Cancer Vaccination

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, cancers can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the cancer vaccination.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Ajani, J. A., J. R. Hecht, et al. (2006). "An open-label, multinational, multicenter study of G17DT vaccination combined with cisplatin and 5-fluorouracil in patients with untreated, advanced gastric or gastroesophageal cancer: the GC4 study." Cancer **106**(9): 1908-16.

BACKGROUND: Gastrin hormone is trophic to in vitro gastric cancer, and the antigastrin antibodies (AGAs) are antiproliferative and antimetastatic. Human gastric cancers overexpress gastrin genes and receptors that react to gastrin's trophic effects. Immunogen G17DT elicits a specific and high-affinity AGA. The authors evaluated G17DT vaccination given with cisplatin plus 5-fluorouracil for the treatment gastric adenocarcinoma. METHODS: In this multicenter, Phase II study, patients received G17DT vaccination intramuscularly on Weeks 1, 5, 9 and 25 and cisplatin plus 5-fluorouracil every 28 days. Eligible patients had untreated, metastatic, or unresectable gastric or gastroesophageal adenocarcinoma with near-normal organ function. The primary endpoint of the study was the over response rate (ORR), and secondary endpoints included overall survival (OS), safety, and the impact of successful vaccination on patient outcome. RESULTS: In total, 103 patients were enrolled in 5 countries. Seven patients who were overdosed inadvertently with 5-fluorouracil (a major protocol violation) were removed from the analysis. The confirmed ORR was 30% in 79 patients who were evaluated for response. The median time-to-progression (TTP) was 5.4 months, and the median survival (MS) was 9.0 months (n = 96 patients). Sixty-five of 94 patients who were vaccinated (69%) had 2 consecutive AGA titers of > or =1 units (successfully vaccinated patients or immune-responders). The TTP was longer in immune-responders than in immune-nonresponders (P = .0005). Similarly, the MS was longer in immune-responders than in immune-nonresponders (10.3 months vs. 3.8 months; P < or =.0001). In a multivariate analysis, successful vaccination was an independent OS prognosticator (P = .0001). G17DT did not have an adverse effect on safety. CONCLUSIONS: The results demonstrated that successful G17DT vaccination was correlated with longer TTP and MS. AGA response was an independent OS prognosticator. A Phase III evaluation of G17DT in gastric cancer is warranted.

Amato, R. J., N. Drury, et al. (2008). "Vaccination of prostate cancer patients with modified vaccinia ankara delivering the tumor antigen 5T4 (TroVax): a phase 2 trial." J Immunother **31**(6): 577-85.

The attenuated vaccinia virus, modified vaccinia Ankara, has been engineered to deliver the tumor antigen 5T4 (TroVax). TroVax has been evaluated in an open-label phase 2 trial in hormone refractory prostate cancer patients in which the vaccine was administered either alone or in combination with granulocyte macrophage-colony stimulating factor (GM-CSF). The comparative safety and immunologic and clinical efficacy of TroVax alone or in combination with GM-CSF was determined. Twenty-seven patients with metastatic hormone refractory prostate cancer were treated with TroVax alone (n=14) or TroVax+GM-CSF (n=13).

5T4-specific cellular and humoral responses were monitored throughout the study. Clinical responses were assessed by quantifying prostate-specific antigen concentrations and measuring changes in tumor burden by computer-assisted tomography scan. TroVax was well tolerated in all patients with no serious adverse events attributed to vaccination. Of 24 immunologically evaluable patients, all mounted 5T4-specific antibody responses. Periods of disease stabilization from 2 to >10 months were observed. Time to progression was significantly greater in patients who mounted 5T4-specific cellular responses compared with those who did not (5.6 vs. 2.3 mo, respectively). There were no objective clinical responses seen in this study. In this study, the combination of GM-CSF with TroVax showed similar clinical and immunologic responses to TroVax alone. The high frequency of 5T4-specific immune responses and relationship with enhanced time to progression is encouraging and warrants further investigation.

Amato, R. J., W. Shingler, et al. (2009). "Vaccination of renal cell cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) alone or administered in combination with interferon-alpha (IFN-alpha): a phase 2 trial." J Immunother **32**(7): 765-72.

Attenuated vaccinia virus, modified vaccinia Ankara (MVA) has been engineered to deliver the tumor antigen 5T4 (TroVax). MVA-5T4 has been evaluated in an open-label phase 2 trial in metastatic renal cell cancer patients in which the vaccine was administered alone or in combination with interferon-alpha-2b (IFN-alpha). The safety, immunologic, and clinical efficacy of MVA-5T4 with or without IFN-alpha was determined. Twenty-eight patients with metastatic renal cell cancer were treated with MVA-5T4 alone (13) or plus IFN-alpha (15). The 5T4-specific cellular and humoral responses were monitored throughout the study. Clinical responses were assessed by measuring changes in tumor burden by computed tomography or magnetic resonance imaging scan. MVA-5T4 was well tolerated with no serious adverse event attributed to vaccination. Of 23 intent-to-treat patients tested for immune responses postvaccination, 22 (96%) mounted 5T4-specific antibody and/or cellular responses. One patient treated with MVA-5T4 plus IFN-alpha showed a partial response for >7 months, whereas an additional 14 patients (7 receiving MVA-5T4 plus IFN and 7 receiving MVA-5T4 alone) showed periods of disease stabilization ranging from 1.73 to 9.60 months. Median progression free survival and overall survival for all intent-to-treat patients was 3.8 months (range: 1 to 11.47 mo) and 12.1 months (range: 1 to 27 mo), respectively. MVA-5T4 administered alone or in combination with IFN-alpha was well tolerated in all patients. Despite the high frequency of 5T4-specific immune responses, it is not possible to conclude that patients are receiving clinical benefit. The results are encouraging and warrant further investigation.

Amato, R. J., W. Shingler, et al. (2008). "Vaccination of renal cell cancer patients with modified vaccinia ankara delivering tumor antigen 5T4 (TroVax) administered with interleukin 2: a phase II trial." Clin Cancer Res **14**(22): 7504-10.

PURPOSE: The attenuated vaccinia virus modified vaccinia ankara (MVA) has been engineered to deliver the tumor antigen 5T4 (TroVax). TroVax has been evaluated in an open-label phase II trial in metastatic renal cell cancer patients in which the vaccine was administered in combination with interleukin-2 (IL-2). The safety, immunologic, and clinical efficacy of TroVax in combination with IL-2 was determined. EXPERIMENTAL DESIGN: Twenty-five patients with metastatic renal cell cancer were treated with TroVax plus IL-2. 5T4-specific cellular and humoral responses were monitored throughout the study. Clinical responses were assessed by measuring changes in tumor burden by computed tomography or magnetic resonance imaging scan. RESULTS: TroVax was well tolerated with no serious adverse event attributed to vaccination. Of 25 intention-to-treat patients, 21 mounted 5T4-specific antibody responses. Two patients showed a complete response for > 24 months and one a partial response for > 12 months. Six patients had disease stabilization from 6 to > 21 months. Median progression-free survival (PFS) and overall survival (OS) were > 3.37 months (range, 1.50- > 24.76) and > 12.87 months (range, 1.90- > 24.76), respectively. A statistically significant relationship was detected between the magnitude of 5T4-specific antibody responses and PFS and OS. CONCLUSION: TroVax in combination with IL-2 was safe and well tolerated in all patients. The high frequency of 5T4-specific immune responses and good clinical response rate are encouraging and warrant further investigation.

Amin, A., L. C. Benavides, et al. (2008). "Assessment of immunologic response and recurrence patterns among patients with clinical recurrence after vaccination with a preventive HER2/neu peptide vaccine: from US Military Cancer Institute Clinical Trials Group Study I-01 and I-02." Cancer Immunol Immunother **57**(12): 1817-25.

BACKGROUND: E75, a HER2/neu immunogenic peptide, is expressed in breast cancer (BCa). We have performed clinical trials of E75 + GM-CSF vaccine in disease-free, node-positive and node-negative BCa patients at high recurrence risk

and recurrences were noted in both control and vaccine groups. METHODS: Among the 186 BCa patients enrolled, 177 completed the study. Patients were HLA typed; the HLA-A2(+)/A3(+) patients were vaccinated; HLA-A2(-)/A3(-) patients were followed as controls. Standard clinicopathological factors, immunologic response to the vaccine, and recurrences were collected and assessed. RESULTS: The control group recurrence rate was 14.8 and 8.3% in the vaccinated group (P = 0.17). Comparing the 8 vaccinated recurrences (V-R) to the 88 vaccinated nonrecurrent patients (V-NR), the V-R group had higher nodal stage (> or = N2: 75 vs. 5%, P = 0.0001) and higher grade tumors (%grade 3: 88 vs. 31%, P = 0.003). The V-R group did not fail to respond immunologically as noted by equivalent dimer responses and post-DTH responses. Compared to control recurrent patients (C-R), V-R patients trended toward higher-grade tumors and hormone-receptor negativity. C-R patients had 50% bone-only recurrences, compared to V-R patients with no bone-only recurrences (P = 0.05). Lastly, V-R mortality rate was 12.5% compared with 41.7% for the C-R group (P = 0.3). CONCLUSIONS: The vaccinated patients who recurred had more aggressive disease compared to V-NR patients. V-R patients had no difference in immune response to the vaccine either in vitro or in vivo. V-R patients, when compared to C-R patients, trended towards more aggressive disease, decreased recurrence rates, decreased mortality, and no bone-only recurrences.

Andersen, M. H., R. B. Sorensen, et al. (2008). "Cancer treatment: the combination of vaccination with other therapies." Cancer Immunol Immunother **57**(11): 1735-43.

Harnessing of the immune system by the development of 'therapeutic' vaccines, for the battle against cancer has been the focus of tremendous research efforts over the past two decades. As an illustration of the impressive amounts of data gathered over the past years, numerous antigens expressed on the surface of cancer cells, have been characterized. To this end, recent years research has focussed on characterization of antigens that play an important role for the growth and survival of cancer cells. Anti-apoptotic molecules like survivin that enhance the survival of cancer cells and facilitate their escape from cytotoxic therapies represent prime vaccination candidates. The characterization of a high number of tumor antigens allow the concurrent or serial immunological targeting of different proteins associated with such cancer traits. Moreover, while vaccination in itself is a promising new approach to fight cancer, the combination with additional therapy could create a number of synergistic effects. Herein we discuss the possibilities and prospects of vaccination when combined with other treatments. In this regard, cell death upon drug exposure may be immunogenic or non-immunogenic depending on the specific chemotherapeutics. Also, chemotherapy represents one of several options available for clearance of CD4+ Foxp3+ regulatory T cells. Moreover, therapies based on monoclonal antibodies may have synergistic potential in combination with vaccination, both when used for targeting of tumor cells and endothelial cells. The efficacy of therapeutic vaccination against cancer will over the next few years be studied in settings taking advantage of strategies in which vaccination is combined with other treatment modalities. These combinations should be based on current knowledge not only regarding the biology of the cancer cell per se, but also considering how treatment may influence the malignant cell population as well as the immune system.

Anonychuk, A. M., C. T. Bauch, et al. (2009). "A cost-utility analysis of cervical cancer vaccination in preadolescent Canadian females." BMC Public Health **9**: 401.

BACKGROUND: Despite the fact that approximately 70% of Canadian women undergo cervical cancer screening at least once every 3 years, approximately 1,300 women were diagnosed with cervical cancer and approximately 380 died from it in 2008. This study estimates the effectiveness and cost-effectiveness of vaccinating 12-year old Canadian females with an AS04-adjuvanted cervical cancer vaccine. The indirect effect of vaccination, via herd immunity, is also estimated. METHODS: A 12-health-state 1-year-cycle Markov model was developed to estimate lifetime HPV related events for a cohort of 12-year old females. Annual transition probabilities between health-states were derived from published literature and Canadian population statistics. The model was calibrated using Canadian cancer statistics. From a healthcare perspective, the cost-effectiveness of introducing a vaccine with efficacy against HPV-16/18 and evidence of cross-protection against other oncogenic HPV types was evaluated in a population undergoing current screening practices. The base-case analysis included 70% screening coverage, 75% vaccination coverage, $135/dose for vaccine, and 3% discount rate on future costs and health effects. Conservative herd immunity effects were taken into account by estimated HPV incidence using a mathematical model parameterized by reported age-stratified sexual mixing data. Sensitivity analyses were performed to address parameter uncertainties. RESULTS: Vaccinating 12-year old females (n = 100,000) was estimated to prevent between 390-633 undiscounted cervical

cancer cases (reduction of 47%-77%) and 168-275 undiscounted deaths (48%-78%) over their lifetime, depending on whether or not herd immunity and cross-protection against other oncogenic HPV types were included. Vaccination was estimated to cost $18,672-$31,687 per QALY-gained, the lower range representing inclusion of cross-protective efficacy and herd immunity. The cost per QALY-gained was most sensitive to duration of vaccine protection, discount rate, and the correlation between probability of screening and probability of vaccination. CONCLUSION: In the context of current screening patterns, vaccination of 12-year old Canadian females with an ASO4-ajuvanted cervical cancer vaccine is estimated to significantly reduce cervical cancer and mortality, and is a cost-effective option. However, the economic attractiveness of vaccination is impacted by the vaccine's duration of protection and the discount rate used in the analysis.

Atanackovic, D., N. K. Altorki, et al. (2008). "Booster vaccination of cancer patients with MAGE-A3 protein reveals long-term immunological memory or tolerance depending on priming." Proc Natl Acad Sci U S A **105**(5): 1650-5.

We previously reported results of a phase II trial in which recombinant MAGE-A3 protein was administered with or without adjuvant AS02B to 18 non-small-cell lung cancer (NSCLC) patients after tumor resection. We found that the presence of adjuvant was essential for the development of humoral and cellular responses against selected MAGE-A3 epitopes. In our current study, 14 patients that still had no evidence of disease up to 3 years after vaccination with MAGE-A3 protein with or without adjuvant received an additional four doses of MAGE-A3 protein with adjuvant AS02B. After just one boost injection, six of seven patients originally vaccinated with MAGE-A3 protein plus adjuvant reached again their peak antibody titers against MAGE-A3 attained during the first vaccination. All seven patients subsequently developed even stronger antibody responses. Furthermore, booster vaccination widened the spectrum of CD4(+) and CD8(+) T cells against various new and known MAGE-A3 epitopes. In contrast, only two of seven patients originally vaccinated with MAGE-A3 protein alone developed high-titer antibodies to MAGE-A3, and all these patients showed very limited CD4(+) and no CD8(+) T cell reactivity, despite now receiving antigen in the presence of adjuvant. Our results underscore the importance of appropriate antigen priming using an adjuvant for generating persistent B and T cell memory and allowing typical booster responses with reimmunization. In contrast, absence of adjuvant at priming compromises further immunization attempts. These data provide an immunological rationale for vaccine design in light of recently reported favorable clinical responses in NSCLC patients after vaccination with MAGE-A3 protein plus adjuvant AS02B.

Ault, K. and K. Reisinger (2007). "Programmatic issues in the implementation of an HPV vaccination program to prevent cervical cancer." Int J Infect Dis **11 Suppl 2**: S26-8.

BACKGROUND: Cervical cancer remains an important health problem even in countries with effective cervical screening programs. HPV vaccines offer great potential for primary prevention of cervical cancer and other HPV-related diseases. PERSPECTIVES: Eventual implementation of an HPV vaccination program raises several key issues, including universal vs. targeted vaccinations, the age and gender of vaccine recipients, the acceptability of this vaccine to health care providers, adolescents, and parents, and the effect of this vaccine on cervical cancer screening. These issues were explored among symposium attendees during an interactive question-and-answer session using computerized voting pads. CONCLUSIONS: Preventative HPV vaccination programs should ideally be executed universally in both women and men with an emphasis on children and adolescents prior to their first sexual experience. Parent education on HPV disease and vaccine efficacy and safety will be critical to the acceptability of HPV vaccination for their children. HPV vaccination will not eliminate the need for Pap screening. Further research will be needed to develop rational and cost-effective cervical surveillance programs for women protected by HPV vaccines.

Avigan, D., B. Vasir, et al. (2004). "Fusion cell vaccination of patients with metastatic breast and renal cancer induces immunological and clinical responses." Clin Cancer Res **10**(14): 4699-708.

PURPOSE: Dendritic cells (DCs) are potent antigen-presenting cells that are uniquely capable of inducing tumor-specific immune responses. We have conducted a Phase I trial in which patients with metastatic breast and renal cancer were treated with a vaccine prepared by fusing autologous tumor and DCs. EXPERIMENTAL DESIGN: Accessible tumor tissue was disrupted into single cell suspensions. Autologous DCs were prepared from adherent peripheral blood mononuclear cells that were obtained by leukapheresis and cultured in granulocyte macrophage colony-stimulating factor, interleukin 4, and autologous plasma. Tumor cells and DCs were cocultured in the presence of polyethylene glycol to generate the fusions. Fusion cells were quantified by determining the percentage of cells that coexpress tumor and DC markers. Patients were vaccinated with

fusion cells at 3-week intervals and assessed weekly for toxicity, and tumor response was assessed at 1, 3, and 6 months after completion of vaccination. RESULTS: The vaccine was generated for 32 patients. Twenty-three patients were vaccinated with 1 x 10(5) to 4 x 10(6) fusion cells. Fusion cells coexpressed tumor and DC antigens and stimulated allogeneic T-cell proliferation. There was no significant treatment-related toxicity and no clinical evidence of autoimmunity. In a subset of patients, vaccination resulted in an increased percentage of CD4 and CD8+ T cells expressing intracellular IFN-gamma in response to in vitro exposure to tumor lysate. Two patients with breast cancer exhibited disease regressions, including a near complete response of a large chest wall mass. Five patients with renal carcinoma and one patient with breast cancer had disease stabilization. CONCLUSIONS: Our findings demonstrate that fusion cell vaccination of patients with metastatic breast and renal cancer is a feasible, nontoxic approach associated with the induction of immunological and clinical antitumor responses.

Avritscher, E. B., C. D. Cooksley, et al. (2007). "Cost-effectiveness of influenza vaccination in working-age cancer patients." Cancer **109**(11): 2357-64.

BACKGROUND: Despite recommendations to immunize all patients at an increased risk of influenza complications, the vaccine utilization among high-risk nonelderly adults remains low and its cost-effectiveness is unclear. In the current study, the authors analyzed the cost-effectiveness of influenza vaccination in working-age (ages 20-64 years) cancer patients. METHODS: The authors developed a decision-analytic model, from the societal perspective, using epidemiologic, vaccine effectiveness, resource utilization, cost, survival, and utility data from published sources, supplemented with data collected from the authors' own institutional accounting system. Two strategies were compared: influenza vaccination of working-age cancer patients and no vaccination. The base-case patient was assumed to be a 51-year-old cancer patient (the mean age for the National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER] population of working-age patients within 5 years of cancer diagnosis). RESULTS: The effectiveness of the influenza vaccine was 6.02 quality-adjusted life-years (QALYs) at a cost of $30.10. The effectiveness of the no vaccination strategy was 6.01 QALYs at a cost of $27.86. Compared with the no vaccination strategy, the incremental cost-effectiveness ratio of vaccinating working-age cancer patients would be $224.00 per QALY gained. Using the benchmark of $50,000 per QALY, the model was only sensitive to changes in cancer survival (threshold of 2.8 months). CONCLUSIONS: The influenza vaccine is cost-effective for working-age cancer patients with a life expectancy of >or=3 months. All working-age cancer patients who are within 5 years of cancer diagnosis and have a life expectancy of at least 3 months should be vaccinated against influenza.

Barbuto, J. A., L. F. Ensina, et al. (2004). "Dendritic cell-tumor cell hybrid vaccination for metastatic cancer." Cancer Immunol Immunother **53**(12): 1111-8.

Dendritic cells are the most potent antigen-presenting cells, and the possibility of their use for cancer vaccination has renewed the interest in this therapeutic modality. Nevertheless, the ideal immunization protocol with these cells has not been described yet. In this paper we describe the preliminary results of a protocol using autologous tumor and allogeneic dendritic hybrid cell vaccination every 6 weeks, for metastatic melanoma and renal cell carcinoma (RCC) patients. Thirty-five patients were enrolled between March 2001 and March 2003. Though all patients included presented with large tumor burdens and progressive diseases, 71% of them experienced stability after vaccination, with durations up to 19 months. Among RCC patients 3/22 (14%) presented objective responses. The median time to progression was 4 months for melanoma and 5.7 months for RCC patients; no significant untoward effects were noted. Furthermore, immune function, as evaluated by cutaneous delayed-type hypersensitivity reactions to recall antigens and by peripheral blood proliferative responses to tumor-specific and nonspecific stimuli, presented a clear tendency to recover in vaccinated patients. These data indicate that dendritic cell-tumor cell hybrid vaccination affects the natural history of advanced cancer and provide support for its study in less advanced patients, who should, more likely, benefit even more from this approach.

Barnabas, R. V., P. Laukkanen, et al. (2006). "Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses." PLoS Med **3**(5): e138.

BACKGROUND: Candidate human papillomavirus (HPV) vaccines have demonstrated almost 90%-100% efficacy in preventing persistent, type-specific HPV infection over 18 mo in clinical trials. If these vaccines go on to demonstrate prevention of precancerous lesions in phase III clinical trials, they will be licensed for public use in the near future. How these vaccines will be used in countries with national cervical cancer screening

programmes is an important question. METHODS AND FINDINGS: We developed a transmission model of HPV 16 infection and progression to cervical cancer and calibrated it to Finnish HPV 16 seroprevalence over time. The model was used to estimate the transmission probability of the virus, to look at the effect of changes in patterns of sexual behaviour and smoking on age-specific trends in cancer incidence, and to explore the impact of HPV 16 vaccination. We estimated a high per-partnership transmission probability of HPV 16, of 0.6. The modelling analyses showed that changes in sexual behaviour and smoking accounted, in part, for the increase seen in cervical cancer incidence in 35- to 39-y-old women from 1990 to 1999. At both low (10% in opportunistic immunisation) and high (90% in a national immunisation programme) coverage of the adolescent population, vaccinating women and men had little benefit over vaccinating women alone. We estimate that vaccinating 90% of young women before sexual debut has the potential to decrease HPV type-specific (e.g., type 16) cervical cancer incidence by 91%. If older women are more likely to have persistent infections and progress to cancer, then vaccination with a duration of protection of less than 15 y could result in an older susceptible cohort and no decrease in cancer incidence. While vaccination has the potential to significantly reduce type-specific cancer incidence, its combination with screening further improves cancer prevention. CONCLUSIONS: HPV vaccination has the potential to significantly decrease HPV type-specific cervical cancer incidence. High vaccine coverage of women alone, sustained over many decades, with a long duration of vaccine-conferred protection, would have the greatest impact on type-specific cancer incidence. This level of coverage could be achieved through national coordinated programmes, with surveillance to detect cancers caused by nonvaccine oncogenic HPV types.

Barrou, B., G. Benoit, et al. (2004). "Vaccination of prostatectomized prostate cancer patients in biochemical relapse, with autologous dendritic cells pulsed with recombinant human PSA." Cancer Immunol Immunother **53**(5): 453-60.

This study was conducted in prostate cancer patients in biochemical relapse after radical prostatectomy, to assess the feasibility, safety, and immunogenicity of therapeutic vaccination with autologous dendritic cells (DCs) pulsed with human recombinant prostate-specific antigen (PSA) (Dendritophage-rPSA). Twenty-four patients with histologically proven prostate carcinoma and an isolated postoperative rise of serum PSA (>1 ng/ml to 10 ng/ml) after radical prostatectomy were included. The patients received nine administrations of PSA-loaded DCs by combined intravenous, subcutaneous, and intradermal routes over 21 weeks. Postbaseline blood tests were performed at months 1, 3, 6, 9, and 12 (PSA levels), at months 6 and 12 (circulating prostate cancer cells), at month 6 (anti-PSA IgG and IgM antibodies), and at up to eight time points before, during, and after immunization (PSA-specific T cells). Circulating prostate cancer cells detected in six patients at baseline were undetectable at 6 months and remained undetectable at 12 months. Eleven patients had a postbaseline transient PSA decrease on one to three occasions, predominantly occurring at month 1 (7 patients) or month 3 (2 patients). Maximum PSA decrease ranged from 6% to 39%. PSA decrease on at least one occasion was more frequent in patients with low Gleason score (p=0.016) at prostatectomy and with positive skin tests at study baseline (p=0.04). PSA-specific T cells were detected ex vivo by ELISpot for IFN-gamma in 7 patients before vaccination and in 11 patients after vaccination. Of the latter 11 patients, 5 had detectable T cells both before and during the vaccination period, 4 only during the vaccination period, while 2 patients could for technical reasons not be assessed prevaccination. No induction of anti-PSA IgG or IgM antibodies was detected. There were no serious adverse events or otherwise severe toxicities observed during the trial. Immunization with Dendritophage-rPSA was feasible and safe in this cohort of patients. An immune response specific for PSA could be detected in some patients. A notable effect was the disappearance of circulating prostate cells in all patients who were RT-PCR positive before vaccination.

Bayas, J. M., L. Costas, et al. (2008). "Cervical cancer vaccination indications, efficacy, and side effects." Gynecol Oncol **110**(3 Suppl 2): S11-4.

Due to the limited contact of the human papillomavirus (HPV) with the immune system, past infection does not guarantee lasting protection. Two preventive vaccines (Gardasil and Cervarix) that can impede persistent HPV infection and its consequences are now available. They use structural L1 capsular proteins obtained by genetic recombination and antigens for genotypes 16 and 18, which are responsible for around 70% of cases of uterine cancer worldwide. Evaluation of their protective efficacy is based on the capacity of the vaccine to prevent persistent infection and cervical intraepithelial neoplasia (CIN). Phase I and II trials showed the safety of these vaccines and their capacity to produce very-high titers of antibodies (low or non-existent after natural infection). Phase II and III trials have confirmed these aspects and shown an efficacy of nearly 100% in the protocol analysis in preventing infection and the CIN associated with oncogenic

vaccine genotypes. Some trials have also shown cross-protection against infections produced by other genotypes (such as 45 and 31). The optimal vaccination strategy is vaccination of girls aged 8-14 years. Other strategies should include the catch-up of adolescent and women not yet sexually-active, as well as the vaccination of sexually-active women. The progressive development of primary prevention strategies should coexist with secondary prevention with redesigned screening programs. The successful development of vaccination programs will require the support of public health authorities, the coordination of health workers from different areas and increased public awareness.

Bernhardt, S. L., M. K. Gjertsen, et al. (2006). "Telomerase peptide vaccination of patients with non-resectable pancreatic cancer: A dose escalating phase I/II study." Br J Cancer **95**(11): 1474-82.

Patients with inoperable pancreatic cancer have a dismal prognosis with a mean life expectancy of 3-6 months. New treatment modalities are thus urgently needed. Telomerase is expressed in 85-90% of pancreas cancer, and immunogenic telomerase peptides have been characterised. A phase I/II study was conducted to investigate the safety, tolerability, and immunogenecity of telomerase peptide vaccination. Survival of the patients was also recorded. Forty-eight patients with non-resectable pancreatic cancer received intradermal injections of the telomerase peptide GV1001 at three dose levels, in combination with granulocyte-macrophage colony-stimulating factor. The treatment period was 10 weeks. Monthly booster vaccinations were offered as follow-up treatment. Immune responses were measured as delayed-type hypersensitivity skin reaction and in vitro T-cell proliferation. GV1001 was well tolerated. Immune responses were observed in 24 of 38 evaluable patients, with the highest ratio (75%) in the intermediate dose group. Twenty-seven evaluable patients completed the study. Median survival for the intermediate dose-group was 8.6 months, significantly longer for the low- ($P = 0.006$) and high-dose groups ($P = 0.05$). One-year survival for the evaluable patients in the intermediate dose group was 25%. The results demonstrate that GV1001 is immunogenic and safe to use. The survival data indicate that induction of an immune response is correlated with prolonged survival, and the vaccine may offer a new treatment option for pancreatic cancer patients, encouraging further clinical studies.

Bharat, A., N. Benshoff, et al. (2008). "Characterization of the role of CD8+T cells in breast cancer immunity following mammaglobin-A DNA vaccination using HLA-class-I tetramers." Breast Cancer Res Treat **110**(3): 453-63.

INTRODUCTION: Mammaglobin-A(mam-A) is expressed in over 80% of human breast tumors. We recently reported that mam-A DNA vaccination resulted in breast cancer immunity in a preclinical model. Here we investigated whether mam-A HLA-class-I tetramers could be used to monitor and define the role of CD8(+)cytotoxic T-lymphocytes(CTL) in mediating breast cancer immunity following mam-A DNA vaccination. STUDY DESIGN: Mam-A DNA vaccination was performed in HLA-A2(+)huCD8(+)transgenic mice. HLA-A2 tetramers carrying the immunodominant mamA2.1 peptide were used to monitor CD8(+)CTL. Human breast cancer colonies were developed in immunodeficient SCID-beige mice. ELISPOT was used to correlate frequency of mamA2.1 tetramer(+)CD8(+)T cells and IFN-gamma production [spots per million cells (spm)] in human subjects. RESULTS: Vaccination of HLA-A2(+)huCD8(+) mice with mam-A DNA vaccine, but not empty vector, led to the expansion of mamA2.1 tetramer(+)CD8(+)T-cells in peripheral blood (<0.5% pre-vaccination compared to >2.0% post-vaccination). CD8(+)T cells from vaccinated mice specifically lysed UACC-812(HLA-A2(+)/mam-A(+), 25% lysis) but not MDA-MB-415(HLA-A2(-)/mam-A(+)) or MCF-7(HLA-A2(+)/mam-A(-)) breast cancer cells. Adoptive transfer of purified CD8(+)T cells from vaccinated mice into immunodeficient SCID-beige mice with established human breast cancer colonies led to tetramer(+)CD8(+)T-cell infiltration with regression of UACC-812 but not MCF-7 tumors. HLA-A2(+) breast cancer patients revealed increased frequency of mamA2.1 tetramer(+)CD8(+)T-cells compared to normal controls (2.86 +/- 0.8% vs. 0.71 +/- 0.1%, $P = 0.01$) that correlated with the IFN-gamma response to mamA2.1 peptide (48.1 +/- 20.9 vs. 2.9 +/- 0.8 spm, $P = 0.03$). CONCLUSIONS: CD8(+)T-cells are crucial in mediating breast cancer immunity following mam-A DNA vaccination. Mam-A HLA-class-I tetramers can be effectively used to monitor development of CD8(+)T-cells following mam-A vaccination.

Bolonaki, I., A. Kotsakis, et al. (2007). "Vaccination of patients with advanced non-small-cell lung cancer with an optimized cryptic human telomerase reverse transcriptase peptide." J Clin Oncol **25**(19): 2727-34.

PURPOSE: To evaluate the immunological and clinical response as well as the safety of the optimized peptide telomerase reverse transcriptase p572Y (TERT572Y) presented by HLA-A*0201 in patients with advanced non-small-cell lung cancer (NSCLC). PATIENTS AND METHODS: Twenty-two patients with advanced NSCLC and residual (n =

8) or progressive disease (PD; n = 14) following chemotherapy and/or radiotherapy received two subcutaneous injections of the optimized TERT572Y peptide followed by four injections of the native TERT572 peptide administered every 3 weeks. Peptide-specific immune responses were monitored by enzyme-linked immunosorbent spot assay and/or TERT572Y pentamer staining. RESULTS: Twelve (54.5%) of 22 patients completed the vaccination program. Toxicity consisted primarily of local skin reactions. TERT572-specific CD8+ cells were detected in 16 (76.2%) of 21 patients after the second vaccination, and 10 (90.9%) of 11 patients after the sixth vaccination. Stable disease (SD) occurred in eight (36.4%) of 22 vaccinated patients, with three (13.6%) having had PD before entering the study. The median duration of SD was 11.2 months. After a median follow-up of 10.0 months, patients with early developed immunological response (n = 16) had a significantly longer time to progression and overall survival (OS) than nonresponders (n = 5; log-rank tests P = .046 and P = .012, respectively). The estimated median OS was 30.0 months (range, 2.8 to 40.0 months) and 4.1 months (range, 2.4 to 10.9 months) for responders and nonresponders, respectively. CONCLUSION: TERT572Y peptide vaccine is well tolerated and effective in eliciting a specific T cell immunity. Immunological response is associated with prolonged survival. These results are encouraging and warrant further evaluation in a randomized study.

Brill, T. H., H. R. Kubler, et al. (2009). "Therapeutic vaccination with an interleukin-2-interferon-gamma-secreting allogeneic tumor vaccine in patients with progressive castration-resistant prostate cancer: a phase I/II trial." Hum Gene Ther **20**(12): 1641-51.

Immunotherapy with whole cell cancer vaccines has been tested in various tumor types. This study investigated the safety profile and antitumor activity of an allogeneic prostate carcinoma cell line, LNCaP, expressing recombinant human interleukin-2 and human interferon-gamma. Thirty HLA-A*0201-matched patients with progressive, castration-resistant prostate cancer received four intradermal injections on days 1, 15, 29, and 92, and then every 90 days, as long as no tumor progression occurred. Three patients received a dose level of 7.5 million cells, and 27 patients received 15 million cells per injection. The primary study criteria were safety and the difference in prostate-specific antigen doubling time (PSA-DT), determined in the pretreatment phase (before the start of vaccination) and in the trial treatment phase (during vaccination). No dose-limiting or autoimmune toxicity was seen. During vaccination there was a significant prolongation of the PSA-DT compared with the prevaccination period (prolongation from 63 to 114 days; $p < 0.01$; intention to treat). In addition, results showed a period of PSA stabilization of at least 12 weeks, together with stable bone scans in 12 of 30 patients, and 3 patients sustained a >50% decrease in PSA versus baseline. The median overall survival time from first vaccination was 32 months (mean value, 34 months). Immune monitoring revealed T cell stimulation in the majority of patients. This vaccine strategy was found to be safe and well tolerated and was accompanied by prolongation of PSA-DT. The results of this trial warrant clinical development of this vaccine.

Brinkman, J. A., A. S. Caffrey, et al. (2005). "The impact of anti HPV vaccination on cervical cancer incidence and HPV induced cervical lesions: consequences for clinical management." Eur J Gynaecol Oncol **26**(2): 129-42.

Cervical cancer is the second most common cause of cancer-related deaths in women worldwide. Screening for cervical cancer is accomplished utilizing a Pap smear and pelvic exam. While this technology is widely available and has reduced cervical cancer incidence in industrialized nations, it is not readily available in third world countries in which cervical cancer incidence and mortality is high. Development of cervical cancer is associated with infection with high risk types of human papillomavirus (HPV) creating a unique opportunity to prevent or treat cervical cancer through anti-viral vaccination strategies. Several strategies have been examined in clinical trials for both the prevention of HPV infection and the treatment of pre-existing HPV-related disease. Clinical trials utilizing prophylactic vaccines containing virus-like particles (VLPs) indicate good vaccine efficacy and it is predicted that a prophylactic vaccine may be available within the next five years. But, preclinical research in this area continues in order to deal with issues such as cost of vaccination in underserved third world populations. A majority of clinical trials using therapeutic agents which aim to prevent the progression of pre-existing HPV associated lesions or cancers have shown limited efficacy in eradicating established tumors in humans possibly due to examining patients with more advanced-stage cancer who tend to have decreased immune function. Future trends in clinical trials with therapeutic agents will examine patients with early stage cancers or pre-invasive lesions in order to prevent invasive cervical cancer. Meanwhile, preclinical studies in this field continue and include the further exploration of peptide or protein vaccination, and the delivery of HPV antigens in DNA-based vaccines or in viral vectors. Given that cervical cancers are caused by the human

papillomavirus, the prospect of therapeutic vaccination to treat existing lesions and prophylactic vaccination to prevent persistent infection with the virus are high and may be implemented in the near future. The consequences for clinical management may include a significant reduction in the frequency of Pap smear screening in the case of prophylactic vaccines, and the availability of less invasive and disfiguring treatment options for women with pre-existing HPV associated lesions in the case of therapeutic vaccines. Implementation of both prophylactic and therapeutic vaccine regimens could result in a significant reduction of health care costs and reduction of worldwide cervical cancer incidence.

Brunsvig, P. F., S. Aamdal, et al. (2006). "Telomerase peptide vaccination: a phase I/II study in patients with non-small cell lung cancer." Cancer Immunol Immunother **55**(12): 1553-64.

PURPOSE: A phase I/II study was conducted to investigate the safety, tolerability and clinical response to vaccination with a combination of telomerase peptides GV1001 (hTERT: 611-626) and HR2822 (hTERT: 540-548) in patients with non-small cell lung cancer. EXPERIMENTAL DESIGN: Twenty-six patients with non-small cell lung cancer received intradermal administrations of either 60 nmole (112 microg) or 300 nmole (560 microg) GV1001 in combination with 60 nM (68.4 microg) HR2822 and granulocyte macrophage-colony stimulating factor. The treatment period was 10 weeks. Booster vaccinations with 300 nM GV1001 were offered as follow-up. Monitoring of blood samples, clinical examination and radiological staging were performed regularly. Immune responses were measured as delayed-type hypersensitivity skin reaction and in vitro T cell proliferation. Bone marrow function was monitored in long time survivors. RESULTS: The treatment was well tolerated with minor side effects. No bone marrow toxicities were observed in long time survivors with immune responses. Immune responses against GV1001 were detected in 11 of 24 evaluable patients during the primary regimen and in additional two patients following booster injections. Two patients responded to HR2822. Cloned GV1001-specific CD4+ T cells displayed a Th1 cytokine profile and recognized autologous antigen presenting cells pulsed with recombinant telomerase protein. A complete tumor response was observed in one patient who developed GV1001-specific cytotoxic T cells that could be cloned from peripheral blood. CONCLUSION: The results demonstrate that GV1001 and HR2822 are immunogenic and safe to use in patients with NSCLC. Induction of GV1001-specific immune responses may result in objective tumor responses. Based on these initial encouraging results, further clinical studies of GV1001 in NSCLC patients are warranted.

Burgdorf, S. K., M. H. Claesson, et al. (2009). "Changes in cytokine and biomarker blood levels in patients with colorectal cancer during dendritic cell-based vaccination." Acta Oncol **48**(8): 1157-64.

INTRODUCTION. Immunotherapy based on dendritic cell vaccination has exciting perspectives for treatment of cancer. In order to clarify immunological mechanisms during vaccination it is essential with intensive monitoring of the responses. This may lead to optimization of treatment and prediction of responding patients. The aim of this study was to evaluate cytokine and biomarker responses in patients with colorectal cancer treated with a cancer vaccine based on dendritic cells pulsed with an allogeneic melanoma cell lysate. MATERIAL AND METHODS. Plasma and serum samples were collected prior to vaccination and continuously during treatment. GM-CSF, IL-2, IL-6, TNF-alpha, IFN-gamma, IL-4, IL-8, IL-1b, IL-5, IL-10, IL-12, MIP-1b, IP-10 and Eotaxin were analyzed in a multiplex assay with a Luminex 100 instrument. CEA and TIMP-1 were analysed on ELISA platforms. RESULTS. Patients achieving stable disease showed increasing levels of plasma GM-CSF, TNF-alpha, IFN-gamma, IL-2, and IL-5. Patients with progressive disease showed significant increase in CEA and TIMP-1 levels, while patients with stable disease showed relatively unaltered levels. CONCLUSION. The increased levels of key pro-inflammatory cytokines in serum of patients who achieved stable disease following vaccination suggest the occurrence of vaccine-induced Th1 responses. Since Th1 responses seem to be essential in cancer immunotherapy this may indicate a therapeutic potential of the vaccine.

Castellsague, X., A. Schneider, et al. (2009). "HPV vaccination against cervical cancer in women above 25 years of age: key considerations and current perspectives." Gynecol Oncol **115**(3 Suppl): S15-23.

OBJECTIVE: Vaccination of young women (15-25 years of age) against human papillomavirus (HPV) has been shown to be very efficacious in preventing the development of moderate or severe cervical precancerous lesions associated with HPV-16 or -18. As the highest rates of new infections with high-risk (i.e., oncogenic) HPV types occur in the first years following sexual debut, most existing guidelines and recommendations advise on vaccinating young girls. We consider oncogenic HPV infection and the risk of developing cervical cancer in women over 25 years of age and whether they would also benefit from vaccination against HPV. METHODS: We reviewed all available literature on oncogenic HPV infection

and the risk of developing cervical cancer in women over 25 years of age. RESULTS: HPV vaccination is likely to be beneficial to sexually active women due to their continuous risk of acquiring new HPV infections and of developing cervical intraepithelial neoplasia (CIN) and cervical cancer. Clinical trial data show that the HPV-16/18 AS04-adjuvanted vaccine is safe and immunogenic in women up to the age of 55 years, whilst preliminary data with the quadrivalent vaccine demonstrated evidence of safety, immunogenicity and high-level efficacy in women 24 to 45 years of age. HPV vaccination in women over 25 years of age is already approved in several countries, and these women are individually seeking advice on vaccination from healthcare professionals. The predicted reduction in cost benefit of vaccination with increasing age, however, is likely to limit the implementation of routine vaccination beyond the late 20s. CONCLUSION: The priority of routine vaccination programmes must be to target girls and young women, with catch-up programmes that extend to age 25/26 when resources allow. For sexually active women over the age of 25, HPV vaccination can be considered on an individual basis, as most will have the potential to benefit from vaccination.

Castro, F., B. Leal, et al. (2009). "Vaccination with Mage-b DNA induces CD8 T-cell responses at young but not old age in mice with metastatic breast cancer." Br J Cancer **101**(8): 1329-37.

BACKGROUND: Elderly individuals react less efficiently to vaccines than do adults, mainly because of T-cell unresponsiveness. In this study, we analysed whether tumour-associated antigen (TAA)-specific CD8 T-cell responses could be induced by vaccination in old mice with metastatic breast cancer. METHODS: The effect of pcDNA-3.1- and Listeria-based vaccines, expressing TAA Mage-b, on Mage-b-specific immune responses was tested in spleens and draining lymph nodes (LNs) of mild (4TO7cg) and aggressive (4T1) syngeneic metastatic mouse breast tumour models at young (3 months) and old (20 months) age. RESULTS: Interferon gamma and interleukin-2 levels increased significantly in draining LNs and spleens of Mage-b-vaccinated mice compared with those in control groups at young but not old age in both mouse tumour models. A significant increase was observed in the number of IFNgamma-producing Mage-b-specific CD8 T cells after Mage-b vaccination in the 4T1 model at young but not old age. This correlated with a reduced protective effect of Mage-b vaccination against metastatic breast cancer at old compared with young age. CONCLUSIONS: The absence of CD8 T-cell responses after Mage-b vaccination and the accompanying reduced protection against metastatic breast cancer in old compared with young mice point towards the need for tailoring cancer vaccination to older age.

Cavallo, F. (2005). "5th European conference on Progress in Vaccination Against Cancer. 20-21 September 2005, Athens, Greece." Expert Opin Biol Ther **5**(12): 1647-51.

'Progress In Vaccination Against Cancer' (PIVAC) examines the latest advances in tumour immunology and their clinical applications. Previous conferences were held in Blaubeuren, London, Cambridge, Oxford, Copenhagen, Stockholm, Nottingham and Freudenstadt-Lauterbad in the Black Forest. The residential format of these conferences encourages interactions between participants and permits a focussed discussion on the new data and concepts. The main topic of the 5th European PIVAC was the induction and maintenance of an active immune memory against cancer. The results of clinical trials with different cancer vaccines were presented. The correlations between tumour regression and immune response, the role of innate and specific immunity, and ways of enhancing these two arms of the antitumour response were explored. Particular attention was devoted to the presence and function of regulatory T cells as a prelude to improving the design of these trials and understanding why they have produced unimpressive results. A consensus was reached on the need to combine vaccination with strategies for suppressing regulatory T cell function. The immune-escape mechanisms of tumours and the emerging importance of some newly discovered mutations were also fully discussed.

Cavallo, F., R. Offringa, et al. (2006). "Vaccination for treatment and prevention of cancer in animal models." Adv Immunol **90**: 175-213.

Two approaches to immunological intervention in tumor-host interactions in mouse models are discussed in this review. The first is described with reference to experiments in which CD8(+) T lymphocytes are used to kill established transplantable tumors. Peptides and their optimal presentation by dendritic cells and intervention in immune regulatory mechanisms are the key issues for efficient induction of T-killer cell-mediated tumor eradication. The time frame of tumor therapy and the threat imposed by tumor growth in transplantable models and cancer patients require the induction of a robust T-cell reaction. Prevention of the progression of small preneoplastic lesions, on the other hand, requires the significant and prolonged immune protection sought in the second approach. This is based on antibody production and the coordinated activation of multiple low-avidity cell-mediated

mechanisms elicited by DNA vaccination in genetically modified cancer-prone mice, transgenic for a mutant Her-2/neu growth factor receptor expressed at the plasma membrane surface of preneoplastic mammary gland epithelial cells. Vaccination with appropriate DNA formulations results in prolonged immune inhibition of the progression of preneoplastic mammary lesions but is ineffective against established tumors. The use of molecularly defined adjuvants and intervention in immune regulatory mechanisms are critical in both the elicitation of an effective T-cell mediated reaction required for tumor debulking in the first set of models and the induction by vaccination of a sustained immune memory able to prevent the expansion of preneoplastic lesions in genetically cancer-prone mice.

Coupe, V. M., J. van Ginkel, et al. (2009). "HPV16/18 vaccination to prevent cervical cancer in The Netherlands: model-based cost-effectiveness." Int J Cancer **124**(4): 970-8.

We evaluated the cost-effectiveness of HPV16/18 vaccination for girls aged 12 years in The Netherlands in addition to cervical cancer screening. For this purpose, we developed a simulation model that describes the relation between each of the high-risk human papillomavirus (hrHPV) types and cervical disease, allowing the occurrence of multiple type-specific infections. Model parameters were derived from Dutch cohort studies, including a large population-based screening trial, and from the national cervical cancer registry. The model satisfactorily reproduced Dutch data on HPV infection and the presence of cervical lesions. For our base-case scenario in which 85% of the girls aged 12 years were vaccinated against types 16/18 (95% efficacy, lifelong protection), the model predicted a decrease of 60% in the number of cervical cancer cases and cervical cancer deaths indicating that substantial health benefits can be achieved. Health savings were robust against changes in the vaccine efficacy (varied from 85% to 98%) but savings showed a substantial reduction when the efficacy started waning 10 years after vaccination. The discounted costs per quality-adjusted life year (QALY) were euro 19,500/QALY (range euro 11,000 to euro 25,000/QALY) and lied near the cost-effectiveness threshold of euro 20,000/QALY used in The Netherlands. The simulations further showed that vaccination cannot replace screening because vaccination without screening was less effective than screening in preventing cancer in women over 40 years of age. In conclusion, our model results support the implementation of HPV16/18 vaccination in young women in addition to cervical cancer screening.

Cranmer, L. D., K. T. Trevor, et al. (2004). "Clinical applications of dendritic cell vaccination in the treatment of cancer." Cancer Immunol Immunother **53**(4): 275-306.

Dendritic cell (DC) immunotherapy has shown significant promise in animal studies as a potential treatment for cancer. Its application in the clinic depends on the results of human trials. Here, we review the published clinical trials of cancer immunotherapy using exogenously antigen-exposed DCs. We begin with a short review of general properties and considerations in the design of such vaccines. We then review trials by disease type. Despite great efforts on the part of individual investigative groups, most trials to date have not yielded data from which firm conclusions can be drawn. The reasons for this include nonstandard DC preparation and vaccination protocols, use of different antigen preparations, variable means of immune assessment, and nonrigorous criteria for defining clinical response. While extensive animal studies have been conducted using DCs, optimal parameters in humans remain to be established. Unanswered questions include optimal cell dose, use of mature versus immature DCs for vaccination, optimal antigen preparation, optimal route, and optimal means of assessing immune response. It is critical that these questions be answered, as DC therapy is labor- and resource-intensive. Cooperation is needed on the part of the many investigators in the field to address these issues. If such cooperation is not forthcoming, the critical studies that will be required to make DC therapy a clinically and commercially viable enterprise will not take place, and this therapy, so promising in preclinical studies, will not be able to compete with the many other new approaches to cancer therapy presently in development. Trials published in print through June 2003 are included. We exclude single case reports, except where relevant, and trials with so many variables as to prevent interpretation about DC therapy effects.

Danet-Desnoyers, G. A., J. L. Luongo, et al. (2005). "Telomerase vaccination has no detectable effect on SCID-repopulating and colony-forming activities in the bone marrow of cancer patients." Exp Hematol **33**(11): 1275-80.

OBJECTIVES: The telomerase reverse transcriptase hTERT is a widely expressed tumor-associated antigen recognized by cytotoxic T lymphocytes (CTL). We have previously shown that vaccination of cancer patients against hTERT induces functional anti-tumor CTL in vivo, but it is not known whether hTERT vaccination harms normal cells expressing the enzyme, especially hematopoietic stem

cells and progenitors. PATIENTS AND METHODS: We employed colony-forming cell (CFC) assays, long-term in vitro cultures, and nonobese diabetic/severe combined immunodeficient (NOD/SCID) repopulation studies to evaluate the effects of hTERT vaccination on hematopoietic progenitors and stem cells in cancer patients following treatment. RESULTS: Using bone marrow samples obtained from cancer patients before and after vaccination, we found that there was no significant decline in the frequency of granulocyte, macrophage or erythroid CFCs using CFC assays or long-term in vitro cultures. In NOD/SCID mice, human hematopoietic reconstitution was easily detected, without quantitative or qualitative differences between pre- and postvaccine samples. CONCLUSION: These findings suggest that induction of tumor-lytic hTERT-specific T cells in vivo by vaccination does not result in a detectable decline in hematopoietic potential despite the expression of hTERT and major histocompatibility complex class I in bone marrow progenitors and stem cells. Thus, even for self-antigens such as telomerase, tumor immunity does not necessarily involve autoimmunity in normal tissues that share the target.

David, M. P., K. Van Herck, et al. (2009). "Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses." Gynecol Oncol **115**(3 Suppl): S1-6.

OBJECTIVES: Strong and sustained HPV-16 and -18 antibody responses have been observed in previously unexposed women aged 15-25 years vaccinated with the AS04-adjuvanted HPV-16/18 L1 virus-like particle vaccine. While awaiting the extended results of ongoing trials, our objective was to predict the long-term persistence of anti-HPV-16/18 antibodies in vaccinees by applying three statistical models using immunogenicity data from vaccinated women with serum samples collected up to 6.4 years after first vaccination. Two different data lock-points (up to 5.5 years and up to 6.4 years) were used to assess the robustness of the models. METHODS: Three statistical models were applied to estimate the long-term persistence of anti-HPV-16/18 antibodies in 393 women vaccinated with the AS04-adjuvanted HPV-16/18 vaccine. Individual antibody levels for each study participant at each timepoint up to 6.4 years were input to previously published power-law and modified power-law models. The power-law model estimates antibody decay over time. The modified power-law model takes into account both antibody persistence over time and immune memory. A third model, the piece-wise model, fits the data based on three different non-overlapping intervals (between Months 7 and 12, Months 12 and 21, and over 21 months), corresponding to the observed decay of vaccine-induced antibodies. RESULTS: HPV-16 and -18 antibodies peaked at Month 7 and gradually plateaued at Months 18-24 and remained stable through 6.4 years. Mean antibody levels at the last timepoint were several fold higher than those associated with natural infection. All three models predict that HPV-16 and -18 mean antibody levels will remain well above those associated with natural infection for at least 20 years, when using data from 5.5 as well as 6.4 years' follow-up. Predictions are similar for the modified power-law model and improve with longer follow-up for both the power-law and the piece-wise models. CONCLUSIONS: Vaccination with the AS04-adjuvanted HPV-16/18 vaccine is predicted to provide long-term persistence for both HPV-16 and -18 antibodies, independent of the statistical model applied. Model predictions are based on conservative mathematical assumptions. Since the input of longer term data of up to 6.4 years showed an improved profile compared with that for data up to 5.5 years, the predictions of antibody persistence based on population means are conservative when predicting that antibody levels will remain well above levels induced by natural infection for 20 years.

Derhovanessian, E., V. Adams, et al. (2009). "Pretreatment frequency of circulating IL-17+ CD4+ T-cells, but not Tregs, correlates with clinical response to whole-cell vaccination in prostate cancer patients." Int J Cancer **125**(6): 1372-9.

The aim of this study was to determine the prognostic implications of the pretreatment level of Th17 cells compared with regulatory T-cell status in prostate cancer patients receiving active whole cell immunotherapy. Ten-color flow cytometry was used to analyze IL-17-producing CD4(+) T-cells in the peripheral blood of hormone-resistant non-bone metastatic prostate cancer patients prior to immunotherapy with an allogeneic whole-cell vaccine. Surface expression of the chemokine receptors CCR4 and CCR6 was used to further subdivide IL-17-producing cells into subsets with distinct homing properties. The frequency of circulating regulatory T-cells (Tregs), defined as CD3(+)CD4(+)CD127(lo)Foxp3(+)CD25(+) was compared in the same patients. The frequency of CCR4(-)IL-17(+)CD4(+) T-cells prevaccination inversely correlated with time to disease progression (TTP) in 23 prostate cancer patients. Furthermore, responder (R) patients with statistically significant reductions in PSA velocity (PSAV) in response to the immunotherapy (n = 9), showed a Th17 profile similar

to healthy male controls and significantly different from non-responder (NR) patients (n = 14) (i.e., those without any significant reduction in PSAV). In contrast, the frequency of Tregs in peripheral blood in PSA-R (n = 11) and -NR (n = 14) patients was similar (but in both cases, significantly higher than in age-matched healthy men). Accordingly, there was no significant correlation between frequency of Tregs and TTP in these late-stage prostate cancer patients undergoing active immunotherapy. These data imply an important role for IL-17-producing helper T-cells in cancer immunology and highlight their potential use as a pretreatment screen to ensure appropriate treatment is offered to hormone-resistant prostate cancer patients.

Diaz, M., J. J. Kim, et al. (2008). "Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India." Br J Cancer **99**(2): 230-8.

Cervical cancer is a leading cause of cancer death among women in low-income countries, with approximately 25% of cases worldwide occurring in India. We estimated the potential health and economic impact of different cervical cancer prevention strategies. After empirically calibrating a cervical cancer model to country-specific epidemiologic data, we projected cancer incidence, life expectancy, and lifetime costs (I$2005), and calculated incremental cost-effectiveness ratios (I$/YLS) for the following strategies: pre-adolescent vaccination of girls before age 12, screening of women over age 30, and combined vaccination and screening. Screening differed by test (cytology, visual inspection, HPV DNA testing), number of clinical visits (1, 2 or 3), frequency (1 x , 2 x , 3 x per lifetime), and age range (35-45). Vaccine efficacy, coverage, and costs were varied in sensitivity analyses. Assuming 70% coverage, mean reduction in lifetime cancer risk was 44% (range, 28-57%) with HPV 16,18 vaccination alone, and 21-33% with screening three times per lifetime. Combining vaccination and screening three times per lifetime provided a mean reduction of 56% (vaccination plus 3-visit conventional cytology) to 63% (vaccination plus 2-visit HPV DNA testing). At a cost per vaccinated girl of I$10 (per dose cost of $2), pre-adolescent vaccination followed by screening three times per lifetime using either VIA or HPV DNA testing, would be considered cost-effective using the country's per capita gross domestic product (I$3452) as a threshold. In India, if high coverage of pre-adolescent girls with a low-cost HPV vaccine that provides long-term protection is achievable, vaccination followed by screening three times per lifetime is expected to reduce cancer deaths by half, and be cost-effective.

Diefenbach, C. S., S. Gnjatic, et al. (2008). "Safety and immunogenicity study of NY-ESO-1b peptide and montanide ISA-51 vaccination of patients with epithelial ovarian cancer in high-risk first remission." Clin Cancer Res **14**(9): 2740-8.

PURPOSE: The cancer-testis antigen NY-ESO-1 is expressed by >40% of advanced epithelial ovarian cancers and is a promising immunotherapeutic target. In this study, we describe the effects of vaccination with the HLA-A*0201-restricted NY-ESO-1b peptide on patients with epithelial ovarian cancer in high-risk first remission. EXPERIMENTAL DESIGN: After primary surgery and chemotherapy, high-risk epithelial ovarian cancer patients in first clinical remission received NY-ESO-1b peptide and Montanide every 3 weeks for five vaccinations. Tumor expression was evaluated by immunohistochemistry. Toxicity was monitored using National Cancer Institute Common Toxicity Criteria Scale Version 2. NY-ESO-1 specific humoral immunity (ELISA), T-cell immunity (tetramer and ELISPOT), and delayed-type hypersensitivity were assessed on weeks 0, 1, 4, 7, 10, 13, and 16. RESULTS: Treatment-related adverse events included grade 1 fatigue, anemia, pruritus, myalgias, and hyperthyroidism and grade 2 hypothyroidism. There were no grade 3/grade 4 adverse events. Three of four patients (75%) with NY-ESO-1-positive tumor showed T-cell immunity by tetramer (0.6-9.5%) and ELISPOT (range, 35-260 spots). Four of five patients (80%) with NY-ESO-1-negative tumor showed T-cell immunity by tetramer (1.0-12.1%) and/or ELISPOT (range, 35-400 spots). With a median follow-up of 11.3 months, six of nine patients (67%) have recurred, with a median progression-free survival of 13 months (95% confidence interval, 11.2 months-not reached). Three of nine patients remain in complete clinical remission at 25, 38, and 52 months. CONCLUSION: Vaccination of high-risk HLA-A*0201-positive epithelial ovarian cancer patients with NY-ESO-1b and Montanide has minimal toxicity and induces specific T-cell immunity in patients with both NY-ESO-1-positive and NY-ESO-1-negative tumors. Additional study is warranted.

Disis, M. L., D. R. Wallace, et al. (2009). "Concurrent trastuzumab and HER2/neu-specific vaccination in patients with metastatic breast cancer." J Clin Oncol **27**(28): 4685-92.

PURPOSE: The primary objectives of this phase I/II study were to evaluate the safety and immunogenicity of combination therapy consisting of concurrent trastuzumab and human epidermal growth factor receptor 2 (HER2)/neu-specific vaccination in patients with HER2/neu-overexpressing metastatic

breast cancer. PATIENTS AND METHODS: Twenty-two patients with stage IV HER2/neu-positive breast cancer receiving trastuzumab therapy were vaccinated with an HER2/neu T-helper peptide-based vaccine. Toxicity was graded according to National Cancer Institute criteria, and antigen specific T-cell immunity was assessed by interferon gamma enzyme-linked immunosorbent spot assay. Data on progression-free and overall survival were collected. RESULTS: Concurrent trastuzumab and HER2/neu vaccinations were well tolerated, with 15% of patients experiencing an asymptomatic decline in left ventricular ejection fraction below the normal range during combination therapy. Although many patients had pre-existing immunity specific for HER2/neu and other breast cancer antigens while treated with trastuzumab alone, that immunity could be significantly boosted and maintained with vaccination. Epitope spreading within HER2/neu and to additional tumor-related proteins was stimulated by immunization, and the magnitude of the T-cell response generated was significantly inversely correlated with serum transforming growth factor beta levels. At a median follow-up of 36 months from the first vaccine, the median overall survival in the study population has not been reached. CONCLUSION: Combination therapy with trastuzumab and a HER2/neu vaccine is associated with minimal toxicity and results in prolonged, robust, antigen-specific immune responses in treated patients.

Donders, G. G., G. Bellen, et al. (2009). "Change in knowledge of women about cervix cancer, human papilloma virus (HPV) and HPV vaccination due to introduction of HPV vaccines." Eur J Obstet Gynecol Reprod Biol **145**(1): 93-5.

OBJECTIVES: Test knowledge of HPV, cervix cancer awareness and acceptance of HPV vaccination of women now and a year ago. STUDY DESIGN: Questionnaires were filled out by 305 women visiting four gynaecologists of the Regional Hospital Heilig Hart, Tienen, Belgium during two subsequent weeks. Fisher T or Chi(2) were used as statistical methods to compare the data with the survey of 381 women exactly one year before. RESULTS: Knowledge about HPV as a cause of cervix cancer and the presence of a vaccine rose from roughly 50% in 2007 to over 80% in 2008 ($p<0.0001$). Level of education and having daughters, sons or no children no longer influenced the level of knowledge or willingness to accept the vaccine. Most parents favor the age group 12-16 years as an ideal time for vaccination. In contrast with the 2007 survey, women below 26 years had now acquired almost equivalent knowledge to older women about the virus, cervix cancer and the vaccine, but they were far less likely to accept the vaccine due to its cost, unless it would be reimbursed (OR 4.2 (1.6-11) $p=0.0055$). CONCLUSION: One year after introduction of the first two HPV vaccines, over 75% of women attending an ambulatory gynaecology clinic know HPV causes cervix cancer and that you can get vaccinated against it. Compared with a year earlier, young and lower educated women had dramatically improved their knowledge. However, women below 26 years are less prepared to pay the cost for vaccination if it is not reimbursed.

Donders, G. G., M. Gabrovska, et al. (2008). "Knowledge of cervix cancer, human papilloma virus (HPV) and HPV vaccination at the moment of introduction of the vaccine in women in Belgium." Arch Gynecol Obstet **277**(4): 291-8.

AIM: To test the knowledge of women, attending a gynecology clinic, on HPV, cervix cancer awareness and the knowledge and willingness to use HPV vaccine for themselves or their children. SETTING: Routine gynecological and obstetrical care with ambulatory service in a medium-sized general hospital in a small town in Belgium (Heilig Hart Hospital, Tienen). METHODS: Questionnaire to be filled out by 381 consecutive women while in the attendance room for consultation with one of the four gynecologists. Fisher T or Chi(2) were used as statistical methods. RESULTS: Knowledge about HPV as a cause of cervix cancer and the existence of a vaccine was roughly 50%. Women with lower education were more likely to know nothing about the cause of cervix cancer than women with higher education (54 versus 39%, $P = 0.016$). Half of the women were willing to accept the vaccine, whatever the cost price, and 40% required more information or refunding. Compared to women above 40, young age (25 years or less) was a risk factor for poor knowledge of HPV ($P = 0.007$), cervix cancer ($P = 0.016$) and the HPV vaccine ($P = 0.07$), regardless of a higher degree of education (79% postgraduate degree versus 43.4% in the 40+-year-old women, $P = 0.006$). Women with a daughter (64.7%) or a son (69.2%) were more inclined to vaccinate their daughter than women without children (46.3%, $P < 0.0001$). None of the women declined the vaccination because it was meant to protect against a sexually transmitted disease (STD). CONCLUSION: Upon introduction and marketing of the first HPV vaccine, only 50% of women attending a routine gynecology clinic were aware of the role of HPV in cervix cancer and the possibility of getting a vaccination against it. Unexpectedly, despite a high degree of education, young women seem to have a low awareness of cervix cancer, its cause and the preventive measures. Contrary to some women in the USA, Western European women are less likely to decline the HPV

vaccine because it will protect them against STD. In Belgium, women who are childless or poorly educated and especially young women should be the targets of campaigns that motivate them to prevent HPV-induced cervix cancer.

Duval, B., V. Gilca, et al. (2009). "Cervical cancer prevention by vaccination: nurses' knowledge, attitudes and intentions." J Adv Nurs **65**(3): 499-508.

AIM: This paper is a report of a survey: (1) to document nurses' knowledge, attitudes and information needs regarding human papillomavirus prevention and (2) to determine factors associated with their willingness to recommend human papillomavirus vaccines. BACKGROUND: Persistent infection with human papillomavirus has been causally linked to cervical cancer. Two human papillomavirus vaccines have recently been approved for use in more than 65 countries. Nurses' level of support for the prevention of human papillomavirus related diseases by vaccination has not been researched. METHODS: A survey was conducted in 2007. Self-administered questionnaires were mailed to 1799 randomly selected nurses. Descriptive statistics were generated for all variables. Multivariable logistic regression models were estimated to determine variables associated with the willingness to recommend human papillomavirus vaccines. RESULTS: A total of 946 questionnaires were analyzed and showed that: 97% of nurses perceived routinely recommended vaccines as very useful; 93% would support human papillomavirus vaccination if it is publicly funded; 85% would recommend human papillomavirus vaccines to their patients; 33%, 46% and 61% expect the vaccination to permit screening to begin later in life, reduction of the frequency of screening, and reduction of the number of postscreening interventions, respectively. Respondents' knowledge score was 3.8 out of 7. Several modifiable factors, including knowledge, perceived self-efficacy, and societal and colleagues support were associated with willingness to recommend vaccines. CONCLUSION: Most nurses' support human papillomavirus vaccination, but their active involvement should not be taken for granted. Targeted educational efforts are needed to ensure nurses' involvement in the prevention of human papillomavirus-related diseases.

Echchannaoui, H., M. Bianchi, et al. (2008). "Intravaginal immunization of mice with recombinant Salmonella enterica serovar Typhimurium expressing human papillomavirus type 16 antigens as a potential route of vaccination against cervical cancer." Infect Immun **76**(5): 1940-51.

Cervical cancer, the second leading cause of cancer deaths in women, is the consequence of high-risk human papillomavirus (HPV) infections. Toward the development of therapeutic vaccines that can induce both innate and adaptive mucosal immune responses, we analyzed intravaginal (ivag) vaccine delivery of live attenuated Salmonella enterica serovar Typhimurium expressing HPV16L1 as a model antigen. Innate immune responses were examined in cervicovaginal tissues by determining gene expression patterns by microarray analysis using nylon membranes imprinted with cDNA fragments coding for inflammation-associated genes. At 24 h, a wide range of genes, including those for chemokines and Th1- and Th2-type cytokine and chemokine receptors were up-regulated in mice ivag immunized with Salmonella compared to control mice. However, the majority of transcripts returned to their steady-state levels 1 week after immunization, suggesting a transient inflammatory response. Indeed, cervicovaginal histology of immunized mice showed a massive, but transient, infiltration of macrophages and neutrophils, while T cells were still increased after 7 days. Ivag immunization also induced humoral and antitumor immune responses, i.e., serum and vaginal anti-HPV16VLP antibody titers similar to those induced by oral immunization, and significant protection in tumor protection experiments using HPV16-expressing C3 tumor cells. These results show that ivag immunization with live attenuated Salmonella expressing HPV16 antigens modulates the local mucosal gene expression pattern into a transient proinflammatory profile, elicits strong systemic and mucosal immunity against HPV16, and confers protection against HPV16 tumor cells subcutaneously implanted in mice. Examination of the efficacy with which ivag HPV16E7E6 Salmonella induces regression of tumors located in cervicovaginal tissue is warranted.

Engels, E. A., J. Chen, et al. (2004). "Poliovirus vaccination during pregnancy, maternal seroconversion to simian virus 40, and risk of childhood cancer." Am J Epidemiol **160**(4): 306-16.

Before 1963, poliovirus vaccine produced in the United States was contaminated with simian virus 40 (SV40), which causes cancer in animals. To examine whether early-life SV40 infection can cause human cancer, the authors studied 54,796 children enrolled in the US-based Collaborative Perinatal Project (CPP) in 1959-1966, 52 of whom developed cancer by their eighth birthday. Those children whose mothers had received pre-1963 poliovirus vaccine during pregnancy (22.5% of the children) had an increased incidence of neural tumors (hazard ratio = 2.6, 95% confidence interval: 1.0, 6.7; 18 cases) and

hematologic malignancies (hazard ratio = 2.8, 95% confidence interval: 1.2, 6.4; 22 cases). For 50 CPP children with cancer and 200 CPP control children, the authors tested paired maternal serum samples from pregnancy for SV40 antibodies using a virus-like particle enzyme immunoassay and a plaque neutralization assay. Overall, mothers exhibited infrequent, low-level SV40 antibody reactivity, and only six case mothers seroconverted by either assay. Using the two SV40 assays, maternal SV40 seroconversion during pregnancy was not consistently related to children's case/control status or mothers' receipt of pre-1963 vaccine. The authors conclude that an increased cancer risk in CPP children whose mothers received pre-1963 poliovirus vaccine was unlikely to have been due to SV40 infection transmitted from mothers to their children.

Esposito, S., V. Cecinati, et al. (2009). "Influenza vaccination in children with cancer receiving chemotherapy." Hum Vaccin **5**(6): 430-2.

Influenza has a significant clinical impact on pediatric cancer patients because it causes frequent febrile episodes and respiratory tract infections, possibly severe complications, delays in chemotherapy administration and even death, all of which supports the importance of prevention and the widespread use of influenza vaccination. Results from clinical studies show that influenza vaccination can be considered safe in children undergoing chemotherapy and, although weaker than in healthy children, the immune response seems to be sufficient in patients with leukemia or solid tumors even if it is less in children receiving chemotherapy than in those who are not. However, there is an urgent need for universally accepted guidelines concerning the type of vaccine that leads to the best immunological results, the number of administrations, and their timing in relation to the severity of immunosuppression and chemotherapy schedules. Such recommendations, together with a clear demonstration of vaccine efficacy, are also needed to increase influenza vaccination coverage in this high-risk category of patients.

Farkas, A., C. Conrad, et al. (2006). "Current state and perspectives of dendritic cell vaccination in cancer immunotherapy." Skin Pharmacol Physiol **19**(3): 124-31.

Recent progress in the approach towards immunotherapy of cancer consists in molecular definition of tumor antigens, new tools for phenotypical and functional characterization of tumor-specific effector cells and clinical use of novel adjuvants for optimal stimulation of a cancer-specific immune response such as dendritic cells. In spite of these advances and immunological as well as clinical responses in selected patients, mechanisms involved in dendritic-cell-based cancer immunotherapy are still poorly understood. Therefore, a standardized study design and small pilot trials are needed to explore open scientific questions in future clinical trials. This review focuses on the different parameters of dendritic cell biology relevant to cancer immunotherapy and on innovative approaches to hopefully enhance the efficacy of dendritic cell vaccination.

Ferko, N., M. Postma, et al. (2008). "Evolution of the health economics of cervical cancer vaccination." Vaccine **26 Suppl 5**: F3-15.

This paper reviews the history of modelling for cervical cancer vaccination. We provide an interpretation and summary of conclusions pertaining to the usefulness of different models, the predicted epidemiological impact of vaccination and the cost-effectiveness of adolescent, catch-up and sex-specific vaccination strategies. To date, model results predict a critical role for vaccination in reducing the burden of cervical disease, with cost-effectiveness being consistently shown across studies using a common threshold of US $50,000 per QALY, but further clinical and epidemiological data are required to confirm these findings. Through this paper, we aim to provide useful insights for decision-makers as they examine how to best evaluate the potential impact of vaccines against cervical cancer and determine how to best incorporate vaccination into practice.

Feyerabend, S., S. Stevanovic, et al. (2009). "Novel multi-peptide vaccination in Hla-A2+ hormone sensitive patients with biochemical relapse of prostate cancer." Prostate **69**(9): 917-27.

BACKGROUND: A phase I/II trial was conducted to assess feasibility and tolerability of tumor associated antigen peptide vaccination in hormone sensitive prostate carcinoma (PC) patients with biochemical recurrence after primary surgical treatment. METHODS: Nineteen HLA-A2 positive patients with rising PSA without detectable metastatic disease or local recurrence received 11 HLA-A*0201-restricted and two HLA class II synthetic peptides derived from PC tumor antigens subcutaneously for 18 months or until PSA progression. The vaccine was emulgated in montanide ISA51 and combined with imiquimod, GM-CSF, mucin-1-mRNA/protamine complex, local hyperthermia or no adjuvant. PSA was assessed, geometric mean doubling times (DT) calculated and clinical performance monitored. RESULTS: PSA DT of 4 out of 19 patients (21%) increased from 4.9 to 25.8 months during vaccination. Out of these, two patients (11%) exhibited PSA

stability for 28 and 31 months which were still continuing at data cut-off. One patient showed no change of PSA DT during vaccination but decline after the therapy. Three patients had an interim PSA decline or DT increase followed by DT decrease compared to baseline PSA DT. Three of the responding patients received imiquimod and one the mucin-1-mRNA/protamine complex as adjuvant; both are Toll-like receptor-7 agonists. Eleven (58%) patients had progressive PSA values. The vaccine was well tolerated, and no grade III or IV toxicity occurred. CONCLUSION: Multi-peptide vaccination stabilized or slowed down PSA progress in four of 19 cases. The vaccination approach is promising with moderate adverse events. Long-term stability delayed androgen deprivation up to 31 months. TLR-7 co-activation seems to be beneficial.

Franco, E. L., F. Coutlee, et al. (2009). "Integrating human papillomavirus vaccination in cervical cancer control programmes." Public Health Genomics **12**(5-6): 352-61.

Screening with Pap cytology has substantially reduced cervical cancer morbidity and mortality during the last 50 years in high-income countries. Unfortunately, in resource-poor countries, Pap screening has either not been effectively implemented or has failed to reduce cervical cancer rates. Cervical cancer in these countries thus remains a major public health problem. Infection with certain human papillomavirus (HPV) types is now recognized as a necessary cause of this disease and has led to new preventive strategies for cervical cancer. Testing for HPV DNA of oncogenic types is gaining increasing interest and application in cervical cancer screening. It has much greater sensitivity and only slightly lower specificity than Pap cytology. Molecular-based screening will be of particular clinical value in the post-vaccine era in which cervical disease will be a rare event and may escape cytology-based detection. As a primary screening test followed by Pap triage of HPV-positive cases, HPV testing has the potential to improve the overall quality of screening programmes, thus allowing for increased testing intervals, which would lower program costs with acceptable safety. Prophylactic vaccines against the 2 leading oncogenic HPV types (16 and 18) have been recently licensed. In large clinical trials, they have shown excellent safety and nearly 100% efficacy in preventing persistent infections and the cervical pre-cancers due to vaccine HPV types 16 and 18. Combining modern screening techniques and universal prophylactic HPV vaccination is likely to produce the most advanced and cost-effective preventive strategy to fight cervical cancer worldwide.

Franco, E. L. and J. Cuzick (2008). "Cervical cancer screening following prophylactic human papillomavirus vaccination." Vaccine **26 Suppl 1**: A16-23.

The recognition that infection with certain human papillomavirus (HPV) types is a necessary cause of cervical cancer has opened new fronts for the prevention of this disease. Primary prevention is now possible via immunization with highly efficacious HPV vaccines and secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programs. Although universal vaccination of teenagers and young women is a desirable policy cost remains a key obstacle. To achieve cost-effective reductions in the burden of cervical cancer prevention initiatives must consider screening and immunization as integrated and organized approaches that take advantage of HPV testing as primary screening test followed by triage with Pap cytology. This strategy has the added benefit of providing epidemiological surveillance of vaccinated populations.

Franco, E. L., J. Cuzick, et al. (2006). "Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination." Vaccine **24 Suppl 3**: S3/171-7.

Human Papillomavirus (HPV) vaccines will likely have an impact as a preventive strategy for cervical cancer. Screening for precancerous lesions cannot be discontinued because vaccination will not protect against HPV types not included in the first generation of vaccines. Moreover, protection for the target types, 16 and 18, which are responsible for most cases of cervical precancerous lesions and cancer, and 6 and 11, which are responsible for a substantial proportion of low-grade lesions, cannot be expected to be absolute, and the likely implementation of HPV vaccination in young women will not impact older groups initially. Cervical cancer control programs will need to be re-evaluated because the addition of HPV vaccination will make the existing approach of high-frequency screening by cytology too costly and inefficient for most public health budgets. Simply making cytology screening less frequent may not be a viable strategy in light of potential problems that may plague cytology performance in conditions of low lesion prevalence. HPV testing has the performance characteristics that would make it an ideal primary screening test in such conditions. Cytology should be reserved for triage of HPV-positive cases because it is more likely to perform with sufficient accuracy in high-prevalence conditions. Another advantage of using HPV testing as a primary screening tool is the opportunity to create infection registries that can link test results from the same women over time, thus allowing an efficient and

low-cost strategy to monitor long-term protection among vaccinated women.

Franco, E. L. and A. Ferenczy (2007). "Cervical cancer screening following the implementation of prophylactic human papillomavirus vaccination." Future Oncol **3**(3): 319-27.

The recognition that infection with certain human papillomavirus (HPV) types is a necessary cause of cervical cancer has opened new fronts in the prevention of this disease. Primary prevention is now possible via immunization with highly efficacious HPV vaccines, and secondary prevention has gained impetus with the advent of sensitive HPV-DNA testing to improve traditional Pap cytology screening programs. Although universal vaccination of teenagers and young women is a desirable policy, cost remains a key obstacle. To achieve cost-effective reductions in cervical cancer burden, prevention initiatives must consider screening and immunization as integrated and organized approaches that take advantage of HPV testing as a primary screening test followed by triage with Pap cytology. This strategy has the added benefit of providing immunosurveillance of vaccinated populations.

Franco, E. L. and D. M. Harper (2005). "Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control." Vaccine **23**(17-18): 2388-94.

Universal deployment of organized or opportunistic screening with Pap cytology in high and middle income countries has been the primary reason for the substantial reductions in cervical cancer morbidity and mortality during the last 50 years. However, in many low income countries Pap cytology screening is yet to be effectively implemented or has failed to reduce cervical cancer rates to an appreciable extent. Cervical cancer thus remains a critical public health problem that is second only to breast cancer in overall disease burden for women throughout the world. The fact that infection with certain human papillomavirus (HPV) types is now recognized as a necessary cause of this disease has led to new research fronts on the prevention of cervical cancer. Recent research on the safety and efficacy of candidate prophylactic vaccines against HPV have shown very promising results with nearly 100% efficacy in preventing the development of persistent infections and cervical precancerous lesions. Ongoing clinical studies are expected to provide further evidence of efficacy and will form the basis for licensing of candidate vaccines by the major pharmaceutical companies within 3-6 years. Although the future seems bright on the HPV vaccine front policy makers are strongly cautioned to avoid scaling back cervical cancer screening. It will take many years before we can rationally develop cervical cancer screening strategies that will be cost-effective for the proper surveillance of women protected by HPV vaccination.

Franco, E. L., S. M. Mahmud, et al. (2009). "The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change." Arch Med Res **40**(6): 478-85.

We used modeling approaches to estimate the impact of human papillomavirus (HPV) vaccination on the performance of Pap cytology screening under different assumptions of lesion prevalence and expected changes in sensitivity and specificity likely to prevail post-vaccination. A major driver of the efficiency and costs of screening, the positive predictive value will be severely affected if Pap cytology continues to serve as the primary screening test in the post-vaccination era. Molecular-based screening with an HPV DNA test followed by Pap triage of HPV-positive cases has the potential for circumventing this problem. As a primary screening test, HPV testing can improve the overall quality of screening programs, thus allowing for increased testing intervals that would lower program costs with acceptable safety. Cytology should be reserved for the more labor-efficient task of triaging HPV-positive cases, a situation in which case loads would be "enriched" with smears containing relevant abnormalities. HPV followed by Pap strategy can also serve a secondary role in post-vaccination surveillance.

Franco, E. L., V. Tsu, et al. (2008). "Integration of human papillomavirus vaccination and cervical cancer screening in Latin America and the Caribbean." Vaccine **26 Suppl 11**: L88-95.

Despite substantial efforts to control cervical cancer by screening, most Latin American and Caribbean countries continue to experience incidence rates of this disease that are much higher than those of other Western countries. The implementation of universal human papillomavirus (HPV) vaccination for young adolescent women is the best prospect for changing this situation. Even though there are financial challenges to overcome to implement such a policy, there is broad political support in the region for adopting universal HPV vaccination. The costs of implementing this policy could be largely alleviated by changing cervical cancer control practices that rely on inefficient use of resources presently allocated to cytology screening. In view of the strong evidence base concerning cervical cancer prevention technologies in the region and the expected impact of vaccination on the performance of cytology, we propose a reformulation of cervical cancer screening

policies to be based on HPV testing using validated methods followed by cytologic triage. This approach would serve as the central component of a system that plays the dual role of providing screening and surveillance as integrated and complementary activities sharing centralized resources and coordination.

Garcia-Hernandez Mde, L., A. Gray, et al. (2007). "In vivo effects of vaccination with six-transmembrane epithelial antigen of the prostate: a candidate antigen for treating prostate cancer." Cancer Res **67**(3): 1344-51.

Immunotherapy may provide an alternative treatment for cancer patients, especially when tumors overexpress antigens that can be recognized by immune cells. The identification of markers and therapeutic targets that are up-regulated in prostate cancer has been important to design new potential treatments for prostate cancer. Among them, the recently identified six-transmembrane epithelial antigen of the prostate (STEAP) is considered attractive due to its overexpression in human prostate cancer tissues. Our study constitutes the first assessment of the in vivo effectiveness of STEAP-based vaccination in prophylactic and therapeutic mouse models. Two delivery systems, cDNA delivered by gene gun and Venezuelan equine encephalitis virus-like replicon particles (VRP), both encoding mouse STEAP (mSTEAP) and three vaccination strategies were used. Our results show that mSTEAP-based vaccination was able to induce a specific CD8 T-cell response against a newly defined mSTEAP epitope that prolonged the overall survival rate in tumor-challenged mice very significantly. This was achieved without any development of autoimmunity. Surprisingly, CD4 T cells that produced IFNgamma, tumor necrosis factor-alpha (TNF-alpha), and interleukin-2 (IL-2) played the main role in tumor rejection in our model as shown by using CD4- and CD8-deficient mice. In addition, the presence of high IL-12 levels in the tumor environment was associated with a favorable antitumor response. Finally, the therapeutic effect of STEAP vaccination was also assessed and induced a modest but significant delay in growth of established, 31 day old tumors. Taken together, our data suggest that vaccination against mSTEAP is a viable option to delay tumor growth.

Garcia-Hernandez Mde, L., A. Gray, et al. (2008). "Prostate stem cell antigen vaccination induces a long-term protective immune response against prostate cancer in the absence of autoimmunity." Cancer Res **68**(3): 861-9.

Prostate stem cell antigen (PSCA) is an attractive antigen to target using therapeutic vaccines because of its overexpression in prostate cancer, especially in metastatic tissues, and its limited expression in other organs. Our studies offer the first evidence that a PSCA-based vaccine can induce long-term protection against prostate cancer development in prostate cancer-prone transgenic adenocarcinoma mouse prostate (TRAMP) mice. Eight-week-old TRAMP mice displaying prostate intraepithelial neoplasia were vaccinated with a heterologous prime/boost strategy consisting of gene gun-delivered PSCA-cDNA followed by Venezuelan equine encephalitis virus replicons encoding PSCA. Our results show the induction of an immune response against a newly defined PSCA epitope that is mediated primarily by CD8 T cells. The prostates of PSCA-vaccinated mice were infiltrated by CD4-positive, CD8-positive, CD11b-positive, and CD11c-positive cells. Vaccination induced MHC class I expression and cytokine production [IFN-gamma, tumor necrosis factor-alpha, interleukin 2 (IL-2), IL-4, and IL-5] within prostate tumors. This tumor microenvironment correlated with low Gleason scores and weak PSCA staining on tumor cells present in hyperplastic zones and in areas that contained focal and well-differentiated adenocarcinomas. PSCA-vaccinated TRAMP mice had a 90% survival rate at 12 months of age. In contrast, all control mice had succumbed to prostate cancer or had heavy tumor loads. Crucially, this long-term protective immune response was not associated with any measurable induction of autoimmunity. The possibility of inducing long-term protection against prostate cancer by vaccination at the earliest signs of its development has the potential to cause a dramatic paradigm shift in the treatment of this disease.

Garland, S. M. (2009). "Can cervical cancer be eradicated by prophylactic HPV vaccination? Challenges to vaccine implementation." Indian J Med Res **130**(3): 311-21.

Cervical cancer is the first cancer to be shown to be 100 per cent attributable to a virus; oncogenic human papillomaviruses (HPV), particularly types 16 and 18, collectively worldwide contribute to 70 per cent squamous cell carcinomas, 85 per cent of adenocarcinomas. Cervical cancer is the second commonest cancer of women, yet largely preventable with high-quality, well-organized screening of the appropriate population. Screening programmes are either nonexistent, or function opportunistically in many poorer countries, resulting in high incidence and mortality. Recently developed, prophylactic HPV vaccines against HPV 16, 18, as cervical cancer preventative vaccines, in phase 3

clinical trials have been shown, to be highly efficacious, safe and immunogenic. With the potential for cross protection against related HPV types, estimates for prevention are in the order of 75 to 80 per cent. Thus a further option exists in the battle to reduce these cancers in women. Challenges however include implementing a vaccination programme with wide coverage to the target populations to be a successful public health tool, integration and maintenance of current screening programmes where they are in existence, the need for reduced costs of the current vaccines, long-term immunogenicity (will there be a need for further doses?), appropriate education messages to the general community, governments, as well as the medical profession.

Giaccone, G., C. Debruyne, et al. (2005). "Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study)." J Clin Oncol **23**(28): 6854-64.

PURPOSE: Bec2 is an anti-idiotypic antibody that mimics GD3, a ganglioside that is expressed on the surface of tumor cells and is of neuroectodermal origin. We assessed whether Bec2/bacille Calmette-Guerin (BCG) vaccination prolongs survival in patients with limited-disease small-cell lung cancer (SCLC) after a major response to chemotherapy and chest radiation. PATIENTS AND METHODS: Patients were randomly assigned to receive five vaccinations of Bec2 (2.5 mg)/BCG vaccine or follow-up. Vaccination was given over a 10-week period. The sample size was targeted to detect an increase in median survival of 40% after random assignment, and stratification was by performance status, response, and institution. Quality of life was assessed by using the European Organisation for Research and Treatment of Cancer instrument. Humoral response was assessed in patients who received vaccination. RESULTS: A total of 515 patients were randomly assigned. The primary toxicities of vaccination were transient skin ulcerations and mild flu-like symptoms. There was no improvement in survival, progression-free survival, or quality of life in the vaccination arm. Median survival from randomization was 16.4 and 14.3 months in the observation and vaccination arms (P = .28), respectively. Among vaccinated patients, a trend toward prolonged survival was observed in those (one third) who developed a humoral response (P = .085). Multivariate analysis showed a positive impact on survival by prior treatment with concomitant chemoradiotherapy, prophylactic cranial irradiation, female sex, low lactate dehydrogenase, and normal platelets. CONCLUSION: Vaccination with Bec2/BCG has no impact on outcome of patients with limited-disease SCLC responding to combined-modality treatment. Vaccination strategies in SCLC may still be warranted using vaccines that produce a better immunologic response.

Goldhaber-Fiebert, J. D., N. K. Stout, et al. (2008). "Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination." J Natl Cancer Inst **100**(5): 308-20.

BACKGROUND: The availability of human papillomavirus (HPV) DNA testing and vaccination against HPV types 16 and 18 (HPV-16,18) motivates questions about the cost-effectiveness of cervical cancer prevention in the United States for unvaccinated older women and for girls eligible for vaccination. METHODS: An empirically calibrated model was used to assess the quality-adjusted life years (QALYs), lifetime costs, and incremental cost-effectiveness ratios (2004 US dollars per QALY) of screening, vaccination of preadolescent girls, and vaccination combined with screening. Screening varied by initiation age (18, 21, or 25 years), interval (every 1, 2, 3, or 5 years), and test (HPV DNA testing of cervical specimens or cytologic evaluation of cervical cells with a Pap test). Testing strategies included: 1) cytology followed by HPV DNA testing for equivocal cytologic results (cytology with HPV test triage); 2) HPV DNA testing followed by cytology for positive HPV DNA results (HPV test with cytology triage); and 3) combined HPV DNA testing and cytology. Strategies were permitted to switch once at age 25, 30, or 35 years. RESULTS: For unvaccinated women, triennial cytology with HPV test triage, beginning by age 21 years and switching to HPV testing with cytology triage at age 30 years, cost $78,000 per QALY compared with the next best strategy. For girls vaccinated before age 12 years, this same strategy, beginning at age 25 years and switching at age 35 years, cost $41,000 per QALY with screening every 5 years and $188,000 per QALY screening triennially, each compared with the next best strategy. These strategies were more effective and cost-effective than screening women of all ages with cytology alone or cytology with HPV triage annually or biennially. CONCLUSIONS: For both vaccinated and unvaccinated women, age-based screening by use of HPV DNA testing as a triage test for equivocal results in younger women and as a primary screening test in older women is expected to be more cost-effective than current screening recommendations.

Goldie, S. (2006). "A public health approach to cervical cancer control: considerations of screening and vaccination strategies." Int J Gynaecol Obstet **94 Suppl 1**: S95-105.

Cervical cancer remains a leading cause of cancer death among women living in low-resource settings. In the last 3 decades, cytologic screening has -in theory -been available and yet more than 6 million women have died of this preventable disease. The necessary resources, infrastructure, and technological expertise, together with the need for repeated screenings at regular intervals, make cytologic screening difficult to implement in poor countries. As noncytologic approaches for the detection of HPV, simple visual screening methods for anogenital lesions caused by HPV, and the availability of an HPV-16/18 vaccine will enhance the linkage between screening and treatment, multiple factors will need to be considered when designing new, or modifying existing prevention strategies. Countryspecific decisions regarding the best strategy for cervical cancer control will need to rely on data from many sources and take into account complex epidemiologic, economic, social, political, and cultural factors, and be made despite uncertainty and incomplete information. A rigorous decision analytic approach using computerbased modeling methods enables linkage of the knowledge gained from empirical studies to real-world situations. This chapter provides an introduction to these methods, reviews lessons learned from cost-effectiveness analyses of cervical cancer screening in developed and developing countries, and emphasizes important qualitative themes to consider in designing cervical cancer prevention policies.

Gonzalez, G., T. Crombet, et al. (2007). "Therapeutic vaccination with epidermal growth factor (EGF) in advanced lung cancer: analysis of pooled data from three clinical trials." Hum Vaccin **3**(1): 8-13.

We have undertaken the analysis of pooled data from three pilot clinical trials of vaccination with Epidermal Growth Factor (EGF) in patients with advanced non small cell lung cancer (NSCLC), addressing particularly the issue of the relationship between immunization and survival. Eighty-three patients with advanced disease were included in three pilot clinical trials and vaccinated with the EGF Vaccine. The trials were designed to evaluate the immunogenicity and safety of the vaccine using different adjuvants, cyclophosphamide pretreatment or not, and different dosage levels of the vaccine. The vaccine elicited specific anti-EGF antibody titers in 83% of subjects, and 49% developed a good anti-EGF antibody response. The adjuvant, the vaccine dose, and cyclophosphamide pretreatment significantly influenced immunogenicity. Patients that seroconverted survived significantly longer than patients who did not. Good antibody responders survived significantly longer than poor responders. Pooled results from these trials confirm that vaccination with EGF is safe and immunogenic in advanced NSCLC patients. The association between good antibody responses and survival consistently appeared in every single trial independently of the specific trial designs. Although these were small pilot nonrandomized clinical trials not intended to confirm therapeutic effect, the survival of the pooled patient population was statistically greater compared with 163 control patients receiving standard treatment.

Goossen, G. M., L. C. Kremer, et al. (2009). "Influenza vaccination in children being treated with chemotherapy for cancer." Cochrane Database Syst Rev(2): CD006484.

BACKGROUND: Influenza infection is a potential cause of severe morbidity in children with cancer, therefore vaccination against influenza is recommended. However, there are conflicting data concerning the immune response to influenza vaccination in children with cancer and the value of vaccination remains unclear. OBJECTIVES: 1. To assess the efficacy of influenza vaccination in stimulating immunological response in children with cancer during chemotherapy, compared to control groups. 2. To assess the efficacy of influenza vaccination in preventing confirmed influenza and influenza-like illness and/or stimulating immunological response in children with cancer treated with chemotherapy, compared to placebo, no intervention or different dosage schedules. 3. To determine the adverse effects associated with influenza vaccination in children with cancer. SEARCH STRATEGY: We searched CENTRAL, MEDLINE (1966 to 2007) and EMBASE (1980 to 2007) up to February 2007. We also searched reference lists of relevant articles and conference proceedings of ICAAC, IDSA, MASCC and SIOP. SELECTION CRITERIA: We considered randomised controlled trials (RCTs) and controlled clinical trials (CCTs) in which the serologic response to influenza vaccination of children with cancer was compared to other control groups. We also considered RCTs and CCTs comparing the effects of influenza vaccination on clinical response and/or immunological response in children with cancer, with placebo, no intervention or different dosage schedules. DATA COLLECTION AND ANALYSIS: Two independent authors assessed the methodological quality of included studies and extracted data. MAIN RESULTS: We included 1 RCT and 8 CCTs (total number of participants=708). None of the included studies reported on clinical outcome. All included studies reported on influenza immunity and adverse reactions to vaccination. In five studies, immune responses to influenza vaccine were compared in 272 children on chemotherapy with 166 children not on chemotherapy. In three studies,

responses to influenza vaccine were assessed in 204 children on chemotherapy compared with responses in 112 healthy children. The measures used to assess immune responses were: a four-fold rise in antibody titre after vaccination, development of haemagglutination inhibition (HI) titre > 32, and pre- and post-vaccination geometric mean titres (GMT). Immune responses in children receiving chemotherapy were consistently weaker (four-fold rise of 25% to 52%) than in those children who had completed chemotherapy (50% to 86%) and in healthy children (71% to 89%). Concerning adverse effects, 359 paediatric oncology patients received influenza vaccine and the side effects described were mild local reactions and low grade fever. No life-threatening or persistent adverse effects were reported. AUTHORS' CONCLUSIONS: Paediatric oncology patients receiving chemotherapy are able to generate an immune response to the influenza vaccine, but it remains unclear whether this immune response protects them from influenza infection or its complications. We are awaiting results from well-designed RCTs addressing the clinical benefit of influenza vaccination in these patients.

Gordon, E. M., J. P. Levy, et al. (2008). "Targeting metastatic cancer from the inside: a new generation of targeted gene delivery vectors enables personalized cancer vaccination in situ." Int J Oncol **33**(4): 665-75.

The advent of pathotropic (disease-seeking) targeting technologies, combined with advanced gene delivery vectors, provides a unique opportunity for the systemic delivery of immunomodulatory cytokine genes to remote sites of cancer metastasis. When injected intravenously, such pathotropic nanoparticles seek out and accumulate selectively at sites of tumor invasion and neo-angiogenesis, resulting in enhanced gene delivery, and thus cytokine production, within the tumor nodules. Used in conjunction with a primary tumoricidal agent (e.g., Rexin-G) that exposes tumor neoantigens, the tumor-targeted immunotherapy vector is intended to promote the recruitment and activation of host immune cells into the metastastic site(s), thereby initiating cancer immunization in situ. In this study, we examine the feasibility of cytokine gene delivery to cancerous lesions in vivo using intravenously administered pathotropically targeted nanoparticles bearing the gene encoding granulocyte/macrophage colony-stimulating factor (GM-CSF; i.e., Reximmune-C). In vitro, transduction of target cancer cells with Reximmune-C resulted in the quantitative production of bioactive and immunoreactive GM-CSF protein. In tumor-bearing nude mice, intravenous infusions of Reximmune-C-induced GM-CSF production by transduced cancer cells and paracrine secretion of the cytokine within the tumor nodules, which promoted the recruitment of host mononuclear cells, including CD40+ B cells and CD86+ dendritic cells, into the tumors. With the first proofs of principle established in preclinical studies, we generated an optimized vector configuration for use in advanced clinical trial designs, and extended the feasibility studies to the clinic. Targeted delivery and localized expression of the GM-CSF transgene was confirmed in a patient with metastatic cancer, as was the recruitment of significant tumor-infiltrating lymphocytes (TILs). Taken together, these studies provide the first demonstrations of cytokine gene delivery to cancerous lesions following intravenous administration and extend the applications of cancer immunization in vivo.

Gravekamp, C. (2009). "The importance of the age factor in cancer vaccination at older age." Cancer Immunol Immunother **58**(12): 1969-77.

Cancer is an age-related disease, and with the graying of the society there is an increasing need to optimize cancer management and therapy to elderly patients. Vaccine therapy for cancer is less toxic than chemotherapy or radiation and could be, therefore, especially effective in older, more frail cancer patients. However, it has been shown that older individuals do not respond to vaccine therapy as well as younger adults. This has been attributed to T cell unresponsiveness, a phenomenon also observed in cancer patients per se. Therefore, research is needed to establish whether age-specific tumor-immunological variables permit optimal use of cancer vaccines and therapy in the elderly. This review summarizes the current knowledge of T cell unresponsiveness in cancer patients and elderly, and the results of cancer vaccination in preclinical models at young and old age. Finally, new directions that may lead to effective cancer vaccination at older age will be proposed.

Gravekamp, C., S. H. Kim, et al. (2009). "Cancer vaccination: manipulation of immune responses at old age." Mech Ageing Dev **130**(1-2): 67-75.

The incidence of cancer has increased over the last decade, mainly due to an increase in the elderly population. Vaccine therapy for cancer is less toxic than chemotherapy or radiation and could be, therefore, especially effective in older, more frail cancer patients. However, it has been shown that older individuals do not respond to vaccine therapy as well as younger adults. This has been attributed to T-cell unresponsiveness, a phenomenon also observed in cancer patients per se. This review summarizes the current knowledge of impaired T-cell responses in cancer patients and the elderly, and the results of cancer vaccination in preclinical models at young and

old age. Finally, various approaches how to manipulate immune responses against cancer by vaccination at older age will be proposed.

Gray, A., A. B. Raff, et al. (2008). "A paradigm shift in therapeutic vaccination of cancer patients: the need to apply therapeutic vaccination strategies in the preventive setting." Immunol Rev **222**: 316-27.

An extraordinary variety of potential therapeutic vaccine strategies directed against a wide variety of tumor antigens has been explored in clinical trials. To date, none of these cancer immunotherapies have been approved by the Food and Drug Administration for use in humans. A significant problem is that the vast majority of such clinical trials are carried out in patients with advanced or metastatic cancer. The immune systems of these patients are considerably compromised as a result of tumor- and treatment-mediated immunosuppression. Even in cases where patients are immunized in the adjuvant setting, where there is minimal residual disease, vaccines directed against tumor-associated antigens have failed to mediate eradication of tumors in the overwhelming majority of cases. Recently, we and others have experimented with administering therapeutic cancer vaccines in the preventive setting. This is achieved by vaccinating at the earliest possible stage of carcinogenesis. These studies have demonstrated that early vaccination is extremely effective in eliciting an anti-tumor immune response that leads to unprecedented improvements in the survival of mice that spontaneously develop cancer. Certain human cancers, notably prostate adenocarcinoma and cervical cancer, can currently be detected at very early stages of carcinogenesis. Therapeutic vaccines are available for these diseases, opening up the possibility of administering vaccinations early to patients diagnosed with pre-malignant lesions to halt disease progression. In addition, new technologies have become available in the past decade that will soon yield very sensitive and specific diagnostic tests for a plethora of other cancers. Earlier detection of these cancers, combined with existing vaccines directed against them, will soon make them targets for therapeutic vaccination in the preventive setting. The ability to immunize patients at the very earliest stages of carcinogenesis, when they have fully competent immune systems, has the potential to cause a paradigm shift in how therapeutic cancer vaccines are tested and used clinically.

Hallermalm, K., S. Johansson, et al. (2007). "Pre-clinical evaluation of a CEA DNA prime/protein boost vaccination strategy against colorectal cancer." Scand J Immunol **66**(1): 43-51.

In preparation for a clinical trial in patients diagnosed with colorectal cancer, a vaccination strategy targeting the carcinoembryonic antigen (CEA) was evaluated in mice using a GMP-produced plasmid DNA vaccine, CEA66, encoding a truncated form of the tumour-associated antigen, CEA. The GMP-produced CEA DNA vaccine was also evaluated for toxicity. Repeated intradermal administration of the GMP-produced vaccine using a novel needle-free jet injection device (Biojector) induced robust CD4 and CD8 T-cell responses in mice, and did not result in any vaccine-related toxicity. In a heterologous DNA prime/protein boost setting, cellular immune responses were of higher magnitude in animals primed with CEA66 DNA than in animals receiving repeated doses of recombinant CEA protein. These responses were further enhanced if recombinant murine granulocyte-macrophage colony-stimulating factor was given as an adjuvant prior to vaccination. In contrast to repeated administration of recombinant CEA protein as a single modality vaccine, the heterologous CEA66 DNA prime/rCEA boost vaccination strategy resulted in a qualitatively broader immune response, and supports clinical testing of this vaccination regimen in humans.

Harada, M., S. Matsueda, et al. (2005). "Vaccination of cytotoxic T lymphocyte-directed peptides elicited and spread humoral and Th1-type immune responses to prostate-specific antigen protein in a prostate cancer patient." J Immunother **28**(4): 368-75.

The authors studied humoral and CD4+ T-cell responses in an HLA-A24+ prostate cancer patient vaccinated with cytotoxic T lymphocyte (CTL)-directed peptides, including a prostate-specific antigen (PSA)248-257 peptide, to understand what kinds of immune responses are elicited in peptide-vaccinated patients. The levels of immunoglobulin G (IgG) reactive to the administered PSA248-257 peptide or the PSA protein were kinetically examined. The level of IgG reactive to the PSA248-257 peptide drastically increased after the peptide vaccination, with a peak after the seventh vaccination, whereas that of IgG reactive to the PSA protein continued to increase throughout the vaccination period. IgG reactive to the PSA protein after the 13th vaccination showed no reactivity to the administered PSA peptides. However, HLA-DRB1*1302-restricted and PSA protein-recognizing TH1-type CD4+ T-cell clone and line, with different specificity, were successfully established from the post-7th and post-13th peripheral blood mononuclear cells, respectively. Both CD4+ T cells produced interferon-gamma in response to naturally processed PSA secreted from prostate cancer cells, whereas their reactivity to the administered PSA248-257 peptide was undetectable or negligible.

These findings indicate that vaccination with CTL-directed peptides, including a PSA-derived peptide, was able to elicit and spread humoral and TH1-type immune responses to the PSA protein.

Harrop, R., N. Connolly, et al. (2006). "Vaccination of colorectal cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) induces immune responses which correlate with disease control: a phase I/II trial." Clin Cancer Res **12**(11 Pt 1): 3416-24.

PURPOSE: The highly attenuated strain of vaccinia virus, modified vaccinia Ankara (MVA), encoding the tumor antigen 5T4 (termed TroVax), has been evaluated in an open-label phase I/II study in colorectal cancer patients. The primary objectives were to assess the safety and immunogenicity of ascending doses of TroVax and to determine the biodistribution of the vector. EXPERIMENTAL DESIGN: TroVax was given to 22 patients with metastatic colorectal cancer. Seventeen patients received doses of TroVax ranging from 5 x 10(7) up to 5 x 10(8) plaque-forming units at 0, 4, and 8 weeks and were considered to be evaluable for assessment of immunologic responses. Both antibody and cellular responses specific for the tumor antigen 5T4 and the viral vector were monitored throughout the study. RESULTS: TroVax was well tolerated in all patients with no serious adverse events attributed to vaccination. Of 17 evaluable patients, 16 showed 5T4-specific cellular responses whereas 14 had detectable antibody levels following vaccination. TroVax was able to boost 5T4-specific immune responses in the presence of MVA neutralizing antibodies. Periods of disease stabilization ranging from 3 to 18 months were observed in five patients, all of whom mounted 5T4-specific immune responses. Furthermore, statistical analysis showed a positive association between the development of a 5T4 (but not MVA) antibody response and patient survival or time to disease progression. CONCLUSION: These data indicate that vaccination with TroVax is safe and well tolerated and that immune responses to 5T4 can be induced without any evidence of autoimmune toxicity. Furthermore, 5T4-specific antibody responses correlate with evidence of disease control.

Harrop, R., N. Drury, et al. (2008). "Vaccination of colorectal cancer patients with TroVax given alongside chemotherapy (5-fluorouracil, leukovorin and irinotecan) is safe and induces potent immune responses." Cancer Immunol Immunother **57**(7): 977-86.

Modified vaccinia Ankara (MVA) encoding the tumor antigen 5T4 (TroVax) has been evaluated in an open label phase II study in metastatic colorectal cancer patients. The primary objective was to assess the safety and immunogenicity of TroVax injected before, during and after treatment with 5-fluorouracil, leukovorin and irinotecan. TroVax was administered to 19 patients with metastatic colorectal cancer. Twelve patients had blood samples taken following each of the six injections and were considered to be evaluable for assessment of immunological responses. Both antibody and cellular responses specific for the tumor antigen 5T4 and the viral vector MVA were monitored throughout the study. Administration of TroVax alongside chemotherapy was safe and well tolerated with no SAEs attributed to the vaccine and no enhancement of chemo-related toxicity. Of the 12 patients who were evaluable for assessment of immune responses, ten mounted 5T4-specific antibody responses with titers ranging from 10 to > 5,000. IFNgamma ELISPOT responses specific for 5T4 were detected in 11 patients with frequencies exceeding one in 1,000 PBMCs in five patients. Eight patients presented with elevated circulating CEA concentrations, six of whom showed decreases in excess of 50% during chemotherapy and four had CEA levels which remained stable for > 1 month following completion of chemotherapy. Of the 19 intention to treat (ITT) patients, one had a CR, six had PRs and five had SD. Potent 5T4-specific cellular and/or humoral immune responses were induced in all 12 evaluable patients and were detectable in most patients during the period in which chemotherapy was administered. These data demonstrate that TroVax can be layered on top of chemotherapy regimens without any evidence of enhanced toxicity or reduced immunological or therapeutic efficacy.

Harrop, R., N. Drury, et al. (2007). "Vaccination of colorectal cancer patients with modified vaccinia ankara encoding the tumor antigen 5T4 (TroVax) given alongside chemotherapy induces potent immune responses." Clin Cancer Res **13**(15 Pt 1): 4487-94.

PURPOSE: The attenuated strain of vaccinia virus, modified vaccinia Ankara (MVA) encoding the tumor antigen 5T4 (TroVax), has been evaluated in an open-label phase II study in metastatic colorectal cancer patients. The primary objective was to assess the safety and immunogenicity of TroVax injected before, during, and after treatment with cycles of 5-fluorouracil, folinic acid, and oxaliplatin. EXPERIMENTAL DESIGN: TroVax was administered to 17 patients with metastatic colorectal cancer. In total, 11 patients were considered to be evaluable for assessment of immunologic responses having received a total of six injections of TroVax, administered before, during, and following completion of chemotherapy. Antibody and cellular responses specific for 5T4 and MVA were monitored

throughout the study. RESULTS: Administration of TroVax alongside 5-fluorouracil, folinic acid, and oxaliplatin was safe and well tolerated with no serious adverse events attributed to TroVax. Ten of the 11 evaluable patients mounted 5T4-specific antibody responses with titers ranging from 10 to >1,000. IFNgamma enzyme-linked immunospot responses specific for 5T4 were detected in 10 patients with precursor frequencies exceeding 1 in 1,000 peripheral blood mononuclear cells in 4 patients. Of the 11 evaluable patients, 6 had complete or partial responses. 5T4-specific immune responses, but not MVA-specific immune responses, correlated with clinical benefit. CONCLUSIONS: Potent 5T4-specific cellular and/or antibody responses were induced in all evaluable patients and were still detectable during the period in which chemotherapy was administered. These results suggest that TroVax can be added to chemotherapy regimens without any evidence of enhanced toxicity or reduced immunologic efficacy and may provide additional clinical benefit.

Havranek, E. G., M. C. Labarthe, et al. (2008). "A novel murine model of allogeneic vaccination against renal cancer." BJU Int **101**(9): 1165-9.

OBJECTIVES: To develop a murine model for whole-cell allogeneic vaccination in renal cancer, as such vaccines aim to direct immune responses against patient tumour cells, due to shared antigens between the vaccine and tumour cells. MATERIALS AND METHODS: A novel murine renal cell line, allogeneic to BALB/c, was developed from a C57BL/6 mouse by primary cell culture (RVIK). It was immortalized by HPV16 E6/E7 and transfected with ras in an attempt to improve its immunogenicity. The cell line was characterized and tested as a vaccine in a BALB/c tumour-protection model after subsequent tumour challenge with autologous RenCa tumour cells. RESULTS: RVIK alone, with no ras induced cross-reactive immunity, providing a valid non-tumorigenic allogeneic whole-cell vaccine model for renal cancer. Ras transfection per se did not improve RVIK immunity. CONCLUSIONS: RVIK is a novel immunogenic murine renal epithelial cell line, which confers protection when used as an allogeneic vaccine. It provides proof of principle for the effectiveness of allogeneic whole-cell vaccines and may therefore form the basis of a useful model of allogeneic vaccination to further optimize vaccination schedules, formulation and adjuvants for a clinical setting.

Hawkins, R. E., C. Macdermott, et al. (2009). "Vaccination of patients with metastatic renal cancer with modified vaccinia Ankara encoding the tumor antigen 5T4 (TroVax) given alongside interferon-alpha." J Immunother **32**(4): 424-9.

Approximately 90% of renal cell tumors overexpress the tumor antigen 5T4. The attenuated strain of vaccinia virus, modified vaccinia Ankara, has been engineered to express 5T4 (TroVax). We conducted an open-label phase 1/2 trial in which TroVax was administered alongside interferon-alpha (IFNalpha) to 11 patients with metastatic renal cell carcinoma. Antigen-specific cellular and humoral responses were monitored throughout the study, and clinical responses were assessed by measuring the changes in tumor burden by computed tomography scan (Response Evaluation Criteria In Solid Tumors). The primary objective was to assess the safety, immunogenicity, and efficacy of TroVax when given alongside IFNalpha. Treatment with TroVax plus IFNalpha was well tolerated with no serious adverse events attributed to TroVax. All 11 patients mounted 5T4-specific antibody responses and 5 (45%) mounted cellular responses. No objective tumor responses were seen, but the overall median time to progression (TTP) of 9 months (range: 2.1 to 26+ mo) was longer than expected for IFNalpha alone. For the 10 clear cell patients the TTP ranged from 3.9 to 26+ months, with a median TTP of 10.4 months. The high frequency of 5T4-specific immune responses and prolonged median TTP for clear cell patients compared with that expected for IFNalpha alone is encouraging and warrants further investigation.

Heinrich, J. E., M. Pollard, et al. (2007). "Vaccination against prostate cancer using a live tissue factor deficient cell line in Lobund-Wistar rats." Cancer Immunol Immunother **56**(5): 725-30.

Reducing expression of the tissue factor gene in prostate adenocarcinoma cells (PAIII) results in a cell line that, in vivo, mimics the growth of wildtype (wt) PAIII. However, instead of continuing to grow and metastasize as wt PAIII tumors do, tissue factor deficient PAIII (TFD PAIII) masses spontaneously regress after several weeks. Although whole cell vaccines are typically inactivated prior to administration to prevent proliferation within the host, numerous studies have suggested that exposure to live, attenuated, whole tumor cells, and the extracellular microenvironment they recruit, increases immunotherapeutic potential. Here, we provide support for this notion, and a strategy through which to implement it, by demonstrating that subcutaneous vaccinations with the TFD PAIII protect the Lobund-Wistar rat against subsequent wt PAIII cell challenge. TFD PAIII immunized rats suffered significantly less metastasis of wt PAIII challenge tumors compared to unvaccinated naive controls rats. These results offer the intriguing possibility that the TFD PAIII vaccine

is an effective system for the prevention and, possibly, the treatment of prostate cancer.

Honma, I., H. Kitamura, et al. (2009). "Phase I clinical study of anti-apoptosis protein survivin-derived peptide vaccination for patients with advanced or recurrent urothelial cancer." Cancer Immunol Immunother **58**(11): 1801-7.

Survivin, a member of the inhibitor of apoptosis protein family, is expressed in many malignant tumors including urothelial cancer but is hardly detectable in normal, differentiated adult tissues. Previously we reported CD8-positive cytotoxic T-lymphocytes (CTLs) were successfully induced by stimulation with survivin-2B80-88 peptide in vitro. We started a phase I clinical study of survivin-2B80-88 peptide vaccination for advanced urothelial cancer patients to assess the safety and efficacy of this vaccination. Nine patients were received vaccination and were evaluated for immunological evaluation, adverse events, and clinical responses. A total of 46 vaccinations were carried out. There was no severe adverse event. HLA-A24/survivin-2B80-88 peptide tetramer analysis revealed a significant increase in the peptide-specific CTL frequency after the vaccination in five patients. Slight reduction of the tumor volume was observed in one patient. Survivin-2B80-88 peptide-based vaccination is safe and should be further considered for potential immune and clinical efficacy in urothelial cancer patients.

Hoops, K. E. and L. B. Twiggs (2008). "Human papillomavirus vaccination: the policy debate over the prevention of cervical cancer--a commentary." J Low Genit Tract Dis **12**(3): 181-4.

The human papillomavirus (HPV) family causes a variety of benign, premalignant, and malignant lesions in men and women. HPV types 16 and 18 are responsible for causing 70% of all cases of cervical cancer each year. Recently, a vaccine that can prevent cervical cancer by protecting women from infection with the most common types of HPV has been made available. Following Food and Drug Administration approval and endorsement by the Centers for Disease Control and Prevention, it is the right and the duty of the state legislatures to implement vaccination programs. This vaccine, a vaccine for a sexually transmitted disease, has stirred a fierce debate. Religion and sexuality have dominated the discussion, and political calculations are inherent to the process; nonetheless, epidemiological analyses are also essential to the decision to mandate the HPV vaccine. HPV vaccine program implementation processes are at many stages in many states, and programs vary widely. Some provide information to families, whereas others allot a range of funding for voluntary vaccination. Virginia is, thus far, the only state to have enacted a mandate. This article discusses the various programs in place, the proposed legislation, and the debate surrounding the political process.

Howlett, R. I., A. B. Miller, et al. (2009). "Defining a strategy to evaluate cervical cancer prevention and early detection in the era of HPV vaccination." Prev Med **48**(5): 432-7.

OBJECTIVE: The purpose of this paper is to outline the short-, medium- and long-term requirements of a strategy to evaluate the impact of HPV immunization and to define a framework to facilitate planning and evaluation. METHOD: This strategy was developed in Ontario from January to August 2008. Literature review was completed to assess existing material relevant to vaccine evaluation, and HPV vaccine specifically. Scientists and epidemiologists within our organization attended meetings to brainstorm and identify key requirements for vaccine evaluation. Other selected internal and external experts were consulted to review preliminary lists of potential indicators and questions for inclusion in an evaluation strategy. RESULTS: Results are reported in three sections--literature review, proposed evaluation framework and data requirements. CONCLUSION: The first vaccine evaluation strategy that integrates primary and secondary prevention of cervical cancer is presented. Among women who are neither screened nor immunized, customized interventions will be required to ensure that they are aware of potential risks and benefits. This evaluation strategy may serve as a useful outline for jurisdictions in Canada and elsewhere. This new paradigm of combined primary and secondary intervention will encourage cooperation for effective evaluation of an integrated approach for control of cervical cancer and other HPV-related disease.

Hueman, M. T., A. Stojadinovic, et al. (2006). "Levels of circulating regulatory CD4+CD25+ T cells are decreased in breast cancer patients after vaccination with a HER2/neu peptide (E75) and GM-CSF vaccine." Breast Cancer Res Treat **98**(1): 17-29.

PURPOSE: We are conducting clinical trials in breast cancer (BrCa) patients to test the HER2/neu peptide vaccine (E75). We have investigated the impact of this vaccine on circulating levels of regulatory T cells (Treg) and the resulting effects on antitumor responses. EXPERIMENTAL DESIGN: Twenty-two blood samples from healthy individuals and from 22 BrCa patients including pre- and post-vaccination samples from seven vaccinated HLA-A2+ patients were stained for CD4, CD25, and CD69 as

well as CD8 and E75:HLA-A2 Ig dimer and quantified by flow cytometry. Cytotoxic activity against HER2/neu+ tumors was measured by 51Cr-release. Serum from BrCa patients and normal subjects were analyzed for TGF-beta levels. RESULTS: BrCa patients have a greater percentage of circulating Treg (CD4+CD25+, 4.45% versus 2.96%; p=0.007) than normal subjects. HLA-A2+ BrCa patients had more Treg compared to the HLA-A2- BrCa patients (CD4+CD25+, 5.63% versus 3.28%; p=0.001). E75 vaccination increased circulating activated CD4+ T cells post-vaccination (CD4+CD69+, 1.23 versus 3.81%; p=0.03). However, T(reg) were significantly reduced after vaccination (CD4+CD25+, 5.31-1.81%; p<0.0001). Furthermore, activated Treg also decreased (CD4+CD25+CD69+, 0.23% versus 0.08%; p=0.06). Importantly, post-vaccination decreases in Treg were temporally associated with increased E75 vaccine-specific CD8+ T cells and corresponding HER2/neu+ tumor cytotoxicity. Serum TGF-beta levels were significantly elevated in BrCa patients compared to normals (3548 pg/ml versus 1007 pg/ml; p=0.007). Four of seven vaccinated patients showed decreased serum TGF-beta levels post-vaccination. CONCLUSIONS: Treg, are increased in BrCa patients along with serum levels of TGF-beta. E75 vaccination resulted in CD4+ recruitment but was associated with a significant decrease in circulating Treg and TGF-beta levels in the majority of the vaccinated patients. Successful cancer vaccination strategies may require the alteration of complex immune interactions.

Jenkins, D. (2008). "A review of cross-protection against oncogenic HPV by an HPV-16/18 AS04-adjuvanted cervical cancer vaccine: importance of virological and clinical endpoints and implications for mass vaccination in cervical cancer prevention." Gynecol Oncol **110**(3 Suppl 1): S18-25.

Human papilloma virus (HPV)-16 and -18 are responsible for approximately 70% of invasive cervical cancers worldwide. Other oncogenic HPV types account for almost all the remainder. Importantly, HPV-45 and -31 account for approximately 10%. HPV-18 and -45, along with HPV-16, are found in over 90% of endocervical adenocarcinomas. HPV-45 is the third most frequent HPV type in cervical carcinoma and adenocarcinoma. The AS04-adjuvanted vaccine Cervarix was developed against HPV-16 and -18 focusing on preventing cervical cancer by inducing durable protection against new infection. In clinical trials, it shows evidence of cross-protection against other important oncogenic HPV types using a range of clinicopathological and virological endpoints. The current evidence suggesting the cross-protective effect comes from its overall impact on precancerous lesions and on 12-month or more persistent oncogenic HPV infection, together with specific evidence of protection against incident and new persistent infection lasting 6 months or more with individual HPV types. The use of virological endpoints for such studies is discussed, in particular for cross-protection evaluation, in view of the lower frequency of many important oncogenic HPV types other than HPV-16 or -18 in precancerous lesions and the frequent presence of multiple HPV infections. Both of these factors complicate the interpretation of type-specific, vaccine-induced protection against cervical intraepithelial neoplasia (CIN) lesions, in which other HPV DNA types are found along with HPV-16 and -18. The observed high level of overall protection against clinicopathological lesions, including CIN2+ in the vaccinated subjects (regardless of their HPV DNA status), predicts a potentially broader impact of the vaccine in the prevention of HPV-related precancers that goes beyond HPV-16 and -18. The prevention of persistent infections by individual types such as HPV-45 provides specific information on the protection against that type, using an alternative endpoint that relates to both precancer and cancer development. Together with sustained protection against HPV-16 and -18, protection against HPV-45 could offer an additional effect on invasive cervical cancer and may have an important impact on endocervical adenocarcinoma, which is not effectively prevented by screening and is becoming increasingly important in young women.

Jo, Y. M., J. Y. Song, et al. (2009). "Dose sparing strategy with intradermal influenza vaccination in patients with solid cancer." J Med Virol **81**(4): 722-7.

Influenza vaccine is considered to reduce influenza-related morbidity and mortality in patients with underlying chronic medical conditions. Because of fear of vaccine shortage during an influenza pandemic, several antigen sparing strategies have been investigated. The immunogenicity of intradermal influenza vaccination with one half the antigenic contents was compared to that of conventional intramuscular vaccination in patients with solid cancer, and adverse events were assessed after vaccination. There was no significant difference between the injection routes in the hemagglutinin inhibition (HI) response and increase in the titer of A/H1N1, A/H3N2, and B 4-6 weeks after the vaccination; seroconversion factors increased by more than 2.5-fold. Seroresponse rates were more than 40% and seroprotection rates were above 70% against all three influenza strains irrespective of the vaccination routes. No serious events were observed, and local

skin reactions were more frequent in the intradermal injection recipients than in the intramuscular recipients (32.7% vs. 9.1%). This study shows that intradermal injection of one half the dose of a commercial influenza vaccine elicits immune responses comparable to those elicited by a full dose of intramuscular vaccine among cancer patients, and it can be tolerated without serious adverse reactions.

Kim, S., J. B. Lee, et al. (2009). "Vaccination with recombinant adenoviruses and dendritic cells expressing prostate-specific antigens is effective in eliciting CTL and suppresses tumor growth in the experimental prostate cancer." Prostate **69**(9): 938-48.

BACKGROUND: Prostate cancer is currently the most commonly diagnosed cancer in men and the second leading cause of cancer-related death in men in the US. Immunological approaches may provide an alternative option for prevention and treatment of prostate cancer. METHODS: To develop vaccine against prostate cancer using mouse model, we constructed three recombinant adenoviruses expressing prostate-specific membrane antigen (rAd/PSMA), prostate stem cell antigen (rAd/PSCA) and six-transmembrane epithelial antigen of the prostate (rAd/STEAP), that were specifically up-regulated in the transgenic murine prostate cancer. RESULTS: Male C57BL/6 mice were immunized by intravenous injection of these recombinant adenoviruses and subsequently by subcutaneous injection of dendritic cells pulsed with TRAMP-C1 tumor lysate. After subcutaneous challenge with TRAMP-C1 cells, tumor growth was significantly delayed in the immunized mice compared to the control group. Surprisingly, significant numbers of STEAP-specific CD8 T cells were detected in the peripheral blood and the spleen of immune mice using MHC I tetramers, and injection of rAd/STEAP alone followed by pulsed DC was sufficient to inhibit tumor growth. Therapeutic vaccination also significantly delayed the growth of pre-established tumors. CONCLUSION: Our results suggest that STEAP is a good immunologic target antigen against prostate cancer and our vaccination regimen successfully elicits anti-tumor CTL responses and suppresses tumor growth. More studies will expedite the development of this vaccine toward clinical application.

Kim-Schulze, S., H. S. Kim, et al. (2008). "Intrarectal vaccination with recombinant vaccinia virus expressing carcinoembronic antigen induces mucosal and systemic immunity and prevents progression of colorectal cancer." J Immunol **181**(11): 8112-9.

The gastrointestinal mucosa contains an intact immune system that protects the host from pathogens and communicates with the systemic immune system. Absorptive epithelial cells in the mucosa give rise to malignant tumors although the interaction between tumor cells and the mucosal immune system is not well defined. The pathophysiology of colorectal cancer has been elucidated through studies of hereditary syndromes, such as familial adenomatous polyposis, a cancer predisposition syndrome caused by germline mutations in the adenomatous polyposis coli tumor suppressor gene. Patients with FAP develop adenomas and inevitably progress to invasive carcinomas by the age of 40. To better delineate the role of mucosal immunity in colorectal cancer, we evaluated the efficacy of intrarectal recombinant vaccinia virus expressing the human carcinoembryonic Ag (CEA) in a murine FAP model in which mice are predisposed to colorectal cancer and also express human CEA in the gut. Mucosal vaccination reduced the incidence of spontaneous adenomas and completely prevented progression to invasive carcinoma. The therapeutic effects were associated with induction of mucosal CEA-specific IgA Ab titers and CD8(+) CTLs. Mucosal vaccination was also associated with an increase in systemic CEA-specific IgG Ab titers, CD4(+) and CD8(+) T cell responses and resulted in growth inhibition of s.c. implanted CEA-expressing tumors suggesting communication between mucosal and systemic immune compartments. Thus, intrarectal vaccination induces mucosal and systemic antitumor immunity and prevents progression of spontaneous colorectal cancer. These results have implications for the prevention of colorectal cancer in high-risk individuals.

Koido, S., E. Hara, et al. (2007). "Dendritic/tumor fusion cell-based vaccination against cancer." Arch Immunol Ther Exp (Warsz) **55**(5): 281-7.

A promising area of investigation is the use of cancer vaccines to eliminate residual tumor cells. Dendritic cells (DCs) are potent professional antigen-presenting cells able to induce primary immune responses. DCs capture and process antigens into peptides and present them to T cells and B cells through MHC class I and II molecules. An alternative approach to the induction of antitumor immunity is the use of fusions of DCs and tumor cells. In this approach, a broad spectrum of tumor-associated antigens, including those known and unidentified, are processed endogenously and presented by MHC class I and II pathways in the context of costimulatory signals. In animal studies, vaccination with DC/tumor fusion cells results in the elimination of established lung metastasis. Preclinical human studies have demonstrated that DC/tumor fusion cells induce antigen-specific polyclonal cytotoxic T-lymphocyte

responses against autologous tumor in vitro. In clinical studies, vaccination of cancer patients with autologous DC/tumor fusion cells is associated with immunological and clinical responses in a subset of patients. Future studies should be investigated to improve the immunogenicity of DC/tumor fusion cell preparations. This review provides a general overview of the DC/tumor fusion cell-based vaccine and summarizes some of the recent advances in this field.

Kono, K., Y. Mizukami, et al. (2009). "Vaccination with multiple peptides derived from novel cancer-testis antigens can induce specific T-cell responses and clinical responses in advanced esophageal cancer." Cancer Sci **100**(8): 1502-9.

We previously identified three novel HLA-A24-restricted epitope peptides, which were derived from three cancer-testis antigens, TTK protein kinase (TTK), lymphocyte antigen 6 complex locus K (LY6K), and insulin-like growth factor (IGF)-II mRNA binding protein 3 (IMP-3), as targets for cancer vaccination against esophageal squamous cell carcinoma (ESCC). To examine the safety, immunogenicity, and antitumor effect of vaccine treatment using a combination of these three peptides, 10 HLA-A2402-positive advanced ESCC patients who failed to standard therapy were enrolled in a phase I clinical trial. Each of the three peptides (1 mg each) was intradermally administered with 1 mL of incomplete Freund's adjuvant to the neck in three separate regions weekly for 5 weeks. The cancer vaccination therapy was well tolerated without any treatment-associated adverse events of grade 3 or 4. The TTK-, LY6K-, and/or IMP-3-specific T-cell immune responses were observed by enzyme-linked immunospot assay in peripheral blood lymphocytes obtained from nine of the 10 ESCC patients after their vaccination. The median survival time after the vaccination was 6.6 months. The vaccination could induce good clinical responses in 50% of the 10 patients. One patient experienced a complete response in hepatic metastasis lasting 7 months, one showed objective responses in all lung metastasis lesions, and three patients revealed a stable disease condition for at least 2.5 months. The cancer vaccine therapy using these three peptides demonstrated satisfactory safety and good immunogenicity as well as promising disease control rate, and therefore warrants further clinical studies.

Kouiavskaia, D. V., C. A. Berard, et al. (2009). "Vaccination with agonist peptide PSA: 154-163 (155L) derived from prostate specific antigen induced CD8 T-cell response to the native peptide PSA: 154-163 but failed to induce the reactivity against tumor targets expressing PSA: a phase 2 study in patients with recurrent prostate cancer." J Immunother **32**(6): 655-66.

We conducted a clinical trial of peptide prostate specific antigen (PSA): 154-163 (155L) vaccination in human leukocyte antigen (HLA)-A2 patients with detectable and rising serum PSA after radical prostatectomy for prostate cancer (Clinicaltrials.gov identifier NCT00109811). The trial was a single dose-level, phase 2 pilot trial of 1 mg of PSA: 154-163 (155L) emulsified with adjuvant (Montanide ISA-51). The primary endpoint was the determination of immunogenicity of the vaccine; secondary outcomes were determination of toxicity and effect on serum PSA. The vaccine was given subcutaneously 7 times on weeks 0, 2, 4, 6, 10, 14, and 18. Peptide-specific CD8 T-cell responses in the peripheral blood mononuclear cells (PBMC) of patients were measured by interferon (IFN)-gamma enzyme-linked immunosorbent spot assay. CD8 T-cell cultures were also established by in vitro stimulation with the peptide presented by autologous dendritic cells. Five patients were enrolled and completed all vaccinations. No IFN-gamma response to PSA: 154-163 (155L) was detected in unfractioned PBMC in any patient either before or after vaccination. Three of 5 patients demonstrated strong IFN-gamma responses to PSA: 154-163 (155L) and native PSA: 154-163 peptides in CD8 T-cell cultures derived from postvaccination PBMC. However, peptide-specific T cells failed to recognize HLA-A2 positive targets expressing endogenous PSA. There were no significant changes in serum PSA level in any subject. No serious adverse events were observed. PSA: 154-163 (155L) is not an effective immunogen when given with Montanide ISA-51. The PSA: 154-163 peptide is poorly processed from endogenous PSA and therefore represents a cryptic epitope of PSA in HLA-A2 antigen-presenting cells.

Krug, L. M., G. Ragupathi, et al. (2004). "Vaccination of patients with small-cell lung cancer with synthetic fucosyl GM-1 conjugated to keyhole limpet hemocyanin." Clin Cancer Res **10**(18 Pt 1): 6094-100.

PURPOSE: Immunotherapy directed toward cell surface antigens may provide a novel approach to the eradication of chemoresistant micrometastatic disease in patients with small-cell lung cancer (SCLC). Studies in SCLC cell lines and human tissues suggest that the ganglioside fucosyl GM1 is an abundant yet specific target. A prior clinical study demonstrated the potent immunogenicity of fucosyl GM-1 derived from bovine thyroid gland, conjugated to keyhole limpet hemocyanin (KLH) and administered with QS-21 adjuvant. EXPERIMENTAL DESIGN: We tested the immunogenicity of three different doses of a synthetic

version of fucosyl-GM1 in patients with SCLC after a major response to initial therapy. The primary end point was to establish the lowest effective dose capable of inducing antibody production. RESULTS: Five of six patients at the 30-microg dose and three of five patients at the 10-microg dose mounted IgM responses of 1:80 or greater. These antibodies were confirmed by flow cytometry in seven of eight cases. None of the patients at the 3-microg dose had titers above 1:80. One patient at the 30-microg dose had an IgG response with a titer of 1:80. The sera from six of the eight responders induced potent complement-mediated cytotoxicity of tumor cells. CONCLUSIONS: Vaccination with the synthetic fucosyl GM1-KLH conjugate induces an IgM antibody response against fucosyl GM1 and tumor cells expressing fucosyl GM1, comparable with the response induced by the bovine derivative. We plan to combine synthetic fucosyl GM1 vaccine at a dose of 30 microg with vaccines against three other antigens-GM2, Globo H, and polysialic acid-to test in patients with SCLC after initial chemotherapy.

Krug, L. M., G. Ragupathi, et al. (2004). "Vaccination of small cell lung cancer patients with polysialic acid or N-propionylated polysialic acid conjugated to keyhole limpet hemocyanin." Clin Cancer Res **10**(3): 916-23.

PURPOSE: Long chain polysialic acid (polySA) is a side chain on embryonal neural cell adhesion molecules that, in the adult, is largely restricted to small cell lung cancer (SCLC). Long chains of polySA are also expressed on group B meningococcus. In this clinical trial, we aimed to elicit an immune response against polysialic acid to target clinically inapparent residual disease in patients with SCLC who had successfully completed initial therapy. EXPERIMENTAL DESIGN: Patients were vaccinated with either 30 micro g unmodified polySA or N-propionylated-polySA (NP-polySA), conjugated to keyhole limpet hemocyanin (KLH) and mixed with 100 micro g of immunological adjuvant QS-21 at weeks 1, 2, 3, 4, 8, and 16. RESULTS: Of the 5 evaluable patients vaccinated with unmodified polySA, only 1 mounted an IgM antibody response to polySA. On the other hand, all 6 of the patients vaccinated with NP-polySA produced IgM antibodies to NP-polySA and these cross-reacted with unmodified polySA in all but 1 case. IgG antibodies to NP-polySA were observed in 5 of the patients, but these did not cross-react with polySA. The presence of IgM antibodies reactive with SCLC cell lines was confirmed in this group by flow cytometry. Complement-dependent lysis of tumor cells could not be demonstrated. However, postimmunization sera induced significant bactericidal activity against group B meningococcus when combined with rabbit complement. CONCLUSIONS: Vaccination with NP-polySA-KLH, but not polySA-KLH, resulted in a consistent high titer antibody response. We are now conducting a de-escalation dosing study with NP-polySA-KLH to better assess the immunogenicity, toxicities, and optimal dose of this vaccine. We plan to incorporate this vaccine as a component of a polyvalent vaccine with GM2, fucosylated GM1, and Globo H to target SCLC.

Kulasingam, S. L., S. Pagliusi, et al. (2007). "Potential effects of decreased cervical cancer screening participation after HPV vaccination: an example from the U.S." Vaccine **25**(48): 8110-3.

A concern with widespread implementation of HPV vaccination programs is that women may mistakenly decide that they do not need to be screened any longer, and thus be less likely to participate in cervical cancer screening, because they view themselves to be at low-risk of developing cervical cancer. We hypothesized that non-participation in screening among vaccinated young women in the 5 years following vaccination may result in missed CIN 2-3 cases that could progress to cancer. For instance, if 50% fewer women 26-30 years old, who were vaccinated, participate in screening in the United States over a 5 year time horizon, there would be approximately 4 women (per 1000) with missed CIN 2-3. On the other hand, non-participation will reduce the number of false-positive screening test results, as non-participation would avoid approximately 27 false-positive test results, with a decrease in follow-up procedures and costs. These results highlight the importance of educating women to ensure continued screening, as well as the need to consider new approaches to screening in the era of vaccination.

Kyte, J. A. (2009). "Cancer vaccination with telomerase peptide GV1001." Expert Opin Investig Drugs **18**(5): 687-94.

Telomerase is highly expressed in essentially all cancer forms, while the expression in normal tissues is restricted. Moreover, telomerase activity is considered indispensable for tumor immortalization and growth. Human telomerase reverse transcriptase (hTERT), the rate-limiting subunit of the telomerase complex, is therefore an attractive target for cancer vaccination. The present review provides an update on the development of GV1001, a peptide vaccine representing a 16-aa hTERT sequence. GV1001 binds multiple HLA class II molecules and harbors putative HLA class I epitopes. The peptide may therefore elicit combined CD4/CD8 T-cell responses, considered important to initiate tumor eradication and long-term memory. Phase I/II trials in advanced pancreatic and

pulmonary cancer patients have demonstrated GV1001-specific T-cell responses in > 50% of subjects, without clinically important toxicity. The results indicate a correlation between development of GV1001-specific responses and prolonged survival. However, as in most cancer vaccine trials, a large proportion of immune responders experience no clinical benefit. Long-term survivors harbor durable GV1001-specific T-cell responses with high IFN-gamma/IL-10 ratios and polyfunctional cytokine patterns. Interestingly, the cytokine profiles do not follow a T(H)1/T(H)2 delineation. Here, the author discusses how immunomonitoring may be improved to discriminate between efficient and pointless immune responses, and which questions to address in the further development of GV1001.

Labarthe, M. C., P. Theocharous, et al. (2008). "A novel murine model of allogeneic vaccination against prostate cancer." Cancer Immunol Immunother **57**(4): 453-65.

Prostate cancer continues to be a major cause of death in men. Surgical and medical treatments of the disease have improved, but metastasic disease remains a significant clinical problem. Novel therapies such as whole cell vaccination offer the potential of treating disease by stimulating the immune system. To study the efficacy of a whole cell vaccine in prostate cancer two strains of mice were used: C57BL/6 (H-2Kb) and C3H/HeJ (H-2K(k)) in combination with four different cell lines. Thus, a model was constructed of allogeneic and syngeneic vaccine, as well as a challenge tumour for each strain. Two novel cell lines were developed during this study. Firstly, the non tumourigeneic PMC-1 was derived from a normal mouse prostate and immortalized with HPV16. Secondly, the tumourigeneic PMC-1 C6ras1p1 was transformed with human ras gene which formed tumours in both SCID and C3H/HeJ mice. Protection, and the nature of the immune response to syngeneic and allogeneic vaccine, in males and females was examined in both strains. Vaccination with both syngeneic and allogeneic irradiated whole cell vaccines induced protection from syngeneic challenge in females. However, no protection was observed when allogeneic vaccine was given to male mice. This correlated with the immune response. Two types of cellular immune responses were generated in females. A NK-mediated response was observed in C57BL/6 mice, whilst C3H/HeJ mice developed a CTL response. Little or no cellular immune response was observed in males. The cytokine profile in C3H/HeJ females was a mixture of Th1 and Th2 whilst a mainly Th1 profile was observed in C57BL/6 mice. Male mice showed a diminished cytokine secretion compared to females which was further depressed after challenge. The difference in immunity was largely as expected, since tolerance to prostate antigens should not normally develop in female mice. However, this makes this model particularly relevant clinically since it directly mimics the human situation and thus may accelerate the development of whole cell vaccines for clinical use.

Lesterhuis, W. J., I. J. de Vries, et al. (2006). "Vaccination of colorectal cancer patients with CEA-loaded dendritic cells: antigen-specific T cell responses in DTH skin tests." Ann Oncol **17**(6): 974-80.

BACKGROUND: Dendritic cells (DCs) are the professional antigen-presenting cells of the immune system. As such they are currently used in clinical vaccination protocols in cancer patients. PATIENTS AND METHODS: We evaluated the ability of mature DCs pulsed with carcinoembryonic antigen (CEA)-peptide to induce CEA-specific T cell responses in patients with resectable liver metastases from colorectal cancer. CEA-specific T cell reactivity was monitored in peripheral blood, biopsies of vaccination sites and post-treatment DTH skin tests, and when available also in resected abdominal lymph nodes and tumor tissue. RESULTS: Ten patients were vaccinated intradermally and intravenously with CEA-peptide pulsed mature DCs three times prior to resection of liver metastases. High numbers of CEA-specific T cells were detected in post-treatment DTH biopsies in seven out of 10 patients, which produced high amounts of interferon (IFN)-gamma upon stimulation with CEA-loaded target cells. These responses were not found in biopsies of first vaccination sites, indicating a de novo T cell induction or at least a strong potentiation by the vaccine. In addition, CEA-specific T cells were detected in a resected lymph node in one patient, but not in peripheral blood or tumor tissue. CONCLUSIONS: Vaccination with CEA-peptide loaded mature DCs induced potent CEA-specific T cell responses in advanced colorectal cancer patients. In this study, antigen-specific T cell responses were readily detected in DTH skin tests, much less in abdominal lymph nodes, and not in peripheral blood and tumor tissue.

Li, H., H. J. Jiang, et al. (2007). "Vaccination with allogeneic GM-CSF gene-modified lung cancer cells: antitumor activity comparing with that induced by autologous vaccine." Cancer Biother Radiopharm **22**(6): 790-8.

OBJECTIVE: The aim of this study was to investigate the whole allogeneic (differing tissue-type) tumor cells as vaccine in the mouse lung cancer model. The immunogenic and antitumor activity of

allogeneic vaccine was compared with that of autologous cancer cell vaccine. METHODS: C57/BL mice inoculated with Lewis lung cancer (LLC) cells were used as the animal model to test the effects of allogeneic vaccination. LA795 and LLC lung cancer cell lines, which were transfected with the mouse granulocyte-macrophage colony-stimulating factor (GM-CSF) gene, were administered as allogeneic and autologous tumor vaccine, respectively. The irradiated tumor cells were administered as subcutaneous vaccines before the tumor challenge. The immunity of cancer vaccine was tested by mouse interferon-gamma (IFN-gamma) enzyme-linked immunospot (ELISPOT) lactate dehydrogenase (LDH) assays. The serum level of IFN-gamma and interleukin (IL)-4 was tested using the enzyme-linked immunosorbent assay method. RESULTS: Prophylactic vaccination with allogeneic LA795 cells protected against the LLC tumor challenge in C57/BL. The tumor growth was inhibited and the survival was accordingly prolonged. The cytotoxicity of the spleen cells or the purified CD(8)(+) T-cells against LLC cells in the mice immunized with either the autologous or allogeneic cancer cell vaccine was significantly increased, relative to that of the control, untreated group ($p<0.05$). ELISPOT IFN-gamma assays showed that spleen cells from mice immunized with LA795 cells could be activated after coculture with irradiated LLC cells. In addition, the serum level of Th1-king cytokine IFN-gamma significantly increased after vaccination; however, no statistically difference was found in Th2-kind cytokine IL-4. CONCLUSIONS: The allogeneic cancer vaccine could induce immune responses and protection against lung cancer, which had no significant difference with that of autologous vaccine.

Li, Y., H. Zeng, et al. (2009). "Vaccination with human pluripotent stem cells generates a broad spectrum of immunological and clinical responses against colon cancer." Stem Cells **27**(12): 3103-11.

The history of immunizing with embryonic materials to generate an antitumor immune response dates back to a century ago. The premise is that cancer cells share the expression of oncofetal antigens with embryonic materials and that the immune response against these antigens in the embryonic tissues is cross-protective against cancer. However, such a practice has never advanced beyond experimental animal settings, because of lack of uniformed source tissues and ethical challenges. With the availability of well-characterized human pluripotent stem cells, it is now possible to ask whether tumor protective immunity could indeed be elicited with stem cells. Herein, we investigated whether vaccination with defined human embryonic stem cells (hESCs) or induced pluripotent stem (iPS) cells was effective against a colon carcinoma. We discovered that vaccination of mice with hESC line H9 generated consistent cellular and humoral immune responses against CT26 colon carcinoma. Protection correlated strongly with the expansion of tumor-responsive and interferon-gamma-producing cells and the profound loss of CD11b(+)Gr-1(+) myeloid-derived suppressor cells in the spleen. No evidence of autoimmunity was observed. We also compared the immunogenicity against colon cancer between a hESC line CT2 and an iPS cell line TZ1 that were generated in the same stem cell facility. We found that the iPS cell line was inferior to the hESC line in conferring tumor protection, suggesting that there is heterogeneity of expression of oncofetal antigens by hESCs and iPS cells. We conclude that the hESC-based vaccine is a promising modality for immunotherapy of cancer.

Liu, K. J., C. C. Wang, et al. (2004). "Generation of carcinoembryonic antigen (CEA)-specific T-cell responses in HLA-A*0201 and HLA-A*2402 late-stage colorectal cancer patients after vaccination with dendritic cells loaded with CEA peptides." Clin Cancer Res **10**(8): 2645-51.

PURPOSE: We intranodally immunized metastatic colorectal carcinoma patients, who had failed standard chemotherapy, with dendritic cells (DCs) pulsed with HLA-A*0201- or HLA-A*2402-restricted carcinoembryonic antigen (CEA) peptides to evaluate the safety of this treatment and the immune response against CEA peptides before and after the treatment. EXPERIMENTAL DESIGN: Six patients with the HLA-A*2402 genotype and 4 patients with the HLA-A*0201 genotype were enrolled. A single CEA peptide (YLSGANLNL) or two CEA peptides (QYSWFVNGTF and TYACFVSNL) were used for patients with the HLA-A*0201 or HLA-A*2402 genotype, respectively. Autologous DCs were generated by culturing adherent mononuclear cells with interleukin 4 and granulocyte macrophage colony-stimulating factor for 6 days. Maturation of DCs was then induced with tumor necrosis factor alpha for 40 h. Mature DCs were pulsed with appropriate CEA peptides for 2 h. After washing, 1 million peptide-pulsed DCs were injected into one inguinal lymph node under sonographic guidance. Each patient received four injections. RESULTS: No grade II/III toxicity or autoimmunity was observed. An increase in the number of CEA-specific T cells after DC vaccination could be detected in 7 of 10 (70%) patients. Two (20%) patients had stable disease for at least 12 weeks. One of these 2 patients experienced a transient decrease in CEA levels during the treatment period and also had the most significant T-cell response against the

immunizing CEA peptides. CONCLUSIONS: These results suggest that our vaccination procedure can generate or boost specific T-cell responses and may provide clinical benefit in certain cancer patients.

Liu, L. N., R. Shivakumar, et al. (2008). "Delivery of whole tumor lysate into dendritic cells for cancer vaccination." Methods Mol Biol **423**: 139-53.

Results from multiple human studies have continued to spur the development of dendritic cells (DCs) as therapeutic vaccines for the treatment of cancer, chronic viral infections, and autoimmune diseases. The antigen-specific activity of DCs is dependent on the ability of the DCs to take up and process tumor-associated antigens for presentation to the immune system. Although immature DCs have been shown to naturally take up tumor-associated antigens by phagocytosis, approaches that significantly affect antigen delivery need further evaluation, especially if such methodologies can be demonstrated to result in the elicitation of more robust and comprehensive immune responses. We have developed a rapid, robust, scalable, and regulatory-compliant process for loading DCs with whole tumor lysate. The use of whole tumor lysate facilitates the generation of a more robust immune response targeting multiple unique antigenic determinants in patient's tumors and likely reduces the tumor's potential of immune escape. We demonstrate that DCs electroloaded with tumor lysate elicit significantly stronger antitumor responses both in a tumor challenge model and in a therapeutic vaccination model for preexisting metastasic disease. These effects are observed in a processing scheme that requires 20- to 40-fold lower amounts of tumor lysate when compared with the standard coincubation/coculture methods employed in loading DCs.

Lollini, P. L., S. Motta, et al. (2006). "Discovery of cancer vaccination protocols with a genetic algorithm driving an agent based simulator." BMC Bioinformatics **7**: 352.

BACKGROUND: Immunological prevention of cancer has been obtained in HER-2/neu transgenic mice using a vaccine that combines 3 different immune stimuli (Triplex vaccine) that is repeatedly administered for the entire lifespan of the host (Chronic protocol). Biological experiments leave open the question of whether the Chronic protocol is indeed the minimal vaccination schedule affording 100% protection, or whether shorter protocols could be applied that would result in the same efficacy. A biological solution would require an enormous number of experiments, each lasting at least one year. Therefore we approached this problem by developing a simulator (SimTriplex) which describes the immune response activated by Triplex vaccine. This simulator, tested against in vivo experiments on HER-2/neu mice, reproduces all the vaccination protocols used in the in vivo experiments. The simulator should describe any vaccination protocol within the tested range. A possible solution to the former open question using a minimal search strategy based on a genetic algorithm is presented. This is the first step toward a more general approach of biological or clinical constraints for the search of an effective vaccination schedule. RESULTS: The results suggest that the Chronic protocol included a good number of redundant vaccine administrations, and that maximal protection could still be obtained with a number of vaccinations approximately 40% less than with the Chronic protocol. CONCLUSION: This approach may have important connotations with regard to translation of cancer immunopreventive approaches to human situations, in which it is desirable to minimize the number of vaccinations. We are currently setting up experiments in mice to test whether the actual effectiveness of the vaccination protocol agrees with the genetic algorithm.

Machlenkin, A., R. Azriel-Rosenfeld, et al. (2007). "Preventive and therapeutic vaccination with PAP-3, a novel human prostate cancer peptide, inhibits carcinoma development in HLA transgenic mice." Cancer Immunol Immunother **56**(2): 217-26.

Conventional treatment of recurrent and metastasized prostate cancer (CaP) remains inadequate; this fact mandates development of alternative therapeutic modalities, such as specific active or passive immunotherapy. Previously, we reported the identification of a novel highly immunogenic HLA-A*0201-restricted Prostatic Acid Phosphatase-derived peptide (PAP-3) by a two-step in vivo screening in an HLA-transgenic (HHD) mouse system. In the present study we aimed at elucidating the efficiency of PAP-3-based vaccine upon active antitumor immunization. To this end we established preventive and therapeutic carcinoma models in HHD mice. The 3LL murine Lewis lung carcinoma clone D122 transduced to express HLA-A*0201 and PAP served as a platform for these models. The HLA-A*0201-PAP-3 complex specific recombinant single chain scFV-PAP-3 antibodies were generated and used to confirm an endogenous PAP processing resulting in PAP-3 presentation by HLA-A*0201. PAP-3 based vaccines significantly decreased tumor incidence in a preventive immunization setting. Therapeutic vaccination of HHD mice with PAP-3 led to rejection of early established tumors and to increase of mouse survival. These results strongly support a therapeutic relevance of the identified CTL epitope

upon active antitumor immunization. The newly established carcinoma model presented herein might be a useful tool for cancer vaccine design and optimization.

Maclean, J., E. P. Rybicki, et al. (2005). "Vaccination strategies for the prevention of cervical cancer." Expert Rev Anticancer Ther **5**(1): 97-107.

Infection with high-risk human papillomaviruses (HPVs) is an essential step in the multistep process leading to cervical cancer. There are approximately 120 different types of HPV identified: of these, 18 are high-risk types associated with cervical cancer, with HPV-16 being the dominant type in most parts of the world. The major capsid protein of papillomavirus, produced in a number of expression systems, self assembles to form virus-like particles. Virus-like particles are the basis of the first generation of HPV vaccines presently being tested in clinical trials. Virus-like particles are highly immunogenic and afford protection from infection both in animal models and in Phase IIb clinical trials. A number of Phase III trials are in progress to determine if the vaccine will protect against cervical disease and, in some cases, genital warts. However, it is predicted that these vaccines will be too expensive for the developing world, where they are desperately needed. Another problem is that they will be type specific. Novel approaches to the production of virus-like particles in plants, second-generation vaccine approaches including viral and bacterial vaccine vectors and DNA vaccines, as well as different routes of immunization, are also reviewed.

Massad, L. S., M. Einstein, et al. (2009). "The impact of human papillomavirus vaccination on cervical cancer prevention efforts." Gynecol Oncol **114**(2): 360-4.

OBJECTIVES: To review concepts, information, obstacles, and approaches to cervical cancer screening and prevention as vaccination against human papillomavirus (HPV) types 16 and 18 is adopted. METHODS: Expert forum, conducted September 12-13, 2008, hosted by the Society of Gynecologic Oncologists, including 56 experts in cervical cancer and titled Future Strategies of Cervical Cancer Prevention: What Do We Need to Do Now to Prepare? RESULTS: The current approach to cervical cancer screening in the U.S. is limited by its opportunistic nature. If given to women before exposure, a vaccine against HPV 16,18 can decrease cervical cancer risk by up to 70%. The impact on abnormal cytology and cervical intraepithelial neoplasia (CIN) will be less but still substantial. As the prevalence of high-grade CIN falls, fewer women with positive screening tests will have truly preinvasive disease. To minimize harm from false positive tests in women who are at low risk for cancer because of early vaccination, later initiation of and longer intervals between screenings are ideal. However, the vaccine is less effective when administered after first intercourse, and delivering and documenting HPV vaccination to girls at optimal ages may prove difficult. CONCLUSIONS: Until population-based data on the performance of cytology, HPV testing, and alternate screening or triage interventions become available, modifying current screening guidelines is premature. Current recommendations to initiate screening as late as age 21 and to screen less often than annually are appropriate for young women known to have been vaccinated before first intercourse.

Matsuzaki, A., A. Suminoe, et al. (2005). "Immune response after influenza vaccination in children with cancer." Pediatr Blood Cancer **45**(6): 831-7.

PURPOSE: To assess the immune response to inactivated trivalent split influenza vaccine in children with cancer. PROCEDURES: Forty-four children with various types of malignancies received two doses of influenza vaccine 2-4 weeks apart. Hemagglutinin-inhibition (HI) antibody titers were determined in paired sera obtained just before the first vaccination and 4 weeks after the second vaccination. RESULTS: Influenza vaccine was administered to all children without any serious adverse effects. Protective titer rates (proportion of patients achieving antibody titers > or =40 among those with pre-vaccination titers <40) and response rates (proportion of patients with fourfold or more antibody rise) were 72% and 65% for H1N1, 60% and 40% for H3N2, and 38% and 46% for influenza B, respectively. However, patients on chemotherapy showed a significantly lower immune response to influenza A than those having completed chemotherapy; protection titer rates were 42% versus 90% for H1N1 ($P = 0.006$) and 25% versus 83% for H3N2 ($P = 0.019$). For influenza B, patients with low IgG showed a lower response rate than those with high IgG (29% vs. 61%, $P = 0.040$). Multivariate analysis revealed that factors significantly associated with a lower immune response were low IgG ($P < 0.001$) and administration of chemotherapy ($P = 0.003$) for H1N1, administration of chemotherapy ($P = 0.008$) for H3N2, and low white blood cell (WBC) count ($P = 0.030$) and low IgG ($P = 0.030$) for influenza B. CONCLUSIONS: Influenza vaccination given to children with cancer was safe and induced immune reaction comparable to healthy children, although patients on chemotherapy and/or with chemotherapy-related conditions had a limited ability to produce a sufficient immune response.

Mazzaferro, V., J. Coppa, et al. (2003). "Vaccination with autologous tumor-derived heat-shock protein gp96 after liver resection for metastatic colorectal cancer." Clin Cancer Res **9**(9): 3235-45.

PURPOSE: Heat shock proteins (HSP) from tumor cells contain the gp96 polypeptide associated with cancer-specific antigenic peptides. Mice that are immunized with HSP/peptide-complex (HSPPC) derived from cancer tissue reject tumor from which HSPs are purified. We tested in humans whether vaccination with HSPPC-gp96 (Oncophage) from autologous liver metastases of colorectal carcinoma induces cancer-specific T-cell responses in patients rendered disease free by surgery. Experimental Design: Twenty-nine consecutive patients underwent radical resection of liver metastases [Memorial Sloan-Kettering Cancer Center (MSKCC) score 1-3 (good prognosis), 18 patients; score 4-5 (bad prognosis), 11 patients] and received autologous tumor-derived HSPPC-96. Two vaccine cycles were administered (four weekly injections followed by four biweekly injections after 8 weeks). Class-I HLA-restricted, anti-colon cancer lines T-cell response was measured by ELISPOT assay on peripheral blood mononuclear cells (PBMCs) obtained before and after vaccination. Feasibility, safety, and possible clinical benefits were also evaluated. RESULTS: Either a de novo induced or a significant increase of preexisting class I HLA-restricted T-cell-mediated anti-colon cancer response was observed in 15 (52%) of 29 patients. Frequency of CD3+, CD45RA+, and CCR7- T lymphocytes increased in immune responders. No relevant toxicity was observed. As expected, patients with good prognosis had a significantly better clinical outcome than those with poor prognosis [2-year overall survival (OS), 89 versus 64%, P = 0.001; disease-free survival (DFS), 46 versus 18%, P = 0.001]. Patients with immune response had a statistically significant clinical advantage over nonresponding subjects (2-year OS, 100% versus 50%, P = 0.001; DFS, 51% versus 8%, P = 0.0001). Occurrence of immune response led to better tumor-free survival, whatever the predicted prognosis was (hazard ratio, 0.11-0.12 with/without stratification; P = 0.0012-0.0003). CONCLUSIONS: HSPPC-96 vaccination after resection of colorectal liver metastases is safe and elicits a significant increase in CD8+ T-cell response against colon cancer. In this limited number of patients, two-year OS and DFS were significantly improved in subjects with postvaccination antitumor immune response, independently from other clinical prognostic factors.

Mennuni, C., S. Ugel, et al. (2008). "Preventive vaccination with telomerase controls tumor growth in genetically engineered and carcinogen-induced mouse models of cancer." Cancer Res **68**(23): 9865-74.

The telomerase reverse transcriptase, TERT, is an attractive target for human cancer vaccination because its expression is reactivated in a conspicuous fraction of human tumors. Genetic vaccination with murine telomerase (mTERT) could break immune tolerance in different mouse strains and resulted in the induction of both CD4+ and CD8+ telomerase-specific T cells. The mTERT-derived immunodominant epitopes recognized by CD8+ T cells were further defined in these mouse strains and used to track immune responses. Antitumor efficacy of telomerase-based vaccination was investigated in two cancer models closely resembling human diseases: the TRAMP transgenic mice for prostate cancer and a carcinogen-induced model for colon cancer. TERT overexpression in tumor lesions was shown in both models by immunohistochemistry, thus reinforcing the similarity of these tumors to their human counterparts. Repeated immunizations with mTERT-encoding DNA resulted in a significant delay of tumor formation and progression in both the prostate cancer and the colon cancer models. Moreover, evaluation of the intratumoral infiltrate revealed the presence of telomerase-specific T cells in vaccinated mice. The safety of vaccination was confirmed by the absence of histomorphologic changes on postnecropsy analysis of several organs and lack of adverse effects on blood cell counts. These results indicate that TERT vaccination can elicit antigen-specific immunosurveillance and imply this antigen as a potential candidate for preventive cancer vaccines.

Met, O., M. Wang, et al. (2006). "The effect of a therapeutic dendritic cell-based cancer vaccination depends on the blockage of CTLA-4 signaling." Cancer Lett **231**(2): 247-56.

Dendritic cells (DCs) were pulsed with the H-2K(b) binding OVA(257-264)-peptide (SIINFEKL), and used as one single-injection vaccine in combination with anti-CTLA-4 monoclonal antibody (mAb) to treat mice inoculated 3 days previously with 3x10(5) E.G7-OVA lymphoma cells. Neither DC vaccination nor CTLA-4 blockage alone prevented tumor growth in tumor challenged mice. In contrast, the combination of one vaccination and injection of anti-CTLA-4 mAb lead to rejection or retarded tumor growth in more than 60% of the mice. The OVA-transgene or the SIINFEKL-epitope was not lost in the progressing tumors of vaccinated mice, however, the highest degree of anti-SIINFEKL reactivity of host CTLs in an IFN-gamma ELISPOT assay was found only in mice showing complete tumor rejection. Vaccinated mice having rejected

E.G7-OVA tumors were capable of rejecting subsequent challenges with 1x10(6) E.G7-OVA tumor cells, and later on these mice even rejected wild-type EL-4 tumor cells indicating that tumor epitope spreading takes place during the process of vaccination-induced E.G7-OVA rejection. In agreement with these observations, mice having rejected E.G7-OVA tumors showed long lasting CTL memory in spleen and bone marrow towards both the SIINFEKL-peptide and other EL-4-derived tumor rejecting epitopes.

Michael, A., G. Ball, et al. (2005). "Delayed disease progression after allogeneic cell vaccination in hormone-resistant prostate cancer and correlation with immunologic variables." Clin Cancer Res **11**(12): 4469-78.

PURPOSE: There are a significant number of patients with asymptomatic hormone-resistant prostate cancer who have increasing prostate-specific antigen (PSA) levels but little or no evaluable disease. The immunogenicity and minimal toxicity associated with cell-based vaccine therapy makes this approach attractive for these patients. EXPERIMENTAL DESIGN: We have evaluated a vaccine comprising monthly intradermal injection of three irradiated allogeneic prostate cell lines (8 x 10(6) cells each) over 1 year. The first two doses were supplemented with bacille Calmette-Guerin as vaccine adjuvant. Twenty-eight hormone-resistant prostate cancer patients were enrolled. Patients were assessed clinically and PSA levels were measured monthly. Radiologic scans (X-ray, computed tomography, and bone scan) were taken at baseline and at intervals throughout the treatment period. Comprehensive monthly immunologic monitoring was undertaken including proliferation studies, activation markers, cytokine protein expression, and gene copy number. This longitudinal data was analyzed through predictive modeling using artificial neural network feed-forward/back-propagation algorithms with multilayer perceptron architecture. RESULTS: Eleven of the 26 patients showed statistically significant, prolonged decreases in their PSA velocity (PSAV). None experienced any significant toxicity. Median time to disease progression was 58 weeks, compared with recent studies of other agents and historical control values of around 28 weeks. PSAV-responding patients showed a titratable T(H)1 cytokine release profile in response to restimulation with a vaccine lysate, while nonresponders showed a mixed T(H)1 and T(H)2 response. Furthermore, immunologic profile correlated with PSAV response by artificial neural network analysis. We found predictive power not only in expression of cytokines after maximal stimulation with phorbol 12-myristate 13-acetate, but also the method of analysis (qPCR measurement of IFN-gamma > qPCR measurement tumor necrosis factor-alpha > protein expression of IFN-gamma > protein expression of interleukin 2). CONCLUSIONS: Whole cell allogeneic vaccination in hormone-resistant prostate cancer is nontoxic and improves the natural history of the disease. Longitudinal changes in immunologic function in vaccinated patients may be better interpreted through predictive modeling using tools such as the artificial neural network rather than periodic "snapshot" readouts.

Naito, M., K. Itoh, et al. (2008). "Dexamethasone did not suppress immune boosting by personalized peptide vaccination for advanced prostate cancer patients." Prostate **68**(16): 1753-62.

BACKGROUND: To evaluate the immunological responses of personalized peptide vaccination combined with low-dose glucocorticoids for advanced hormone refractory prostate cancer (HRPC) patients (pts). METHODS: Eleven pts with advanced HRPC were treated with the vaccination and low-dose glucocorticoids; 6 pts with 10 mg/day of prednisolone (PDL) followed by 1 mg/day of dexamethasone at the time of progression, 1 pt with PDL, and 4 pts with dexamethasone. Peptide-specific cellular and humoral responses were employed to monitor pre- and post- (6th) vaccination samples. RESULTS: The vaccination combined with glucocorticoids was well tolerated with no severe adverse effects. Increments of IgG responses were observed in 1 of 4 or 8 of 10 pts tested who received PDL or dexamethasone, respectively, increment of cytotoxic T lymphocyte activity was observed in 2 of 4 or 5 of 7 pts tested, respectively. Vaccination with PDL or dexamethasone resulted in a decline of PSA (at least 50%) in 1 of 7 or 6 of 10 pts with significantly longer median TTP in the dexamethasone group, respectively. CONCLUSION: Vaccination combined with dexamethasone could be recommended for further clinical trials from both immunological and clinical points of view.

Naud, P., J. Matos, et al. (2006). "Factors predicting intermediate endpoints of cervical cancer and exposure to human papillomavirus (HPV) infections in young women screened as potential targets for prophylactic HPV vaccination in south of Brazil." Eur J Obstet Gynecol Reprod Biol **124**(1): 110-8.

OBJECTIVE: To explore the predictors of intermediate endpoints of cervical cancer in 500 women living in Porto Alegre. STUDY DESIGN: Five hundred randomly selected women (mean age 20.3 years, range 15-25) were screened using PCR detecting 25 HPV types (HPV6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59,

66, 68, 70, and 74). Women were interviewed and serum samples were analysed for antibodies to HPV16 and HPV18 VLPs. Regression models were constructed to analyse predictive factors for (a) HPV PCR status, (b) HPV16-seropositivity, (c) HPV18-seropositivity, and (d) SIL in the PAP smear, used as intermediate endpoints of cervical cancer. RESULTS: Specific HPV types were identified in 137 (27.4%) of the 157 (31.4%) PCR-positive women. PAP test result was the most powerful independent predictor of HPV status in PCR (p = 0.0001), followed by the sexual activity started (p = 0.001) (adjusted OR 34.075, 95% CI: 4.650-249.715). PAP test SIL was independently predicted only by the HPV PCR status (p = 0.0001) (OR 7.561, 95% CI: 2.787-20.514). HPV16 and HPV18 serostatus were the most significant predictors of each other (p=0.0001), and the life-time number of sexual partners was more significant (p=0.001) predictor of HPV16 than HPV18 serostatus (p = 0.049). CONCLUSION: These data are useful in evaluating the exposure status of the women to the risk factors of cervical cancer in south of Brazil.

Nestle, F. O., A. Farkas, et al. (2005). "Dendritic-cell-based therapeutic vaccination against cancer." Curr Opin Immunol **17**(2): 163-9.

Early clinical trials, in which over 1000 cancer patients received dendritic cell (DC) vaccines, tested different vaccine preparations, but they did not always induce sufficient acquired immunity or meet the expected level of tumor regressions. Current studies aim to improve the DC vaccine approach and capture the potential of these cells in order to gain access to lymphoid tissues and induce strong cell-mediated immunity. DC clinical trials are moving towards a more professional environment, in accordance with the latest quality standards. This explains the current need for innovative well designed trials with defined endpoints that induce robust anti-tumor immunity.

Nguyen, C. L., M. L. Salem, et al. (2003). "Mechanisms of enhanced antigen-specific T cell response following vaccination with a novel peptide-based cancer vaccine and systemic interleukin-2 (IL-2)." Vaccine **21**(19-20): 2318-28.

Systemic interleukin-2 (IL-2) therapy has been shown to enhance the clinical efficacy of peptide-based cancer vaccines. However, the mechanisms involved in this complex response remain poorly defined. IL-2 is known to be a potent T cell growth factor, but recent studies suggest that IL-2 is also involved in the regulation of T cell immune responses by increasing the susceptibility of proliferating T cells to apoptosis. Using an adoptive transfer model, we demonstrate that the administration of systemic IL-2 significantly enhances the primary and memory immune responses following peptide-based vaccination. In order to define the mechanisms of IL-2 therapy on the antigen-specific T cell response, the kinetics of T cell proliferation, apoptosis, and trafficking were explored. Systemic IL-2 therapy did not appear to alter the kinetics of T cell proliferation immediately following vaccination, but did prolong the proliferative response. Furthermore, IL-2 therapy did not significantly influence apoptosis of proliferating T cells. Such therapy did, however, potentiate L-selectin (CD62L) downregulation on activated antigen-specific T cells, and altered their trafficking confirming their potential therapeutic value. Our findings support the use of systemic IL-2 following peptide-based vaccination, and suggest that IL-2 therapy enhances the primary and memory immune responses by prolonging the proliferative response and altering the trafficking of antigen-specific T cells.

Nicholson, S., C. C. Bomphray, et al. (2004). "A phase I trial of idiotypic vaccination with HMFG1 in ovarian cancer." Cancer Immunol Immunother **53**(9): 809-16.

INTRODUCTION: An extended phase I trial was conducted in a total of 26 patients with ovarian cancer. The objectives were to assess the safety and tolerability of idiotypic vaccination using the murine monoclonal antibody HMFG1 (anti-MUC1), and to develop robust assays to monitor humoral immune responses generated against either the antibody or MUC1. MATERIAL AND METHODS: All patients had undergone standard debulking surgery (where appropriate) and at least one regimen of platinum-based chemotherapy. Eligibility criteria included: (a) residual disease at the end of chemotherapy, (b) relapsed disease, and (c) pathologically confirmed second complete remission following salvage chemotherapy. Patients received a priming dose of 25 mg of HMFG1 either intravenously or intraperitoneally, followed by up to six intradermal doses of HMFG1 in 10% Alhydrogel at intervals of 1 month. The three dose levels were 0.5 mg, 1 mg and 5 mg. We devised modifications of published protocols for the measurement of anti-idiotypic and anti-MUC1 antibody responses and also extended the use of the IAsys resonant mirror biosensor to measure the kinetics of the idiotypic network response in these patients. RESULTS: There were no serious adverse events at any dose level. The trial confirmed that all doses could be administered safely with minimal toxicity. No clinical responses were seen in patients with evaluable disease. ELISA for anti-idiotypic antibodies (Ab2) showed significant levels in patients who completed the protocol. There were no

significant differences in the levels of Ab2 generated by the different doses of antibody. These results were confirmed by biosensor assays for Ab2, which also showed affinity maturation of the Ab2 response as patients progressed through the vaccination protocol. Biosensor assays also demonstrated no difference in the affinity of Ab2 generated by different booster doses of HMFG1. ELISA for anti-MUC1 antibodies showed less consistent results, with very small but statistically significant rises in anti-MUC1 signals seen in 38% of patients who completed the vaccination regimen. DISCUSSION: The clinical endpoints of safety and tolerability were met. The assays developed for this project have shown reproducibility and may provide surrogate endpoints to assess vaccination for future trials. The use of similar biosensors may be of particular relevance for monitoring of humoral immune responses in other vaccine trials. The low levels of anti-MUC1 antibodies generated may correspond with the lack of clinical efficacy in the few patients with evaluable disease.

Noguchi, M., K. Itoh, et al. (2004). "Immunological monitoring during combination of patient-oriented peptide vaccination and estramustine phosphate in patients with metastatic hormone refractory prostate cancer." Prostate **60**(1): 32-45.

BACKGROUND: Additive antitumor effects could be achieved by combination of immunotherapy and cytotoxic agents with no or minimum suppression. METHODS: Thirteen patients positive for human leukocyte antigen (HLA)-A24 or -A2 with metastatic hormone refractory prostate cancer (HRPC) who had failed to respond to the prior-peptide vaccination were entered in the combined peptide vaccination and estramustine phosphate. Conducted immune monitoring on those 13 patients were mainly peptide-specific cytotoxic T lymphocyte (CTL) precursor analysis by IFN-gamma productions and peptide-reactive IgG by an enzyme-linked immunosorbent assay (ELISA). RESULTS: Grade 3 arrhythmia or cerebral infarction was observed in two cases, and Grade 1 or 2 dermatologic reaction at the vaccination sites was observed in all 13 cases. Eleven patients who received more than one cycle of treatment were eligible for immunological and clinical evaluation. There was no significant immunosuppression in most cases when the peptide and a half dose (280 mg/day) of estramustine were administrated, whereas severe immunosuppression was observed in the first two patients who received both the peptide and a full dose (560 mg/day) estramustine. Augmentation of peptide-specific CTL precursors or peptide-specific IgG was observed in 6 of 11 or 10 of 11 cases, respectively. Ten of 11 patients showed serum prostate-specific antigen (PSA) level decrease from the baseline including 8 patients with a serum PSA level decrease of > or =50%. CONCLUSIONS: These results encouraged the further evaluation of the combination of peptide vaccination and low-dose estramustine phosphate for metastatic HRPC patients.

Noguchi, M., K. Itoh, et al. (2004). "Phase I trial of patient-oriented vaccination in HLA-A2-positive patients with metastatic hormone-refractory prostate cancer." Cancer Sci **95**(1): 77-84.

To evaluate the safety and toxicity of peptide vaccination for patients with metastatic hormone-refractory prostate cancer (HRPC) based on pre-existing peptide-specific cytotoxic T-lymphocyte (CTL) precursors in the circulation, 10 patients positive for human leukocyte antigen (HLA)-A2 with metastatic HRPC were enrolled in a phase I study. Peptide-specific CTL-precursors reactive to 16 kinds of vaccine candidates in the pre-vaccination peripheral blood mononuclear cells (PBMCs) were measured, and patients were followed by vaccination with only positive peptides (up to 4 kinds of peptides). Serum prostate-specific antigen (PSA) levels were monitored regularly. The peptide vaccination was safe and well tolerated with no major adverse effects. The most common toxicities were dermatologic reactions at the injection site. Increased CTL response to peptides was observed in 4 of 10 patients. Anti-peptide IgG was also detected in post-vaccination sera of 7 of 10 patients. One patient showed the disappearance of a pelvic bone metastasis after five vaccinations. Three patients showed a decrease of serum PSA level from the baseline after the vaccination, but no patients showed a serum PSA level decrease of >/= 50%. The median survival duration of study patients was 22 months with follow-up from 3 to 27 months. We consider that the increase in cellular and humoral immune responses, and decrease in PSA level in some patients justify further development of peptide vaccination for metastatic HRPC patients.

Noguchi, M., K. Kobayashi, et al. (2003). "Induction of cellular and humoral immune responses to tumor cells and peptides in HLA-A24 positive hormone-refractory prostate cancer patients by peptide vaccination." Prostate **57**(1): 80-92.

BACKGROUND: To assess the safety and immune response of a peptide-based immunotherapy for patients with hormone-refractory prostate cancer, a phase I clinical trial was conducted. METHODS: This study first investigated whether cytotoxic T-lymphocyte (CTL) precursors reacting to peptide with vaccine candidates (14 peptides for HLA-A24 positive patients) were detectable in the pre-vaccination

peripheral blood mononuclear cells (PBMCs) of ten patients with hormone-refractory prostate cancer. Patients were then vaccinated subcutaneously with only those peptides to which pre-vaccination PBMCs reacted (CTL precursor-oriented peptide vaccine) for up to four kinds of peptides. RESULTS: Overall vaccinations were generally well tolerated, but most patients (nine of ten) developed grade 1 local redness and swelling at the injection site. Increased CTL response to both peptides and cancer cells were observed in four of ten patients. Anti-peptide IgG antibodies were also detected in post-vaccination sera of seven of ten patients. One patient achieved a partial response with an 89% decrease in PSA. Stable disease was demonstrated in five of ten patients (50%) for the median duration of 2 months (range, 2-5 months). There were no objective responses of measurable lesions. CONCLUSIONS: Increase in cellular and humoral immune responses, and decrease in PSA level in some patients support further development of peptide-based immunotherapy for hormone refractory prostate cancer.

Noguchi, M., T. Mine, et al. (2007). "Combination therapy of personalized peptide vaccination and low-dose estramustine phosphate for metastatic hormone refractory prostate cancer patients: an analysis of prognostic factors in the treatment." Oncol Res **16**(7): 341-9.

The aim of this study was to investigate prognostic factors of patients with metastatic hormone refractory prostate cancer (HRPC) under combined administration of personalized peptide vaccination and low-dose estramustine phosphate (EMP). From February 2001 to July 2004, 58 men with metastatic HRPC received the combination therapy of personalized peptide vaccination and low-dose EMP. Conducted immune monitorings for those patients were peptide-specific cytotoxic T lymphocyte (CTL) precursor analysis by interferon-gamma production and peptide-reactive immunoglobulin G (IgG) by an enzyme-linked immunosorbent assay. Clinical responses and survival times were also evaluated. The combination therapy was well tolerated with no major adverse effects. Increased levels of CTL precursors and IgG responses to the vaccinated peptides were observed in 29 of 37 (78%) patients and in 36 of 41 (88%) patients tested, respectively. A prostate-specific antigen decline of at least 50% occurred in 24% of patients. The median survival time was 17 months (95% confidence interval, 12-25 months). Cox proportional hazards analysis showed that a low number of lymphocytes ($p = 0.0075$, odds ratio 2.700), a negative immunological activity response after the vaccination ($p = 0.0185$, odds ratio 2.658), and poor performance status ($p = 0.0347$, odds ratio 2.569) were independent predictors of disease death. These encouraging results show the need for further evaluation of the combination of personalized peptide vaccination and low dose of EMP for metastatic HRPC patients.

Noguchi, M., A. Yao, et al. (2007). "Immunological evaluation of neoadjuvant peptide vaccination before radical prostatectomy for patients with localized prostate cancer." Prostate **67**(9): 933-42.

BACKGROUND: The purpose of this study was to determine the safety and immune responses of pre-operative personalized peptide vaccine for patients with localized prostate cancer. METHOD: Ten human leukocyte antigen (HLA)-A24(+) patients with localized prostate cancer received weekly personalized peptide vaccine for six times with positive peptides (up to four kinds of peptides) from 16 kinds of vaccine candidates, followed by a retropubic radical prostatectomy (RRP). Eight patients with localized prostate cancer receiving RRP served as the control group. The serum prostate-specific antigen (PSA) level, and peptide-specific cytotoxic T lymphocyte (CTL) precursor analysis by interferon-gamma production, and peptide-reactive immunoglobulin G (IgG) using an enzyme-linked immunosorbent assay were monitored during the treatment. Distributions of CD45RO(+) cells, CD8(+) T cells, and CD20(+) B cells in tissue microarray samples were studied using an immunohistochemical technique. RESULT: The peptide vaccination was safe and well tolerated with no major adverse effects. Increased CTL response and the anti-peptide IgG titer were observed in the post-vaccination samples in 8 of 10 or 8 of 10 patients, respectively. The intensity of CD45RO(+) infiltrating cells in the vaccination group was significantly larger than that in the control group. CD8(+) T cell infiltration was seen only in the vaccinated group. CONCLUSION: Increased immune responses, at both the circulation and tumor sites in the vaccinated group, support the further development of personalized peptide vaccines for patients with localized prostate cancer.

Oka, Y., A. Tsuboi, et al. (2009). "WT1 peptide vaccine as a paradigm for "cancer antigen-derived peptide"-based immunotherapy for malignancies: successful induction of anti-cancer effect by vaccination with a single kind of WT1 peptide." Anticancer Agents Med Chem **9**(7): 787-97.

Wilms' tumor gene (WT1) possesses oncogenic functions and is expressed in various kinds of malignancies, which suggests that the gene's product, the WT1 protein, should be one of the most promising cancer antigens. In fact, the WT1 protein was shown to be highly immunogenic in cancer

patients. WT1 peptides that could induce WT1-specific CTLs (WT1 CTL peptides) were identified, and vaccination of cancer patients with these WT1 CTL peptides induced immunological responses, which were assessed by ex vivo immuno-monitoring, such as the tetramer assay, and in vivo immuno-monitoring, such as the peptide-specific delayed type hypersensitivity reaction. The induced immunological responses then led to clinical responses such as solid tumor shrinkage, a decrease in leukemia cells, and reduction of M-protein (multiple myeloma). Long-term stabilization of disease with good quality of life, which might be characteristic of cancer vaccine therapy, was also reported. It is noteworthy that injection with a "single" kind of WT1 peptide elicited an immunological response strong enough to induce a clinical response, indicating that the WT1 peptide vaccine has therapeutic potential. The number of reports of the successful treatment of cancer patients (not only adult but also childhood malignancies) with WT1 vaccination is increasing. Strategies for further improvement in the efficacy of therapy, including combined use of chemotherapy drugs, molecular-target-based drugs, or WT1 helper peptides, are being proposed. WT1 peptide vaccination in an "adjuvant setting" should be considered a promising treatment to protect against progression or relapse of malignancies in cases with minimal residual disease.

Okaji, Y., N. H. Tsuno, et al. (2004). "Vaccination with autologous endothelium inhibits angiogenesis and metastasis of colon cancer through autoimmunity." Cancer Sci **95**(1): 85-90.

Overcoming immune tolerance of tumor angiogenesis should be useful for adjuvant therapy of cancer. We hypothesized that vaccination with autologous endothelium would induce an autoimmune response targeting tumor angiogenesis. To test this concept, we immunized BALB/c mice with a vaccine of glutaraldehyde-fixed murine hepatic sinusoidal endothelial cells (HSEs) in a lung metastasis model of Colon-26 cancer. Vaccination with autologous HSEs induced both preventive and therapeutic anti-tumor immunity that significantly inhibited the development of metastases. ELISA revealed an immunoglobulin response involving IgM and IgG subclasses. These antibodies had a strong affinity for antigens of both murine and human endothelium, and lyzed endothelial cells in the CDC assay. Flow-cytometry and chromium-release cytotoxicity assay revealed a specific CTL response against endothelial cells, which were lyzed in an effector: target ratio-dependent manner. Neither antibodies nor CTLs reacted with Colon-26. The effect of autologous HSEs was more pronounced than that of xenogeneic human umbilical vein endothelial cells (HUVECs), which were tested in the same experimental setting. Our results suggest that vaccination with autologous endothelium can overcome peripheral tolerance of self-angiogenic antigens and therefore should be useful for adjuvant immunotherapy of cancer.

Papewalis, C., M. Wuttke, et al. (2008). "Dendritic cell vaccination with xenogenic polypeptide hormone induces tumor rejection in neuroendocrine cancer." Clin Cancer Res **14**(13): 4298-305.

PURPOSE: No relevant breakthrough has yet been achieved in the identification of tumor antigens in many neuroendocrine cancer types that exist, such as malignant gastrinoma, insulinoma, or medullary thyroid carcinoma. The aim of this study was to proof the concept of dendritic cell immunization with a tumor cell-specific polypeptide hormone as a target molecule in a transgenic mouse model for medullary thyroid carcinoma (Ret/Cal mice). EXPERIMENTAL DESIGN: Ret/Cal mice were repeatedly immunized for up to 6 months with amino acid-modified (xenogenic) calcitonin-pulsed dendritic cells. Xenogenic calcitonin was chosen for immunization due to its higher immunogenicity as compared with murine calcitonin. RESULTS: Lymph nodes from control protein-immunized mice did not show any macroscopic abnormalities, whereas tumor peptide-treated mice revealed in general profoundly enlarged lymph nodes. In tetramer analysis of paratumorous lymph nodes, 1.9% to 3.1% of all infiltrating CD8(+) T cells were specific for one of three tumor epitopes tested. Analysis of the activated IFN-gamma-secreting component in splenic cells revealed an average of 2.8% tumor epitope-specific CD8(+) cells. Immunohistochemistry revealed strong CD8(+) tumor infiltration in calcitonin-vaccinated mice. In addition, these cells also showed strong in vitro lysis capacity at up to 63.3%. Most importantly, calcitonin-immunized mice revealed largely diminished tumor outgrowth (-74.3%) compared with control mice ($P < 0.0001$). Likewise, serum calcitonin levels in calcitonin-vaccinated Ret/Cal mice were lower than in the control group. CONCLUSION: These results have a major effect, as they are the first to establish a role for xenogenic polypeptide hormones as target molecules for immunotherapy in endocrine malignancies.

Parkinson, R. J., M. S. Simms, et al. (2004). "A vaccination strategy for the long-term suppression of androgens in advanced prostate cancer." Eur Urol **45**(2): 171-4; discussion 174-5.

OBJECTIVES: We have previously reported the ability of D17DT (formerly GnRH-DT) vaccination to produce castrate levels of androgens in men with advanced prostate cancer. This study examines the efficacy and tolerability of 3 and 15

micrograms of D17DT in 12 patients with advanced prostate cancer to establish a dose-response relationship. METHODS: 12 patients received either 3 or 15 micrograms of D17DT as 3 deep intramuscular injections over 6 weeks. Outcome was assessed in terms of physical and biochemical evaluations of clinical progression and antibody titres. RESULTS: Significant titres of anti-GnRH antibodies were detected in 2 out of 6 subjects who received 15 micrograms of D17DT; suppression of testosterone to castrate levels accompanied by a significant and prolonged reduction in PSA was also demonstrated. No responses were seen following treatment with 3 micrograms of D17DT. CONCLUSION: The induction of anti-GnRH antibodies through vaccination with 15 micrograms D17DT can produce and sustain castrate levels of testosterone in men with advanced prostate cancer.

Pavlenko, M., A. K. Roos, et al. (2004). "A phase I trial of DNA vaccination with a plasmid expressing prostate-specific antigen in patients with hormone-refractory prostate cancer." Br J Cancer **91**(4): 688-94.

Prostate-specific antigen (PSA) is a serine protease secreted at low levels by normal luminal epithelial cells of the prostate and in significantly higher levels by prostate cancer cells. Therefore, PSA is a potential target for various immunotherapeutical approaches against prostate cancer. DNA vaccination has been investigated as immunotherapy for infectious diseases in patients and for specific treatment of cancer in certain animal models. In animal studies, we have demonstrated that vaccination with plasmid vector pVAX/PSA results in PSA-specific cellular response and protection against tumour challenge. The purpose of the trial was to evaluate the safety, feasibility and biological efficacy of pVAX/PSA vaccine in the clinic. A phase I trial of pVAX/PSA, together with cytokine granulocyte/macrophage-colony stimulating factor (GM-CSF) (Molgramostim) and IL-2 (Aldesleukin) as vaccine adjuvants, was carried out in patients with hormone-refractory prostate cancer. To evaluate the biologically active dose, the vaccine was administered during five cycles in doses of 100, 300 and 900 microg, with three patients in each cohort. Eight patients were evaluable. A PSA-specific cellular immune response, measured by IFN-gamma production against recombinant PSA protein, and a rise in anti-PSA IgG were detected in two of three patients after vaccination in the highest dose cohort. A decrease in the slope of PSA was observed in the two patients exhibiting IFN-gamma production to PSA. No adverse effects (WHO grade >2) were observed in any dose cohort. We demonstrate that DNA vaccination with a PSA-coding plasmid vector, given with GM-CSF and IL-2 to patients with prostate cancer, is safe and in doses of 900 microg the vaccine can induce cellular and humoral immune responses against PSA protein.

Pilla, L., L. Rivoltini, et al. (2009). "Multipeptide vaccination in cancer patients." Expert Opin Biol Ther **9**(8): 1043-55.

Since the identification of tumor associated antigens (TAA) in different tumor histotypes, many vaccination strategies have been investigated, including peptide-based vaccines. Results from the first decade of clinical experimentation, though demonstrating the feasibility and the good toxicity profile of this approach, provided evidence of clinical activity only in a minority of patients, despite inducing immunization in up to 50% of them. In this review, we discuss the different approaches recently developed in order to induce stronger peptide-induced immune-mediated tumor growth control, possibly translating into improved clinical response rates, with specific focus on multipeptide-based anti-cancer vaccines. This strategy offers many advantages, such as the possibility of bypassing tumor heterogeneity and selection of antigen (Ag)-negative clones escaping peptide-specific immune responses, or combining HLA class I- and class II-restricted epitopes, thus eliciting both CD4- and CD8-mediated immune recognition. Notably, advances in Ag discovery technologies permit further optimization of peptide selection, in terms of identification of tumor-specific and unique TAA as well as Ags derived from different tumor microenvironment cell components. With the ultimate goal of combining peptide selection with patient-specific immunogenic profile, peptide based anti-cancer vaccines remain a promising treatment for cancer patients, as attested by of pre-clinical and clinical studies.

Pitts, M., A. Smith, et al. (2009). "Singaporean men's knowledge of cervical cancer and human papillomavirus (HPV) and their attitudes towards HPV vaccination." Vaccine **27**(22): 2989-93.

Little is known of men's knowledge of cervical cancer and its links with human papillomavirus (HPV), or of their attitudes and beliefs about HPV vaccination. This is despite men's sexual behaviour contributing to HPV transmission and their potential role in deciding whether their children are vaccinated against HPV. To address this, a comprehensive survey was conducted in Singapore where plans are underway for an HPV vaccination program. A representative sample of 930 Singaporean men was found to have moderate knowledge of cervical cancer but poor knowledge and awareness of HPV. Although these men showed strong support for HPV vaccination, overall findings highlight the

importance of including men in education campaigns that aim to decrease the incidence of cervical and other HPV-related cancers and to increase the uptake of HPV vaccination.

Plymoth, A., S. Viviani, et al. (2009). "Control of hepatocellular carcinoma through hepatitis B vaccination in areas of high endemicity: perspectives for global liver cancer prevention." Cancer Lett **286**(1): 15-21.

There are approximately 360 millions chronic carriers of Hepatitis B virus worldwide. Patterns of HB carriage are variable from one region to the other. Regions with rates of carriage over 8% are commonly considered as "high endemicity" regions. HB carriers have a very significant lifetime risk of developing chronic liver diseases such as cirrhosis and/or liver cancer (hepatocellular carcinoma, HCC). An efficient HB vaccine is available since the early eighties and has been used since for universal infant vaccination in regions of high endemicity. Observations from Taiwan, where universal infant vaccination was introduced from 1984, show a remarkable, long-lasting protection against carriage and reduction of HCC rates in adolescent and young adults born after the initiation of the programme. Two population-based trials have been set up in the mid-eighties to evaluate lifelong protective effects of infant HB vaccine against liver cancer, in The Gambia (West Africa) and in the area of Qidong, China. In other high-endemicity regions of Asia and Africa, universal infants vaccination has consistently showed a long-lasting high protection against chronic carriage and this is expected to lead to a dramatic decrease of chronic liver disease and liver cancer within the next decades. Here we briefly review the lessons of vaccination programmes and trials in high-endemicity regions, based on data gathered during 15-20years of implementation.

Raez, L. E., P. A. Cassileth, et al. (2004). "Allogeneic vaccination with a B7.1 HLA-A gene-modified adenocarcinoma cell line in patients with advanced non-small-cell lung cancer." J Clin Oncol **22**(14): 2800-7.

PURPOSE: To determine the safety, immunogenicity, and clinical response to an allogeneic tumor vaccine for non-small-cell lung cancer, we conducted a phase I trial in patients with advanced metastatic disease. PATIENTS AND METHODS: We treated 19 patients with a vaccine based on an adenocarcinoma line (AD100) transfected with B7.1 (CD80) and HLA A1 or A2. Patients were vaccinated intradermally with 5 x 10(7) cells once every 2 weeks. Three vaccinations represented one course of treatment. If patients had complete response, partial response, or stable disease, they continued with the vaccinations for up to three courses (nine vaccinations). Immune response was assessed by a change between pre-study and postvaccination enzyme-linked immunospot frequency of purified CD8 T-cells secreting interferon-gamma in response to in vitro challenge with AD100. RESULTS: Four patients experienced serious adverse events that were unrelated to vaccine. Another four patients experienced only minimal skin erythema. All but one patient had a measurable CD8 response after three immunizations. The immune response of six surviving, clinically responding patients shows that CD8 titers continue to be elevated up to 150 weeks, even after cessation of vaccination. Overall, one patient had a partial response, and five had stable disease. Median survival for all patients is 18 months (90% CI, 7 to 23 months), with corresponding estimates of 1-year, 2-year, and 3-year survival of 52%, 30%, and 30%, respectively. HLA matching of vaccine, age, sex, race, and pathology did not bear a significant relation to response. CONCLUSION: Minimal toxicity and good survival in this small population suggest clinical benefit from vaccination.

Ramanathapuram, L. V., T. Hahn, et al. (2005). "Chemo-immunotherapy of breast cancer using vesiculated alpha-tocopheryl succinate in combination with dendritic cell vaccination." Nutr Cancer **53**(2): 177-93.

In this study, we evaluated the efficacy of vesiculated alpha-tocopheryl succinate (Valpha-TOS) in combination with non-antigen pulsed, nonmatured dendritic cells (nmDC) to treat pre-established tumors of the highly metastatic murine mammary cancer cell line 4T1. We demonstrated that Valpha-TOS in combination with non-antigen pulsed nmDC significantly inhibits the growth of established tumors in vivo and prolongs survival of treated mice. In addition, when initiated after resection of the established primary tumor, the combination treatment dramatically inhibits residual metastatic disease. The clinical response achieved with the combination therapy was correlated with increased interferon-gamma and interleukin-4 (IL-4) production by splenic lymphocytes and draining lymph node cells. Interestingly, when used in combination with Valpha-TOS, nmDC were as effective as tumor necrosis factor-alpha matured DC at inhibiting the growth of pre-established tumors. Valpha-TOS-induced cellular factors collected by high-speed centrifugation of supernatant from Valpha-TOS-treated tumor cells caused maturation of DC as evidenced by the up-regulation of co-stimulatory molecules and secretion of IL-12p70. These results demonstrate the potential usefulness of Valpha-TOS + DC chemo-

immunotherapy in treating established primary mammary tumors as well as residual metastatic disease.

Roden, R. B., M. Ling, et al. (2004). "Vaccination to prevent and treat cervical cancer." Hum Pathol **35**(8): 971-82.

Human papillomaviruses (HPVs) are the primary etiologic agents of cervical cancer. Thus, cervical cancer and other HPV-associated malignancies might be prevented or treated by HPV vaccines. Transmission of papillomavirus may be prevented by the generation of antibodies to capsid proteins L1 and L2 that neutralize viral infection. However, because the capsid proteins are not expressed at detectable levels by infected basal keratinocytes or in HPV-transformed cells, therapeutic vaccines generally target nonstructural early viral antigens. Two HPV oncogenic proteins, E6 and E7, are critical to the induction and maintenance of cellular transformation and are coexpressed in the majority of HPV-containing carcinomas. Thus, therapeutic vaccines targeting E6 and E7 may provide the best option for controlling HPV-associated malignancies. Various candidate therapeutic HPV vaccines are currently being tested whereby E6 and/or E7 are administered in live vectors, as peptides or protein, in nucleic acid form, as components of chimeric virus-like particles, or in cell-based vaccines. Encouraging results from experimental vaccination systems in animal models have led to several prophylactic and therapeutic vaccine clinical trials. If these preventive and therapeutic HPV vaccines prove successful in patients, as they have in animal models, then oncogenic HPV infection and its associated malignancies may be controllable by vaccination.

Rogoza, R. M., N. Ferko, et al. (2008). "Optimization of primary and secondary cervical cancer prevention strategies in an era of cervical cancer vaccination: a multi-regional health economic analysis." Vaccine **26 Suppl 5**: F46-58.

With the recent advent of cervical cancer vaccines, many questions relating to the best overall prevention methods for cervical disease are beginning to arise. A Markov model was used across five geographic regions (Canada, The Netherlands, Taiwan, UK, US) to examine the clinical benefits and cost-effectiveness of: (1) vaccination combined with screening, considering changes to screening-related parameters and (2) vaccination combined with screening, considering changes to screening policy. Given the assumptions used in this analysis, adding vaccination to current screening is likely to be cost-effective in the regions studied. When considering vaccination with several plausible changes to screening programmes, locations with the most frequent Papanicolaou smear testing may achieve the most efficiency gains by adopting a less frequent screening interval or incorporating HPV testing into their screening practices. Although it may be beneficial to change screening to maximize efficiency, the most cost-effective strategies for vaccination and screening combinations may not lead to the greatest reductions in cervical cancer; therefore such policy decisions may vary depending on region-specific goals. Finally, new screening paradigms such as primary HPV testing should be considered in future analyses.

Rogoza, R. M., T. A. Westra, et al. (2009). "Cost-effectiveness of prophylactic vaccination against human papillomavirus 16/18 for the prevention of cervical cancer: adaptation of an existing cohort model to the situation in the Netherlands." Vaccine **27**(35): 4776-83.

Cervical cancer is one of the most prevalent cancers among women worldwide. Implementation of an HPV-vaccination strategy targeting the major oncogenic types 16 and 18 that cause cervical cancer is generally expected to significantly reduce the burden of cervical cancer disease. Here we estimate the costs, savings and health gains with the addition of HPV-16/18 vaccination to the already existing Dutch screening programme. In the base-case analysis, it was estimated that implementation of an HPV-16/18 vaccine would result in an incremental cost-effectiveness ratio (ICER) of euro22,700 per life-year gained (LYG). In sensitivity analysis, the robustness of our finding of favourable cost-effectiveness was established. The ICER appeared sensitive to the vaccine price, discount rate and duration of vaccine-induced protection. From our results, it validly follows that immunization of 12-year-old Dutch girls against HPV-16/18 infection is a cost-effective strategy for protecting against cervical cancer.

Romero, P., J. C. Cerottini, et al. (2004). "Monitoring tumor antigen specific T-cell responses in cancer patients and phase I clinical trials of peptide-based vaccination." Cancer Immunol Immunother **53**(3): 249-55.

Numerous phase I and II clinical trials testing the safety and immunogenicity of various peptide vaccine formulations based on CTL-defined tumor antigens in cancer patients have been reported during the last 7 years. While specific T-cell responses can be detected in a variable fraction of immunized patients, an even smaller but significant fraction of these patients have objective tumor responses. Efficient therapeutic vaccination should aim at boosting naturally occurring antitumor T- and B-cell responses

and at sustaining a large number of tumor antigen specific and fully functional effector T cells at tumor sites. Recent progress in our ability to quantitatively and qualitatively monitor tumor antigen specific CD8 T-cell responses will greatly help in making rapid progress in this field.

Roos, A. K., A. King, et al. (2008). "DNA vaccination for prostate cancer." Methods Mol Biol **423**: 463-72.

DNA-based cancer vaccines have been used successfully in mice to induce cytotoxic T lymphocytes (CTLs) specific for prostate antigens. Translation of a prostate-specific antigen (PSA) DNA vaccine into a phase I clinical trial demonstrated that PSA-specific immune responses could be induced but at a significantly lower level compared with those in mice. To enhance the efficacy of DNA vaccination against prostate cancer, we have explored and optimized intradermal electroporation as an effective way of delivering a PSA DNA vaccine. The results demonstrated that intradermal DNA vaccination using low amounts of DNA, followed by two sets of electrical pulses of different length and voltage, effectively induced PSA-specific T cells. Here we describe in detail how to perform intradermal DNA electroporation to induce high gene expression in skin and, more important, how to induce and analyze PSA-specific T cell responses.

Rosato, A., A. Zoso, et al. (2006). "Predicting tumor outcome following cancer vaccination by monitoring quantitative and qualitative CD8+ T cell parameters." J Immunol **176**(3): 1999-2006.

Identification of reliable surrogate predictors for evaluation of cancer vaccine efficacy is a critical issue in immunotherapy. We analyzed quantitative and qualitative CD8+ T cell parameters in a large pool of BALB/c mice that were DNA-vaccinated against P1A self tumor-specific Ag. After immunization, mice were splenectomized and kept alive for a subsequent tumor challenge to correlate results of immune monitoring assays with tumor regression or progression in each individual animal, and to assess the prognostic value of the assays. The parameters tested were 1) percentage of in vivo vaccine-induced tumor-specific CD8+ T cells; 2) results of ELISPOT tests from fresh splenocytes; 3) percentage of tumor-specific CD8+ T cells in culture after in vitro restimulation; 4) in vitro increase of tumor-specific CD8+ T cell population expressed as fold of expansion; and 5) antitumor lytic activity of restimulated cultures. Except for the ELISPOT assay, each parameter tested was shown by univariate statistical analysis to correlate with tumor regression. However, multivariate analysis revealed that only in vitro percentage of Ag-specific CD8+ T cells was an independent prognostic factor that predicted tumor outcome. These findings should be considered in the design of new immune monitoring systems used in cancer immunotherapy studies.

Ruttinger, D., N. K. van den Engel, et al. (2007). "Adjuvant therapeutic vaccination in patients with non-small cell lung cancer made lymphopenic and reconstituted with autologous PBMC: first clinical experience and evidence of an immune response." J Transl Med **5**: 43.

BACKGROUND: Given the considerable toxicity and modest benefit of adjuvant chemotherapy for non-small cell lung cancer (NSCLC), there is clearly a need for new treatment modalities in the adjuvant setting. Active specific immunotherapy may represent such an option. However, clinical responses have been rare so far. Manipulating the host by inducing lymphopenia before vaccination resulted in a magnification of the immune response in the preclinical setting. To evaluate feasibility and safety of an irradiated, autologous tumor cell vaccine given following induction of lymphopenia by chemotherapy and reinfusion of autologous peripheral blood mononuclear cells (PBMC), we are currently conducting a pilot-phase I clinical trial in patients with NSCLC following surgical resection. This paper reports on the first clinical experience and evidence of an immune response in patients suffering from NSCLC. METHODS: NSCLC patients stages I-IIIA are recruited. Vaccines are generated from their resected lung specimens. Patients undergo leukapheresis to harvest their PBMC prior to or following the surgical procedure. Furthermore, patients receive preparative chemotherapy (cyclophosphamide 350 mg/m2 and fludarabine 20 mg/m2 on 3 consecutive days) for induction of lymphopenia followed by reconstitution with their autologous PBMC. Vaccines are administered intradermally on day 1 following reconstitution and every two weeks for a total of up to five vaccinations. Granulocyte-macrophage-colony-stimulating-factor (GM-CSF) is given continuously (at a rate of 50 microg/24 h) at the site of vaccination via minipump for six consecutive days after each vaccination. RESULTS: To date, vaccines were successfully manufactured for 4 of 4 patients. The most common toxicities were local injection-site reactions and mild constitutional symptoms. Immune responses to chemotherapy, reconstitution and vaccination are measured by vaccine site and delayed type hypersensitivity (DTH) skin reactions. One patient developed positive DTH skin tests so far. Immunohistochemical assessment of punch biopsies taken at the local vaccine site reaction revealed a dense lymphocyte infiltrate. Further

immunohistochemical differentiation showed that CD1a+ cells had been attracted to the vaccine site as well as predominantly CD4+ lymphocytes. The 3-day combination chemotherapy consisting of cyclophosphamide and fludarabine induced a profound lymphopenia in all patients. Sequential FACS analysis revealed that different T cell subsets (CD4, CD8, CD4CD25) as well as granulocytes, B cells and NK cells were significantly reduced. Here, we report on clinical safety and feasibility of this vaccination approach during lymphoid recovery and demonstrate a patient example. CONCLUSION: Thus far, all vaccines were well tolerated. The overall trial design seems safe and feasible. Vaccine site reactions associated with infusion of GM-CSF via mini-pump are consistent with the postulated mechanism of action. More detailed immune-monitoring is required to evaluate a potential systemic immune response. Further studies to exploit homeostasis-driven T cell proliferation for the induction of a specific anti-tumor immune response in this clinical setting are warranted.

Saito, H., D. Frleta, et al. (2006). "Dendritic cell-based vaccination against cancer." Hematol Oncol Clin North Am **20**(3): 689-710.

Vaccination against infectious agents represents a success of immunology, although many infectious diseases still evade the immune system, including chronic infections, such as tuberculosis, malaria, and HIV. Further progress is expected through rational design based on increased understanding of how the immune system works, and how the induction of protective immunity is regulated. The same principle applies to cancer vaccines, particularly because cancer is a chronic disease. Owing to their capacity to regulate cellular and humoral immunity, dendritic cells are increasingly used as vaccines; the immunogenicity of antigens delivered on dendritic cells has been shown in cancer patients. A better understanding of how dendritic cells regulate immune responses would allow clinicians to exploit them better to induce effective immunity against cancer.

Sakai, Y., B. J. Morrison, et al. (2004). "Vaccination by genetically modified dendritic cells expressing a truncated neu oncogene prevents development of breast cancer in transgenic mice." Cancer Res **64**(21): 8022-8.

Dendritic cells (DCs) are powerful antigen-presenting cells that process antigens and present peptide epitopes in the context of the major histocompatibility complex molecules to generate immune responses. DCs are being studied as potential anticancer vaccines because of their ability to present antigens to naive T cells and to stimulate the expansion of antigen-specific T-cell populations. We investigated an antitumor vaccination using DCs modified by transfer of a nonsignaling neu oncogene, a homologue of human HER-2/neu, in a transgenic model of breast cancer. BALB-neuT mice develop breast cancers as a consequence of mammary gland-specific expression of an activated neu oncogene. We vaccinated BALB-neuT mice with bone marrow-derived DCs transduced with Ad.Neu, a recombinant adenovirus expressing a truncated neu oncoprotein. The vaccine stimulated the production of specific anti-neu antibodies, enhanced interferon-gamma expression by T cells, and prevented or delayed the onset of mammary carcinomas in the mice. Over 65% of vaccinated mice remained tumor free at 28 weeks of age, whereas all of the mice in the control groups developed tumors. When challenged with a neu-expressing breast cancer cell line, vaccinated tumor-free animals had delayed tumor growth compared with controls. The antitumor effect of the vaccine was specific for expression of neu. Studies showed that CD4+ T cells were required in order to generate antitumor immunity. Importantly, the effectiveness of the vaccine was not diminished by preexisting immunity to adenovirus, whereas the protection afforded by vaccination that used direct injection of Ad.Neu was markedly reduced in mice with anti-adenovirus antibody titers. DCs modified by recombinant adenoviruses expressing tumor-associated antigens may provide an effective antitumor vaccination strategy.

Saleem, A., A. Tristram, et al. (2009). "Prophylactic HPV vaccination: a major breakthrough in the fight against cervical cancer?" Minerva Med **100**(6): 503-23.

Cervical cancer is the second most common female cancer with 500000 new cases and 290000 deaths occurring worldwide per annum. Organized cervical screening programs have reduced the incidence and mortality of cervical cancer. However, in developing countries scarce resources, poverty, lack of infrastructure and disenfranchisement of women have been major hurdles in the effective implementation of routine screening programmes. As a result, 83% of cervical cancers still occur in the developing countries and account for 15% of all female cancers. Epidemiological studies have established a causative role of Human Papillomavi-rus (HPV) infection in the development of cervical cancer. The development and implementation of a prophylactic HPV vaccine will have a major impact on preventing this global disease. However, long-term surveillance of the HPV vaccination program will be required to confirm the expected reduction in cervical cancer incidence. This article reviews the role of HPV

in the development of cancer and the burden of HPV related cancers; types and pharmacokinetics of HPV vaccines; challenges and issues in implementing vaccination programmes; screening in the developing and developed countries and screening options in the post-vaccination era.

Salem, M. L., A. N. Kadima, et al. (2004). "Paracrine release of IL-12 stimulates IFN-gamma production and dramatically enhances the antigen-specific T cell response after vaccination with a novel peptide-based cancer vaccine." J Immunol **172**(9): 5159-67.

Interleukin-12 can act as a potent adjuvant for T cell vaccines, but its clinical use is limited by toxicity. Paracrine administration of IL-12 could significantly enhance the response to such vaccines without the toxicity associated with systemic administration. We have developed a novel vaccine delivery system (designated F2 gel matrix) composed of poly-N-acetyl glucosamine that has the dual properties of a sustained-release delivery system and a potent adjuvant. To test the efficacy of paracrine IL-12, we incorporated this cytokine into F2 gel matrix and monitored the response of OT-1 T cells in an adoptive transfer model. Recipient mice were vaccinated with F2 gel/SIINFEKL, F2 gel/SIINFEKL/IL-12 (paracrine IL-12), or F2 gel/SIINFEKL plus systemic IL-12 (systemic IL-12). Systemic levels of IL-12 were lower in paracrine IL-12-treated mice, suggesting that paracrine administration of IL-12 may be associated with less toxicity. However, paracrine administration of IL-12 was associated with an enhanced Ag-specific T cell proliferative and functional response. Furthermore, paracrine IL-12 promoted the generation of a stable, functional memory T cell population and was associated with protection from tumor challenge. To study the mechanisms underlying this enhanced response, wild-type and gene-deficient mice were used. The enhanced immune response was significantly reduced in IFN-gamma(-/-) and IL-12R beta 2(-/-) recipient mice suggesting that the role of IL-12 is mediated, at least in part, by host cells. Collectively, the results support the potential of F2 gel matrix as a vaccine delivery system and suggest that sustained paracrine release of IL-12 has potential clinical application.

Santin, A. D., S. Bellone, et al. (2006). "HPV16/18 E7-pulsed dendritic cell vaccination in cervical cancer patients with recurrent disease refractory to standard treatment modalities." Gynecol Oncol **100**(3): 469-78.

OBJECTIVE: To evaluate the potential of human papillomavirus (HPV) type 16 and 18 E7 antigen-loaded autologous dendritic cells (DC) as a therapeutic cellular vaccine in a case series of cervical cancer patients harboring recurrent/metastatic disease refractory to standard treatment modalities. METHODS: Autologous monocyte-derived DC were pulsed with recombinant HPV16 E7 or HPV18 E7 oncoproteins and administered to 4 cervical cancer patients. Vaccinations were followed by subcutaneous administration twice daily of low doses of human recombinant interleukin-2 (1 x 10(6) IU/m2) from day 3 to day 7. Safety, toxicity, delayed type hypersensitivity reactions (DTH), clinical responses, and induction of serological and cellular immunity against HPV16/18 E7 were monitored. RESULTS: The vaccine was well-tolerated in all patients and no local or systemic side effects or toxicity were recorded. Three out of four patients were found to be significantly immunocompromised before starting the vaccination treatment, as assessed by DTH with a panel of recall antigens. Specific humoral and cellular CD4+ T cell responses to the E7 vaccine were detected in 2 patients, as detected by ELISA and by IFN-gamma ELISpot assays, respectively. Increased numbers of E7-specific IFN-gamma secreting CD8+ T cells were detected in all patients after vaccination. Swelling and induration (i.e., a positive DTH response) to the intradermal injection of HPV E7 oncoprotein and/or irradiated autologous tumor cells were detected in two patients after six vaccinations. No objective clinical responses were observed. However, both patients who developed a positive DTH to the vaccine experienced a slow tumor progression (i.e., 13 months survival) while DTH unresponsive patients died within 5 months from the beginning of therapy. CONCLUSIONS: Autologous DC pulsed with HPV16/18 E7 proteins can induce systemic B and T cell responses in patients unresponsive to standard treatment modalities. However, treatment-induced immunosuppression may impose severe limitations on the efficacy of active vaccination strategies in late stage cervical cancer patients. DC-based vaccination trials are warranted in immunocompetent cervical cancer patients with early stage disease and/or limited tumor burden, and at significant risk for tumor recurrence or disease progression.

Santin, A. D., S. Bellone, et al. (2008). "Human papillomavirus type 16 and 18 E7-pulsed dendritic cell vaccination of stage IB or IIA cervical cancer patients: a phase I escalating-dose trial." J Virol **82**(4): 1968-79.

The safety and immunogenicity of the human papillomavirus type 16 (HPV16) or HPV18 (HPV16/18) E7 antigen-pulsed mature dendritic cell (DC) vaccination were evaluated for patients with stage IB or IIA cervical cancer. Escalating doses of autologous DC (5, 10, and 15 x 10(6) cells for

injection) were pulsed with recombinant HPV16/18 E7 antigens and keyhole limpet hemocyanin (KLH; an immunological tracer molecule) and delivered in five subcutaneous injections at 21-day intervals to 10 cervical cancer patients with no evidence of disease after they underwent radical surgery. Safety, toxicity, delayed-type hypersensitivity (DTH) reaction, and induction of serological and cellular immunity against HPV16/18 E7 and KLH were monitored. DC vaccination was well tolerated, and no significant toxicities were recorded. All patients developed CD4(+) T-cell and antibody responses to DC vaccination, as detected by enzyme-linked immunosorbent spot (ELISpot) and enzyme-linked immunosorbent assays (ELISA), respectively, and 8 out of 10 patients demonstrated levels of E7-specific CD8(+) T-cell counts, detected by ELISpot during or immediately after immunization, that were increased compared to prevaccination baseline levels. The vaccine dose did not predict the magnitude of the antibody or T-cell response or the time to detection of HPV16/18 E7-specific immunity. DTH responses to intradermal injections of HPV E7 antigen and KLH were detected for all patients after vaccination. We conclude that HPV E7-loaded DC vaccination is safe and immunogenic for stage IB or IIA cervical cancer patients. Phase II E7-pulsed DC-based vaccination trials with cervical cancer patients harboring a limited tumor burden, or who are at significant risk of tumor recurrence, are warranted.

Sato, Y., H. Shomura, et al. (2003). "Immunological evaluation of peptide vaccination for patients with gastric cancer based on pre-existing cellular response to peptide." Cancer Sci **94**(9): 802-8.

There is no standard treatment modality for advanced gastric cancer (GC) at the present time. To develop a new treatment modality, we investigated the immunological responses of advanced GC patients (n = 13, 9 non-scirrhous and 4 scirrhous types) vaccinated with peptides to a regimen under which pre-vaccination peripheral blood mononuclear cells (PBMCs) were screened for their reactivity in vitro to each of 14 peptides on HLA-A24 or 16 peptides on -A2 allele, then only the reactive peptides (maximum: 4) were administered in vivo. This regimen was generally well tolerated, although grade I levels of fever and local skin reactions were observed in several patients. Delayed-type hypersensitivity (DTH) to the vaccinated peptides was observed in 4 patients. Increased cellular and humoral immune responses to the vaccinated peptides were observed in post-vaccination PBMCs from 4 of 8 patients and in post-vaccination sera of 8 of 10 patients tested, respectively. Prolonged survival was observed in patients showing cellular and humoral immune responses to the vaccinated peptides in the post-vaccination samples, including all 4 patients with the scirrhous type. These results encourage further development of peptide-based immunotherapy for GC patients.

Shih, N. Y., H. Y. Yang, et al. (2009). "Conditioning vaccination site with irradiated MIP-3alpha-transfected tumor cells enhances efficacy of dendritic cell-based cancer vaccine." J Immunother **32**(4): 363-9.

Macrophage inflammation protein-3alpha (MIP-3alpha) is a chemokine expressed in inflamed tissue and capable of inducing migration of immature dendritic cells (DCs) or Langerhans cells. We postulated that conditioning vaccination sites with MIP-3alpha might enhance the efficacy of subsequently administered DC-based cancer vaccines. Our results demonstrate that subcutaneously injection of irradiated tumor cells expressing MIP-3alpha induces substantial cell infiltration to the injection site. Vaccination of irradiated tumor cells expressing MIP-3alpha followed by DCs pulsed with irradiated tumor cells can effectively suppress tumor growth in animals, which is significantly better than vaccination with irradiated MIP-3alpha-producing tumor cells or DCs pulsed with tumor cells alone. The protective effect was most evident when the MIP-3alpha-producing tumor cells and DC-based vaccines were injected at the same site. These results support the notion that this combination vaccination strategy might generate a more effective immune response to suppress the growth of tumor cells in animals.

Sigurdsson, K., H. Sigvaldason, et al. (2009). "The efficacy of HPV 16/18 vaccines on sexually active 18-23 year old women and the impact of HPV vaccination on organized cervical cancer screening." Acta Obstet Gynecol Scand **88**(1): 27-35.

OBJECTIVE: Evaluate the efficacy of catch-up HPV vaccination in sexually active young women and the potential impact of HPV vaccines on the practice of organized screening. SAMPLE: (1) Women enrolled in the Future II study and (2) from a separate population-based study in Iceland. METHODS: (1) Analysis of cytological and histological results and colposcopic examinations among 710 women, aged 18-23, with less than five sexual partners, irrespectively of baseline HPV status at enrolment. (2) The impact on screening practice as determined by evaluating the distribution of 12 oncogenic HPV types in 582 cervical intraepithelial lesions (CIN 2-3) and cancer cases. MAIN OUTCOME MEASURES: (1) Distribution of evaluated parameters according to age at enrolment. (2) Age distribution of four HPV groups, within age

classes and HPV groups: mean time to development of lesions, mean time to development of CIN 2-3+, cumulative frequency for CIN 2-3+ lesions after the last normal smear. RESULTS: (1) After an average 52 months of post-enrolment follow-up, significant reductions in all evaluated parameters were observed in women aged 18-19 at enrolment. (2) Among women <25 years, the proportion of cases with only HPV 16/18 was significantly lower and the proportion containing HPV16/18 plus > or =1 out of 10 non-vaccine HPV types (31/33/45/52/58/35/39/51/56/59) was higher than at age 25-49. The proportion of cases containing only the non-vaccine types was the same within all age groups. Cases with HPV 16/18 and some non-vaccine types decreased significantly with age and accumulated more slowly after the last negative smear. CONCLUSIONS: Catch-up vaccination of younger women should be considered in the context of sexual practices and the effects of prevalent disease on observed vaccine efficacy. Current data do not support a change in the lower age limit or screening intervals for women.

Sinibaldi Vallebona, P., G. Rasi, et al. (2004). "Vaccination with a synthetic nonapeptide expressed in human tumors prevents colorectal cancer liver metastases in syngeneic rats." Int J Cancer **110**(1): 70-5.

In previous studies, the antigen CSH-275 (RTNKEASIC) was found expressed in tissue specimens from colorectal cancer but not in normal colonic mucosa. It was also naturally expressed in the DHD-K12 experimental colorectal cancer in BDIX rats. In this study, we describe the effect of vaccination with the synthetic nonapeptide CSH-275 in preventing tumor growth in a model closely mimicking the clinical situation of liver metastases, after surgical resection of primary colorectal cancer. A vaccination protocol using CSH-275, conjugated with complete or incomplete Freund's adjuvant, was carried out to determine the effect in preventing the progression of liver metastases induced by DHD-K12 cells injected in the splenic vein (preventive vaccine). An additional vaccination procedure was carried out to determine the effect on s.c. tumor growth (therapeutic vaccine). A significant improvement in survival along with the prevention of liver metastases formation and reduced growth of s.c. tumor were observed. CSH-275 vaccination resulted in a significant increase in CTL activity against autologous DHD-K12 cells in DHD-K12 tumor-bearing rats and the generation of a CTL response against DHD-K12 cells in DHD-K12 naive rats. Vaccination also induced massive infiltration of CD8(+) cells in tumor. These results demonstrate that CSH-275 is a new molecular target for colorectal cancer immunotherapy; it is also an excellent candidate for preclinical studies because it is naturally expressed on tumors in a fully competent syngeneic animal, which reproduces the clinical pattern of cancer progression.

Spies, C. D., M. Kip, et al. (2008). "Influence of vaccination and surgery on HLA-DR expression in patients with upper aerodigestive tract cancer." J Int Med Res **36**(2): 296-307.

Major surgery is associated with an increased risk of post-operative immunosuppression and infections. We investigated the influence of influenza vaccination on cell-mediated immune responses in cancer patients undergoing either surgical or conservative therapy. Forty patients with an upper aerodigestive tract tumour were allocated to either a surgical or non-surgical treatment course. Patients within each group were randomized to the vaccination or non-vaccination group. Vaccination was performed twice before surgery or conservative treatment. Human leucocyte antigen receptor (HLA-DR) expression on monocytes was analysed by flow cytometry. In the surgical patients, HLA-DR expression on day 1 after surgery decreased in both the vaccinated and non-vaccinated groups. Vaccinated non-surgical patients showed significantly increased HLA-DR expression levels compared with the non-vaccinated patients. This pilot study demonstrated that vaccination increased monocyte HLA-DR expression in conservatively-treated cancer patients whereas surgery abrogated this response. Vaccination before surgery, therefore, might not help to maintain immune reactivity after surgery.

Suzuki, T., T. Fukuhara, et al. (2005). "Vaccination of dendritic cells loaded with interleukin-12-secreting cancer cells augments in vivo antitumor immunity: characteristics of syngeneic and allogeneic antigen-presenting cell cancer hybrid cells." Clin Cancer Res **11**(1): 58-66.

Cancer immunotherapy by fusion of antigen-presenting cells and tumor cells has been shown to induce potent antitumor immunity. In this study, we characterized syngeneic and allogeneic, murine macrophage/dendritic cell (DC)-cancer fusion cells for the antitumor effects. The results showed the superiority of allogeneic cells as fusion partners in both types of antigen-presenting cells in an in vivo immunotherapy model. A potent induction of tumor-specific CTLs was observed in these immunized conditions. In addition, the immunization with DC-cancer fusion cells was better than that with macrophage-cancer fusion cells. Both syngeneic and allogeneic DC-cancer fusion cells induced higher levels of IFN-gamma production than macrophage-cancer fusion cells. Interestingly, allogeneic DC-

cancer fusion cells were superior in that they efficiently induced Th1-type cytokines but not the Th2-type cytokines interleukin (IL)-10 and IL-4, whereas syngeneic DC-cancer fusion cells were powerful inducers of both Th1 and Th2 cytokines. These results suggest that allogeneic DCs are suitable as fusion cells in cancer immunotherapy. To further enhance the antitumor immunity in the clinical setting, we prepared DCs fused with IL-12 gene-transferred cancer cells and thus generated IL-12-secreting DC-cancer fusion cells. Immunization with these gene-modified DC-cancer fusion cells was able to elicit a markedly enhanced antitumor effect in the in vivo therapeutic model. This novel IL-12-producing fusion cell vaccine might be one promising intervention for future cancer immunotherapy.

Svane, I. M., A. E. Pedersen, et al. (2007). "Vaccination with p53 peptide-pulsed dendritic cells is associated with disease stabilization in patients with p53 expressing advanced breast cancer; monitoring of serum YKL-40 and IL-6 as response biomarkers." Cancer Immunol Immunother **56**(9): 1485-99.

p53 Mutations are found in up to 30% of breast cancers and peptides derived from over-expressed p53 protein are presented by class I HLA molecules and may act as tumor-associated epitopes in cancer vaccines. Nineteen patients were available for first evaluation after 6 vaccinations; 8/19 evaluable patients attained stable disease (SD) or minor regression while 11/19 patients had progressive disease (PD), indicating an effect of p53-specific immune therapy. This was supported by: (1) a positive correlation between p53 expression of tumor and observed SD, (2) therapy induced p53 specific T cells in 4/7 patients with SD but only in 2/9 patients with PD, and (3) significant response associated changes in serum YKL-40 and IL-6 levels identifying these biomarkers as possible candidates for monitoring of response in connection with DC based cancer immunotherapy. In conclusion, a significant fraction of breast cancer patients obtained SD during p53-targeting DC therapy. Data encourage initiation of a randomized trial in p53 positive patients evaluating the impact on progression free survival.

Svane, I. M., A. E. Pedersen, et al. (2004). "Vaccination with p53-peptide-pulsed dendritic cells, of patients with advanced breast cancer: report from a phase I study." Cancer Immunol Immunother **53**(7): 633-41.

Peptides derived from over-expressed p53 protein are presented by class I MHC molecules and may act as tumour-associated epitopes. Due to the diversity of p53 mutations, immunogenic peptides representing wild-type sequences are preferable as a basis for a broad-spectrum p53-targeting cancer vaccine. Our preclinical studies have shown that wild-type p53-derived HLA-A2-binding peptides are able to activate human T cells and that the generated effector T cells are cytotoxic to human HLA-A2+, p53+ tumour cells. In this phase I pilot study, the toxicity and efficacy of autologous dendritic cells (DCs) loaded with a cocktail of three wild-type and three modified p53 peptides are being analysed in six HLA-A2+ patients with progressive advanced breast cancer. Vaccinations were well tolerated and no toxicity was observed. Disease stabilisation was seen in two of six patients, one patient had a transient regression of a single lymph node and one had a mixed response. ELISpot analyses showed that the p53-peptide-loaded DCs were able to induce specific T-cell responses against modified and unmodified p53 peptides in three patients, including two of the patients with a possible clinical benefit from the treatment. In conclusion, the strategy for p53-DC vaccination seems safe and without toxicity. Furthermore, indications of both immunologic and clinical effect were found in heavily pretreated patients with advanced breast cancer. An independent clinical effect of repeated administration of DCs and IL-2 can not of course be excluded; further studies are necessary to answer these questions.

Svane, I. M., A. E. Pedersen, et al. (2008). "Alterations in p53-specific T cells and other lymphocyte subsets in breast cancer patients during vaccination with p53-peptide loaded dendritic cells and low-dose interleukin-2." Vaccine **26**(36): 4716-24.

We have previously established a cancer vaccine using autologous DCs, generated by in vitro stimulation with IL-4 and GM-CSF, and pulsed with six HLA-A*0201 binding wild-type p53 derived peptides. This vaccine was used in combination with low-dose interleukin-2 in a recently published clinical Phase II trial where 26 HLA-A2+ patients with progressive late-stage metastatic breast cancer (BC) were included. Almost 1/3rd of the patients obtained stable disease or minor regression during treatment with a positive correlation to tumour over-expression of p53. In the present study, we performed a comprehensive analysis of the effector stage of the p53-specific CD8+ T cells by the use of Dextramer Technology and multicolour FACS. Pre- and post-treatment blood samples from eight BC patients were analysed. Independent of clinical outcome p53-specific T cells were phenotypic distinctly antigen experienced (CD44high, CCR-7low and CD62Llow). Furthermore, fresh blood from 18 cancer patients included in the vaccination trial were prospectively examined for more general treatment associated

quantitative and qualitative changes in T cell subpopulations. We found that the frequency of CD4+ CD25high regulatory T cells was almost doubled after only 4 weeks of weekly vaccination and low-dose IL-2. In addition, a decrease in the percentage of CD27highCCR-7high CD4/CD8 naive T cells was measured particularly in patients with progressive disease during vaccination. Finally, prior to immunotherapy a higher percentage of both CD28 and CD27 positive CD8naive/early effector memory T cells were present in chemotherapy-treated patients.

Svane, I. M., M. L. Soot, et al. (2003). "Clinical application of dendritic cells in cancer vaccination therapy." Apmis **111**(7-8): 818-34.

During the last decade use of dendritic cells (DC) has moved from murine and in vitro studies to clinical trials as adjuvant in cancer immunotherapy. Here they function as delivery vehicles for exogenous tumor antigens, promoting an efficient antigen presentation. The development of protocols for large-scale generation of dendritic cells for clinical applications has made possible phase I/II studies designed to analyze the toxicity, feasibility and efficacy of this approach. In clinical trials, DC-based vaccination of patients with advanced cancer has in many cases led to immunity and in selected patients to tumor regression. However, the majority of clinical trials are still in phase I, and interpretations are hampered by pronounced variation in study design related to technical aspects of DC preparation, treatment and schedule, monitoring of immune response, and clinically relevant endpoints, including toxicity and response evaluation. This paper aims to review the technical aspects and clinical impact of vaccination trials, focusing on the generation of DC-based vaccines, evaluation of immunologic parameters and design of clinical trials necessary to meet the need for good laboratory and clinical practice.

Takedatsu, H., K. Yoshimoto, et al. (2005). "Immunological evaluation of vaccination of peptides derived from epithelial cancer-related antigens in two patients with hematological malignancy." Int J Oncol **26**(6): 1605-12.

Recent advances in tumor immunology have resulted in identification of many epithelial cancer-related antigens and peptides applicable to specific immunotherapy. We and others have reported that several epithelial cancer-related antigens are also expressed in hematological malignancies. Two patients with hematological malignancy (multiple myeloma and chronic lymphocytic leukemia) were vaccinated with peptides derived from epithelial cancer-related antigens to evaluate the immune responses to peptides under a personalized peptide vaccination regimen. There was no adverse event except for local skin reaction at the injection site. The peptide vaccination augmented both peptide-specific CTLs cytotoxic to hematological malignant cells in post-vaccination peripheral blood mononuclear cells and peptide-specific IgG in post-vaccination sera. A transient but obvious decrease of malignant cells was observed at the early phase of the vaccination in both cases. Vaccines consisting of peptides derived from epithelial cancer antigens safely increased anti-tumor cell activity in patients with hematological malignancies. These results may provide a scientific rationale in use of epithelial cancer-related antigens for specific immunotherapy to patients with hematological malignancies.

Tamir, A., E. Basagila, et al. (2007). "Induction of tumor-specific T-cell responses by vaccination with tumor lysate-loaded dendritic cells in colorectal cancer patients with carcinoembryonic-antigen positive tumors." Cancer Immunol Immunother **56**(12): 2003-16.

BACKGROUND: Dendritic cells (DCs) are the most effective antigen-presenting cells. In the last decade, the use of DCs for immunotherapy of cancer patients has been vastly increased. High endocytic capacity together with a unique capability of initiating primary T-cell responses have made DCs the most potent candidates for this purpose. Although DC vaccination occasionally leads to tumor regression, clinical efficacy, and immunogenicity of DCs in clinical trials has not been yet clarified. The present study evaluated the safety and effectiveness of tumor-lysate loaded DC vaccines in advanced colorectal cancer (CRC) patients with carcinoembryonic antigen (CEA) positive tumors. RESULTS: Six patients HLA-A*0201-positive were vaccinated with autologous DCs loaded with tumor lysates (TL) together with tetanus toxoid antigen, hepatitis B, and influenza matrix peptides. Two additional patients were injected with DCs that were generated from their sibling or parent with one haplotype mismatch. All patients received the vaccines every 2 weeks, with a total of three intra-nodal injections per patient. The results indicated that DC vaccination was safe and well tolerated by the patients. Specific immune responses were detected and in some patients, transient stabilization or even reduction of CEA levels were observed. The injection of haplotype mismatched HLA-A*0201-positive DCs resulted in some enhancement of the anti-tumor response in vitro and led to stabilization/reduction of CEA levels in the serum, compared to the use of autologous DCs. CONCLUSION: Altogether, these results suggest that TL-pulsed DCs may be an effective vaccine method in

CRC patients. Elimination of regulatory mechanisms as well as adjustment of the vaccination protocol may improve the efficacy of DC vaccination.

Tanaka, S., M. Harada, et al. (2003). "Peptide vaccination for patients with melanoma and other types of cancer based on pre-existing peptide-specific ctotoxic T-lymphocyte precursors in the periphery." J Immunother **26**(4): 357-66.

Identification of antigenic peptides expressed on cancer cells enables us to treat cancer patients with peptide-based immunotherapy. Although optimal protocols for peptide-based vaccines have not yet been elucidated, boosting the immune system could be a better approach than priming the immune system to elicit prompt and potent peptide-specific T-cell responses in cancer patients. Kinetic analysis revealed that peptide-reactive CTLs increased after peptide vaccination in 7 of 14 patients. Immunoglobulin G (IgG) reactive to the administered peptides was detected in 2 patients before vaccination, although it became detectable in 8 of the other 12 patients after the peptide vaccination. Stable disease for more than 6 months was observed in five patients (one with melanoma and four with other types of cancer); all of these patients showed increased levels of peptide-specific IgG. These results indicate that peptide vaccination of patients showing evidence of pre-existing peptide-specific CTL precursors can be applied in further clinical trials aimed at the treatment of melanoma and other types of cancer.

Taylor, M., L. M. Bolton, et al. (2007). "Breast cancer is a promising target for vaccination using cancer-testis antigens known to elicit immune responses." Breast Cancer Res **9**(4): R46.

INTRODUCTION: Cancer-testis antigens (CTAGs) are expressed solely in germ cells and in malignant tissues. They are targets of immune responses mediated by cytotoxic T cells in some cancers, and there is much interest in developing vaccines that induce these responses. The purpose of the present study was to ascertain the frequency of expression of CTAGs in breast cancer. METHODS: Breast tumours were collected sequentially in the Southampton Tumour Bank from donors who had given written informed consent. Stored samples where there was sufficient material were sampled in sequence. An initial series of 42 tumours was screened for expression of 17 different CTAGs. A second panel of 40 tumours was screened for the expression of those antigens present in the first panel. RESULTS: Ninety-three per cent of tumours in the first series expressed at least one CTAG, and 62% expressed the single antigen CTAG1. Eighty per cent of tumours in the second series expressed at least one CTAG, 50% expressing CTAG1. Tumours exhibiting higher risk features tended to express more CTAGs. CONCLUSION: More than two-thirds of breast cancers would be covered by a vaccine directed against just three CTAGs - CTAG1, BAGE1, and MAGEA10 - all of which are known to be targets of cytotoxic-T-lymphocyte responses.

Thiry, N., C. De Laet, et al. (2009). "Cost-effectiveness of human papillomavirus vaccination in Belgium: do not forget about cervical cancer screening." Int J Technol Assess Health Care **25**(2): 161-70.

OBJECTIVES: The cost-effectiveness of adding a human papillomavirus (HPV) vaccination program in 12-year-old females to the recommended cervical cancer screening in Belgium is examined. Moreover, the health and economic consequences of a potential decline in screening uptake after initiation of a HPV vaccination program are investigated. METHODS: A static Markov model is developed to estimate the direct effect of vaccination on precancerous lesions and cervical cancers. RESULTS: Vaccination is estimated to avoid 20 percent of the cervical cancers occurring in a 12-year-old girls' cohort and to cost 32,665 euro per quality-adjusted life-year (QALY) gained (95 percent credibility interval [CrI]: 17,447 euro to 68,078 euro), assuming a booster injection after 10 years, a limited duration of protection and discounting costs and effects at 3 percent and 1.5 percent, respectively. Assuming lifelong protection, HPV vaccination is estimated to cost 14,382 euro (95 percent CrI: 9,238 euro to 25,644 euro) per QALY gained, while avoiding 50 percent of the cervical cancer cases. In the base-case, a 10 percent reduction in screening compliance after vaccination obliterates the effect of vaccination on cervical cancer cases avoided, whereas further declines in the level of screening compliance even turned out to be detrimental for the cohort's health, inducing a mean loss in QALYs and life-year gained compared with the situation prevaccination. CONCLUSIONS: An HPV vaccination program should only be considered if the level of screening after vaccination can be maintained.

Thomas-Kaskel, A. K. and H. Veelken (2009). "Dendritic-cell vaccination for prostate cancer." Immunotherapy **1**(1): 63-72.

Vaccination with tumor antigen-loaded dendritic cells has been one of the most frequently applied immunotherapeutic strategies in prostate cancer. Immunological effects have been observed in a majority of patients, while clinical effects have been modest and transient. Advances in the understanding of the interplay between cancer and the immune

system have generated new concepts in tumor immunology and immunotherapy that might aid in the improvement of vaccine effectiveness. The combination of immunotherapy with conventional treatment modalities and targeting of immunosuppressive mechanisms has demonstrated improved immunological and clinical results that warrant further investigation.

Thomas-Kaskel, A. K., R. Zeiser, et al. (2006). "Vaccination of advanced prostate cancer patients with PSCA and PSA peptide-loaded dendritic cells induces DTH responses that correlate with superior overall survival." Int J Cancer **119**(10): 2428-34.

Prostate stem cell antigen (PSCA) and prostate-specific antigen (PSA) are overexpressed in most prostate cancers. PSCA- and PSA-derived, HLA-A2 binding peptides are specific targets for T-cell responses in vitro. One patient had a complete disappearance of lymphadenopathy despite rising PSA. Four patients with SD and 1 progressor developed a positive DTH after the 4th vaccination. With a median survival of all patients of 13.4 months, DTH-positivity was associated with significantly superior survival ($p = 0.003$). HLA tetramer analysis detected high frequencies of peptide-specific T cells after 2 vaccinations in 1 patient who was also the sole responder to concomitant hepatitis B vaccination as an indicator of immune competence and survived 27 months after start of vaccination. Vaccination with PSA/PSCA peptide-loaded, autologous DCs may induce cellular responses primarily in immunocompetent patients, which appear to be associated with clinical benefit. Testing of DC-based vaccination is warranted for patients at earlier stages of prostate cancer.

Torne, A., I. Alonso, et al. (2008). "Clinical role of cervical cancer vaccination: when and whom to vaccinate?" Gynecol Oncol **110**(3 Suppl 2): S15-6.

The recent development of two highly effective vaccines against persistent infection by the 2 most important types of human papillomavirus (HPV) (16 and 18) and against high grade premalignant lesions (CIN2+) has opened a new scenario for the primary prevention of cervical cancer. The optimum target population for vaccination should be individually defined taking the following into account: 1) the efficacy of the vaccine, 2) the epidemiological context and 3) the vaccination programs available in each country. To achieve the maximum preventive benefits, the vaccine should be administered before the initiation of sexual relations. So, the HPV vaccine should be integrated in the school vaccination programs of adolescents together with other vaccines. The vaccination of sexually active women may considerably increase the speed with which results in the fight against this disease will be achieved. Developed countries will probably consider the vaccination of these women, although vaccination strategies and the efforts to reach this population will be conditioned by the resources of each country and by the estimations of the cost-efficacy relationship in each situation. Women with a previous history of premalignant cervical disease or with an abnormal screening test should not be excluded from the potential benefits which the vaccine may provide. There is no contraindication for the administration of the vaccine in immunosupressed women. However, it is still unknown under what specific circumstances of immunosuppression the immunogenicity of the vaccine may be affected and there are currently ongoing studies for an answer to this question.

Vetter, K. M. and S. E. Geller (2007). "Moving forward: human papillomavirus vaccination and the prevention of cervical cancer." J Womens Health (Larchmt) **16**(9): 1258-68.

In June 2006, the Food and Drug Administration (FDA) approved the first human papillomavirus (HPV) vaccine. The vaccine was subsequently recommended by the Centers for Disease Control and Prevention's (CDC) Advisory Committee for Immunization Practices (ACIP) for routine vaccination of 11-12-year-old girls and catch-up vaccination of females 13-26 years of age. With the approval of the first HPV vaccine, cervical cancer now has a primary prevention tool. However, the availability of an HPV vaccine will not change the course of cervical cancer in this country unless there is both widespread demand by and access for the targeted populations. Demand will require recognition of the need for protection against HPV infection as well as a positive perception of the vaccine as safe and efficacious. General knowledge of HPV and its relationship to cervical cancer is limited; some parents and healthcare providers are hesitant to vaccinate preadolescent girls. Access to the expensive vaccine will not be increased without addressing financial constraints. Although the Vaccines for Children (VFC) program has added HPV to its vaccine plan, not all private insurers have approved coverage, and the uninsured and underinsured may have limited access. Moving forward will require a well-planned and executed public information campaign by trusted sources and the development of a comprehensive vaccine administration program. Although mandates would assure the broadest coverage, controversies surrounding mandates may deter work toward broad coverage. States should focus on developing a comprehensive program and then return to the

mandate issue if coverage does not meet public health objectives.

Victora, G. D., A. Socorro-Silva, et al. (2009). "Immune response to vaccination with DNA-Hsp65 in a phase I clinical trial with head and neck cancer patients." Cancer Gene Ther **16**(7): 598-608.

DNA-hsp65, a DNA vaccine encoding the 65-kDa heat-shock protein of Mycobacterium leprae (Hsp65) is capable of inducing the reduction of established tumors in mouse models. We conducted a phase I clinical trial of DNA-hsp65 in patients with advanced head and neck carcinoma. In this article, we report on the vaccine's potential to induce immune responses to Hsp65 and to its human homologue, Hsp60, in these patients. Twenty-one patients with unresectable squamous cell carcinoma of the head and neck received three doses of 150, 400 or 600 microg naked DNA-hsp65 plasmid by ultrasound-guided intratumoral injection. Vaccination did not increase levels of circulating anti-hsp65 IgG or IgM antibody, or lead to detectable Hsp65-specific cell proliferation or interferon-gamma (IFN-gamma) production by blood mononuclear cells. Frequency of antigen-induced IL-10-producing cells increased after vaccination in 4 of 13 patients analyzed. Five patients showed disease stability or regression following immunization; however, we were unable to detect significant differences between these patients and those with disease progression using these parameters. There was also no increase in antibody or IFN-gamma responses to human Hsp60 in these patients. Our results suggest that although DNA-hsp65 was able to induce some degree of immunostimulation with no evidence of pathological autoimmunity, we were unable to differentiate between patients with different clinical outcomes based on the parameters measured. Future studies should focus on characterizing more reliable correlations between immune response parameters and clinical outcome that may be used as predictors of vaccine success in immunosuppressed individuals.

Vonderheide, R. H. (2007). "Universal tumor antigens for cancer vaccination: targeting telomerase for immunoprevention." Discov Med **7**(39): 103-8.

Despite their much-heralded clinical potential, therapeutic cancer vaccines have thus far failed to achieve the necessary clinical benchmarks to allow their regulatory approval. In contrast, vaccination against infectious pathogens represents one of the biggest achievements of modern medicine, and in certain cases such as vaccines against the human papilloma virus or hepatitis B virus, vaccination may impact the development of cancer. To the extent that these two approaches differ as immunotherapy vs. immunoprevention, the challenge is to rethink the types of non-viral antigens that are currently being targeted in cancer vaccines. Immunological analysis suggests that the telomerase reverse transcriptase hTERT is a widely applicable target recognized by T lymphocytes and a prototype for a novel class of universal tumor antigens. Findings from initial clinical trials demonstrate that hTERT-specific immune responses can be safely induced in cancer patients. If the amplitude and duration of cellular immunity against hTERT can be optimized without toxicity in humans, then an opportunity exists to test hTERT vaccination as a way to reduce the risk of cancer recurrence in patients or even the risk of developing cancer in otherwise healthy individuals.

Vonderheide, R. H., S. M. Domchek, et al. (2004). "Vaccination of cancer patients against telomerase induces functional antitumor CD8+ T lymphocytes." Clin Cancer Res **10**(3): 828-39.

PURPOSE: High-level expression of the telomerase reverse transcriptase (hTERT) in >85% of human cancers, in contrast with its restricted expression in normal adult tissues, points to hTERT as a broadly applicable molecular target for anticancer immunotherapy. CTLs recognize peptides derived from hTERT and kill hTERT+ tumor cells of multiple histologies in vitro. Moreover, because survival of hTERT+ tumor cells requires functionally active telomerase, hTERT mutation or loss as a means of escape may be incompatible with sustained tumor growth. EXPERIMENTAL DESIGN: A Phase I clinical trial was performed to evaluate the clinical and immunological impact of vaccinating advanced cancer patients with the HLA-A2-restricted hTERT I540 peptide presented with keyhole limpet hemocyanin by ex vivo generated autologous dendritic cells. RESULTS: As measured by peptide/MHC tetramer, enzyme-linked immunospot, and cytotoxicity assays, hTERT-specific T lymphocytes were induced in 4 of 7 patients with advanced breast or prostate carcinoma after vaccination with dendritic cells pulsed with hTERT peptide. Tetramer-guided high-speed sorting and polyclonal expansion achieved highly enriched populations of hTERT-specific cells that killed tumor cells in an MHC- restricted fashion. Despite concerns of telomerase activity in rare normal cells, no significant toxicity was observed. Partial tumor regression in 1 patient was associated with the induction of CD8+ tumor infiltrating lymphocytes. CONCLUSIONS: These results demonstrate the immunological feasibility of vaccinating patients against telomerase and provide rationale for targeting self-antigens with critical roles in oncogenesis.

Wada, H., E. Sato, et al. (2008). "Analysis of peripheral and local anti-tumor immune response in esophageal cancer patients after NY-ESO-1 protein vaccination." Int J Cancer **123**(10): 2362-9.

NY-ESO-1 antigen is a prototype of a class of cancer/testis antigens. We carried out a clinical trial using NY-ESO-1 whole protein as a cancer vaccine for 13 advanced cancer patients. We have recently reported that vaccine elicited humoral and cellular immune responses in 9 cancer patients including 4 esophageal cancer patients, and clinical responses were also observed in 4 of 5 evaluable patients. In this study, we analyzed the responses in 8 esophageal cancer patients including 4 newly enrolled patients. Patients were injected subcutaneously at biweekly intervals with NY-ESO-1 recombinant protein formulated with cholesterol-bearing hydrophobized pullulan. Induction of antibody, and CD4 and CD8 T-cell responses were observed in 7, 7 and 6 patients, respectively, out of 8 patients. 1 PR, 2 SD and 2 mixed clinical responses were observed in 6 evaluable patients. No significant adverse events were observed. Furthermore, we analyzed NY-ESO-1 and MHC class I expression and the infiltration of immune cells into tumor samples obtained before and after vaccination from 4 patients by immunohistochemistry. The results showed 2 patients with disappearance of CD4 and CD8 T-cell infiltration, 1 patient with increase in the number of CD68(+) macrophages and 1 patient with tumor antigen loss in the progressive tumors following vaccinations. The induction of NY-ESO-1 immunity and some preferable clinical outcomes were observed in esophageal cancer patients by vaccination with NY-ESO-1. However, the tumors grew eventually by various mechanisms after vaccination.

Wada, S., T. Tsunoda, et al. (2005). "Rationale for antiangiogenic cancer therapy with vaccination using epitope peptides derived from human vascular endothelial growth factor receptor 2." Cancer Res **65**(11): 4939-46.

Angiogenesis is a critical mechanism for tumor progression. Multiple studies have suggested that tumor growth can be suppressed if tumor angiogenesis can be inhibited using various types of antiangiogenic agents. Recent studies in mouse systems have shown that tumor angiogenesis can also be inhibited if cellular immune response could be induced against vascular endothelial growth factor receptor 2 (VEGFR2), which is one of the key factors in tumor angiogenesis. In this study, we examined the possibility of developing this novel immunotherapy in clinical setting. We first identified the epitope peptides of VEGFR2 and showed that stimulation using these peptides induces CTLs with potent cytotoxicity in the HLA class I-restricted fashion against not only peptide-pulsed target cells but also endothelial cells endogenously expressing VEGFR2. In A2/Kb transgenic mice that express alpha1 and alpha2 domains of human HLA-A*0201, vaccination using these epitope peptides in vivo was associated with significant suppression of the tumor growth and prolongation of the animal survival without fatal adverse effects. In antiangiogenesis assay, tumor-induced angiogenesis was significantly suppressed with the vaccination using these epitope peptides. Furthermore, CTLs specific to the epitope peptides were successfully induced in cancer patients, and the specificities of the CTLs were confirmed using functional and HLA-tetramer analysis. These results in vitro and in vivo strongly suggest that the epitope peptides derived from VEGFR2 could be used as the agents for antiangiogenic immunotherapy against cancer in clinical settings.

Wallace, L. S. and K. A. Ache (2009). "Hear all about it: nightly television news coverage of cervical cancer vaccination in the United States." J Low Genit Tract Dis **13**(3): 154-8.

OBJECTIVE: To examine the content of human papillomavirus (HPV)-related vaccination information presented during nightly national television news broadcasts in the United States. MATERIALS AND METHODS: A retrospective content analysis of HPV vaccination coverage on 5 major nightly US television networks from 2002 to 2007. The Vanderbilt Television News Archive was searched for keywords "Gardasil," "cervical cancer vaccination," "human papillomavirus vaccine," and "HPV vaccination." Each television news broadcast was categorized as follows: segment length (in seconds), network (American Broadcasting Company, Columbia Broadcasting Company, National Broadcasting Company, Cable News Network, or Fox Broadcasting Company), year of broadcast (2002-2007), and (4) presentation type. Air dates were plotted on a timeline to depict trends and linkages to 5 seminal events surrounding the development, efficacy, and controversy regarding HPV vaccination. RESULTS: During the 6-year period, a total of 27 HPV-related vaccination news broadcasts aired. News broadcasts ranged from 10 to 250 seconds, lasting an average of close to 2 minutes (mean +/- SD, 127.0 +/- 66.1 seconds). Most broadcasts presented information pertaining to HPV and cervical cancer, information on vaccine labeling, impact of the vaccine, and raised issues or concerns about the vaccine. More than half (66.7%) of news broadcasts were directly related to 5 seminal events surrounding the development, efficacy, and controversy regarding HPV vaccination. CONCLUSION: All 5 networks included within the Vanderbilt Television News Archive aired HPV

vaccination content, with National Broadcasting Company and Columbia Broadcasting Company broadcasting most of the news stories during this time period. As compared with other medical-related information presented on national nightly television news during this time period, HPV vaccination received a modest amount of coverage.

Waller, J., L. A. Marlow, et al. (2006). "Mothers' attitudes towards preventing cervical cancer through human papillomavirus vaccination: a qualitative study." Cancer Epidemiol Biomarkers Prev **15**(7): 1257-61.

Prophylactic vaccines against human papillomavirus (HPV) types causing cervical cancer will soon be available. Success of the vaccine relies on parents' willingness to vaccinate their prepubescent daughters. We explored mothers' attitudes towards vaccination. Twenty-four mothers of girls ages 8 to 14 years took part in four focus groups. Discussions covered attitudes to vaccination in general, cancer vaccines, vaccines for sexually transmitted infections (STI), and the HPV vaccine. Discussions were recorded, transcribed, and analyzed thematically. Mothers were broadly provaccination. Some were excited about a cancer vaccine, although there were fears that it might lead to unhealthy behaviors (e.g., smoking). STI vaccines got a mixed reception. Enthusiasm was moderated by concerns about an increase in risky sexual behavior. When provided with information about the HPV vaccine, women were in favor of protecting their daughters from cervical cancer, abnormal Papanicolaou results and, potentially, from cervical screening. Some worried about an increase in promiscuity and risk of other STIs. There was disagreement about the age at which girls should be vaccinated. Although some women thought this question should be medically driven, others were concerned about discussing the vaccine with young girls and preferred to wait until they were older. In conclusion, mothers were broadly in favor of HPV vaccination but had reservations, particularly about vaccinating girls as young as 10. Larger-scale quantitative work is needed to assess acceptability at the population level. If the vaccine is introduced, information provision is likely to be key to ensuring parents understand the rationale for vaccinating at a young age.

Wang, K. L. (2007). "Human papillomavirus and vaccination in cervical cancer." Taiwan J Obstet Gynecol **46**(4): 352-62.

Cervical cancer is not only the most frequently reported cancer among women, but also the most common female genital tract neoplasm in Taiwan. Early detection is effective, because the development, maintenance and progression of precursor lesions (cervical intraepithelial neoplasia [CIN]) evolve slowly into invasive cancer, typically over a period of more than 10 years. It is now recognized that human papillomavirus (HPV) infection is a necessary cause for over 99% of cervical cancer cases. Advances in the understanding of the causative role of HPV in the etiology of high-grade cervical lesions (CIN 2/3) and cervical cancer have led to the development, evaluation and recommendation of HPV-based technologies for cervical cancer prevention and control. The prevention of HPV infection before the onset of CIN is now possible with recently available prophylactic HPV vaccines, e.g. the quadrivalent Gardasil (Merck & Co., NJ, USA) and bivalent Cervarix (GlaxoSmithKline, London, UK). This review article provides an up-to-date summary of recent studies and available information concerning HPV and vaccination in cervical cancer.

Wang, X., J. P. Wang, et al. (2005). "Prime-boost vaccination with plasmid and adenovirus gene vaccines control HER2/neu+ metastatic breast cancer in mice." Breast Cancer Res **7**(5): R580-8.

INTRODUCTION: Once metastasis has occurred, the possibility of completely curing breast cancer is unlikely, particularly for the 30 to 40% of cancers overexpressing the gene for HER2/neu. A vaccine targeting p185, the protein product of the HER2/neu gene, could have therapeutic application by controlling the growth and metastasis of highly aggressive HER2/neu+ cells. The purpose of this study was to determine the effectiveness of two gene vaccines targeting HER2/neu in preventive and therapeutic tumor models. METHODS: The mouse breast cancer cell line A2L2, which expresses the gene for rat HER2/neu and hence p185, was injected into the mammary fat pad of mice as a model of solid tumor growth or was injected intravenously as a model of lung metastasis. SINCP-neu, a plasmid containing Sindbis virus genes and the gene for rat HER2/neu, and Adeno-neu, an E1,E2a-deleted adenovirus also containing the gene for rat HER2/neu, were tested as preventive and therapeutic vaccines. RESULTS: Vaccination with SINCP-neu or Adeno-neu before tumor challenge with A2L2 cells significantly inhibited the growth of the cells injected into the mammary fat or intravenously. Vaccination 2 days after tumor challenge with either vaccine was ineffective in both tumor models. However, therapeutic vaccination in a prime-boost protocol with SINCP-neu followed by Adeno-neu significantly prolonged the overall survival rate of mice injected intravenously with the tumor cells. Naive mice vaccinated using the same prime-boost protocol

demonstrated a strong serum immunoglobulin G response and p185-specific cellular immunity, as shown by the results of ELISPOT (enzyme-linked immunospot) analysis for IFNgamma. CONCLUSION: We report herein that vaccination of mice with a plasmid gene vaccine and an adenovirus gene vaccine, each containing the gene for HER2/neu, prevented growth of a HER2/neu-expressing breast cancer cell line injected into the mammary fat pad or intravenously. Sequential administration of the vaccines in a prime-boost protocol was therapeutically effective when tumor cells were injected intravenously before the vaccination. The vaccines induced high levels of both cellular and humoral immunity as determined by in vitro assessment. These findings indicate that clinical evaluation of these vaccines, particularly when used sequentially in a prime-boost protocol, is justified.

Weide, B., C. Garbe, et al. (2008). "Plasmid DNA- and messenger RNA-based anti-cancer vaccination." Immunol Lett **115**(1): 33-42.

Tumor cells (over-) express specific antigens which allow them to be recognized and destroyed by the immune system. Triggering anti-tumor immunity in cancer patients by specific vaccination is foreseen as a safe and versatile method to control cancer. As a source of antigen, whole tumor cells, nucleic acids, proteins or derived peptides have been used. This review focuses on the utilization of vaccines based on plasmid DNA (pDNA) and messenger RNA (mRNA) coding for tumor associated antigens. Both vectors (pDNA and mRNA) are grouped under the designation "minimal nucleic acid vector" or MNAV. The current knowledge on anti-tumor vaccination based on MNAV-encoded tumor antigens, methods of delivery, principles of production and optimization is discussed. Furthermore, an up-to-date summary of published clinical trials using MNAV for the vaccination against solid tumors is given. Recent preclinical and early phase clinical trials demonstrate promising synergies between vaccination and other treatments such as chemotherapy or non-specific immune enhancement regimens. Combining optimized MNAV formulations and parallel adjuvant treatments could allow to turn MNAV-based vaccines into efficient anti-tumor immunotherapies in humans.

Weise, J. B., K. Csiszar, et al. (2008). "Vaccination strategy to target lysyl oxidase-like 4 in dendritic cell based immunotherapy for head and neck cancer." Int J Oncol **32**(2): 317-22.

Overexpression of lysyl oxidase (LOX) is associated with the invasive potential of metastatic breast and head and neck cancer (HNC) cells and reduced metastasis-free and overall survival. Recently, we have demonstrated up-regulation of a new member of the LOX family, lysyl oxidase-like 4 (LOXL4), in invasive HNC revealed a significant correlation between LOXL4 expression and local lymph node metastases and higher tumour stages. The objective of this study was to examine whether cellular LOXL4 may provide an effective target for cell-meditated immunotherapy in invasive tumours associated with LOXL4 overexpression. As a feasibility study we expressed LOXL4 mRNA in immature dendritic cells derived from human peripheral blood mononuclear cells (PBMC). LOXL4 protein expression was ascertained using Western blotting and immunocytochemistry with polyclonal rabbit anti-LOXL4 antibody. The successfully transfected immature dendritic cells (DCs) were induced to mature with GM-CSF, IL-4, IL-1beta, TNF-alpha, IL-6, and PGE2, and then used to stimulate T cell enriched non-adherent fraction of PBMC. LOXL4 specific T cell stimulation induced cytotoxic T lymphocyte (CTL) response was monitored using IFN-gamma secretion from the non-adherent PBMC fraction exposed to mature, LOXL4 transfected DCs acting as the antigen presenting target cells. LOXL4-DC stimulated T cells produced higher IFN-gamma secretion compared to unstimulated T cells and T cells stimulated with untransfected DCs, in the presence of the pan-DR-epitope (PADRE). These initial results demonstrated the potential for LOXL4-transfected DCs to serve as efficient tumour vaccine and support their suitability as a vaccination strategy applicable to cancer patients with tumour specific up-regulation of LOXL4.

Wenandy, L., R. B. Sorensen, et al. (2008). "RhoC a new target for therapeutic vaccination against metastatic cancer." Cancer Immunol Immunother **57**(12): 1871-8.

Most cancer deaths are due to the development of metastases. Increased expression of RhoC is linked to enhanced metastatic potential in multiple cancers. Consequently, the RhoC protein is an attractive target for drug design. The clinical application of immunotherapy against cancer is rapidly moving forward in multiple areas, including the adoptive transfer of anti-tumor-reactive T cells and the use of "therapeutic" vaccines. The over-expression of RhoC in cancer and the fact that immune escape by down regulation or loss of expression of this protein would reduce the morbidity and mortality of cancer makes RhoC a very attractive target for anti-cancer immunotherapy. Herein, we describe an HLA-A3 restricted epitope from RhoC, which is recognized by cytotoxic T cells. Moreover, RhoC-specific T cells show cytotoxic potential against HLA-matched cancer cells of different origin. Thus,

RhoC may serve as an important and widely applicable target for anti-cancer immunotherapeutic strategies.

Wentzensen, N. and S. J. Klug (2009). "Cervical cancer control in the era of HPV vaccination and novel biomarkers." Pathobiology **76**(2): 82-9.

Infections with human papillomaviruses (HPV) are a necessary, but not sufficient cause of cervical cancer. Cervical cancer develops over a long time through precursor lesions that can be detected by cytological screening. The majority of these lesions regress spontaneously without treatment. The challenge of cervical cancer screening is to detect the lesions that have a high risk of progression. Since the recently introduced vaccination against HPV cannot provide 100% protection, cervical cancer screening programs must continue. It is assumed that the reduction of precancers related to vaccination will have a negative impact on the efficiency of current screening programs. Therefore, participation rates need to be increased and current screening modalities should be improved. Several promising biomarkers have been described that might improve cervical cancer screening, but currently, high-quality studies on their efficiency are lacking.

Wheeler, C. M., W. C. Hunt, et al. (2009). "Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States." J Natl Cancer Inst **101**(7): 475-87.

BACKGROUND: Limited data are available describing human papillomavirus (HPV) genotype distributions in cervical cancer in the United States. Such studies are needed to predict how HPV vaccination and HPV-based screening will influence cervical cancer prevention. METHODS: We used the New Mexico Surveillance, Epidemiology, and End Results Registry to ascertain cases of in situ (n = 1213) and invasive (n = 808) cervical cancer diagnosed during 1985-1999 and 1980-1999, respectively, in the state of New Mexico. HPV genotyping was performed using two polymerase chain reaction-based methods on paraffin-embedded tissues from in situ and invasive cancers and on cervical Papanicolaou test specimen from control subjects (ie, women aged 18-40 years attending clinics for routine cervical screening [n = 4007]). Relative risks for cervical cancer were estimated, and factors associated with age at cancer diagnosis and the prevalence of HPV genotypes in cancers were examined. RESULTS: The most common HPV genotypes detected in invasive cancers were HPV type 16 (HPV16, 53.2%), HPV18 (13.1%), and HPV45 (6.1%) and those in in situ cancers were HPV16 (56.3%), HPV31 (12.6%), and HPV33 (8.0%). Invasive cancer case subjects who were positive for HPV16 or 18 were diagnosed at younger ages than those who were positive for other carcinogenic HPV genotypes (mean age at diagnosis: 48.1 [95% confidence interval {CI} = 46.6 to 49.6 years], 45.9 [95% CI = 42.9 to 49.0 years], and 52.3 years [95% CI = 50.0 to 54.6 years], respectively). The proportion of HPV16-positive in situ and invasive cancers, but not of HPV18-positive cancers, declined with more recent calendar year of diagnosis, whereas the proportion positive for carcinogenic HPV genotypes other than HPV18 increased. CONCLUSIONS: HPV16 and 18 caused the majority of invasive cervical cancer in this population sample of US women, but the proportion attributable to HPV16 declined over the last 20 years. The age at diagnosis of HPV16- and HPV18-related cancers was 5 years earlier than that of cancers caused by carcinogenic HPV genotypes other than HPV16 and 18, suggesting that the age at initiation of cervical screening could be delayed in HPV-vaccinated populations.

Yanagimoto, H., T. Mine, et al. (2007). "Immunological evaluation of personalized peptide vaccination with gemcitabine for pancreatic cancer." Cancer Sci **98**(4): 605-11.

The aim of the present study was to investigate the safety and immune responses of personalized peptide vaccination when administered with gemcitabine (GEM) in advanced pancreatic cancer (APC) patients. Thirteen patients with APC were enrolled. Pre-vaccination with peripheral blood mononuclear cells and plasma was carried out to examine cellular and humoral responses to 25 or 23 peptides in human leukocyte antigen A24+(+) or A2++(+) patients, respectively. Only the reactive peptides (maximum of four) were then administered weekly at three different dose settings: 1, 2 and 3 mg of peptide. GEM was administered at 1000 mg/m(2) per week for 3 weeks, followed by 1 week of rest. The combination therapy was well tolerated. Grade 3 toxicities were: anemia (three patients), neutropenia (two patients) and thrombocytopenia (two patients). Of these 13 patients, 11 (85%) showed clinical responses, such as reduction in tumor size and/or level of tumor markers. Augmentation of peptide-specific cytotoxic T lymphocyte activity against pancreatic cancer cells was observed at each dose level, whereas the increment of peptide-specific IgG antibodies was dependent on peptide dose. GEM did not inhibit the immune responses induced by personalized peptide vaccinations, and this new type of immunochemotherapy combination is recommended for further clinical study in APC patients.

Yasuda, T., T. Kamigaki, et al. (2006). "Dendritic cell-tumor cell hybrids enhance the induction of cytotoxic T lymphocytes against murine colon cancer: a comparative analysis of antigen loading methods for the vaccination of immunotherapeutic dendritic cells." Oncol Rep **16**(6): 1317-24.

Dendritic cells (DCs) have been used successfully for inducing effective anti-tumor immune responses in advanced cancer patients undergoing tumor-specific immunotherapy. Appropriate antigen pulsing is a crucial parameter for optimizing the efficacy of immunotherapy as well as anti-tumor protection therapy. Using a murine colon cancer model, we evaluated the anti-tumor efficacy of four different preparations of DC vaccines that contained either a whole tumor or its derivatives, including i) DCs pulsed with tumor lysate, ii) DCs pulsed with necrotic tumor cells, iii) DCs pulsed with apoptotic tumor cells, and iv) DC-tumor cell fusion hybrids. Our data show that DC-tumor cell fusion hybrids and DCs pulsed with irradiated apoptotic tumor cells were more potent than DCs with freeze-thawed necrotic tumor cells for the induction of protective anti-tumor responses. The vaccination of DCs pulsed with tumor lysate failed to elicit any anti-tumor effect. In animals administered with higher doses of a tumor-cell challenge, DC-tumor cell fusion hybrids elicited the most effective anti-tumor response. Among the preparations tested, mice immunized with DC-tumor cell fusion hybrids resulted in the greatest induction of cytotoxicity as measured by the cytotoxic T lymphocyte activity of both the splenocytes and the Thy1.2-positive T lymphocytes. Furthermore, the in vitro production of IFN-gamma polarized to the Th1 cytokine responses was highest in the splenocytes derived from mice vaccinated with DC-tumor cell fusion hybrids. Our results suggest that DC-tumor cell fusion hybrids are more potent inducers of protection against solid tumors, such as colon cancer, than other antigen-loading strategies using whole tumor cell materials.

Yi, H., Y. Rong, et al. (2006). "Improved efficacy of DNA vaccination against breast cancer by boosting with the repeat beta-hCG C-terminal peptide carried by mycobacterial heat-shock protein HSP65." Vaccine **24**(14): 2575-84.

Studies have demonstrated that active-specific immunotherapy has potential for controlling mammary tumor progression. Human chorionic gonadotropin (hCG) is expressed and extremely sensitive, easily detectable and highly correlated with breast cancer. We developed a gene vaccine using a plasmid vector to deliver the six copies of 10-amino acid residues of beta-hCG 109-118 and beta hCG C-terminal 37-amino acid (CTP37). BALB/c female mice were immunized with a combination of pCR-HBc-X6-betahCGCTP37 DNA vaccine and HSP-X6-betahCGCTP37 protein vaccine. pCR-HBc-X6-betahCGCTP37 DNA vaccine were injected intramuscularly three times, on days -46,-25 and -11 and HSP-X6-betahCGCTP37 protein were applied two times, 21 and 14 days before tumor cell challenge. We assessed a combined DNA and protein vaccine for its effect of against murine EMT6 mammary tumor cells. In this study, animals vaccinated DNA vaccination boosting with the repeat beta-hCG C-terminal peptide carried by mycobacterial heat-shock protein HSP65 induced higher avidity antibodies and effectively inhibited the growth of tumor, compared with treatment using DNA alone or BCG priming HSP-X6-betahCGCTP37 protein boosting. The data presented demonstrate that improve immunogenicity of DNA vaccination by boosting with the repeat beta-hCG C-terminal peptide carried by mycobacterial heat-shock protein HSP65, which should prove useful in the development of new DNA vaccine against growth factors for cancer immunotherapy.

Zbar, A. P., H. Thomas, et al. (2005). "Immune responses in advanced colorectal cancer following repeated intradermal vaccination with the anti-CEA murine monoclonal antibody, PR1A3: results of a phase I study." Int J Colorectal Dis **20**(5): 403-14.

BACKGROUND AND AIMS: The aim was to determine the toxicity, clinical and immune responses to the murine monoclonal anti-carcinoembryonic antigen (CEA) antibody, PR1A3, in patients with advanced colorectal cancer. MATERIALS AND METHODS: Fifteen patients with advanced colorectal cancer received either 0.5-, 1.0- or 5.0-mg doses of PR1A3 mixed with 10% w/v Alum adjuvant (Superfos Biosector, Denmark) intradermally at 4-week intervals for 3 months. Patient serum was assessed for anti-idiotypic (Ab2), anti-anti-idiotypic (Ab3) and human anti-mouse antibody (HAMA) reactivity. Peripheral blood mononuclear cell (PBMC) proliferation with phytohaemagglutinin (PHA), CEA and PR1A3, stimulated IL-2, IL-4 and IFN-gamma levels and PR1A3-stimulated IL-2 receptor expression during immunotherapy were determined. Comparisons were made with 16 age-matched controls without malignant disease. RESULTS: Hyperimmune sera from 12 of the 15 patients showed Ab2 reactivity with no detectable Ab3 responses. Strong HAMA reactivity was recorded in 7 of the 15 cases with no adverse clinical effect. Delayed-type hypersensitivity (DTH) responses developed in 12 of the 15 patients. Pre-treatment PBMC proliferation with PHA was subnormal in each patient compared with controls,

becoming normal (or supranormal) in all patients during immunisation (P<0.001). PBMC proliferation with CEA and PR1A3 increased during immunotherapy (P<0.001) along with stimulated production of IL-2, IFN-gamma and IL-2 receptor expression. Progressive disease was observed in 14 of the 15 patients with minimal toxicity. CONCLUSION: PR1A3 generated limited idiotypic responses but robust DTH reactivity in most patients. In vitro PBMC proliferation with mitogens and recall antigens is greatly increased during the course of immunisation, with a shift in stimulated cytokine profile.

Zhang, D., Y. Chen, et al. (2006). "MG7 mimotope-based DNA vaccination for gastric cancer." Expert Rev Vaccines **5**(2): 223-31.

Gastric cancer is still one of the leading causes of cancer-related death worldwide. Prevention and treatment of gastric cancer through vaccination has been difficult owing to lack of a specific target and poor immunity. A number of vaccination strategies have been used to augment immune responses against gastric cancer and some progress has been made. In a series of studies, the authors have focused on gastric cancer vaccination approaches based on MG7 mimotopes, which are mimicry epitopes selected from phage-displayed oligopeptide libraries with a gastric cancer cell-specific monoclonal antibody, MG7-Ab. Strategies employed in these studies include viral or plasmid vectors in combination with carrier sequence or unmethylated CpG with synthetic peptides in nanoemulsion. The results demonstrated that MG7 mimotopes could effectively and specifically induce both cellular and humoral immune reactions and in vivo antitumor responses. In particular, a four-MG7 mimotope DNA vaccine was found to elicit much stronger antitumor immune responses in mice compared with its single-mimotope counterpart. These encouraging findings might pave the way for the development of novel MG7 antigen-based vaccination approaches for human gastric cancer. The review also discusses other immune-enhancing vaccination strategies for gastric cancer.

Zoller, M. (2003). "Immunotherapy of cancer by active vaccination: does allogeneic bone marrow transplantation after non-myeloablative conditioning provide a new option?" Technol Cancer Res Treat **2**(3): 237-60.

The critical role of antigen-specific T cells in cancer immunotherapy has been amply demonstrated in many model systems. Though success of clinical trials still remains far behind expectation, the continuous improvement in our understanding of the biology of the immune response will provide the basis of optimized cancer vaccines and allow for new modalities of cancer treatment. This review focuses on the current status of active therapeutic vaccination and future prospects. The latter will mainly be concerned with allogeneic bone marrow cell transplantation after non-myeloablative conditioning, because it is my belief that this approach could provide a major breakthrough in cancer immunotherapy. Concerning active vaccination protocols the following aspects will be addressed: i) the targets of immunotherapeutic approaches; ii) the response elements needed for raising a therapeutically successful immune reaction; iii) ways to achieve an optimal confrontation of the immune system with the tumor and iv) supportive regimen of immunomodulation. Hazards which one is most frequently confronted with in trials to attack tumors with the inherent weapon of immune defense will only be briefly mentioned. Many question remain to be answered in the field of allogeneic bone marrow transplantation after non-myeloablative conditioning to optimize the therapeutic setting for this likely very powerful tool of cancer therapy. Current considerations to improve engraftment and to reduce graft versus host disease while strengthening graft versus tumor reactivity will be briefly reviewed. Finally, I will discuss whether tumor-reactive T cells can be "naturally" maintained during the process of T cell maturation in the allogeneic host. Provided this hypothesis can be substantiated, a T cell vaccine will meet a pool of virgin T cells in the allogeneically reconstituted host, which are tolerant towards the host, but not anergised towards tumor antigens presented by MHC molecules of the host.

Zubor, P., J. Danko, et al. (2007). "Low affordability may limit the effect of cervical cancer vaccination in central and eastern European countries." J Clin Oncol **25**(34): 5534-7.

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