marker, PCNA, and HER2/neu were significantly reduced in the mammary glands of protected mice.
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A phase I trial in patients with solid tumours using autologous dendritic cells loaded with mannan-conjugated recombinant MUC1 protein

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We report the results of a Phase I immunotherapy trial (1) aimed to elicit reproducible cellular immunity using autologous cultured dendritic cells (DC) loaded with Mucin 1 (MUC1) antigen *ex vivo* before injection. MUC1 is a glycoprotein frequently expressed in large quantities by adenocarcinoma cells. Recombinant MUC1 protein (FP) when conjugated to mannan (M-FP) is rapidly taken up by DC and macrophages. We previously reported trials using the direct injection of MFP to patients (pts), obtaining variable T-cell and antibody responses but no effects on disease progression (2).
Eligible patients had MUC1 positive solid tumours, age >18yrs, PS 0–1 with adequate haematological, renal and hepatic function, and no autoimmune disorders. Ten pts underwent leukapheresis on 3 occasions every 4 weeks with average yield $2.8x10^9$ PBMC. DC were derived from plastic-adherent PBMC by culture with 500 U/mL IL-4 and 500 U/mL GM-CSF for 6 days, being pulsed with 10 ug/mL M-FP on day 5. The harvested cells were injected at i.d. and s.c. sites.
Nine of the 10 pts completed the 12 week study, evaluable for toxicity, immunological endpoints and efficacy; 3 were followed-up for 6 months and another 5 for 12 months post-trial. Patients were injected three times with DC/M-FP. Two patients (renal and ovarian carcinoma) who were clearly progressive at study entry, received additional i.d. injections starting 9 and 11 months from initial treatment, first using freshly harvested DC/M-FP then thawed cryopreserved M-FP pulsed cells. They have had a prolonged period of stable disease (>30 months) with ongoing treatment at 3 monthly intervals.
There was no treatment-related toxicity although 2 pts developed marginal anti-thyroid and nuclear antibodies, respectively. Measured immune responses are Th1-type. All pts developed DTH-like responses at injection sites, confirmed by skin biopsies in 5, after the second or third DC/M-FP injections which were recurrent with each additional injection. Different from earlier trials using direct injection of M-FP (2), all pts showed significant vaccine-specific T cell immunity as IFNγ production by both CD4 and CD8 cells to MUC1 antigen (Elispot), and only 3 pts maintained or had an increase in low titre antibody responses. The results indicate that i.d. injection of DC loaded with mannan-conjugated cancer antigen induce consistent immune responses.

References

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Induction of anti-tumor immunity by an anti-idiotype antibody mimicking human HER2/Neu

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Our goal is to apply an anti-idiotype (Id) based vaccine approach for the treatment of HER2/Neu positive human cancer. Amplification and/or over-expression of HER2/Neu occurs in multiple human malignancies and is associated with a poor prognosis. The HER2/Neu proto-oncogene is a suitable target for cancer immunotherapy. We have developed and characterized a murine monoclonal anti-Id antibody, 6D12 that mimics a specific epitope of HER2/Neu and can be used as a surrogate antigen for HER2/Neu. In this study, the efficacy of 6D12 as a tumor vaccine was evaluated in a murine tumor model. In this model, the murine tumor cell line EL4 was transfected with the human HER2/Neu gene (EL4-Her) and injected into syngeneic, immuno-competent C57BL/6 ($H\text{-}2^b$) mice. Immunization of naïve mice with 6D12 conjugated with keyhole limpet hemocyanin and mixed with Freund's adjuvant or 6D12 combined with the adjuvant QS-21 induced anti-6D12 as well as anti-HER2/Neu immunity. The immune sera from mice reacted with the antigen positive SKBR3 cells by ELISA and FACS analysis. The anti-HER2/Neu specific antibodies in the mice sera also demonstrated strong reactivity with EL4-Her cells, but no reactivity at all with parental EL4 cells by FACS analysis showing specificity of the binding. In *in vitro* culture, immune sera killed HER2/Neu positive tumor cells by antibody dependent cellular cytotoxicity (ADCC). Mice immunized with 6D12 were protected against a challenge with lethal doses of EL4-Her, whereas no protection was observed when 6D12 vaccinated mice were challenged with HER2 negative EL4 cells or when mice were vaccinated with an unrelated anti-Id antibody and challenged with EL4-Her cells. These data suggest that the anti-Id 6D12 vaccine can induce protective HER2/Neu specific antitumor immunity and may serve as a potential network antigen for the treatment of patients with HER2/Neu positive tumors. Supported by the NIH grant R01CA91878.

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Allogeneic whole cell vaccination significantly delays disease progression in hormone-relapsed prostate cancer: final data from a phase II study

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Immunotherapy of cancer is under active development and is particularly appealing for patients with asymptomatic hormone-relapsed prostate cancer (HRPC), in whom conventional treatments offer no survival advantage.
We have evaluated a vaccine comprised of three irradiated allogeneic prostate cell lines ($8x10^6$ cells each) for intradermal injection into draining lymph node basins. The treatment period was one year; the first two doses were supplemented with BCG as vaccine adjuvant at a two-week interval, followed by monthly doses of cells alone. A total of 28 HRPC patients were enrolled on the study using conventional entry criteria of failed hormonal therapy, absence of detectable bone metastases plus the ability to mount a delayed-type hypersensitivity (DTH) response to at least one of a panel of common recall antigens.
Two patients were protocol violators and did not form part of the intention-to-treat (ITT) population. 11 of the 26 patients in the ITT population showed statistically significant decreases in their rate of prostate specific antigen (PSA) release. Median time to disease progression (TTP) was assessed using standard clinical and radiological parameters and was 58 weeks in the ITT population compared with historical control values of ca. 25 weeks. No significant side effects were recorded and quality of life remained unchanged throughout the entire course of treatment.
Immunological analysis showed clear evidence of immune activation after vaccination. Responding patients demonstrated a titratable T_H1 cytokine release profile in response to restimulation with a vaccine lysate, whilst non-responders demonstrated a mixed T_H1 and T_H2 response. An unvaccinated control group did not show any notable vaccine specific cytokine responses. Furthermore, immunological profile, as defined by cell surface markers, maximal cytokine production and proliferation, has been shown to correlate with PSA response using Artificial Neural Network (ANN) analysis.
In conclusion, this study represents evidence of the potential efficacy of whole cell allogeneic vaccination in HRPC and a randomised double-blind study is in preparation.

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Multi-epitope peptide vaccine and co-administration of IL-12 prevents tumor growth in Her-2 transgenic mice

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New approaches in cancer treatment are based on the development of vaccines directed against tumor-associated antigens, thereby guaranteeing effective antitumor immune responses.
In a previous study, we selected putative B cell epitopes (P4, P6, P7) derived from the extracellular domain of Her-2/neu. Immunization of BALB/c mice with these peptides gave rise to Her-2/neu specific antibodies, which elicited strong antitumor activity *in vitro*.
The aim of the present study was to evaluate whether peptide immunization also prevent tumor growth *in vivo*. Female FVB mice transgenic for c-*neu* were immunized with a multiepitope vaccine consisting of the three described peptides coupled to tetanus toxoid. The immunizations were performed with or without addition of the Th1 promoting cytokine