Dr. Stéphanie McArdle
Senior Research Scientist in Tumour Immunology

‘Towards the development of a prostate cancer vaccine’
Identifying where research is needed

**Cancer Picked Up**

Will it PROGRESS?

Flow Cytometry

**High PSA**

TRUS Biopsy

**Cancer NOT Picked Up**

Further INVESTIGATIONS?

ELISA Test

**Aggressive**

Cancer Picked Up

**Immune MARKERS?**

To identify immune response for aggressive disease

**Patient NOT responding to hormonal treatment.**

**VACCINE?**

To TREAT the disease

TRUS / TRANS biopsies were taken from all the patients and were found to be either:

1. Benign / Benign
2. Cancer / Cancer
3. Benign / Cancer

www.ntu.ac.uk/vangeest
The centre focuses on two key approaches to the treatment of patients with cancer:

- Improving the diagnosis and management of breast and prostate cancers (mainly via our Biomarker programme)

- Developing effective vaccines and immunotherapies that will significantly improve the survival rates and quality of life for cancer sufferers (via our Immunology programme).
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What is a Biomarker?

“a measurable characteristic that reflects the severity or presence of some disease state”

“a parameter that can be used to measure the progress of disease or the effects of treatment”
Where can we find cancer biomarkers?

**Biological Samples**
- Patient serum
- Patient blood cells
- Patient fresh tissue
- Patient archived tissue
- Patient urine
- Prostate cancer cell lines

**Dataset Mining**
- Publicly available Data Sets
- Gene Expression Arrays
- Gene Micro-Array
- Mass Spectrometry
- Flow Cytometry
What is a Bioinformatics?

Computer-based techniques for analysing and ‘making sense’ of complex datasets and enabling us to ‘Spot the Difference’
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IMMUNOLOGY AND IMMUNOTHERAPY PROGRAMME

- cancer and the immune system -

Core Activities

- Better understanding the relationship(s) between cancer and the immune system
- Development of novel cancer vaccines
Assessing the Immune system of prostate cancer patients

Assessment of
- Suppressive cells (MDSC/Treg)
- Presence of Antigen specific circulating T cells
- NK cell subset

Overview of the Immune system

HLA-A2 typing

Serum assessed for
- HSP90a and B7-H3
- Proteomics
- NK soluble markers

Cells frozen first or not
Immune Profiling
MYELOID-DERIVED SUPPRESSOR CELLS (MDSCs)

Heterogenous population of immune cells with strong immunosuppressressive activities

28/04/2014
Important steps to consider when designing a vaccine

1) Need to choose an “ideal” antigen, then chose which part of the antigen will be the “active” ingredient.

2) Choose a delivery system (i.e. long peptide, DNA vector, Immunobody, Shigella etc.)

3) Choose the most appropriate adjuvant (i.e. GM-CSF, Poly-IC, CpG, IRX.)
1) Prostate Cancer Antigens used in clinical trial

- PSA,
- PSMA,
- PSCA,
- six-transmembrane epithelial antigen of the prostate,
- NY-ESO
- PAP
- HER2/neu
2) Delivery systems

- Adenovirus
- Vaccinia/fowlpox virus (PROSTVAC / TRICOM: B7, ICAM-1 and LFA-3)
- Naked DNA vaccine with vector such as pVAX
- DC precursor cells transfected with PAP (Sipuleucel-T (PAP)
- Whole cell vaccine (GVAX® Two irradiated prostate cancer: LNCaP and PC3)
- **Immunobody™**
- Shigella
The major advantage of the Immunobody® technology is that the Fc component of the engineered antibody will be recognised by the high affinity CD64 receptor present on dendritic cells.
A novel prostate acid phosphatase-based peptide vaccination strategy induces antigen-specific T-cell responses and limits tumour growth in mice.

Effect on Vaccine-Specific T cells

Effect on Tumour Infiltrating Cells

Saif J et al, European Journal of Immunology 2013
In the Press..

Vaccine that turns off prostate cancer could save thousands of lives

By Sarah Knapton
Science Correspondent

A VACCINE that prevents prostate cancer is a step closer after scientists discovered a protein that stops tumour growth in 90 percent of cases.

Researchers at Nottingham Trent University found that injecting part of a tumour protein into the cells surrounding the tumour accelerates the level of activity in the body’s immune system. The immune system then prevents the tumour growing any further, effectively “switching off” the cancer.

Prostate cancer is the most common cancer for men in Britain, where more than 40,000 cases are diagnosed each year and more than 10,000 men die of the disease each year. The majority of men with prostate cancer live more than 10 years after being diagnosed.

“Developing cancer vaccines that can overcome the capacity of tumours to evade the immune system is essential for the development of new therapies for aggressive disease,” said Dr Stephanie McAllister, the lead researcher at the university’s John van Geest Cancer Research Centre. “The only vaccine that currently exists for prostate cancer uses the blood of a sufferer. It is hoped to make the antibody that can be injected to activate the immune system to target the cancer.”

Scientists said the new vaccine would be cheaper to produce and could be given to patients in a relatively simple formulation.

Although the discovery has so far only been made in the laboratory and tested on mice, scientists hope to begin clinical trials soon.

Dr Ian Fraser, the director of research at Prostate Cancer UK, said: “These are truly exciting research results that are promising for the future. However, they are at a very early stage and much more work needs to be done before this could become a viable treatment.”

The research was published in the European Journal of Immunology.

Male Cancer Hope

A PROTEIN that could help fight prostate cancer has been found by scientists. Prostate acid phosphatase, which occurs in 90 percent of prostate tumours, may trigger the body’s own immune system to fight against the cancer.

Researchers at Nottingham Trent University have developed a vaccination strategy involving a series of injections that appears to act against tumour growth. They believe their findings could lead to the development of a vaccine.

Research centre director Professor Robert Rees said: “We are encouraged by the findings.”

Prostate cancer is the most common form of cancer in UK men, affecting around 40,000 men a year, and killing more than 10,000.

Hope for prostate cancer vaccine

Jon Unsworth-Thomas

Scientists believe they may have made the breakthrough for a new prostate cancer vaccine after discovering how a protein can be used to combat the disease.

Researchers at Nottingham Trent University found that the protein – prostata acid phosphatase (PAP) – can be used to stimulate the body’s immune system to target tumour cells.

Prostate cancer is the most common form of cancer in men, killing more than 35,000 in Britain every year.

The new study, published in the European Journal of Immunology, focused on a portion of the PAP protein – known as PAP 248 – and found it was capable of preventing and reducing tumour growth in mice in pre-clinical trials. It also protected against established prostate tumours.

Scientists believe their findings could lead to the development of a cost-effective injectable treatment that will stimulate a faster acting and longer lasting immune response in people suffering from the potentially lethal tumours.

Stephanie McAllister, lead researcher, said: “Our findings demonstrate that PAP 248 is a promising candidate for further development of PAP-based cancer vaccines. It is capable of triggering an immune attack against prostate cancer cells and providing protection against established prostate tumours.”

John Rees, director of research at Prostate Cancer UK, said: “The findings could lead to a new generation of immunotherapies.”

Daily Telegraph, Sat 14th December 2013

The Sunday Times
Sun 15th December 2013
2) Delivery systems

- Adenovirus
- Vaccinia/fowlpox virus (PROSTVAC / TRICOM: B7, ICAM-1 and LFA-3)
- Naked DNA vaccine with vector such as pVAX
- DC precursor cells transfected with PAP (Sipuleucel-T (PAP)
- Whole cell vaccine (GVAX® Two irradiated prostate cancer: LNCaP and PC3)
- Immunobody
  - Shigella
The Shiga toxin B-subunit targets antigen in vivo to dendritic cells and elicits anti-tumor immunity

Benoit Vinger et al., Olivier Addaoui et al., Delphine Patin et al., Steffen Jang et al., Protal Srichani et al., Ludovic Freyburger et al., Cheryl Foppo et al., Anita Seppanen et al., Mohamed Amessou et al., Françoise Quintin-Colonna et al., Wolf Herman Fridman et al., Ludger Johannes et al., and Eric Tartour et al.
TRAMP a useful model of spontaneous prostate cancer

Prostate cancer, tumor immunity and a renewed sense of optimism in immunotherapy

Nicolò Rigamonti · Matteo Bellone

The TRAMP mouse as a model for prostate cancer.

Hurwitz AA¹, Foster BA, Allison JP, Greenberg NM, Kwon ED.

Characterization of preclinical models of prostate cancer using PET-based molecular imaging.

Add tumour associated peptides to PBMC

Presence of Antigen specific circulating T cells
Where do we go from here?

- Assess other delivery systems and other PAP sequences (AICR grant).
- Compare their pre-clinical efficacy using transplantable and spontaneous prostate cancer models (TRAMP C1 cells versus TRAMP mice).
- Assess the presence of circulating T-cells in the blood of prostate benign / cancer patients (before and after combined hormone/radiotherapy).
- Phase-I clinical trial.
John van Geest
Cancer Research Centre
Nottingham Trent University

Hugh's Story
Nottingham Trent University

Cracking the cancer code
www.ntu.ac.uk/vangeest
Key findings:
• Patients reported significant reductions in psychological distress associated with prostate cancer
• The percentage of free PSA was significantly improved when the entire group of 30 participants was analysed
• Intensive nutrition and lifestyle changes modulate gene expression in the prostate.

In short:
Although we can’t change our DNA, we do have the ability to control our lifestyle, leading to epigenetic changes that can influence us both positively and negatively

*Men enrolled in the study:
- Mean age of 62.3 years
- Mean PSA of 4.8ng/ml
- Gleason 6
A total of 93 volunteers with serum PSA 4 to 10 ng/ml and cancer Gleason scores less than 7

• None of the experimental group patients but 6 control patients underwent conventional treatment due to an increase in PSA and/or progression of disease on magnetic resonance imaging.

• PSA decreased 4% in the experimental group but increased 6% in the control group (p = 0.016).

**Conclusions**
Intensive lifestyle changes may affect the progression of early, low grade prostate cancer in men. Further studies and longer term follow up are warranted.
Alternative Therapies

Clinical Events in Prostate Cancer Lifestyle Trial: Results From Two Years of Follow-Up

Joanne Frattaroli, Gerdi Weidner, Ann M. Dnistrian, Colleen Kemp, Jennifer J. Daubenmier, Ruth O. Marlin, Lila Crutchfield, Loren Yglesias, Peter R. Carroll, and Dean Ornish

OBJECTIVES
Previous research has demonstrated that patients with prostate cancer participating in the Prostate Cancer Lifestyle Trial had a reduction in prostate-specific antigen (PSA) levels, inhibition of LNCaP cell growth, and fewer prostate cancer-related clinical events at the end of 1 year compared with controls. The aim of this study was to examine the clinical events in this trial during a 2-year period.

METHODS
The Prostate Cancer Lifestyle Trial was a 1-year randomized controlled clinical trial of 93 patients with early-stage prostate cancer (Gleason score ≤7, PSA ≤10 ng/mL) undergoing active surveillance. The patients in the experimental arm were encouraged to adopt a low-fat, plant-based diet, to exercise and practice stress management, and to attend group support sessions. The control patients received the usual care.

RESULTS
By 2 years of follow-up, 13 of 49 (27%) control patients and 2 of 43 (5%) experimental patients had undergone conventional prostate cancer treatment (radical prostatectomy, radiotherapy, or androgen deprivation, \( P < .05 \)). No differences were found between the groups in other clinical events (eg, cardiac), and no deaths occurred. Three of the treated control patients but none of the treated experimental patients had a PSA level of ≥10 ng/mL, and 1 treated control patient but no treated experimental patients had a PSA velocity of >2 ng/mL/y before treatment. No significant differences were found between the untreated experimental and untreated control patients in PSA change or velocity at the end of 2 years.

CONCLUSIONS
Patients with early-stage prostate cancer choosing active surveillance might be able to avoid or delay conventional treatment for at least 2 years by making changes in their diet and lifestyle. UROLOGY 72: 1319–1323, 2008. © 2008 Elsevier Inc.
Key International Collaborations

- TUM (Technische Universität München)
- HELMHOLTZ Association
- CIIC (Cancer Immunology and Immunotherapy Center)
- Université Paris Descartes
- Ospedale San Raffaele

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