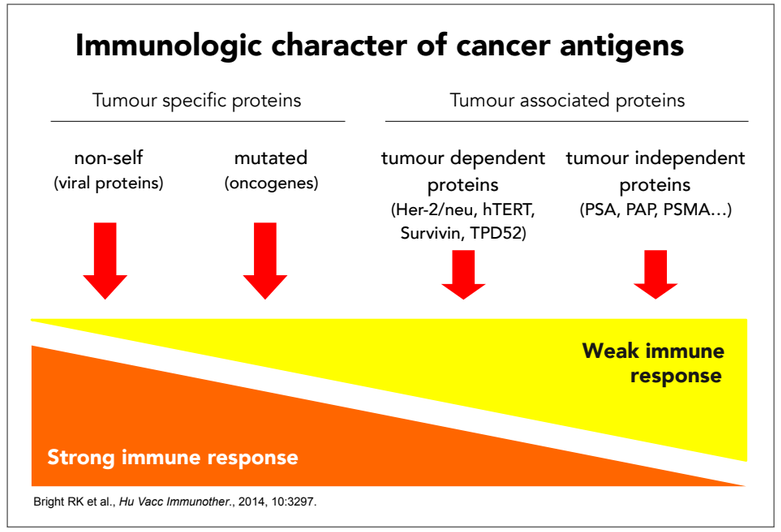
Arming the immune system for the war on cancer

The use of antibodies and the immune system to fight cancer has been an area of intensive research, with only modest successes. **Professor Robert Bright** and his team at the Health Sciences Center of Texas Tech University have made great strides in identifying novel antigens for vaccine targeting and uncovering the mechanisms which may impede effective vaccine-induced immunity.

The immune system is a powerful weapon in the host's armoury against infection and, to some extent, tumours. Innate immunity to certain factors is coupled with an adaptive response from B and T cells, which is developed over the lifetime of the individual, carefully regulated for the correct response to a given situation. Survival of the host relies on an efficient and vigorous response to presented antigens, while the prevention of autoimmune diseases relies on the attenuation of these responses, and a robust recognition of self.

UNLOCKING THE BODY'S ARMOURY

Tumours present a certain problem in that, although they are incredibly damaging to a host and require a robust response from the immune system, they stem from host tissues and are therefore difficult to identify as a threat. Precisely what makes tumours so problematic is that the usual controls on their growth and proliferation have become circumvented often by overexpressed oncogenic proteins enabling them to replicate freely.



Bright RK et al., *Hu Vacc Immunother.*, 2014, 10:3297.

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A NEW TARGET IN THEIR SIGHTS

Professor Robert Bright has identified how overexpressed elements might actually be the target that cancer immunologists have been seeking. Many tumours overexpress antigens that mark them as self to the immune system. Normal cells express these at low levels in order to keep the immune system's sights off them, but tumours from breast to prostate cancers have them in abundance. This is partly what has made them so easy to identify, but Prof Bright's team have shown that one in particular, known as D52, has the potential to be a therapeutic target.

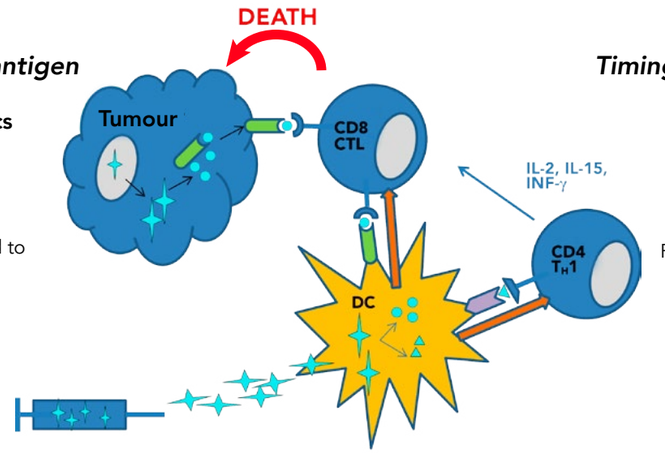
Clearly, the ideal target would be an antigen that is only found in tumours, allowing the immune system to be targeted to that molecule alone and bring the big guns to bear. However, this approach has had limited success so far, so more research is needed to identify broader targets. What Professor Bright's team have discovered is that D52 is not only overexpressed in many tumours, but it also has a vital role to play in tumourigenesis itself. The protein has been implicated in metastasis and proliferation, with the consequent reduction in survival rates of individuals in which this overexpression occurs.

Finding the target is only the first step in developing an effective vaccine, however. Studies by the team into how such a vaccine would perform in animal models of the disease, showed a surprisingly high hit rate given the self-nature of the antigen D52, at 50-75% tumour rejection, but not 100% as hoped. Obviously, something was getting in the way of effectively targeting the immune response to this challenge.

DEPLOYING THE COUNTERMEASURES

Following further investigations, the team deduced that unique populations of regulatory T cells (a subpopulation of T cells which modulate the immune system) are responsible ▶

Cancer vaccination targeting overexpressed oncogenic tumour-self antigens



Character of the antigen

Critical characteristics of next gen tumor-self antigens

Increased expression in tumour cells compared to normal cells facilitated discovery

Demonstrable, indispensable role in oncogenesis

Vaccine induction of tumour-specific CD8+ CTLs

Timing of administration

Vaccine administration for <u>low to no</u> tumour burden

Following surgical removal of primary tumour

Following early detection of minimal disease

Genetic "predisposition" and demonstrable risk (traditional prophylaxis?)

for suppressing the immune response. When these cells, known as CD25 T-regs (because of the biomarkers they express), were reduced in the animal model, the immune system of these animals rejected a tumour challenge. Importantly this did not have any impact on immune memory as a second challenge one hundred days later was similarly rejected.

Professor Bright has reviewed the extensive literature on the role of T-regs in tumour immunity and autoimmune diseases, concluding that further study of this least characterised of the regulatory lymphocytes is required to fully understand their role in tumour immunity. He has identified early evidence which shows that there may be distinct populations of T-regs, yet to be described, which do not display any of the already known markers in other T-reg cells. These may well be precisely the populations which play such a vital role in maintaining tolerance to the self-antigens commonly overexpressed in tumours.

A PERFECT DELIVERY SYSTEM

Having identified a target and taken out the existing defence mechanisms, the next stage is to develop a suitable vaccine and delivery method which can bring the immune system's payload to bear on the malignant growth. For the first of these, Professor Bright has identified that an effective vaccine for this type of challenge is best composed of either the antigenic protein with chemical or molecular adjuvants – to enhance its immunogenicity – or recombinant DNA which codes for the protein to be expressed intracellularly.

Professor Bright identifies the next stage as a key factor which is currently limiting the development of these types of therapies. The ideal position is to be able to develop a vaccine which can be administered to prevent the development of cancer, but in human clinical trials it is currently only possible to administer such experimental compounds to those with late stage tumours which have resisted other therapies.

Professor Bright's research seeks to prevent tumours from forming in the common cancers which overexpress the D52 protein"

PREVENTION IS BETTER THAN CURE

If disease vaccines were only tested on those with full-blown infection, then the small pox vaccine would have never been deemed effective and the disease would still be a major public health problem.

Instead, the ideal situation is for vaccines to be created which can protect people against developing cancer in the first place. One such recent success story is the vaccine for human papillomavirus, which is responsible for 70% of cervical cancer, as well as other cancers. By immunising girls against the virus, it is hoped that most cancers will be prevented in later life. In a more direct way, Professor Bright's research seeks to prevent tumours from forming in the common cancers which overexpress the D52 protein.

Professor Bright is a leading researcher in the field of immunology, particularly as it relates to cancer therapy. Because of this, he also serves as an expert reviewer for several scientific journals including the *Journal of Immunology*. As such, he is perfectly placed to drive this research forward, bringing new promise to a field that has struggled to find success in the fight against cancer.

Q&A

What prevents the immune system from being a more effective control of tumours?

Immune surveillance theories argue for and support the notion that the immune system does effectively control tumours. Evidence for this is the relative low incidence of cancers in young adults as compared to older adults whose immune systems naturally diminish in function. The phenomenon of spontaneous regressions may also attribute to immune control of tumours. The safety and regulatory mandate of treating late stage existing tumours limits immune efficacy, similar to a polio patient not benefiting from the polio vaccine. Treating existing tumours also brings into play the immune suppressive tumour microenvironment, another obstacle for immune system control of tumours.

Why did you first start investigating D52 as a possible target?

For decades, cancer vaccine research was limited by efforts to find cancer causing viruses to target tumour-specific viral proteins. Most cancers are not caused by viruses, mandating the search for a different class of vaccine targets. Early on we developed methods to generate tumour and normal cell cultures from prostate cancer patients and used methods for detecting differential gene expression, and discovered D52. For this effort, we considered proteins that were not tumour specific but tumour associated, even if expression was detected in normal cells. Increased cancer expression and oncogenic function was important and describes the nature of D52.

How do regulatory T cells prevent the vaccine from working?

Regulatory T cells act as guardians of the immune system within the immune system, to safely regulate immune responses and prevent autoimmunity. The suppressive function of regulatory T cells is not completely understood and is an area of intense research. What is clear is that they protect against untoward immune responses against self-proteins to prevent autoimmunity. Overexpressed tumour associated proteins like D52 are tumour-self antigens and thus naturally targeted by regulatory T cells to regulate and prevent potential autoimmunity. Managing this regulation in combination with vaccination will be important for maximum effective immunologic control of tumours.

What might an effective D52 vaccine mean for public health strategies?

D52 is likely an oncogenic driver for most cancers, and necessary for aggressive cancer growth. This suggests cancers are "addicted" to D52 and must have it to survive, so targeting it by vaccination would be a strategy that should remain effective over time. Loss of efficacy is a concern for many cancer treatment strategies. D52 vaccination could be applied in combination with current antibody based immune therapies, specific small molecule therapies or existing chemotherapies to augment the treatment efficacy. The lack of debilitating side effects with long lasting efficacy over many years makes active cancer immune therapy (vaccination) very attractive.

What are the next steps for your group in developing this vaccine strategy further?

D52 is a tumour-self protein. As such it is important to better define the unique CD8 regulatory T cells elicited by D52 vaccination. Combination approaches to temporarily inhibit the suppressive function of these cells, with D52 vaccination may maximise anti-tumour immune responses. Models of early cancer detection that enable surgical removal of small local tumours followed by D52 vaccination to prevent aggressive recurrences and lethal metastases would address realistic, clinical applications. Interestingly, D52 vaccination has not elicited unwanted, harmful autoimmunity. Solving this understudied aspect of self-discrimination will be an important advance in the development of next generation cancer vaccines.

Detail

RESEARCH OBJECTIVES

Professor Bright's research focuses on tumour immunity with an emphasis on the development of vaccines against cancer. His research over the last two decades has explored Tumour Self-Protein TP(D52) as the target for vaccine formulation, with recent focus on TP(D52) eliciting a unique subset of CD8+ T cells.

FUNDING

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BIO

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