The jigsaw puzzle: Brian McGuinness and Theodora Harold

Unlocking the potential of PSMA as a cancer target

As far back as the ancient Egyptian and Greek civilisations, patients with cancer were treated with radical surgical intervention. Astonishingly, it was not until the late 1800s when the discovery of X-rays and their use for the treatment of tumours provided the first modern therapeutic approach in medical oncology. For the ensuing 40-50 years, mainstream treatment options remained centred on these and other radical interventions, aimed at the complete eradication of the disease prior to metastasis. However, the frequent failure to remove all of the tumour mass, the devastating physical trauma of the surgical or radiological intervention itself, the metastatic spread of the tumour or any combination of these factors habitually resulted in high patient morbidity and/or mortality.

Cancer therapy has made huge progress since the days of radical surgical and radiological interventions. Chemotherapy came of age during and after the Second World War and still is a standard of care in many therapeutic settings. However, treating cancer patients with chemotherapy is frequently a fine balance between being able to administer enough drug to kill the tumour before reaching the maximum tolerated dose or indeed a dose that kills the patient.

A third phase in the evolution of cancer therapy has been the emergence of biologics. Arguably, biologic agents have transformed the cancer treatment landscape. Most recently, biologics have allowed us to take advantage of our growing understanding of the complex dual role that the immune system plays in both protecting against tumour growth while also shaping tumour immunogenicity by promoting the selection of tumour cells which are equipped to avoid the host's immune response.

In this article, we review the biologic landscape and explain why our company, Crescendo Biologics, is interested in prostate specific membrane antigen (PSMA) as a cancer target.

Biologic immunotherapies designed to manipulate the immune system to reactivate an antitumor immune response and overcome the pathways leading to tumour-escape have been transformative for some patients with advanced disease. Early approaches to cancer immunotherapy included the use of cytokines such as IL-2 to modulate immune cell function, but high-dose IL-2 can cause capillary leakage and a sepsis-like syndrome which can result in multi-organ failure [1]. More latterly antibodies targeting immune checkpoint inhibitors such as CTLA-4, PD-1 or PD-L1, act by taking the brakes off of the anti-tumour immune response, while antibodies such as utomilumab or urelumab have been developed which are capable of agonising the T cell co-stimulatory receptor CD137 (4-1BB) thereby driving potent T cell activation. Each approach is capable of delivering extremely effective immune-mediated cancer cell death (and some potentially 'curative' outcomes). However, each is also associated with its own assortment of treatment-limiting, organ-specific inflammatory side effects.

Combination therapy is a cornerstone of modern cancer treatment. Scheduled polytherapy, comprising combination interventions, has delivered significant enhancements in therapeutic potency and concomitant improvements in side effects in some cancers. However, along with enhanced therapeutic potency, simple combination therapy can also expose patients to a collection of the side effects associated with each of the individual agents thereby reducing therapeutic index.

It is well accepted therefore, that in the face of ever more potent therapeutic agents, in order to improve patient outcomes further, it is necessary to refine the targeting of existing approaches to limit the exposure of healthy, non-cancerous tissue to their effects.

Antibody-based molecules have been the most successful class of drug for delivery of therapeutic 'payloads' (be that a small molecule toxin, a radionuclide or biologic immunotherapy etc) to tumour cells. For this approach to be most effective however, the delivery agent must bind to tumour cells but not to healthy normal tissue by means of a cancer specific marker. Also, the targeted delivery of 'payload' must kill tumour cells without causing damage to normal tissue.

The critical success factors for such a targeted approach are summarised in Table 1.

It is a measure of the attractiveness of the targeted approach that there are a very large number of cancer-associated markers currently being assessed by drug developers for use in a variety of different therapeutic formats including radiotherapies, antibody drug conjugates (ADCs), targeted RNA therapeutics, cellular therapies, such as CAR T cell therapies, and various T or NK cell engaging bispecifics. The degree to which each cancer marker in development meets the criteria listed in Table 1 varies considerably, but there are few if any that, in our opinion, have better credentials overall than prostate specific membrane antigen (PSMA).

The importance of PSMA

PSMA is a relatively large (750 amino acid) type II transmembrane glycoprotein which acts as a folate hydrolase. There are at least five important features of this antigen. First, PSMA is expressed in up to 95% of prostate cancer, at all grades of disease with a strong positive correlation

Table 1. Criteria for a successful cancer marker

A cancer marker should:
✔ be a tumour specific antigen and ideally not expressed on healthy tissue;
✔ not be shed from the tumour surface to any great extent;
✔ be amenable to the generation of a targeting binder;
✔ be expressed broadly within a cancer, at all stages of the disease, and across a range of different cancers;
✔ exhibit stability of expression, with no long-term down-modulation in response to therapy.

between expression level and disease severity. Second, the expression of the antigen extends to metastases in lymph nodes and bone which means that not only is PSMA an excellent marker for targeted therapy but it is also ideal for use in diagnostic imaging. Third, PSMA internalises, but its expression is not down-modulated (current standard of care may even be associated with upregulation of PSMA expression). Fourth, low levels of shed or soluble PSMA can be detected in serum from healthy and diseased individuals. And finally, normal tissue expression is restricted to prostate epithelial cells, with some limited relatively low-level expression also reported in a small number of additional tissues including duodenum, colon and kidney tubules.

PSMA is an established marker for prostate cancer and prostate cancer is still the second most common cancer in men worldwide. It is behind only lung cancer in prevalence, which is one of the leading causes of cancer death in men in the US and UK [2,3]. The prognosis for patients with late stage prostate cancer is very poor and there is a need for new, effective theranostic agents, in particular for metastatic disease which has become resistant to androgen deprivation therapy. There are a limited number of approved therapies for metastatic castrate-resistant prostate cancer (mCRPC). As of September 2019, the US Food and Drug Administration had approved six, which were able to show an improvement in overall survival in men with mCRPC[4]. These are docetaxel, sipuleucel-T, abiraterone, enzalutamide, cabazitaxel and radium-223. However, the development pipeline for mCRPC is rich and PSMA features highly as a tumour specific antigen across multiple targeted agents, including radioligands, CAR T cell therapies and various CD3-based bispecific molecules.

Importantly, high frequencies of PSMA expression are also commonly found on cancer cells and/or the neovasculature (normal vasculature does not express PSMA) in a range of other solid tumours beyond prostate cancer[5]. These include breast, lung, colorectal and renal cell carcinoma, all of which are indications with high unmet medical need. This hitherto overlooked observation has subsequently been confirmed by our company where, in addition to prostate cancer, we have verified high level PSMA expression in the primary tumour and/or endothelium of cancers including squamous cell carcinoma of the lung and renal cell carcinoma. Thus, it is now clear that PSMA's excellent tumour specific antigen credentials extend further than many realised and there is the very real potential to use PSMA targeting to deliver highly potent immuno-modulatory agents to bring therapeutic benefit to a broad range of cancer patients.

The final piece of the jigsaw that has unlocked the broad potential of PSMA-specific therapeutics is the arrival of the latest generation of antibody-based targeting formats. These new kids on the block can facilitate an entirely novel bispecific-based approach to delivering cancer-specific cytotoxicity.

The 'Humabody' molecules created by our company are one such example of a new, targeted therapeutic format. Our lead product, CB307, is a bispecific T cell-enabling therapeutic. Containing a single binding domain for each of PSMA and CD137 (4-1BB) and a human serum albumin binding domain for half-life extension, CB307 is able to deliver targeted activation of tumour-specific T cells only in the tumour. CD137 is a member of the tumour necrosis factor receptor superfamily which is upregulated on the surface of activated T cells already primed to recognise antigen.

If CD137 is subsequently clustered (normally by binding to its trimeric ligand) on activated T cells recognising tumour antigen, it can deliver a costimulatory signal enhancing their cytotoxic activity, as well as causing them to proliferate and survive (a memory-like effect).

Unlike traditional bivalent monoclonal antibody formats, CB307 has only a single binding site for CD137 and as such, when it binds to CD137 *alone* it will not cause it to cluster. Only when CB307 binds simultaneously to both sufficient PSMA in the tumour and CD137 on activated T cells in the tumour will the co-engagement drive clustering of CD137 and co-stimulation of T cells programmed to recognise tumour. This drives a double layer of safety: CB307 only activates T cells that are already directed against the tumour and it only activates them in the tumour microenvironment. This mechanism of action drives a broad, long-lasting anti-cancer response and contrasts with CD3-based bispecifics which result in short-lived pan-T cell activation associated with dose-limiting toxicities. It also contrasts with the tumour-independent CD137 co-stimulation by regular monoclonal antibodies with their associated organ-specific inflammatory side effects.

The need for tumour-targeted therapies

The evolutionary trajectory of cancer therapeutics has produced ever more potent cytotoxic agents delivered in ever more complex combination regimens. While this has resulted in a steady enhancement in benefit to patients, the improved potency of mono- and polytherapy has often come with more challenging side effects. This has driven the need for tumour-targeted therapies. With its excellent credentials for tumour specificity and an expression profile that spans a range of key cancers with high unmet need, PSMA is an excellent cancer marker for targeting by the latest generation of potent immuno-modulatory therapeutics, such as Crescendo Biologics' CD137 (4-1BB) x PSMA bispecific.

References:

1. Lucy Boyce Kennedy MD & April K. S. Salama MD. A review of cancer immunotherapy toxicity. *CA: A Cancer Journal for Clinicians* (Jan 2020) Wiley Online Library https://doi.org/10.3322/caac.21596 https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21596

2. Website for the American Cancer Society (https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html)

3. Website for Cancer Research UK (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero)

4. Food and Drug Administration, Drugs@FDA: FDA Approved Drug Products, (n.d.). https://www.accessdata.fda.gov/scripts/cder/daf/

5. Fragomeni R.A.S, Amir T, Sheikhbahaei S, Harvey S.C., Javadi M.S., Solnes L.B.,Kiess A.P., Allaf M.E., Pomper M.G., Gorin M.A., and Rowe S.P. Imaging of Non prostate Cancers Using PSMA-Targeted Radiotracers: Rationale, Current State of the Field, and a Call to Arms *J Nucl Med* (2018); 59:871–877

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