Title: Prostate specific membrane antigen (PSMA) from diagnostic to therapeutic target: radionuclide therapy comes of age in prostate cancer

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Without doubt, molecular imaging using PET/CT directed against prostate specific membrane antigen (PSMA) has generated much interest for its impressive accuracy in detecting prostate cancer, particularly for biochemical recurrence[1]. PSMA expression is up regulated in advanced prostate cancer, including metastatic castration resistant prostate cancer (mCRPC), and provides a novel therapeutic target for radionuclide therapy directed towards PSMA-avid disease.

Radionuclide therapy relies on the identification of a suitable tumour associated 'target' and an appropriate 'vehicle' that can bind to this with high selectivity and specificity to allow delivery of a therapeutic radionuclide. PSMA represents an excellent target for radionuclide therapy of prostate cancer, having high expression on tumour cells and minimal or absent expression on most normal tissues. It is present on most prostate cancers and expression is increased in higher grade, advanced and metastatic cancers[2]. Extra-prostatic expression is limited to the small bowel, proximal renal tubules and salivary glands but expression in these tissues is 100-1000 times less than that seen in cancer cells. Another favorable attribute of PSMA is that it is rapidly 'internalised' by cells following ligand binding and this serves to concentrate the molecule with any attached radionuclide inside cells, thus increasing tumour absorbed dose.

A number of radionuclide therapies have been developed recently in prostate cancer that target PSMA, using either antibodies targeting its extracellular structure, or small molecules targeting its enzymatic site and both show

promising activity in the clinic. Antibody directed radionuclide therapy targeting PSMA has largely focused on J591, a fully humanised monoclonal antibody, and in early phase clinical studies ^{177}Lu J591 demonstrates modest efficacy but also dose limiting haematological toxicity [3]. The explanation for this is that whole antibodies are large molecules that penetrate poorly into tumours, reducing absorbed dose and therefore effectiveness, and also clear slowly from the circulation leading to prolonged irradiation of the bone marrow. Antibody 'fragments', smaller molecules that retain the antigen-binding domain of whole antibodies, appear to have a more favorable biodistribution and might be expected to have an improved therapeutic ratio.

Small molecule inhibitors of PSMA by comparison are tiny molecules and are much more agile in tissues. They accumulate rapidly in tumours leading to high tumour absorbed doses, and also clear rapidly from the circulation limiting haematological toxicity. Being rapidly excreted through the kidneys dose limiting renal toxicity might be expected, however experience gained from many years of treating neuroendocrine tumours (NET) with radionuclide therapy has shown this can be avoided. Radiolabelled somatostatin analogues used in the treatment of NET are also small molecules cleared rapidly through the kidneys and minimal renal toxicity occurs providing they are labeled with 'shorter-range' β emitters such as ^{177}Lu , and also given with concomitant amino acid infusions that reduce renal uptake. To date acute renal toxicity has not been reported using radiolabelled inhibitors of PSMA and radiation dosimetry studies that measure absorbed dose in the kidneys indicate that multiple cycles of therapy will not exceed their radiation 'tolerance' so late renal toxicity is unlikely. In numerous retrospective series radiolabelled small molecules targeting PSMA labeled with β emitting radionuclides have demonstrated impressive clinical efficacy with limited acute toxicity in cohorts of heavily pre-treated patients.

In the largest of the reported series of 145 patients treated across 12 centres a PSA fall of greater than 50% was reported in 45% of patients and in 40% this was observed after a single treatment. Toxicity was largely haematological (G3-4) in 12% of patients and mild to moderate xerostomia in 8%[4].

Improvement in the efficacy of these treatments is to be expected as the techniques for patient selection and administration are refined. Additional benefits might also be seen with their combination with radio-sensitising chemotherapy, an approach that is already applied in radionuclide therapy of NET. Radiation may enhance anti-tumour immune responses by the release of tumour antigens leading to abscopal effects. Exploration of potential synergy between external beam radiation and PD1 inhibitors is underway and combination of these agents with radionuclide therapies targeting PSMA is worthy of further investigation. Synergy between radionuclide therapy and PARP inhibitors has recently been demonstrated in vitro in the treatment of NET[5]. The combination of small molecule inhibitors with alternative radionuclides either α or Auger emitters that have different radiobiological characteristics to β emitters also look promising and may offer advantages in the treatment of resistant, small volume and micro metastatic disease[6].

And what of the targeting of other molecular targets on prostate cancer? The bombesin receptor is also highly expressed in prostate cancer and peptide antagonists have already been shown to be a promising PET imaging agent in prostate cancer [7]. And where might PSMA-directed radionuclide therapy sit in the broader landscape of prostate cancer other than end stage disease? Therapy may be more effective given earlier in the course of the disease including the castration sensitive setting, exploring the known synergy between radiation and androgen deprivation. Radionuclide therapy might also be an effective adjuvant therapy given alongside surgery and radiotherapy in localised but high-risk disease.

Therefore it appears that PSMA shows great promise not just in detecting prostate cancer, but also as a target for radionuclide therapy, providing another option for the management of mCRPC, and perhaps even earlier disease. Whilst early retrospective data are encouraging, prospective studies are needed to confirm these results. We have recently completed recruitment of a phase II study of 30 patients (ACTRN12615000912583) and expect analysis of the primary endpoint data later this year. Ultimately, larger multi-centre

randomised controlled studies will be needed to establish this as a mainstream option for men with advanced prostate cancer.

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