Comparison of PSMA and GPC-1 Technologies Useful in Prostate Cancer Diagnosis and Therapy

The success of an antibody therapeutic relies on its specific expression in tumor, with limited or no expression in normal tissue. In prostate cancer, Prostate Specific Membrane Antigen (PSMA) has been targeted clinically for both imaging and therapy. Overexpressed in the prostate tumors of some individuals, it has allowed successful imaging using ^{68}Ga-PSMA-PET and therapy using ^{177}Lu-PSMA or ^{177}Lu-J591. However, not all patients tumors express PSMA, leaving 10-30% of patients with late stage metastatic disease who do not respond to PSMA-directed therapy. Moreover, PSMA is not only expressed in tumor tissue, but is also expressed in a variety of normal tissues. Immunohistochemistry studies have shown PSMA to be expressed in the kidney, testis, ovary, brain, salivary gland, small intestine, lacrimal glands, colon, liver, spleen, breast, skeletal muscle and benign fractures, as well as malignancies of these tissues (Farag et al, 2020), which means that targeting PSMA using radiation leads to exposure of normal tissue to radiation and subsequent tissue damage and associated side effects. Glypican-1 is a new tumor targeting molecule that is expressed in a variety of deadly solid tumors of high unmet need (including prostate, brain, bladder, esophageal, pancreas, mesothelioma and cervical). What makes Glypican-1 such a promising therapeutic target is its lack of expression in normal tissue (confirmed by the FIH clinical trial completed with Miltuximab®). Moreover, targeting of Glypican-1 with antibody therapeutics has proven completely safe in numerous animal studies, as well as the human study of Miltuximab®. Clinically, GPC-1 is a particularly exciting target, as expression of GPC-1 has been associated with poor clinical prognosis and aggressive tumors, in several solid tumors including pancreatic, esophageal and glioblastoma. Furthermore, we have evidence to suggest potential synergy between GPC-1 directed therapy and standard of care therapies such as chemotherapy and radiotherapy.

GPC-1 as a Therapeutic Target in Prostate Cancer

Expression of GPC-1 in prostate cancer is well established and correlates with Gleason score (Russell et al. 2004, Truong et al. 2016, Levin et al. 2018), in line with the known role of GPC-1 in tumor growth, invasion and metastasis. Targeting of PSMA with ^{68}Ga-PSMA-PET and ^{177}Lu-PSMA or ^{177}Lu-J591 has shown promise for imaging and therapy of prostate cancer respectively. However, these are not applicable to patients whose tumors do not overexpress PSMA, with some 10-30% of patients with late stage metastatic castrate resistant prostate cancer failing to respond, indicating the need for improved or additional therapies (Emmett et al. 2017, Hofman et al. 2018, Brauer et al. 2017).

Largely, “tumor antigens” are expressed at low level on normal tissue or moderately expressed in a limited number of normal tissues. Indeed, PSMA, which has high expression in prostate cancer, is also expressed in normal tissue, including moderate expression in salivary glands, lacrimal glands and minimal expression in other normal tissues such as small intestine and proximal renal tubules (Will et al. 2017, Holland et al. 2010). During PSMA targeted therapy for prostate cancer, radiation to other organs that also express PSMA can cause related side effects (Emmett et al. 2017). The main side effects observed, which are attributed to targeting of PSMA expressed in normal tissue, include dry mouth, nausea, and thrombocytopenia. Alternatively, expression of GPC-1 is absent in normal adult tissue (Kato et al. 2020, Russell et al. 2004). Studies using GPC-1 targeting antibody MIL-38 indicate no cross-reactivity with normal tissue (20 normal cadaveric tissues screened from 1-2 donors) (Russell et al. 2014). Importantly, GPC-1 is not required for normal adult homeostasis (Jen et al. 2009) and the safety of targeting of GPC-1 has been well established in multiple mouse models (Matsuzaki et al. 2018, Kato et al. 2020, Harada et al. 2017). For example, safety studies in mice delivering an anti-GPC-1 antibody (50mg/kg) that recognizes mouse GPC-1, showed no adverse effects (Matsuzaki et al. 2018, Harada et al. 2017). A phase I first-in-human clinical trial of Miltuximab® targeting GPC-1, at a total antibody dose of 25mg, proved safe (Campbell et al. 2019). Thus, targeting of GPC-1 using Miltuximab® may represent an attractive option for those patients not suitable for, or who have failed, PSMA directed therapy.

GPC-1 – A Novel Targeting Antigen with Great Potential for the Therapy of Solid Tumors

Structure: GPC-1 is one of six members of the vertebrate family of glypicans, a family of cell surface proteoglycans, consisting of a core protein covalently linked to heparan sulfate (HS) side chains, all encoded by separate genes (Wang et al. 2019). Glypican-1 exists on the surface of cells attached by a glycosylphosphatidylinositol (GPI) anchor.

Function in cancer: The role of GPC-1 is thought to be developmental (Litwack et al. 1998), with expression restricted in normal adult tissue (Kato et al. 2020, Russell et al. 2004) and its expression is not required for normal adult homeostasis (Jen et al. 2009). Glypican-1 is expressed on tumor cells, controlling growth factor signalling. Acting on these pathways, GPC-1 promotes tumor and cancer stromal cell growth, tumor cell invasion and metastasis (Lund et al. 2020). GPC-1 is known to be overexpressed in a variety of solid tumors and is associated with poor clinical prognosis and an aggressive phenotype, which is perhaps not surprising, given its known role in tumor biology. The biology of GPC-1 in several of these solid tumors has been investigated, with a wealth of evidence in pancreatic cancer (Kleef et al. 1998, Whipple et al. 2012).

Clinical Novelty: The clinical novelty and potential of targeting GPC-1 lies not only in its excellent tumor specific expression profile and proven safety, but in its expression in a variety of solid tumors with high unmet need. Glypican-1 is expressed in prostate tumors (80% of tumors; Russell et al. 2004), bladder (Russell et al. 2004), pancreatic (Lu et al. 2017), breast (Matsuda et al. 2008), esophageal (Hara et al. 2016), cervical (Matsuzaki et al 2018), mesothelioma (Amatya et al. 2018) and brain (glioblastoma; Saito et al. 2017). Playing a critical role in tumor invasion and metastasis, targeting of GPC-1 may allow targeting of a more aggressive phenotype of tumor. Work performed with our collaborators has shown that knockdown of GPC-1 can inhibit the establishment of metastases in a mouse model of prostate cancer. High GPC-1 expression has been associated with poor survival and clinical outcomes, in some solid tumors such as oesophageal, glioblastoma and pancreatic (Hara et al. 2016, Saito et al. 2017, Lu et al. 2017). In the First in Human clinical trial of Miltuximab®, targeting was observed in patients that had failed enzalutamide therapy – potentially a more aggressive tumor (Sabanathan et al. EJNMMI Research, submitted 2020).

Moreover, there is potential for combination therapies between existing therapeutic drugs such as chemotherapeutics or external beam radiation, and GPC-1 targeted therapy. Knockdown of GPC-1 in chemo-resistant glioblastoma cell lines restores the tumor cell's responsivity to chemotherapy (Listik et al. 2020), suggestive of potential synergy with chemotherapy or use in chemo-resistant tumors. Work performed in collaboration with Weill Cornell has shown that GPC-1 expression may be up-regulated in prostate cancer cell lines resistant to radiotherapy (unpublished data).

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