# Glypican-1 Target Summary

## 1. Protein structure

Glypican-1 (GPC-1) is a cell surface proteoglycan linked via a GPI anchor. It has two N-linked glycosylation sites at residues 79 and 116 and three Heparan sulfate attachment sites at residues 486, 488 and 490 [1]. GPC-1 has 14 cross-linked cysteines and the crystal structure shows 14 alpha helices and 3 major loops [2].

Soluble forms of GPC-1 have been detected [3], although these are of relatively low concentration (~20-30ng/ml) [4]. Other studies indicate GPC-1 is expressed on exosomes from different cancers, particularly pancreatic cancer [5].

## 2. GPC-1 is not detected in normal tissue and knockout is viable

Immunohistochemistry studies using well characterised anti-GPC-1 antibodies demonstrate GPC-1 protein is not detectable in normal adult tissue [6,7]. The GPC-1 knockout mouse is viable, with a minimal brain phenotype indicating that GPC-1 is not essential for either development or normal homeostasis [8]. The lack of expression of GPC-1 in normal adult tissue is supported by the excellent safety profiles of anti-GPC-1 therapies, including CAR-T [6,9,10].

## 3. GPC-1 upregulates a variety of cancer pathways

GPC-1 acts as a co-receptor for a variety of growth factors including FGFb, VEGFa, TGFb, WNT, BMPs. These growth factor pathways in turn activate MEK/Erk kinase, PI3 Kinase/AKT, Smad2/3, b-catenin among others [1]. Knockdown of GPC-1 reduces adhesion, migration, proliferation and anchorage independent growth *in vitro* [11,12], and tumour growth *in vivo* in xenograft [4,13] and spontaneous tumour models [14].

## 4. GPC-1 is overexpressed in multiple solid tumours

GPC-1 is overexpressed in multiple solid tumours, including bladder [15,16], breast [17,18], cervical [19], cholangiocarcinoma [20], colorectal [21], gastroesophageal [12], squamous esophageal [22], glioblastoma [23], hepatocellular [24], squamous non-small lung [25], mesothelioma [26], ovarian [27], pancreatic [28–30], prostate cancers [7] and uveal melanoma [31].

Reported rates of GPC-1 positivity in tumours range from 50% in glioblastoma to a 100% in mesothelioma and squamous non-small lung cancers.

## 5. High GPC-1 expression is associated with poor prognosis

Overexpression of GPC-1 is associated with poor prognosis in bladder [31], cervical [31], cholangiocarcinoma [20], colorectal [32], gastroesophageal [12], squamous esophageal [22,33], hepatocellular [24,34,35], non-small cell lung [31], mesothelioma [31], ovarian [31]and pancreatic cancers [29,36] as well as uveal melanoma .

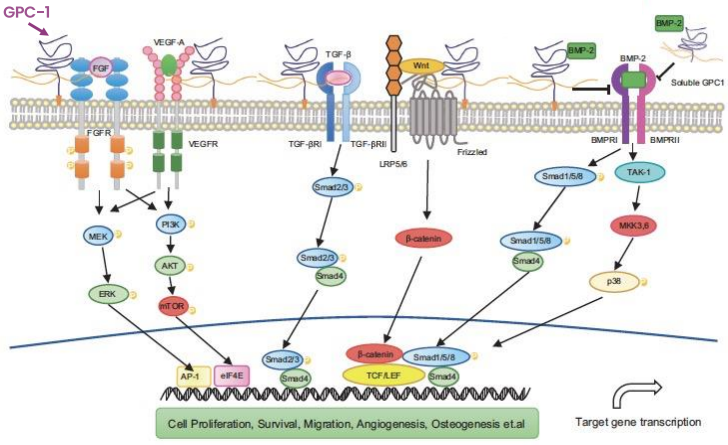
# 6. GPC-1 is an excellent target for targeted radiotherapy

GPC-1 has the following characteristics that make it an excellent radiopharmaceutical target for $^{177}$Lu-directed therapies:

1. Novel solid tumour cancer target with extensive publications characterising its role in cancer biology
2. Undetectable protein expression in normal adult tissues
3. GPC-1 is not required for normal homeostasis (knockout is viable)
4. Overexpression in a large number of solid tumours with high unmet medical need (with different expression profile from GPC-3)
5. High GPC-1 expression correlates with poor patient prognosis in multiple cancers
6. Excellent preclinical safety profile for anti-GPC-1 therapies supported by four independent research groups
7. Preclinical studies indicate optimal anti-cancer activity achieved with "armed" anti-GPC-1 antibody (radiolabelled or antibody drug conjugate)
8. Preclinical efficacy and safety demonstrated with $^{89}$Zr (imaging) and $^{177}$Lu (therapeutic) labelled Miltuximab®
9. First in human clinical trial of Miltuximab® imaging agent showed an excellent safety profile with no drug related adverse events
10. Biodistribution in patients very similar to radiolabelled MAbs such as J591, Herceptin – no off-target binding observed
11. Biodistribution from FIH trial allows calculation of safe dosages for Phase Ib for $^{89}$Zr and $^{177}$Lu-Miltuximab®
12. Chosen therapeutic isotope $^{177}$Lu isotope has a well understood safety profile from 20+ years of use

GPC-1 regulates cancer growth, migration and invasion *in vitro* and in *vivo* via interaction with variety of growth factors including FGFb, VEGFa, TGFb, WNT, BMPs. Unlike other therapeutic antibody targets such as EGFR (Cetuximab), or HER2 (Trastuzumab), the GPC-1 knockout is viable, indicating that it is nor essential for normal development homeostasis.

From 1995 - 2024, there were 1041 publications in PubMed listed using the search term "Glypican 1 and cancer", with >50 publications per year since 2010.

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