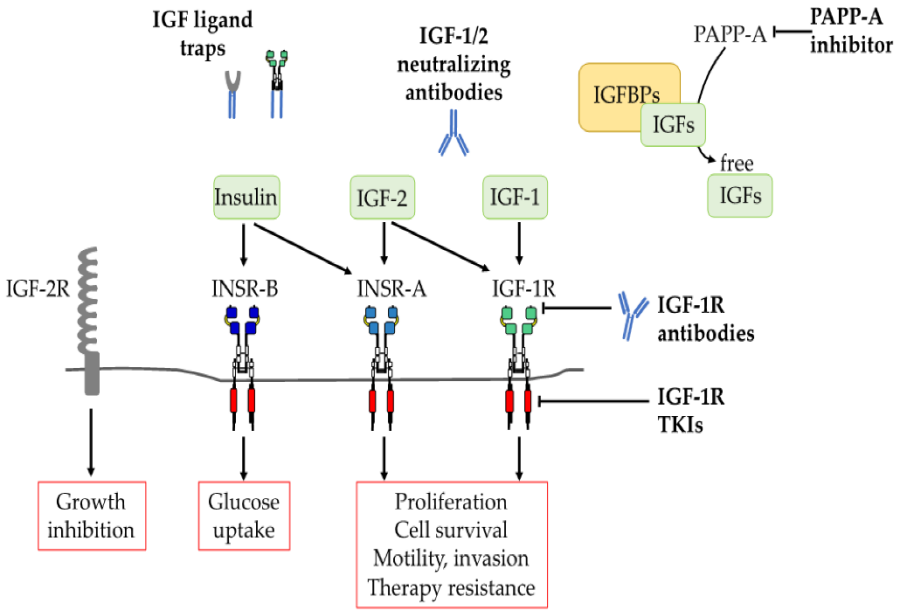
AnshLabs

PAPP-A Neutralizing antibody (1/41): A tool for longevity, cancer, kidney disease, diabetes , CVD etc.

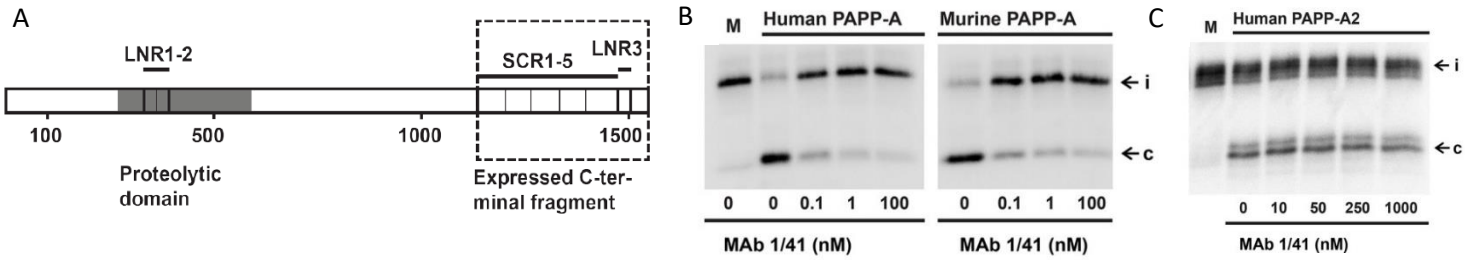
Scientific enquiry: Kannan Alpadi DVM. PhD, Director Scientific Affairs kalpadi@anshlabs.com

The role of insulin-like growth factors (IGFs) in the development and progression of a broad range of epithelial cancers is well documented and investigational compounds targeting the IGF axis have been developed for cancer therapeutics. Monoclonal antibodies directed against the IGF-I receptor (IGF-IR), which transduces IGF-I and IGF-II signaling in cells, have been evaluated. Although conceptually sound, the clinical experience to date using these antibodies in unselected patients with various cancers has been largely disappointing. This can be explained by the broad-based activity of said antibodies (IGF-IR is ubiquitous and serves essential functions in normal tissues), lack of effect on IGF-II mitogenic signaling through insulin receptor isoform A (InsR-A), and secondary hormonal and metabolic derangements. Alternative means of inhibiting IGF signaling was proposed to target pregnancy-associated plasma protein-A (PAPP-A). PAPP-A is a novel metalloprotease of the metzincin superfamily. PAPP-A enhances IGF action through specific cleavage of inhibitory IGF binding proteins, primarily IGFBP-4, resulting in increased IGF bioavailability. It also has the potential to increase local IGF-II available for activation of InsR-A, an insulin receptor that is prevalent in tumor tissue and mediates a mitogenic signal. Therapeutic inhibition of PAPP-A proteolytic activity would effectively both IGF-I and IGF-II (but not insulin) signaling, thereby enhancing efficacy but limiting metabolic toxicity.



Overview of therapeutic strategies developed to inhibit the insulin like growth factor (IGF) axis[1]

1.Targeting the proteolytic activity of PAPP-A towards IGFBP-4[2]

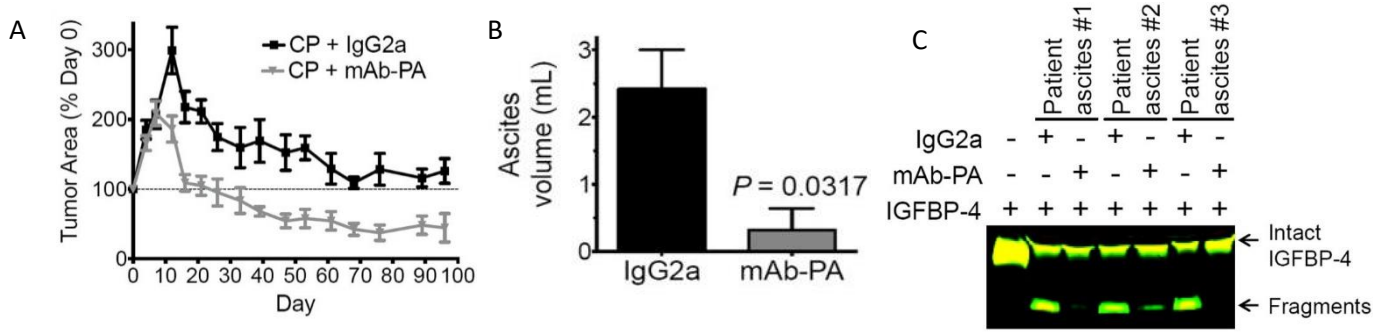


A. Schematic outline of the 200 kDa 1547-residue human PAPP-A subunit. The LNR3 module is 100% conserved between mouse and man. B. Inhibition of cleavage of radiolabeled IGFBP-4 by recombinant human PAPP-A (left panel) and recombinant murine PAPP-A (200 pM, right panel) by using mAb 1/41. Please note that in this experiment, C-terminally tagged IGFBP-4 was used, causing the N- and C-terminal cleavage fragments to co-migrate. Intact IGFBP-4 (i) and the co-migrating cleavage fragments (c) are indicated. C, MAb 1/41 does not inhibit cleavage of radiolabeled IGFBP-5 by recombinant human PAPP-A2 .

Available ANSH LABS ELISA assays (Human and Mouse) :

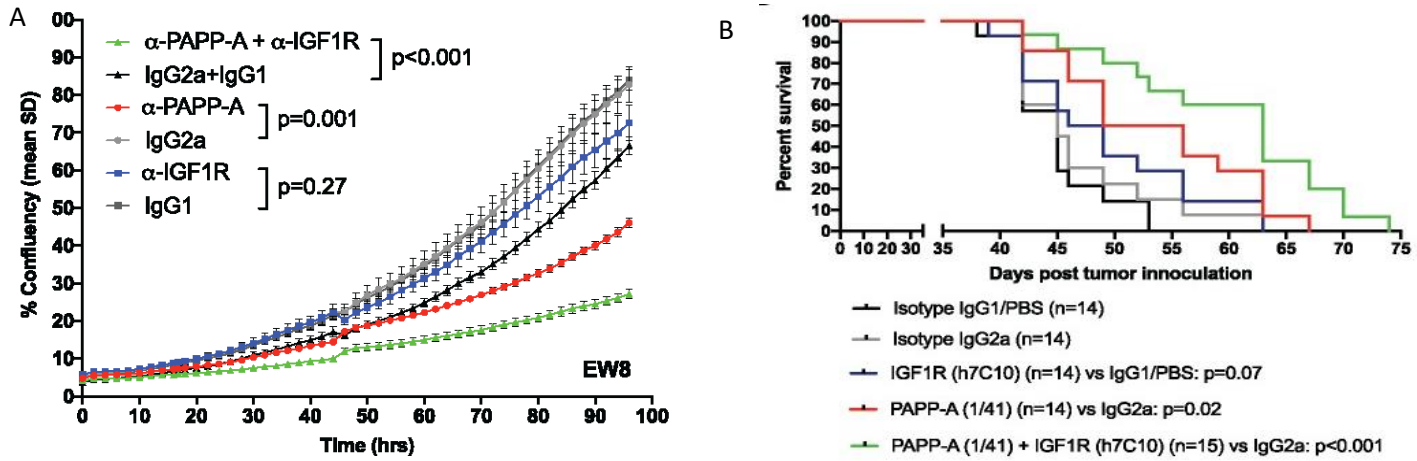
PAPP-A	PAPPA2	IGF-I Total, free	IGF-II	IGFBP2	IGFBP3 Intact, total	IGFBP4 Intact, total	IGFBP5	STC2

2. Targeting PAPP-A in Ovatar mice models with ascites development[3]



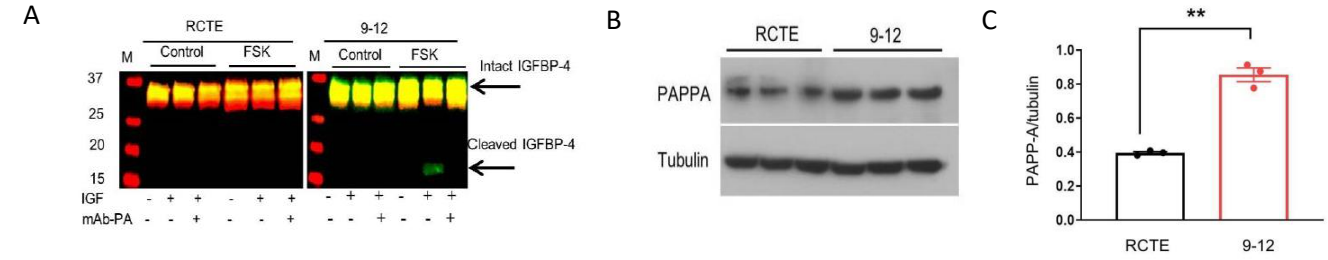
A. Tumor growth in response to platinum chemotherapy combined with mAb-PA [CP + mAb-PA, gray line] vs. IgG2a [CP + IgG2a, black line] (n = 10/group). B. PAPP-A blockade attenuates ovarian ascites progression in mice C. Western blot analysis of effective inhibition of IGFBP-4 proteolysis by mAb-PA in human ascites fluid.

3. Role of pregnancy-associated plasma protein A (PAPP-A) on growth of Ewing sarcoma (EWS) cell lines ex vivo[4].



A. Impact of neutralizing anti-PAPP-A (mAb 1/41) and/or anti-IGF-1R (mAb h7C10) or isotype controls on cell growth over time as measured by confluency in EW8 cell line. B. Effect of pregnancy-associated plasma protein A (PAPP-A) inhibition ± IGF-1R blockade on tumor growth and survival in a Ewing sarcoma (EWS) xenograft model in vivo.

4. PAPP-A regulation of IGF-1 contributes to polycystic kidney disease pathogenesis[5]



Proteolytic assay of PAPP-A mediated IGFBP4 using cell free conditioned media of RCTE (Human renal cortical tubular epithelial cells) and 9-12 (ADPKD cystic epithelial cells) cells treated with cAMP-stimulating agent FSK or vehicle for 72 hours. Conditioned medium was incubated for 72 hours at 37 °C with IGFBP4 without (−) or with (+) pre-complexing to IGF, and without (−) or with (+) the addition of inhibitory mAb-PA 1/41 antibody. Western blot analysis of PAPP-A protein levels in (RCTE) and ADPKD cystic epithelial cells (9-12). graph shows quantification relative to tubulin.

References: *1. Cells. 2019 Aug 14;8(8), 2. Oncotarget. 2014 Feb 28;5(4):1014-25 3. Mol Cancer Ther. 2015 Apr; 14(4): 973–981. 4. J Natl Cancer Inst. 2019 Sep; 111(9): 970–982. 5. JCI Insight. 2020 Jan 28. pii: 135700. doi: 10.1172/jci.insight.135700*