

# PI-88 AND NOVEL HEPARAN SULFATE MIMETICS BLOCK ANGIOGENESIS

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## INTRODUCTION

- PI-88 is a heparan sulfate (HS) mimetic angiogenesis inhibitor (see the box below)
- Currently in multiple phase II clinical trials in a range of solid tumors
- Pharmacokinetic and biological activities of several new HS mimetics with defined pentasaccharide backbones have been evaluated
- Several novel HS mimetics have been developed that block heparanase and VEGF function. From this series PG500 & PG501 are discussed in detail

### Summary of Results

- Compounds inhibit heparanase activity and bind to the angiogenic growth factors (VEGF, FGF-1, FGF-2) with similar affinity to PI-88
- Compounds inhibited tube formation in the Matrigel™ tube formation assay
- In cell-based assays, the compounds were not cytotoxic to human umbilical vein endothelial cells
- Following preliminary pharmacokinetic results, PG500 and PG501 were chosen as representative compounds for evaluation in two murine models of FGF-2 induced angiogenesis, along with PI-88

## SUMMARY OF PI-88

- PI-88 consists of sulfated monophosphorylated mannose oligosaccharides
- Developed as an antagonist of HS interactions with angiogenic growth factors (VEGF, FGF-1 and FGF-2) and as an inhibitor of heparanase, an endoglycosidase that cleaves HS in the extracellular matrix and basement membranes
- First in class heparanase inhibitor
- PI-88 blocks angiogenesis, tumor growth and metastasis in a variety of tumor models
- Toxicity of PI-88 has been assessed in rats and cynomolgus monkeys
- Five phase I and two phase II clinical trials have been completed to date under an IND
- Demonstrated acceptable safety profile (daily SC self administration) with promising signs of patient benefit
- Four phase II trials are ongoing

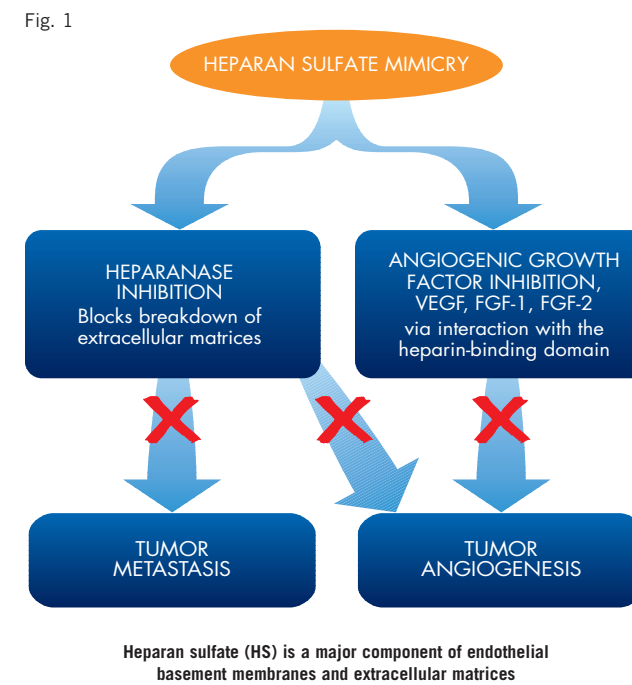
## KEY COMPLETED PI-88 TRIALS UNDER IND

Study	Phase	Treatment	Key Points
Self administered SC in advanced cancer patients	Phase I	Dose escalation for 4 days every fortnight and 4 days every week	<ul style="list-style-type: none"> <li>42 pts recruited (25 male) with median age of 55 years</li> <li>MTD 250 mg/day 4 days in every 7</li> <li>38 evaluable pts, 1 PR, 14 SD for 3 months or longer (39.4% disease control)</li> <li>2 pts still on PI-88 treatment for 47 and 55 months respectively</li> </ul>
Self administered SC in multiple myeloma patients	Phase II	PI-88 dose determined via doubling APTT levels	<ul style="list-style-type: none"> <li>Paraprotein marker study – 19 patients recruited</li> <li>Disease stabilization – 41% of pts evaluable for 8 weeks or longer</li> </ul>
Self administered SC in advanced melanoma patients	Phase II	PI-88, 250 mg/day 4 days in every 7	<ul style="list-style-type: none"> <li>44 pts recruited</li> <li>9 months median survival led to initiation of first line trial in combination with DTIC (dacarbazine)</li> <li>11pts with SD at end of C2, 1 PR and 5 SD at the end of cycle 4</li> </ul>

## CURRENT PI-88 CLINICAL TRIALS UNDER IND – PHASE II

Study	Treatment	Key Points
Primary liver cancer (Post resection hepatocellular carcinoma)	3-arm study: 2 dose levels of PI-88 and control	<ul style="list-style-type: none"> <li>Trial commenced July 2004</li> <li>Approx. 343 pts to be recruited</li> <li>172 pts recruited to date for stage 1</li> </ul>
NSCLC second line treatment	2-arm study: Combined therapy Taxotere® (docetaxel) with and without self administration of PI-88	<ul style="list-style-type: none"> <li>Trial commenced February 2004</li> <li>100 pts to be recruited</li> <li>95 pts recruited to date</li> </ul>
Metastatic melanoma first-line treatment	2-arm study: Combined therapy DTIC, with and without self administration of PI-88	<ul style="list-style-type: none"> <li>Trial commenced May 2005</li> <li>Up to 118 pts to be recruited</li> <li>Dose escalation lead-in safety study</li> <li>Randomized stage will assess the benefit of the addition of PI-88</li> </ul>
Androgen-independent prostate cancer	2-arm study: Self administration of PI-88 combined with Taxotere® (docetaxel)	<ul style="list-style-type: none"> <li>Trial commenced in August 2005</li> <li>90 pts to be recruited</li> <li>Dose escalation lead-in safety study</li> <li>Randomized stage will assess combination at two different dose regimens in combination with Taxotere®</li> </ul>

## MODE OF ACTION



## GROWTH FACTOR BINDING AND HEPARANASE INHIBITION

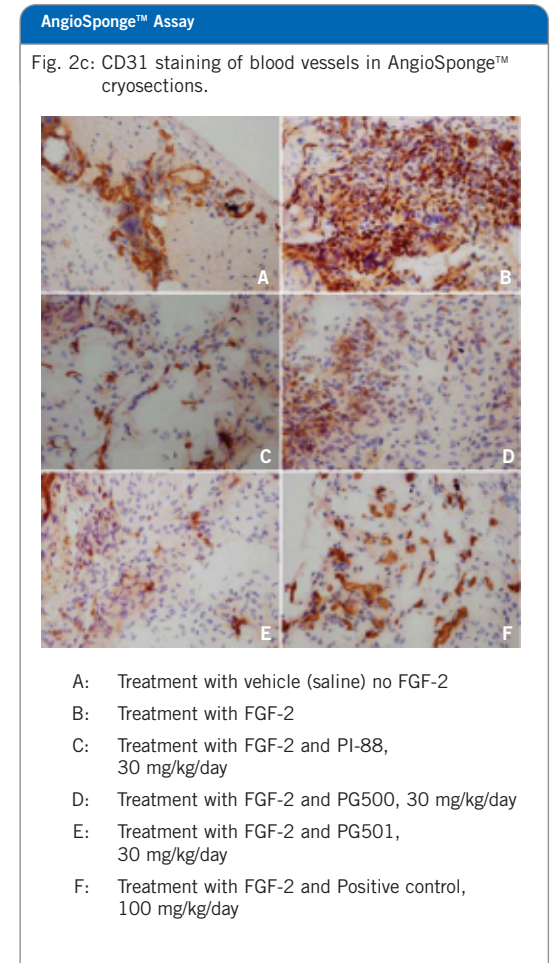
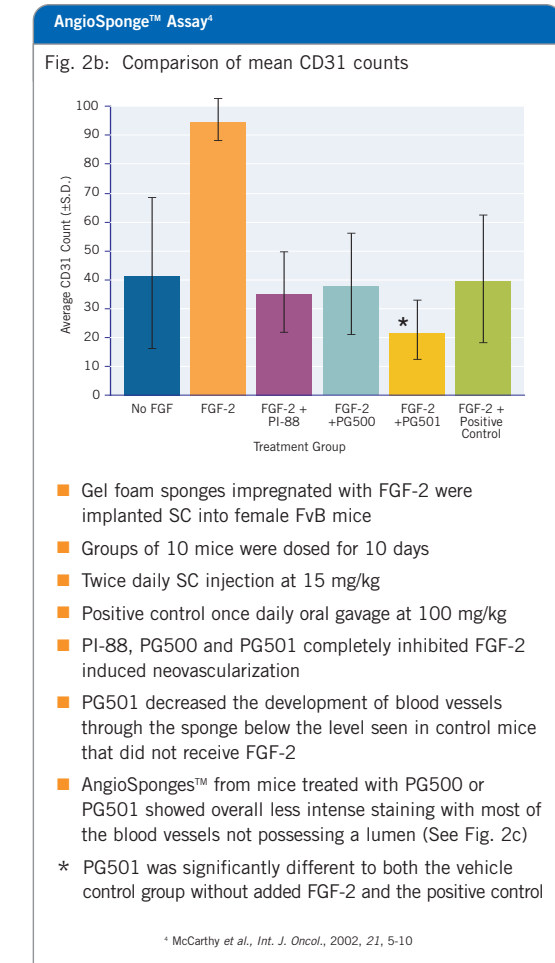
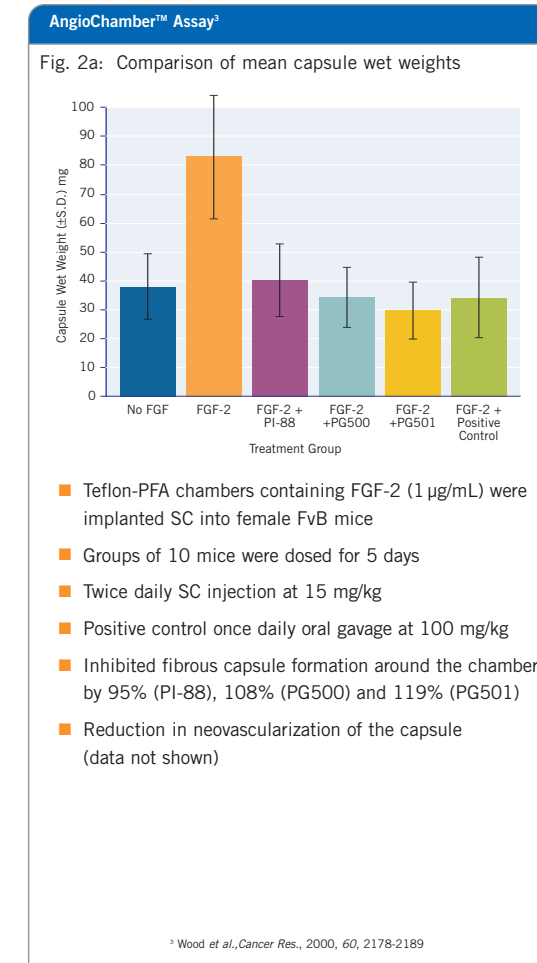
Compound	*K <sub>i</sub> , VEGF (nM)	*K <sub>i</sub> , FGF-1 (nM)	*K <sub>i</sub> , FGF-2 (nM)	*K <sub>i</sub> , Heparanase (nM)
PG500	1.72 ± 0.19	0.12 ± 0.03	86 ± 7	450 ± 120
PG501	1.67 ± 0.11	0.14 ± 0.001	68.3 ± 2.9	410 ± 100
PI-88	1.9 – 6.9	0.25 – 0.86	82 – 140	240 ± 30

\* The binding affinities of these compounds for the angiogenic growth factors FGF-1, FGF-2 and VEGF were determined using a BIAcore (surface plasmon resonance) solution affinity assay<sup>1</sup>

+ Compounds were tested for their ability to inhibit human platelet heparanase. The assays were performed using a microcon ultrafiltration assay which relies on the principle of physically separating HS digested by heparanase from native HS to determine heparanase activity<sup>2</sup>

<sup>1</sup> Cochran et al., J. Med. Chem., 2003, 46, 4601-4608  
<sup>2</sup> Karoli et al., J. Med. Chem., 2005, 48, 8229-36

## EVIDENCE OF IN VIVO ANTI-ANGIOGENIC ACTIVITY IN ANGIOCHAMBER™ AND ANGIOSPONGE™ MODELS



## PHARMACOKINETIC STUDY DATA

Compound	AUC <sub>0-12h</sub> (µg·eq·h/mL)	t <sub>1/2</sub> (h)	Cl (mL/h/kg)
PG500	12.6 ± 1.2	0.83 ± 0.02	199 ± 13.2
PG501	29.7 ± 3.4	1.1 ± 0.09	83.6 ± 9.1
PI-88	9.6 ± 1.9	0.83 ± 0.09	250 ± 27.6

- Preliminary pharmacokinetic data were obtained following intravenous administration of [<sup>3</sup>S]-labeled compounds to groups (n=4) of male Sprague Dawley rats (mean values ±SD)
- PG501 displayed altered pharmacokinetic behavior compared with PI-88 and was cleared three times more slowly than PI-88

## CONCLUSIONS

- Lead anti-metastatic, anti-angiogenic compound PI-88 is currently in four phase II clinical trials
- Novel easily synthesized HS mimetics have been developed with improved *in vitro* and possibly *in vivo* angiogenesis inhibition
- Pharmacokinetic studies indicate it is possible to improve pharmacokinetic properties while retaining or enhancing biological activity
- Compounds PG500 and PG501 show promising anti-angiogenic activity which warrants further investigation
- Further preclinical angiogenesis, pharmacokinetic and tumor model studies are planned