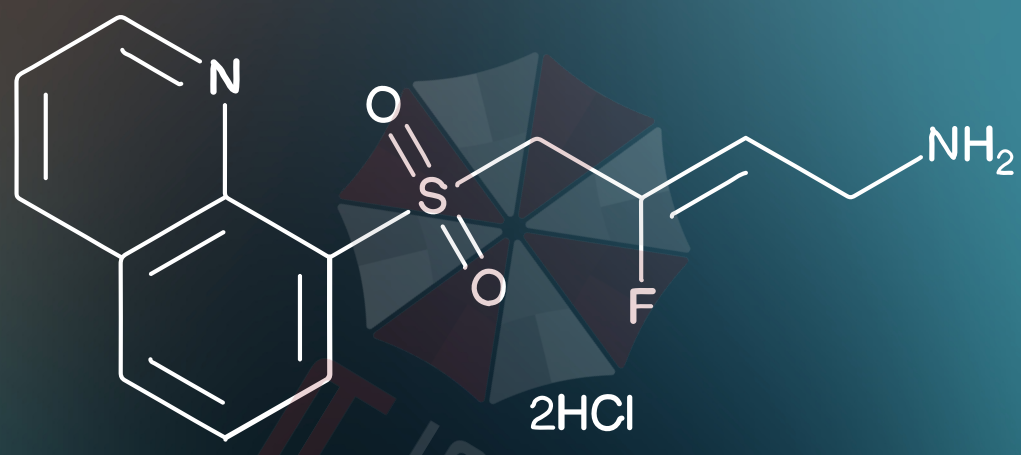

PXS-5505:
A Pan-Lysyl Oxidase Inhibitor with Potential in Fibrosis and Solid Tumors

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PXS is a selective inhibitor for LOX and LOXL1-4 over other recombinant human lysyl oxidases. (IC50s = >30 μM for all). The lysyl oxidase family is critical to the biogenesis of connective tissue through catalyzing the oxidative deamination of lysine residues in tropocollagen monomers thereby stabilizing them into fibrils and fibers. In mammals, there are five family homologs: lysyl oxidase (LOX) and lysyl oxidase-like 1 to 4 (LOXL1–LOXL4). Each family member shares a conserved catalytic C-terminal domain critical to their crosslinking activity, with tissue-specific expression patterns thought to play important roles in determining their exact biological function. All enzymes are suspected to be involved in scar formation, although it is not clear if one or more play a more fundamental role. The inhibitory concentrations are reported as follows:

C50

0.493 μM (fibroblast LOX)

0.159 μM (rh LOXL1)

0.57 μM (rh LOXL2)

0.18 μM (rh LOXL3)

0.19 μM (rh LOXL4)

It was first envisioned as an auxiliary treatment option for pancreatic adenocarcinoma and potentially for other cancer types. Many solid tumor are accompanied by a growth of fibrous connective tissue in the area of the tumor. Antistromal therapies that target or blunt the development of tumor desmoplasia are an emerging area with a substantial and immediate translational impact for enhancing therapy efficacy and improving survival.

PXS-5505 was tested in mice which developed pancreatic cancer as an add on to classical chemotherapy. It was found that PXS-5505 is well tolerated for 6 months in preclinical toxicity studies and >6 months in mouse pancreatic cancer models with no adverse side effects. In mouse and human in vivo models of pancreatic cancer, PXS-5505 reduces collagen deposition and tumor stiffness and improves perfusion of agents into the primary tumor site. In the mouse model, PXS-5505 reduces spontaneous metastasis to other organs and most notably the liver, a major site of metastatic dissemination in patients. These in vivo findings match the in vitro organotypic data showing reductions in local invasion. Furthermore, addition of PXS-5505 to gemcitabine treatment extends survival by approximately 45% and decreases metastatic deposits within the liver compared to gemcitabine alone.[1]

After the initial study in PXS-5505 in mice, further studies on humans are being conducted on patients with a condition called myelofibrosis (MF). Affected patients suffer from a loss of functional bone marrow which is replaced by connective tissue.

In one study, PXS-5505 demonstrated an excellent safety profile and was well tolerated in healthy human subjects. PK/PD properties are consistent with preclinical data and support once or twice daily >100 mg dosing over 14 days. PXS-5505 achieves long-lasting, strong inhibition of lysyl oxidases. Based on previous mouse studies, it is possible that LOX levels would be higher in MF patients when compared to age-matched controls. This study did not report the effectiveness of PXD-5505 in MF.[2] However, another study reported preliminary positive findings on efficacy in MF.[3]

In an additional study, patients will receive PXS-5505 200mg BID for up to 52 weeks or until progressive disease, unacceptable toxicity, dose limiting toxicity or withdrawal of consent. Fifteen pts are planned to be enrolled in this phase of the study. Results have not been published.[4]

In a disease that often leads to myelofibrosis, polycythemia vera, PXS-5505 was also investigated. All 9 patients showed stable reticulin fibrosis at each visit; collagen fibrosis was reduced in 5/9 patients. Hematological parameters were stable; 7/10 had stable/improved hemoglobin and 8/10 had stable/improved platelets over 24 weeks.[5]

PXS-5505 has been successfully used a variety of mouse models of fibrosis. PXS-5505 exhibited anti-fibrotic effects in the skin mouse model, reducing dermal thickness and α- smooth muscle actin. Similarly, in the bleomycin-induced mouse lung model, PXS-5505 reduced pulmonary fibrosis toward normal levels, mediated by its ability to normalize collagen/elastin crosslink formation. PXS-5505 also reduced fibrotic extent in models of the ischemia-reperfusion heart, the unilateral ureteral obstruction kidney, and the CCl4- induced fibrotic liver. PXS-5505 consistently demonstrates potent anti-fibrotic efficacy in multiple models of organ fibrosis.[6]

PXS-5505 was also tested in an animal model of atrial fibrillation (AF), a radiological condition, which can be caused by overgrowth of connective tissue in the heart. PXS- 5505 prevented fibrosis without reducing AF inducibility in model mice but exacerbated AF and fibrosis in sham mice. Hence, the applicability in this field remains questionable.

In all clinical studies PXS-5505 is used as an oral agent, although it is probably suitable to penetrate skin as well due to its small size. However, it has not been reported in that use and a later report on the quite similar PXS-4787 indicates that PXS-5505 might also be instable in topical formulations.

A study with a different lysyl oxidase inhibitor BAPN (β-aminopropionitrile) in rats has shown that oral intake of the compound can lead to increased penis length increase when combined with a vacuum device. This is likely due to the reason that the integrity of the penis is partially due to the so called tunica albuginea, a fibrous sheath of connective tissue, which consists of collagen fibers which are crosslinked using lysyl oxidases. If the oxidases are inhibited, the collagen crosslinking is reduced and the mechanical stability diminishes, leading to a greater volume increase of the corpora cavernosa and the corpus spongiosum, which fill with blood.[7] It is likely that similar results can be achieved in rats using PXS-5505, due to its similar pharmacological actions. No reports on topical applications exist to this day, but a topical application might reduce systemic side effects of lysyl oxidase inhibitors.

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