

## Pankind 2026 Scientific Meeting

### Poster Abstract Form

#### Targeting Pain Pathways in Pancreatic Cancer: Validation of CXCL12-CXCR4 Axis

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**Introduction:** Pancreatic cancer (PC) pain is debilitating and affects the efficacy of cancer treatments. Current therapies offer only transient relief, underscoring the need for novel therapeutic targets. Neural hypertrophy, neuritis (infiltration of nerve sheaths by mast cells), and pancreatic stellate cell (PSC) generated fibrosis are postulated to mediate pain in PC. Chemokines are involved in pancreatic inflammation, thus may contribute to pain. Hence, we hypothesised that PC pain is driven by CXCL12 secreted from PSCs binding to CXCR4 receptors on mast cells, leading to neural hypertrophy and neuritis resulting in pain.

**Methods:** (i) Mouse PSCs were co-cultured with mast cells, and the expression of CXCR4 and CXCL12 was assessed by RT-PCR.

(ii) PSCs, mast cells and dorsal root ganglion (DRG) neurons were co-cultured and incubated with CXCL12 inhibitor (200mM) and/or CXCR4 inhibitor (AMD3100, 100ng/mL). We assessed their effects on mast cell (chymase) and PSC activation (collagen), nerve injury (AFT3), and pain markers (substance P) by RT-PCR. ELISA quantified histamine levels in the cell secretions.

**Results:** CXCL12 and CXCR4 inhibitors significantly downregulated Chymase expression in PSC+mast cell co-cultures ( $p<0.05$ ). In the triple co-culture, AMD3100 significantly downregulated chymase, collagen, and ATF3 ( $p<0.05$ ). Substance P expression in neuron+mast cell co-culture showed a trend to increase. Lastly, histamine levels were significantly upregulated ( $p<0.05$ ) in PSC+mast cell culture and significantly decreased in all treatment groups ( $p<0.05$ ).

**Conclusion:** PSC-DRG-Mast cell interactions promote an inflammatory/neural injury milieu mediated by the CXCL12-CXCR4 axis, suggesting a potential novel therapeutic target for alleviating PC pain.