Elucidating mechanisms of endocrine-exocrine signaling in obesity-driven pancreatic cancer

Cathy Garcia/ Aarthi Venkat
PhD. Candidates
Muzumdar Lab/ Krishnaswamy Lab
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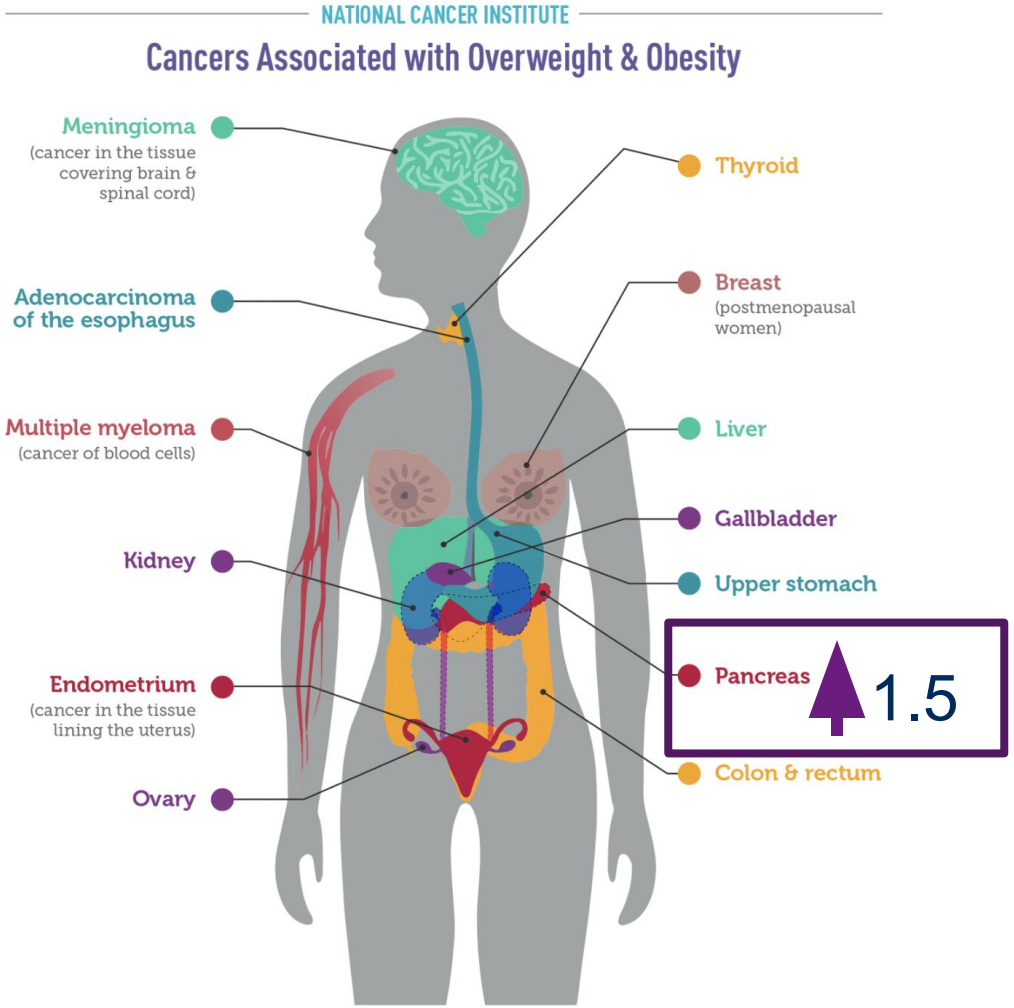
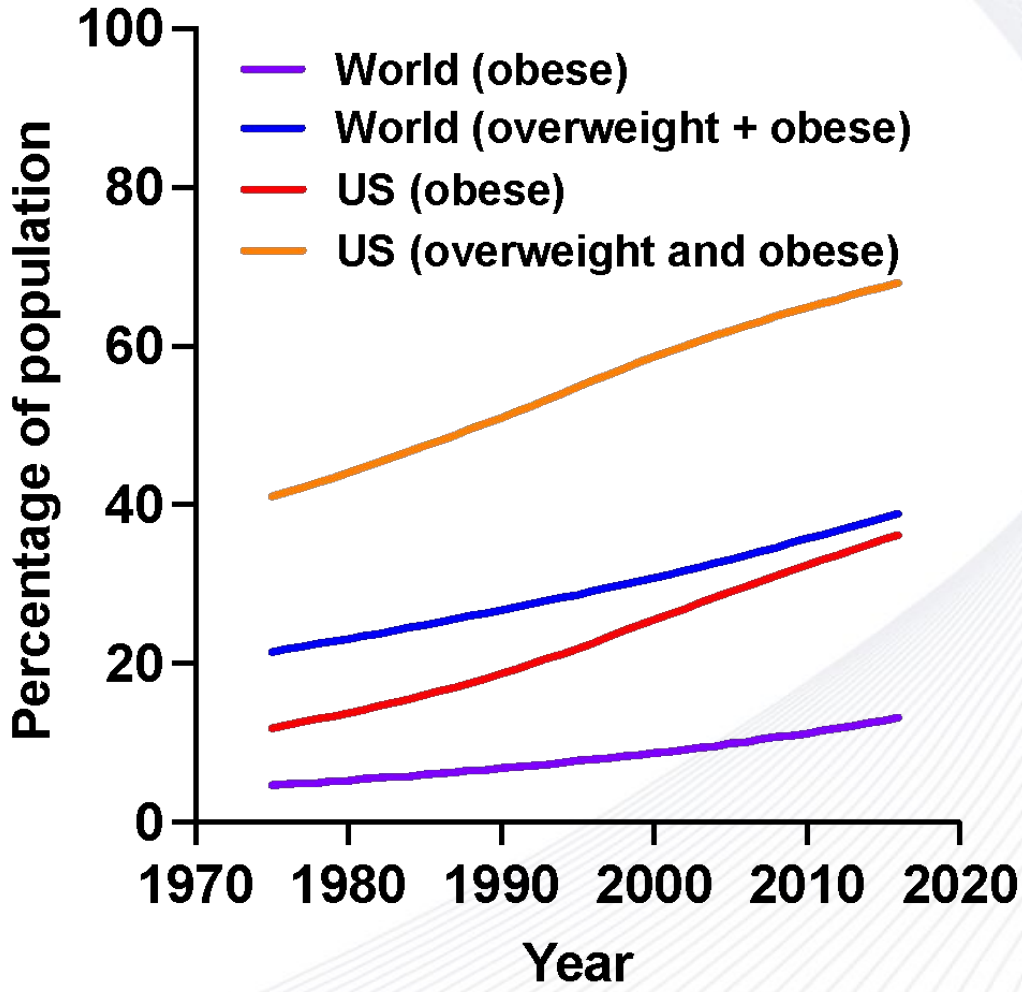
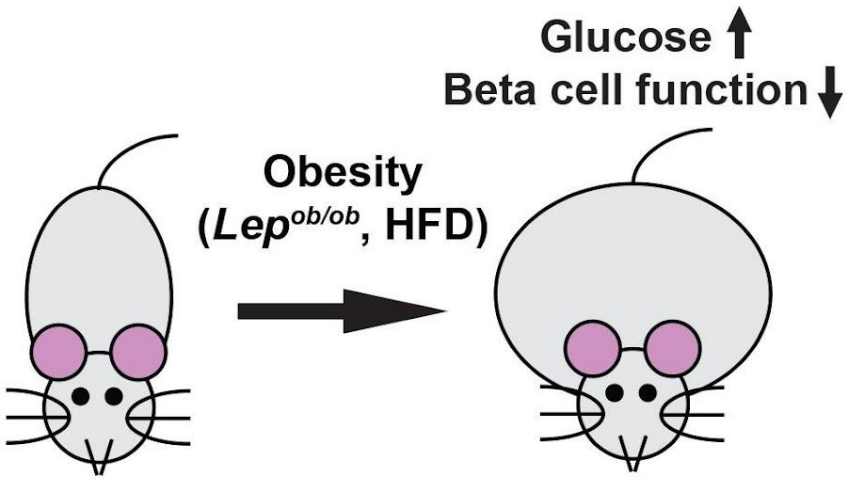
Obesity as a risk factor for PDAC

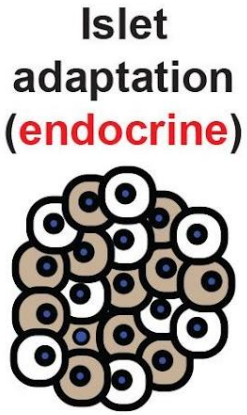


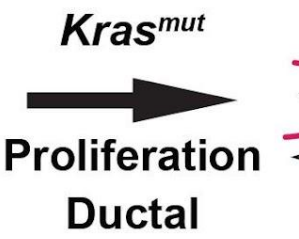


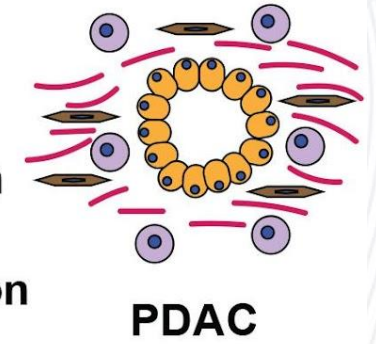
Obesity promotes pancreatic cancer development



Obesity drives pancreatic cancer



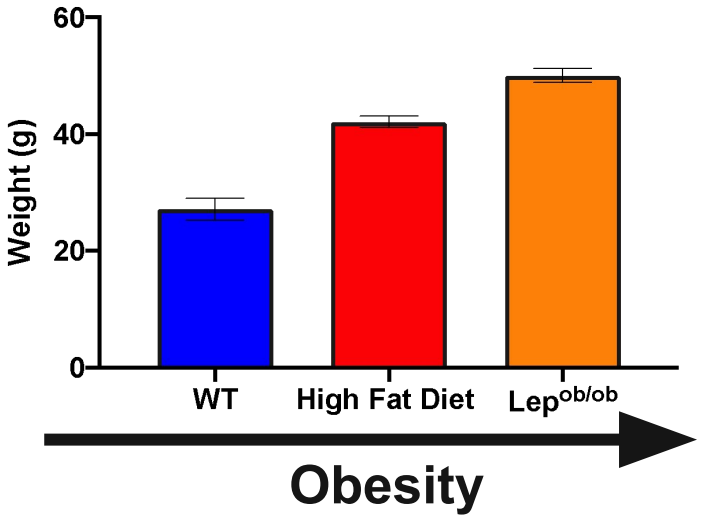


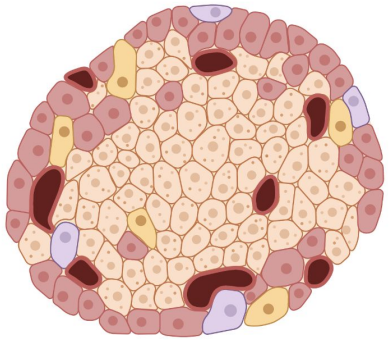


Changes in Hormone expression

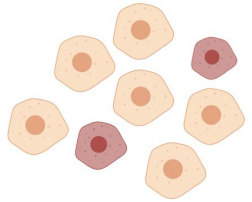
Hormones promote pancreatic cancer

Aberrant hormone expression in β cells of obese mice

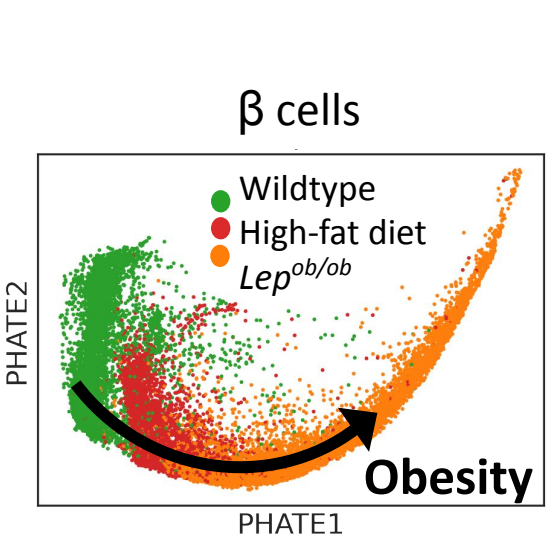


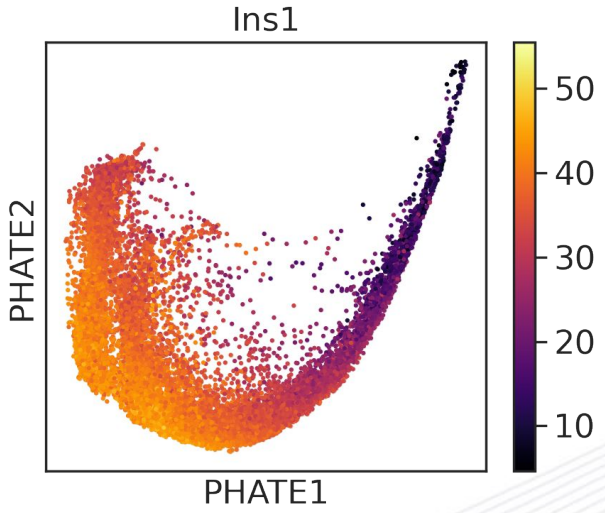


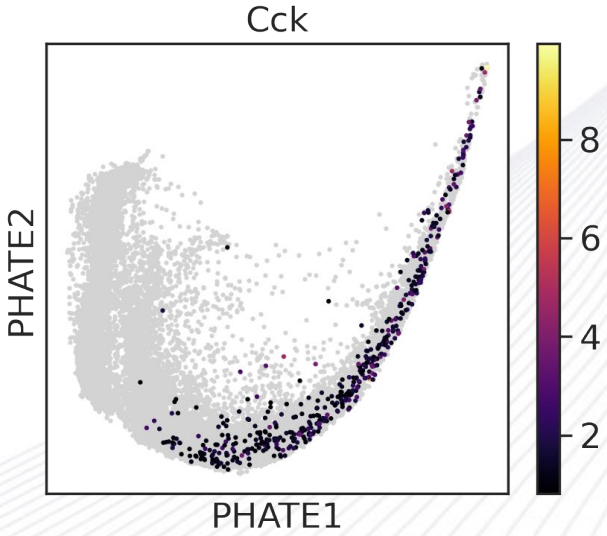
Isolated Islets



Single-cell RNA seq

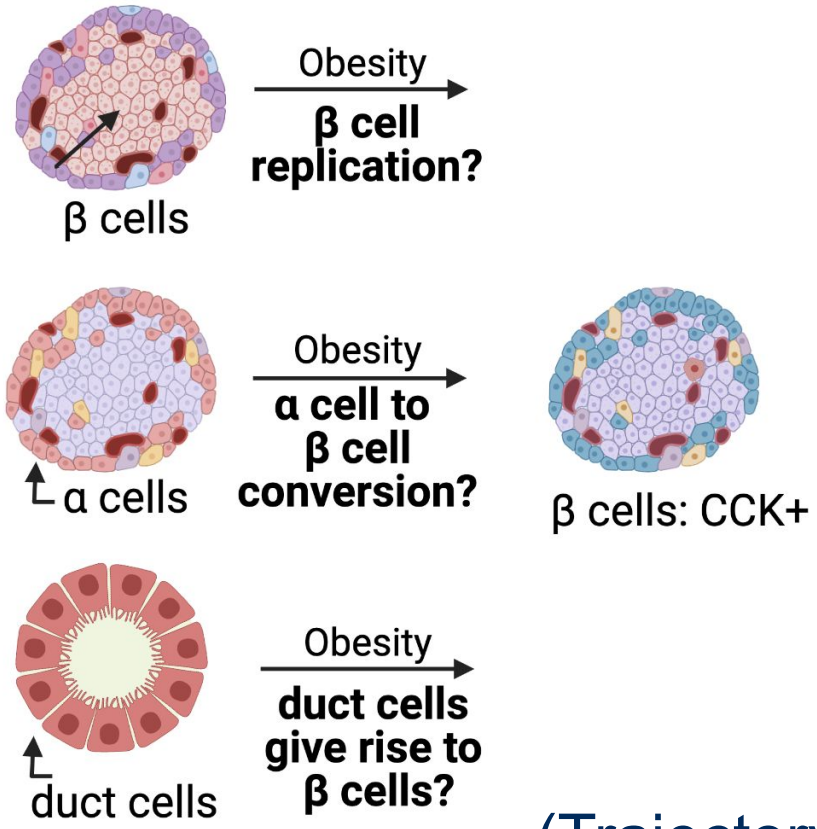




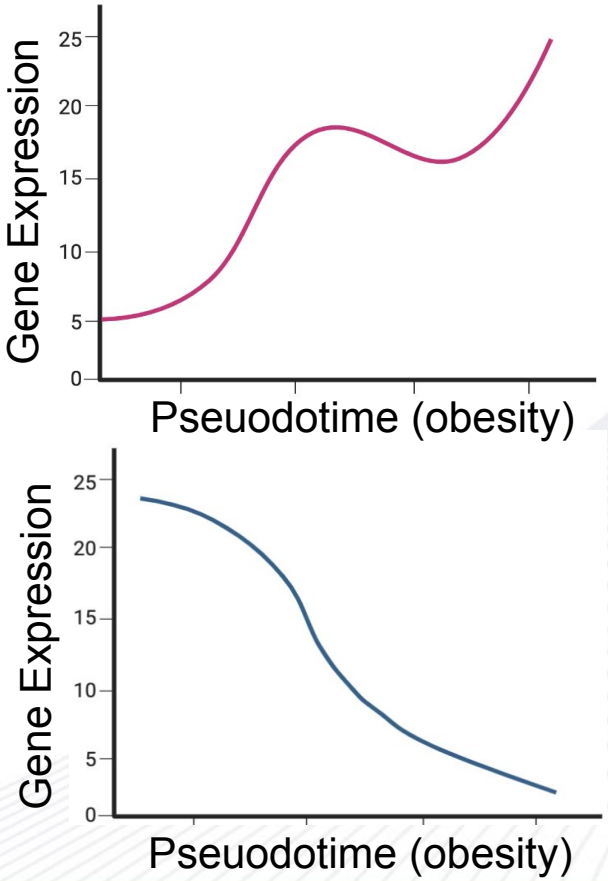


Elucidate the cellular and molecular mechanisms of islet adaptation to obesity, which promotes PDAC progression

I. Identify cell-of-origin that gives rise to β cells mis-expressing hormones

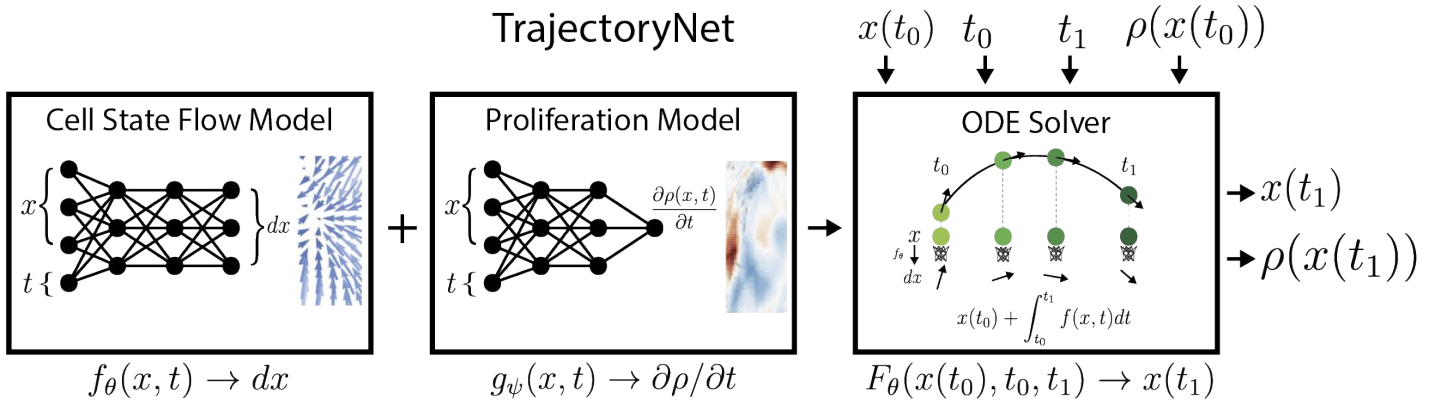


II. Identify transcriptional changes that occur in β cells as obesity progresses



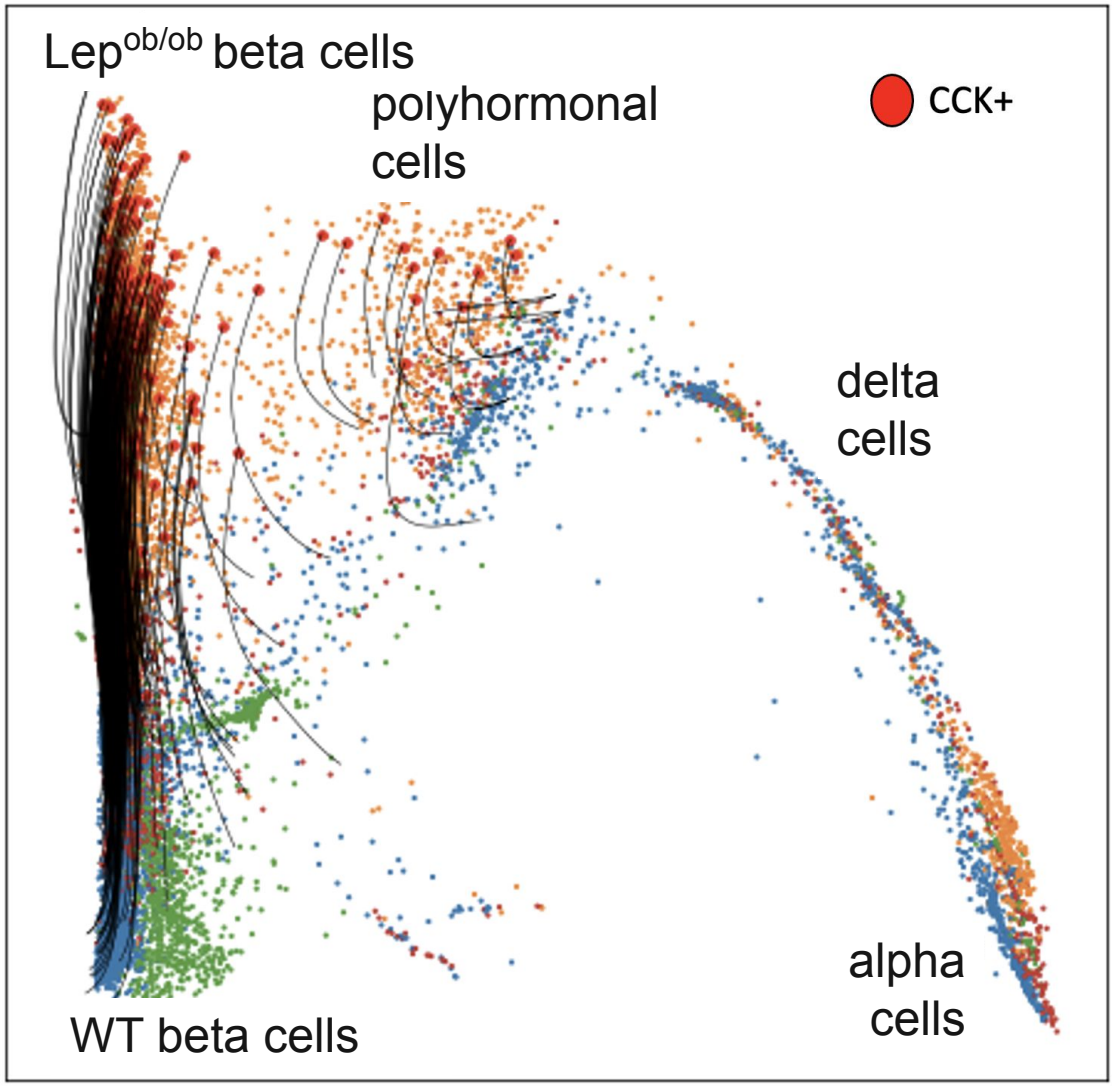
(TrajectoryNet & AAnet)

TrajectoryNet learns continuous cell-specific trajectories with neural ODE-based optimal transport

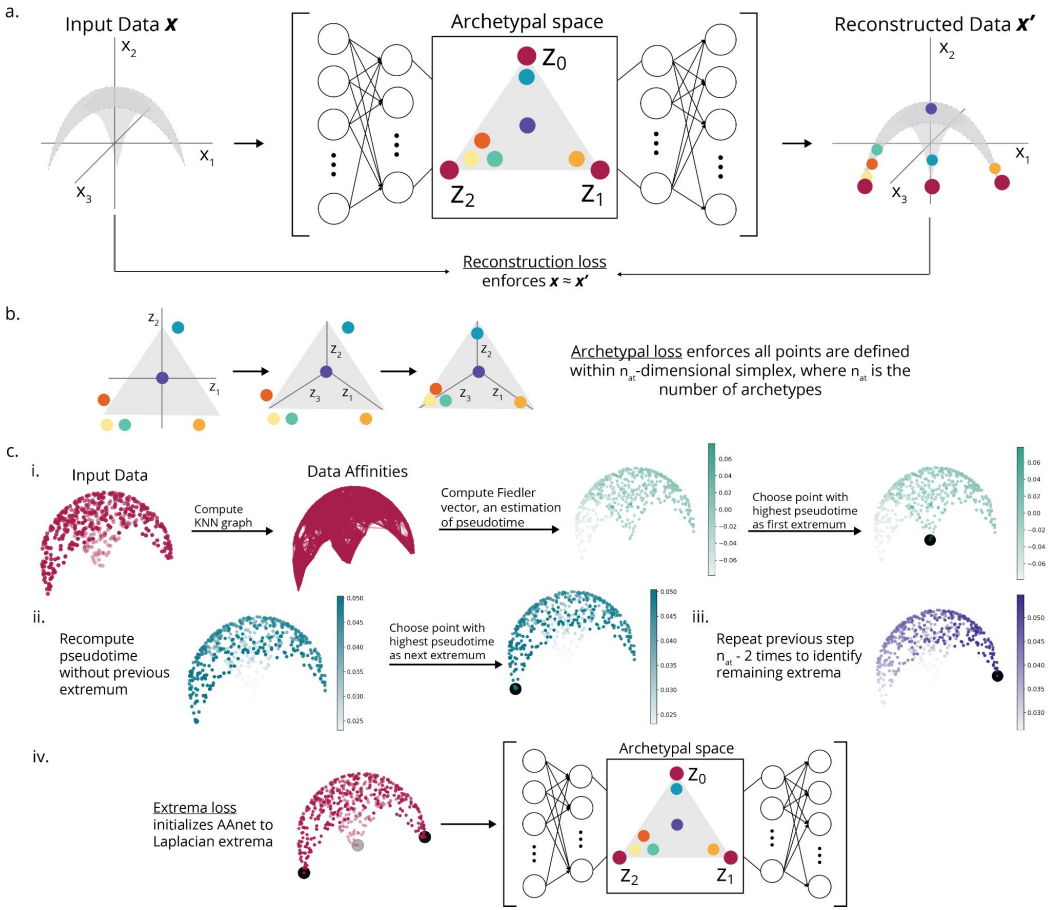


TrajectoryNet interpolates population flows between distant timepoints

Identify the cell-of-origin that gives rise to β cells mis-expressing hormones (CCK)



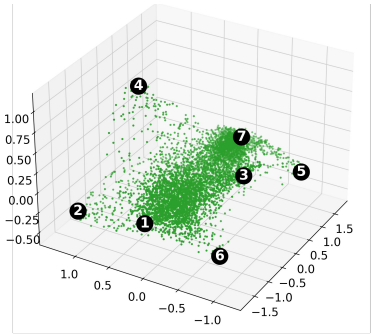
AAnet enables characterization of cells with respect to archetypes, or extreme states

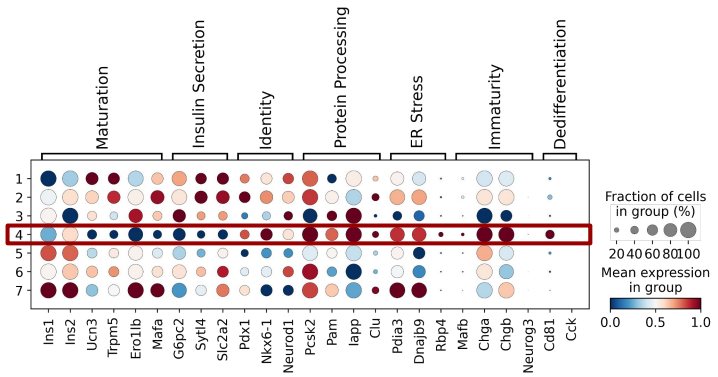


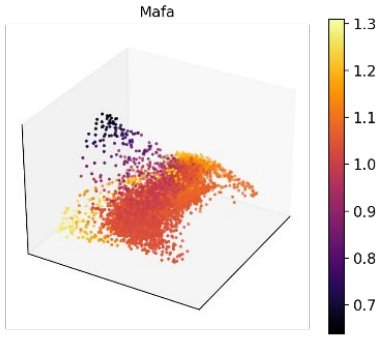
AAnet learns archetypes by transforming data into space bound by a simplex

AAnet learns archetypical β cell states within each condition

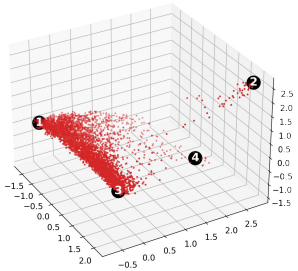
β cells of wildtype mice

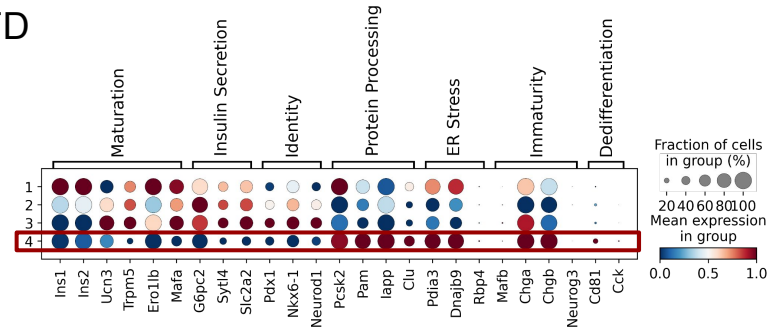


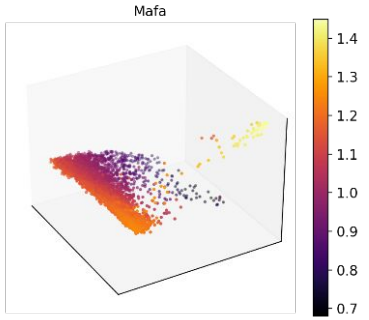




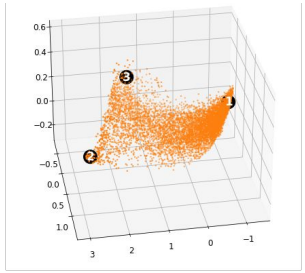
β cells of mice fed a HFD

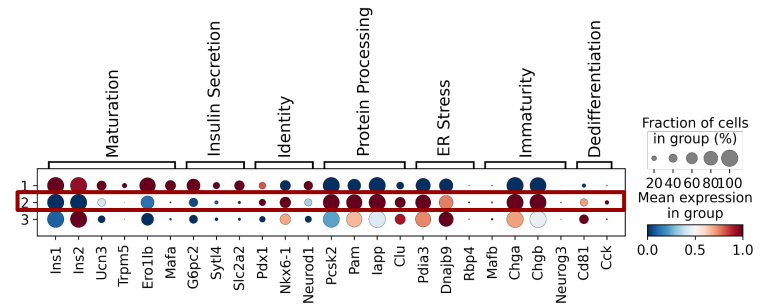


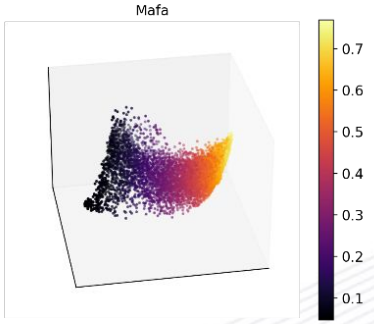




β cells of *Lep*$^{ob/ob}$ mice

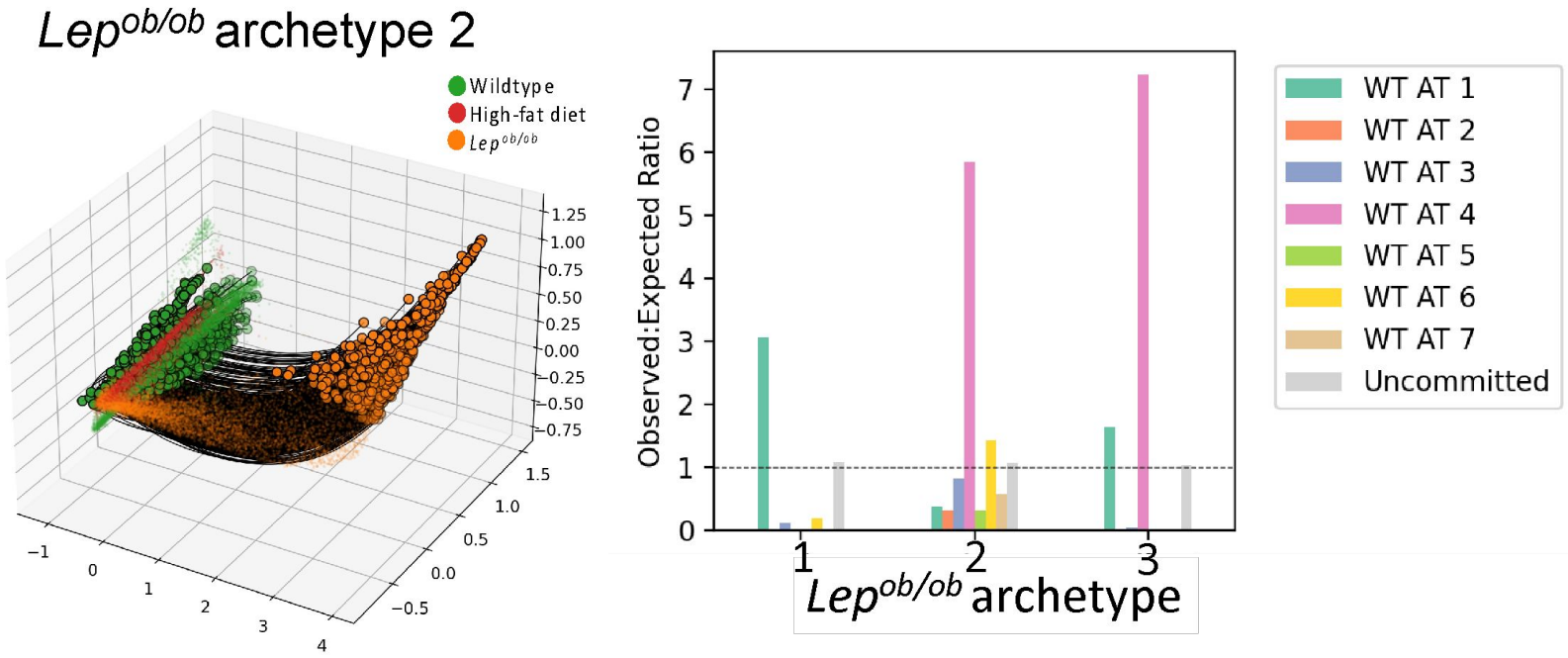


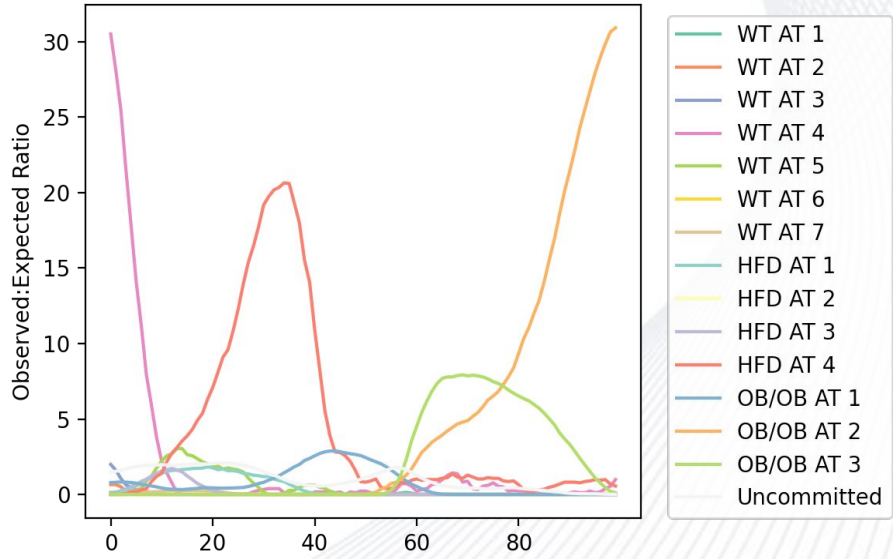




Each condition shows a β cell state characterized by low insulin secretion and high immaturity/stress

CCK+ cells arise from immature wildtype β cells (virgin β cells)

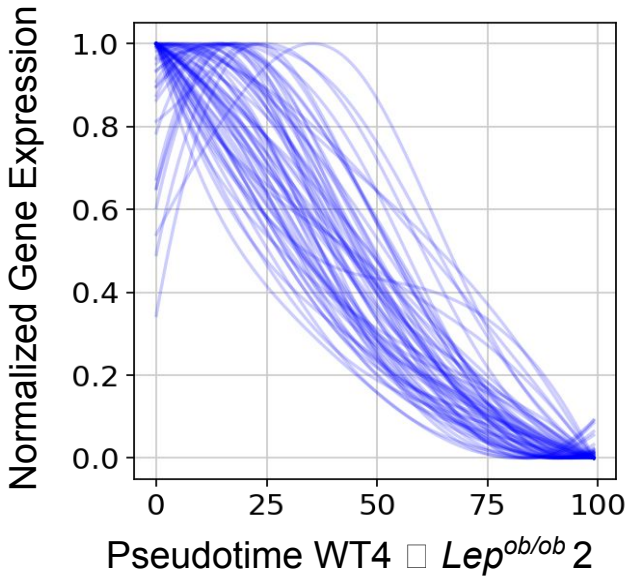


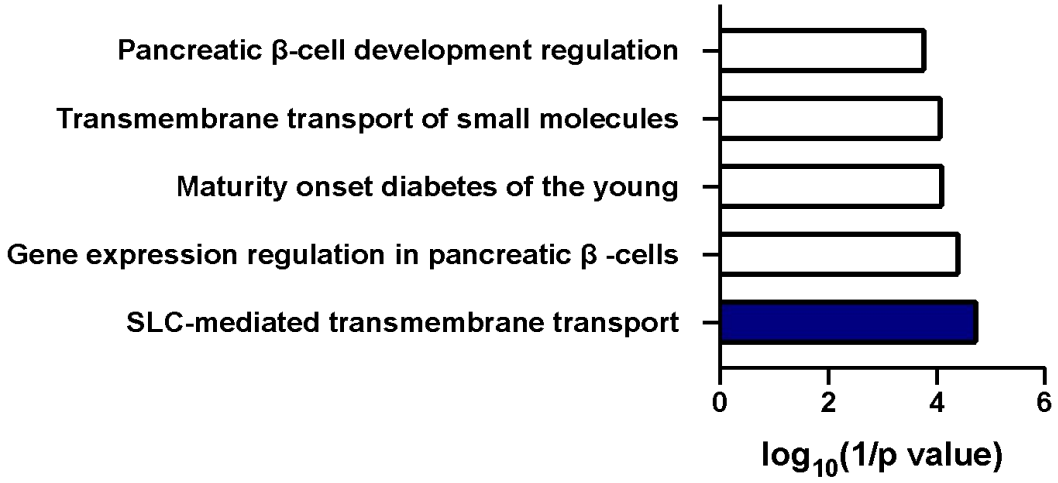


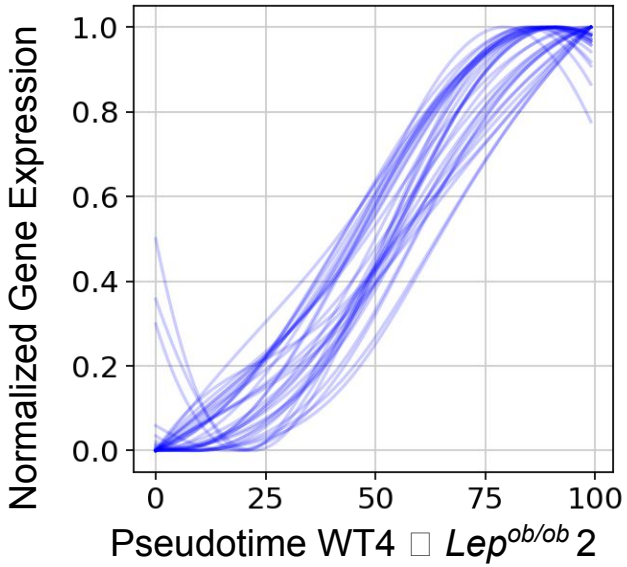
Lep$^{ob/ob}$ archetype 2 arises from wildtype archetype 4

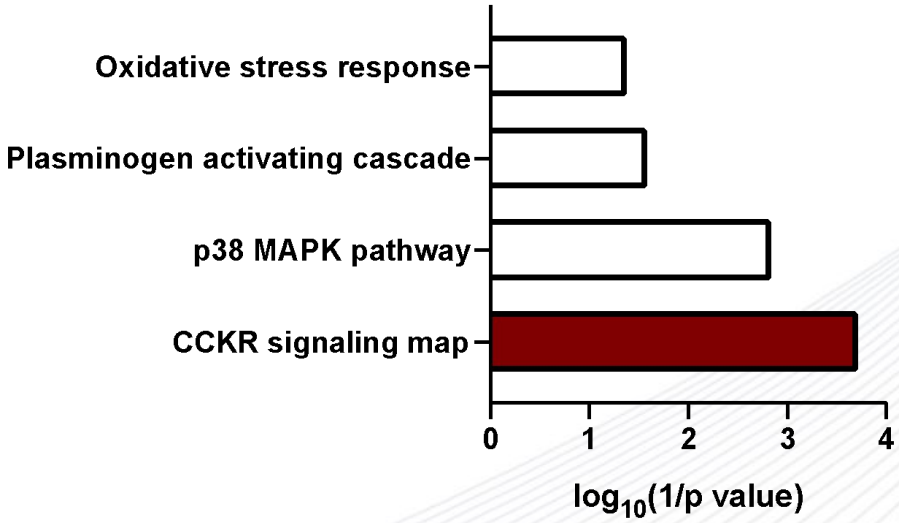
Wildtype AT4 → Highfat diet AT4 → *Lep*$^{ob/ob}$ AT2

Loss of β cell identity and increased stress response to obesity



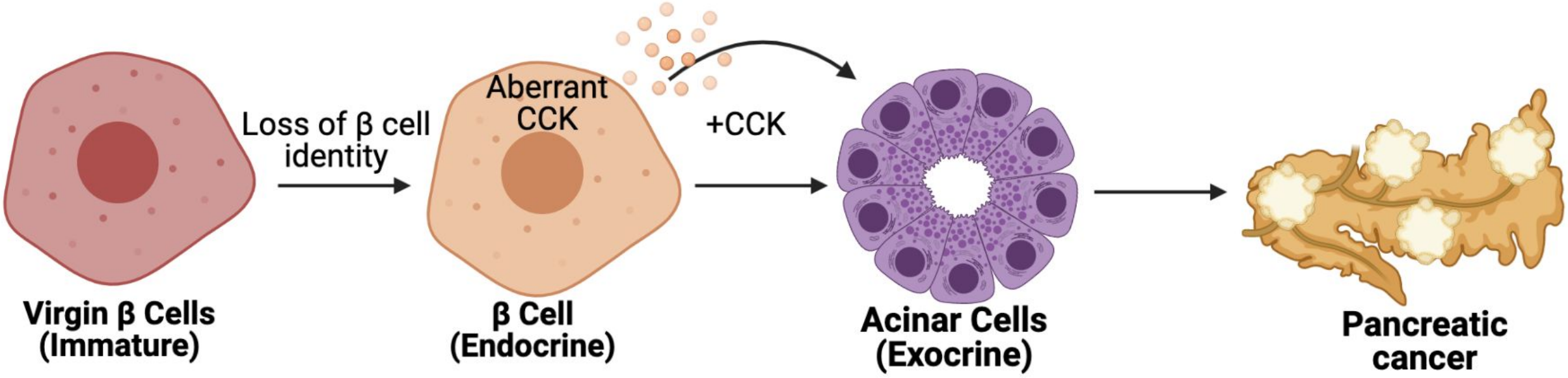






Unpublished with Smita Krishnaswamy (Yale)

Conclusions and Future Directions



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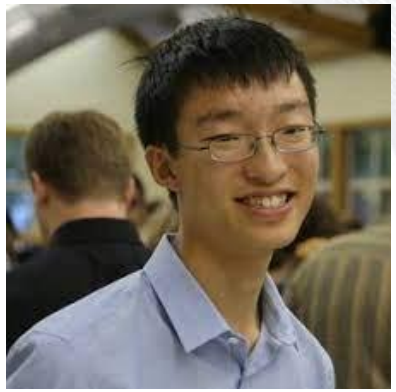

Krishnaswamy Lab
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Thesis Committee:
Smita Krishnaswamy
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