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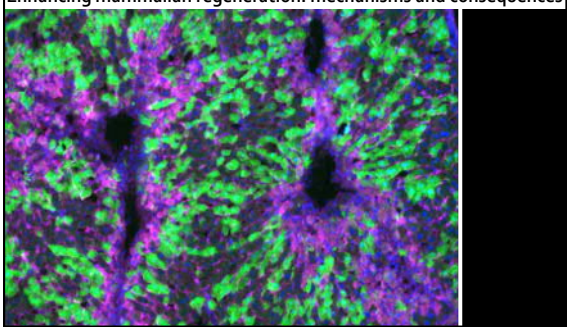
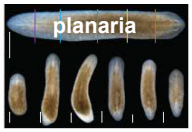
RESEARCH INSTITUTE
AT UT SOUTHWESTERN

Enhancing mammalian regeneration: mechanisms and consequences

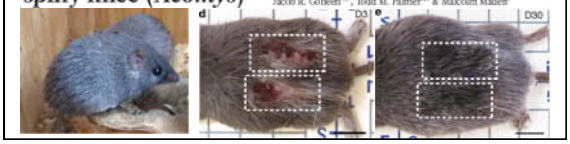


Animals have vastly different regenerative capabilities

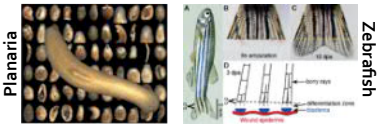


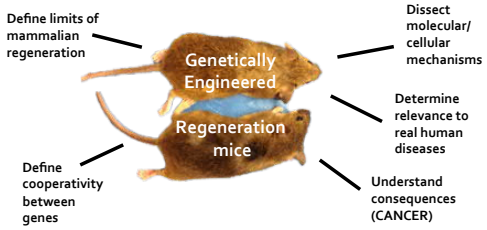
Skin shedding and tissue regeneration in African spiny mice (*Acomys*)

Ashley W. Seifert[1,2,3], Stephen G. Kiama[2], Megan G. Seifert[1,2], Jacob R. Goheen[3,4], Todd M. Palmer[2,3] & Malcolm Maden[2]

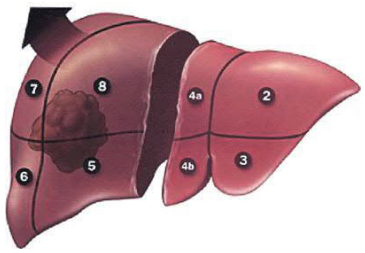


Genetic experiments in regenerative mammals



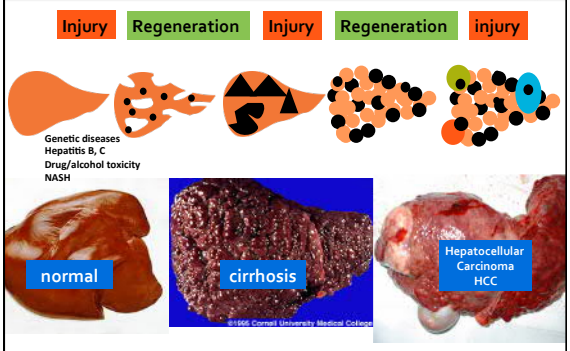


The liver is an exceptionally regenerative organ

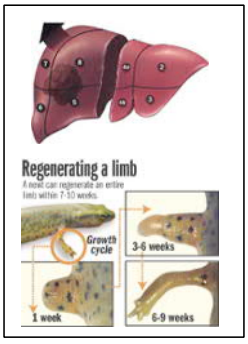


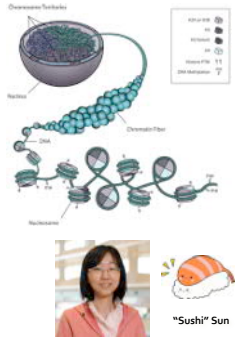
BUT even the liver has its limits

Chronic liver injury leads to cirrhosis and cancer



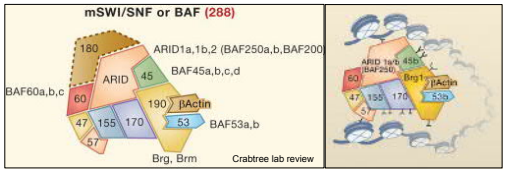
Is chromatin state plasticity a factor in regeneration?





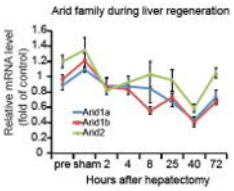
"Sushi" Sun

Do chromatin remodelers influence regeneration?

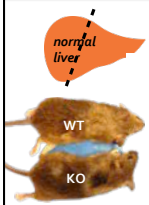


Arid1a turns on in aging liver

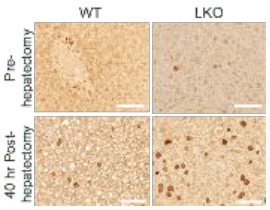
Arid family during liver regeneration

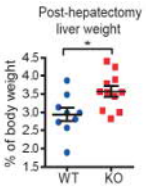


Mice without *Arid1a* have improved liver regeneration

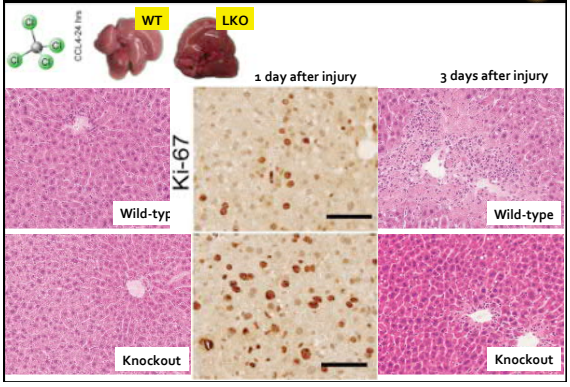


Ki-67+ proliferating cells

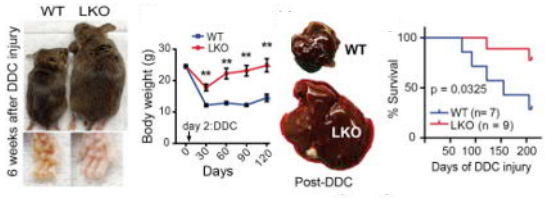




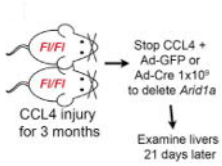
Arid1a deficient mice sustain less necrosis



Loss of *Arid1a* blocks biliary injury

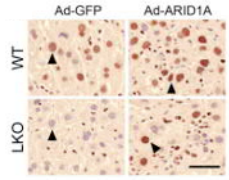


Improved regeneration occurs after equal levels of injury

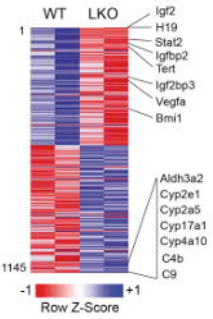


The same is true for hepatectomy and DDC injuries

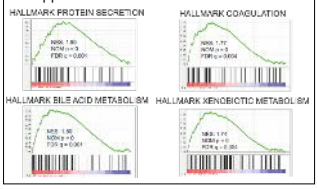
Human *ARID1A* overexpression blocks liver proliferation



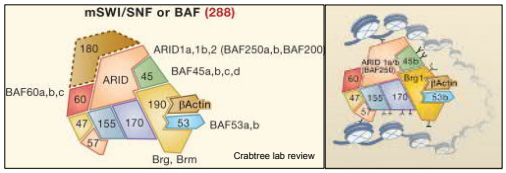
LKO livers show reduced maturation



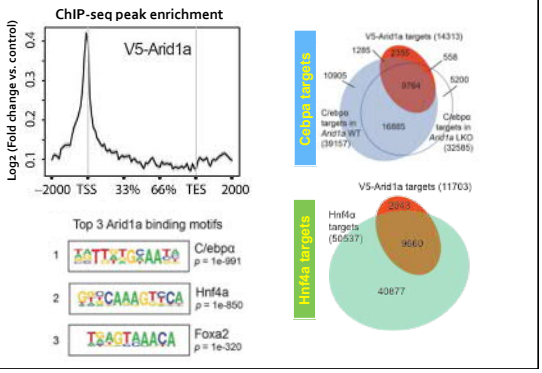
GSEA analysis of RNA-seq at baseline:
Increased differentiation in WT mice
Suppressed differentiation in LKO mice



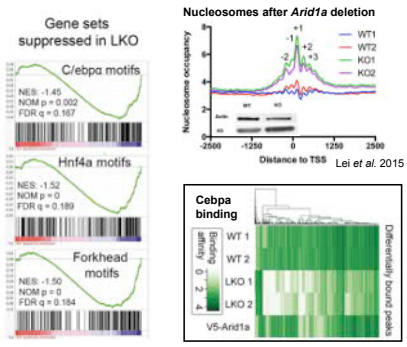
Do chromatin remodelers influence regeneration?



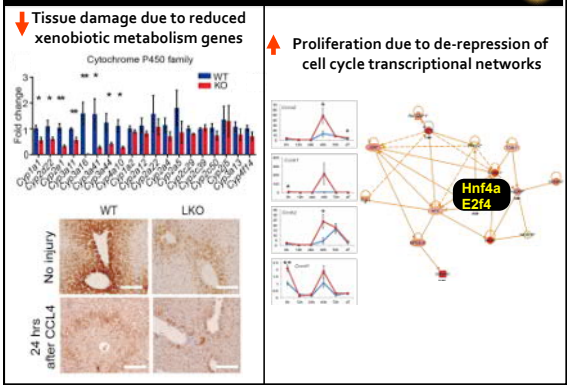
Arid1a is enriched on promoters of hepatic lineage genes



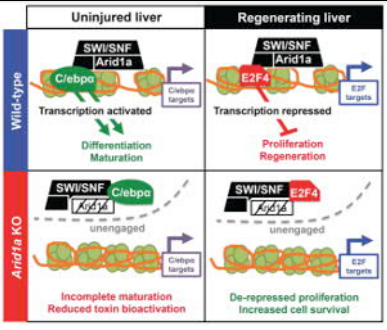
Arid1a loss restricts C/ebpa access



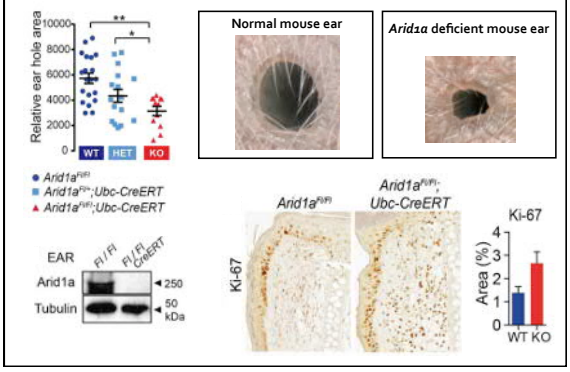
Dual transcriptional effects regulate injury/regeneration



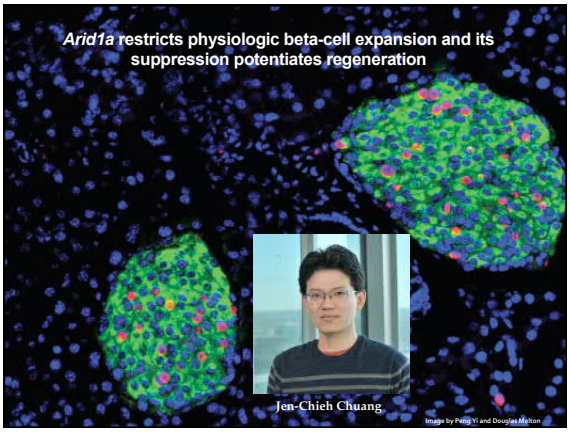
Working model



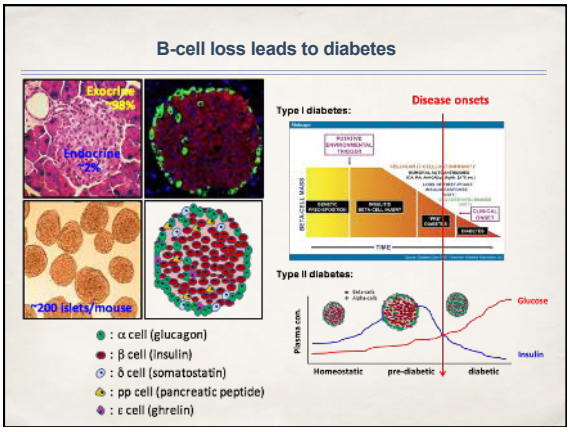
Arid1a has restricts tissue repair in other tissues



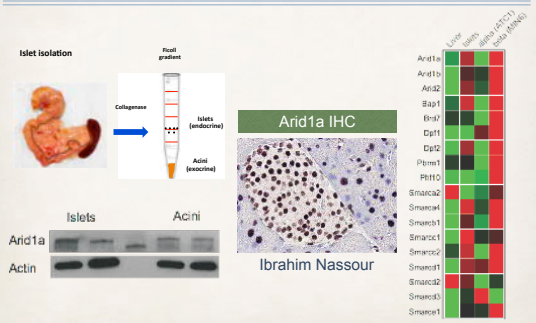
Arid1a restricts physiologic beta-cell expansion and its suppression potentiates regeneration



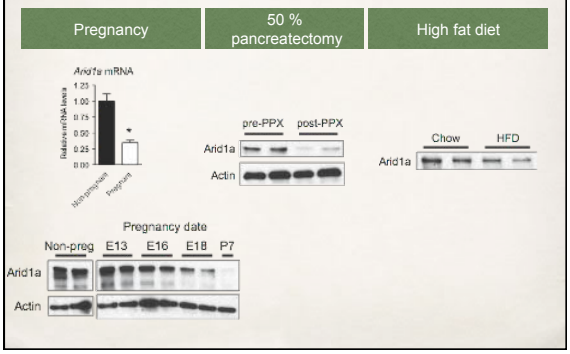
B-cell loss leads to diabetes



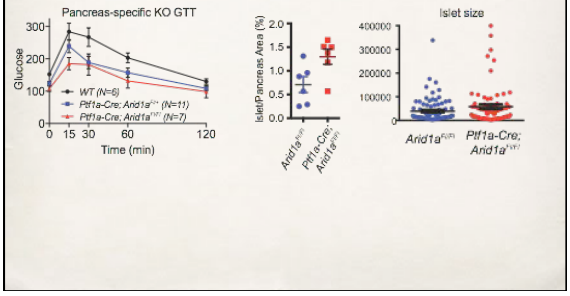
Arid1a is highly expressed in pancreatic islets



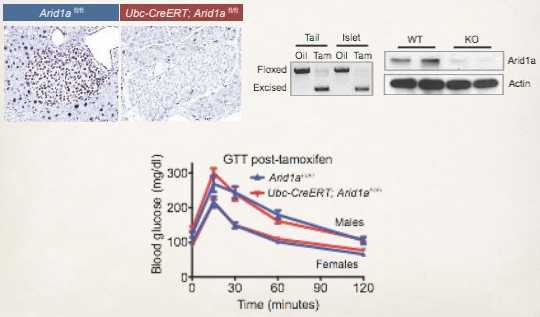
Arid1a is suppressed during physiological β-cell expansion



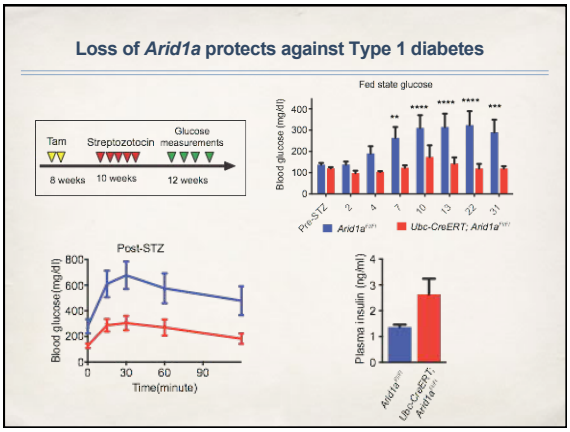
Arid1a deletion in whole pancreas leads to β-cell expansion during development



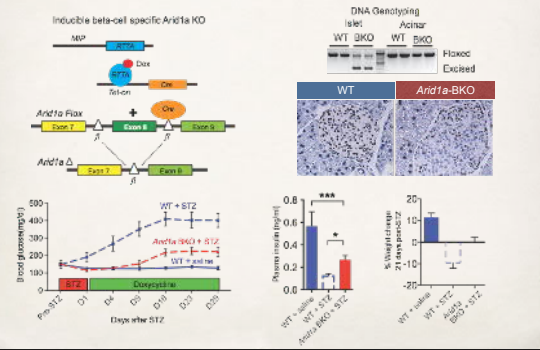
Global adult deletion of *Arid1a* does not affect β-cell mass or glucose clearance at basal state



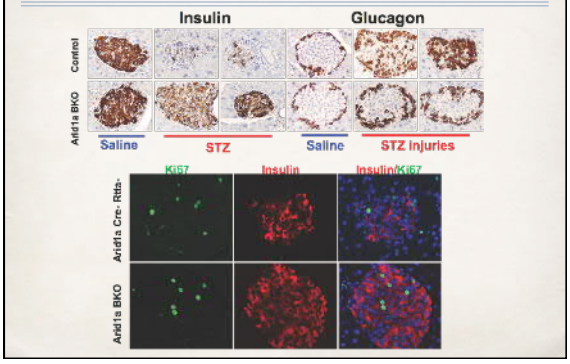
Loss of *Arid1a* protects against Type 1 diabetes



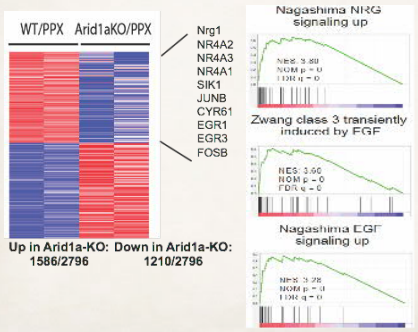
!-cell specific *Arid1a* deletion *after* STZ could reduce the development of diabetes, modeling a therapeutic approach



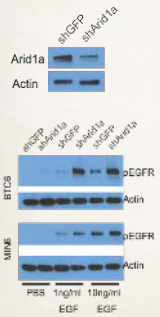
Arid1a loss mediates increased proliferation in !-cells



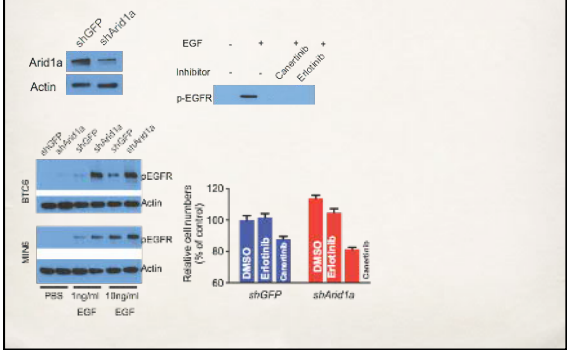
Islet transcriptome reveals increase NRG/EGF signaling in *Arid1a* KO



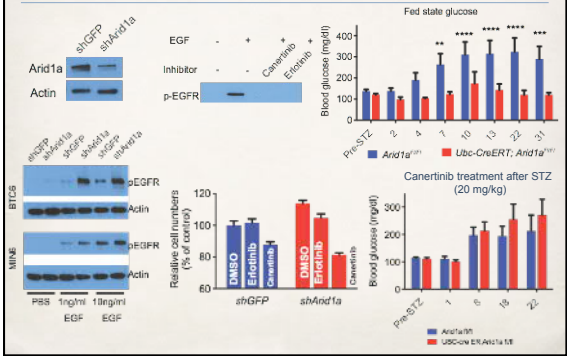
Arid1a deficient !-cells are more sensitive to EGF



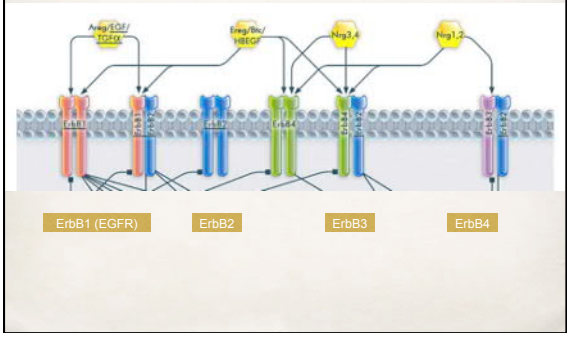
EGFR inhibition abrogates increase in proliferation and receptor phosphorylation after *Arid1a* KD in !-cell lines



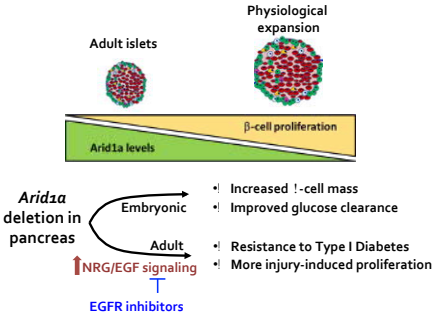
EGFR inhibition in vivo abolishes anti-diabetic effect of *Arid1a* loss



ErbB family of receptors



Arid1a is a regulator of β-cell homeostasis and may uncover a new pathway for β-cell regeneration



Conclusions

1. Regeneration can be improved through changes in single genes.
2. *Arid1a* loss leads to increased regenerative capacity in multiple tissues.
3. Using these models, determine how regenerative capacity impacts organ function, aging, and cancer.

Acknowledgements

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