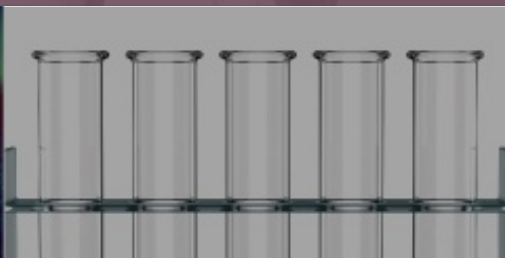




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at Scripps Research

The Hunt for Regenerative Medicines

Michael J. Bollong, PhD
Department of Chemistry
Scripps Research

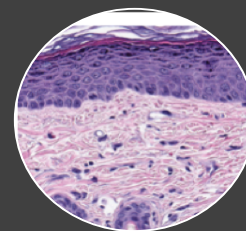
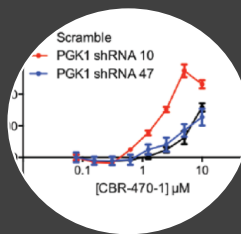
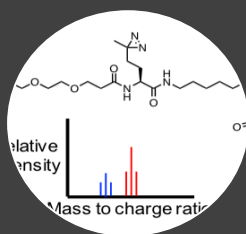
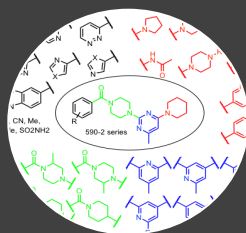


Outline

- Introduction to chemical genetics and induced proliferation
- A therapeutic drug candidate that promotes lung regeneration
- Manipulating organ size control pathway for regenerative repair
 - Chronic wounds
 - Heart failure



A chemical genetics-based approach to biological discovery



Cell-based, high throughput small molecule screening

Medicinal chemistry

MS-enabled target identification

Mechanism of action studies

Proof of concept rodent studies

Therapeutic lead molecules

 **Calibr**
at Scripps Research

New biological insights

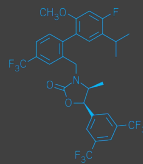
 **Scripps Research**
Chemistry



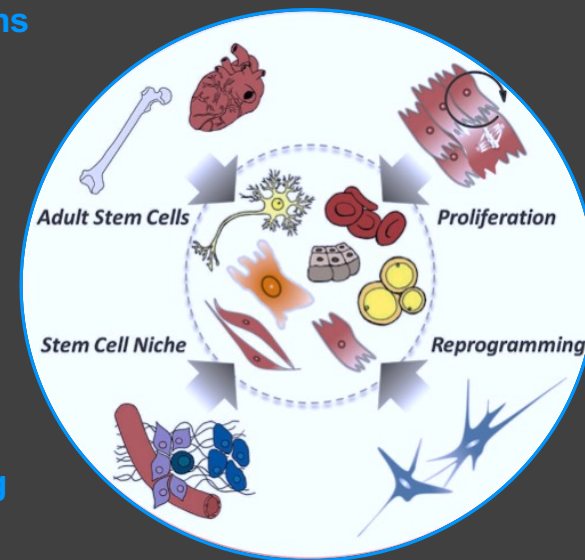
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Small molecule drugs for regenerative medicine

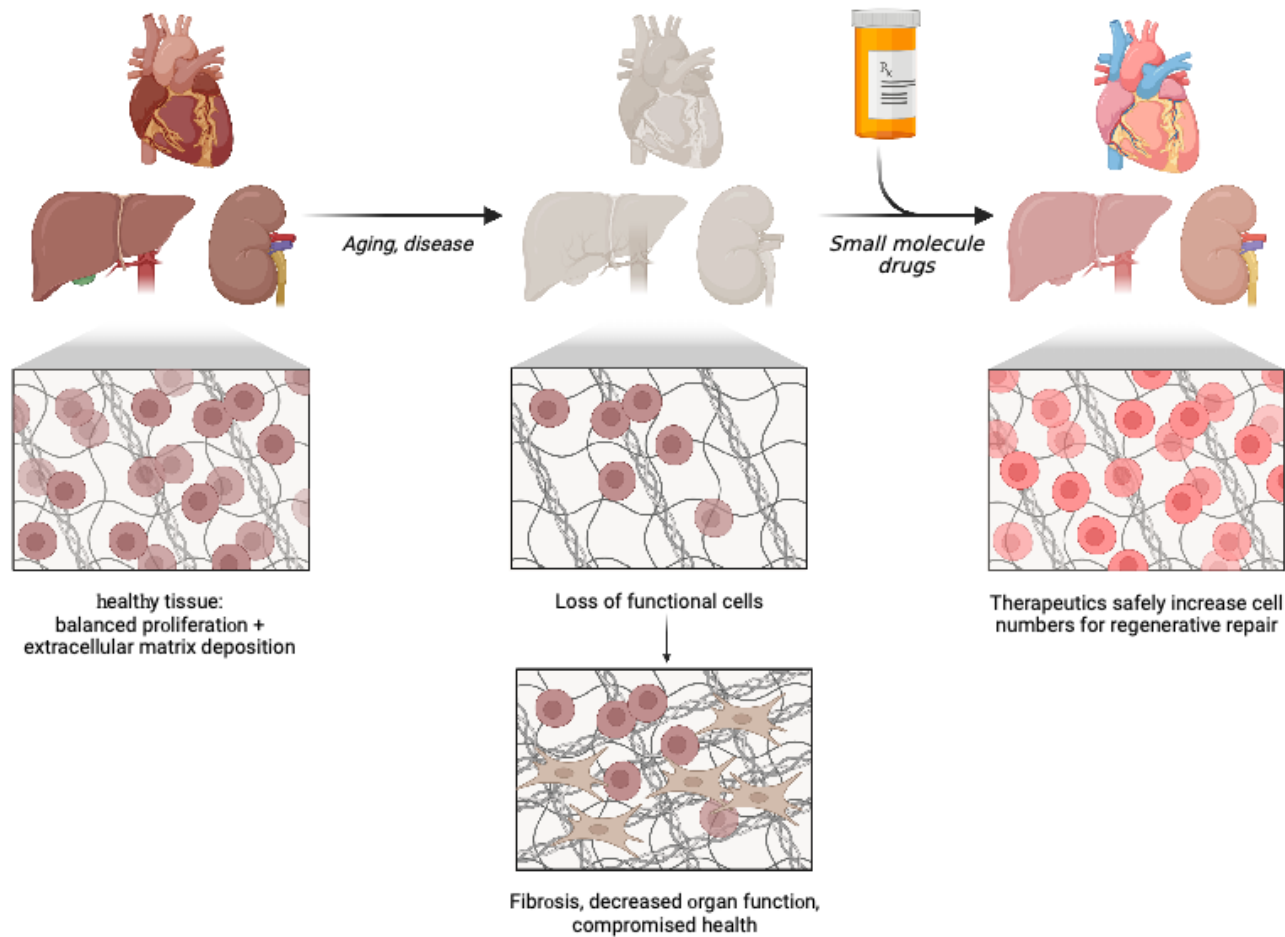
Small molecules identified by phenotypic chemical screens



Induced proliferation, differentiation, remodeling



Regenerative organ repair requires cellular proliferation



Outline

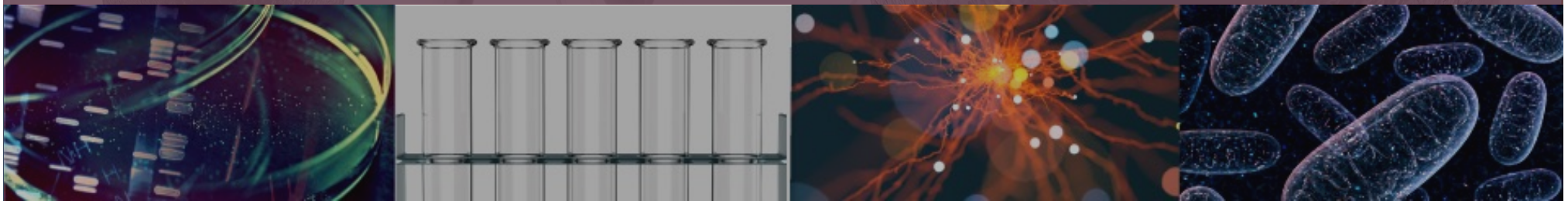
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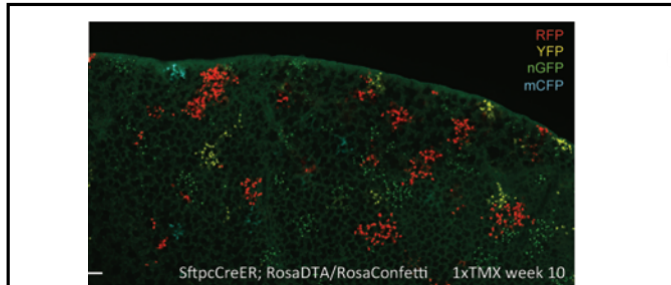
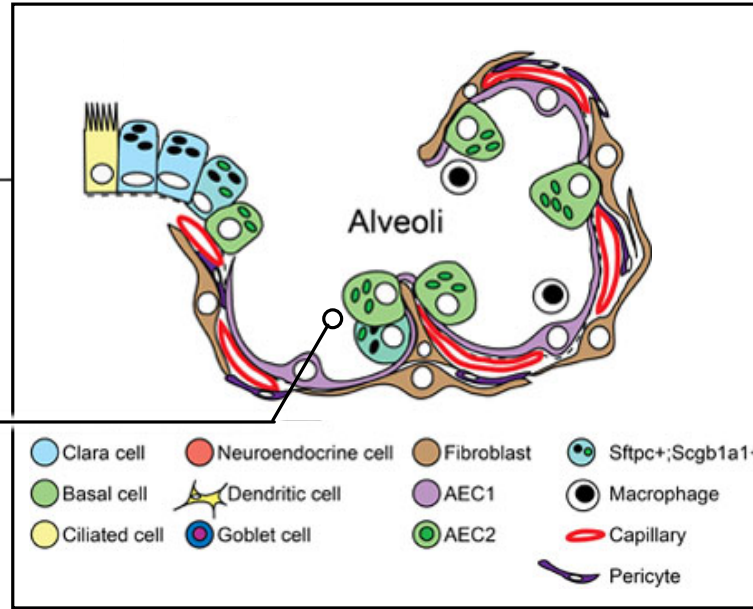
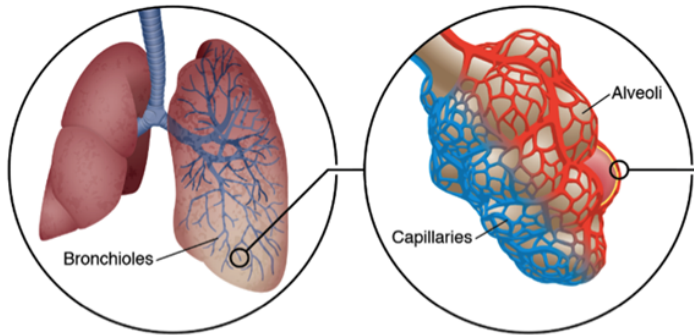


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Regeneration of the lower airway



AEC2s are the stem cells of the lower airway



AEC2 – <10% area, 60% of total cells, cuboidal, surfactant production, source of AEC1 cells

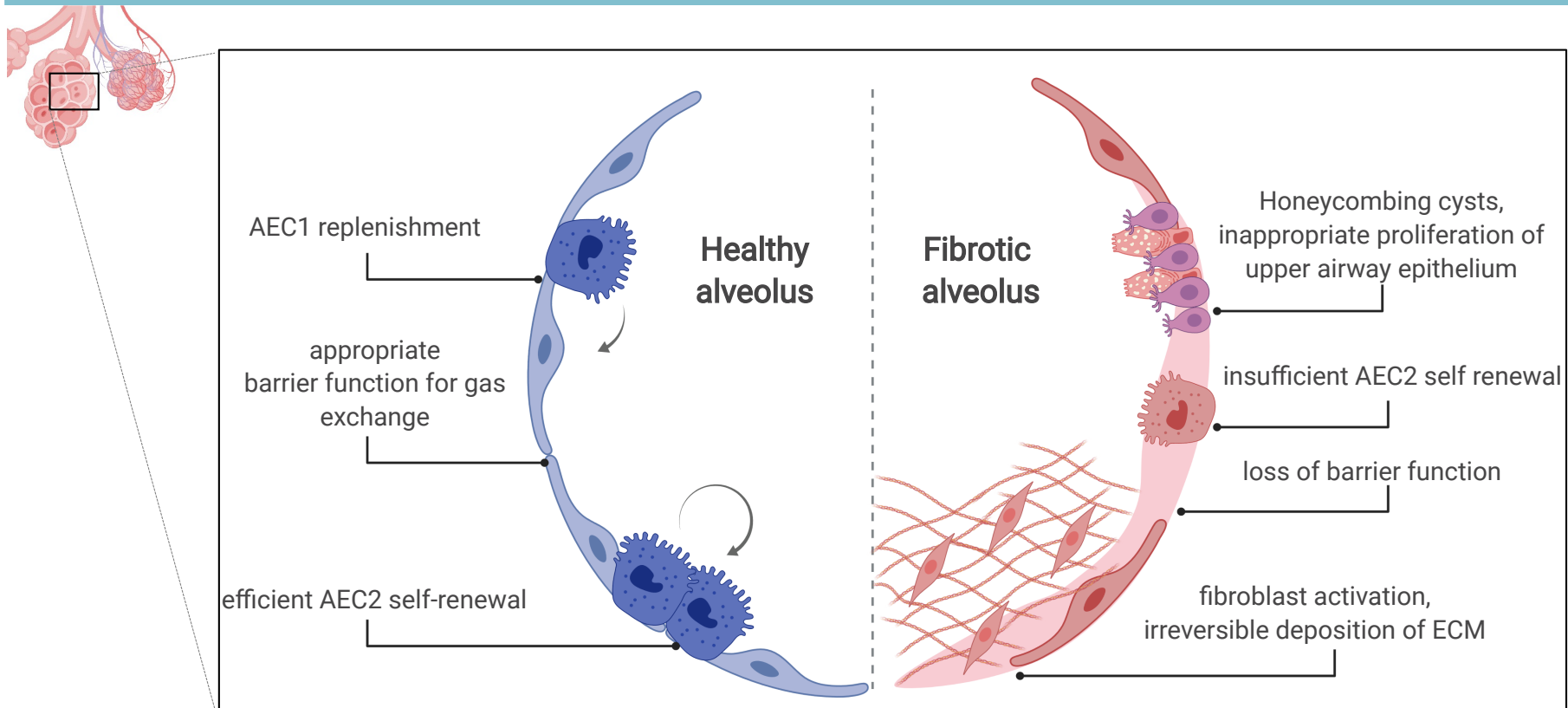
AEC1 – >90% area, gas exchange

AEC2s are stem/progenitors of the lower airway

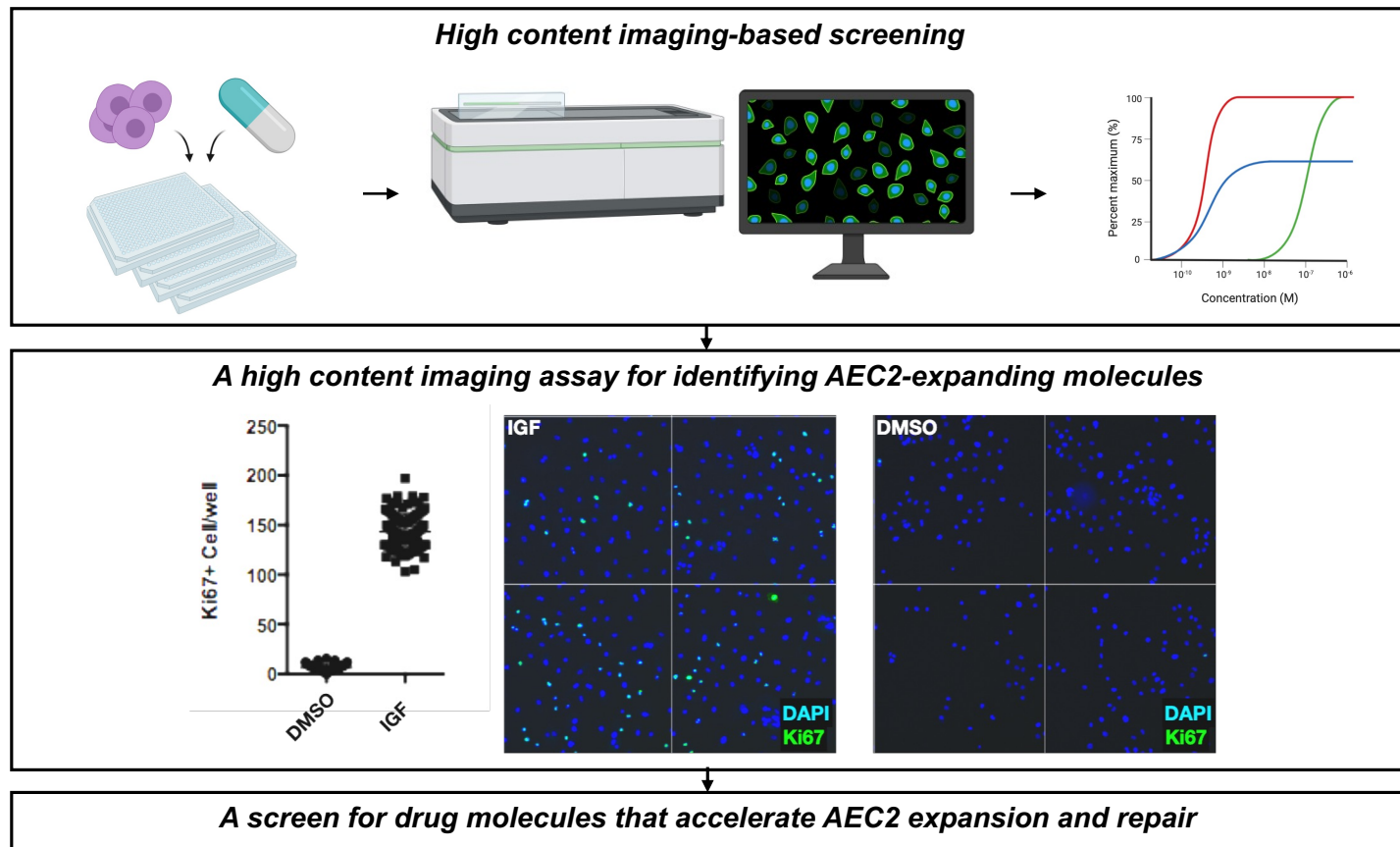
- Clonal proliferation after partial genetic ablation
- 3D clonal growth and differentiation *in vitro*



Ineffective AEC2 proliferation and differentiation is causative of Idiopathic Pulmonary Fibrosis (IPF)



Screening for small molecules that expand lung stem cells



DPP4 inhibitors are widely used medications for T2D



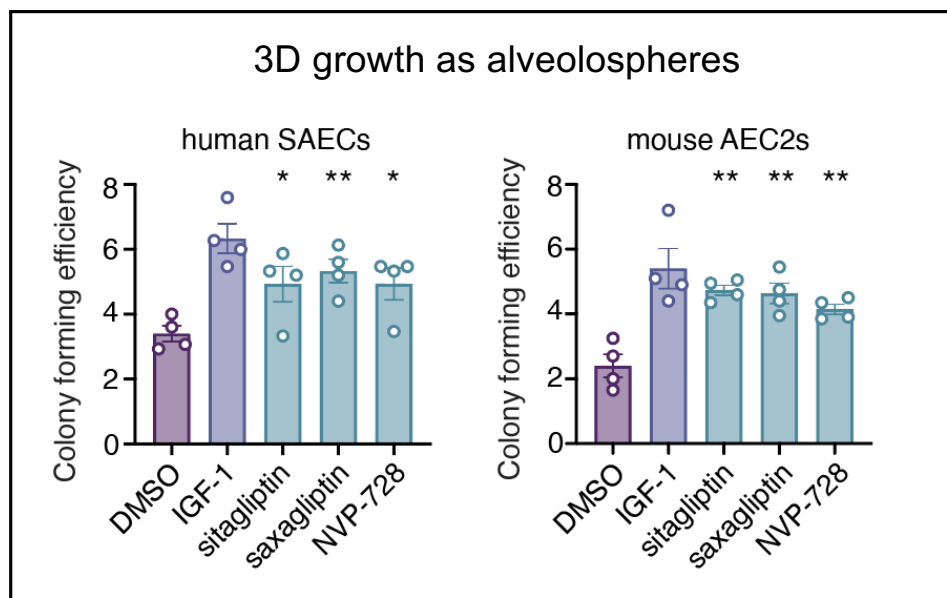
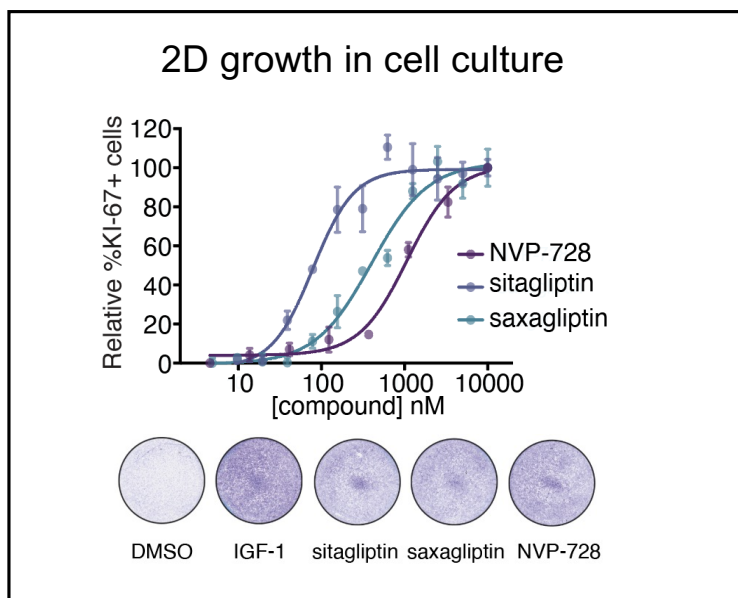
8.9M prescriptions in USA

Dipeptidyl peptidase-4 (DPP4) inhibitors

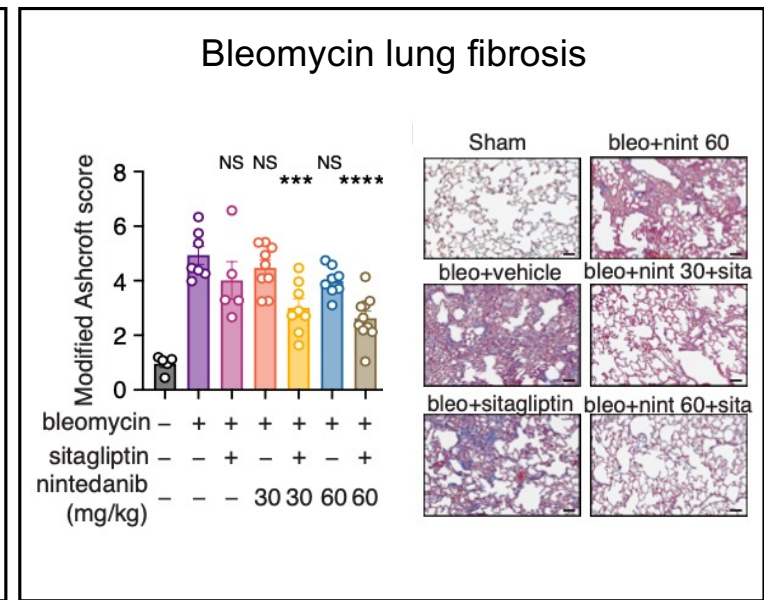
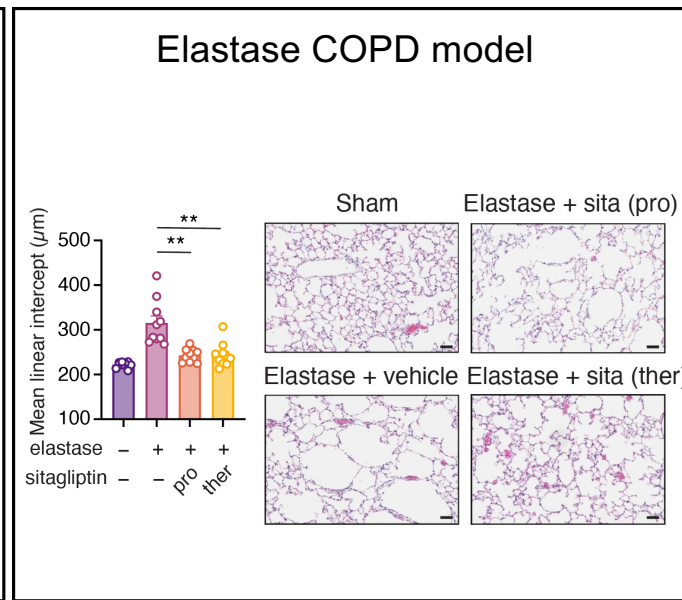
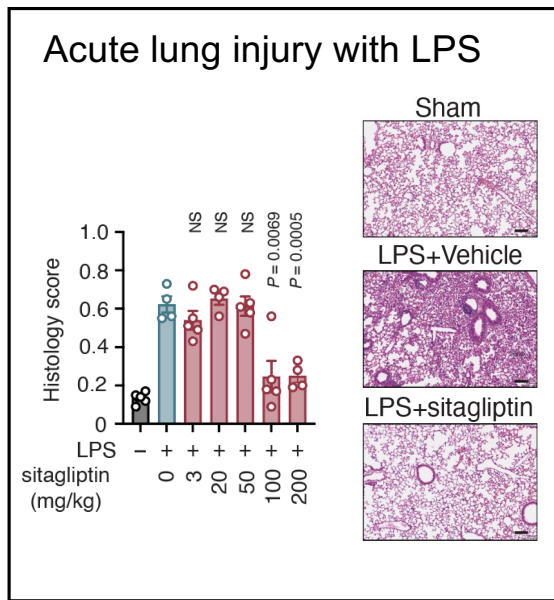
- Increase incretin hormone levels to control blood glucose in Type 2 Diabetes
- Front line T2D medication (>0.4 Billion patients worldwide)
- 4 FDA approved 'gliptins': Januvia (Sitagliptin), Onglyza (Saxagliptin), Tradjenta (Linagliptin), and Nesina (Alogliptin)
- Very widely used; millions of patients in USA
- Minimal adverse effects



DPP4 inhibitors expand AEC2s in cell culture

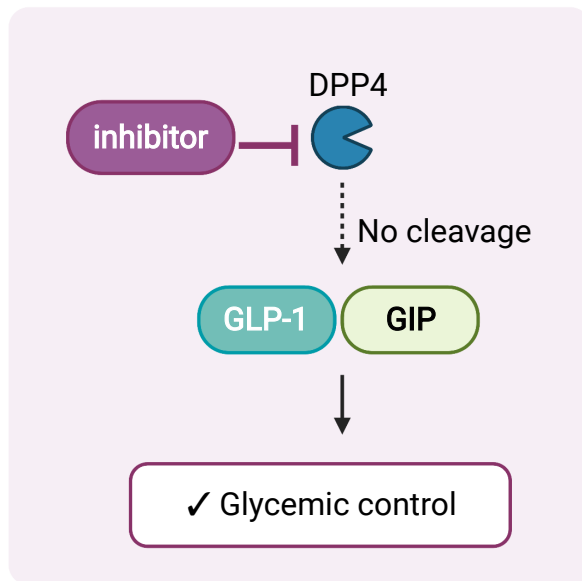


High dose Sitagliptin inhibits lung disease in mouse

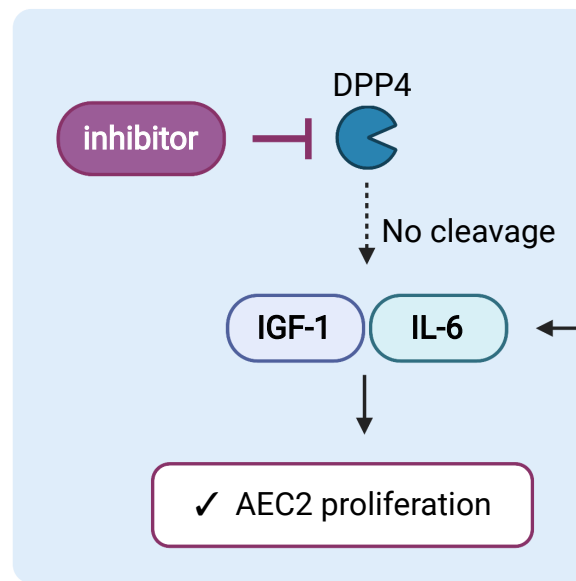


A different set of factors are degraded by DPP4 in the lung

Anti-diabetic effect



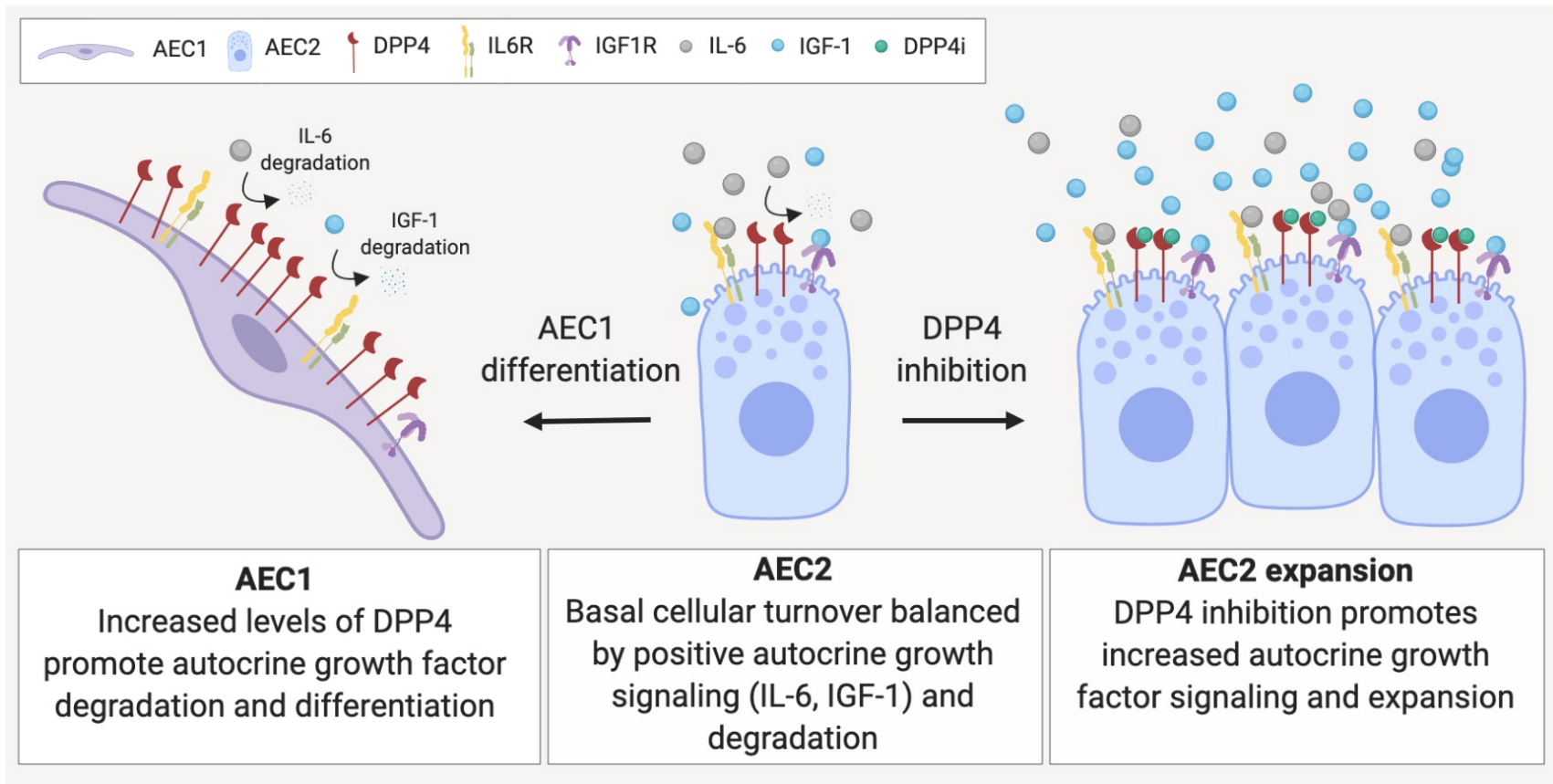
AEC2 expansion effect



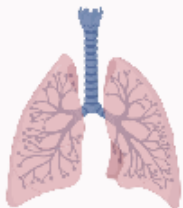
Different substrates degraded by DPP4 in the lung



DPP4 tunes the availability of growth factors to control AEC2 expansion



Why can't we directly repurpose gliptins for treating lung disease?



Problem

- DPP4 activity in the lung compartment is critical
- 5-20x the approved clinical dose to achieve therapeutic drug exposure in lung

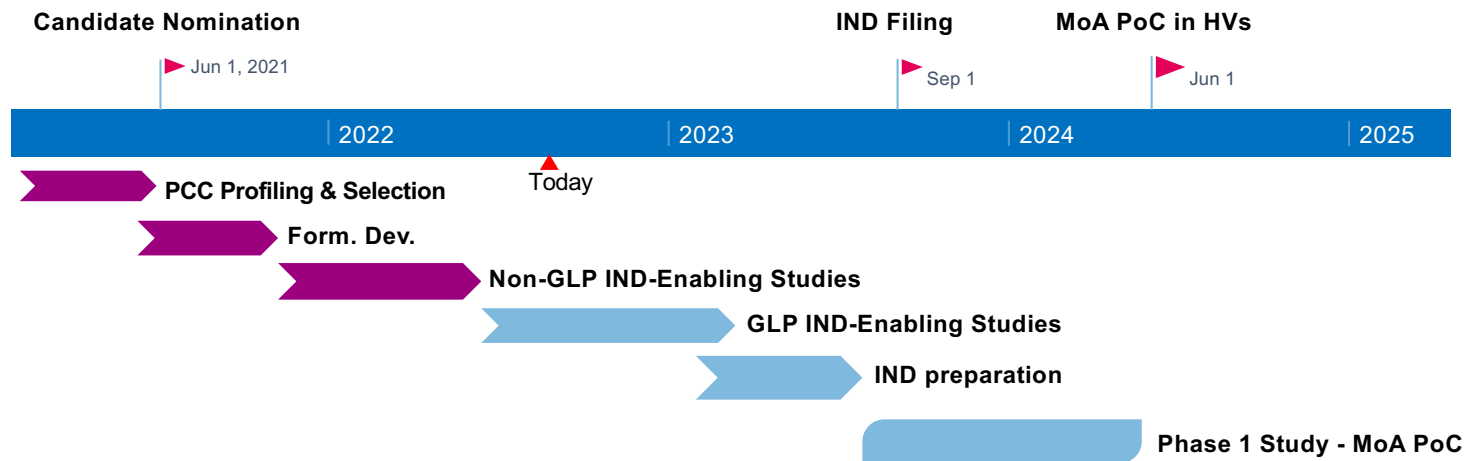


Solution

- Direct delivery of a lung retained molecule for continuous drug exposure at the site of action
- >10x less drug required
- Very minimal peripheral exposure
- Once weekly dosing; < 10 m nebulization



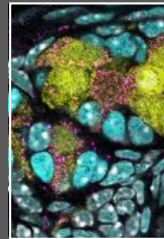
Timeline to the clinic



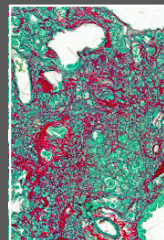
Impact



The only regenerative approach to treating lung disease



Augmenting the body's endogenous repair capacity through a safe repurposing mechanism



Potential therapies for other lung diseases: COVID 19, COPD



Outline

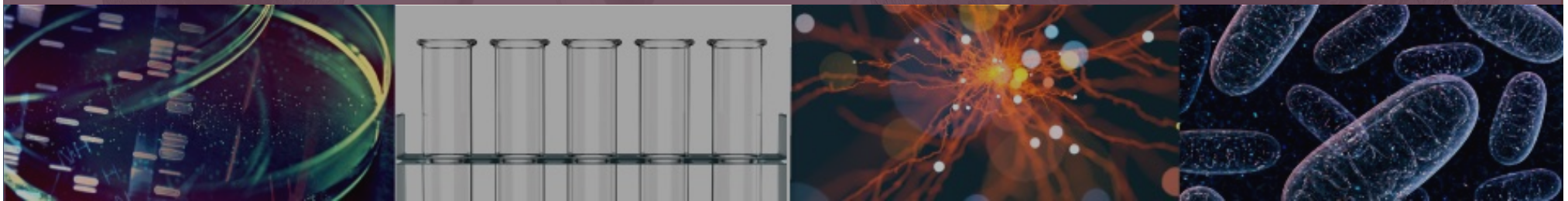
- Introduction to chemical genetics and induced proliferation
- A therapeutic drug candidate that promotes lung regeneration
- **Manipulating organ size control pathway for regenerative repair**
 - Chronic wounds
 - Heart failure





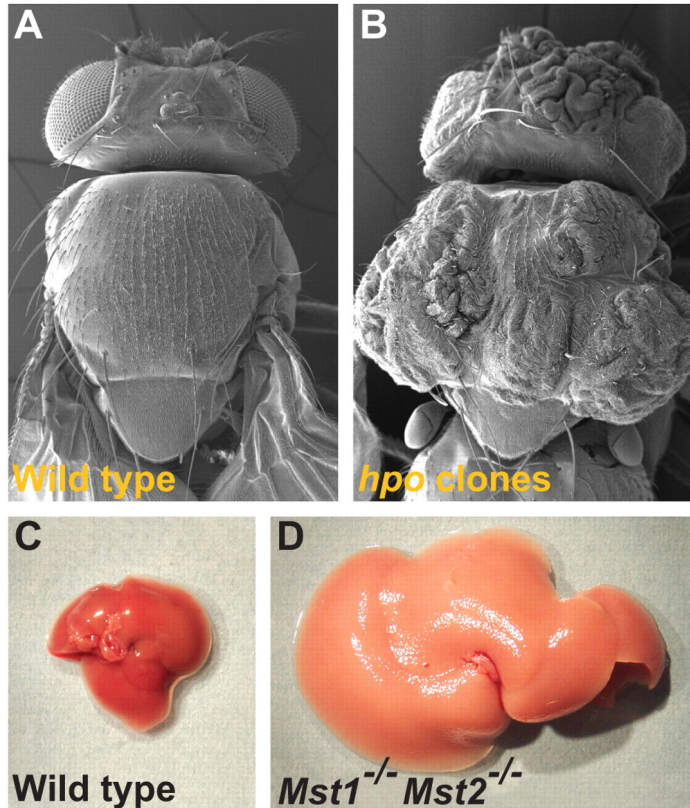
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Manipulating organ size control pathways for regenerative repair

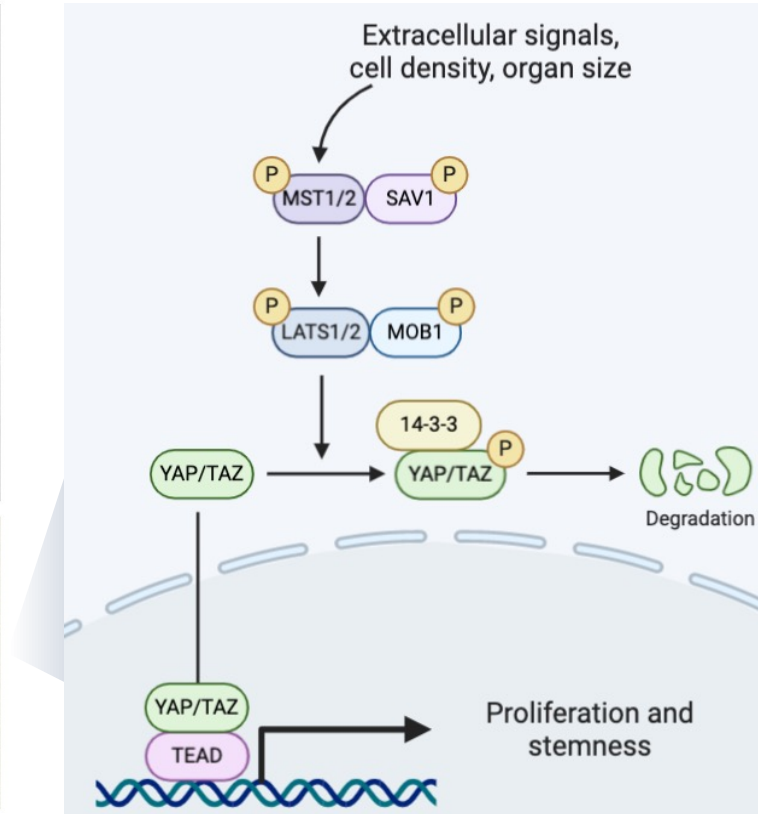


The Hippo-YAP pathway controls organ size in animals

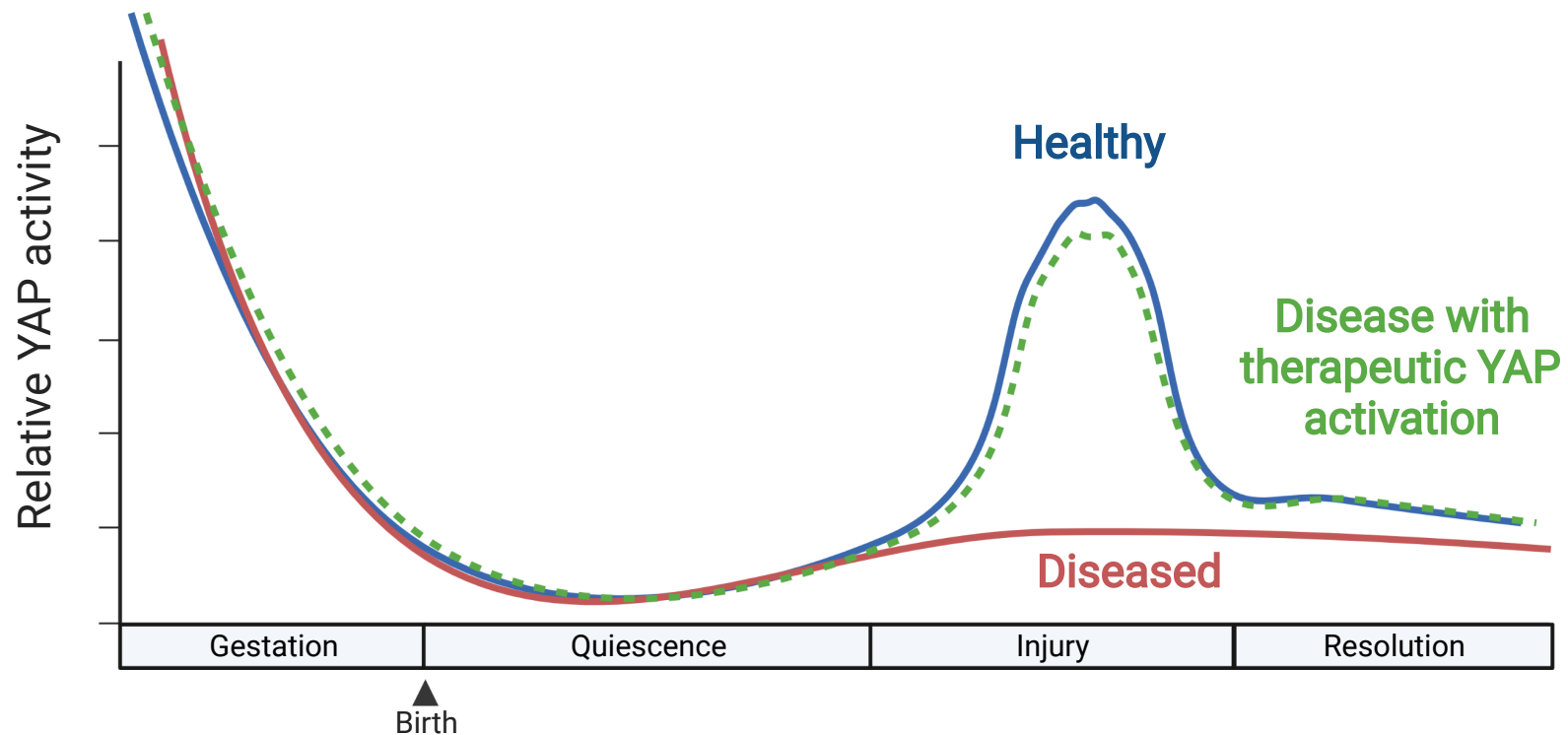
A conserved pathway controls organ size



Molecular logic of Hippo signaling

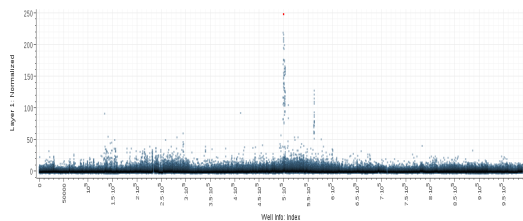
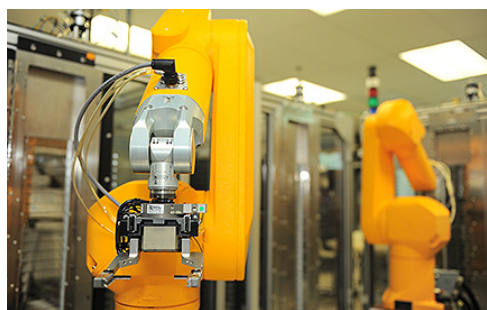


YAP is transiently activated for normal repair and regeneration

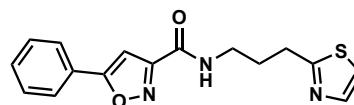


Identifying small molecules that activate YAP

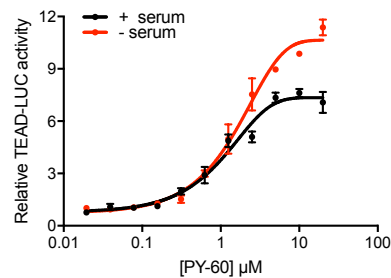
Testing >700k compounds



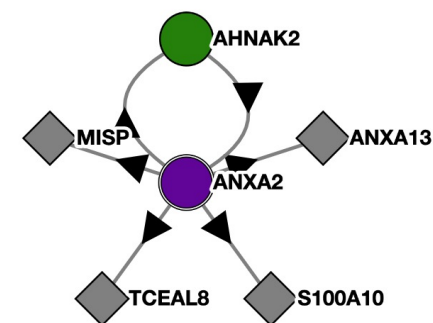
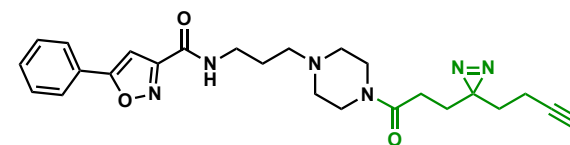
Identification of small molecule activator of YAP



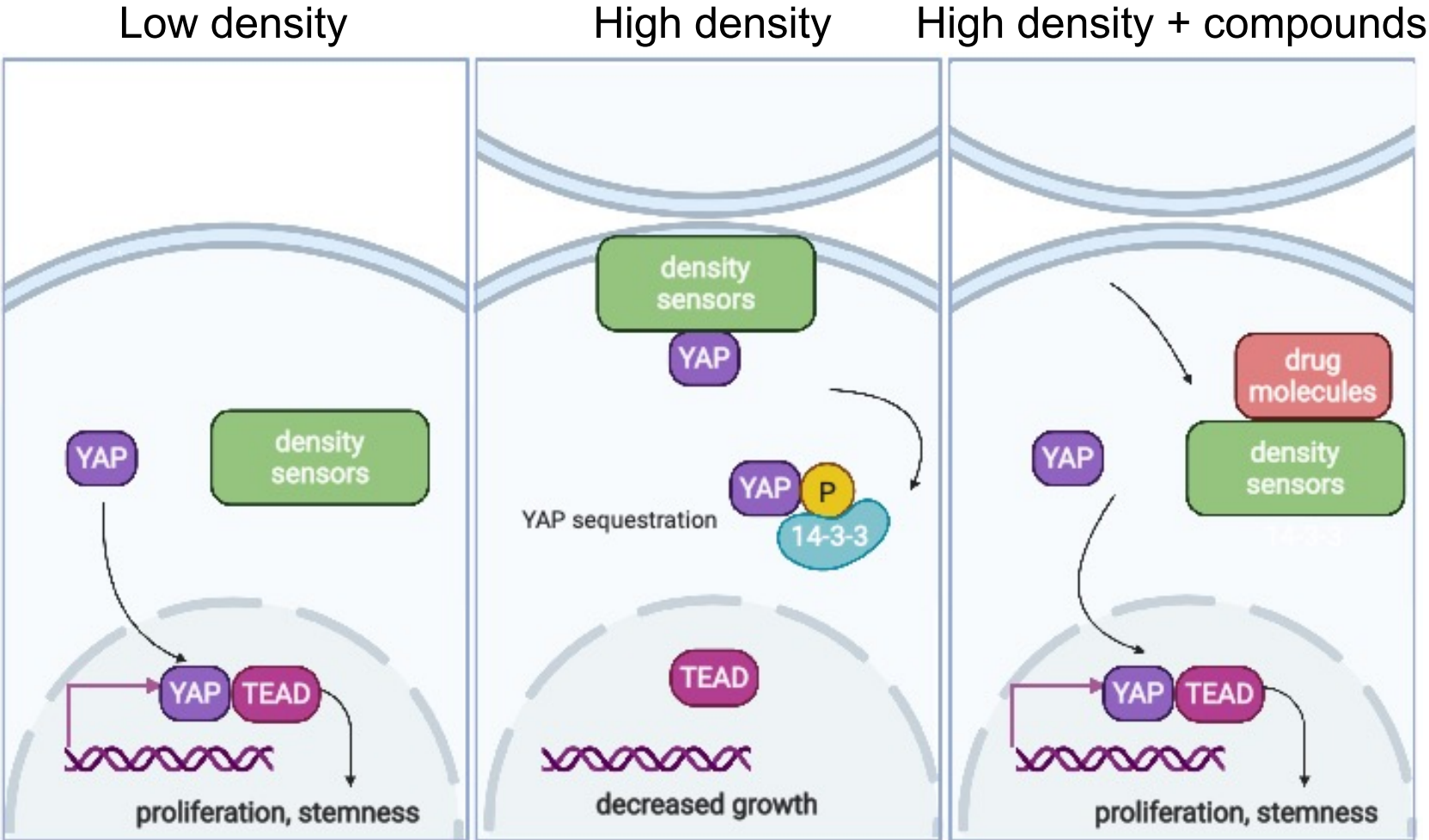
PY-60



Mechanism deconvolution



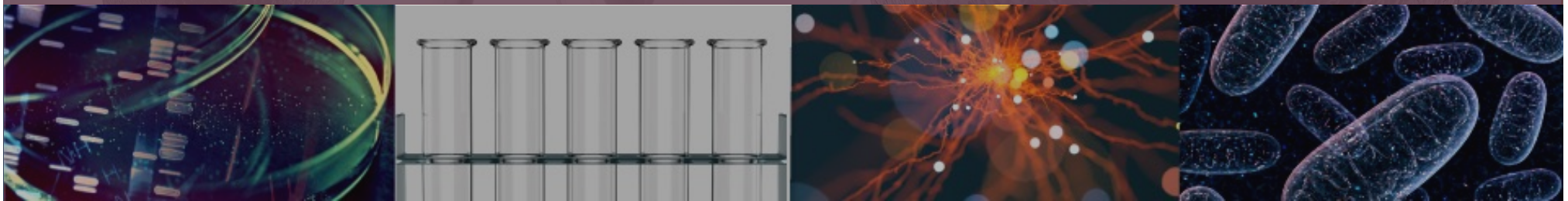
Compounds target density sensing machinery of cells



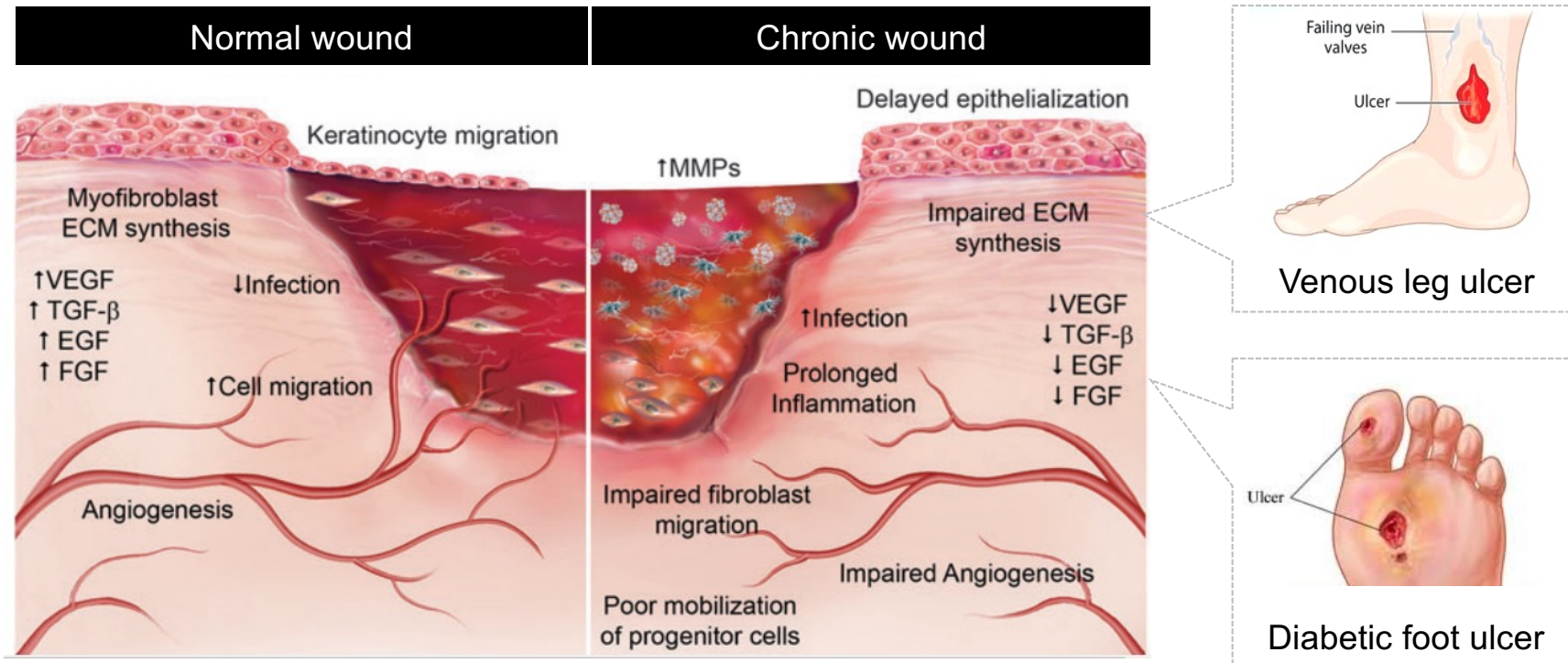


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Activating YAP for healing chronic wounds



Chronic wounds: an unmet medical need driven by insufficient tissue repair



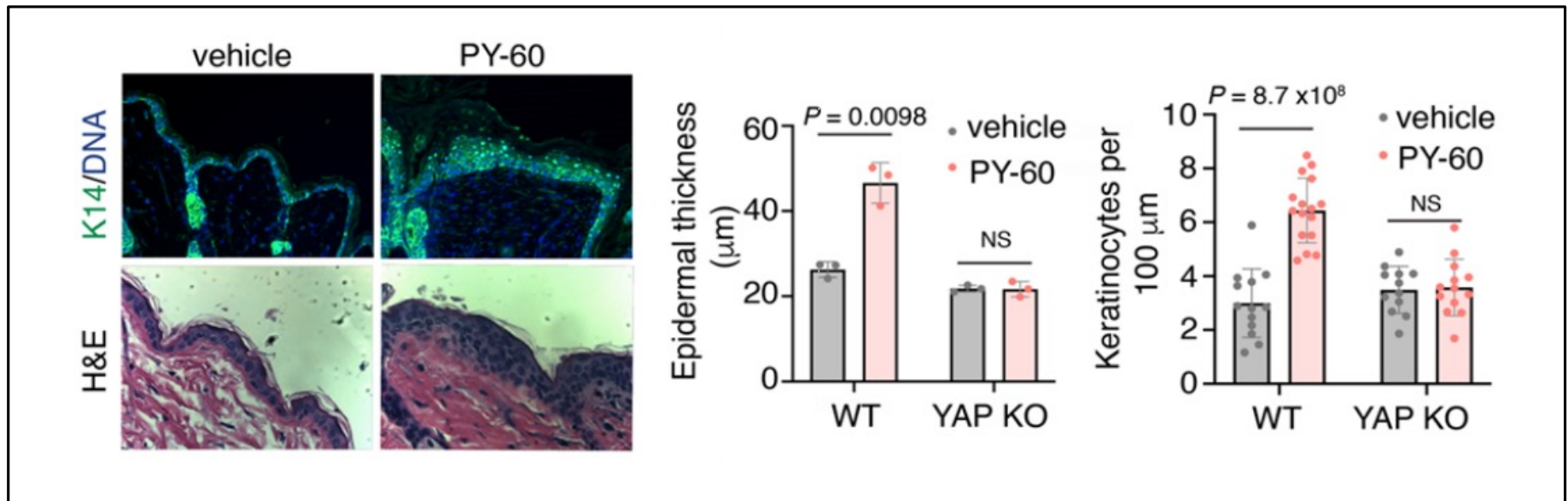
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PMID: 28614678



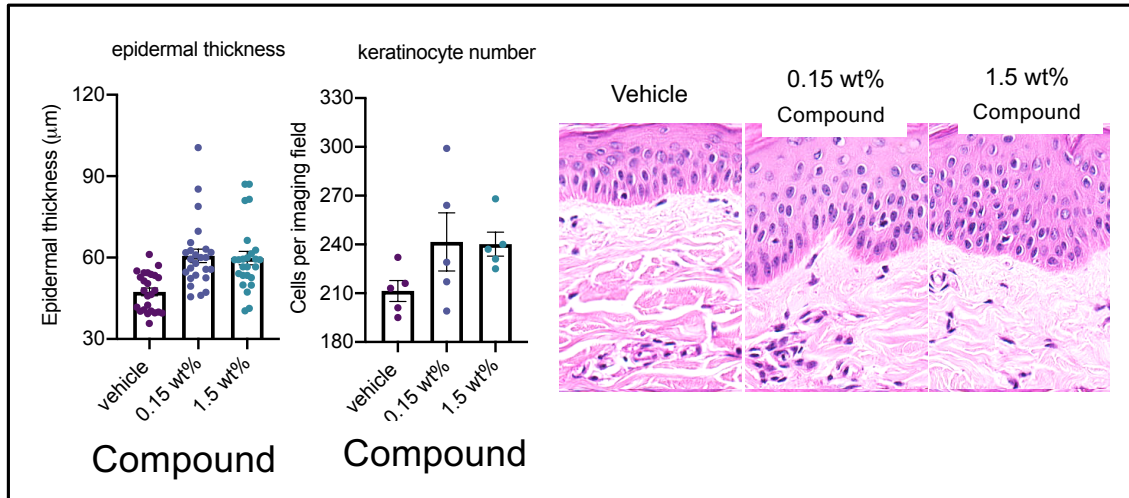
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Topical PY-60 treatment promotes YAP dependent keratinocyte expansion in the mouse

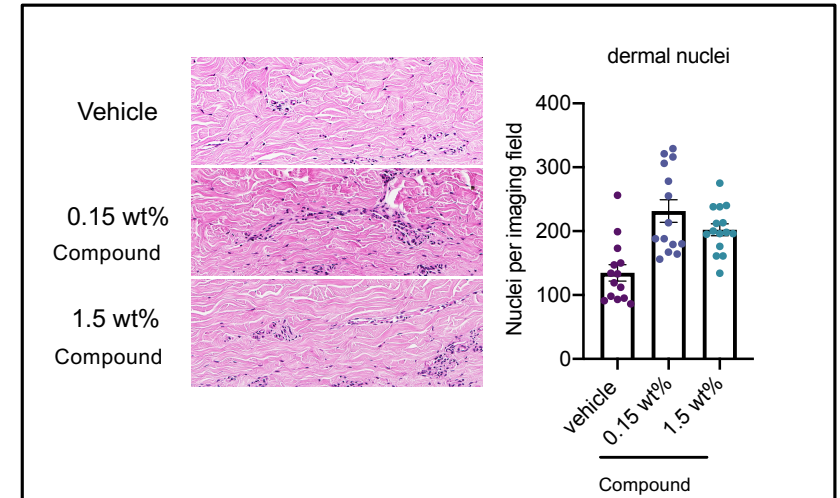


YAP-driven proliferation in pigs

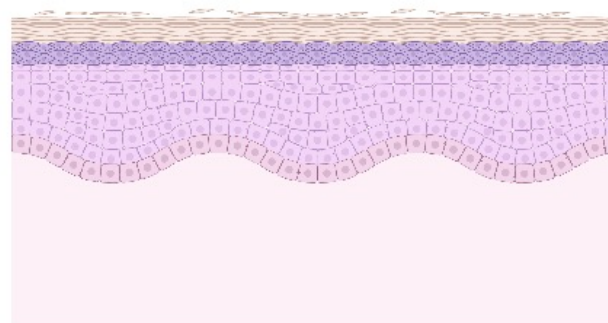
Epidermal thickening



Dermal thickening

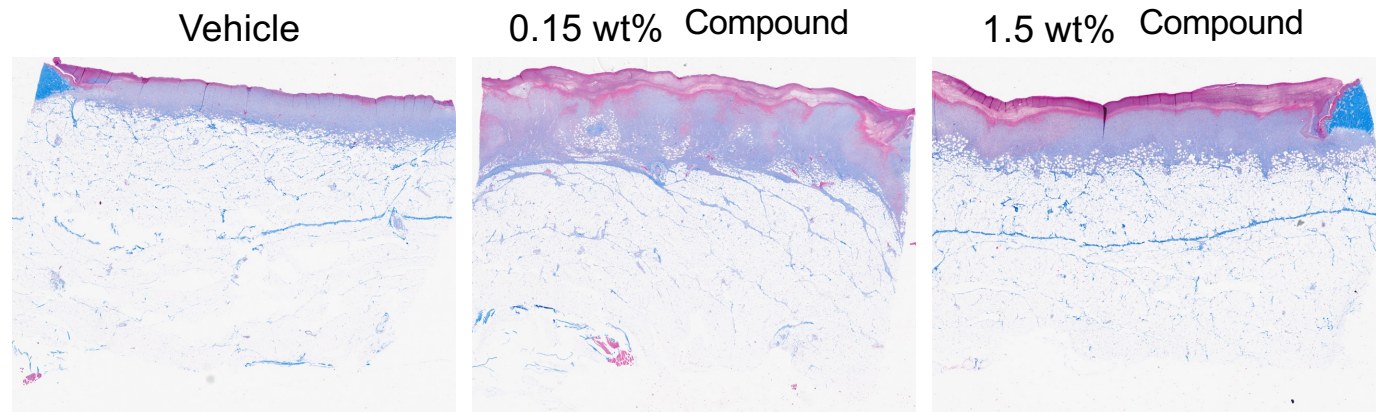
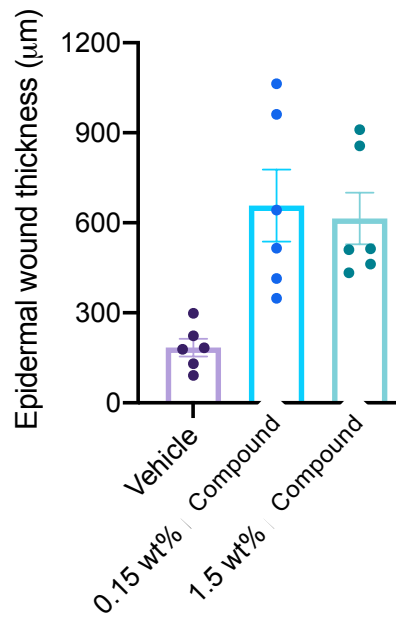


Epidermis
(keratinocytes,
barrier function)

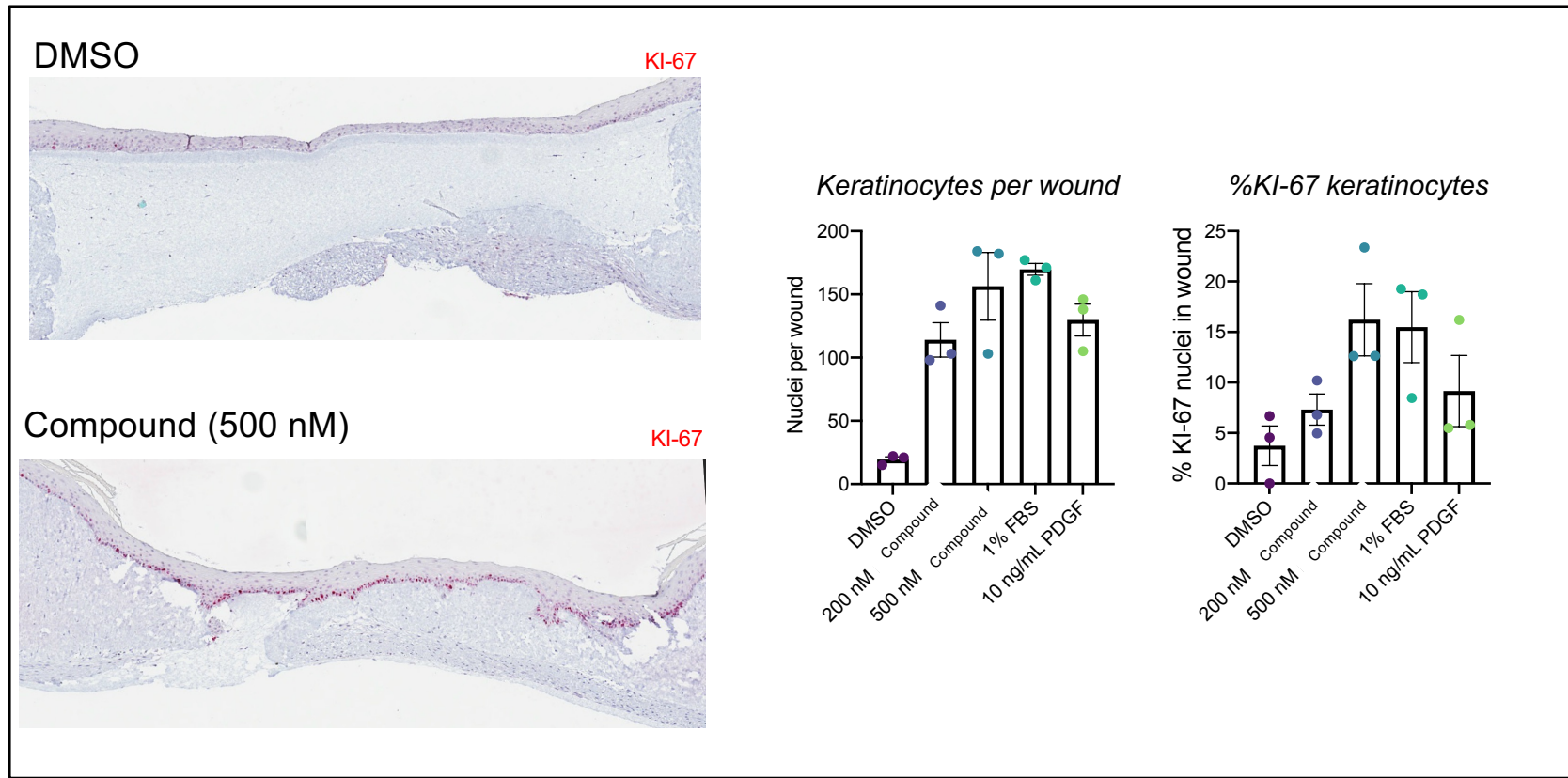


Dermis
(connective tissue)

YAP activation promotes epidermal thickening in pig wound healing models



Pharmacological YAP activation accelerates wound healing in human skin equivalents

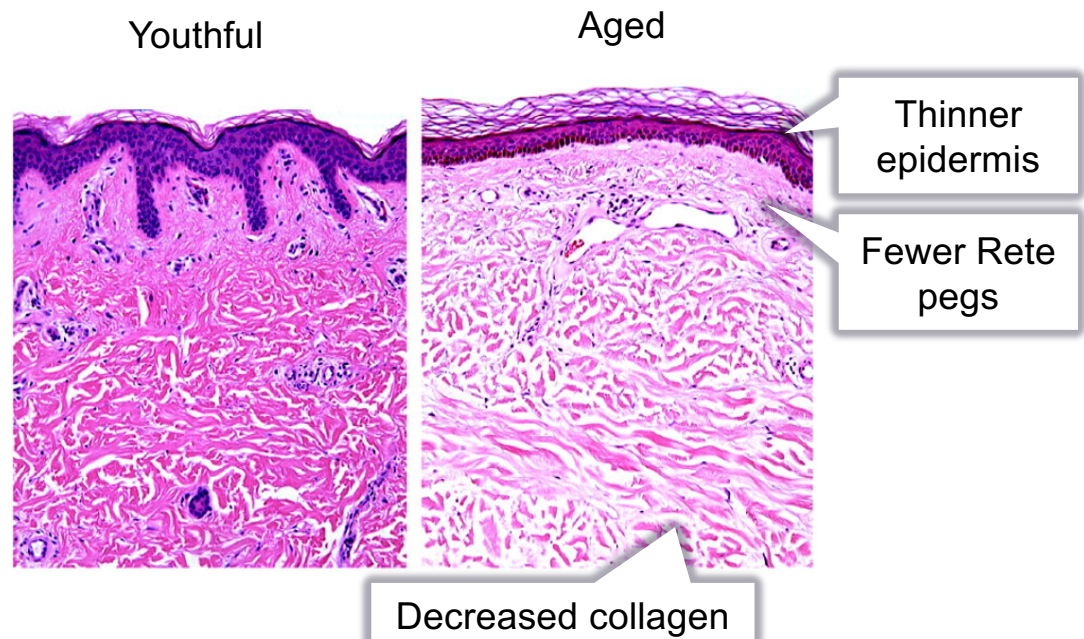


Senile purpura: a potential indication for topical YAP activators

Senile purpura: easily bruised skin with excessive tearing associated with aging



Aging decreases rete pegs, epidermal thickness, collagen bundling

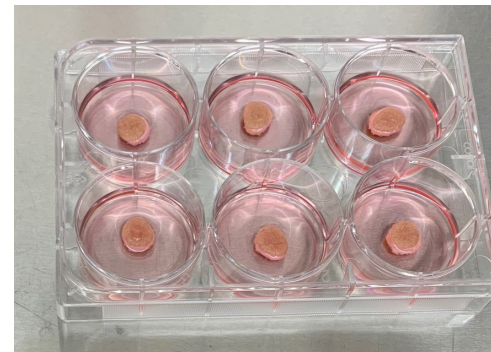
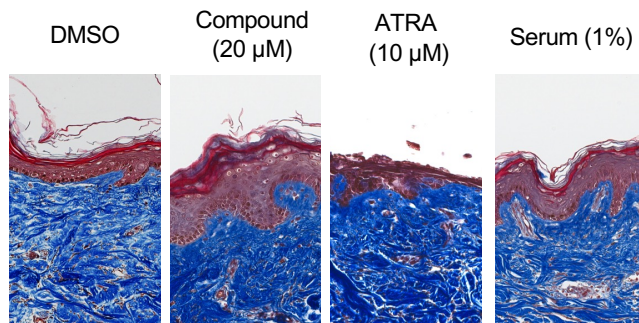
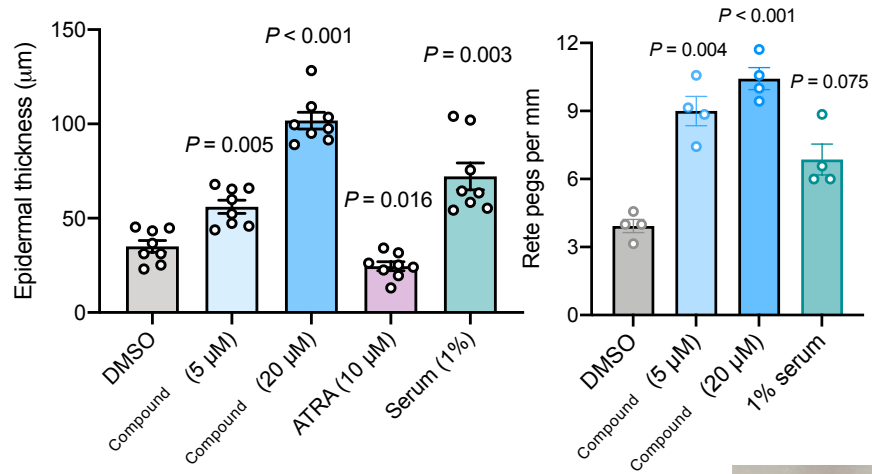


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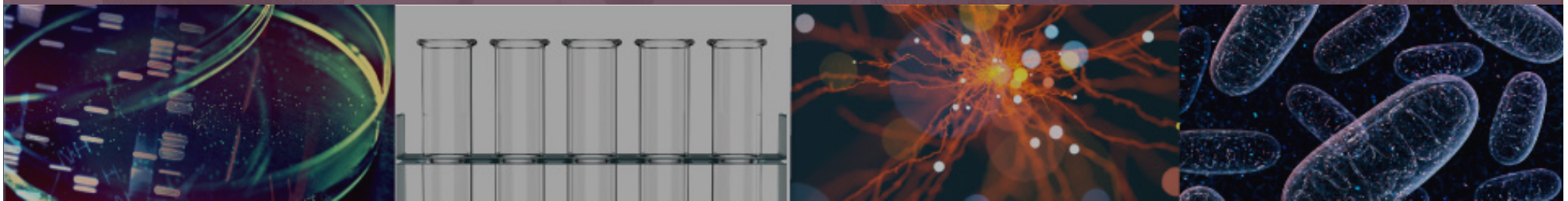
Efficacy of a YAP activator in human skin explants



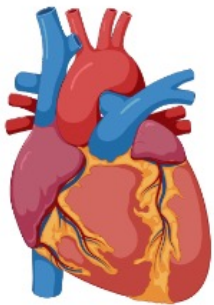


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Activating YAP for heart failure



Heart failure is a tremendous unmet medical need



Healthy

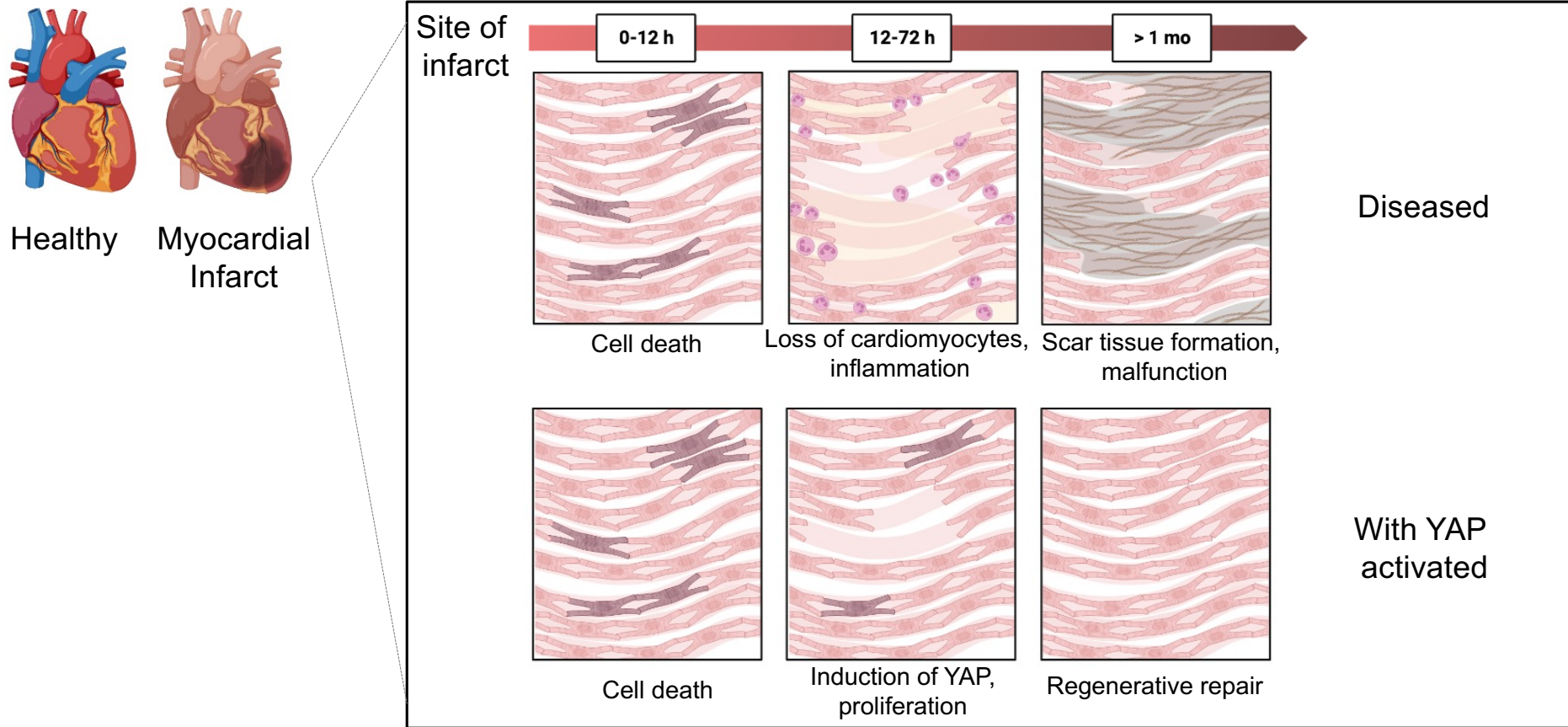


Myocardial
Infarct

- Nearly 5 million Americans (1-2% of the population) suffer from heart failure; 10% of those over 70 yrs. old
- Heart failure is a \$30 billion dollar US healthcare burden
- Current drugs only delay progression but do not stop disease or heal damage



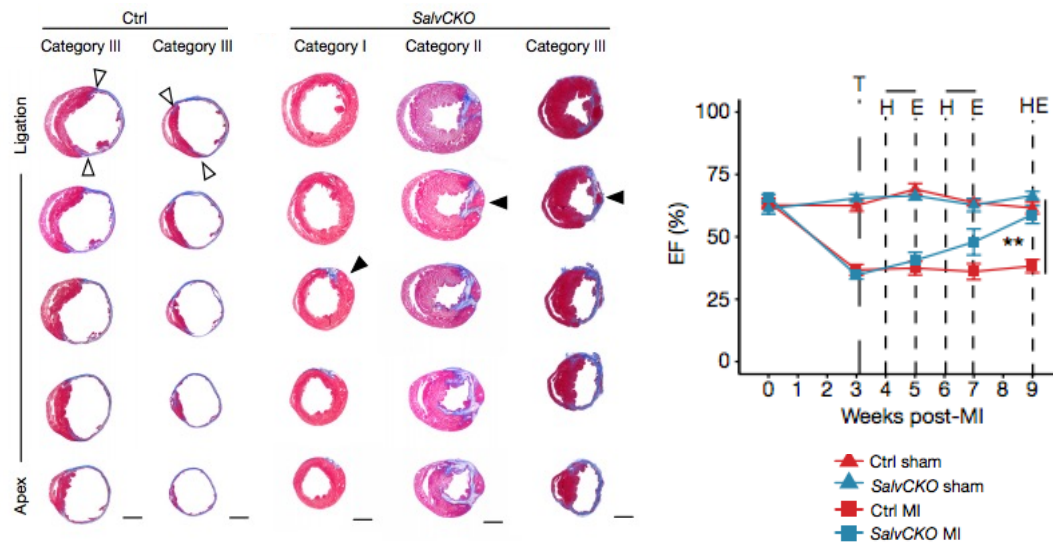
Heart failure derives from an irreversible loss of cardiomyocytes after MI



Genetic activation of YAP promotes regenerative cardiac repair in mice and pigs

Martin lab, Nature 2017

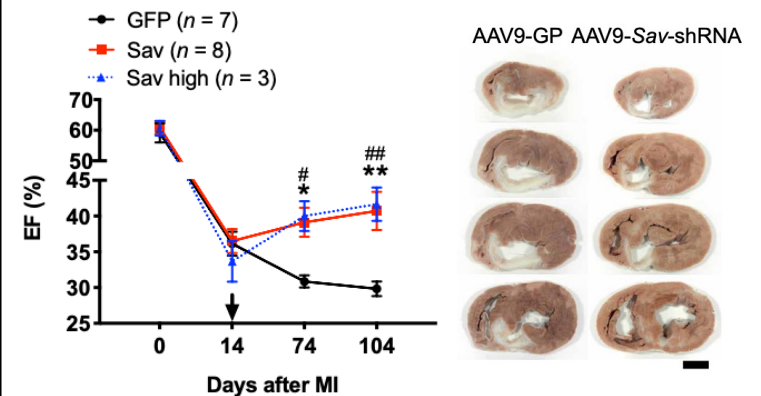
Genetic YAP activation *reverses* heart failure in mouse through regenerative cardiomyocyte growth (3 weeks after myocardial infarction)



PMID: 28976966

Martin lab, Science Translational Medicine 2021

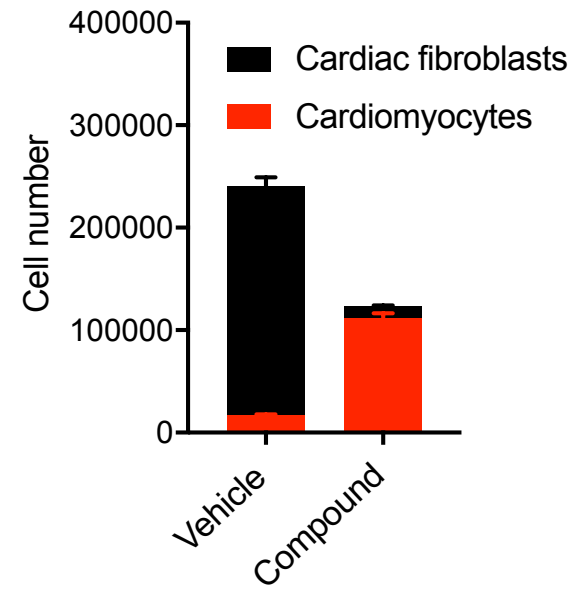
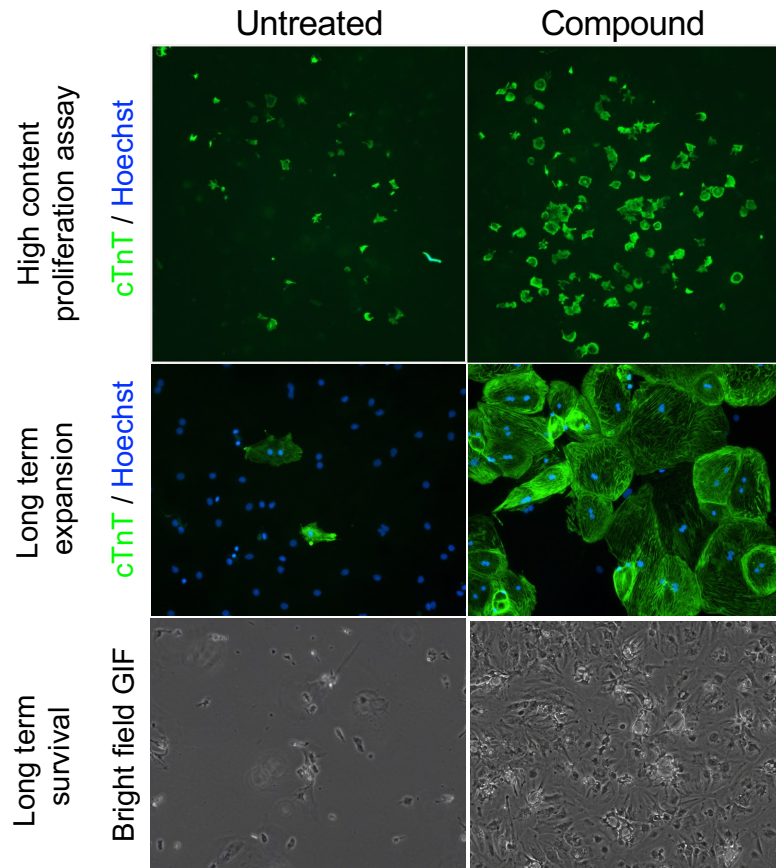
Genetic YAP activation *reverses* heart failure in pigs through regenerative cardiomyocyte growth (2 weeks after MI, durable reversal over 100 days)



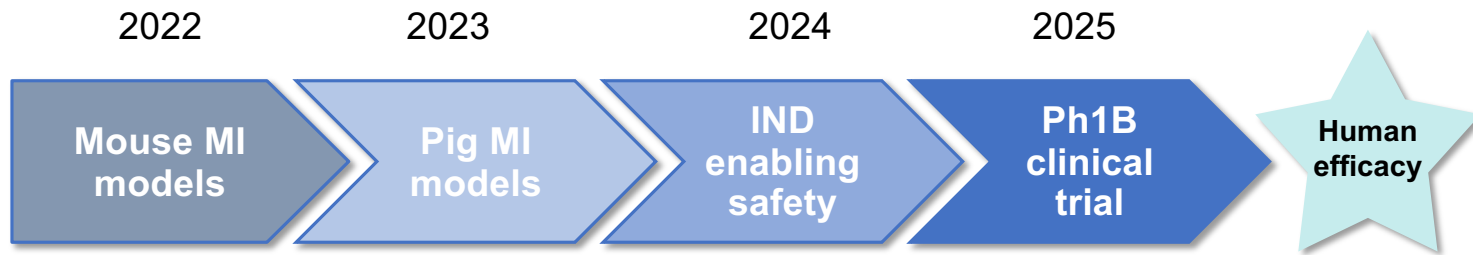
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A YAP activator promotes and selective expansion of cardiomyocytes



Next steps towards a regenerative therapy for HF



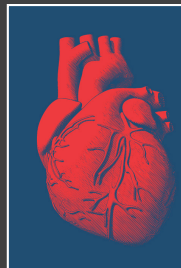
Impact



Augmenting repair by targeting the pathway controlling organ size



A regenerative approach to treating diabetic foot ulcers



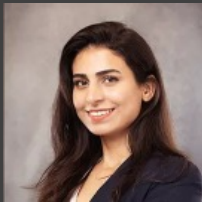
A regenerative approach to treating heart failure

Acknowledging the Bollong Lab and the Scripps Research community

Maya
Bulos



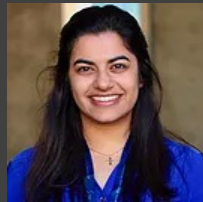
Fereshte
Ghorbani



Edyta
Grzelak



Lara
Ibrahim



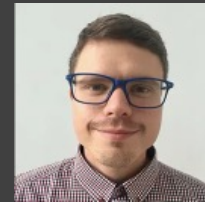
Kayla
Nutsch



Sida
Shao



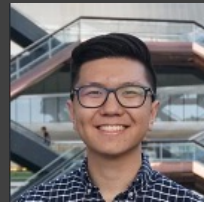
Greg
Specht



Caroline
Stanton



Tiger
You



Schultz Lab, Scripps
Wiseman Lab, TSRI
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Cravatt Lab, TSRI
Kelly Lab, TSRI
Teijaro Lab, TSRI
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Noble Lab, Cedars
Saghatelian Lab, Salk

Arnab Chatterjee, Calibr
Case McNamara, Calibr
Kristen Johnson, Calibr
Sean Joseph, Calibr
Jeff Chen, Calibr
Van Nguyen-Tran, Calibr
Janelle Stricker, Calibr