Targeting Cholesterol to Accelerate Chronic Wound Healing: Statin-Loaded Hydrogel Improves Healing Outcomes in Preclinical Models

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Jozic Lab

Conflicts of Interest

- The underlying technology US2025/0367164 A1 (Dec 4, 2025).
- COO for AdaptBio Therapeutics (antibody mimetics for inflammatory skin diseases). *No scientific overlap with this talk.*

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Collaborators (Miami)

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Collaborators (External)

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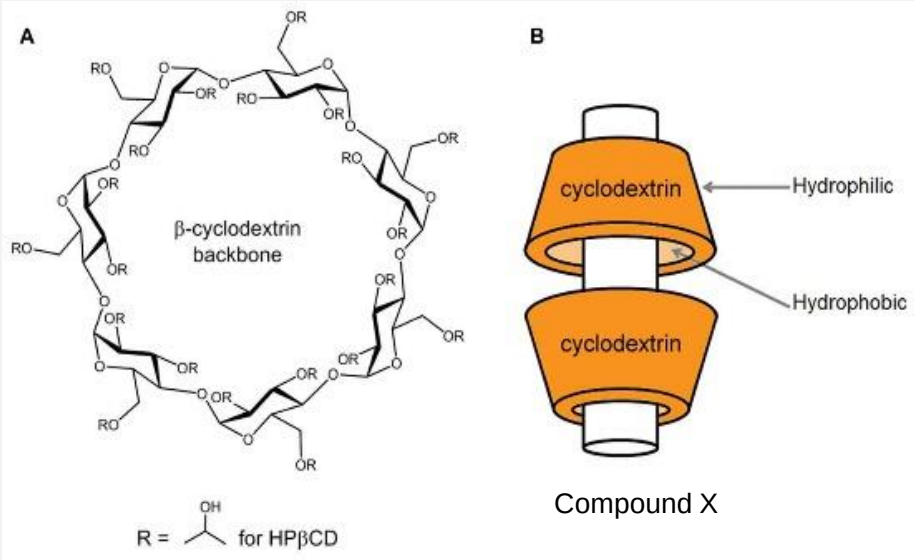
American Diabetes Association.
1122JDFPM07

NIH
AR083526

UNDERLYING TECHNOLOGY

- Gelatin and hyaluronic acid-based hydrogels
- Utilize cyclodextrin (CD) to form **inclusion complexes**, delivering compounds of interest to the wound and protecting them from degradation
- Nesting Doll Model - Enhance solubility, improve stability, allow for controlled release
- Multi-pronged approach to accelerating wound closure:

    1. Increasing cell migration and wound re-epithelialization
    2. **Modulating inflammatory response**
    3. **Decreasing wound infection**
    4. Increasing angiogenesis

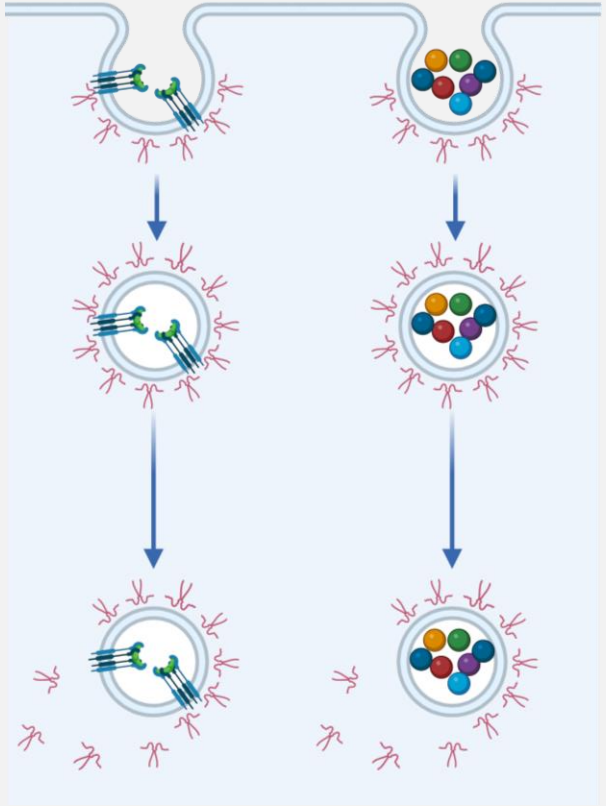


Examples of FDA approved CD-inclusion complexes

1. Food industry (encapsulation of volatile compounds to prevent oxidation and evaporation)
2. Controlled release of antimicrobial agents from inclusion complexes
3. Stabilization of retinol and Vit-C in cosmeceutical creams
4. Solubility enhancement of NSAIDs and antifungals
5. Encapsulation of slow-release agrochemicals (pesticides)

Mechanism of Action

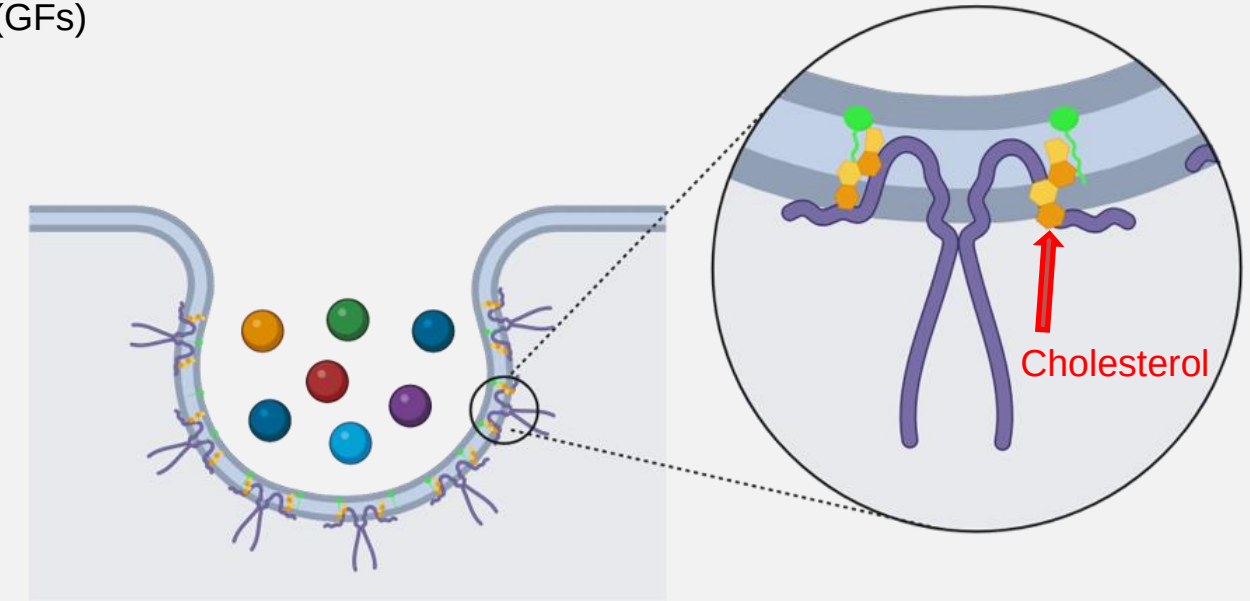
- Cyclodextrins remove cholesterol from membranes
- Caveolae are specialized membrane domains rich in ***cholesterol*** and sphingomyelin
- Disrupting membrane cholesterol inhibits **caveolin** proteins and prevents formation of caveolae



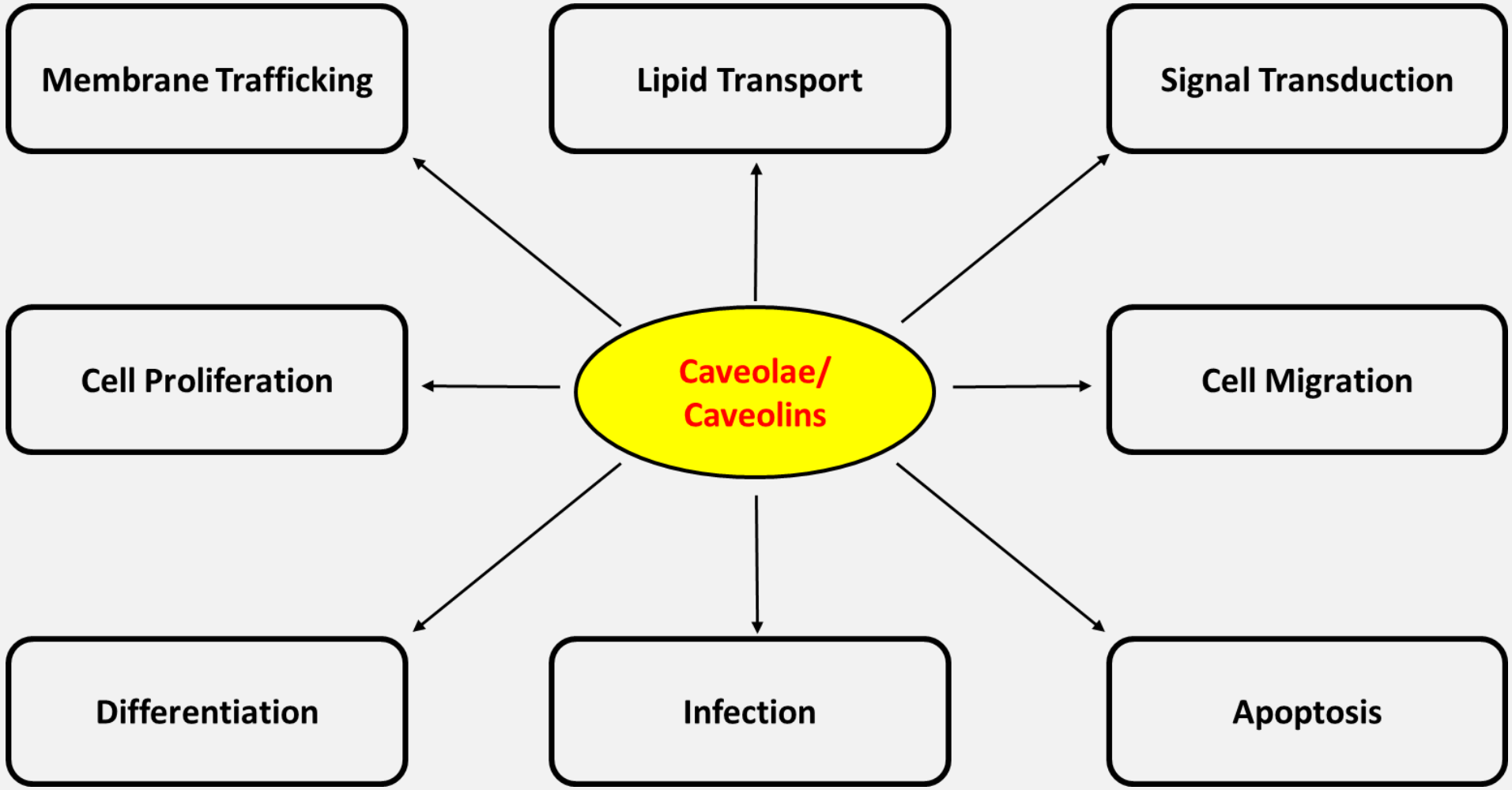
Caveolin 1 (Cav1)

Growth factors (GFs)

GF receptors



CAVEOLAE AND CAVEOLINS AS UNIVERSAL TARGETS IN DERMATOLOGY



Egger et al., (*2020*) Experimental Dermatology

WHY SHOULD YOU CARE ABOUT CAVEOLAE AS THERAPEUTIC TARGETS?

1. Cutaneous wound healing
2. Infection
3. Alopecia
4. Psoriasis
5. Hidradenitis suppurativa
6. Skin aging
7. Atopic and contract dermatitis
8. Basal and squamous cell carcinoma
9. Cutaneous fibroses
10. Blistering skin diseases (pemphigus)
11. Others?

> Commun Biol. 2021 Jun 18;4(1):757. doi: 10.1038/s42003-021-02298-5.

Glucocorticoid-mediated induction of caveolin-1 disrupts cytoskeletal organization, inhibits cell migration and re-epithelialization of non-healing wounds

Ivan Jozic [1], Beatriz Abdo Abujamra [2], Michael H Elliott [3], Tongyu C Wikramanayake [2], Jelena Marjanovic [2], Rivka C Stone [2], Cheyanne R Head [2], Irena Pastar [2], Robert S Kirsner [2], Fotios M Andreopoulos [4 5], Juan P Musi [4], Marjana Tomic-Canic [6 7]

> Mol Ther. 2019 Nov 6;27(11):1992-2004. doi: 10.1016/j.ymthe.2019.07.016. Epub 2019 Jul 30.

Pharmacological and Genetic Inhibition of Caveolin-1 Promotes Epithelialization and Wound Closure

Ivan Jozic [1], Andrew P Sawaya [1], Irena Pastar [1], Cheyanne R Head [1], Lulu L Wong [1], George D Glinos [1], Tongyu Cao Wikramanayake [1], Harold Brem [2], Robert S Kirsner [1], Marjana Tomic-Canic [3]

Case Reports > JID Innov. 2023 Aug 14;3(6):100223. doi: 10.1016/j.xjidi.2023.100223. eCollection 2023 Nov.

Upregulation of Caveolae-Associated Proteins in Lesional Samples of Hidradenitis Suppurativa: A Case Series Study

Neil Seth [1], Beatriz Abdo Abujamra [1], Maria Boulina [2], Hadar Lev-Tov [1], Ivan Jozic [1]

Review > Exp Dermatol. 2020 Feb;29(2):136-148. doi: 10.1111/exd.14068. Epub 2020 Jan 10.

The importance of caveolins and caveolae to dermatology: Lessons from the caves and beyond

Andjela N Egger [1], Ali Rajabiestarabadi [1], Natalie M Williams [1], Sydney R Resnik [1], Joshua D Fox [1], Lulu L Wong [1], Ivan Jozic [1]

> Arch Dermatol Res. 2024 Jun 5;316(6):330. doi: 10.1007/s00403-024-03153-3.

Upregulation of caveolae-associated structural proteins in the hair follicle bulge of lichen planopilaris and frontal fibrosing alopecia

Alessandra Anzai [1], Beatriz Abdo Abujamra [2], Valéria Aoki [3], Ivan Jozic [2]

> Biomedicines. 2021 May 19;9(5):572. doi: 10.3390/biomedicines9050572.

A Cell Membrane-Level Approach to Cicatricial Alopecia Management: Is Caveolin-1 a Viable Therapeutic Target in Frontal Fibrosing Alopecia?

Ivan Jozic [1], Jérémy Chéret [1], Beatriz Abdo Abujamra [1], Mariya Miteva [1], Jennifer Gherardini [1 2], Ralf Paus [1 2 3]

> Radiat Oncol. 2024 Jun 26;19(1):82. doi: 10.1186/s13014-024-02472-z.

Single-cell transcriptional analysis of irradiated skin reveals changes in fibroblast subpopulations and variability in caveolin expression

Lionel E Kameni [1], Michelle Griffin [1], Charlotte E Berry [1 2], Siavash Shariatzadeh [1], Mauricio A Downer Jr [1], Caleb Valencia [1], Alexander Z Fazilat [1], Rahim Nazerali [1], Arash Momeni [1], Michael Januszyk [3 4], Michael T Longaker [1 5], Derrick C Wan [6 7]

Case Reports > JID Innov. 2024 Feb 1;4(2):100265. doi: 10.1016/j.xjidi.2024.100265. eCollection 2024 Mar.

Downregulation of Caveolae-Associated Proteins in Psoriasis: A Case Series Study

Deborah A Lin [1], Beatriz Abdo Abujamra [1], Stephanie Revah [1], Leigh Nattkemper [1], Brian Morrison [1], Paolo Romanelli [1], Ivan Jozic [1]

> Cell Mol Life Sci. 2024 Oct 16;81(1):435. doi: 10.1007/s00018-024-05472-0.

Alpha-hemolysin promotes internalization of Staphylococcus aureus into human lung epithelial cells via caveolin-1- and cholesterol-rich lipid rafts

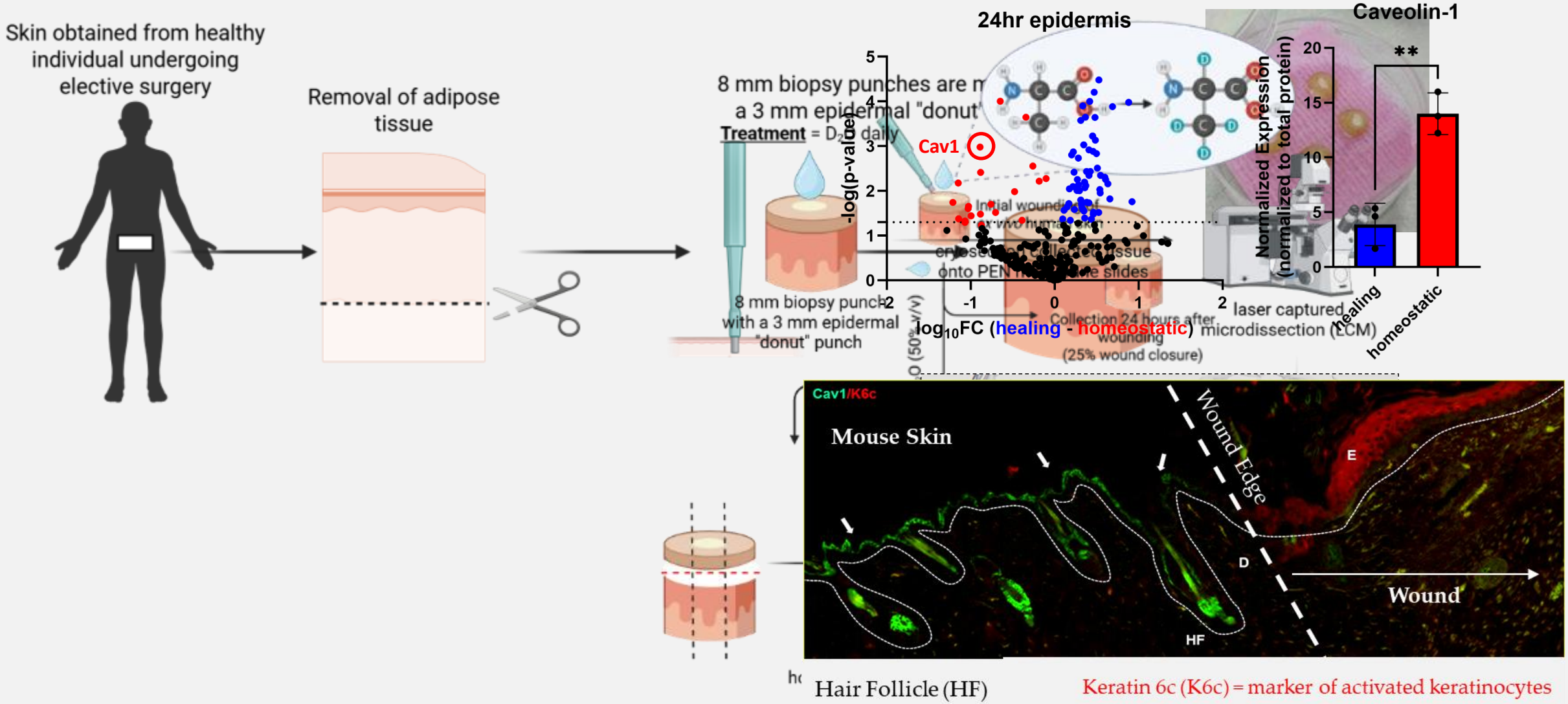
Oliver Goldmann [1], Julia C Lang [# 1 2], Manfred Rohde [3], Tobias May [4], Gabriella Molinari [3], Eva Medina [5]

> Cytojournal. 2024 Nov 15:21:42. doi: 10.25259/Cytojournal_76_2024. eCollection 2024.

Increased caveolin 1 by human antigen R exacerbates *Porphyromonas gingivali*-induced atherosclerosis by modulating oxidative stress and inflammatory responses

Fang Miao [1], Yangyang Lei [2], Yunfei Guo [1], Yongxia Ma [2], Ye Zhang [1], Binbin Jia [2]

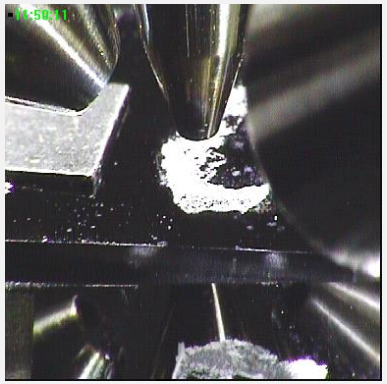
What is the evidence for the involvement of caveolae in Cutaneous wound healing?

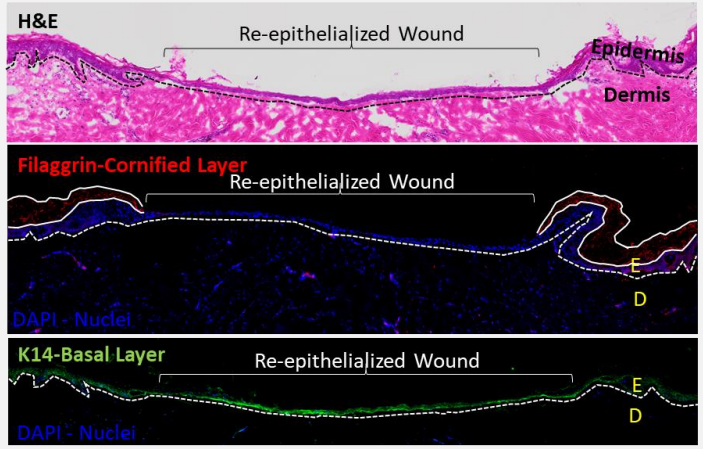


Jozic et al., (2019) Molecular Therapy

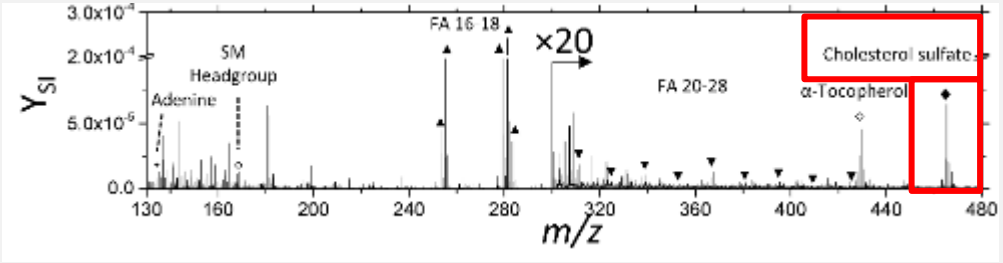
Does downregulation of Cav1 correlate with diminished cholesterol levels?

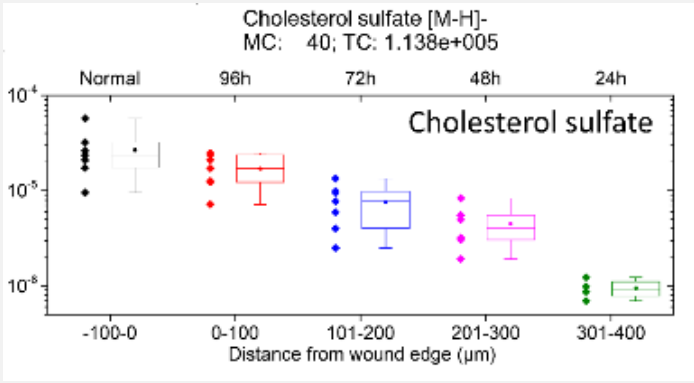
TOF-SIMS Imaging



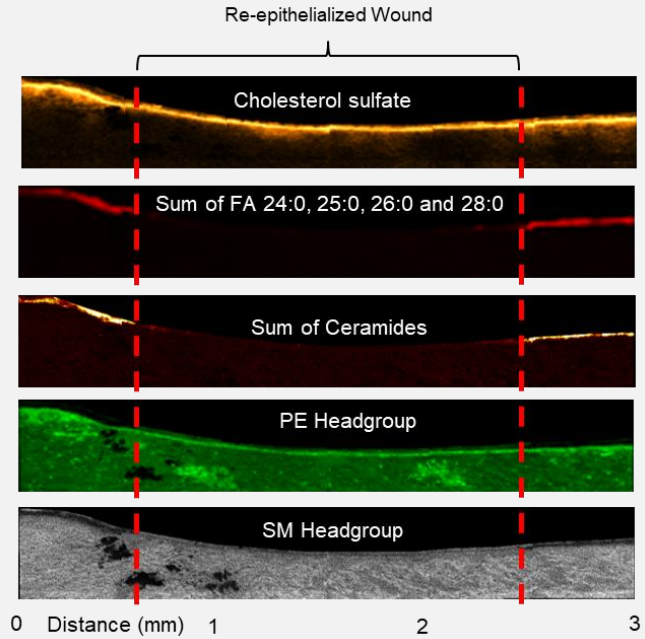


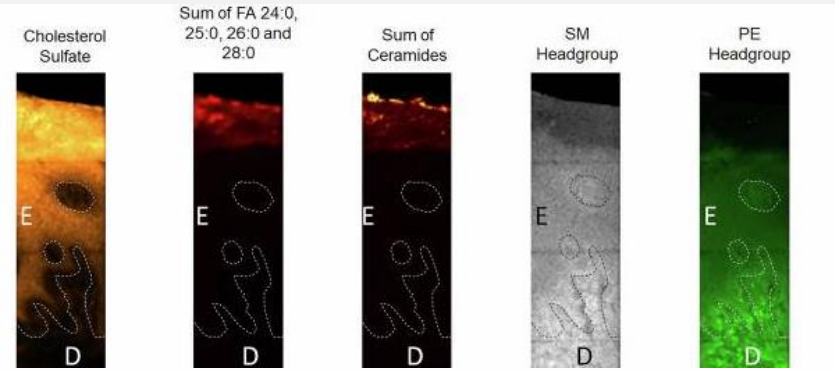
Analysis of lipidomic fingerprints

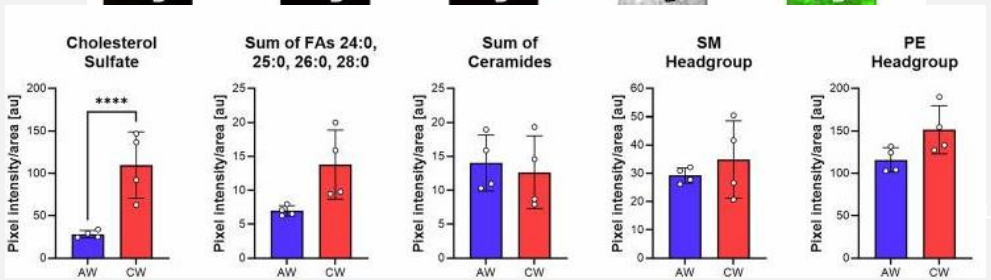




What about chronic wounds?



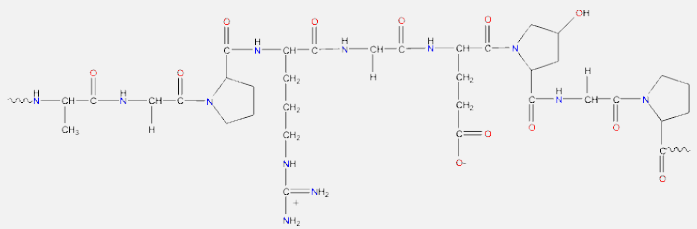




Castellanos et al., (2020) Anal Chem

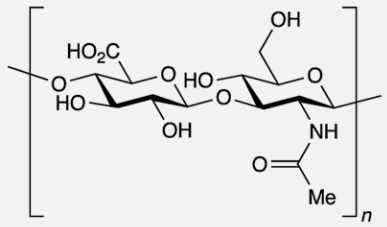
Majranovic et al., (2025) Nat Regen Med

LOGICALLY WE STARTED OFF WITH CYCLODEXTRIN-STATIN HYDROGEL FIRST



gelatin

+



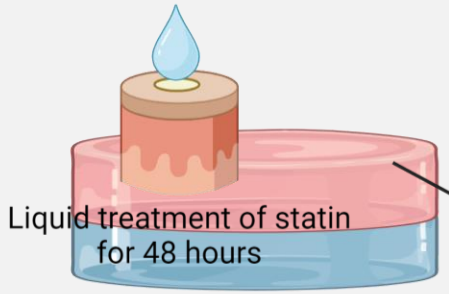
hyaluronic acid

+

> Wound Repair Regen. 2016 Mar;24(2):454-57. doi: 10.1111/wrr.12400. Epub 2016 Feb 5.

Statins may be associated with six-week diabetic foot ulcer healing

Joshua D Fox [1], Katherine L Baquerizo-Nole [2], Flor Macquhae [1], Ingrid Herskovitz [1], Jeremy B Freedman [3], Loretta Vileikyte [4], David J Margolis [5], Robert S Kirsner [1]



Liquid treatment of statin for 48 hours

Hydrogel with statins complexed in HβCD treatment for 24 and 48 hours

SLOW degrading

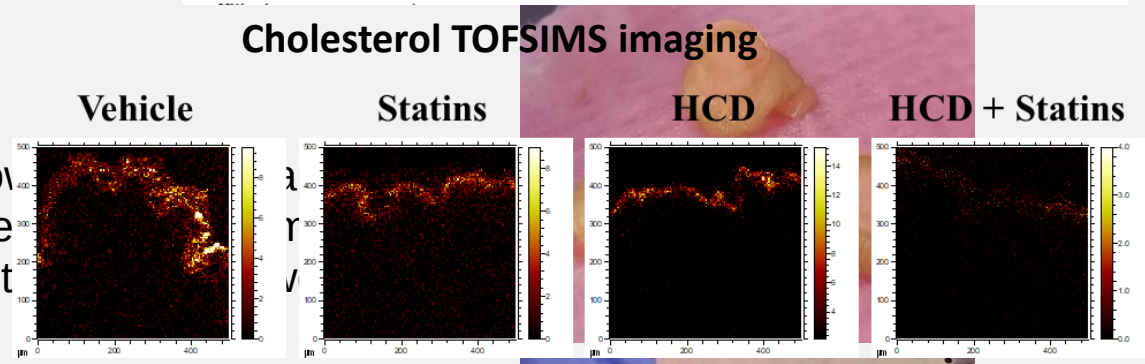
Cryosectioning

grading

TOFSIMs for statin metabolites

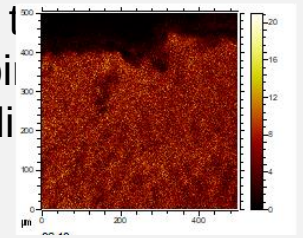
Slo
Tre
Later t

Cholesterol TOFSIMS imaging

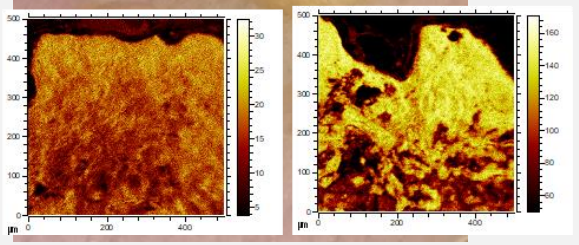


a) Topical Statin

Burst-like therapy
Immediate t
Early time poi
heali



b) HCD/Statin Hydrogel



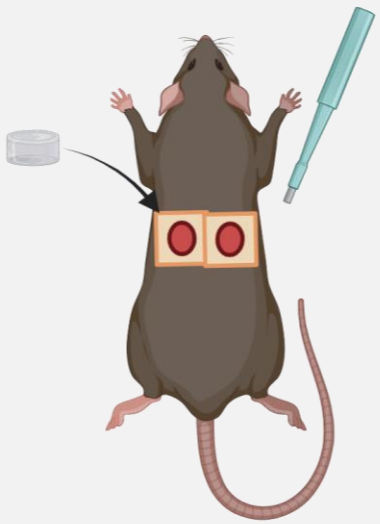
HCD – 2-hydroxypropyl-β-cyclodextrin

DO CYCLODEXTRIN-STATIN HYDROGELS ACCELERATE WOUND HEALING IN VIVO?

Murine Wound Models

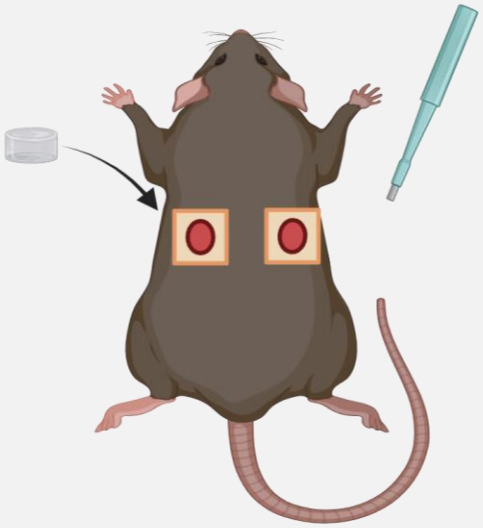
Acute

Db/+ Wounded Mouse Model



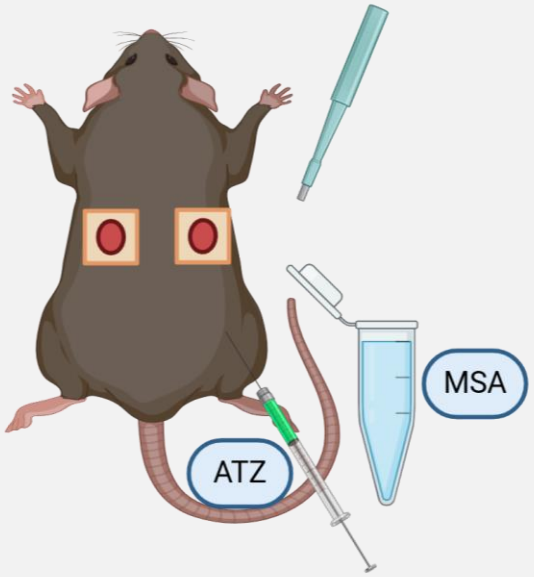
Delayed

Db/db Wounded Mouse Model

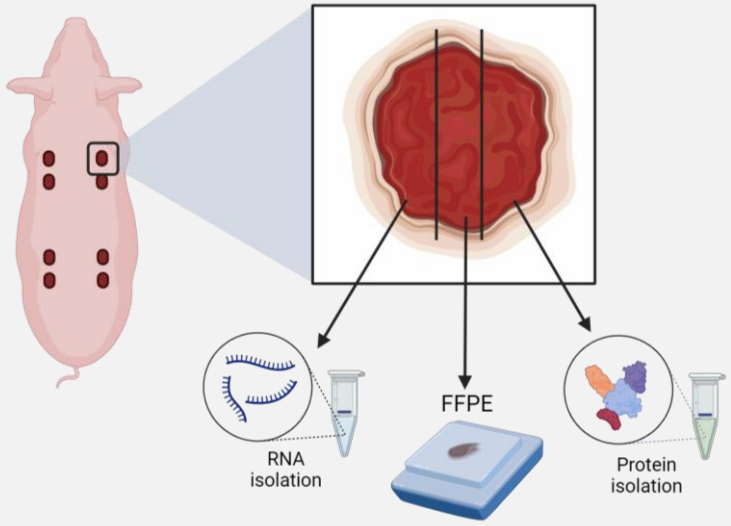


Chronic-like

Db/db Chronic Wounded Mouse Model



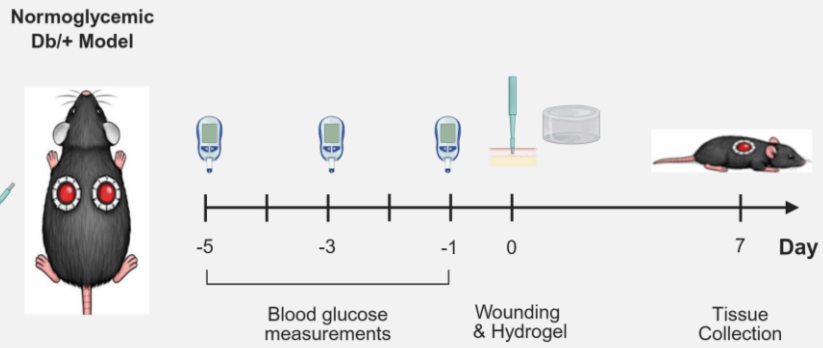
Porcine Wound Model

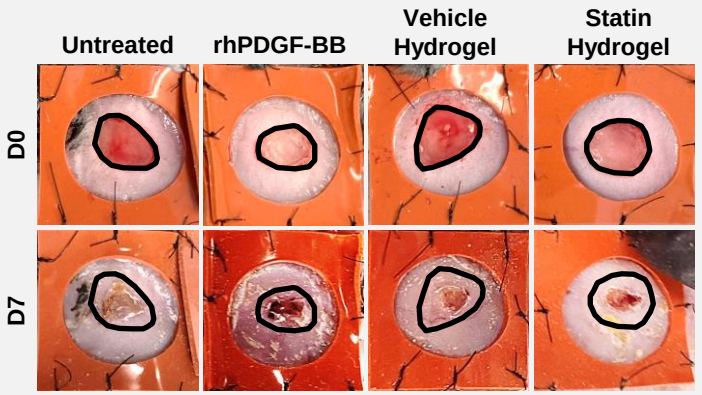


n = 3 mice/treatment/ collection day
2 wounds/mouse

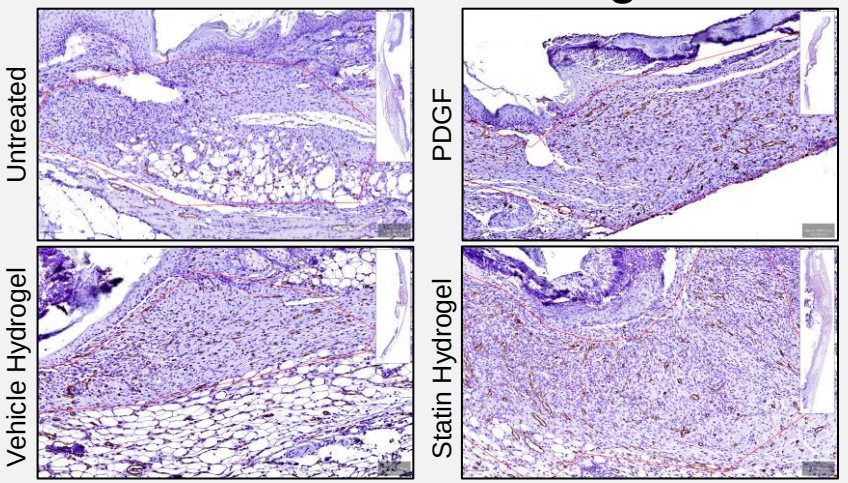
ATZ = 3-amino-1,2,4-triazole (*catalase inhibitor*)
MSA = mercaptosuccinic acid (*glutathione peroxidase inhibitor*)

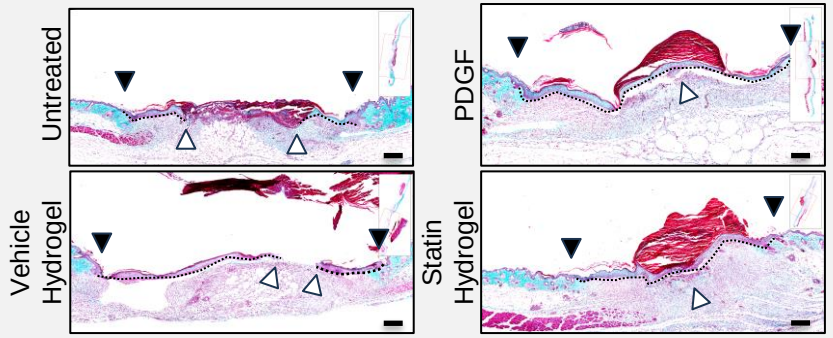
Evidence Mouse Models

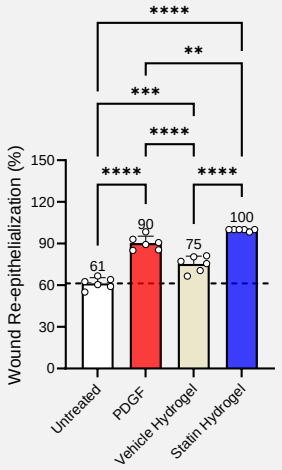


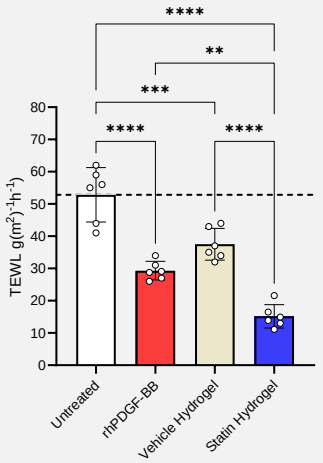


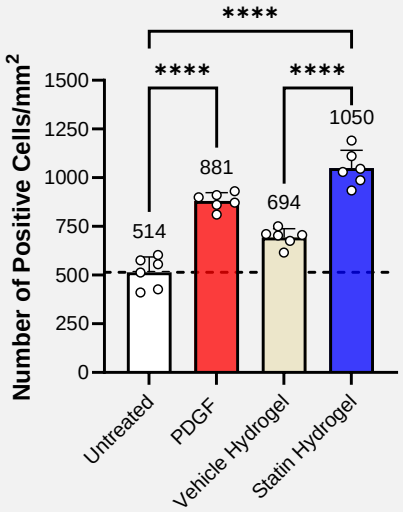
CD31 Staining



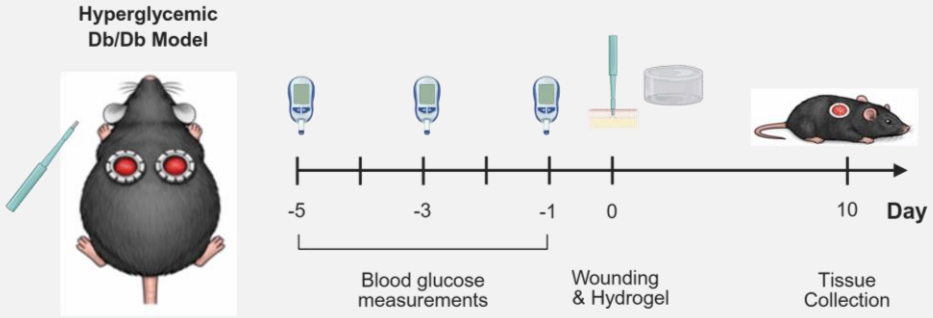


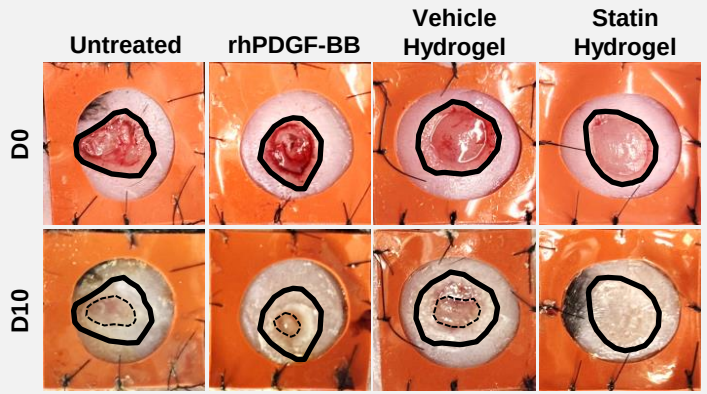


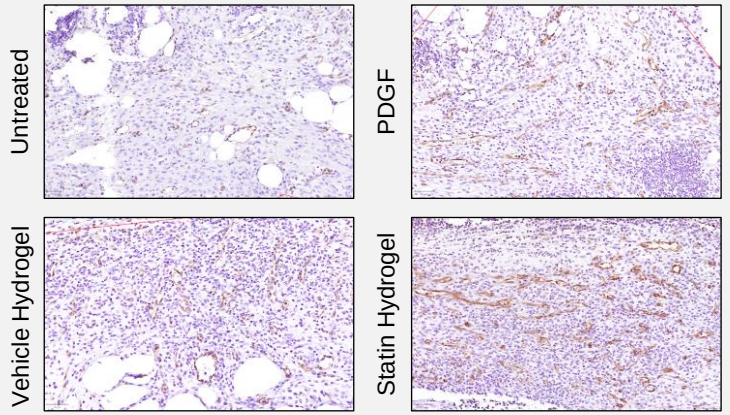


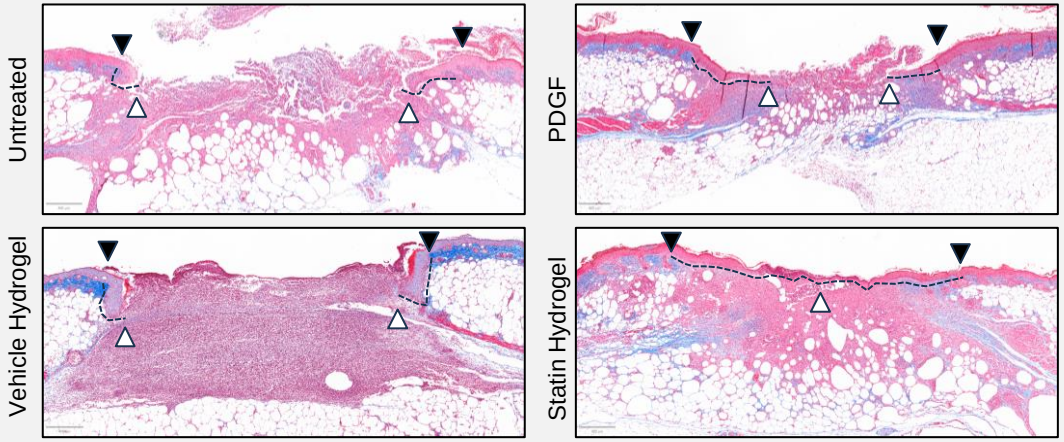


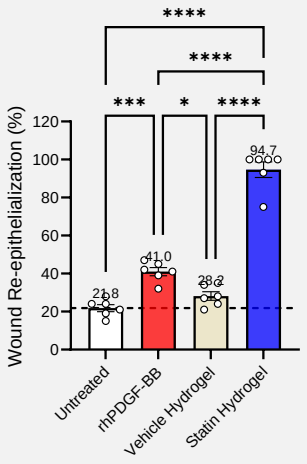
Better Efficacy in More Diabetic Mouse Models

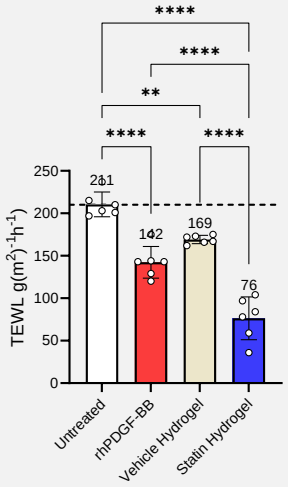


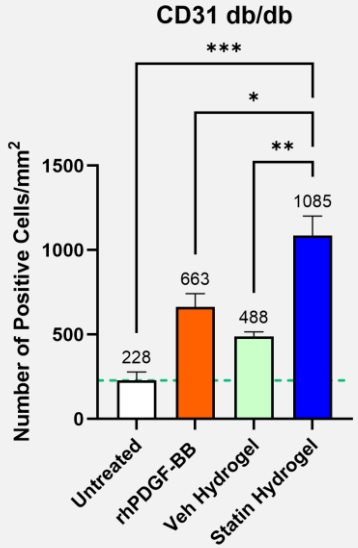




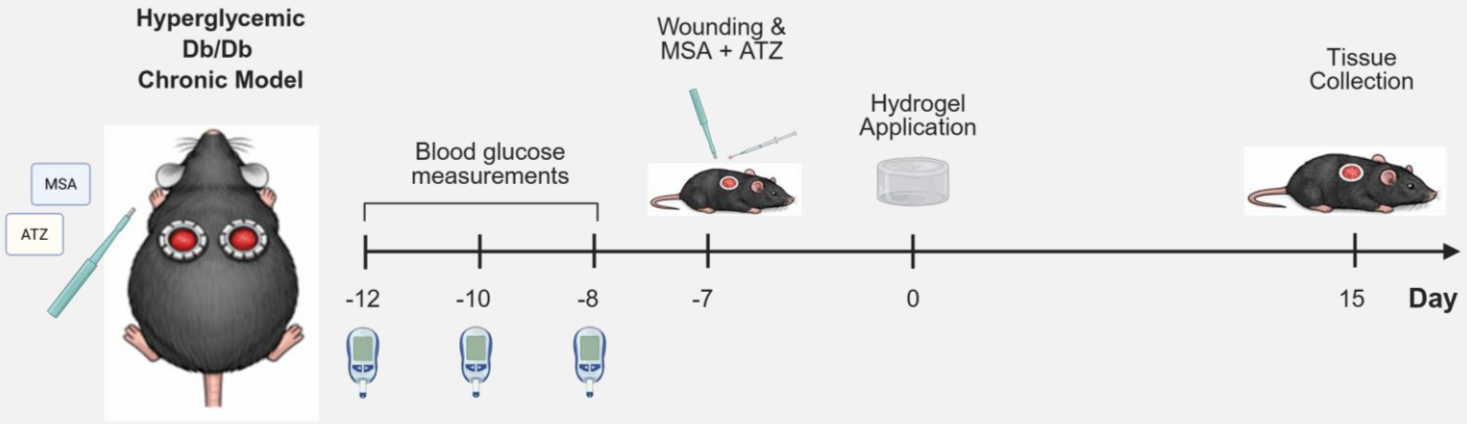


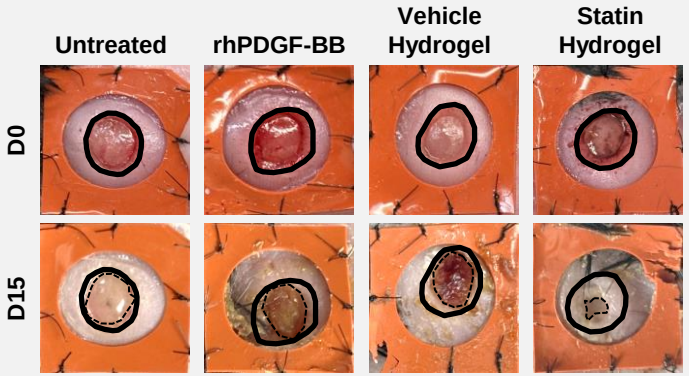


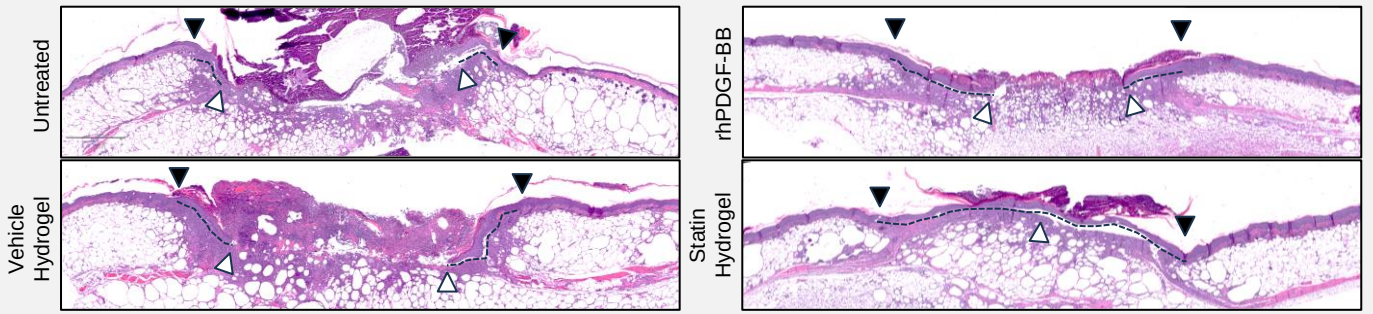


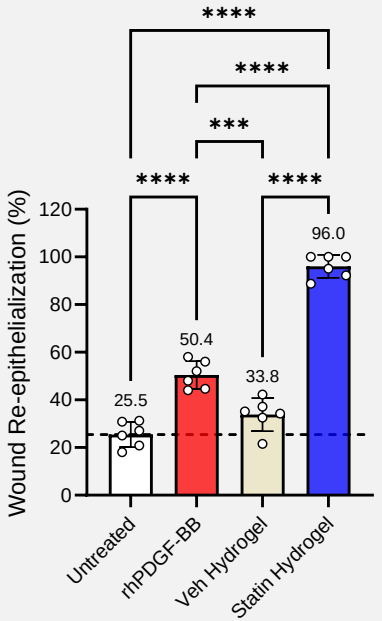


Best Efficacy in a Chronic-Like Diabetic Mouse Model

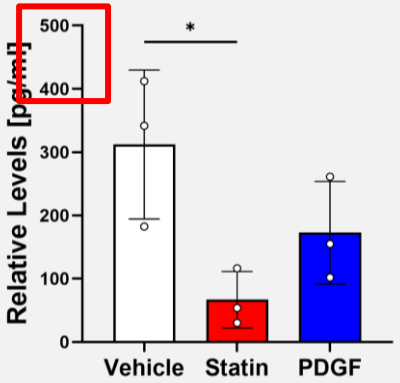
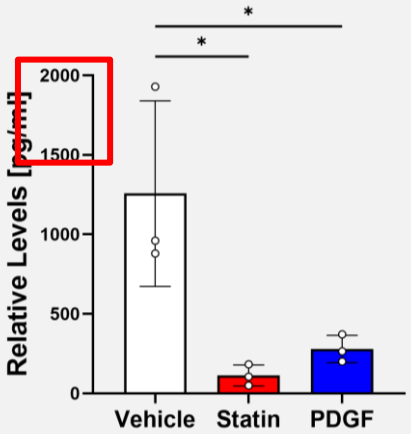
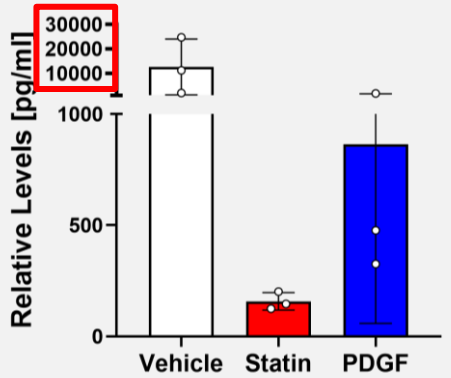
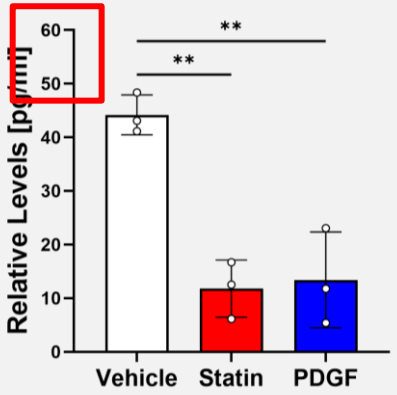
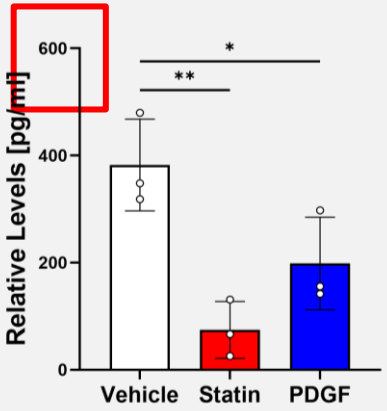
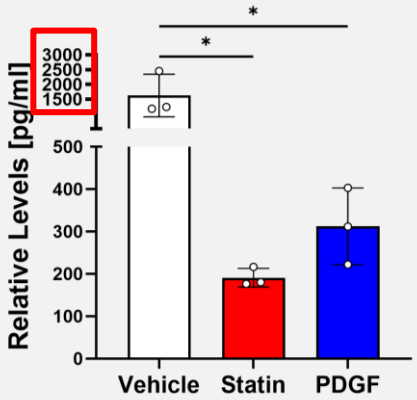






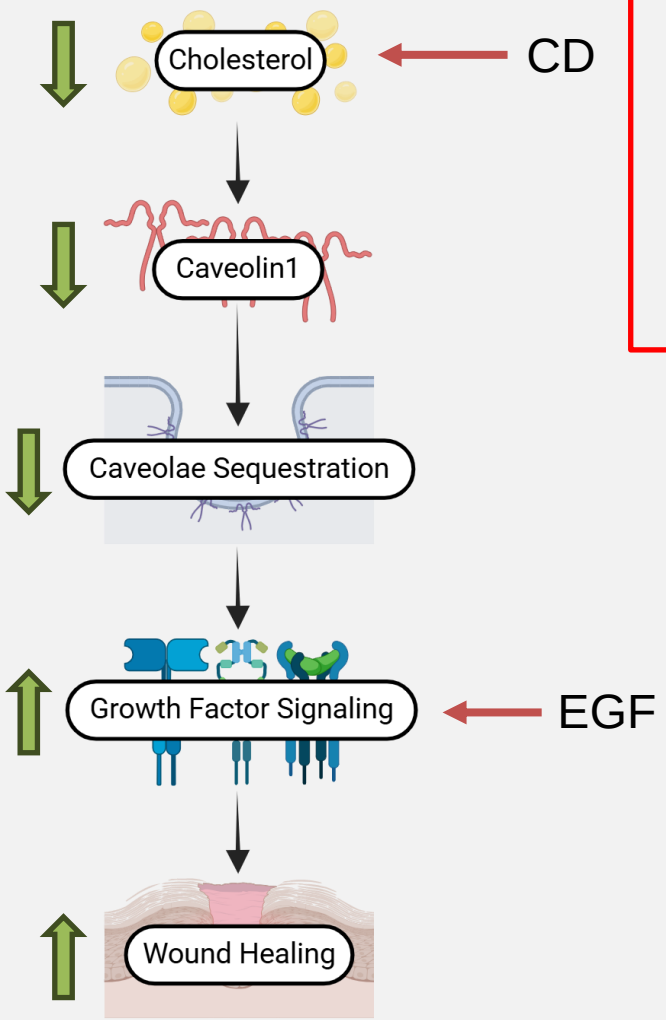


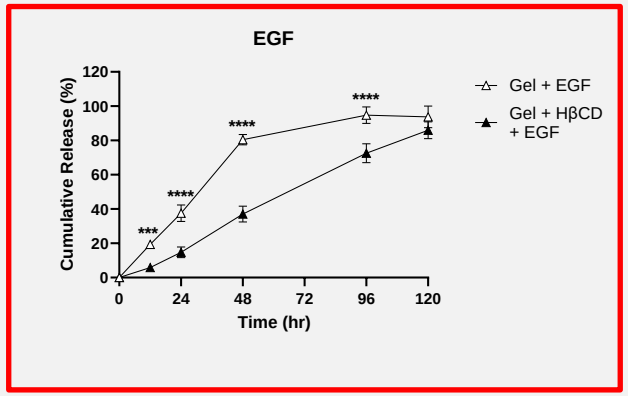
CYCLODEXTRIN-STATIN HYDROGELS AUGMENT LEVELS OF INFLAMMATORY CYTOKINES

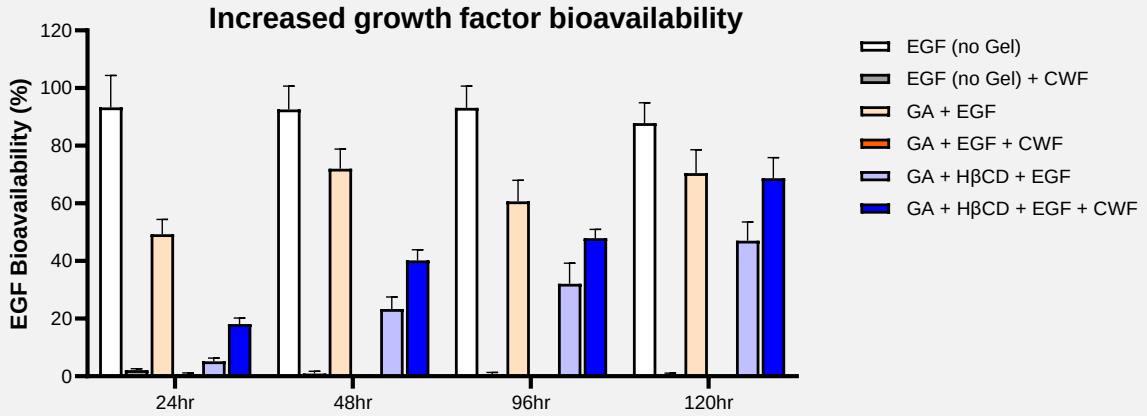
	Db/+ Wounded Mouse Model	Db/db Wounded Mouse Model	Db/db Chronic Wounded Mouse Model
IFNγ			
TNFα			

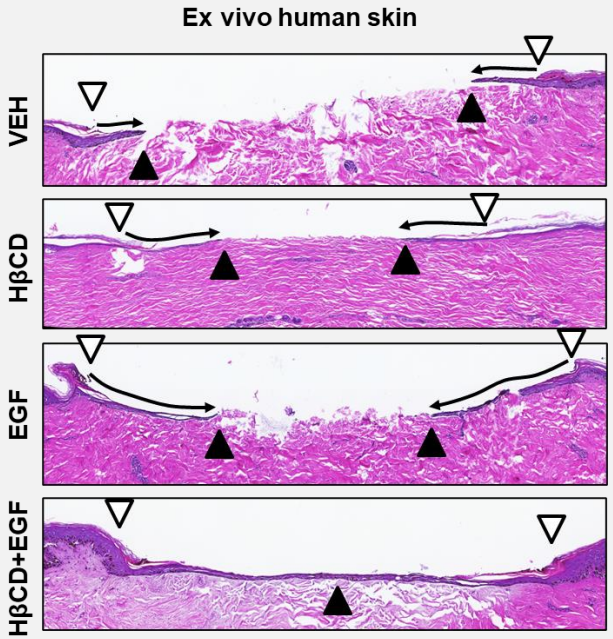
The statin hydrogels have a more pronounced effect as the models get more *chronic*-like

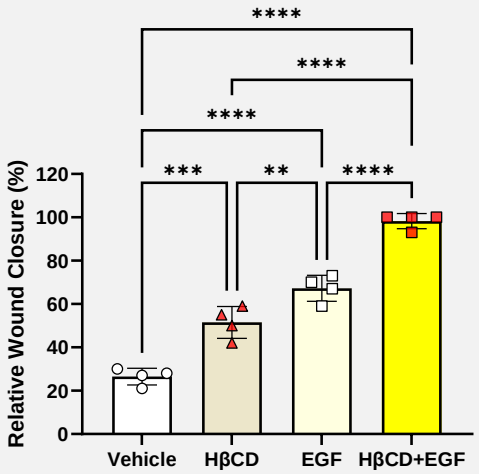
POTENTIAL PLUG-AND-PLAY PLATFORM ADAPTABILITY?

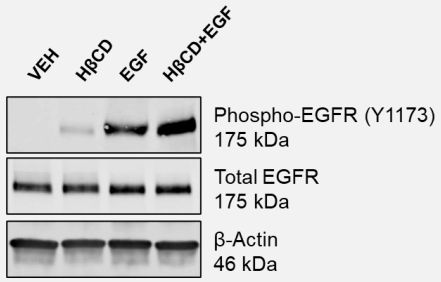


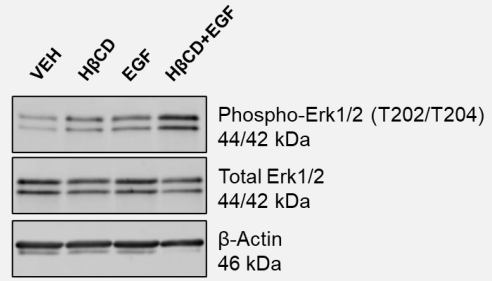












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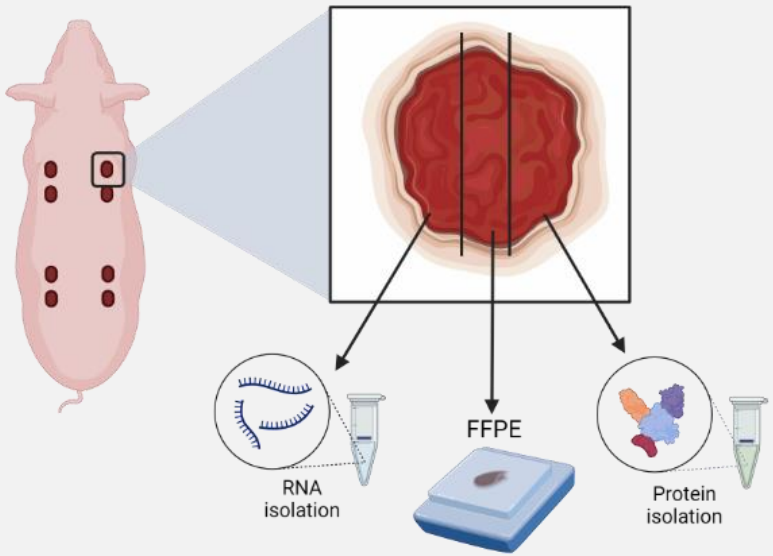
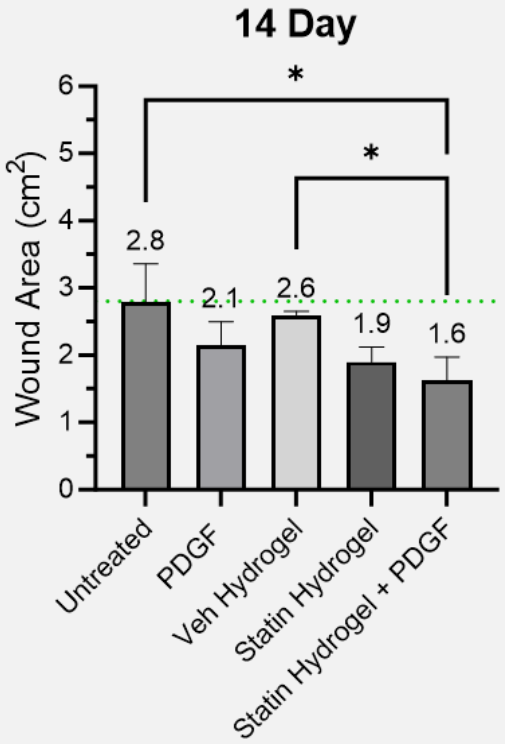
CWF – Simulated Chronic Wound Fluid
GA – Gelatin/Hyaluronic acid hydrogel
HβCD – 2-hydroxypropyl-beta-cyclodextrin

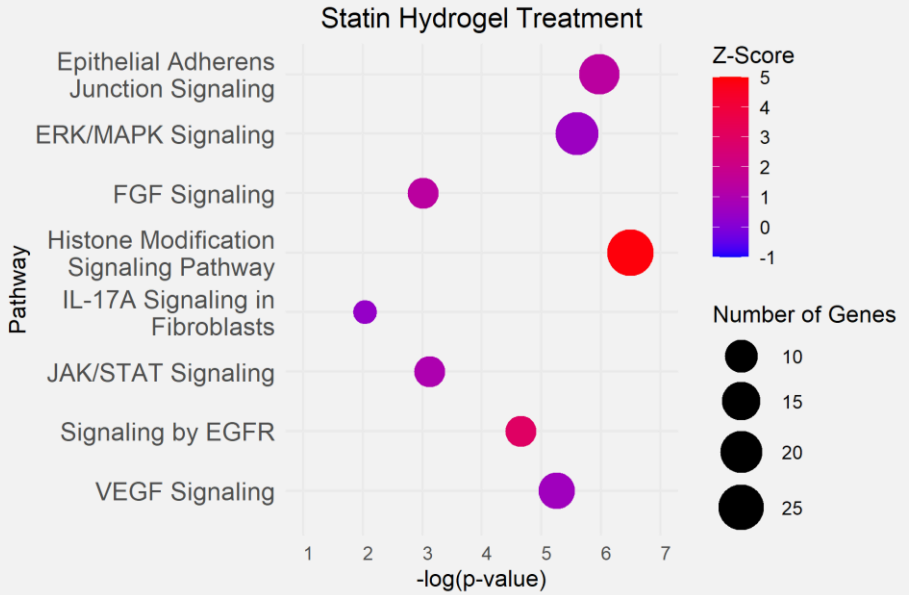
Majranovic et al., 2025 Nat Regen Med

What about a combinatorial approach of Statin + Growth Factor



Re-epithelialization

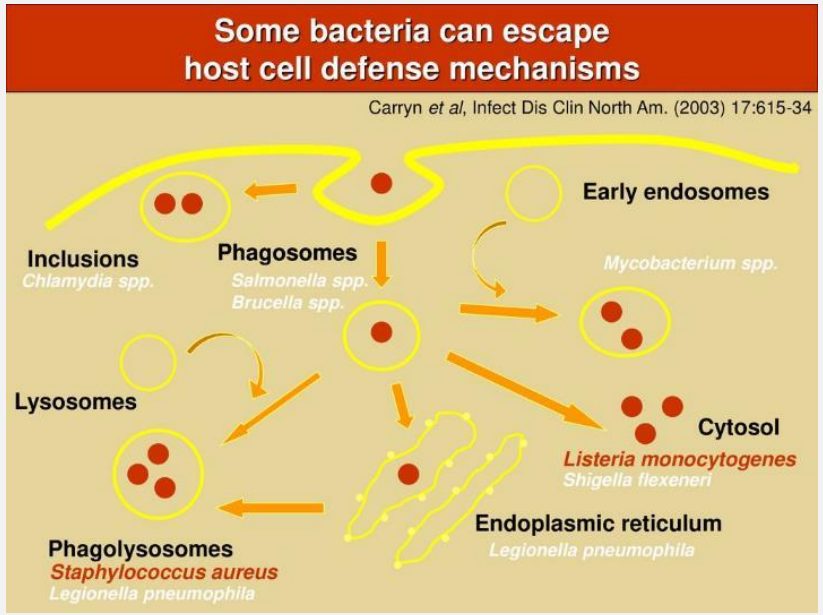




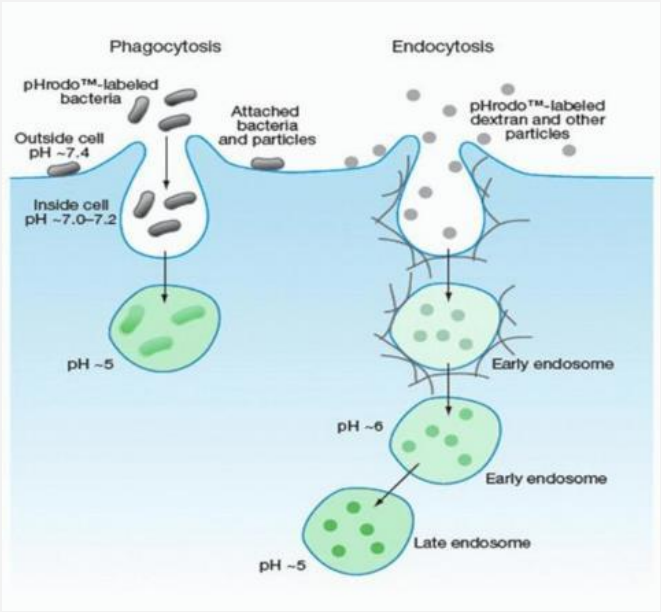
Treatment groups:

1. Untreated
2. PDGF hydrogel
3. Vehicle hydrogel
4. Statin hydrogel
5. Statin + PDGF hydrogel

WHAT ABOUT PATHOGEN INTERNALIZATION?

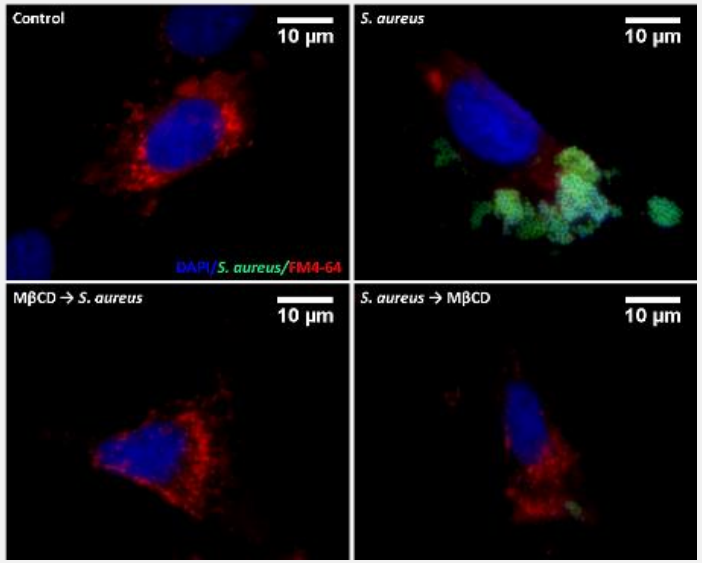


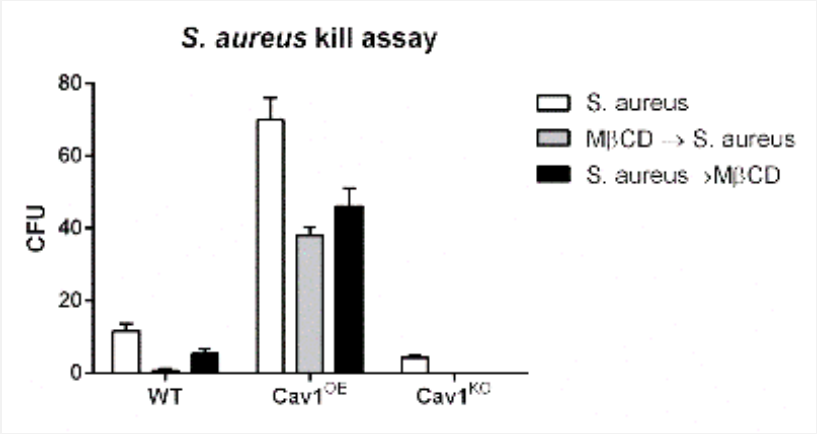
Cav1 has been previously demonstrated to regulate internalization of *Pseudomonas aeruginosa* and other skin pathogens



pHrodo iFL STP ester only fluoresces at low pH

In vitro human keratinocytes

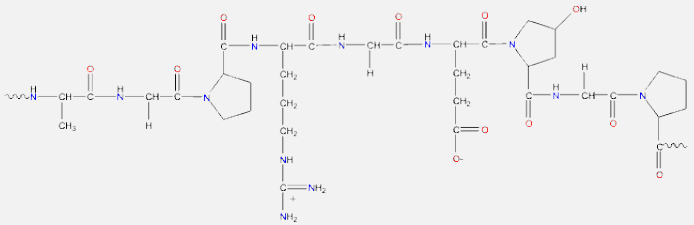




Summary Regarding CD-Statin Hydrogels

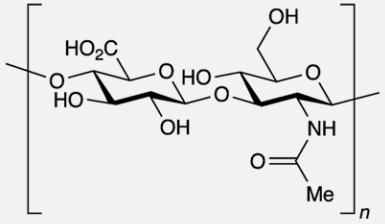
- Accelerate healing in multiple pre-clinical animal models
- Appear to exhibit better efficacy as the models become more chronic
- May help in expulsion of intracellular bacteria
- Provide a plug-and-play platform for other compounds of interest

Potential Platform with Plug-and-Play adaptability



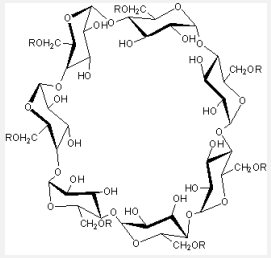
gelatin

+



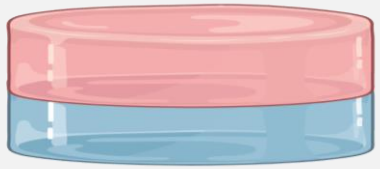
hyaluronic acid

+



Cyclodextrin

+ ?

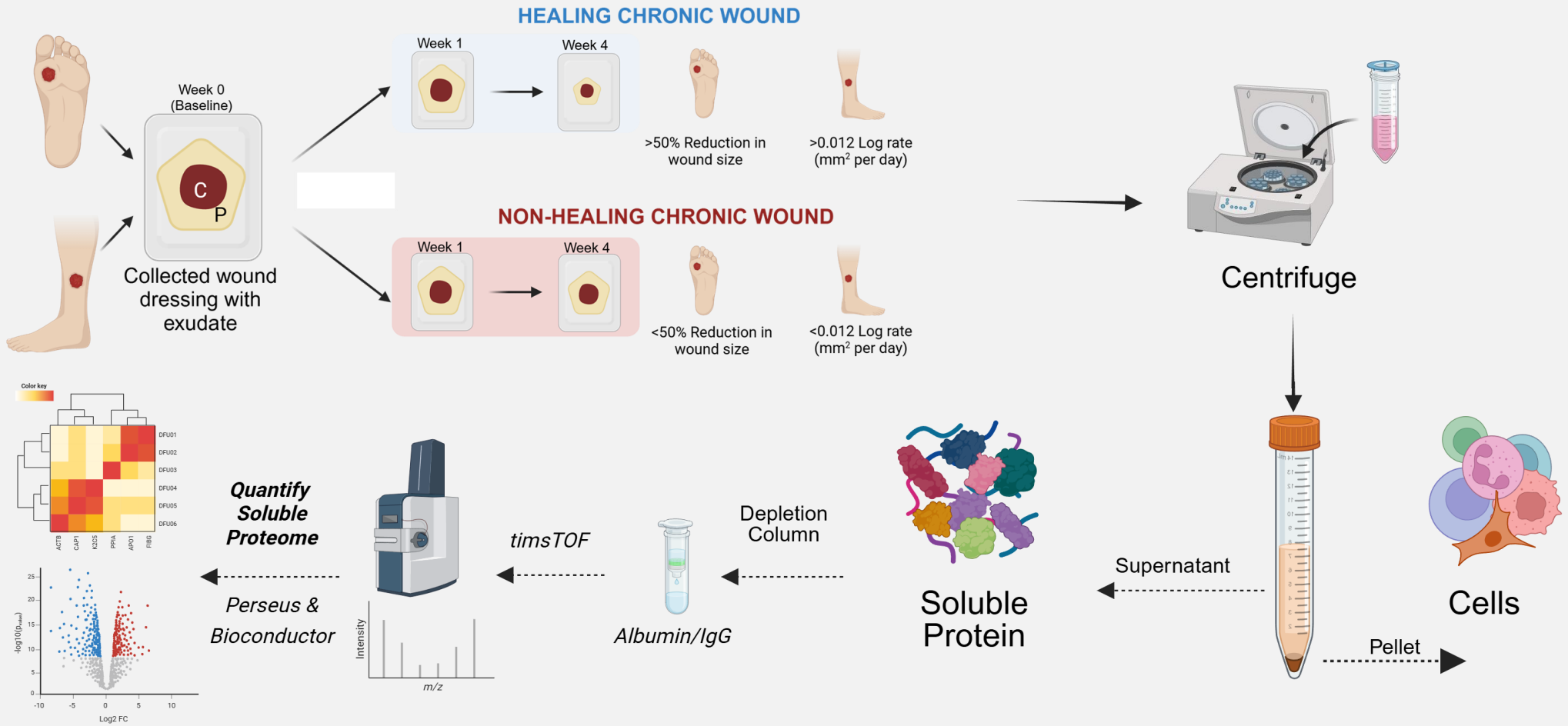


SLOW degrading → Slow-release therapy
Treatment over time
Later time points of wound healing → Statins?
Growth factors?
Angiogenic peptides?
Stem-cell attractants?
Anti-fibrotic agents?

FAST degrading → Burst-like therapy
Immediate treatment
Early time point of wound healing → Antibiotic/AMPs?
Analgesic?
Anti-inflammatory agents?

How to incorporate adaptability and personalized treatment?

Proteomic profiling of wound exudate captured by discarded wound dressings may help guide treatment options



Soto et al., 2025 Mol Cell Proteomics

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Questions?

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