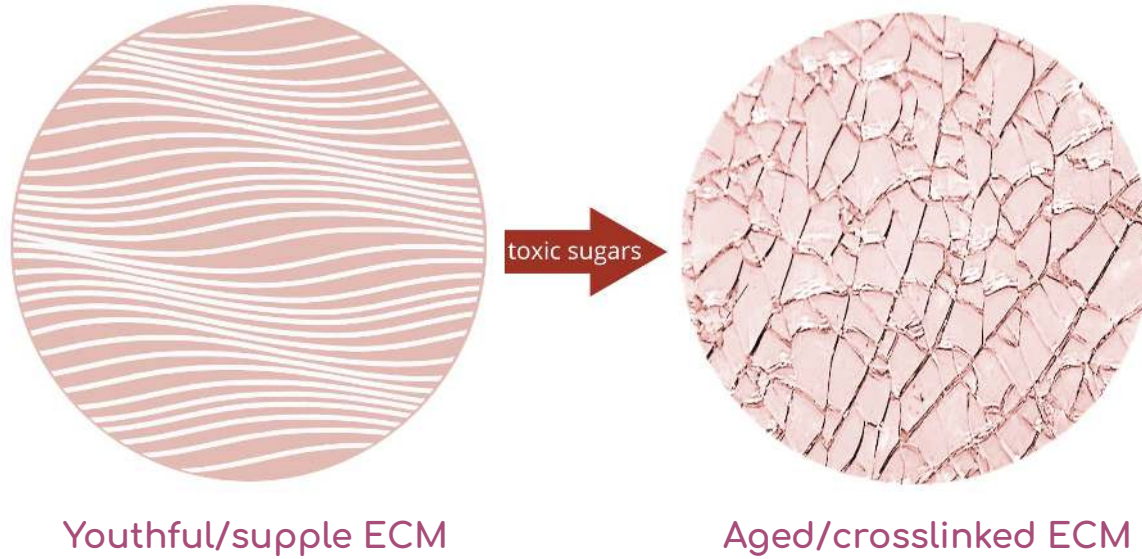hack-age

We are a goal-driven association of passionate individuals unified by a vision: **rejuvenation of the extracellular matrix**

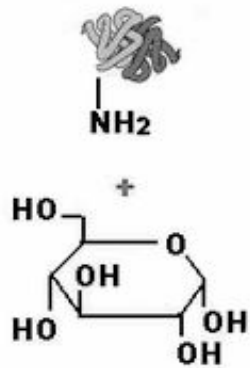# Glycation

Youthful/supple ECM → toxic sugars → Aged/crosslinked ECM

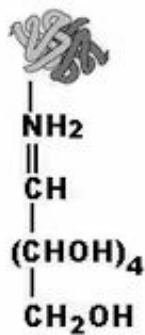# REVERSIBILITY OF THE GLYCATION DAMAGE
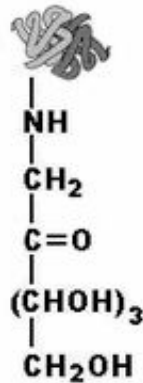
Minutes | Hours | Weeks | Years

Blood sugar ⇌ Schiff's base ⇌ Amadori product ⇒ Adducts and crosslinks: glucosepane, crossline, GOLD, MOLD

AGEs

(Advanced Glycation End products)

AGEs: crosslinks

Crosslinks accumulation

- As a part of aging, crosslinks accumulate in the matrix
- Glucosepane is the major AGE in humans

Decline of collagen solubility

- Aging is associated with deterioration of the enzymatic ability to cleave collagen fibrils that interrupt matrix renewal

Targets

REVERSIBILITY OF THE GLYCATION DAMAGE
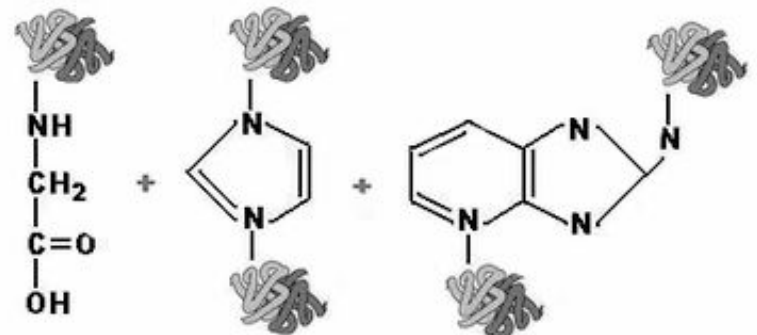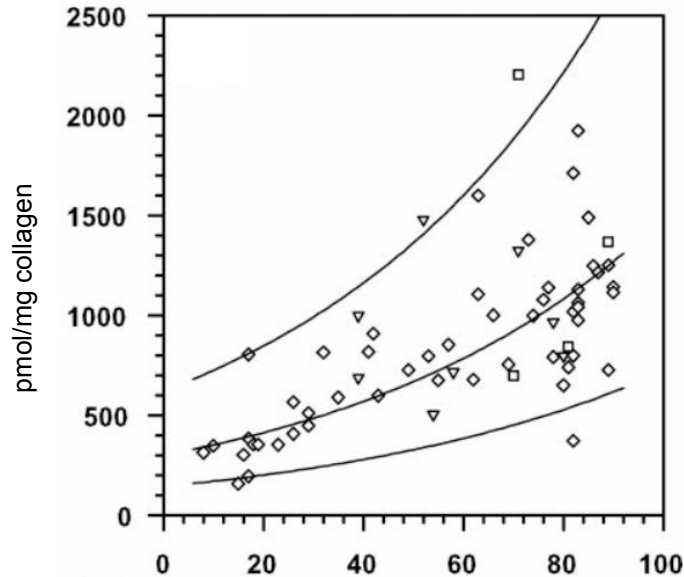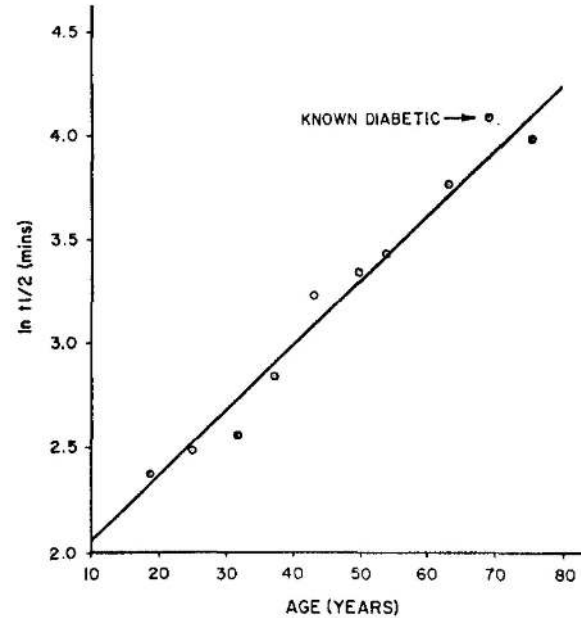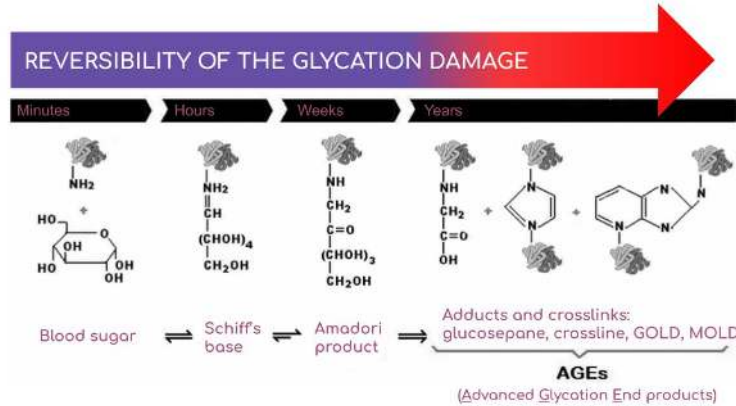
Minutes | Hours | Weeks | Years

Blood sugar ⇌ Schiff's base ⇌ Amadori product ⇌ Adducts and crosslinks: glucosepane, crossline, GOLD, MOLD

AGEs
(Advanced Glycation End products)

Precursors	→	Early glycation products	→	Advanced glycation end products
Dicarbonyls, transition metals, ROS, etc.		Schiff's bases, Amadori products, etc.		CML, CEL, hydroimidazolones, crosslinks, etc.

Our approach: development tracks

HACK01

De novo enzyme engineering

HACK02

Database search and in silico screen

HACK03

In silico directed evolution of deglycases

HACK04

Glo1 therapeutics: small molecules, biologics, etc.
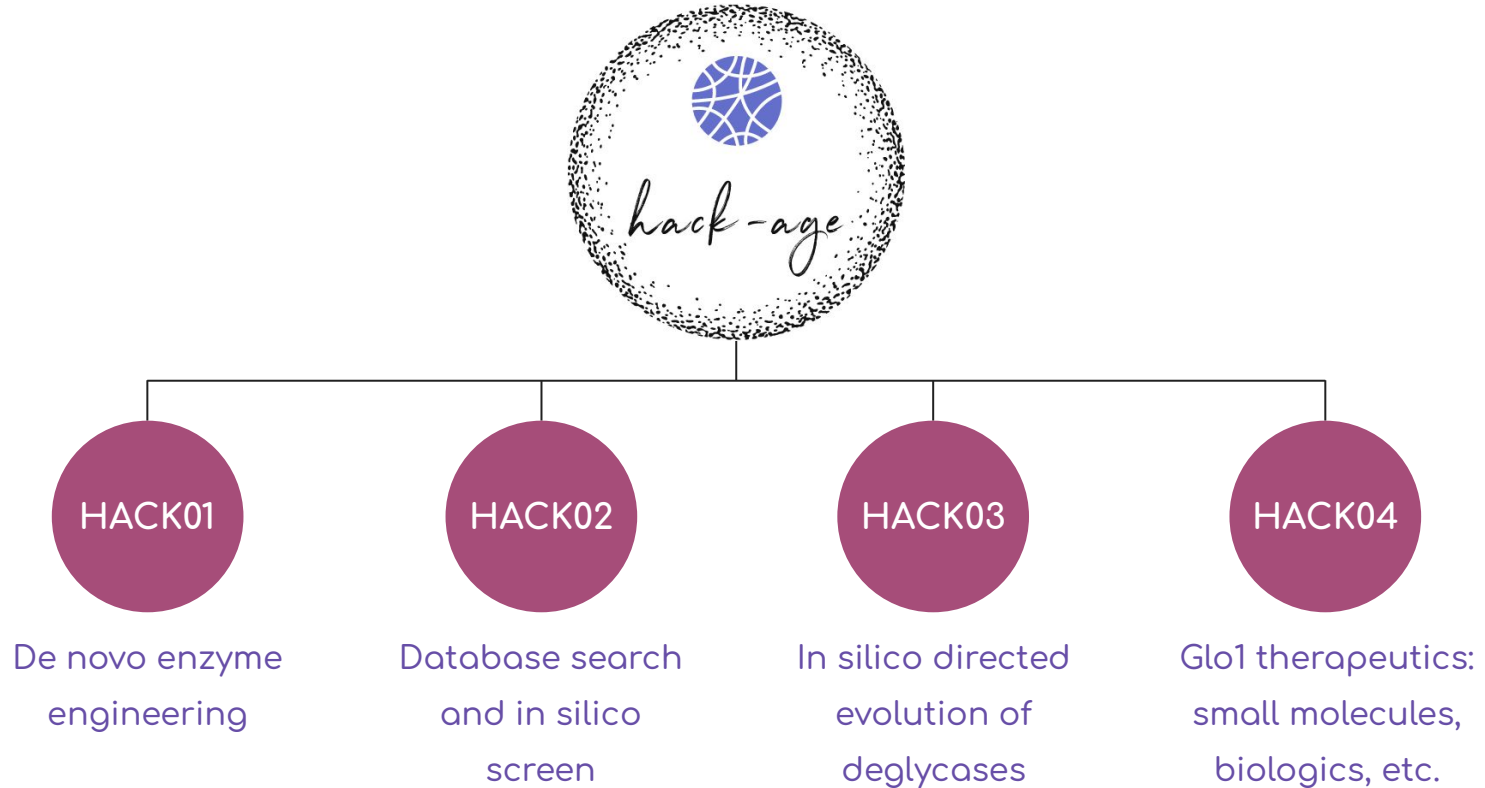
HACK02: metagenomic space
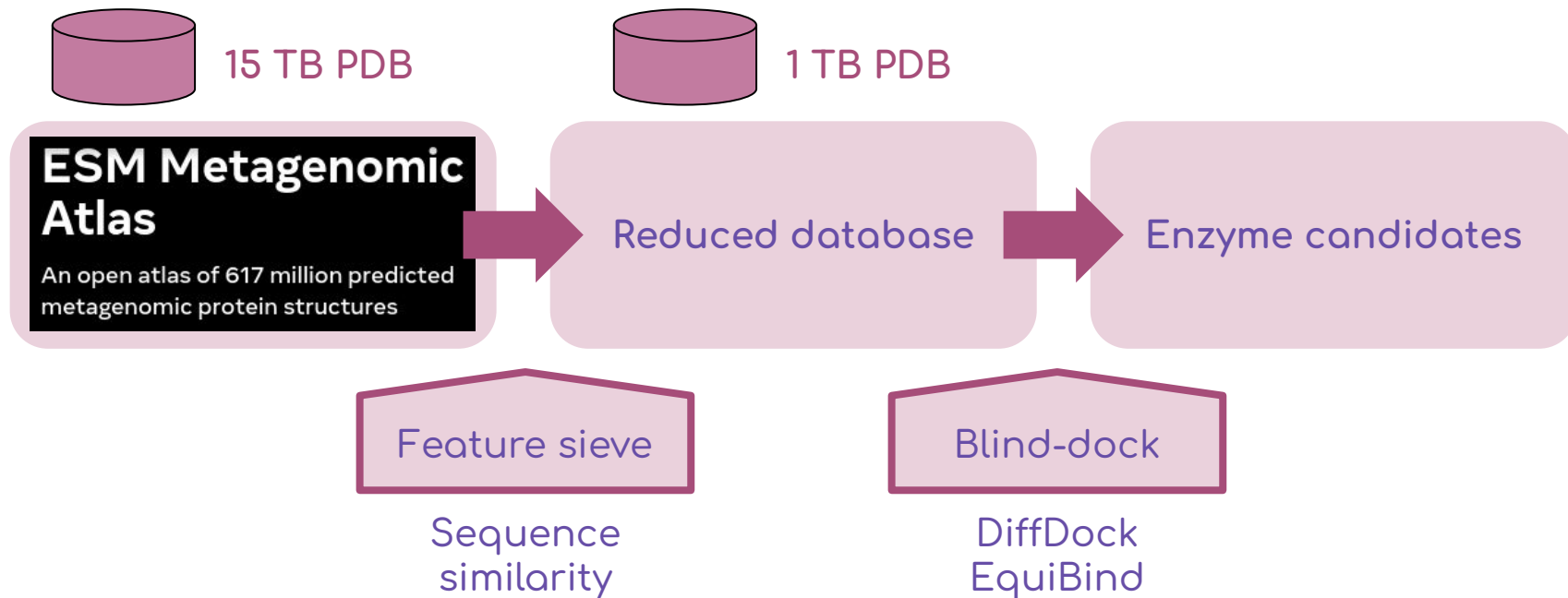
HACK03: directed evolution
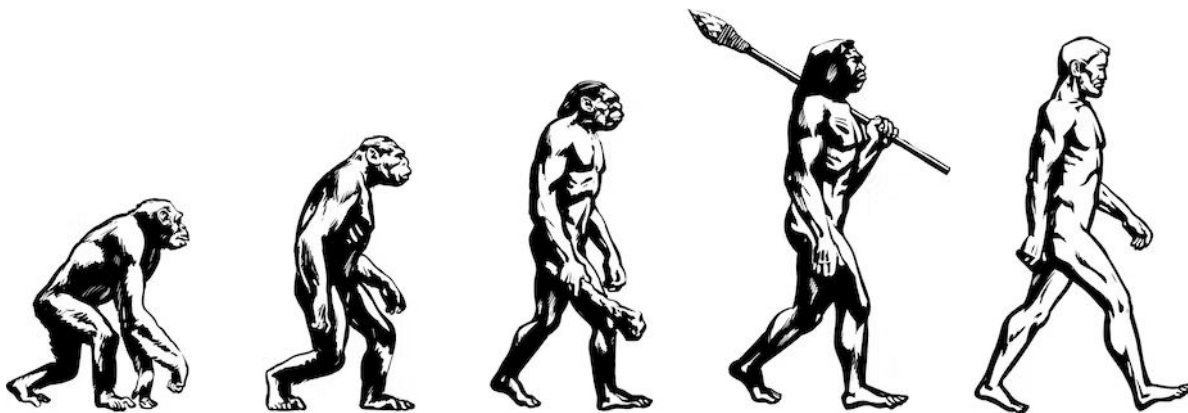
Directed evolution	→	3D conformation prediction	→	Molecular docking

MutaGAN
CADEE

AlphaFold
ESMFold

DiffDock
EquiBind

Known deglycating enzymes
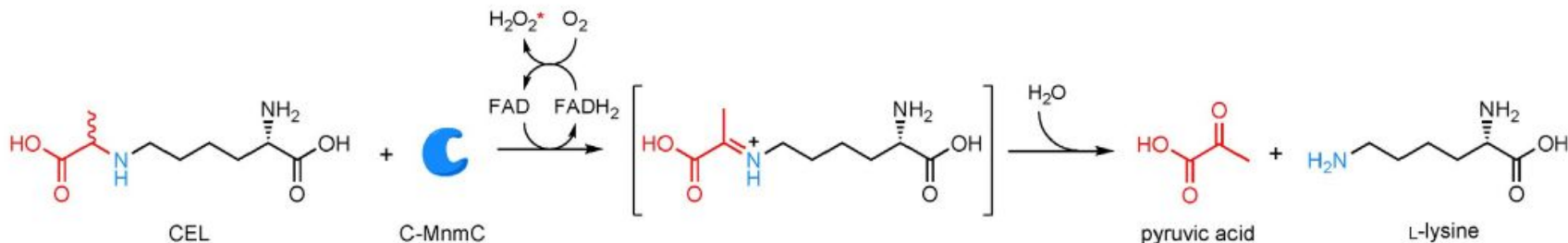
- MnmC

- DJ-1/PARK7
- GATD3A
- Glyoxalase II

Biocatalytic Reversal of Advanced Glycation End Product Modification

Nam Y. Kim,[a, b] Tyler N. Goddard,[a, b] Seungjung Sohn,[a] David A. Spiegel,[a, c] and Jason M. Crawford*[a, b, d]

HACK01: building an active site from scratch

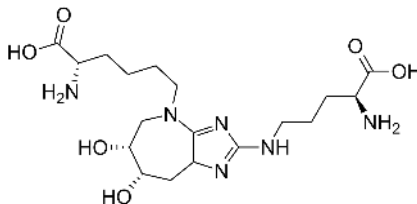1. Identify targetable glucosepane fragments

2. Hypothesize a reaction that can be applied on the fragments
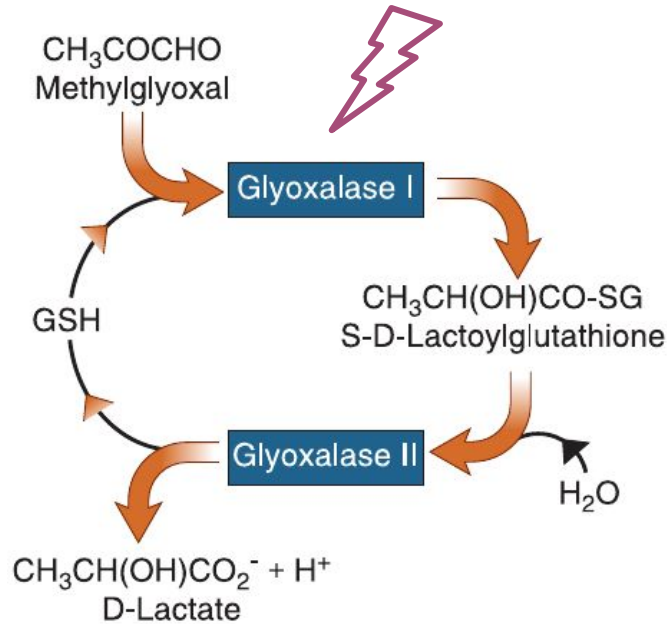
3. Use QM/MM modeling to build an active site given the reaction and the substrate

4. Extrapolate the active site topology on the full amino acid sequence

HACK04: Glo1 engineering

- DKD is characterized by ↓ Glo1:
  - nephropathy in Glo1-deficient mice
  - ↑ MGO in diabetic patients

- Overexpression of Glo1:
  - alleviates nephropathy in experimental models

Delivery of engineered Glo1 more efficient at removing toxic methylglyoxal into diabetic kidneys

Plans

Short-term:
- A running directed evolution platform
- Candidates for all four tracks by EOY 2023

Medium-term:
- Wetlab validation of candidates in 2024
- Pre-clinical leads by mid-2025

We hack age.