hack-age

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

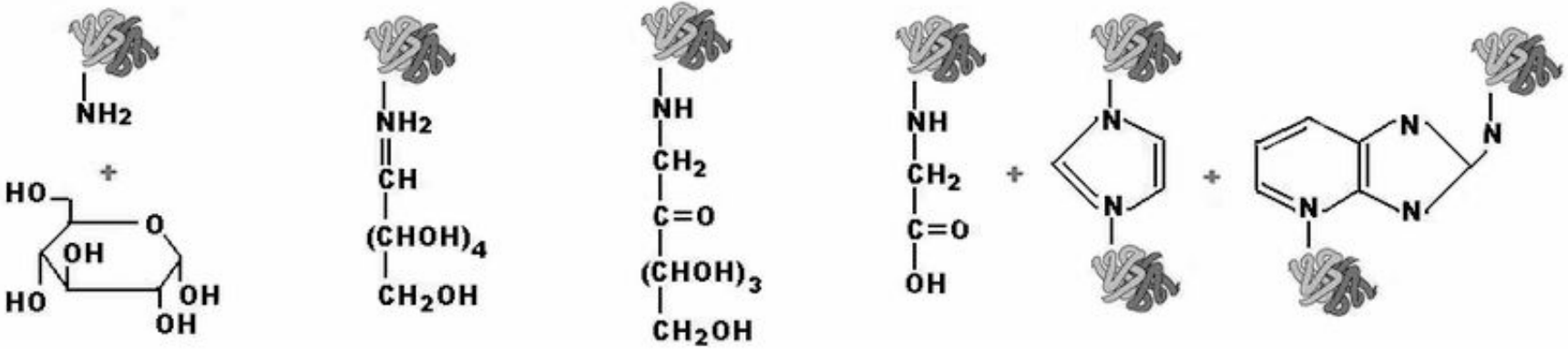
Glycation

Youthful/supple ECM

Aged/crosslinked ECM

REVERSIBILITY OF THE GLYCATION DAMAGE

Minutes | Hours | Weeks | Years

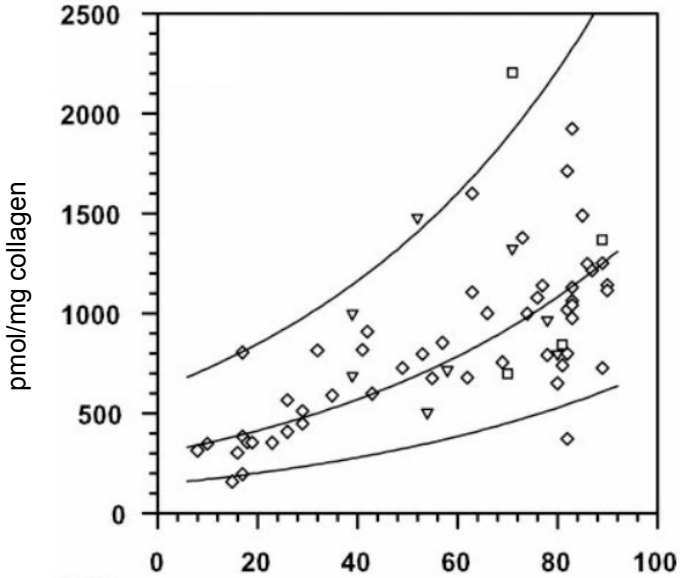


Blood sugar ⇌ Schiff's base ⇌ Amadori product ⇒ Adducts and crosslinks: glucosepane, crossline, GOLD, MOLD

AGEs

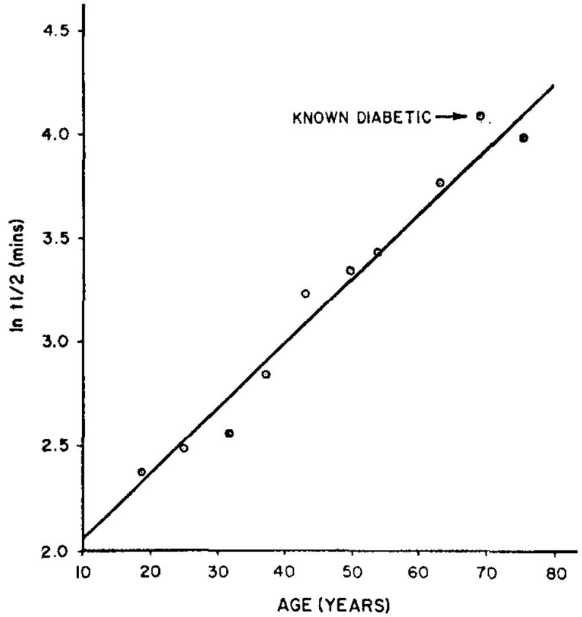
(Advanced Glycation End products)

AGEs: crosslinks



Crosslinks accumulation

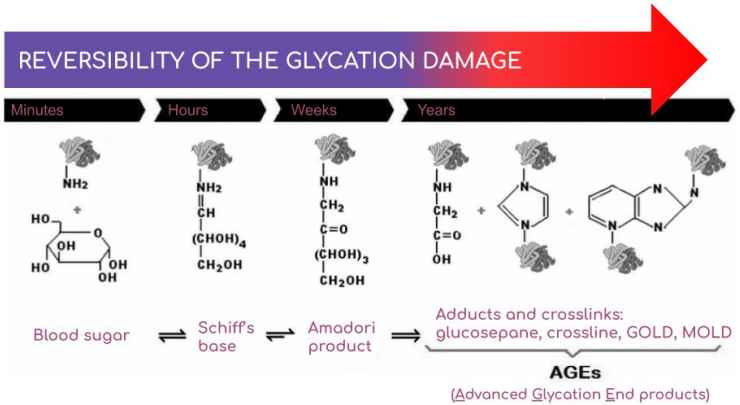
- As a part of aging, crosslinks accumulate in the matrix
- Glucosepane is the major AGE in humans



Decline of collagen solubility

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

Targets



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

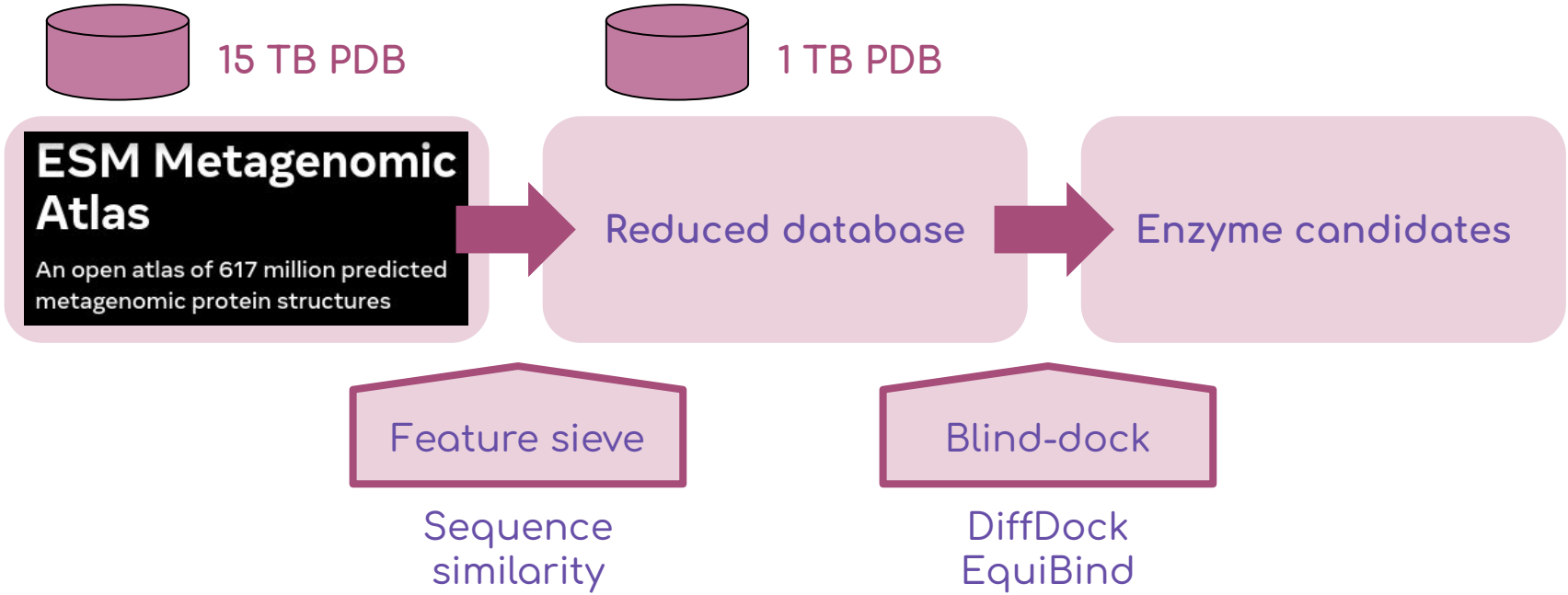
HACK03

In silico directed evolution of deglycases

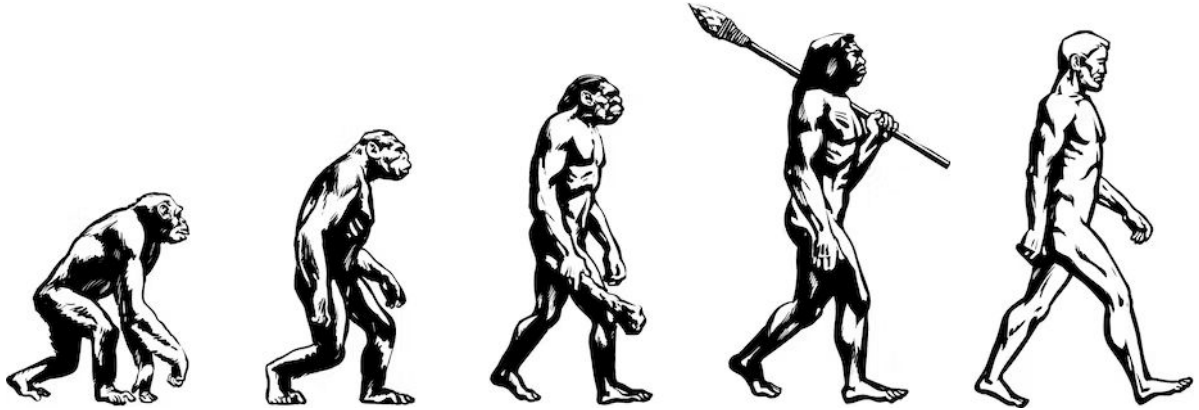
HACK04

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

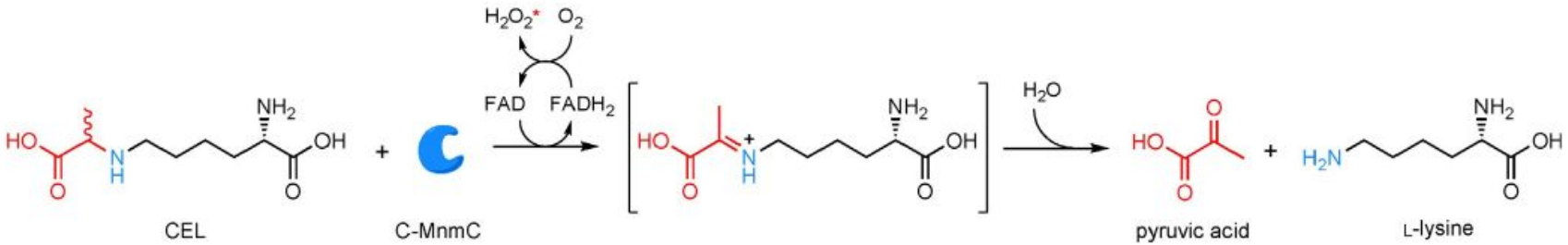
- DJ-1/PARK7
- GATD3A
- Glyoxalase II

ChemPubSoc Europe DOI: 10.1002/cbic.201900158 CHEMBIOCHEM Full Papers

VIP *Very Important Paper*

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]



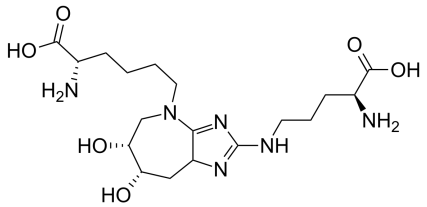
HACK01: building an active site from scratch

1. Identify targetable glucosepane fragments

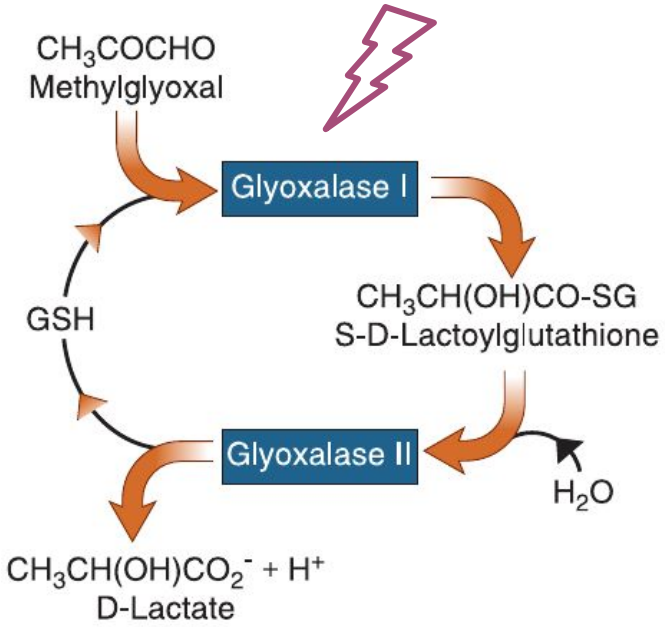
2. Hypothesize a reaction that can be applied on the fragments

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.