Digital Organs and Cells: Systems Biology Approaches for Translational Applications

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FOUNDATION FOR LIVER RESEARCH

THE ROGER WILLIAMS INSTITUTE OF LIVER STUDIES

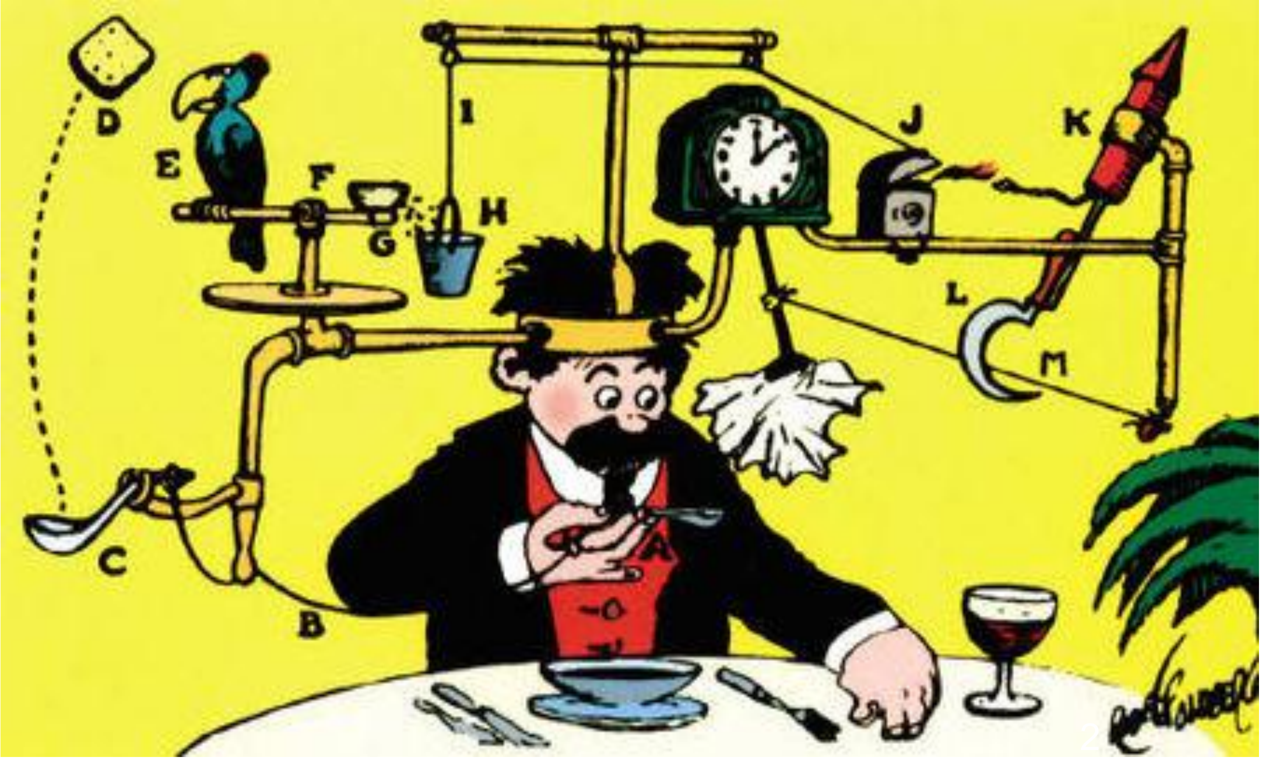
KING'S College LONDON

Systems Biology & Systems Medicine

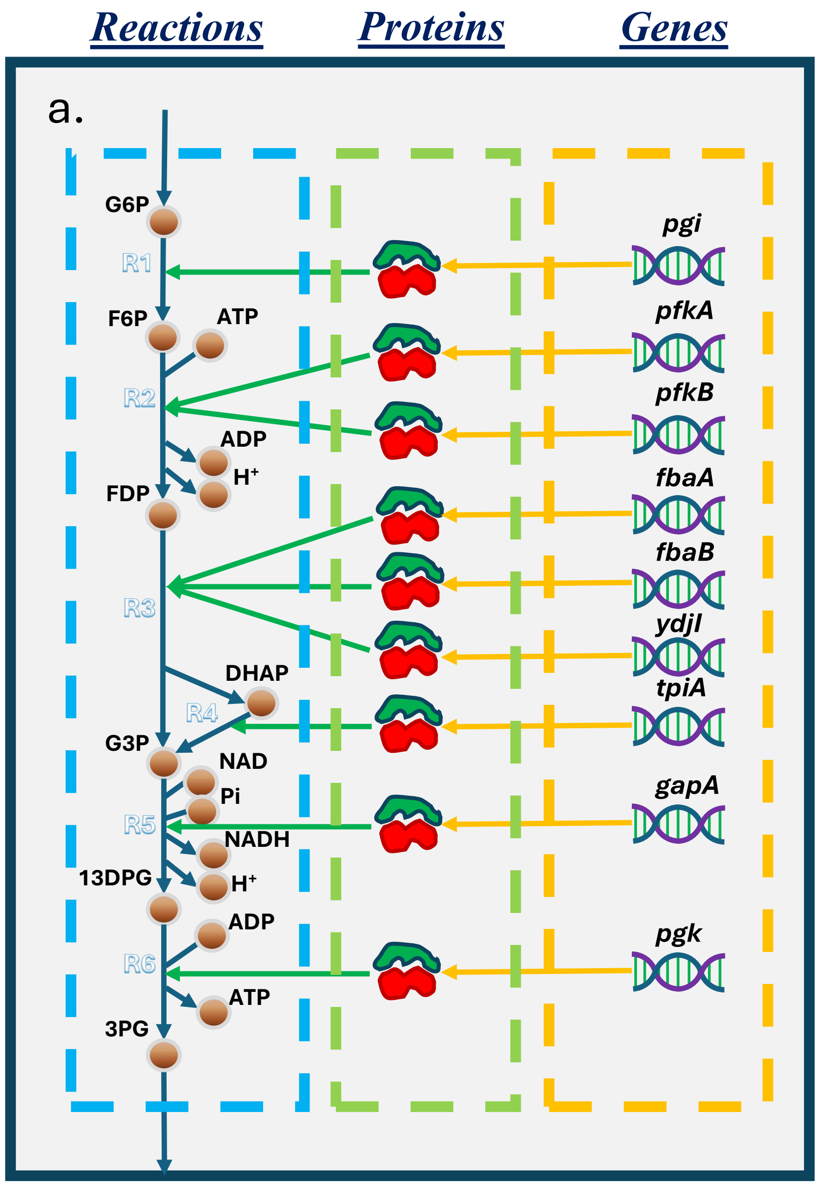
- Evolution created enormously complicated organisms and this random and chaotic process only work in particular environment.
- Over the years complicated circuits are built on top of this complex structure.
- To study and understand this complexity is a challenging task.

Rube Golberg's inventions

- ✓ Number of components
- ✓ Individual dynamics
- ✓ Their connection
- ✓ System dynamics



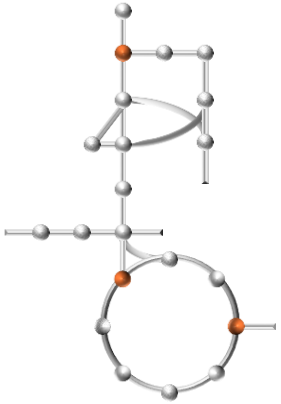
Genome-scale metabolic models



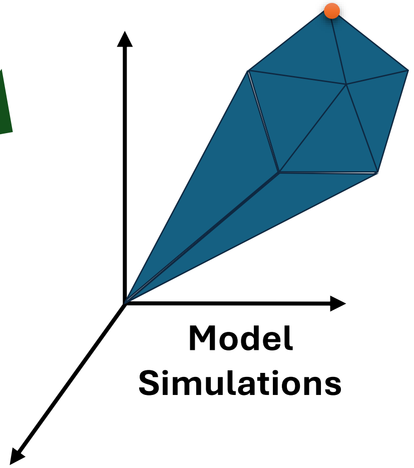
Stochiometric matrix

	R1	R2	R3	R4	R5	R6
G6P	-1	0	0	0	0	0
F6P	1	-1	0	0	0	0
FDP	0	1	-1	0	0	0
DHAP	0	0	1	-1	0	0
G3P	0	0	1	1	-1	0
13DPG	0	0	0	0	1	-1
3PG	0	0	0	0	0	1
ATP	0	-1	0	0	0	1
ADP	0	1	0	0	0	-1
NADH	0	0	0	0	1	0
NAD	0	0	0	0	-1	0
H^+	0	1	0	0	1	0
Pi	0	0	0	0	-1	0

Zhang et al (2016), Front. Physiol., 6: 413

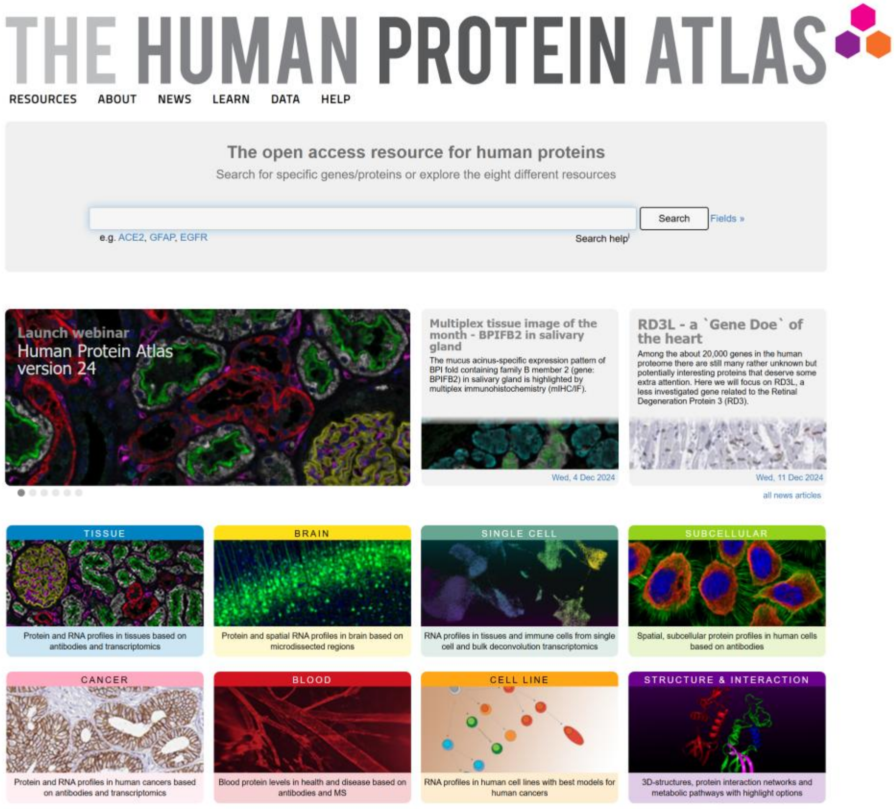


Network dependent Analysis

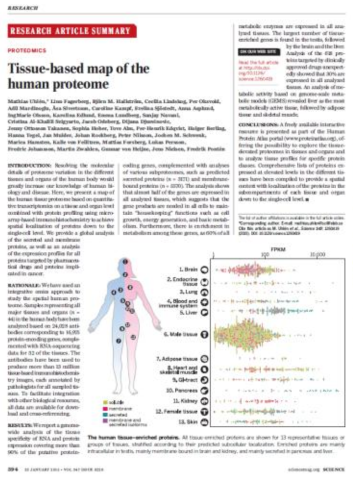


Model Simulations

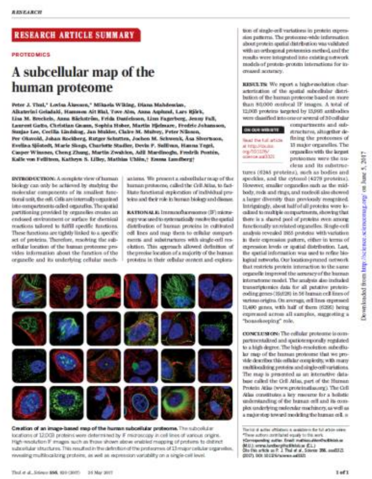
The Human Protein Atlas



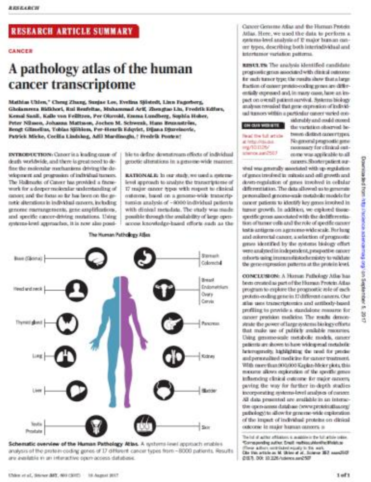
www.proteinatlas.org



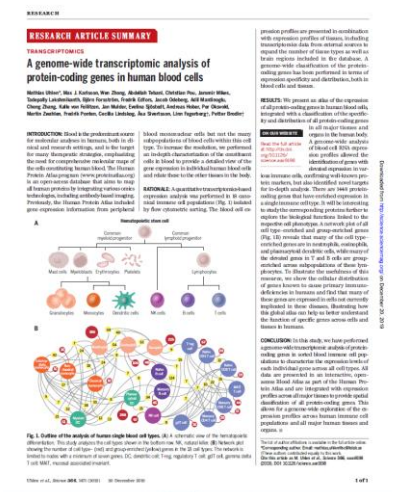
Tissue Atlas
Science, 2015



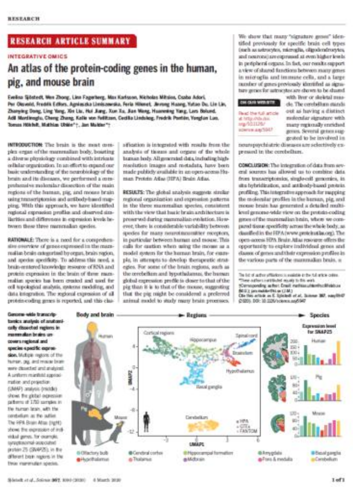
Subcellular Atlas
Science, 2017



Pathology Atlas
Science, 2017

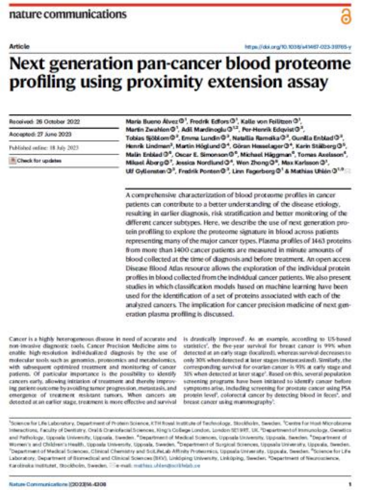


Blood Atlas
Science, 2019

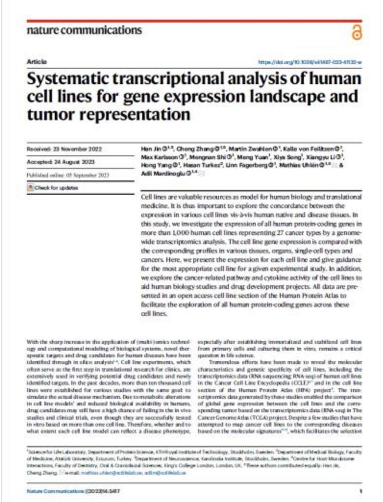


Brain Atlas
Science, 2019

Single Cell Type Atlas
Science Adv., 2021

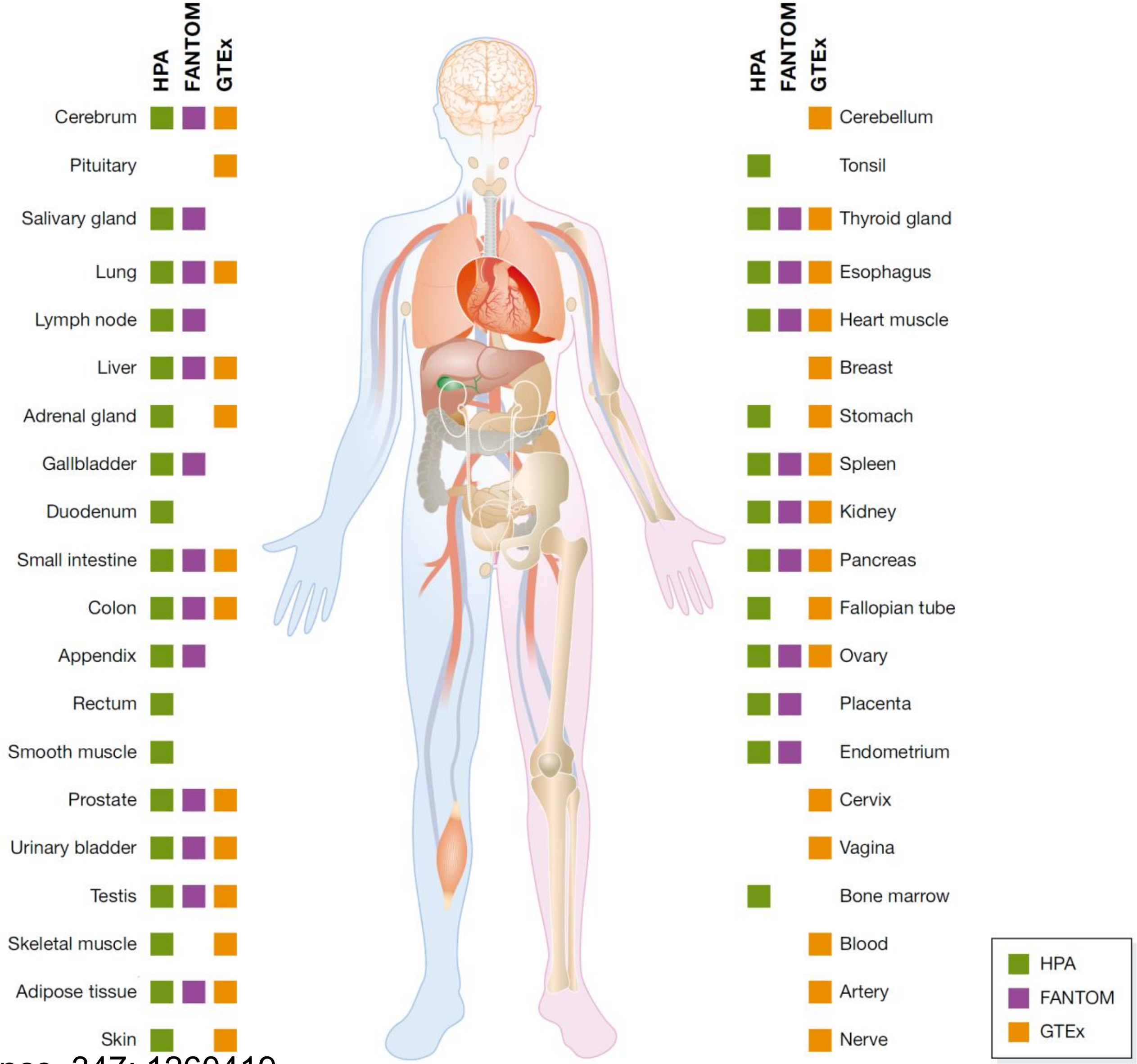


Disease Atlas
Nature Com., 2023



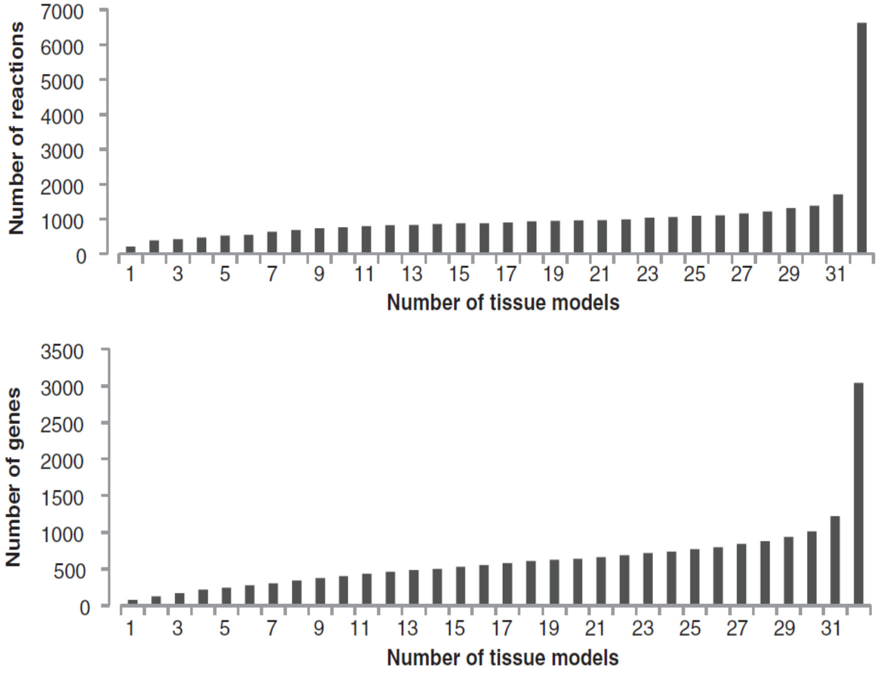
Cell Line Atlas
Nature Com., 2023

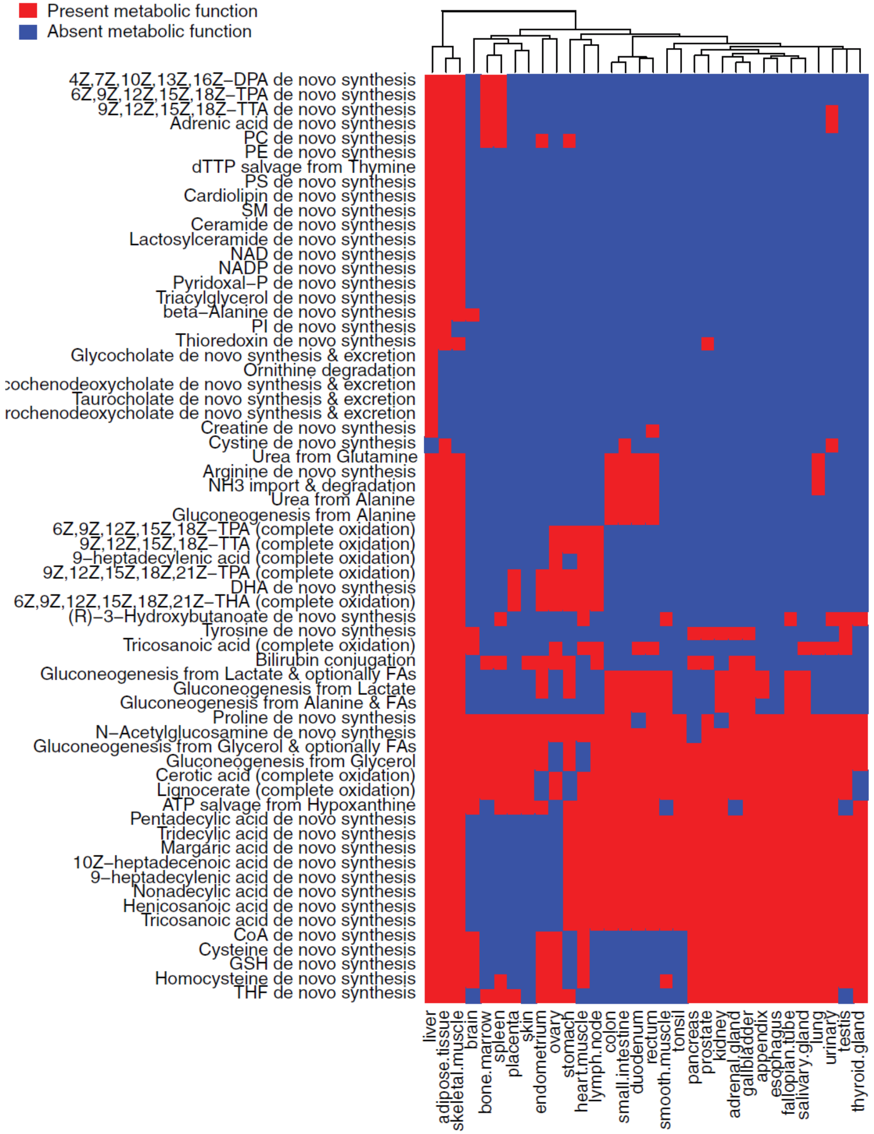
The Human Protein Atlas



Uhlen et. al (2015), Science, 347: 1260419

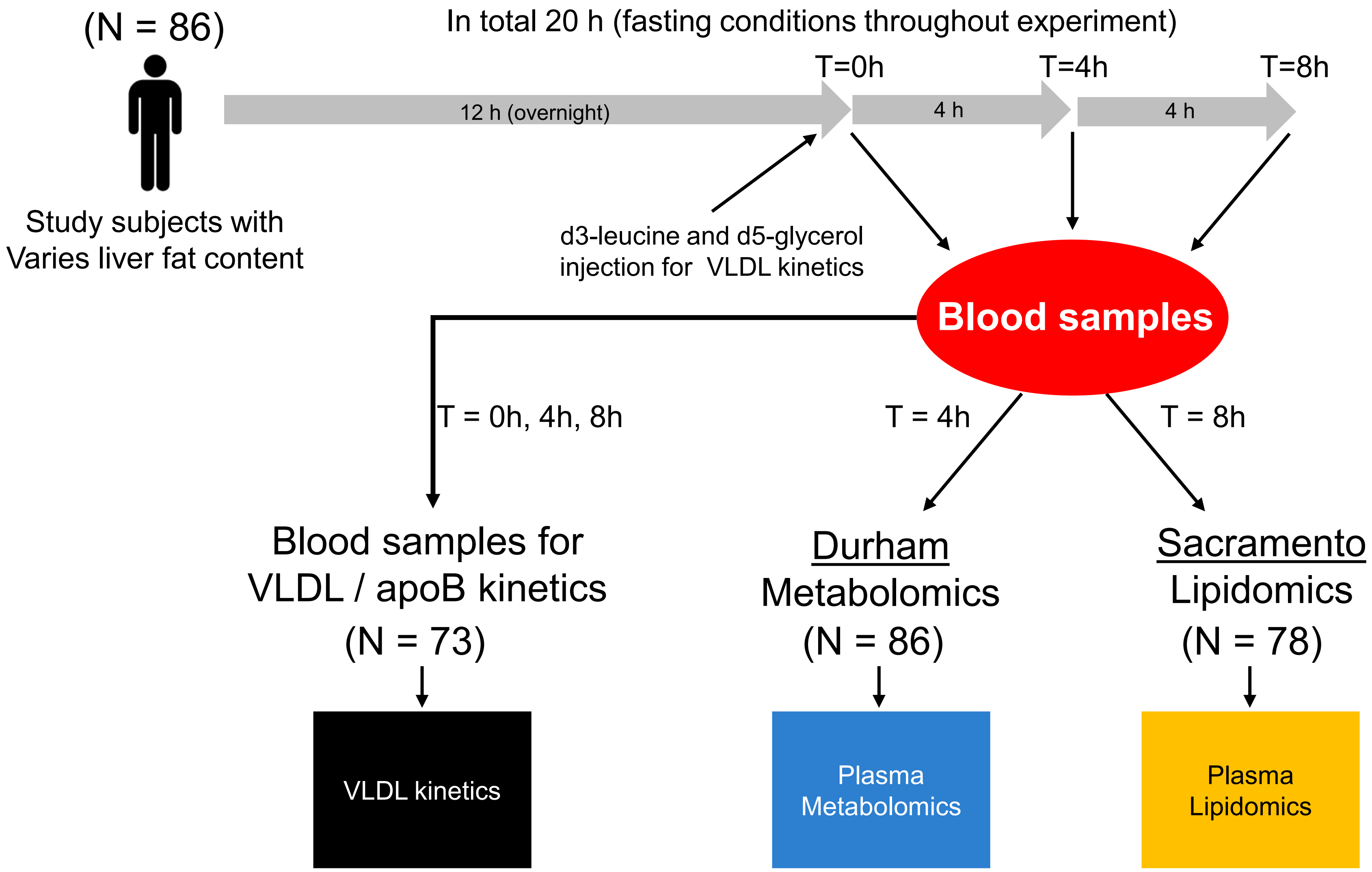
Human Tissue GEMs based on proteomics and transcriptomics data





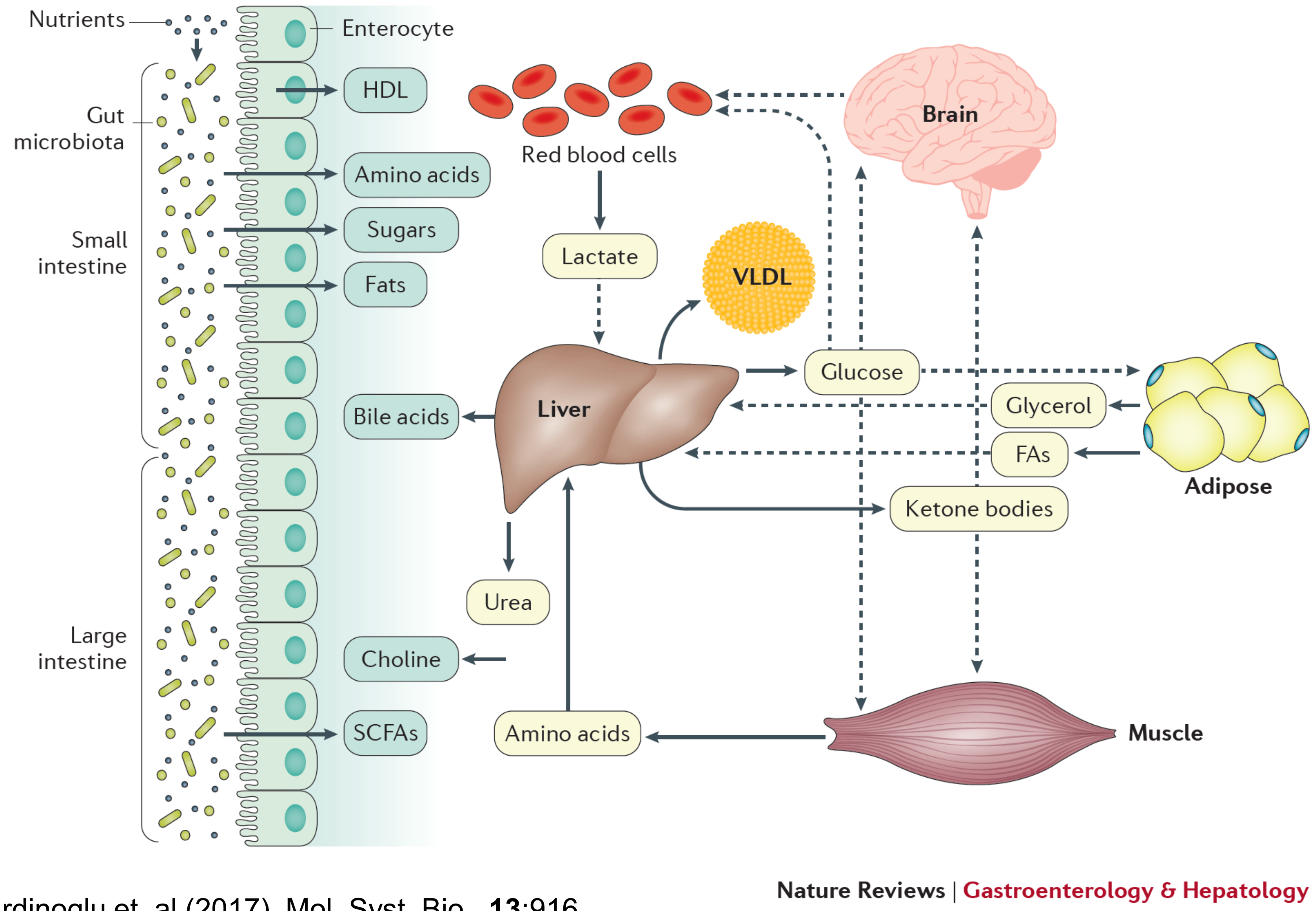
Uhlen et. al (2015), Science, 347: 1260419

Subjects with NAFLD



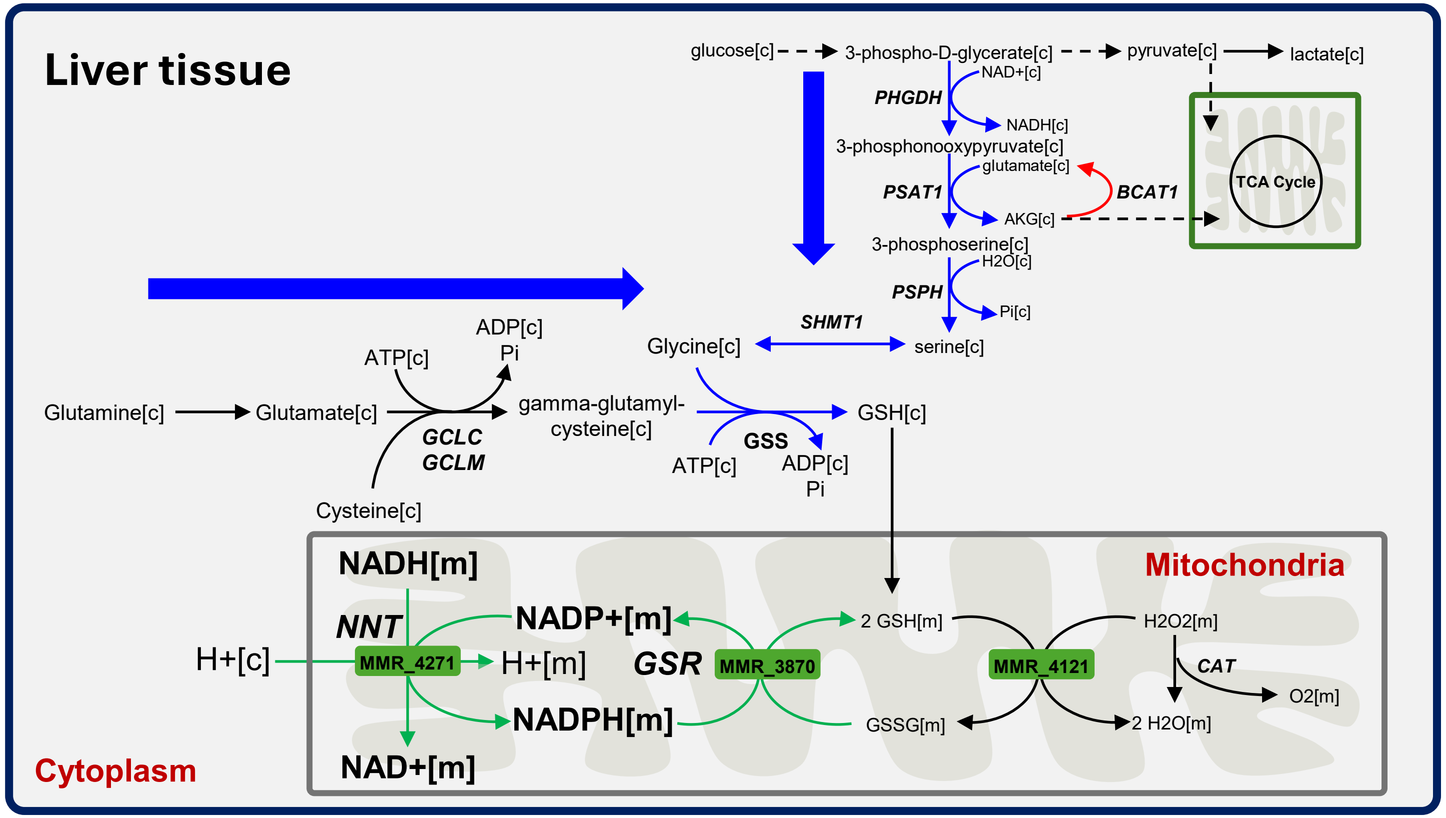
Mardinoglu et. al (2017), Mol. Syst. Bio., **13**:916

Construction of digital human liver using advanced metabolic modeling



Mardinoglu et. al (2017), Mol. Syst. Bio., **13**:916

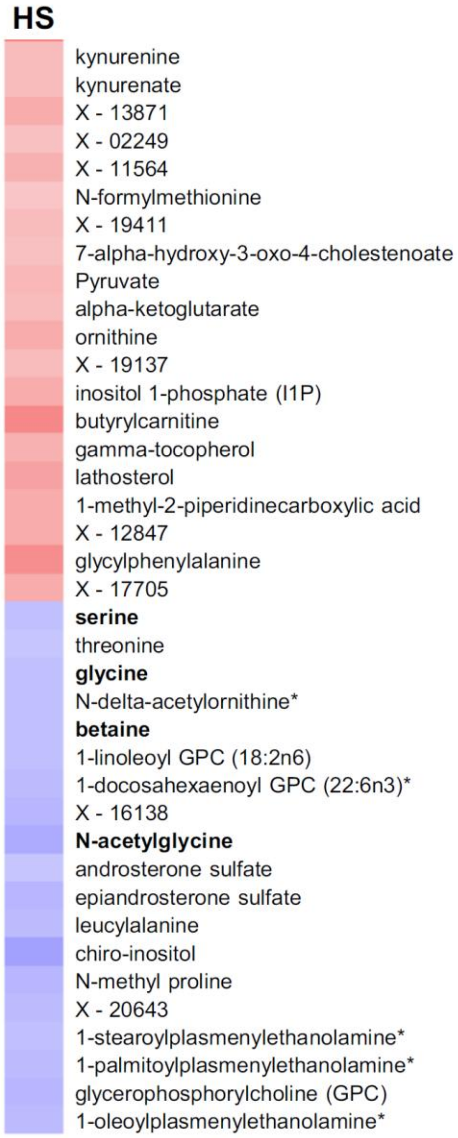
Correlation of intracellular fluxes with liver fat



Blue colour indicates down regulation of the genes.

Serine
Glycine
Betaine
Nacetylglycine

Blood



Mardinoglu et. al (2017), Mol. Syst. Bio., **13**:916

Human serine supplementation for two weeks

Clinical variable	Baseline n=6	After serine n=6	P-value
Liver fat (%)	26.8 ± 6.0	20.4 ± 7.0	**<0.05**
Age (years)	56.7 ± 5.2	56.7 ± 5.2	-
Weight (kg)	103.0 ± 14.3	103.0 ± 13.9	-
Body Mass Index (BMI) (kg/m^2)	32.5 ± 2.70	32.5 ± 2.60	-
Alanine aminotransferase (ALT) (U/L)	50.8 ± 15.2	37.6 ± 5.3	**<0.05**
Aspartate aminotransferase (AST) (U/L)	34.5 ± 8.10	27.4 ± 8.4	**<0.05**
Alkaline phosphatase (ALP) (U/L)	76.3 ± 17.2	71.3 ± 17.9	**<0.05**
γ -Glutamyl transferase (µGT) (U/L)	63.8 ± 12.9	62.3 ± 16.3	0.30
Fasting plasma glucose (mmol/L)	6.57 ± 1.41	6.33 ± 1.41	0.25
Fasting plasma insulin (FPI) (pmol/L)	46.3 ± 33.8	34.7 ± 25.2	0.23
HOMA-IR	2.15 ± 1.85	1.54 ± 1.49	0.18
LDL cholesterol (mmol/L)	3.68 ± 0.80	3.85 ± 0.94	0.50
HDL cholesterol (mmol/L)	1.00 ± 0.21	1.02 ± 0.18	0.30
Plasma triglycerides (TG) (mmol/L)	6.90 ± 6.65	3.63 ± 1.81	0.13
Total cholesterol (mmol/L)	6.23 ± 1.49	5.85 ± 1.15	0.18
Bilirubin (µmol/L)	7.33 ± 4.11	6.48 ± 3.94	0.13

Mardinoglu et. al (2017), Mol. Syst. Bio., **13**:916

Phase I: Calibration study with CMCS

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Article

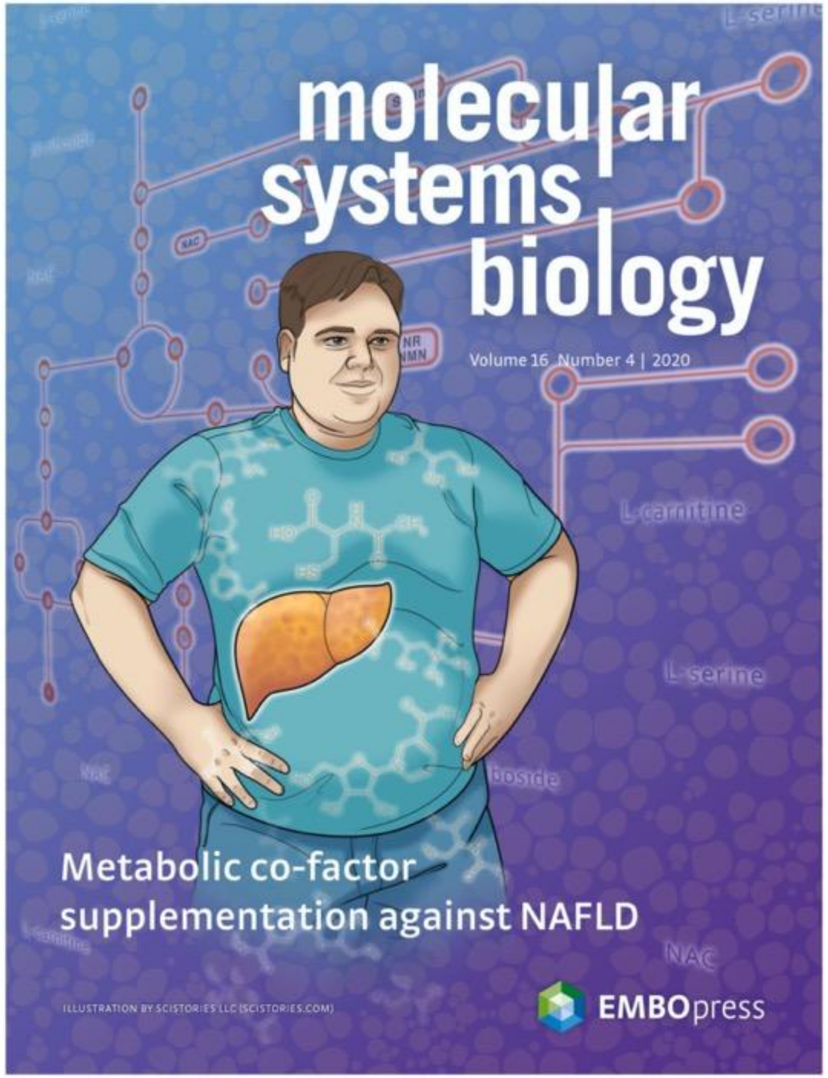
TRANSPARENT PROCESS

OPEN ACCESS

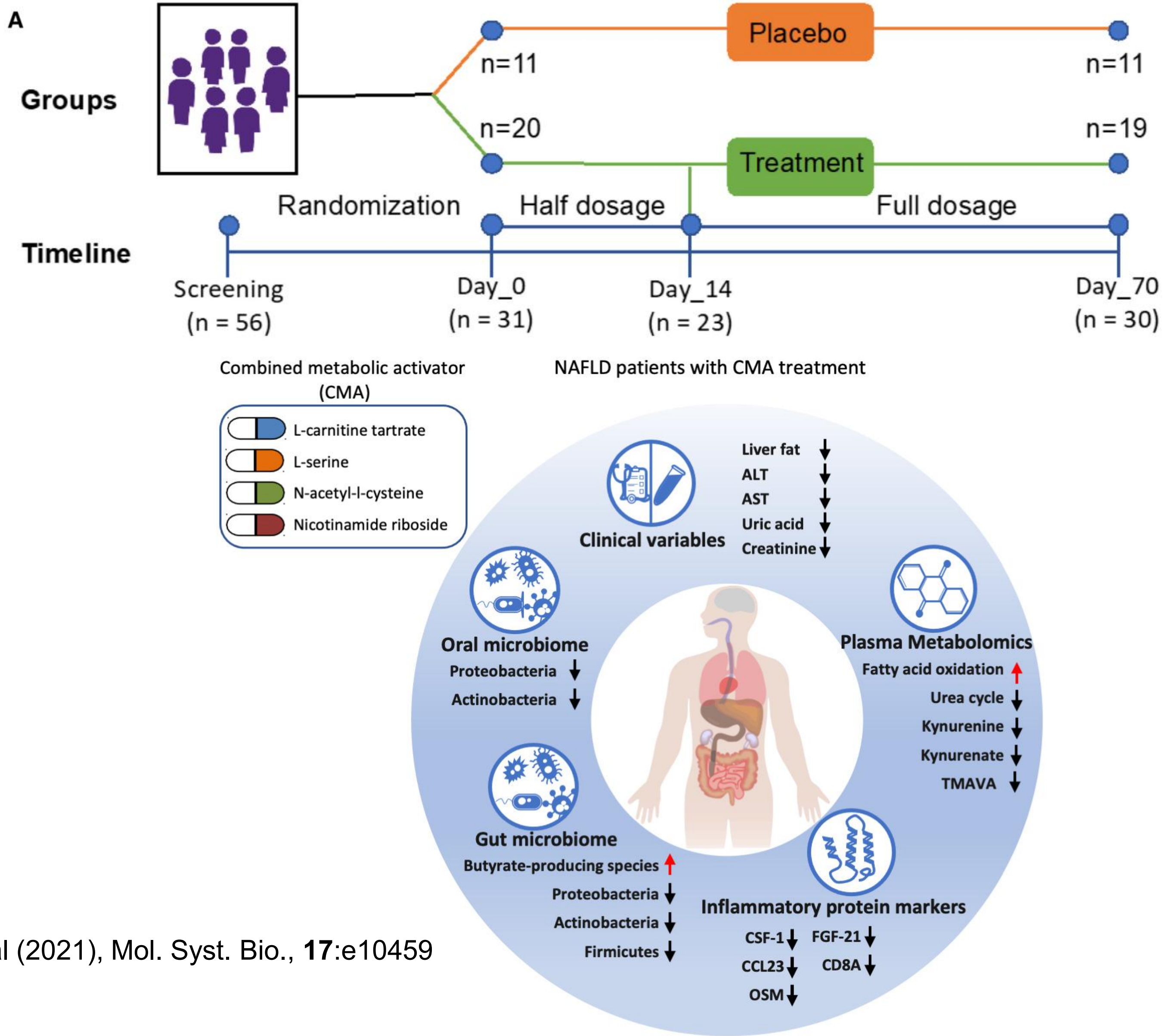
molecular systems biology

The acute effect of metabolic cofactor supplementation: a potential therapeutic strategy against non-alcoholic fatty liver disease

Cheng Zhang[1,2,†], Elias Bjornson[3,4,†], Muhammad Arif[1,†], Abdellah Tebani[1], Alen Lovric[1,‡,§], Rui Benfeitas[1,¶], Mehmet Ozcan[1], Kajetan Juszczak[1], Woonghee Kim[1], Jung Tae Kim[1], Gholamreza Bidkhori[5], Marcus Ståhlman[3], Per-Olof Bergh[3], Martin Adiels[3], Hasan Turkez[6], Marja-Riitta Taskinen[7], Jim Bosley[8], Hanns-Ulrich Marschall[3], Jens Nielsen[4], Mathias Uhlén[1], Jan Borén[3,*] & Adil Mardinoglu[1,5,**]



Phase II: Treatment of NAFLD patients with CMCS



Zeybel et. al (2021), Mol. Syst. Bio., **17**:e10459

T regulatory cells & therapeutics

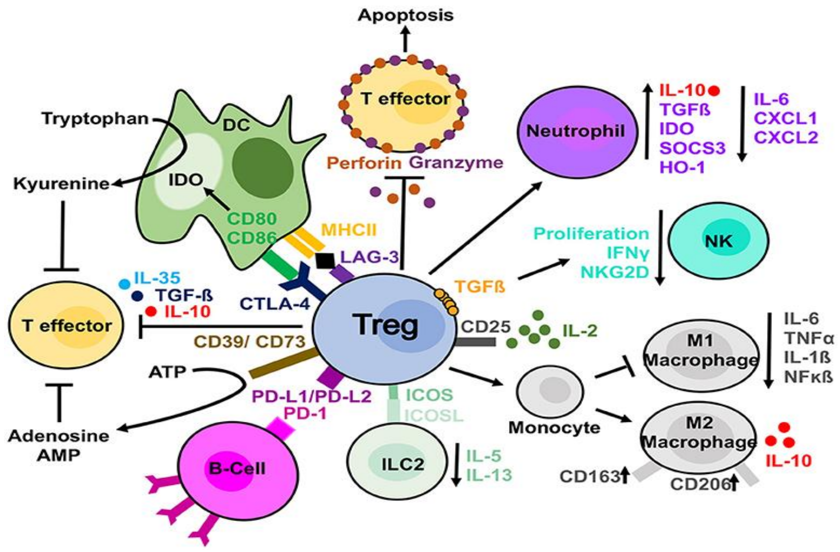
Tregs Functional Roles

- **Tolerance to Self-Antigens:** Prevent autoimmunity by suppressing self-reactive T cells
- **Regulation of Inflammation:** Control the intensity and duration of immune responses
- **Immune Homeostasis:** Maintain balance and prevent overactive immune responses

Main indications of Treg therapy

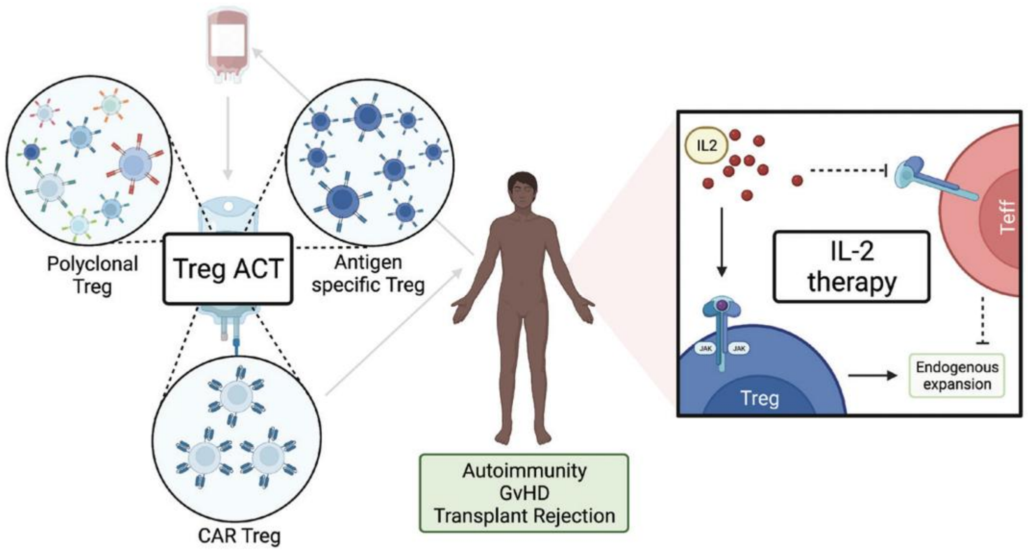
- Transplant tolerance
- Treatment of autoimmune diseases

Tregs MOAs



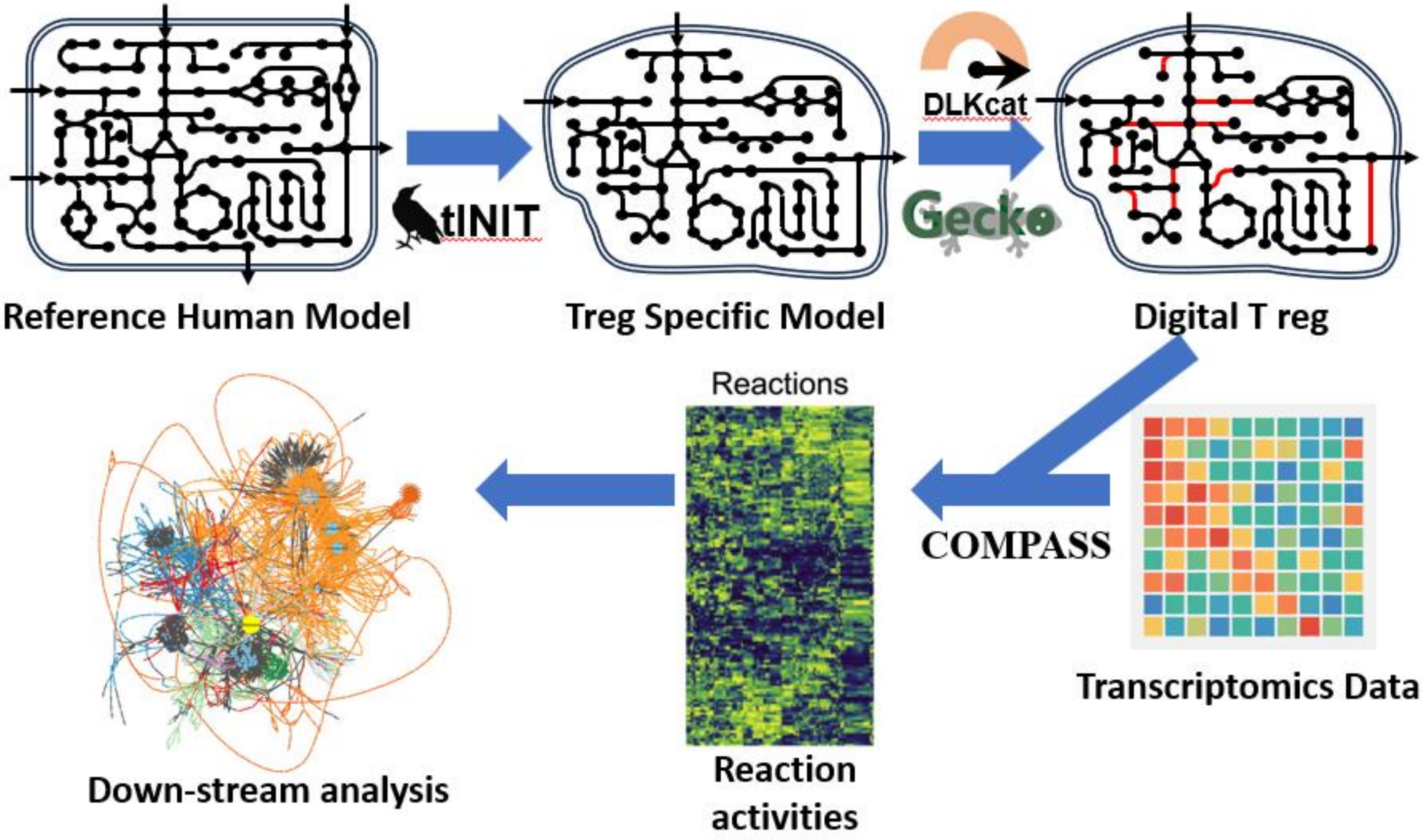
Romano M, et al. Front Immunol 2019

Treg therapy approaches that have progressed into clinical trials

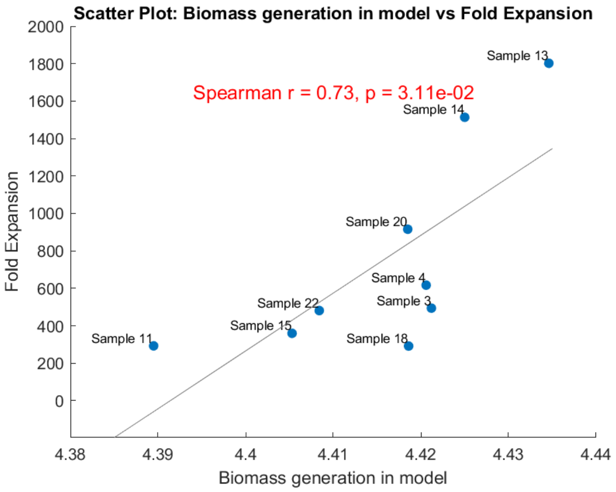


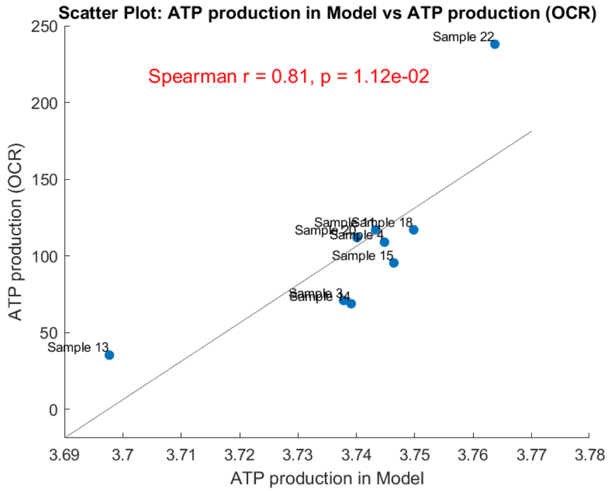
McCallion O et al. Clinical and Experimental Immunology, 2023

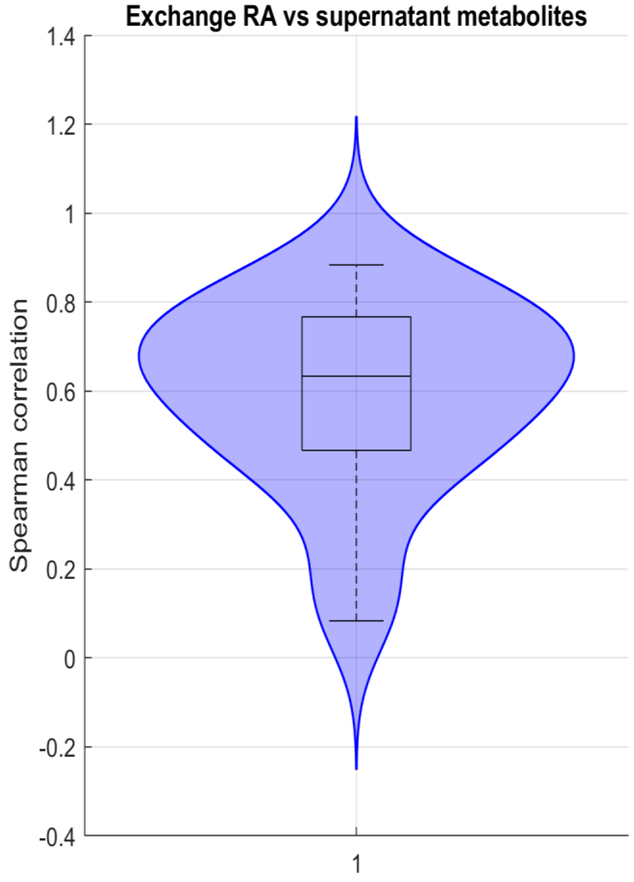
Construction of digital human regulatory T cells using advanced metabolic modeling

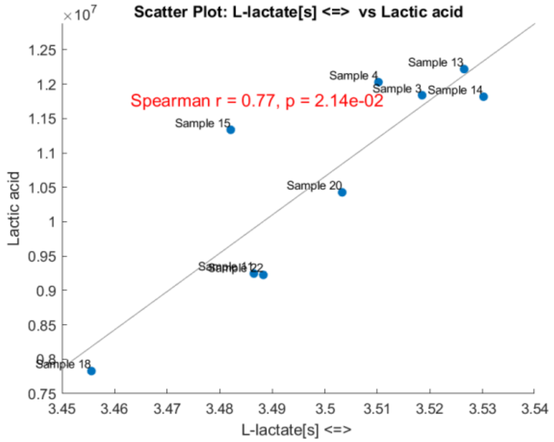


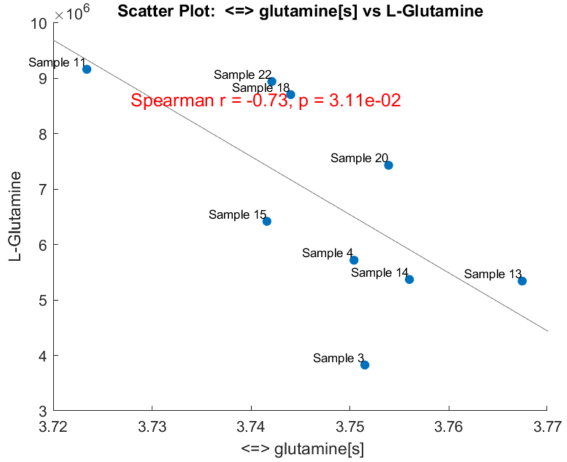
Digital T reg cells accurately predicted experimental data



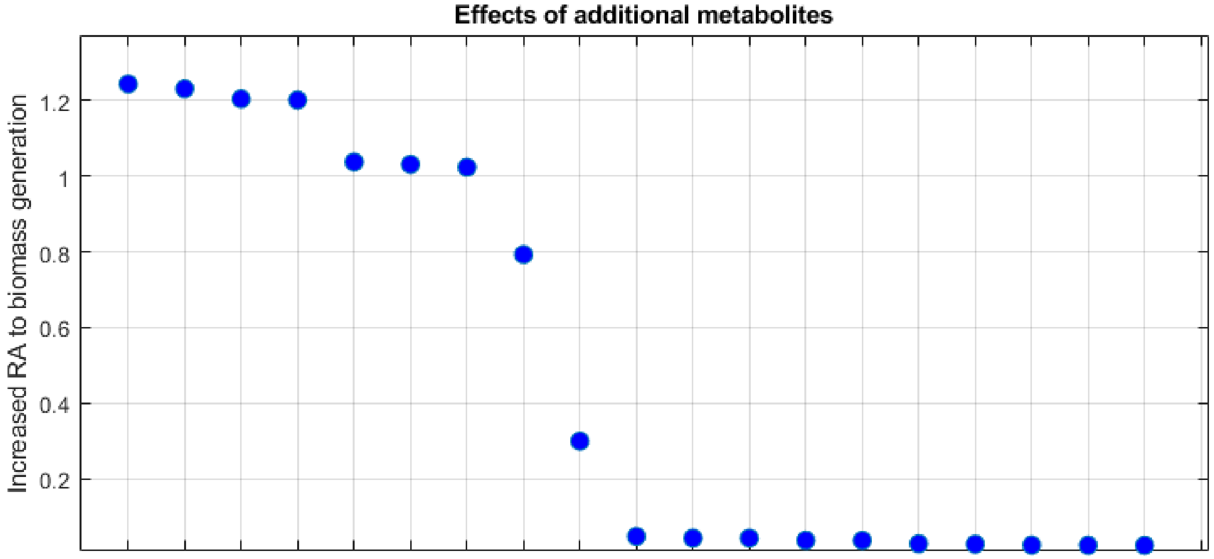


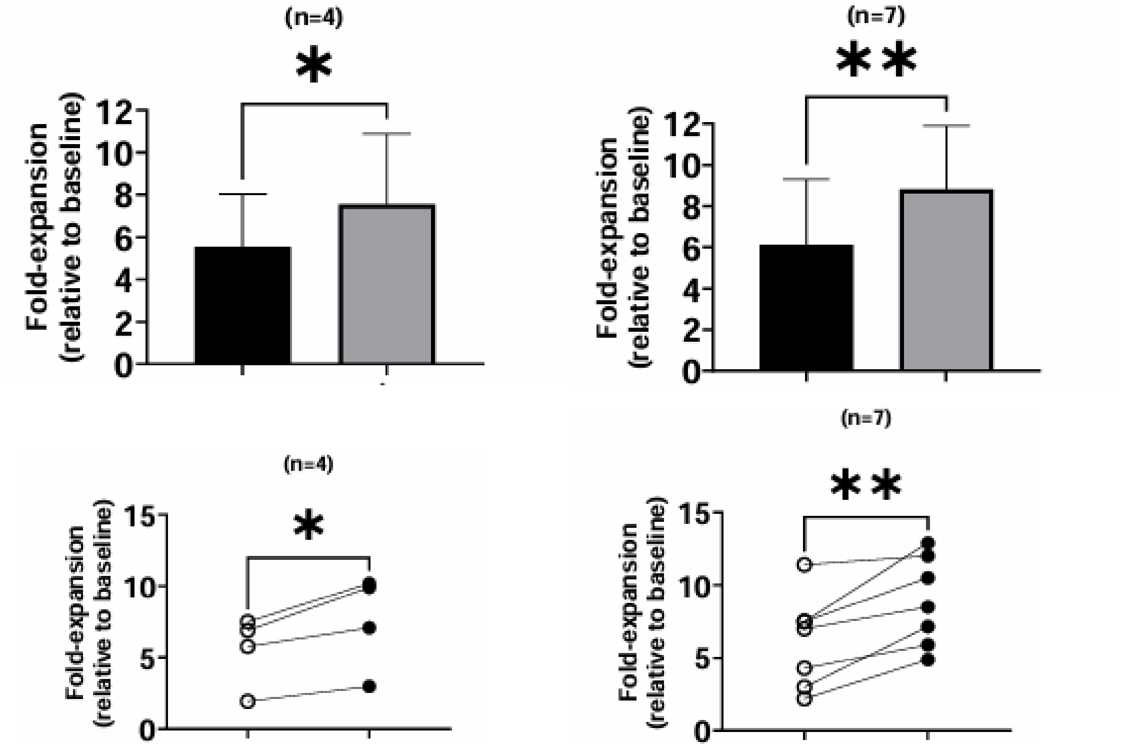






Digital T reg cell allows prediction of metabolic addition that could improve ex vivo fold expansion





Ideas for potential collaborations

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HORIZON-HLTH-2025-STAYHLTH-01-01
"Digital Human Immune System for Personalized Therapy Design"
Collaboration Concept:
- Develop personalized immune system models using plasma transcriptomics and metabolomics data integrated with AI-driven metabolic modeling.
- Combine UK computational expertise (genome-scale metabolic models, MOFA+ integration) with Korean cell expansion protocols and EU clinical cohorts and advanced imaging technologies.
- Create predictive avatars that simulate individual patient responses to immunotherapies, autoimmune treatments, and metabolic interventions.

Expected Outcome:
A validated digital human platform for personalized immunotherapy design, reducing clinical trial failures by 40% and enabling precision medicine for immune diseases.

2. Metabolically-Enhanced Multi-Cell Therapy Manufacturing Platform

HORIZON-HLTH-2025-01-IND-01
"Optimising ATMP Manufacturing"
- Establish next-generation manufacturing facilities for Tregs, CAR-T cells, and therapeutic macrophages using metabolic optimization principles.
- Integrate UK metabolic modeling (fatty acid supplementation, pathway prediction) with Korean cell expansion expertise and EU GMP manufacturing facilities and bioreactor technologies.
- Develop AI-driven quality control systems that monitor and adjust metabolic conditions in real-time during cell expansion.

Expected Outcome:
50% reduction in manufacturing time, enhanced cell potency/stability, and standardized protocols for multi-cell therapy production across Korea-EU facilities.

Acknowledgement

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Prof. Andrew J Walley

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Prof. Michael Snyder
Dr Brian D Piening

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Dr Resat Cinar
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University of Leipzig
Prof. Matthias Blüher

If you have questions, you are welcome to contact me via
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