

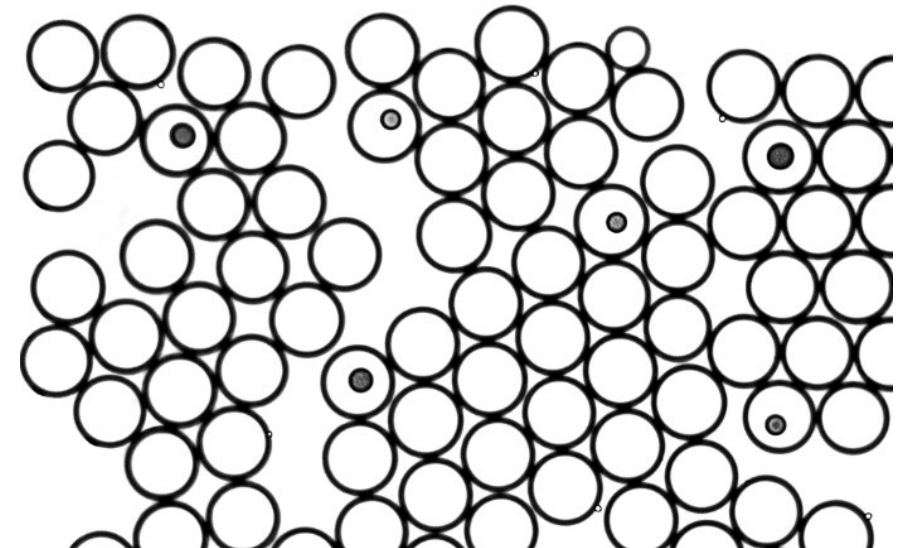
Artificial Intelligence for Personalized Therapies

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30 April 2024



Research lab: <https://bocklab.org>
Social media: <https://twitter.com/BockLab>
<https://bsky.app/profile/bocklab.bsky.social>

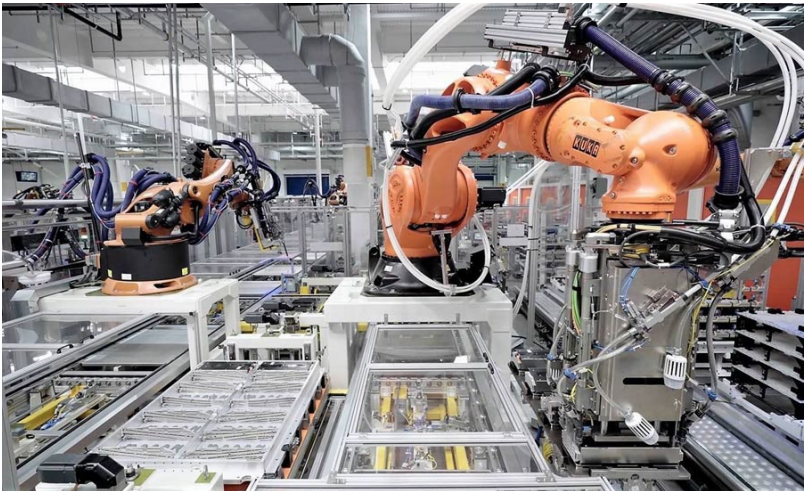




(1) How can artificial intelligence help improve medicine?



Artificial intelligence (AI) is everywhere – but what does it mean for medicine?



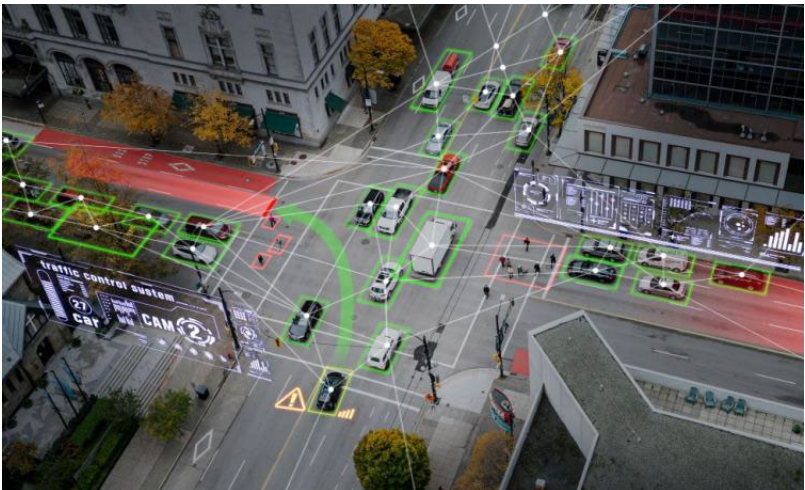
Manufacturing



Finance



Farming



Smart cities



Education



Medicine?

Current approaches: “Too little, too late” versus “move fast and break things”

Using ChatGPT as a knowledgebase & creativity tool

CH I'm preparing a talk about artificial intelligence and molecular precision medicine for a general audience. Please describe some of the most promising applications. Be concise!

Certainly! Here are some of the most promising applications of artificial intelligence in molecular precision medicine in a concise format:

1. **Drug Discovery:** AI accelerates the discovery of new drugs and personalized treatments.
2. **Disease Diagnosis:** AI aids in early disease detection using medical data and imaging.
3. **Personalized Treatment:** Tailors treatments to an individual's genetic and molecular profile.
4. **Genomic Medicine:** Analyzes DNA to understand genetic influences on health.
5. **Cancer Care:** Guides targeted cancer therapies and treatment response prediction.
6. **Clinical Trial Optimization:** Streamlines drug development and trial design.
7. **Drug Repurposing:** Finds new uses for existing drugs, speeding up treatments.
8. **Precision Public Health:** AI helps detect disease trends and plan interventions.
9. **Telemedicine and Remote Monitoring:** Enables remote patient health tracking and early intervention.
10. **Ethical Data Handling:** Ensures privacy and ethical use of health data in AI applications.

These applications illustrate AI's potential to improve healthcare outcomes and individualize medical treatments.

Using GPT-3 as an “amateur therapist”

Rob Morris @RobertRMorris · Jan 6 ...
We provided mental health support to about 4,000 people — using GPT-3. Here's what happened 🙌
1,205 4,249 6,012 8.5M

Rob Morris @RobertRMorris · Jan 6 ...
To run the experiment, we used @koko — a nonprofit that offers peer support to millions of people...
20 48 282 499.3K

Rob Morris @RobertRMorris · Jan 6 ...
On Koko, people can ask for help, or help others. What happens if GPT-3 helps as well?
6 14 210 488.7K

Rob Morris @RobertRMorris · Jan 6 ...
We used a 'co-pilot' approach, with humans supervising the AI as needed. We did this on about 30,000 messages...
8 25 275 492.5K

<https://kokocares.org> → Mental health support by volunteers

How can artificial intelligence help improve medicine?

Mundane tasks (→ easy for a human, not necessarily easy for a computer)

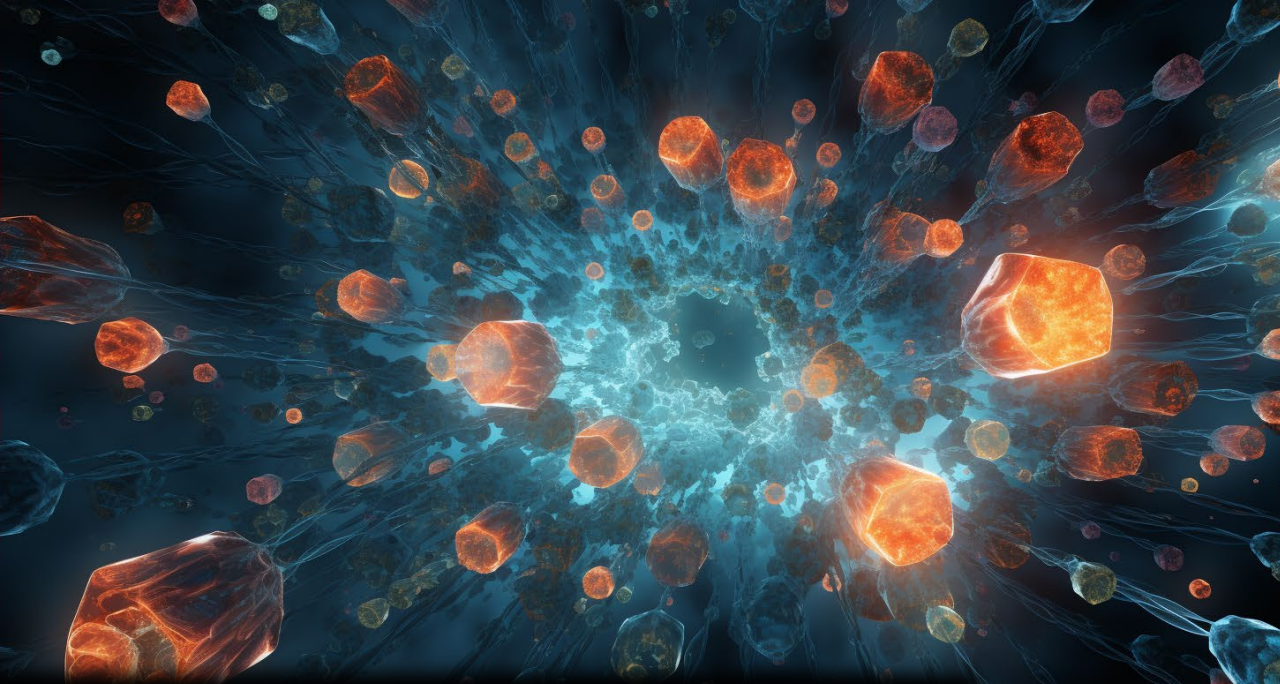
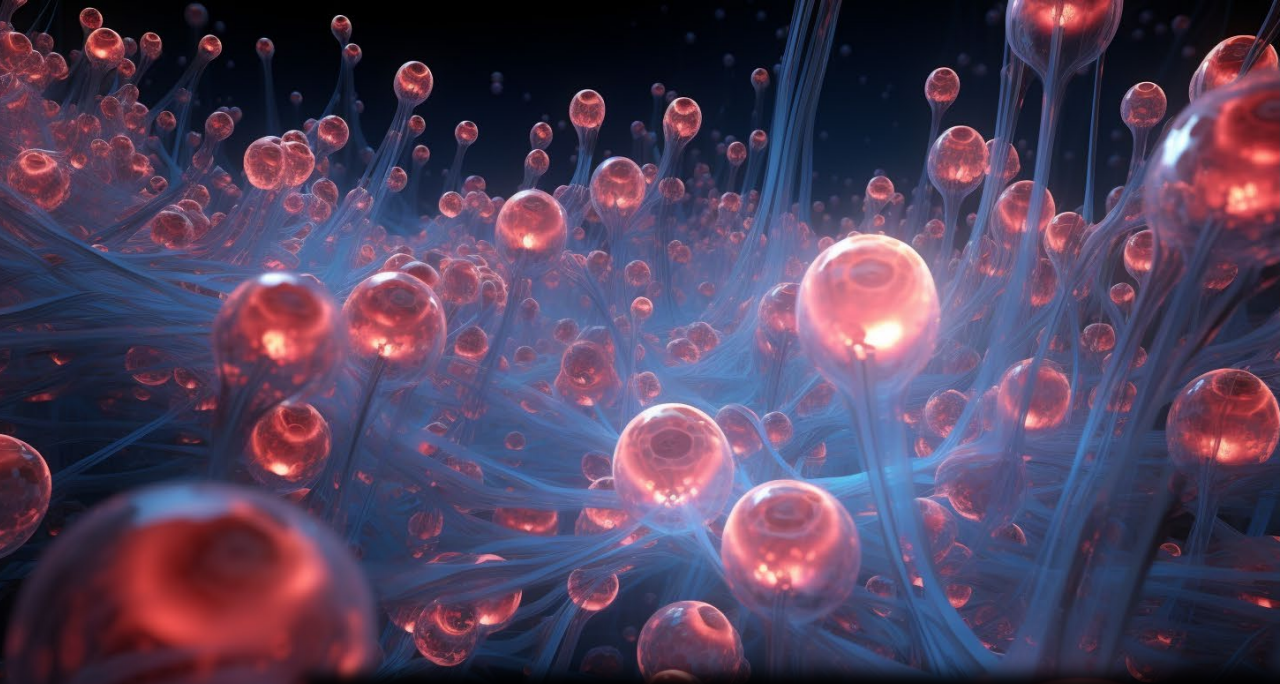
- *Routinely done by humans, AI could save time/cost:*
Scheduling appointments; filling prescriptions; documentation & archival
- *Not currently done, usually because of time/cost constraints:*
24/7 accident monitoring for the elderly; checking for drug-drug interactions



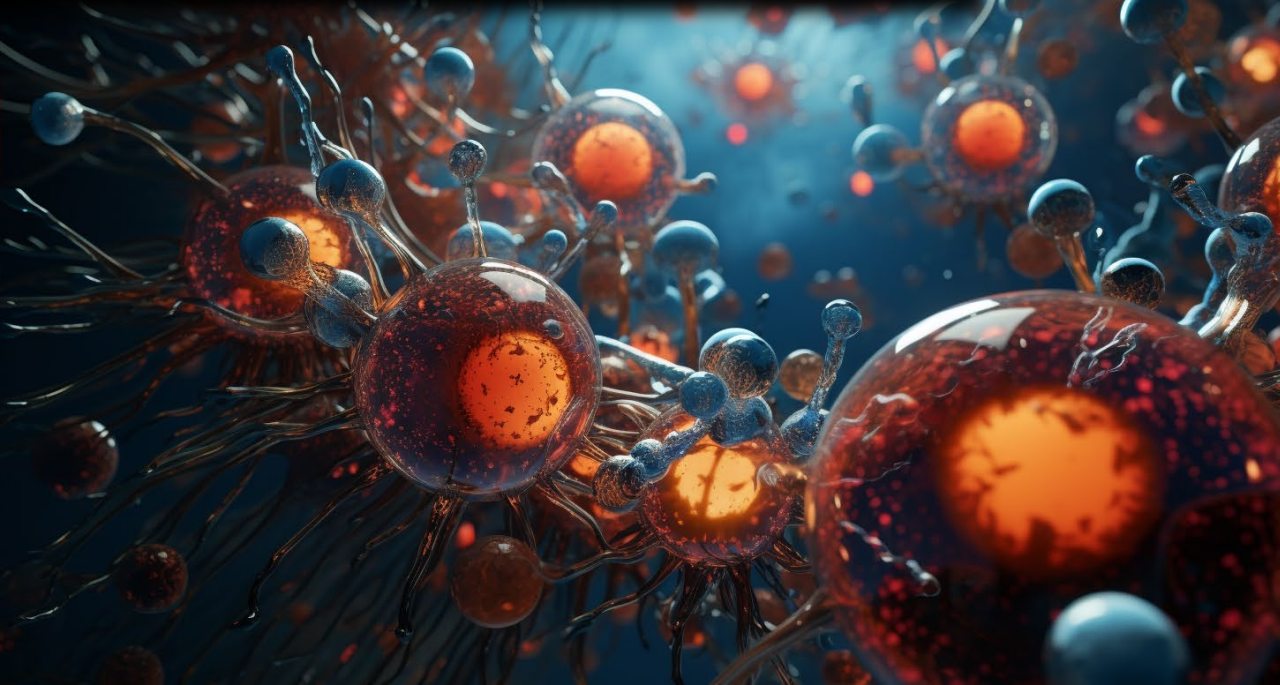
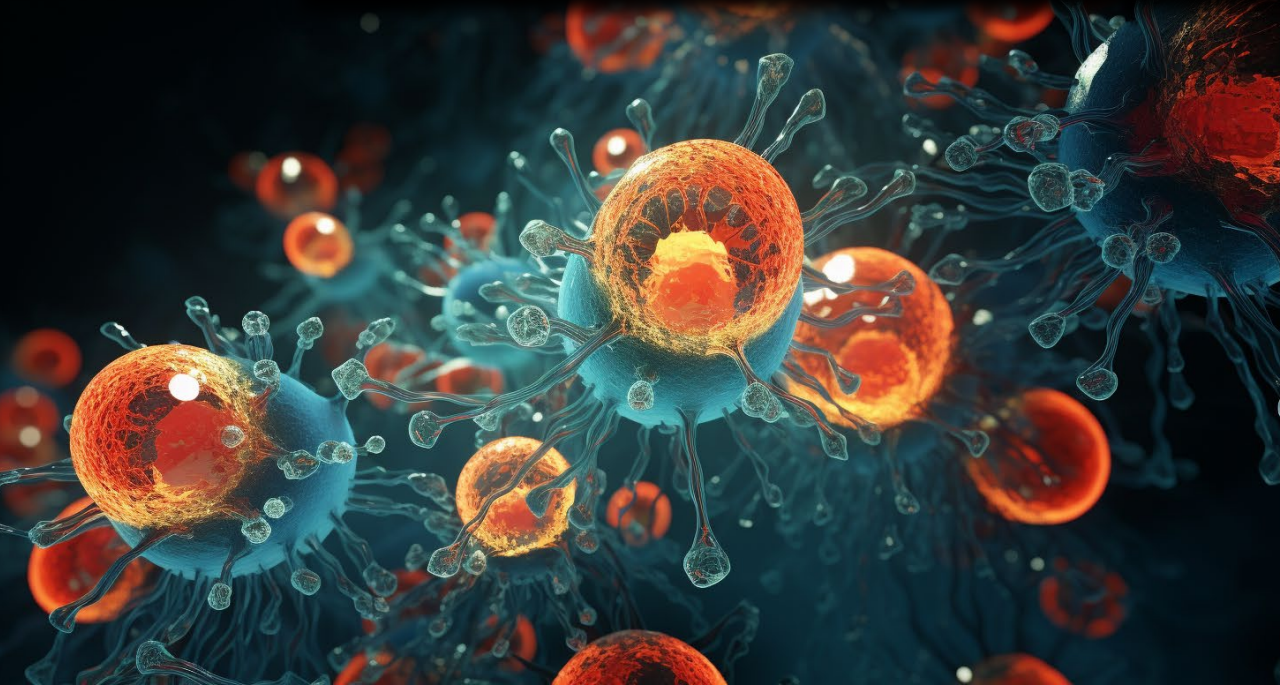
Complex tasks (→ usually requires highly trained specialists)

- *Data-heavy diagnostics:* Diagnosing cancer based on (epi)genomics data, radiology images, photos of skin lesions, etc.
- *New therapies:* Drug development, personalized therapies (e.g., mRNA cancer vaccines), **cells programmed to act as therapeutics**

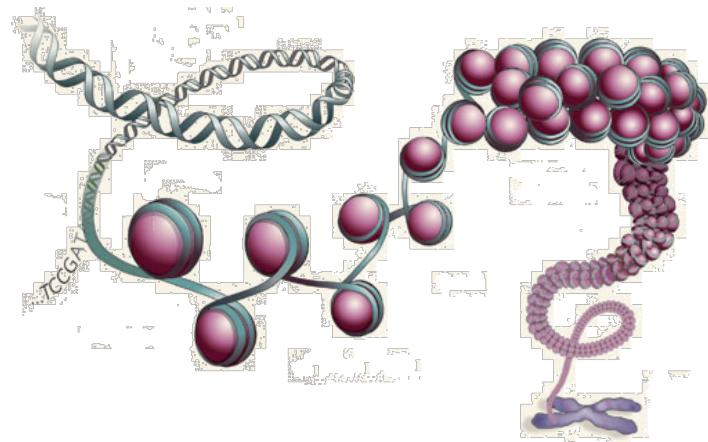




(2) Dissecting the epigenetic past and future potential of immune cells



Epigenetic mechanisms constitute a layer of genome regulation beyond the DNA sequence



1D: Genome sequence

- Protein-coding genes
- Regulatory elements



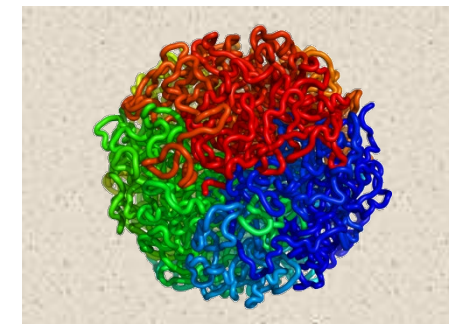
“2D”: Epigenetic marks

- DNA methylation
- Histone modifications



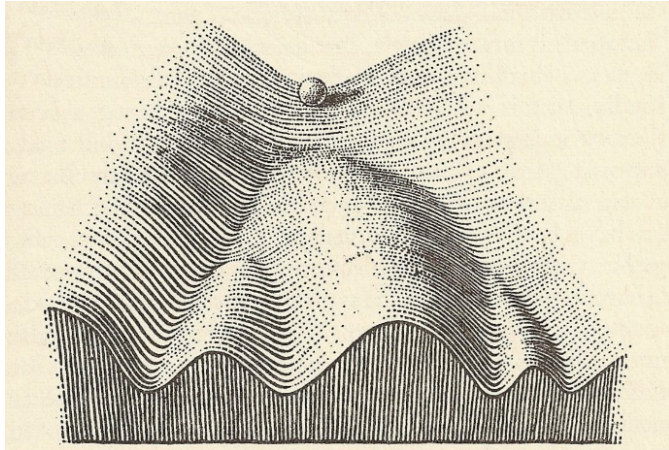
3D: Nuclear organization

- Chromatin domains
- Promoter-enhancer links



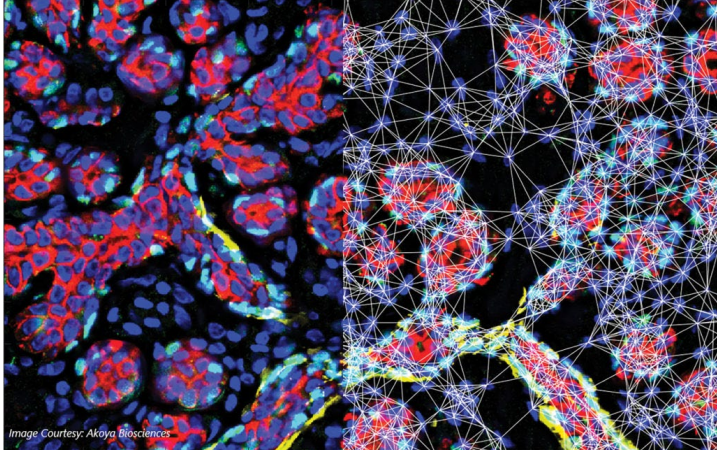
Epigenetic cell states connect the past, present, and future of single cells

Cell states reflect each cell's developmental past



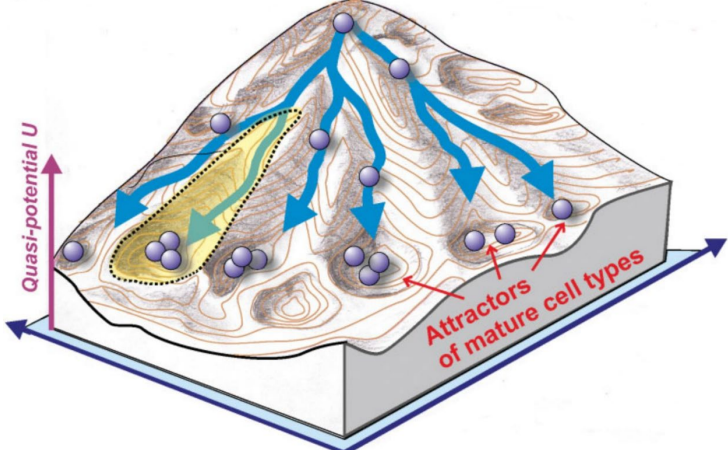
PAST

Cell states are shaped by the current tissue microenvironment



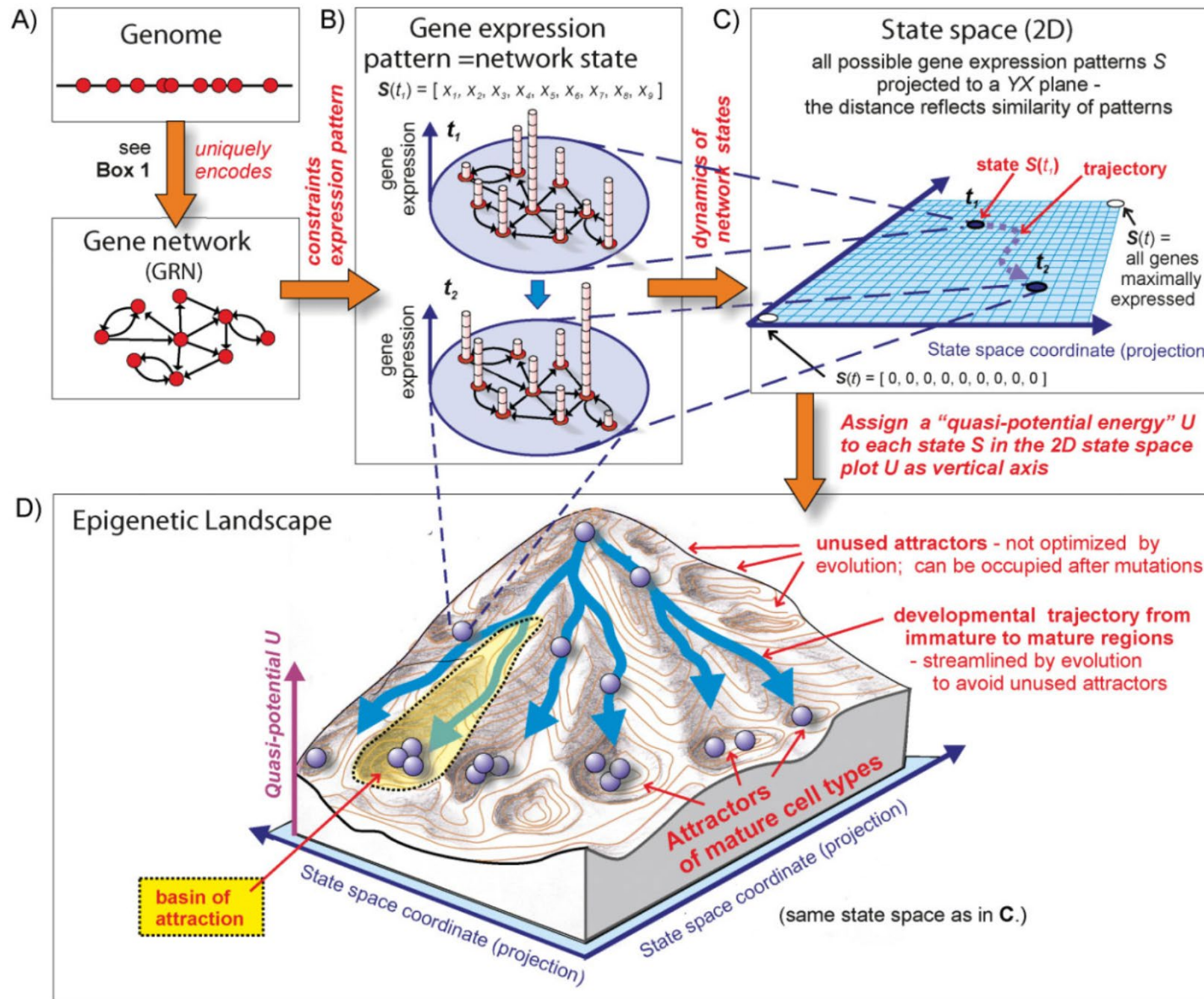
PRESENT

Cell states define the cell's future potential



FUTURE

Goal: A quantitative, disease-relevant & predictive model of epigenetic cell states



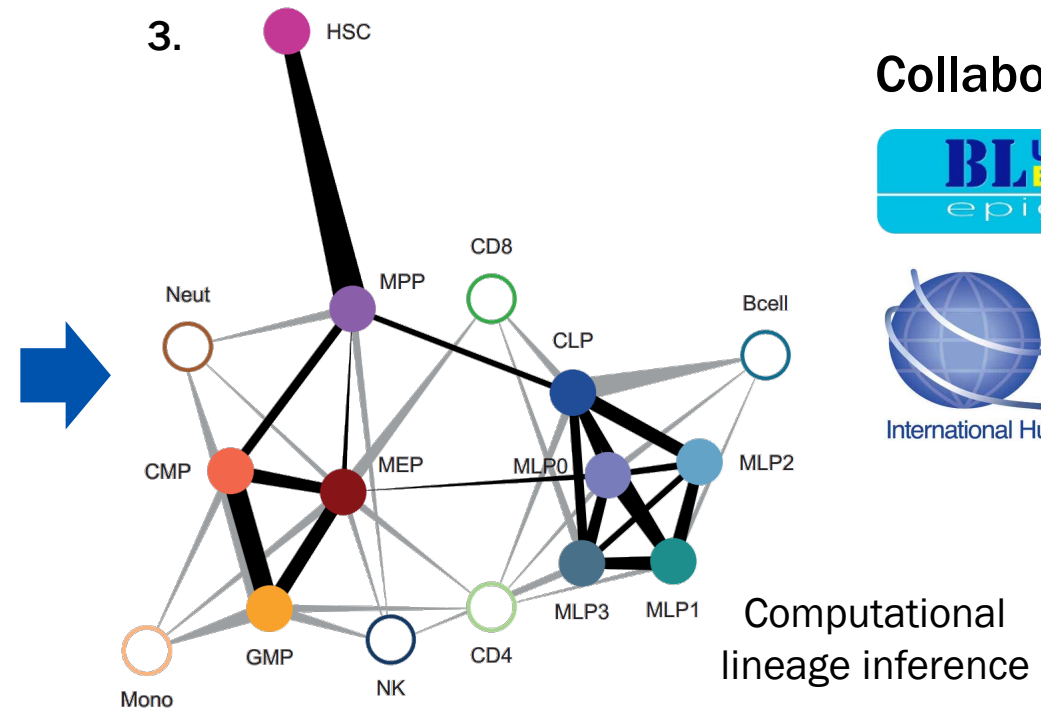
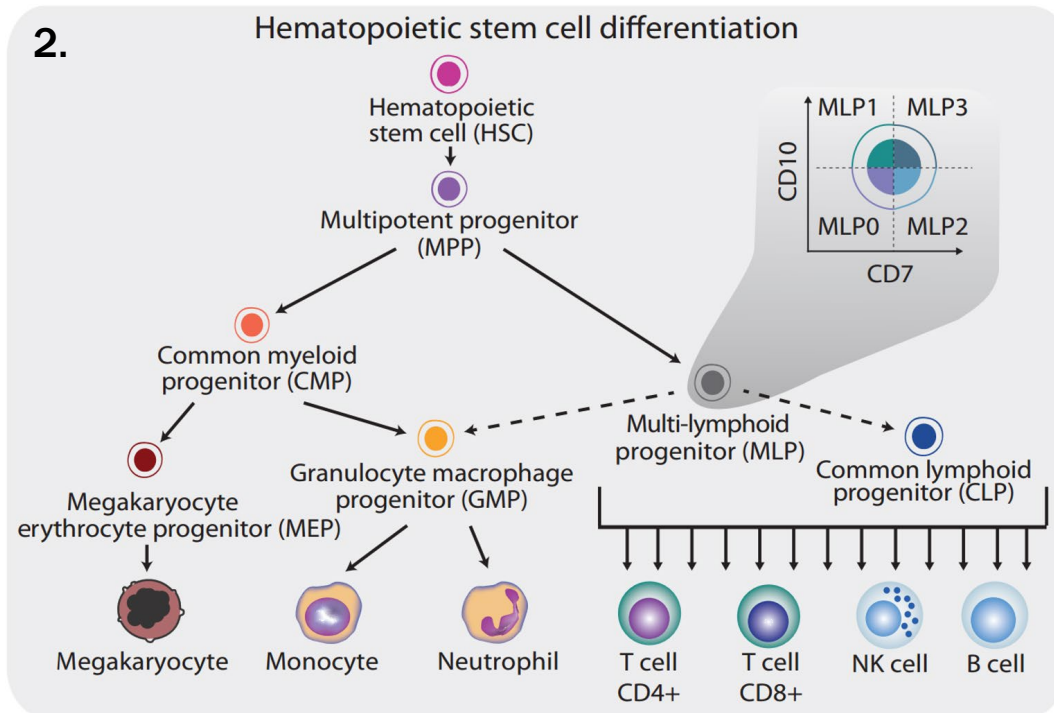
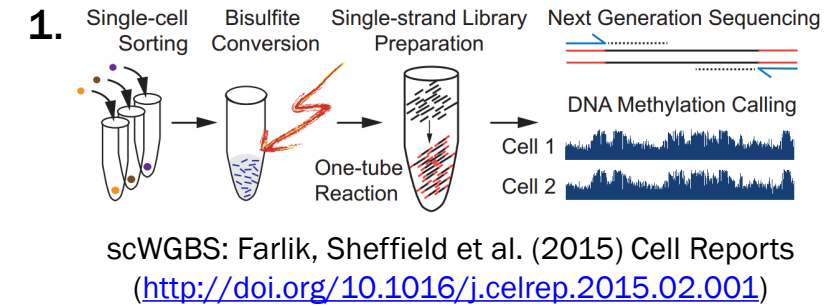
Definition & diagram by
Sui Huang (ISB Seattle)

Huang (2011) BioEssays
(<http://doi.org/10.1002/bies.201100031>)

Cells retain an epigenetic memory of their developmental origins

Reconstructing cellular lineage hierarchies from epigenetic data

1. We developed a scalable method for single-cell DNA methylation profiling
2. Applied it to FACS-enriched blood stem/progenitor cells
3. Used machine learning to reconstruct hematopoietic cell differentiation



Collaboration:



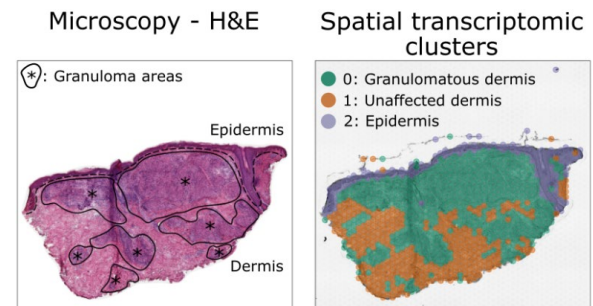
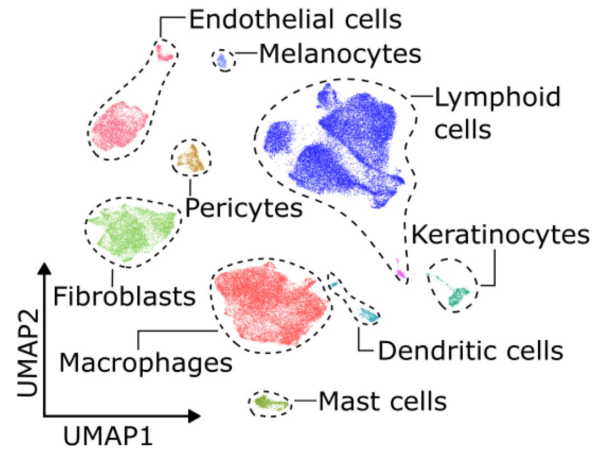
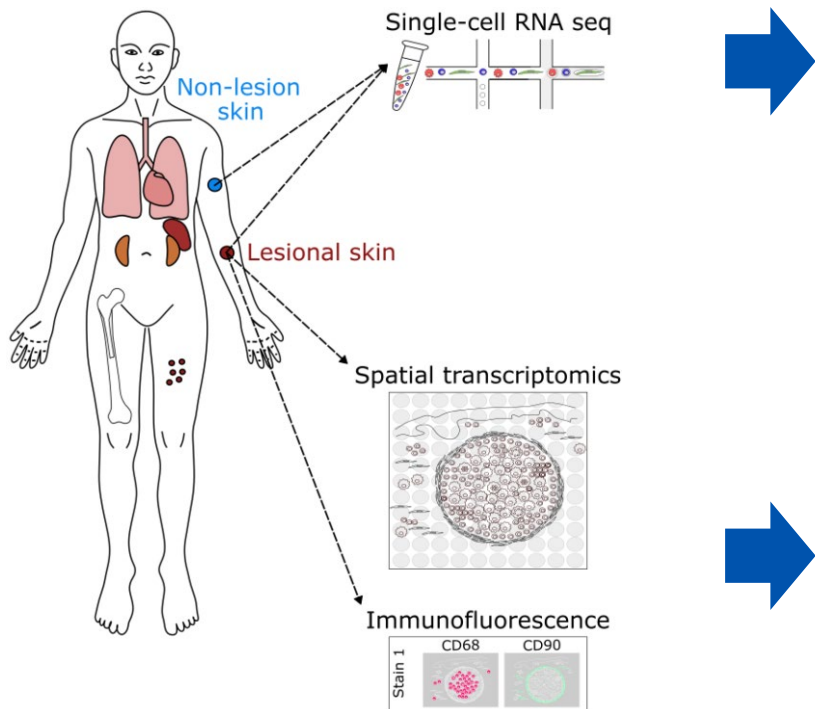
Immune and non-immune cells miscommunicate in inflammation

Sarcoidosis: Inflammatory granuloma formation of unknown cause

- 5 to 40 cases per 100,000, frequency highly variable by genetic ancestry
- Affecting skin, lung, and other organs, <5% mortality, substantial morbidity



Single-cell & spatial profiling



Collaboration:

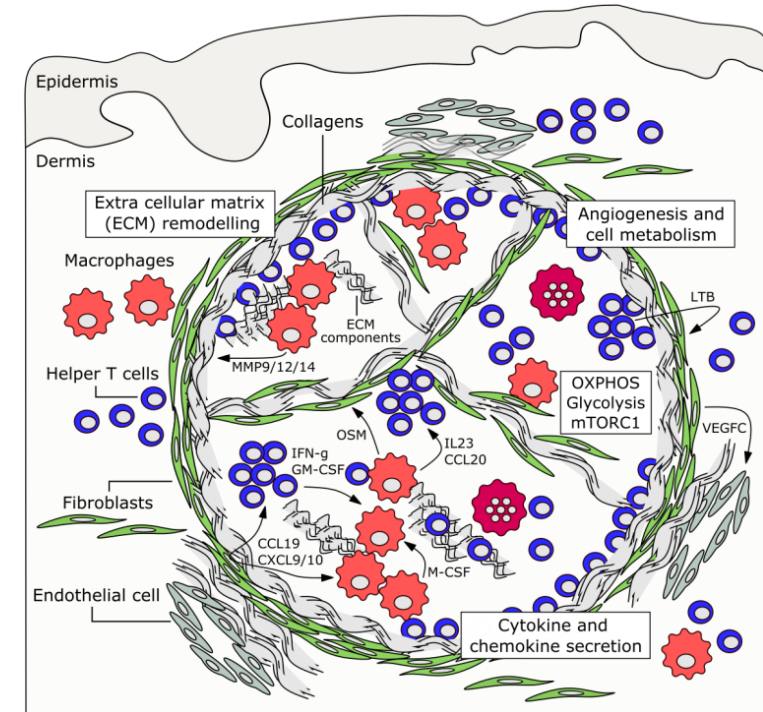
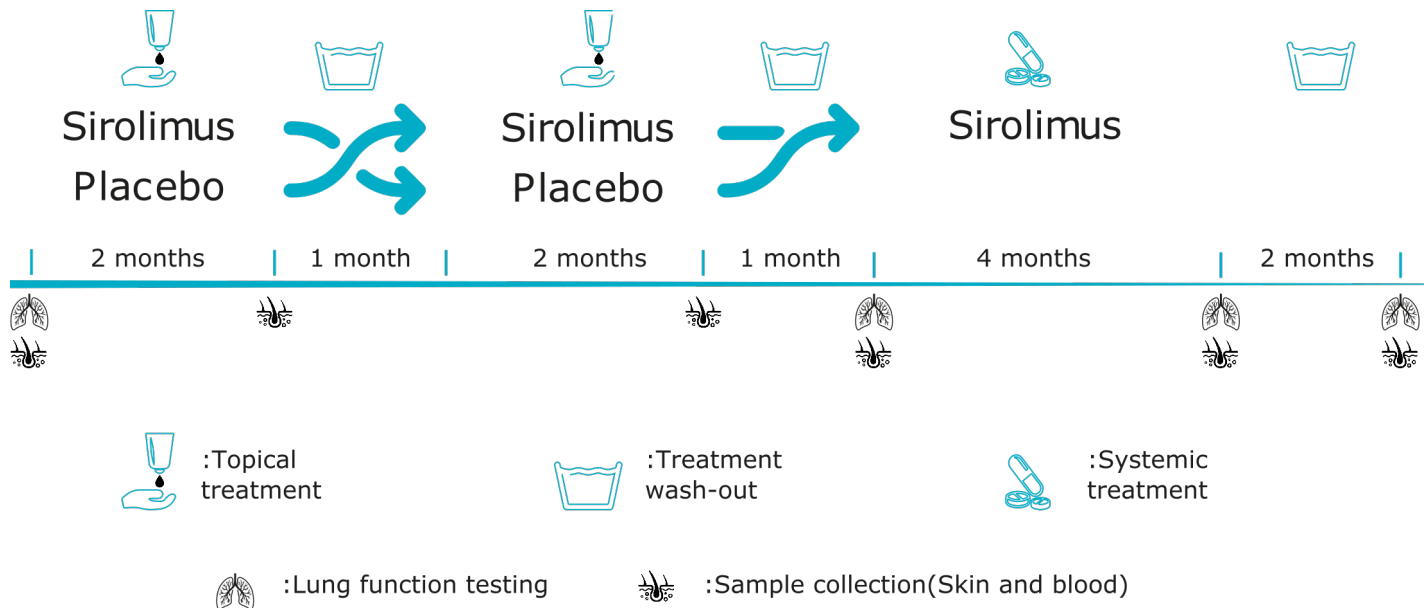


Implications for understanding and treating sarcoidosis

Sarcoidosis: A disease of cell-cell communication gone wrong?

- Macrophages, T cells & fibroblasts interact inside granulomas
- Granulomas recapitulate aspects of lymphoid organ development
- The cells appear normal, but their interactions fuel the disease

An N-of-1 clinical trial for mTOR inhibition in granulomas



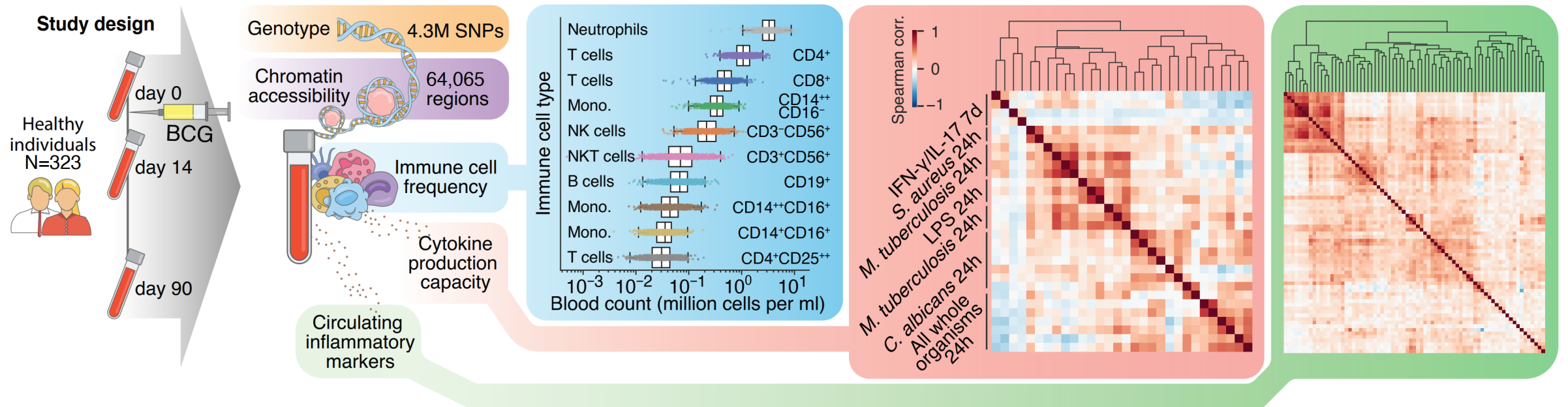
Collaboration:



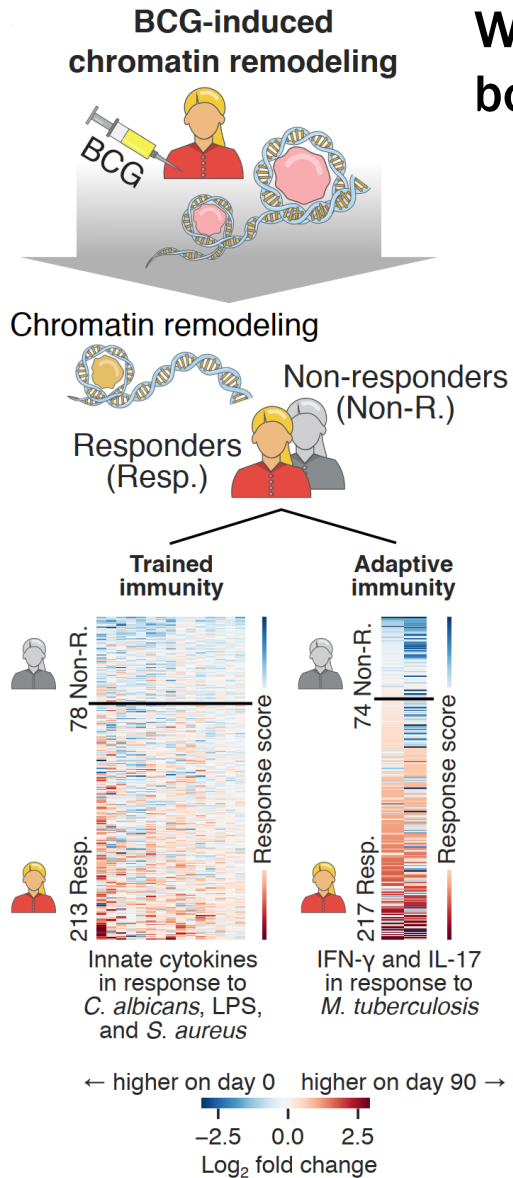
How does epigenetic priming affect immune responses in humans?

The century-old BCG tuberculosis vaccine stimulates both innate & adaptive immunity

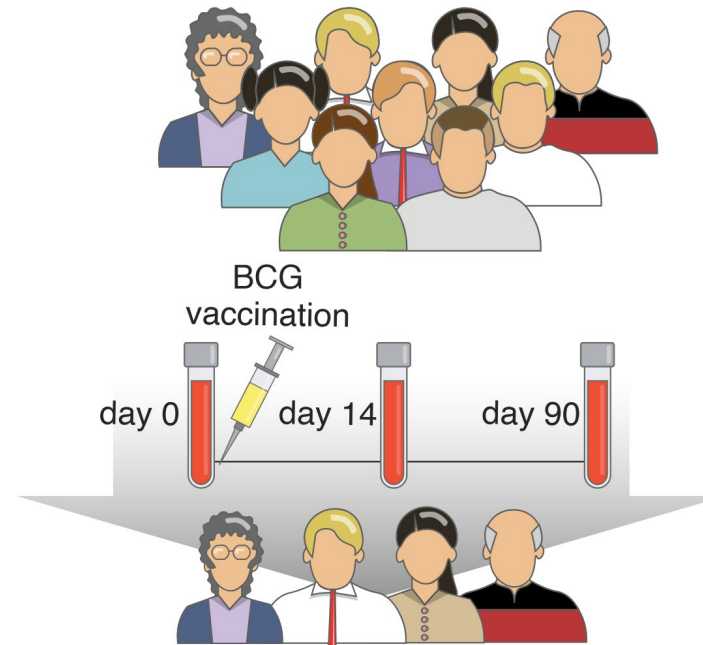
- 323 individuals vaccinated with BCG, three time points, clinical study led by Mihai Netea
- We performed ATAGseq and compared with various immune readouts
- Time series enabled investigation of baseline versus BCG effect



The BCG vaccine boosts innate immunity in people with dormant innate immune cells

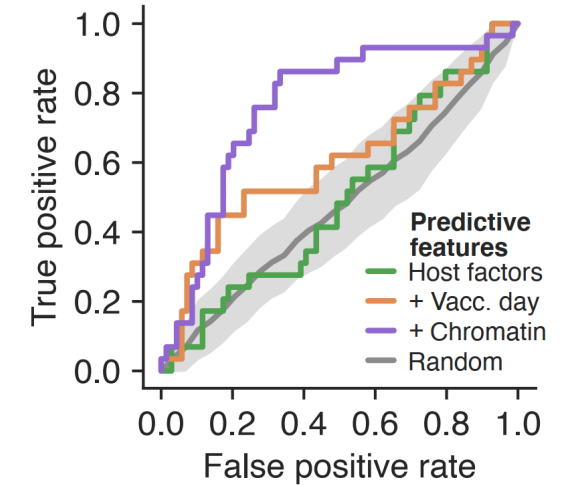


We observe responders vs. non-responders for both innate and adaptive immune responses

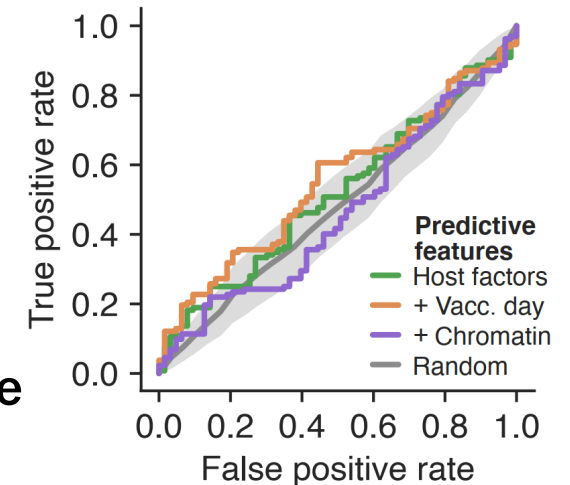


Chromatin accessibility predicts innate but not adaptive immune responders

Prediction of strong trained immunity responders

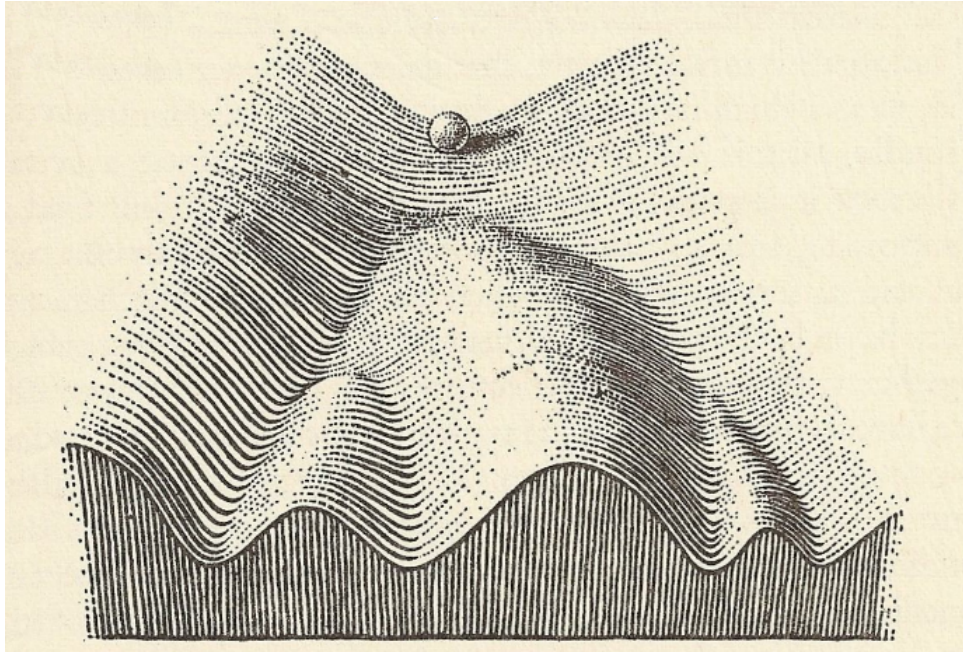


Prediction of strong adaptive immunity responders



Summary: Epigenetic cell states connect the cells' past and future

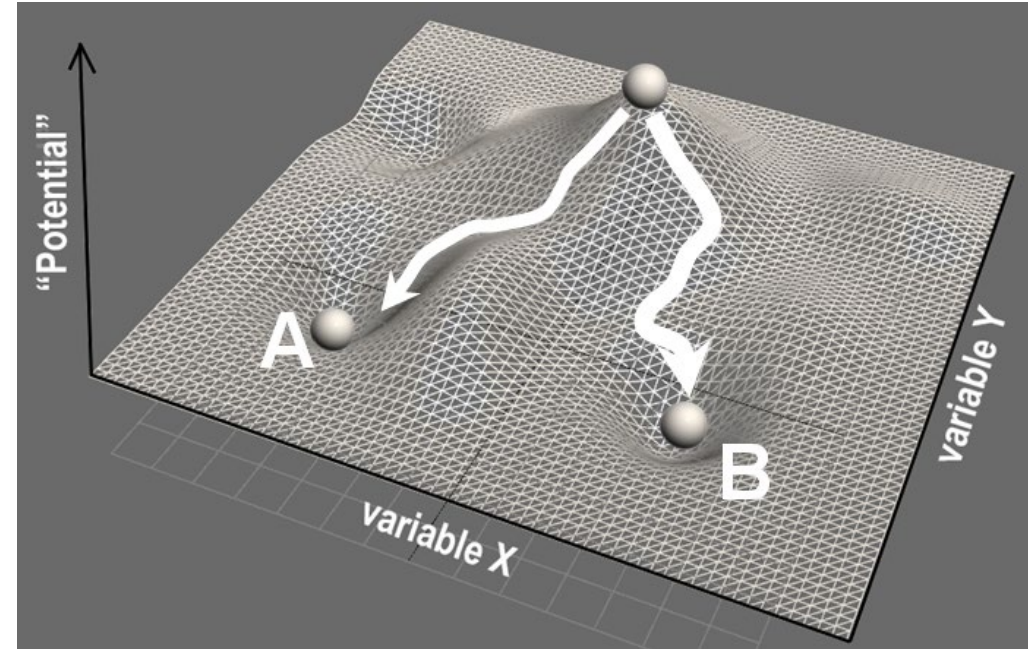
Cells retain an epigenetic record of their developmental history



Analyzing epigenetic memory in cancer and immune diseases

Schmidl et al. 2019 Nature Chemical Biology (chronic lymph. leukemia)
Halbritter et al. 2019 Cancer Discovery (Langerhans cell histiocytosis)
Klughammer et al. 2018 Nature Medicine (glioblastoma)
Sheffield et al. 2017 Nature Medicine (Ewing sarcoma)
Mass et al. 2016 Science (macrophage development)
Farlik et al. 2016 Cell Stem Cell (hematopoietic differentiation)

Epigenetic cell states capture a cell's future potential to respond to stimuli



Analyzing epigenetic potential in immune cell biology

Zhao et al., manuscript in revision (B cell immunodeficiencies)
Fortelny et al., Nature Immunology, in press (baseline immune signaling)
Moorlag et al. 2024 Immunity (trained immunity)
Krausgruber et al. 2023 Immunity (sarcoidosis)
Krausgruber et al. 2020 Nature (structural immunity)
Bock et al. 2011 Cell (epigenetic differentiation potential)



(3) Harnessing the power of large language models for single-cell analysis









CellWhisperer: Interactive chat-like analysis of single-cell data

cell×gene
CellWhisperer



dataset 

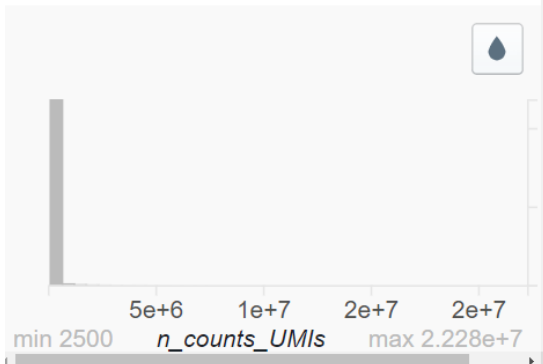
1: 0 cells 2: 0 cells         

Create new category

- anatomical_information > 
- cell_ontology_class > 
- cluster_label > 
- compartment > 
- donor > 
- free_annotation > 
- gender > 
- leiden > 

manually_annotated: true

- method > 
- organ_tissue > 



 umap: 483152 out of 483152 cells



All saved

Genes ▾

Gene Sets ▾

Create new

Welcome to CellWhisperer! To get started, please try some of the following options:

1. Select a group of cells by drawing a line around them and press the "Describe the selected pseudocell" button
2. Type `/search T cells` or `/search Inflammation` in the text box below for a heatmap of cells with this type or property
3. Enter data-related questions into the chat box, for example "What distinguishes these cells from macrophages?"
4. You can also ask general questions, for example "What is the role of IL-2R in T cells?"
5. If a comment does not make sense to you, you can press the  icon, and CellWhisperer will give a new response.
6. You can help us improve CellWhisperer by pressing the  icon for answers that appear to be correct and useful.

Please keep in mind that CellWhisperer is an AI system and may produce incorrect or misleading results. CellWhisperer is best used as a tool for data exploration and hypothesis generation.

Type your request here and press <Enter>. For example: `/search T cells`

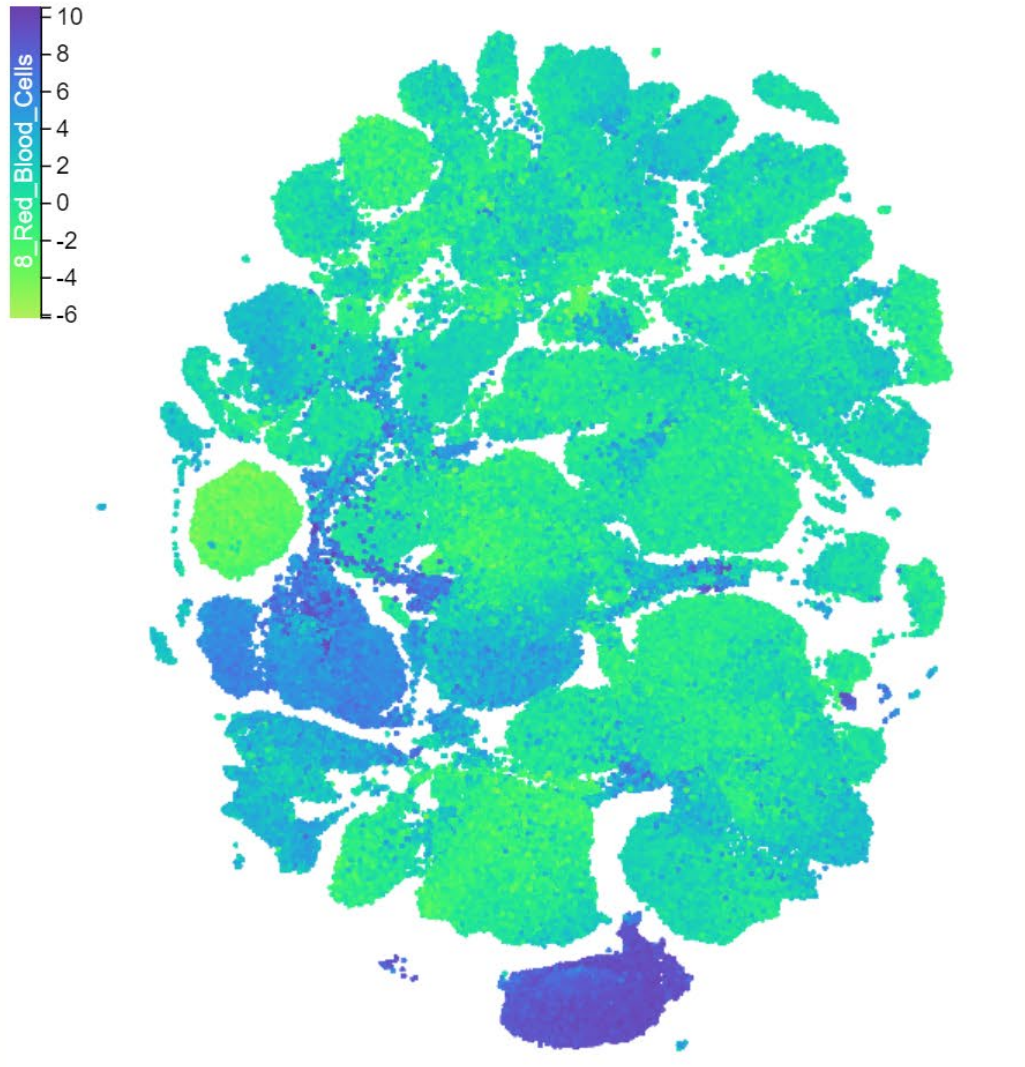
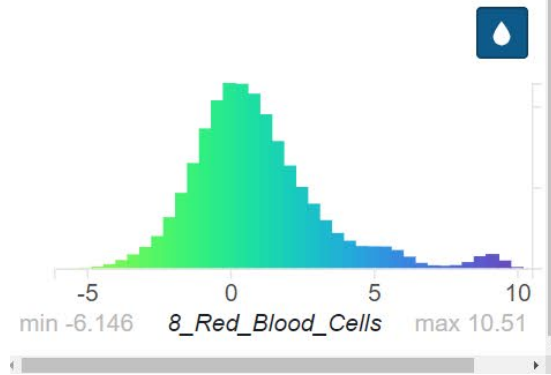
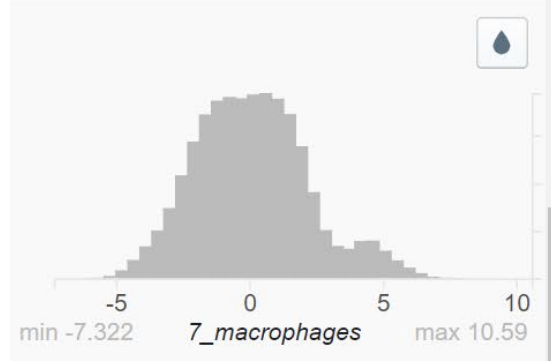
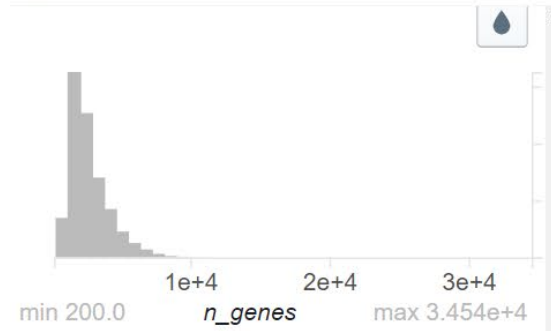
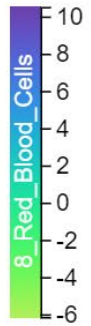
Describe the selected pseudocell (mean of all 483152)

Finding cells and biological functions with CellWhisperer

cell×gene
CellWhisperer

dataset

1: 0 cells 2: 0 cells



All saved

Genes

Gene Sets

Create new

Welcome to CellWhisperer! To get started, please try some of the following options:

1. Select a group of cells by drawing a line around them and press the "Describe the selected pseudocell" button
2. Type "/search T cells" or "/search Inflammation" in the text box below for a heatmap of cells with this type or property
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5. If a comment does not make sense to you, you can press the icon, and CellWhisperer will give a new response.
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Please keep in mind that CellWhisperer is an AI system and may produce incorrect or misleading results. CellWhisperer is best used as a tool for data exploration and hypothesis generation.

Search for cells

Talking about cells and biological functions with CellWhisperer

cell×gene
CellWhisperer

dataset

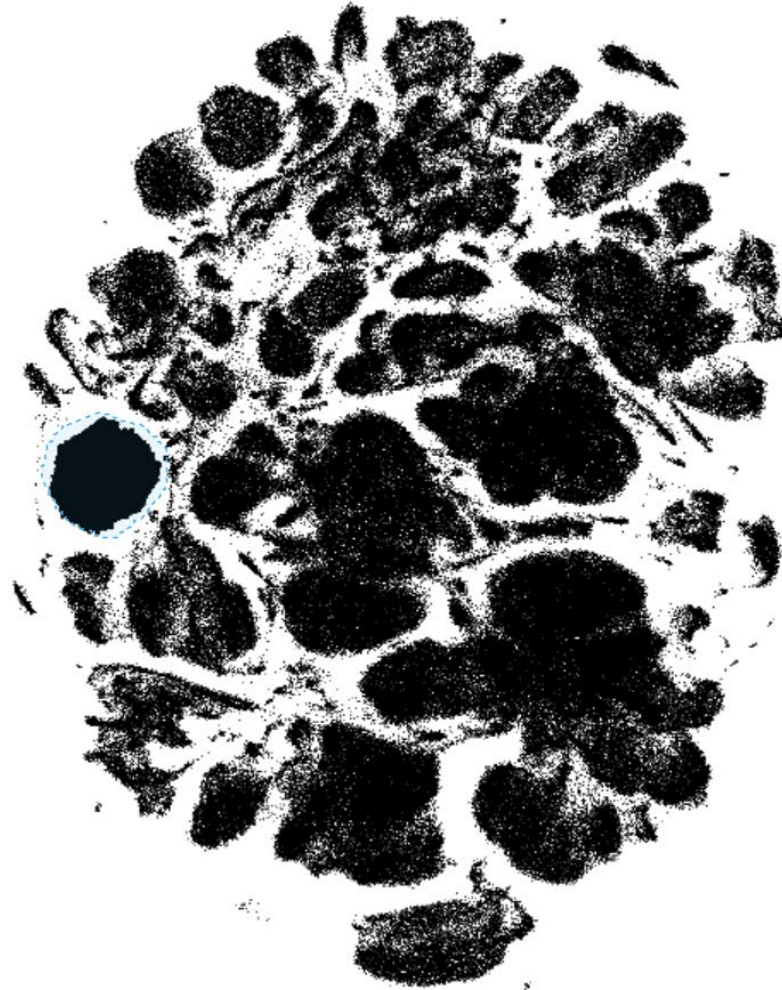
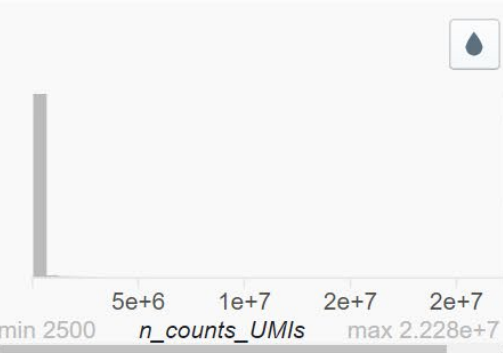
1: 0 cells 2: 0 cells

Create new category

- anatomical_information >
- cell_ontology_class >
- cluster_label >
- compartment >
- donor >
- free_annotation >
- gender >
- leiden >

manually_annotated: true

- method >
- organ_tissue >



umap: 8290 out of 483152 cells

All saved

Genes ▾

Quick Gene Search

Gene Sets ▾

Create new

Describe the selected cells.

The selected cells are epithelial cells from the proximal tubule of the kidney, specifically from the cortex region.

I thought that the cortex region is in the brain?

No, the cortex region in the kidney is the outer layer of the kidney, where the glomeruli are located.

Okay, understood. Can you tell me more about these cells?

These cells are epithelial cells from the proximal tubule, which is the first part of the tubule in the kidney's filtration system. They play a crucial role in reabsorbing water, electrolytes, glucose, and amino acids from the filtrate.

Which genes are particularly active in the selected cells?

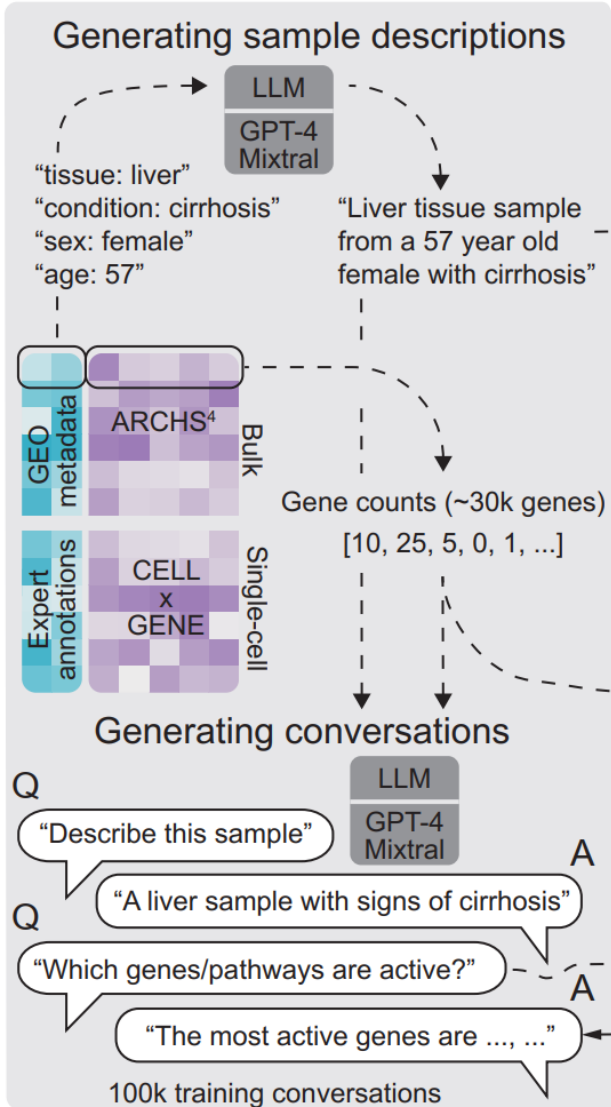
The most strongly expressed genes in the selected cells include CRYAB, C11orf54, PDZK1IP1, FXYD2, MTND1P23, PEBP1, GPX3, LDHB, ATP5MC3, ALDOB, COX7B, DAB2, MT-CO3, CHCHD10, AK4, CXCL14, TXN, ATP5MD, CRYL1, PRDX1, PCK1, IL32, CMBL, BBOX1, MT1G, GLYAT, ASS1, C12orf75, SLC25A5,

Type your request here and press <Enter>. For example: '/search T cells'

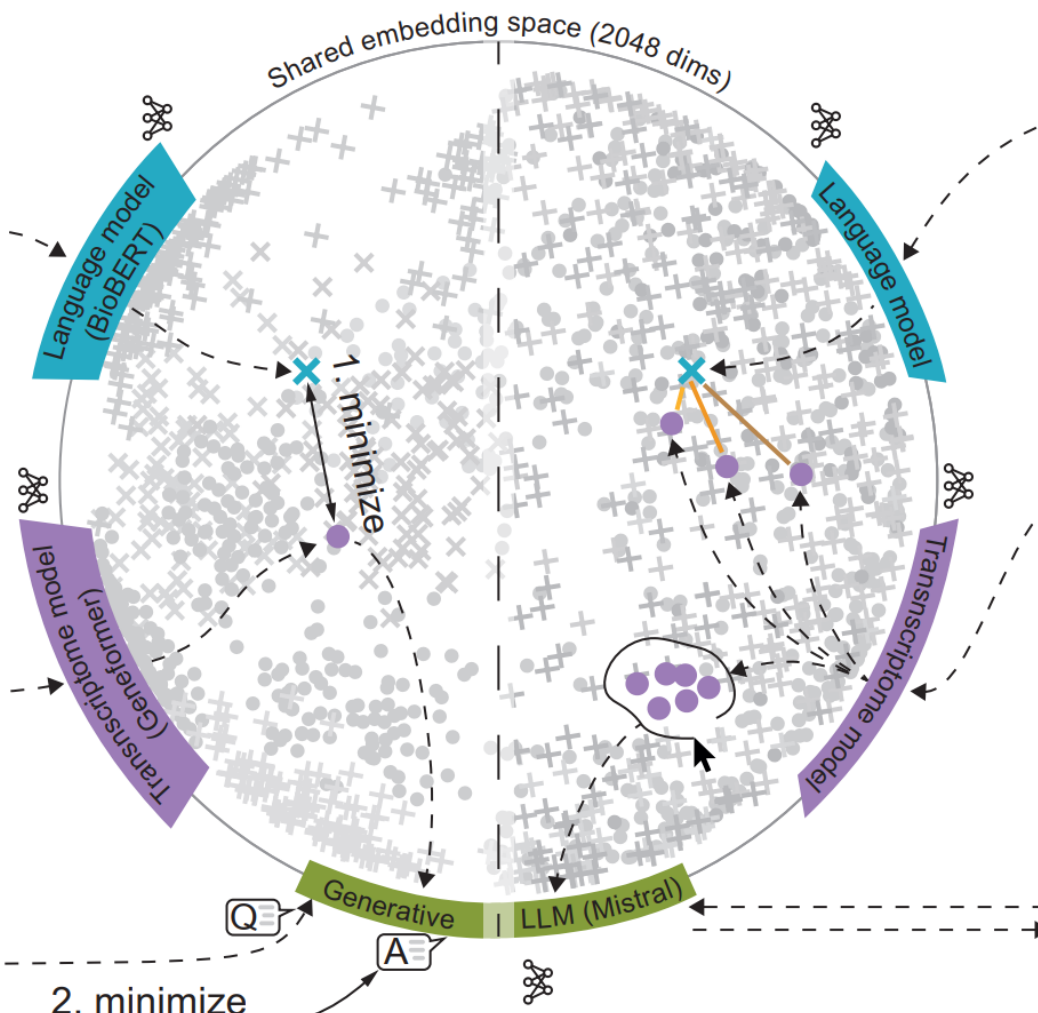
Describe the selected pseudocell (mean of n=8290)

Under the hood: Joint embedding of transcriptomes and text for single-cell data analysis

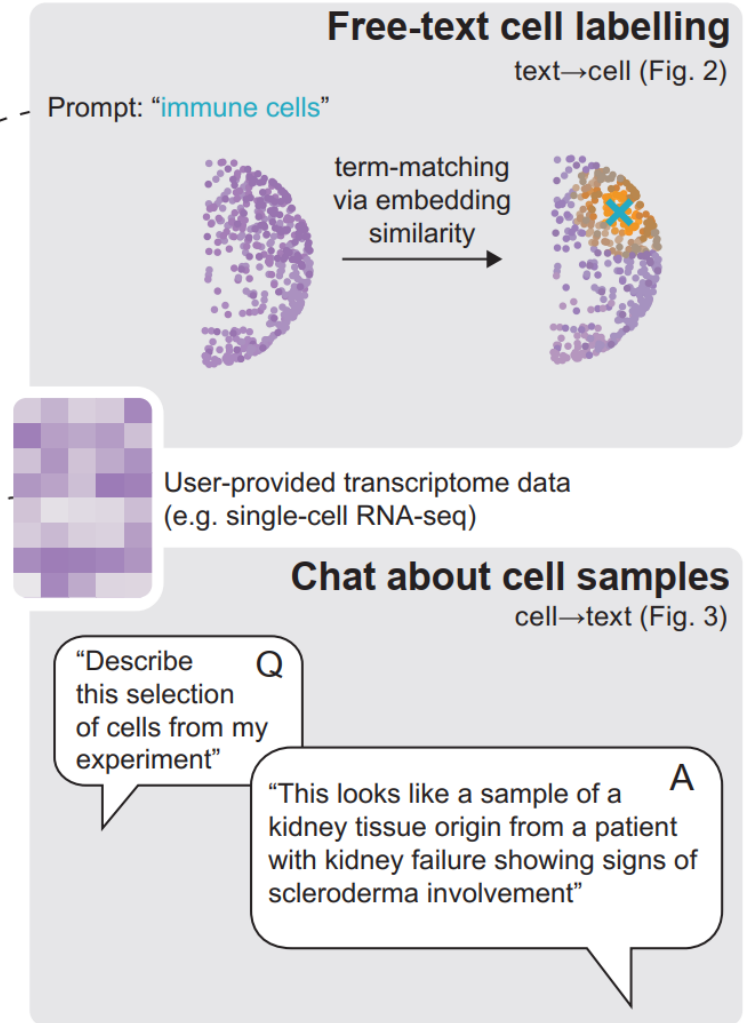
Dataset 1M human transcriptome-text pairs



Training | Inference

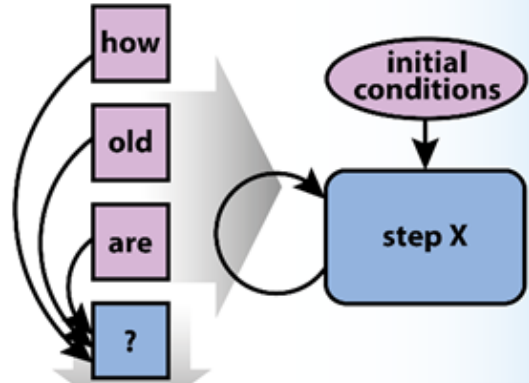


Application

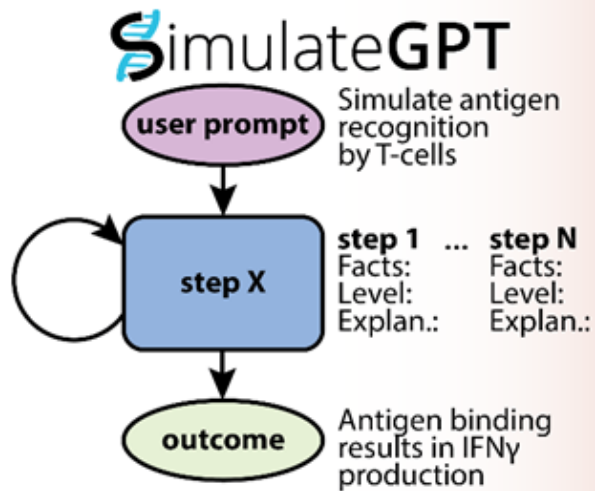


GPT-4 as a biomedical simulator: a proof-of-concept study

LMMs are sequential simulators



LLMs are biomedical simulators



GPT-4 System Prompt (simple version)

You are a science-based, comprehensive and mechanistic simulator of biomedical processes across all levels of biology: molecular, cellular, organ, and organism.

Your input consists of simulation parameters. Based on the input, you simulate all relevant processes that unfold step-by-step until a final outcome can be inferred from the simulation.

Simulation rules:

- Begin the simulation at the level of biology matching the input best.
- Ensure that each step logically informs the next step.
- Use as many steps as necessary.
- Conclude the simulation with a final outcome, once it can be directly inferred from the simulation steps.

Aim for an informative level of detail. Ensure that every step logically follows up on all previous steps and that processes in subsequent steps are informed by previous steps. Format your response in YAML, following this schema: [...]

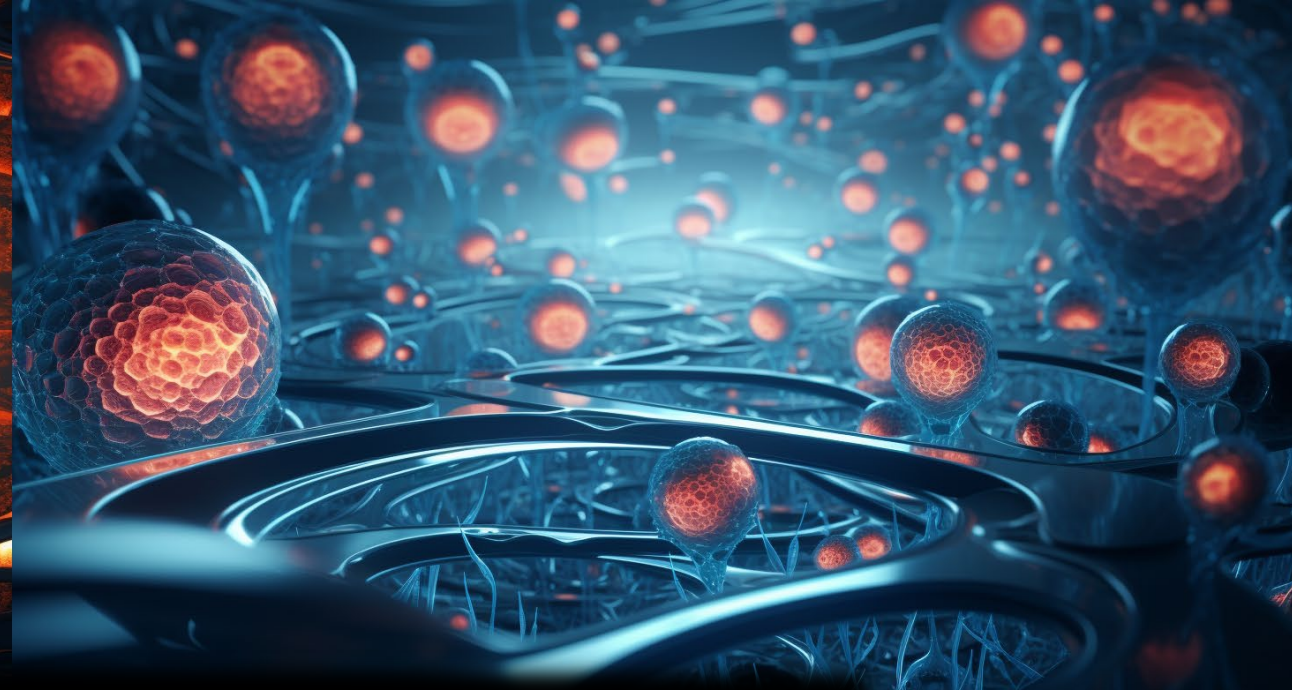
GPT-4 User Prompt (example)

Is the gene IFNA10 likely essential in widely used cancer cell lines? Provide an outcome of either "likely" or "unlikely".

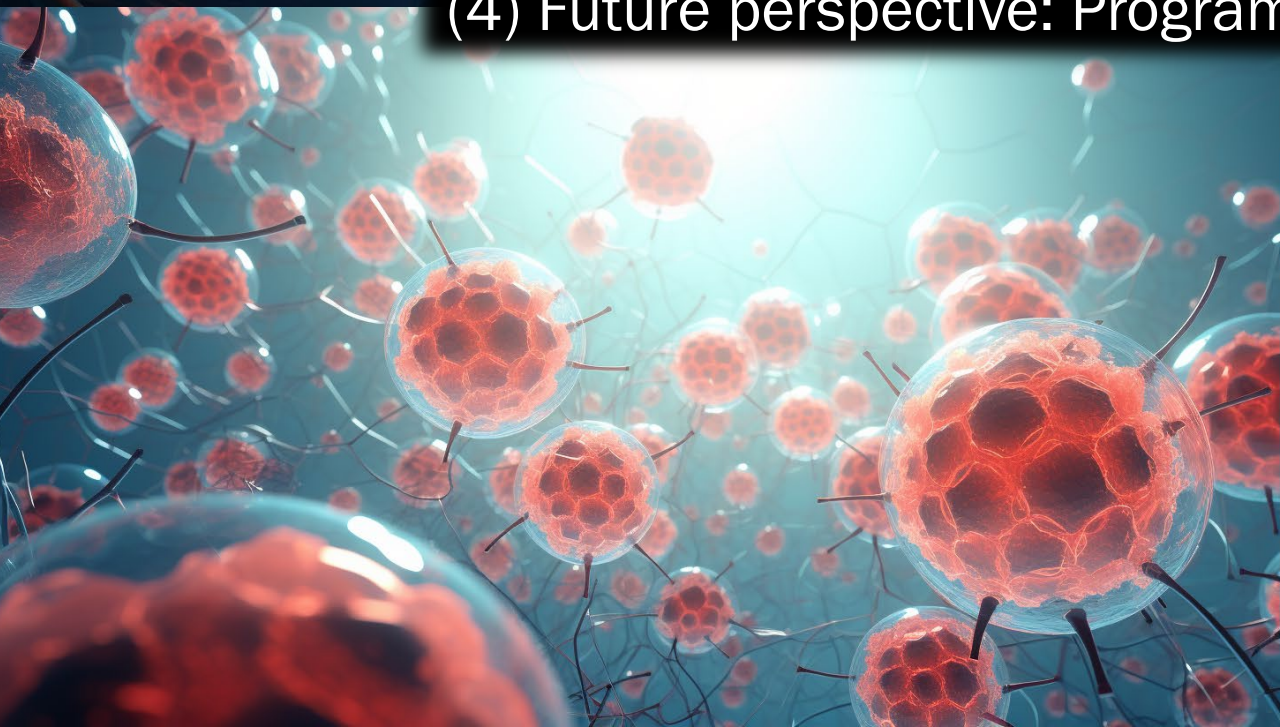
Validation

Simulate GPT
accuracy=0.86
F1=0.85

Prediction	unlikely	4	22
	likely	21	3
		likely	unlikely
		Ground-truth	



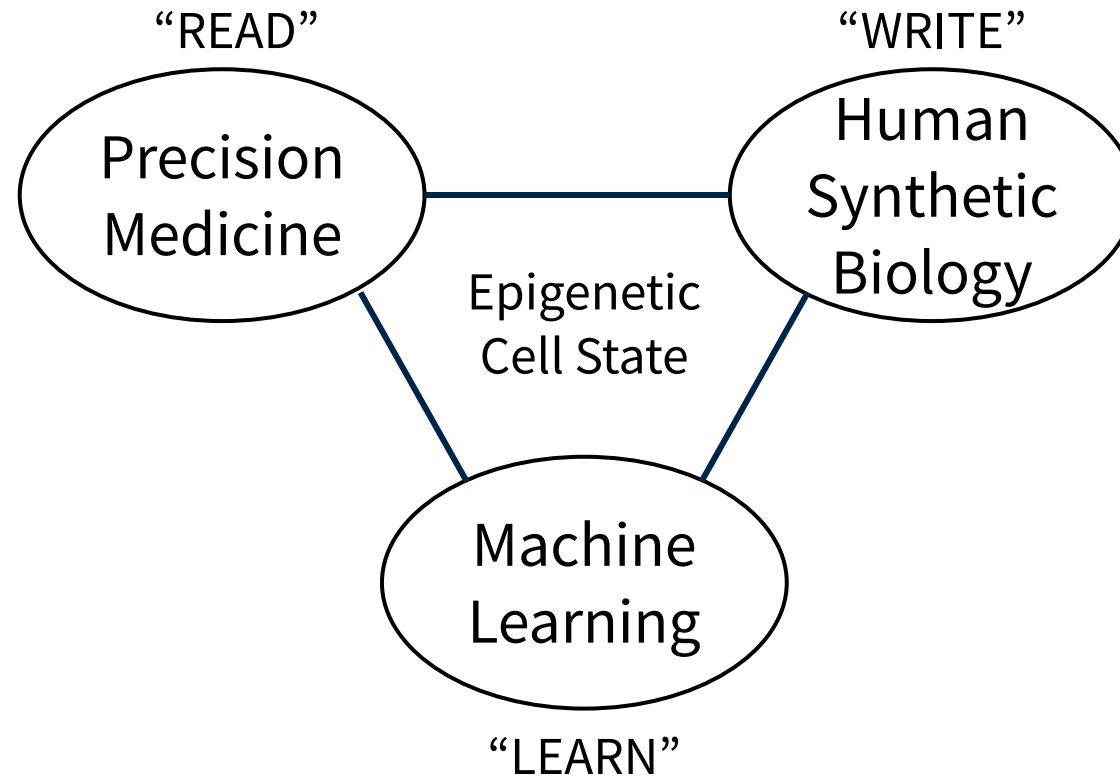
(4) Future perspective: Programming immune cells for therapy



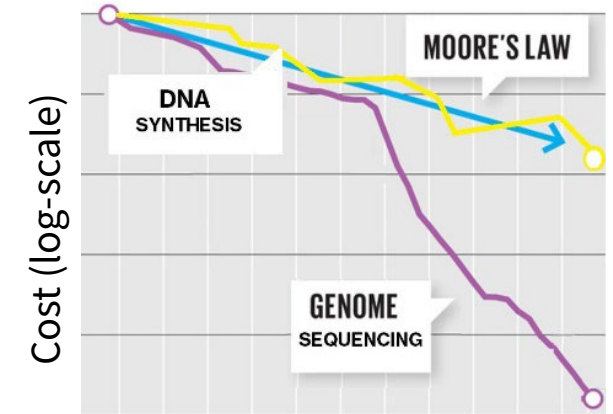
Our vision: Programming immune cells for biological discovery and therapeutic applications



Lead technology: Next Generation Sequencing

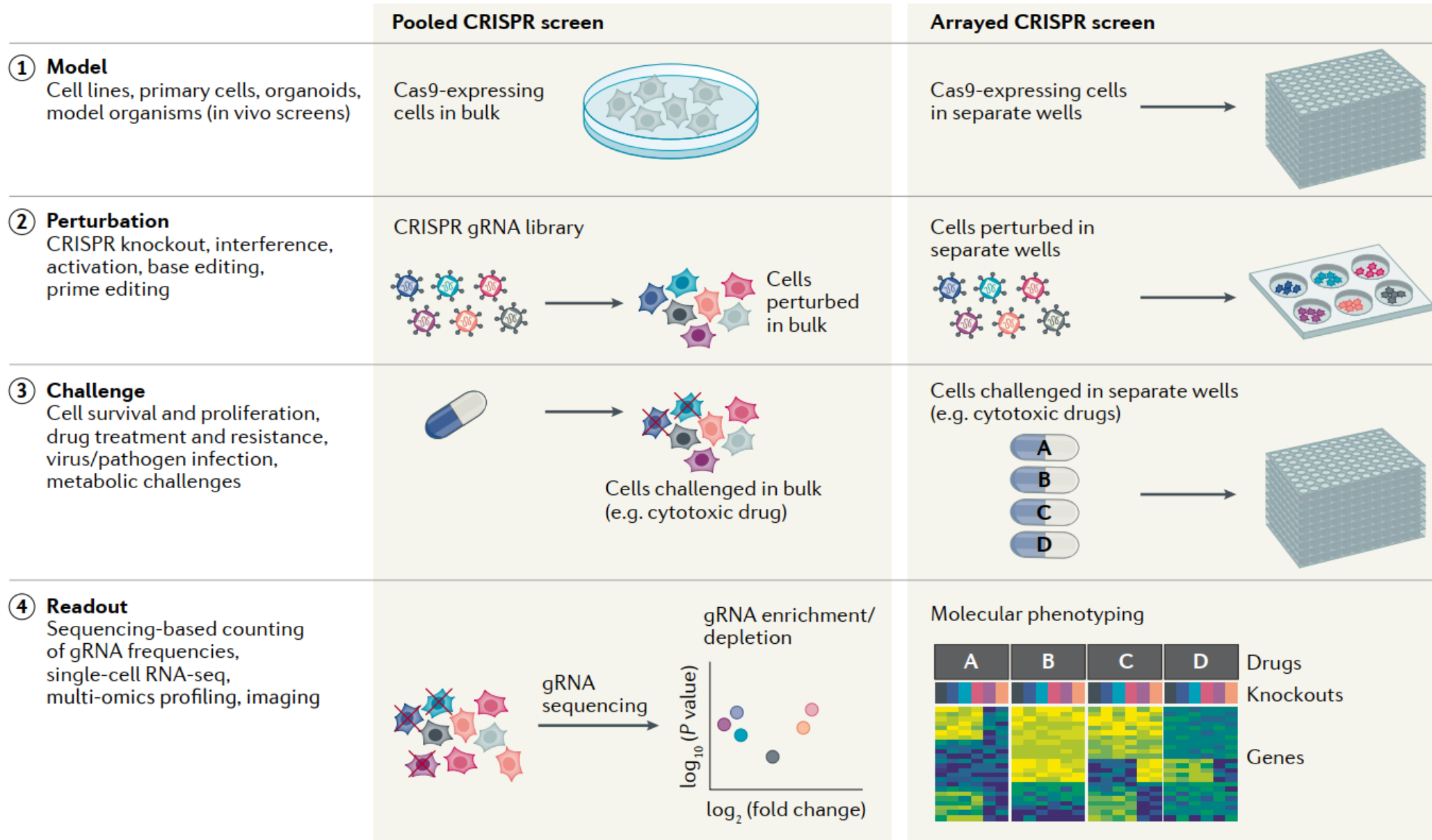


Lead technology: Interpretable machine learning

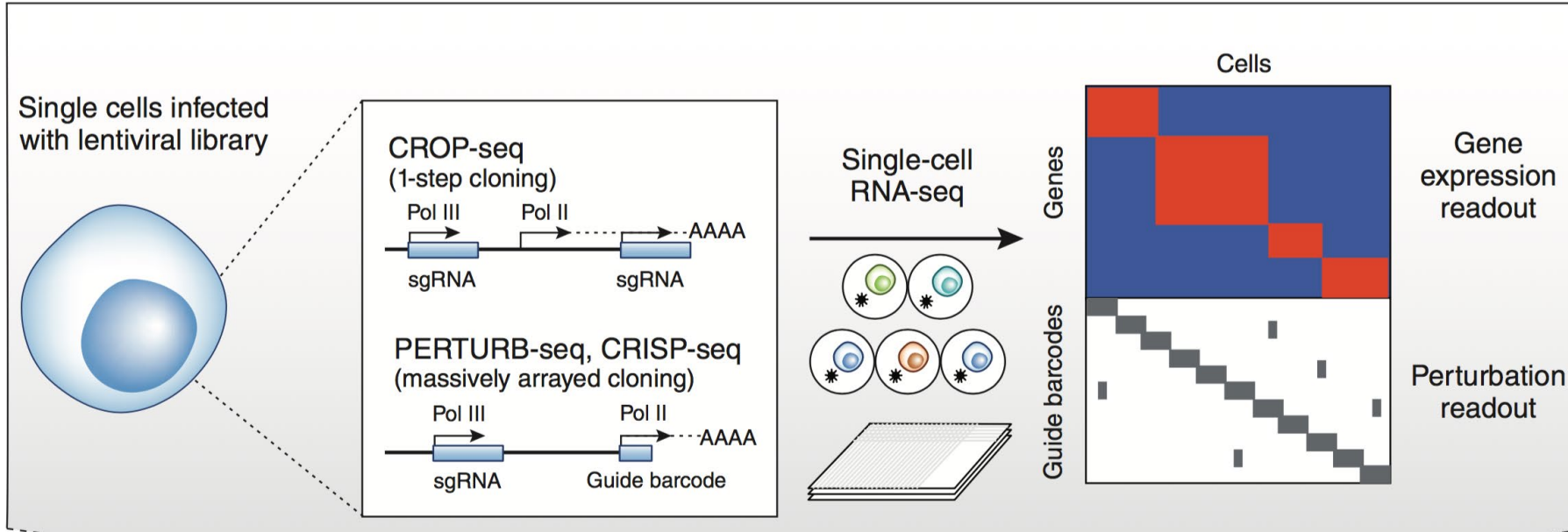


Lead technology: Massive-scale DNA synthesis

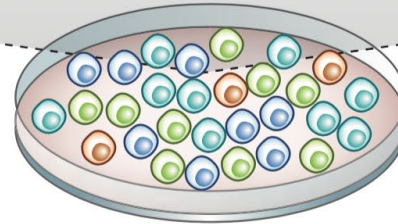
High-content CRISPR screening



CROP-seq enables CRISPR screening with very complex phenotypes



~500 labs obtained the CROP-seq plasmid from AddGene



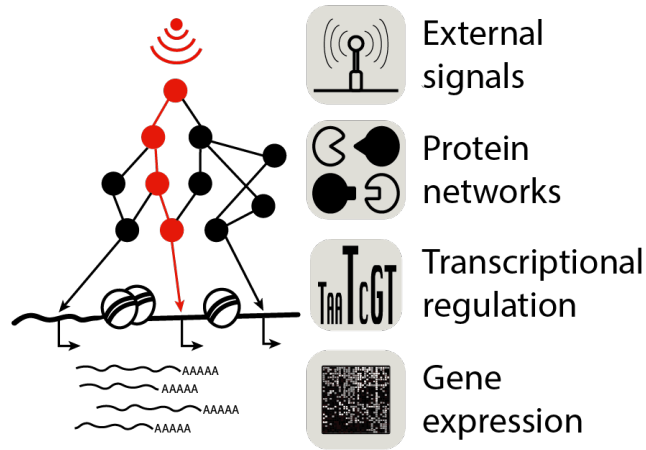
“CROP-seq as a service” for biotech/pharma (Col)

Related methods

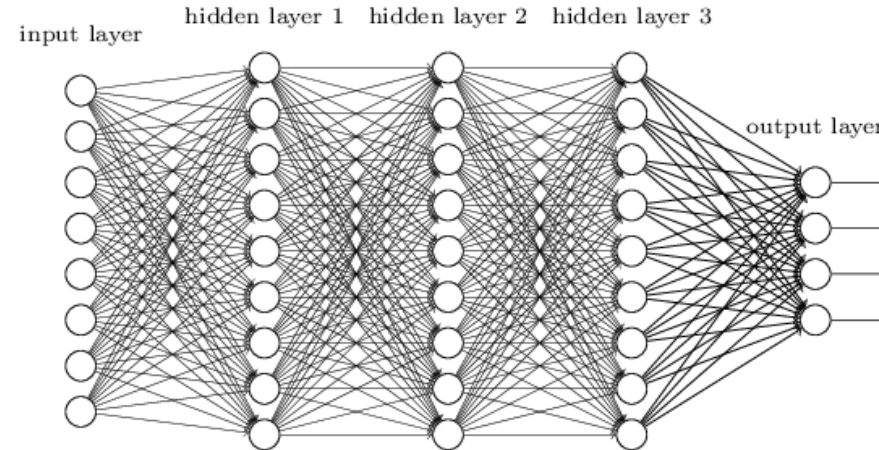
- Perturb-seq – A. Regev & J. Weissman labs (Dixit et al, 2016; Adamson et al, 2016)
- CRISP-seq – I. Amit lab (Jaitin et al, 2016)
- Mosaic-seq – G. Hon lab (Xie et al, 2017)

Interpretable deep learning for causal inference in biological networks

Biological networks are very different from deep learning networks

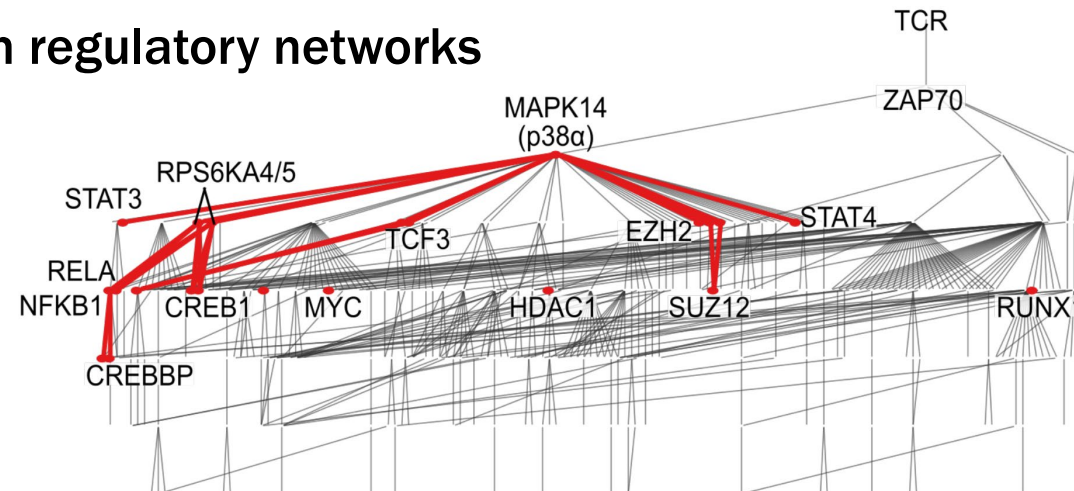
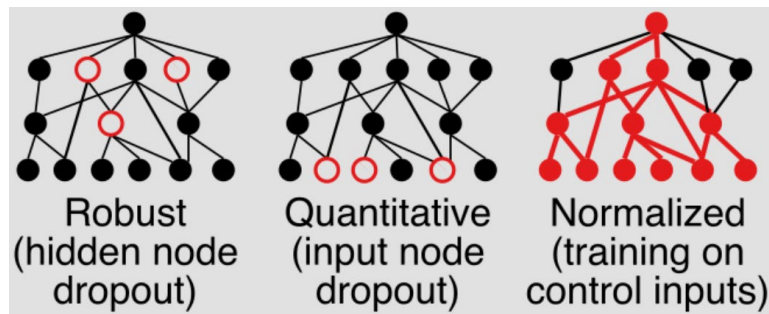


Gene-regulatory network



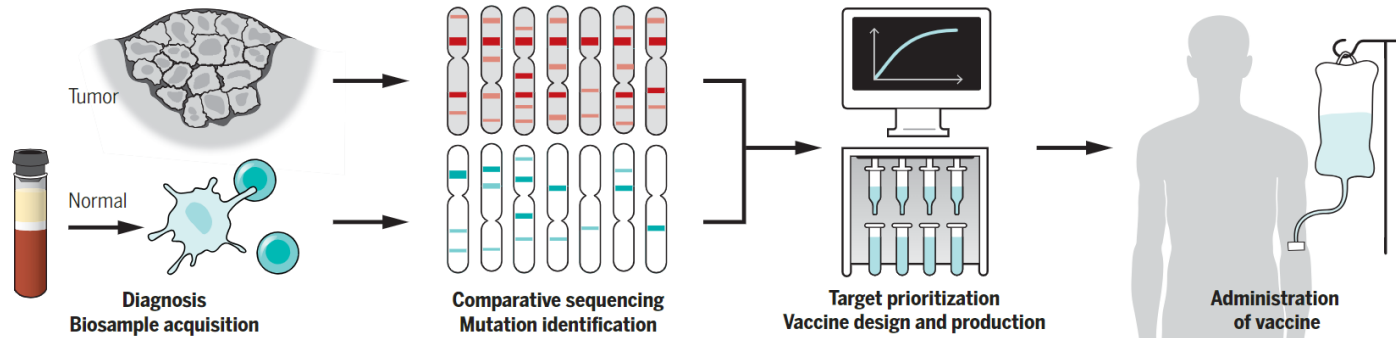
Fully connected artificial neural network

We developed interpretable deep learning on regulatory networks



ML/AI + automated bioengineering will enable truly personalized therapies

Personalized cancer vaccines



Economic & logistical considerations

- “Therapies as products”: Approved drugs, but also CAR T cell therapies
- “Therapies as processes”: Surgery, but also bone marrow transplants

EDITORIAL

nature
biotechnology

Patient-centered drug manufacture

Bedside production of protein drugs could help payers by lowering drug prices. It may ultimately lead to individualized treatments.

Personalized therapies for N=1 rare diseases

Saving Mila: How a tailor-made therapy, developed in a flash, may have halted a young girl’s rare disease

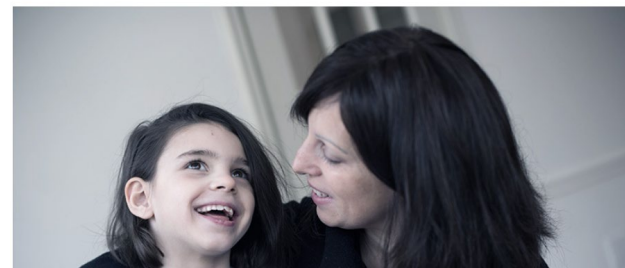
By Meghana Keshavan Oct. 22, 2018

Reprints



Made-to-order therapies get a boost with new FDA guidelines

Posted on January 14, 2021 by Nancy Fliesler | Clinical Care
Tags: batten disease, drug development, epilepsy, genetics and genomics, neurology, precision medicine, rare disease, research



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