Modern Tools to Meet the Challenges of Preclinical Translation to the Clinic

Maximizing GSP and Emerging Technologies

Steven Novick, Senior Director
Head of Nonclinical Statistics, Takeda

June, 2025

Better Health, Brighter Future

Admission and Acknowledgments

I don’t work on many projects anymore…

Thanks to these members from the Takeda preclinical stats team:

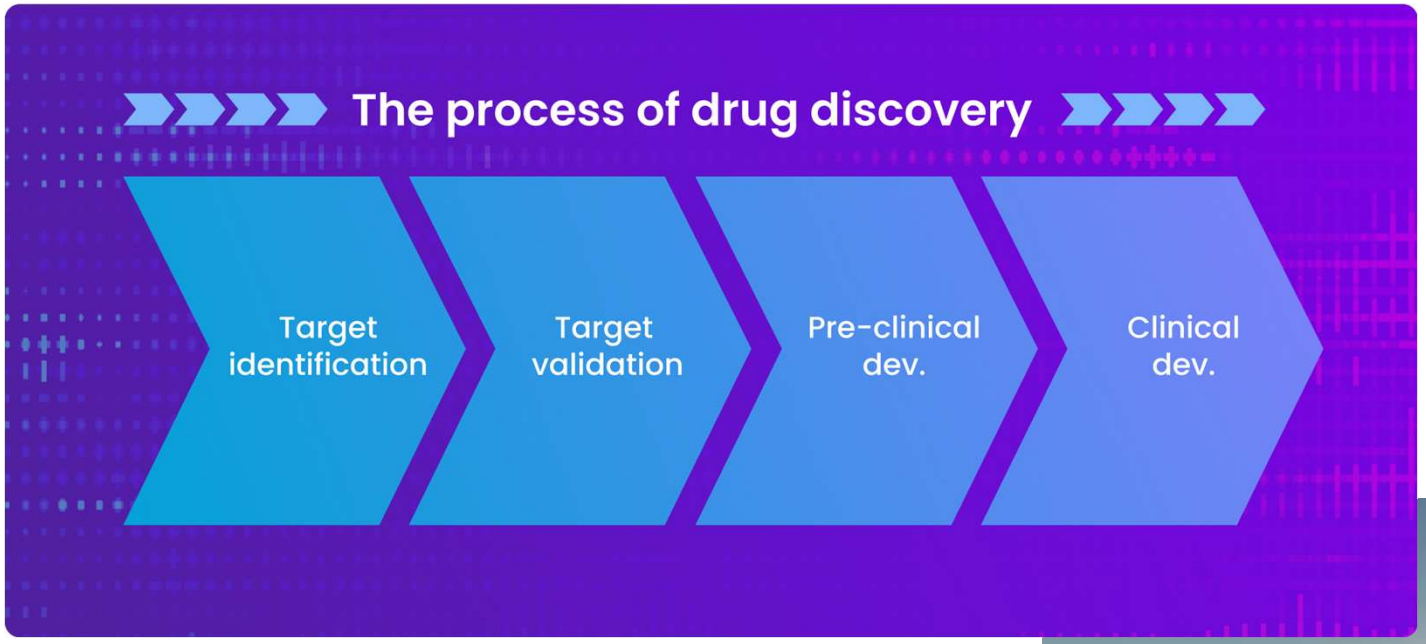
- Pietro Artoni
- Reuben Retnam
- Yue Yang

…I also asked ChatGPT

Pharmaceutical Companies make drugs!

Discovering Drugs is a difficult task

90% of clinical drugs fail (Sun et al, 2022)

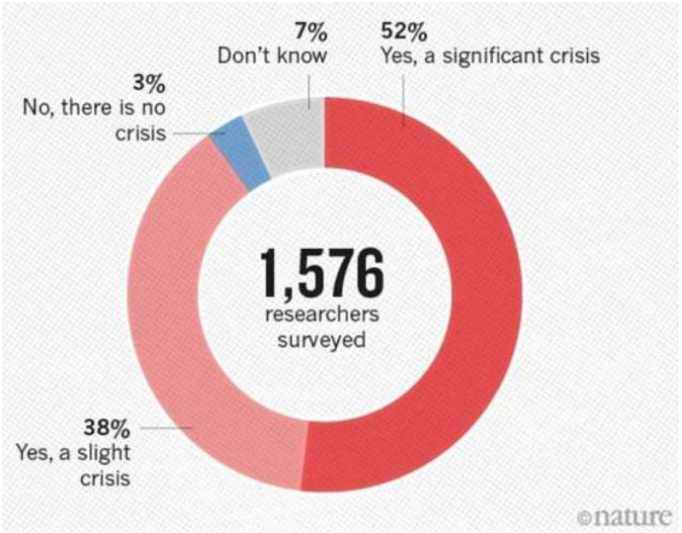


Long journey

- Target ID (TI)
- Target validation (TV)
- Hit ID (HI)
- Lead Optimization (LO)

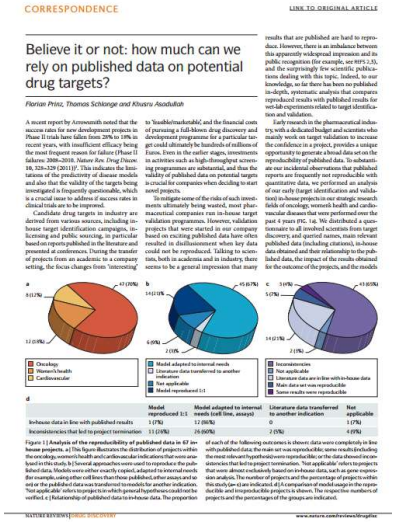
2010s: Lack of replicable results motivated GSP

Baker et al 2016 Nature



- 70% failed to replicate another scientists experiments
- 50% failed to replicate their own experiments

Findings confirmed in only 14 out of 67 studies (21%)


CORRESPONDENCE

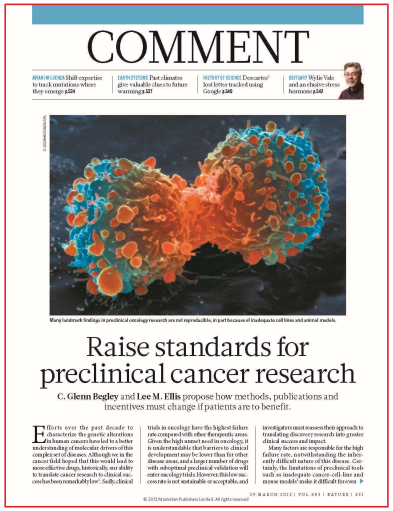
LINK TO ORIGINAL ARTICLE

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

Prinz F, Schlange T, Asadullah K (2011). *Nat Rev Drug Discov* 10(9): 712.

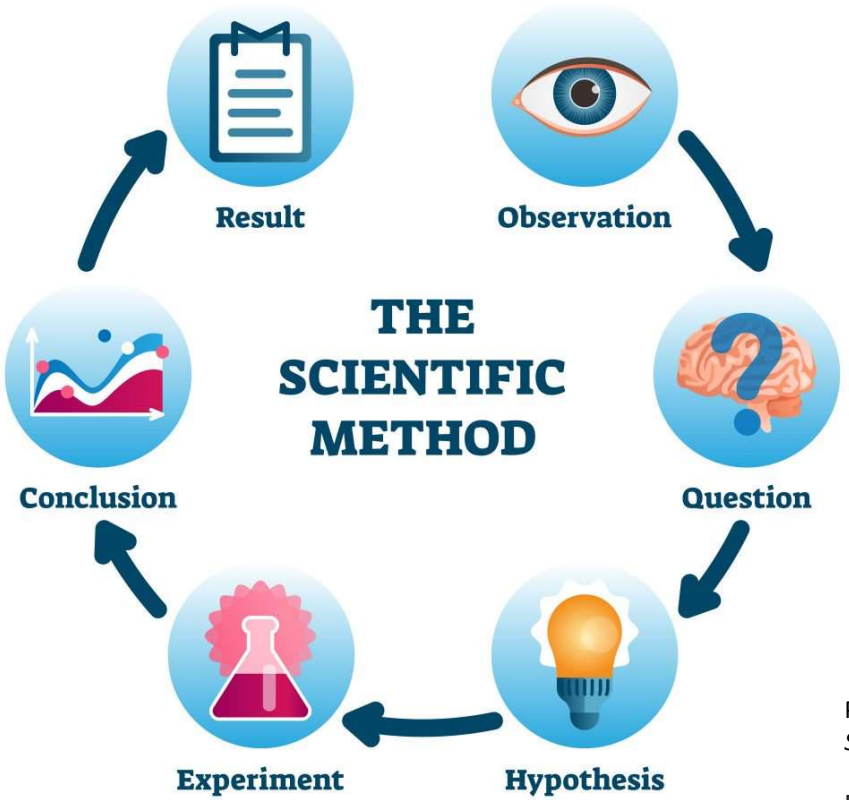
Findings confirmed in only 6 out of 53 studies (11%)


COMMENT

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

Begley CG, Ellis LM (2012). Drug development: *Nature* **483**(7391)**:** 531-533.



We operate under
The Scientific Method

Good statistical Practice (GSP) adds *statistical rigor and confidence* to the scientific method

- ➔ Interpretable results
- ➔ Reproducible
- ➔ Confidence in findings

Preece, D. A. "**Good Statistical Practice**." *Journal of the Royal Statistical Society. Series D (The Statistician)*, vol. 36, no. 4, 1987, pp. 397–408. *JSTOR*, https://doi.org/10.2307/2348838.

Reynolds PS. Between two stools: preclinical research, reproducibility, and statistical design of experiments. BMC Res Notes. 2022 Feb 21;15(1):73. doi: 10.1186/s13104-022-05965-w. PMID: 35189946; PMCID: PMC8862533.

Percie du Sert, N., Hurst, V., Ahluwalia, A. *et al.* **The ARRIVE guidelines 2.0**: Updated guidelines for reporting animal research. *BMC Vet Res* **16**, 242 (2020). https://doi.org/10.1186/s12917-020-02451-y

Good Statistical Practice

Study Design

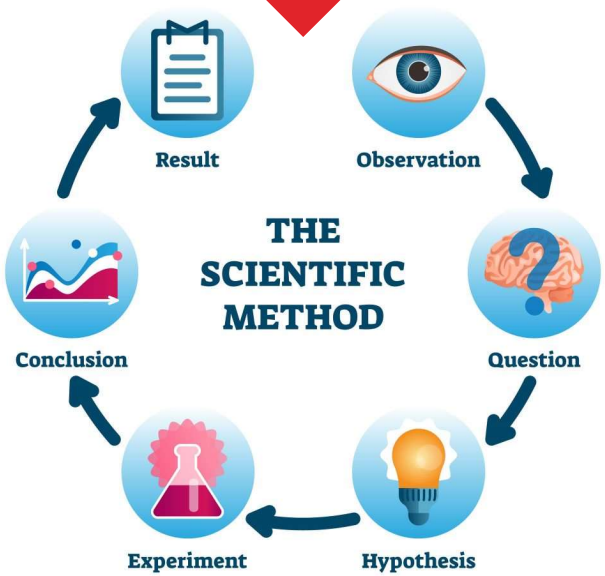
Statistical Analysis Plan (SAP)

Reproducibility Interpretability (R&I)

Efficiency

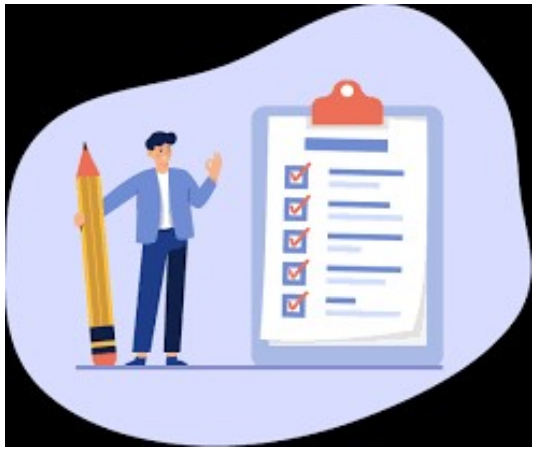
Confidence

R&I



Good Statistical Practice

Purpose of Study	√
Outcome Measurements + signal window	√
Success criteria	√
Controls/comparators	.
Experimental design	.
Estimation/testing strategy	.
Decision criteria	.
Sample size justification	.
Randomization into groups	.
Sample processing order	√
Blinding	√
Monitoring	√



https://arriveguidelines.org/

*A*nimal *R*esearch: *R*eporting of *In V*ivo *E*xperiments

ARRIVE guidelines

The ARRIVE guidelines (Animal Research: Reporting of *In Vivo* Experiments) are a checklist of recommendations for the full and transparent reporting of research involving animals – maximising the quality and reliability of published research, and enabling others to better scrutinise, evaluate and reproduce it.

ARRIVE guidelines ›

The ARRIVE guidelines embody GSP

GSP Alone is Not Enough

Remember:

90% of clinical drugs fail (Sun et al, 2022)

The root issues:

- *Poor reproducibility*
- *Statistical inefficiencies*
- ***Misalignment of preclinical models with human biology***

In vitro to Animal

Animal to Human

AstraZeneca's 5Rs

Right Target
Right Tissue
Right Safety
Right Patient
Right Commercial

Find the right target

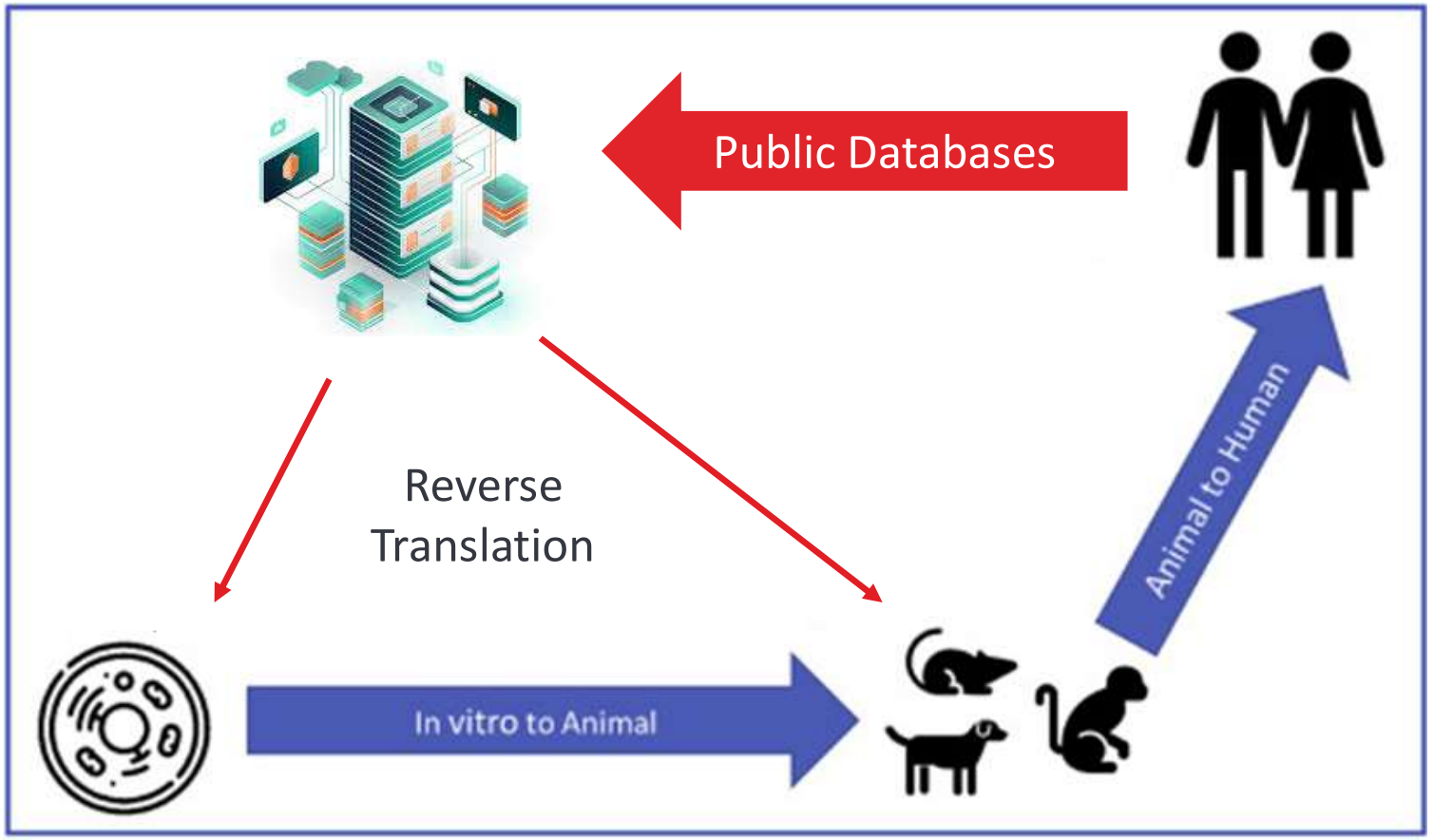
Difficult before 2008…

President George W. Bush signs H.R. 493, the Genetic Information Nondiscrimination Act of 2008, Wednesday, May 21, 2008, in the Oval Office. White House photo by Eric Draper.

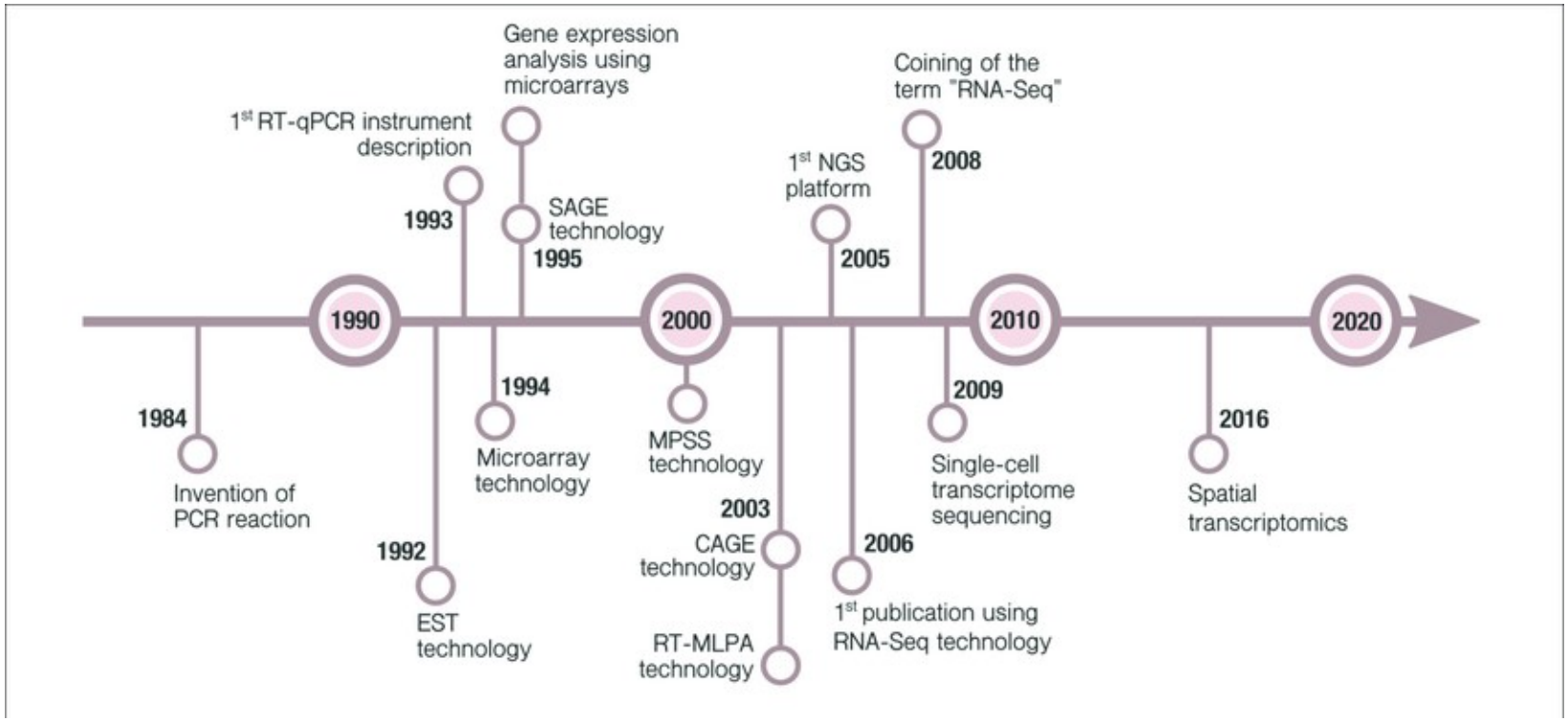
Genetic Information Nondiscrimination Act of 2008

Omics, pre-2008

Modern omics



Timeline of gene-expression assays



Martinez-Perez et al (2022)

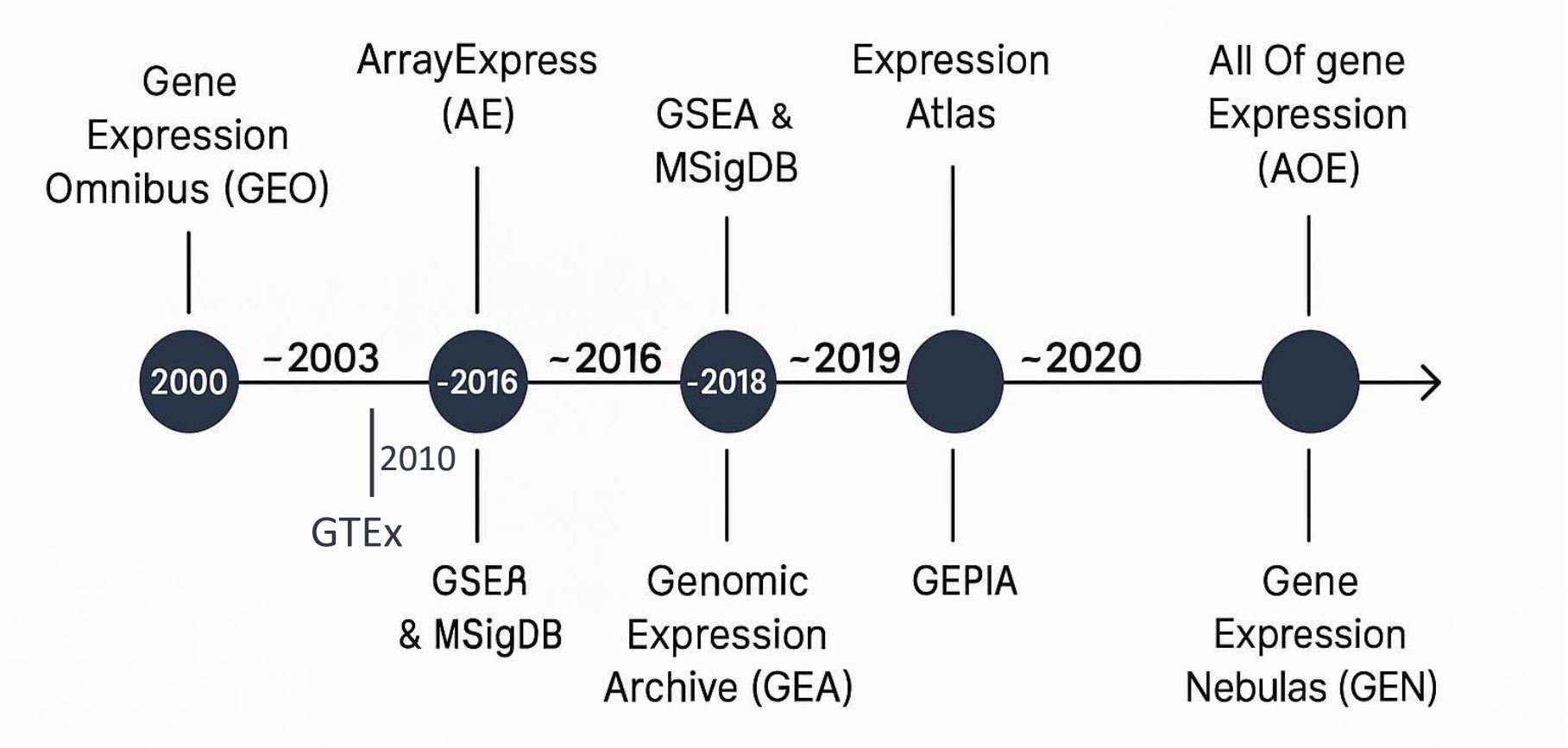
Patients reluctant to provide genetic data

2008

Citizens pay for analysis of DNA

Ancestry DNA
My Heritage
Etc.

Public databases of gene-expression data

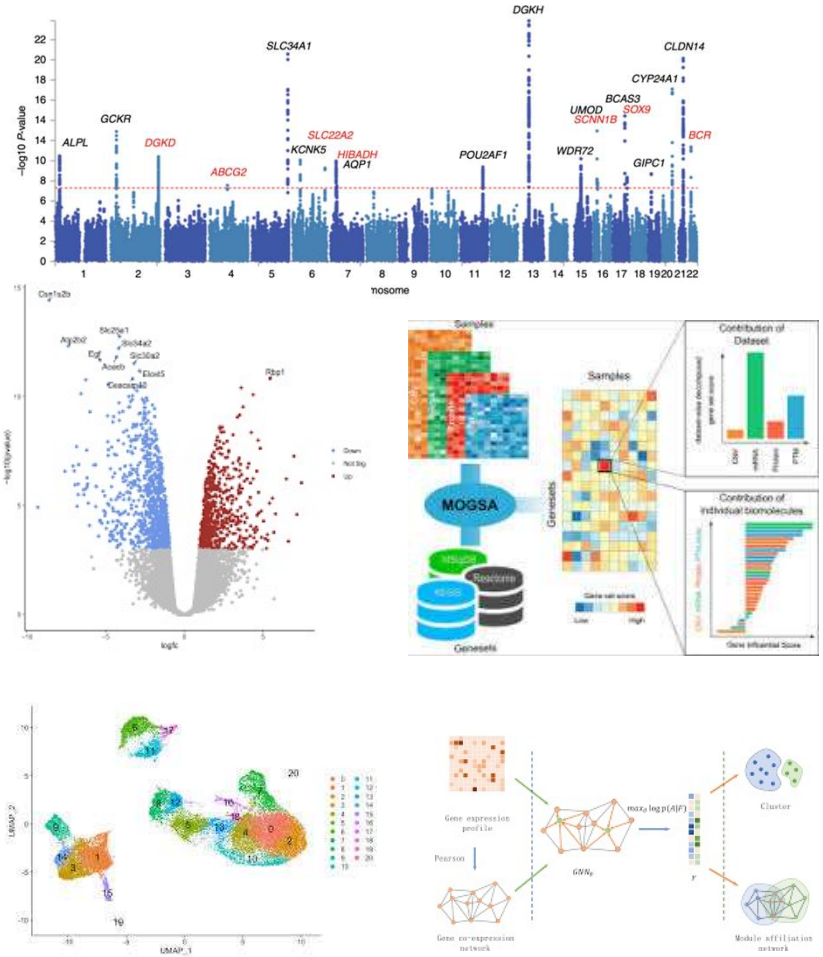


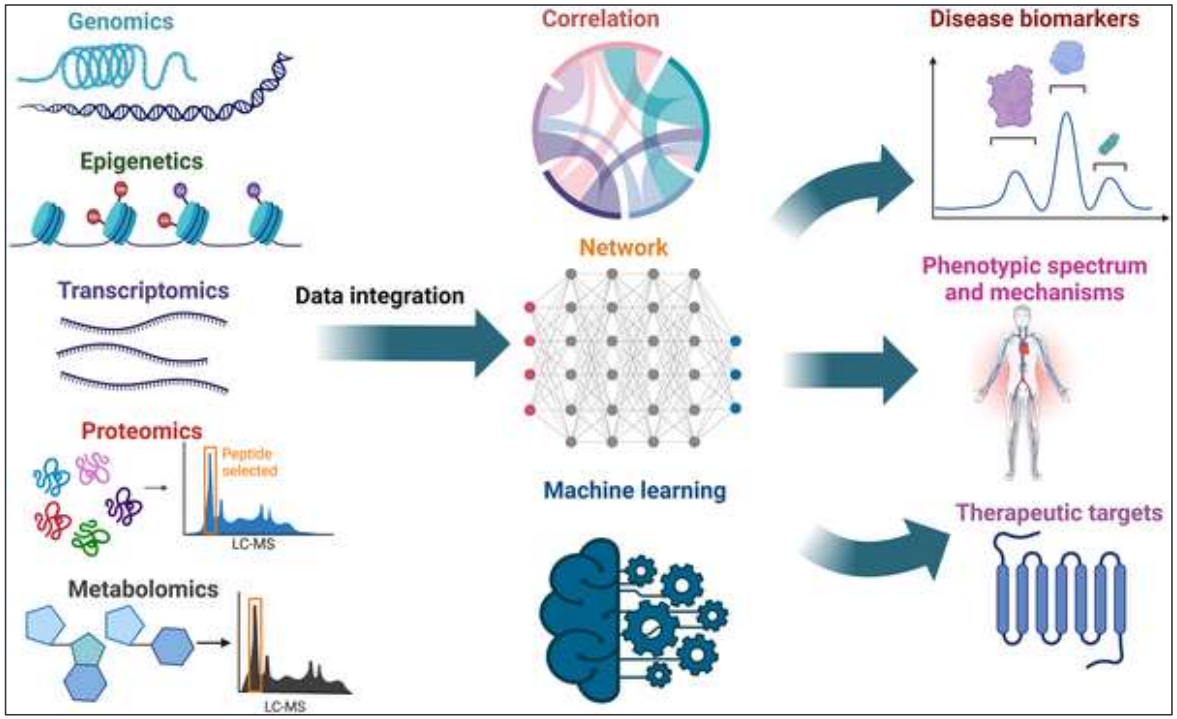
Types of omics data

- Genomics
- Epigenomics
- Phenomics
- Glycome
- Singe-cell RNA sequencing
- Proteomics
- Metabolomics
- DNA reference sequences
- Lipidome
- Transcriptomics
- Metagenomics
- Pharmacogenomics
- RNA sequencing

List pulled from Google search, 27-April-2025

Data integration, Multiomics





Chen et al (2020). “Applications of multi-omics analysis in human diseases.” MedComm

Traditional ‘omics analyses are [now] more meaningful

1. Differential Expression Analysis
2. Pathway Enrichment Analysis
3. Network Analysis
4. Genome-Wide Association Studies (GWAS)

In many cases, we collect selective panels of gene/protein expression data

Given benchmarks against human results,

➔ more confidence in novel findings

Reverse Translated Biomarkers for Enhanced Translation

Alzheimer's Disease

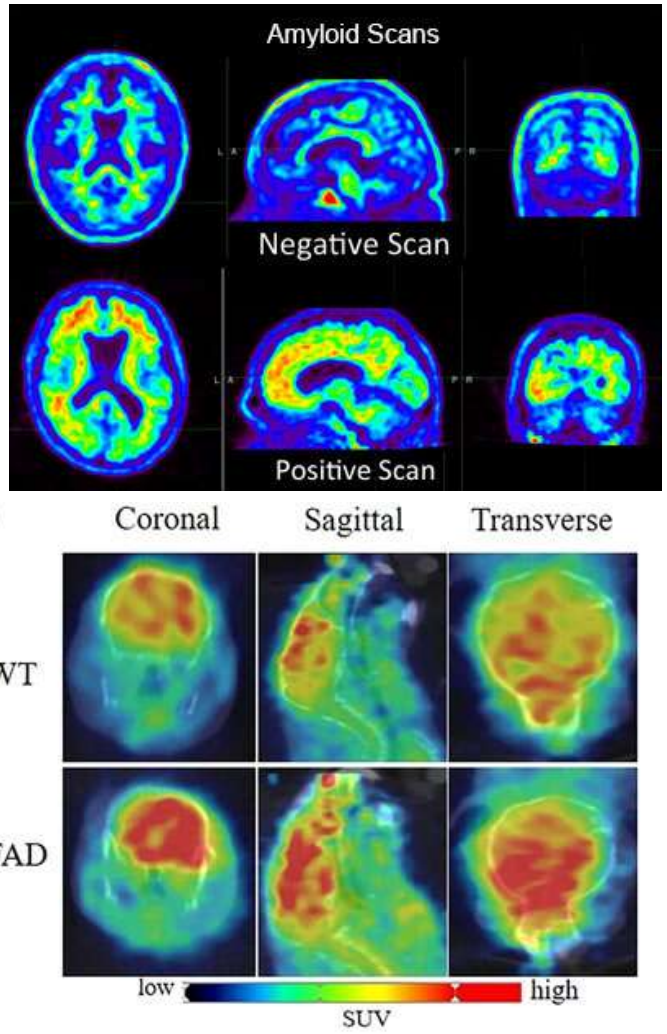
- Clinical studies show accumulation of amyloid-beta plaques in human brain

Led to development of mouse model

- Mimics amyloid-beta pathology (e.g., 5xFAD, APP/PS1 transgenics)

Human

Mouse: 5xFAD



https://radiology.ucsf.edu/patient-care/services/specialty-imaging/alzheimer

Damuka N, Irmen RE, Krizan I, Miller M, Gollapelli KK, Bhoopal B, Deep O, Bansode A, Lockhart SN, Orr ME, Jadiya P, Bashetti N, Kumar JVS, Mintz A, Whitlow CT, Craft S, Macauley SL, Solingapuram Sai KK. Exploring microtubule dynamics in Alzheimer's disease: Longitudinal assessment using [^{11}C]MPC-6827 PET imaging in rodent models of Alzheimer's-related pathology. Alzheimers Dement. 2024 Sep;20(9):6082-6093. doi: 10.1002/alz.14083. Epub 2024 Jul 5. PMID: 38967283; PMCID: PMC11497705.

Psoriasis (chronic autoimmune skin disease)

- Clinical studies found IL-17A and IL-23 cytokines highly elevated in psoriatic skin and blood
- Correlation with disease severity (PASI score — Psoriasis Area and Severity Index)

Led to development of mouse model to drive IL-17A/IL-23 activation

Mimics human psoriasis →

IL-17A Antibody on C57BL/6 Mice

Li, Q., Liu, W., Gao, S. *et al.* Application of imiquimod-induced murine psoriasis model in evaluating interleukin-17A antagonist. *BMC Immunol* **22**, 11 (2021). https://doi.org/10.1186/s12865-021-00401-3

Deciding on the right target

Multiparameter Optimization (MPO)

Decision theory technique to simultaneously optimize a set of factors against an objective

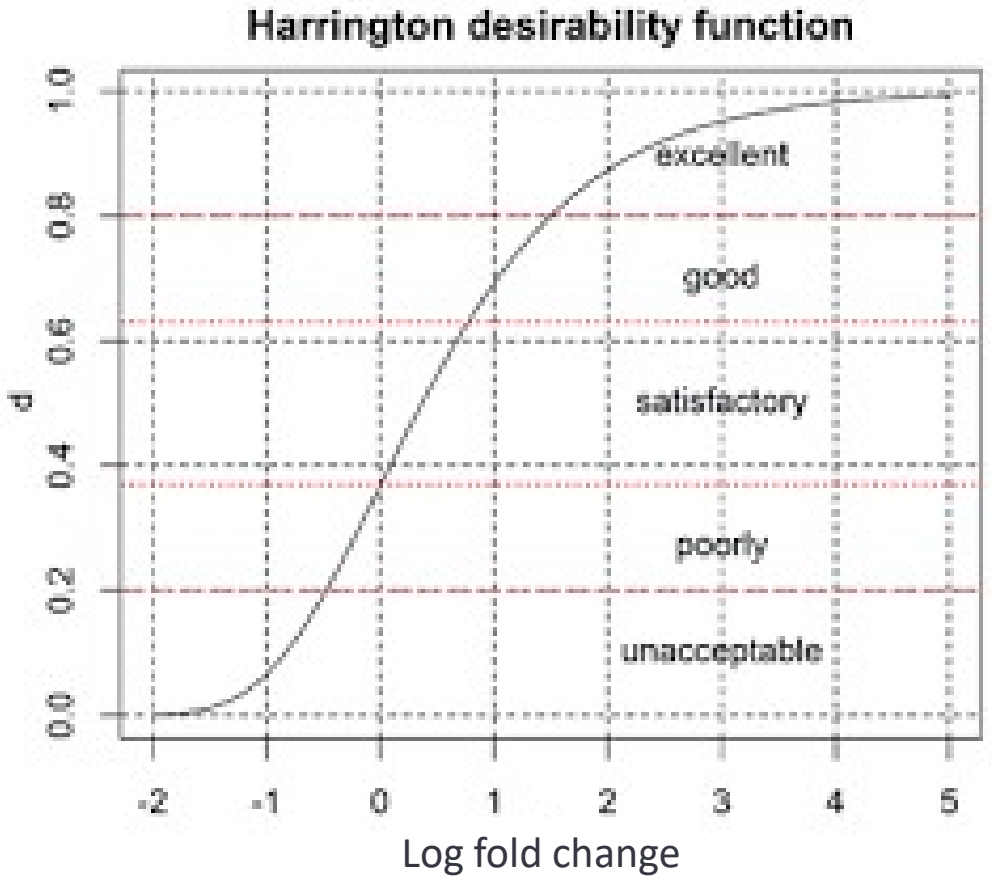
Rank order alternatives

	Alternative			Criterion Weights
	1	2	3	
Efficacy	##	##	##	##
Safety	##	##	##	##
Quality of Life	##	##	##	##
Functional Status	##	##	##	##
Dosing Convenience	##	##	##	##
Price	##	##	##	##
Cost-Effectiveness	##	##	##	##
Budget Impact	##	##	##	##

Scores Reflecting Performance

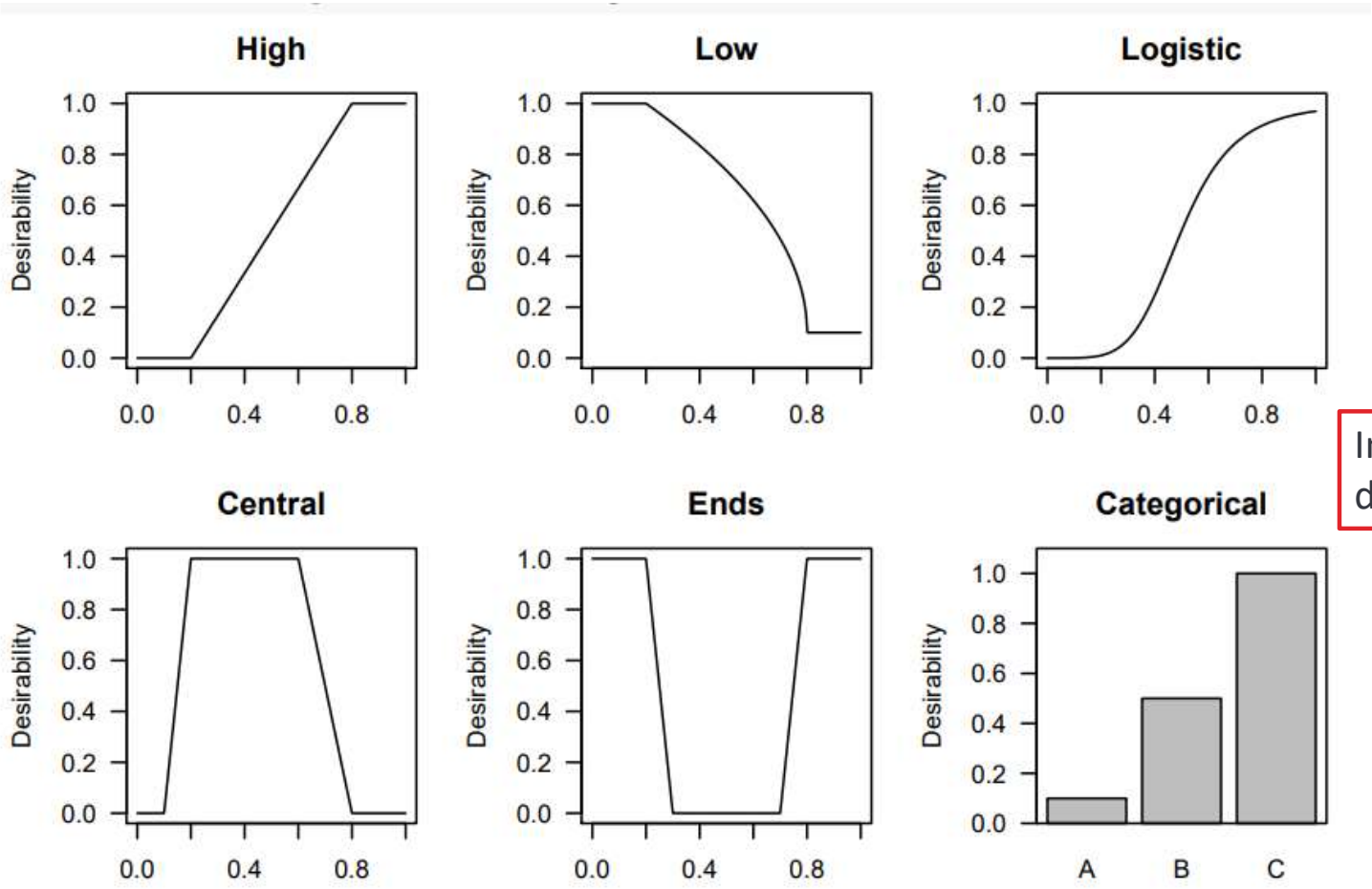
Harrington, E.C. (**1965**) The Desirability Function. Industrial Quality Control, 21, 494-498.

Each feature is matched with a desirability function



Desirability: $0 < d < 1$

Subjectively chosen



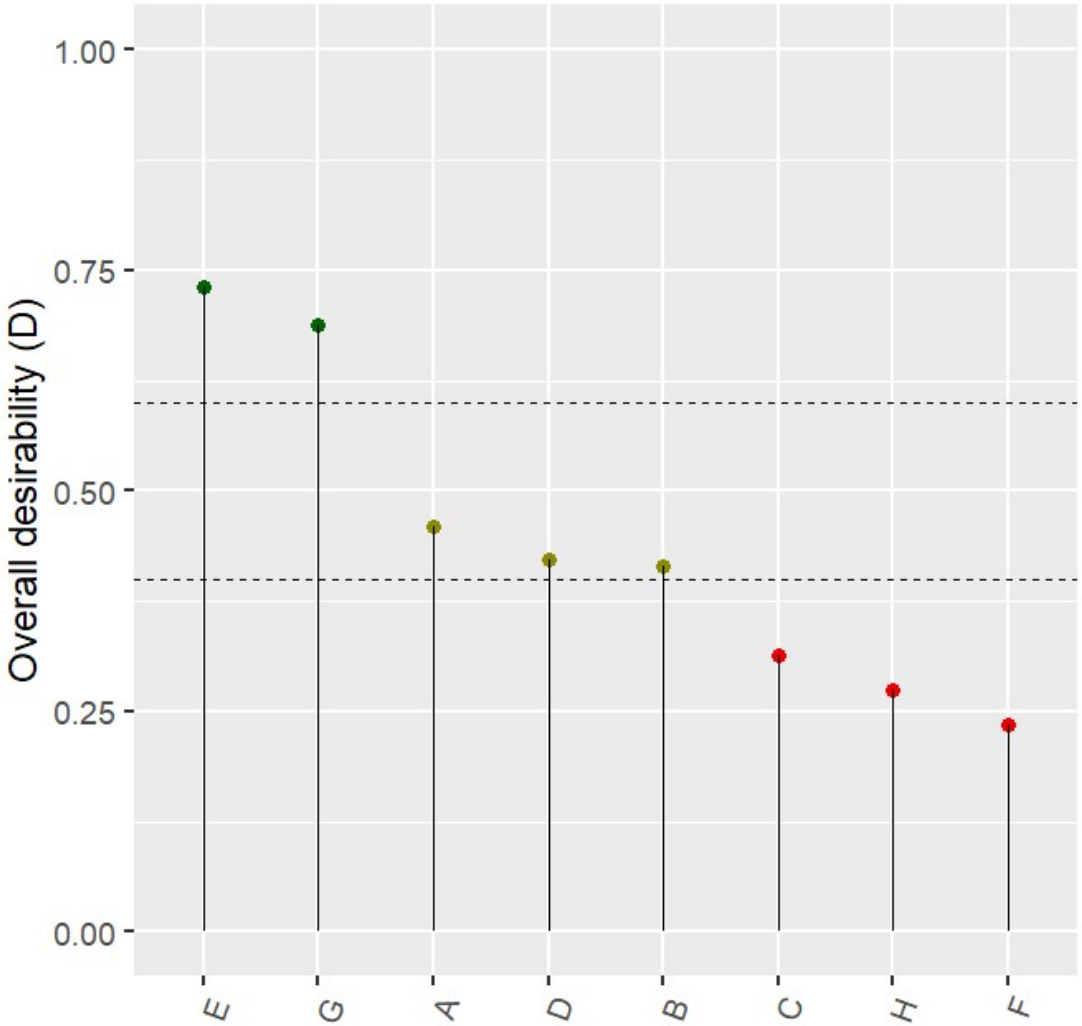
Infinite variety of desirability functions

Source: https://cran.r-project.org/web/packages/desiR/vignettes/Gene_ranking.pdf

Overall desirability

	Value					desirability				
Target	Log2 FC gene1	Log2 FC gene2	Corr	# Articles	Market ($B)	Log2 FC gene1	Log2 FC gene2	Corr	# Articles	Market
						2x	1x	1x	0.5x	0.25x
A	0.617	1.116	0.410	0	7	0.48	0.59	0.41	0.20	1.00
B	1.199	-0.871	0.357	1	2	0.96	0.10	0.36	0.40	0.29
C	0.015	1.500	0.579	3	7	0.10	0.77	0.58	0.80	1.00
D	0.699	0.074	0.883	1	1	0.62	0.13	0.88	0.40	0.14
E	1.864	0.633	0.806	4	5	1.00	0.31	0.81	1.00	0.71
F	0.208	0.964	0.437	0	7	0.10	0.50	0.44	0.20	1.00
G	0.850	1.137	0.478	3	7	0.81	0.61	0.48	0.80	1.00
H	0.041	2.315	0.375	1	6	0.10	0.94	0.38	0.40	0.86

Overall D = weighted geometric mean

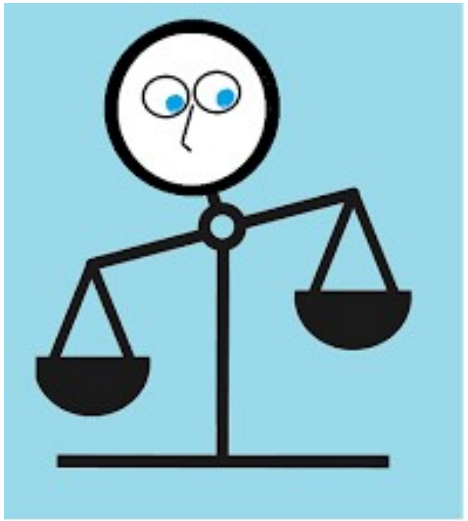


Target	Desirability
E, G	0.6 – 1 [Top choices]
A, B, D	0.4 – 0.6 [Grey area]
C, F, H	0 – 0.4 [Avoid these]

Subjective, but still great

MPO significantly enhances decision-making in preclinical drug development

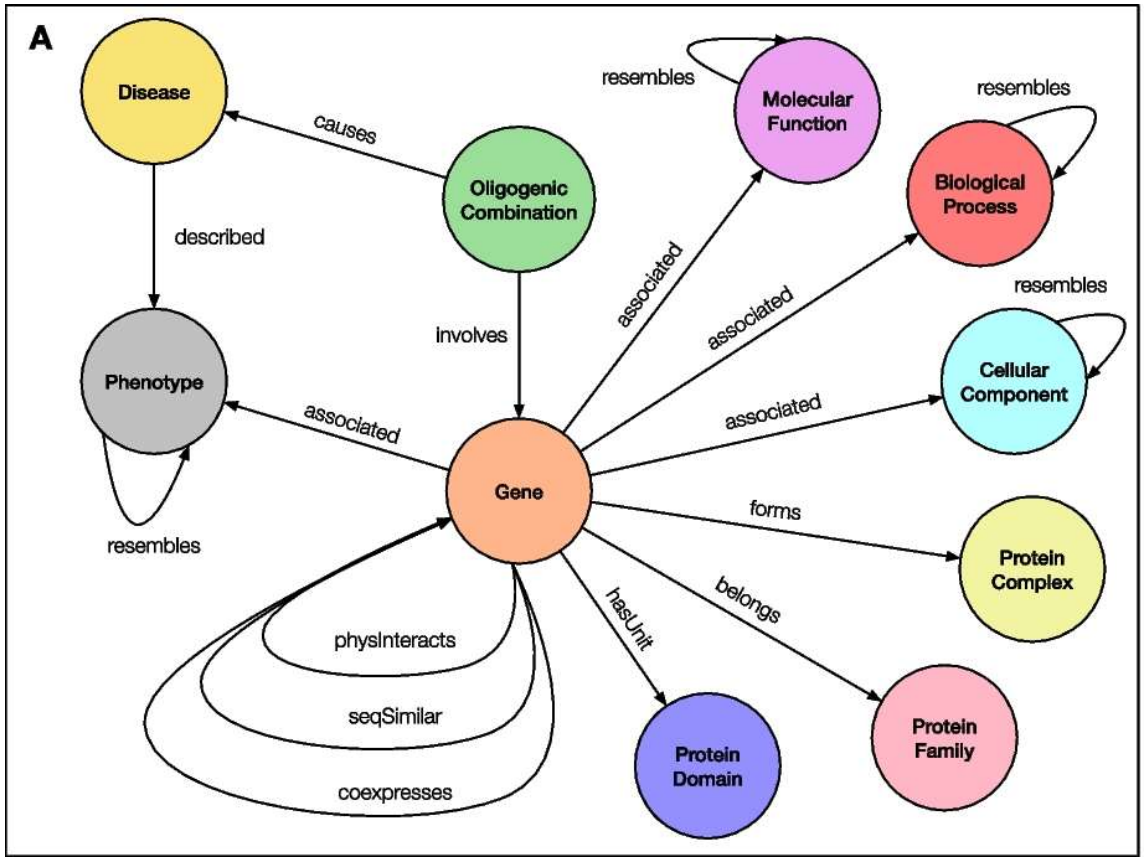
- Integrates expert knowledge, study data
- Evaluates trade offs among multiple targets or attributes
- Further refinement steps, such as compound diversity analyses and LLM-augmented summaries of evidence



Machine Learning and AI

Photo is of Secretary of Education, Linda McMahon at Educators Convention in San Diego, April 8, 2025

Knowledge Graphs (KG)



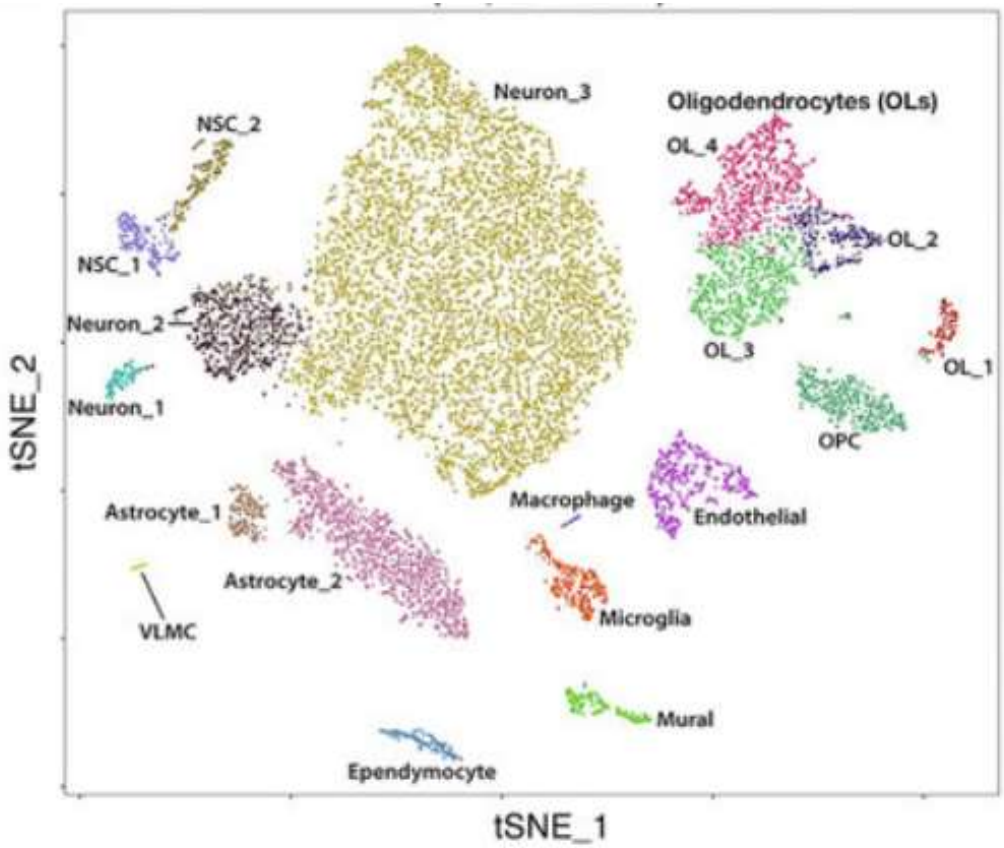
- Links explicit knowledge with inferred relationships
- Genes/proteins/disease are nodes
- Relationships are edges

By analyzing connections, KGs can uncover hidden or non-obvious relationships, identifying potential targets

+ predictive analytics can suggest new drug-target connections or repurpose existing drugs

Renaux et al (2023). A knowledge graph approach to predict and interpret disease-causing gene interactions. *BMC Bioinformatics*

Find the right tissue



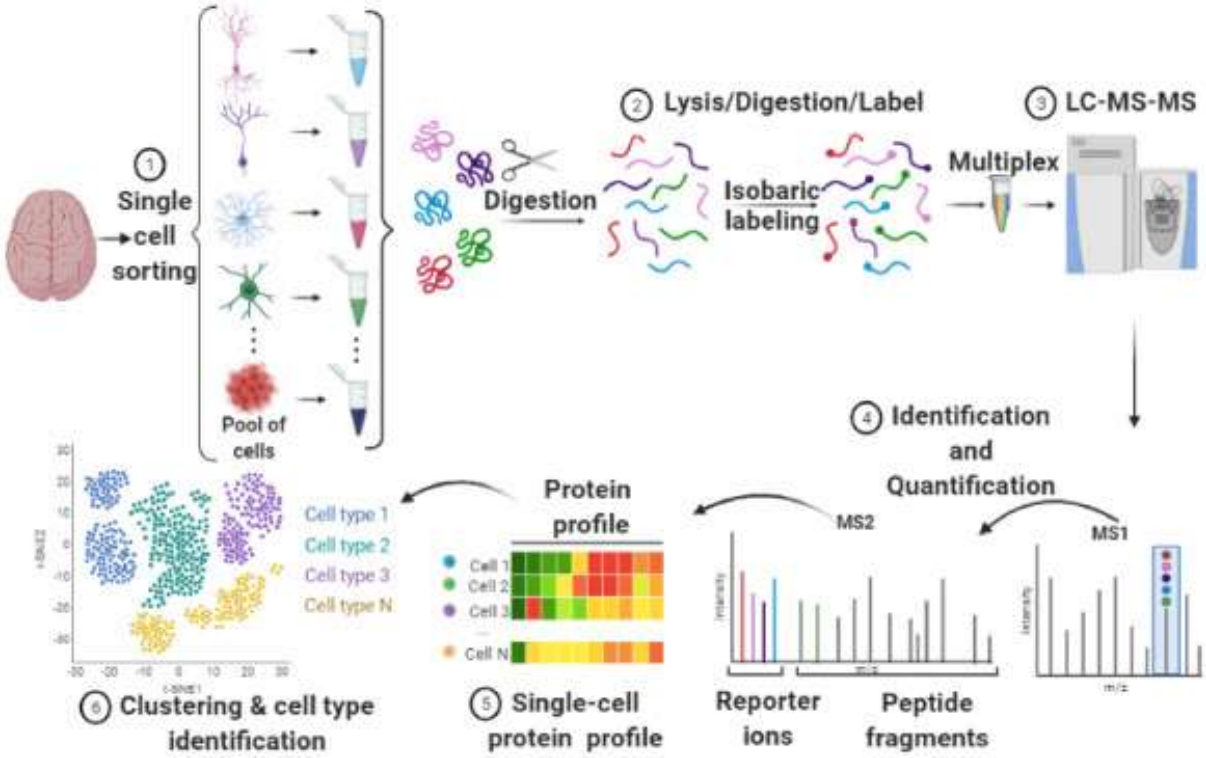
Analysis of single cell RNAseq

- Classifiers to determine cell types
- Spatial Tx

Fewer false pos/neg in
DEG associated with cell types

Avey et al (2018). “Single-Cell RNA-Seq Uncovers a Robust Transcriptional Response to Morphine by Glia.” Cell Rep.

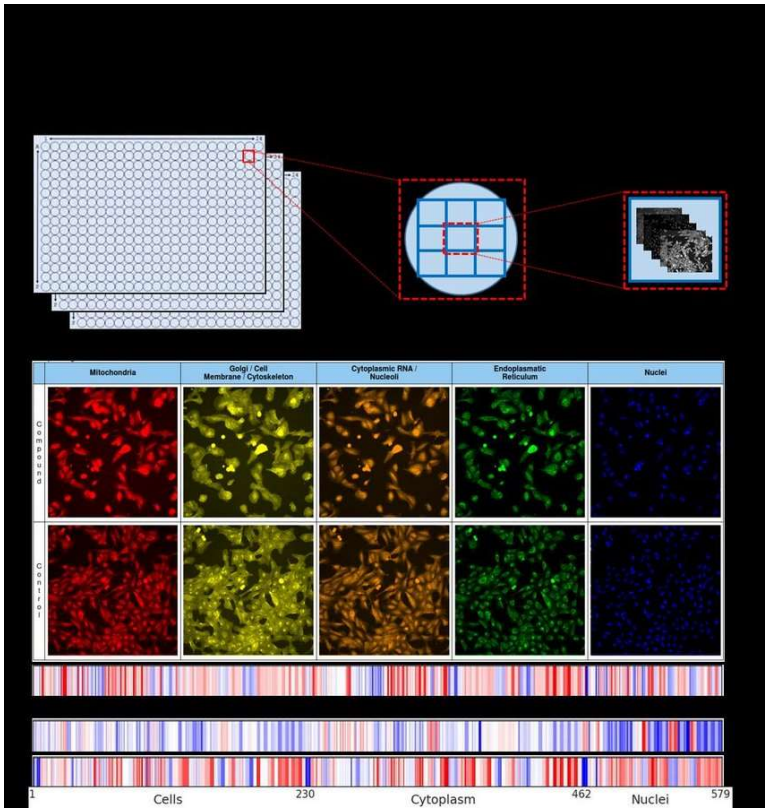
Single cell proteomics



Goto-Silva L, Junqueira M. Single-cell proteomics: A treasure trove in neurobiology. Biochim Biophys Acta Proteins Proteom. 2021 Jul;1869(7):140658. doi: 10.1016/j.bbapap.2021.140658. Epub 2021 Apr 12. PMID: 33845200.

Given the right target and tissue…

Digital Hit Screening



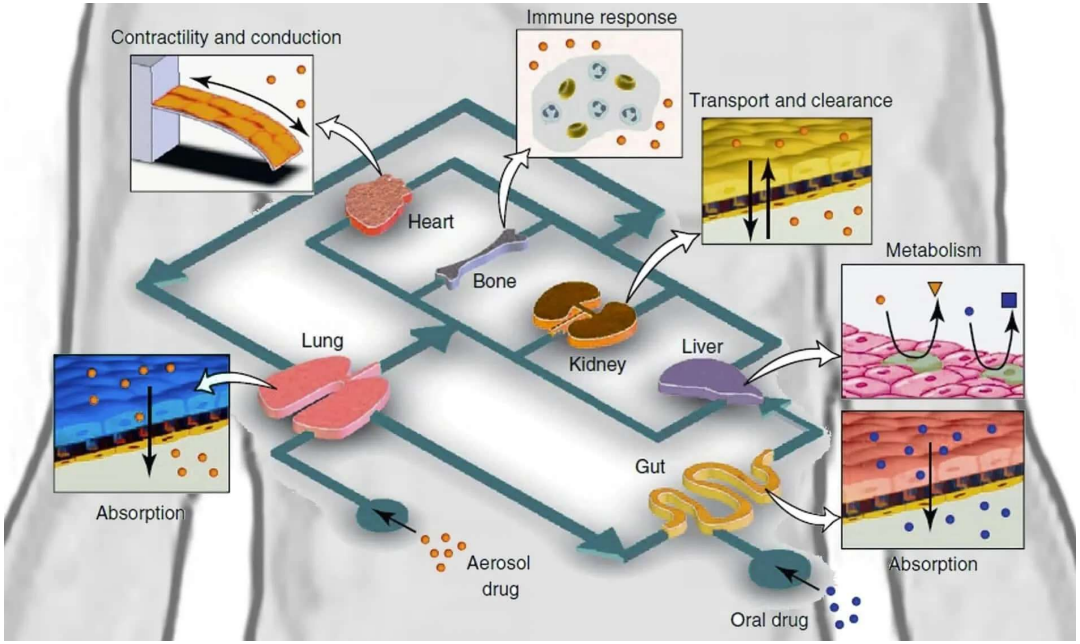
Cell Painting for hit screening, drug repurposing

Provides profile cellular phenotypes that dye organelles or cellular components.

Microscopy + image analysis
Differentiate cellular morphology

Gally et al (2020)
Identifying bioactivity of pseudo-natural products using the Cell Painting assay

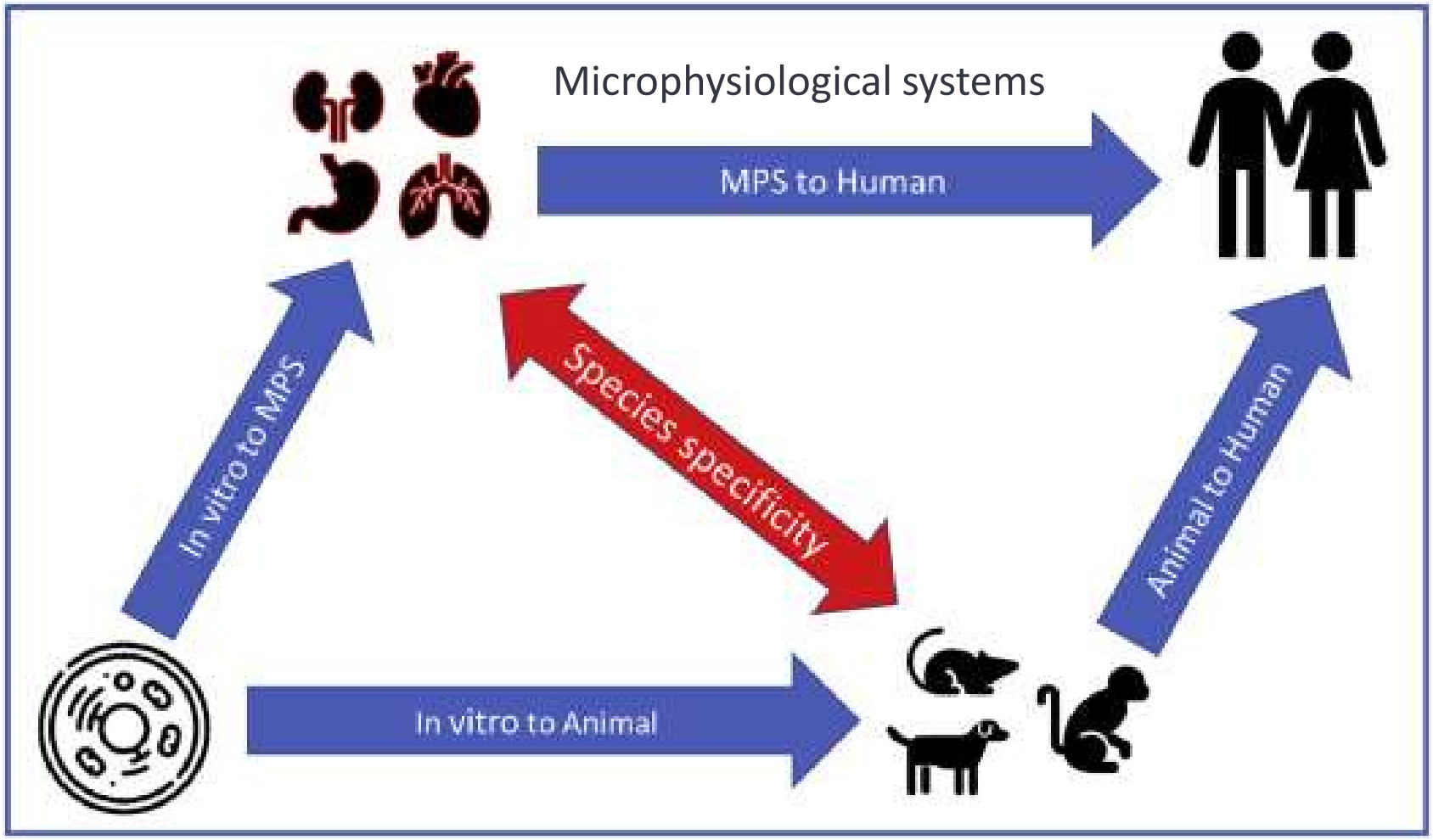
Organs on a chip



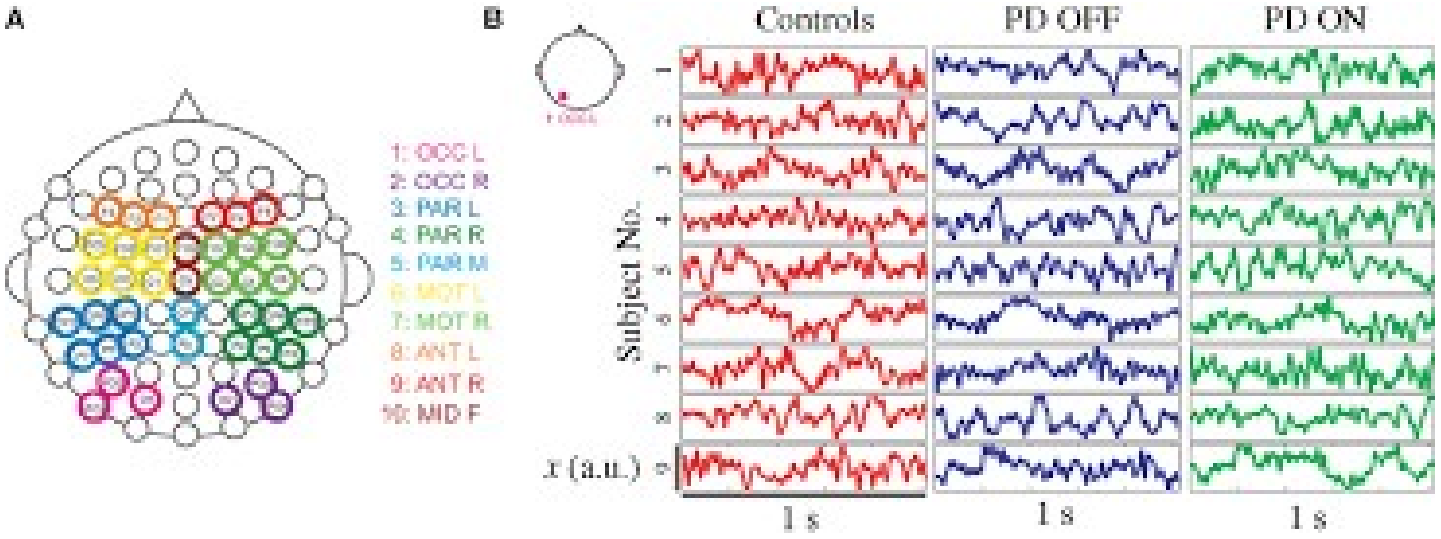
Traditional 2D cell cultures often fail to capture human-disease biology effectively. Enter 3D-organoid cultures and organs-on-chip platforms, which have brought us closer to mimicking human tissue functionality

Predict side effects and human toxicity and associated mechanisms

Modern translation



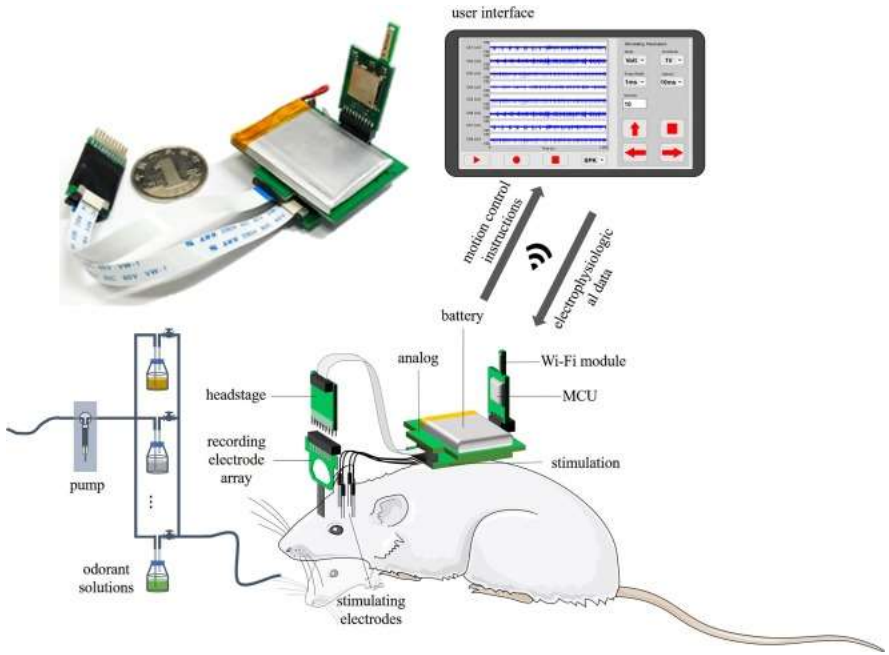
Digital biomarkers



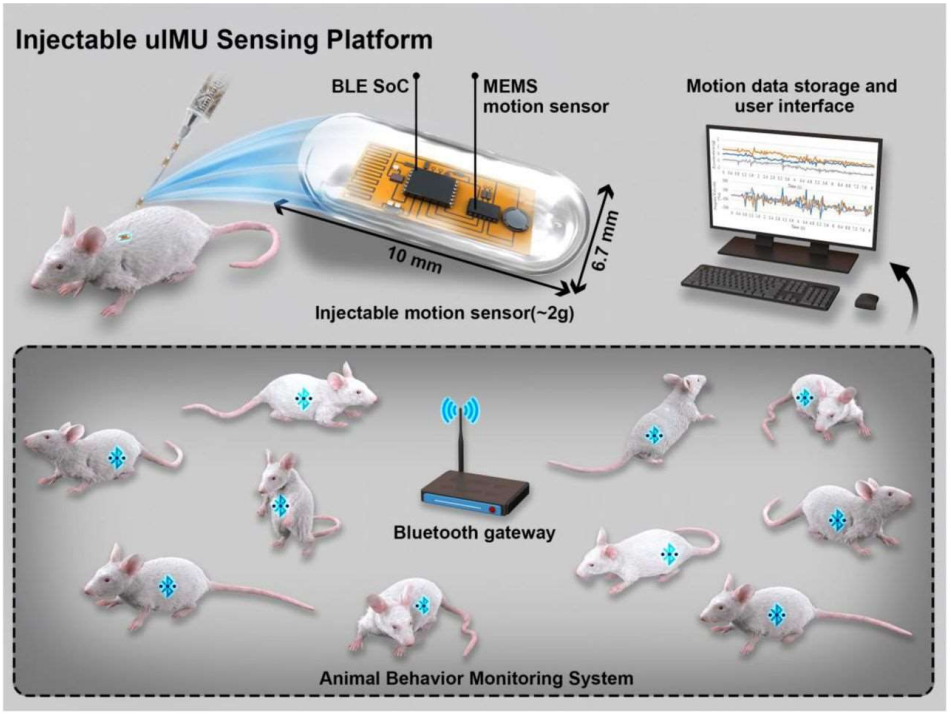
EEG data for Parkingson's, epilepsy

Lainscsek et al (2013)

Non-Linear Dynamical Analysis of EEG Time Series Distinguishes Patients with Parkinson's Disease from Healthy Individuals

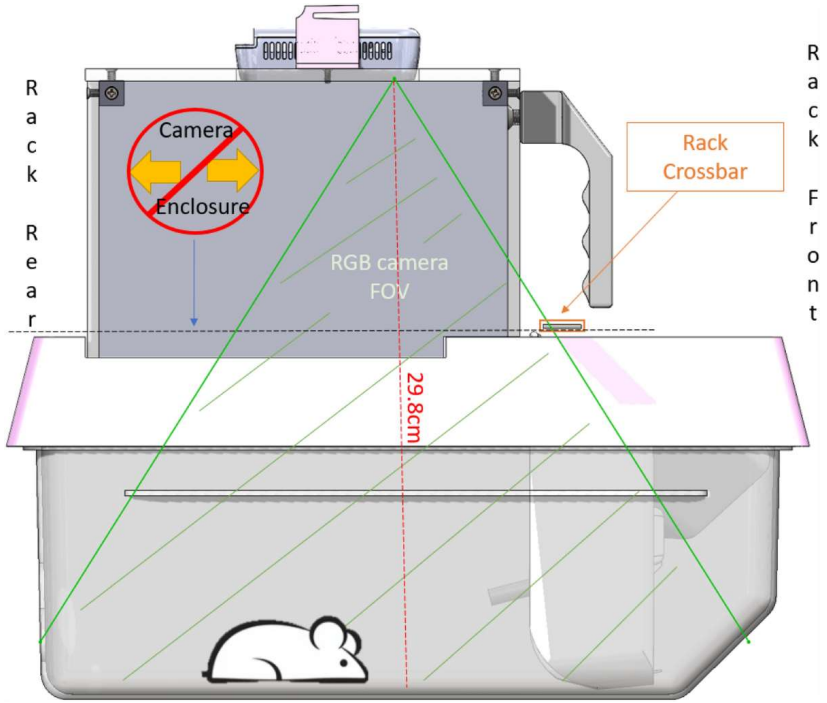


Zhang, et al (2018)
A wearable system for olfactory electrophysiological recording and animal motion control



Chen et al (2020)
Wireless AI-Powered IoT Sensors for Laboratory Mice Behavior Recognition

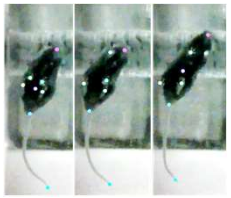
Enhanced Translation: Behavioral Phenotyping



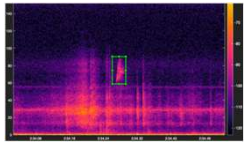
AI driven models of physiological and behavioral signals

Preclinical

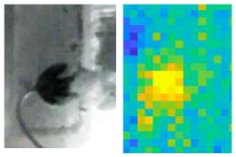
Quadruped gait



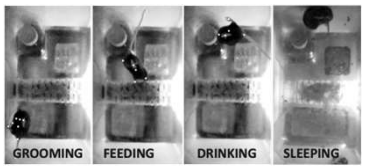
Ultrasonic Vocalizations



Temperature monitoring



Core behaviors



Clinical

Biped gait

Speech biomarkers

Temperature monitoring

Quality of life

- Translating *video* motor phenotyping of behavioral information
- Provides quantitative measurements of gait and complex behaviors in home cage

Grooming

Eating

Walking

Rearing

Drinking

Leveraging AI tools on AWS Insight:

- deeplabcut (tracking)
- b-soid (ethology)

Feature extraction & statistical modeling

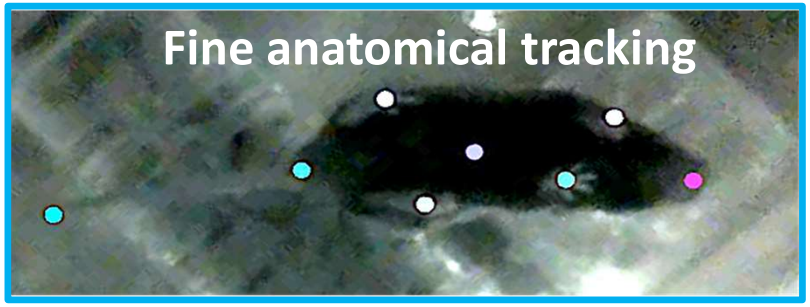
Neurodegenerative diseases

T Tremor: shaking, usually starting on one side

R Rigidity: stiffness of the limbs, neck, or trunk

A Akinesia: loss or impairment in power of voluntary movement

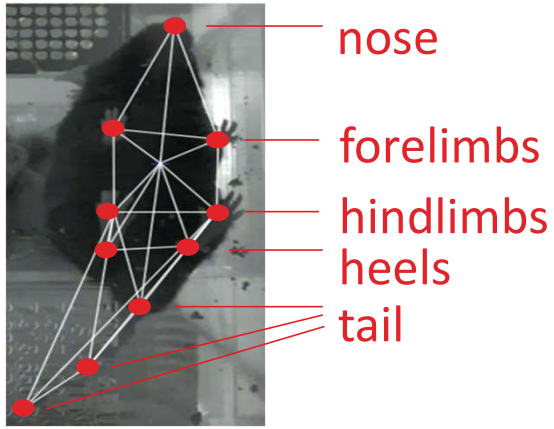
P Posture and balance



Reverse translation

Inflammation Model

Ear scratching



Key Takeaways

- Statistical rigor is essential via GSP
- GSP alone is insufficient to sustain a successful preclinical pipeline
- Sets of tools that take advantage of troves of data
- Knowledge Graph, LLM, or generative AI
- New Approach Methodologies (NAMs): Organs on a chip
- Reverse translation

THANK YOU!

Takeda

Better Health, Brighter Future