Integration of Omics-Based Technologies in Drug Target Discovery

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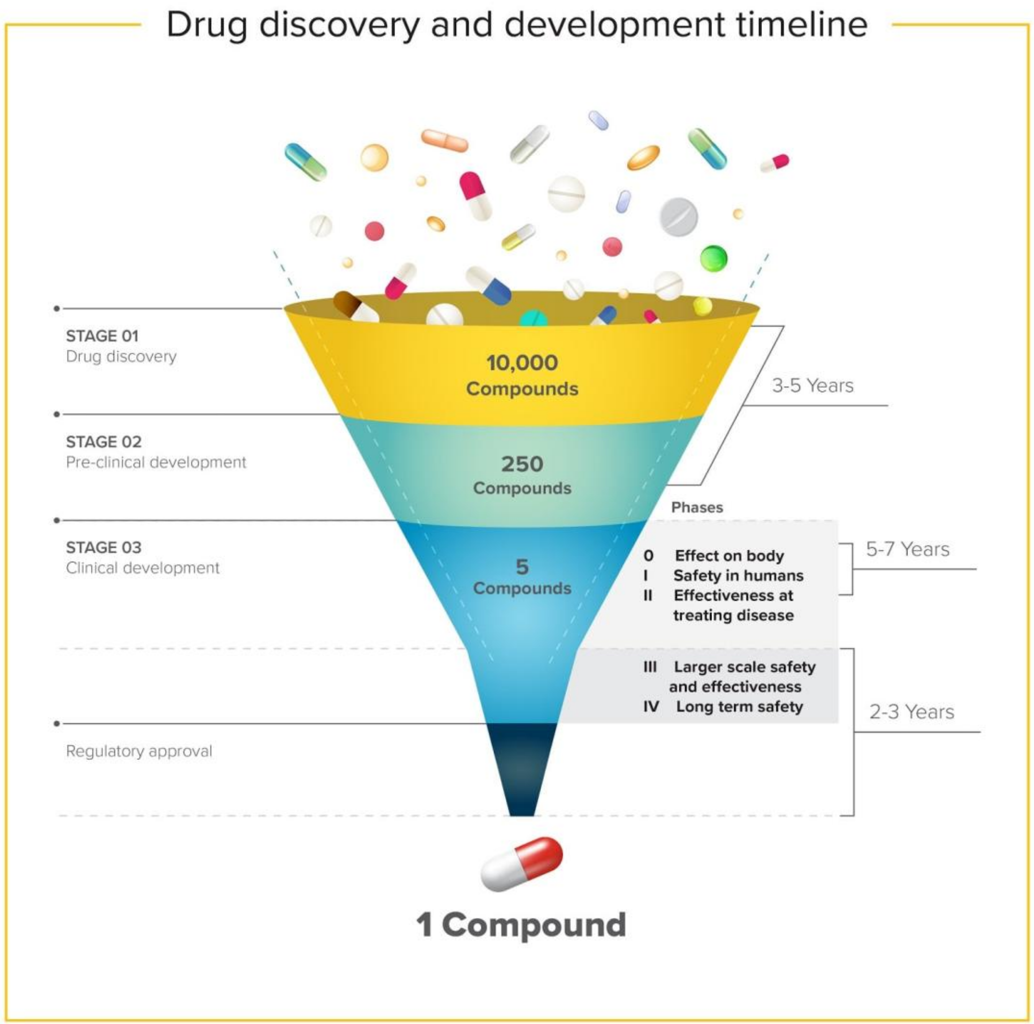
Drug discovery

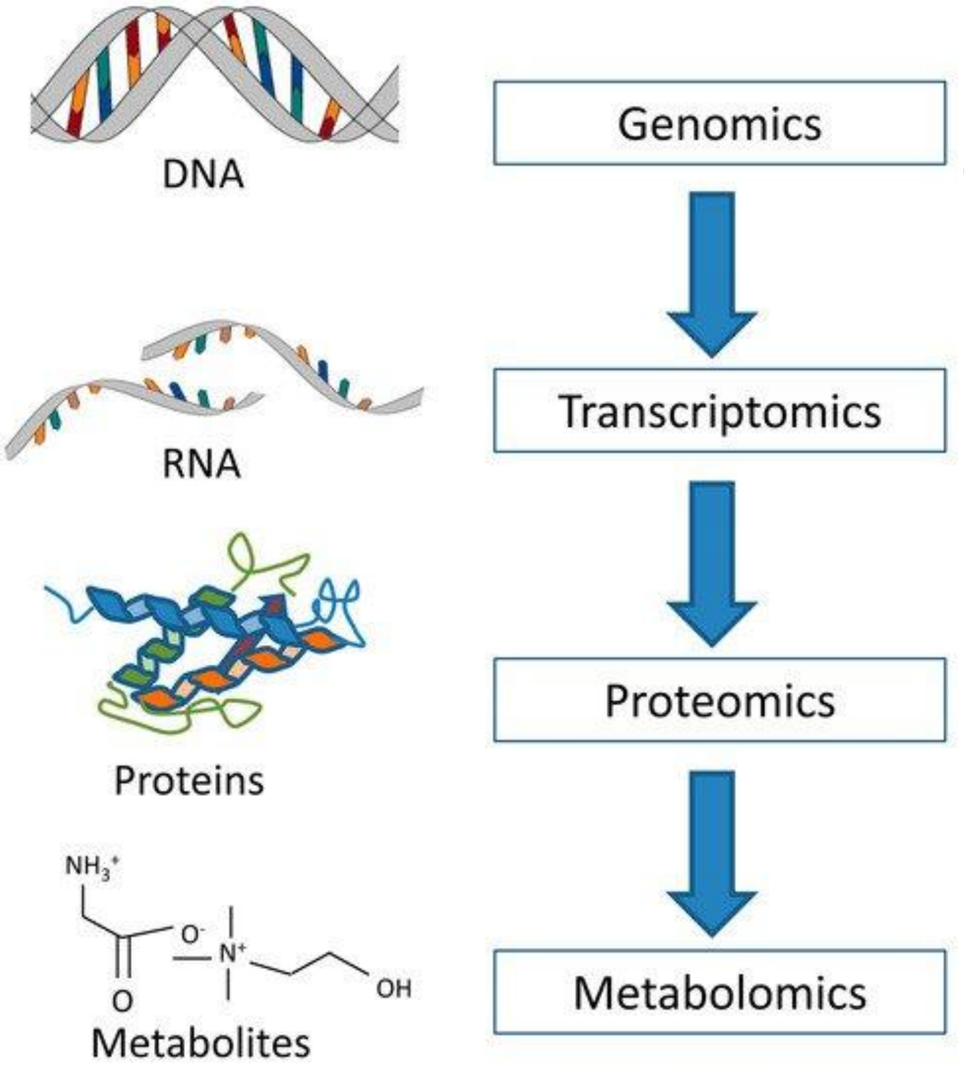
- Advancing a single drug from concept to market→ exceeds 1 billion US dollars.
- Traditional drug discovery processes→ **costly**, time-consuming, and **very risky**.
- Omics-based technologies can **accelerate** drug discovery and provide novel, clinically valid targets.


Drug discovery and development timeline

www.yourgenome.org

Omics?

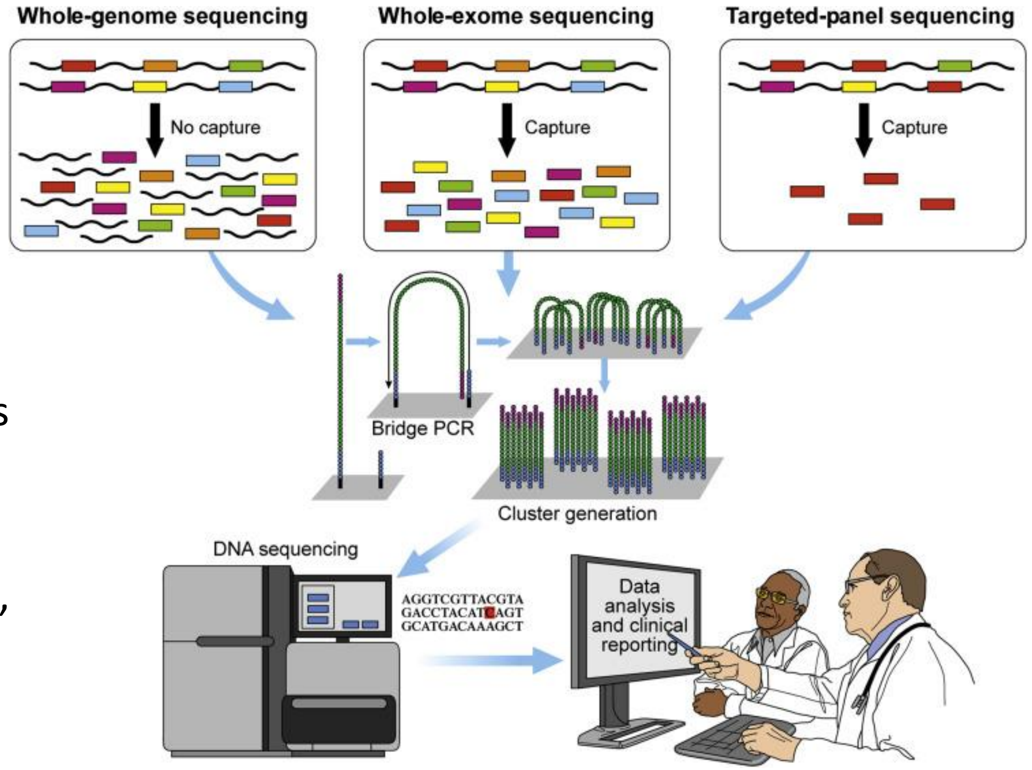
- Omics refers to various disciplines in biology such as genomics, proteomics, metabolomics, metagenomics, and transcriptomics.
- The suffix -omics added to a molecular term implies a comprehensive, or global, assessment of a **set of molecules**.
- Omics provides collective characterization and quantification of pools of biological molecules.
- These approaches allow a **deep investigation** of the structure, function, and dynamics of a cell, tissue, or organism.



Haukaas *et al.*, Metabolites, 2017

Genomics

- Genomics: the genetic mapping and DNA sequencing of sets of genes or the complete genomes of selected organisms.
- One of the earliest applications for drug target discoveries.
- Genomics can provide evidence of causation→ ++ clinical trial success.
- Identification of disease-associated mutations: assess risk for diseases and discover effective drug targets.
- Sequencing technologies are extensively used to identify variants: **SNPs**, INDELs, and SVs.
- For example, genetic hypertriglyceridemia can be caused by biallelic loss-of-function in the LPL, APOC2, APOA5, LMF1, and GPIHBP1 genes.



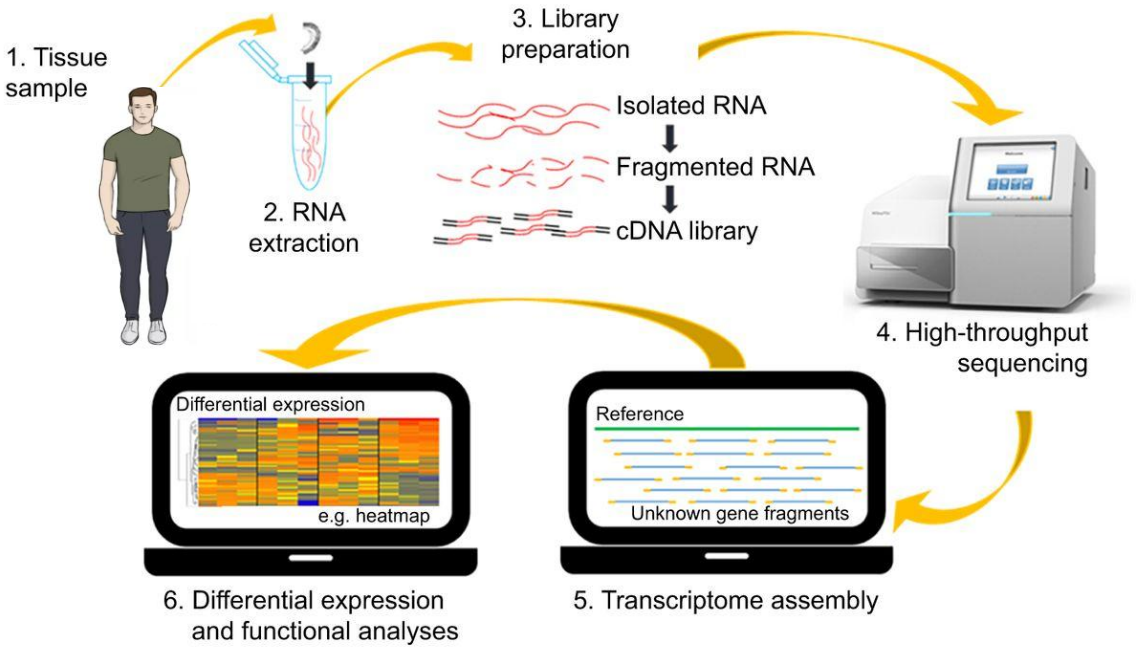
Klein & Foroud, Symposium on Precision Medicine, 2017

Pharmacogenomics

- To study the impact of genetic variations on drug response and drug metabolism→ **patient stratification**.
- A patient’s response to drug treatment could be linked to the SNP genomic profile.
- Pharmacogenomics could guide the drug development process: assess the efficacy and drug-related toxicity.
- It helps determine which available drugs are suitable for a particular patient in a daily clinical setting→ safer and more powerful medicines.
- For example, the effectiveness of clopidogrel (antiplatelet drug) is influenced by variations in the CYP2C19 gene, which encodes an enzyme involved in the drug’s metabolism.

Transcriptomics

- Transcriptomics is the study of the complete set of RNA transcripts **at a given time**.
- Gene expression profiling is mainly used to evaluate potential adverse effects at an early stage in drug development.
- Transcriptomics is widely used to support alternative methods for chemical risk assessment.
- Transcriptomics and pharmacogenomics data could be combined to ensure drug safety.

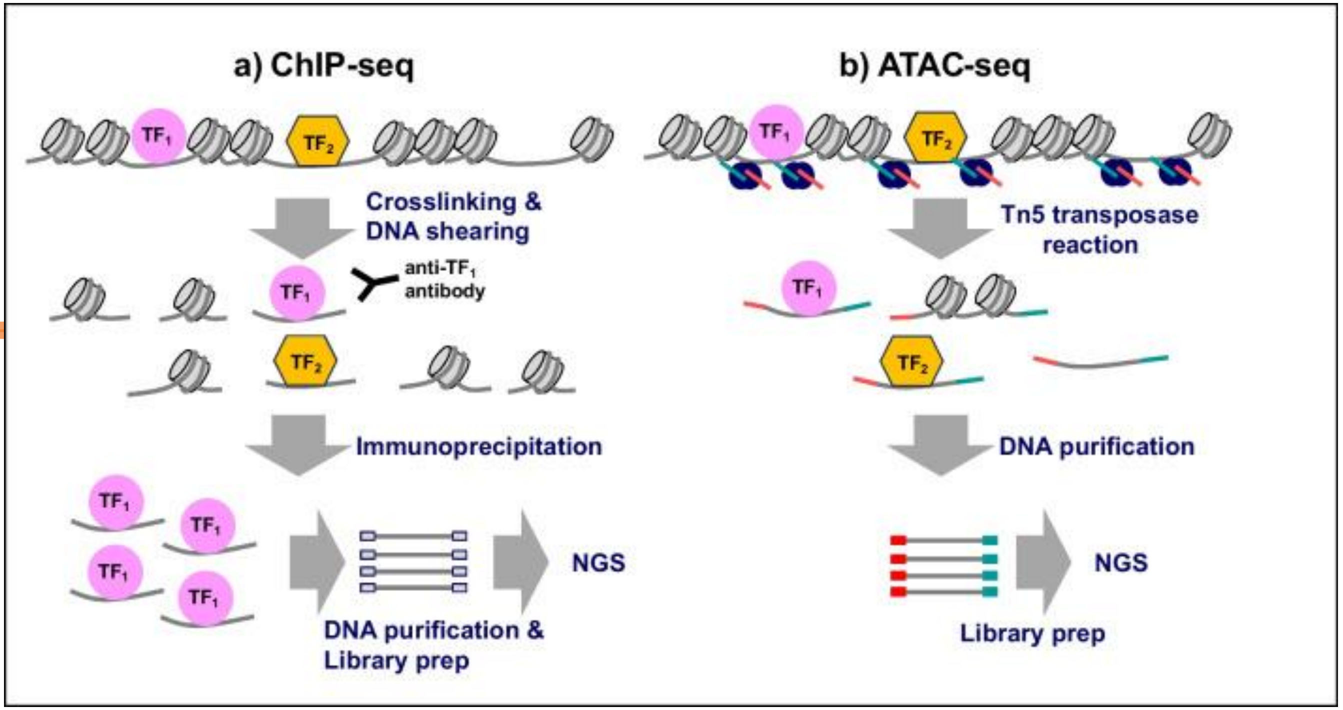


https://www.rna-seqblog.com/

The field is rapidly expanding with NGS technologies: RNA sequencing (bulk or single-cell RNA-Seq)

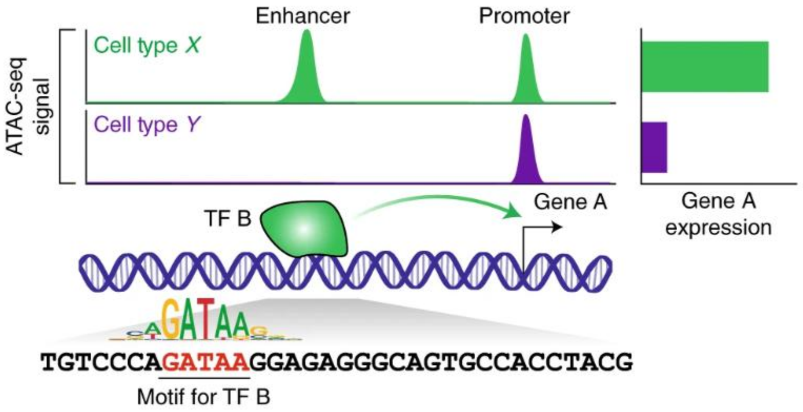
Epigenomics

- Epigenomics is the study of epigenetic modifications to DNA and histone proteins that regulate gene expression without altering the underlying DNA sequence.



Hojo and Ohba., Curr Osteoporos Rep, 2023

- Example techniques: ChIP-Seq (Chromatin Immunoprecipitation Sequencing), Bisulfite Sequencing, Methylation Arrays, ATAC-Seq (Assay for Transposase-Accessible Chromatin with Sequencing).



Grandi et al., Nature protocols, 2022

- ATAC-Seq is an advanced epigenomic tool that provides insights into chromatin structure and accessibility.

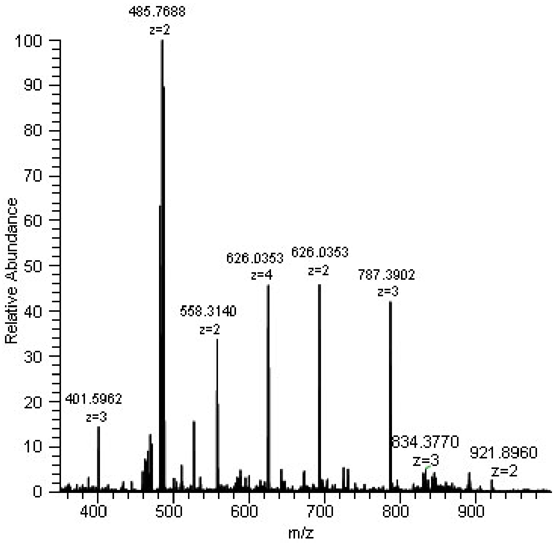
Proteomics

- Proteomics → analysis of the entire protein content of a cell, tissue, or organism under a specific condition.
- Proteomics mainly includes protein expression profiling, functional proteomics, and phospho-proteomics.

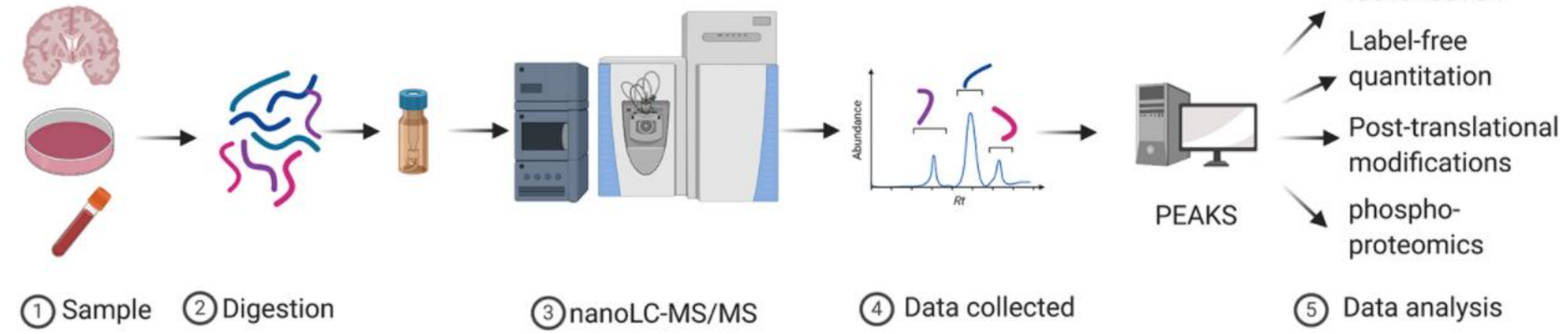
Proteomics can be used to :

1. identify and validate druggable proteins
2. study drug efficacy and toxicology
3. disease stratification

Mass spectrometry is the technique of choice for proteome analysis→ mass-to-charge ratio (m/z)



Protein and peptide identification

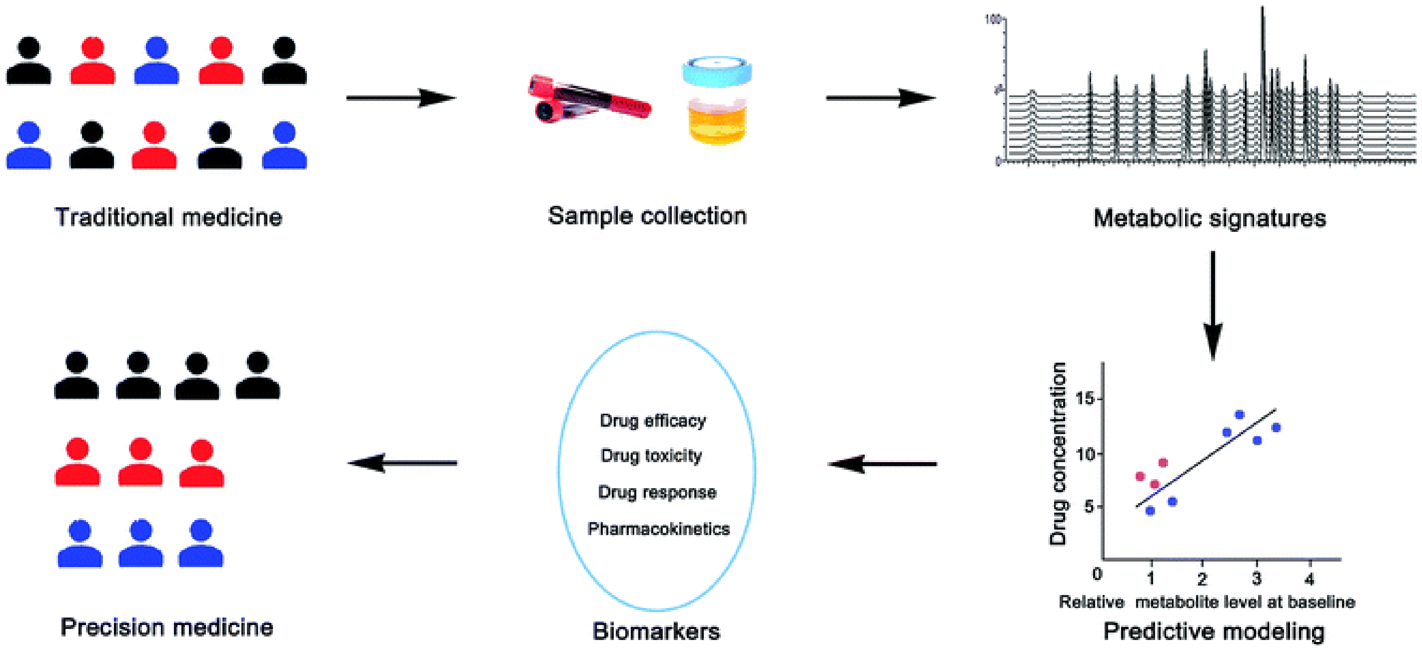


Metabolomics

- Metabolomics is the study of all the metabolites present in a cell, tissue or organism under different treatments or conditions.

- It provides an overview of the metabolic status and global biochemical events associated with a cellular or biological system.

- Branches of metabolomics: lipidomics, glycomics, pharmacometabolomics…

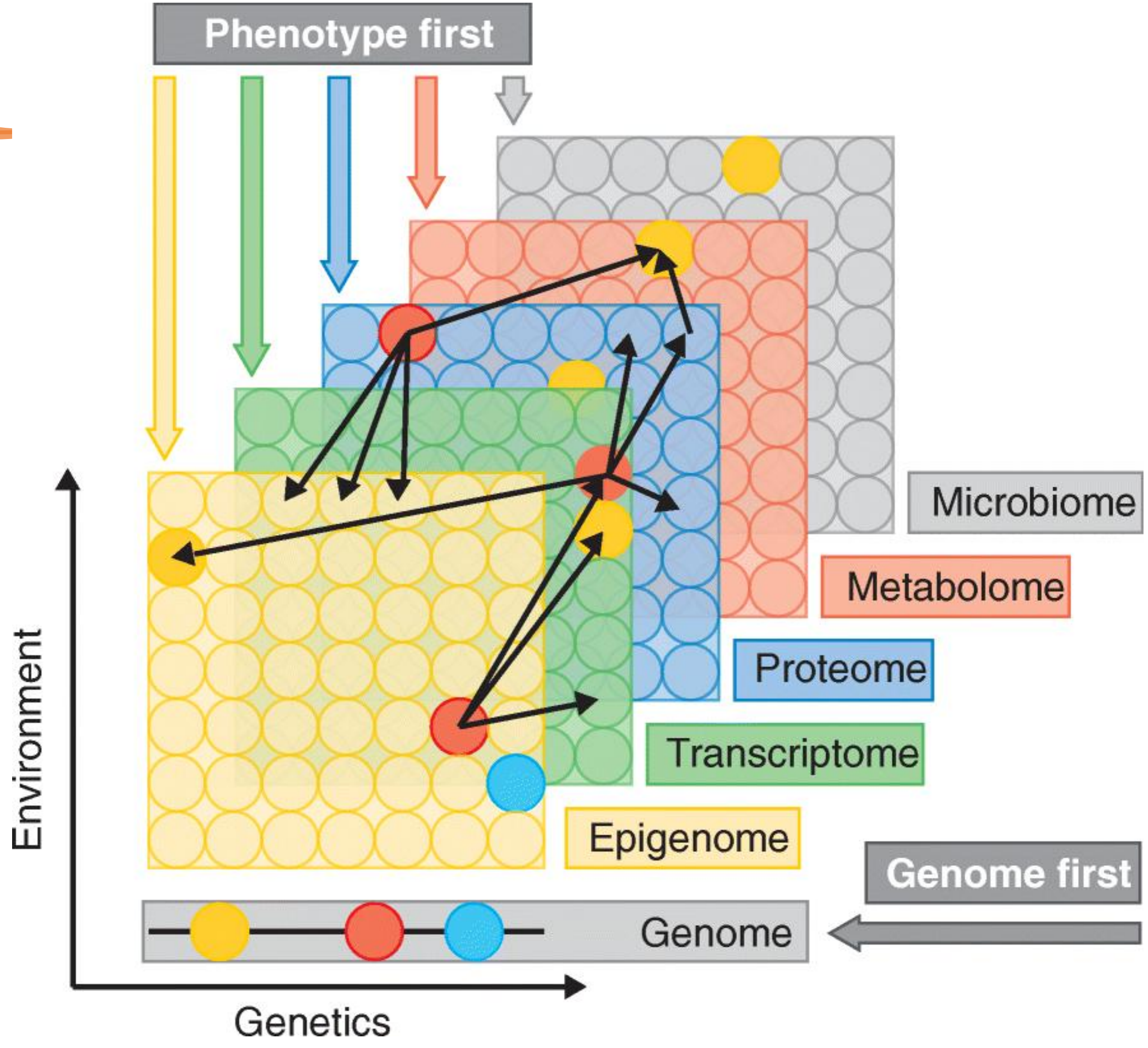


Zhang et al., RSC Advances, 2020

- Metabolomics has contributed to identifying metabolic causes and biomarkers for chronic diseases such as diabetes, Alzheimer disease, atherosclerosis and cancer.

Multi-Omics

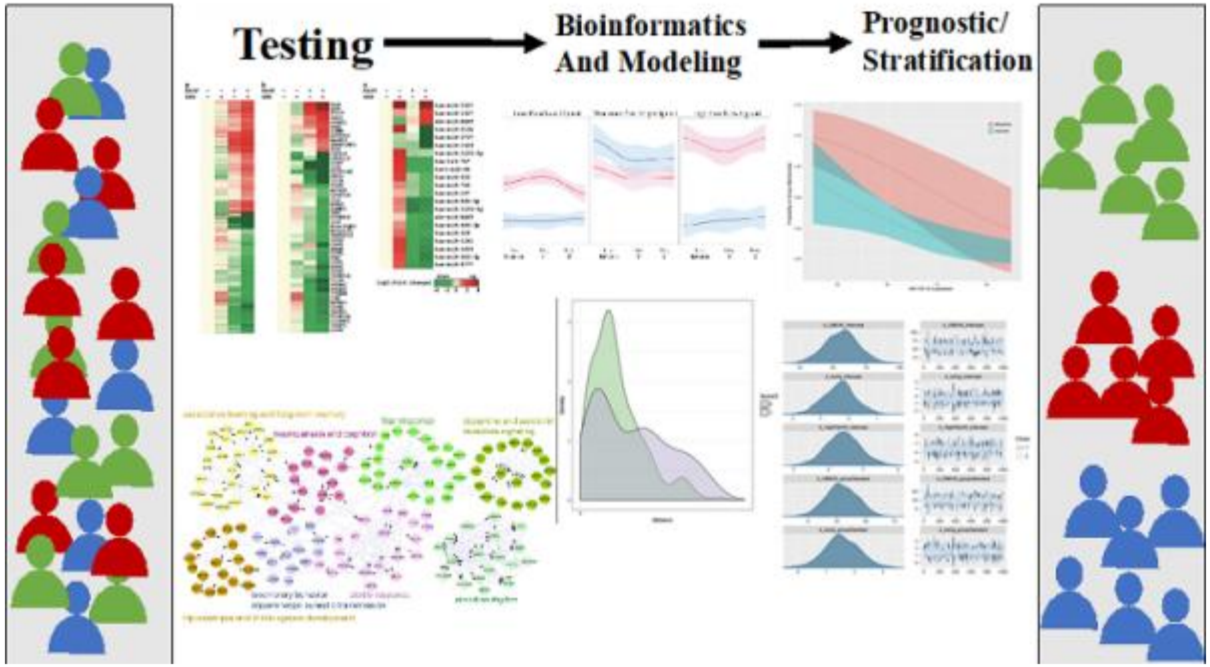
- A disease represents complex interactions between genetic, phenotypic, and environmental factors acting in complementary roles to define a global biological function.
- A single layer of omics is not enough→ integrated analysis of multi-omics data is required.
- Multi-omics approach → combining data sets from different omics studies.
- Multi-omics approaches can be grouped into three categories according to the initial focus: “genome first”, “phenotype first”, and “environment first”.
- Data integration across multiple omics layers is related to the study design→ 2 frequent approaches: correlation or co-mapping.



Hasin *et al*. Genome Biology, 2017

Bioinformatics

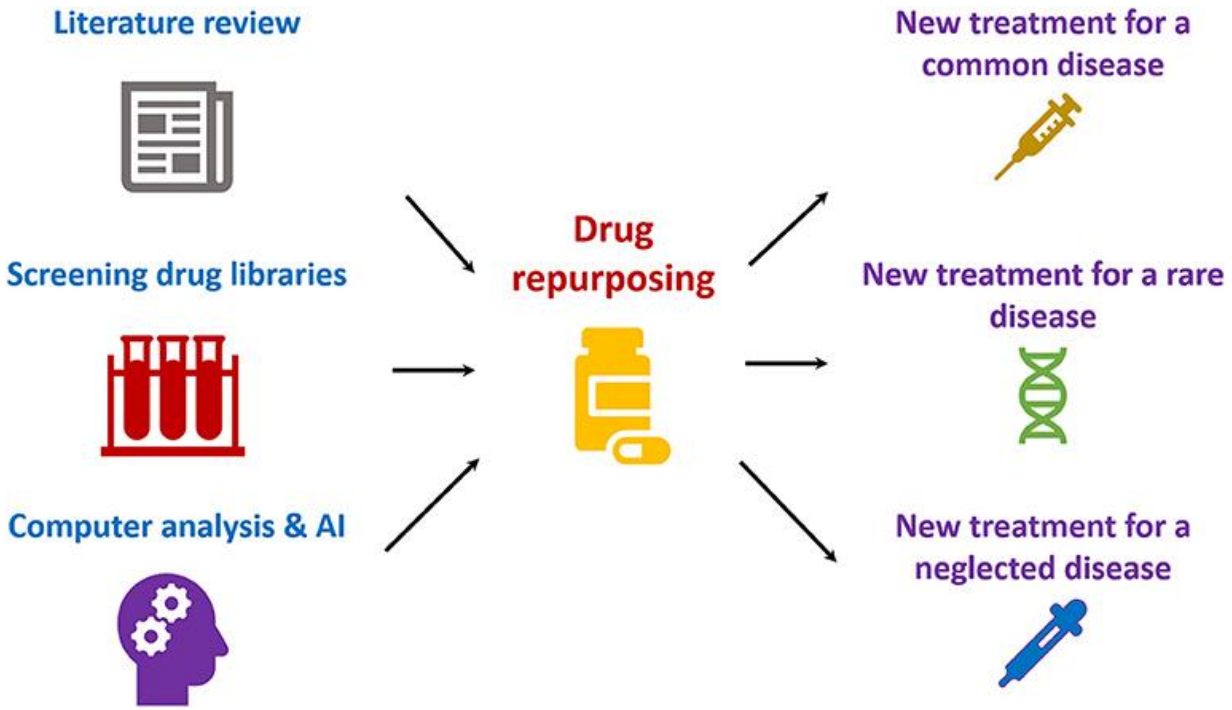
- Bioinformatics → application of tools of computation to analyze biological data.
- Omics platforms result in large, complex “data-rich” outputs→ concurrent development of bioinformatics methodology for data integration and interpretation.
- Multi-omics data need to be explored and used by computational analysis and mining tools.
- Unprecedented increases in free open-source software and publicly available resources giving access to Omics-related data.
- !!! Multiple challenges and limitations related to data quality, standardization, reproducibility, interpretation, and validation!!!



www.wrair.army.mil

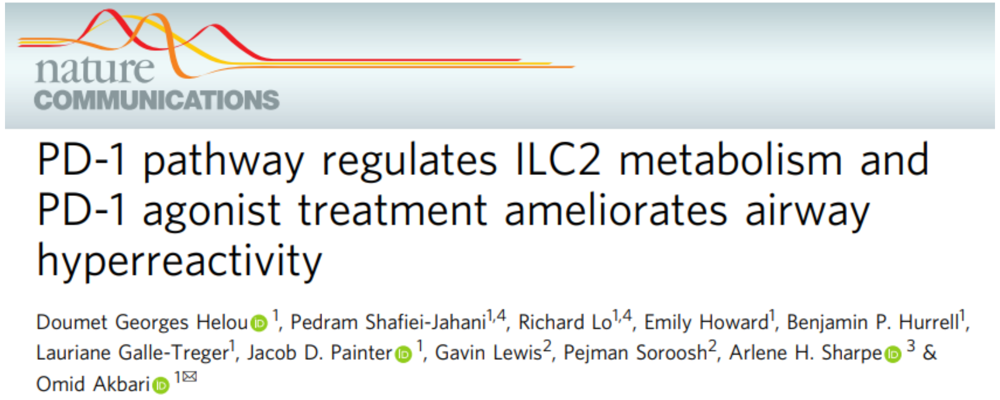
Omics in drug repurposing

- Multi-omics screening methods could be useful for drug reuse.
- For comprehensive repurposing, various computer-based approaches are involved in the integration of disease phenotypes and targets.
- Approaches involved in drug repositioning can be classified as drug-oriented, target-oriented, and disease-oriented…
- DSP-1181 is the first drug designed by artificial intelligence to enter clinical trials → multi-omics screening approach in less than 12 months.
- Since then, several companies have had their clinical development accelerated through AI-enabled solutions.



Mourenza *et al*. Frontiers, 2021

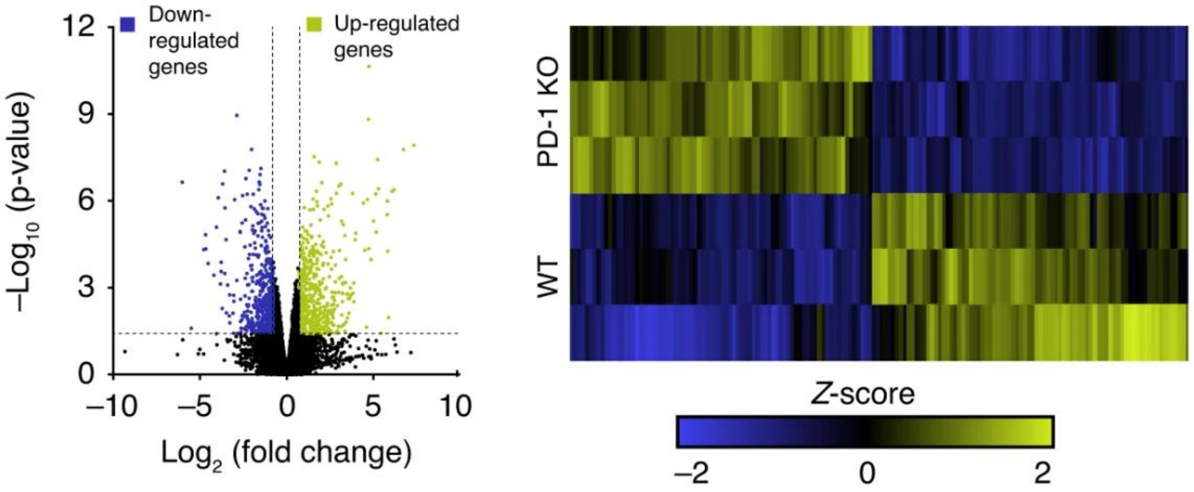
Omics in fundamental research

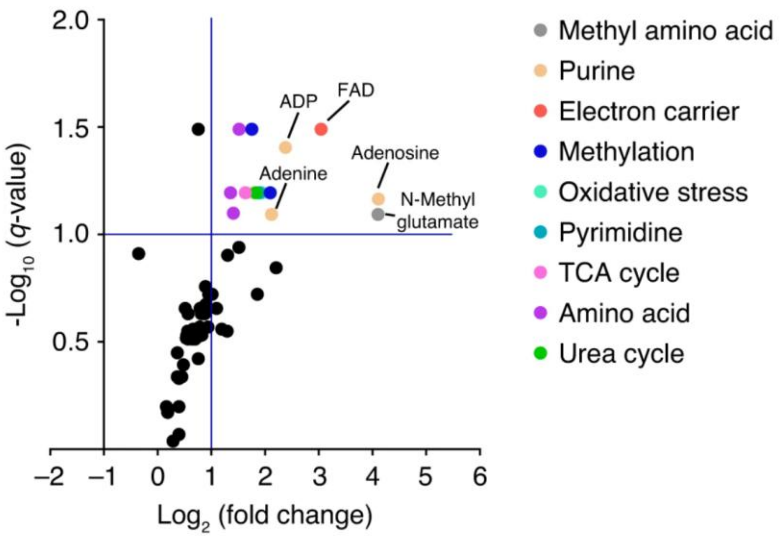


nature COMMUNICATIONS

PD-1 pathway regulates ILC2 metabolism and PD-1 agonist treatment ameliorates airway hyperreactivity

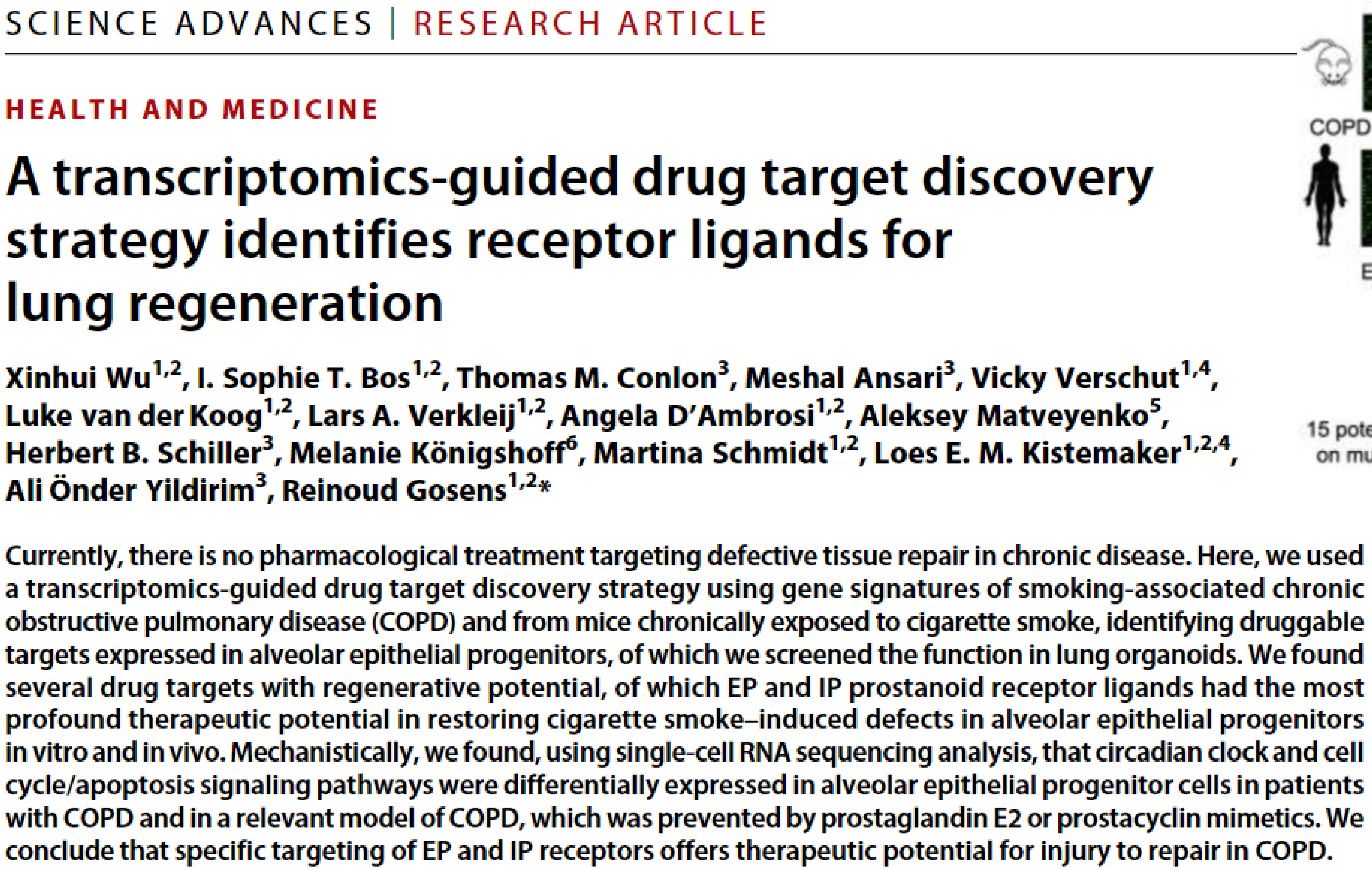
Doumet Georges Helou[1], Pedram Shafiei-Jahani[1,4], Richard Lo[1,4], Emily Howard[1], Benjamin P. Hurrell[1], Lauriane Galle-Treger[1], Jacob D. Painter[1], Gavin Lewis[2], Pejman Soroosh[2], Arlene H. Sharpe[3] & Omid Akbari[1]✉





- Transcriptomics and metabolomics approaches were used in this study to investigate the molecular mechanisms related to the immune checkpoint PD-1.
- This multi-omics approach (transcriptomics and metabolomics) allowed the discovery of a new biomarker in allergic asthma and the development of a PD-1 agonist!

Omics in translational research



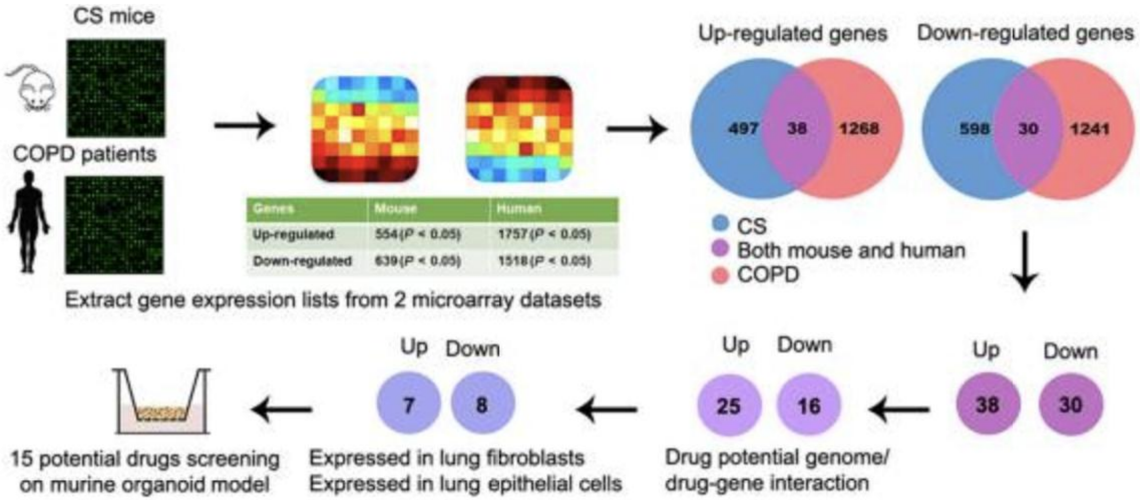
SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

A transcriptomics-guided drug target discovery strategy identifies receptor ligands for lung regeneration

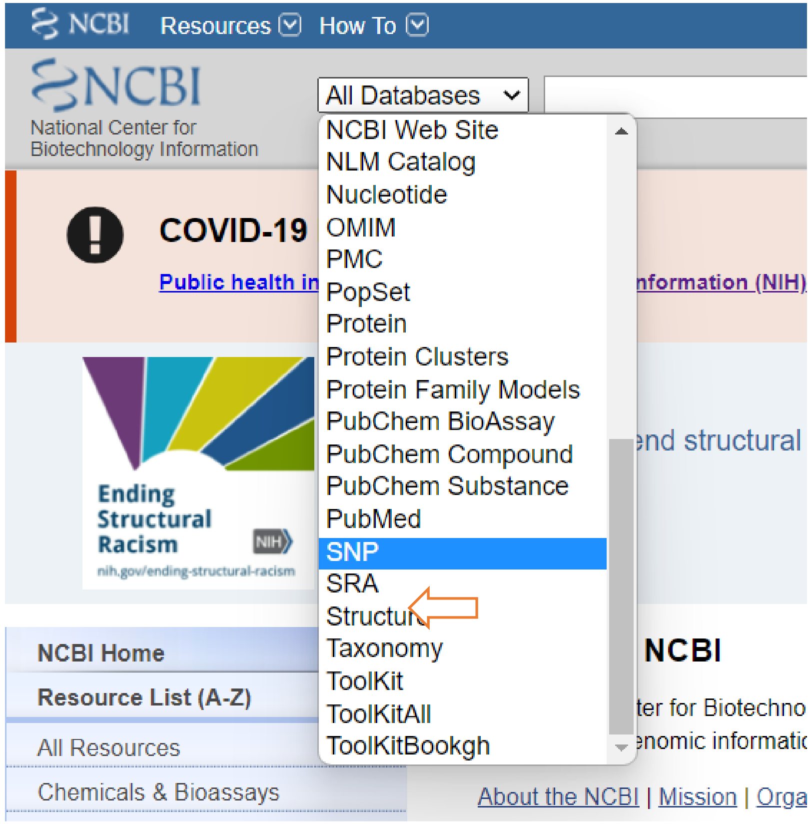
Xinhui Wu[1,2], I. Sophie T. Bos[1,2], Thomas M. Conlon[3], Meshal Ansari[3], Vicky Verschut[1,4], Luke van der Koog[1,2], Lars A. Verkleij[1,2], Angela D'Ambrosi[1,2], Aleksey Matveyenko[5], Herbert B. Schiller[3], Melanie Königshoff[6], Martina Schmidt[1,2], Loes E. M. Kistemaker[1,2,4], Ali Önder Yildirim[3], Reinoud Gosens[1,2]*

Currently, there is no pharmacological treatment targeting defective tissue repair in chronic disease. Here, we used a transcriptomics-guided drug target discovery strategy using gene signatures of smoking-associated chronic obstructive pulmonary disease (COPD) and from mice chronically exposed to cigarette smoke, identifying druggable targets expressed in alveolar epithelial progenitors, of which we screened the function in lung organoids. We found several drug targets with regenerative potential, of which EP and IP prostanoid receptor ligands had the most profound therapeutic potential in restoring cigarette smoke–induced defects in alveolar epithelial progenitors in vitro and in vivo. Mechanistically, we found, using single-cell RNA sequencing analysis, that circadian clock and cell cycle/apoptosis signaling pathways were differentially expressed in alveolar epithelial progenitor cells in patients with COPD and in a relevant model of COPD, which was prevented by prostaglandin E2 or prostacyclin mimetics. We conclude that specific targeting of EP and IP receptors offers therapeutic potential for injury to repair in COPD.



Genes	Mouse	Human
Up-regulated	554 ($P < 0.05$)	1757 ($P < 0.05$)
Down-regulated	639 ($P < 0.05$)	1518 ($P < 0.05$)

Online Omics data exploration

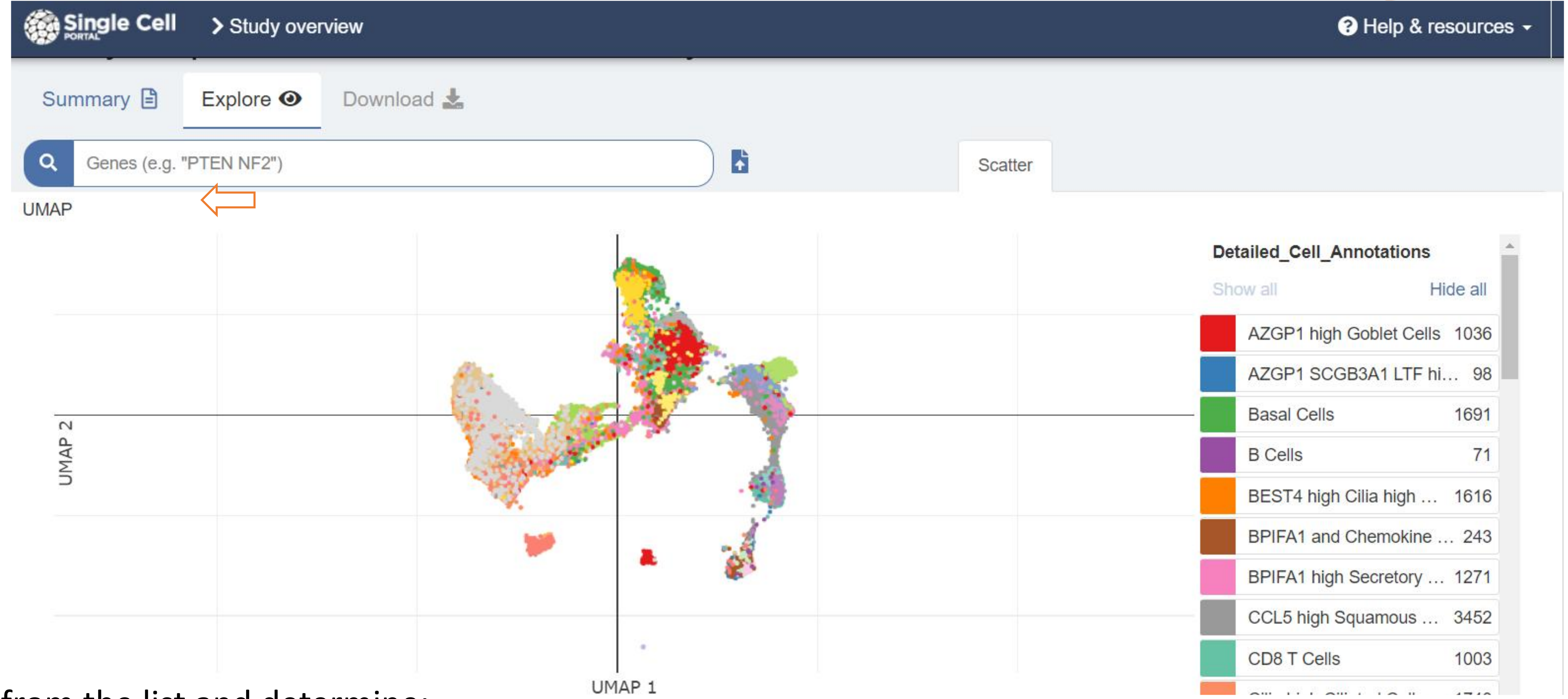


Choose a random gene and determine the variation type of 1 SNP, position, functional consequence, and clinical significance (CFTR?)

scRNA-seq → expression profiles of **individual cells**

Online Omics data exploration: scRNAseq

CLEC5A
CLEC10A
JAG1
FAM20C
IL1R1
B3GNT5
RRAGD
DAB2
CA2
ADAM9
FCER1A
PGD
CTSB
EMILIN2
CAPG

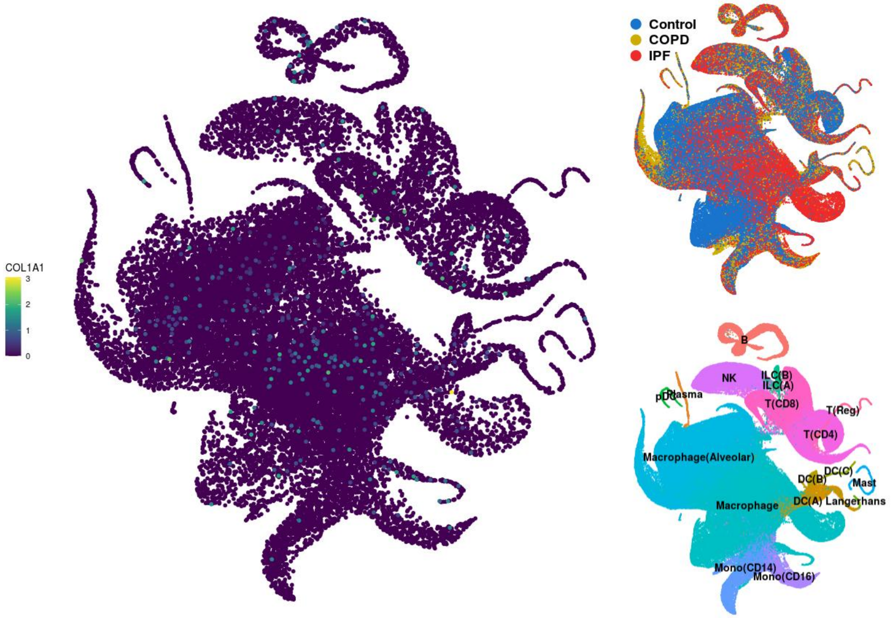


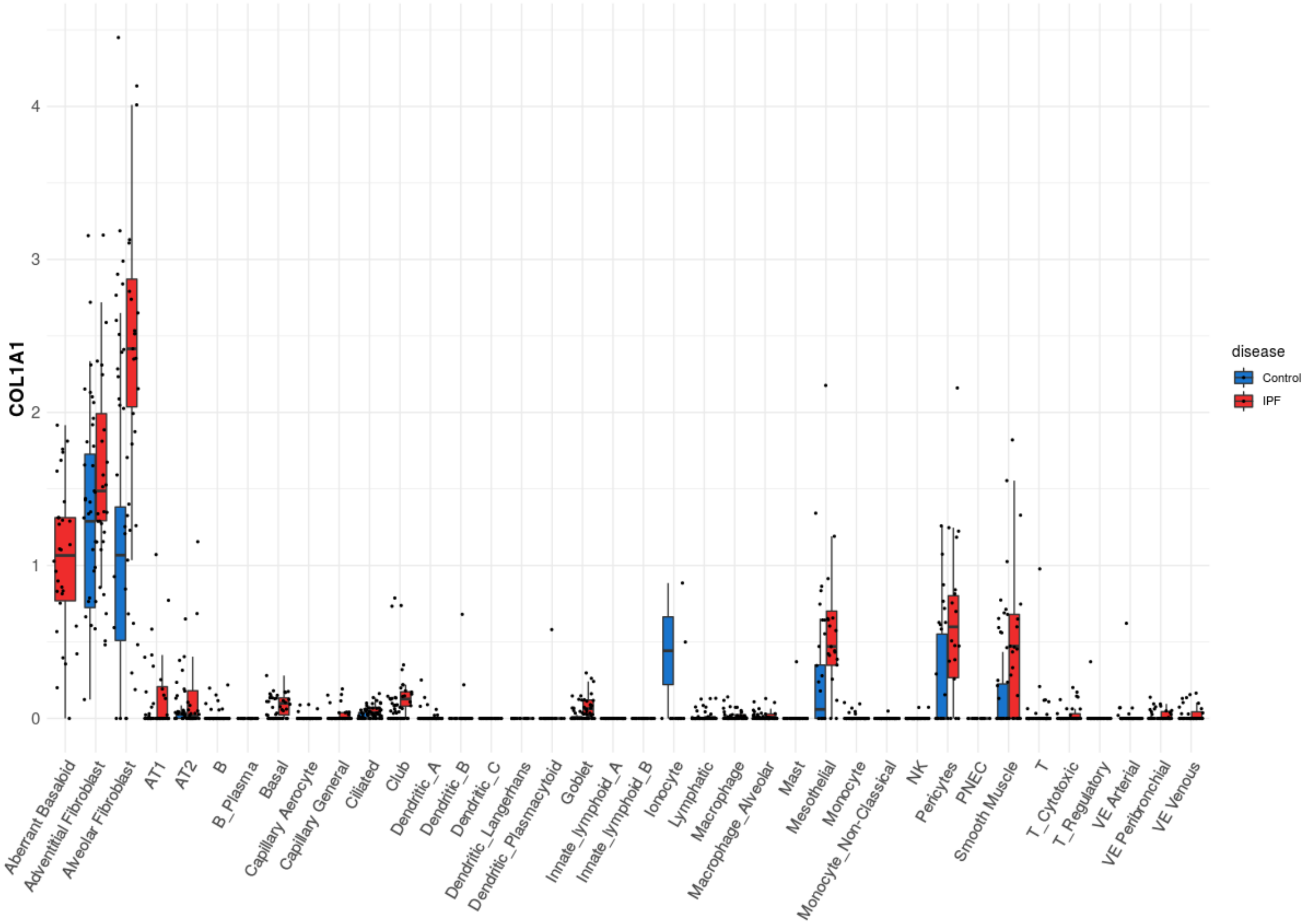
Detailed_Cell_Annotations

■	AZGP1 high Goblet Cells	1036
■	AZGP1 SCGB3A1 LTF hi…	98
■	Basal Cells	1691
■	B Cells	71
■	BEST4 high Cilia high …	1616
■	BPIFA1 and Chemokine …	243
■	BPIFA1 high Secretory …	1271
■	CCL5 high Squamous …	3452
■	CD8 T Cells	1003

Choose a gene from the list and determine: modulation in covid (up or downregulated), cell population, gender-related differences…

Online Omics data exploration: scRNAseq





Go to http://ipfcellatlas.com/ to start exploring a new disease: Idiopathic pulmonary fibrosis

Conclusions

- Omics-based technologies are promising the discovery of new therapeutic targets through the improved understanding of the molecular mechanisms of diseases.
- New methodologies are prompting a shift from traditional “hypothesis-driven” to “discovery-based” research, from “traditional” to “personalized” medicine.
- Many obstacles and hurdles are facing the integration of omics technologies: experimental/technical, analytical, and financial.
- The future of drug discovery hinges on integrating emerging omics technologies through robust bioinformatics platforms, advanced data analysis techniques, and AI-driven insights.

Thank you!