Biyoinformatiğe Giriş
Temel Konular

Uğur Sezerman

Acıbadem Üniversitesi

ACIBADEM
ÜNİVERSİTESİ

HUMAN GENOME PROJECT

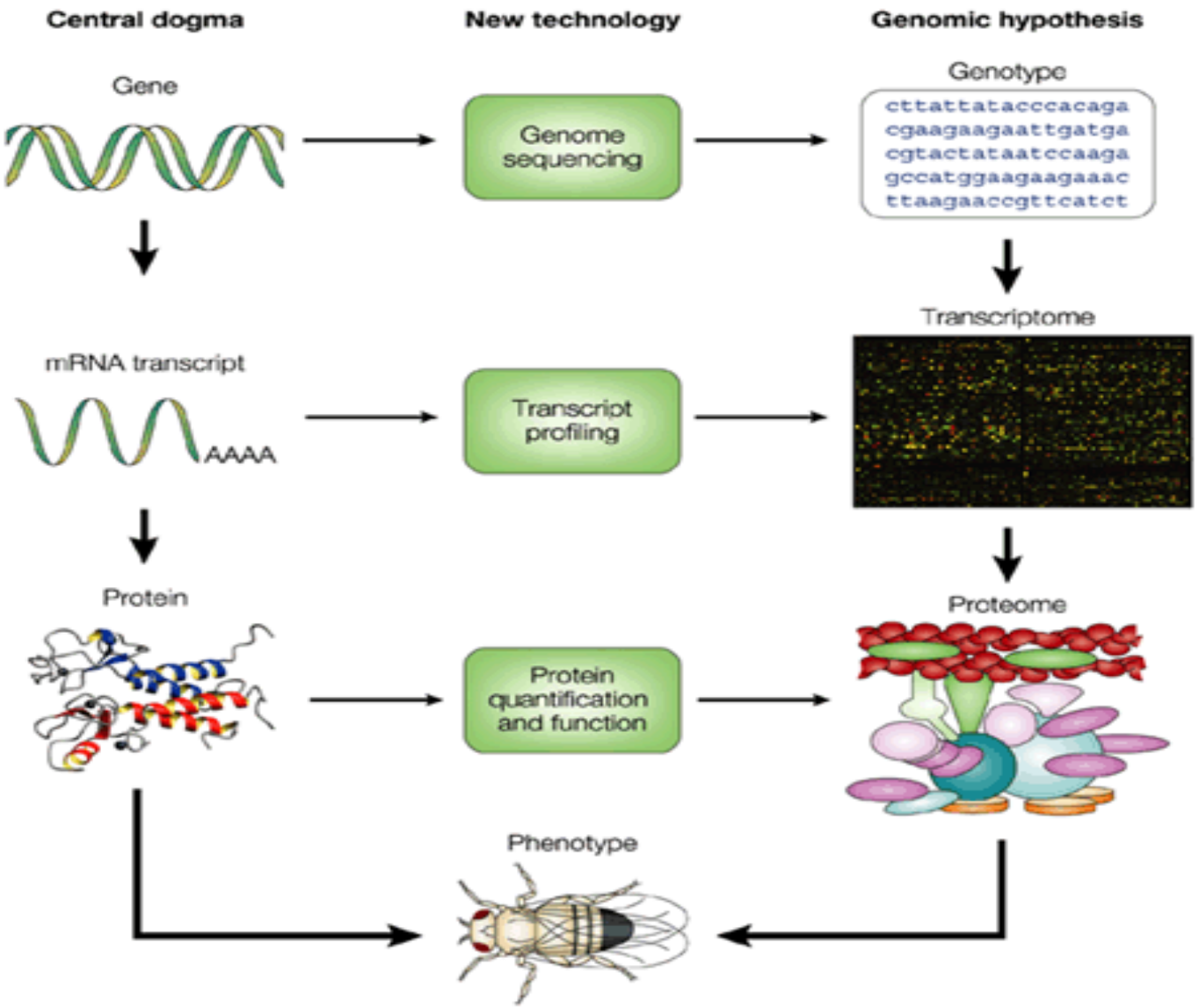
Goals:

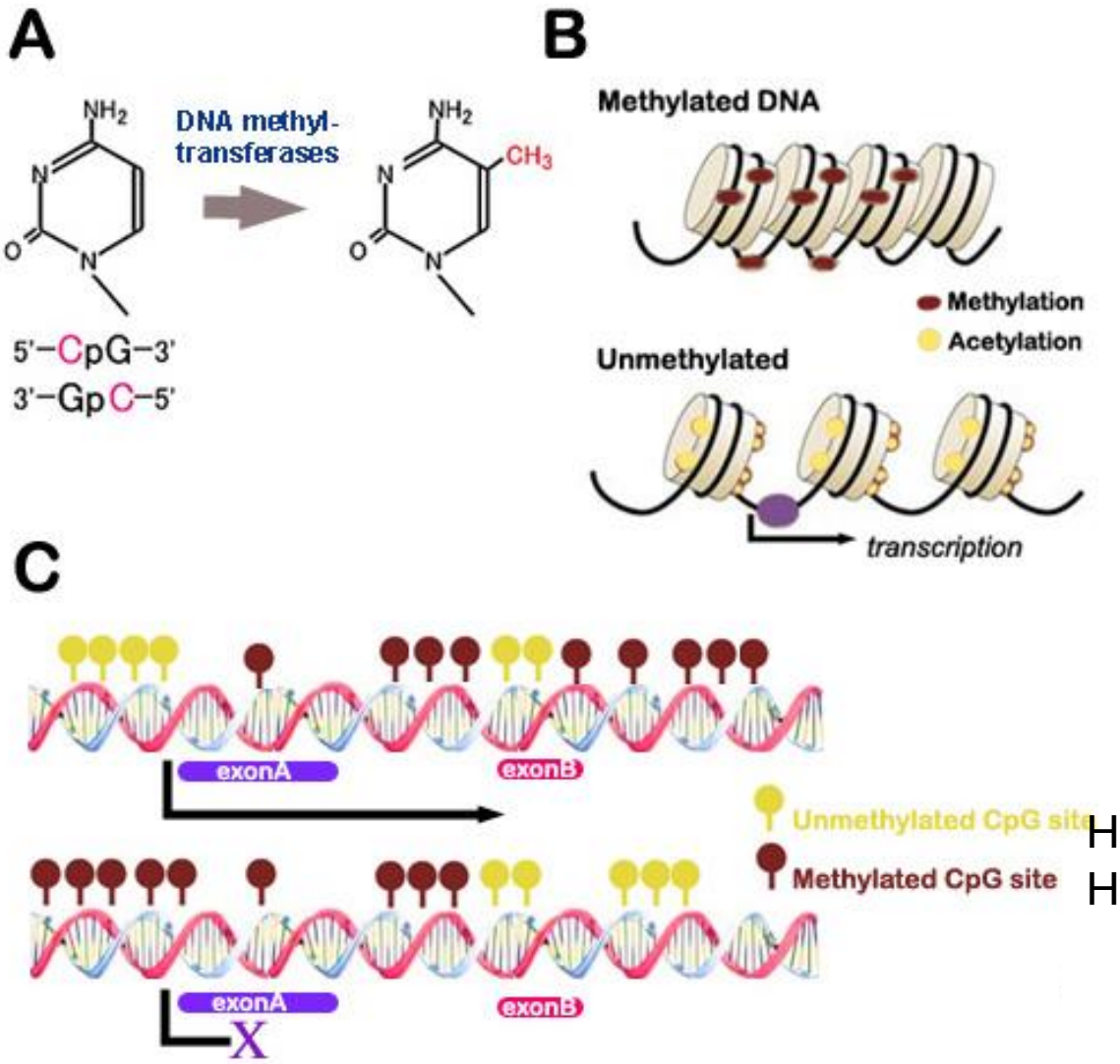
- identify all the approximate 30,000 genes in human DNA,
- determine the sequences of the 3 billion chemical base pairs that make up human DNA,
- store this information in databases,
- improve tools for data analysis,
- transfer related technologies to the private sector, and
- address the ethical, legal, and social issues (ELSI) that may arise from the project.

Milestones:

- 1990: Project initiated as joint effort of U.S. Department of Energy and the National Institutes of Health
- June 2000: Completion of a working draft of the entire human genome (covers >90% of the genome to a depth of 3-4x redundant sequence)
- February 2001: Analyses of the working draft are published
- April 2003: HGP sequencing is completed and Project is declared finished two years ahead of schedule

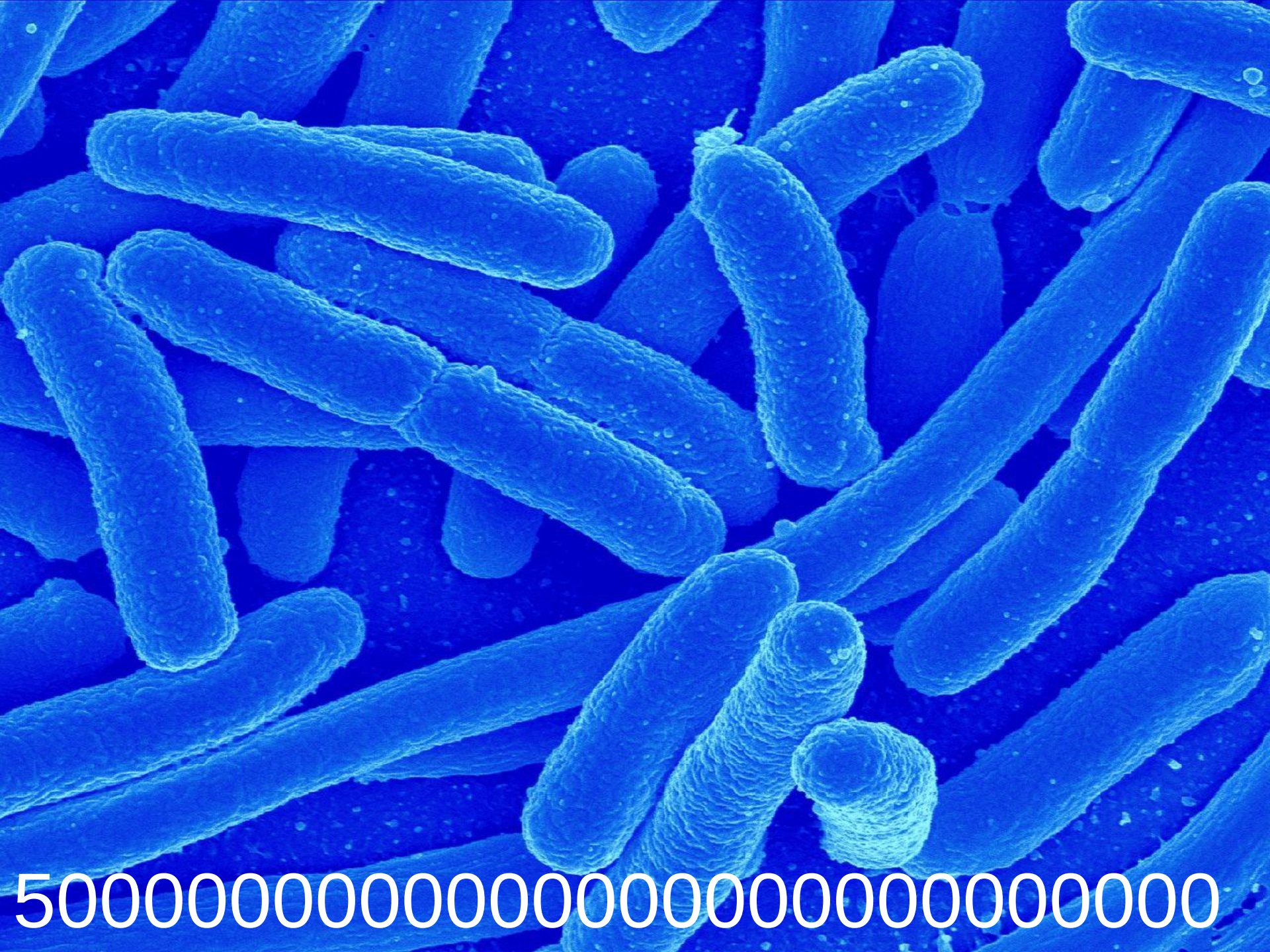
http://doegenomes.org
http://www.sanger.ac.uk/HGP/overview.shtml


Central dogma
New technology
Genomic hypothesis
Gene
Genome sequencing
Genotype
cttattatacccacaga
cgaagaagaattgatga
cgtactataatccaaga
gccatggaagaagaaac
ttaagaaccgttcatct
mRNA transcript
AAAA
Transcript profiling
Transcriptome
Protein
Protein quantification and function
Proteome
Phenotype
Nature Reviews | Genetics



Hypomethylation
Hypermethylation

http://www.cellscience.com/reviews7/Taylor1.jpg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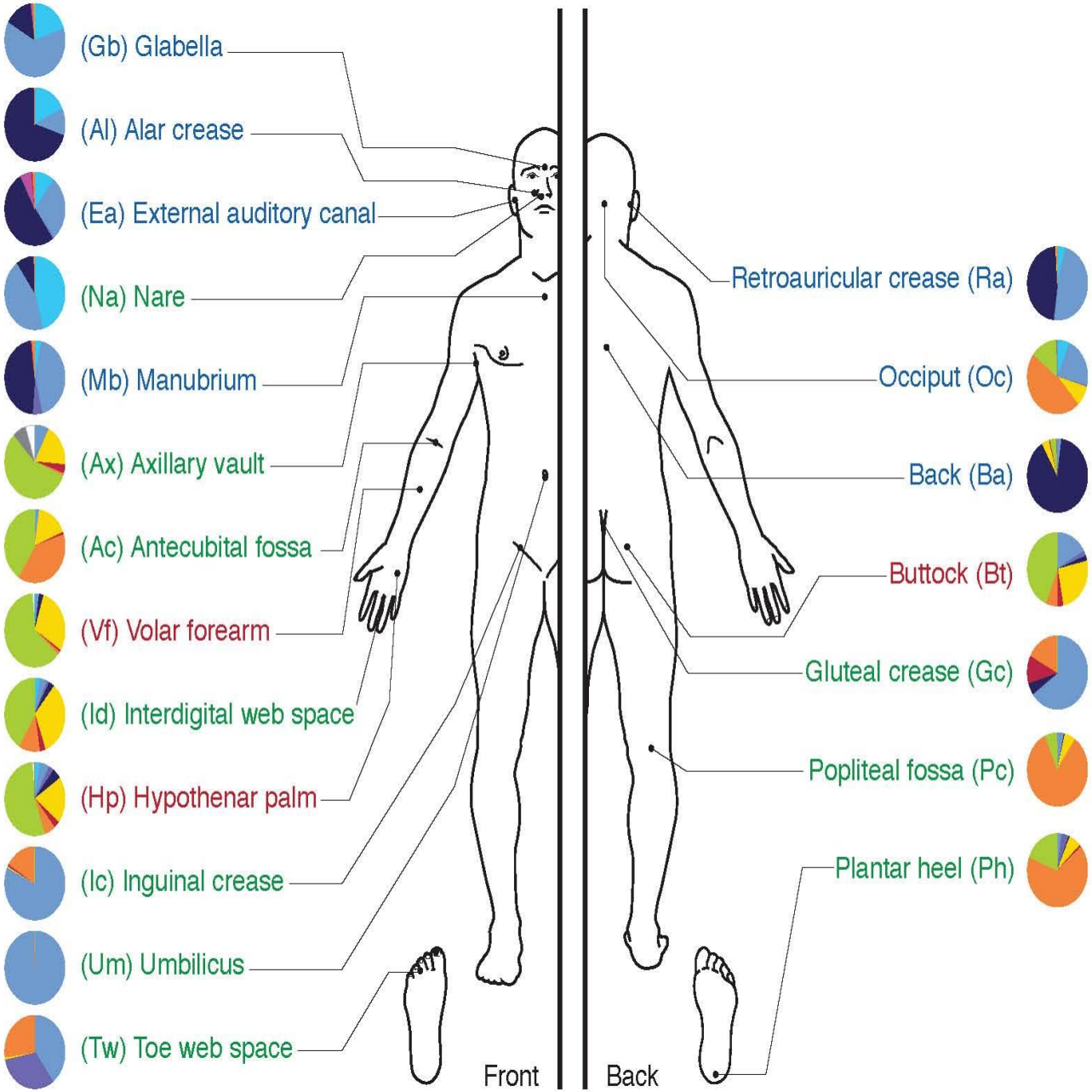
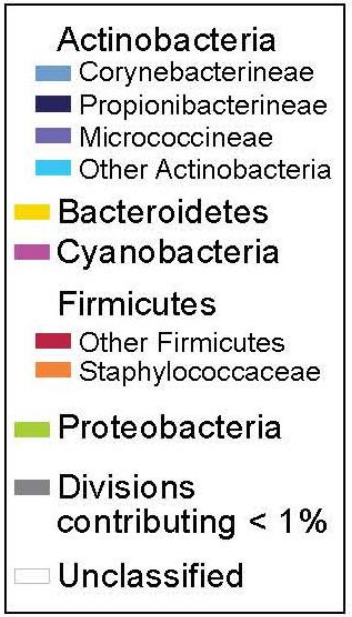
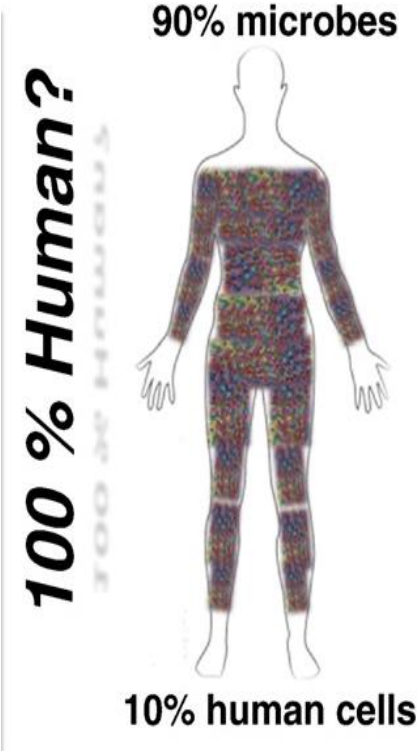
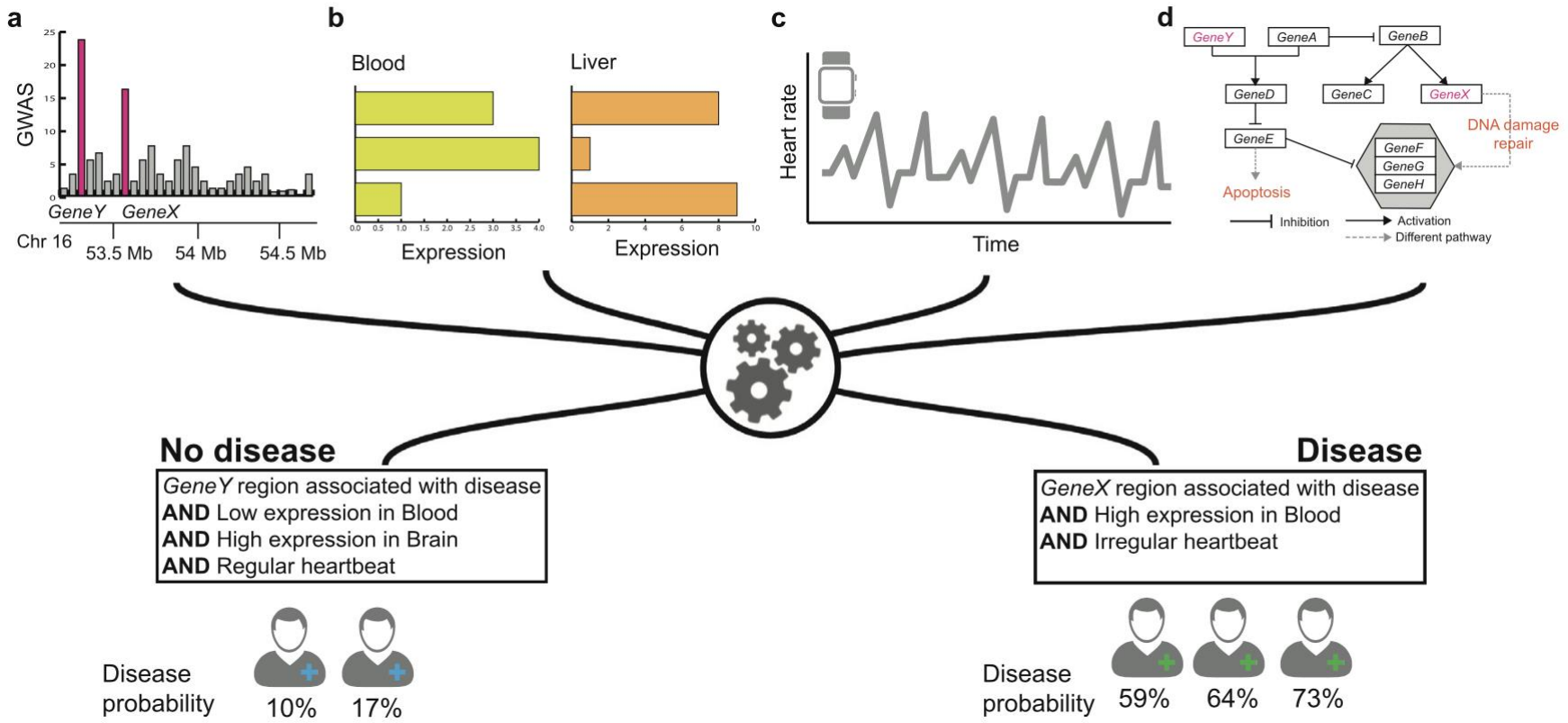






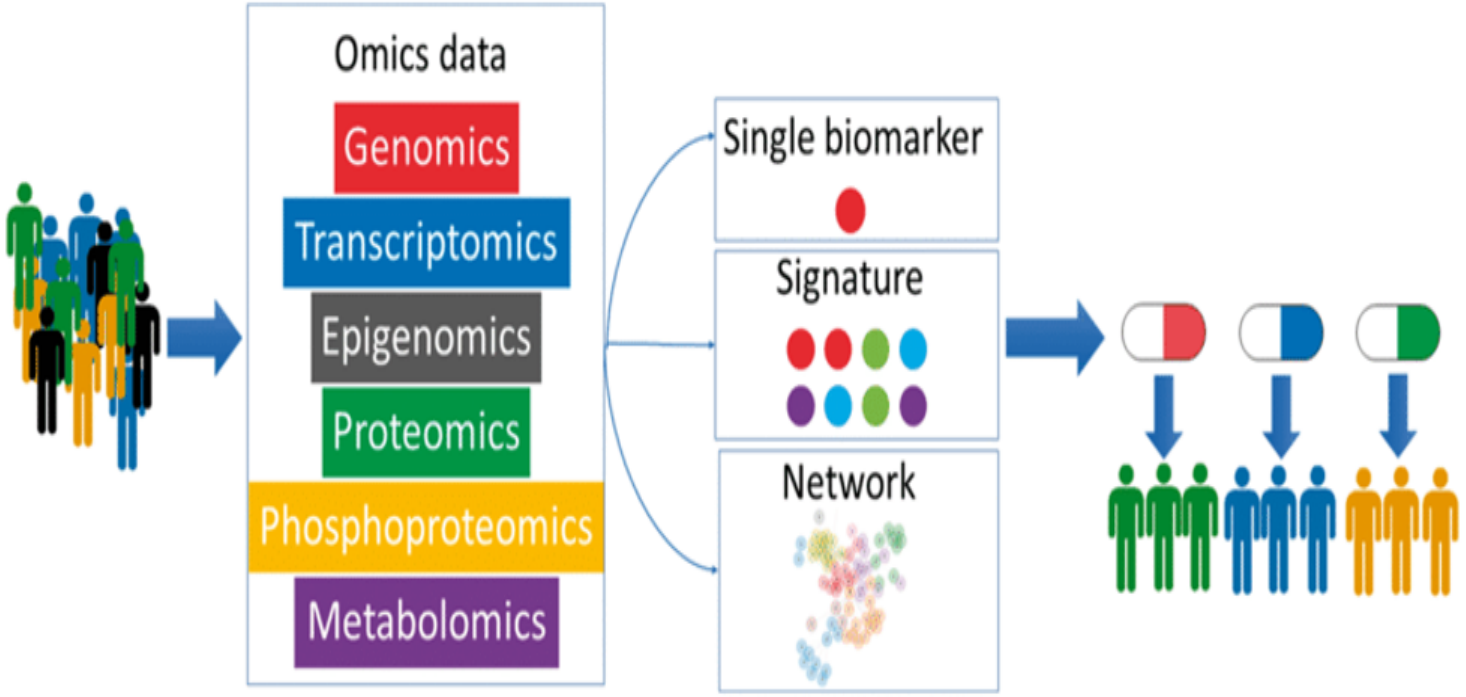
We Are Really More Bug than

AI/ML in Translational Medicine



Zitnik M, Nguyen F, Wang B, Leskovec J, Goldenberg A, Hoffman MM. Machine Learning for Integrating Data in Biology and Medicine: Principles, Practice, and Opportunities. Inf Fusion. 2019;50:71-91.

single cell omics in personalized medicine applications



Personalized medicine

- represents one of the major clinical outcomes of omics applications.

https://
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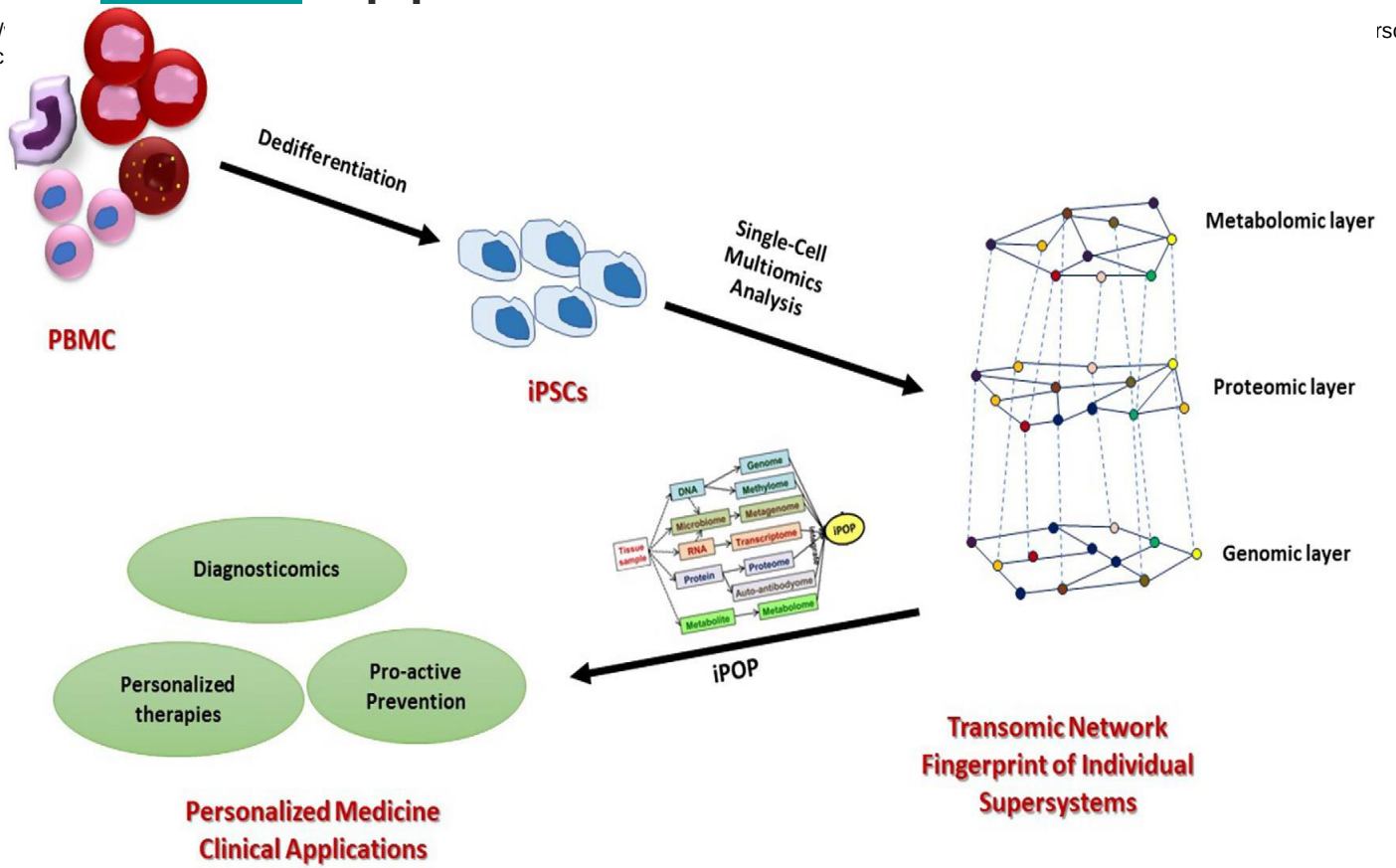
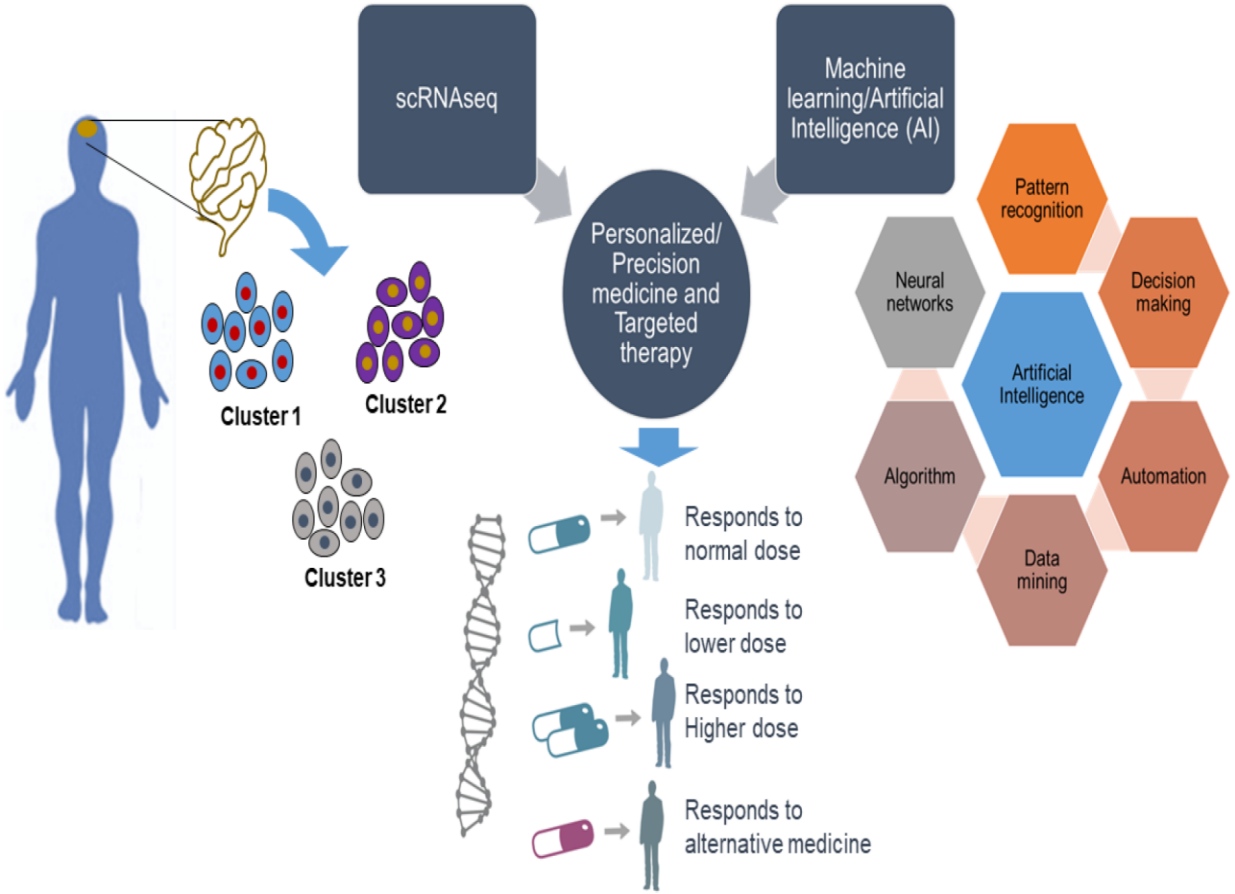
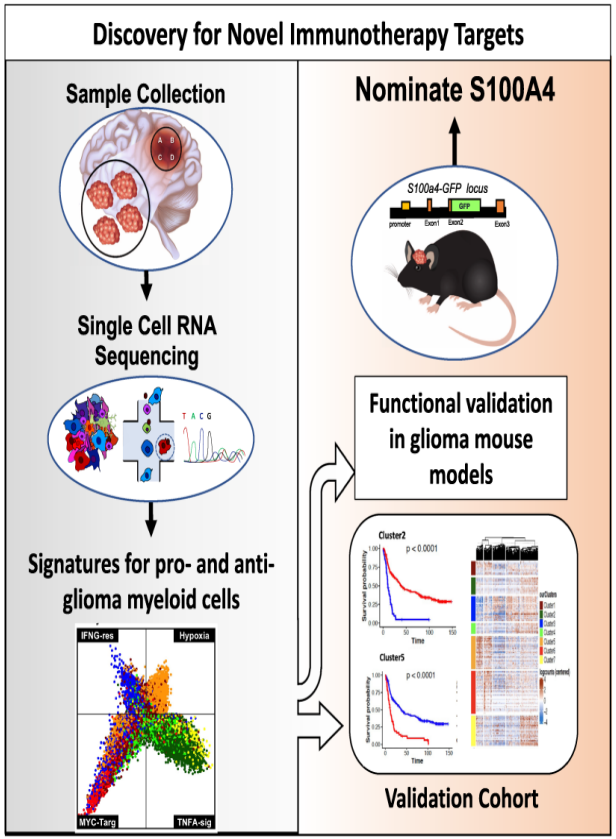


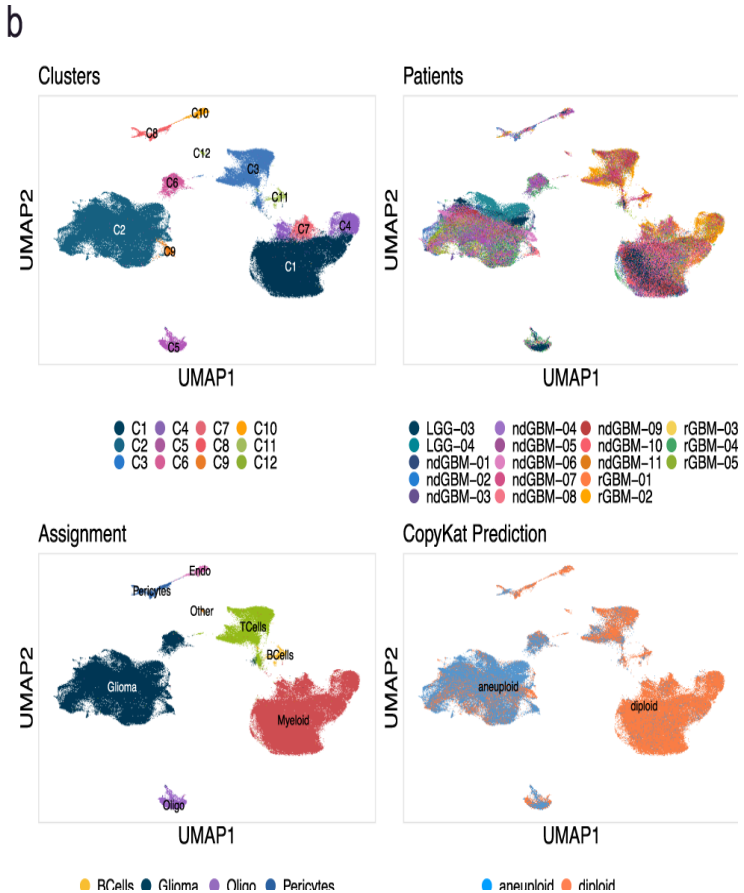
scRNA and personalized medicine



https://www.mdpi.com/2073-4409/9/8/1751/htm

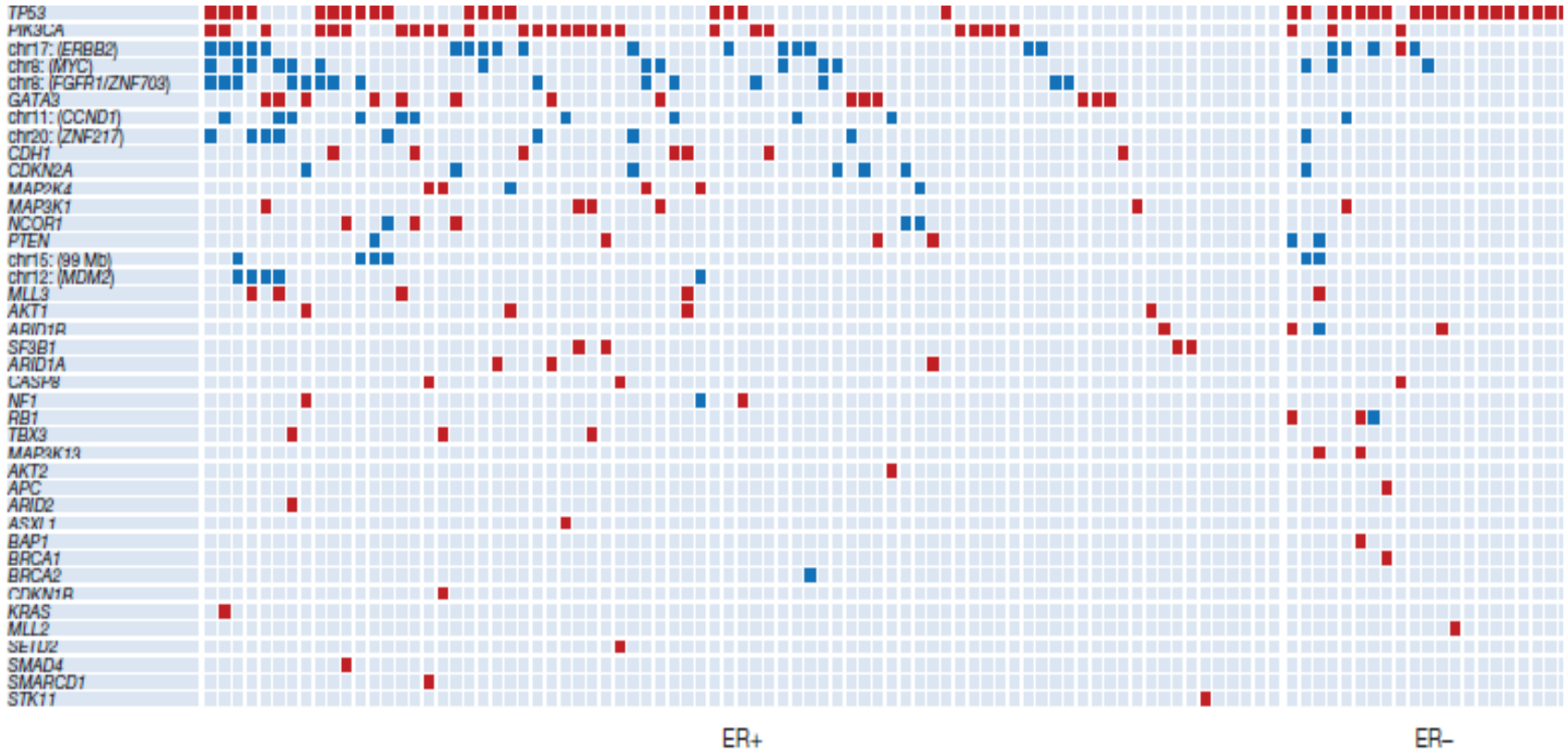
Single-cell analysis of human glioma and immune cells identifies S100A4 as an immunotherapy target





Frequent cancers include high number of very rare genomic segments

- Somatic mutation
- Copy Number Variation



(whole genome sequencing breast cancers)

Stephens, Nature, 2012

Transplantation Immunology Related OMICS studies

Multi-omics network characterization reveals novel microRNA biomarkers and mechanisms for diagnosis and subtyping of kidney transplant rejection. Transl Med 19, 346 (2021). https://doi.org/10.1186/s12967-021-03025-8

- Kidney transplantation is an optimal method for treatment of end-stage kidney failure. However, kidney transplant rejection (KTR) is commonly observed to have negative effects on allograft function. MicroRNAs (miRNAs) are small non-coding RNAs with regulatory role in KTR genesis, the identification of miRNA biomarkers for accurate diagnosis and subtyping of KTR is therefore of clinical significance for active intervention and personalized therapy.
- In this study, an integrative bioinformatics model was developed based on multi-omics network characterization for miRNA biomarker discovery in KTR. Compared with existed methods, the topological importance of miRNA targets was prioritized based on cross-level miRNA-mRNA and protein–protein interaction network analyses. The biomarker potential of identified miRNAs was computationally validated and explored by receiver-operating characteristic (ROC) evaluation and integrated “miRNA-gene-pathway” pathogenic survey.

- Three miRNAs, *i.e.,* miR-145-5p, miR-155-5p, and miR-23b-3p, were screened as putative biomarkers for KTR monitoring. Among them, miR-155-5p was a previously reported signature in KTR, whereas the remaining two were novel candidates both for KTR diagnosis and subtyping. The ROC analysis convinced the power of identified miRNAs as single and combined biomarkers for KTR prediction in kidney tissue and blood samples. Functional analyses, including the latent crosstalk among HLA-related genes, immune signaling pathways and identified miRNAs, provided new insights of these miRNAs in KTR pathogenesis.
-

Integrative Omics Analysis Unravels Microvascular Inflammation-Related Pathways in Kidney Allograft Biopsies

URL=https://www.frontiersin.org/article/10.3389/fimmu.2021.738795
DOI=10.3389/fimmu.2021.738795

- In solid-organ transplantation, microRNAs (miRNAs) have emerged as key players in the regulation of allograft cells function in response to injury. To gain insight into the role of miRNAs in antibody-mediated rejection, a rejection phenotype histologically defined by microvascular inflammation, kidney allograft biopsies were subjected to miRNA but also messenger RNA (mRNA) profiling. Using a unique multistep selection process specific to the BIOMARGIN study (discovery cohort, N=86; selection cohort, N=99; validation cohort, N=298), six differentially expressed miRNAs were consistently identified: miR-139-5p (down) and miR-142-3p/150-5p/155-5p/222-3p/223-3p (up). Their expression level gradually correlated with microvascular inflammation intensity. The cell specificity of miRNAs target genes was investigated by integrating their *in vivo* mRNA targets with single-cell RNA sequencing from an independent allograft biopsy cohort. Endothelial-derived miR-139-5p expression correlated negatively with MHC-related genes expression. Conversely, epithelial-derived miR-222-3p overexpression was strongly associated with degraded renal electrolyte homeostasis and repressed immune-related pathways. In immune cells, miR-150-5p regulated NF-κB activation in T lymphocytes whereas miR-155-5p regulated mRNA splicing in antigen-presenting cells. Altogether, integrated omics enabled us to unravel new pathways involved in microvascular inflammation and suggests that metabolism modifications in tubular epithelial cells occur as a consequence of antibody-mediated rejection, beyond the nearby endothelial compartment.
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Advanced Genomics-Based Approaches for Defining Allograft Rejection With Single Cell Resolution

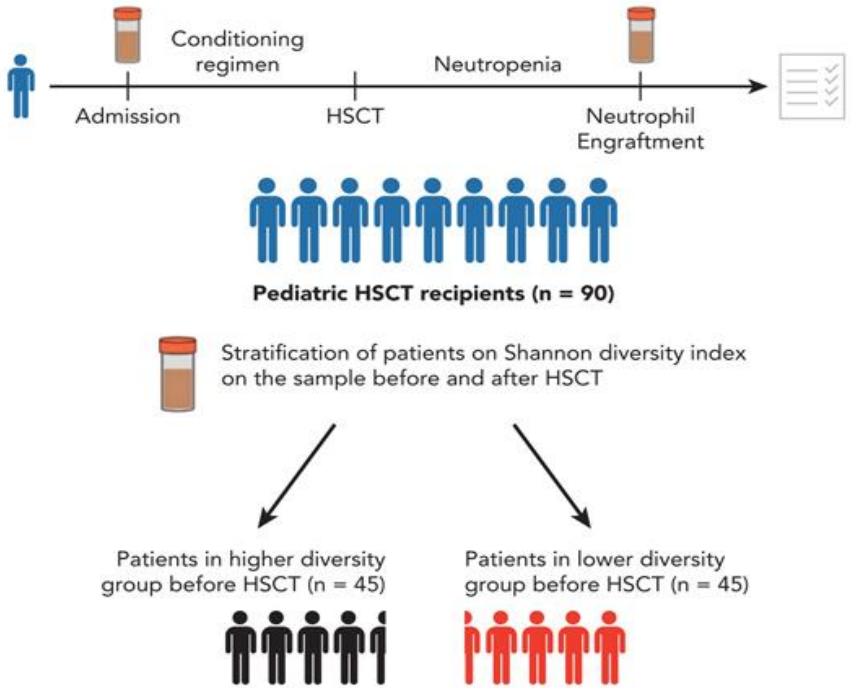
URL=https://www.frontiersin.org/article/10.3389/fimmu.2021.750754
DOI=10.3389/fimmu.2021.750754

- Solid organ transplant recipients require long-term immunosuppression for prevention of rejection. Calcineurin inhibitor (CNI)-based immunosuppressive regimens have remained the primary means for immunosuppression for four decades now, yet little is known about their effects on graft resident and infiltrating immune cell populations. Similarly, the understanding of rejection biology under specific types of immunosuppression remains to be defined. Furthermore, development of innovative, rationally designed targeted therapeutics for mitigating or preventing rejection requires a fundamental understanding of the immunobiology that underlies the rejection process. The established use of microarray technologies in transplantation has provided great insight into gene transcripts associated with allograft rejection but does not characterize rejection on a single cell level. Therefore, the development of novel genomics tools, such as single cell sequencing techniques, combined with powerful bioinformatics approaches, has enabled characterization of immune processes at the single cell level. This can provide profound insights into the rejection process, including identification of resident and infiltrating cell transcriptomes, cell-cell interactions, and T cell receptor α/β repertoires. In this review, we discuss genomic analysis techniques, including microarray, bulk RNAseq (bulkSeq), single-cell RNAseq (scRNAseq), and spatial transcriptomic (ST) techniques, including considerations of their benefits and limitations. Further, other techniques, such as chromatin analysis via assay for transposase-accessible chromatin sequencing (ATACseq), bioinformatic regulatory network analyses, and protein-based approaches are also examined. Application of these tools will play a crucial role in redefining transplant rejection with single cell resolution and likely aid in the development of future

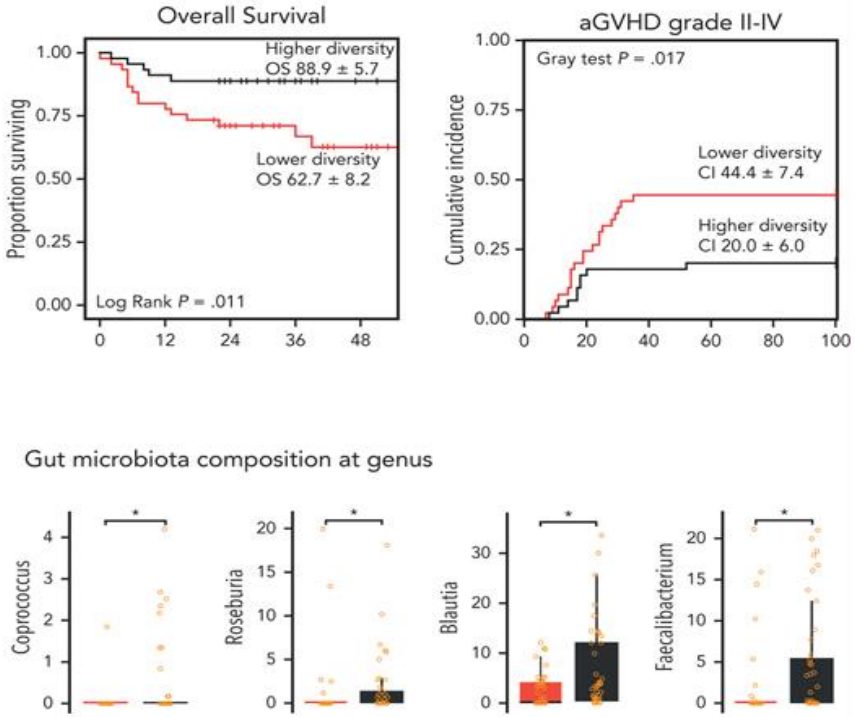
  immunomodulatory therapies in solid organ transplantation.

Gut Microbiota Diversity Before Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) as a Predictor of Mortality in Children

Patients and Methods



Main Outcomes



Conclusion: Higher pre-transplant microbiota diversity correlates with better overall survival, a lower incidence of acute GVHD, and a higher abundance of short-chain fatty acid (SCFA)-producing taxa.

*Masetti et al. DOI: 10.1182/**blood**.2023020026*

***Blood* Visual Abstract**

MHC – Peptide Binding Prediction Algorithms

- Major histocompatibility complex (MHC) molecules play a pivotal role in the immune system by presenting peptides to T cells, initiating immune responses against pathogens and cancer cells.
- The ability to model and predict the antigens capable of MHC presentation is pivotal in manipulating the immune system and devising therapeutic interventions.
- Computational prediction algorithms serve as indispensable tools for estimating peptide-MHC binding affinity, offering insights into antigen presentation and immune responses.

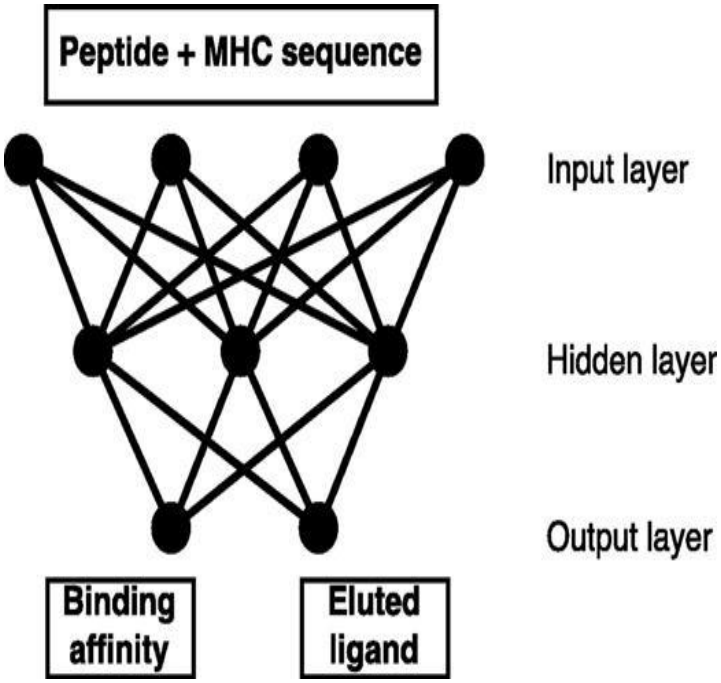
Simple Motif-Based Models

- Based on the observation that MHC molecules have binding preferences in terms of simple binding motifs.
- **SYFPEITHI prediction model**: Statistics from MHC-I eluted ligand data (EL data) is used to estimate differential scoring of the amino acid propensity depending on the peptide position.
- **MHC binding predictions based on ARB matrices:** Directly predict IC_{50} values. Measured binding data from single substitution analogs of known ligands are used for calculating the scores.

Machine Learning Models

- **Artificial Neural Network based Models:**
  - Stabilized Matrix Method (SMM).
  - High order regression models: SVMHC, SVRMHC and NetHMC.
- **Hidden Markov Models:**
  - S-HMM
- **Support Vector Machines:**
  - Salomon et al. (2006)
  - Cui et al. (2006)

Machine Learning Models



- **NetMHCpan v4.0:**
  - Class I MHC ligand elution assays from the IEDB database.
  - NNAlign training (sequence alignment based NN approach) with insertions and deletions (3) was extended by adding a second output neuron.

- **Prospective Tracking of Donor-Reactive T-Cell Clones in the Circulation and Rejecting Human Kidney Allografts**

- **Dynamically Driven Allostery in MHC Proteins: Peptide-Dependent Tuning of Class I MHC Global Flexibility**

- Meydan, C., Otu, H.H. & Sezerman, O.U. Prediction of peptides binding to MHC class I and II alleles by temporal motif mining.
- *BMC Bioinformatics* **14,** S13 (2013). https://doi.org/10.1186/1471-2105-14-S2-S13

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