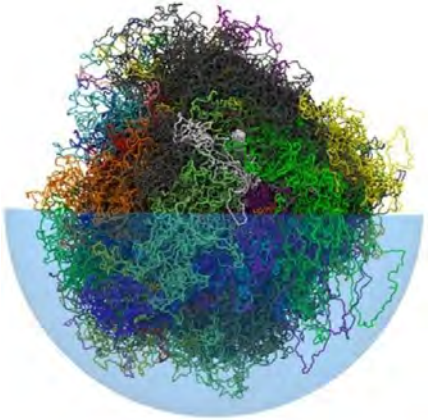
4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

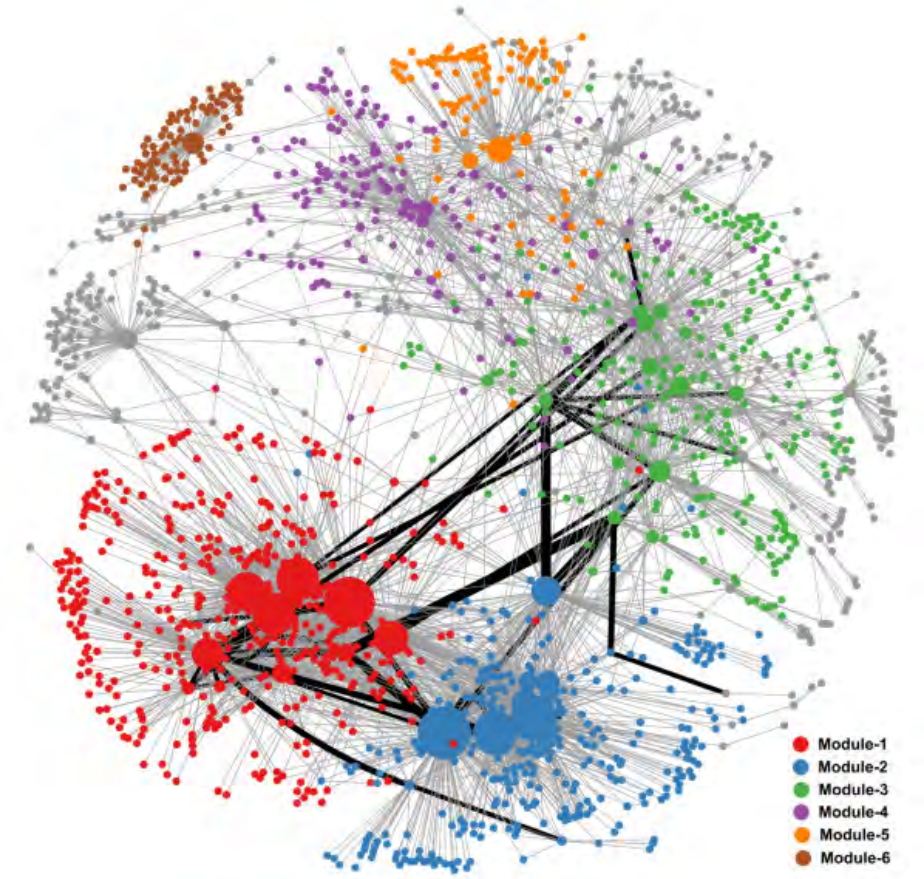


Βιολογία συστημάτων (Systems Biology) στα ρευματικά νοσήματα

25.06.2022

Άγγελος Μπανός – Μεταδιδακτορικός ερευνητής (Εργαστήριο Αυτοανοσίας και Φλεγμονής, ΙΙΒΕΑΑ)

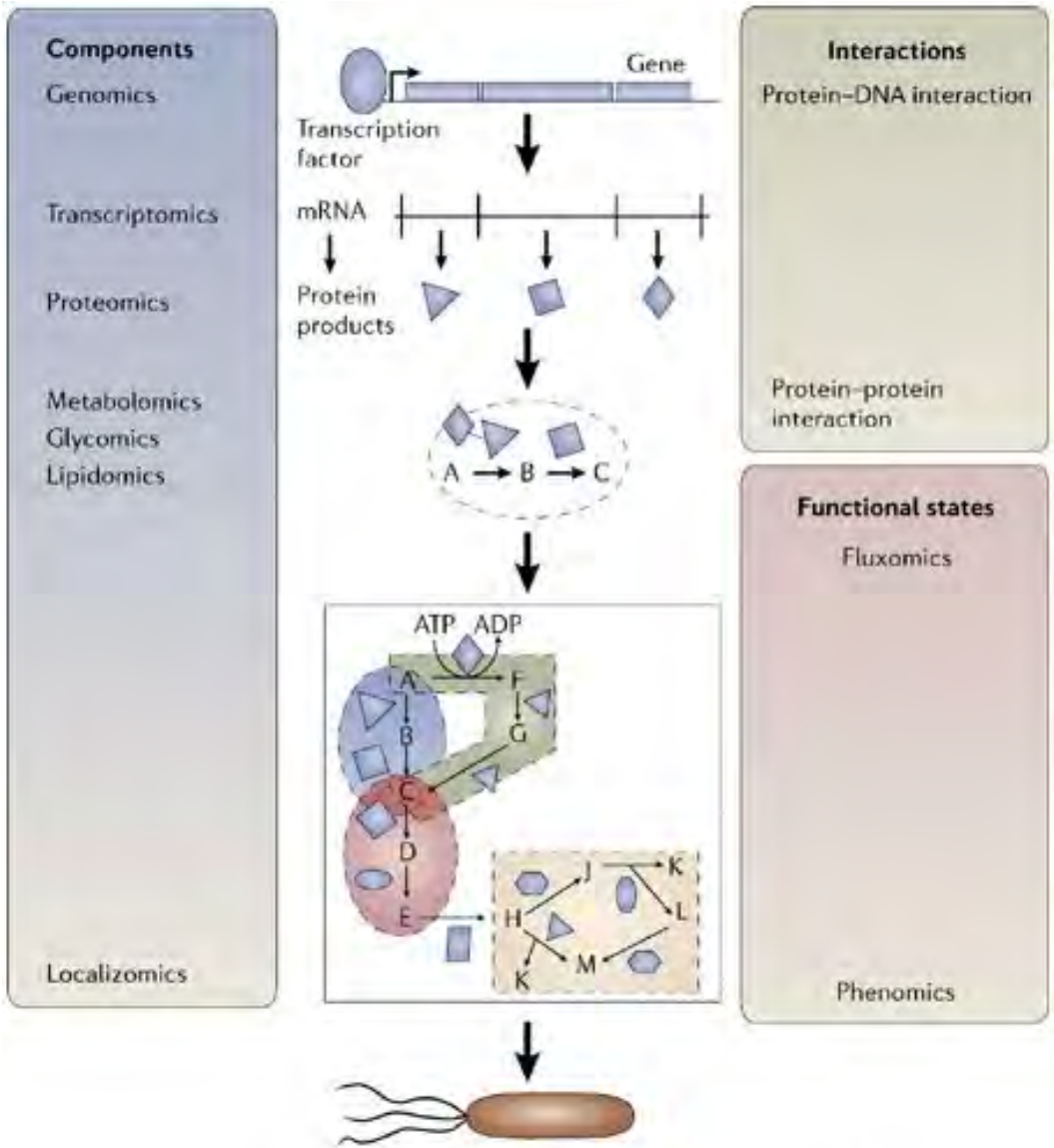
Omics
Big data/Next Generation Techniques



Gene regulatory networks in Hepatocellular Carcinoma

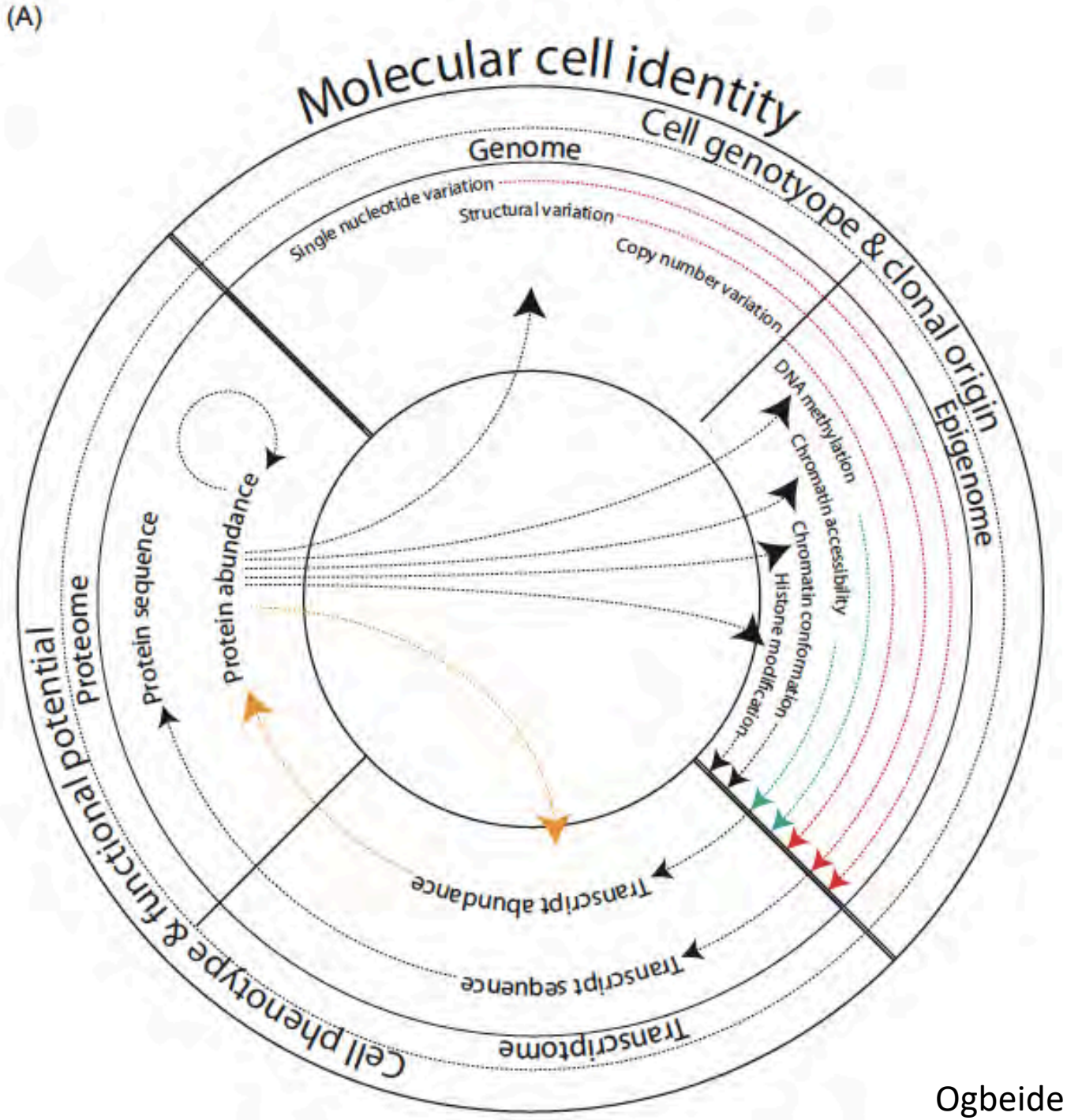
-Omics: Large scale dataset in specific species of biomolecules or biological entities (wholistic approach)

Gu et al, BMC Syst Biol. 2012

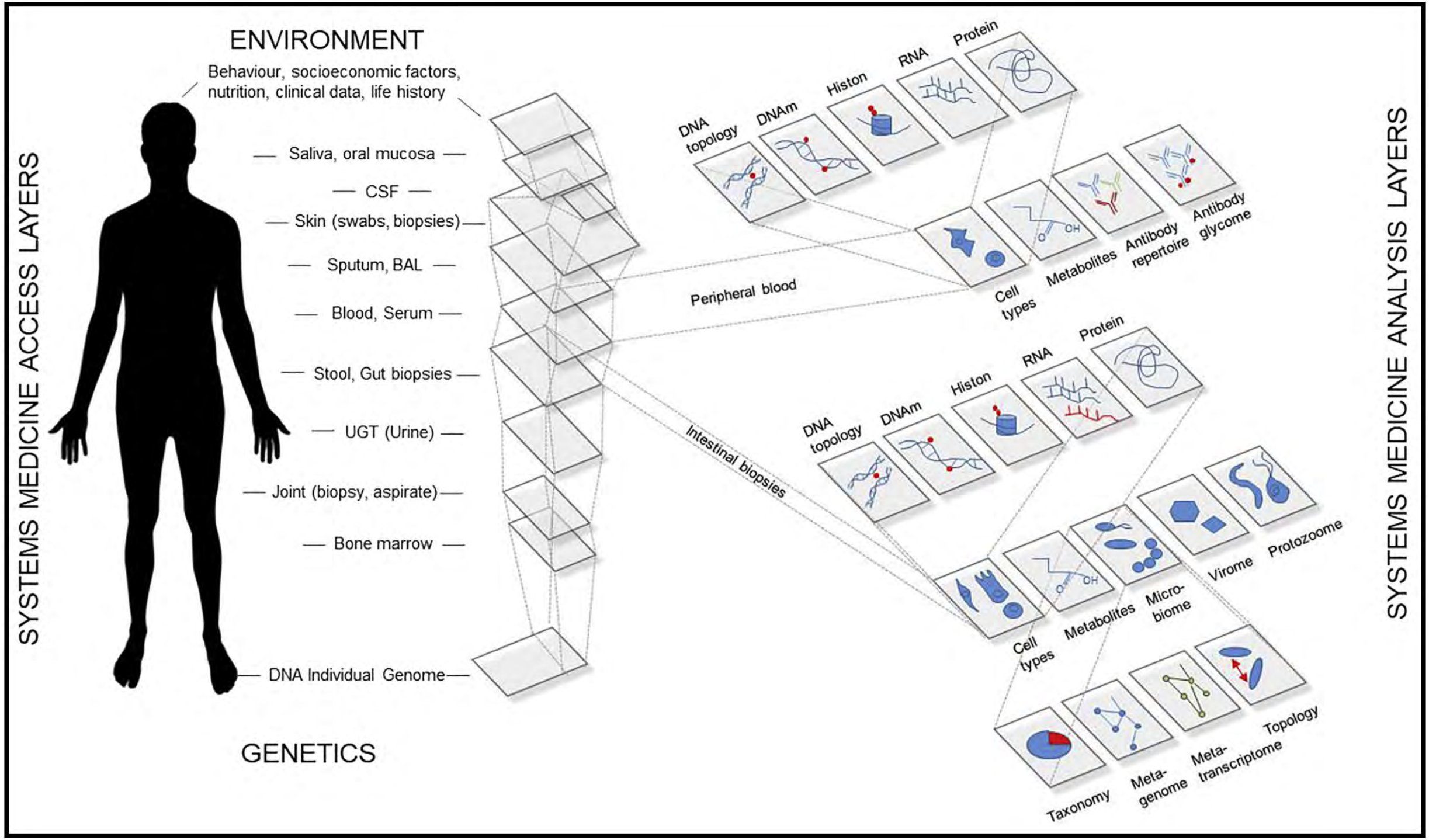


- Serial layers of –omics
- Elucidation of mechanisms
- Pathophysiological maps
- Casuality
- Therapeutical targets
- Personalized medicine

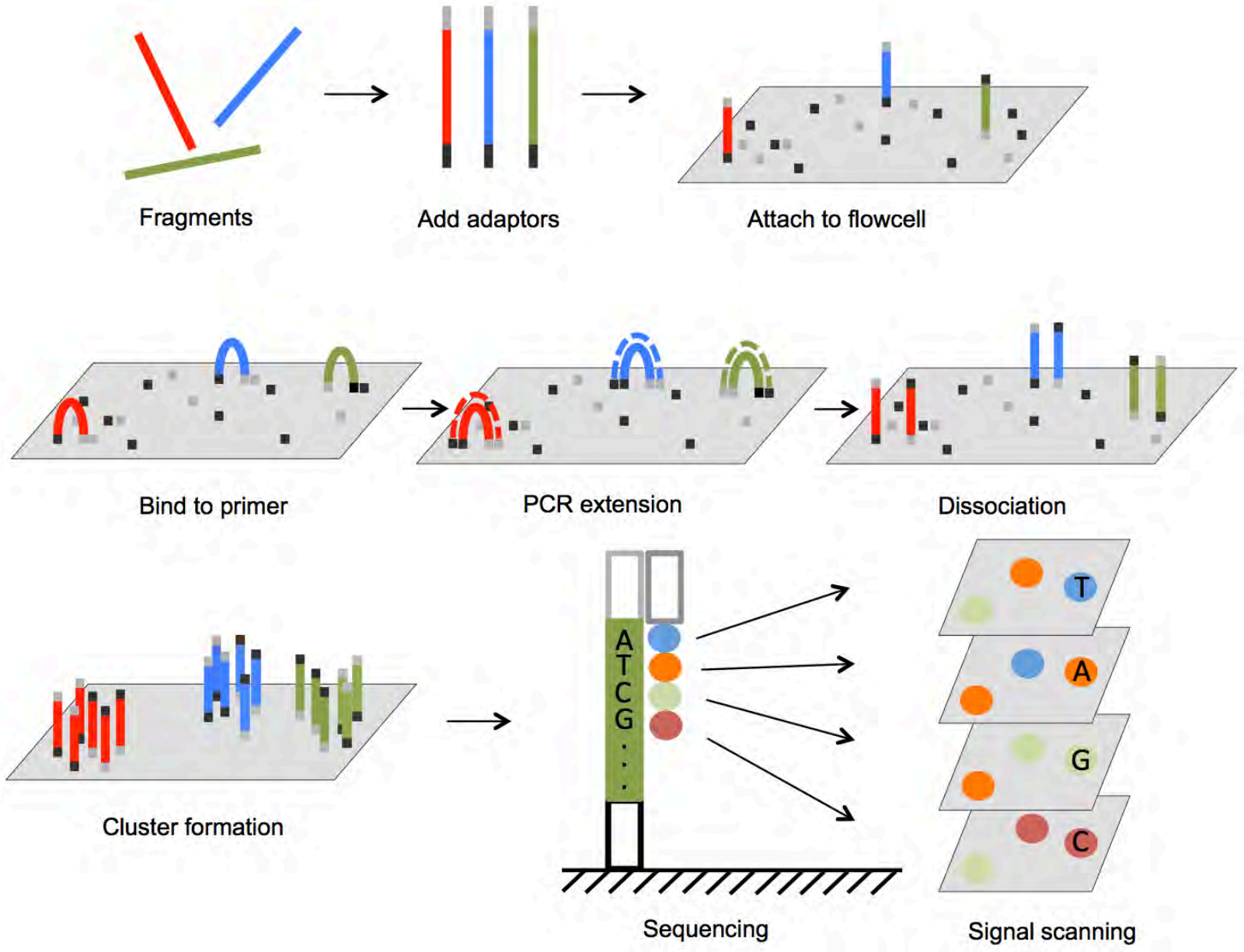
Joyce, A. Nat Rev Mol Cell Biol **7,** 198–210 (2006)



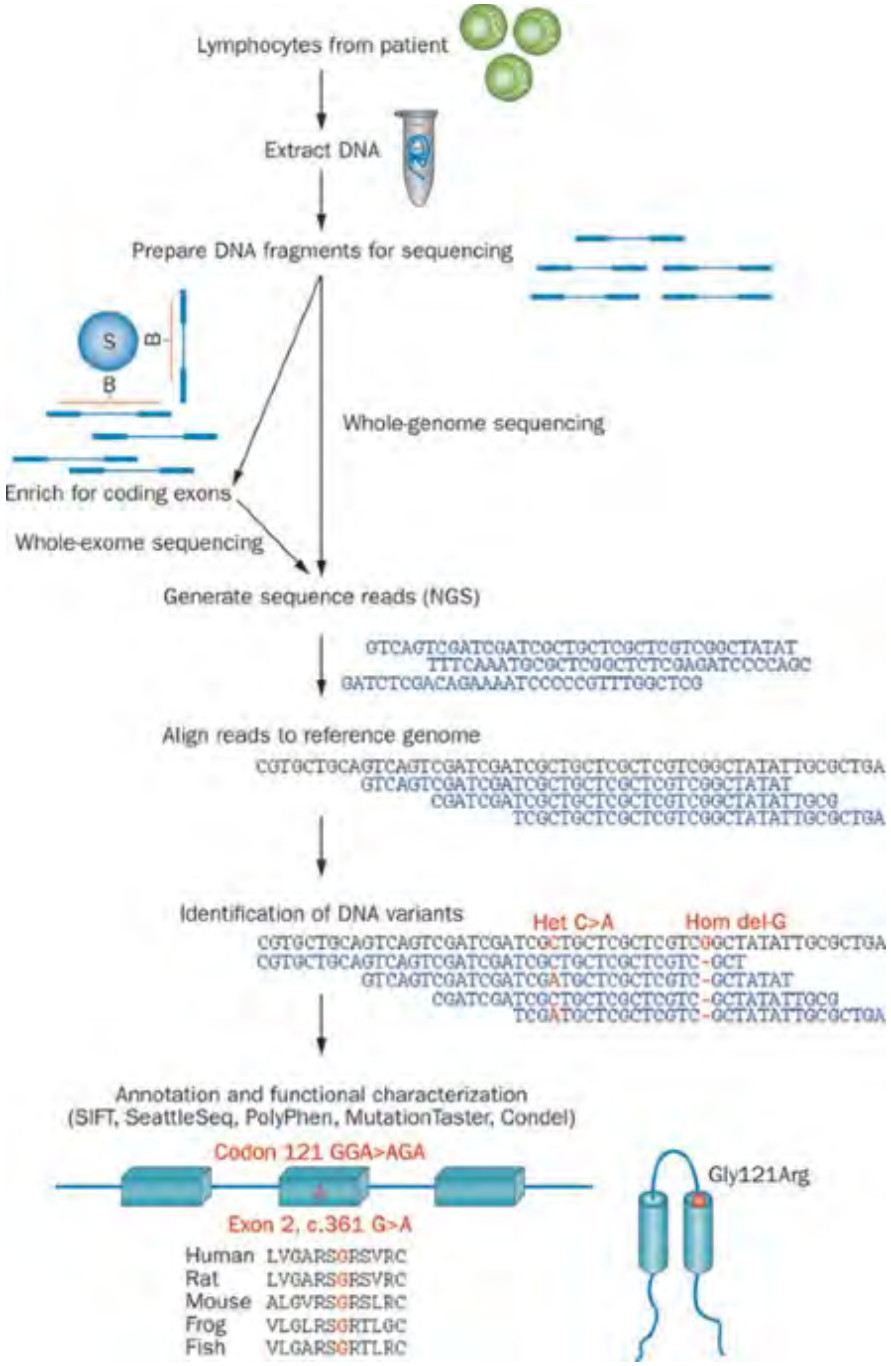
Ogbeide S, et al. Trends Genet(22) 2022


ENVIRONMENT
Behaviour, socioeconomic factors, nutrition, clinical data, life history
SYSTEMS MEDICINE ACCESS LAYERS
Saliva, oral mucosa
CSF
Skin (swabs, biopsies)
Sputum, BAL
Blood, Serum
Stool, Gut biopsies
UGT (Urine)
Joint (biopsy, aspirate)
Bone marrow
DNA Individual Genome
GENETICS
Peripheral blood
Intestinal biopsies
DNA topology
DNAm
Histon
RNA
Protein
Cell types
Metabolites
Antibody repertoire
Antibody glycome
Microbiome
Virome
Protozoome
Taxonomy
Metagenome
Metatranscriptome
Topology
SYSTEMS MEDICINE ANALYSIS LAYERS

NGS technology

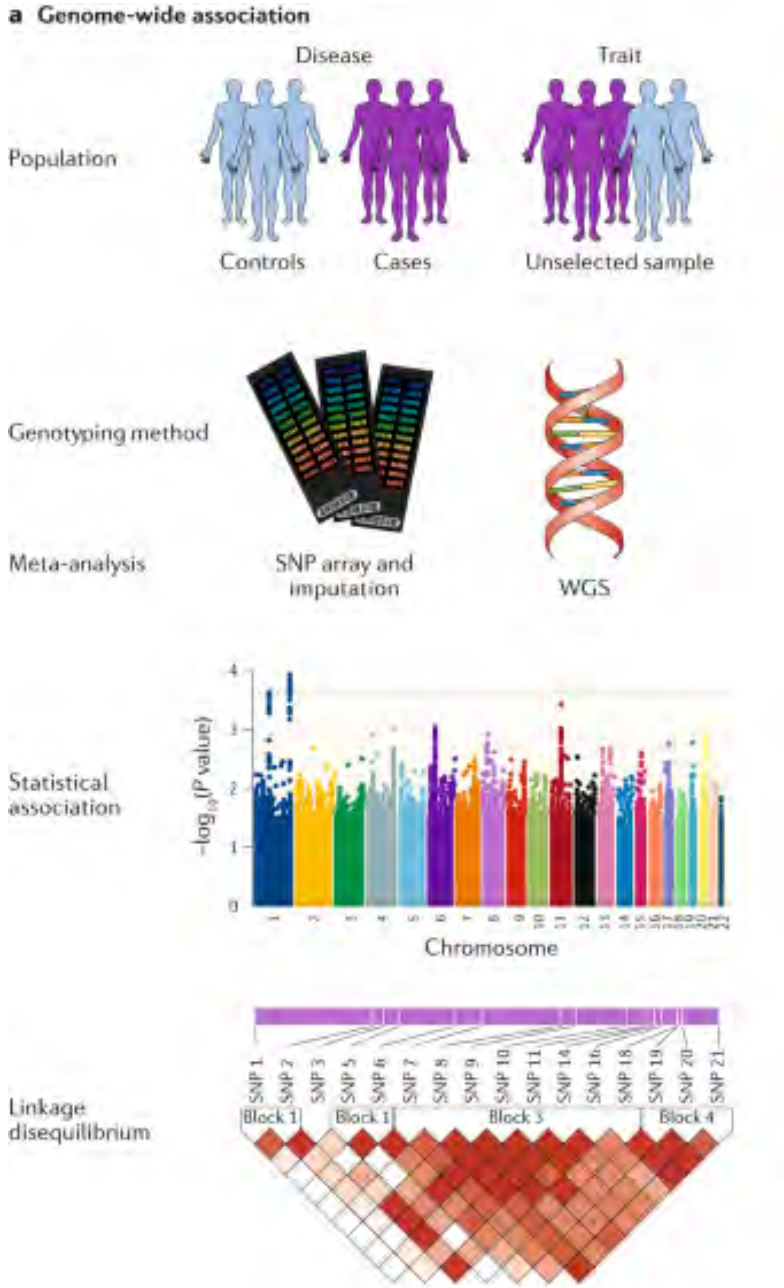


Genetic load of rheumatic diseases



GWAS Studies

Whole Genome/Exome Sequencing



Genetic predisposition in EGPA

ARTICLE

https://doi.org/10.1038/s41467-019-12515-9 OPEN

Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status

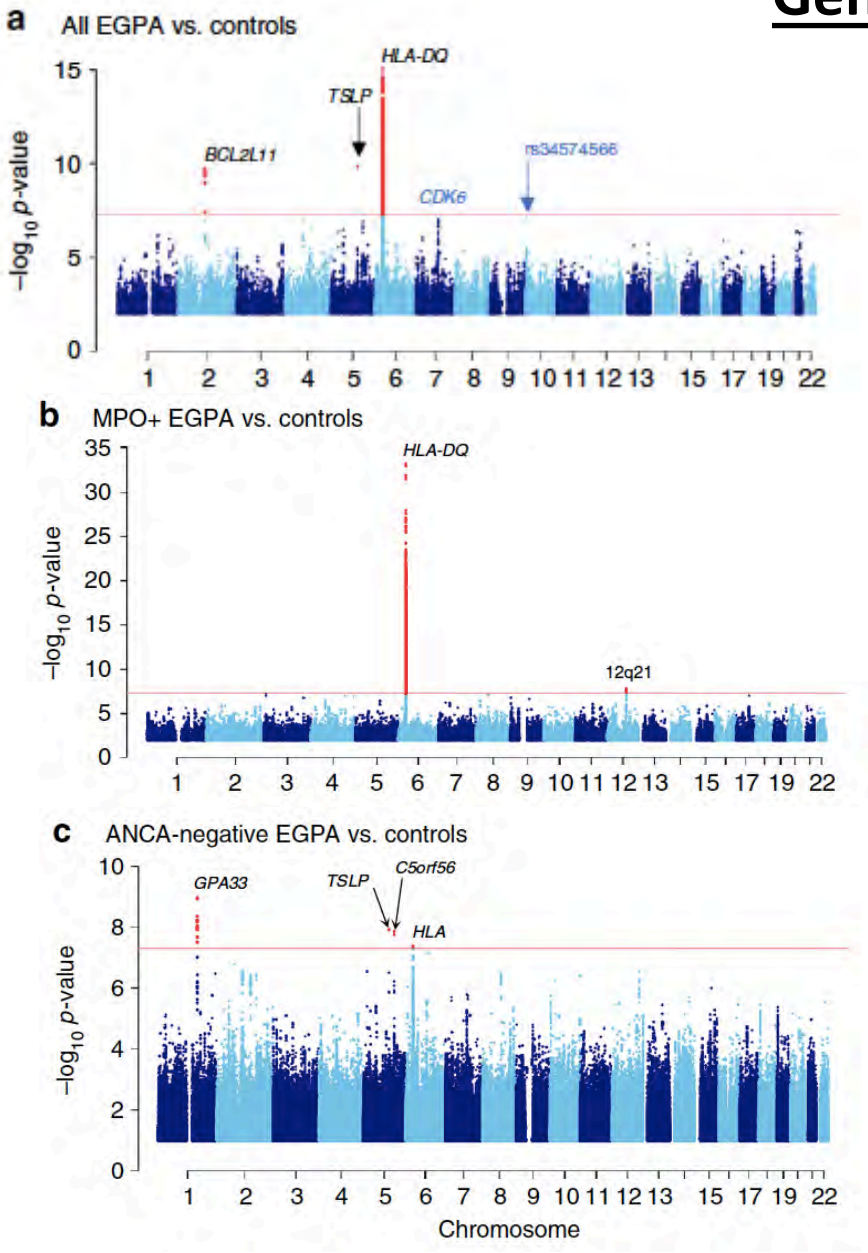
Paul A Lyons et al.#

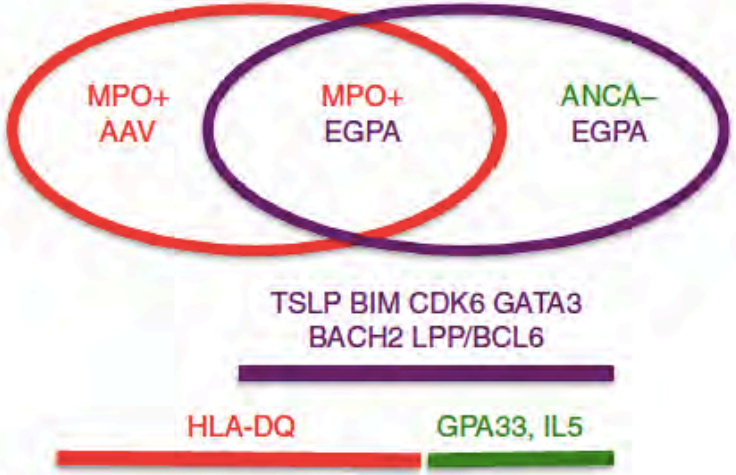
Table 2 Genetic associations with EGPA

						Total EGPA *N* = 534			MPO+EGPA *N* = 159		ANCA −ve EGPA *N* = 352	
Chr	Variant rsid	Gene/ Region	Cont maf	Case maf	OR	LMM *P*	Meta OR	Meta *P*	MPO OR	MPO *P*	OR	*P*
2	rs72946301	*BCL2L11*	0.1	0.17	1.66	$\mathbf{1.9\times10^{-10}}$	1.81	$\mathbf{9.0\times10^{-11}}$	1.89	7.7×10^{-5}	1.76	3.6×10^{-7}
5	rs1837253	*TSLP*	0.26	0.17	1.42	$\mathbf{1.5\times10^{-10}}$	1.52	$\mathbf{5.2\times10^{-11}}$	1.46	0.0008	1.53	$\mathbf{1.2\times10^{-8}}$
6	rs9274704	*HLA-DQ*	0.17	0.27	1.98	$\mathbf{8.2\times10^{-16}}$	2.01	$\mathbf{1.2\times10^{-20}}$	5.68	$\mathbf{1.1\times10^{-28}}$	1.32	0.004
10	rs34574566	*10p14*	0.31	0.24	0.73	8.0×10^{-8}	0.7	$\mathbf{2.9\times10^{-8}}$	0.66	0.0004	0.7	9.9×10^{-6}
7	rs42041	*CDK6*	0.24	0.31	1.32	1.9×10^{-6}			1.34	0.014	1.36	9.7×10^{-5}
5	rs11745587†	*IRF1/IL5*	0.35	0.4	1.31	2.1×10^{-7}			1.16	0.17	1.47	$\mathbf{1.8\times10^{-8}}$
6	rs6454802	*BACH2*	0.4	0.31	0.8	2.2×10^{-6}			0.81	0.024	0.74	3.8×10^{-6}
3	rs9290877	*LPP*	0.3	0.38	1.27	4.7×10^{-6}			1.48	0.0007	1.24	0.0006
1	rs72689399	*GPA33*	0.01	0.03	2.7	6.7×10^{-7}			0.89	0.96	5.34	$\mathbf{1.1\times10^{-9}}$
6	rs6931740	*HLA*	0.39	0.25	0.62	$\mathbf{1.7\times10^{-10}}$			0.55	1.6×10^{-5}	0.61	$\mathbf{4.2\times10^{-8}}$
12	rs78478398	*12q21*	0.03	0.05	0.59	0.0017			0.17	$\mathbf{1.7\times10^{-8}}$	0.81	0.37

Nat Commun. 2019 Nov 12;10(1):5120.

Genetic predisposition in EGPA

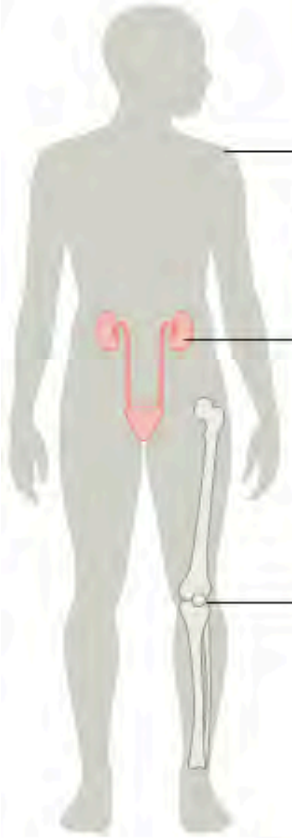




	% of patients with feature		
Clinical feature	MPO+ AAV (non EGPA)	MPO+ EGPA	ANCA– EGPA
Glomerulonephritis	85	29*	9
Neuropathy	20	79*	57
Asthma	n.d.	100	100
Eosinophilia	4.5	100	100
Pulmonary hemorrhage	17	4	4
Ear nose or throat	32	81	88
Pulmonary infiltrates	20	45	61*
Cardiac involvement	3	15	30*
Rituximab response	98	80	38

Nat Commun. 2019 Nov 12;10(1):5120.

Molecular Taxonomy in Rheumatic Diseases



SSc (skin)

Groups	Immune and inflammatory response	Proliferation	Fatty acids and lipid biosynthesis mechanisms	Heterogenous functions	Disease severity
dcSSc	Low	High	Low	Medium	Low
lcSSc	Low	Low	Medium	High	Low
dcSSc and lcSSc	High	Low	Medium	Medium	High

Lupus nephritis (glomeruli)

Groups	Interferon	Fibrosis	Glomerulosclerosis
I	Low	High	High
II	High	Low	Low

RA (synovial tissue)

Groups	Immune and inflammatory response	Complement activation	Fibroblast de-differentiation	Repair and remodelling	Disease severity
RA-Ia	High	Low	Low	Low	High
RA-Ib	High	High	Low	High	High
RA-II	Low	Low	High	High	Low

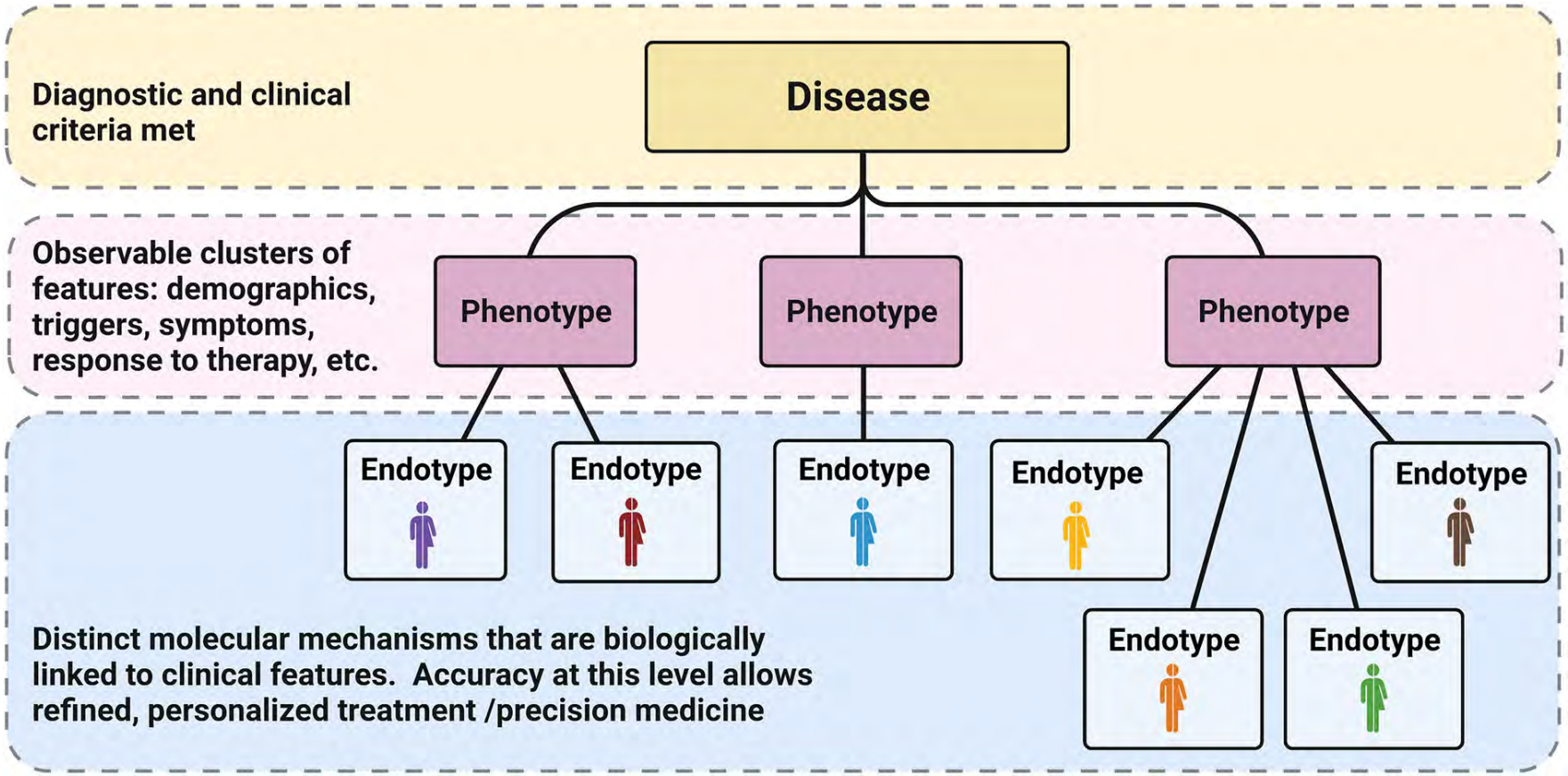
SLE versus RA (synovial tissue)

Groups	Interferon	ECM homeostasis
SLE	High	Low
RA	Medium	Medium

Molecular taxonomy based on transcriptome analysis

Barturen G, et al. Nat Rev Rheumatol. 2018

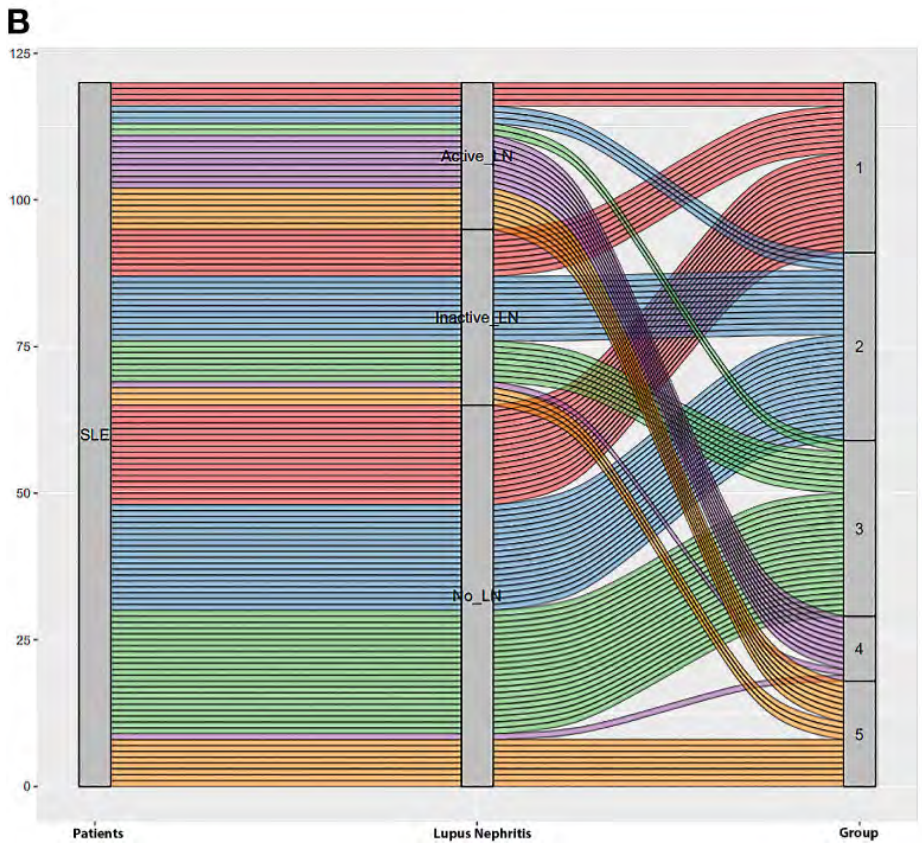
Molecular Disease Endotypes

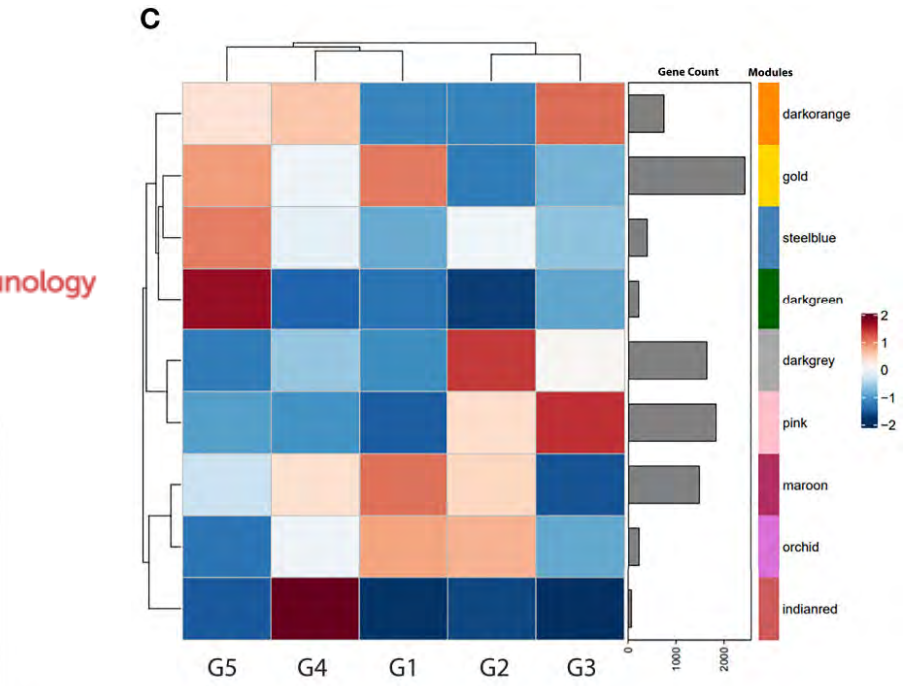


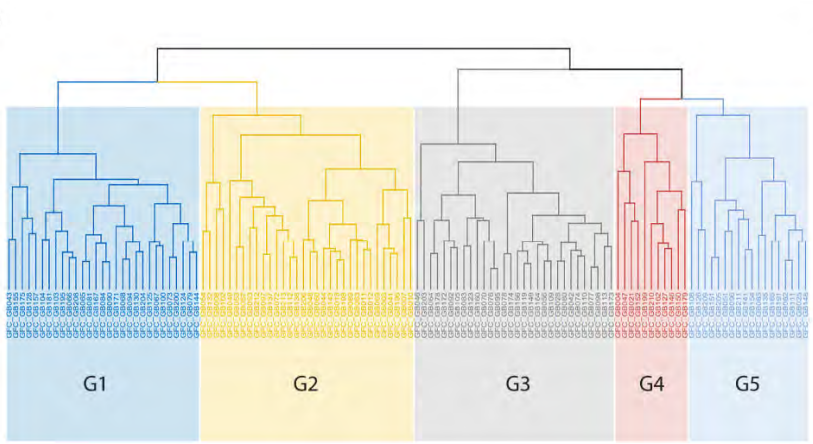
Proper SP, et al. Front Immunol. 2021 Aug 18;12:720746

Molecular Taxonomy of Systemic Lupus Erythematosus Through Data-Driven Patient Stratification: Molecular Endotypes and Cluster-Tailored Drugs

frontiers | Frontiers in Immunology







- 5 SLE endotypes characterized by a unique gene module enrichment pattern.
- Neutrophilic signature consisted primarily of patients with active LN
- B-cell group included patients with constitutional features.
- Patients with moderate severity and serologic activity exhibited a signature enriched for metabolic processes.
- Mild disease was distributed in 2 groups, exhibiting enhanced basic cellular functions, myelopoiesis, and autophagy

Garantziotis P, et al. Front Immunol. 2022 May 9;13:860726.

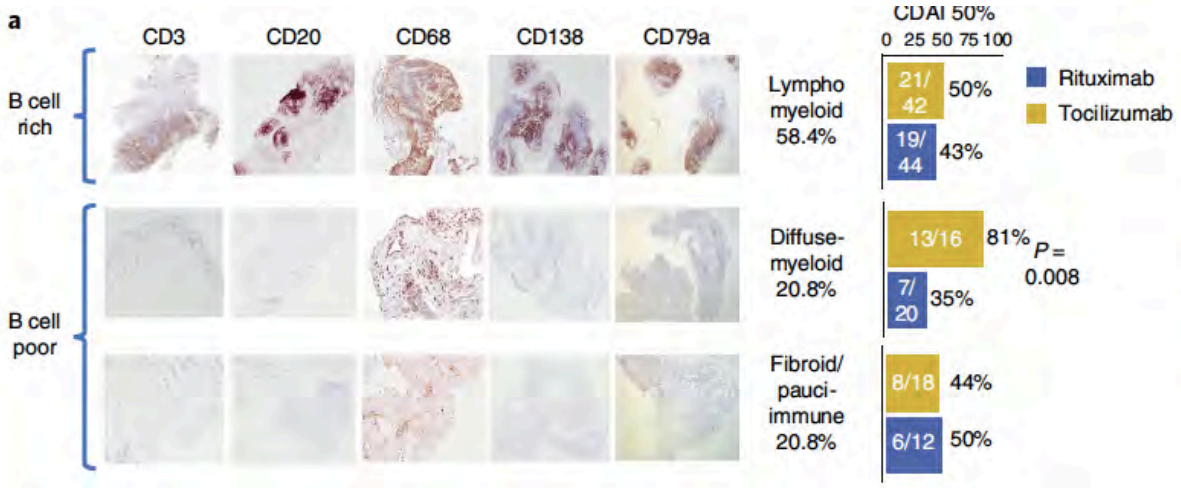
Biopsy-based disease endotyping before and after therapy in RA reveals diverse clinical and treatment–response phenotypes

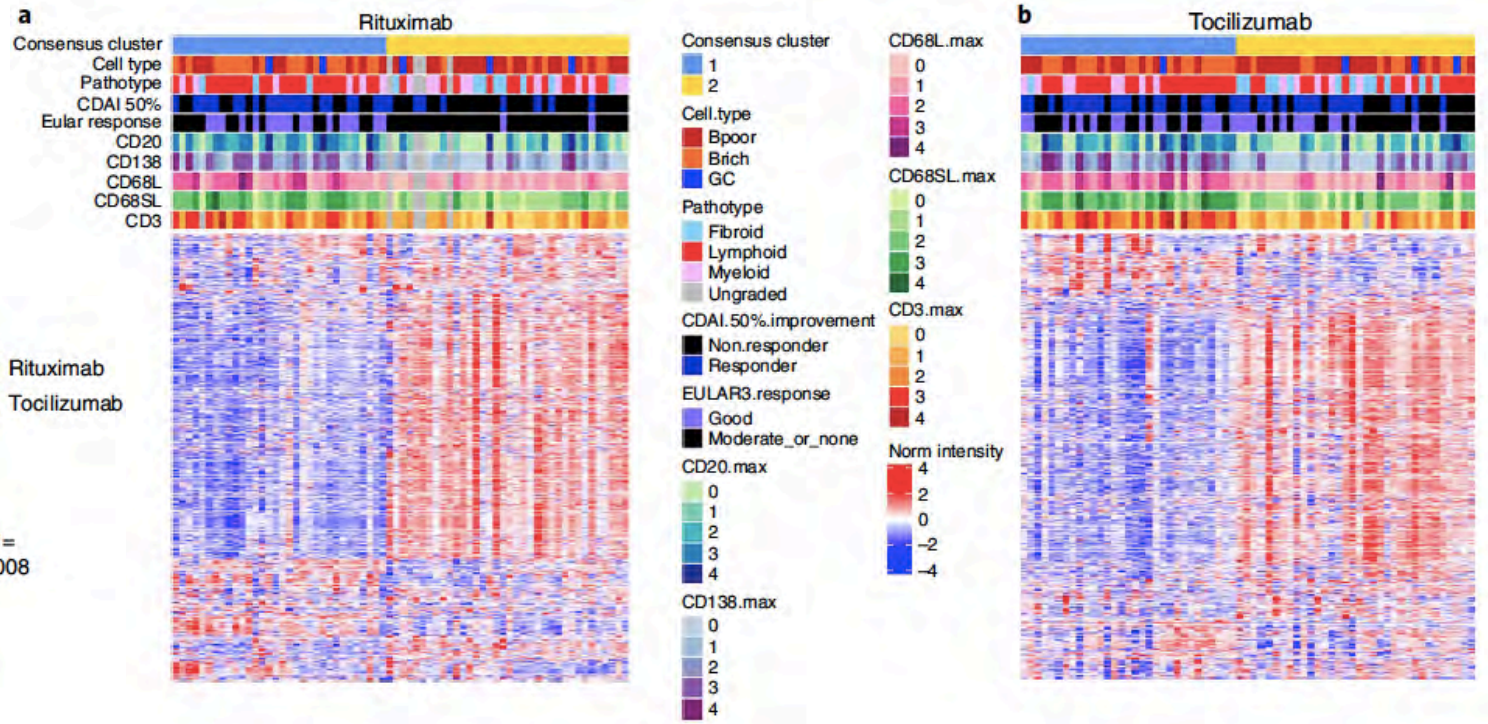
ARTICLES
https://doi.org/10.1038/s41591-022-01789-0
nature medicine

Check for updates

OPEN

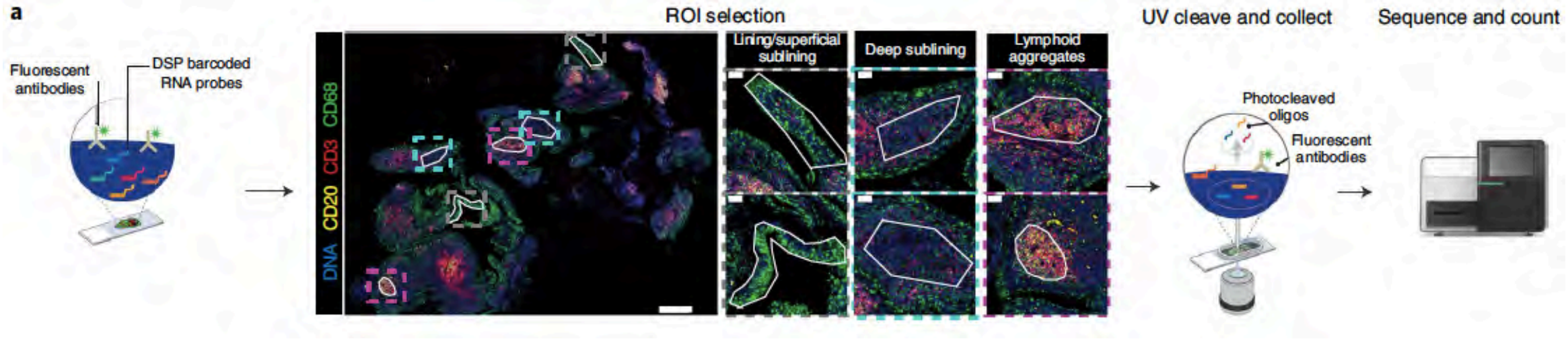
Rituximab versus tocilizumab in rheumatoid arthritis: synovial biopsy-based biomarker analysis of the phase 4 R4RA randomized trial

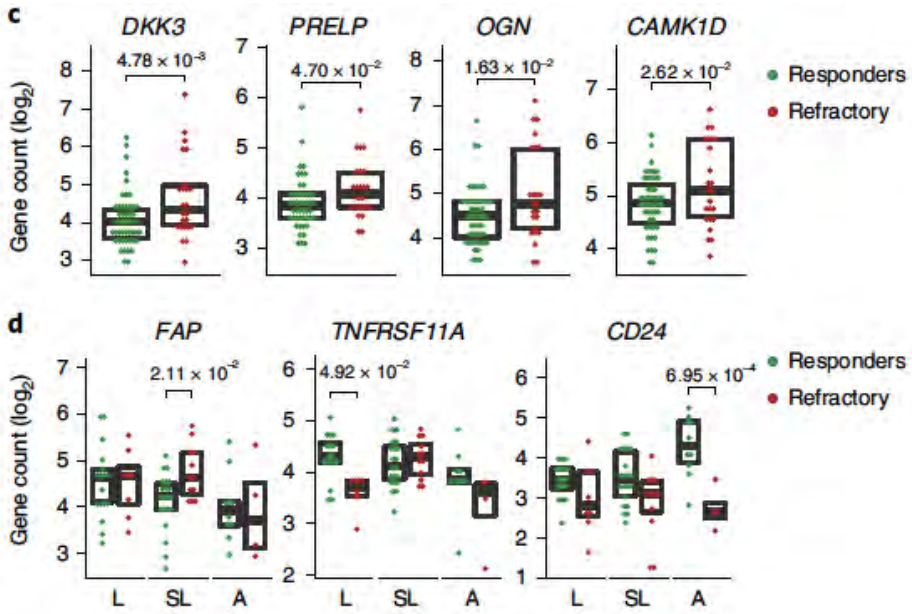


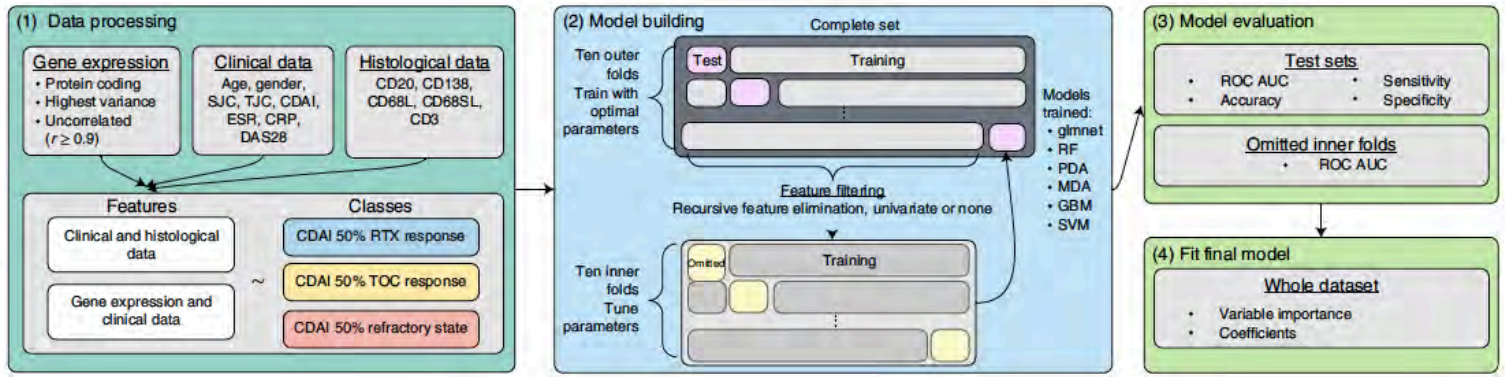


Rivellese F, et al. Nat Med. 2022 Jun;28(6):1256-1268

The future of Transcriptomics and Personalized Medicine – Spatial Transcriptomics

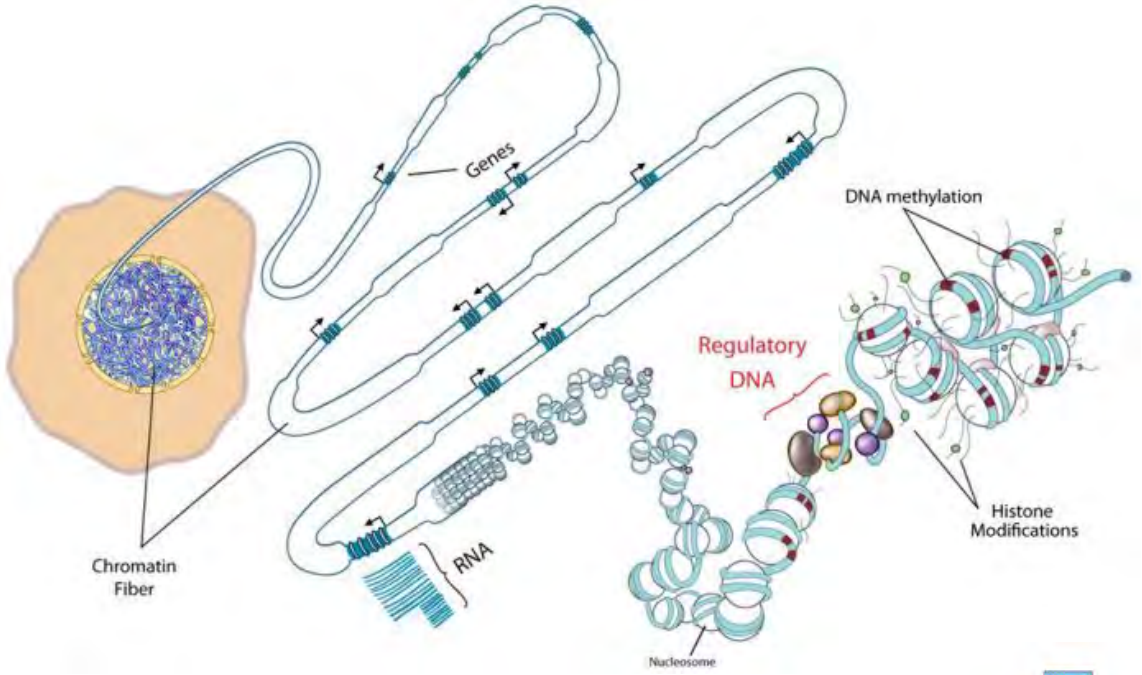


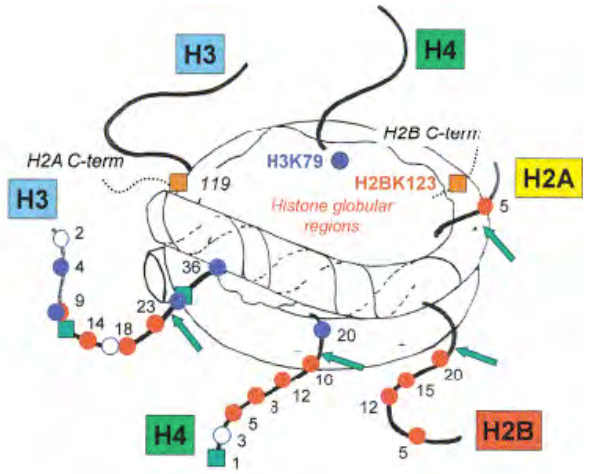


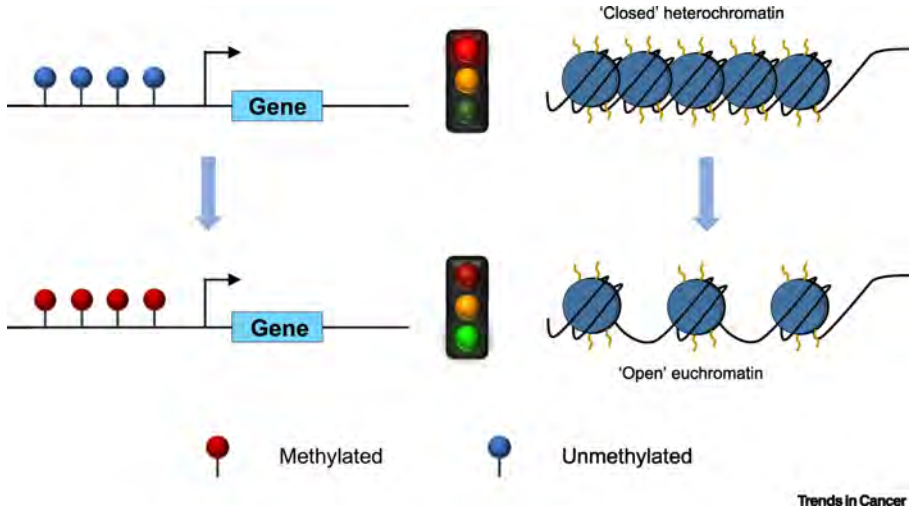


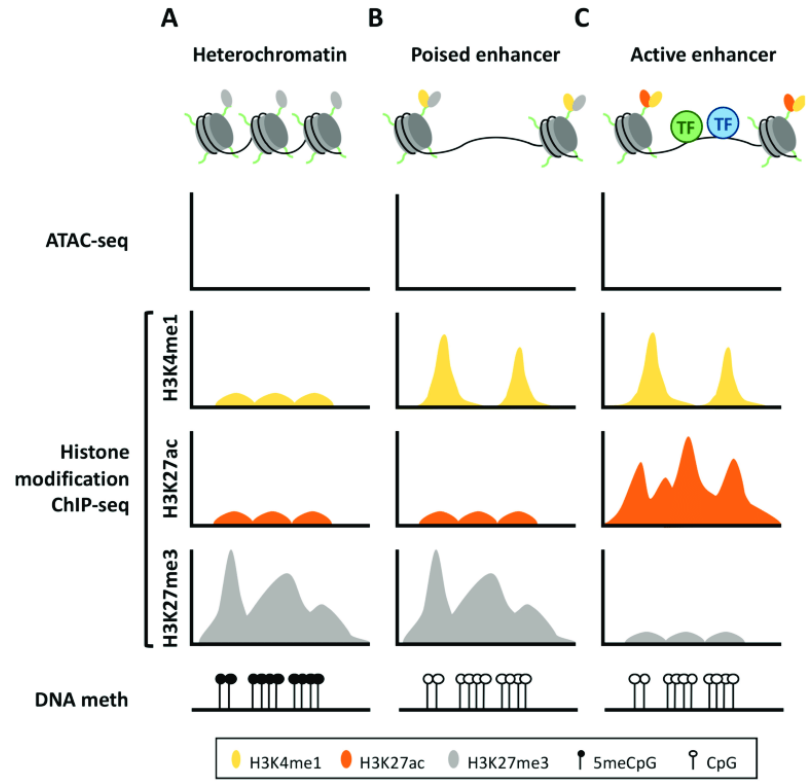
Rivellese F, et al. Nat Med. 2022 Jun;28(6):1256-1268

Epigenetics – Past and Response of the cell



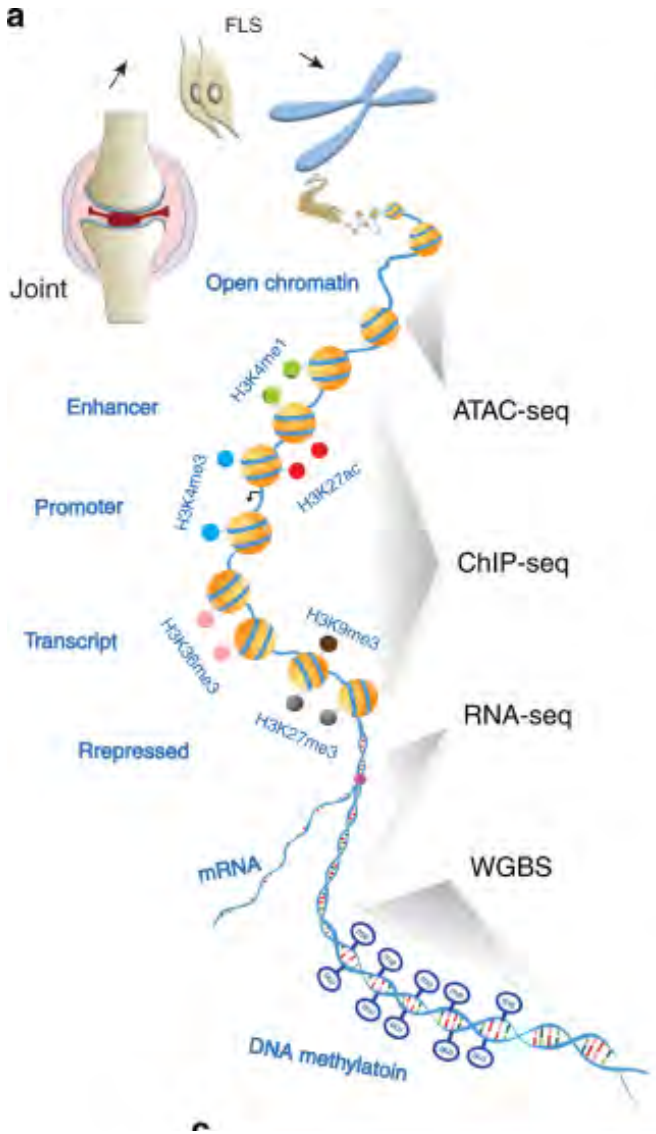


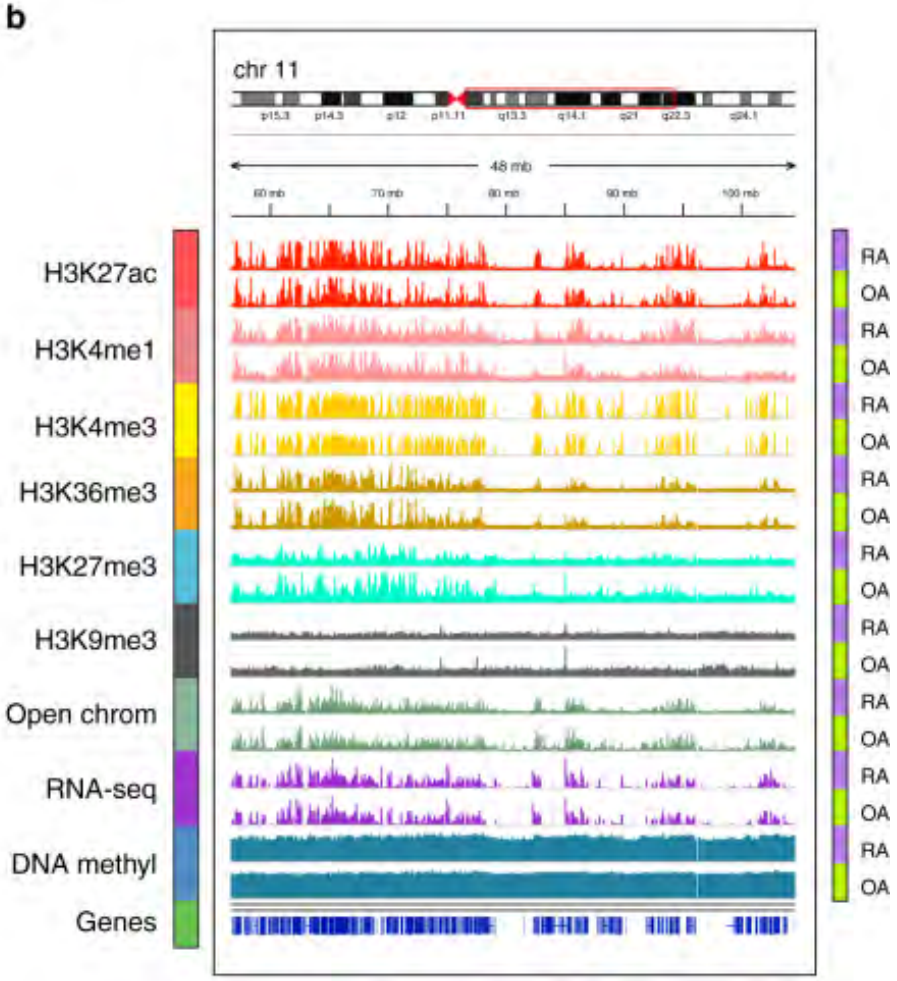




ARTICLE
DOI: 10.1038/s41467-018-04310-9 OPEN

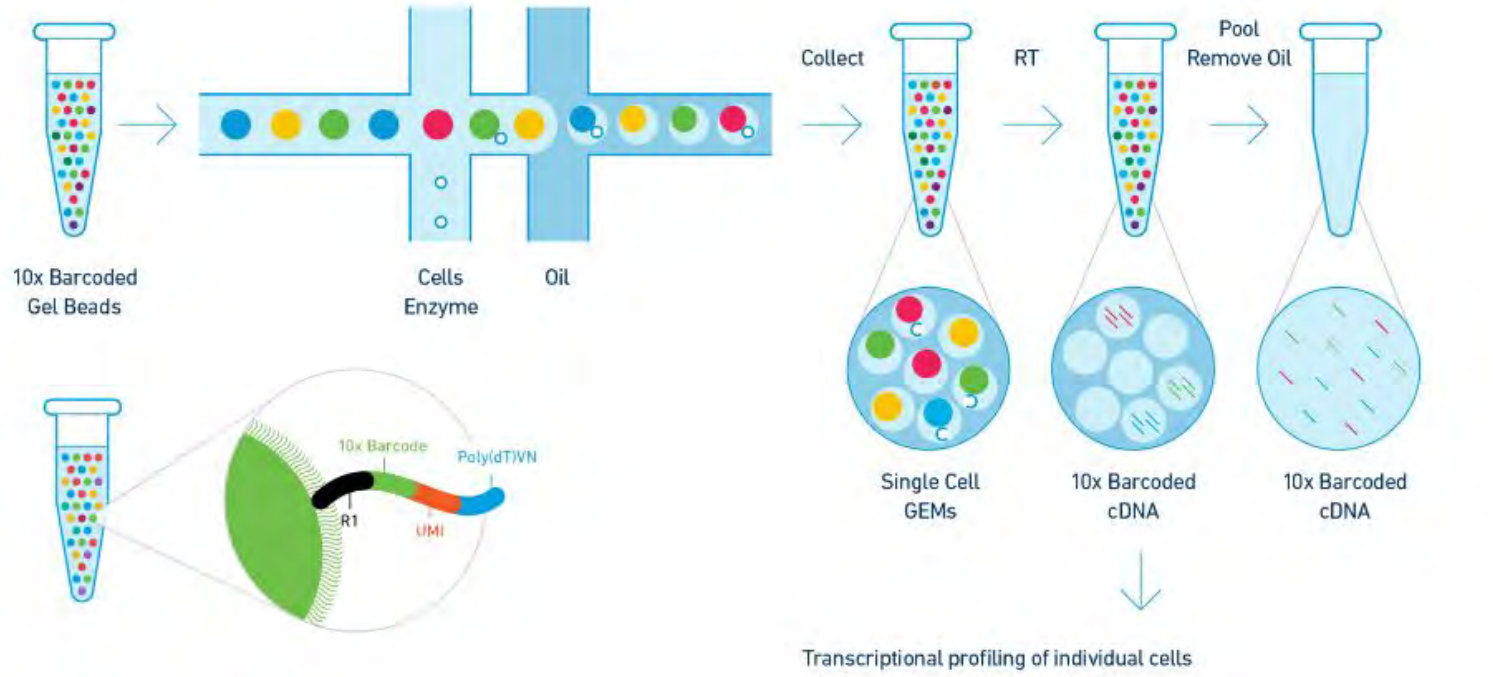
Comprehensive epigenetic landscape of rheumatoid arthritis fibroblast-like synoviocytes

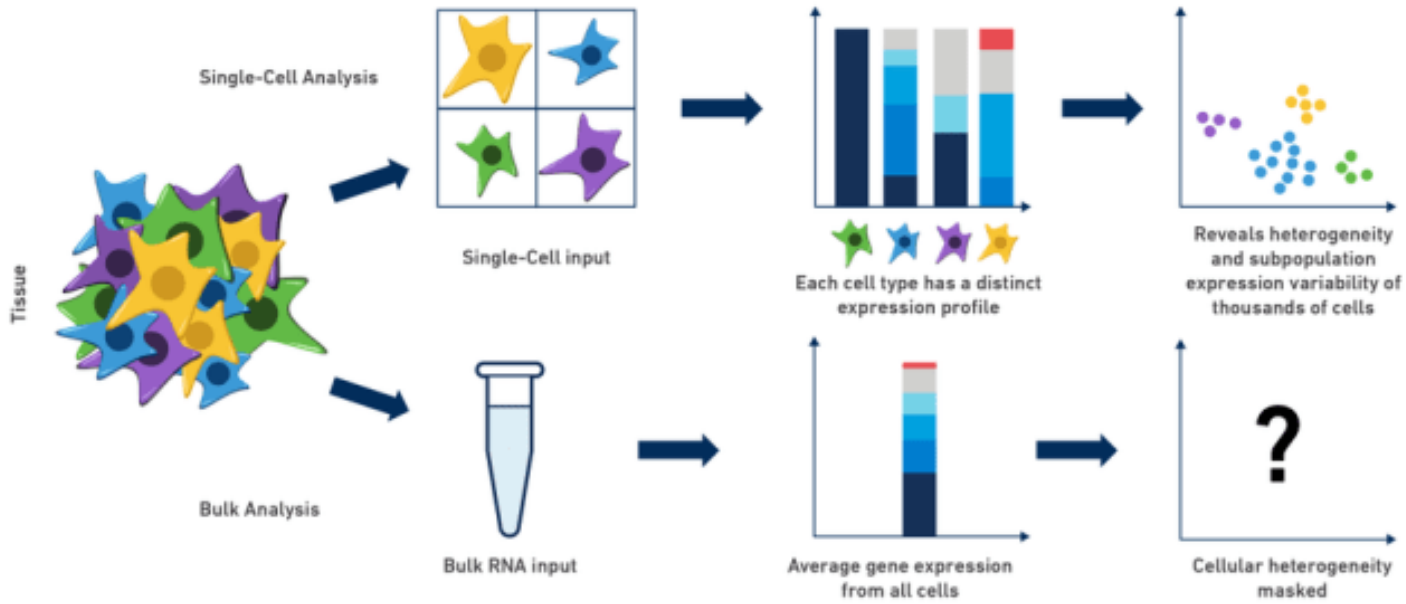




- Characterization of DMERs
- Differentially modified epigenetic regions
- Integration of different omics
- Epigenetic landscape sets new light on the genetic load and its pathophysiological mechanisms

Ai R, et al. Nat Commun. 2018

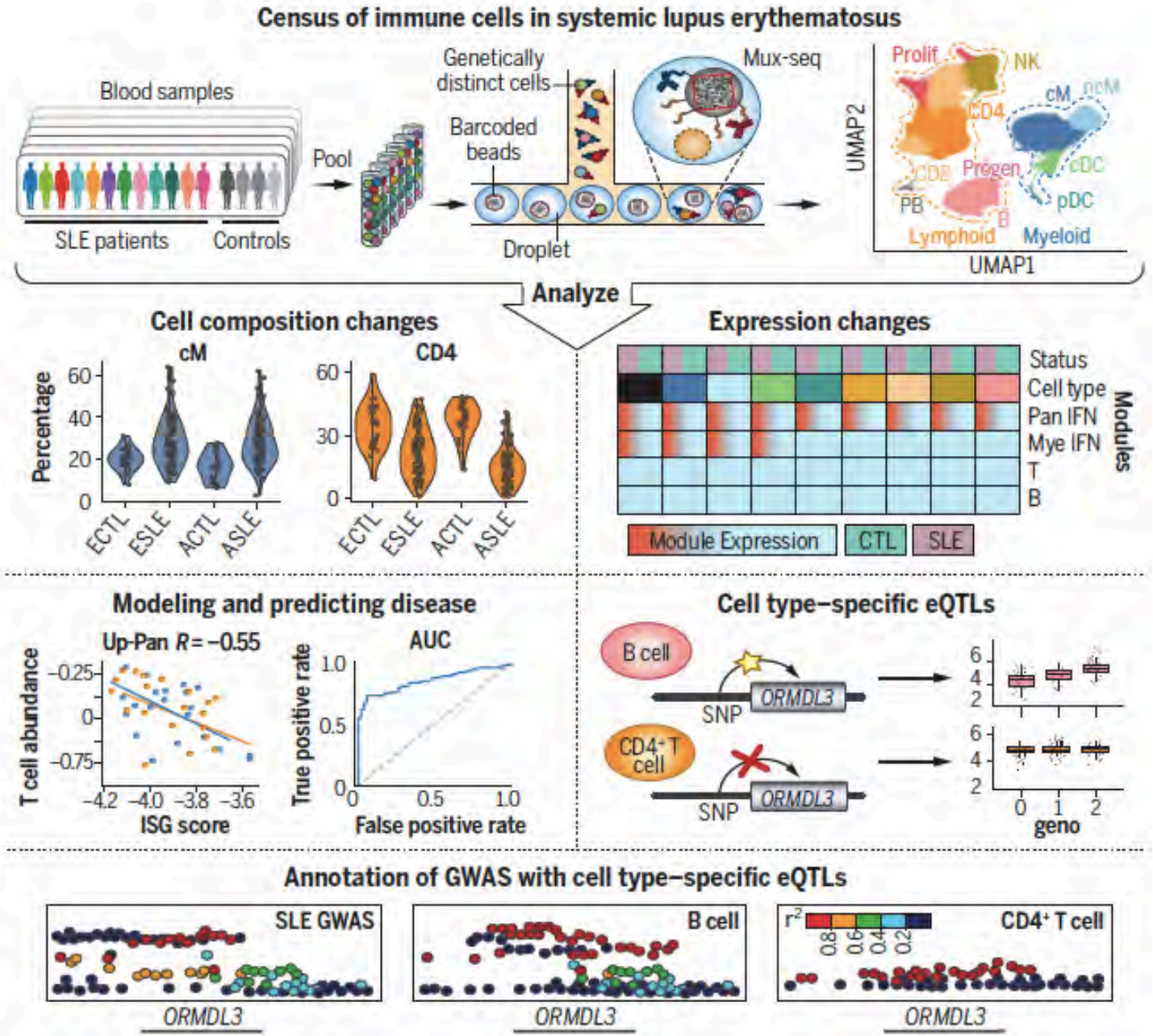




Single Cell Technology

- Through almost all –omics layers
- Fighting heterogeneity with a previously proposed “uniform” population
- Characterization of effector and driver/”causal” cells

10x Genomics

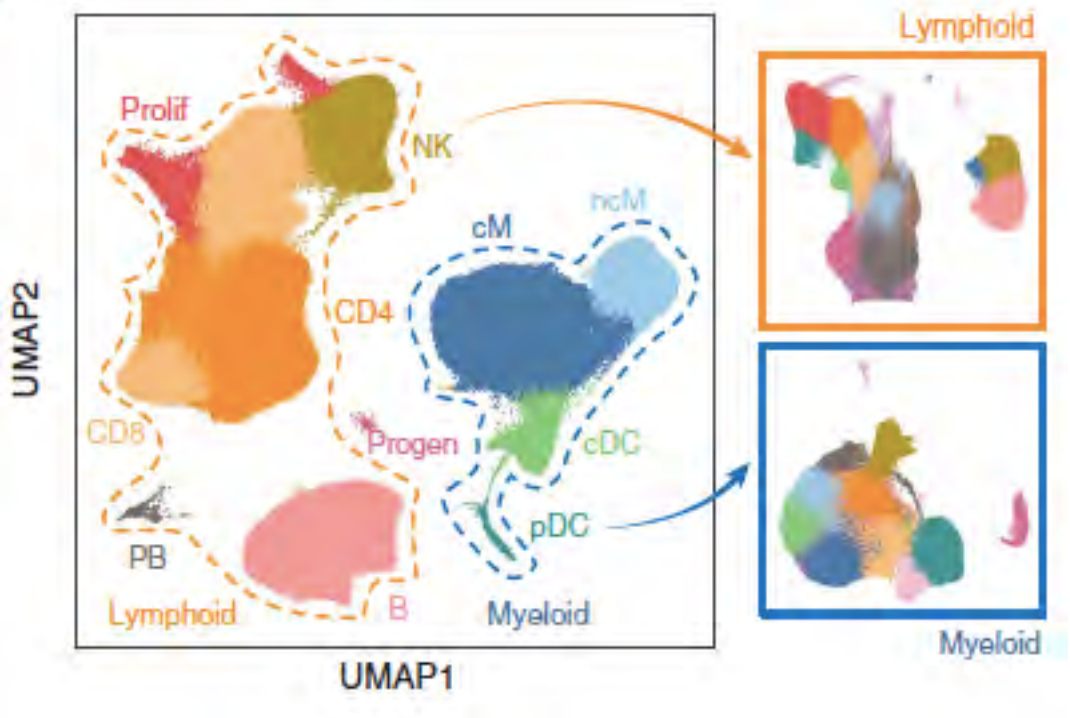


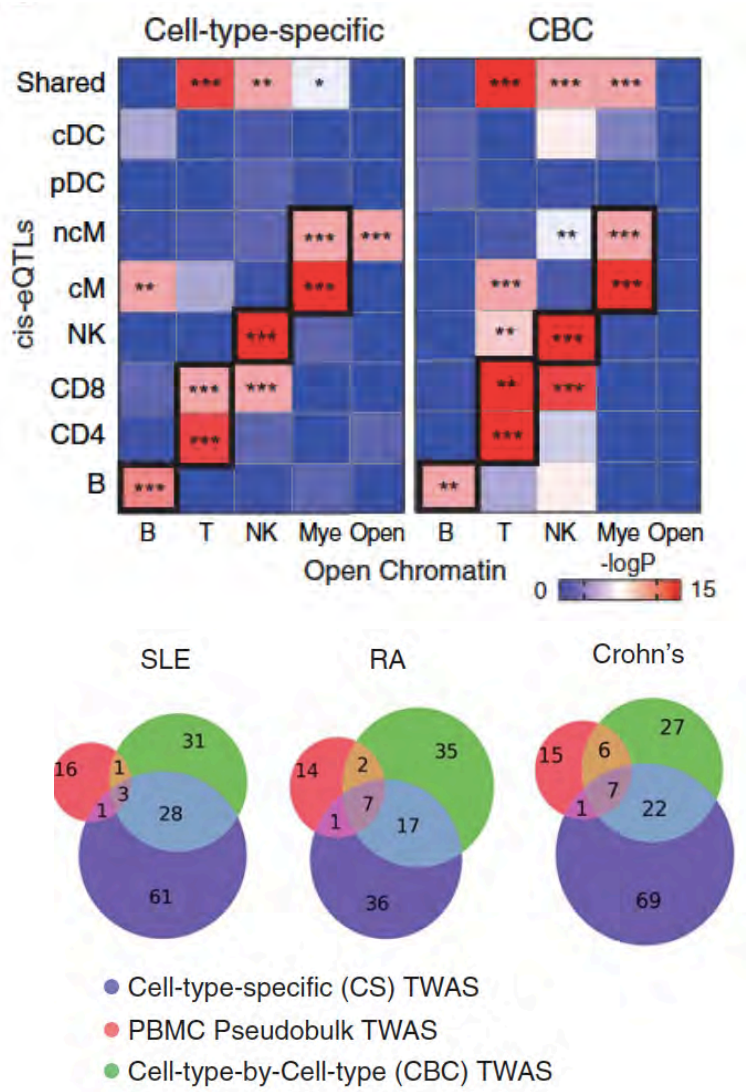
IMMUNOGENOMICS

Single-cell RNA-seq reveals cell type–specific molecular and genetic associations to lupus

- Unique maps of cell heterogeneity within hundreds of patients
- Integration with genetic and epigenetic layer
- Cell-type specific effects
- Gene modules for disease prediction

Perez et al., Science 376, 153 (2022)



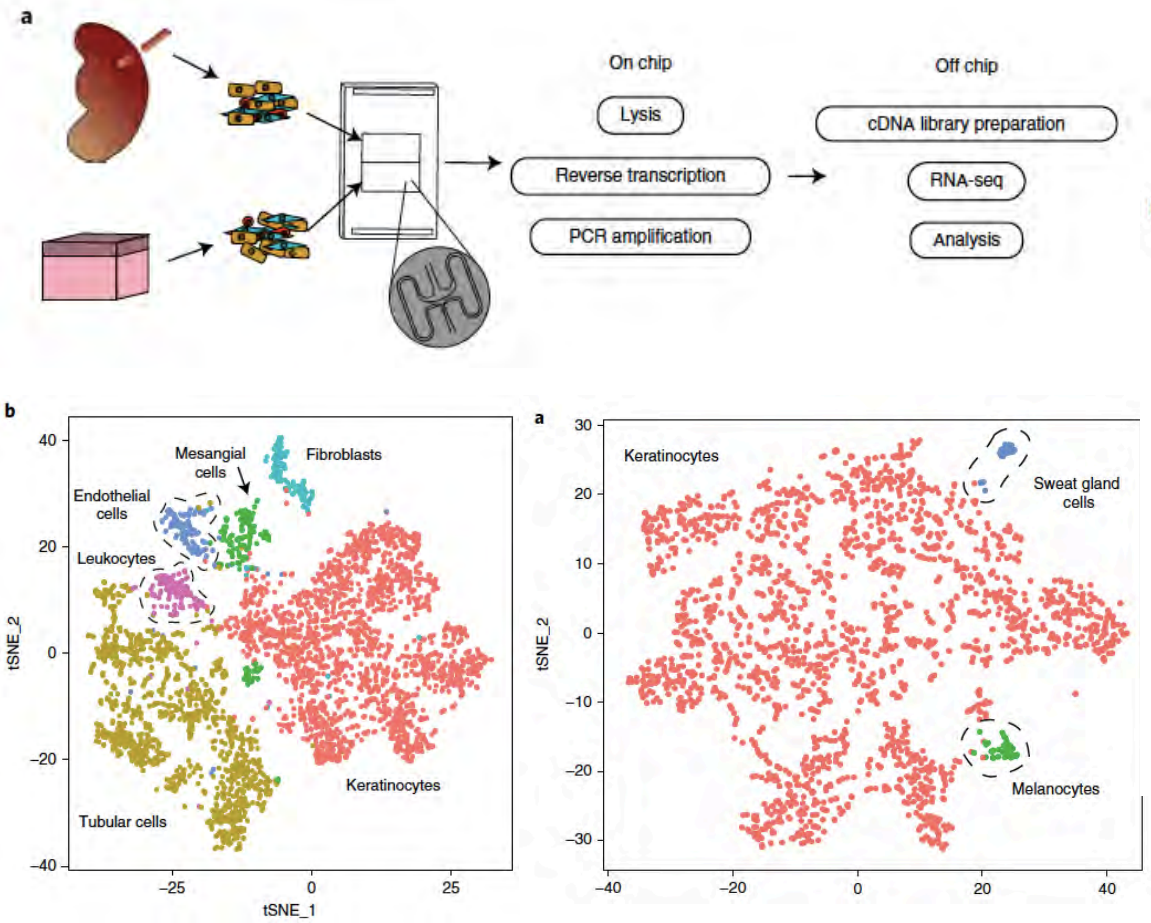


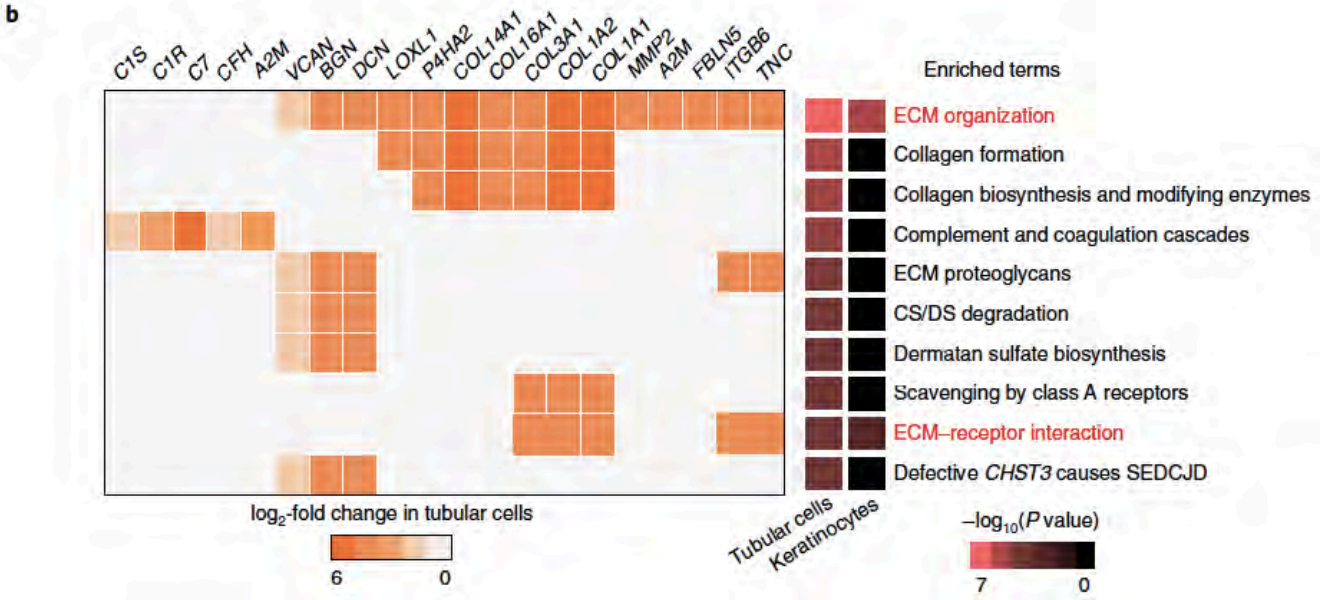
- Single cell analysis of 1.2 million cells derived of SLE PMBCs reveals gene modules driving into molecular subtypes of the disease

- Omics integration leads to better understanding of genome wide disease-specific reprogramming

Perez et al., Science 376, 153 (2022)

Personalized medicine through accesible tissue single cell approach

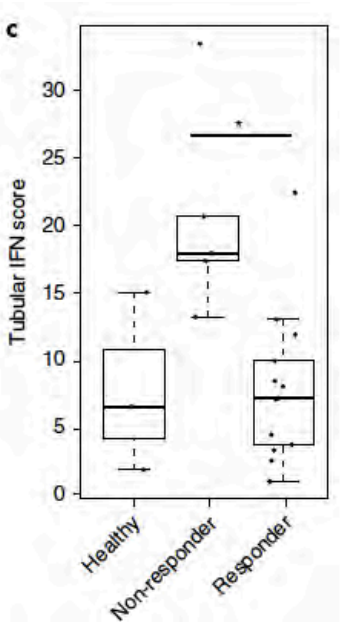


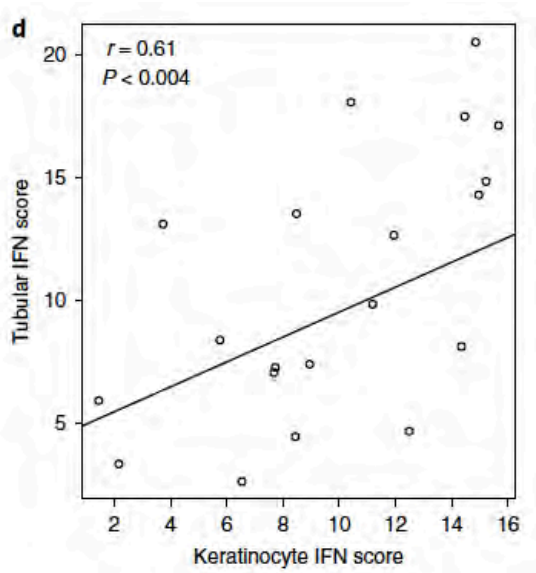


Der, E. et al. *Nat Immunol* **20,** 915–927 (2019).

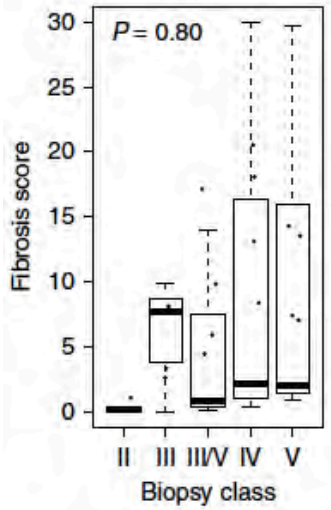
Personalized medicine through accesible tissue single cell approach

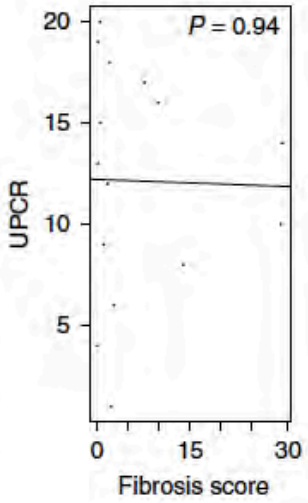
Type-I IFN score

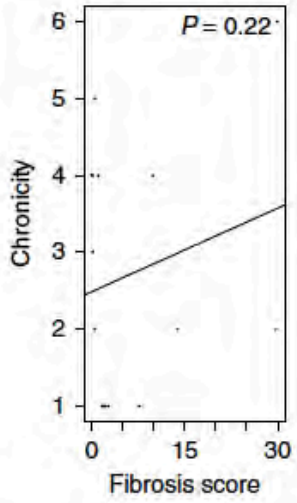


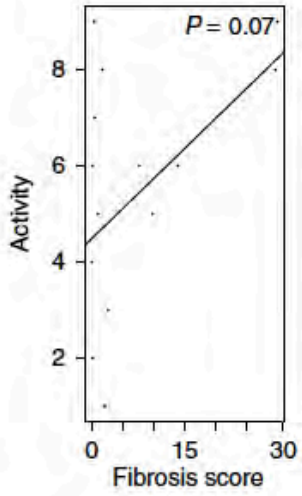


Fibrotic score



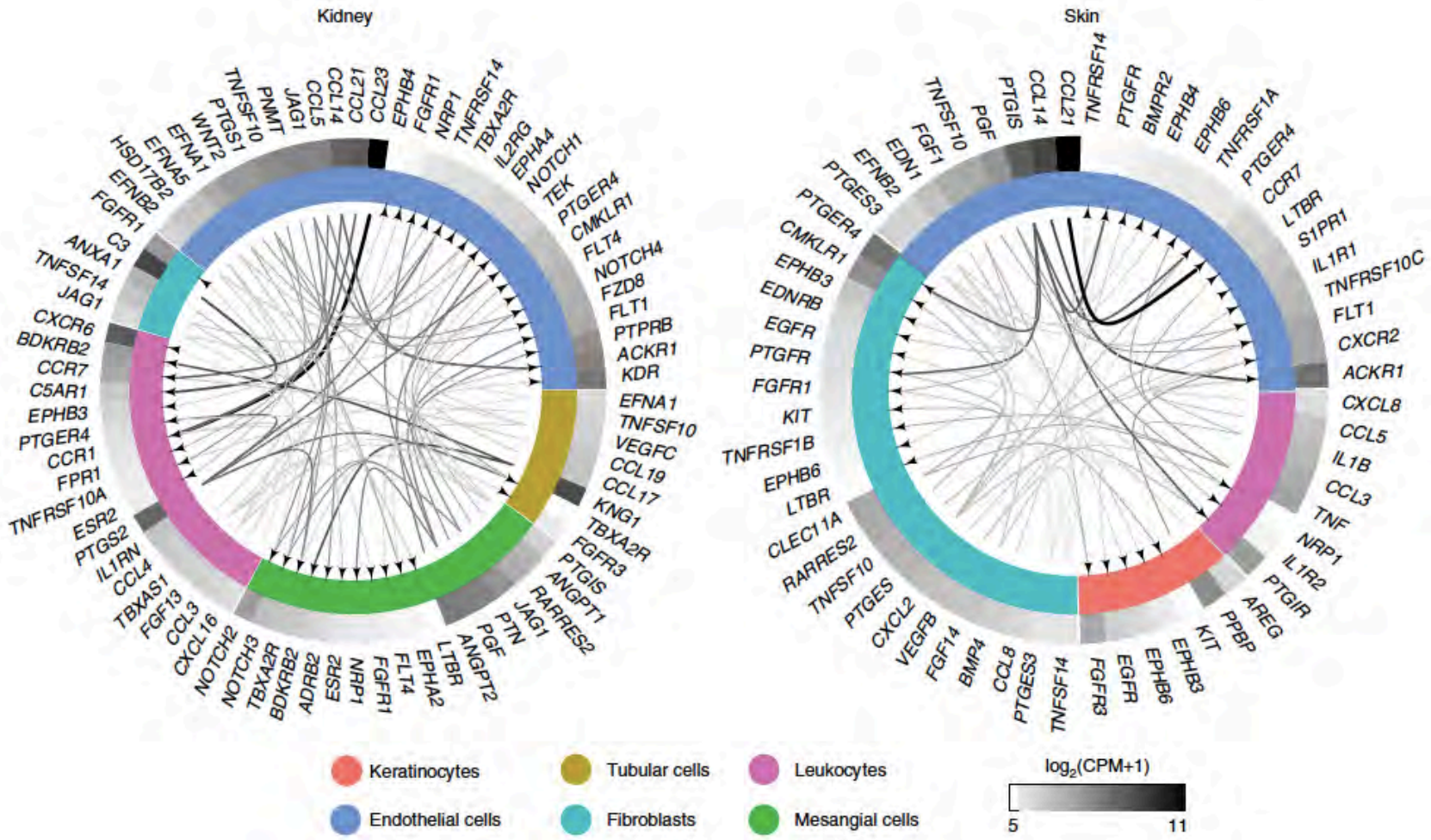






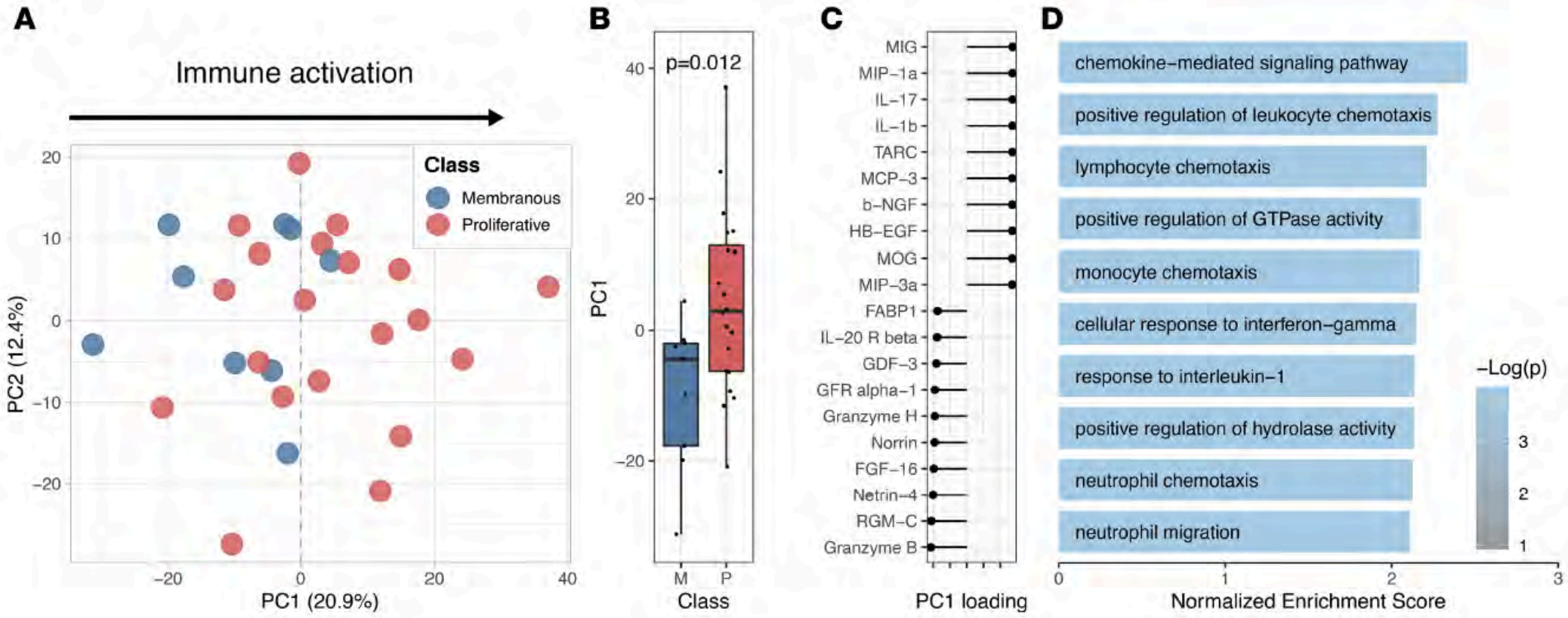
Der, E. et al. *Nat Immunol* **20,** 915–927 (2019).

Personalized medicine through accesible tissue single cell approach



Der, E. et al. *Nat Immunol* **20,** 915–927 (2019).

Proteomics analysis in urine leads to stratification of SLE patients according to kidney damage



Fava a. et al, *JCI Insight*. 2020;5(12):e138345

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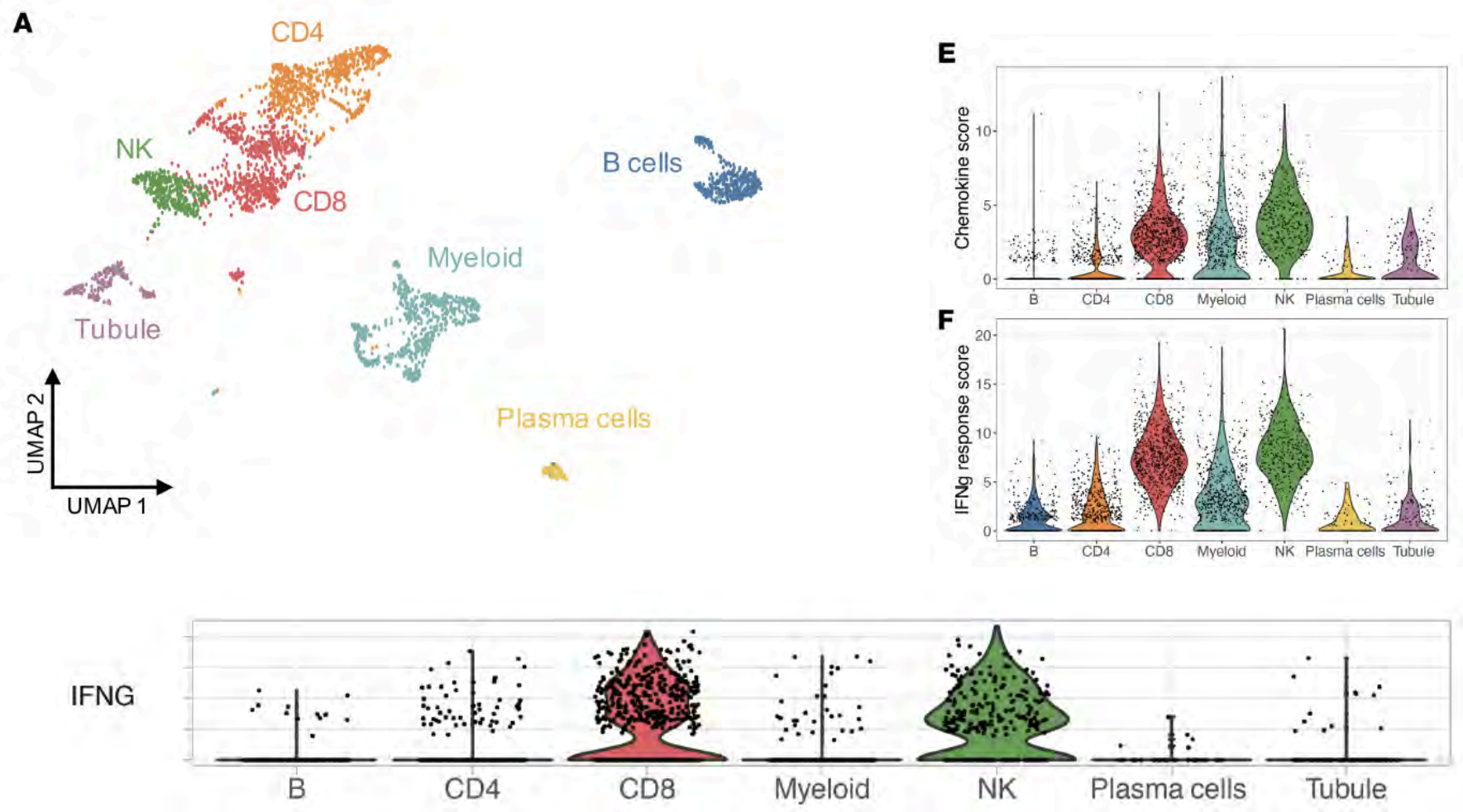

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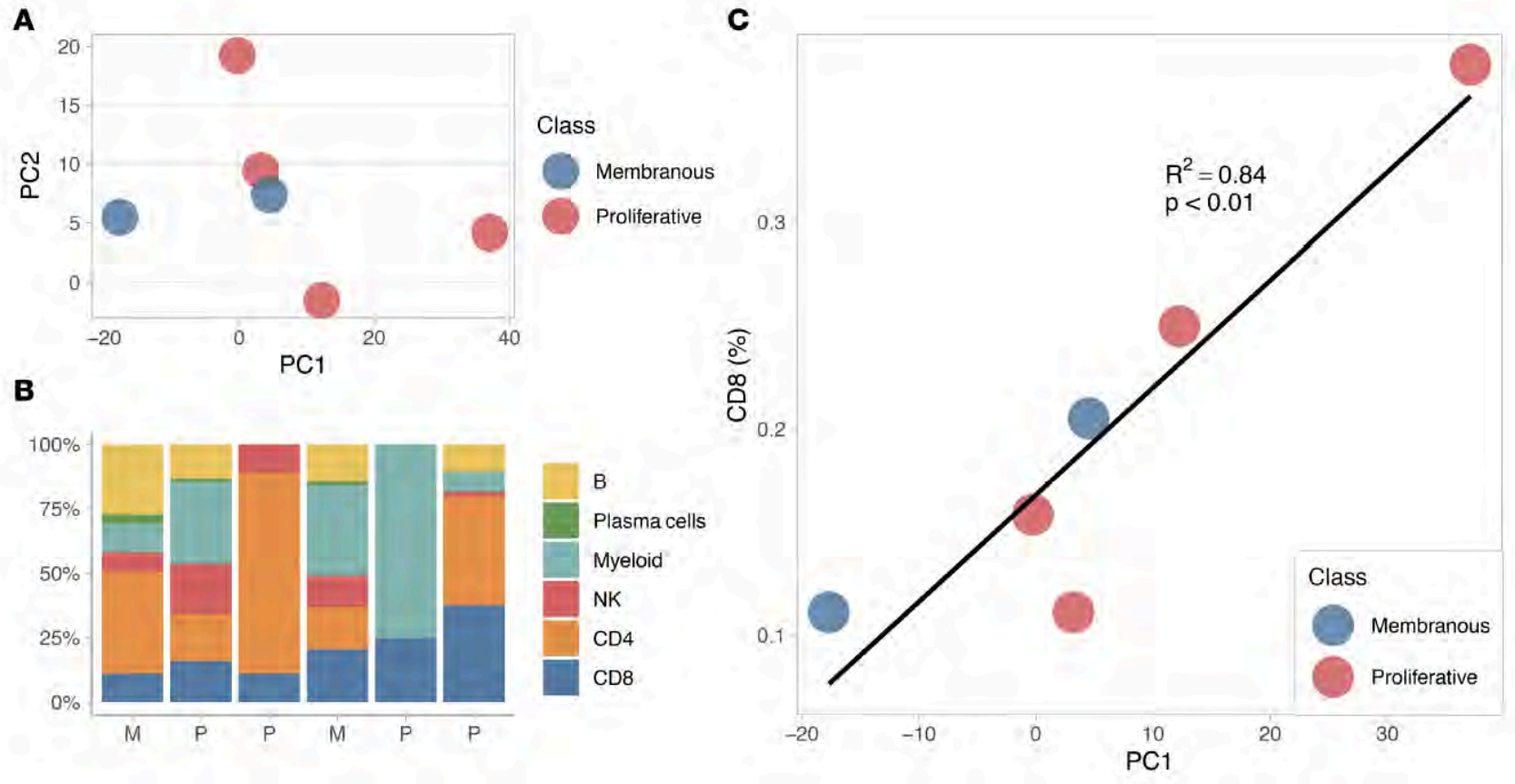

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Take-home messages

- Systems Medicine initiates a new era in Rheumatology, providing novel tools in clinical practice
- Pathophysiological mechanisms, previously unknown are elucidated though –omics
- Genetic basis of each disease is seen through a new lens
- Single cell studies are conquering almost all rheumatic diseases from various aspects
- Personalized medicine is based solely on systems approach
- Future studies will analyze spatial cell characteristics of causal and inflemed tissues

THANK YOU