PABLO COTO SEGURA

DERMATOLOGÍA. HOSPITAL VITAL ÁLVAREZ-BUYLLA (MIERES)

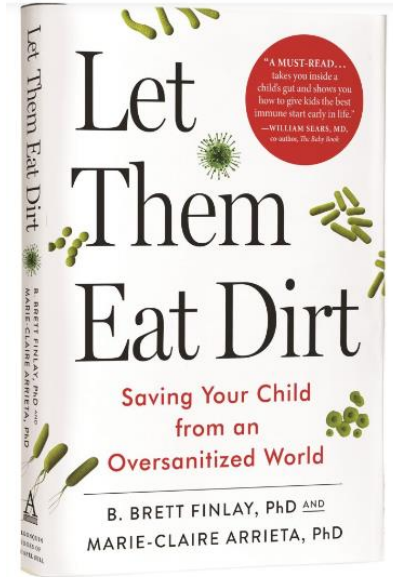
Perlas en investigación traslacional

- Butler, D. Translational research: Crossing the valley of death. *Nature* **453**, 840–842 (2008). https://doi.org/10.1038/453840

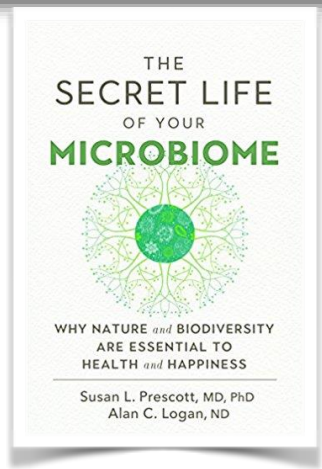
- ¿Tienen influencia la dieta en la Psoriasis?
- ¿Hay alguna relación entre mis problemas intestinales y mi dermatitis atópica?
- ¿me merece la pena tomar probióticos?


The Economist
The Catholic church's unholy mess
Paul Ryan: the man with the plan
Generation Xhausted
China, victim of the Olympics?
On the origin of specie
Microbes maketh man
How 90% of the cells in your body are bacteria, the benefits of faecal transplants and other things you would rather not know before breakfast

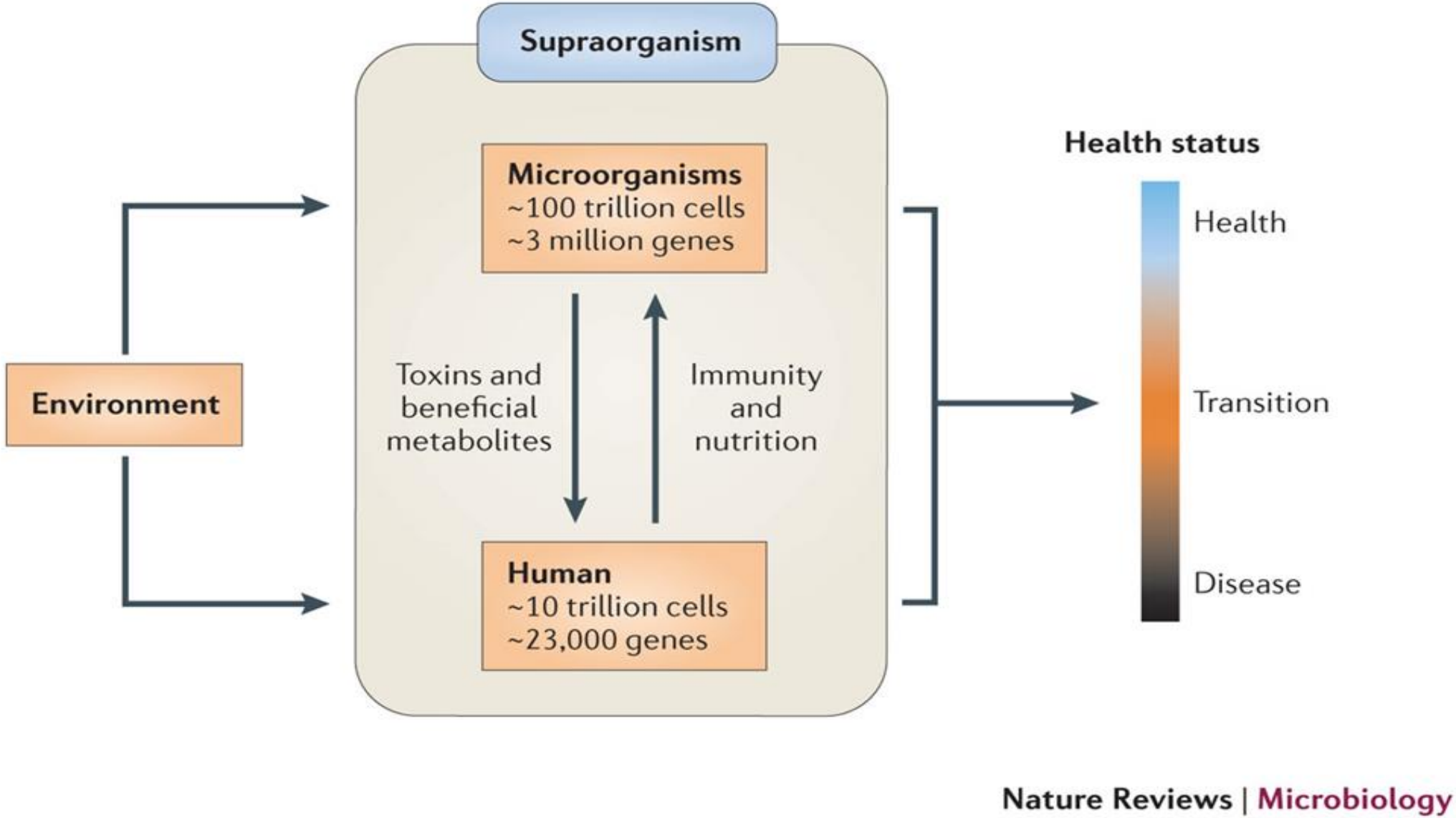

nature
QUANTUM COMPUTERS
Choosing the hardware
SUPERCONDUCTORS
Going organic
NUCLEAR PROLIFERATION
Ban laser uranium enrichment?
OUR OTHER GENOME
A gene catalogue of the human gut microbiome


Let Them Eat Dirt
"A MUST-READ... takes you inside a child's gut and shows you how to give kids the best immune start early in life."
—WILLIAM SEARS, MD, co-author, The Baby Book
Let Them Eat Dirt
Saving Your Child from an Oversanitized World
B. BRETT FINLAY, PhD AND MARIE-CLAIRE ARRIETA, PhD


nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
How early life shapes the infant gut microbiome and risk of disease
PAGES 583 & 589
SECURITY BLANKET
SPACE
REACHING FOR THE MOON
Plans for a permanent lunar base gather momentum
PAGE 474
NEUTRINO PHYSICS
THE HEART OF THE SUN
Neutrino detector probes solar nuclear reactions
PAGES 496 & 505
CAREERS
SATISFACTION IN SCIENCE?
Nature's salary survey takes the pulse of the workplace
PAGE 511
NATURE.COM

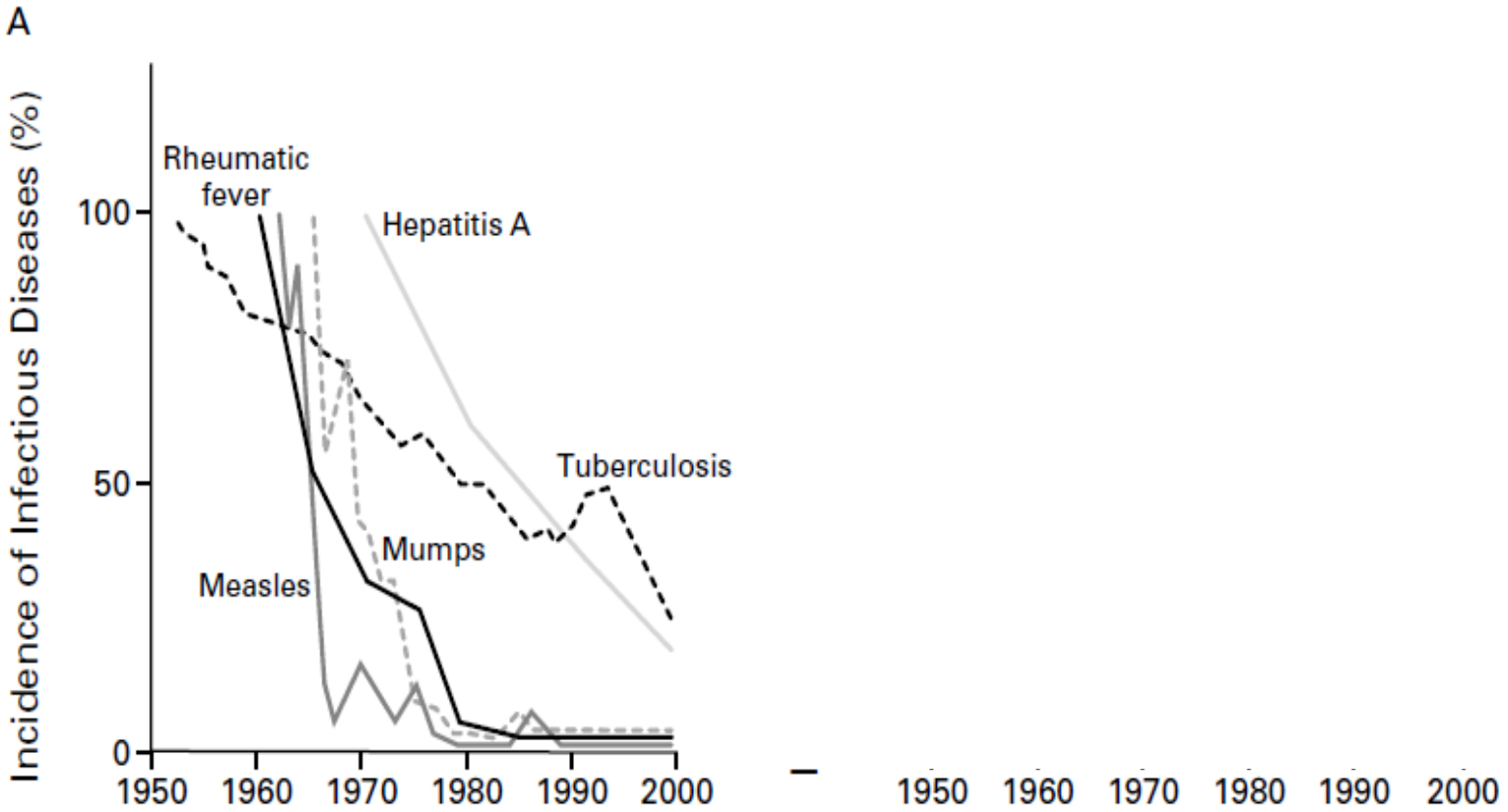

THE SECRET LIFE OF YOUR MICROBIOME
WHY NATURE and BIODIVERSITY ARE ESSENTIAL TO HEALTH and HAPPINESS
Susan L. Prescott, MD, PhD
Alan C. Logan, ND


nature
FELLOW TRAVELLERS



Nature Reviews Microbiology 11, 639–647 2013

Enfermedades infecciosas vs autoinmunes



Bach. NEJM 2002; 347: 911.

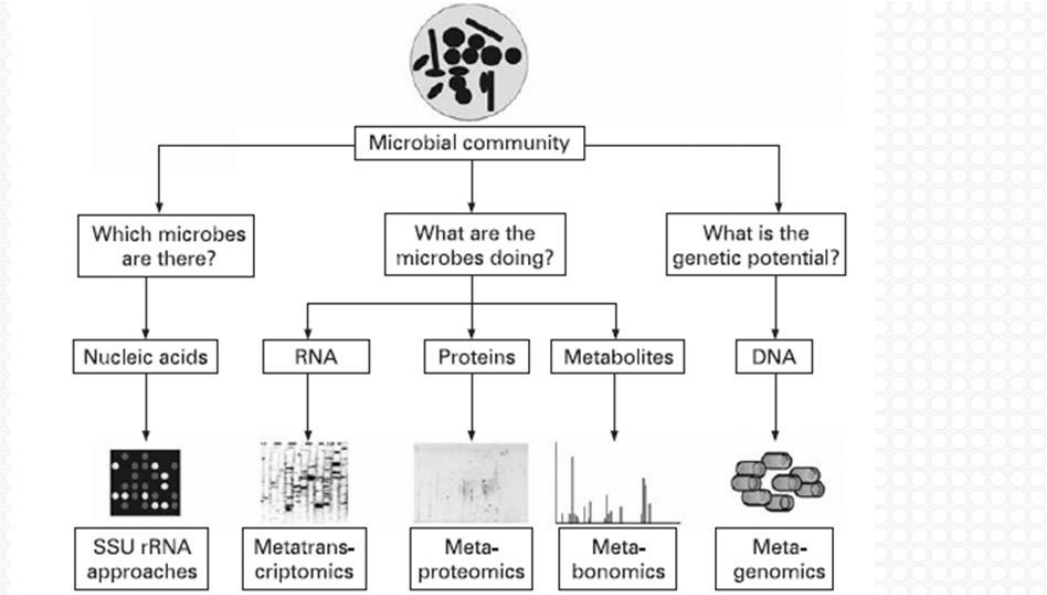
GENERAL DERMATOLOGY

BJD
British Journal of Dermatology

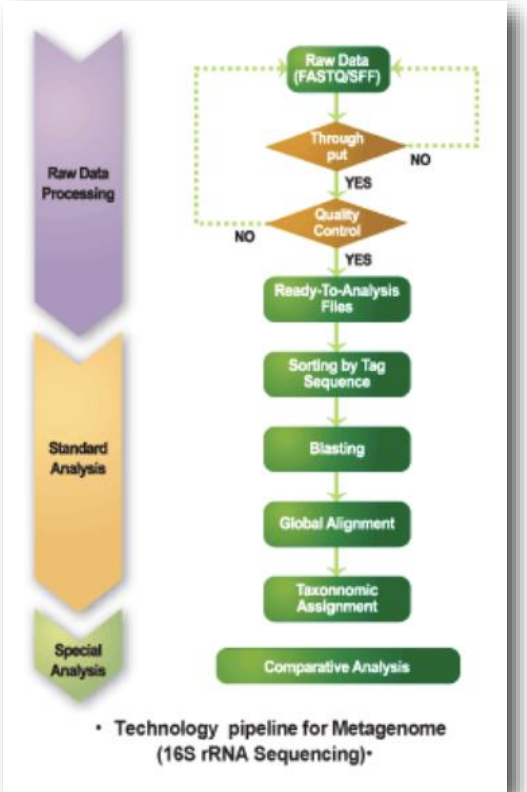
Gut microbiota dysbiosis in a cohort of patients with psoriasis

C. Hidalgo-Cantabrana,[1] J. Gómez,[2] S. Delgado,[1] S. Requena-López,[3] R. Queiro-Silva,[4] A. Margolles,[1] E. Coto,[2] B. Sánchez[1] and P. Coto-Segura[5]

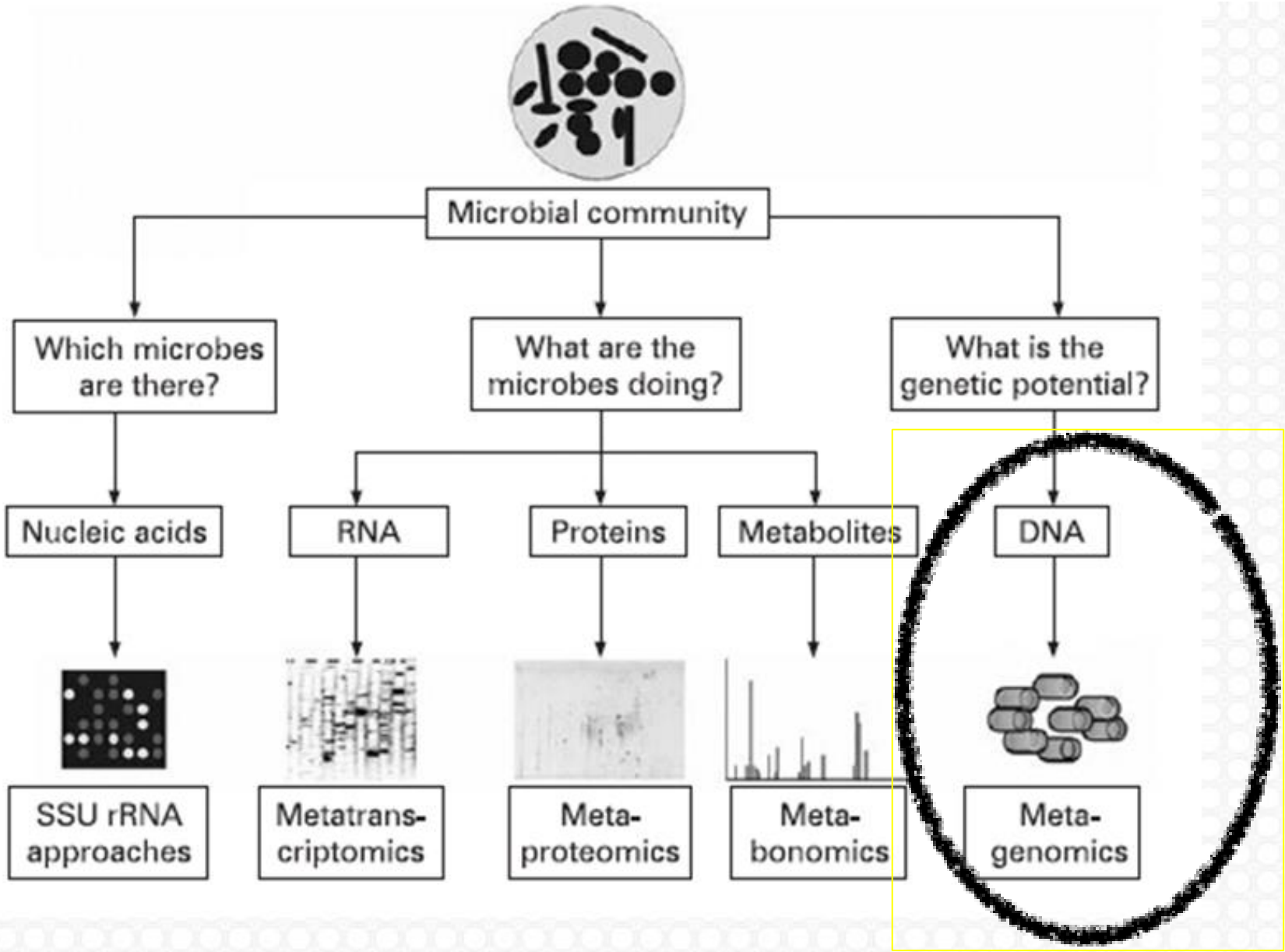
HIPÓTESIS: una disbiosis en la microbiota intestinal puede tener un papel en el desarrollo de la enfermedad psoriásica y desencadenar una respuesta inflamatoria aberrante que puede estar conectada con la piel.



Zoetendal, Gut 2008



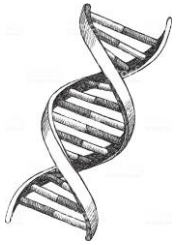
• Technology pipeline for Metagenome (16S rRNA Sequencing)•



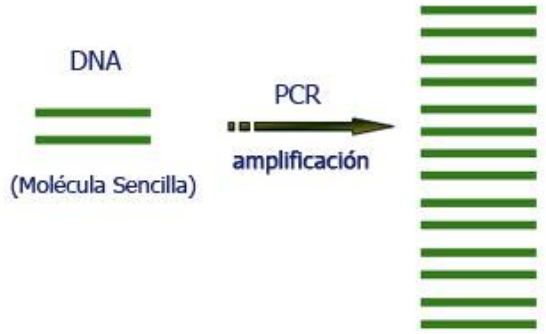
Zoetendal, Gut 2008

Workflow análisis metagenómico

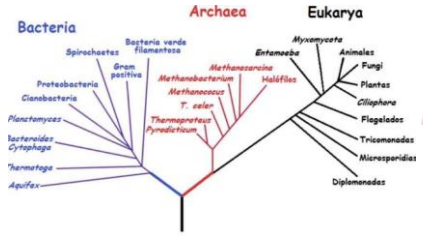
Obtención de la muestra (10 gr suficiente!!!)



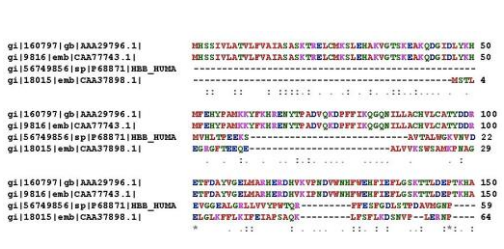
Extracción del DNA



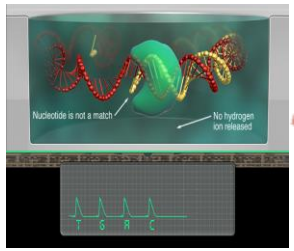
Amplificación del DNA 16 s



Corrección de errores
Comparación secuencias
Trazado árbol filogenético



Análisis bioinformático de la secuencia de datos con Qiime2 y SILVA database

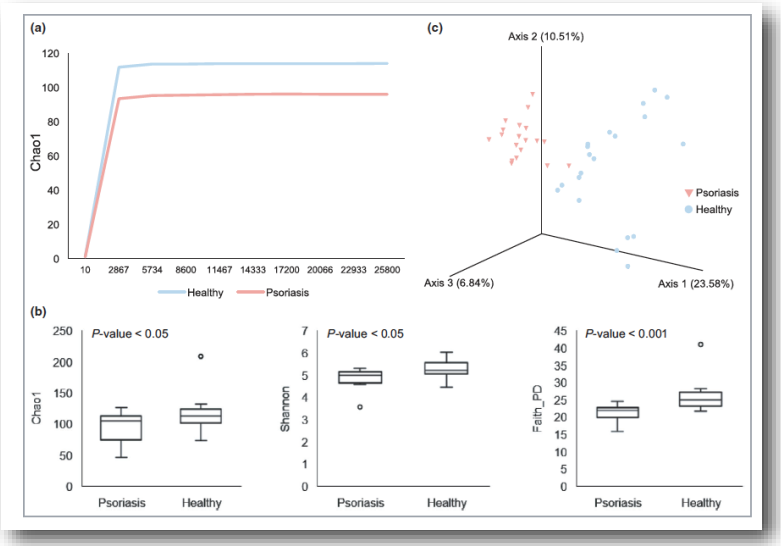


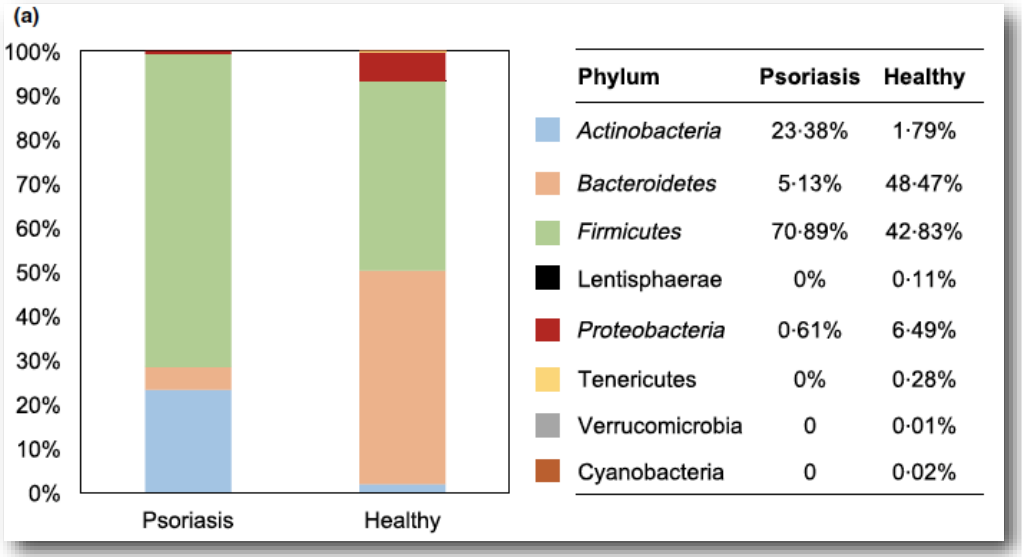
Secuenciación del amplicon Ion Torrent
Single end reads

GENERAL DERMATOLOGY

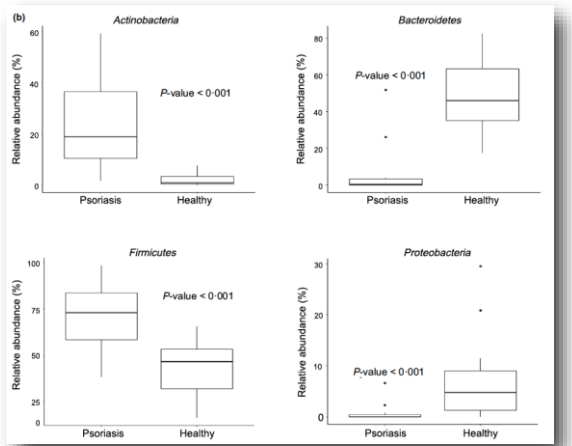
BJD
British Journal of Dermatology

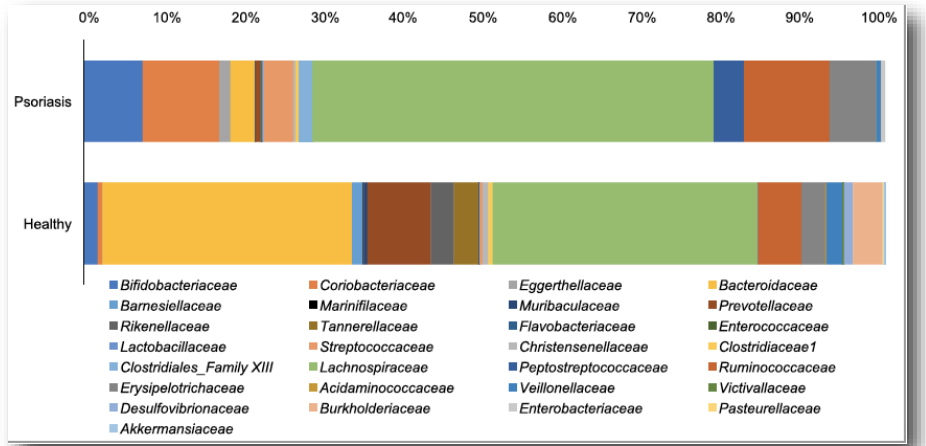
Gut microbiota dysbiosis in a cohort of patients with psoriasis





Phylum	Psoriasis	Healthy
Actinobacteria	23·38%	1·79%
Bacteroidetes	5·13%	48·47%
Firmicutes	70·89%	42·83%
Lentisphaerae	0%	0·11%
Proteobacteria	0·61%	6·49%
Tenericutes	0%	0·28%
Verrucomicrobia	0	0·01%
Cyanobacteria	0	0·02%





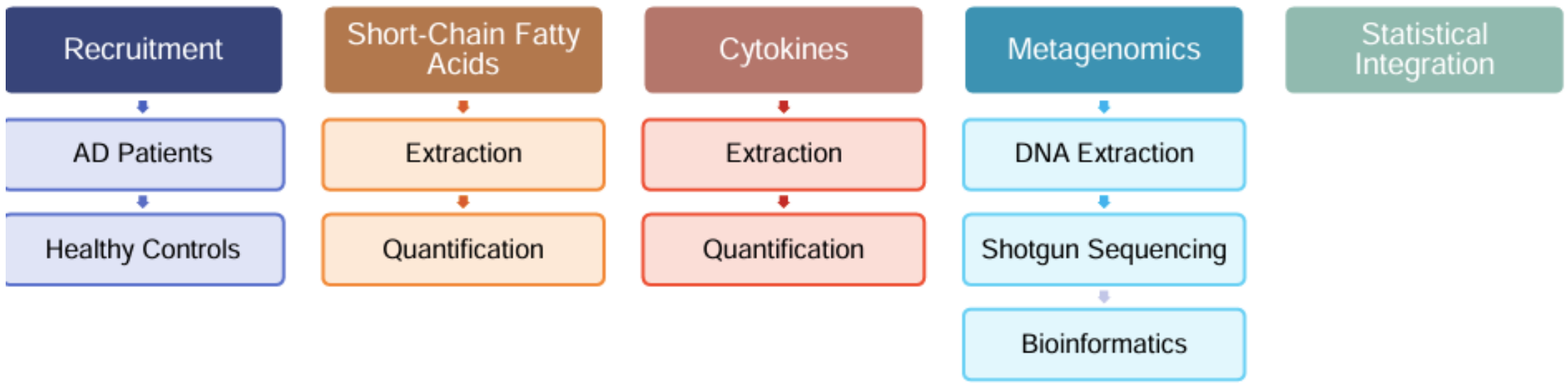

¿Y qué más?

Study of Intestinal Microbiota in Patients with Atopic Dermatitis

General Objetives

1. To analyze the **gut microbiota composition** of patients with atopic dermatitis, from a stool sample, through shotgun sequencing and bioinformatic analysis, comparing it with a healthy control group of similar gender and age distribution.

2. To study the **functional profile of the gut microbiota** of patients with atopic dermatitis from the metagenomes obtained by shotgun sequencing the fecal microbiota (objective 1), by identifying microbial metabolic pathways and comparing them with healthy individuals.


Recruitment
AD Patients
Healthy Controls
Short-Chain Fatty Acids
Extraction
Quantification
Cytokines
Extraction
Quantification
Metagenomics
DNA Extraction
Shotgun Sequencing
Bioinformatics
Statistical Integration

Metagenomic Analysis

DNA Extraction

- QIAamp® PowerFecal® Pro DNA Kit (Qiagen)

Sequencing

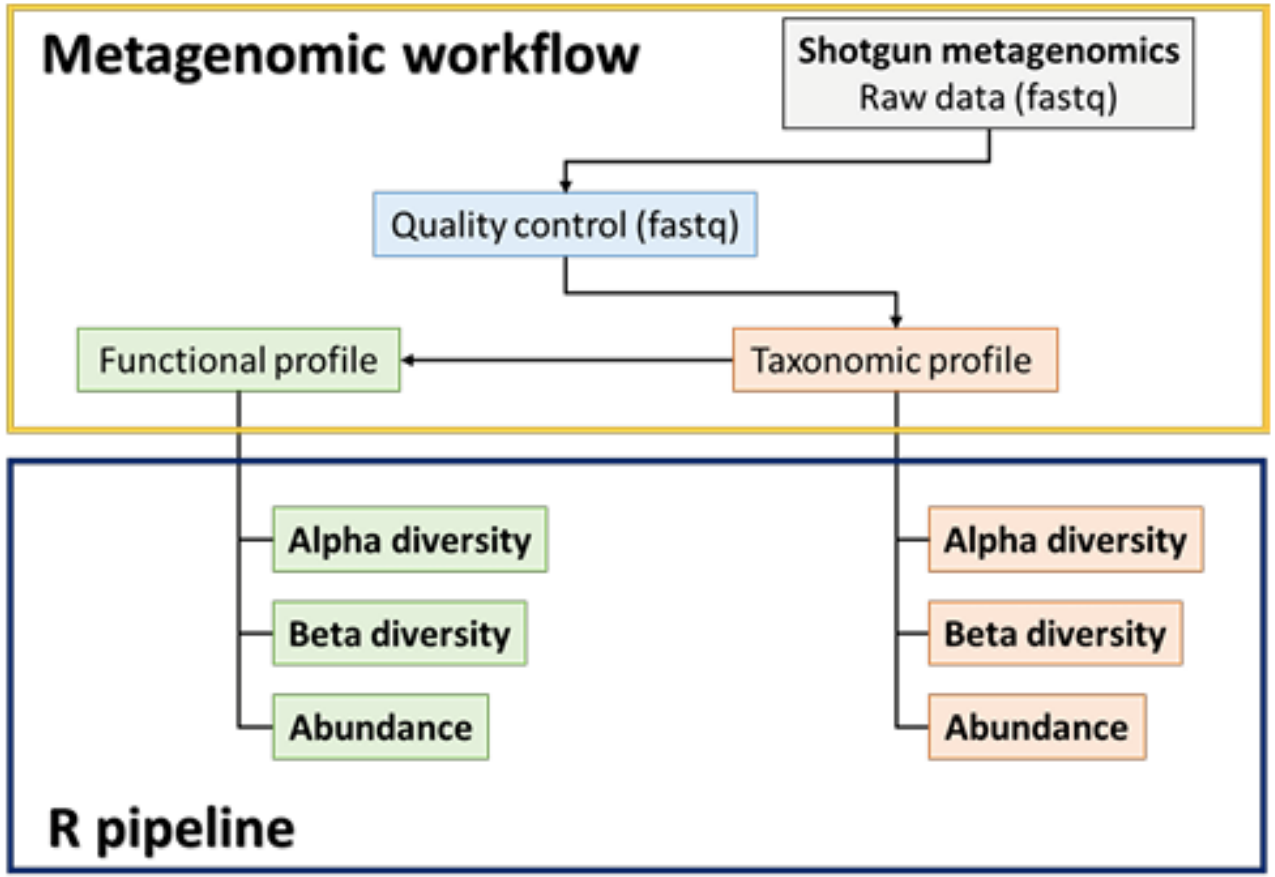
- Illumina
- Shotgun metagenomics:

  150 pb paired end

  20 Million reads per size

Bioinformatic Analysis

- Quality control and filtering
- Taxonomic assignment
- Functional assignment
- Statistical analysis



References
Blanco-Míguez et al. 2023 Nat Biotechnol. doi: 10.1038/s41587-023-01688-w

Shotgun sequencing steps

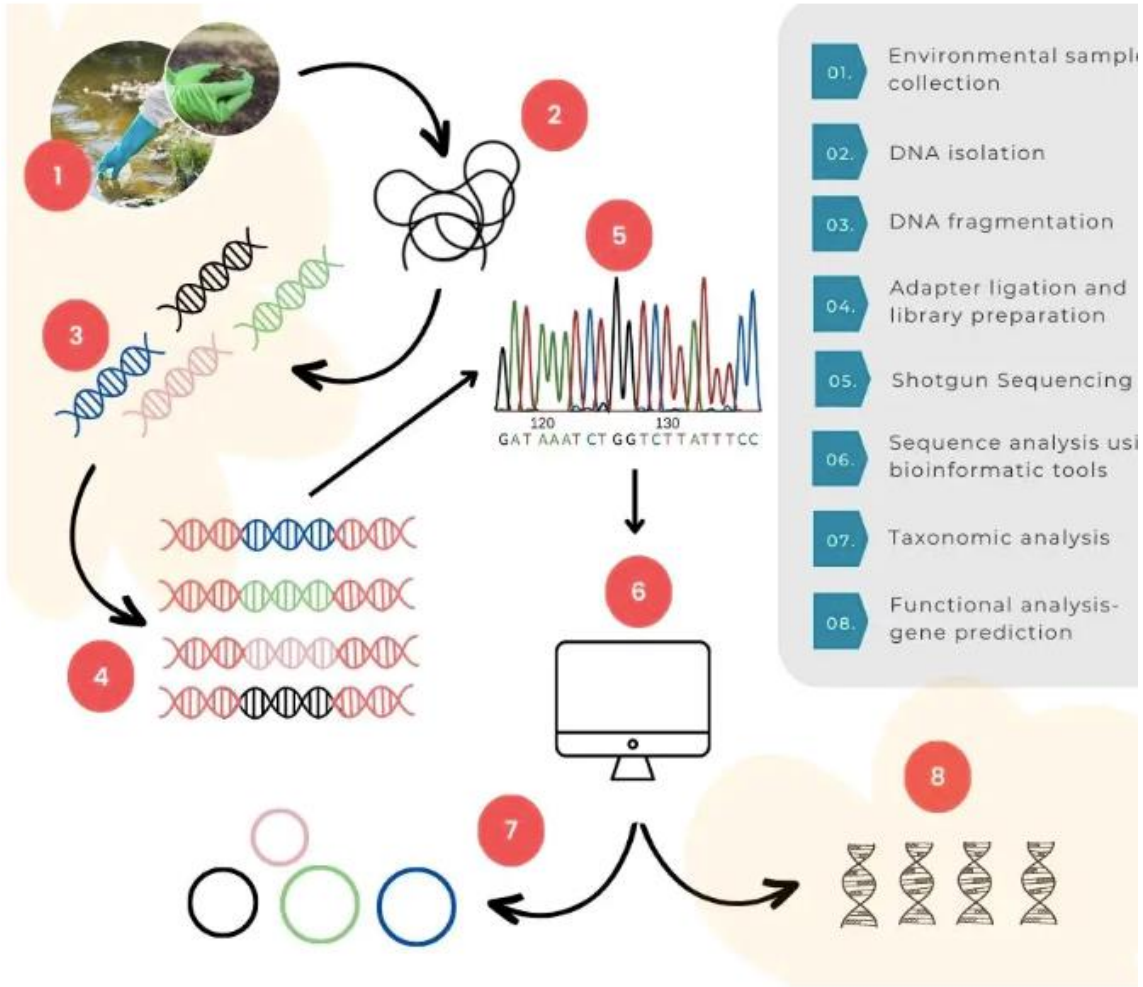
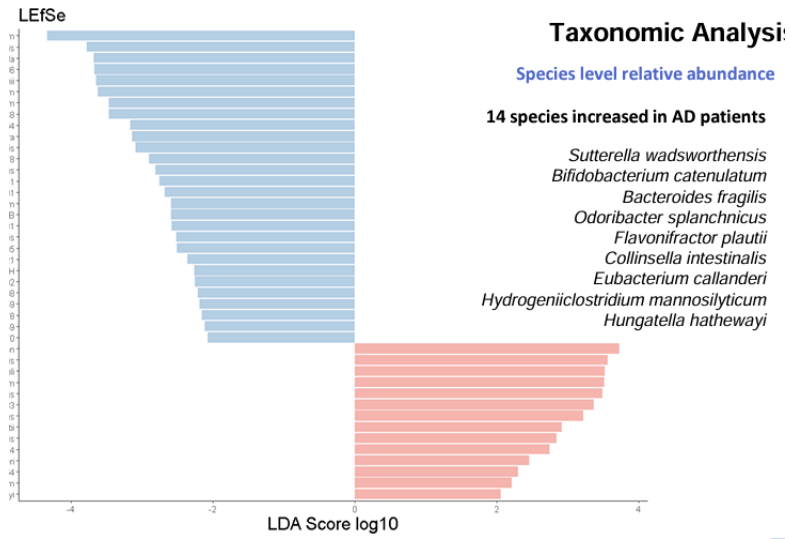
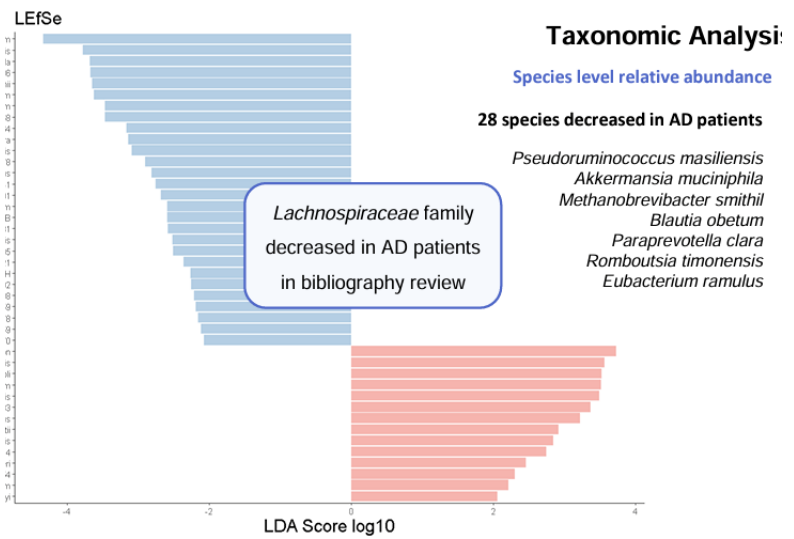
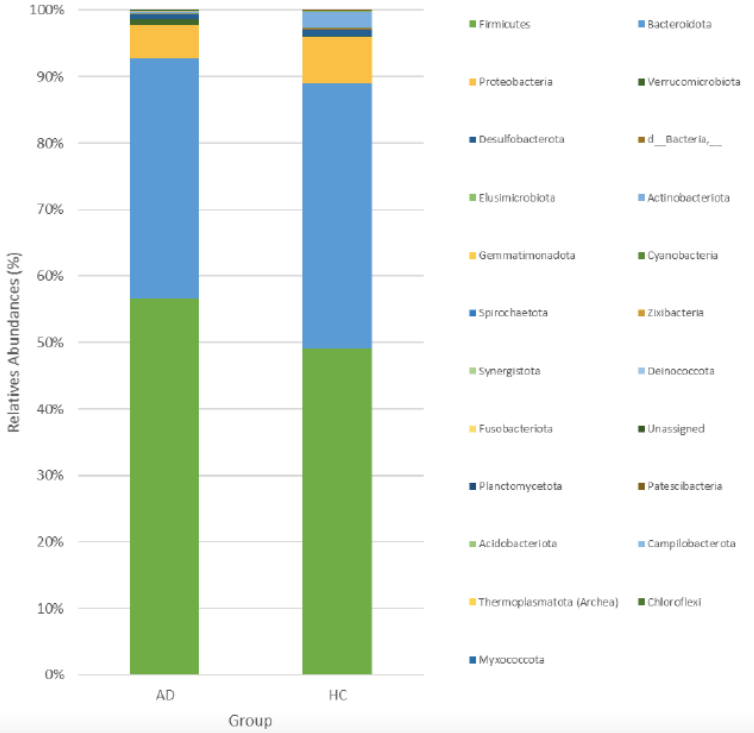
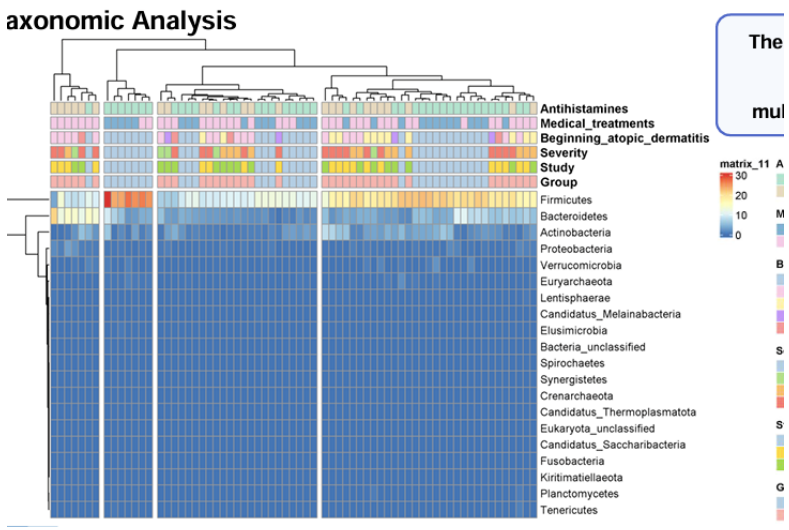


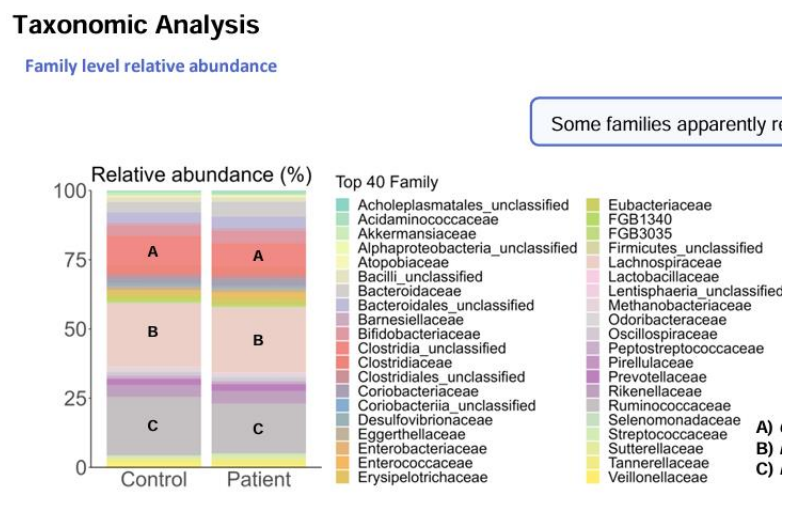
Illustration of the general scheme of shotgun sequencing for metagenomic analysis.



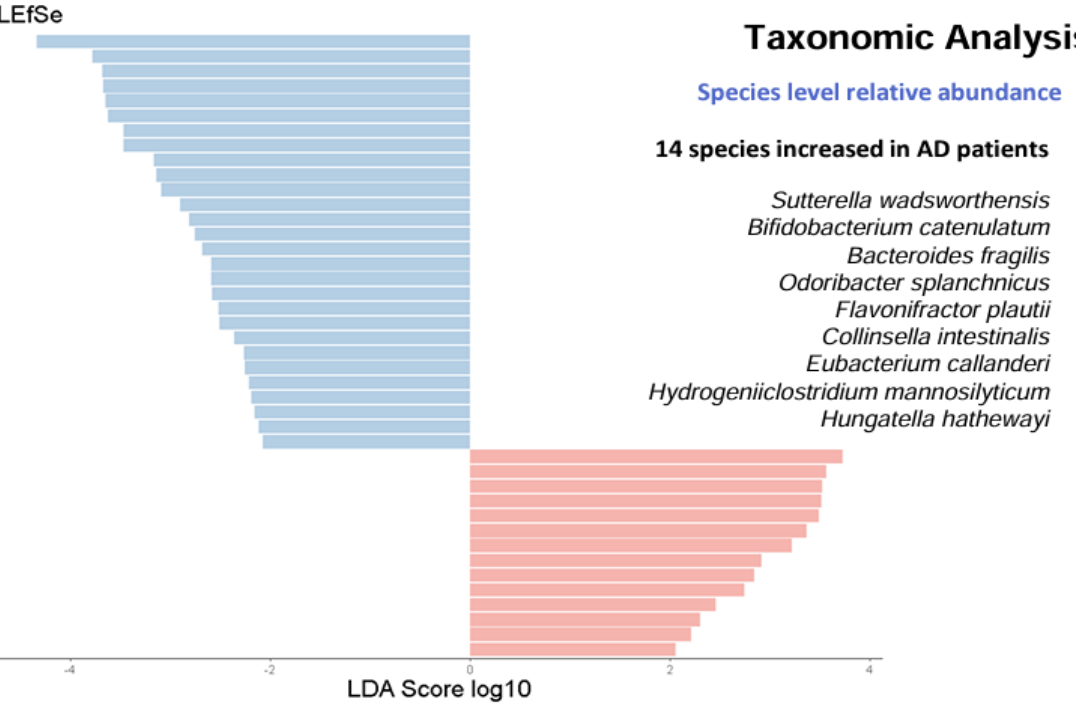


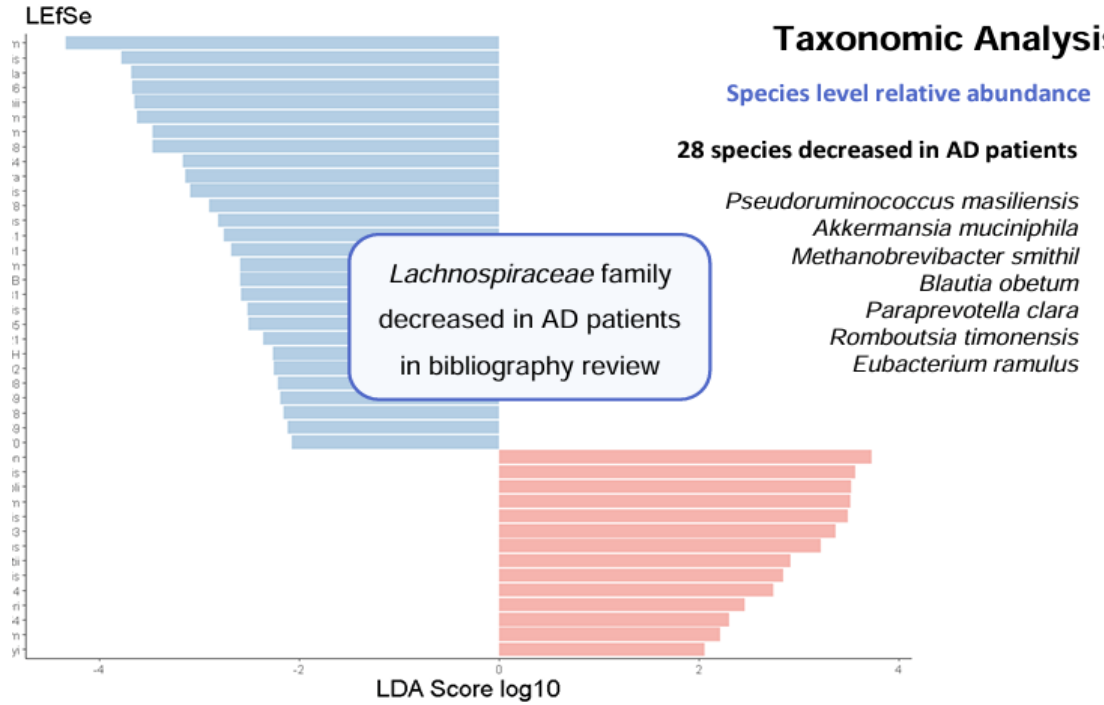


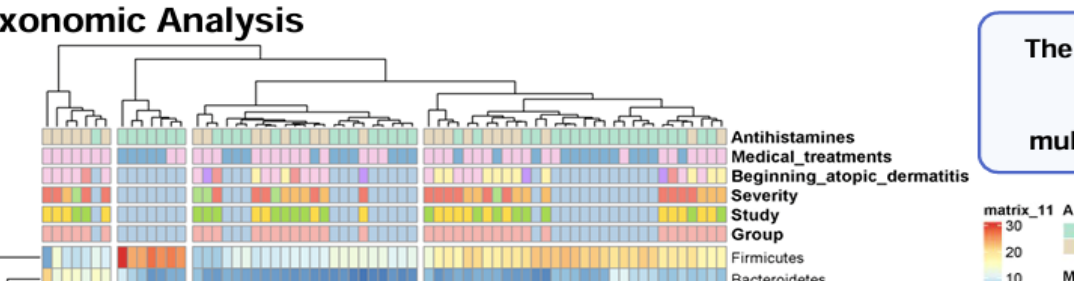


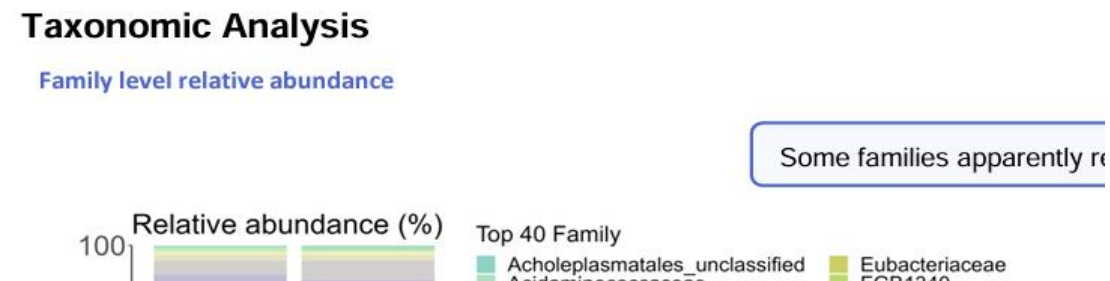


Análisis taxonómico


LEfSe
Taxonomic Analysis
Species level relative abundance
14 species increased in AD patients
Sutterella wadsworthensis
Bifidobacterium catenulatum
Bacteroides fragilis
Odoribacter splanchnicus
Flavonifractor plautii
Collinsella intestinalis
Eubacterium callanderi
Hydrogeniiclostridium mannosilyticum
Hungatella hathewayi
-4
-2
0
2
4
LDA Score log10


LEfSe
Taxonomic Analysis
Species level relative abundance
28 species decreased in AD patients
Pseudoruminococcus masiliensis
Akkermansia muciniphila
Methanobrevibacter smithil
Blautia obetum
Paraprevotella clara
Romboutsia timonensis
Eubacterium ramulus
Lachnospiraceae family
decreased in AD patients
in bibliography review
-4
-2
0
2
4
LDA Score log10


xonomic Analysis
The
mul
Antihistamines
Medical_treatments
Beginning_atopic_dermatitis
Severity
Study
Group
Firmicutes
matrix_11
30
20

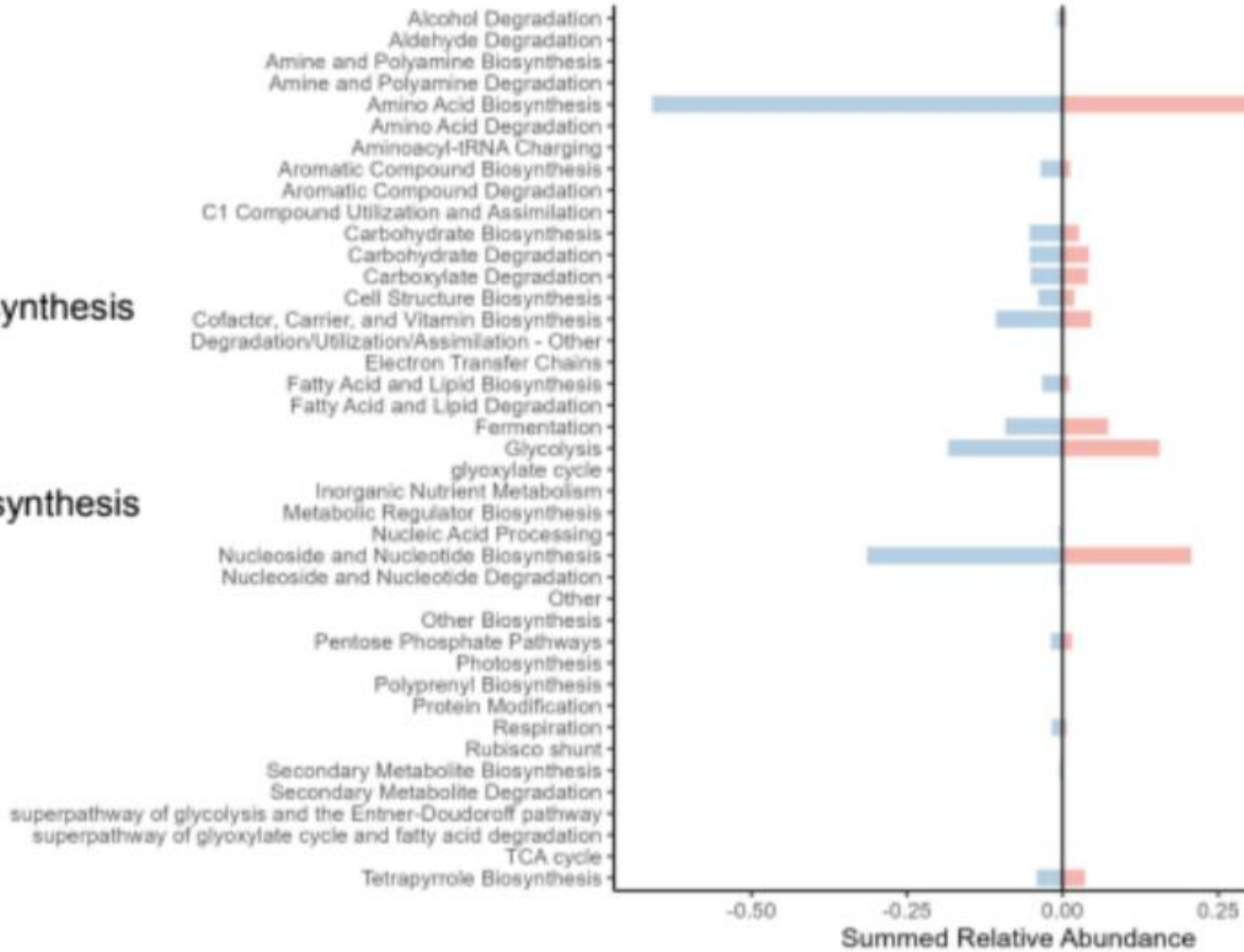

Taxonomic Analysis
Family level relative abundance
Some families apparently r
Relative abundance (%)
100
Top 40 Family
Acholeplasmatales_unclassified
Eubacteriaceae

Functional Analysis

Metabolic pathways abundance

Decreased in AD patients

- Amino acids biosynthesis
- Cofactor, carrier and vitamin biosynthesis
- Fatty acid and lipid biosynthesis
- Energy metabolism
  - Nucleotide and nucleoside biosynthesis
  - Glycolysis
  - Fermentation



Conclusions

- The quantification of short-chain fatty acids and cytokines in fecal samples did not show significant differences between atopic dermatitis patients and healthy individuals.
- The patients with AD showed a lower number of OTUs detected, implying a lower bacterial diversity both in richness and in homogeneity.
- The bacterial families *Methanobacteriaceae*, *Ruminococcaceae*, *Lachnospiraceae*, and *Akkermansiaceae* are significantly decreased in AD patients.
- Several metabolic pathways are decreased in AD patients, including amino acid biosynthesis, cofactor, carrier and vitamin biosynthesis, fatty acids and lipids biosynthesis, and energy metabolism.
- This study lays the groundwork for more comprehensive studies providing one of the first taxonomic and functional metagenomic analysis on fecal microbiota in atopic dermatitis in adults.

Future perspectives

- Possible **targets for microbiome modulation**

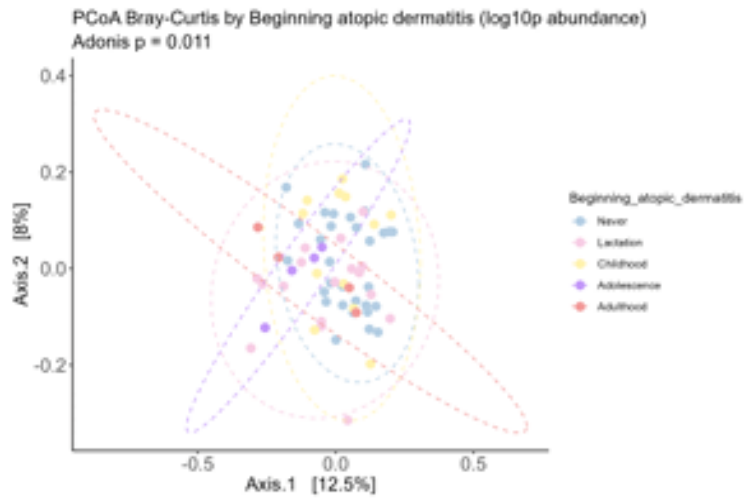
Bacterial populations

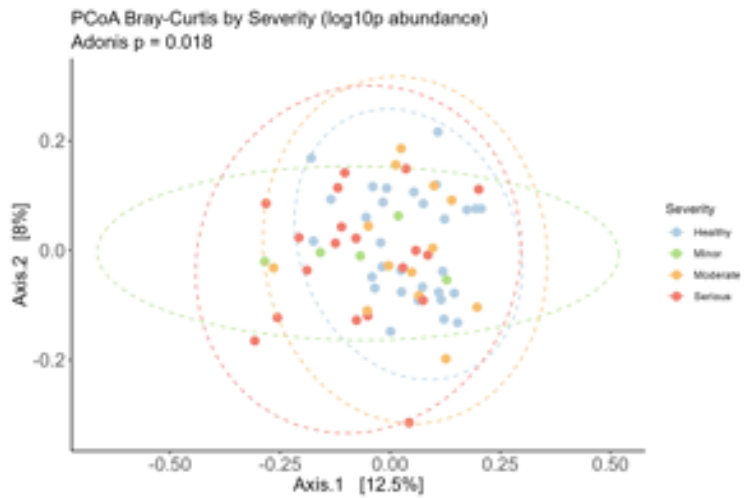
- *Methanobacteriaceae*
- *Ruminococcaceae*
- *Lachnospiraceae*
- *Akkermansiaceae*

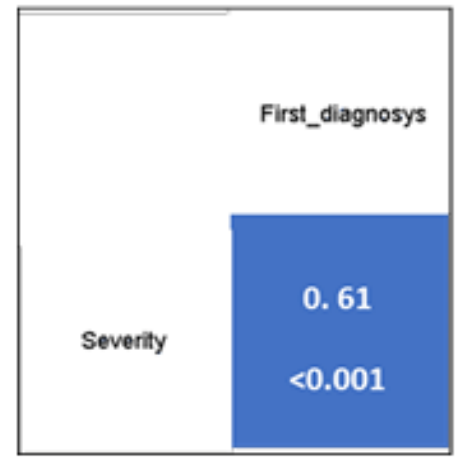
Metabolic routes

- Amino acid biosynthesis
- Vitamin biosynthesis
- Lipid biosynthesis
- Energy metabolism

- **Diagnosis during lactation** is related with changes in the microbiome respect to controls, but also with the seve the disease, which makes it an **interesting target population**







- **Early monitoring and modulation** of these bacterial features seems essential to fight against atopic dermatitis

Conclusions

- The quantification of short-chain fatty acids and cytokines in fecal samples did not show significant differences between atopic dermatitis patients and healthy individuals.
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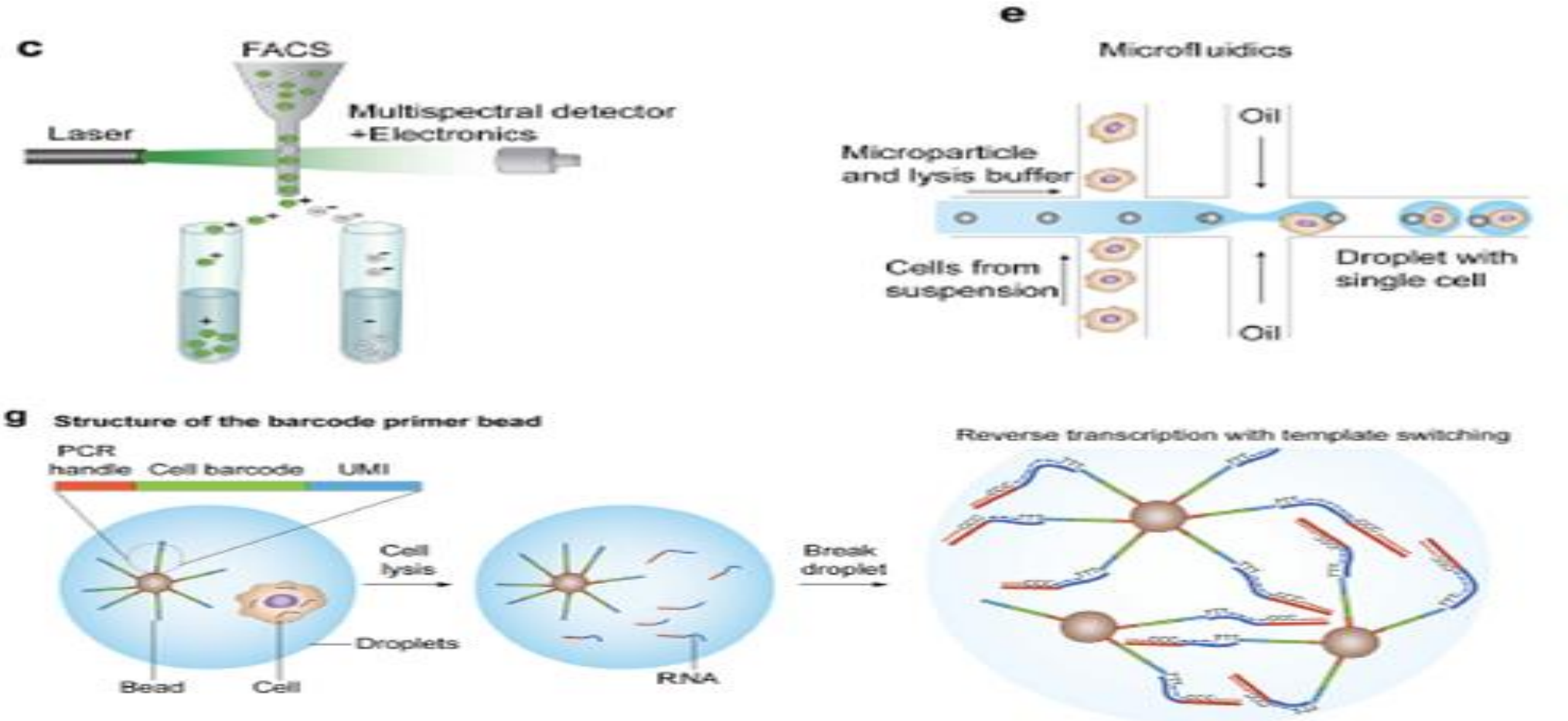
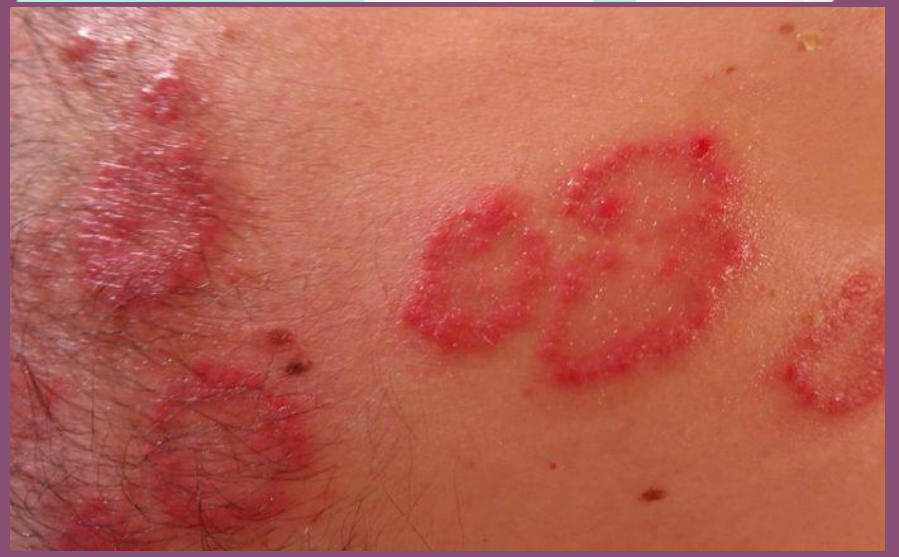


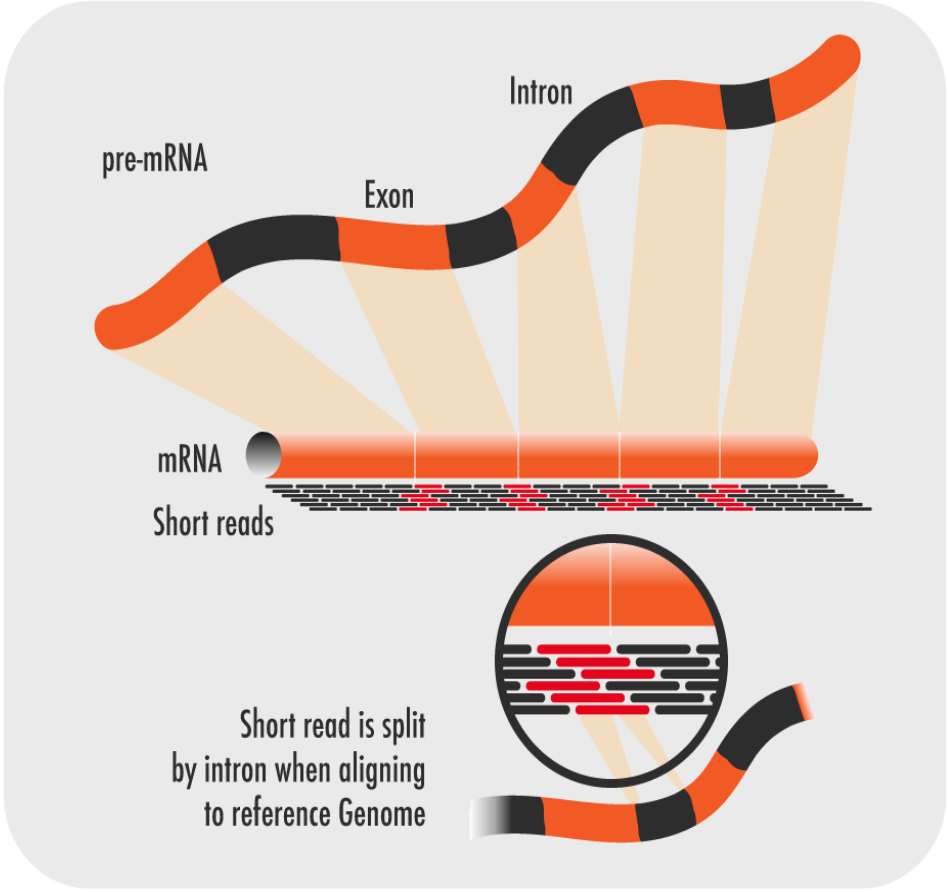
Hwang, B., Lee, J. H., & Bang, D. (2018). Single-cell RNA sequencing technologies and bioinformatics pipelines. *Experimental & molecular medicine*, *50*(8), 1-14. (editado)

- ¿Qué zona de la placa tiene potencial para iniciar todo el proceso inflamatorio?



¿Qué es el RNAseq?

- RNA-seq :observación de transcritos resultantes del empalme alternativo, modificación postranscripcional, fusiones génicas, mutaciones/SNPsy cambios de expresión de genes a lo largo del tiempo.
  - el proceso implica la obtención de RNA total, la RNA Seq puede ayudar a caracterizar poblaciones diferentes de RNA como miRNA, tRNA, y rRNA5 Esta tecnología, además, también puede servir para determinar las fronteras exón / intrón y verificar o enmendar regiones 5 'y 3'.
  - bioinformática asociada a las tecnologías NGS es por tanto una disciplina joven, y carente de estandarización a la hora de abordar un problema. Es por ello que es común que distintos investigadores programen cada uno su propia solución a una misma en la mayoría de casos, igual de válidas las distintas herramientas desarrolladas.

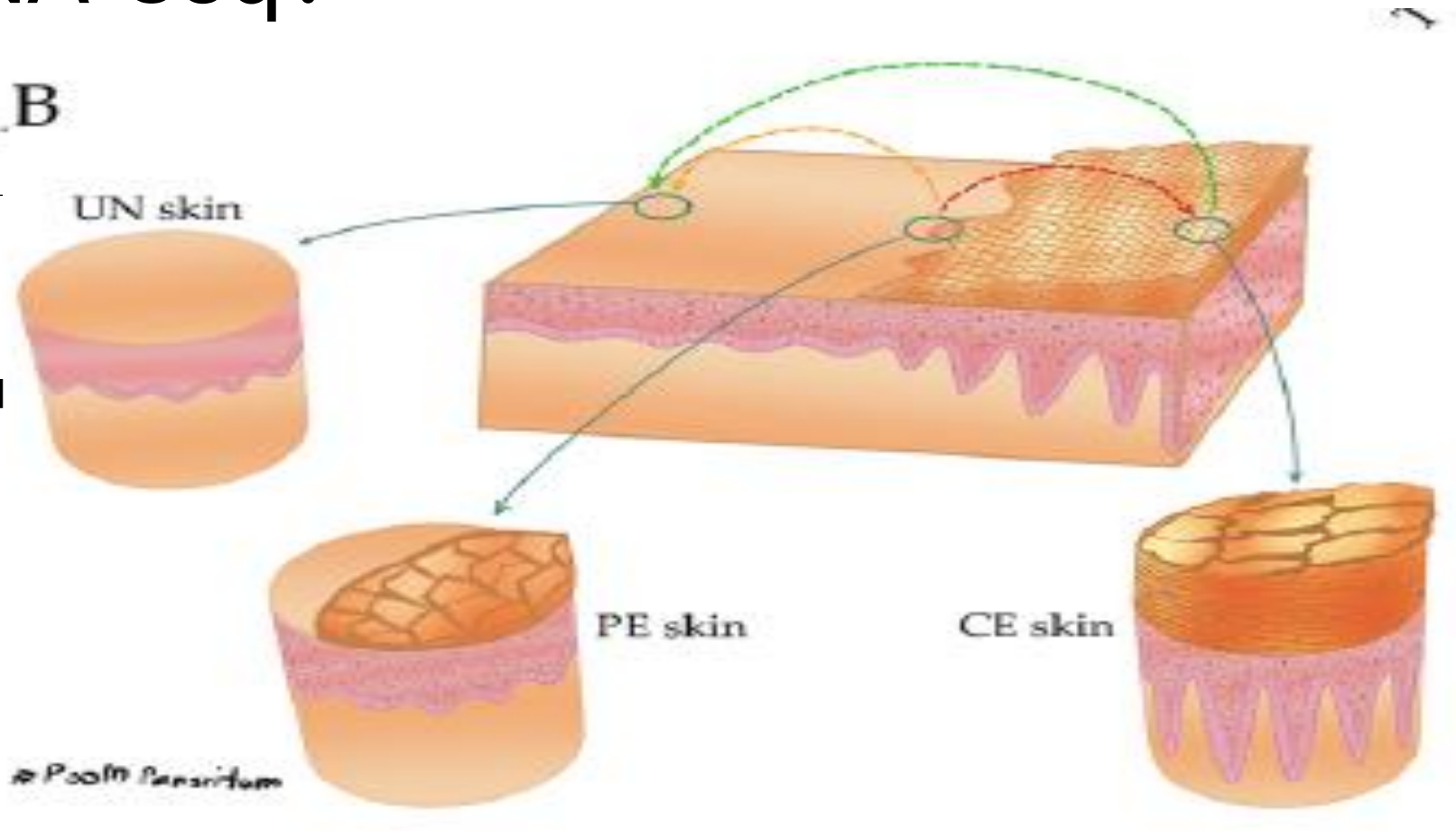


Hwang, B., Lee, J. H., & Bang, D. (2021). Author Correction: Single-cell RNA sequencing technologies and bioinformatics pipelines. *Experimental & molecular medicine*, *53*(5), 1005. https://doi.org/10.1038/s12276-021-

¿Qué es scRNA-seq?

- Tecnología que permite la disección de la expresión génica a la resolución de una sola célula.

- La aplicación Single-Cell RNA-Seq proporciona perfiles transcripcionales que permite comprender a nivel de una sola célula qué genes se expresan, en qué cantidades y cómo difieren los niveles de expresión entre las miles de células contenidas en una muestra



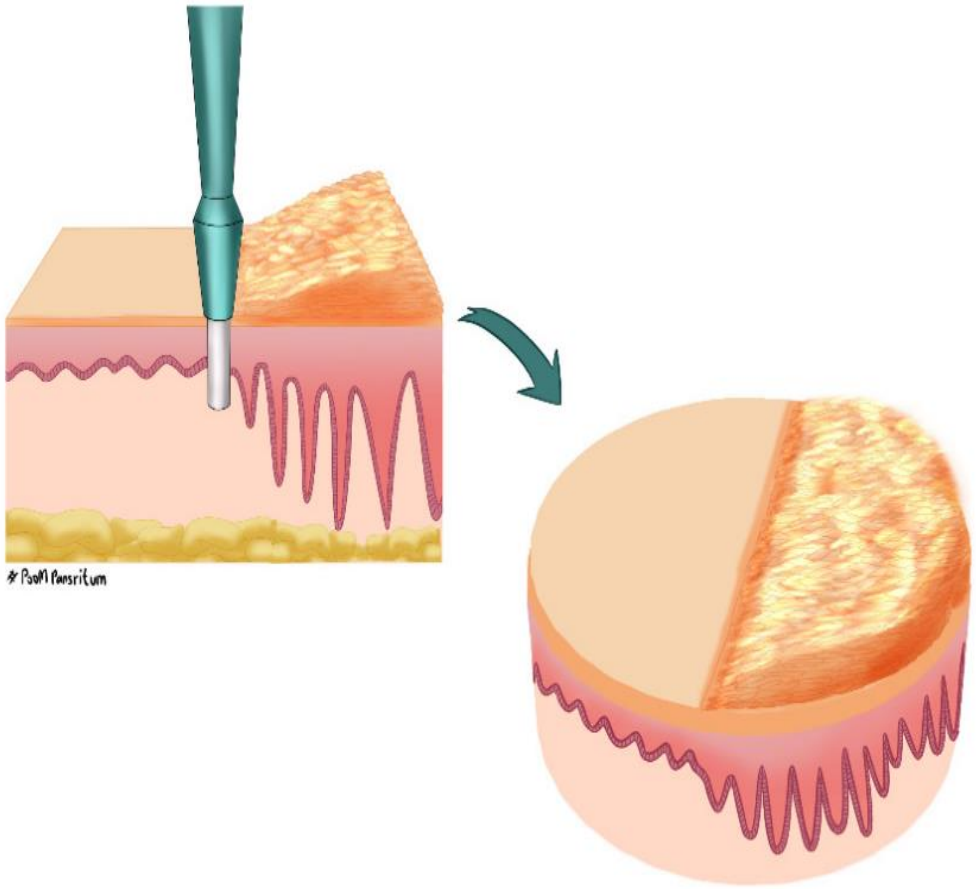
Ventajas RNA-seq

Superioridad frente a otras tecnologías, como la hibridacion de microarrays, para detector nuevas trancripciones

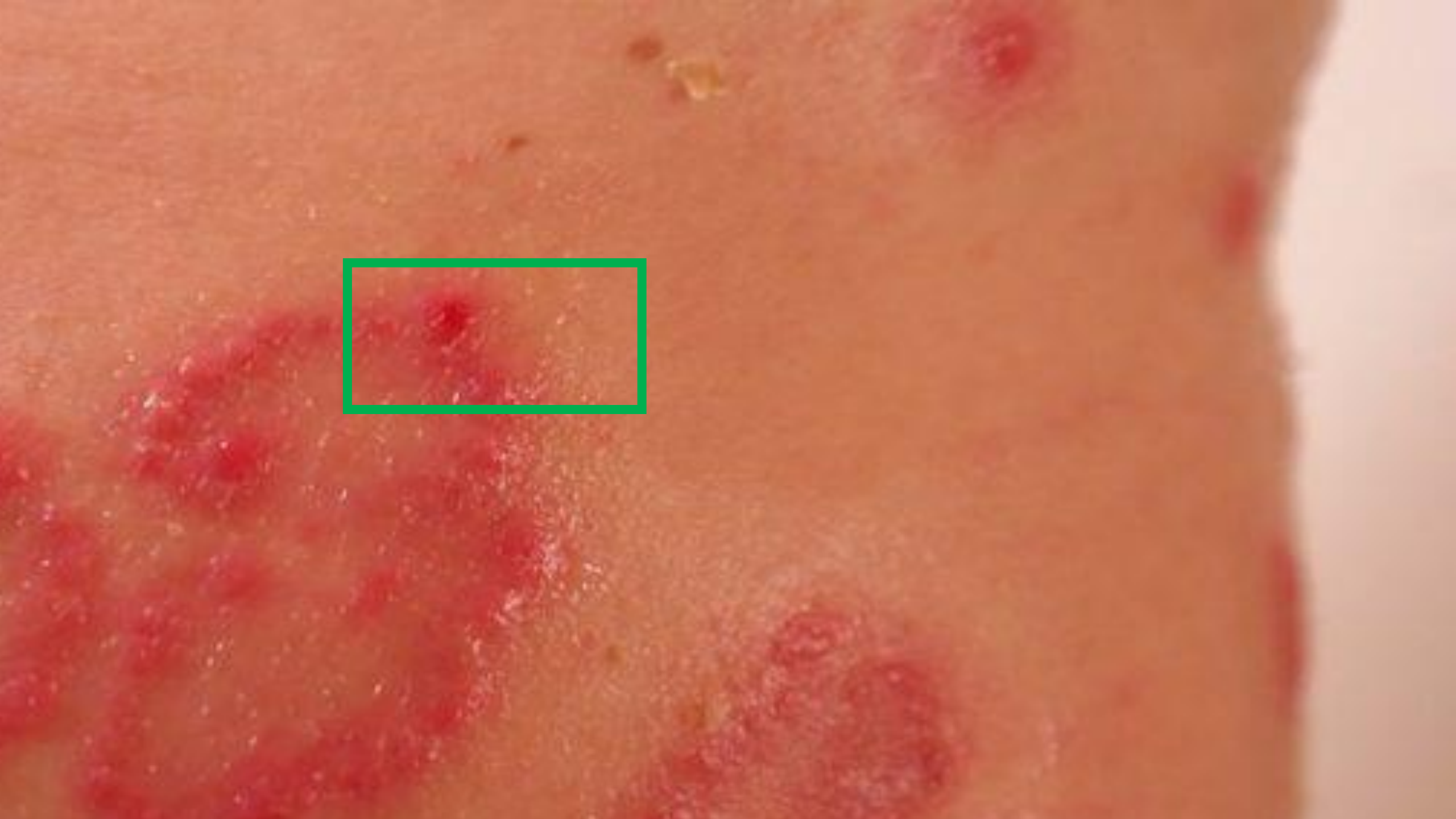
Elimina el ruido experimental, que si ocurre con la hibridación cruzada o subestándar en microarrays

No limitado a secuencias genómicas

Son cuantificables

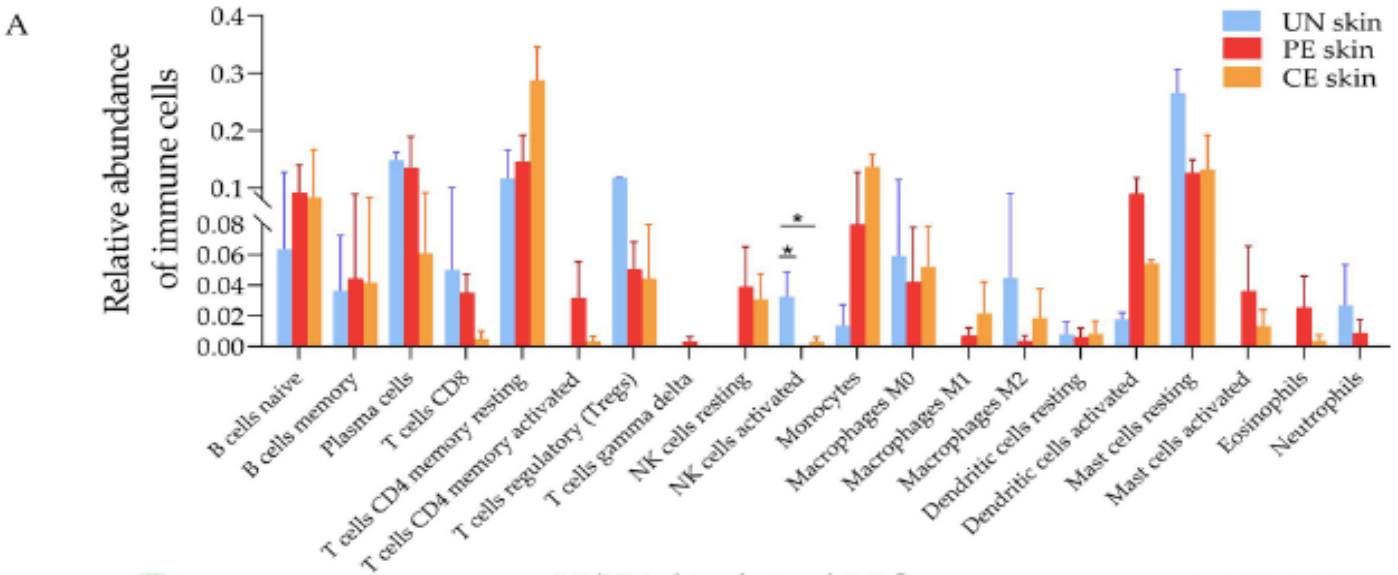


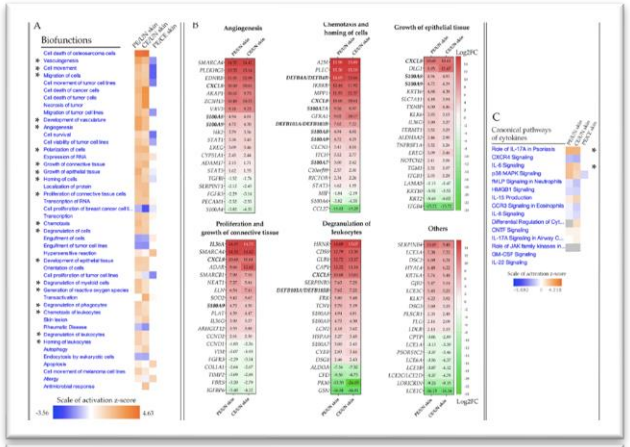
Hwang, B., Lee, J. H., & Bang, D. (2021). Author Correction: Single-cell RNA sequencing technologies and bioinformatics pipelines. *Experimental & molecular medicine*, *53*(5), 1005. https://doi.org/10.1038/s12276-021-



Las placas psoriásicas no son uniformes, por lo que resulta interesante examinar los perfiles de expresión génica de distintas zonas de las placas que aún no han sido completamente exploradas.

En 2021, se publicó la primera secuenciación de ARN unicelular (scRNA-seq) de piel psoriásica que reveló el perfil de expresión del ARNm de diferentes subconjuntos de células inmunitarias y las distintas capas de queratinocitos





Published in final edited form as:

J Allergy Clin Immunol. 2021 November ; 148(5): 1281–1292. doi:10.1016/j.jaci.2021.04.021.

Single-cell transcriptomics applied to emigrating cells from psoriasis elucidate pathogenic vs. regulatory immune cell subsets

Jaehwan Kim, MD, PhD[1,2,*], Jongmi Lee, MD, PhD[1], Hyun Je Kim, MD, PhD[3,4], Naoya Kameyama, PhD[3], Roya Nazarian, MD[2], Evan Der, PhD[5], Steven Cohen, MD, MPH[2], Emma Guttman-Yassky, MD, PhD[3], Chaim Putterman, MD[5,6,7], James G. Krueger, MD, PhD[1,*]

Kim, J., Lee, J., Kim, H. J., Kameyama, N., Nazarian, R., Der, E., Cohen, S., Guttman-Yassky, E., Putterman, C., & Krueger, J. G. (2021). Single-cell transcriptomics applied to emigrating cells from

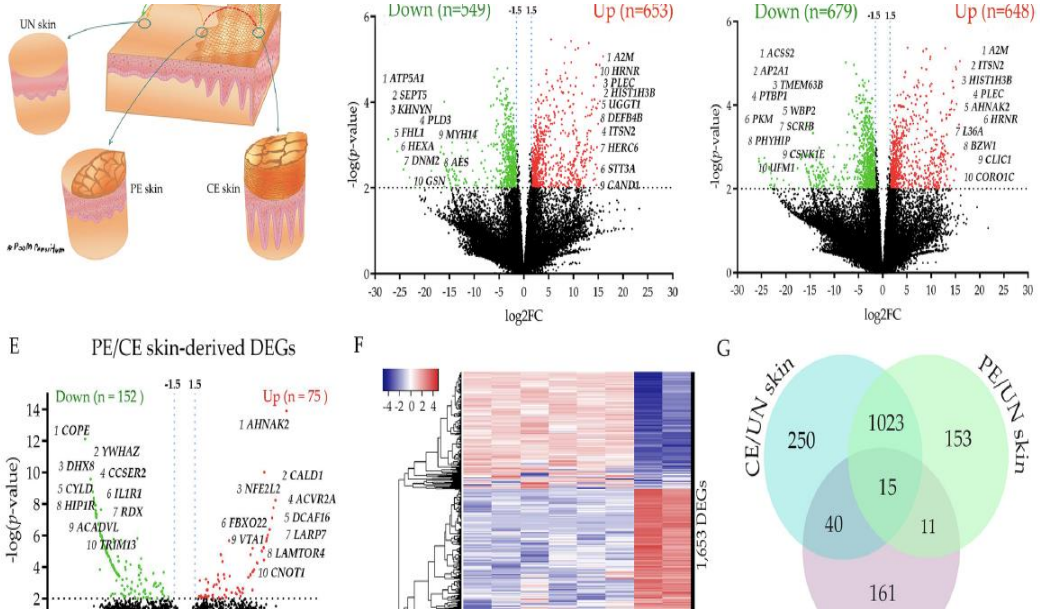
International Journal of
Molecular Sciences

MDPI

Article

Transcriptomic Profiling of Peripheral Edge of Lesions to Elucidate the Pathogenesis of Psoriasis Vulgaris

Suphagan Boonpethkaew [1], Jitlada Meephansan [1,*], Onjira Jumlongpim [1], Pattarin Tangtanatakul [2], Wipasiri Soonthornchai [3], Jongkonnee Wongpiyabovorn [4], Ratchanee Vipanurat [5] and Mayumi Komine [6]



In contrast, the largest subset of IL-17-producing T-cells isolated from psoriasis lesions are those that are IL-17F$^+$ IL-10$^-$. This population (presumptive IL-17F/F producers) constitutes 53% of T17 T-cells and is about 5-fold more frequent than cells co-producing IL-17A and IFN$_\gamma$. High expression of cytokines such as IL-1B, CSF-2, LTA, IL-24 and IL-34 likely identifies a different inflammatory potential from cells exposing IL-17A and IFN$_\gamma$. Interestingly, this subset has the highest expression of the IL-23 receptor, so it might be the most strongly affected by therapeutic IL-23 antagonists. Perhaps this subset also stems from inflammatory conversion of Tregs, as FoxP3 has the highest expression among all T17 cells. While a recent report found some human blood T-cells synthesized only IL-17F after culture in polarizing conditions[45], we believe this is the first report of a unique and

With our new single-cell approach, we found cutaneous T17 cell subsets with highly differing transcriptomes depending on IL-17A vs. IL-17F expression and IFN$_\gamma$ vs. IL-10 expression: 1) IL-17A$^+$ IFN$_\gamma^+$ T17 cells, 2) IL-17A$^+$ IFN$_\gamma^-$ T17 cells, 3) IL-17A$^+$ IL-17F$^+$ T17 cells, 4) IL-17F$^+$ IL-10$^-$ T17 cells and 5) IL-17F$^+$ IL-10$^+$ T17 cells (Fig 3B). The T17 cell subset that most conforms with current pathogenic subsets[6, 22–24] is the IL-17A$^+$ IFN$_\gamma^+$ population, synthesizing high levels of TNF, IL-26 and IL-36G and mostly within CD8$^+$ T-cells that co-express cytotoxic markers (Tc17 T-cells).

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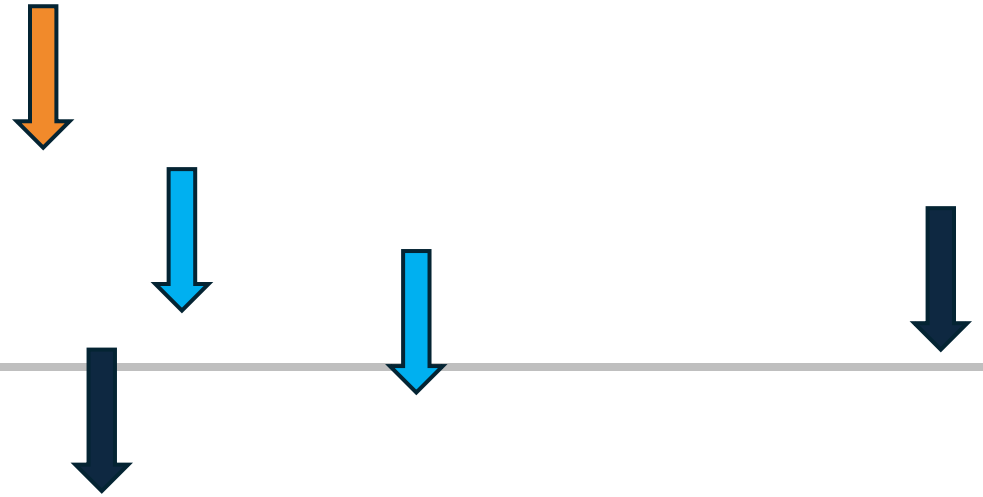

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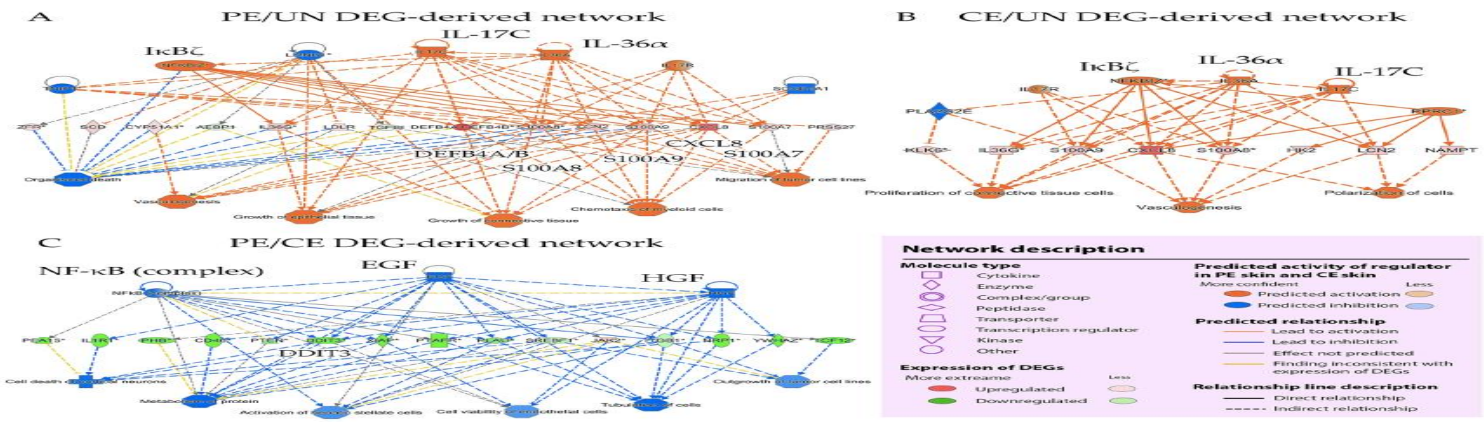

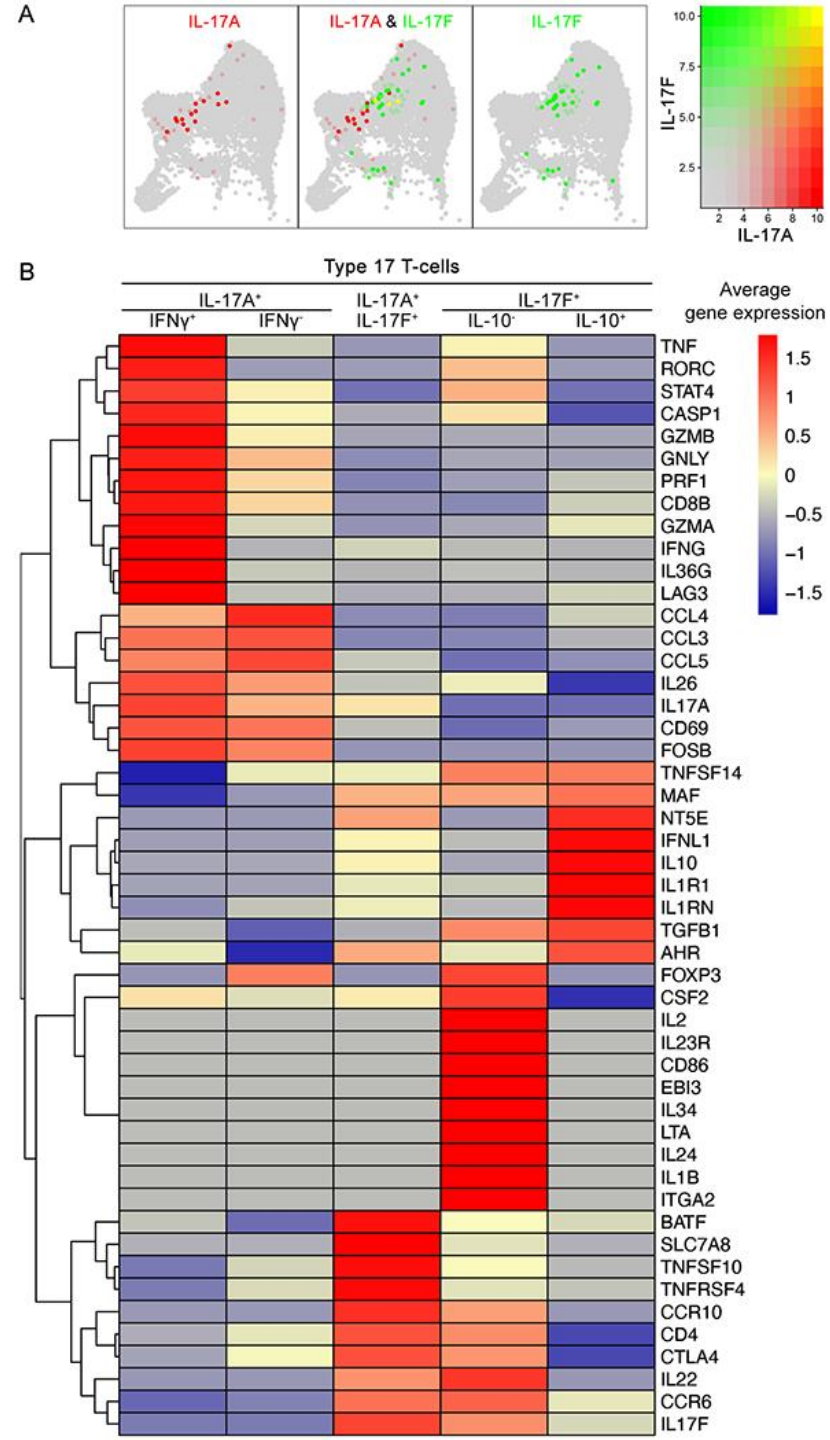

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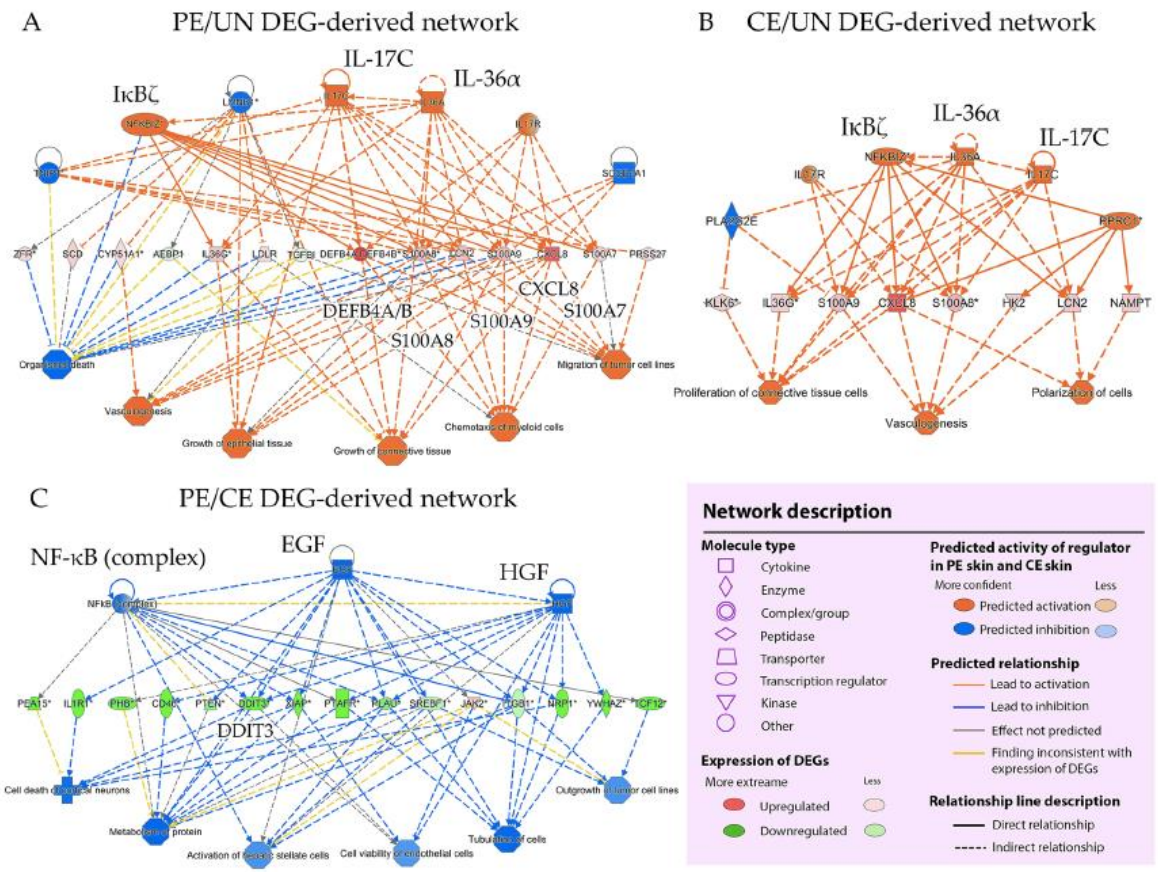
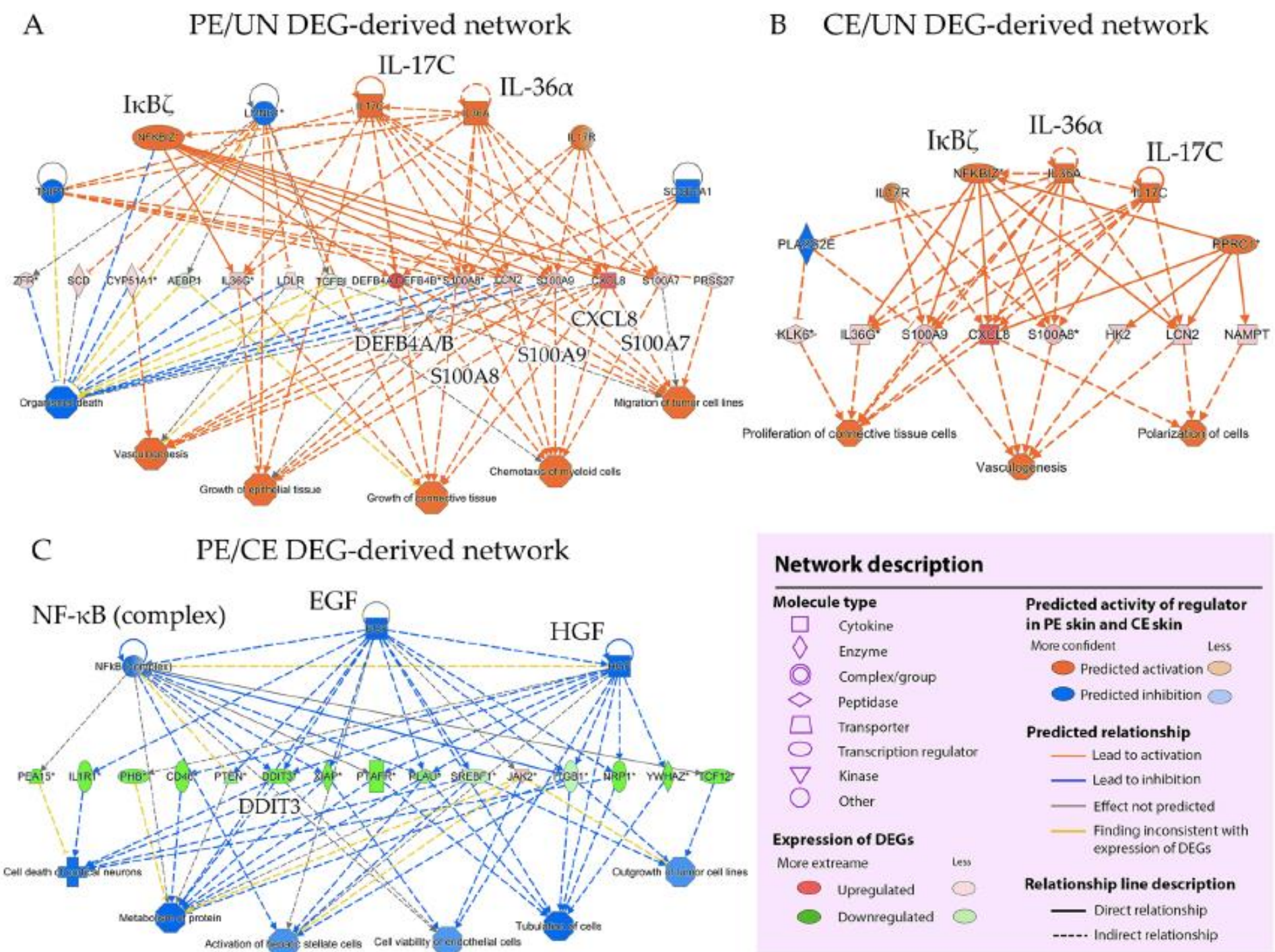
- La piel PE contenía **moléculas iniciadoras de la inflam**ación, como **S100A7** y S**100A15**, e **impulsores de la inflamación**, como la interleucina **(IL)-36α**.
- La **señalización de la IL-6** era más activa en la piel **PE** que en la CE.
- La IL-8, la S100A7, la S100A8, la S100A9 y la β-defensina-2 humana se regularon con un patrón similar en ambas zonas.
- Sin embargo, la piel **PE creó una red inflamatoria más activa** y las funciones derivadas, como la **quimiotaxis** y la **angiogénesis**, fueron más prominentes que en la piel CE.
- Por el contrario, la piel **CE, en la que el factor de crecimiento epidérmico y el factor de crecimiento de hepatocitos** aumentaron su actividad, resultó ser más estable.



Boonpethkaew S, Meephansan J, Jumlongpim O, Tangtanatakul P, Soonthornchai W, Wongpiyabovorn J, Vipanurat R, Komine M. Transcriptomic Profiling of Peripheral Edge of Lesions to Elucidate the Pathogenesis of Psoriasis Vulgaris. Int J Mol Sci. 2022 Apr 30;23(9):4983. doi: 10.3390/ijms23094983. PMID: 35563374; PMCID: PMC9101153.



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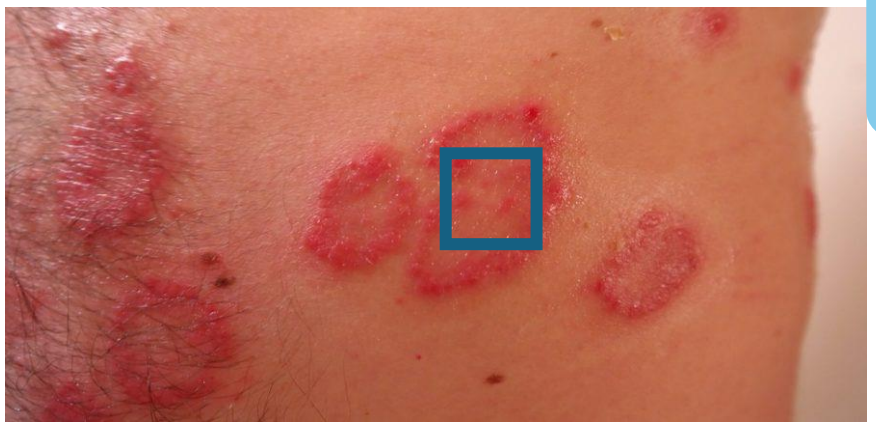
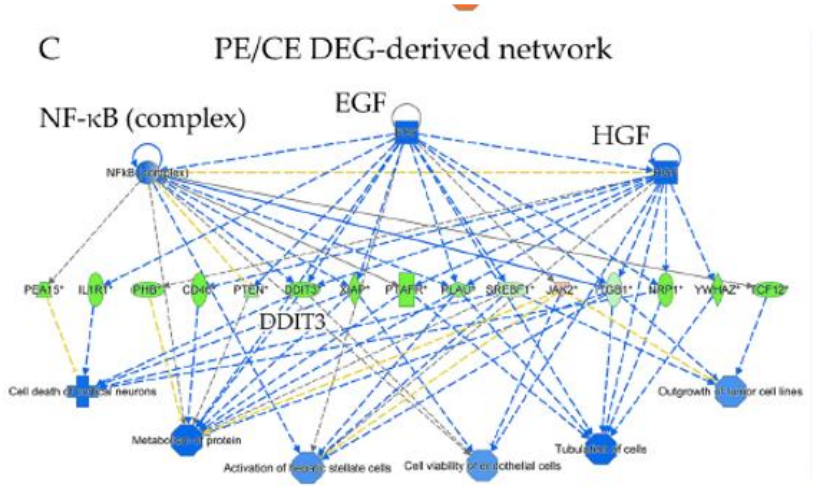


El EGFR se expresa en la zona central de las placas psoriásicas y promueve la proliferación de Qc y la angiogenesis

Además, el EGF puede suprimir la expresión del ARNm de la IL-6 y la IL-1β, lo que sugiere una alteración del entorno de diferenciación Th17, y puede suprimir la expresión del ARNm de la IL-17A

El HGF es secretado por los fibroblastos dérmicos. Promueve la proliferación de los Qc e induce la expresión de VEGF , promoviendo así la angiogénesis, que podría ayudar a mantener las placas formadas.

Sin embargo, la sobreproducción de HGF reduce la inflamación psoriásica a través de la supresión de la expresión de ARNm de citoquinas clave (IFN-γ, IL-17A, IL-17 F e IL-23) en las lesiones psoriásicas lo que puede dar lugar a la estabilización, y posterior regresión de la placa



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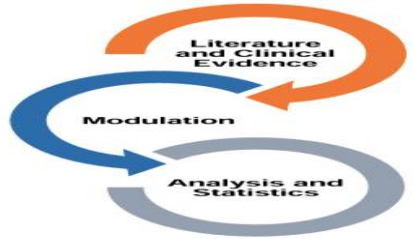


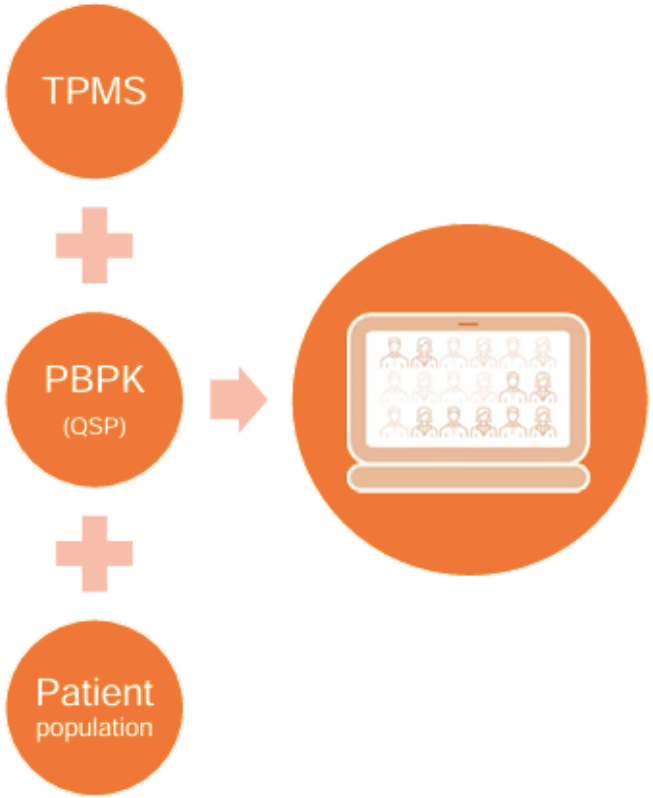
In Silico Clinical Trial | Approach

Integrates

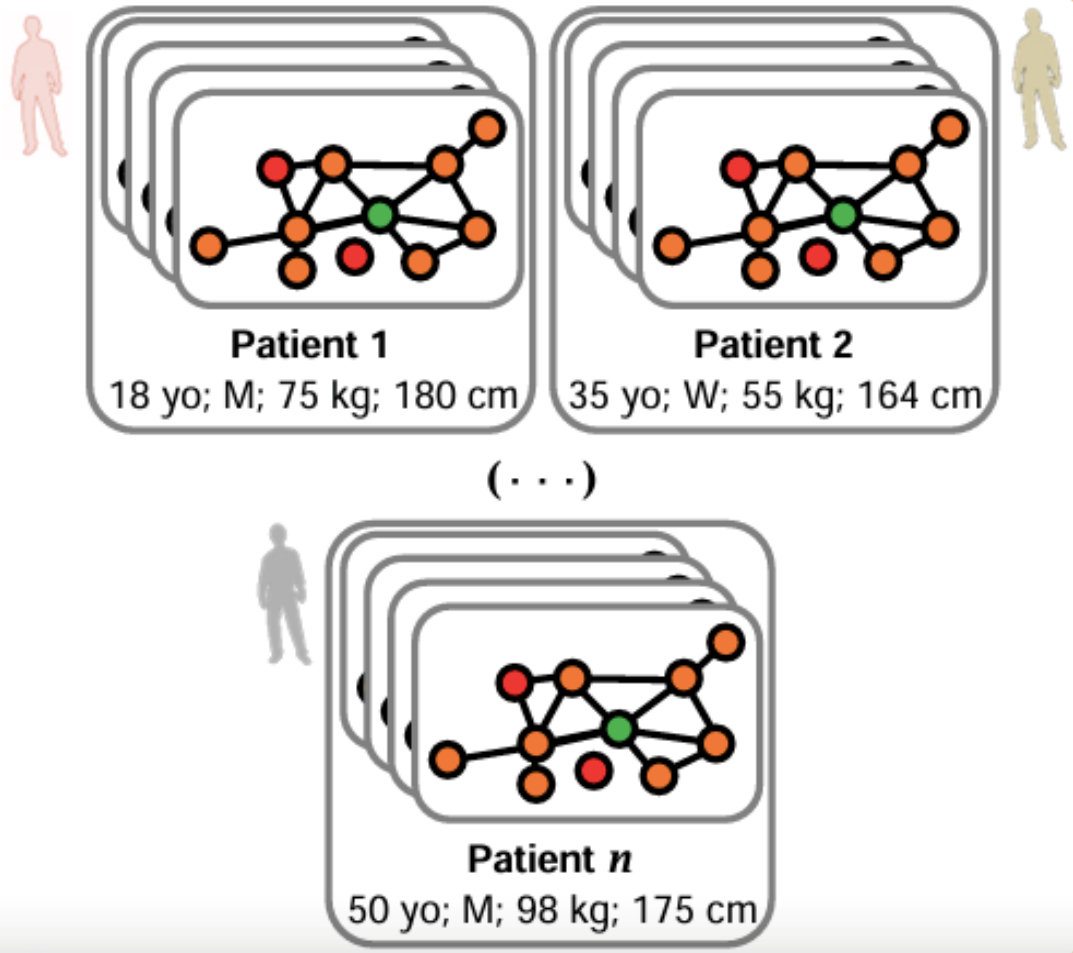
- Systems Biology-based models (TPMS)
- Pharmacokinetic modelling (PBPK)
- Virtual patient population (includes population characteristics)

Captures

- Individual and tissue specific drug response:
  - Demographics
  - Metabolism
  - Protein and gene changes



In Silico Clinical Trial | Outcomes

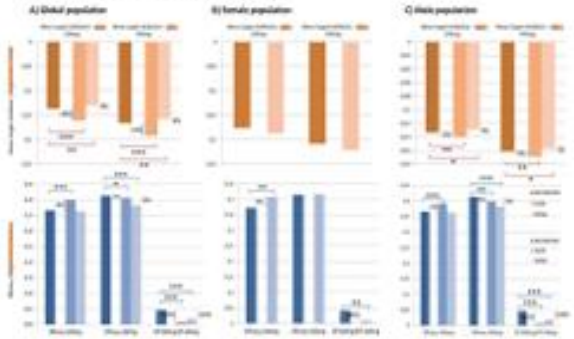


Molecular characterization of the Drug

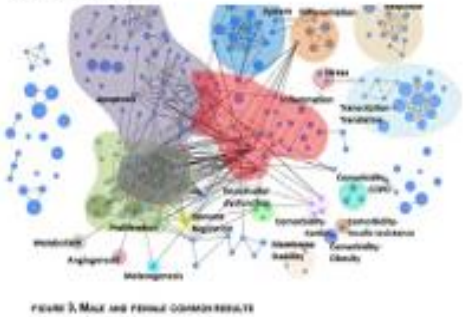
- Each patient includes **various** mathematical models.
  - Corresponds to the **various pathways** in each subject related to that drug.
- In each, the signal is propagated according to the **stimulus activation**.
  - **PBPK and demographics** modulate activation.
- **Various response sets** are assessed. Depending on clinical variables of interest.

In Silico Clinical Trial | Outcomes

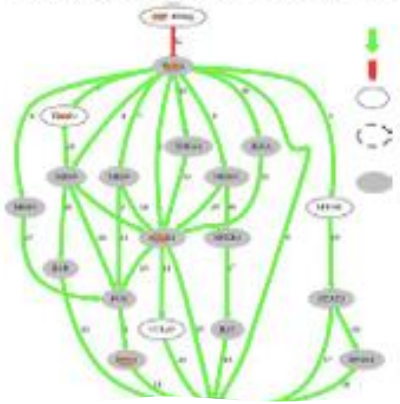
1 Classical **statistical analysis** or by Machine Learning.



2 **Pathology contextualization** (by subsets of patients or biomarker patterns).



3 Exploration the **mechanism of action** of the drug (including subsets of patients).



3. PROJECT EXECUTION

Literature-based disease characterisation

Definition of the condition motives

The main pathophysiological processes known to be involved in AD.

Definition of each motive at protein level

Protein/gene candidates to be condition effectors whose activity (or lack thereof) is functionally associated with the development of the condition.

PubMed

AD network

("Atopic dermatitis" [Title] OR "AD" [Title] ("neurodermatitis" [Title] OR "Atopic neurodermatitis" [Titl OR "atopic eczema" [Title] OR "infantile eccema" [Title] ("chronic eczema" [Title] OR "prurigo nodularis" [Title] ("hand chronic eczema" [Title]) AND ("pathogenesis" [Title] ("pathophysiology" [Title] OR "molecular" [Title]) AND Revie [ptyp]

- Retrieved in the last 10 years

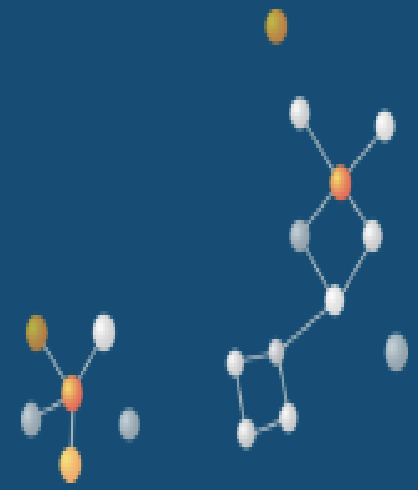
Publicly available AD patients expression data

GEO Gene Expression Omnibus +

Potential designs:

- **Validation and completion of the literature-based characterisation**
- **Generation of a disease molecular fingerprint**
- **Help better model AD pathophysiological model**

AD signature

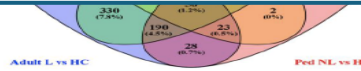


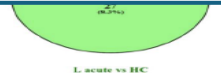
topic dermatitis molecular characterisation through the scientific literature-based revision and, analysis of publicly available gene expression data from atopic dermatitis patients

Adult L vs Healthy control	2376	1087	1289

DEGs in different comparatives of GSE36842 dataset
logFC > 1: upregulated DEGs, logFC < -1: downregulated DEGs.
Those comparatives shaded in blue were the ones used for the enrichment analysis.

Comparatives*	Number of DEGS	DEGS logFC > 1	DEGS logFC < -1
NL vs healthy control	224	17	207
L chronic vs NL	0	0	0
L chronic vs healthy control	139	45	94
L acute vs NL	0	0	0
L acute vs healthy control	111	15	96
L acute vs L chronic	0	0	0





a) Lesional phenotype has more DEGs than non-lesional phenotype. Most non-lesional DEGs are shared with those in lesional phenotypes. Most adult and pediatric DEGs are unique
b) Non-lesional is the one with the most unique DEGs. Lesional chronic has more unique DEGs than the lesional acute comparative.

1 Differential expression analysis

Identify genes that exhibited significant expression changes between the experimental conditions of GSE107361 and GSE36842

Criteria
- (|LogFC|) > 1
- FDR < 0.05

Comparative	Number of DEGs	Upregulated DEGs	Downregulated DEGs
Pediatric NL vs Healthy control	931	223	708
Pediatric L vs Pediatric NL	620	348	272
Pediatric L vs Healthy control	2094	783	1311
Adult NL vs Pediatric NL	2734	1290	1444
Adul NL vs Healthy control	1065	321	744
Adult L vs Pediatric L	2872	1405	1467
Adult L vs Adult NL	227	142	85
Adult L vs Healthy control	2376	1087	1289

Comparatives	Number of DEGS	Upregulated DEGs	Downregulated DEGs
NL vs healthy control	224	17	207
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L acute vs healthy control	111	15	96
L acute vs L chronic	0	0	0

2 Enrichment analysis

Overexpression/Hypergeometric analysis

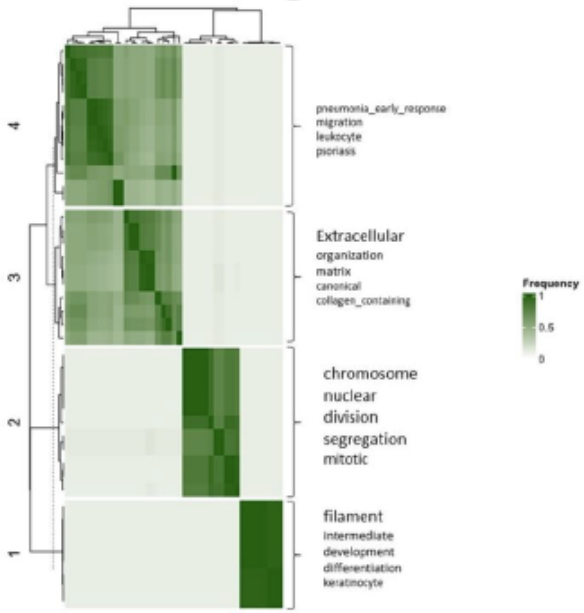
Discover what processes characterise the pathophysiology of atopic dermatitis

Criteria
Processes comprising an original protein size between 10 and 500.

Phenotypes of interest
- Adult patients
- Pediatric patients
- Non-lesional samples
- Acute samples (Lesional)
- Chronic samples (Lesional)

3 Clustering of enrichment results

Compute similarities among sets



4.1. RESULTS» DISEASE CHARACTERISATION

Literature-based disease characterisation

Definition of the condition motives

The main pathophysiological processes known to be involved in AD.

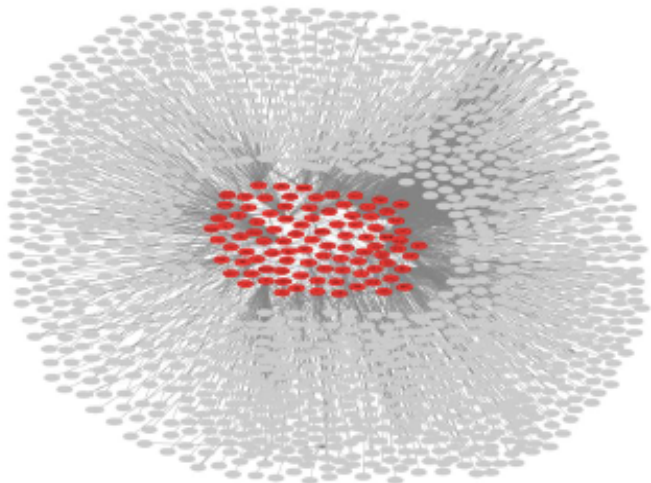
Definition of each motive at protein level

Protein/gene candidates to be condition effectors whose activity (or lack thereof) is functionally associated with the development of the condition.

** See Excel file AtopicDermatitis_ConditionCharacterisation*

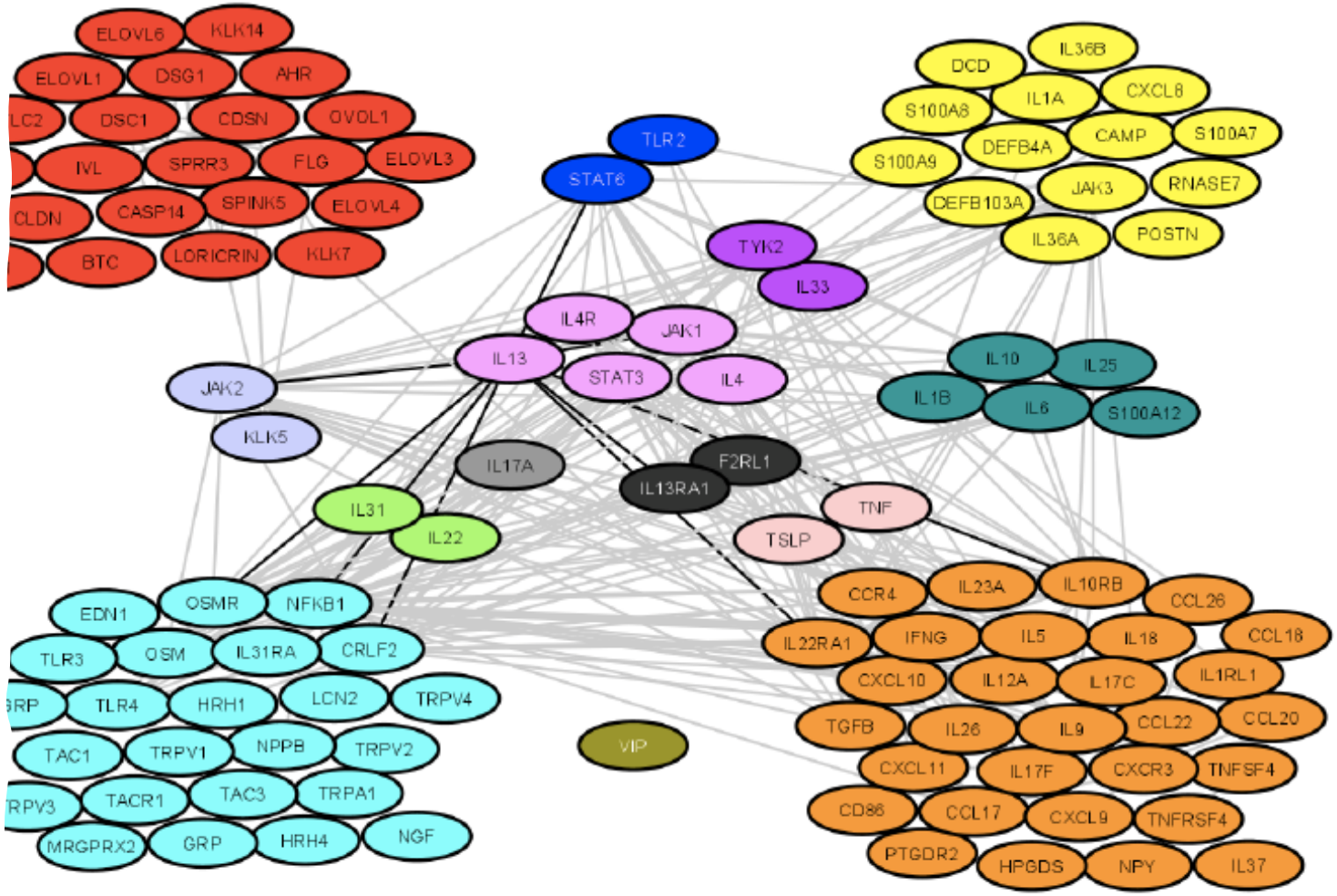
	MOTIVE	# PROTEINS
1	Epidermal barrier dysfunction (C;S)	36
2	Innate immunity dysregulation (C)	30
3	Adaptative immunity dysregulation (C;S)	68
3.1	Th2-derived inflammation (C;S)	29
3.2	Th22-derived inflammation (C;S)	8
3.3	Th1-derived inflammation (C;S)	9
3.4	Th17-derived inflammation (C;S)	13
4	Pruritus and itch (C;S)	37
	Total unique protein number	114

2 of these proteins come from the associated publications revision of the filtered datasets (highlighted in bold in the Excel file).



AD protein interactome

4.1. RESULTS» DISEASE CHARACTERISATION

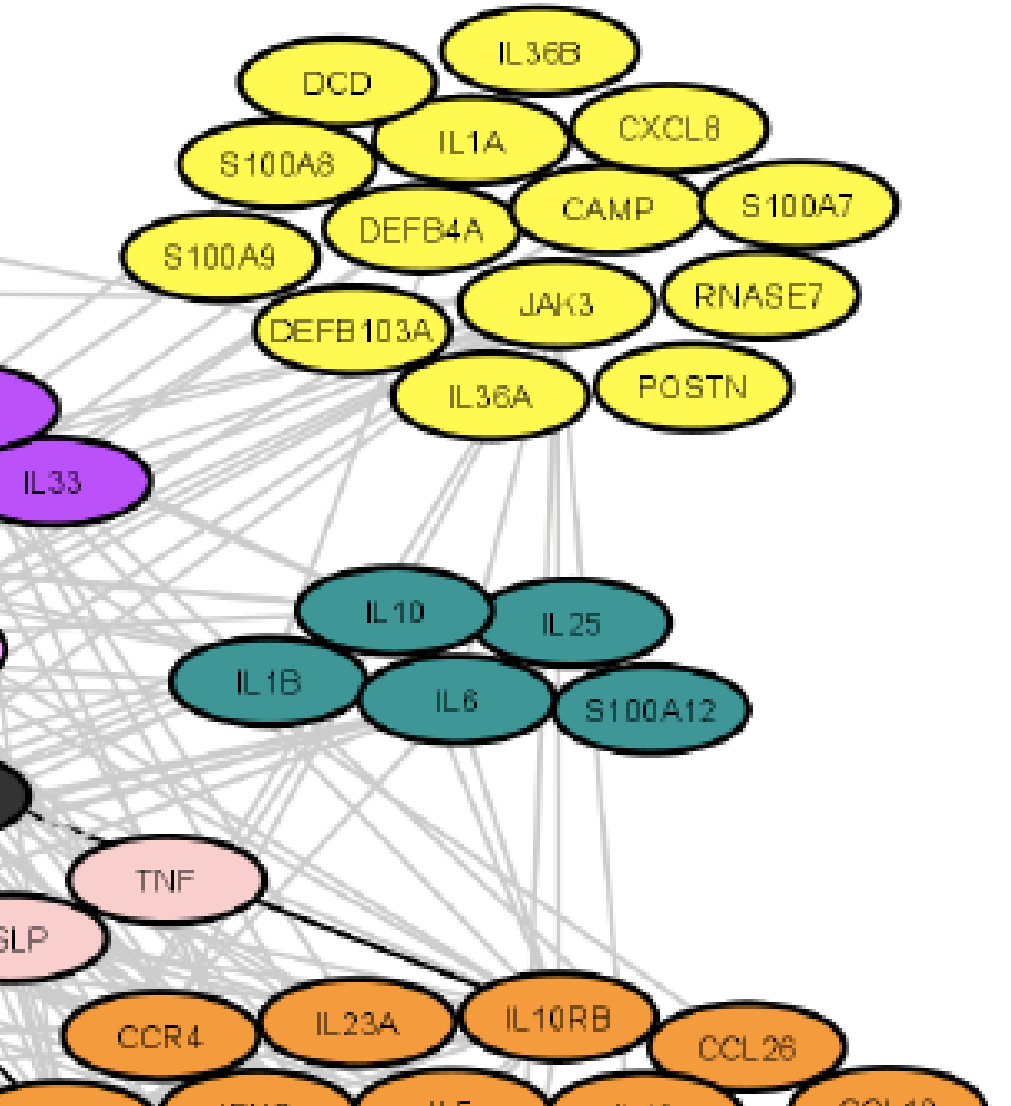


- EBD
- II
- AI
- P
- EBD;II
- EBD;AI
- EBD;P
- II;AI
- II;P
- AI;P
- EBD;II;AI
- EBD;AI;P
- II;AI;P
- EBD;II;AI;P

EBD: Epidermal barrier disruption; II: innate immunity; AI: adaptative immunity; P: pruritus

- 5 proteins involved in all motives. 2 of them of the JAK/STAT cascade, the other 3 are IL-13, IL-4 and its receptor IL-4R. They seem to be core proteins in AD.
- Black edges show connections between IL13 and all atopic dermatitis motives
- High interconnection between motives, specially innate immunity, adaptative immunity and pruritus and itch.
- Epidermal barrier disruption motive is not connected with any motive, only interconnected with themselves.

SE CHARACTERISATION



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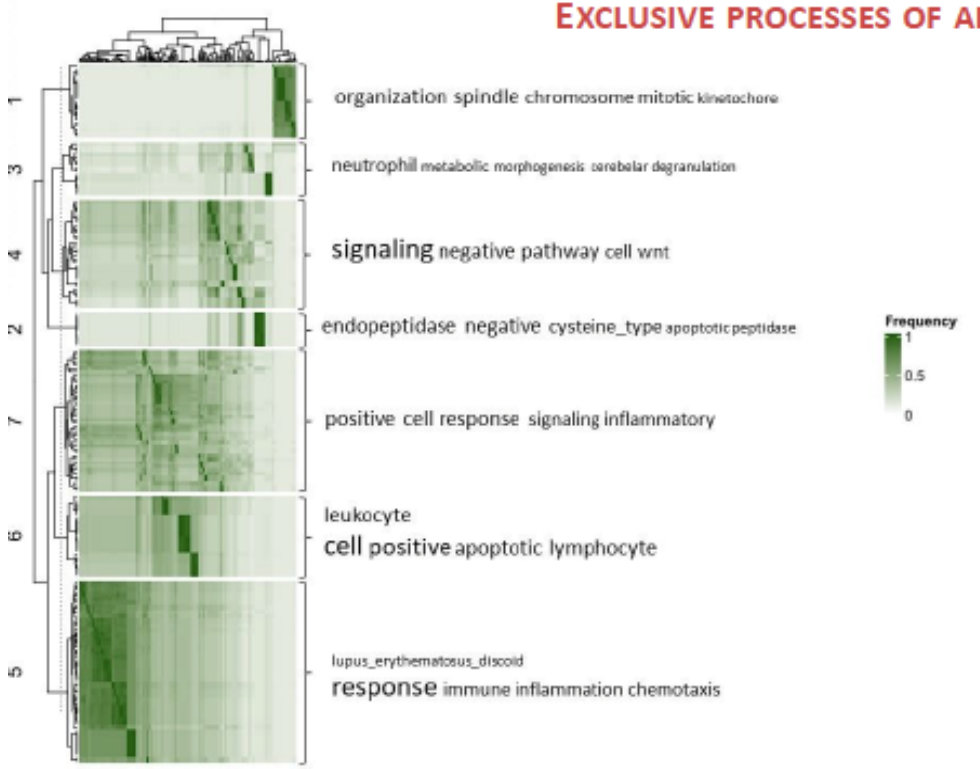
- Epidermal barrier disruption motive is not connected with any motive, only interconnected with themselves.

4.3. RESULTS» Enrichment of adult vs. Pediatric signatures

Exclusive processes of adult lesional patients vs healthy control.

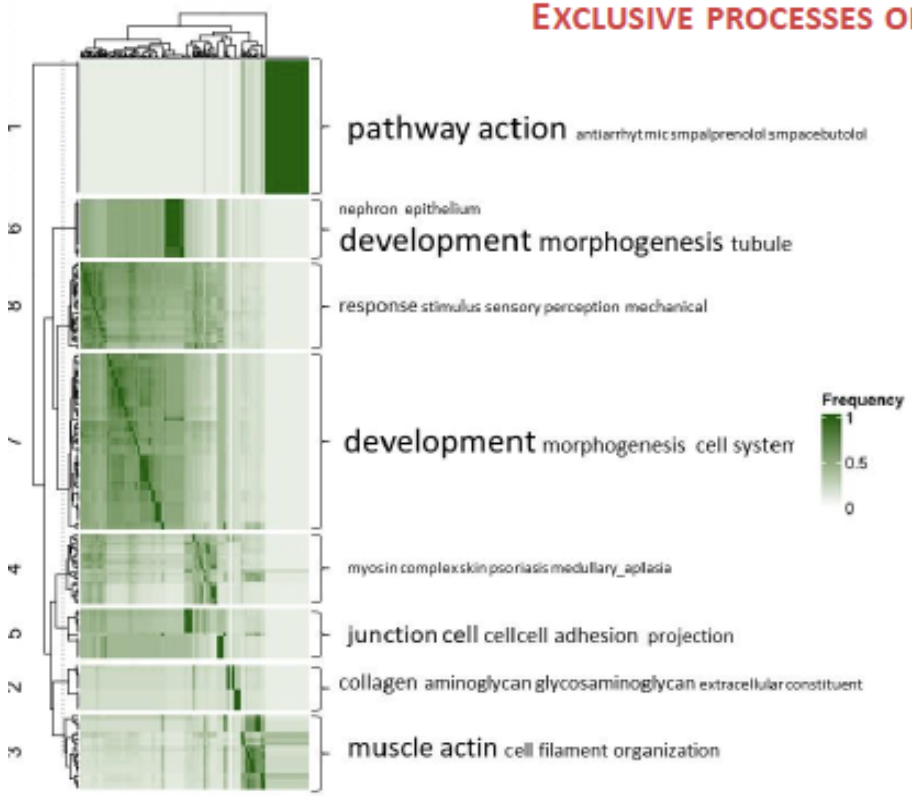


200 PROCESSES				
Process	Epidermal barrier disruption	Innate immunity dysregulation	Adaptative immunity dysregulation	Pruritus and itch
Cluster 1. Cell division				✓
Cluster 2. Peptidases activity	✓			
Cluster 3. Antigen presentation, neutrophil-mediated activity		✓	✓	✓
Cluster 4. Signaling pathways			✓	
Cluster 5. Inflammatory response and chemokine response.		✓	✓	
Cluster 6. T cell activation			✓	
Cluster 7. Inflammation and T cell response		✓	✓	

The processes present **only** in adult lesional samples are: cell division, peptidases activity, antigen processing and presentation, neutrophil-mediated immunity, signaling pathways, inflammation and T cell activation, all included in the following AD characterisation motives: epidermal barrier disruption, innate immunity dysregulation, adaptative immunity dysregulation and pruritus and itch. First of all, these results unravel what processes are present in an adult atopic dermatitis patient. Moreover, cell division, antigen processing and T-cell activation processes have also appeared in common results, which means a higher involvement in adult patients than in pediatric patients, since they have not resulted enriched in pediatric populations. However, endopeptidases activity and signaling pathways (such as NFKB or IFNG signaling pathways) are processes enriched only in adult patients, suggesting its implication in adult patients and not in pediatric ones.

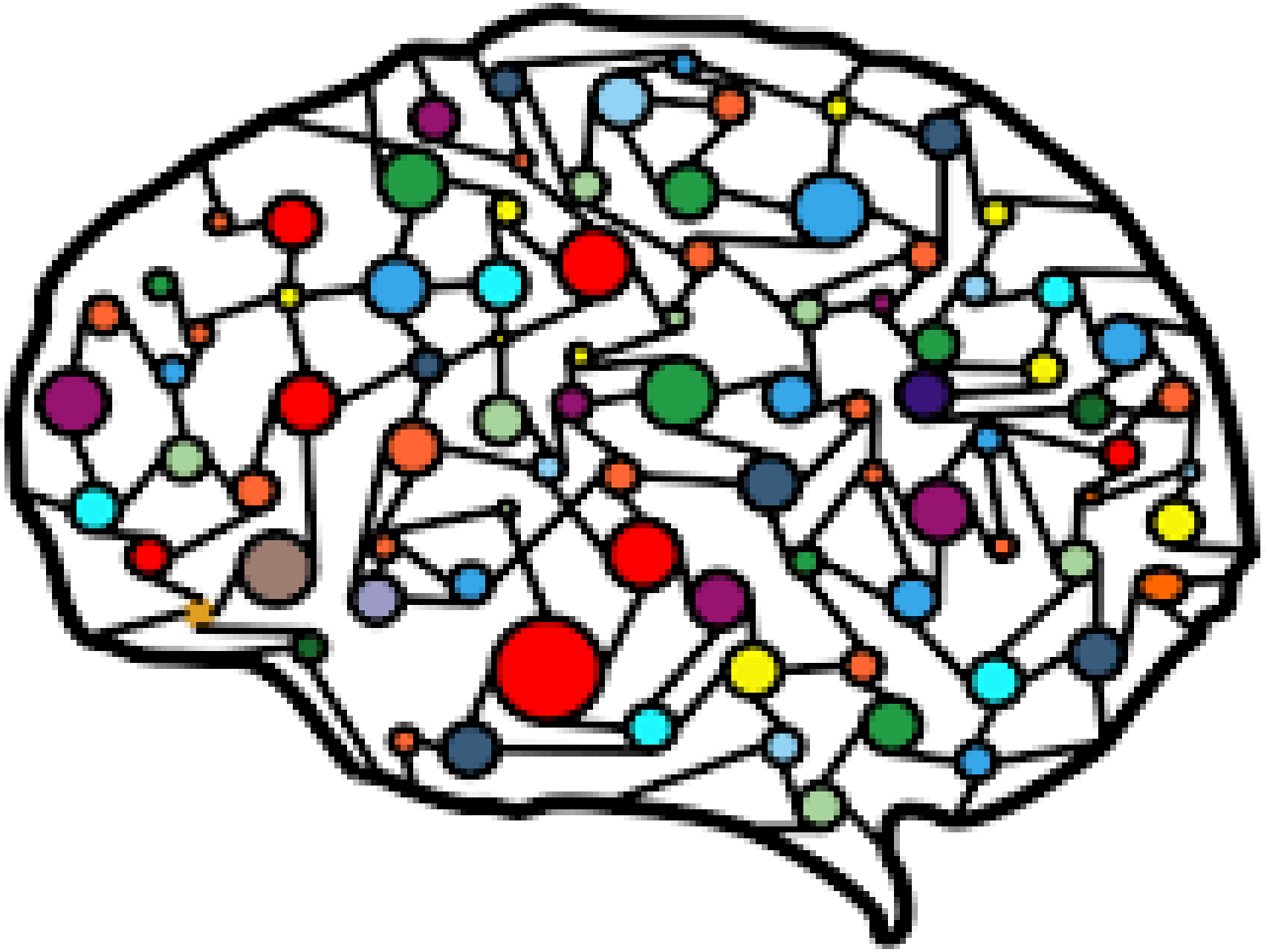
4.3. RESULTS» ENRICHMENT OF ADULT VS. PEDIATRIC SIGNATURES

EXCLUSIVE PROCESSES OF PEDIATRIC LESIONAL PATIENTS VS HEALTHY CONTROL.



249 PROCESSES				
Process	Epidermal barrier disruption	Innate immunity dysregulation	Adaptative immunity dysregulation	Pruritus and itch
Cluster 1. Heart drugs				
Cluster 2. Collagen organization	✓			
Cluster 3. Collagen organization and muscle cell action	✓			
Cluster 4. Cornification of cornified envelope and antimicrobial humoral response	✓	✓		
Cluster 5. Cell-cell junction.	✓			
Cluster 6. Kidney and nephron development.	✓?			
Cluster 7. Morphogenesis	✓			
Cluster 8. Receptor complexes and angiogenesis	✓	✓	✓	✓

The processes present **only** in pediatric lesional samples are: extracellular matrix structure, muscle cell differentiation, humoral response, cell-cell junction, morphogenesis and angiogenesis, some of them included in all AD characterisation motives. However, muscle cell differentiation, morphogenesis and angiogenesis are not covered by our characterisation, because they are not fully studied in an atopic dermatitis environment. Humoral response is a process involved in all phenotype's pathologies. Both ECM and cell junction processes are involved in common analyses and in only pediatric, but not in only adult, suggesting a higher role in the present population. Finally, the other processes (muscle cell differentiation, morphogenesis and angiogenesis) are features of pediatric patients, not involved in adult pathology.



Artificial neuronal networks (ANNs)-based prediction

ANN value	ANN category	Associated p-value
> 92.19%	VERY HIGH	≤ 0.01
91.88%-77.56%	HIGH	0.01-0.05
77.12%-70.73%	MEDIUM-HIGH	0.05-0.1
70.59%-63.01%	MEDIUM	0.1-0.15
62.52%-48.21%	LOW-MEDIUM	0.15-0.2
< 47.61%	LOW	≥ 0.2

Drug Name	Drug Equivs	GLOBAL	Epidermal barrier dysfunction	Innate immunity dysregulation	Adaptative immunity dysregulation	Pruritus and itch
IL13	IL13	71.41%	71.43%	74.55%	76.73%	86.39%

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nature computational science

Perspective

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Digital twins in medicine

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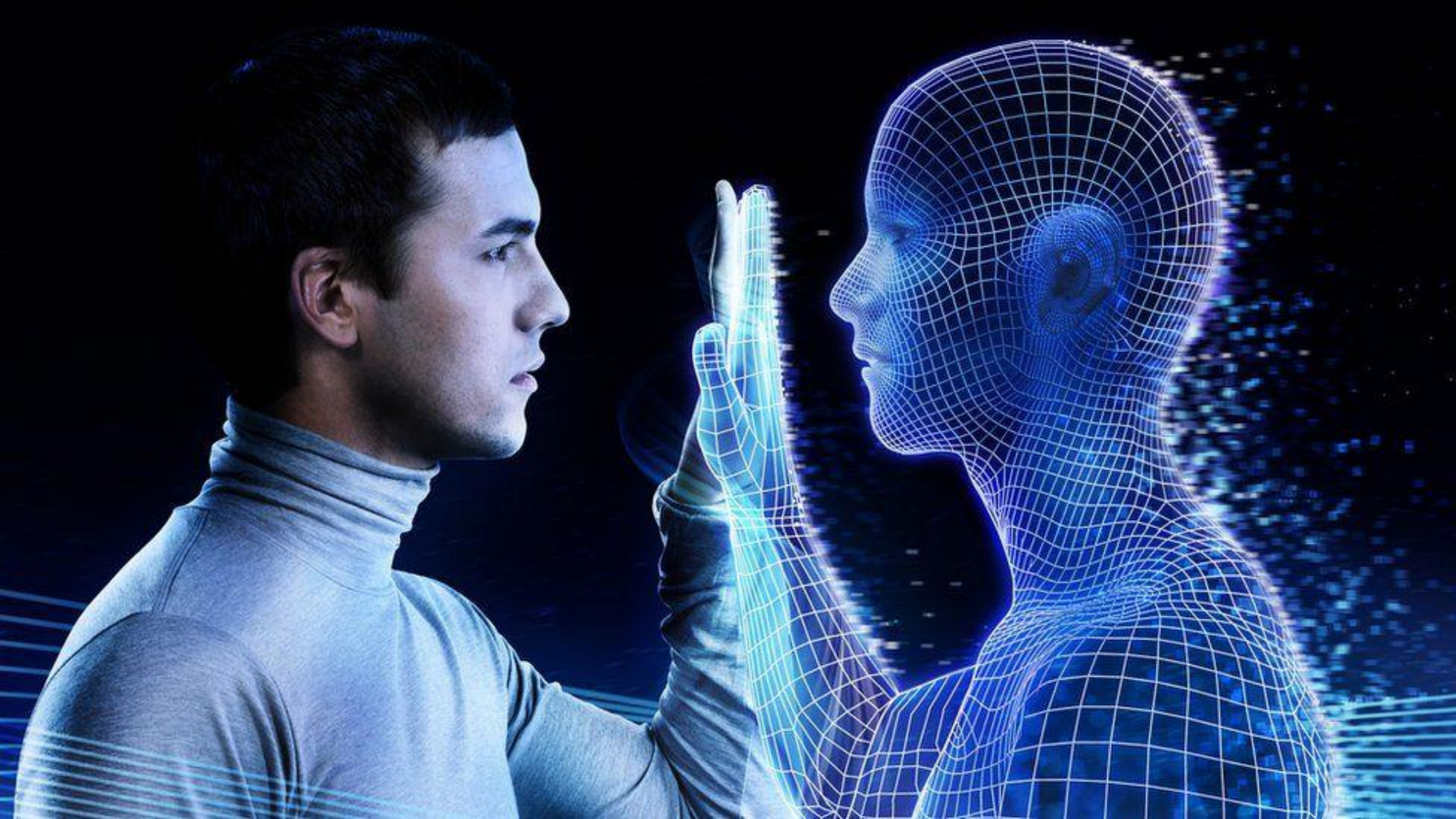
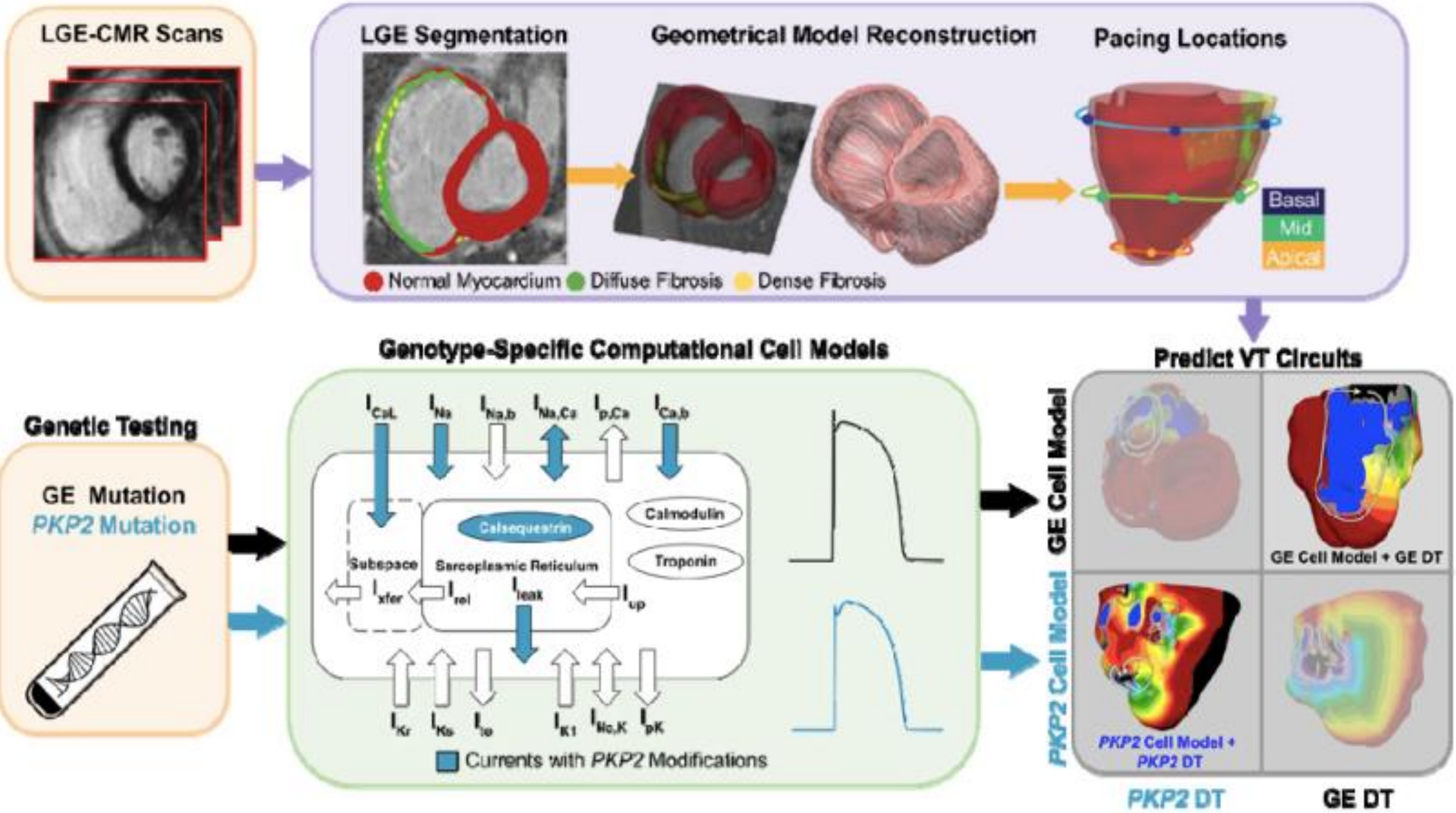
Check for updates

R. Laubenbacher[1], B. Mehrad[1], I. Shmulevich[2] & N. Trayanova[3]

Medical digital twins, which are potentially vital for personalized medicine, have become a recent focus in medical research. Here we present an overview of the state of the art in medical digital twin development, especially in oncology and cardiology, where it is most advanced. We discuss major challenges, such as data integration and privacy, and provide an outlook on future advancements. Emphasizing the importance of this technology in healthcare, we highlight the potential for substantial improvements in patient-specific treatments and diagnostics.




LGE-CMR Scans
LGE Segmentation
Geometrical Model Reconstruction
Pacing Locations
Basal
Mid
Apical
Normal Myocardium
Diffuse Fibrosis
Dense Fibrosis
Genetic Testing
GE Mutation
PKP2 Mutation
Genotype-Specific Computational Cell Models
Calsequestrin
Calmodulin
Troponin
Subspace
Sarcoplasmic Reticulum
Currents with PKP2 Modifications
Predict VT Circuits
GE Cell Model
PKP2 Cell Model
GE Cell Model + GE DT
PKP2 Cell Model + PKP2 DT
PKP2 DT
GE DT

Computational and Systems Biology

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Reviewed Preprint

Revised by authors after peer review.

About eLife's process

Reviewed preprint version 2
October 6, 2023 (this version)

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July 18, 2023

Yingnan Zhang, Kelly Zhang, Adityo Prakosa, Cynthia James, Stefan L Zimmerman, Richard Carrick, Eric Sung, Alessio Gasperetti, Crystal Tichnell, Brittney Murray, Hugh Calkins, Natalia Trayanova

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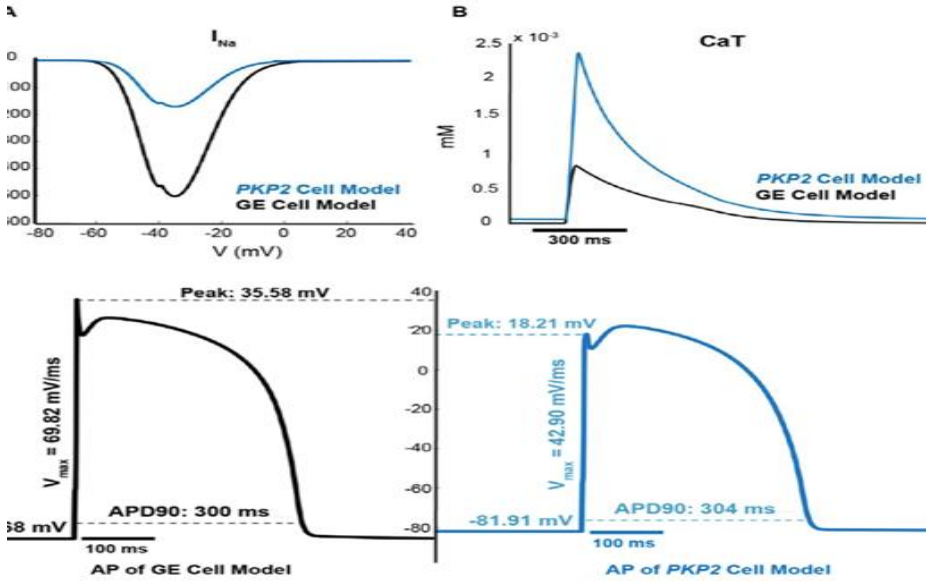
A
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GE Cell Model
V (mV)
B
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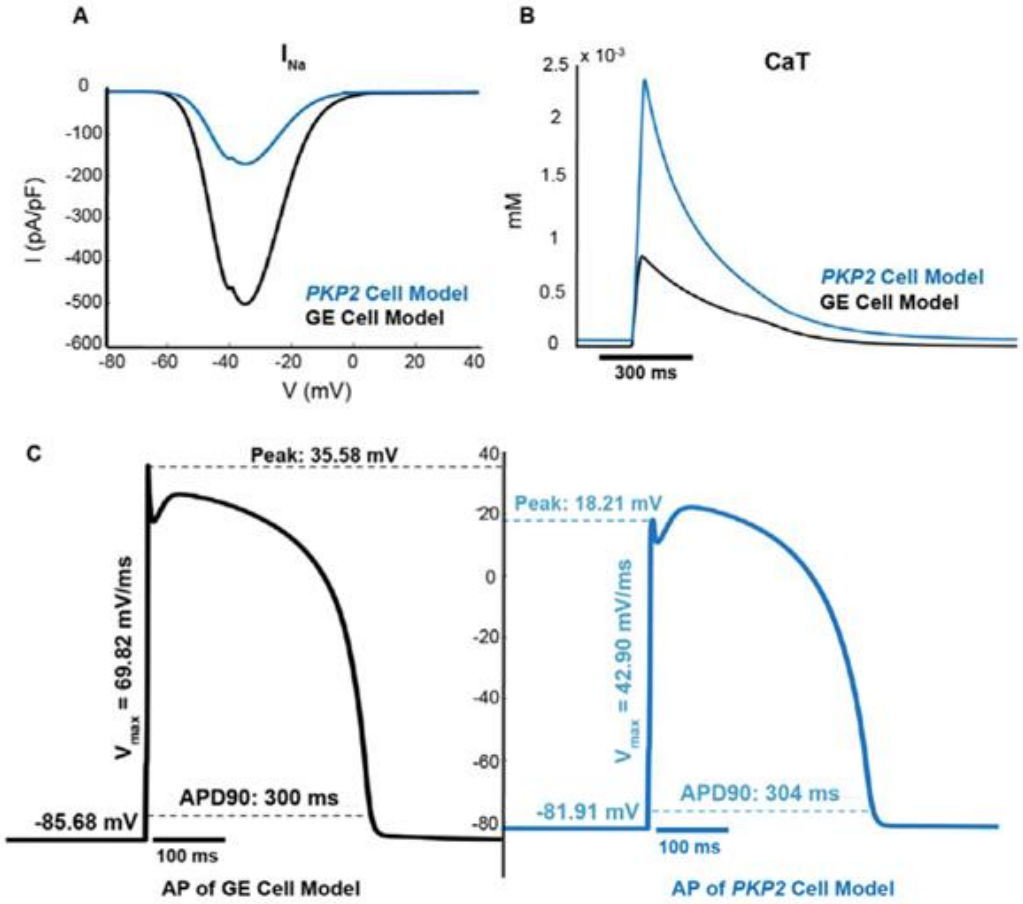
PKP2 Cell Model
GE Cell Model
300 ms
Peak: 35.58 mV
V_{max} = 69.82 mV/ms
APD90: 300 ms
100 ms
AP of GE Cell Model
Peak: 18.21 mV
V_{max} = 42.90 mV/ms
-81.91 mV
APD90: 304 ms
100 ms
AP of PKP2 Cell Model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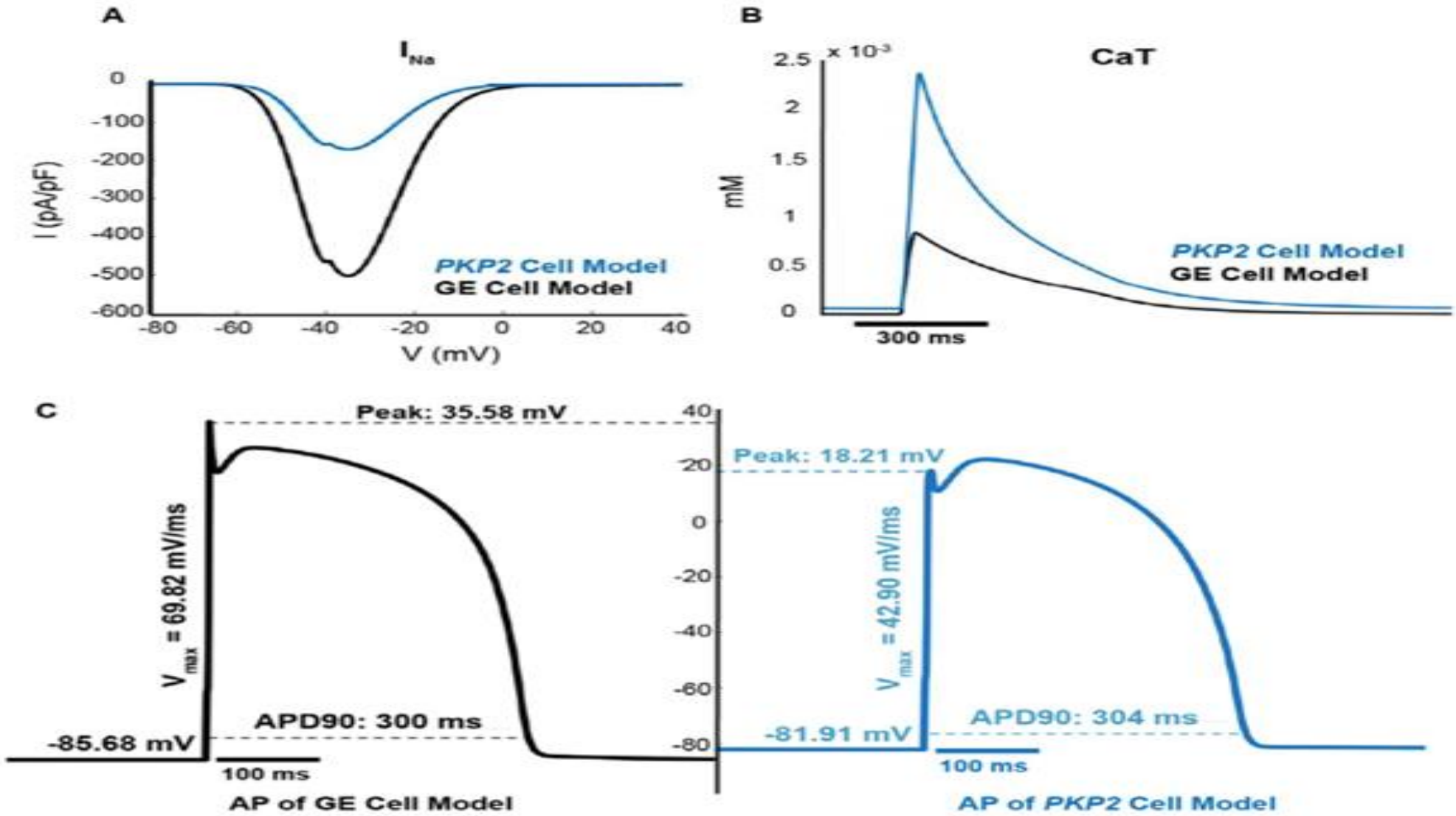
A
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PKP2 Cell Model
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PKP2 Cell Model
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AP of PKP2 Cell Model

PERLAS PARA LLEVAR A CASA..

- Veremos muchos artículos que estudian el metagenoma…hacernos la pregunta de ¿qué importan esas diferencias?→ estudios que realicen SHOTGUN METAGENOMICS
- SINGLE CELL-RNAseq puede proporcionar nuevos insights sobre los mecanismos fisiopatogenicos
- IN SILICO CLINICAL TRIAL y DIGITAL TWIN para ”democratizar” fm, enf raras…

Muchas gracias

PABLO COTO SEGURA

DERMATOLOGÍA. HOSPITAL VITAL ÁLVAREZ-BUYLLA (MIERES)