

Biomaterials & Immune System Responses

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Quick Definitions

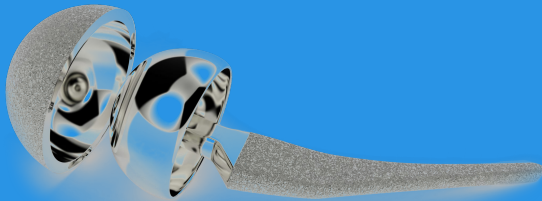
1. **Biomaterials** - an engineered material to interact with the human body
2. **Foreign Objects** - the medical devices: titanium knee, silicone implants, etc.
3. **Immune System** - protect the body fight infections and viruses

Medical Devices

Examples

Joint Replacements

Artificial implants that replace damages and restore mobility



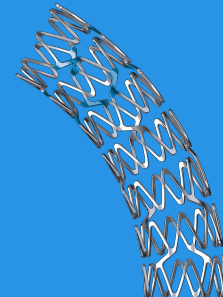
Pacemakers

Devices implanted in the chest to regulate heart rhythms




Stents

Small mesh tubes inserted into blood vessels to keep them open and maintain blood flow



What is the current problem?

What do we want to know?



This project explores how different implant materials influence immune response and how data science can be used to predict material compatibility for more personalized and biocompatible medical devices

Materials Currently Used



Titanium

- Ideal for bone integration
- Lightweight



Silicon

- Extremely Flexible
- Used primarily in implants



Collagen

- Natural Protein
- Wound Healing

Immune Response

ACCEPT

REJECT

- Non-threatening
- Triggers healing-oriented immune reaction
- Healing cytokines
- Tissue integrates
- Minimal inflammation
- Long-term stability

- Seen as a foreign invader
- Activates strong response
- Inflammatory cytokines are released
- Leads to tissue damage, fibrosis, or scarring
- Increases risk of implant failure

Common Genes

TLR4

- recognizes foreign or damaged material
- triggers strong innate immune activation

CD86

- activates T cells and initiates adaptive immune response
- High potential for implant rejection

IFIT1

- interferon stimulated gene
- Can signal immune stress after implant exposure

STAT1

- activated by interferons
- often elevated in response to foreign materials like implants

RELA

- regulates inflammatory responses
- switch in both immune activation and resolution

STAT6

- promotes anti-inflammatory macrophage activity
- support tissue repair

IL6

- cytokine protein
- inflammation and immune response

CCL2

- attracts immune cells
- involved in inflammation
- can promote tissue remodeling

NFKB1

- regulator of immune response
- Balances pro and anti-inflammatory signaling-

Implant Strategies

Traditional

- Immune Rejection
 - Treats implant as threat
 - Leads to damage
- SOLUTION:** immuno-suppressants
 - Temporarily reduce Immune response
- **RISKS**
 - Organ damage
 - Complications

Current Focus

- Engineering Better Implants
 - Materials that cooperate with Immune cells
- Inspired by natural biomaterials
- Lower rejection, promote healing

Future Vision

- Immune-informed Design
 - Predictive models to guide implant development
- Fully personalized and adaptive biomaterials

All Databases ▾

Search

NCBI Home

Resource List (A-Z)

All Resources

Chemicals & Bioassays

Data & Software

DNA & RNA

Domains & Structures

Genes & Expression

Genetics & Medicine

Genomes & Maps

Homology

Literature

Proteins

Sequence Analysis

Taxonomy

Training & Tutorials

Variation

Welcome to NCBI

The National Center for Biotechnology Information advances science and health by providing access to biomedical and genomic information.

GEO - Gene Expression Omnibus

Submit

Deposit data or manuscripts into NCBI databases



Download

Transfer NCBI data to your computer



Learn

Find help documents, attend a class or watch a tutorial



Develop

Use NCBI APIs and code libraries to build applications



Analyze

Identify an NCBI tool for your data analysis task



Research

Explore NCBI research and collaborative projects



Popular Resources

PubMed

Bookshelf

PubMed Central

BLAST

Nucleotide

Genome

SNP

Gene

Protein

PubChem

NCBI News & Blog

Beta Now Live! New & Improved Homepage Design

NCBI is excited to introduce a fresh look and feel to the Database of Genotypes and Phenotypes (dbGaP).

Now Available: Updated Bacterial and Archaeal Reference Genome Collections

Rejection of Titanium Implants

German University 2021

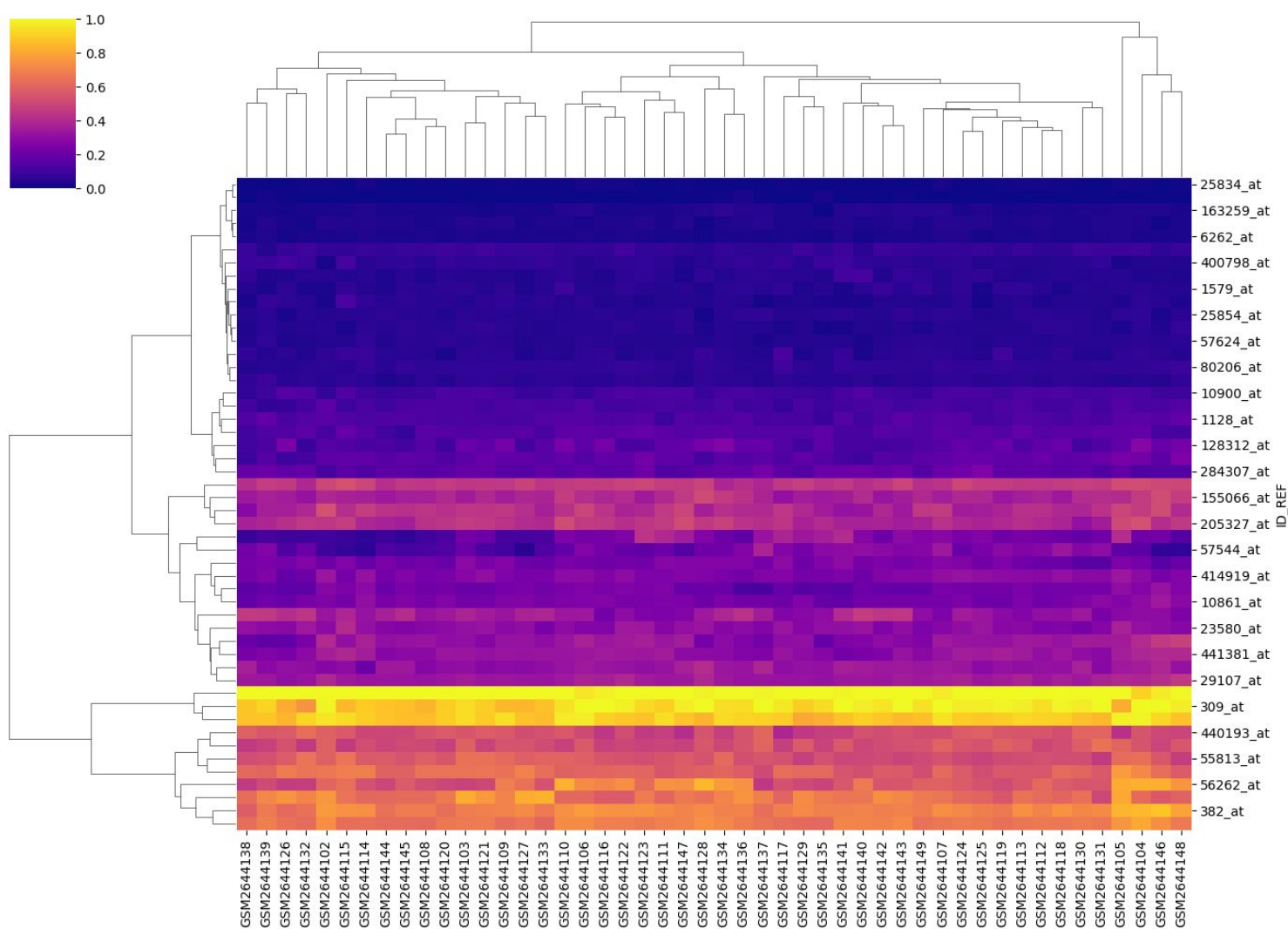


Macrophages - a type of white blood that works in the immune system

- Helps the body fight bacterial or viral infections

Two discs treated 3 ways

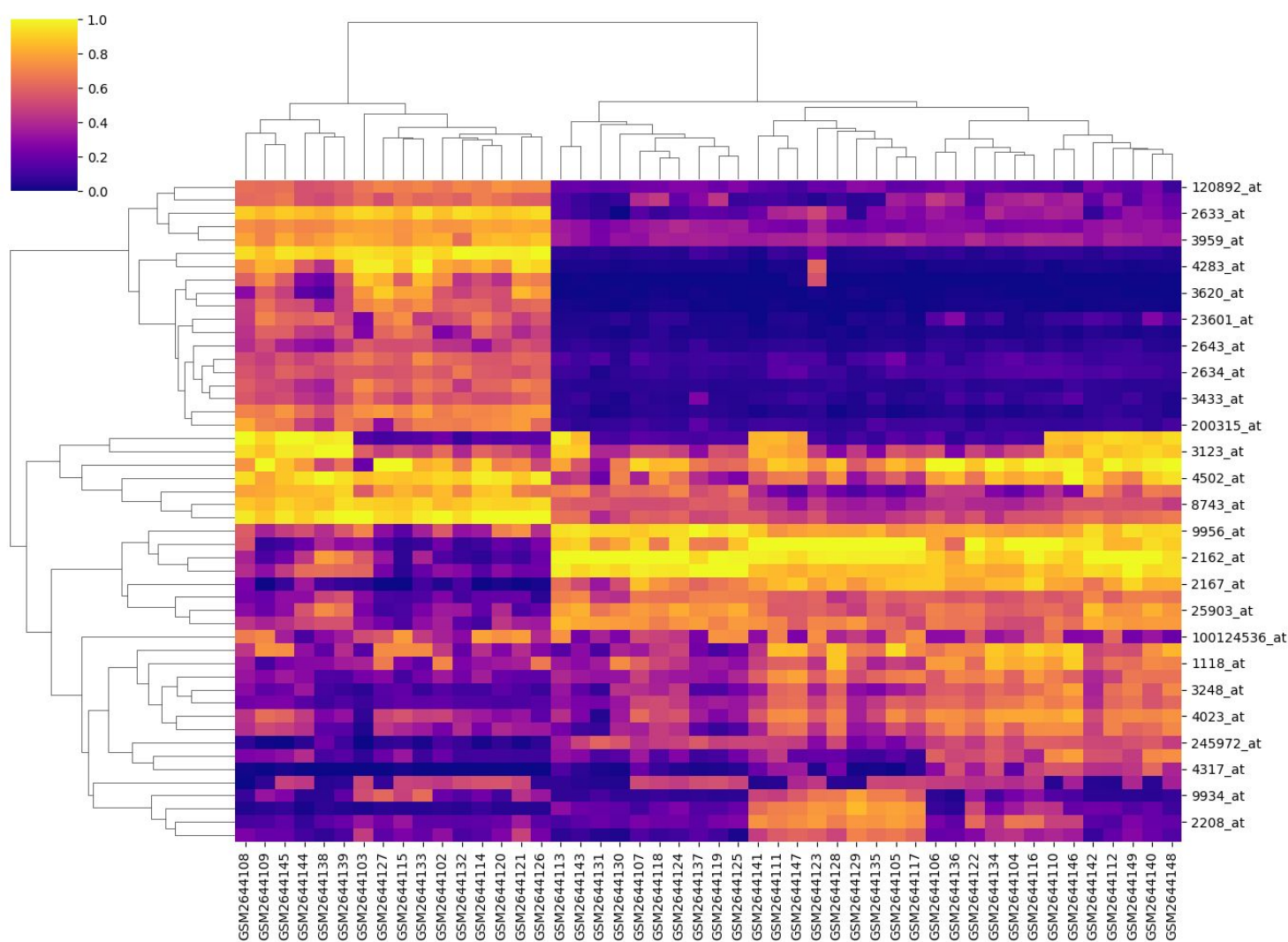
1. Control
2. Interferon Gamma (IFN- γ)
 - a. stimulate the inflammatory or pre rejection environment
3. Interleukin - 4 (IL- 4)
 - a. body accepts the implant



50 Randomly Selected Genes

Heatmap- shows
magnitude of values
based on colors

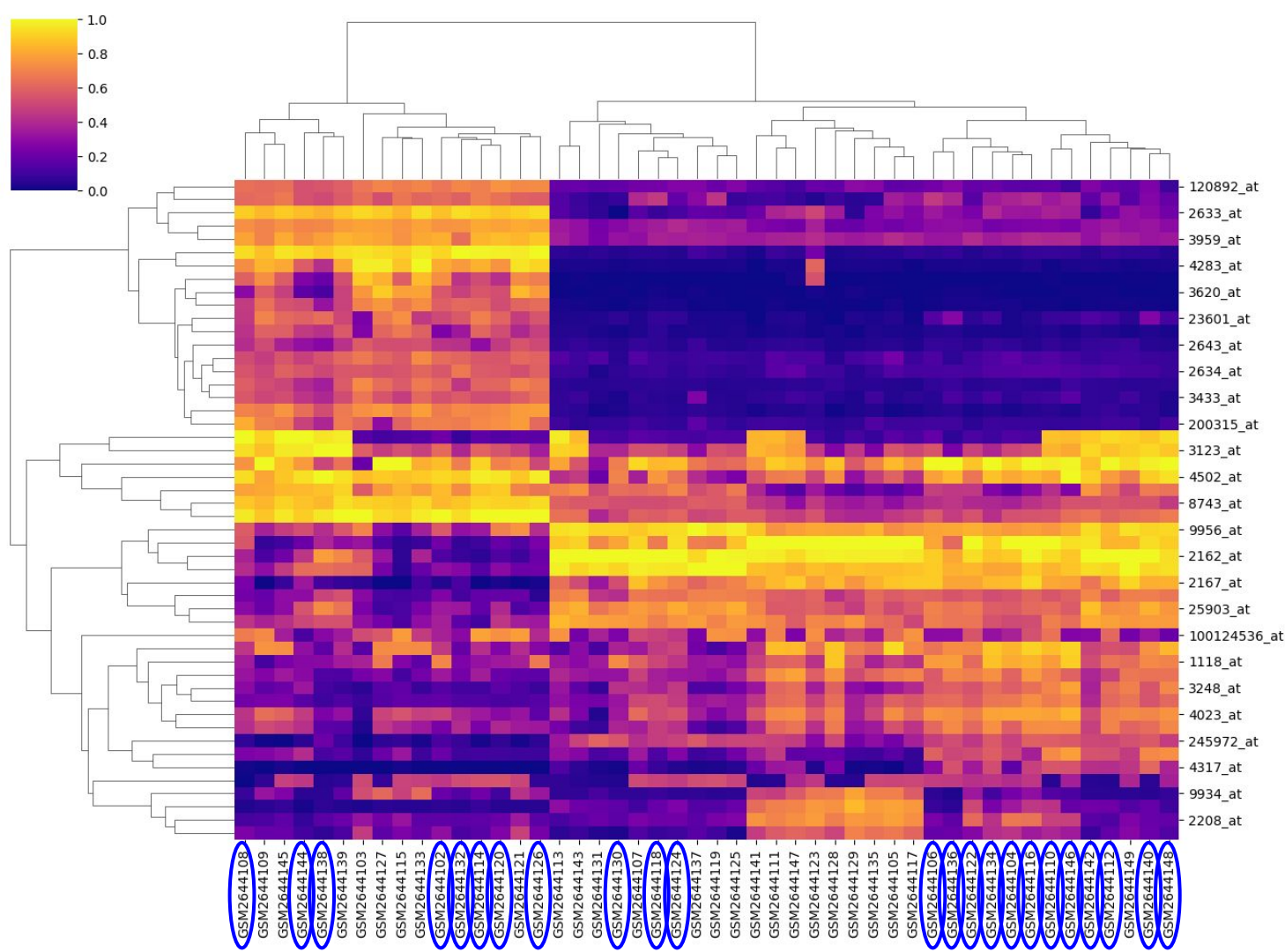
Higher gene
expression → light
color (yellow)



50 Highest Variance Genes

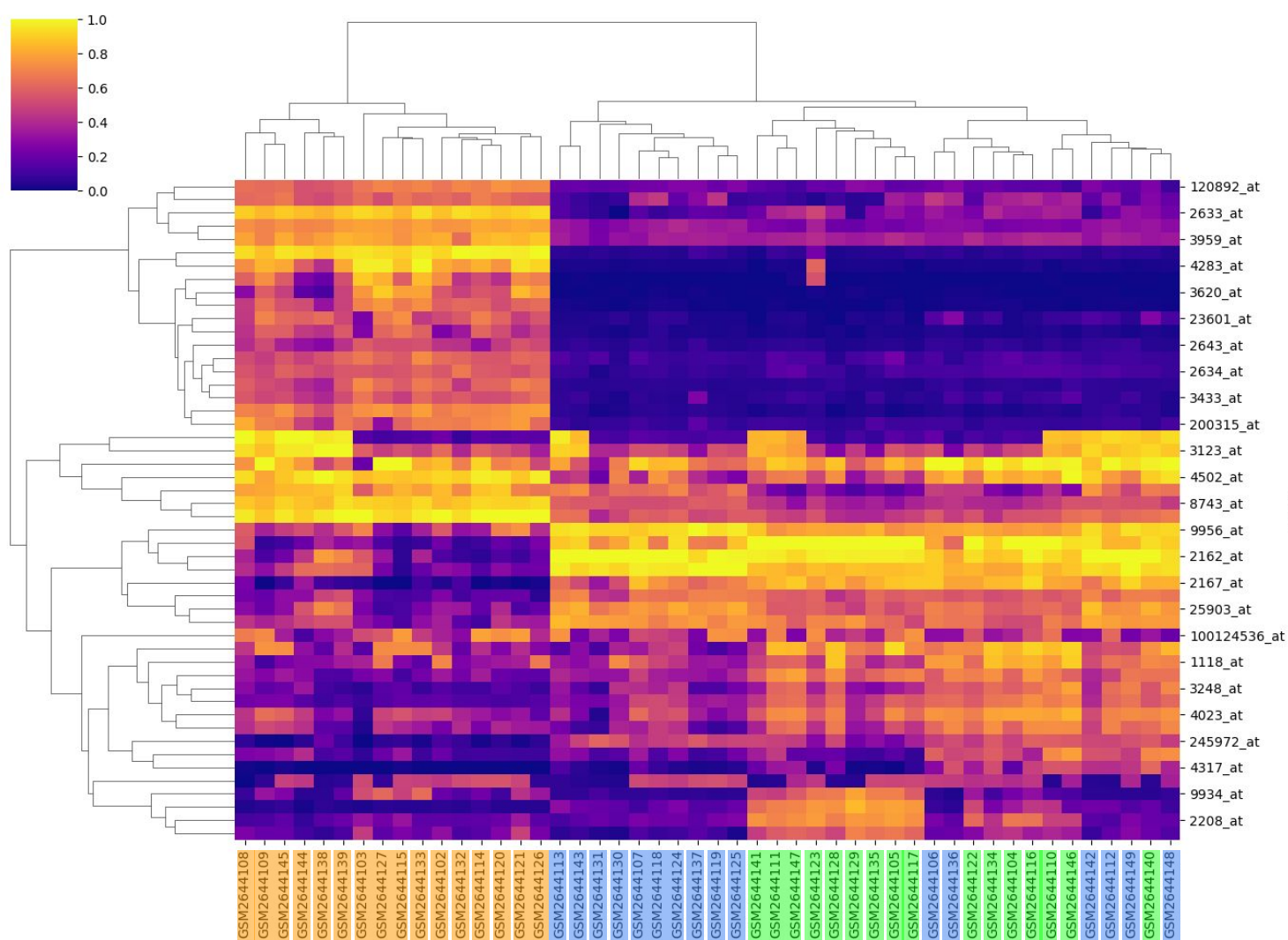
Variance - how spread out the gene expressions are

$$s^2 = (1 / (n - 1)) \times \sum (x_i - \bar{x})^2$$



50 Highest Variance Genes

Porous Titanium Disc

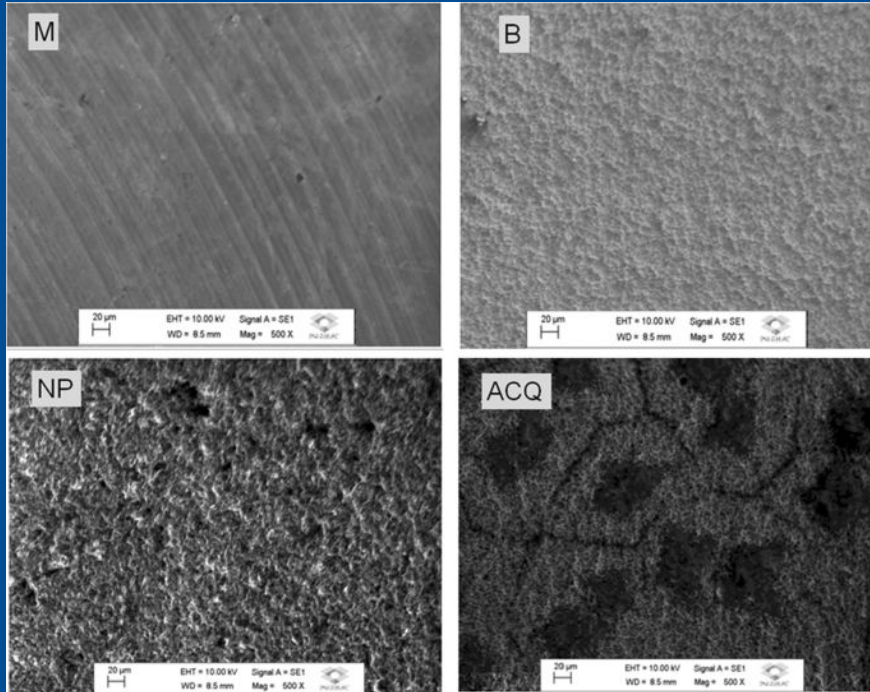


50 Highest Variance Genes

- IFN Gamma Stimulation
- IL Stimulation
- No Stimulation

Topography Reactions

Spanish University 2010 → 2019



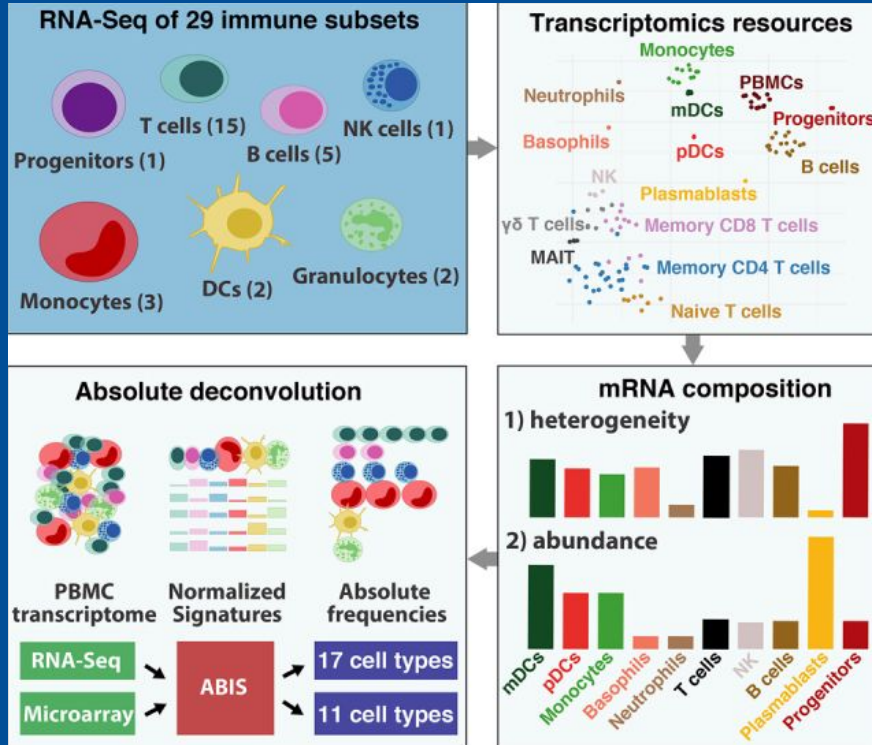
Topography - the surface of a material

- Can affect the effectiveness and acceptance of the medical device or implant

Research tested genes when exposed to a rough titanium surface and a smoother fluoride treated titanium surface

Immune Cell Profiling

German Medical Center 2019



Peripheral blood mononuclear cell - type of white blood cell

- Essential to immune response

Performed RNA sequencing to more accurately measure gene expression in these cells

Genes of Interest

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IL6

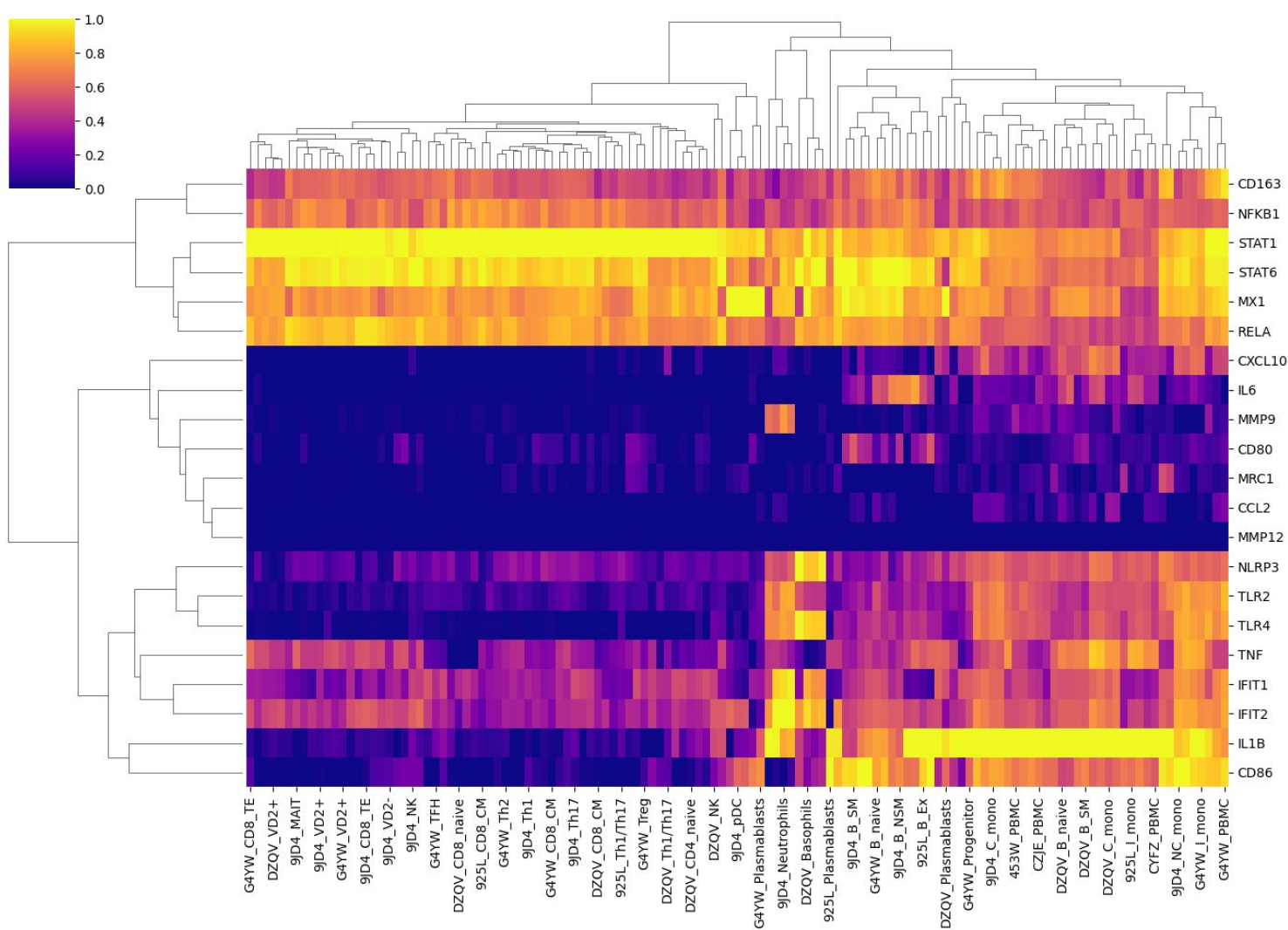
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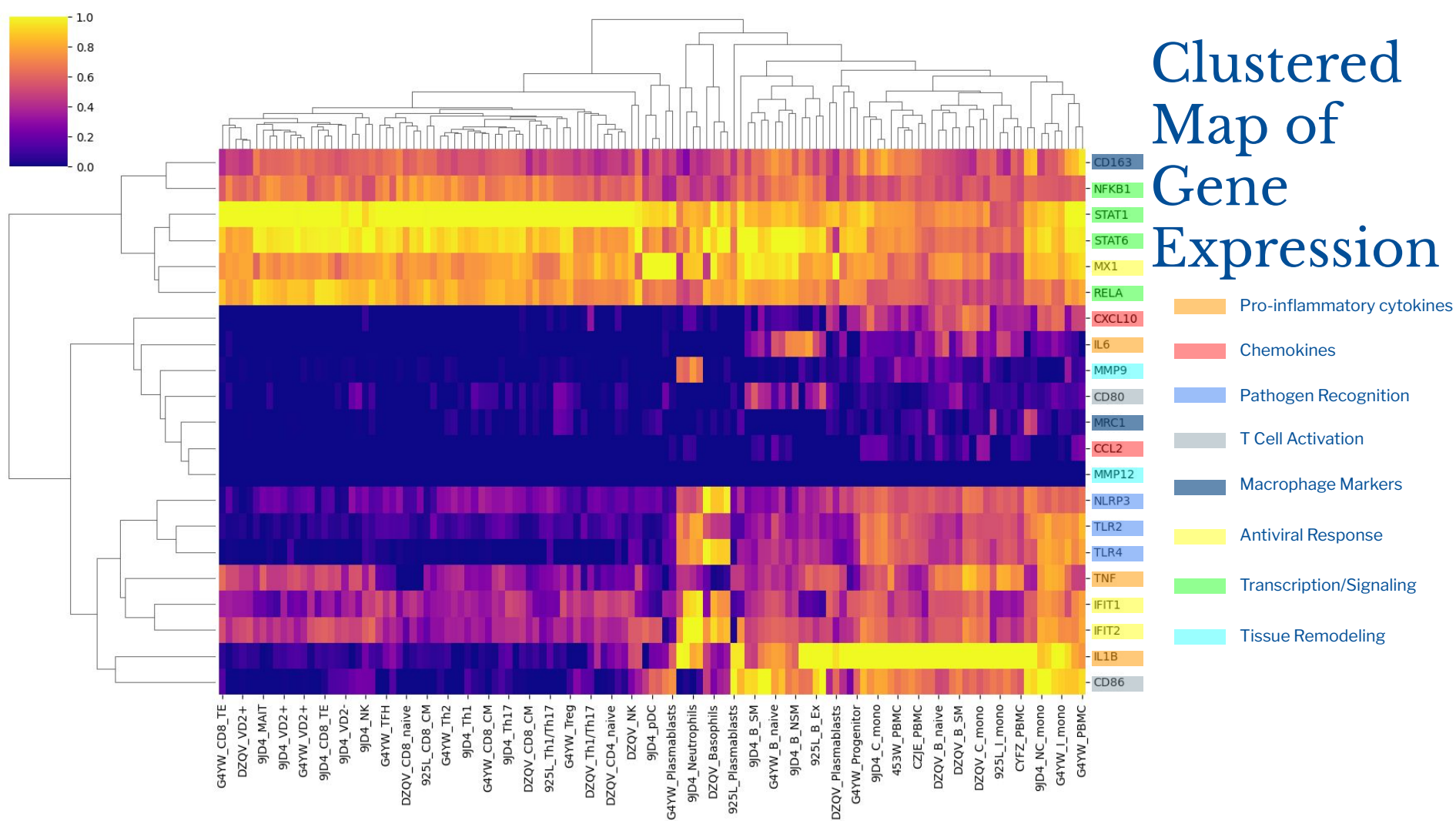
NFKB1

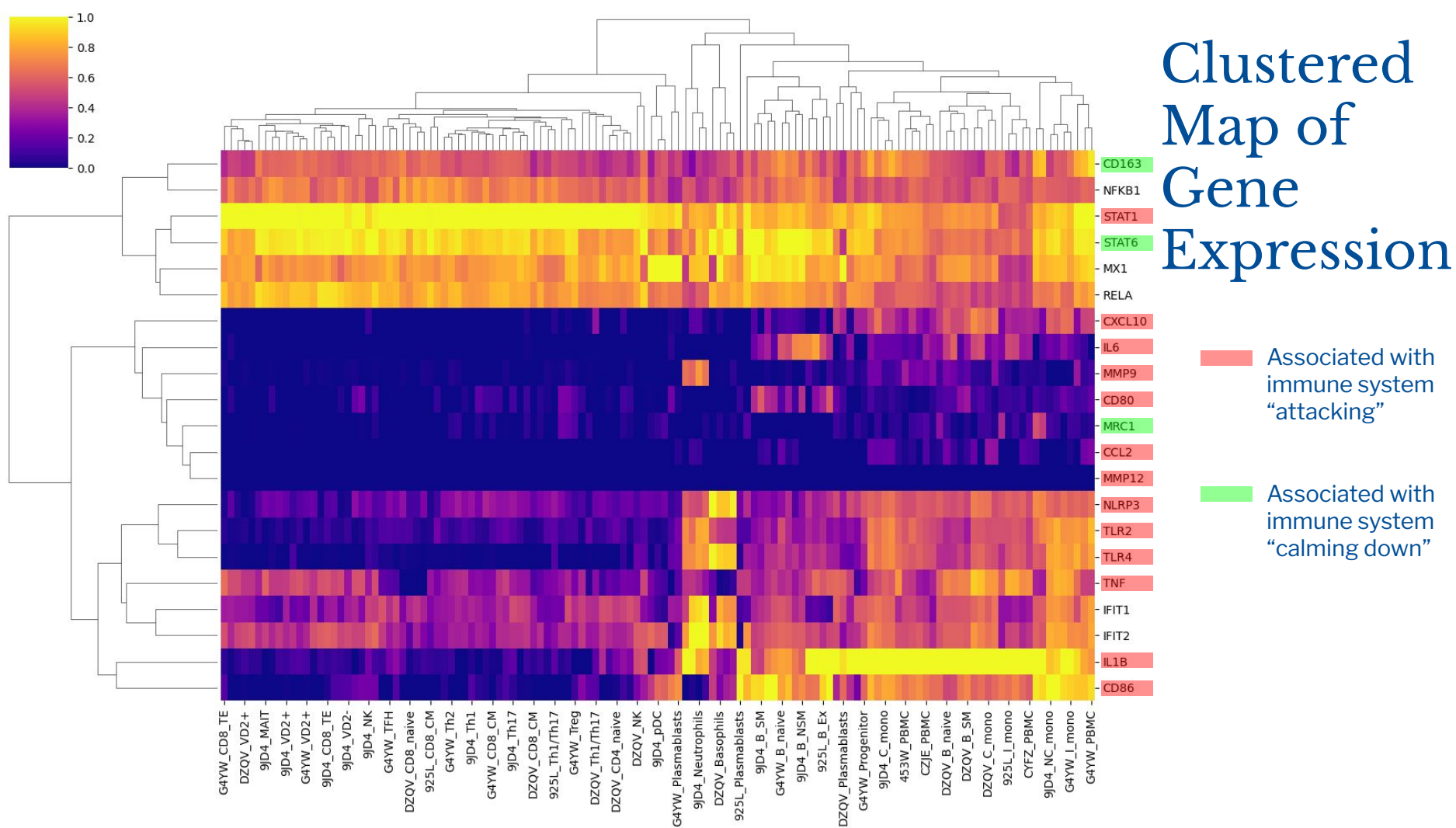
- regulator of immune response
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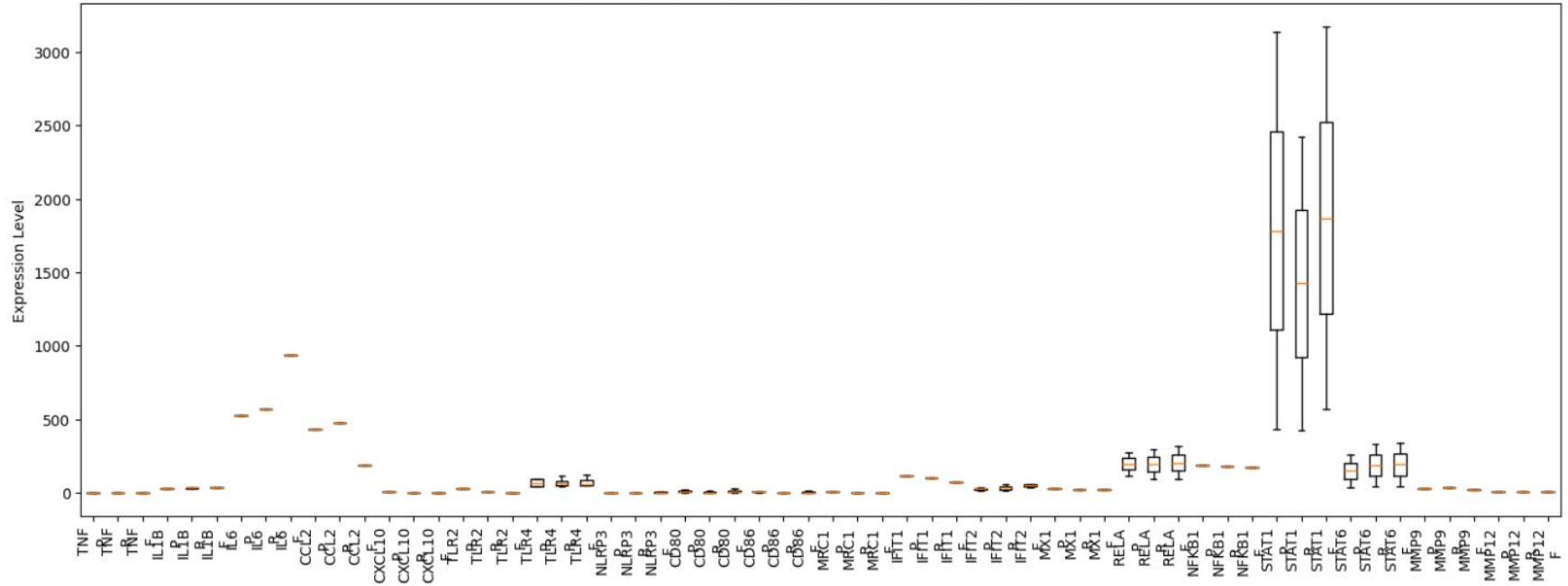
Clustered Map of Gene Expression

- Genes on y axis selected from topography study
- Gene expression data from immune systems profiling study
- Sampled & predicted cell type on x axis
 - Found computationally

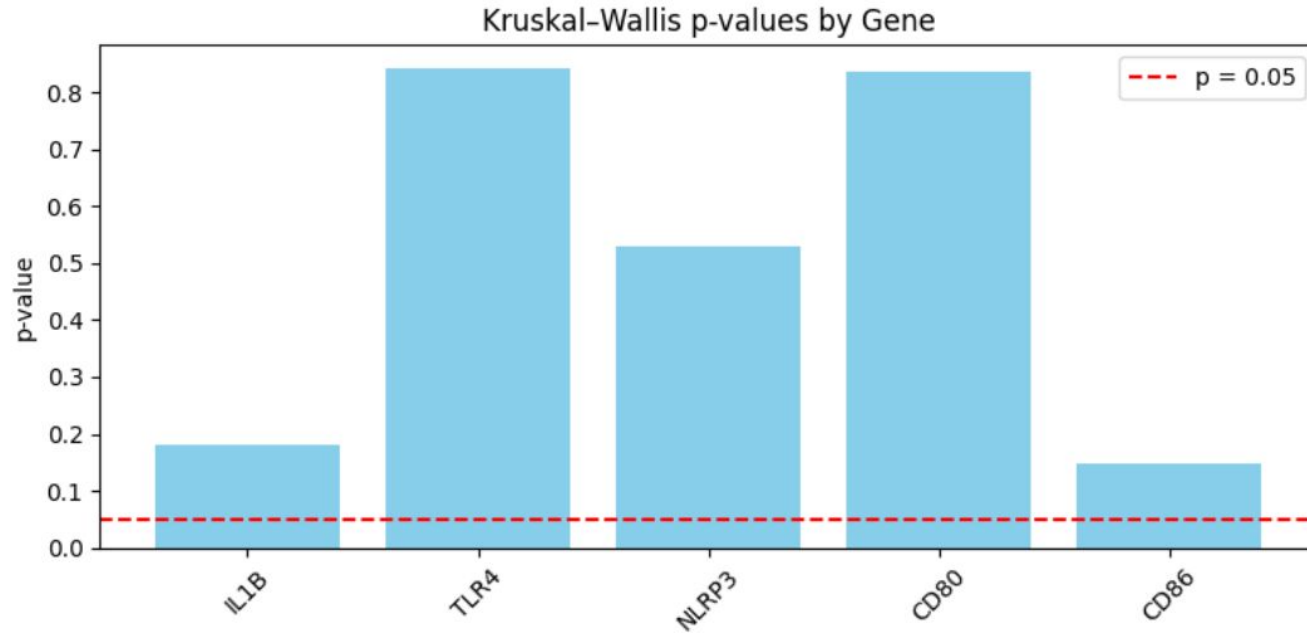




P = Polished, R = Rough, F = Fluoride

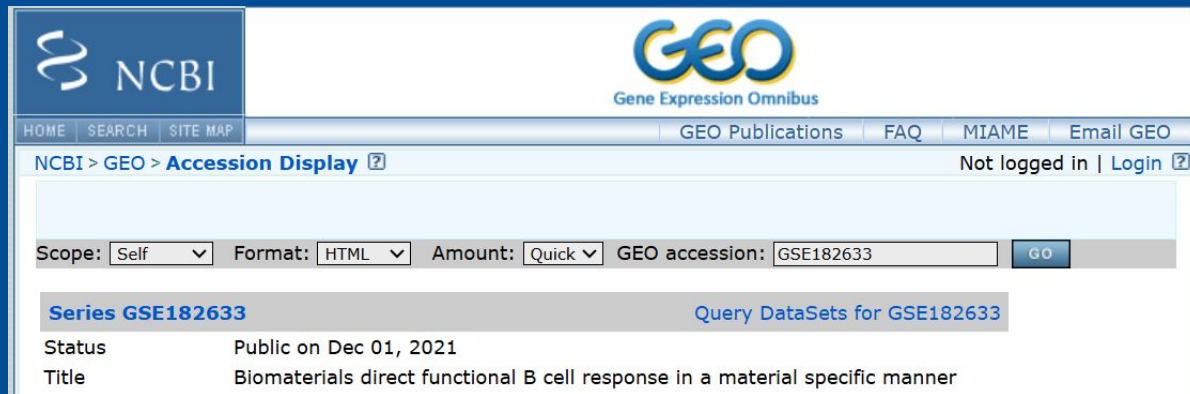


- Shows which genes look different between the surfaces
- STAT1 is a key transcription factor that gets activated cytokines, and stress or inflammation
- CD86 has one of the lowest expression levels



- Shows which differences are likely real using Kruskal-Wallis Test
- Would need more samples to confirm possible treatment effect

Methods



The screenshot shows the NCBI GEO website interface. At the top, there's the NCBI logo and the GEO Gene Expression Omnibus logo. Below the navigation bar, the breadcrumb trail reads "NCBI > GEO > Accession Display". The main search area contains a form with the following fields: "Scope" set to "Self", "Format" set to "HTML", "Amount" set to "Quick", and "GEO accession" set to "GSE182633". A "GO" button is next to the accession number. Below the search bar, the results for "Series GSE182633" are displayed, including a link to "Query DataSets for GSE182633". The status is "Public on Dec 01, 2021" and the title is "Biomaterials direct functional B cell response in a material specific manner".

Series GSE182633	
Status	Public on Dec 01, 2021
Title	Biomaterials direct functional B cell response in a material specific manner

Find the datasets - we found
GEO the most helpful

Read the study, identify
variables, what can this
study show us?

Clean the data organize
ideas, find the best way to
display it

Analyze the graph in the
context of the study, what
does this show?



Results

Gene Expression

Genes react to varied materials and varied stimulations

High Variance

Variance can be related to immune systems activity

Topography

Rough surface can spike inflammatory genes like STAT1

Early Detection

Genes can help observe acceptance or rejection of implants

Next Steps

- Find more data
- Expand material analyzation
- Create tests that can trace certain genes to a negative or positive reaction

What would we do if we had more time?



Future Plans



A decorative graphic on the left side of the slide consisting of several blue hexagons of different shades (dark blue and light blue) arranged in a geometric pattern.

Thank you!

Any questions?

References

1. *MICROARRAY-BASED GENE EXPRESSION ANALYSIS OF HUMAN OSTEOLASTS IN RESPONSE TO ROUGHNESS AND FLUORIDE TREATMENT OF TITANIUM IMPLANTS*. Refine.bio. (n.d.).
<https://www.refine.bio/experiments/GSE22217/microarray-based->
2. U.S. National Library of Medicine. (2021, February 10). *Geo accession viewer*. National Center for Biotechnology Information.
<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE99445>
3. JH, E. (2021, December 1). *Geo accession viewer*. National Center for Biotechnology Information.
https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE182633&utm_source
4. U.S. Department of Health and Human Services. (2023, October 23). *New insight into the immune response forges a path toward improved medical implants*. National Institute of Biomedical Imaging and Bioengineering.
<https://www.nibib.nih.gov/news-events/newsroom/new-insight-immune-response-forges-path-toward-improved-medical-implants>
5. Kim A;Downer MA;Berry CE;Valencia C;Fazilat AZ;Griffin M; A. M. C. C. A. M. (2023, December 11). *Investigating immunomodulatory biomaterials for preventing the foreign body response*. Bioengineering (Basel, Switzerland).
<https://pubmed.ncbi.nlm.nih.gov/38136002/>
6. *MICROARRAY-BASED GENE EXPRESSION ANALYSIS OF HUMAN OSTEOLASTS IN RESPONSE TO ROUGHNESS AND FLUORIDE TREATMENT OF TITANIUM IMPLANTS*. Refine.bio. (n.d.).
<https://www.refine.bio/experiments/GSE22217/microarray-based->
7. August 7, 2024 • Portland. (2024, August 7). *Une's Eva Rose Balog delivers "genius" presentation to audience of Maine Science Enthusiasts*. University of New England.
<https://www.une.edu/news/2024/unes-eva-rose-balog-delivers-genius-presentation-audience-maine-science-enthusiasts>

Current Research Findings

- Natural Biomaterials are Showing Promise
- Problems with Synthetic Materials
- Advanced Modeling of Immune Response

Gene Expression & Variance

How do they relate and how did we calculate?

Variance - how spread out the gene expressions are

$$s^2 = (1 / (n - 1)) \times \sum (x_i - \bar{x})^2$$

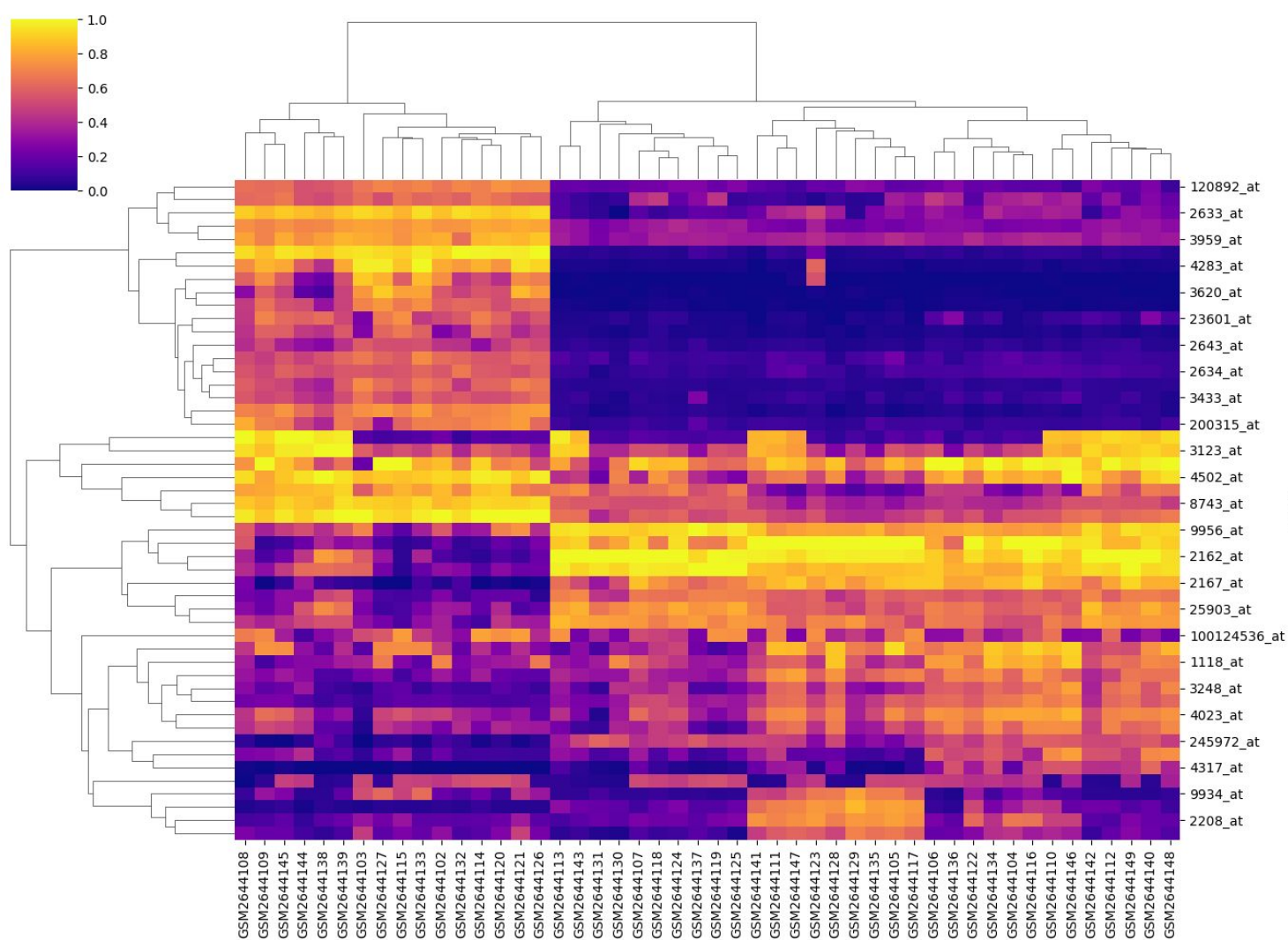
- s^2 is the sample variance
- n is the number of observations
- x_i is each individual value
- \bar{x} is the mean of all values
- Σ means "sum over all"

Coding:

#calculate the variance of each row

#sorted gene variance from highest to lowest

#took top 50 from there



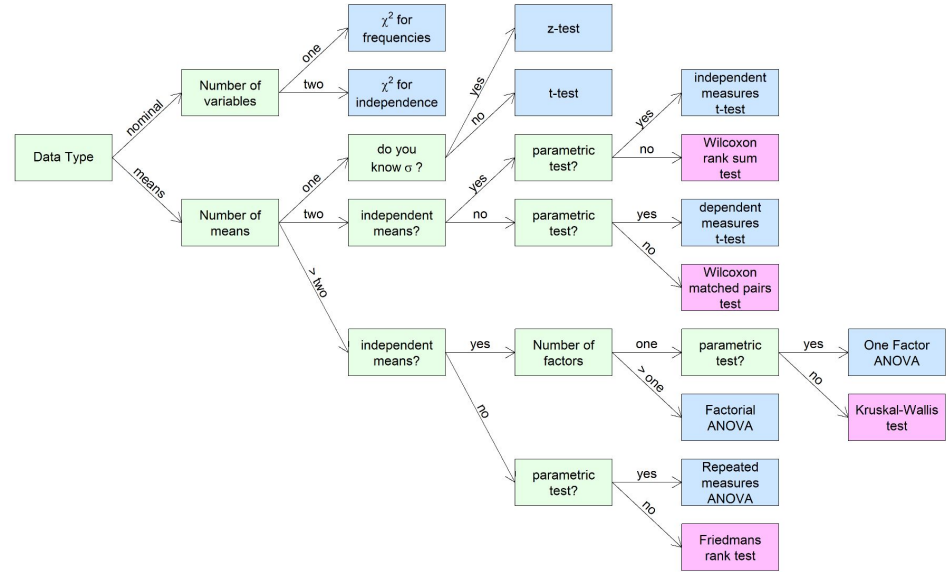
50 Highest Variance Genes

#data is still gene
expression

#values are just
selected to only be
the genes with
highest variance

ID_REF

Statistical Analysis



Statistical Analysis

- Some immune-related genes (like STAT1, IL6) look more active with certain treatments
- But visual differences in gene expression can be misleading
- To confirm if these differences are real, we ran a Kruskal-Wallis test
- This test compares the average expression levels of each gene across the three treatment groups (polished, rough, fluoride-treated)

Studies with these datasets

Mapping of γ/δ T cells reveals V δ 2+ T cells resistance to senescence

- To explore how aging affects T cell subsets
 - stress response
- These T cells are uniquely resilient to age-associated decline
- Used RNA-Seq data enabled analysis of gene expression various T cells

Xu W, Monaco G, Wong EH, Tan WLW, Kared H, Simoni Y, Tan SW, How WZY, Tan CTY, Lee BTK, Carbajo D, K G S, Low ICH, Mok EWH, Foo S, Lum J, Tey HL, Tan WP, Poidinger M, Newell E, Ng TP, Foo R, Akbar AN, Fülöp T, Larbi A. Mapping of γ/δ T cells reveals V δ 2+ T cells resistance to senescence. EBioMedicine. 2019 Jan;39:44-58. doi: 10.1016/j.ebiom.2018.11.053. Epub 2018 Dec 7. PMID: 30528453; PMCID: PMC6354624.

Limitations

- Not all datasets included results or the informations that we thought they would
- We had to narrow down our question to be completed in the 1 week timeslot
- Finding datasets that displayed data that was relevant