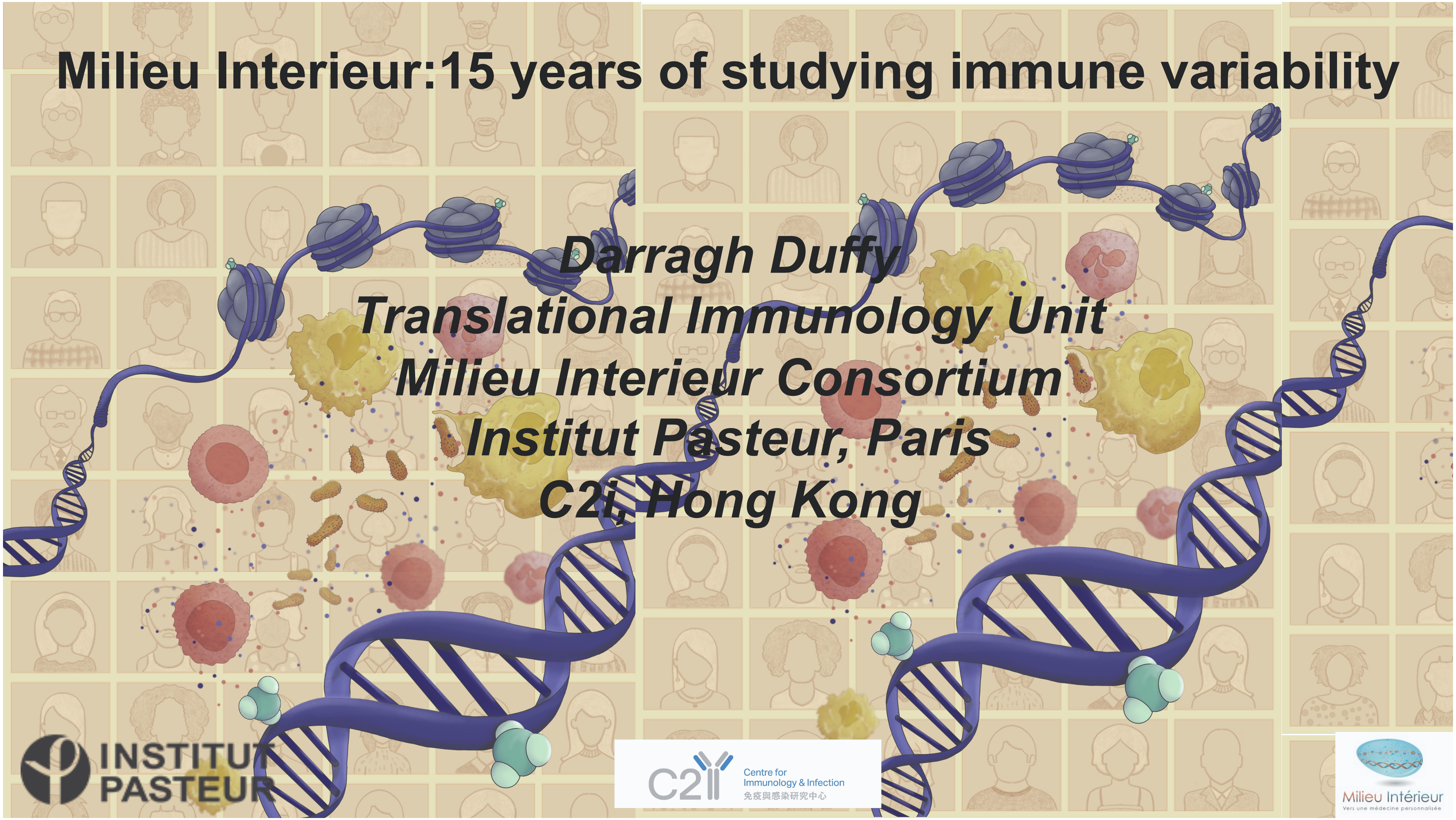
Milieu Interieur:15 years of studying immune variability



Darragh Duffy

Translational Immunology Unit

Milieu Interieur Consortium

Institut Pasteur, Paris

C2i, Hong Kong

INSTITUT PASTEUR

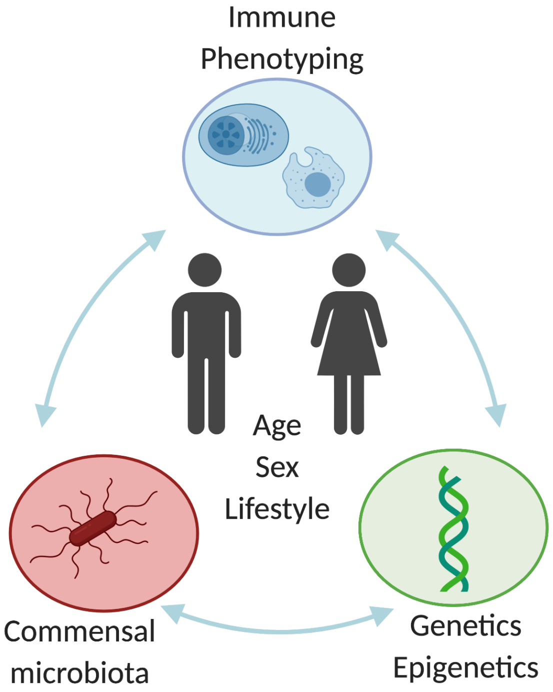
C2i
Centre for
Immunology & Infection
免疫與感染研究中心

Milieu Intérieur
Vers une médecine personnalisée

Milieu Interieur: concept and objectives

- ✓ Immune responses are highly variable
- ✓ We can dissect what causes this variance in healthy state
- ➢ **Hypothesis: A better understanding of this variability can identify new strategies for managing disease & health**

Claude Bernard 1813-1878



Immune Phenotyping

Age
Sex
Lifestyle

Commensal microbiota

Genetics
Epigenetics

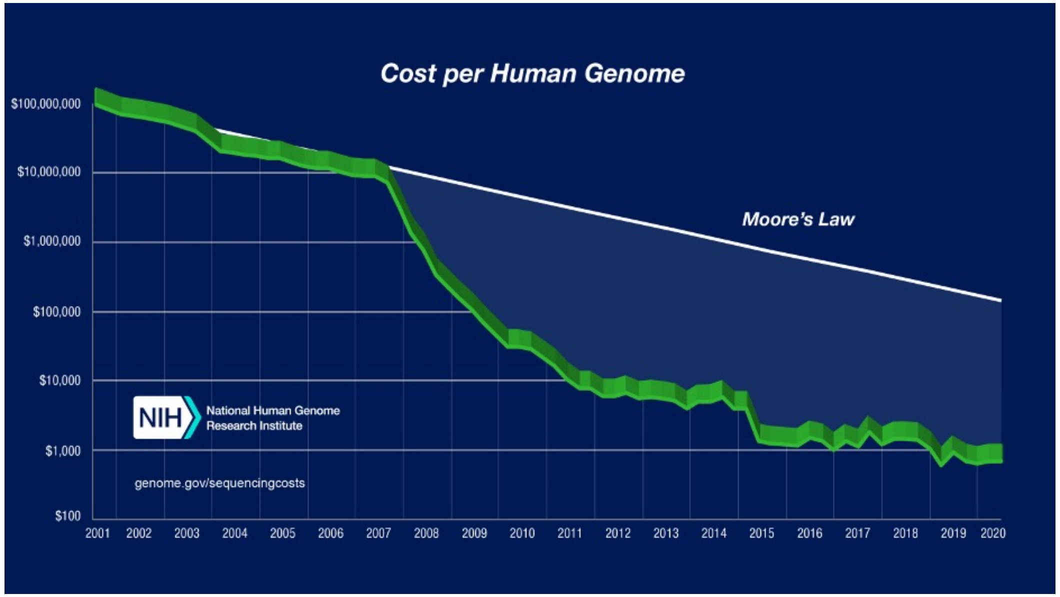
Matthew Albert

Lluis Quintana-Murci

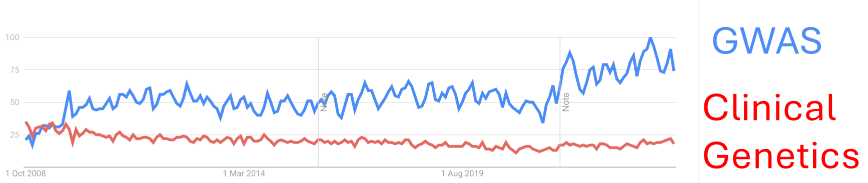
- ✓ Vaccine response
- ✓ Outcome to infection
- ✓ Cancer immunotherapy
- ✓ Autoimmunity / Allergy
- ✓ Neurologic disease and degenerations

"La fixité du milieu intérieur est la condition de la vie libre et indépendante"

Revolution in genomics has not lead to revolution in genetic clinical testing….

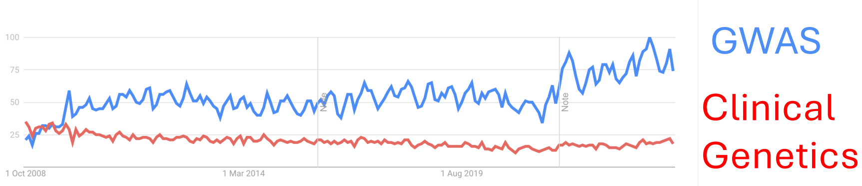


Google search trends since 2008



Revolution in genomics has not lead to revolution in genetic clinical testing….

Google search trends since 2008



39 FDA approved pharmacogenomic Biomarkers

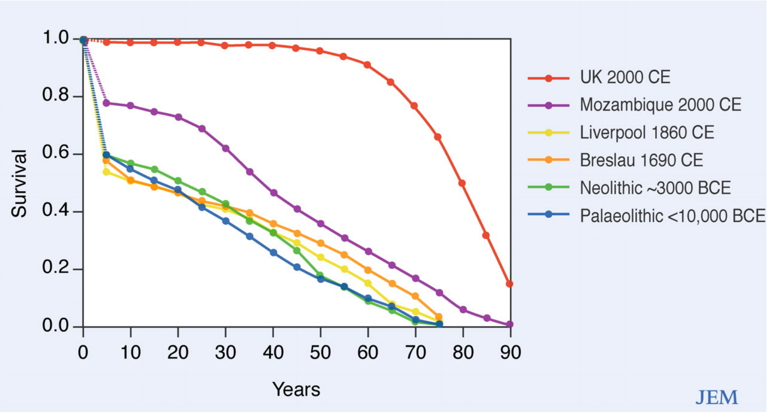
Biomarker	*Disease Area*
ALK	Oncology
Antithrombin III deficiency	Hematology
APOE2	Metabolic, Endocrinology
BRAF	Oncology
C-Kit	Oncology
CCR5	Antivirals
CD20 antigen	Oncology
CD25	Oncology
CD30	Oncology
CFTR (G551D)	Pulmonary
Chromosome 5q	Hematology
CYP1A2	Gastroenterology
CYP2C19	Multiple
CYP2C9	Analgesics, Hematology
CYP2D6	Multiple
DPD	Oncology
EGFR	Oncology
ER	Oncology
ER &/ PGR	Oncology
ERBB2 (HER2)	Oncology
Factor V Leiden (FV)	Oncology
FIP1L1-PDGFRα	Oncology
G6PD	Antiinfectives
HGPRT	Transplantation
HLA-B*1502	Neurology
HLA-B*5701	Antivirals
IL28B	Antivirals
KRAS	Oncology
LDL receptor	Metabolic & Endocrinology
NAT1; NAT2	Cardiovascular
NAT1; NAT2	Antiinfectives
PDGFR	Oncology
Ph Chromosome	Oncology
PML/RARα	Oncology
Prothrombin mutations (F2)	Oncology
TPMT	Rheumatology
UCD	Gastroenterology
UGT1A1	Oncology
VKORC1	Hematology

Only 5 for infectious disease

Biomarker	*Disease Area*	*Drug*
CCR5	HIV	Maraviroc
G6PD	Malaria	Chloroquine
HLA-B*5701	HIV	Abacavir
IL28B	HCV	Peginterferon alfa-2b, Boceprevir, Teleprevir
NAT1; NAT2	TB	Rifampin, Isoniazid, and Pyrazinamide

Genetics reflects our evolutionary history & environment our modern present

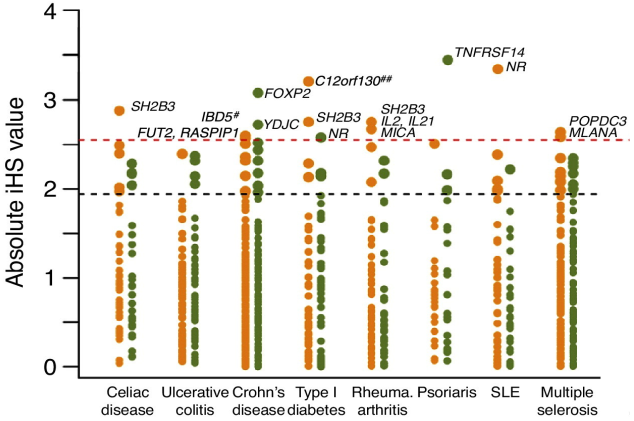
Life expectancy ~25 years
(pre-industrial revolution)



Clean water &
Environments
Antibiotics
Vaccines

Rich diets
Alcohol & smoking
Sedentary lifestyles
Pollution

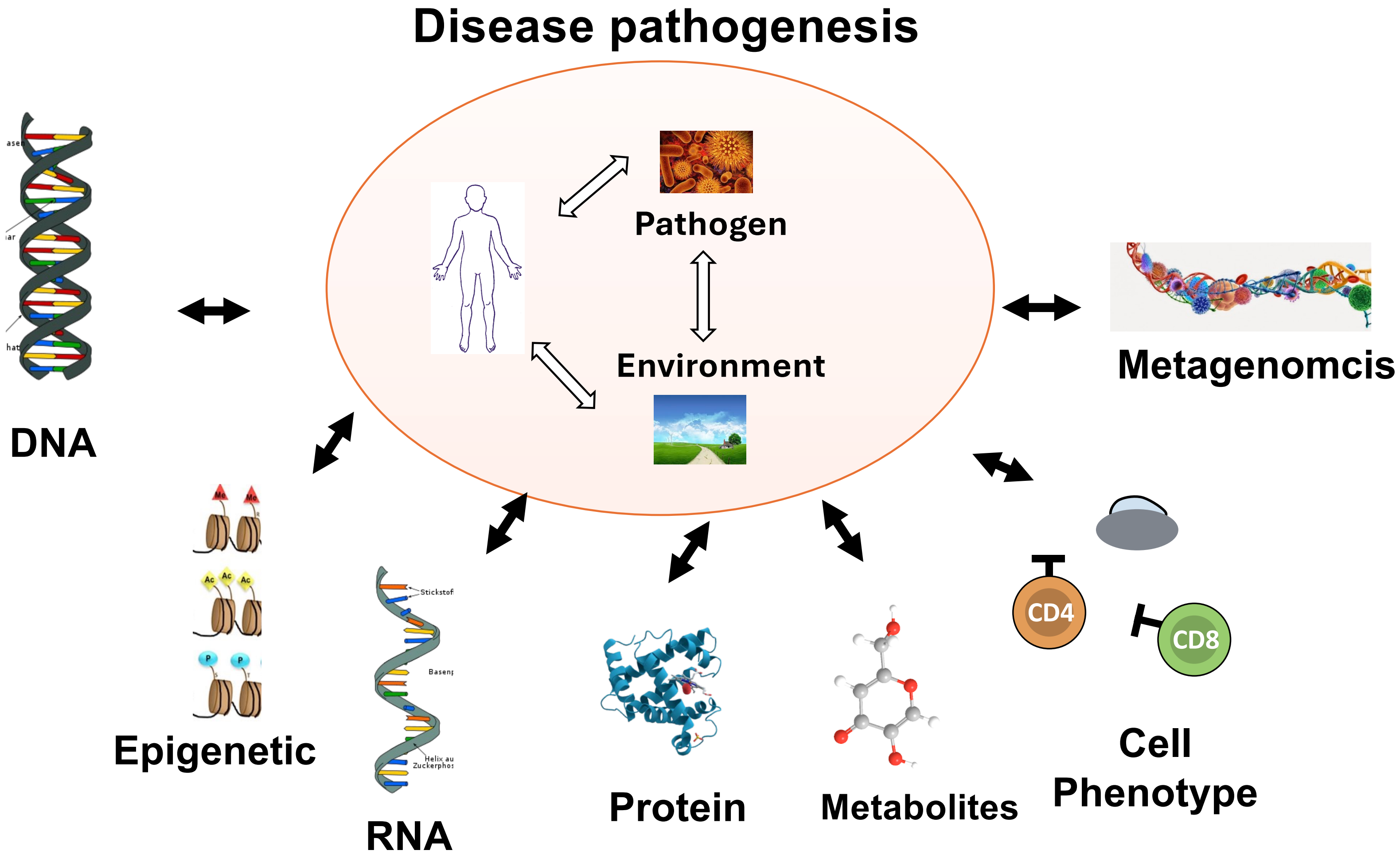
Genes with recent evolutionary selection
→ autoimmune/inflammatory diseases



Casanova & Abel JEM 2015

Brinkworth & Barreiro COI 2014

Binary approach to identify correlates to treatment response



Disease pathogenesis

Pathogen

Environment

DNA

Metagenomcis

Epigenetic

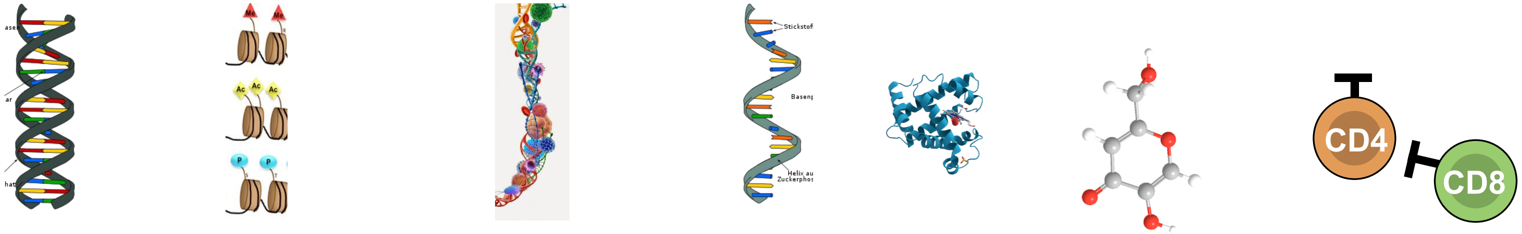
RNA

Protein

Metabolites

Cell Phenotype

Milieu Interieur: integrated systems biology approach

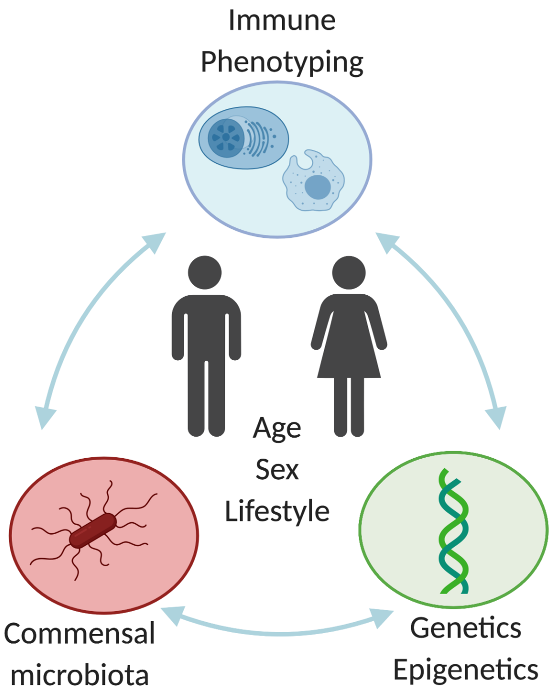


DNA **Epigenetic** **Metagenomcis** **RNA** **Protein** **Metabolites** **Cells**

Intermediate phenotypes

1. Define the “normal boundaries” of a functional healthy immune response & identify outliers
2. Associate natural immune variance with physiological, environmental, & genetic factors
3. Comparison studies in disease populations

How to define “healthy” ?



Immune Phenotyping

Age

Sex

Lifestyle

Commensal microbiota

Genetics

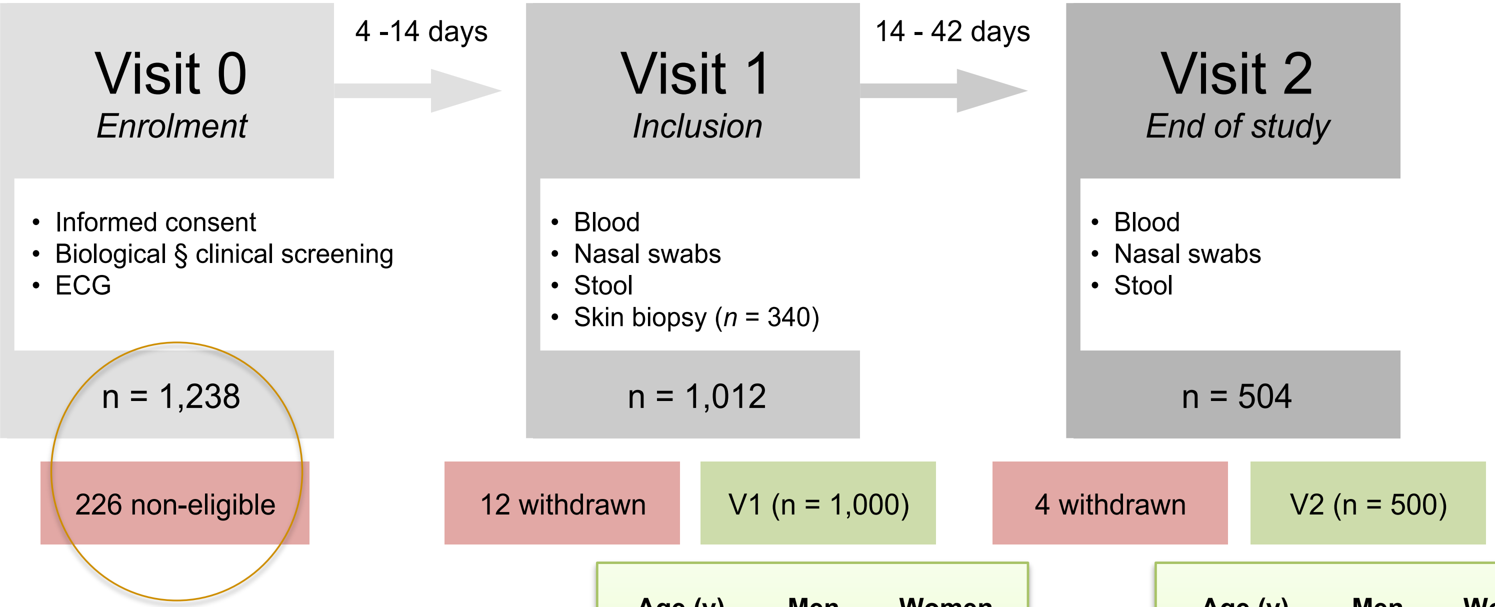
Epigenetics

Inclusion Criteria	**Exclusion criteria** *(for complete list see Supplementary Text)*
- Subjects considered as healthy by the investigator based on medical history, clinical examination, laboratory results and ECG[§] - Availability for all scheduled visits at the investigational site. - Healthy male or female aged between 20 and 69 (included) years - Metropolitan French origin for 3 generations - 18.5 ≤BMI ≤ 32 kg/m² - Ability to give their informed consent in writing - Must understand spoken and written French - Affiliated to the French social security or assimilated regimens - Registered on the French “Fichier des Volontaires se prêtant à la Recherche Biomédicale (VRB)”*	- Relatedness to previously recruited individuals in the study cohort - Travel in (sub-)tropical countries within the last 3 months - For women: pregnant or breastfeeding or intending to become pregnant or peri-menopausal - Any physical exercise within the last 8 hours before inclusion (V1) and before (V2) - Subjects following a special diet for medical reasons - Alcohol abuse - Illicit drug use or substance abuse within 3 months prior to inclusion - Presence of evidence of neurological or psychiatric diagnoses - Severe/chronic/recurrent pathological conditions - Chronic administration of immunosuppressants or other immune-modifying drugs within the 6 months prior to the inclusion - Receipt of any vaccination 3 months before the inclusion - Receipt of blood products or immunoglobulins within 3 months prior the inclusion - Hemoglobin measurement less than 10.0 g/dL for women and less than 11.5 g/dL for men - Platelet count less than 120.000/mm3 - ALT and/or AST > 3 times the upper limit of the norm[†] - Allergy to lidocaine

Thomas *et al* (Clinical Immunology 2015)

Recruitment of 1000 healthy donors

- Donors recruited at one site in Rennes (Biotrial) from September 2012 – July 2013



4 -14 days

14 - 42 days

Visit 0
Enrolment

- Informed consent
- Biological § clinical screening
- ECG

n = 1,238

226 non-eligible

Visit 1
Inclusion

- Blood
- Nasal swabs
- Stool
- Skin biopsy (*n* = 340)

n = 1,012

12 withdrawn

V1 (n = 1,000)

Age (y)	Men	Women
20 – 29	100	100
30 – 39	100	100
40 – 49	100	100
50 – 59	100	100
60 – 69	100	100

Visit 2
End of study

- Blood
- Nasal swabs
- Stool

n = 504

4 withdrawn

V2 (n = 500)

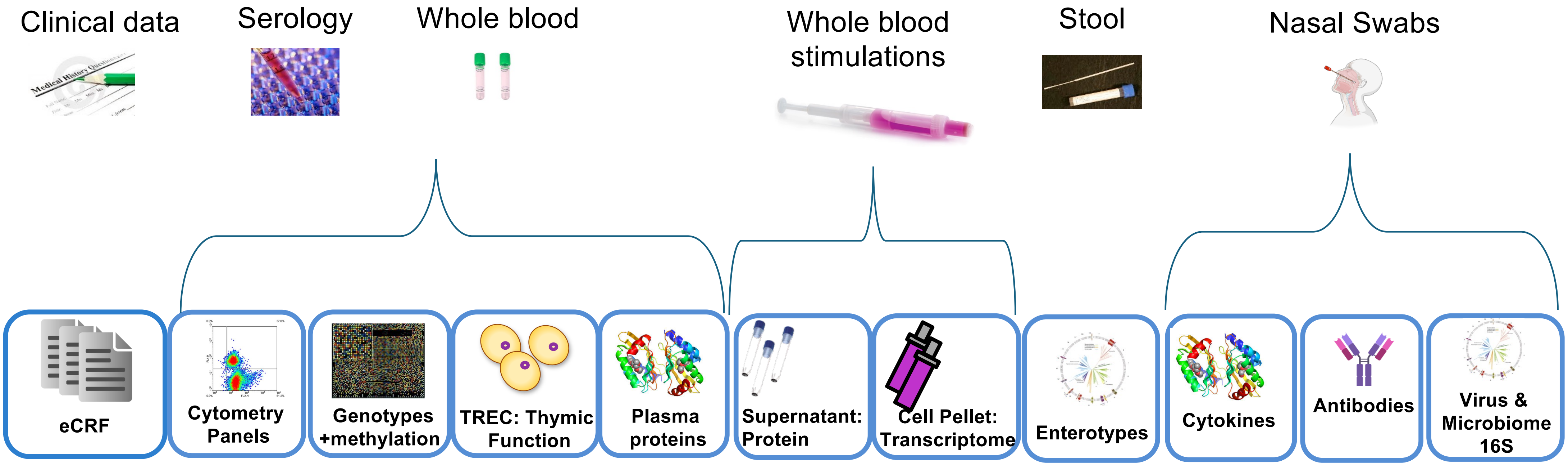
Age (y)	Men	Women
20 – 29	50	50
30 – 39	50	50
40 – 49	50	50
50 – 59	50	50
60 – 69	50	50

Thomas *et al* (Clinical Immunology 2015)

Establishing a rich healthy donor biobank and data warehouse

Milieu Intérieur
Vers une médecine personnalisée

1,000 Healthy donors
Well-defined healthy state
500 men/women
20-69 yrs



Clinical data
Serology
Whole blood
Whole blood stimulations
Stool
Nasal Swabs

- **eCRF**
- **Cytometry Panels**
- **Genotypes +methylation**
- **TREC: Thymic Function**
- **Plasma proteins**
- **Supernatant: Protein**
- **Cell Pellet: Transcriptome**
- **Enterotypes**
- **Cytokines**
- **Antibodies**
- **Virus & Microbiome 16S**

C2I Centre for Immunology & Infection
免疫與感染研究中心

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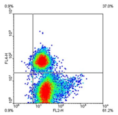
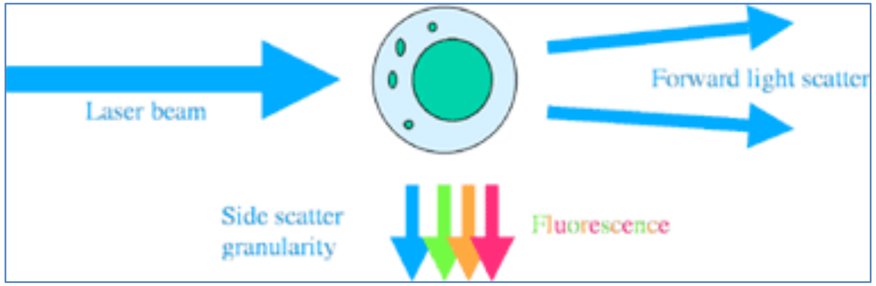
Flow cytometry – characterising multi-parameter cellular populations

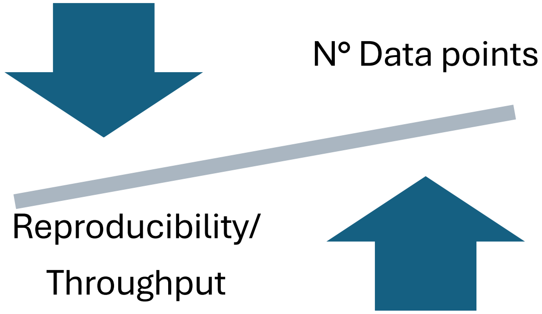


10 Cytometry Panels



Standard Flow (8-12 colours)

CyTOF – Mass Spec based (>50)



N° Data points

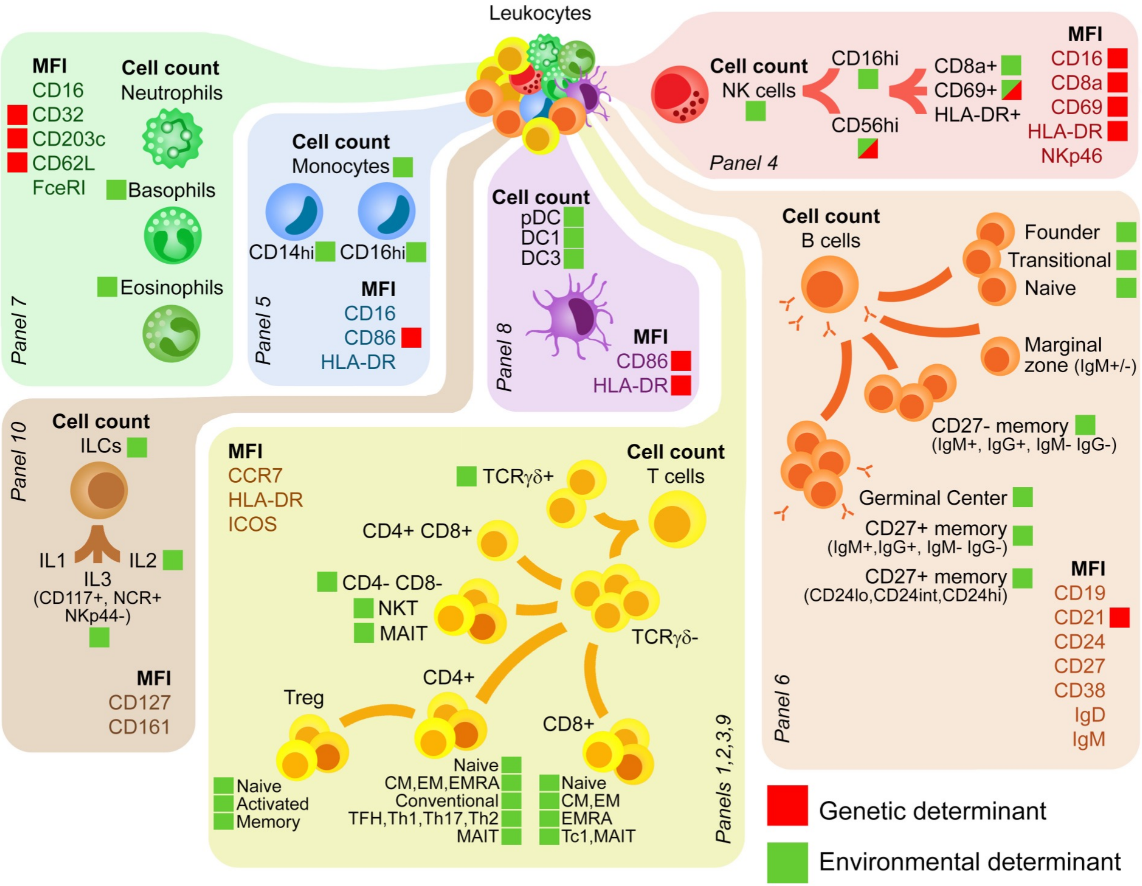
Reproducibility/
Throughput

Genetic and environmental determinants of circulating immune cells

Milieu Intérieur
Vers une médecine personnalisée

x10 panels 8 colour flow cytometry

- 74 subpopulations quantified
- 89 cell surface marker expression



Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

Milena Hasan

Etienne Patin

Jacob Bergstedt

Vincent Rouilly

What does an effect size measure ?

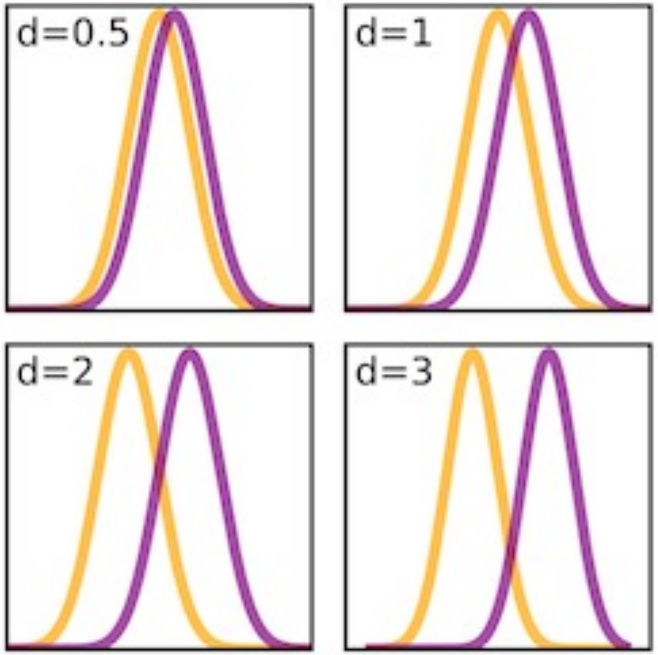
Significance*: tells how likely it is that a result is due to chance*

Effect size*: tells you how important the result is*

Cohen's *d* = $(x_1 - x_2) / s$

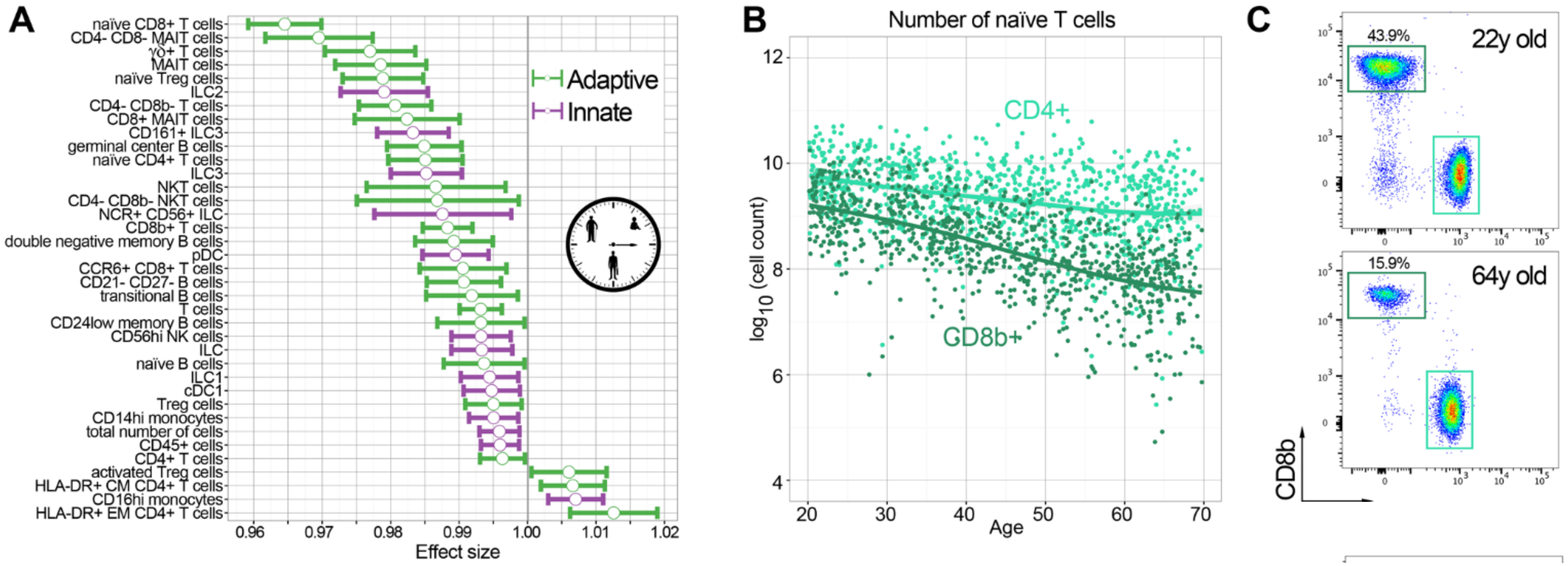
x_1 and x_2 are the sample means of group 1 and group 2,

s is the standard deviation of the population from which the two groups were taken



Dissecting environmental determinants of Immune cells - Age

42/74 subsets affected by age



→ No increase with age of memory T cells

→ Stronger decline with age of naïve CD8+ T cells, with respect to CD4+ (3.5% and 1.5% per year, respectively)

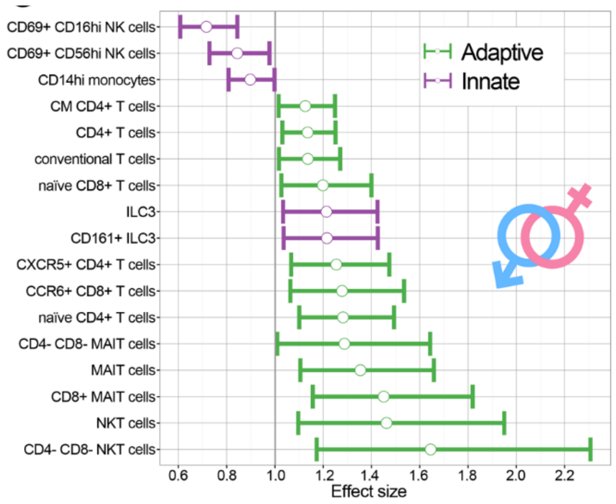
→ CD8+ T cells are more susceptible to homeostatic cytokines and/or the production of CD4+ T cells is preferentially enhanced in the human thymus?

Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

Dissecting environmental determinants of Immune cells - Sex

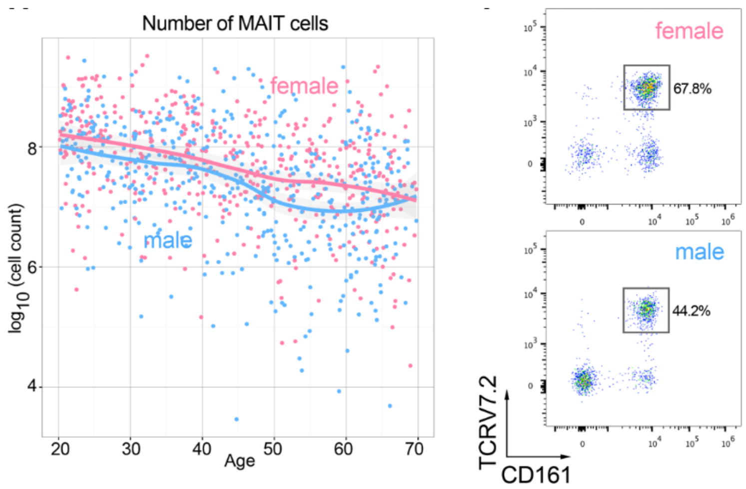
Milieu Intérieur
Vers une médecine personnalisée

17/74 subsets different between sexes



MAIT cells

Sex effect 1.39/Age effect 0.97

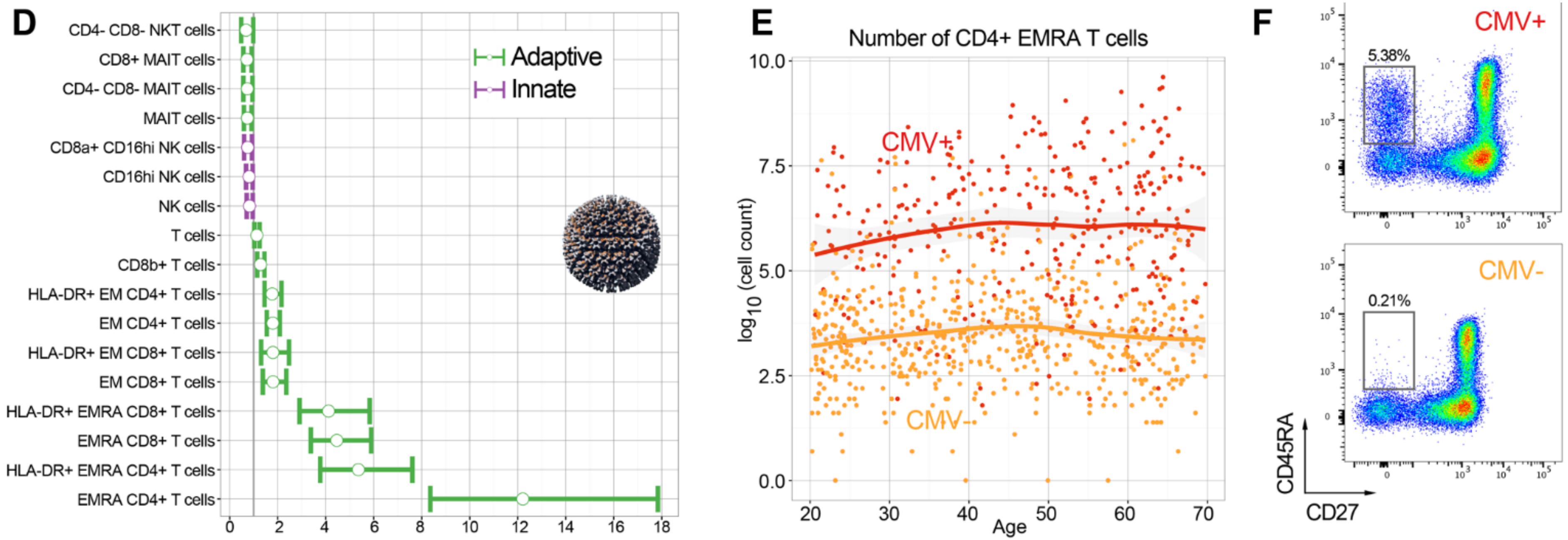


→ Women have greater numbers of MAIT cells, NK T cells, naive CD4+ T cells, ILC3

→ Men have greater numbers of $CD14^{hi}$ monocytes, NK cell subsets

Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

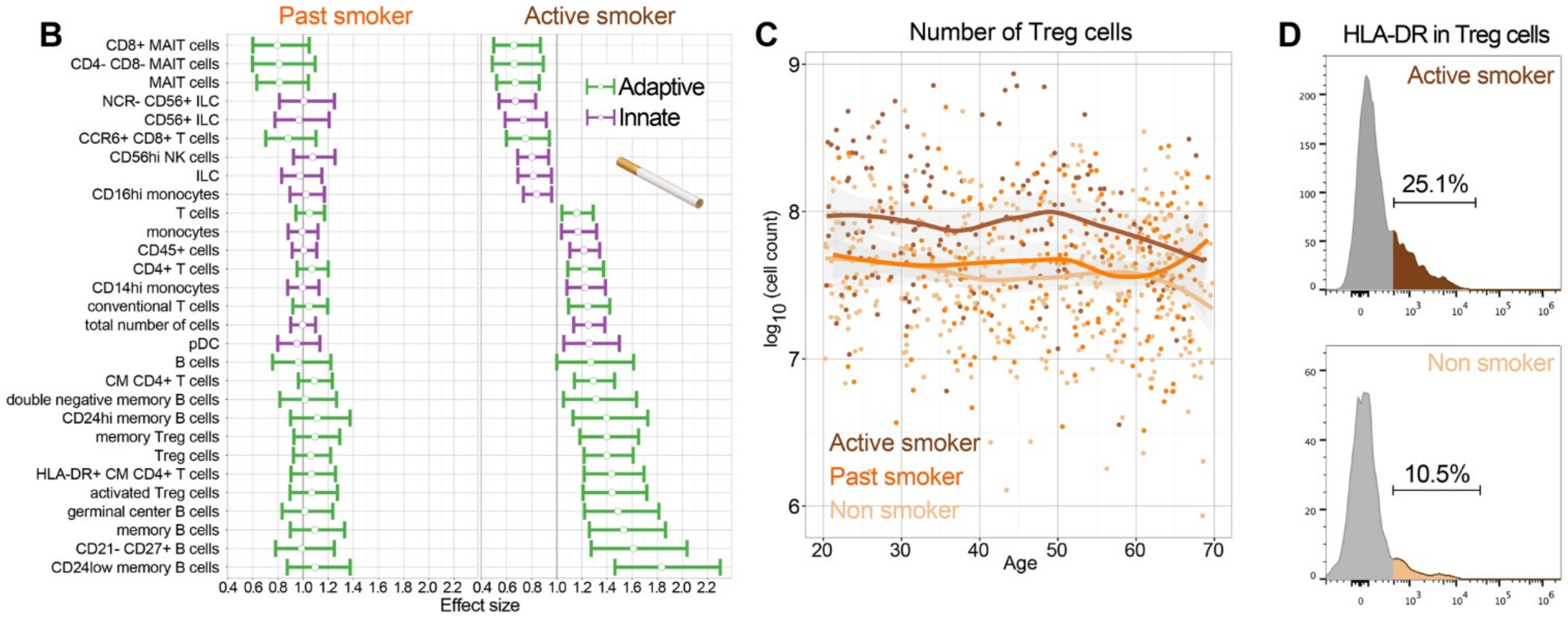
Dissecting environmental determinants of Immune cells - CMV



→ CMV seropositivity associates with the presence CD4+ and CD8$^+$ T_{EM} and T_{EMRA} compartments, but not naïve T cells and T_{CM} compartments, suggesting independent regulation of the naïve and EM/EMRA T cell pools

Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

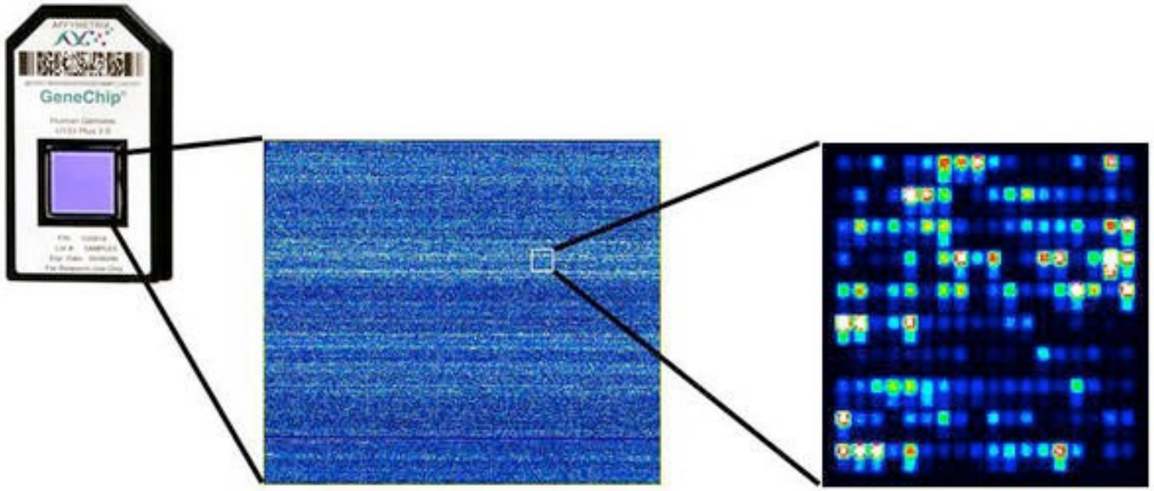
Dissecting environmental determinants of Immune cells - Smoking



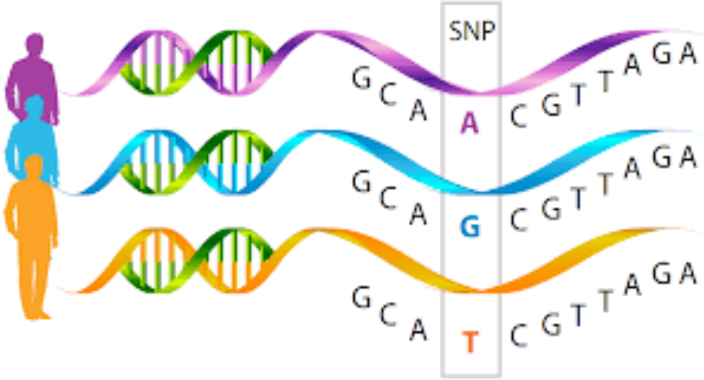
→ The increase in Treg cells may contribute to the diminished Th1 immunity observed in smokers, and the increased susceptibility to bacterial infection

Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

Genome wide association studies -GWAS



SNP: Single Nucelotide Polymorphims: 10^6 differences within 10^9 nucleotides estimated to account for 90% genetic variability in humans

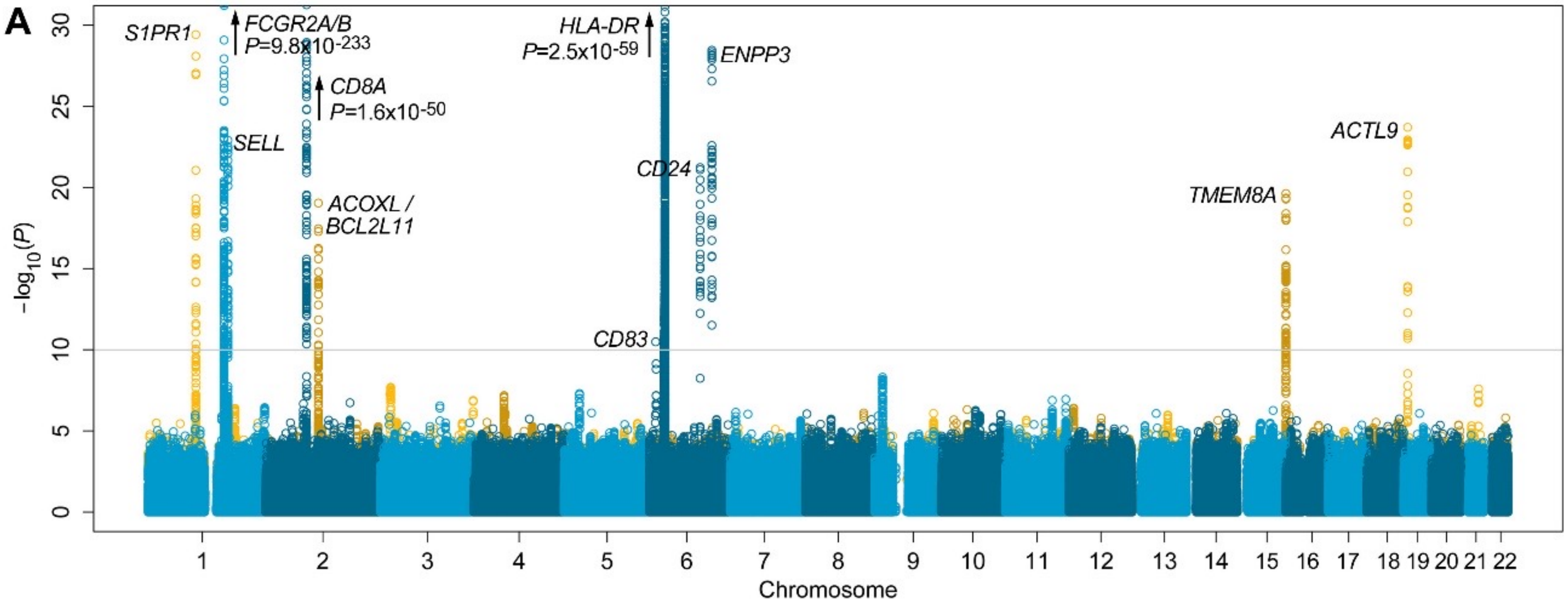


Genome wide association studies -GWAS

GWAS Catalog: a quality controlled, manually curated, literature-derived collection of all published genome-wide association studies with at least 100,000 SNPs and all SNP-trait associations with p-values $< 1.0 \times 10^{-5}$

www.ebi.ac.uk/gwas

Dissecting genetic determinants of Immune cells



→ 14 independent loci are genome-wide significant ($P < 10^{-10}$), of which 11 are novel

→ 10 are local pQTLs of cell-surface expression of immune cell markers (CD32a/b, CD62L, CD24, CD8a, HLA-DR, CD203c)

→ 4 are *trans*-acting QTLs associated with either cell counts and MFIs (*S1PR1, BCL2L11, TMEM8A, ACTL9*)

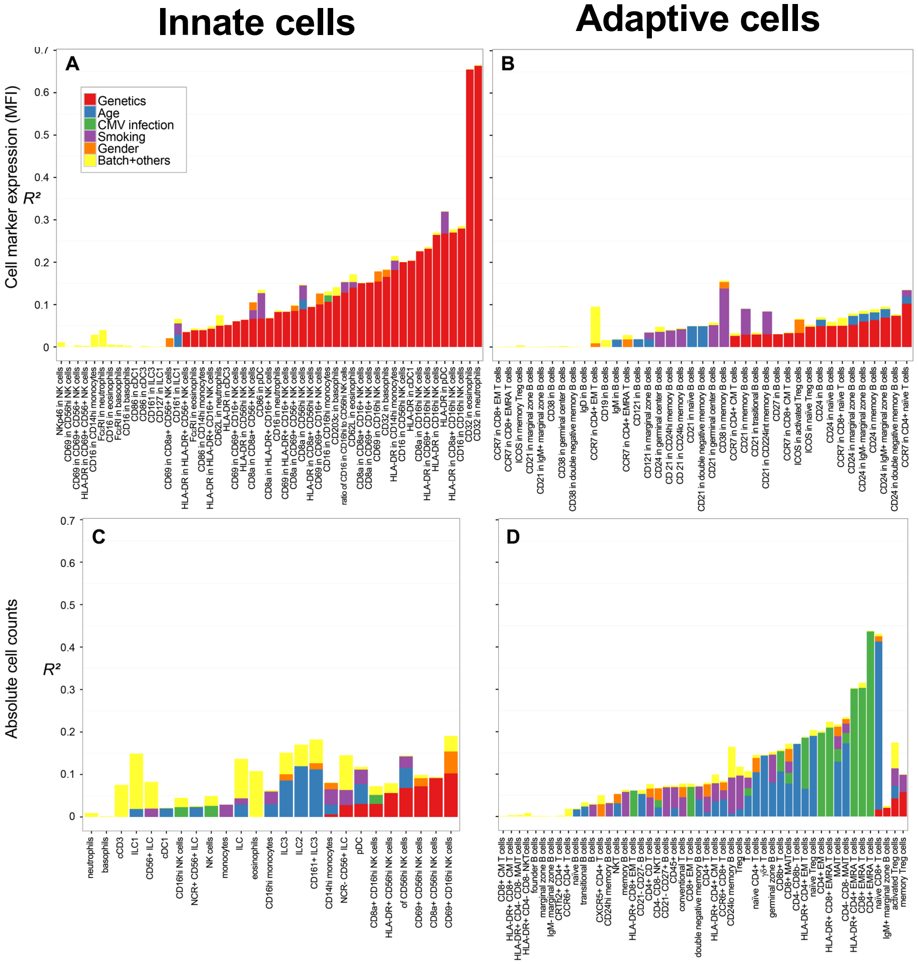
Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

Variation in innate immune cells is driven by genetic factors

Milieu Intérieur
Vers une médecine personnalisée

Linear mixed models applied to each Immune cell phenotype

- 🟥 Genetics
- 🟦 Age
- 🟩 CMV infection
- 🟪 Smoking
- 🟧 Gender
- 🟨 Batch+others



MFI

Absolute Cell counts

Patin E, Hasan M, Bergstedt J, Rouilly V et al (Nat Imm 2018)

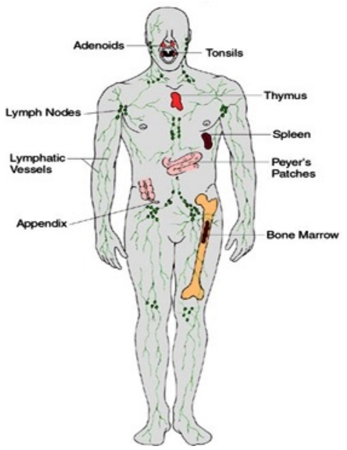
Can we identify the same genetic and environmental associations for induced immune responses?

Standardized profiling of induced immune responses

How is your immune system feeling today ?

Robust Diagnostics for Cardiology

- ✓ Blood pressure
- ✓ Electrocardiogram
- ✓ Cholesterol testing



Assessing the Health of your Immune System

???

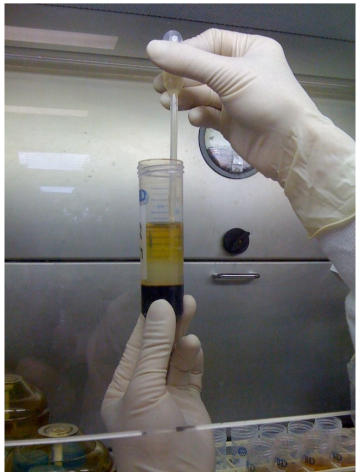
TruCulture: standardized immunomonitoring

Standardization of immunophenotyping

- Recent progress in standardizing immunophenotyping readouts

- Sample source and preparation equally important to reduce technical variability

➔ Particularly for studying **induced immune responses**



Current "bronze standard" based on PBMC stimulation
➔source of huge variability through

- Transport of blood (eg time, temperature)
- Ficoll separation of leukocytes
- Freeze/Thaw of cells
- Removal of granulocytes, platelets, plasma

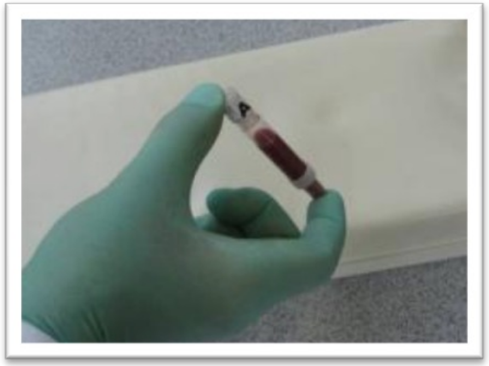
Setting up a TruCulture

TruCulture: syringe based device for whole blood collection and incubation

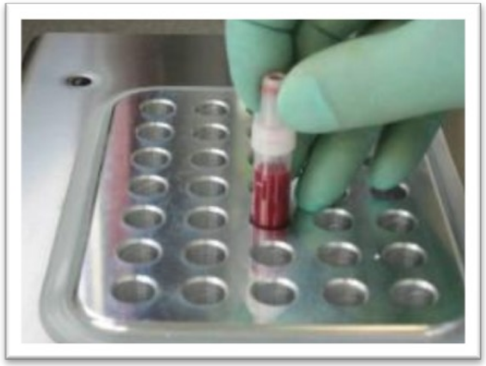
A) Pre-fill tubing with blood

B) Pull, until it “clicks”

C) Break away plunger



D) Mix gently 3x (end-over-end)



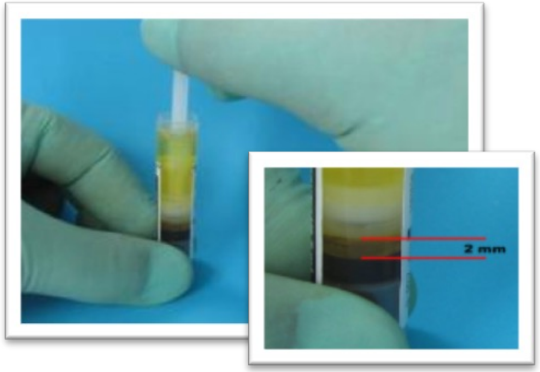
E) Incubate for defined time (1-48hrs)

Harvesting a TruCulture

TruCulture: syringe based device for whole blood collection and incubation

1) Assemble valve separator

2) Insert valve separator



3) Push down, leave 1-2 mm between septum and cells

4) Remove rod and discard;
close tube and freeze at -20°C
(or aliquot supernatant for stabilizing RNA)

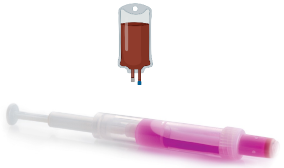
Whole blood maintains granulocytes, platelets & plasma matrix

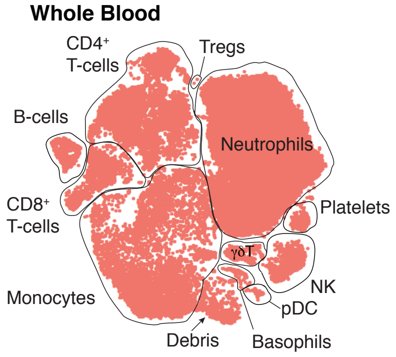
Milieu Intérieur
Vers une médecine personnalisée

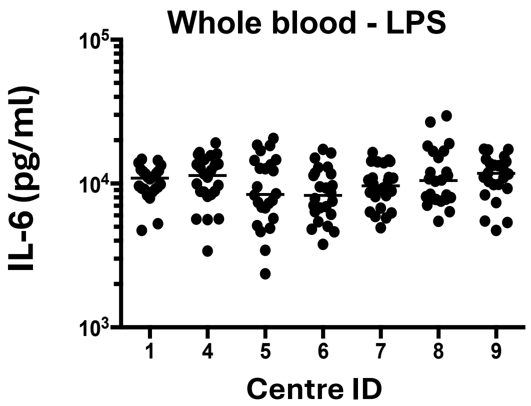
Whole blood maintains neutrophils/platelets

Whole blood shows less technical variability

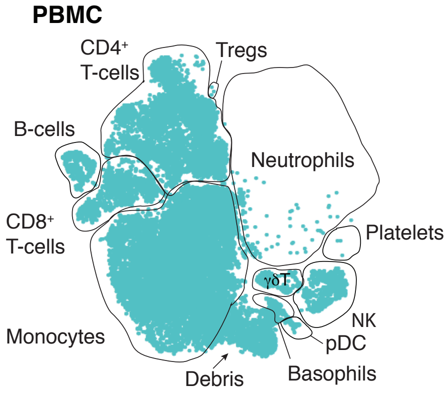
Whole Blood

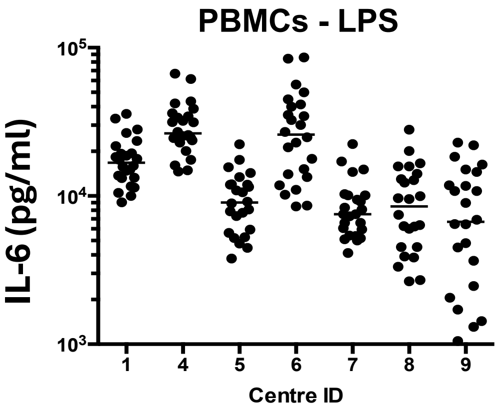



Whole Blood


Whole blood - LPS

PBMCs

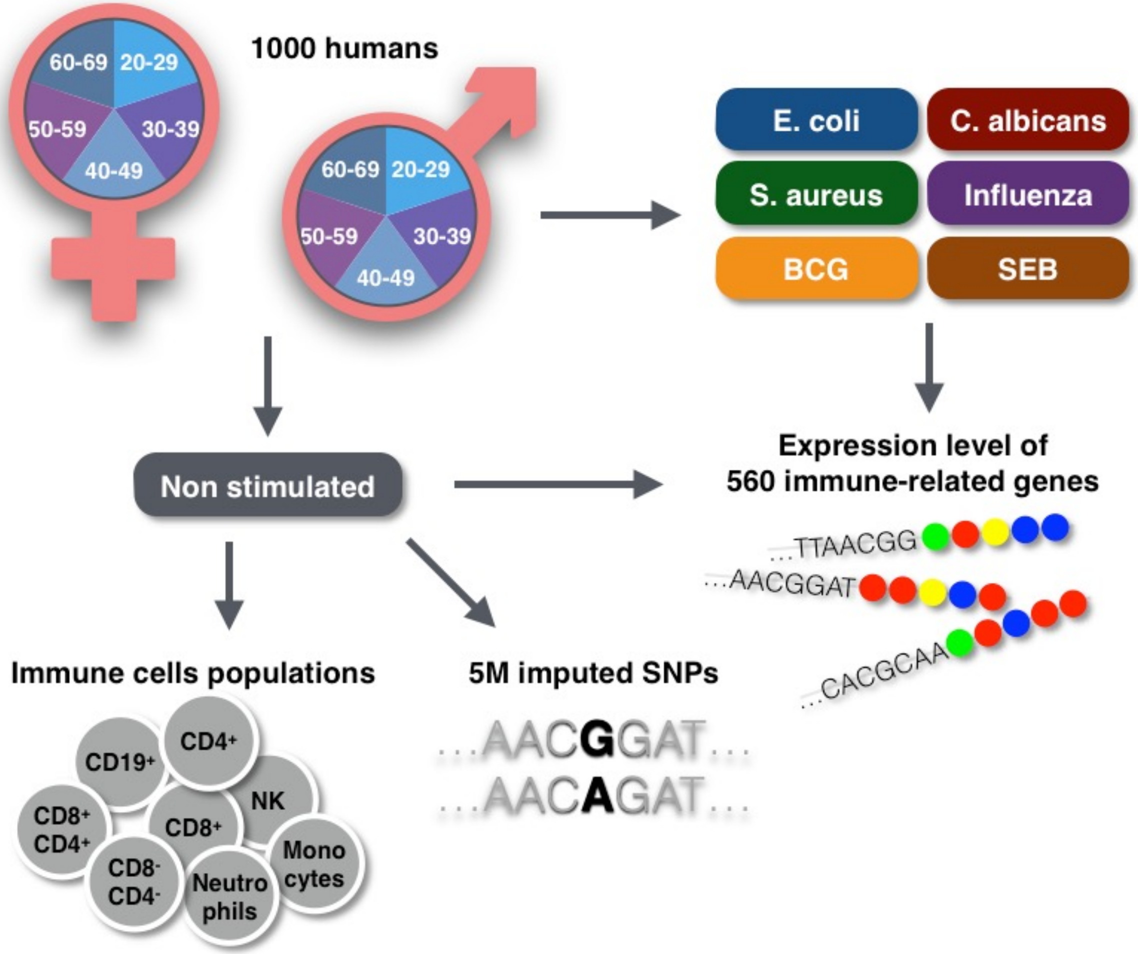

PBMC

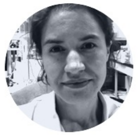

PBMCs - LPS

Brodin, Duffy, Quintana Immunity 2019

Duffy D *et al* Clin Imm 2017

Studying variability in induced transcriptomic responses to microbial stimuli





Alejandra Urrutia

Bruno Charbit

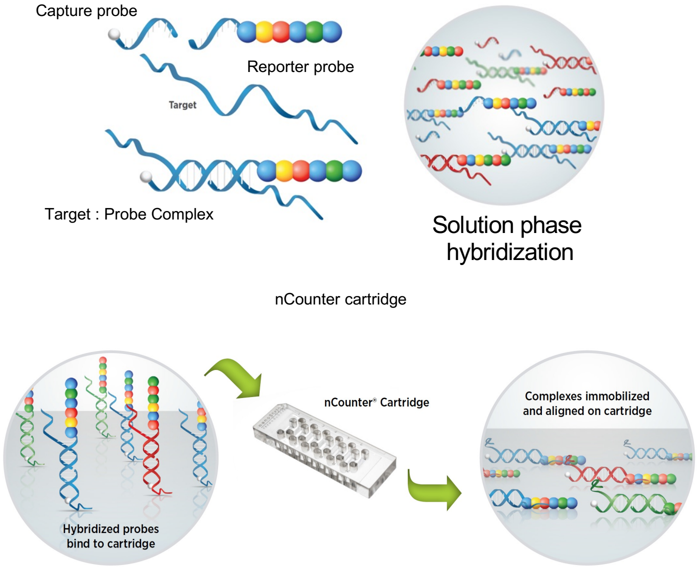
Celine Posseme

Barbara Piasecka

Standardization of mRNA signatures

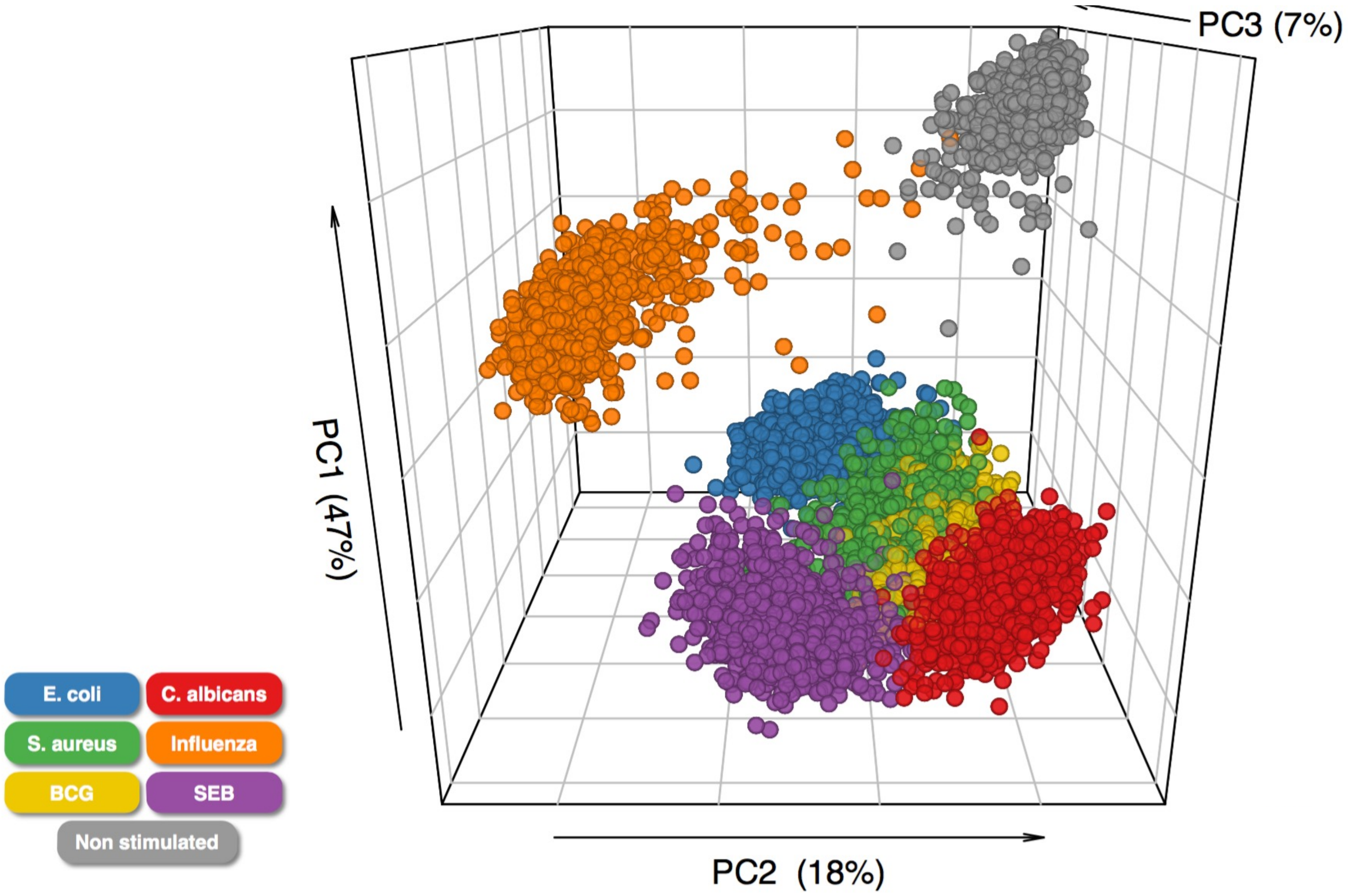
Hybridisation Arrays

No amplification step



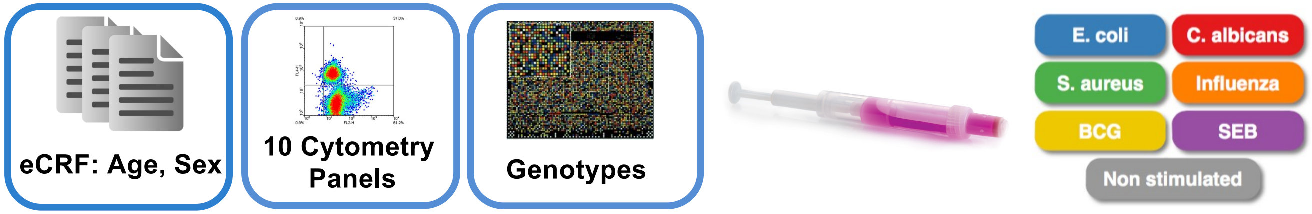
Technology	Method	Gene set	Adaptable for use with whole blood
Fluidigm Biomark	Microfluidic-based PCR	80 genes	• cDNA preparation required = pre-analytical bias • PCR reaction inhibited by presence of heparin
Nanostring nCounter	RNA Hybridization	780 genes	• **Absolute counts** • **suitable for partially extracted RNA**
Affymetrix	cDNA Hybridization	**Whole genome**	• requirement for high quality RNA • cDNA preparation required = pre-analytical bias
Ion Torrent	NGS	**Whole genome**	• requirement for high quality RNA • globin RNA dominate read count (90% of total RNA)

Differential changes in expression induced by stimulations

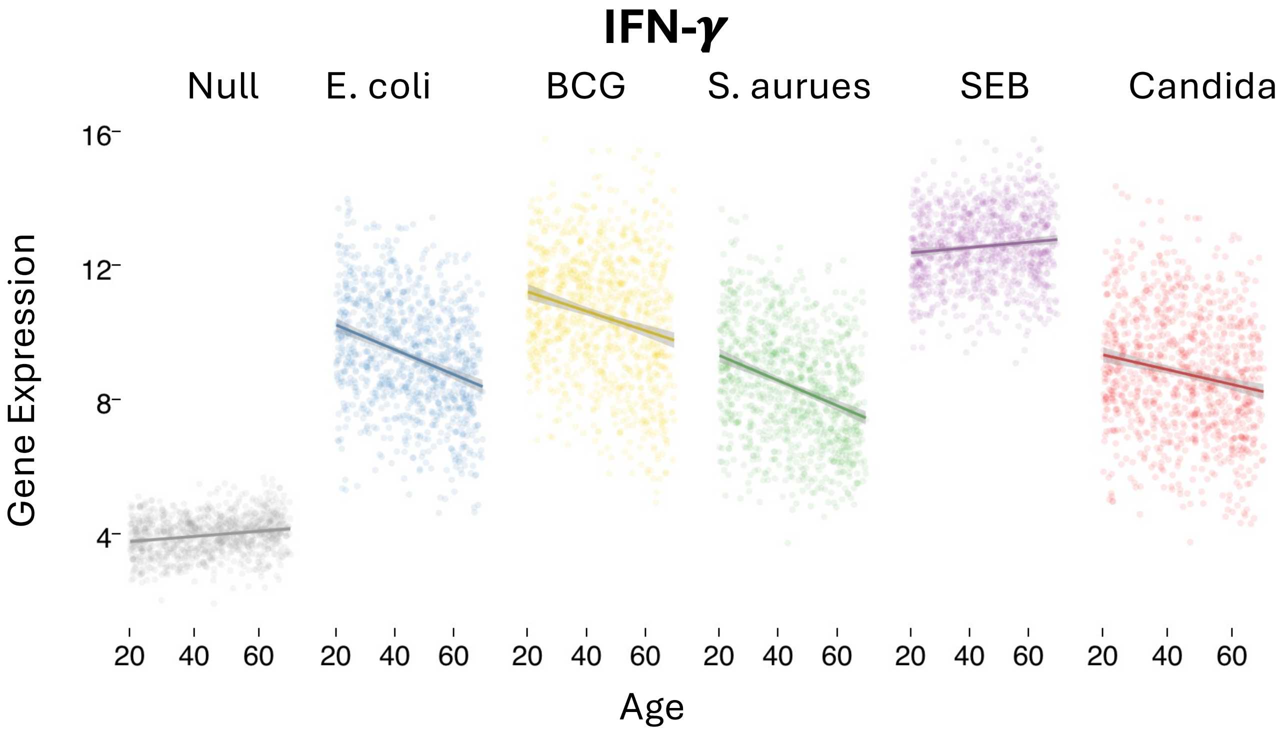


Piasecka B, Duffy D et al (PNAS 2017)

Age associated changes in induced gene expression in healthy donors



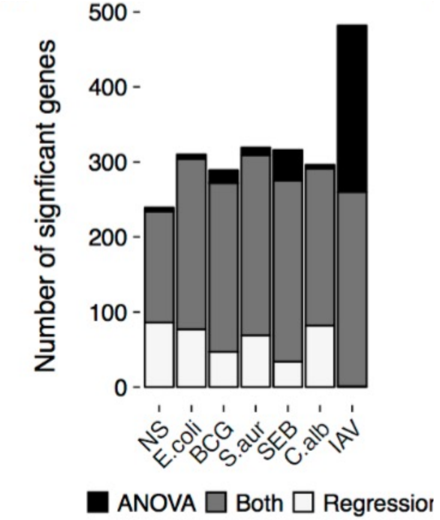
473/560 genes show a significant age associated effect (FDR<0.01, n=1,000)



Piasecka B, Duffy D et al (PNAS 2017)

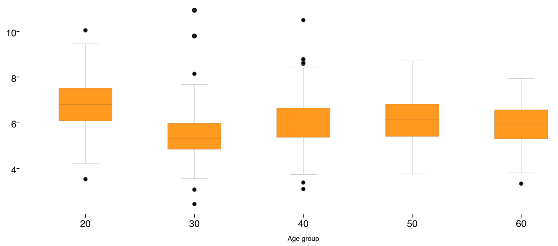
Age associated changes in influenza induced gene expression

Age associations



87 genes
20-29yr > 30-39yr
Tukey HSD test; p < 0.05
Enriched in innate response genes
(p = 6.5 x 10^{-3} InnateDB)

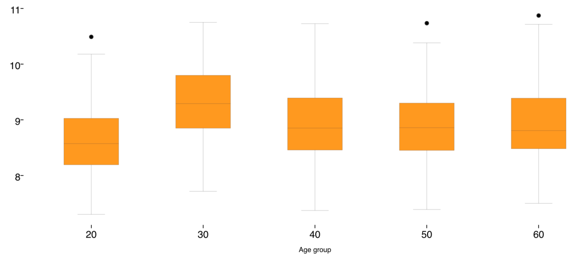
IFNa2



Age Group (per decade)

119 genes
20-29yr > 30-39yr
Tukey HSD test; p < 0.05

FcGRT



Age Group (per decade)

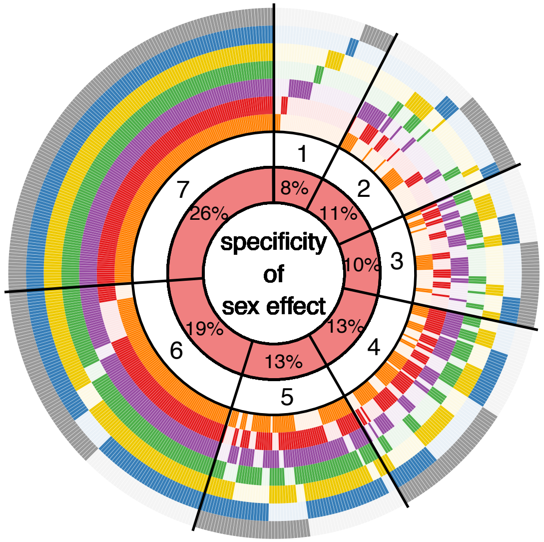
H1N1 (A/PR/8/34 strain)

Hypothesis: Reflects pre-existing serological immunity in 30yr+ donors (Nat Imm Sobolev 2015)
and a H1N1 antigenic shift around 1983
Or
Reflects real age related differences in response to influenza (Sci Imm HIPC-CHI 2017)

Piasecka B, Duffy D et al (PNAS 2017)

Integration of clinical, flow cytometry, genetics & transcriptomic responses

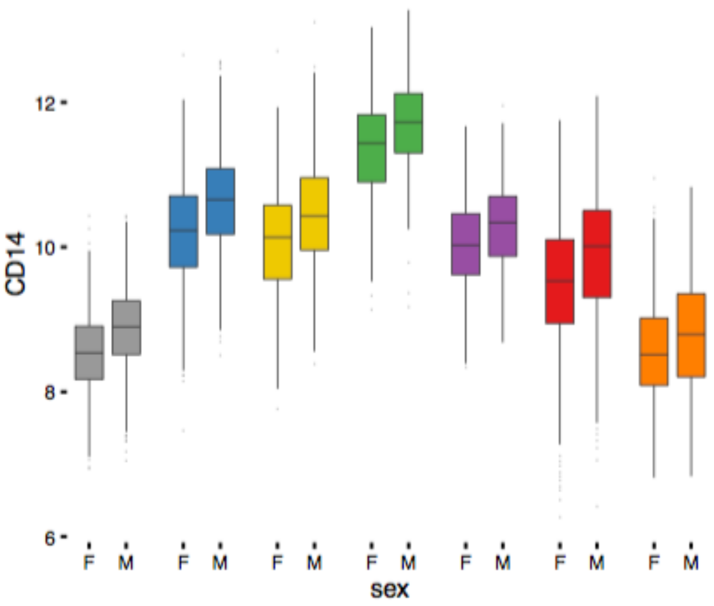
Sex effects are more common across stimuli – 48% shared across 5 stimuli



509/560 genes: (FDR<0.01)

E. coli **C. albicans**
S. aureus **Influenza**
BCG **SEB**
Non stimulated

Common sex association (CD14)



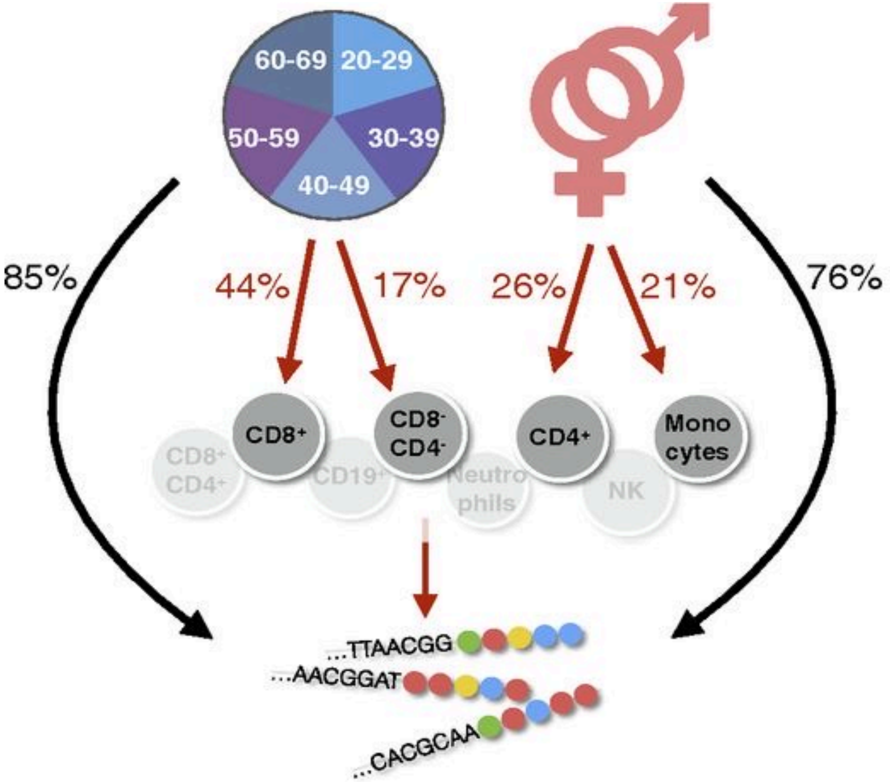
Piasecka B, Duffy D et al (PNAS 2017)

Testing direct versus indirect effects of age and sex on immune responses

Are age and sex directly affecting gene expression changes or are these changes mediated through cellular changes ?

Structural equation modelling

Each age/sex associated gene: model with 8 indirect effects (each cell type) & one direct effect



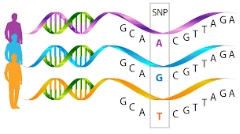
Piasecka B, Duffy D et al (PNAS 2017)

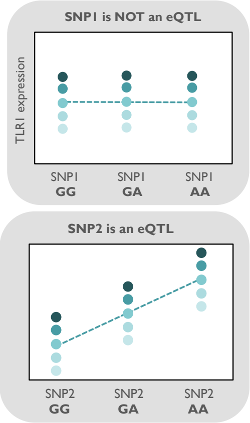
How to identify genetic associations with immune responses ?

Milieu Intérieur
Vers une médecine personnalisée

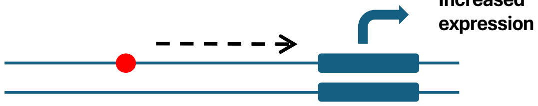
Quantitative Trait Loci mapping (QTL)

$5x10^6$ SNPs

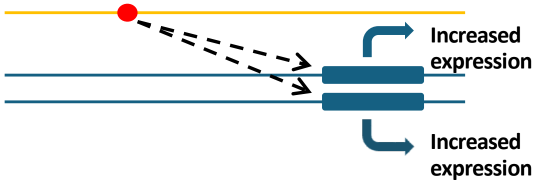




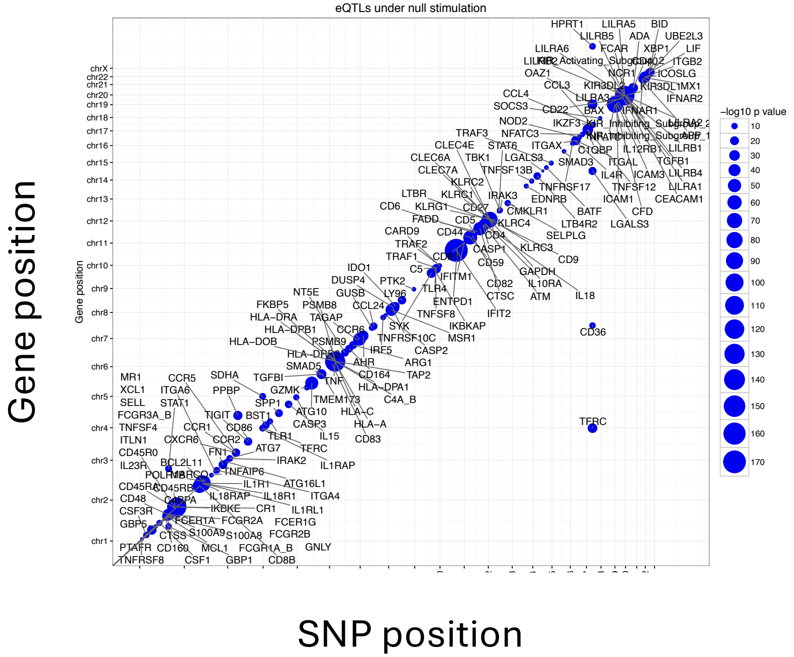
Cis-regulation



Trans-regulation

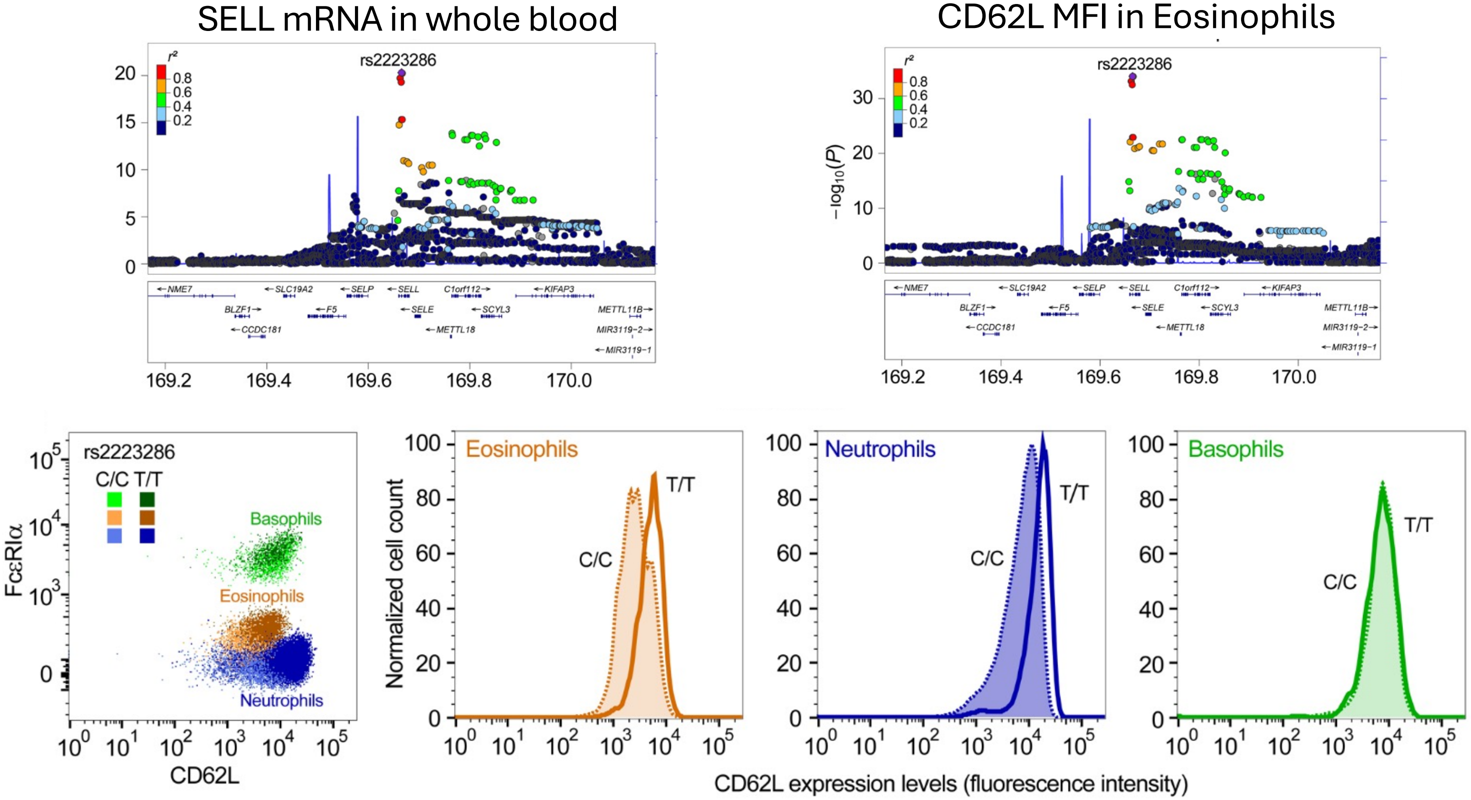


Null control



Piasecka B, Duffy D et al (PNAS 2017)

Integrating transcriptional & flow cytometry data sets to identify cellular determinants of genetics


SELL mRNA in whole blood

CD62L MFI in Eosinophils

→ Cell specific pQTLs: MFI in eosinophils ($P = 9.2x10^{-35}$) and neutrophils ($4.6x10^{-14}$) but not in basophils

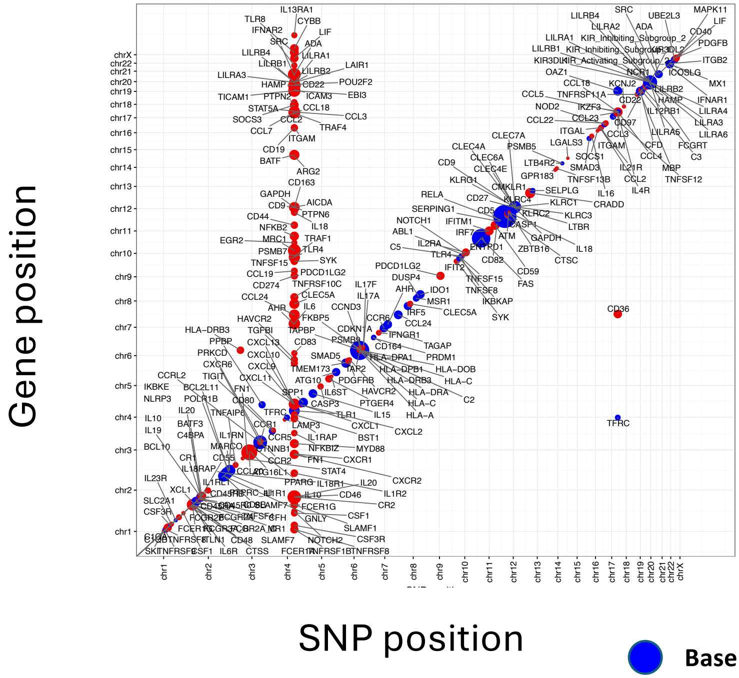
TT alllele: higher expression in monocytes/lower in B cells (Fairfax Nat Gen 2012)

Piasecka B, Duffy D et al (PNAS 2017)

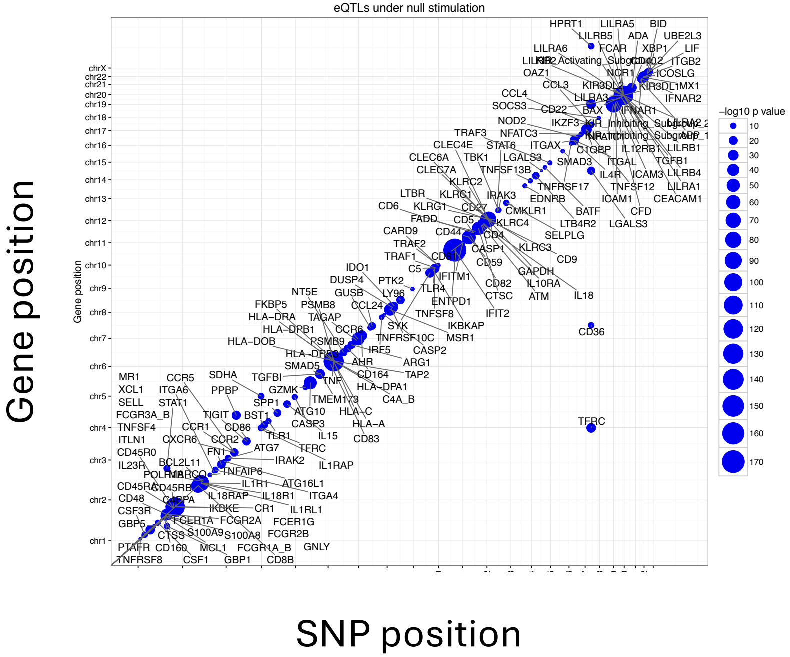
Mapping Quantitative Trait Loci (eQTL) identifies novel genetic associations

Milieu Intérieur
Vers une médecine personnalisée

BCG stimulation



Null control



● **Baseline QTL**

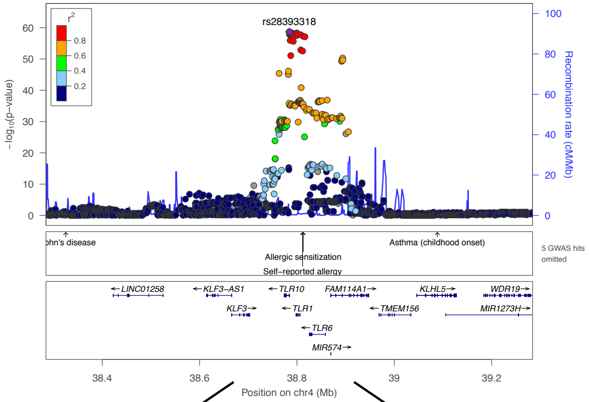
● **Response QTL**

Piasecka B, Duffy D et al (PNAS 2017)

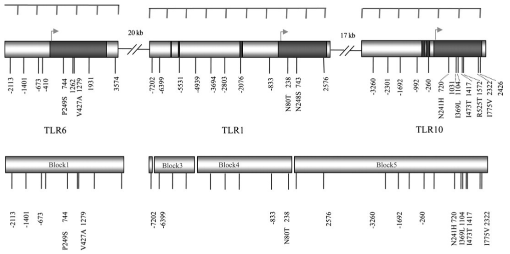
TLR 10/1/6: master regulator of bacterial induced expression

Milieu Intérieur
Vers une médecine personnalisée

Genetic variability in Europeans



TLR 10 / 1 / 6 genetic locus

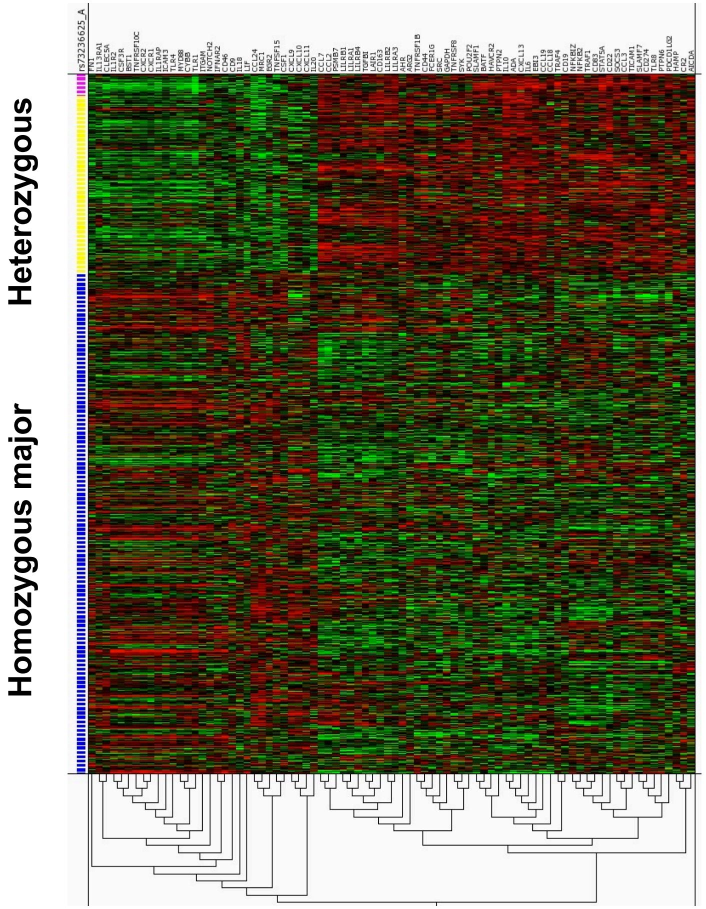


Pro-inflammatory

(e.g, IL18, TLRs,)

Anti-inflammatory

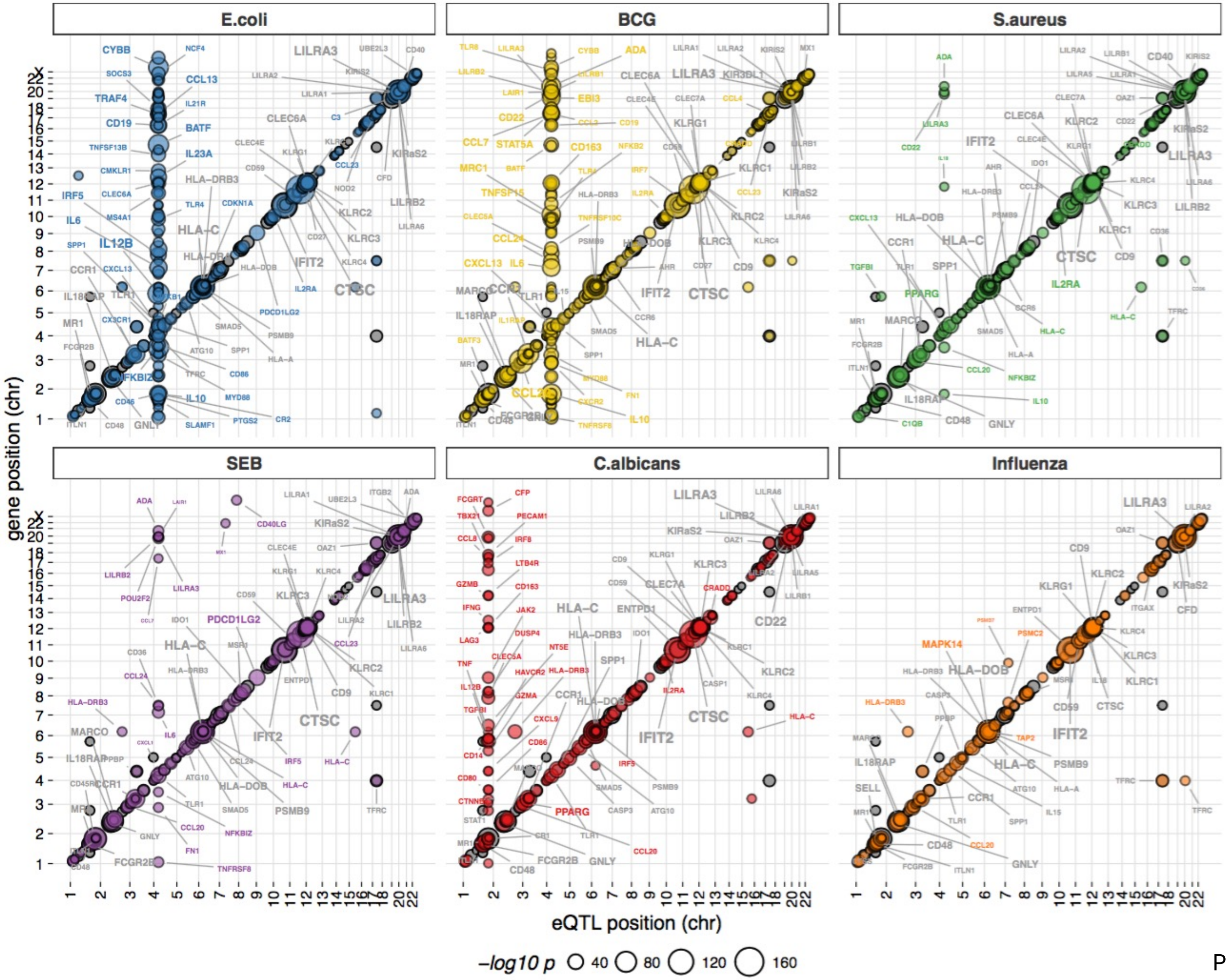
(e.g., IL-10, IL10, LILR)



(Quach *et al* Cell 2016)

Mapping stimuli specific Quantitative Trait Loci (eQTL)

Milieu Intérieur
Vers une médecine personnalisée



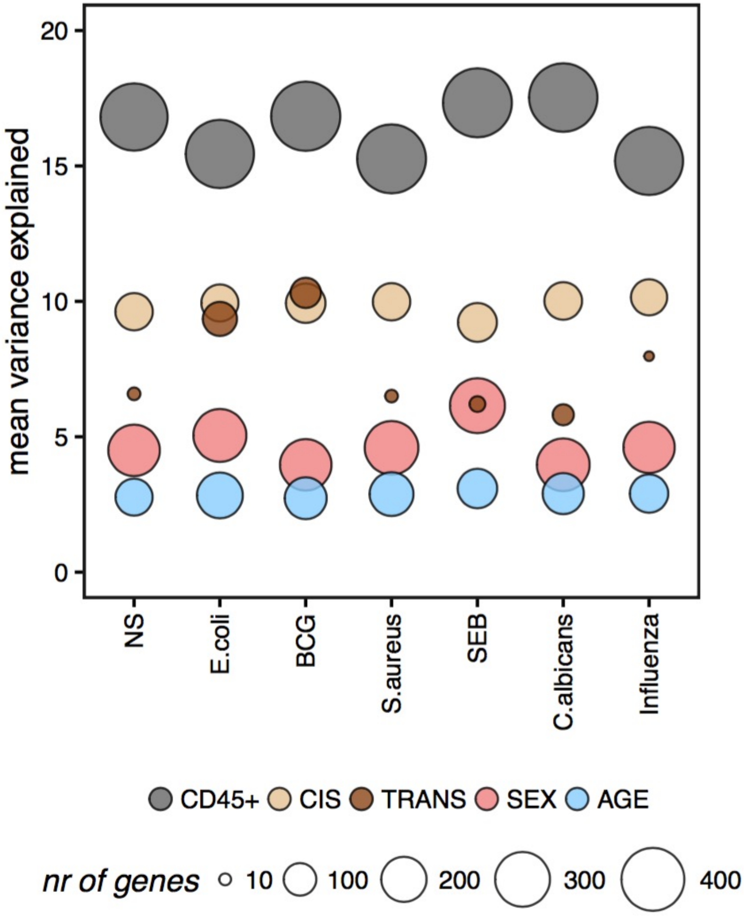
Piasecka B, Duffy D et al (PNAS 2017)

Dissecting factors responsible for gene expression variance

- Cellular composition accounts for largest proportion of gene expression variance in whole blood

- Genetics affects high percentage of genes with Medium-strong effect

- Age & sex affect numerous genes but to lower degree



Piasecka B, Duffy D et al (PNAS 2017)

Identification of novel environmental – immune response associations

Milieu Intérieur
Vers une médecine personnalisée

Whole blood stimulation

1,000 Healthy donors

12 stimuli

13 cytokines by Luminex

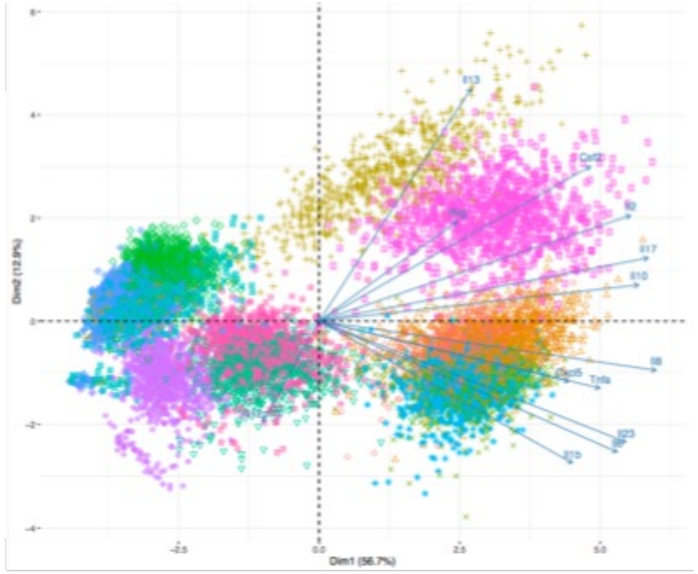
Cytokines
- IFNg
- TNF
- IL1b

T-cell
- SEB
- CD3+CD28

Viral
- PolyIC
- Influenza

Microbial
- *E.coli*
- LPS
- BCG
- *C.albicans*

- Control



CXCL5
GM-CSF
IFN-G
IL-1B
TNF
IL-2
IL-6
IL-8
IL-10
IL-12p70
IL-13
IL-17
IL-23

Identification of novel environmental – immune response associations

Milieu Intérieur
Vers une médecine personnalisée

Violaine
Saint-Andre

Whole blood
stimulation

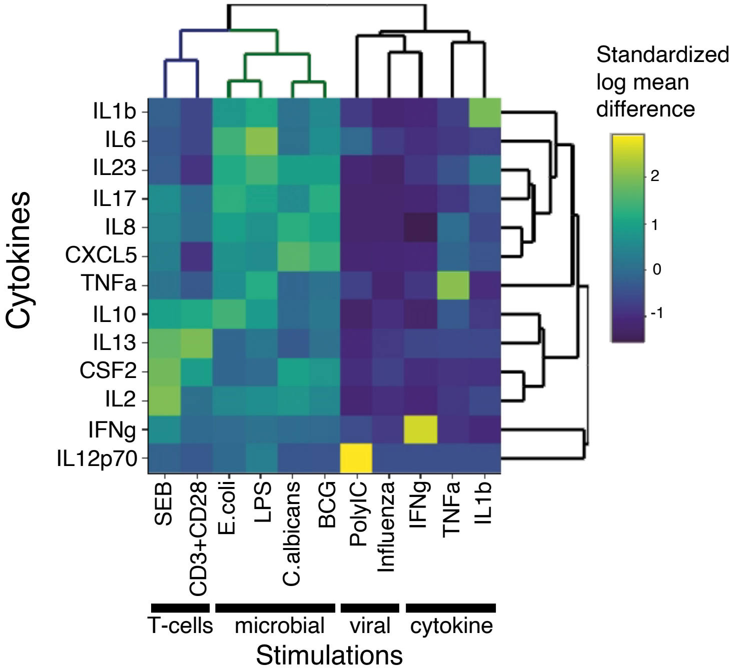
1,000 Healthy donors

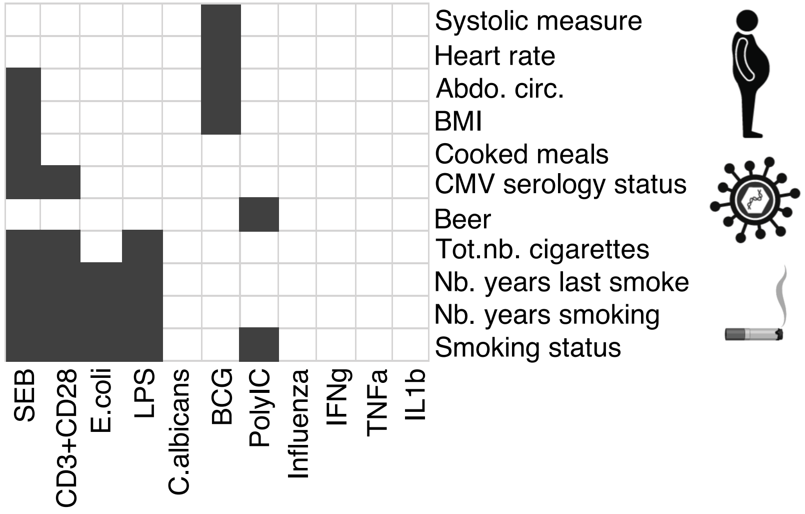
12 stimuli

Associate with 140 environmental factors (CRF)

(Age and Sex corrected)

→ 11 factors significantly associated (adj-P val LRT < 0.01)



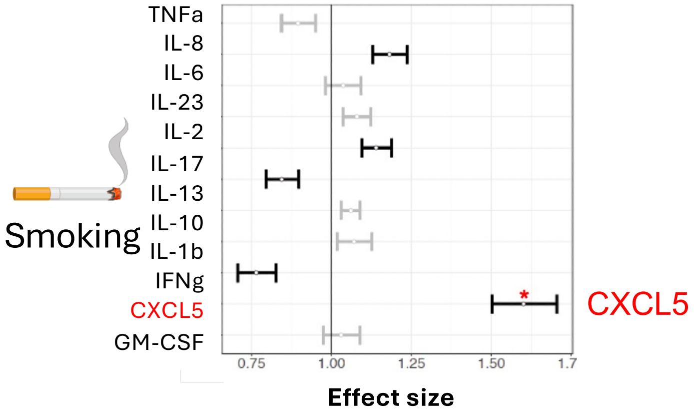


	SEB	CD3+CD28	E.coli	LPS	C.albicans	BCG	PolyIC	Influenza	IFNg	TNFa	IL1b
Systolic measure						■					
Heart rate						■					
Abdo. circ.	■					■					
BMI	■					■					
Cooked meals	■										
CMV serology status	■	■									
Beer							■				
Tot.nb. cigarettes	■	■		■							
Nb. years last smoke	■	■	■	■							
Nb. years smoking	■	■	■	■							
Smoking status	■	■	■	■			■				

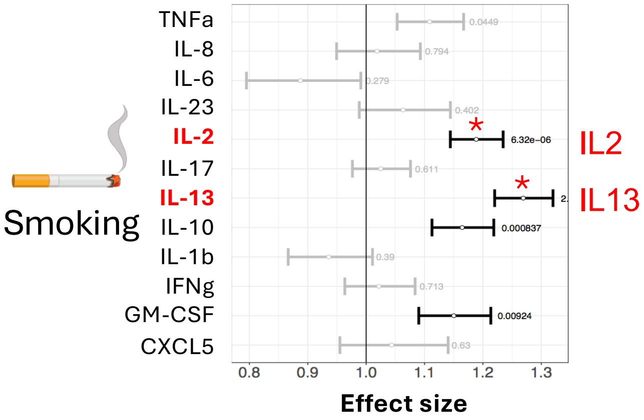
Saint-Andre, et al (Nature 2024)

Smoking differentially affects innate and adaptive immune responses

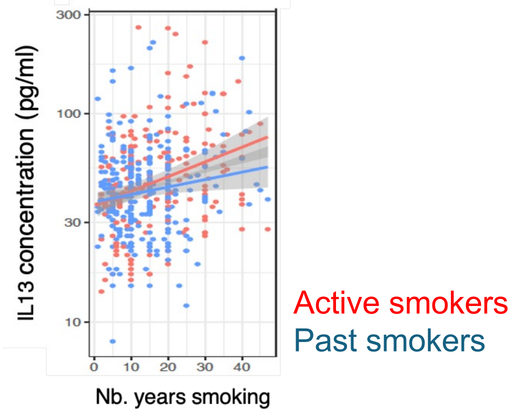
E. coli stimulation



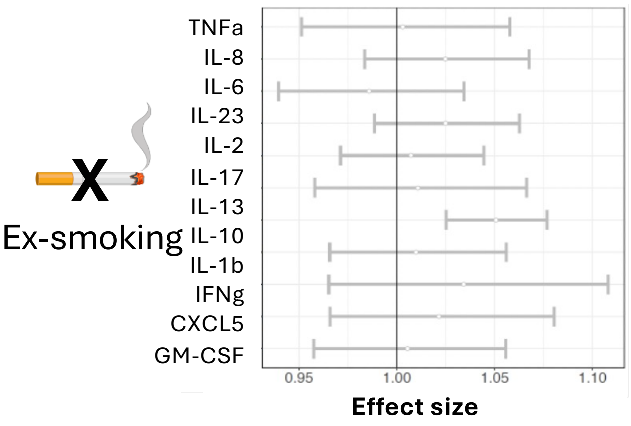
SEB stimulation



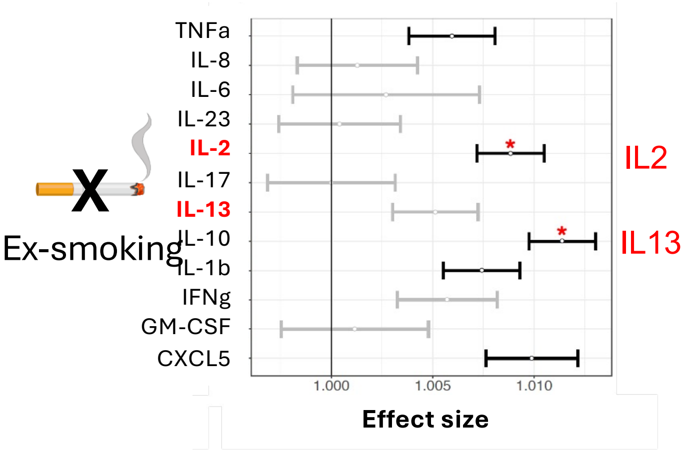
SEB stimulation



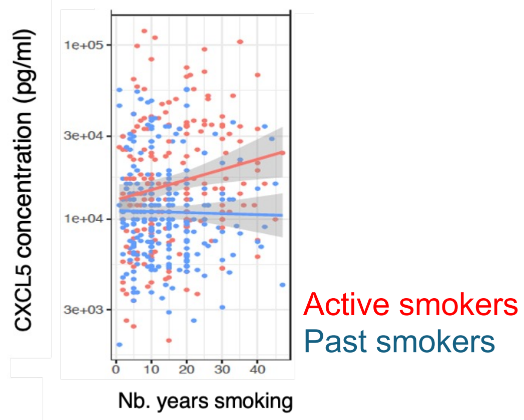
E. coli stimulation



SEB stimulation



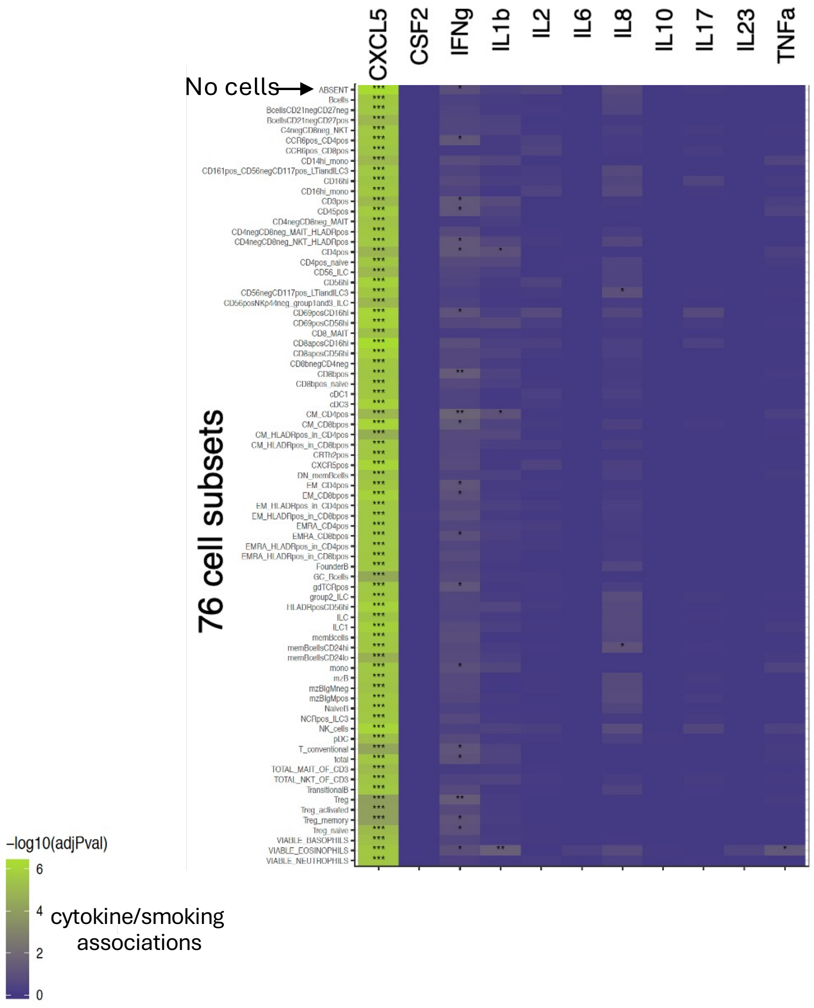
E. coli stimulation



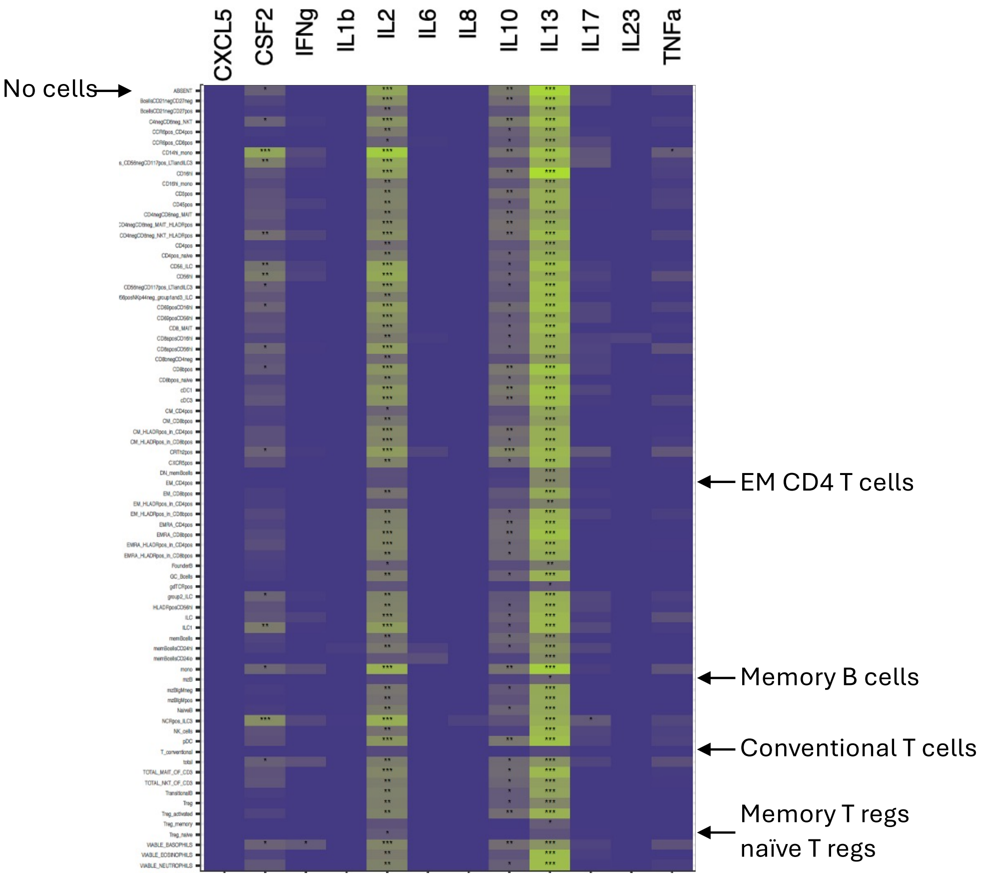
Saint-Andre, et al (Nature 2024)

Identification of cellular mediators of smoking effects on cytokines

E. Coli stimulation- smoking associations



SEB stimulation – smoking associations



Saint-Andre, et al (Nature 2024)

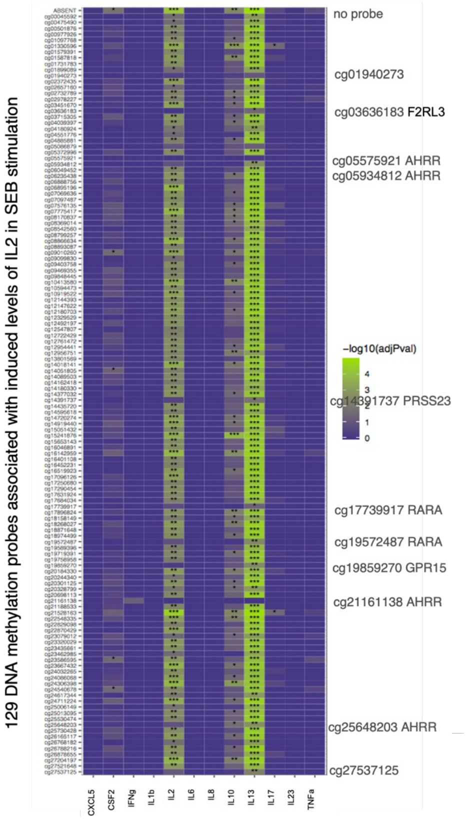
Epigenetic mediation of past smoking effect

Hypothesis: The past effect of smoking acting through long lived B & T cells is epigentically mediated

Blood methylome 850k CpG sites – **2416 directly** (not through cellular associations) associated with **smoking** (Bergstedt et al, Nat Com 2022)

→ **129** significantly associated with **IL2 in SEB** stimulation (BY adj-pval of LRT < 0.001)

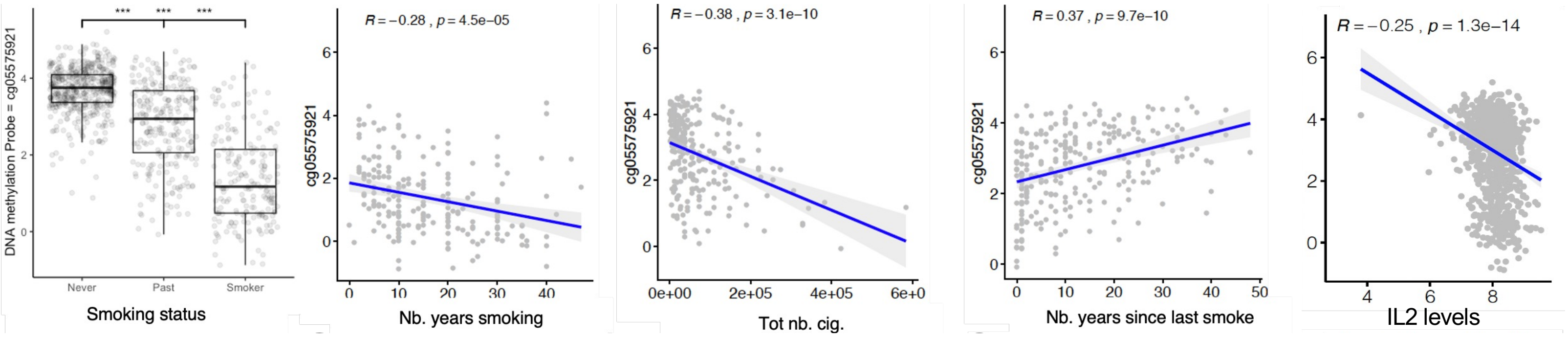
SEB – smoking associations



→ 11 probes removed association of IL2/IL13 and smoking:

AHRR (Aryl Hydrocarbon Receptor Repressor)
F2RL3 & *GPR15* (G protein-coupled receptors)
RARA (Retinoic acid receptor)
PRSS23 (serine protease)

AHRR DNA methylation



Saint-Andre, et al (Nature 2024)

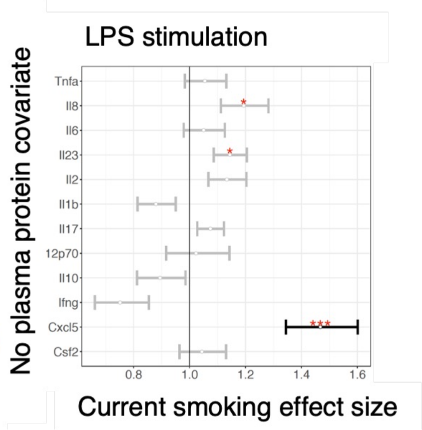
Non cellular mediators of active smoking on inflammatory responses

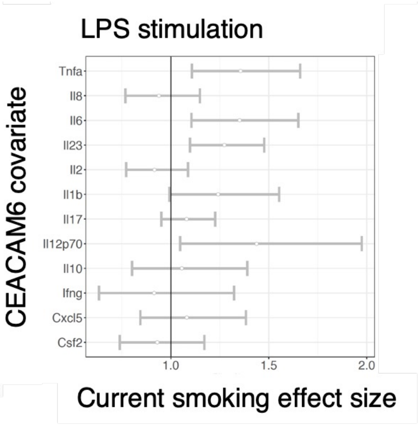
Milieu Intérieur
Vers une médecine personnalisée

Hypothesis: If no cellular mediator of active smoking effect on CXCL5 can we identify a soluble factor

326 plasma proteins measured by Luminex in subset of 400 donors (Caron *et al*, Genome Med 2022)

→ CEACAM6 protein removed active smoking effect on CXCL5 in LPS/E. coli stimulation





CEACAM6

- Glycosylphosphatidylinositol (GPI)-linked cell surface protein
- Expressed by neutrophils, macrophages, & lung/intestinal epithelial cells
- Elevated in multiple cancers

Hypothesis

- Smoking leads to elevant CEACAM6 in the blood

→ increases inflammatory response of neutrophils

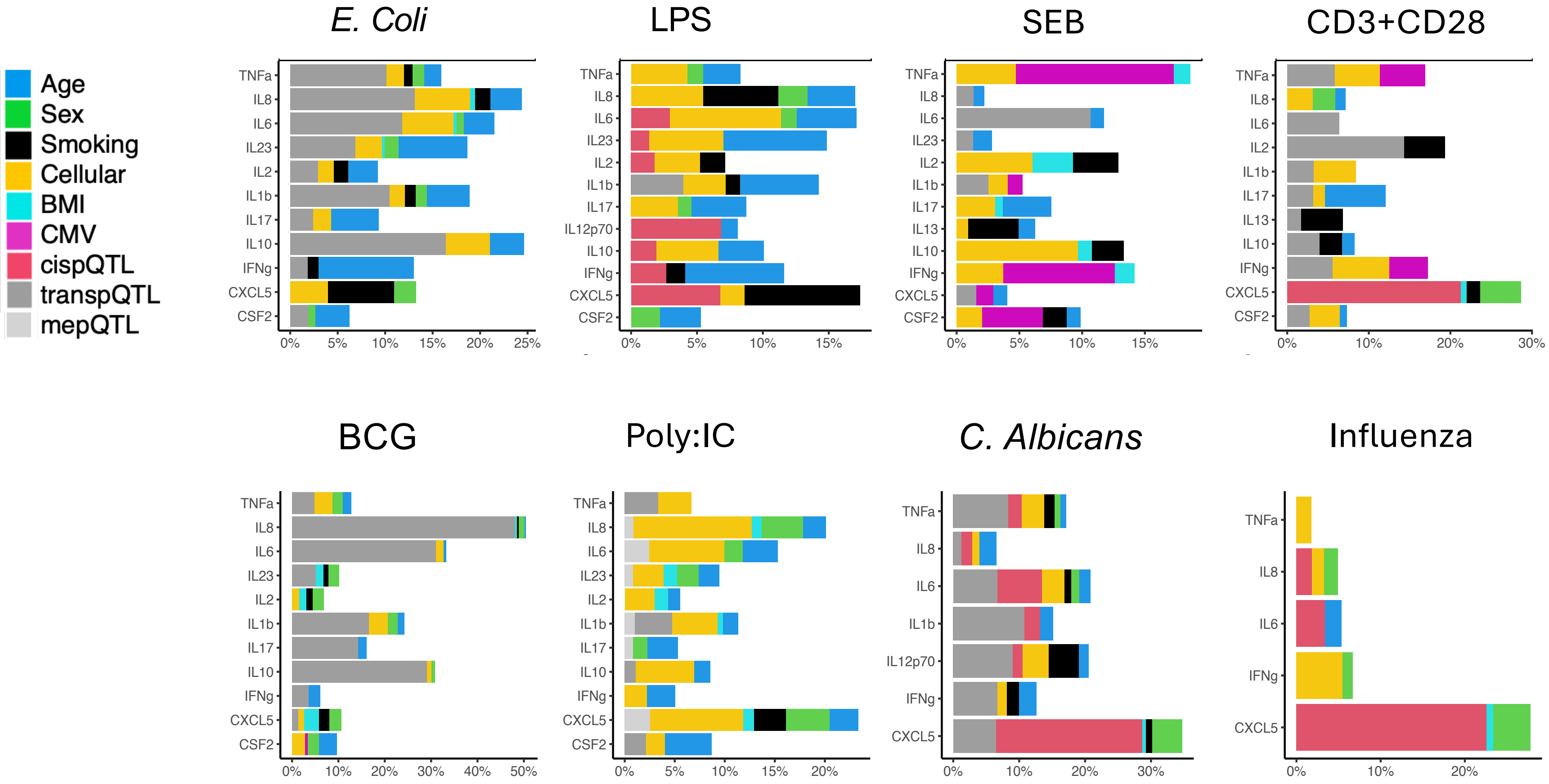
May explain the contradictory findings of smoking and COVID-19 ?

Saint-Andre, et al (Nature 2024)

Summary of environmental and genetic effects on cytokine responses

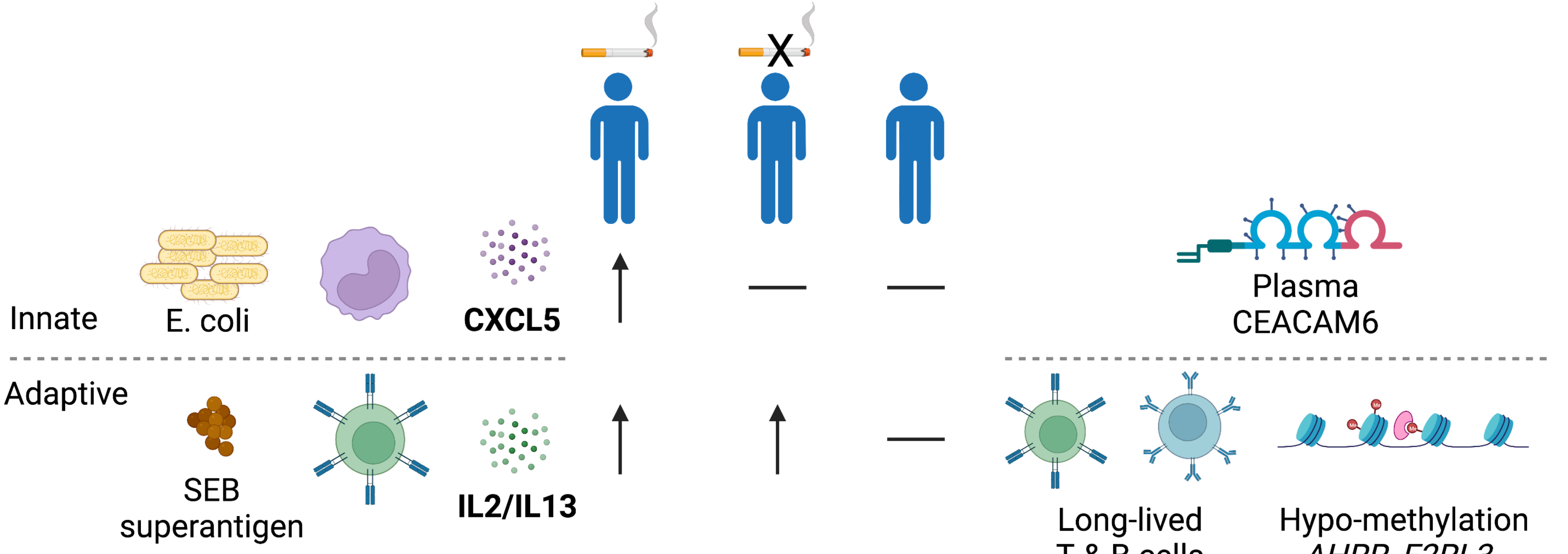
Milieu Intérieur
Vers une médecine personnalisée

Linear regression models including all identified signifcant effects on cytokine responses



Saint-Andre, et al (Nature 2024)

Summary of smoking findings



			Smokers	Ex-smokers	Never smoked	
Innate	E. coli	**CXCL5**	↑	—	—	Plasma CEACAM6
Adaptive	SEB superantigen	**IL2/IL13**	↑	↑	—	Long-lived T & B cells Hypo-methylation *AHRR, F2RL3, GPR15, RARA, PRSS23*

The international journal of science / 22 February 2024

nature

SMOKE ALARM

How smoking alters the immune response even years after quitting

(artwork by Bertsy Goic)

Saint-Andre, et al (Nature 2024)

Ongoing impact of Milieu Interieur - media

Milieu Intérieur
Vers une médecine personnalisée

Widespread international press coverage from Nature paper on smoking-imune effects (Saint-Andre *et al*)

Le Monde
SCIENCES · BIOLOGIE
Le tabac affaiblit la réponse immunitaire, même dix ou quinze ans après son arrêt
Chez les anciens fumeurs, l'immunité apparaît fragilisée, même des années après l'arrêt du tabac, montre une étude de l'Institut Pasteur, publiée dans la revue « Nature ».
Par Florence Rosier
Publié le 14 février 2024 à 17h04, modifié le 19 février 2024 à 14h44 · Lecture 3 min. · Read in English

France Inter
RECHERCHE MÉDICALE
Le tabagisme nuit à l'immunité sur le long terme, selon une étude de l'Institut Pasteur
Par La rédaction numérique de France Inter
Publié le jeudi 15 février 2024 à 06h08 | 2 min | PARTAGER

France Culture
Tabac : l'immunité des anciens fumeurs reste altérée longtemps après l'arrêt
Mercredi 21 février 2024
ÉCOUTER (4 MIN)

Europe 1
Accueil > Santé
Tabac et système immunitaire : des effets néfastes 15 ans après l'arrêt de la cigarette

RTL
2 min de lecture
Fumer a un effet sur le système immunitaire, même des années après avoir arrêté
Selon des scientifiques de l'Institut Pasteur, le tabagisme pourrait avoir une influence sur la réponse immunitaire pendant 10 ou 15 ans.

Courrier international
SCIENCES ET ENVIRONNEMENT • TABAC
Santé. Les effets de la cigarette sur le système immunitaire peuvent durer des années
Une étude récente met en évidence un lien entre le tabagisme et une altération de la réponse immunitaire, même longtemps après l'arrêt de la cigarette.

Libération
Accueil / Société / Santé
Santé
Cigarette : de nouvelles études éclairent les effets du tabac sur l'espérance de vie et les défenses immunitaires
D'après deux récentes publications scientifiques, l'espérance de vie remonte presque au niveau des non-fumeurs après dix ans d'abstinence. Des perturbations du système immunitaire peuvent toutefois persister plusieurs années après l'arrêt.

Sciences et Avenir
SCIENCES ET AVENIR > SANTÉ
SANTÉ
Comment le tabac perturbe le système immunitaire sur le long terme
Par Marie Parra le 14.02.2024 à 17h10

dentaire365
Le tabac a des effets à long terme sur le système immunitaire
Une étude menée par des chercheurs de l'Institut Pasteur révèle une mémoire à long terme des effets du tabagisme sur l'immunité.
Par Agnès Taupin, publié le 14 février 2024

Le Parisien
Société, Santé
Le tabagisme détériore la santé et l'immunité pour des années après l'arrêt, selon des études
Selon les scientifiques, l'immunité adaptative, construite au fur et à mesure des infections, reste lésée pendant des années après avoir arrêté de fumer.

Le Point
Tabac et immunité : des effets néfastes 10 à 15 ans après l'arrêt de la cigarette
Selon une étude de l'Institut Pasteur, parue ce mercredi, le tabac pourrait avoir autant d'influence sur certaines réponses immunitaires que l'âge, le sexe ou les variables génétiques.
Par Caroline Douteau

HuffPost
Life 17/02/2024 08:30
Tabagisme : après l'arrêt de la cigarette, le système immunitaire reste affecté plusieurs années

L'Express
e le système immunitaire
eur vient de mettre en évidence l'impac
uteurs de cette découverte qui fait la u

Les Echos
immunitaire, même des années après avoir arrêté de fumer

Le Quotidien du Médecin
Accueil > Spécialités > Immunologie
Le tabagisme altère le système immunitaire long terme
PAR DR IRÈNE DROGOU - PUBLIÉ LE 14/02/2024

Santé magazine
Selon une étude, le tabac altère l'immunité jusqu'à 15 ans après l'arrêt de la cigarette

nature
nature > news > article
NEWS | 14 February 2024
Smoking scars the immune system for years after quitting
A cigarette habit and previous infection with a common virus both have important effects on the immune system.
By Heidi Ledford

CNN health
Smoking's effects on the immune system can last years, study finds
By Jen Christensen, CNN
4 minute read · Published 11:00 AM EST, Wed February 14, 2024

Radio-Canada Ohdio
ÉMISSIONS | LES ANNÉES LUMIÈRE | RATTRAPAGE DU 18 FÉVR. 2024 : LE MAGNÉTISME COMME OUTIL POUR LIVRER LA CHIMIOT
Tabac : des effets s'installent pour longtemps dans nos cellules
Écouter le segment 11 min

EL PAÍS
Ciencia / Materia
TABACO >
Fumar es el factor que más altera las defensas, incluso años después de dejarlo
Un ingenioso experimento, con 1.000 personas de una misma ciudad analizadas a fondo, revela los desconocidos efectos persistentes del tabaquismo

Неделя Новостей
Среда, 21 Февраля 2024
Курение необратимо разрушает иммунную систему
Некоторые негативные последствия сохраняются в течение многих лет после того, как человек отказывается от курения.

科普｜最新研究揭示吸烟如何改变免疫系统，戒烟后会发生什么？

第一财经

吸烟是影响人类健康的危险因素。它不仅与多种癌症、心血管疾病和呼吸系统疾病有关，最新研究发现，吸烟还可以直接影响人体免疫系统的功能。

《自然》杂志2月15日发表的一篇题为《吸烟改变适应性免疫并对人体产生持久影响》的研究，法国巴斯德研究所通过对1000名参与者血液样本的免疫反应测试发现，吸烟可以改变人体对细菌和病毒的免疫反应，吸烟者即使在戒烟多年后也容易患上更多的疾病和感染。

BioArt
Nature | 戒烟后吸烟对适应性免疫反应的影响依然存在
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Article
Smoking changes adaptive immunity with persistent effects

TODAY
Study shows how smoking can gravely harm the immune system

le Scienze
edizione italiana di Scientific American
16 febbraio 2024
Fumare può compromettere la funzione del sistema immunitario, anche anni dopo aver smesso
di Alejandra Manjarrez/Scientific American

SINC
OTRAS ESPECIALIDADES MÉDICAS
Fumar provoca cambios en la respuesta inmunitaria que persisten tras dejarlo
Un equipo del Instituto Pasteur de París ha estudiado los efectos en las defensas de más de 100 factores ambientales en 1.000 personas. Los resultados revelan que el tabaquismo es el que más influye, ya que produce alteraciones en la inmunidad innata, la adaptativa y cambios epigenéticos que se pueden mantener durante décadas.

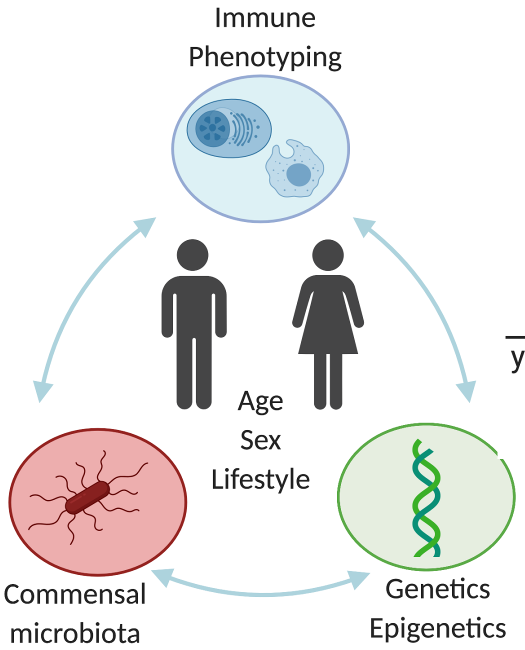
NATIONAL GEOGRAPHIC ESPAÑA
CIENCIA | MEDICINA
Confirmado: el tabaco altera las defensas, incluso años después de haberlo dejado
Un nuevo estudio revela que los fumadores generan un entorno inflamatorio generalizado que hace que la respuesta inmunitaria resulte poco eficaz cuando sufren una infección.
Actualizado a 15 de febrero de 2024, 18:00

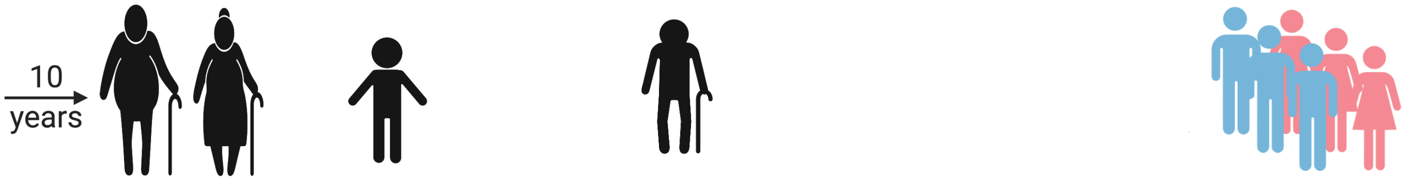
The ongoing evolution of Milieu Interieur

Milieu Intérieur
Vers une médecine personnalisée

Extending the MI approach to more integration, deeper phenotyping, other ages & populations

- Compare population level aging effects with individual level variation
- Compare immune variability with and within other populations





ATRACTion
(Imagine)
2-8 yrs

TILDA
(Trinity)
>75 yrs

University
of Tartu

Healthy Human Global Project (HHGP)
Institut Pasteur Senegal
Institut Pasteur Hong Kong

ATRACTion
Vers une médecine personnalisée

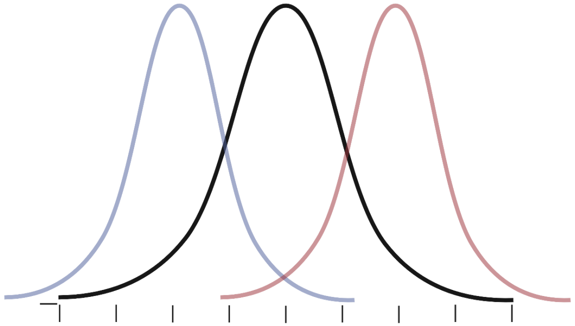
tilda
Staidéar Fadaimseartha na
hÉireann um Dhul in Aois
The Irish Longitudinal
Study on Ageing

SYS AGE

Healthy
Human
Global
Project

How does immune variability impact disease risk, drug or vaccine response

Normal distribution of immune responses



Tuberculosis
(Tom Scriba)

Urinary Tract Infection
(Molly Ingersoll)

Viral resistance
(Jamie Sugrue/Cliona O’Farrelly)

Type I diabetes
(Kristin Tarbell)

COVID-19
(Trinity College Dublin/Hopital Cochin)

Pertusis
(Julie Toubiana)

Multiple Sclerosis
(Frederique Michel)

Spondyloarthritis
(Lars Rogge)

Vaccine responsiveness
COVID-19 – C2i/HK
Influenza – H2020 Incentive

Sarcoidosis
(Karim Sacre)

Juvenile Dermatomytis
(Mathieu Rodero/Cyril Gitaux)

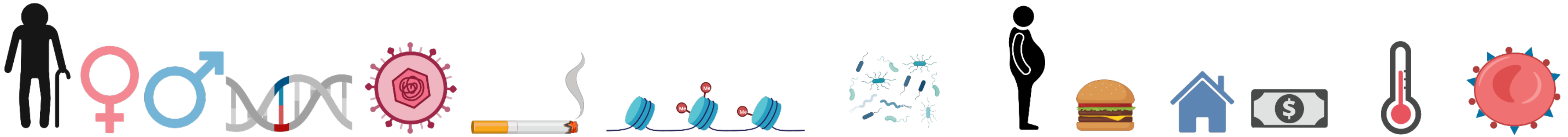
Cancer immunotherapy
(Nader Yatim/Celeste Lebbe)

ITP
(Richard Lee/Charlotte Bradbury)

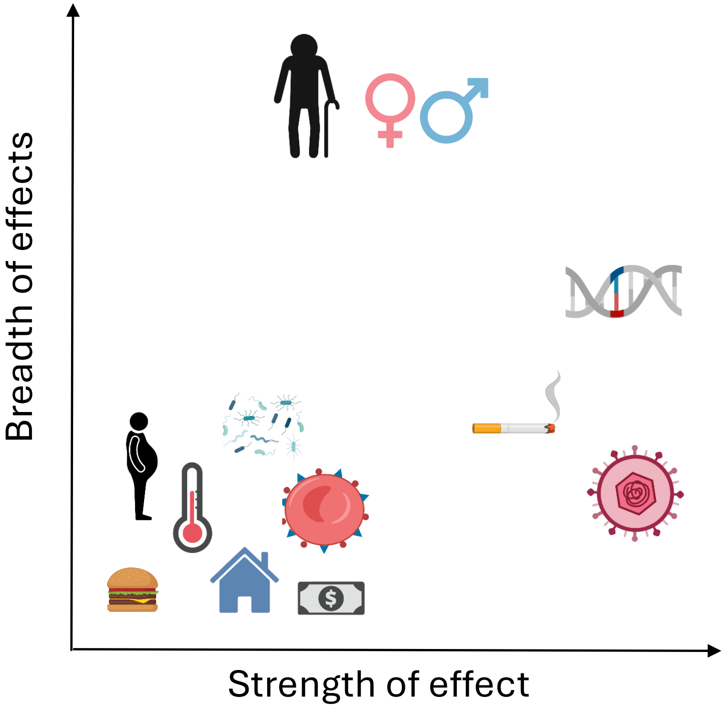
Lupus
(JP Herbeuvel/Anne-Sophie Korganow)

Duffy et al, Clin Inf Dis 2018
Rodrigues et al, Diabetologia 2020
Menegatti et al, Ann Rheum Dis 2021
Devi-Marulkar et al, Frontiers Imm 2021
Llibre et al, Frontiers 2022
Sugrue et al, Cell Reports 2022
Smith et al, Nat Comms 2022

Conclusion - why are immune responses different between individuals



Age **Sex** **Genetics** **CMV** **Smoking** **Epigenetics** **Microbiome** **BMI** **Diet** **Social status** **Temp** **Blood type**



- Immune responses are highly diverse & variable
- Widespread effects of age, sex & host genetics
- Specific & strong effects of smoking & CMV infection
- Many other specific environmental factors important
- Results can be context specific

Ongoing work

- Need to include other ages & diverse populations
- Need to asesse age*sex*genetic*environment interactions
- Longitudinal assessment required
- Comparison with patient populations

“Art is I, Science is We” Claude Bernard 1865




Translational Immunology

Anthony Bertrand
Vincent Bondet
Melanie Briard
Auxence Desrentes
Florian Dubois
Jingwen Fan
Mercè Guzman Vendrell
Elizabeth Maloney
Thomas Moreau
Farah Rahal
Quentin Richier
Marie Robert
Vincent Rouilly (Datactix)
Alexandra Serris
Arcange Shannon
Jamie Sugrue
Violaine Saint-Andre
Etienne Villain
MC Vougny

Trinity College Dublin/St James

Nollaig Bourke
Colim Bergin
Niall Conlon
Adam Dyer
Federica Giangrazi
Cliona Ni Cheallaigh
Cliona O’Farrelly
Matt McElheron
Cian Reid
Liam Townsend

Past lab members

Chloe Albert
Bruno Charbit
Tom Dott
Tinaia Evita Lou
Alba Llibre Serradell
Celine Posseme
Andre Rodriguez
Nikaia Smith
Divya Unni
Nader Yatim

Mucosal Inflammation & Immunity

Léa Deltourbe
Molly Ingersoll

Human Evolutionary Genetics

Auerlie Bisaux
Anthony Jaquaniello
Etienne Patin
Maxime Rotival
Marwan Sharawy
Lluis Quintana-Murci

Innate Immunity

James Di Santo
Jean Marc Doisne
Eva Eleftheri
Toshiki Eri
Pedro Goncalves
Gosia Mni

CBUTechS

Slobodan Culina
Milena Hasan

Infectious Disease Epidemiology & Analytics

Michael White

C2i, Hong Kong/IP HK

Roberto Bruzzone
Hebie Chen
Raven Cheng
Peter Chung
Jessica Denecke
Rosanna Fong
Rex Hung
Ashley Li

Theodora Luk
Jimmy Lai
Minnie Lo
Max Hui
Cheska Li
Anna Lee
Leo Poon
Simon Muller

Wilson Ng
Malik Peiris
Rachel Telford
Christy Wong
Grace Wu
Christy Wong
Jeffrey Yu
Amandine Schneider

CNRS

Mattheiu Rodero
Cyril Gitiaux

APHP

Karim Sacre

IP Senegal

Fatoumata DIENE SARRI
Babacar DIOUF
Cheikh LOUCOUBAR
Aniick MANSOUROU
Ronald PERRAUT
Aissatou TOURE
Marie-Louise VARELA

Milieu Interieur Consortium
Lluis QUINTANA MURCI
Darragh DUFFY
Matthew AILBERT
Laurent ABEL (Necker)
Andres ALCOVER
Hughues ASCHARD
Philippe BOUSSO
Nollaig BOURKE (TCD)
Petter BRODIN (Karolinksa)
Pierre BRUHNS
Nadeine CERF-BENSUSSAN (Imagine)
Ana CUMANO
Caroline DEMANGEL
Christophe D’ENFERT
Ludovic DERIANO
Marie-Agnes DILLIES
James DI SANTO
Gérard EBERL
Jost ENNINGA
Jacques FELLAY (EFL)
Ivo GOMPERTS-BONECA
Milena HASAN
Magnus FONTES (Roche)
Serge HERCBERG (Université Paris)
Molly INGERSOLL
Rose ANNE KENNY (TCD)
Olivier LANTZ (Curie)
Gunilla KARLSSON HEDESTAM (Karolinska)
Frederique MICHEL
Hugo MOUQUET
Cliona O’FARRELLY (TCD)
Etienne PATIN
Antonio RAUSELL (Imagine)
Lars ROGGE
Anavaj SAKUNTABHAI
Olivier SCHWARTZ
Benno SCHWIKOWSKI
Spencer SHORTE
Fréderic TANGY
Antoine TOUBERT (St Louis)
Mathilde TOUVIER Université Paris)
Marie-Noelle UNGHEUER
Christophe ZIMMER

Thanks for your attention !

darragh.duffy@pasteur.fr
https://www.linkedin.com/in/darragh-duffy/
@darraghduffy.bsky.social

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