Franco-Brazilian Health Workshop-
June 11th 2025

Team MEETiCs

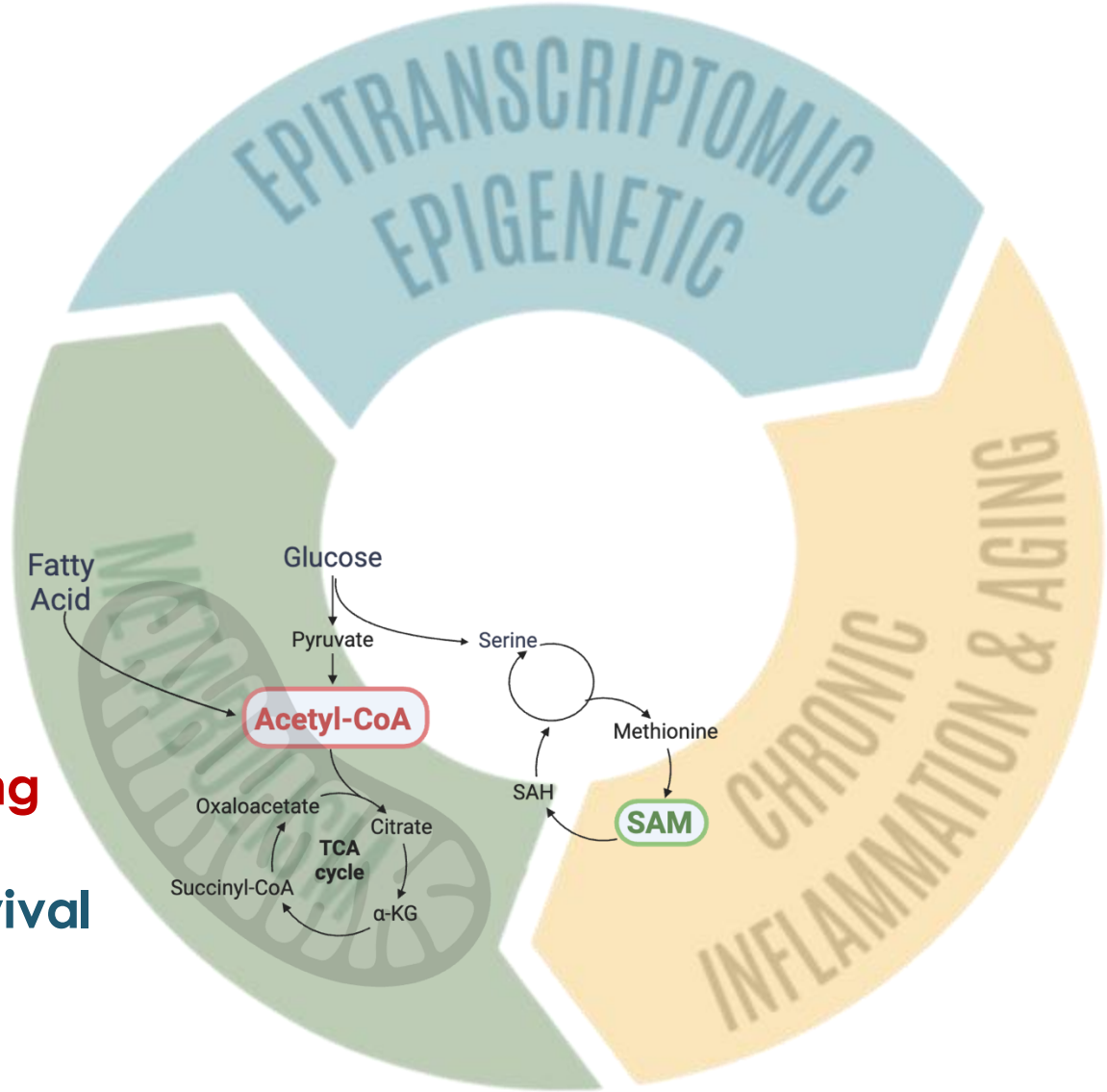
Metabolic, Epigenetic and Epitranscriptomic interplay in T cells during Chronic inflammation, infection & Senescence

Anne S. Dejean, PhD
anne.dejean@inserm.fr



Toulouse Institute for Infectious and Inflammatory Diseases

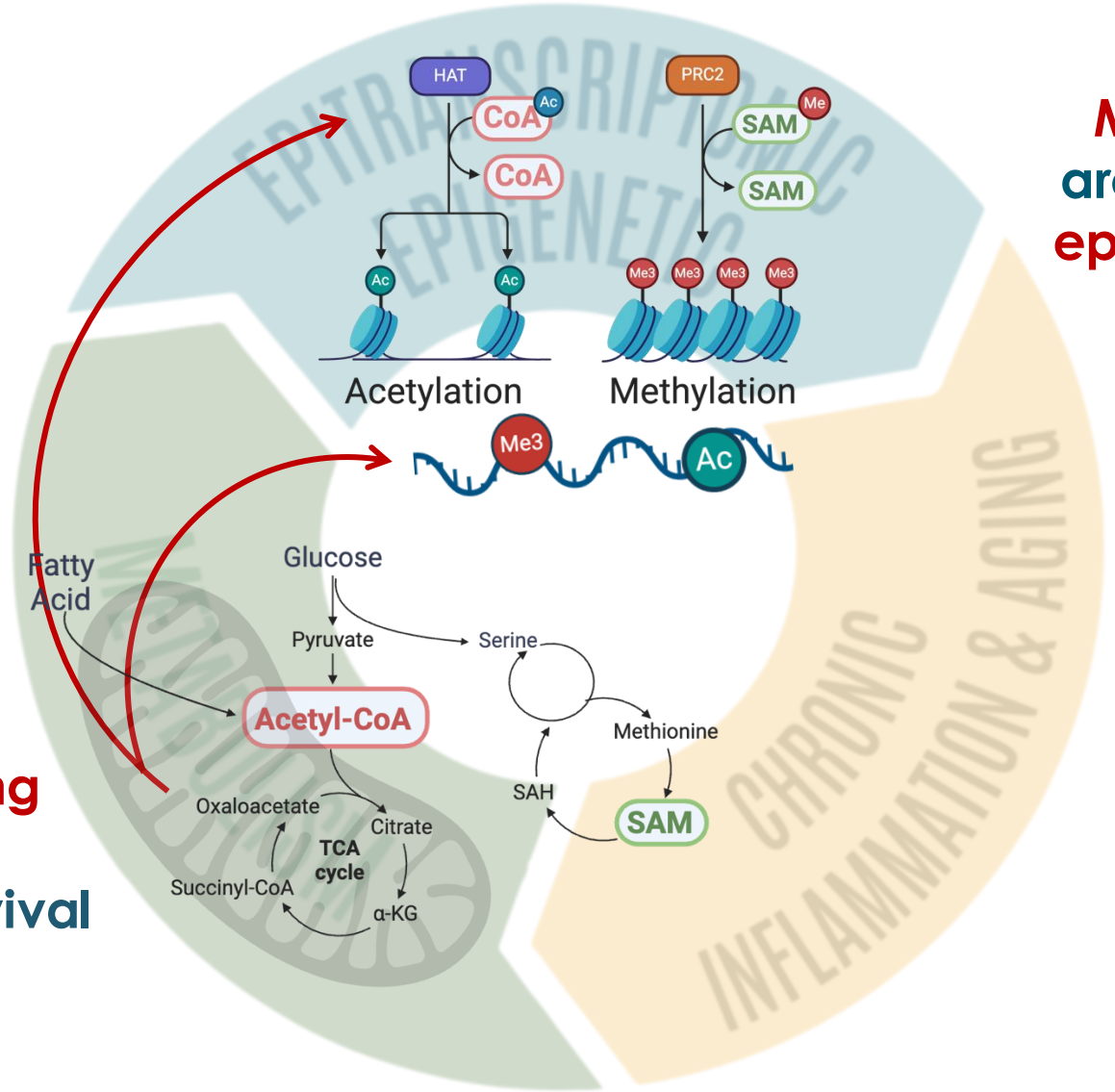
Team MEETiCs



Metabolic remodeling
T cell activation,
differentiation and survival

Metabolic sensors
(mTOR, Myc, HIF1a, AMPK…)
are key regulators of T cell Immunity

Team MEETiCs

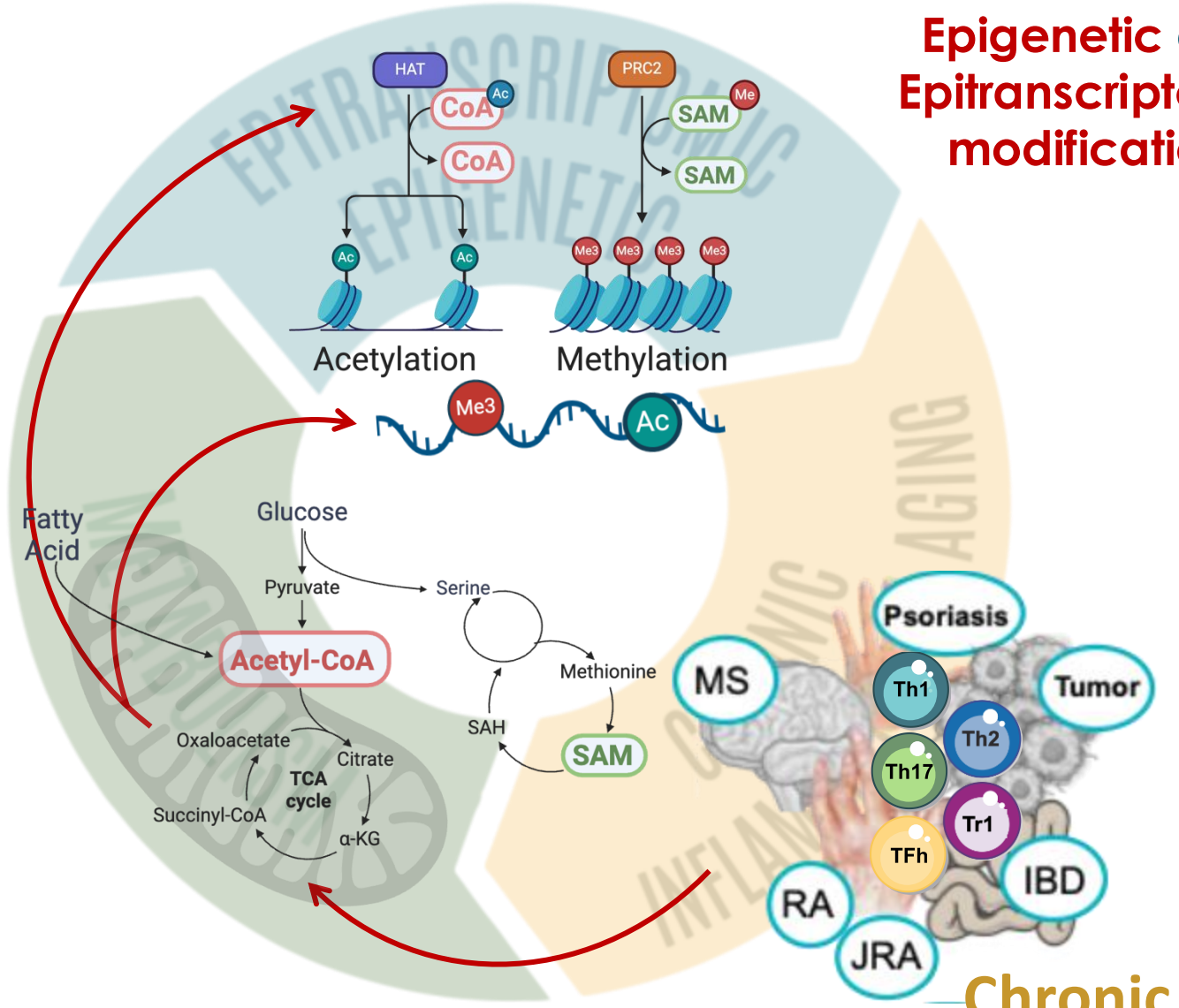


Metabolic intermediates are used in epigenetic and epitranscriptomic programs

Metabolic remodeling T cell activation, differentiation and survival

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Epigenetic and Epitranscriptomic modifications

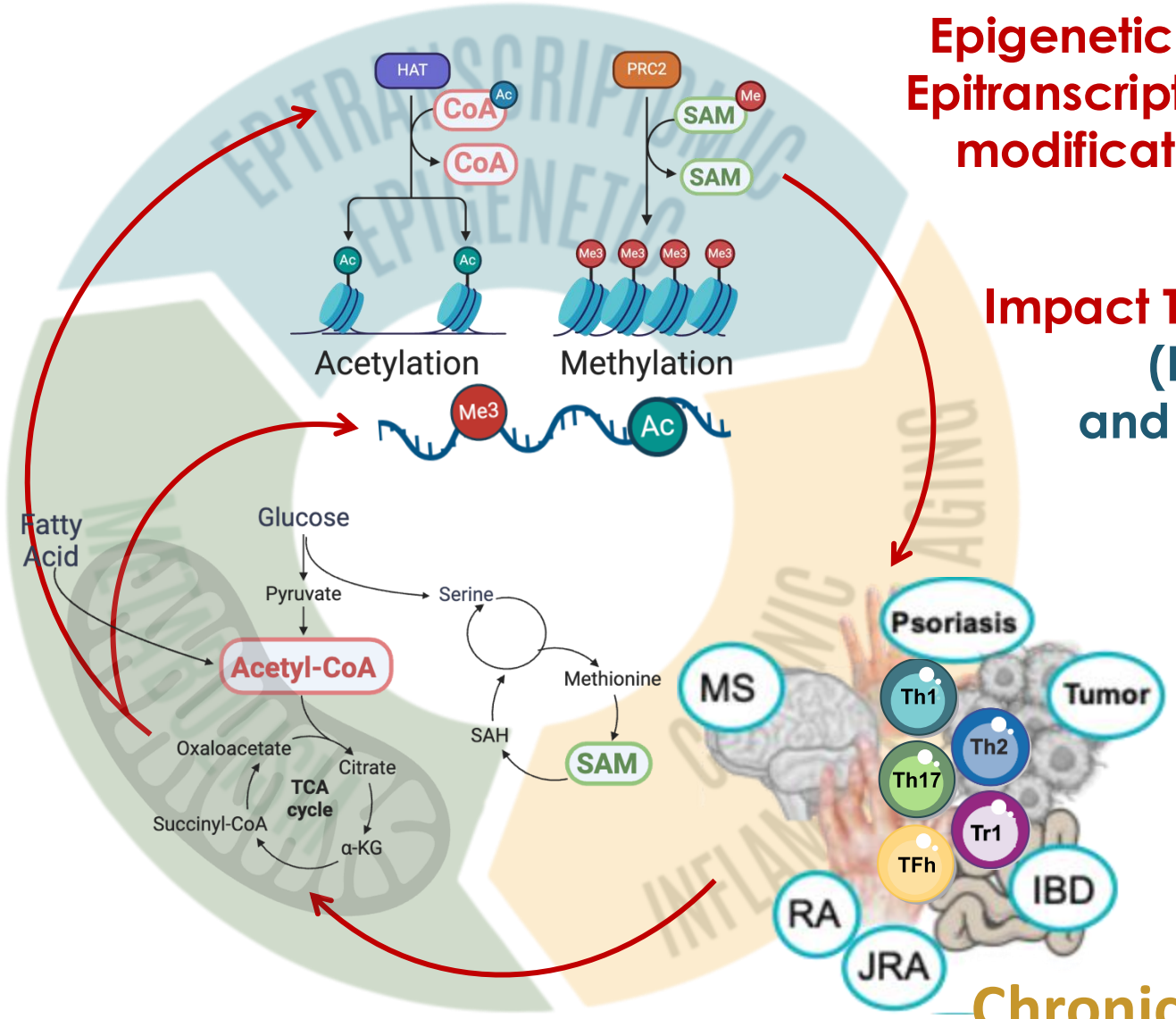


Metabolic alterations

T cells undergo metabolic stress

Chronic Inflammation, Infection & aging

Team MEETiCs



Epigenetic and Epitranscriptomic modifications

Impact T cell fate/function (Exhaustion and senescence)

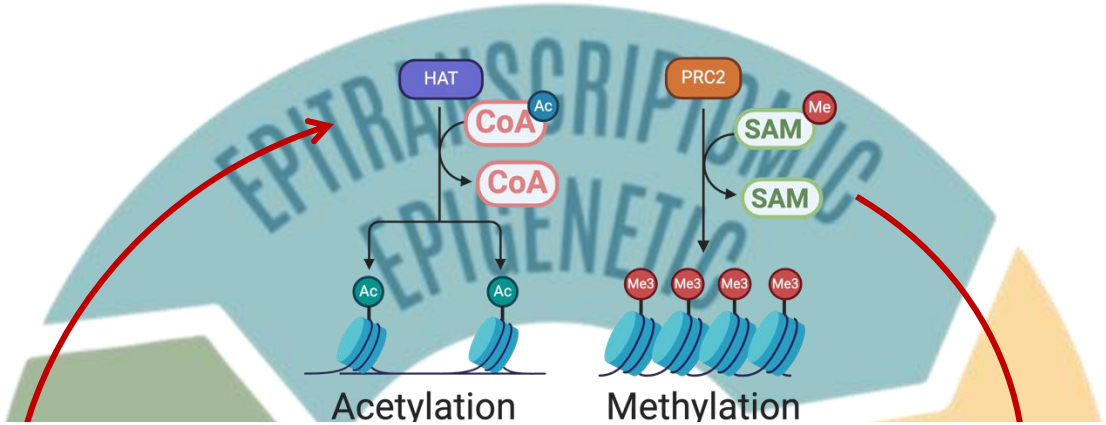
Metabolic alterations

T cells undergo metabolic stress

Chronic Inflammation, Infection & aging

Changes in DNA methylation are hallmarks of aging and chronic diseases

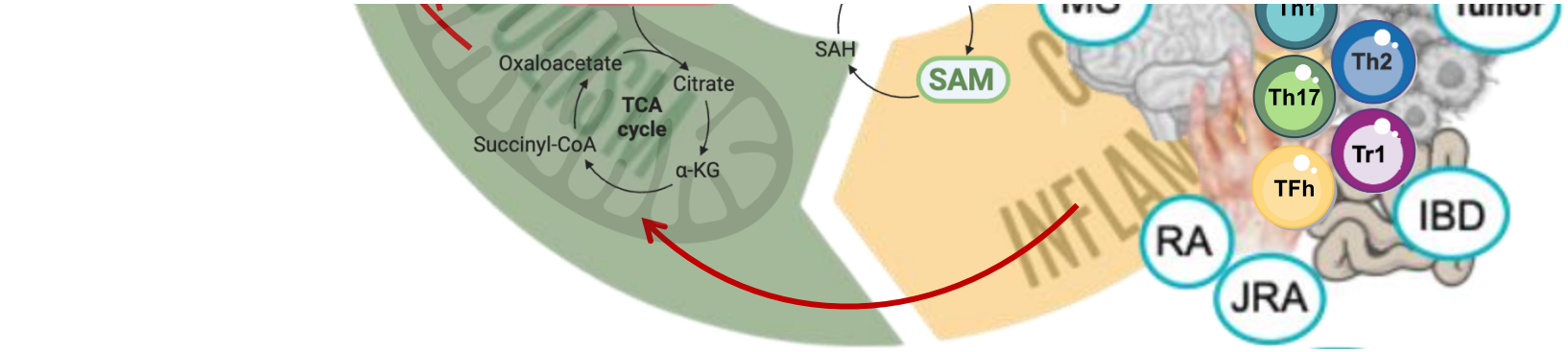
Team MEETiCs



How does metabolic stress affect epigenetic or epitranscriptomic landscapes?

Consequences on T cell fate and function?

Contribution to chronic inflammation and accelerated aging?



Team MEETiCs

Axe2: Identification of novel epigenetic and epitranscriptomic actors in CD4+ T cell functions



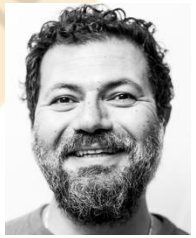
V. ADOUE (CNRS)
Molecular studies
Bio-informatic
Epigenetic/Epitranscriptomic

Axe1: New T cell metabolic regulators in chronic inflammation and cancer



A. DEJEAN (INSERM)
T cell subsets & function
Transcription factors
Animal models

Axe3: Metabolic fitness of T cells in chronic infection and aging



H. El COSTA (INSERM)
Translational research
Immunometabolism
Chronic infection & Aging

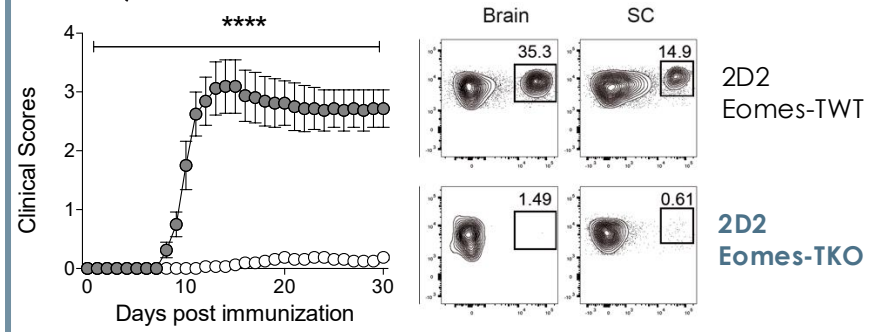
Initial Collaboration: Role of Eomes in Neuroinflammation

Eomes
Inflammatory disease (MS, RA) cancer

Eomes+ CD4 T cells accumulate in **inflamed tissues**

EAE

Eomes$^{fl/fl}$ -CD4cre mice



☑ **Eomes-KO CD4 T cells failed to induce EAE**



E. Joulia et al. (PhD), J. Exp. Med. 2024

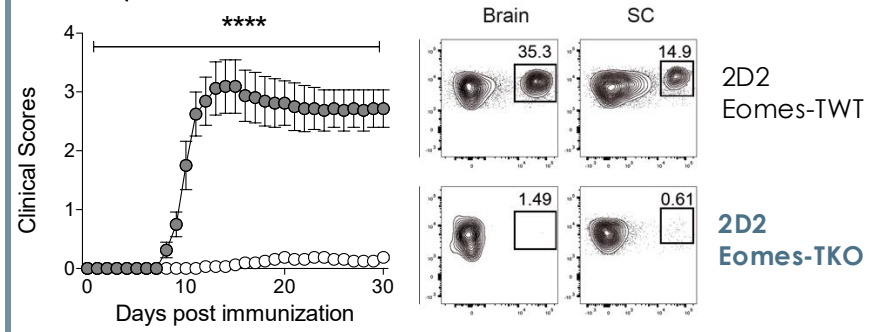
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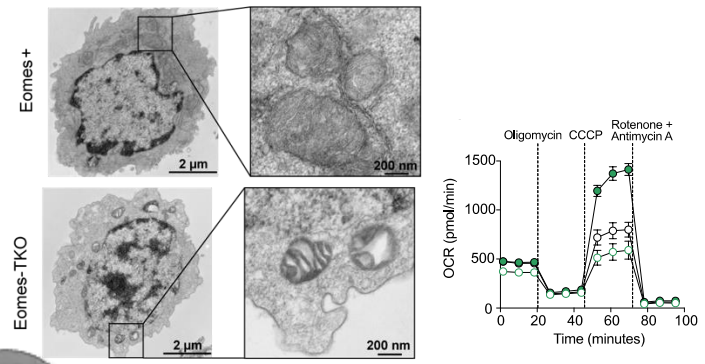
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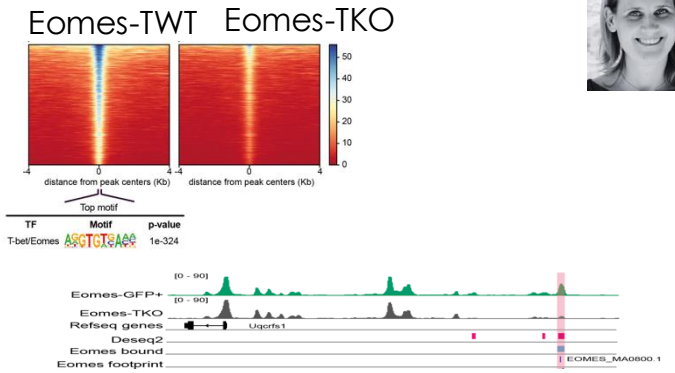
Mechanisms involved?

Metabolic studies



Epigenetic studies

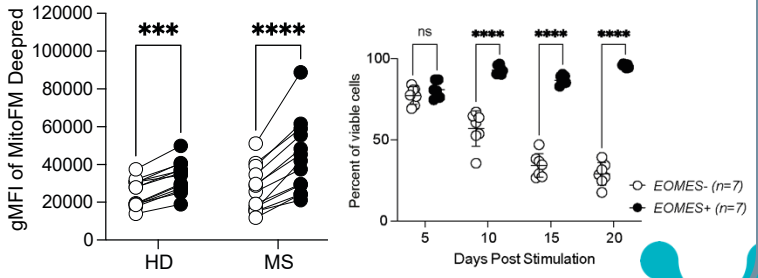
CUT&RUN ATAC-Seq





Translational studies
MS patients







E. Joulia et al. (PhD), J. Exp. Med. 2024

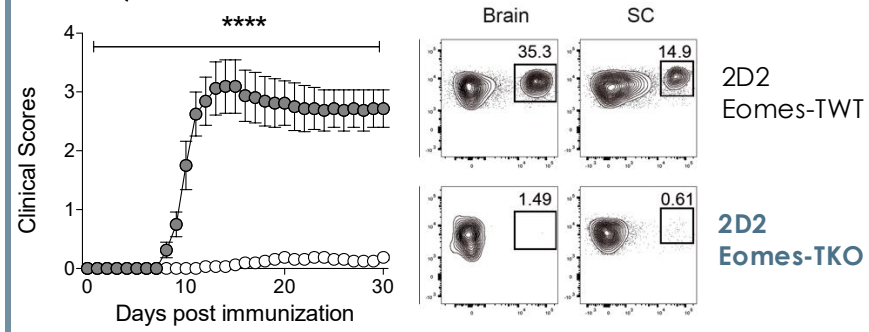
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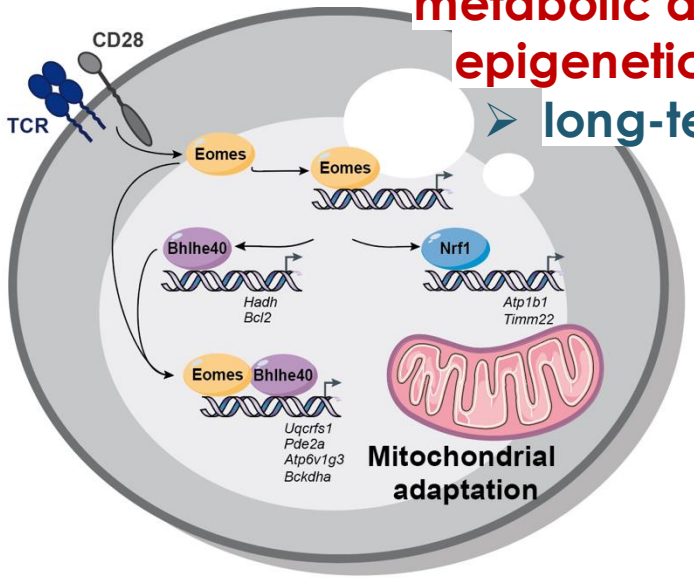
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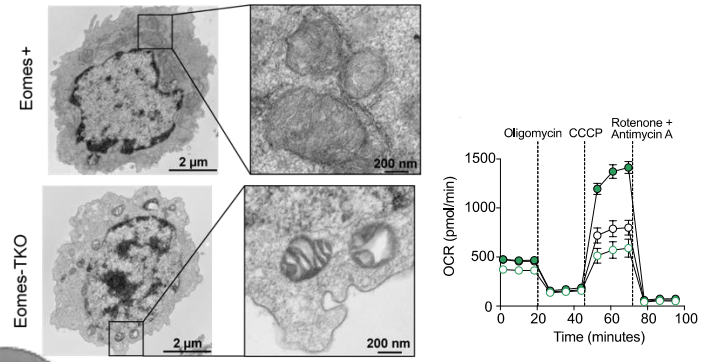
Eomes: key regulator of CD4 T cell metabolic adaptation and epigenetic remodeling

➢ long-term survival



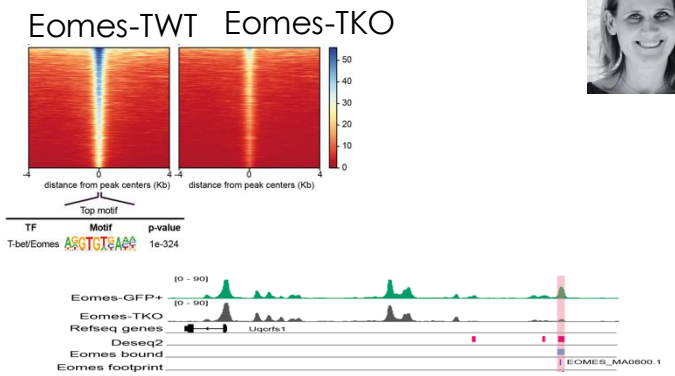
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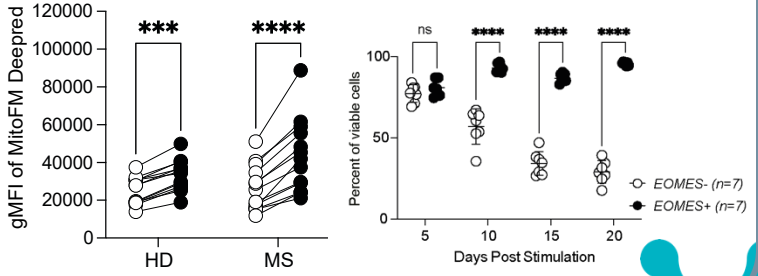
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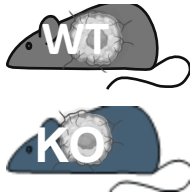




E. Joulia et al. (PhD), J. Exp. Med. 2024

Axe 1: New T cell metabolic regulators in cancer

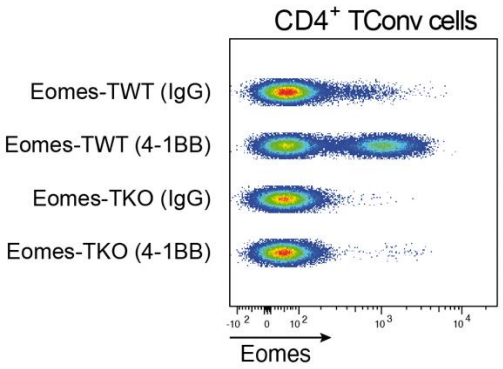
Multiple Myeloma

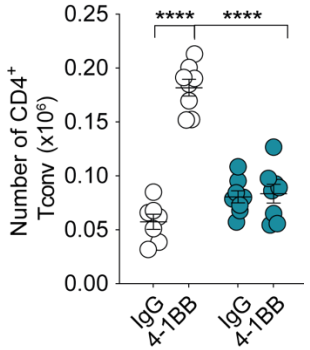


Eomes$^{fl/fl}$ – CD4-Cre mice

4-1BB Agonist

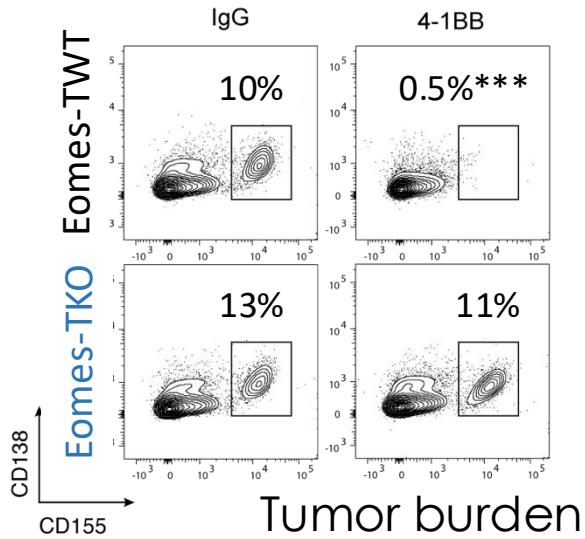
CD4 TILs





↑ Proliferation
↑ IFNg/cytotoxicity
↑ Exhaustion
=Tumor rejection

KO
=No response





A. Agesta (PhD), Immunity, In revision

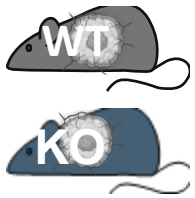
Collaborations: Ludovic Martinet & Liliana Lucca CRCT, Toulouse

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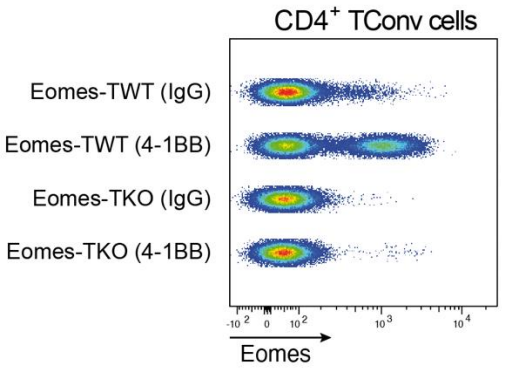
Multiple Myeloma

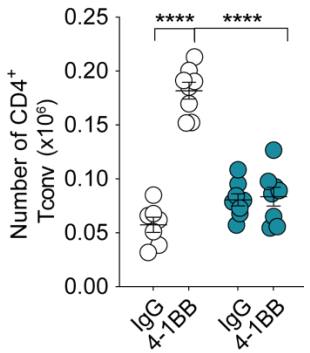
4-1BB Agonist

CD4 TILs



Eomes$^{fl/fl}$ – CD4-Cre mice

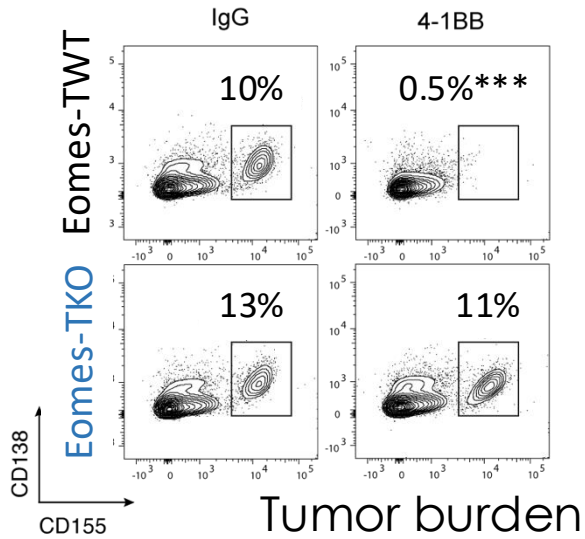




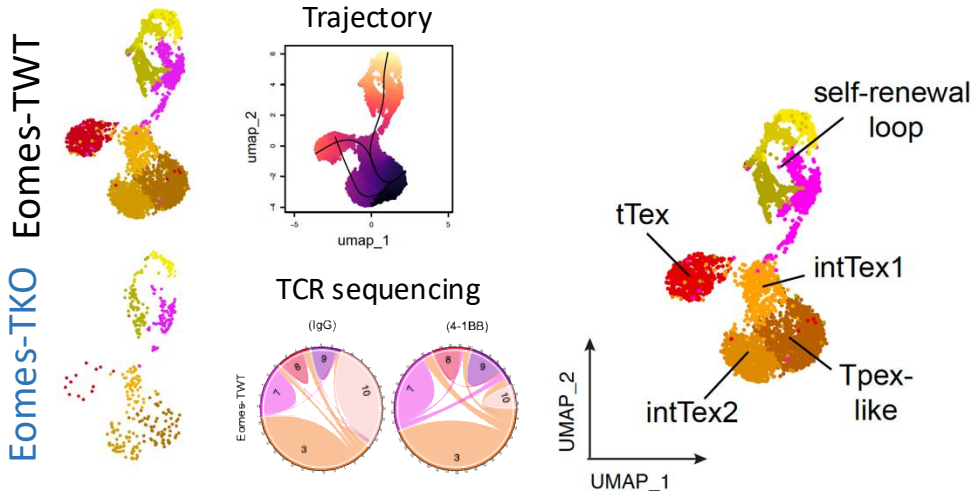
↑ Proliferation
↑ IFNg/cytotoxicity
↑ Exhaustion
=Tumor rejection

WT

KO
=No response



Tumor burden



☑ **Eomes is critical for exhausted CD4+ T cell maintenance** (metabolic fitness and resistance to cytotoxicity)

☑ **Identification of Tpex-like CD4 T cells:**

- ✓ **Self renewal capacity**
- ✓ **Give rise to effector-like Tex** (IFNg+, GzmB+, CD107a+)
- ✓ **Exhibit antitumoral properties** (even in absence of CD8 T cells)

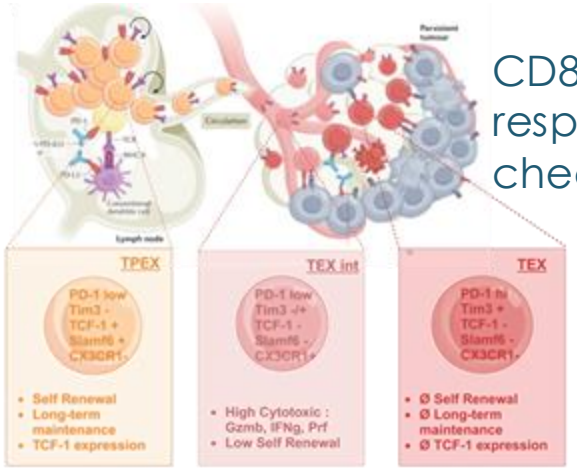
☑ **Characterization of the exhausted CD4 T cell lineage**



A. Agesta (PhD), Immunity, In revision

Collaborations: Ludovic Martinet & Liliana Lucca CRCT, Toulouse

Axe 1: New T cell metabolic regulators in cancer



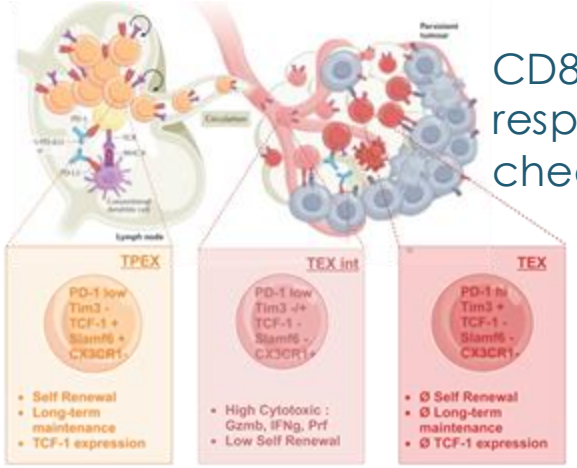
CD8 T_{PEX} mediate the response to Immune checkpoint Inhibitors (ICI)

Utzschneider, D et al. (2016) Immunity. & Im, S. J. et al. (2016) Nature



C. Ferrand (PhD)

Axe 1: New T cell metabolic regulators in cancer



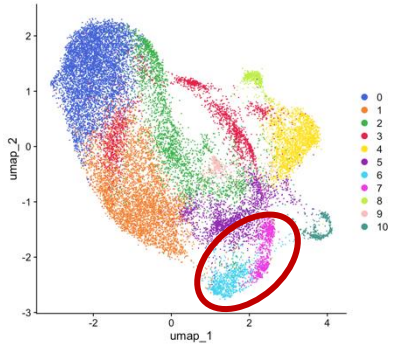
CD8 T_{PEX} mediate the response to Immune checkpoint Inhibitors (ICI)

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Melanoma patients prior and after ICI

CD4 T cells



- ☑ Eomes
  PDCD1, HAVR2, LAG3
  GzmK, IFNγ
- ☑ Tpex/Tex signatures

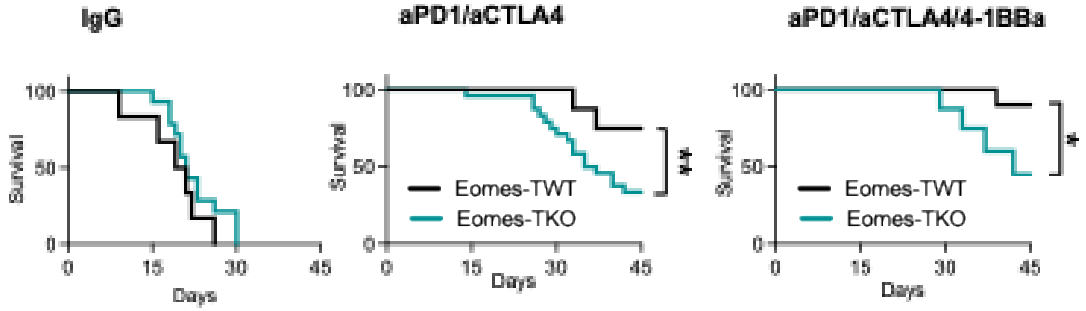
- ☑ Most expended clusters post-ICI treatment
- ☑ Enriched in neo-antigen specificity TCR



$Eomes^{fl/fl}$ –CD4-Cre mice

Melanoma
B16-Ova





☑ **Eomes expression in T cells controls sensitivity to ICI**

- ☐ Role of CD4Tpex/Tex cells
- ☐ Define the metabolic switch associated with their maintenance in tumor and t-dLN
- ☐ Understand how metabolic adaptation impacts TIL functions through epigenetic modifications

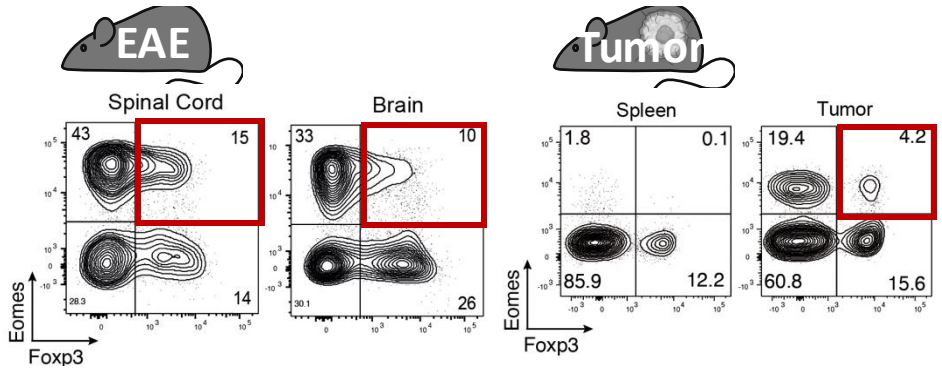


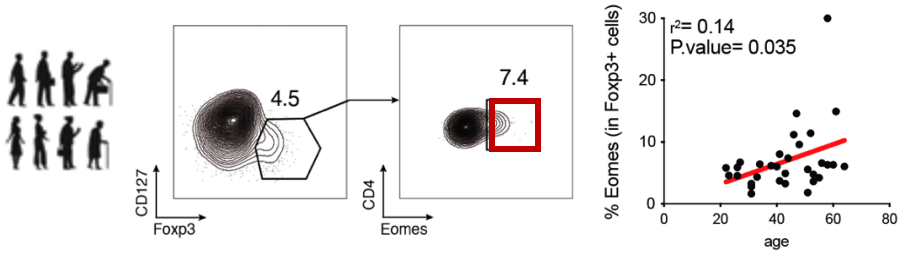
C. Ferrand (PhD)

Collaboration: Benjamin Lu & Harriet Kluger, Yale, USA

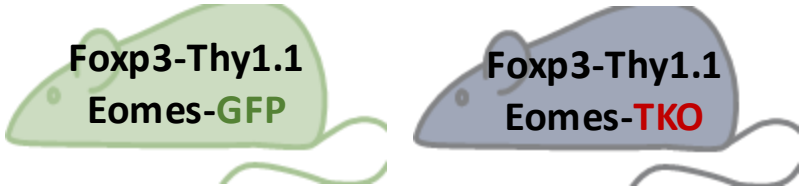
Axe 1: New T cell metabolic regulators in chronic inflammation and cancer

Eomes in Tregs?



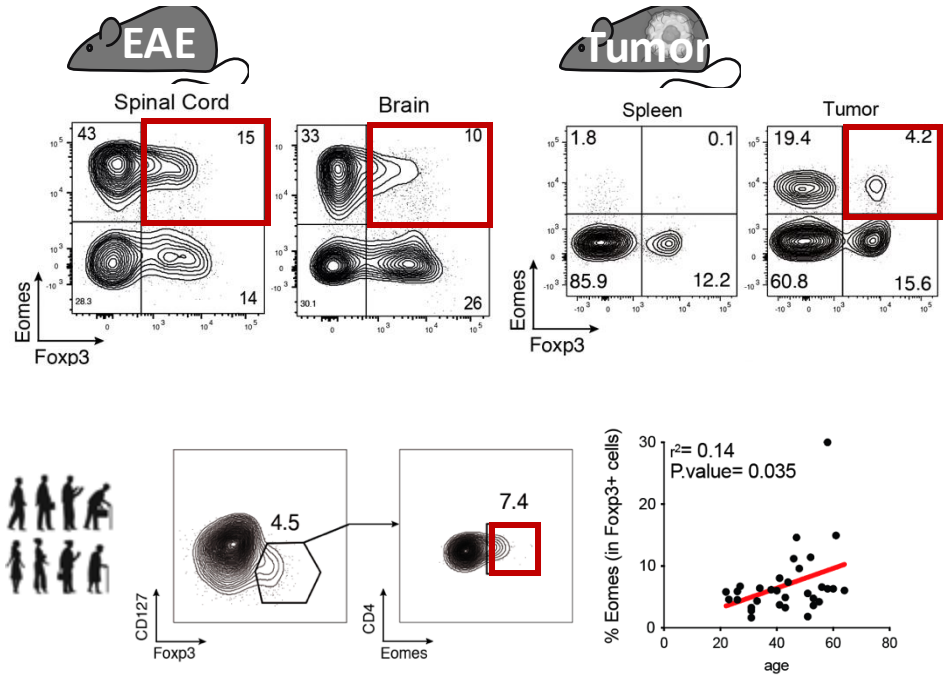


☑ **Tregs co-expressing Foxp3 and Eomes are found in inflammatory conditions**

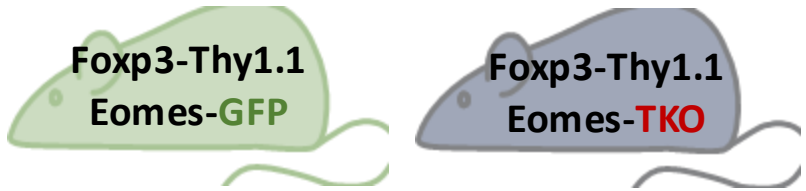


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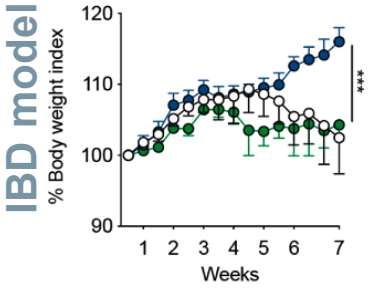
Despite normal Foxp3 expression

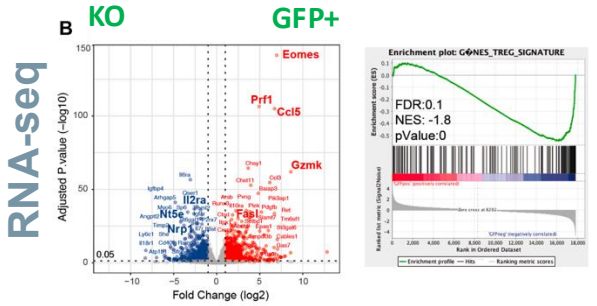
R. Peroceschi (PhD)
In preparation



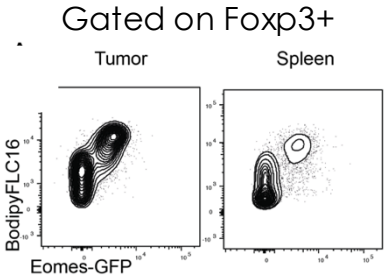
☑ **Enhanced plasticity** (IFNγ/TNF/cytotoxicity)

☑ **Decreased Treg suppressive function**





☑ **Loss of Treg signature genes**



☑ **Enhanced Lipid accumulation**

- ☐ Contribution to chronic inflammation and aging
- ☐ Molecular mechanisms whereby Eomes impacts Treg identity
- ☐ Define the metabolic switch associated with Eomes expression in Tregs



L. Esteban (AI)

Team MEETiCs

Axe2: Identification of novel epigenetic and epitranscriptomic actors in CD4+ T cell functions



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Molecular studies
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Epigenetic/Epitranscriptomic

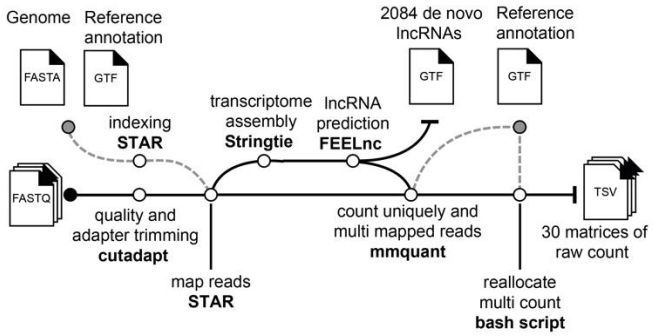
Axe1: New T cell metabolic regulators in chronic inflammation and cancer

Axe3: Metabolic fitness of T cells in chronic infection and aging

Axe2: Novel epigenetic and epitranscriptomic actors in CD4+ T cell functions

Bioinformatic studies (RNAseq Tregs/Th subsets)

New bioinformatic pipeline dedicated to lncRNA



Recruitment of
chromatin modifiers
Enhancer/promoter loops

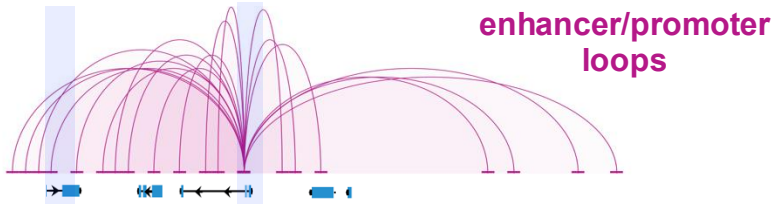
☑ **~2000 new lncRNA in CD4+ T cells**

☑ **49 lncRNA are Treg specific**

Adoue V et al. in preparation (resource paper)

☑ Identification of Lcincr

HiChIP in Tregs



Garp is involved in active TGFβ conversion

GWAS study

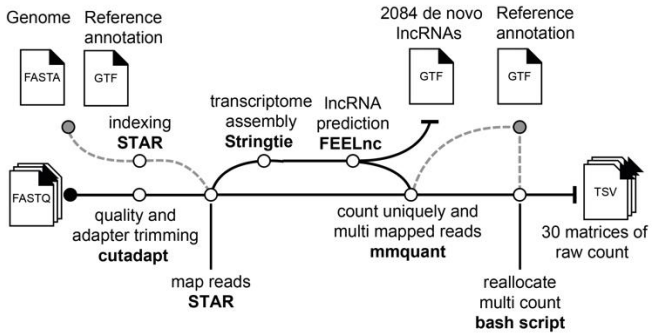
Allergic diseases
Chronic inflammation



Axe2: Novel epigenetic and epitranscriptomic actors in CD4+ T cell functions

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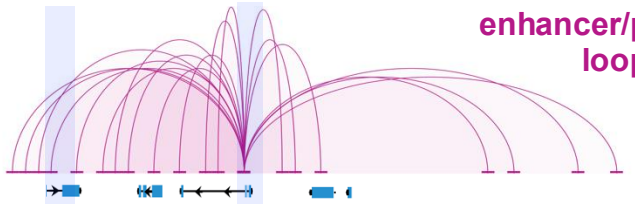
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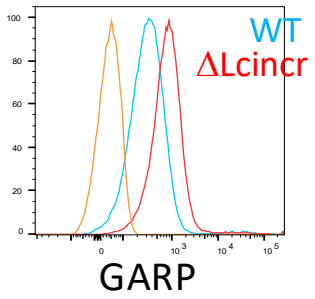
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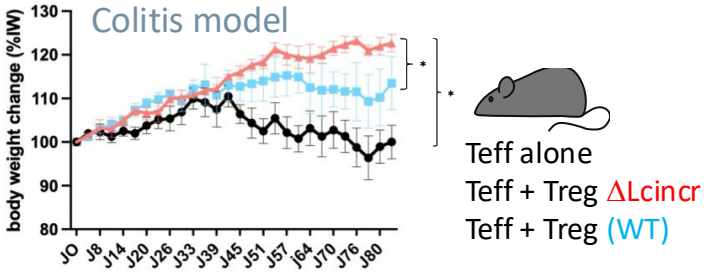


CRISPR/Cas9 deletion of Lcincr in iTreg/Th2



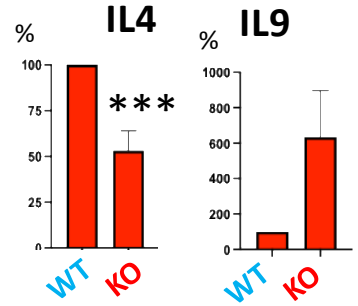
☑ **Lcincr, repressor of Garp**

iTreg



☑ **Enhanced Foxp3 and TGFβ Suppressive functions**

Th2



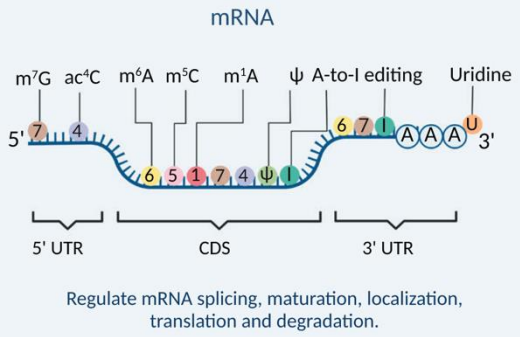
☑ **Decreased Th2/enhanced Th9**

☐ Impact in allergic and inflammatory diseases

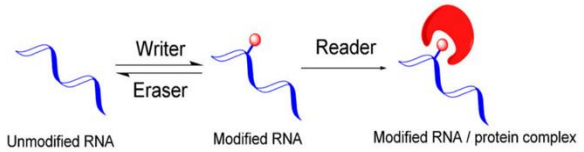
☐ Identify the genes/pathways altered by its deletion
RNAseq WT/KO in Th subset
HiChIP comparing WT vs Lcincr-KO Th cells

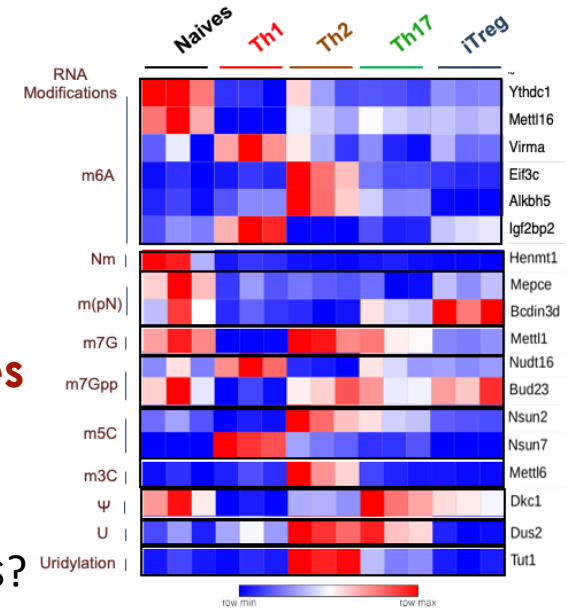
Axe2: Novel epigenetic and epitranscriptomic actors in CD4+ T cell functions

Epitranscriptomic modifications are dynamic and reversible



>170 modifications





- ☑ **Th specific expression of Epitranscriptomic enzymes**

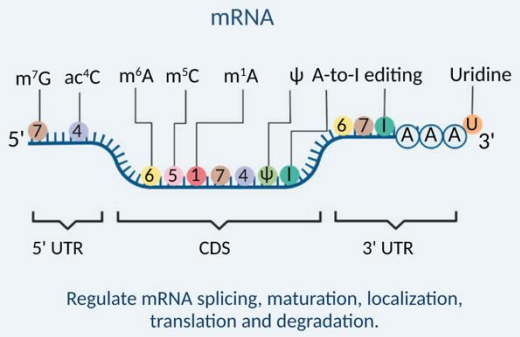
- ☐ Role in CD4+ T cell subsets?
- ☐ Which genes are targeted?
- ☐ Function (splicing, translation, expression)



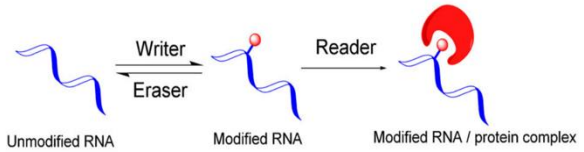
M. Le Teuff (IE)

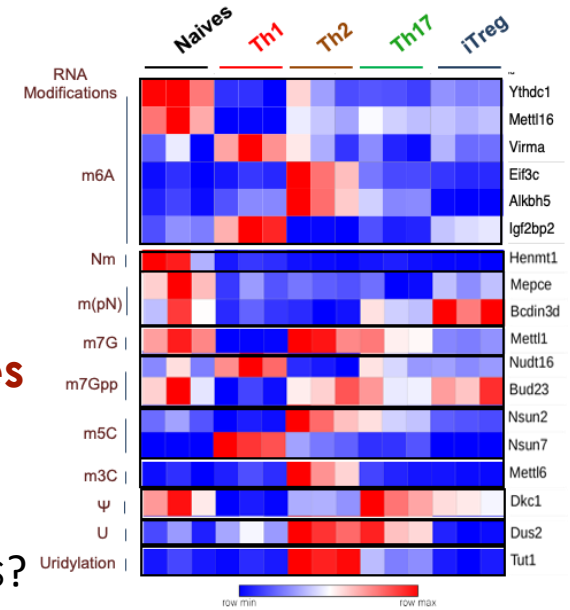
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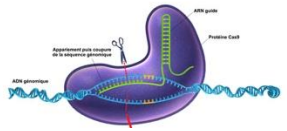
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- ☐ Function (splicing, translation, expression)



M. Le Teuff (IE)

1) *In vitro* screen (CRISPR/Cas9)

(specific Th subset expression and GWAS association)

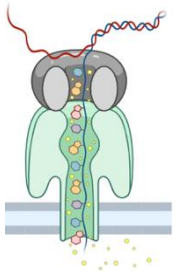


2) *In vivo* confirmation



EAE/Asthma/Colitis

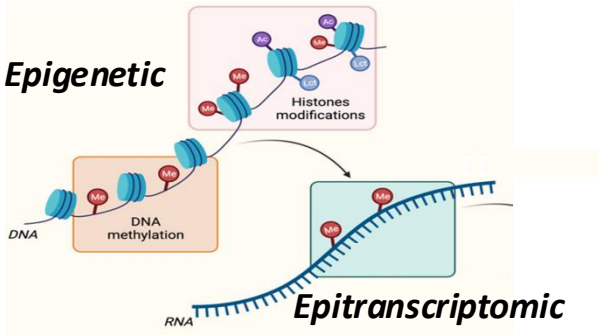
3) Deciphering molecular mechanisms



- Native RNA sequencing (nanopore)
- iCLIP-seq
- Ribo-seq



4) Epitranscriptomics & epigenetics interactions

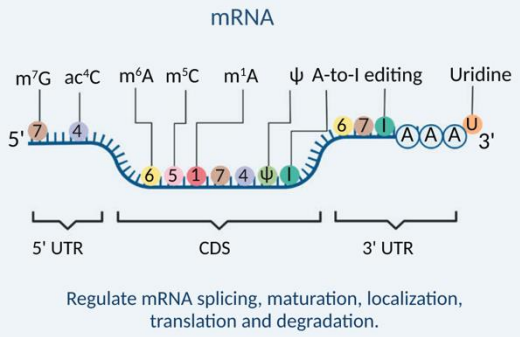


N. Hakim (PhD)

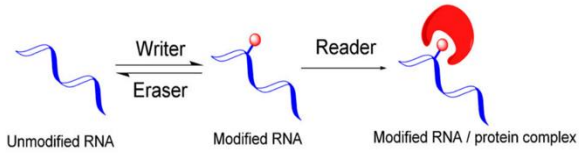


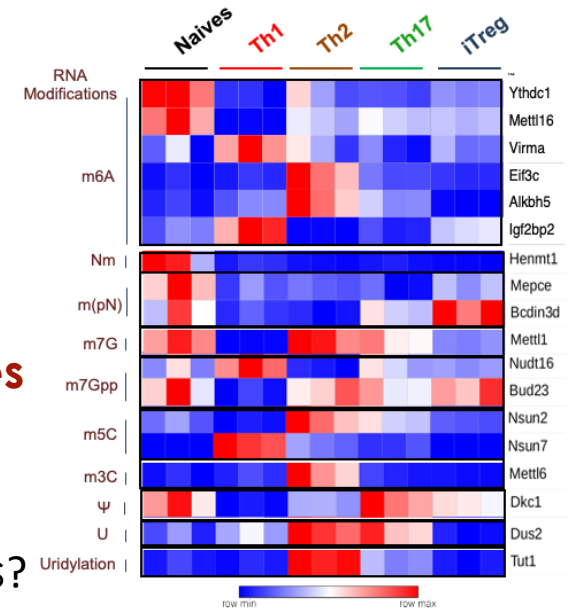
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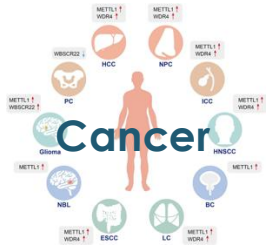
☑ **Th specific expression of Epitranscriptomic enzymes**

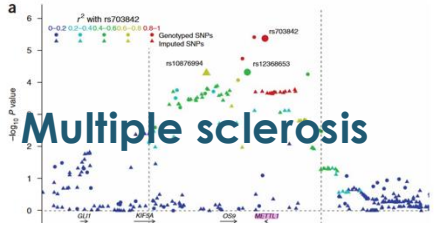
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M. Le Teuff (IE)

METTL1 is an m7G writer



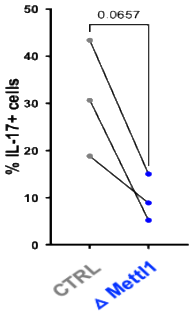


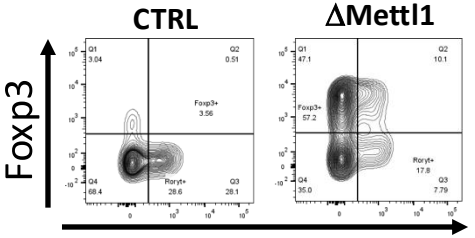


- association with cancers and susceptibility locus for MS
- diminished with senescence and aging

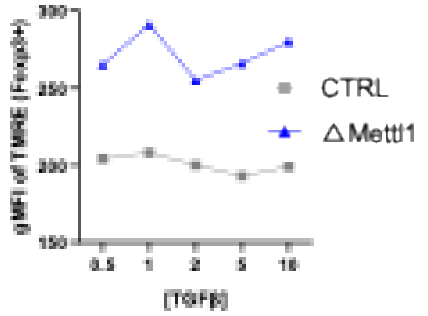
1) In vitro CRISPR/Cas9 deletion of Mettl1

Th17





Tregs



☑ **Decreased Th17/Increased Foxp3 expression**



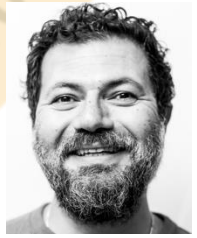
Mettl1$^{fl/fl}$ x CD4-Cre mice x Foxp3-ERT2Cre

Team MEETiCs

Axe2: Identification of novel epigenetic and epitranscriptomic actors in CD4+ T cell functions

Axe1: New T cell metabolic regulators in chronic inflammation and cancer

Axe3: Metabolic fitness of T cells in chronic infection and aging



H. El COSTA (INSERM)

Translational research

Immunometabolism

Chronic infection & Aging

Axe 3: Metabolic fitness of T cells in chronic infection and aging

T cells play a role in the systemic aging process



TFAM$^{fl/fl}$-CD4Cre

Desdín-Micó G. Science, 2020

Mitochondrial dysfunction of T cells
Systemic senescence
Features of aging (cognitive, metabolic and cardiovascular impairments)

What about in Human?

Inspire-T cohort > 70 years old

IHU HealthAge
GEROSCIENCE & PREVENTION

Frailty Index/ Intrinsic Capacity score

Frail   Robust

Bioenergy profile of immune cells
(using Scenith methods)

Collaboration: L. Martinet, I2MC, Toulouse

Axe 3: Metabolic fitness of T cells in chronic infection and aging

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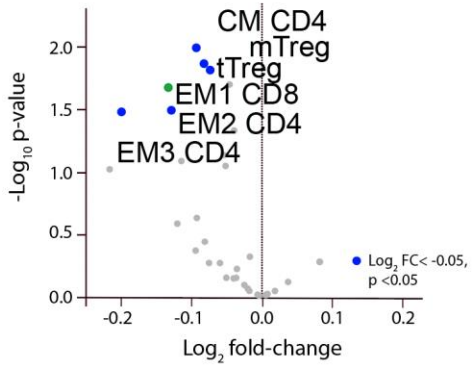
IHU HealthAge – Geroscience & Prevention

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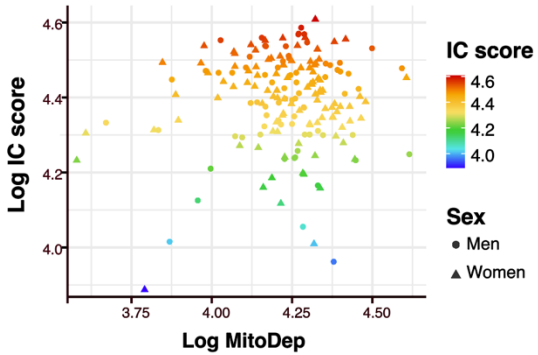
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Bioenergy profile of immune cells
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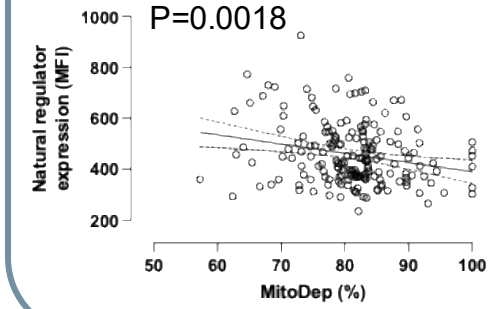
Frailty Index



Intrinsic Capacity



☑ **Decreased MitoDep in CD4 T cells is associated with functional decline**



Mitochondrial regulator (**X**)

Impact on CD4 T cell Functions and aging ?

Collaboration: L. Martinet, I2MC, Toulouse

Axe 3: Metabolic fitness of T cells in chronic infection and aging

T cells play a role in the systemic aging process



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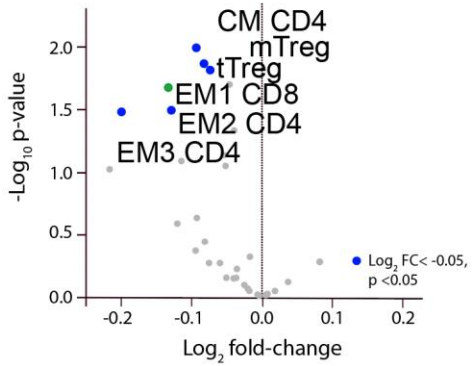
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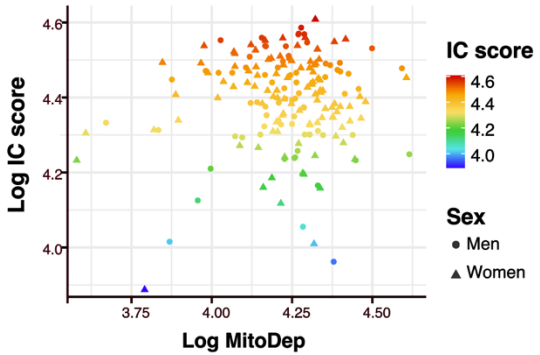
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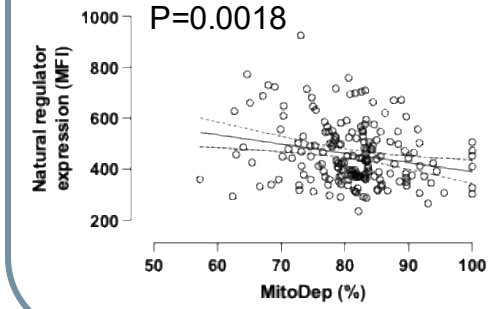
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Impact on CD4 T cell Functions and aging ?

☐ Longitudinal analysis (5 years) 

1) Determine at which age the decline is observed

2) Assess whether mitodep in CD4 T cell can predict functional decline.

Axe 3: Metabolic fitness of T cells in chronic infection and aging

T cells play a role in the systemic aging process



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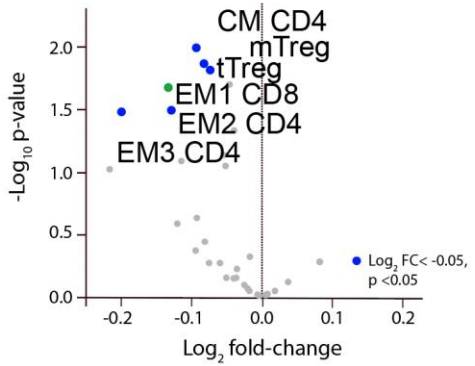
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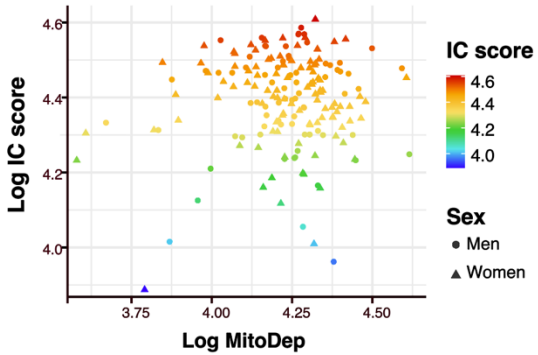
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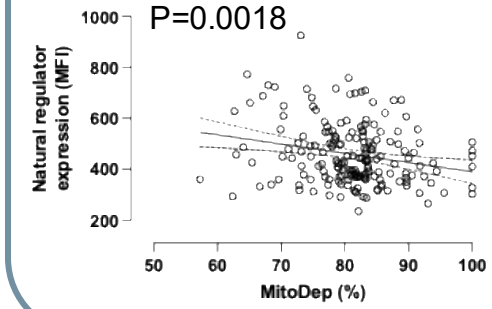
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Other metabolic regulators (Mettl1/Eomes)

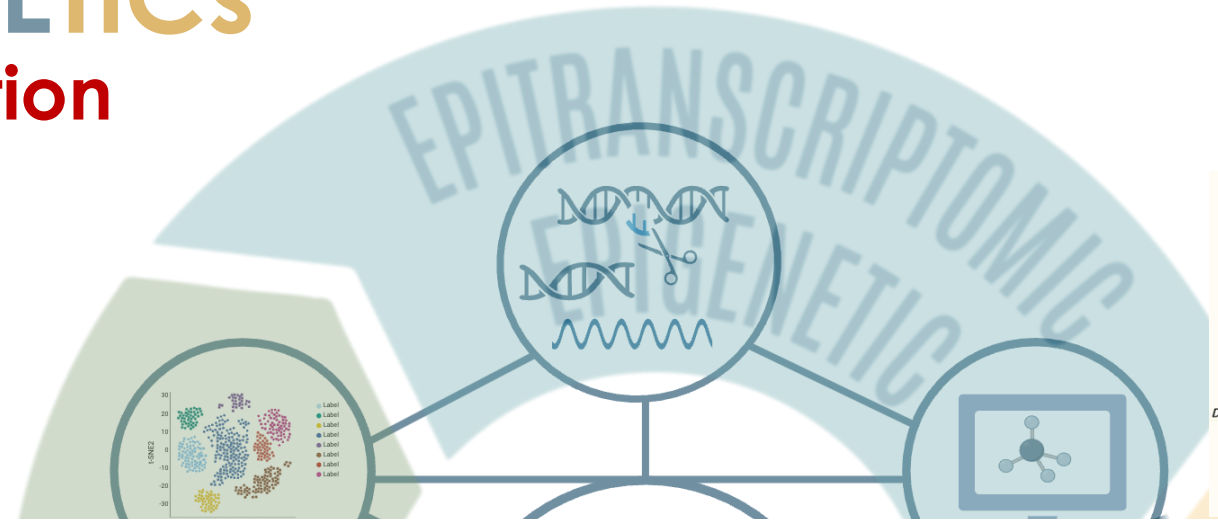
Team MEETiCs

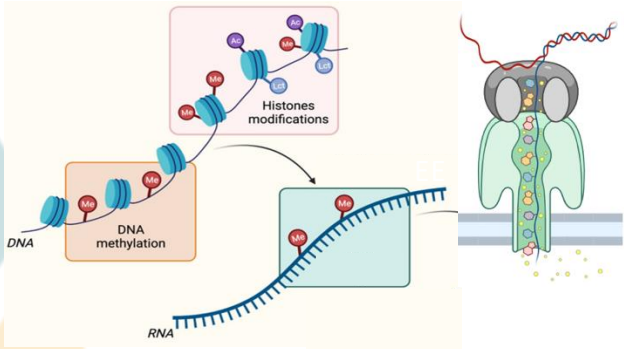
Data integration

Epitranscriptomic
Epigenetic
Native RNA-seq

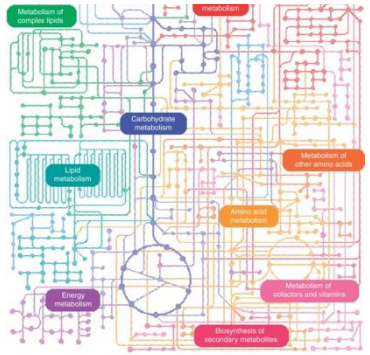
Transcriptomic





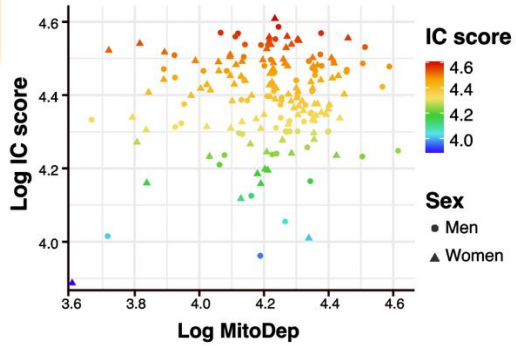


How the interplay between metabolic, epigenetic and epitransctranscriptomic impact T cell response and contribute to the severity of Chronic inflammation and Scenencence



Metabolomic





Bioenergy profile of immune cells

Team MEETiCs



Collaborations

