5TH EDITION
METABOLISM & CANCER
22-24 Nov 2023, Nice, FR

Importance of metabolism in mast cells regulation: from allergy to leukemia

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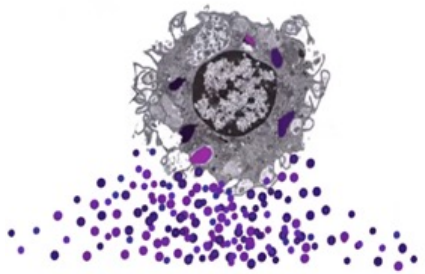
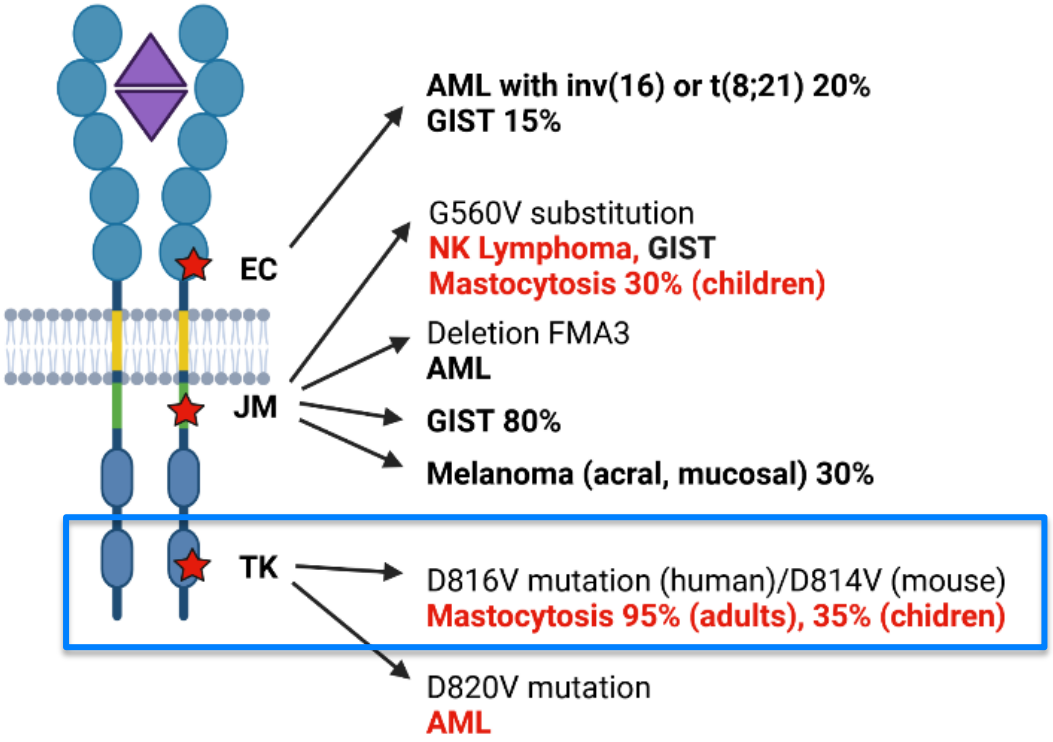
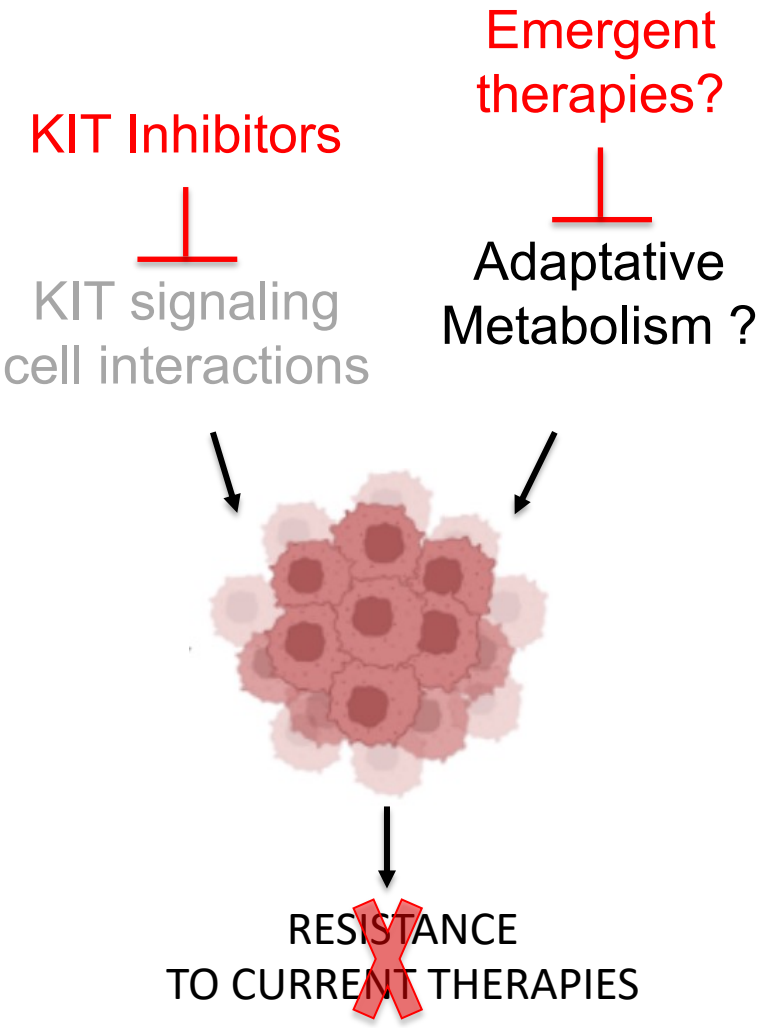
Cancer Research Center of Marseille (CRCM) – U1068



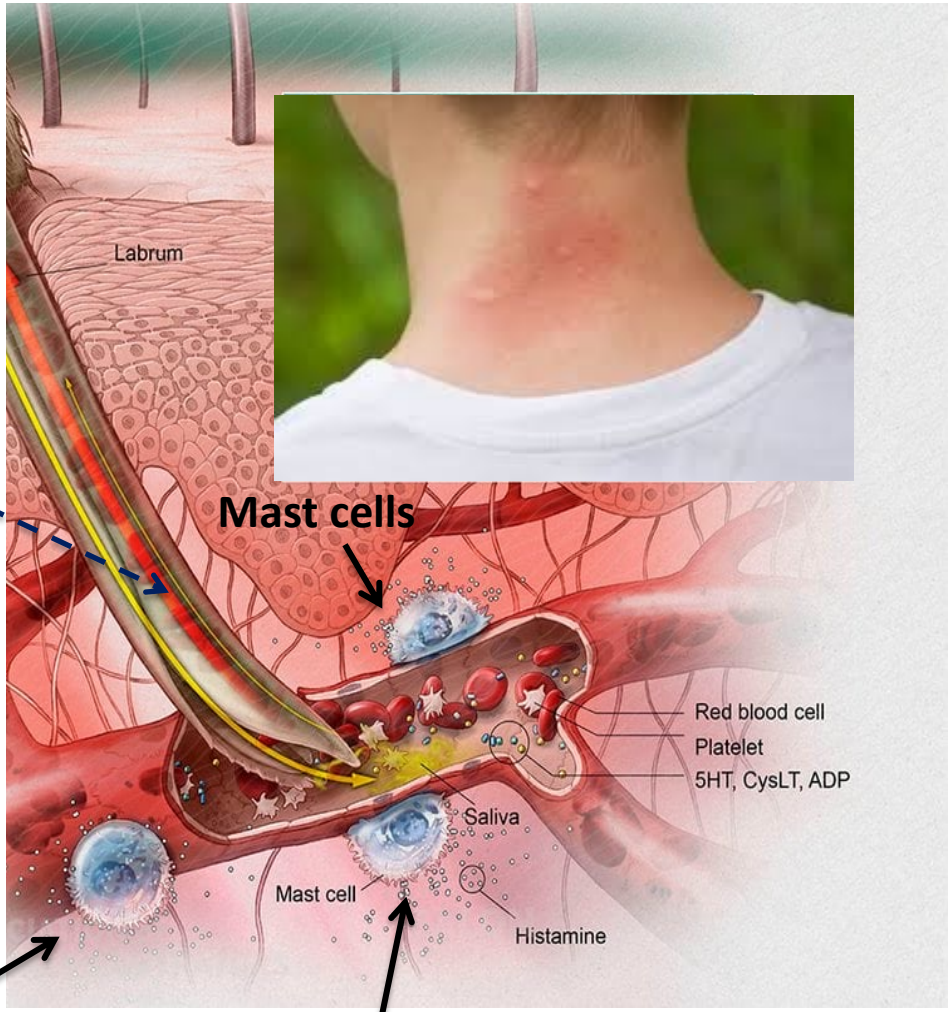
Research gap: the specific metabolic underpinings of KIT-driven oncogenic progression are largely undefined



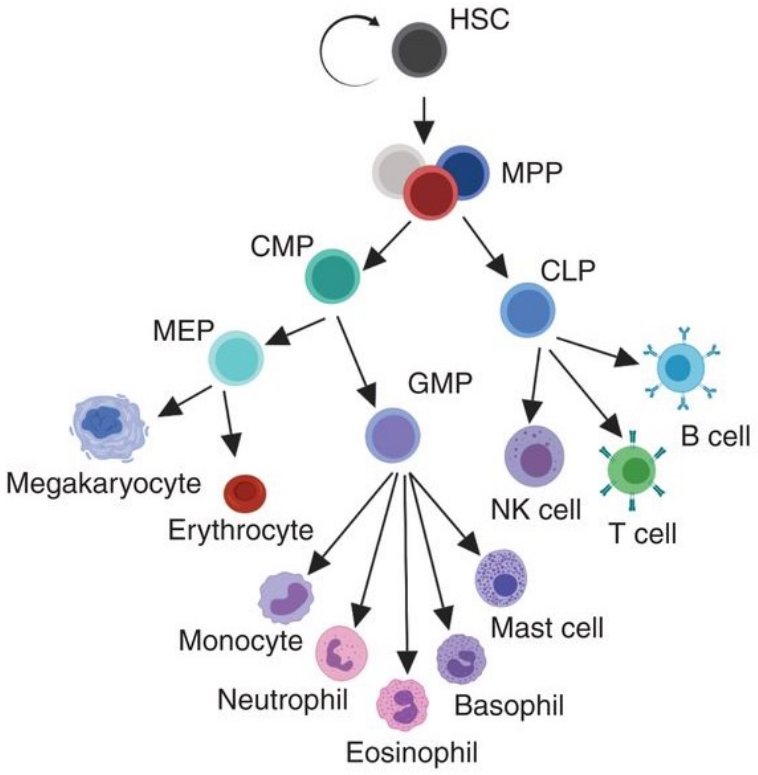


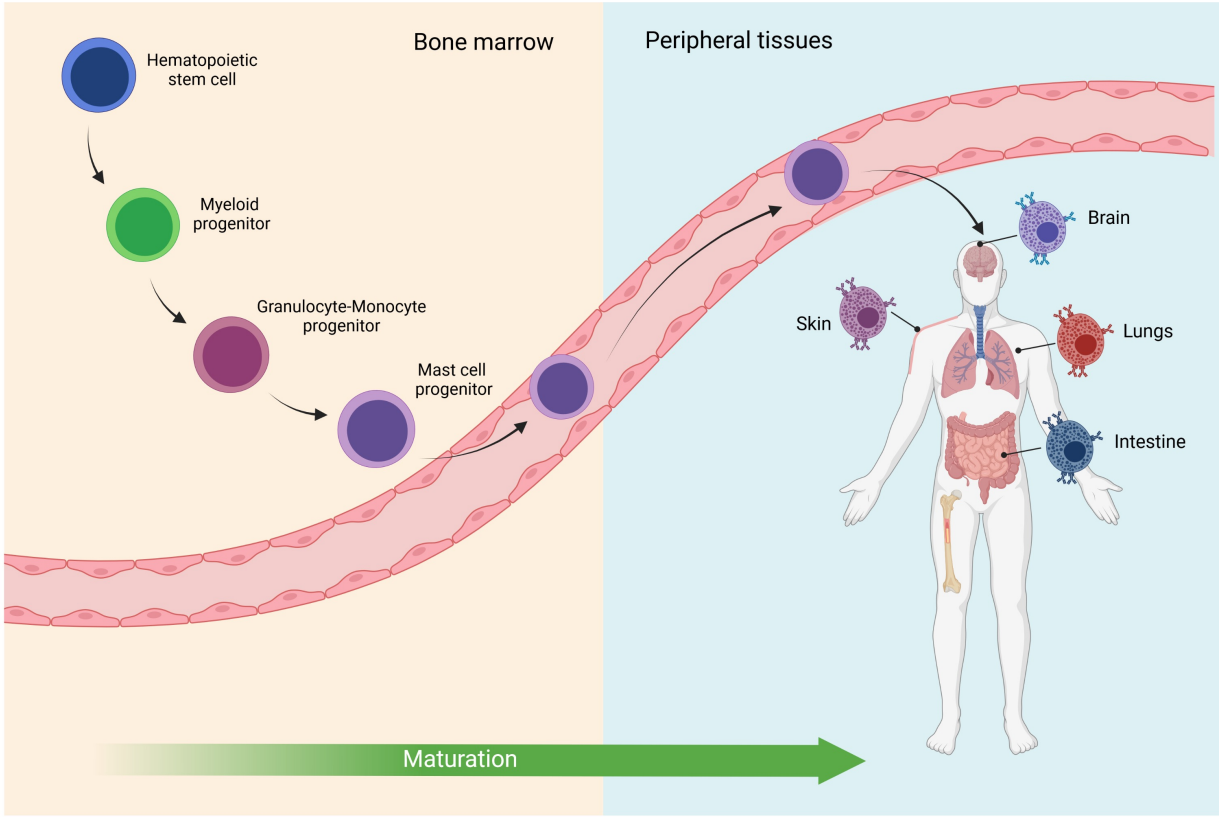
Development of strategies to leverage KIT-driven metabolic dependencies when KIT inhibitors treatment fails.

Mast cells are sentinels of the innate immune system

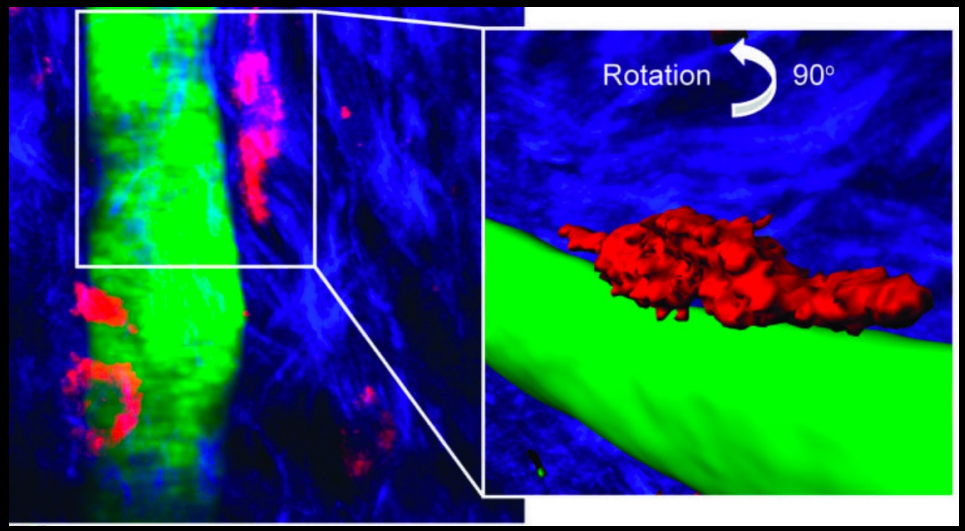


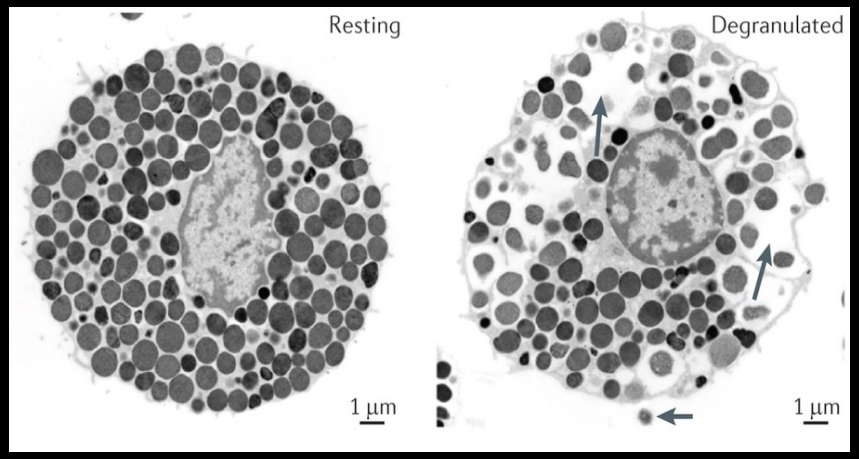
Mast cells differentiate from hematopoietic stem cells in the bone marrow



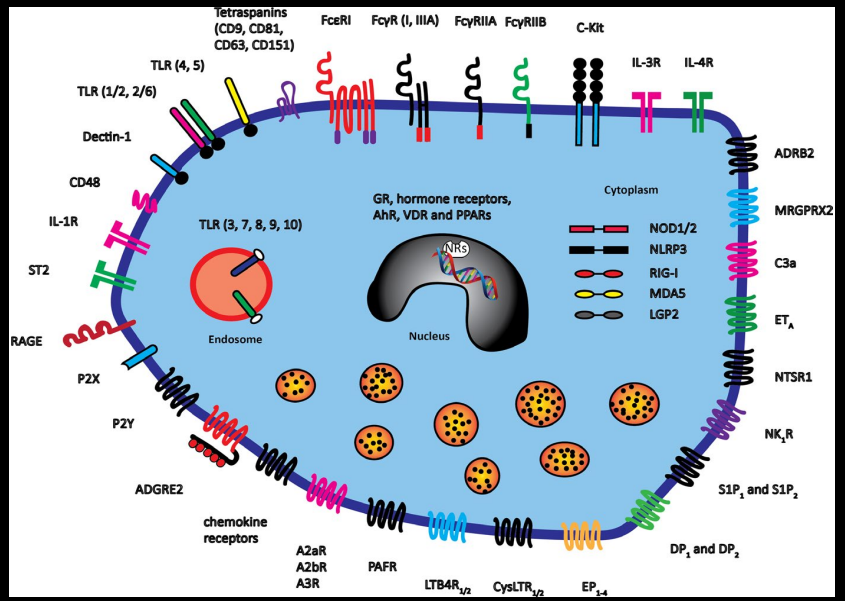


Mast cells are sentinels with strategic location



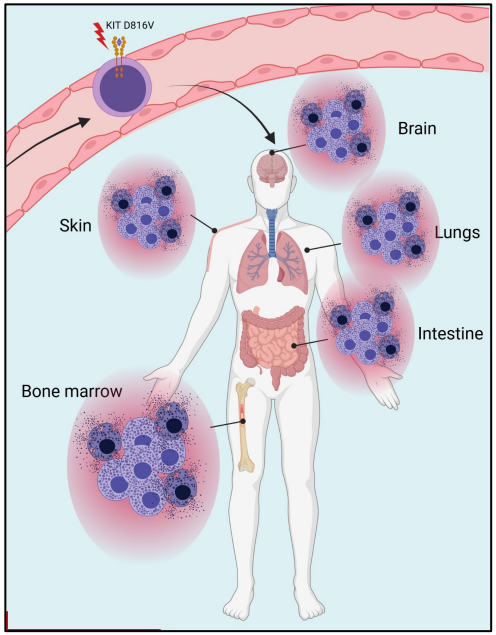


Redegeld F et al., Immunol Reviews, 2018
Gaudizio N et al., J Clin Invest, 2016



WHO classification: Systemic mastocytosis spectrum

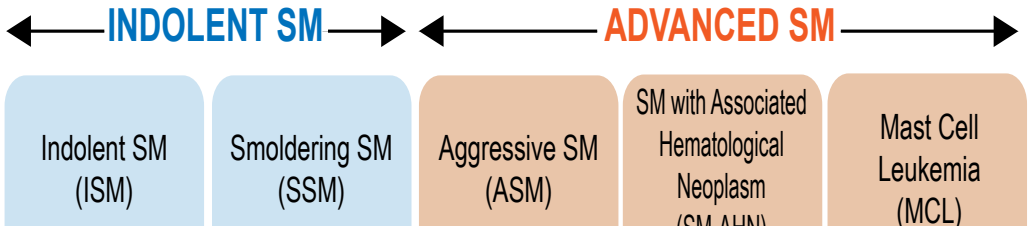
Abnormal accumulation and activation of neoplastic mast cells in one or more organs, mostly the bone marrow.



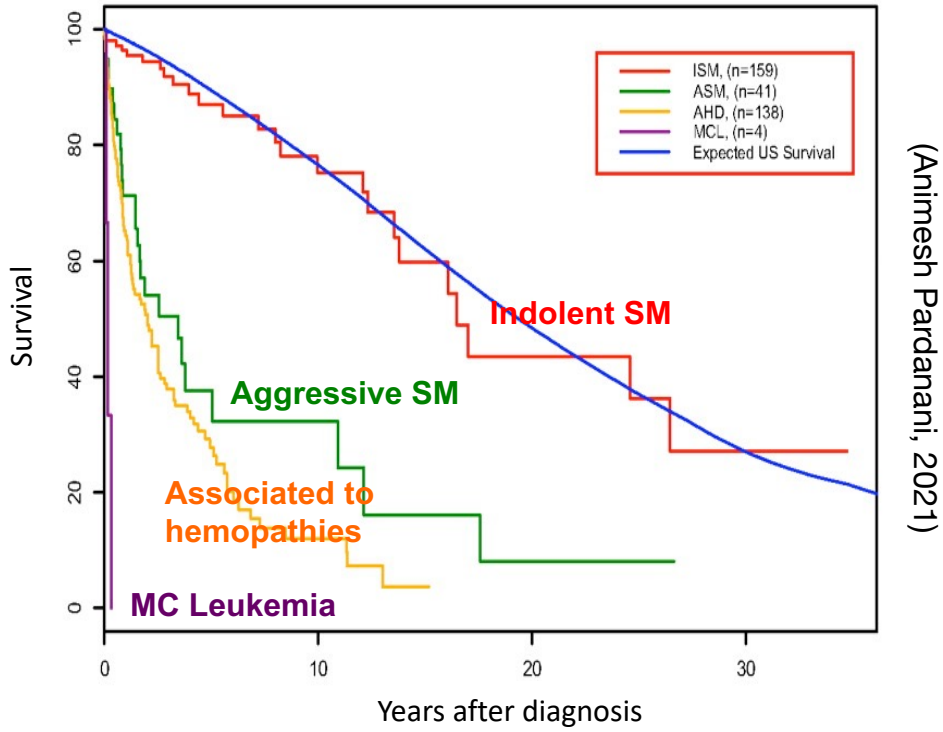
Tyrosine kinase inhibitors

Partial efficacy of TKIs

(Lübke et al., 2019; Laine, et al, 2011)



MC organ infiltration - MC related organ damages

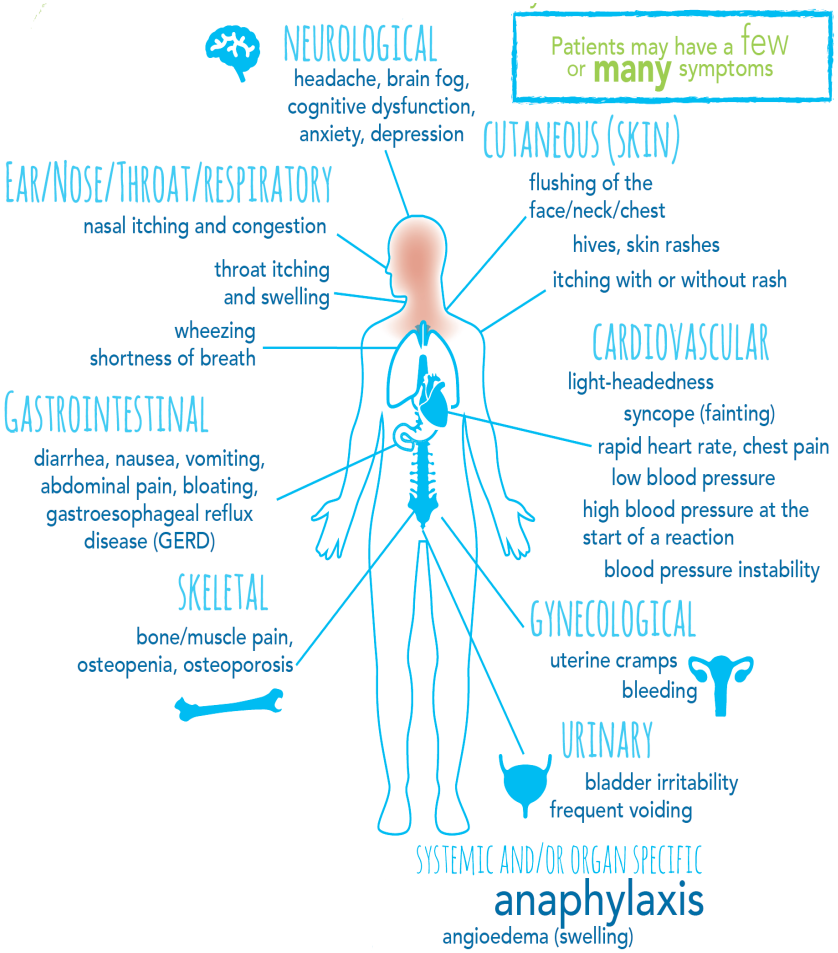


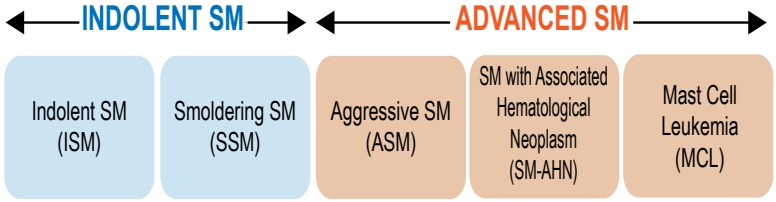
(Animesh Pardanani, 2021)

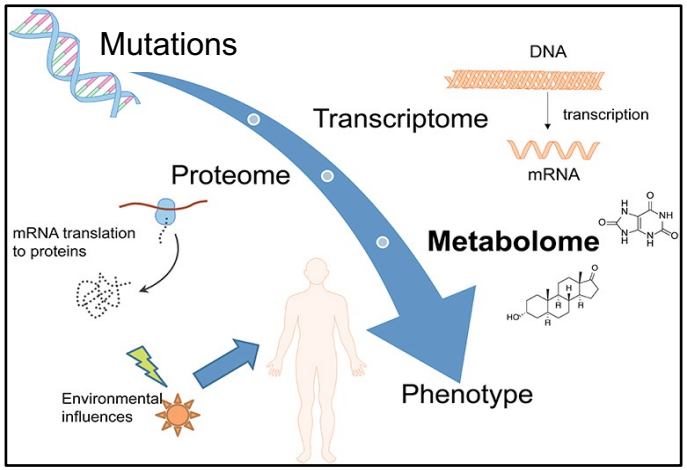
There is a need to find new therapies not KIT-centered.

Mastocytosis is a systemic disease: is it possible to stratify patients according to their diagnosis by a metabolomic approach?

Hypothesis: Altered metabolism could be a good approach to study this systemic disease.







A plasma metabolomic profiling is able to discriminate SM patients according to disease aggressiveness

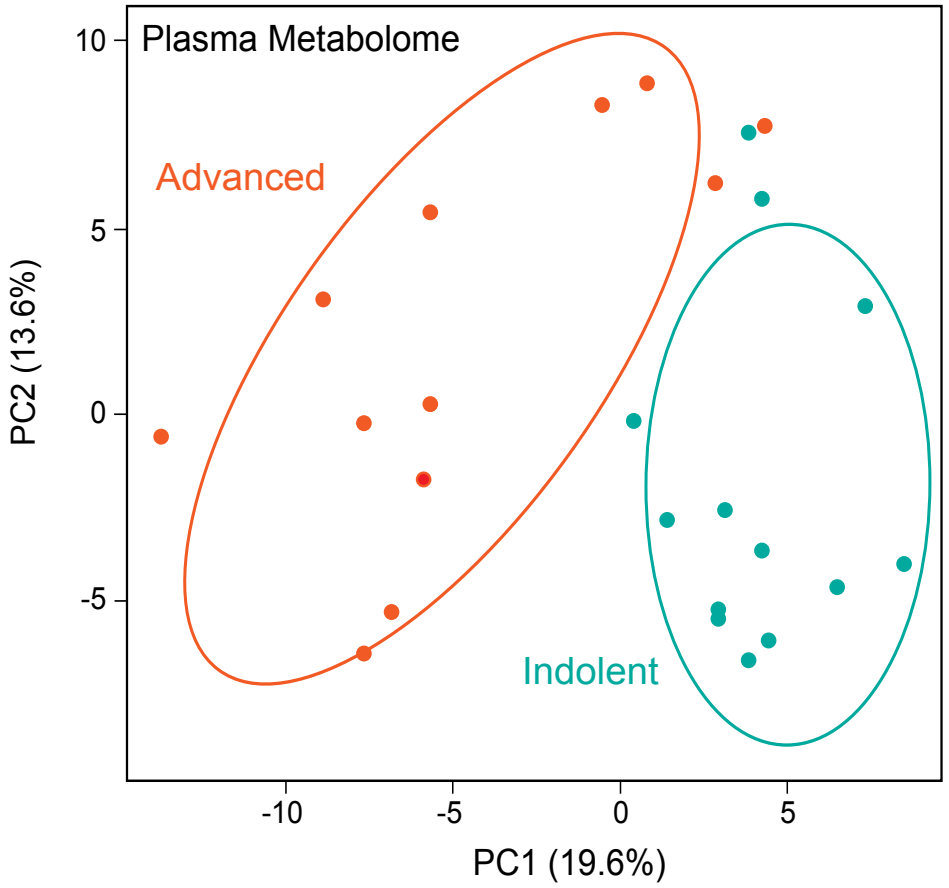
Centre de référence des mastocytoses CEREMAST

CEREMAST cohort

Plasma collection

Polar Metabolite extraction

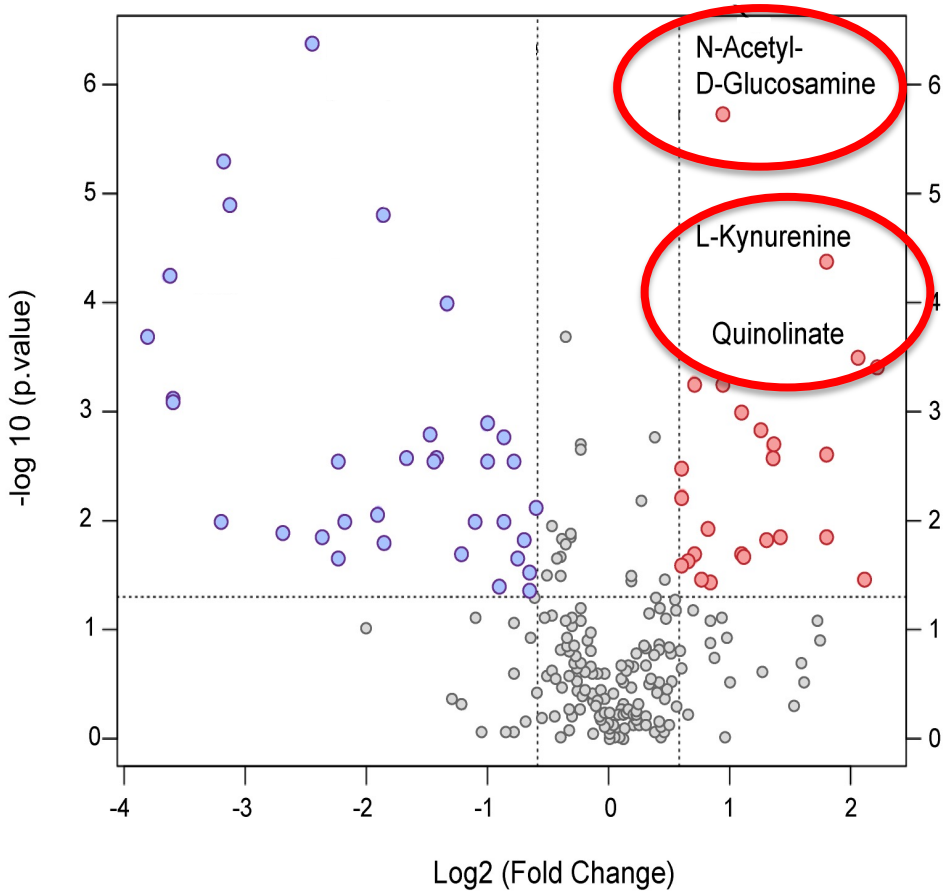
LC-MS/MS Analysis



Collaboration: John M Asara (BIDMC, Boston)
BIDMC-Harvard Mass Spectrometry Facility.

Most discriminant metabolites between indolent and advanced SM

Patient plasma metabolome
SM Indolentes/Avancées



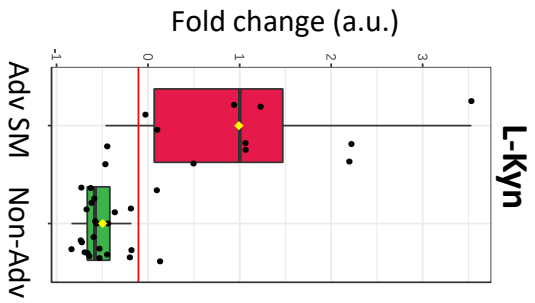
GlcNAc is a mast-cell chromatin-remodeling oncometabolite that promotes SM aggressiveness by TF glycosylation.

Agopian J et al, Blood, 2021
Brenet F, Patent WO2022/180236

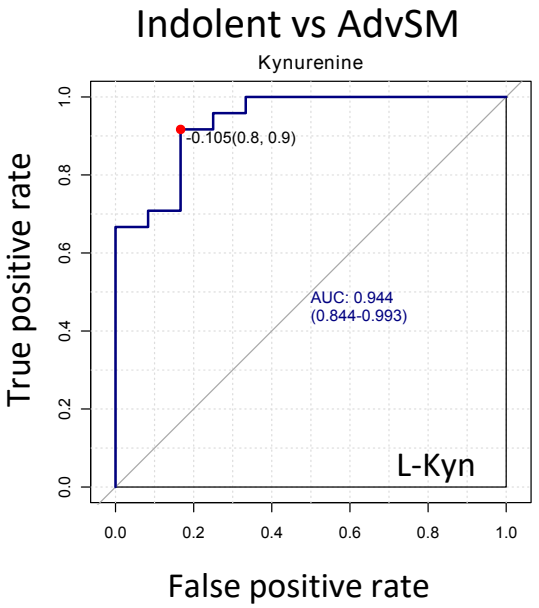
What is the impact of the kynurenine pathway on MC functions?

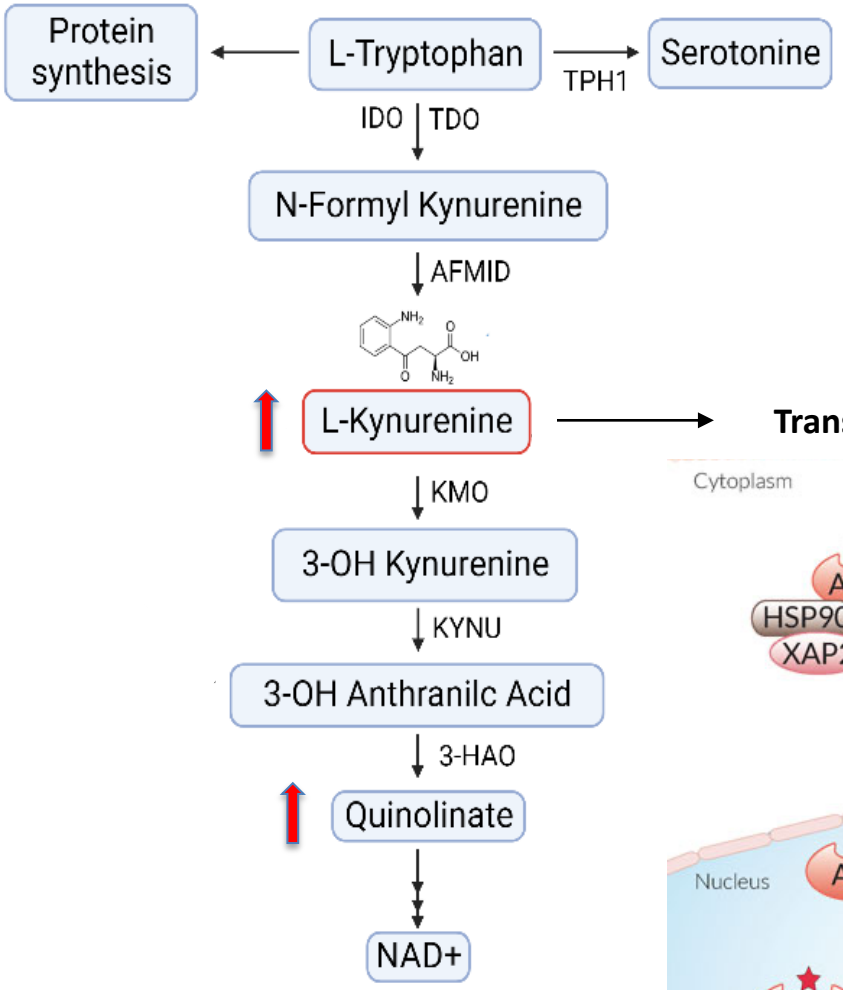
The L-Kyn pathway: Tryptophane catabolism

FOLD CHANGE

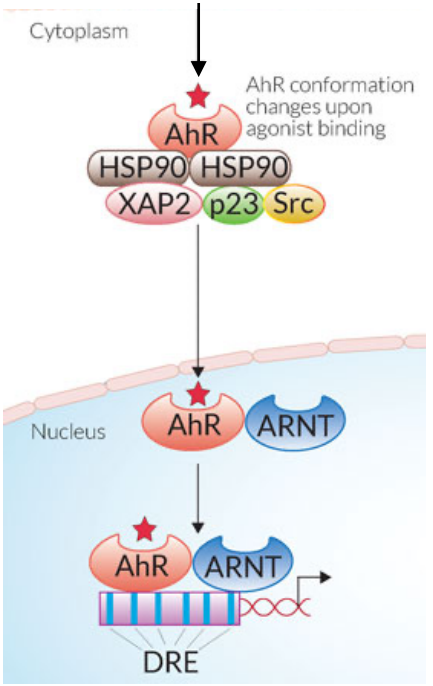


ROC CURVE





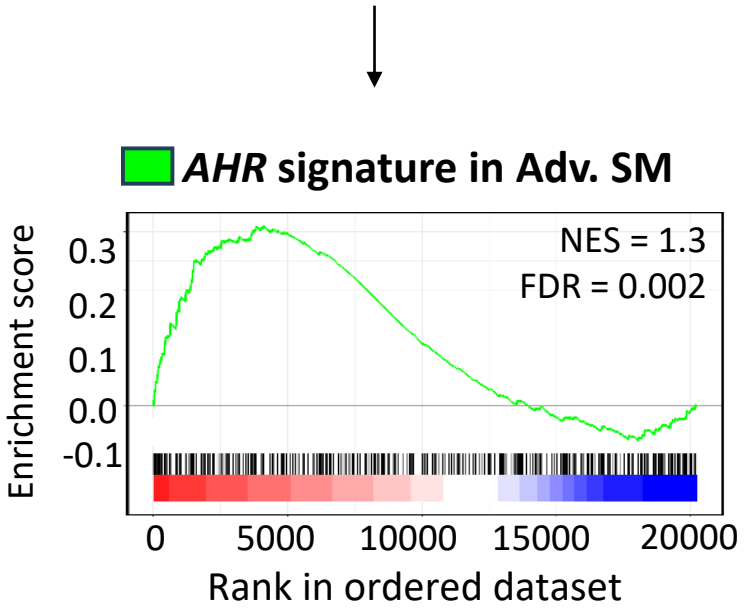
Transcription

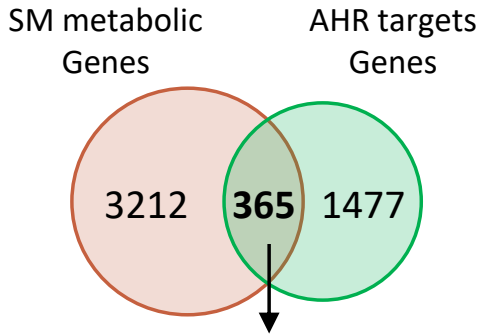


Is the L-Kyn pathway active in patients bone marrow mast cells?

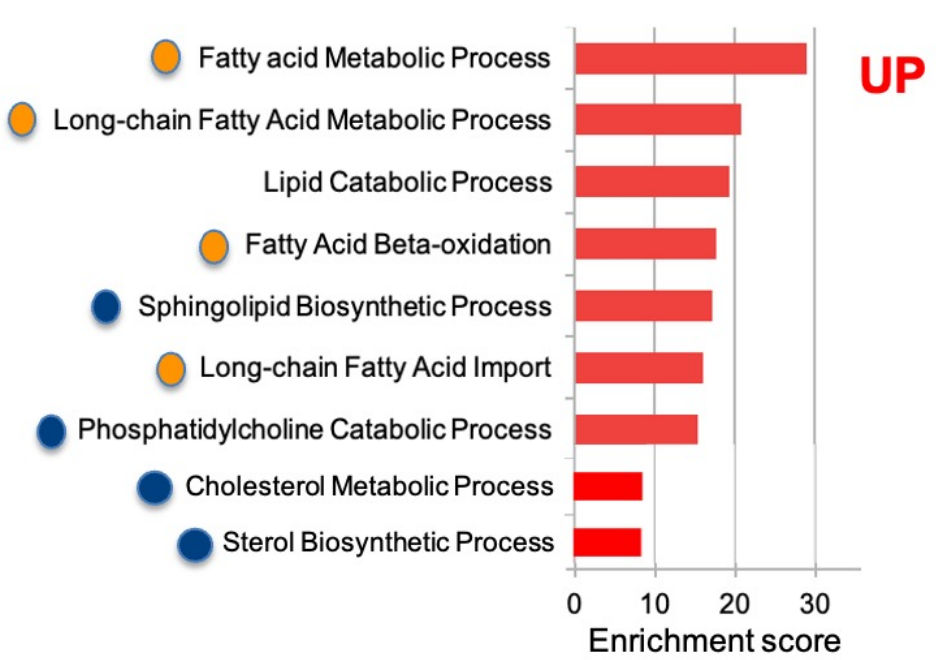
FACS sorted patient BM mast cells
($CD117^{hi}/CD34^{-}/CD45^{+}/CD14^{-}$)

ISM vs CTRL/Adv SM vs CTRL





Metabolic AHR signature



Activation of L-Kyn/AHR axis has 2 types of impact on lipid metabolism.

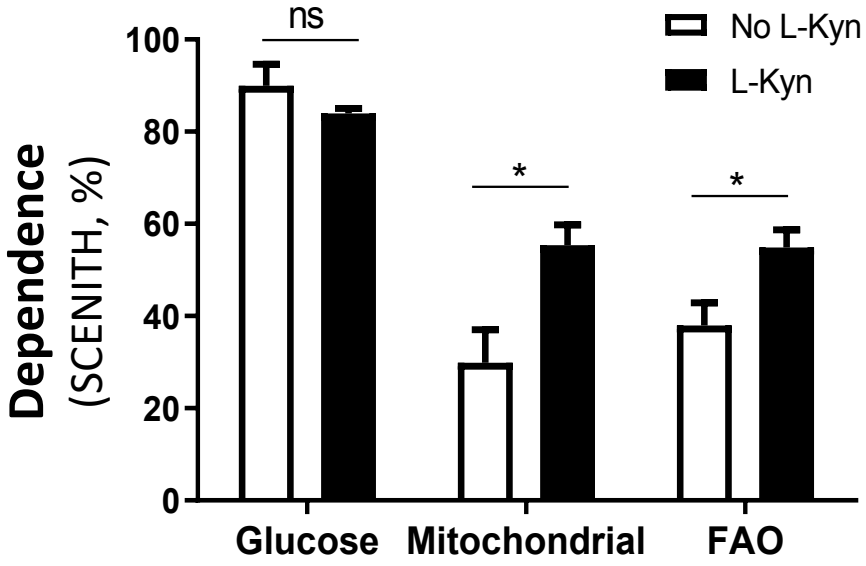
- Fatty acid catabolism/Import
- Membrane lipids

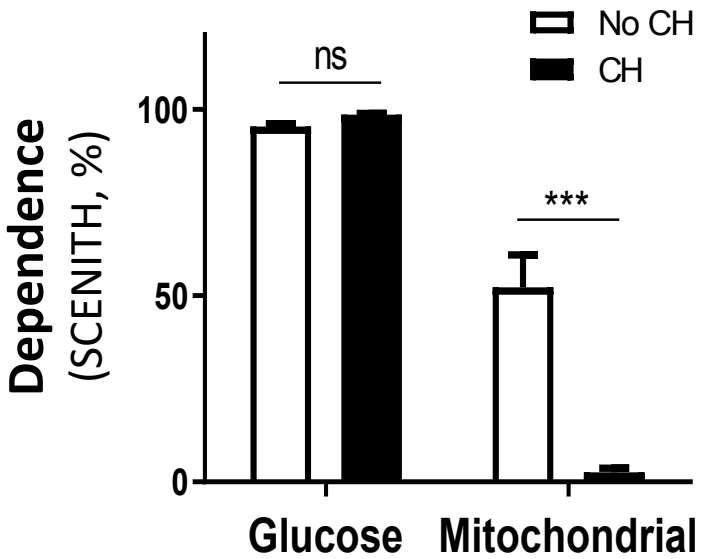
Collaboration: Alberto Orfao (CIC, Salamanca, Spain)

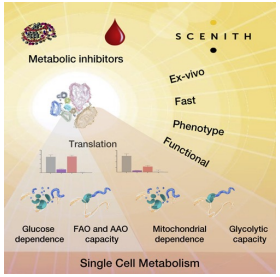
Impact of L-Kyn on MC metabolism and functions?

Function 1: MC metabolism

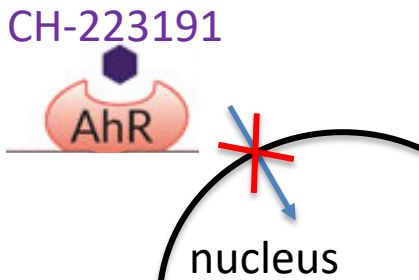
L-Kyn induces an AHR-metabolic dependence to fatty acids catabolism in human neoplastic mast cells





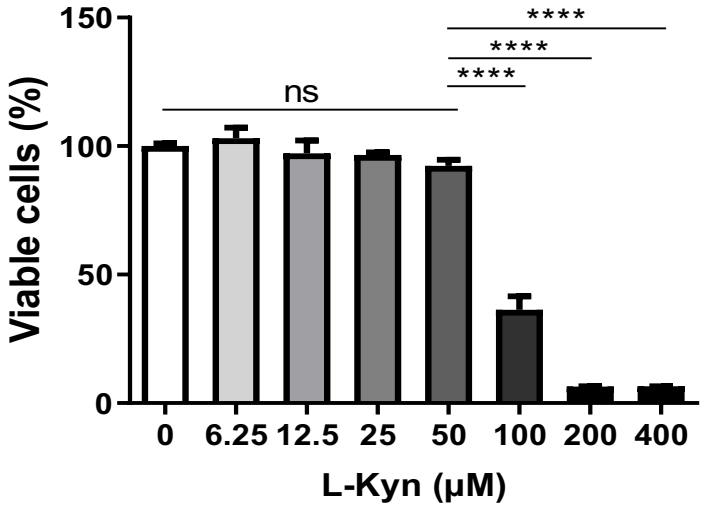


Collaboration: Rafael Argüello (CIML, Marseille)
SCENITH: Argüello RJ et al., Cell Metabolism, 2020.

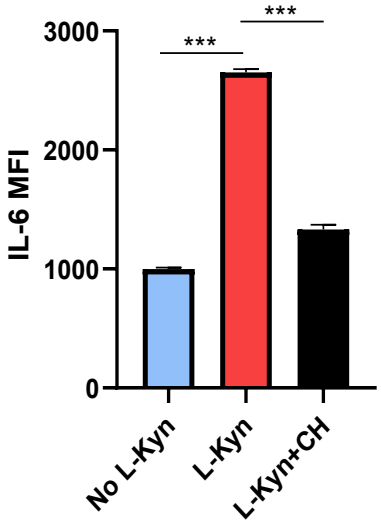


Functions: Proliferation and degranulation

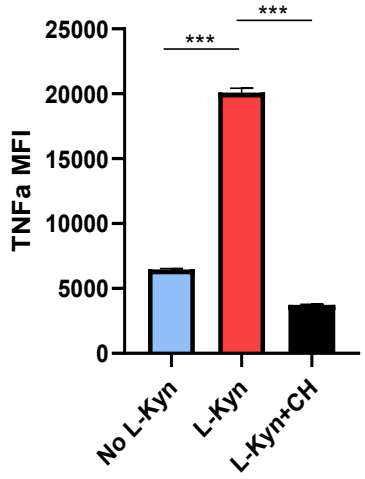
PROLIFERATION



RELEASE OF INFLAMMATORY CYTOKINES



IL-6

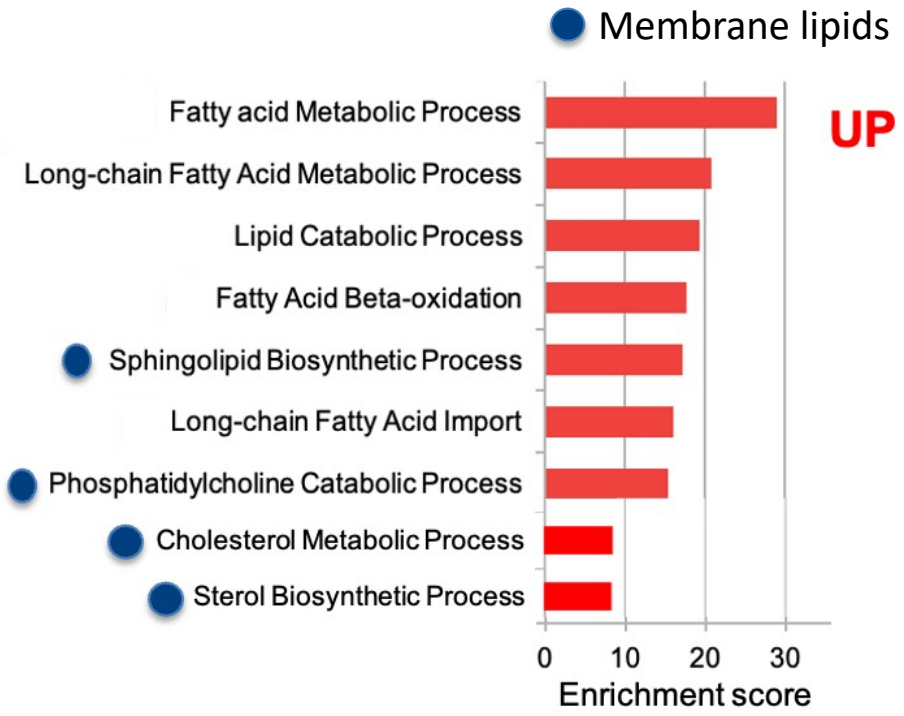


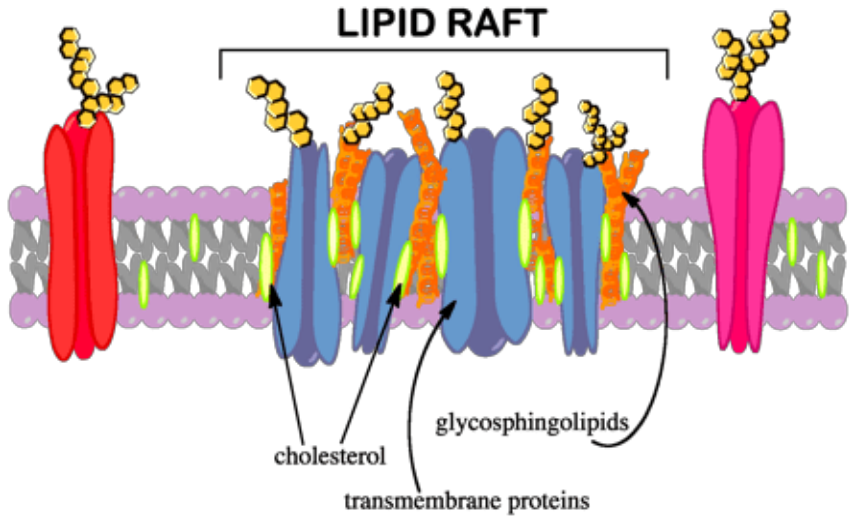
TNF-a

L-Kyn increases acute inflammatory responses *in vitro*

Impact of L-Kyn
on membrane lipid composition?

Metabolic AHR signature

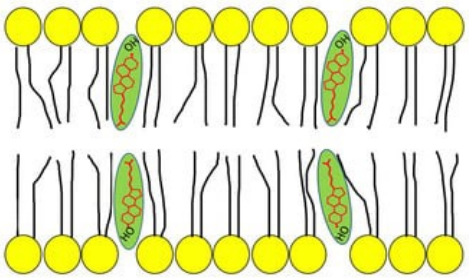


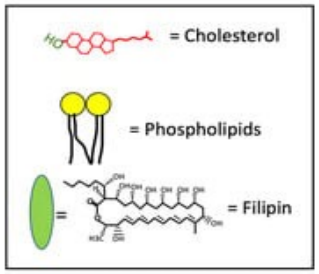


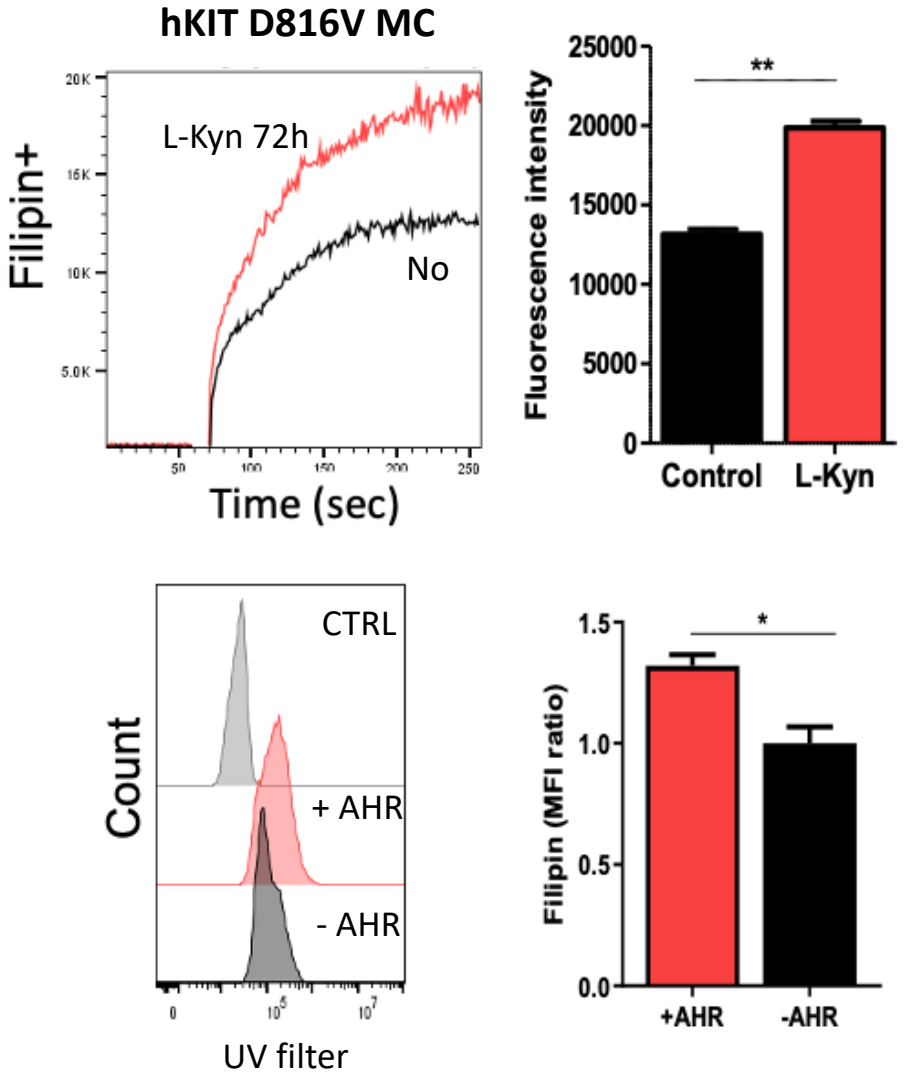
L-Kyn/AHR axis promotes the formation of these specialized microdomains?

The L-Kyn/AHR axis increases cholesterol levels in neoplastic MC membranes

Filipin labeling



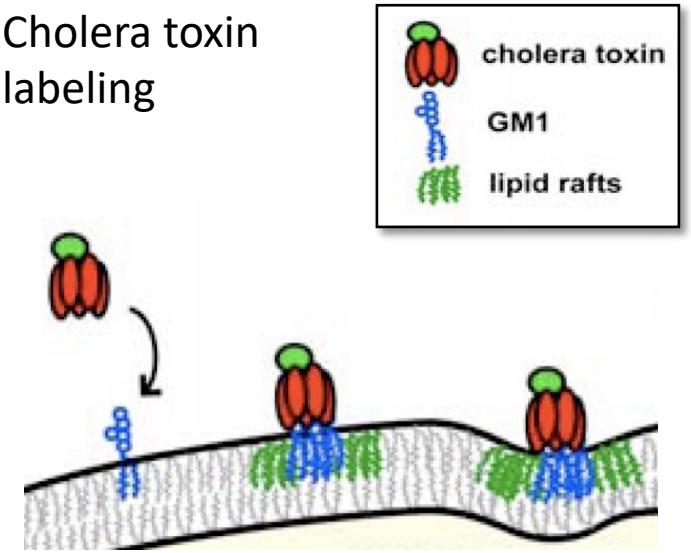


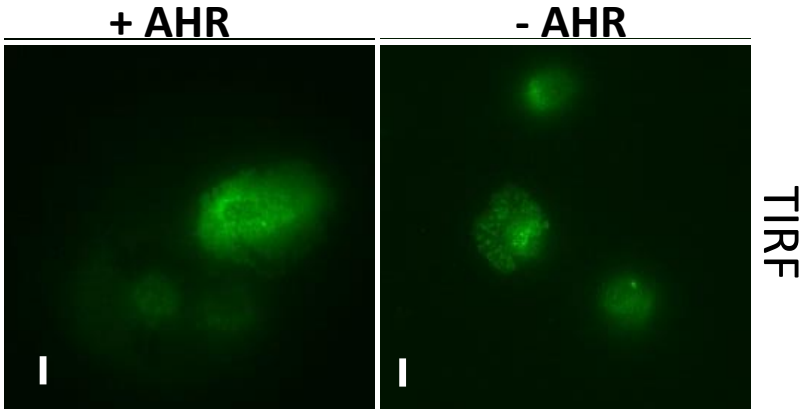


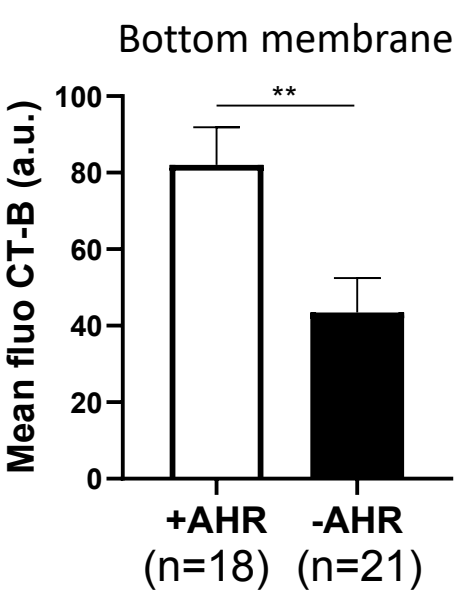
Collaboration: Yannick HAMON (CIML, Marseille)

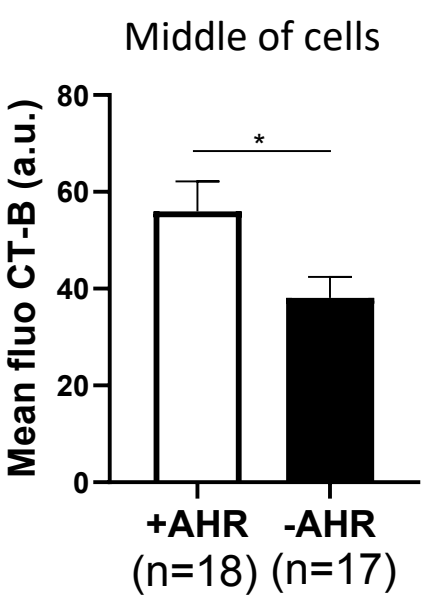
The L-Kyn/AHR axis increases sphingolipid (GM1) levels in neoplastic MC membranes

Cholera toxin labeling







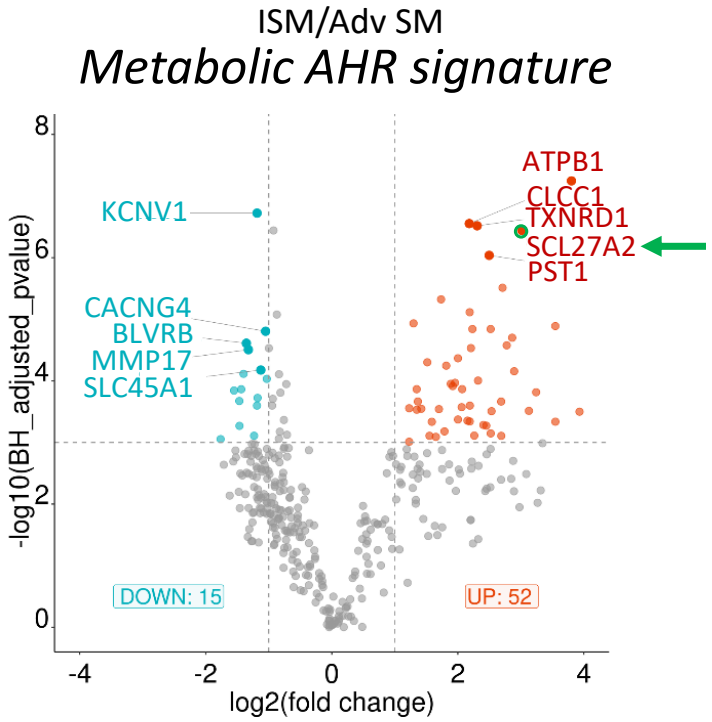


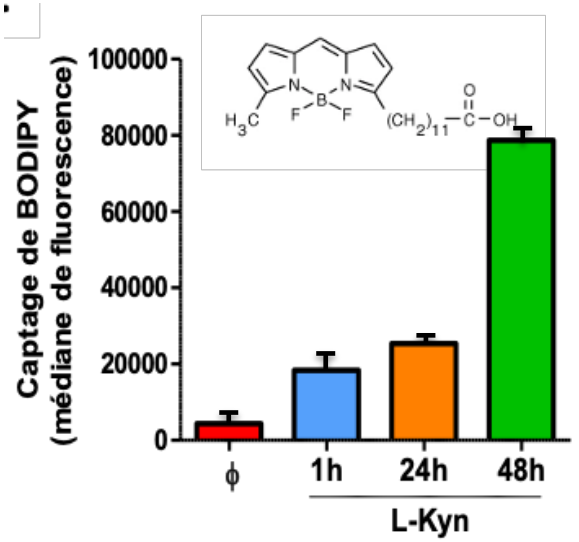
Collaboration: Arnauld Sergé, Loriane Maillot (LAI, Marseille)

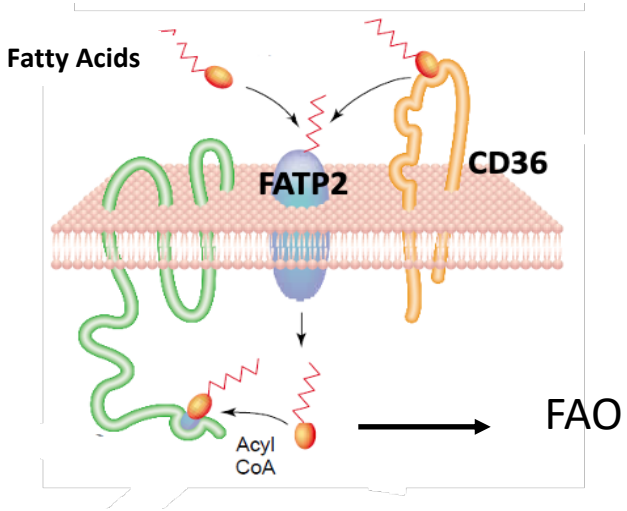
Total internal reflection fluorescence (TIRF) microscopy

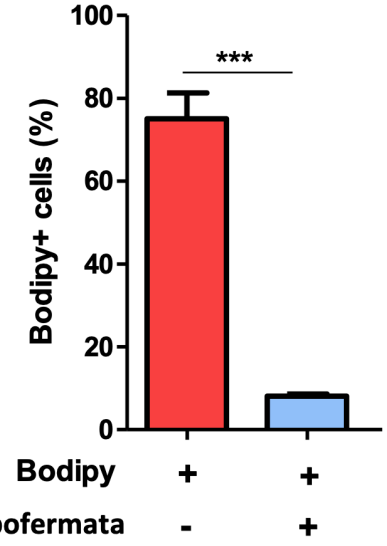
Is it possible to find a relevant potential therapeutic target that would be related to lipid raft and FAO?

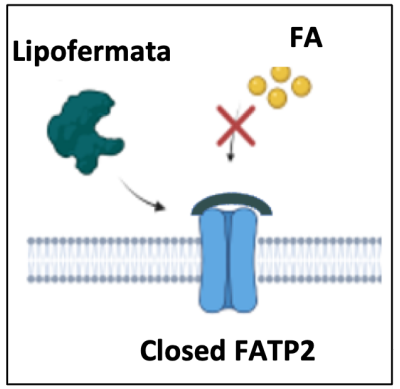
SCL27A2 (FATP2) regulates L-Kyn-mediated fatty acid uptake in neoplastic MC





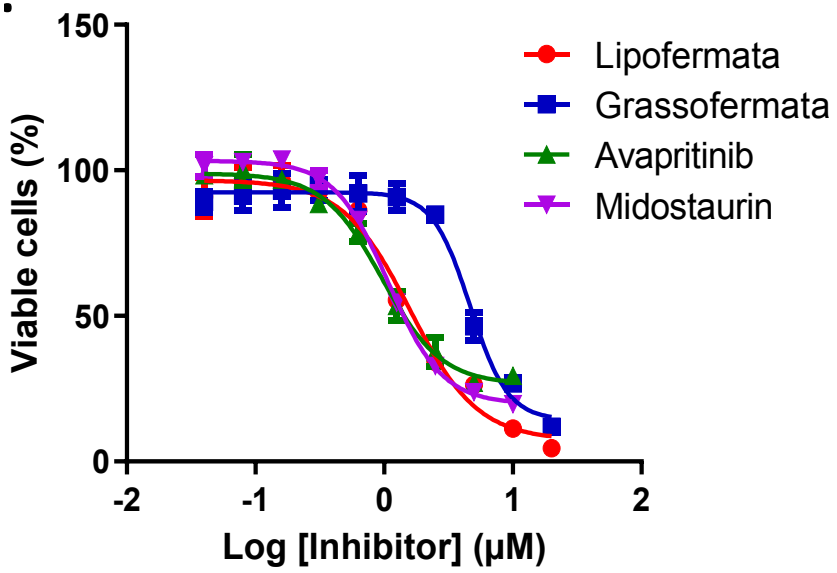






Impact of FATP2 inhition on mast cell proliferation and degranulation

PROLIFERATION



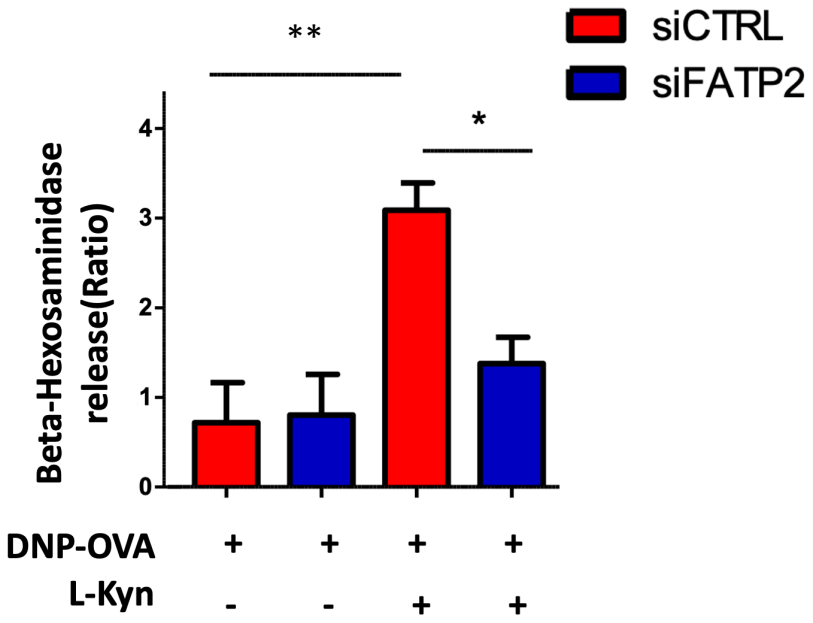
IC_{50} (µM)	Lipofermata	Grassofermata	Avapritinib	Misostaurin
HMC1.2	1,62	4,67	0,97	1,08

Avapririnib

Midostaurin

KIT inhibitors

DEGRANULATION



Take home messages and perspectives

How does L-Kyn contribute to SM aggressiveness?

- L-Kyn is a circulating **biomarker of SM aggressiveness** that modulates MC functions.

- L-Kyn induces an **AHR-metabolic dependence to FA catabolism** in neoplastic MC as well as **unrestrained inflammatory responses**.

- L-Kyn induces a significant **shift in the lipid composition of mast membranes** suggesting **an increase of lipid rafts** and membrane rigidity that enhances membrane receptor signaling (FATP2, KIT, FceRI).

- L-Kyn increases FATP2 expression and **FA uptake in MCs**.

- FATP2 inhibition is a potential therapeutic target that has additive effect with KIT inhibitors (ongoing in pre-clinical mice models and patients samples).

THANK YOU

DE SEPULVEDA TEAM @ CRCM

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Sébastien Létard
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  - Michel Arock (ENS Cachan)
  - Julien ROSSIGNOL (Necker, Paris)
  - Leïla Maouche-Chrétien (Institut Imagine)

CRCM, Marseille

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  - Paraskevi Kousteridou
- **Integrative Bioinformatics Platform**
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  - Samuel Granjeaud
- **CRCM TrGET platform**
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  - Rémy Castellano
  - Armelle Goubard

- **US and EUROPE**
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  - Alberto Orfao (CIC, Salamanca)
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  - Loriane Maillot
- **CIML, Marseille**
  - Rafael Argüello