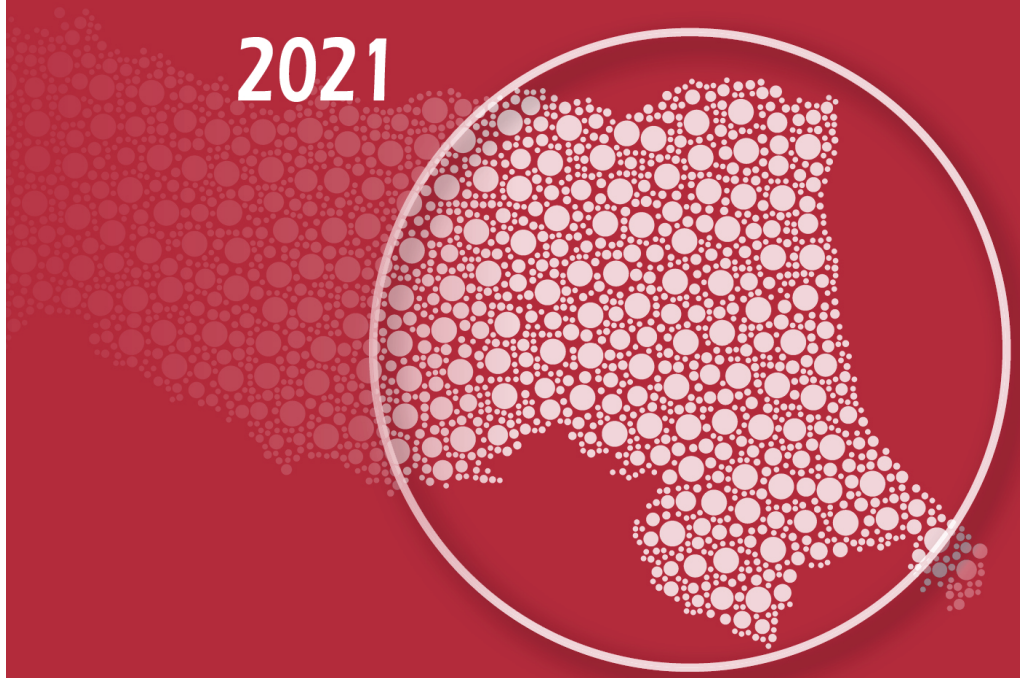


Progetto Ematologia Romagna

The interplay between leukemic cells and bone marrow microenvironment

Valentina Salvestrini

Istituto di Ematologia Seragnoli

DISCLOSURE STATEMENT

Valentina Salvestrini, PhD

- Nothing to disclose

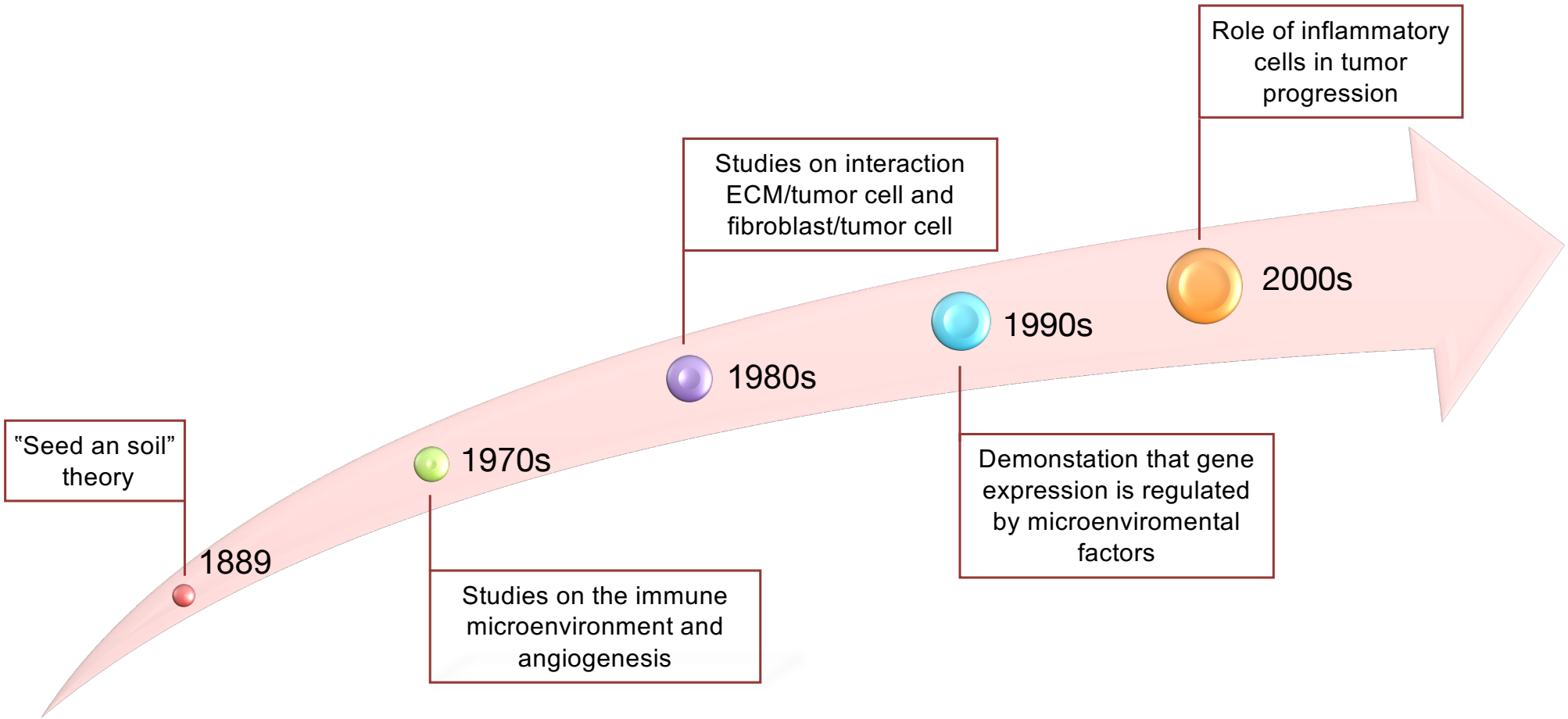
"Seed and soil" hypotesis

"The seed of plants are carried in all direction; but they live and grow only if they fall on congenial soil"

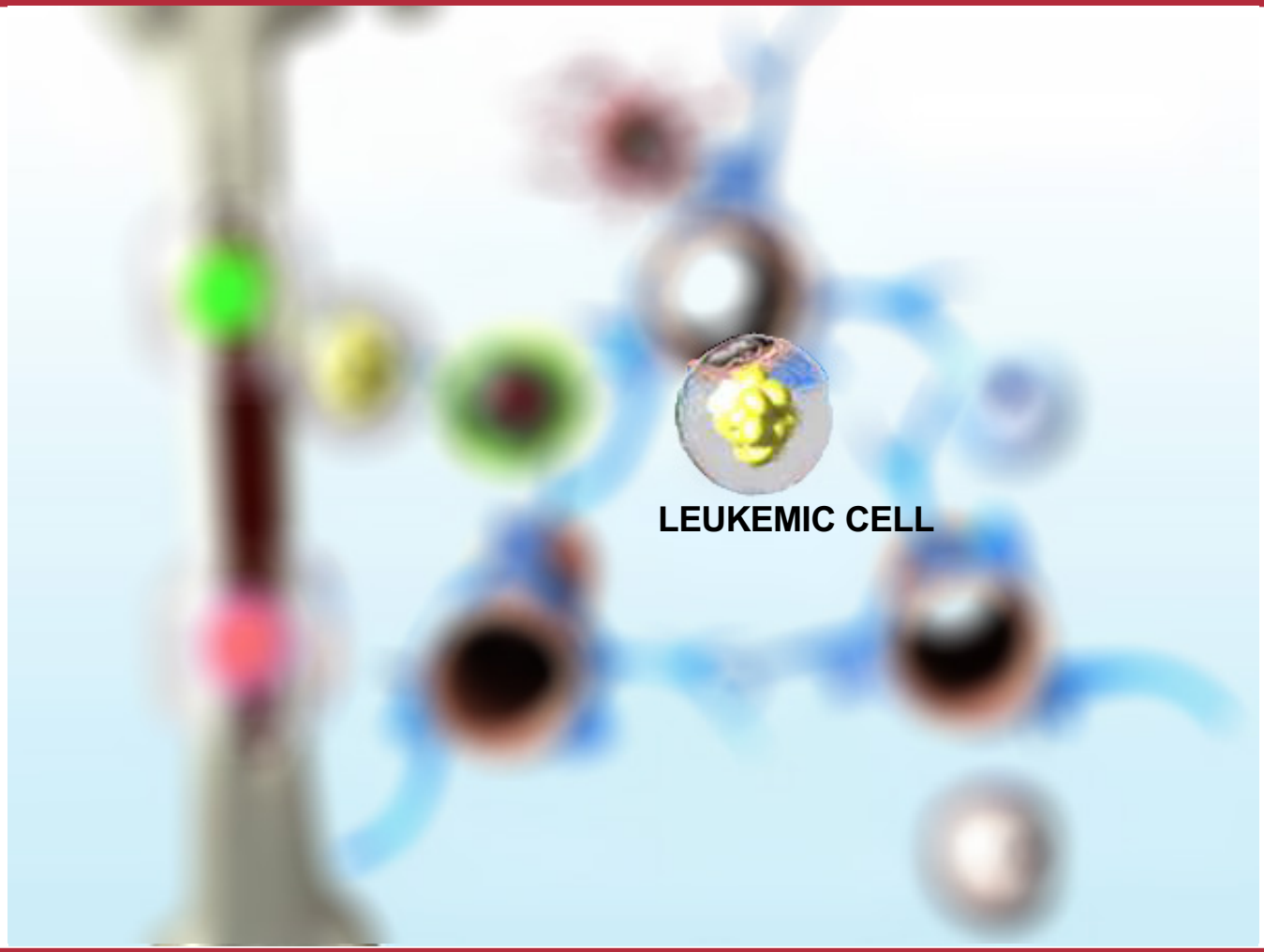
- Paget 1889

The succesful growth of metastatic cells depends on the interaction and properties of cancer cells (seed) and their potential target organs (soil)

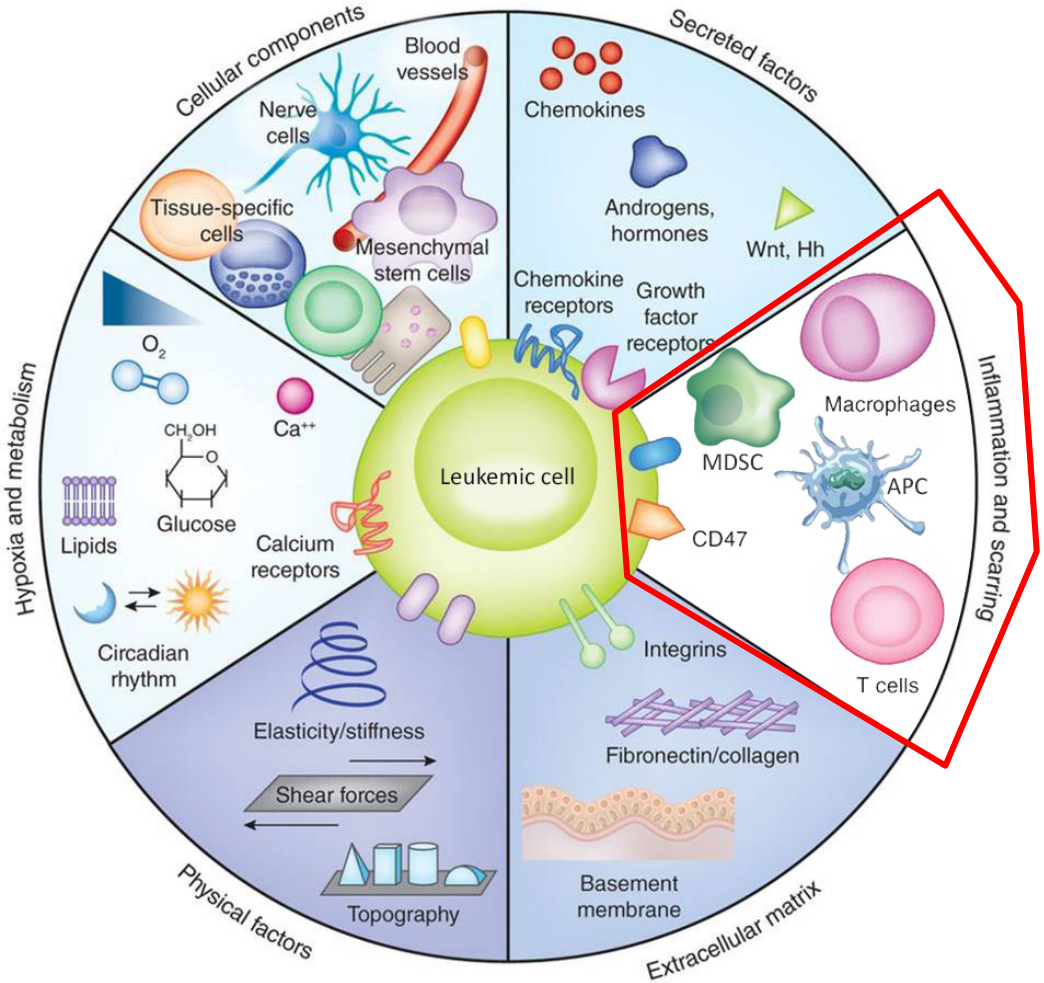
The Tumor Microenvironment: the making of a paradigm



We change the depth of focus…



The Leukemia Microenvironment



Modified, Lane SW et al Nat Biotechnol. 2014

The immune landascape in AML

IMMUNOREACTIVITY

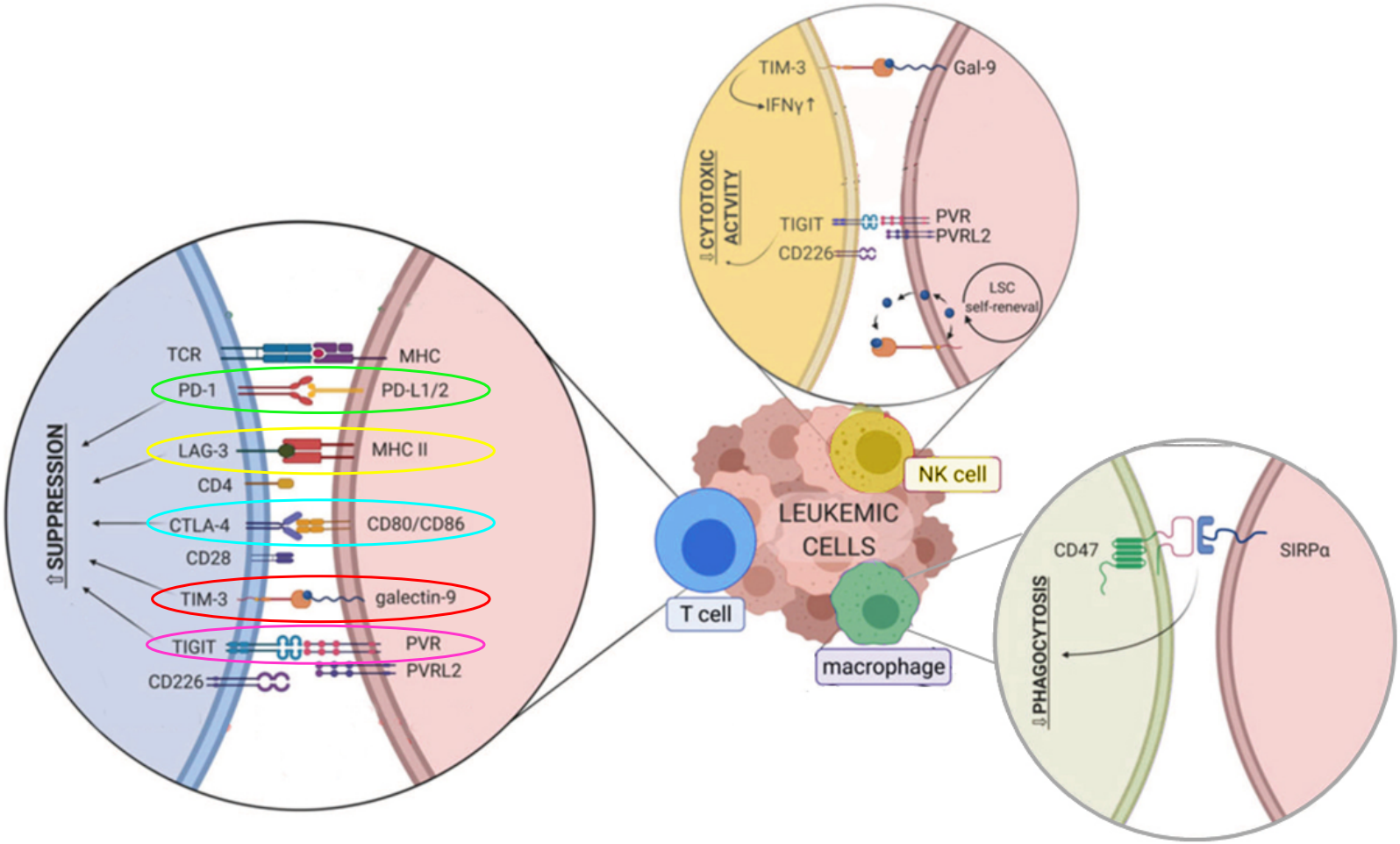
IMMUNOTOLERANCE

1. Increased Treg cell number
2. Increased T cell exhaustion, such as through upregulation of immune checkpoint ligands and receptors, and senescence
3. Diminished function of T helper and alteration in cytokine production
4. Deregulated anti-leukemic NK-mediated cytotoxicity
5. Increased myeloid derived suppressor cell and M2-like macrophage populations

Leukemia immune modulation mechanisms:

1. Cell-cell interaction and receptor-ligand interaction
2. Immunosuppressive soluble factors
3. Immunometabolism

1. Cell-cell interaction and receptor-ligand interaction



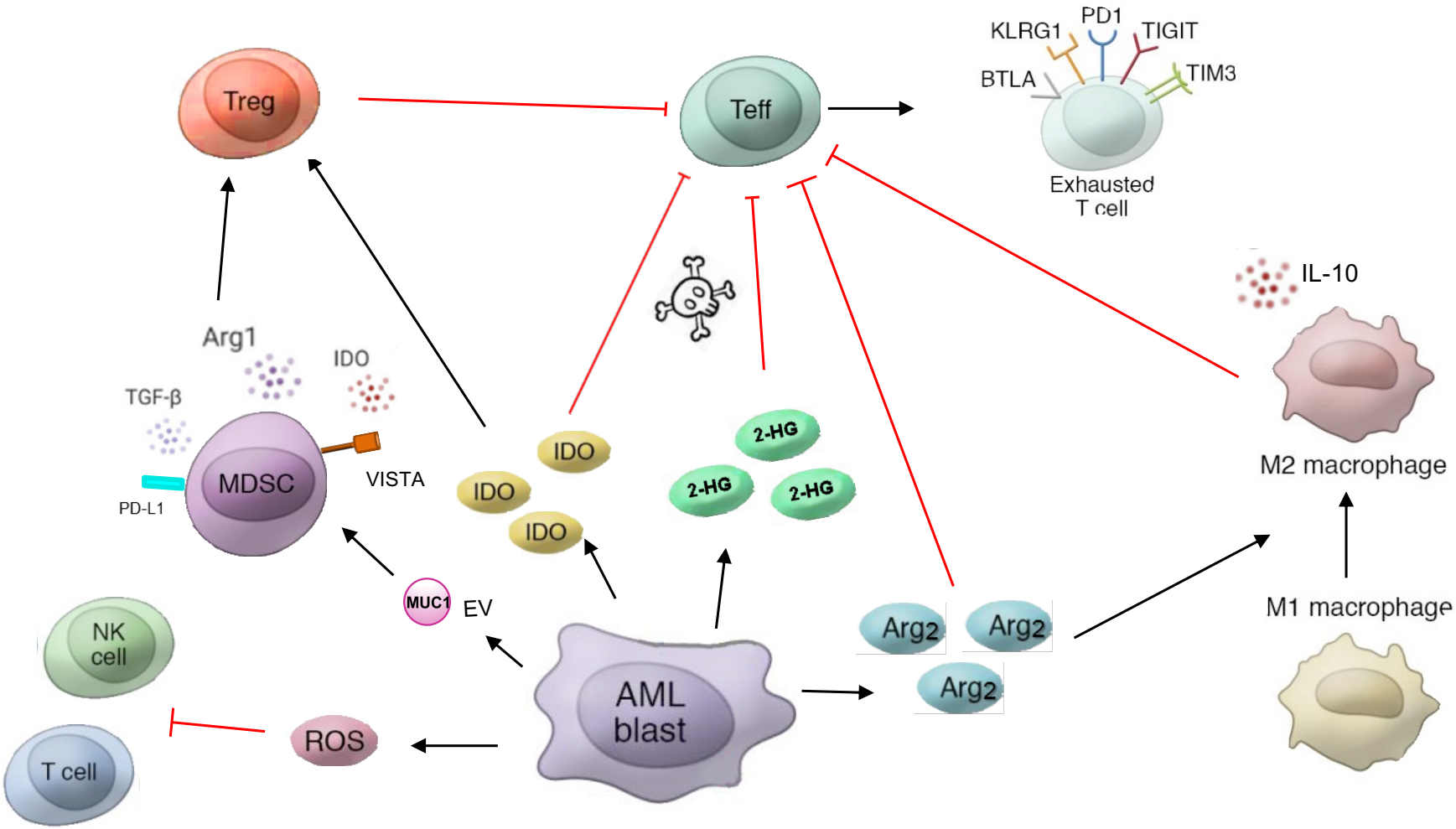
Swalter J et al. Cancers. 2021 Mar 10;13(6):1203

Clinical Trials of drugs and treatments that target immunosuppressive factors in AML

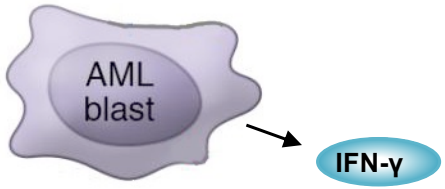
Target	Drug	Phase	Trial Number (clinicaltrials.gov)	Malignancy
PD-L1	Avelumab	1–2	NCT03390296	AML
		1–2	NCT02767063	CML
	Atezolizumab	1	NCT02892318, NCT03922477	AML
		1–2	NCT03730012	AML
	Durvalumab	2	NCT02775903	AML
PD-1	Nivolumab	1	NCT01822509	CML, AML
		1	NCT02011945	CML
		1	NCT04361058	AML
		1–2	NCT03825367	AML
		2	NCT02397720, NCT02464657, NCT02275533, NCT02532231	AML
	Pembrolizumab	1	NCT02981914, NCT03969446, NCT03286114	AML
		1–2	NCT03761914, NCT02996474 NCT03769532, NCT02768792	AML
		2	NCT02845297, NCT04284787, NCT02708641	AML
	PDR001	1	NCT03066648	AML
	Tislelizumab	2	NCT04541277	AML
CTLA-4	Ipilimumab	1	NCT00060372	CML, AML
		1	NCT03912064, NCT01757639 NCT01757639, NCT02890329	AML
PD-1 + CTLA-4	Nivolumab + ipilimumab	1	NCT01822509, NCT03600155	CML, AML
		2	NCT02397720	AML
TIM-3	MBG453	1	NCT03940352, NCT03066648	AML
		2	NCT04150029	AML
CD47	ALX148	1–2	NCT04755244	AML
	Magrolimab	1–2	NCT04435691	AML
	IBI188	1–2	NCT04485052	AML
	TJ011133	1–2	NCT04202003	AML
CD25 (Treg)	ADCT-301	2	NCT04639024	AML
arginine	PEG-BCT-100 (recombinant arginase 1)	2	NCT02899286	AML

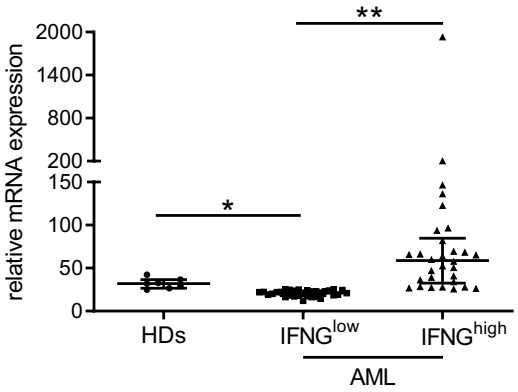
Swalter J et al. Cancers. 2021 Mar 10;13(6):1203

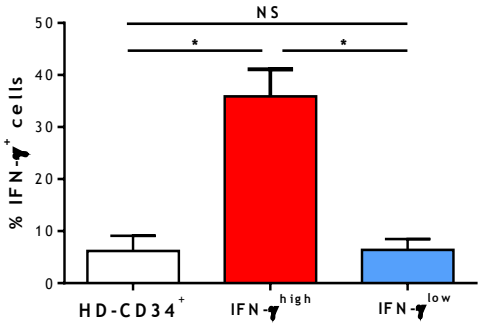
2. Immunosuppressive soluble factors



Release of IFN-γ by AML cells remodels bone marrow microenvironment

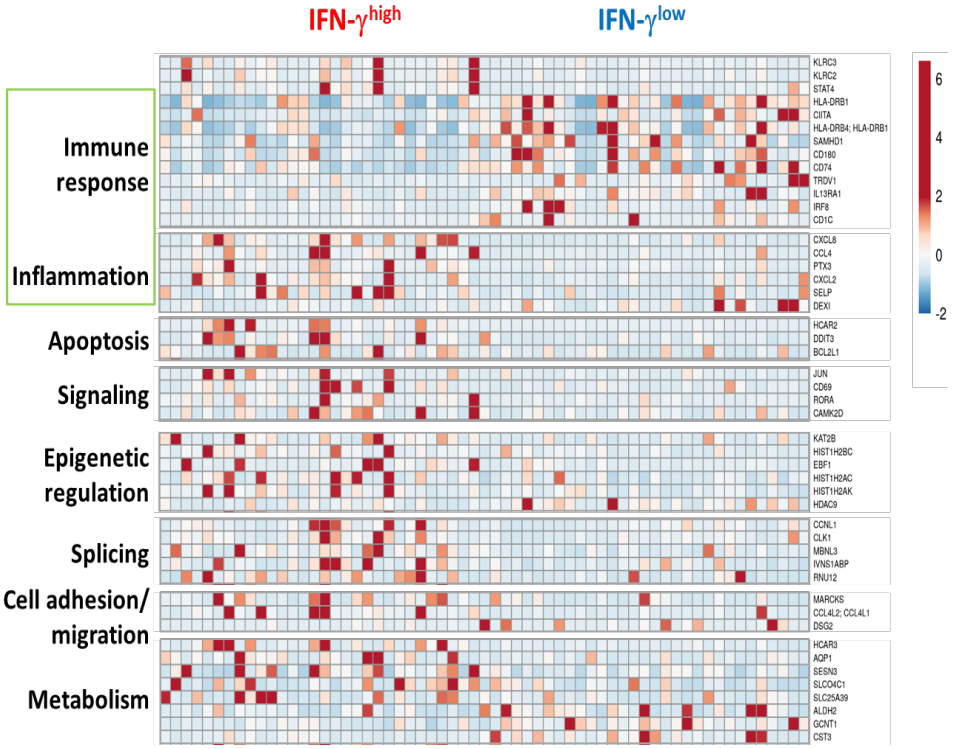






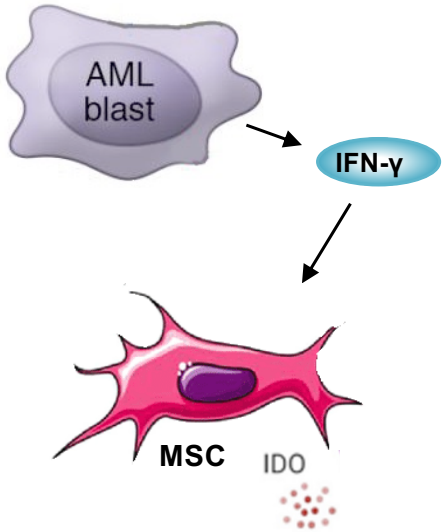
40% AML patients secrete high level of IFN-γ

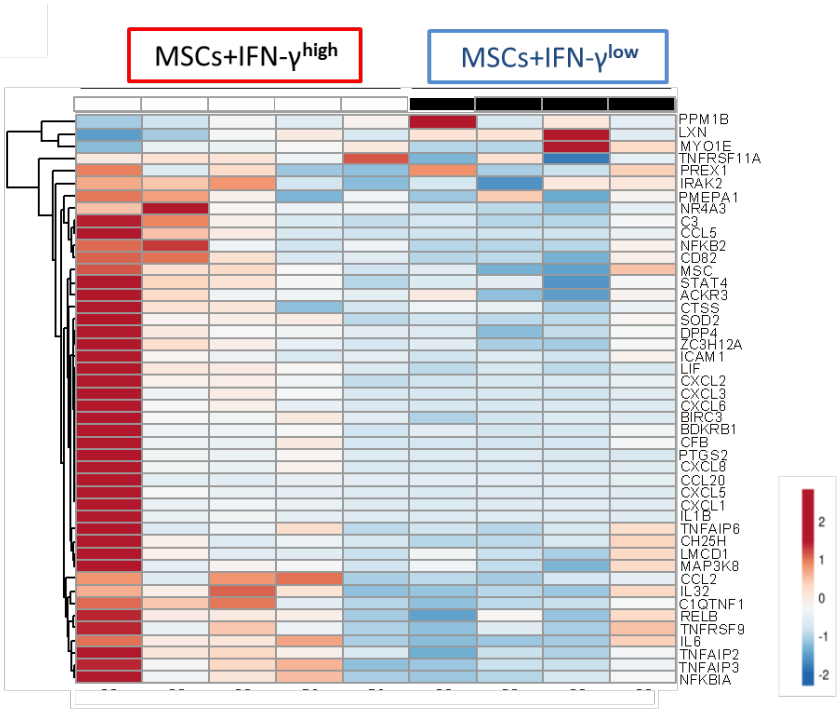
IFNγ^{high}AML cells are enriched in IFN-γ signaling, inflammatory and immune-response pathways

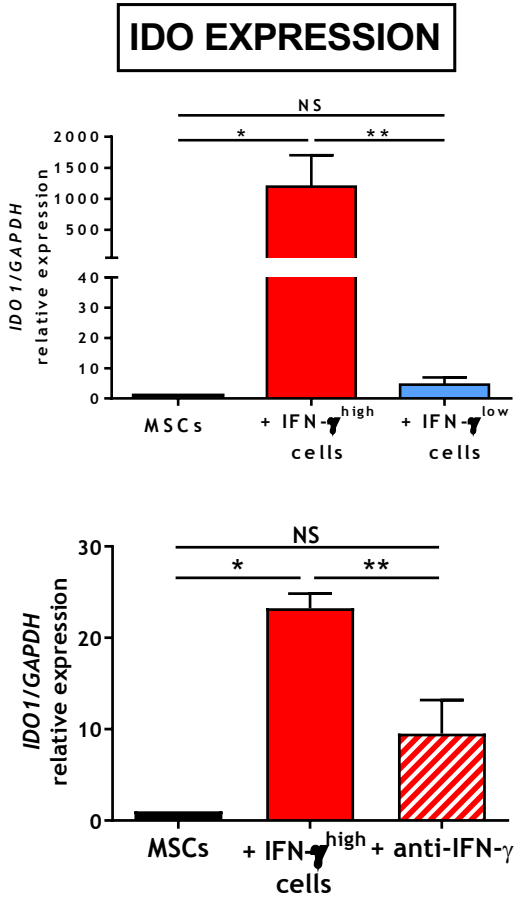


Corradi G et al. In preparation

IFNγ^{high}AML cells upregulate immune-suppressive genes in MSCs, which overexpressed IDO

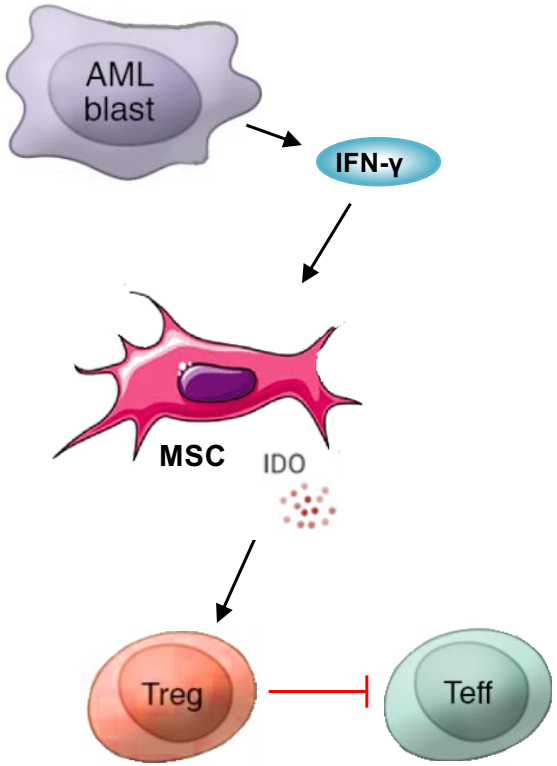




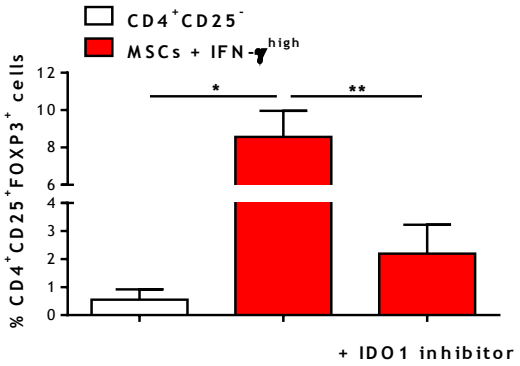


Corradi G et al. In preparation

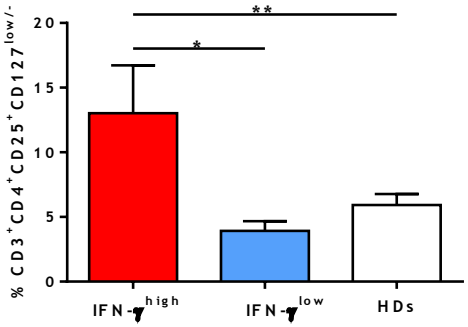
Release of IFN-γ by AML cells remodels bone marrow immune microenvironment by inducing regulatory T cells



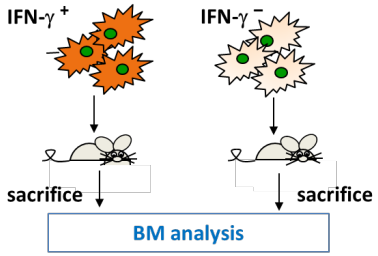
Tregs *in vitro*

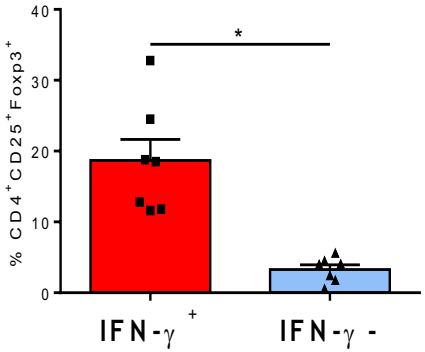


Tregs *ex vivo*



Tregs *in vivo*





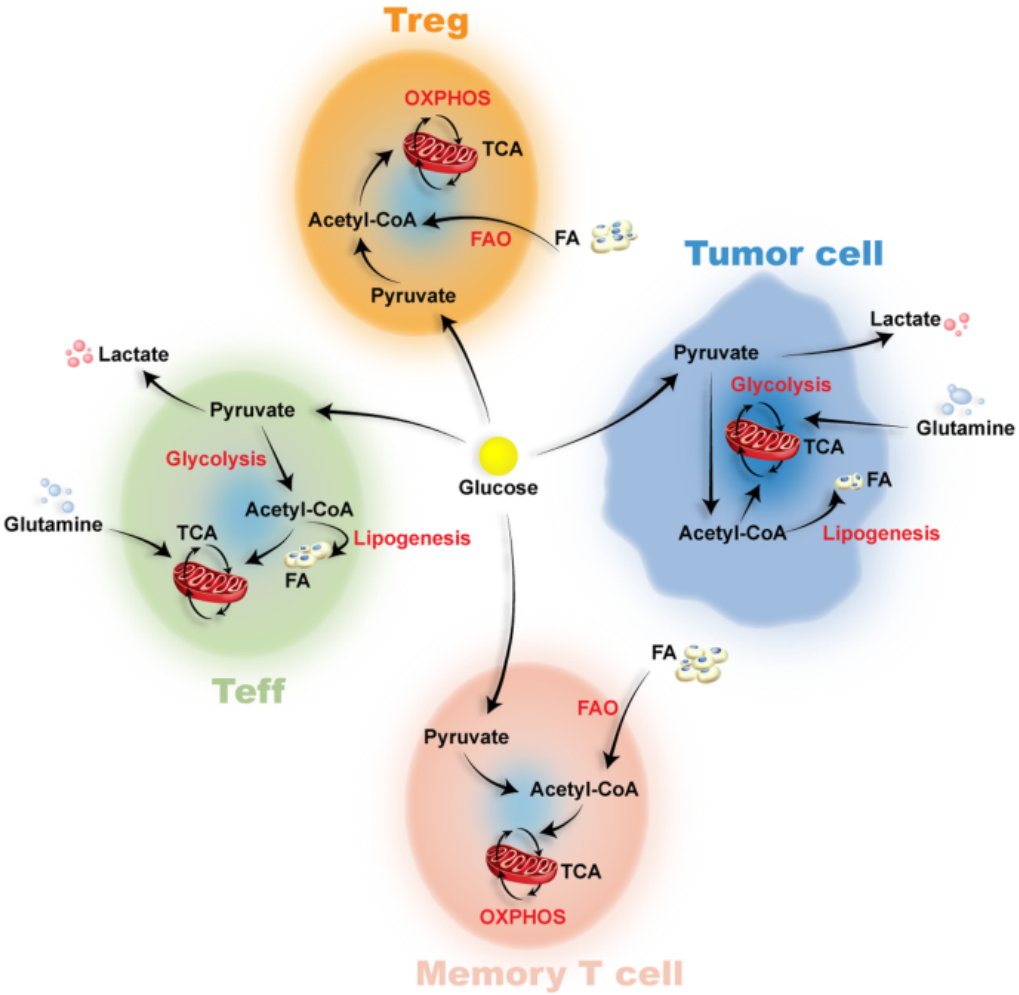
Corradi G et al. In preparation

3. The immunometabolism

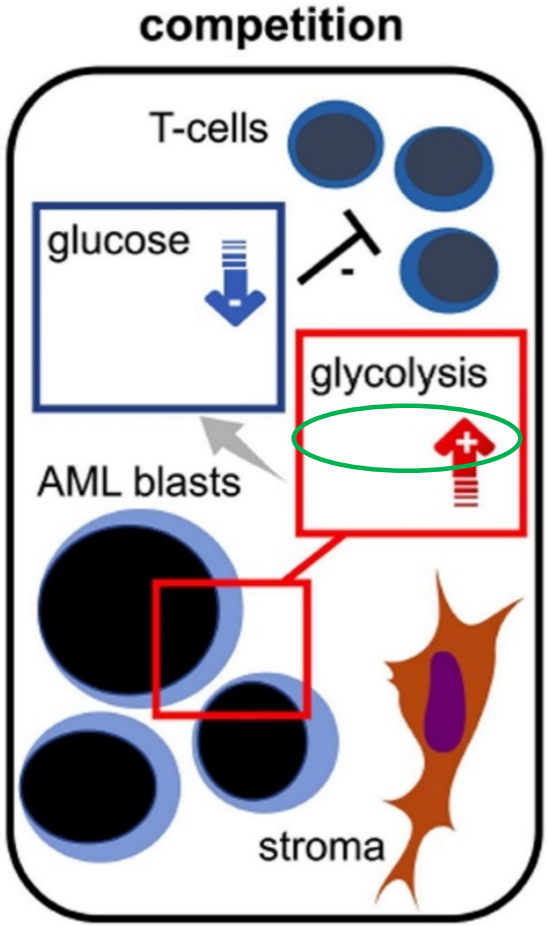
AML metabolic alterations could be linked to immunoregulation:

- Competition over substrated
- Abundant release of bioactive metabolites

Microenviromental metabolic remodelling



The immunometabolic interplay in AML: competition for substrates



Cell Metabolism
Clinical and Translational Report
CellPress

Increased Tumor Glycolysis Characterizes Immune Resistance to Adoptive T Cell Therapy

Tina Cascone,[1] Jodi A. McKenzie,[2,11] Rina M. Mbofung,[2,12] Simone Punt,[2] Zhe Wang,[2,13] Chunyu Xu,[2] Leila J. Williams,[2] Zhiqiang Wang,[3] Christopher A. Bristow,[4] Alessandro Carugo,[4] Michael D. Peoples,[4] Lerong Li,[5] Tatiana Karpinets,[6] Lu Huang,[2] Shruti Malu,[2,14] Caitlin Creasy,[2] Sara E. Leahey,[2] Jiong Chen,[7] Yuan Chen,[2] Helen Pelicano,[8] Chantale Bernatchez,[2] Y.N. Vashisht Gopal,[2] Timothy P. Heffernan,[4] Jianhua Hu,[7] Jing Wang,[5] Rodabe N. Amaria,[2] Levi A. Garraway,[9,14] Peng Huang,[8] Peiying Yang,[10] Ignacio I. Wistuba,[6] Scott E. Woodman,[2] Jason Roszik,[2,6] R. Eric Davis,[3,8] Michael A. Davies,[2] John V. Heymach,[1] Patrick Hwu,[2,*] and Weiyi Peng[2,15,*]

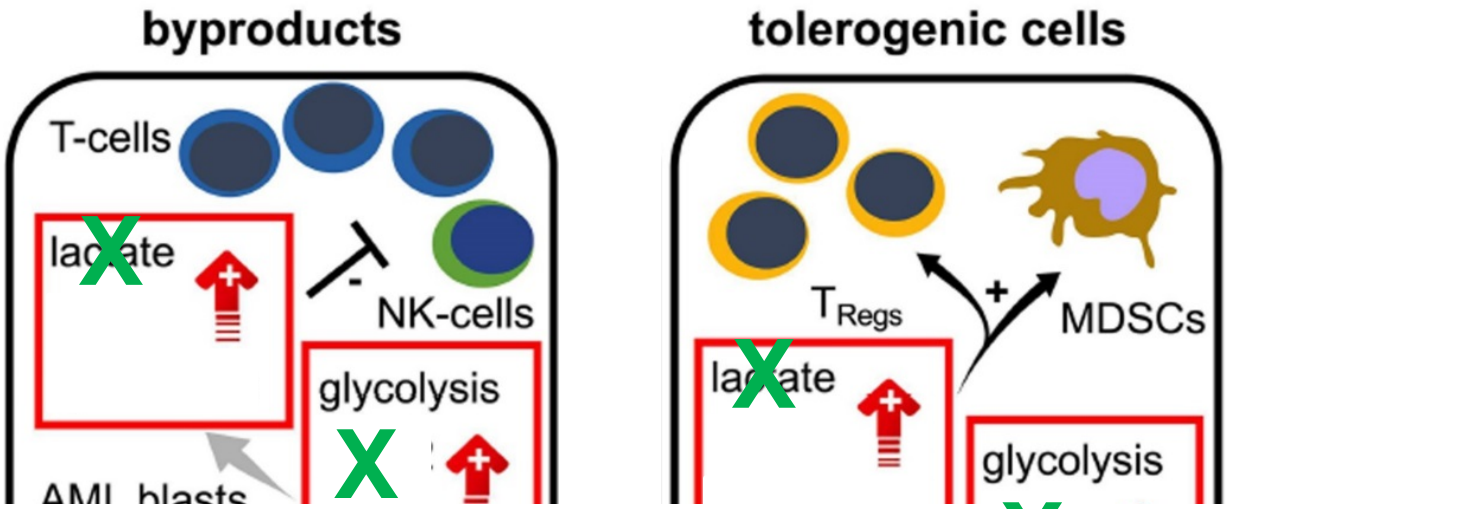
[1]Institute of Immunology and Immunotherapy, University of Birmingham Birmingham, United Kingdom
[2]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[3]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom
[4]Bio-cancer Treatment International Ltd, Hong Kong

Increased tumor intrinsic glycolytic activity is associated with poor response to melanoma patients to ACT

Glycolysis inhibition increased the ACT efficacy

Mougiakakos D, et al.Front Oncol. 2019; 9: 1166

The immunometabolic interplay in AML: production of bioactive metabolites



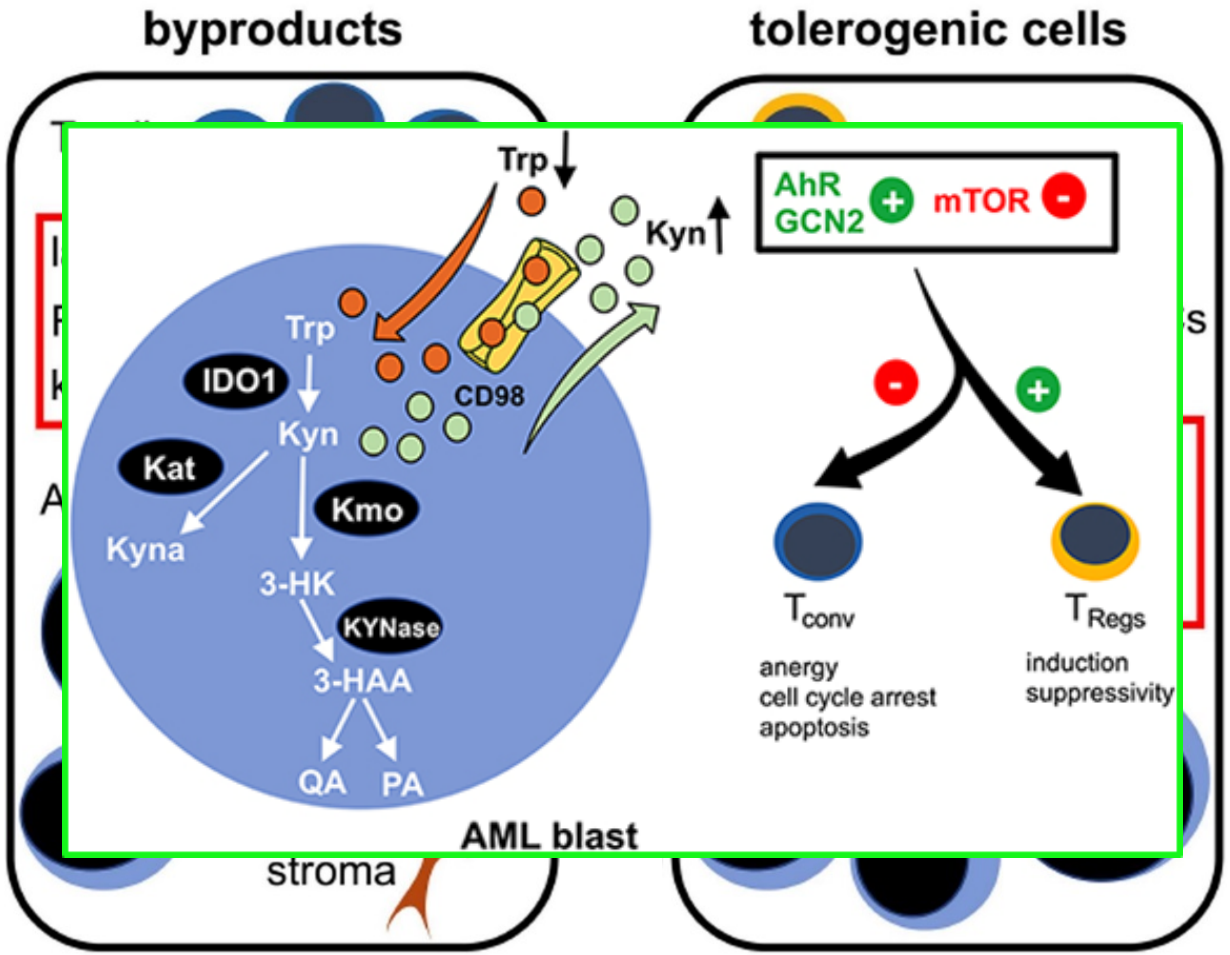
CLINICAL TRIALS AND OBSERVATIONS

Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial

Mats Brune, Sylvie Castaigne, John Catalano, Kurt Gehlsen, Anthony D. Ho, Wolf-Karsten Hofmann, Donna E. Hogge, Bo Nilsson, Reuven Or, Ana I. Romero, Jacob M. Rowe, Bengt Simonsson, Ruth Spearing, Edward A. Stadtmauer, Jeff Szer, Elisabeth Wallhult, and Kristoffer Hellstrand

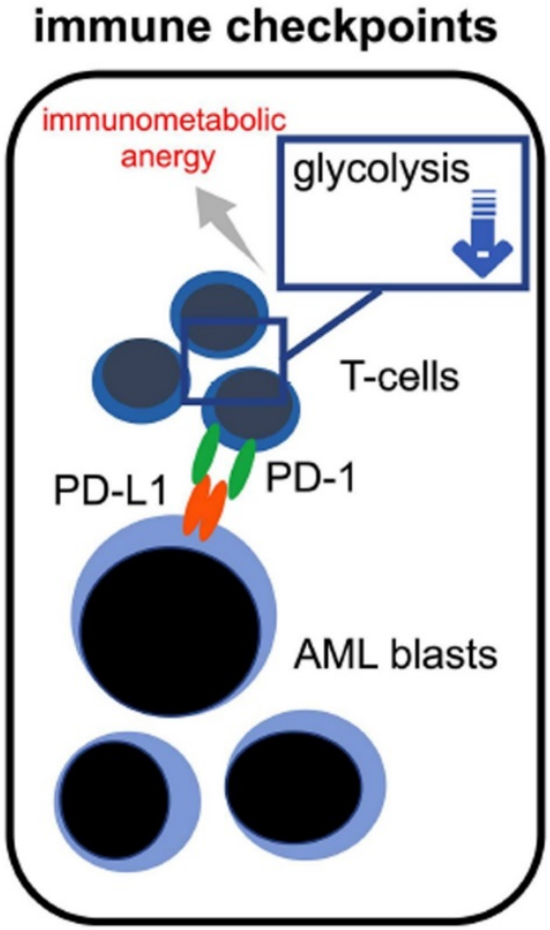
Mougiakakos D, et al.Front Oncol. 2019; 9: 116

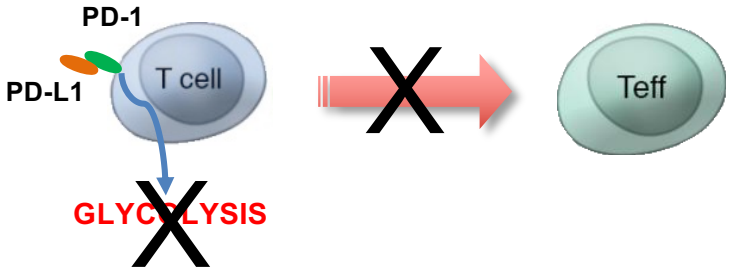
The immunometabolic interplay in AML: production of bioactive metabolites

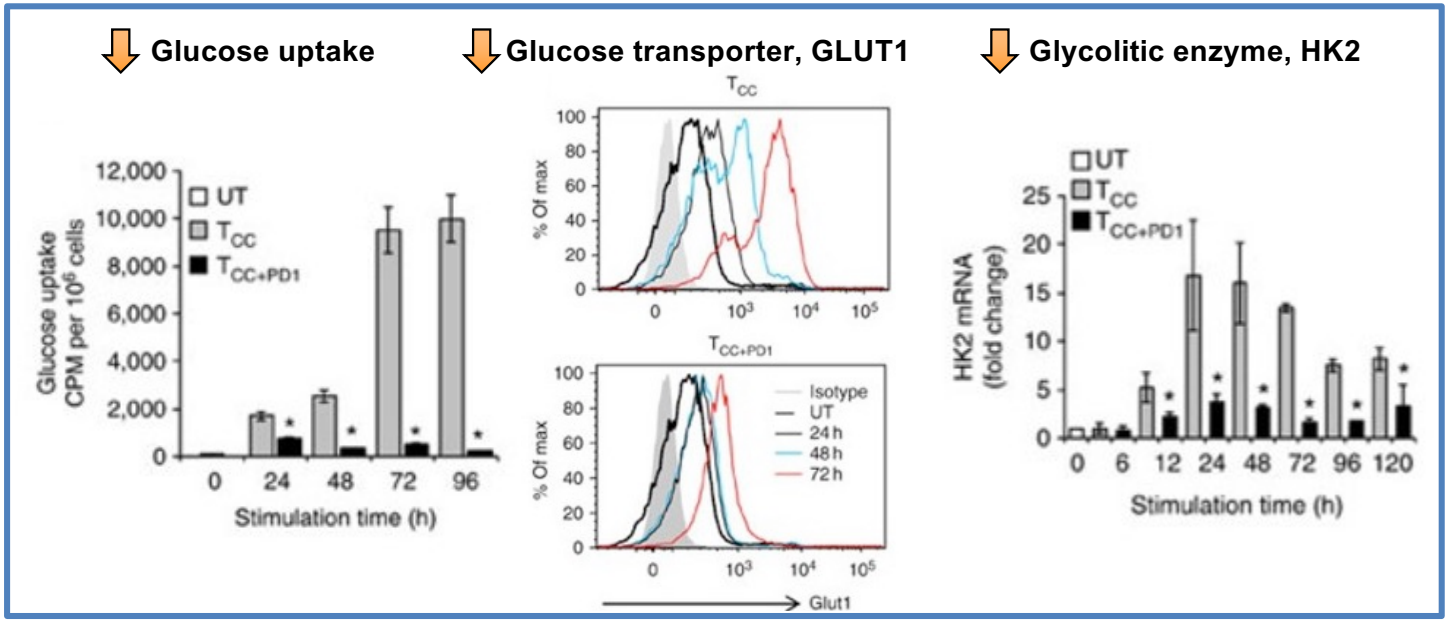


Mougiakakos D, et al.Front Oncol. 2019; 9: 1166

The immunometabolic interplay in AML







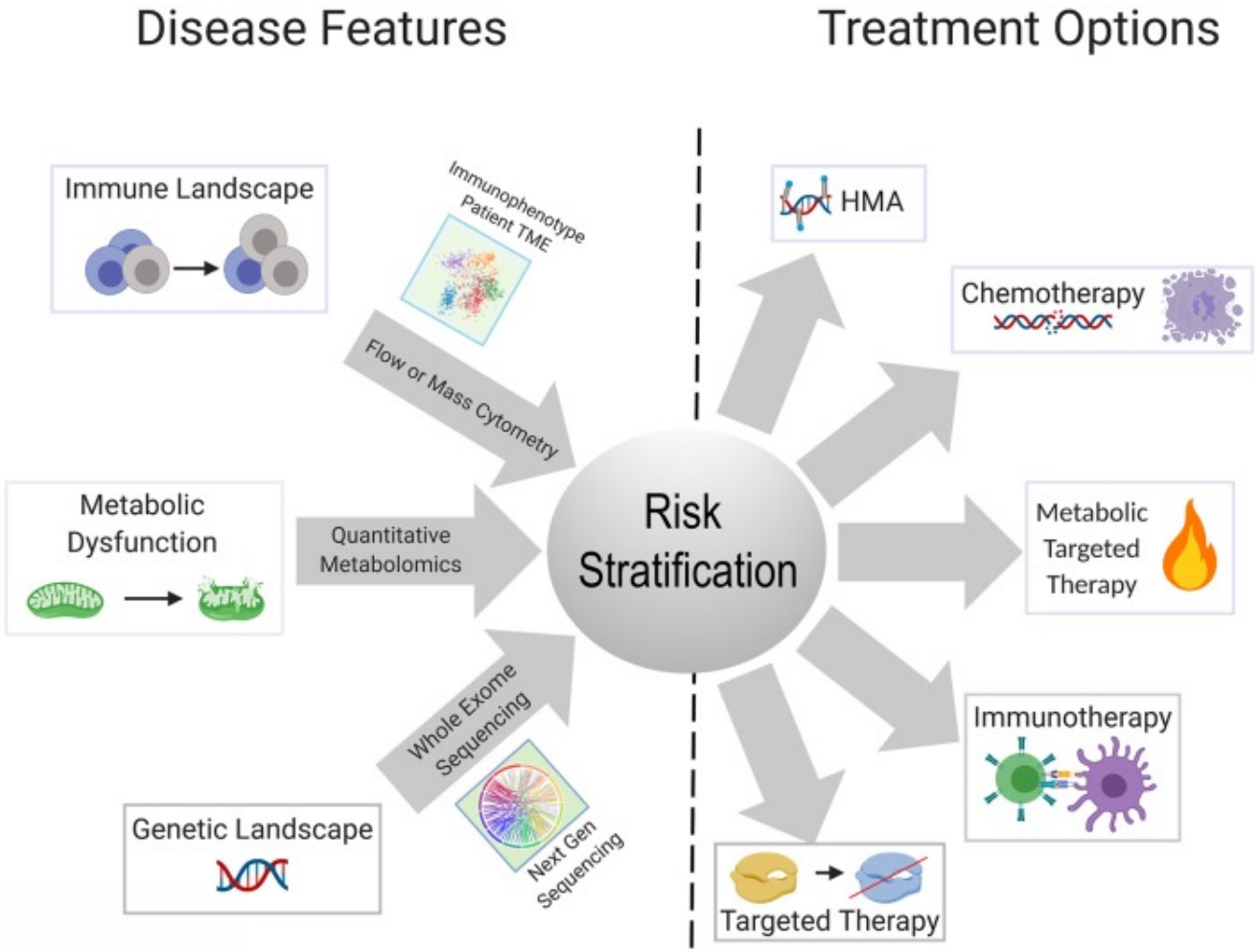
Mougiakakos D, et al.Front Oncol. 2019; 9: 1166
Patsoukis N et al. Nat Commun. 2015 Mar 26;6:6692

Resistance to therapies is largely influenced by the composition of the immunological microenvironment

Do new drugs alter leukemia cross-talk with immune system?

YES

- Interferons treatment increases PD-L1 expression
- MEK inhibitors reduce PD-L1 expression
- Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents
- Patients non-responders to chemotherapy increase TIM3 and Gal9
- …….



Mendez LM, et al.Front Oncol. 2019; 9: 1162

2021

TANKS TO…

Sabina Sangaletti
Barbara Bassani
Mario Colombo
Istituto Nazionale dei tumori, Milano

Giorgia Simonetti
Martina Pazzaglia
Maria Chiara Fontana
Giovanni Martinelli
IRST, Meldola

Marilena Ciciarello
Giulia Corradi
Dorian Forte
Darina Očadlíková
Valentina Pensato

Antonio Curti
Cell Therapy lab

Gianluca Cristiano
Jacopo Nanni
Cristina Papayannidis
Stefania Paolini
Chiara Sartor
Letizia Zannoni
AML group

Lorenza Bandini
Emanuela Ottaviani
Molecular Biology

Istituto 'Seragnoli'
Director: Prof. Michele Cavo

Jayakumar Vadakekolathu
Sergio Rutella
Nottingham Trent University, UK

Alessandro Gulino
Claudio Tripodo
University of Palermo

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SEZIONE DI BOLOGNA
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Thank you