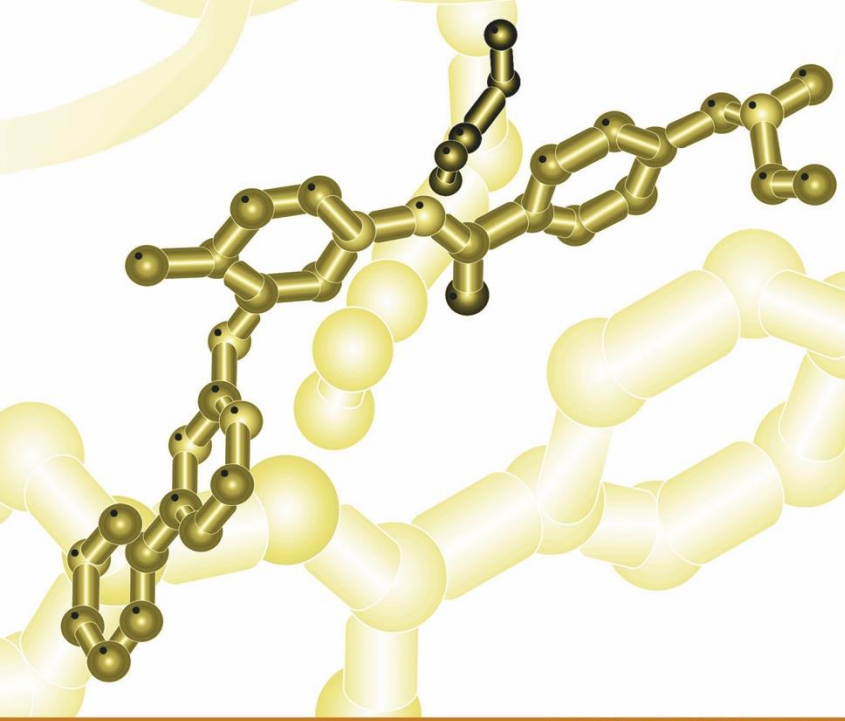
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI
SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna



New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

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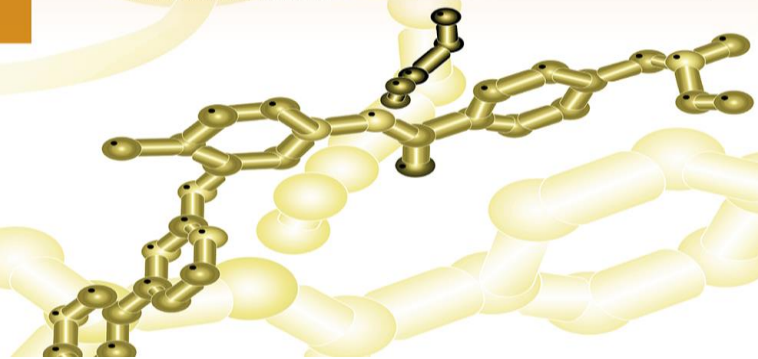

New Drugs in Hematology

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Disclosures of Marilena Ciciarello

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
none							

Immunotherapy in AML: targeting immunosuppressive microenvironment

Marilena Ciciarello, PhD

CNR Institute of Molecular Genetics
IRCCS Istituto Ortopedico Rizzoli
Alma Mater Studiorum - University of Bologna

Cancer immunotherapy history

live and inactivated bacteria

1891
William Coley

Cytokines therapy

1976
IL-2

Adoptive cell therapy

1985
TILs

1998 CAR-T

Cancer vaccines

1991-1994
Melanoma antigens

IC inhibitors

1992-1996
αPD1 & αCTLA4
antibodies

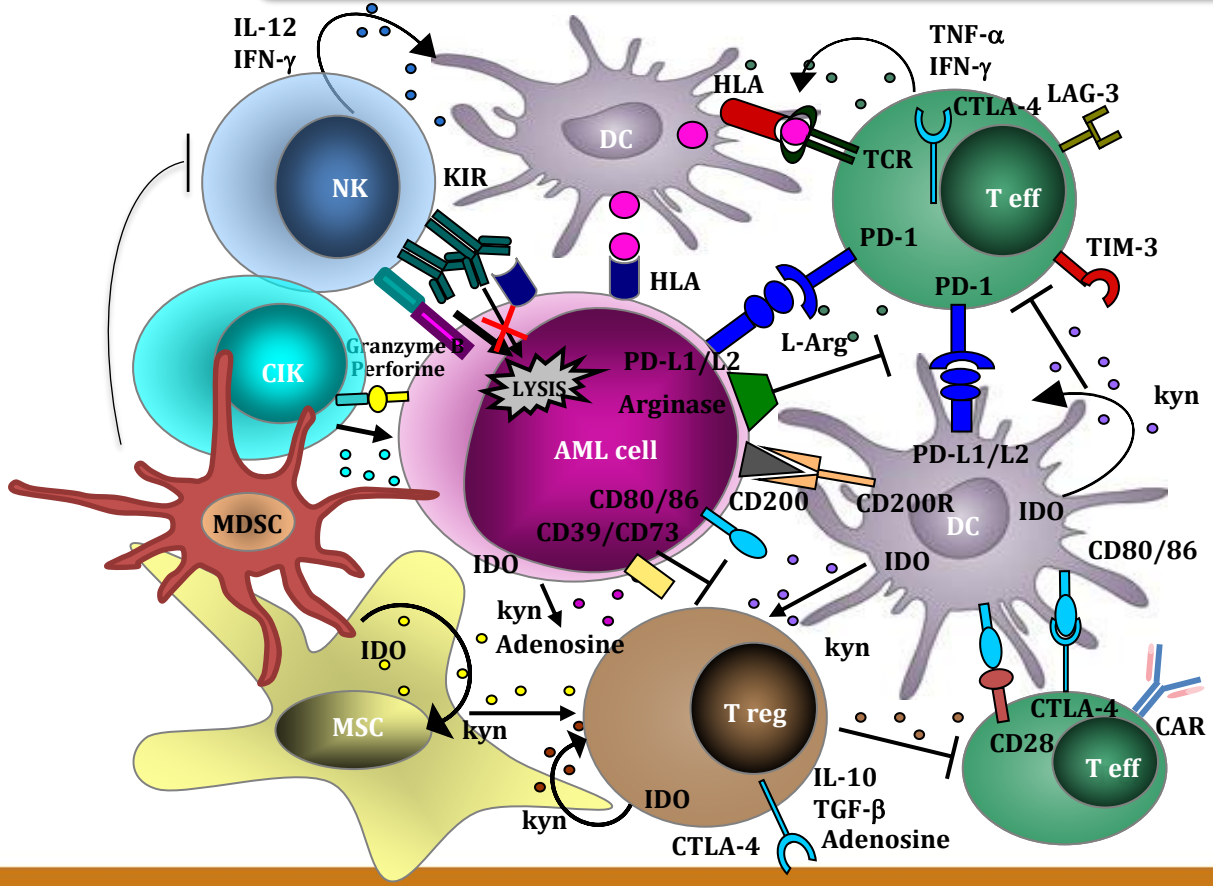
Honjo &Allison
2018 Nobel prize

Oncolytic virus

2012-2015
T-vec

Adapted from Zhang & Zhang 2020

stromal/immune ME in AML



Immune suppressive mechanisms

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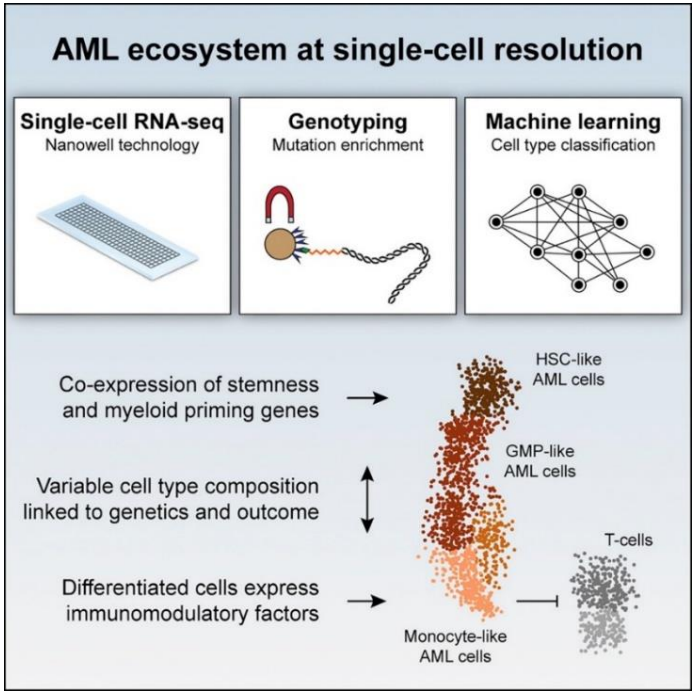
- Modulation of ICs
- Loss tumor antigen expression

Extrinsic

- Innate immune response (e.g., Suppression of NK-mediated cytotoxity; DCs inhibition by immature NKs)
- Disfuntional exhausted T cells (PD1, TIM3)
- Increased T regs
- Immunesuppressive CKs' production

Adapted from D. Ocadlikova

Single-Cell RNA-seq reveals AML hierarchies relevant to disease progression and immunity

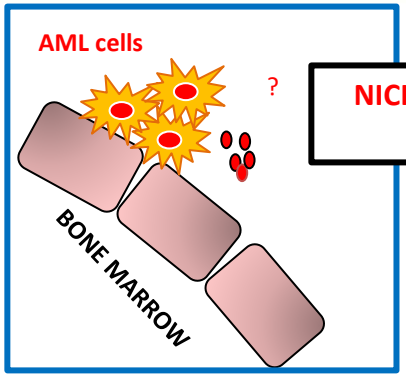


Differentiated malignant AML cells contribute to the immunosuppressive microenvironment

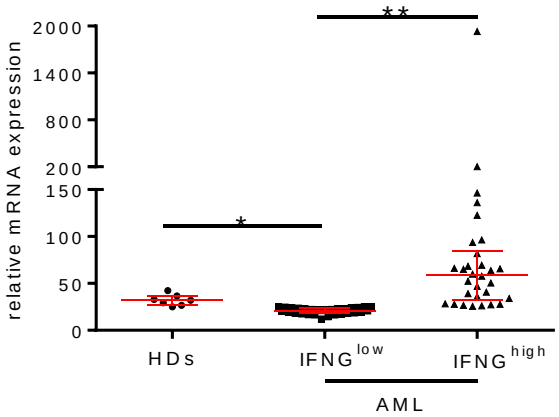
- inhibit T-cell activation
- contribute to altered T-cell phenotypes
- express **immunomodulatory genes**

Van Galen P, Cell, Volume 176, 2019, Pages 1265-1281

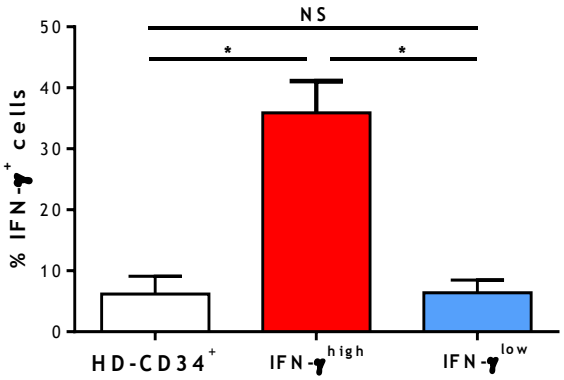
IFN-γ is specifically produced by AML cells

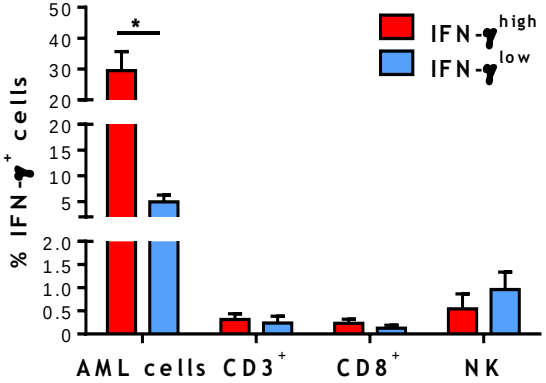


Gene chip data



Flow cytometry

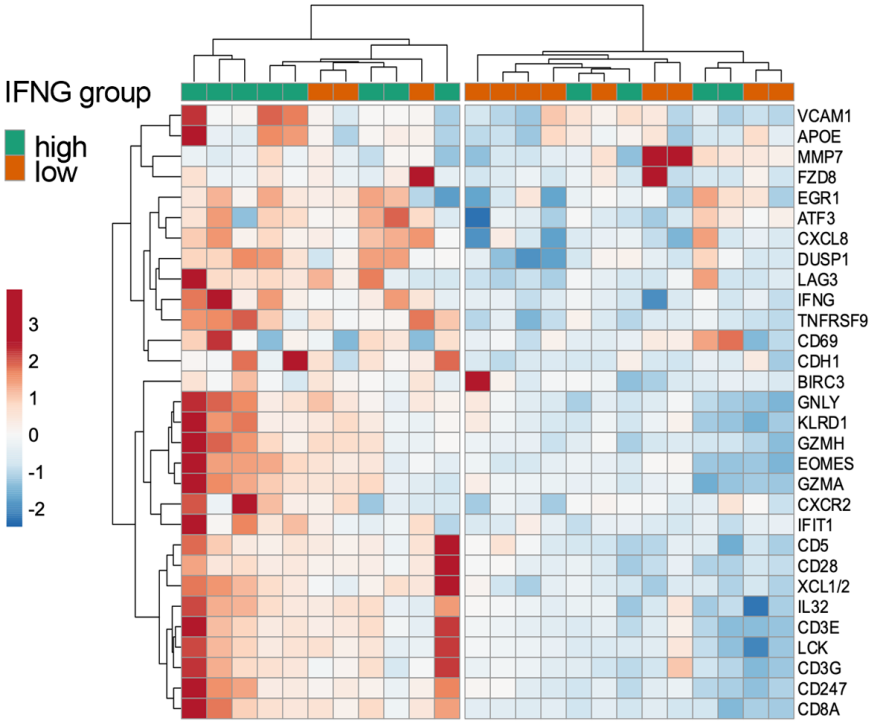




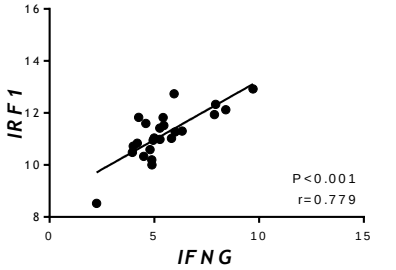
Corradi et al., Clin Cancer Res. 2022; 28:3141-3155

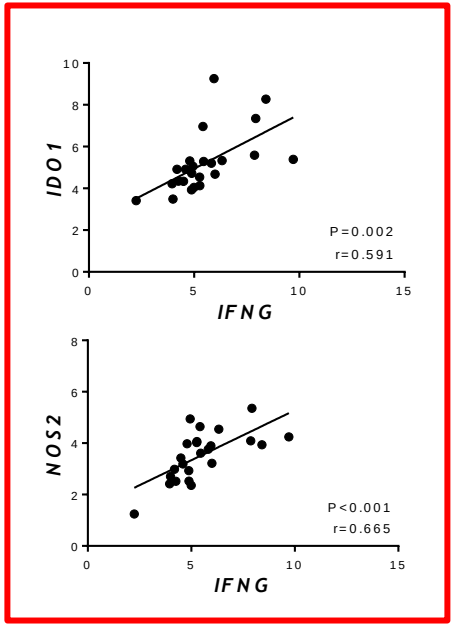
IFN-γ^{high} AML cells hold an inflammatory and immune gene signature

NanoString



Gene expression correlations

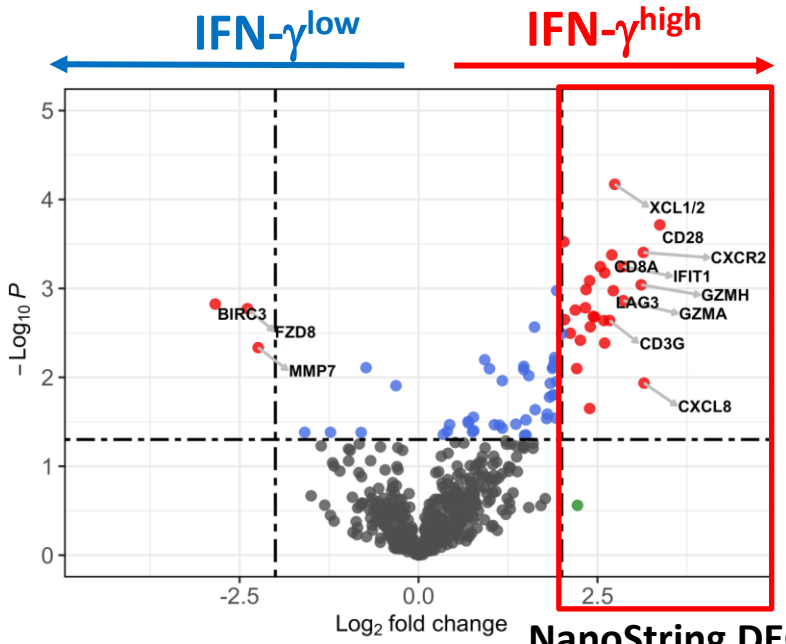




immune-tolerance genes

Corradi et al., Clin Cancer Res. 2022; 28:3141-3155

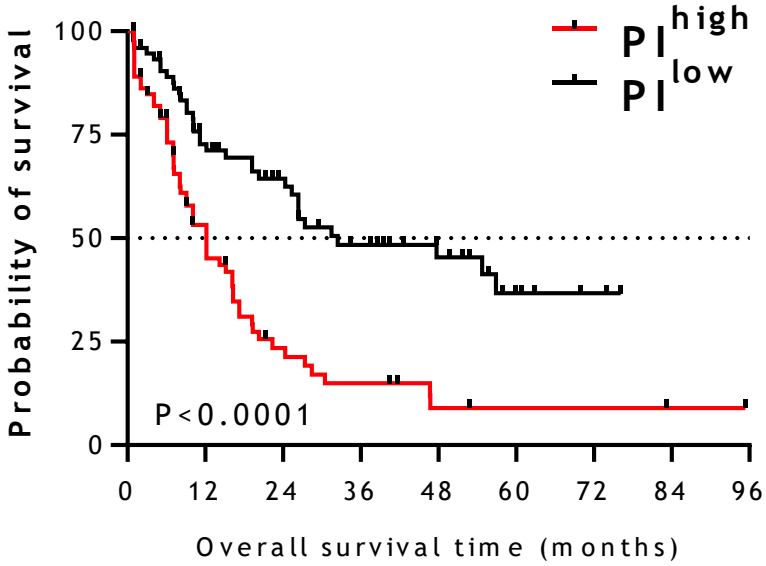
IFN-γ signature results poor overall survival in AML patients



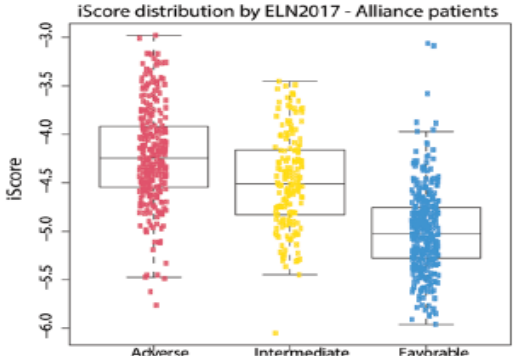
NanoString DEGs

Prognostic index (PI)

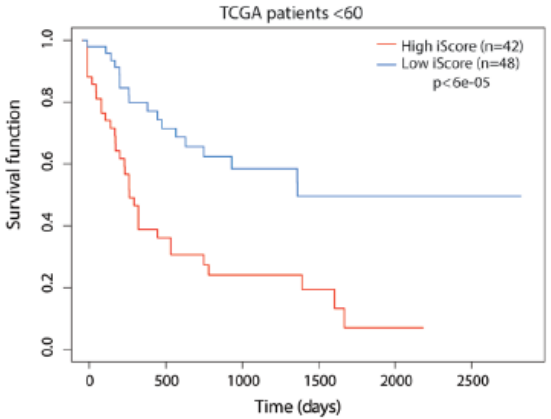
TGCA

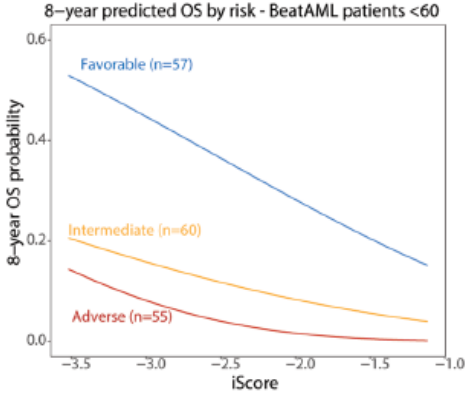


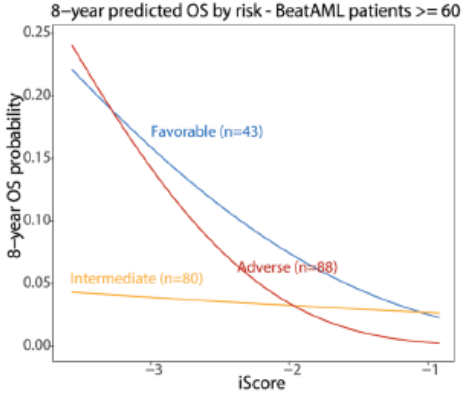
Corradi et al., Clin Cancer Res. 2022; 28:3141-3155



High inflammatory score is associated with adverse ELN risk group and prognostically stratifies AML patients





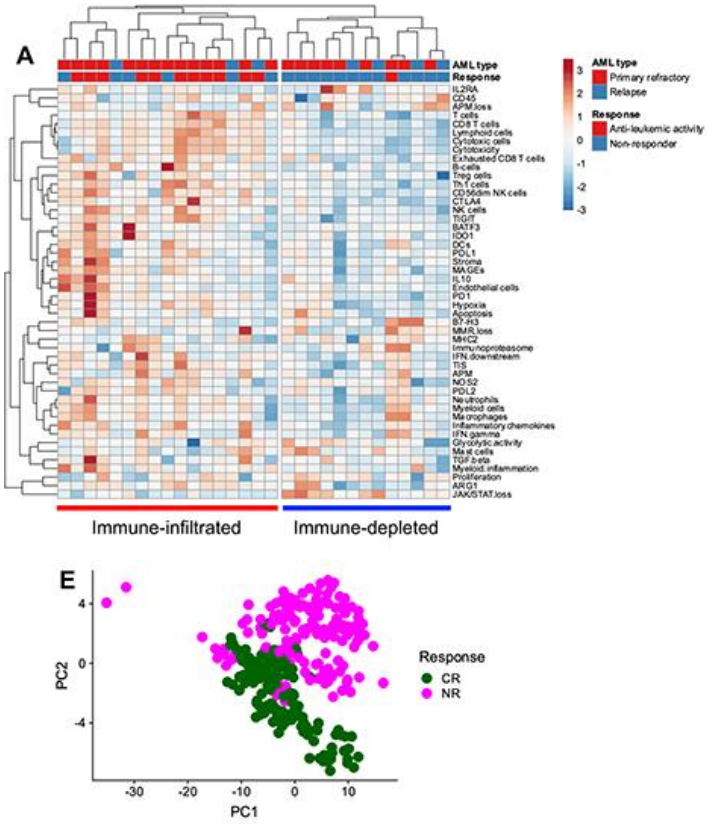


Lasry A et al, Nature Cancer, January 2023, 27-42

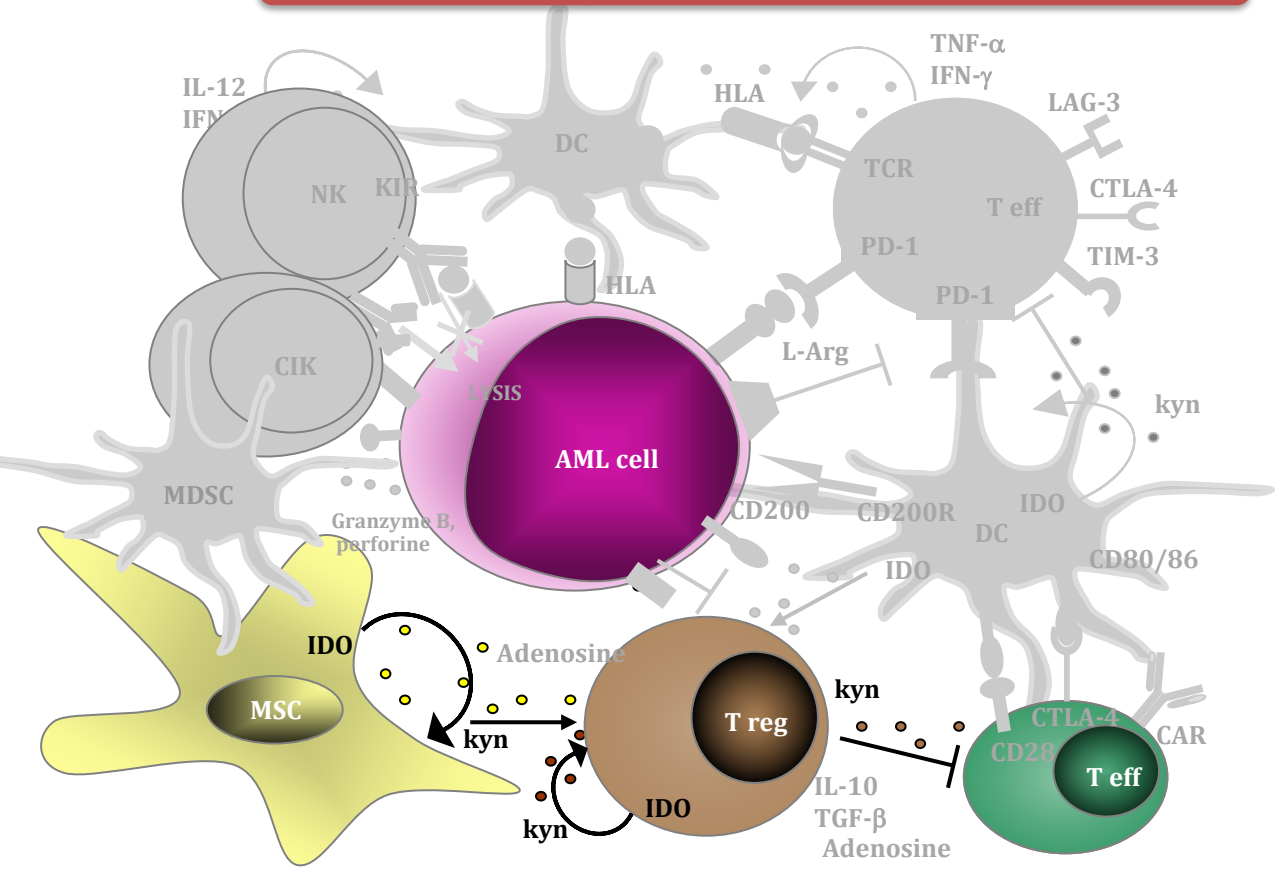
Sci Transl Med. 2020 June 03; 12(546): . doi:10.1126/scitranslmed.aaz0463.

Immune landscapes predict chemotherapy resistance and immunotherapy response in acute myeloid leukemia

Jayakumar Vadakekolathu[1], Mark D. Minden[2], Tressa Hood[3], Sarah E. Church[3], Stephen Reeder[1], Heidi Altmann[4], Amy H. Sullivan[3], Elena J. Viboch[3], Tasleema Patel[5], Narmin Ibrahimova[2], Sarah E. Warren[3], Andrea Arruda[2], Yan Liang[3], Thomas H. Smith[3], Gemma A. Foulds[1], Michael D. Bailey[3], James Gowen-MacDonald[3], John Muth[6], Marc Schmitz[7,8,9], Alessandra Cesano[3], A. Graham Pockley[1,10], Peter J.M. Valk[11], Bob Löwenberg[11], Martin Bornhäuser[4,8,9], Sarah K. Tasian[5], Michael P. Rettig[12], Jan Davidson-Moncada[6], John F. DiPersio[12], Sergio Rutella[1,10,*]



stromal/immune ME in AML



Immune suppressive mechanisms

Intrinsic

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Extrinsic

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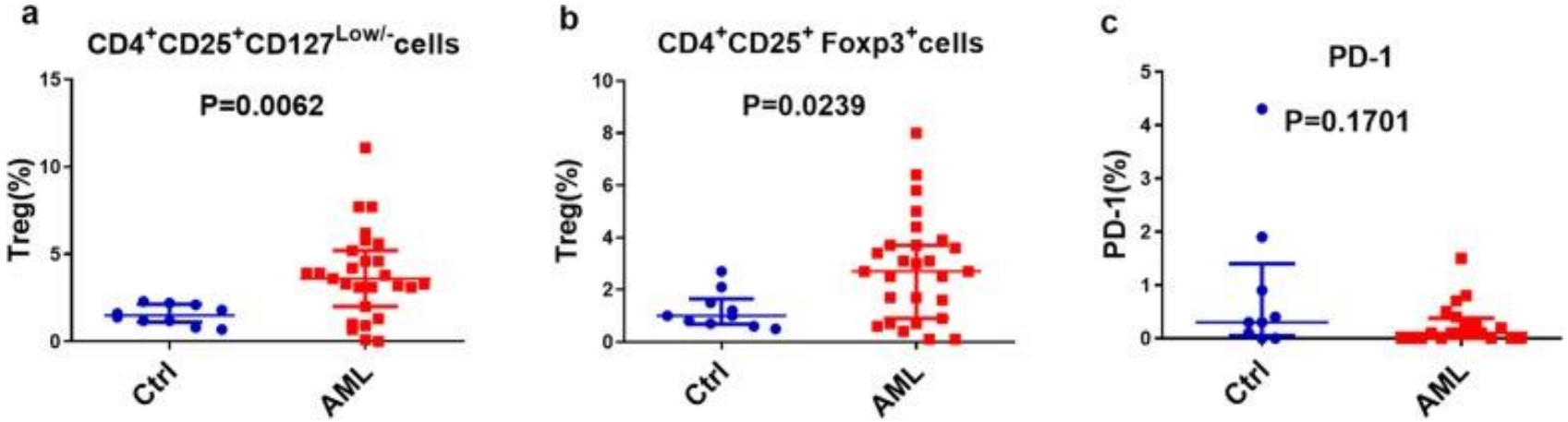
- Disfuntional exhausted T cells (PD1, TIM3)
- **Increased T regs**
- Immunesuppressive CKs' production

Adapted from D. Ocadlikova

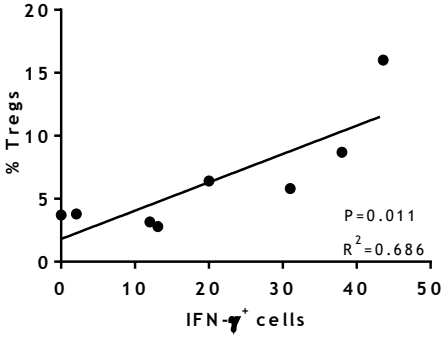
T regs are increased and hyperfunctional in de novo AML

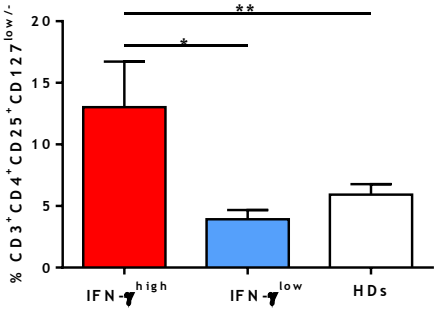


Wang Y et al, BMC Cancer. 2020; 20: 472

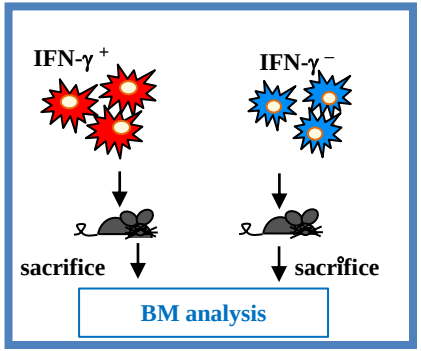
IFN-γ production by AML cells results in high BM Tregs

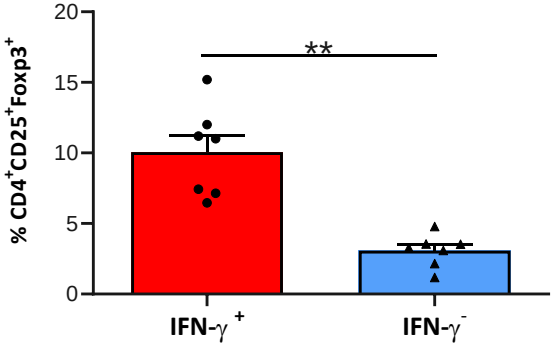
Tregs in AML patients





Tregs in MICE





Corradi et a., Clin Cancer Res. 2022; 28:3141-3155

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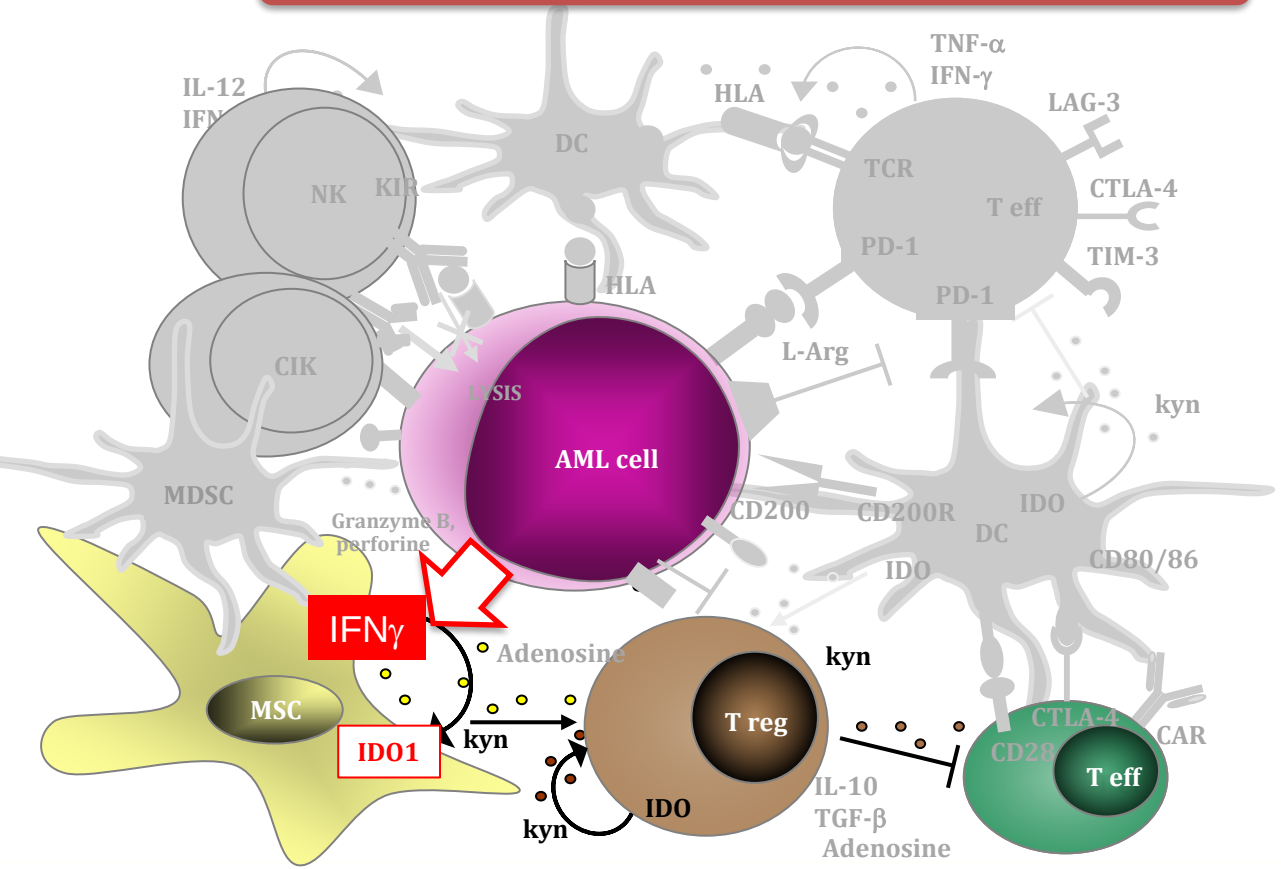

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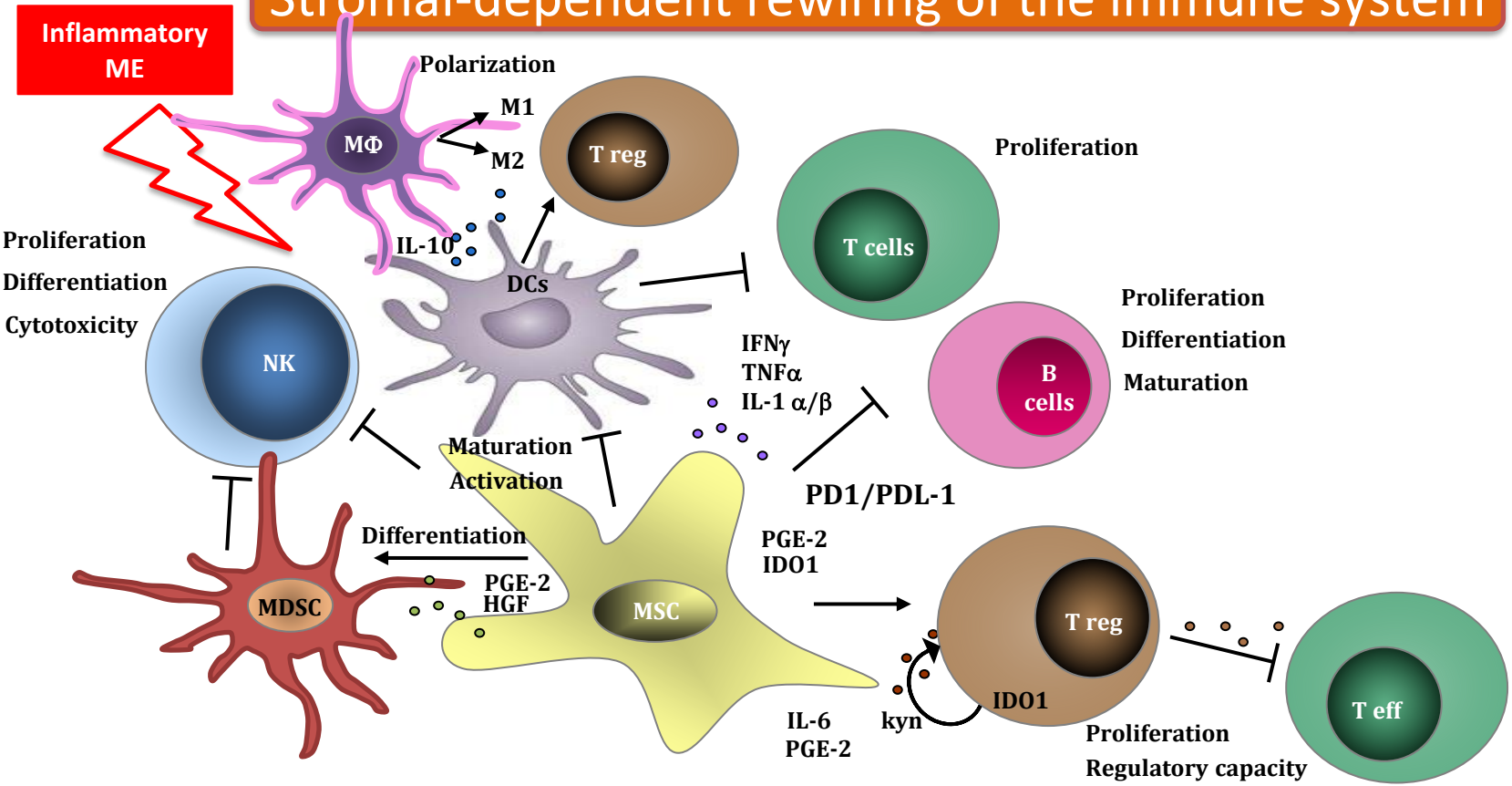
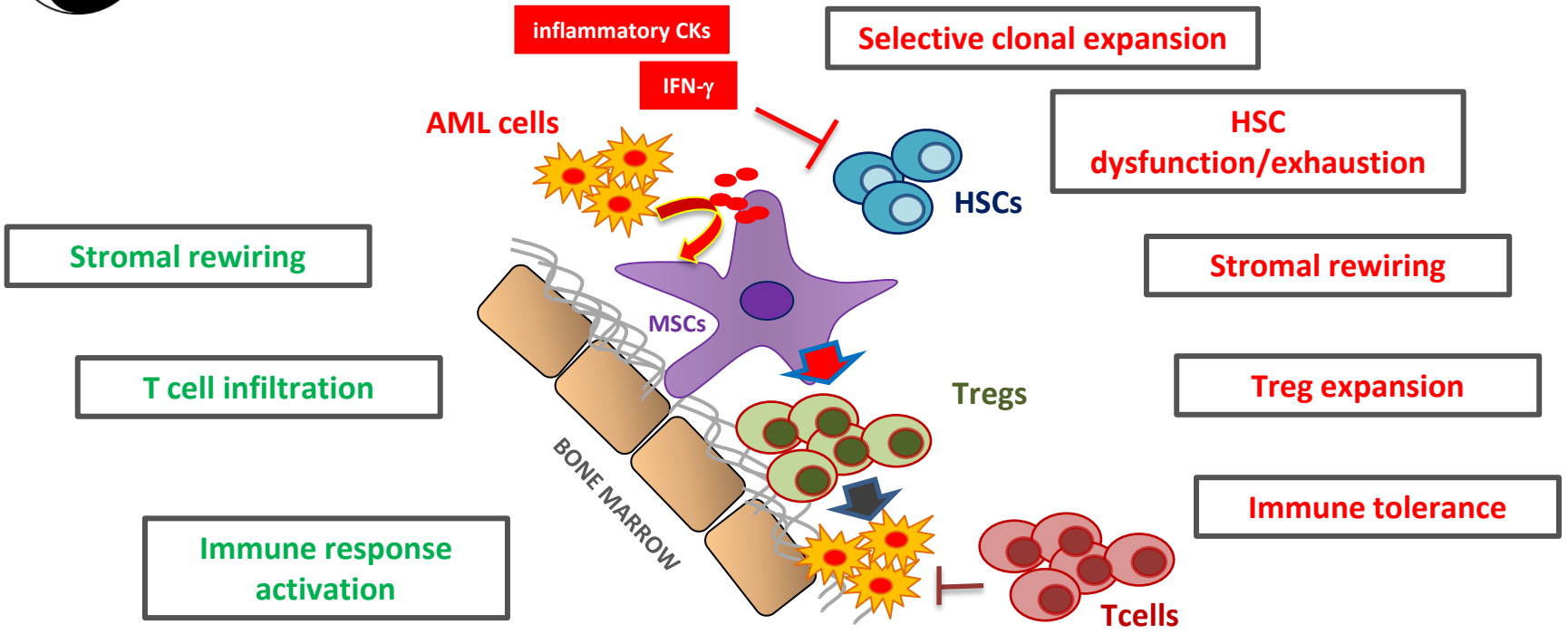
- **Stromal-dependent rewiring?**

Adapted from D. Ocadlikova

Stromal-dependent rewiring of the immune system



Inflammation and AML



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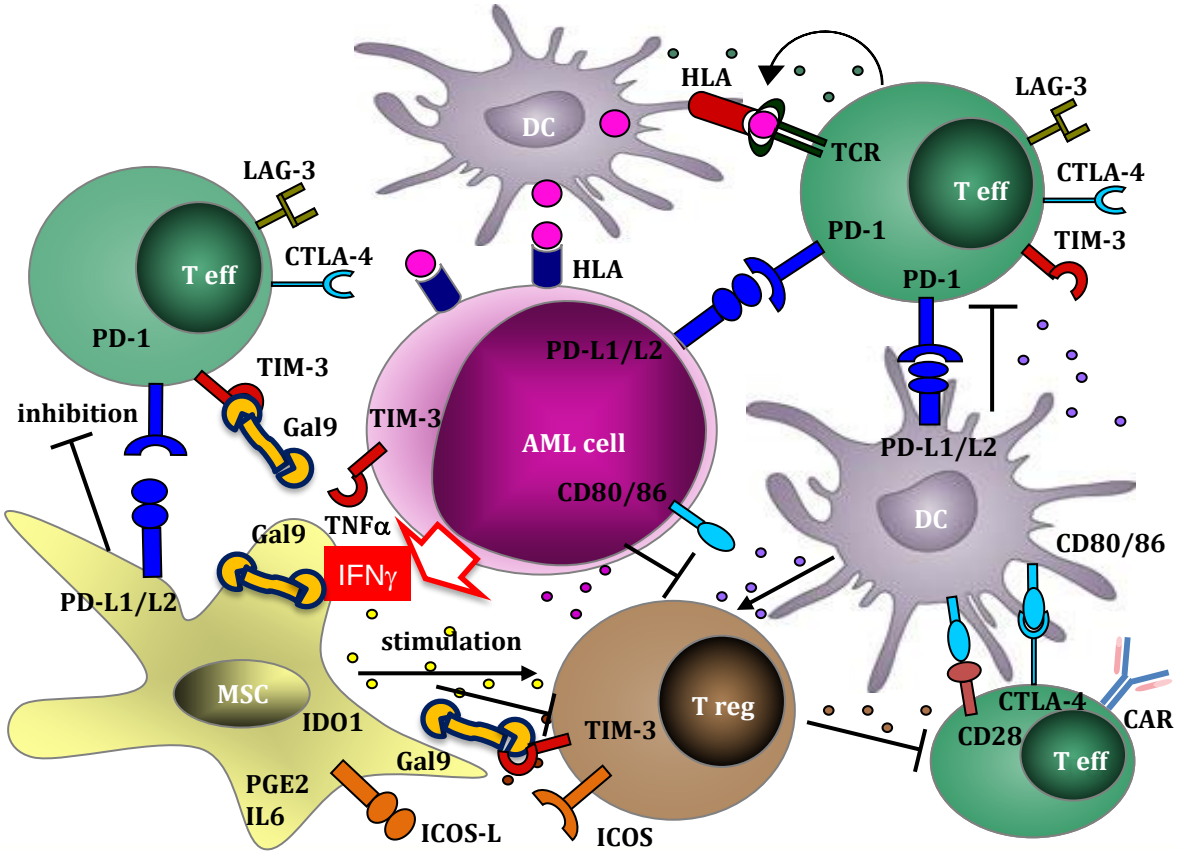

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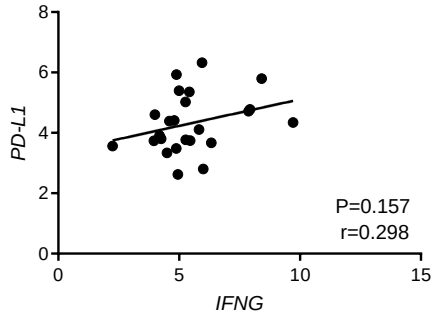
- **Modulation of ICs**

Adapted by D. Ocadlikova

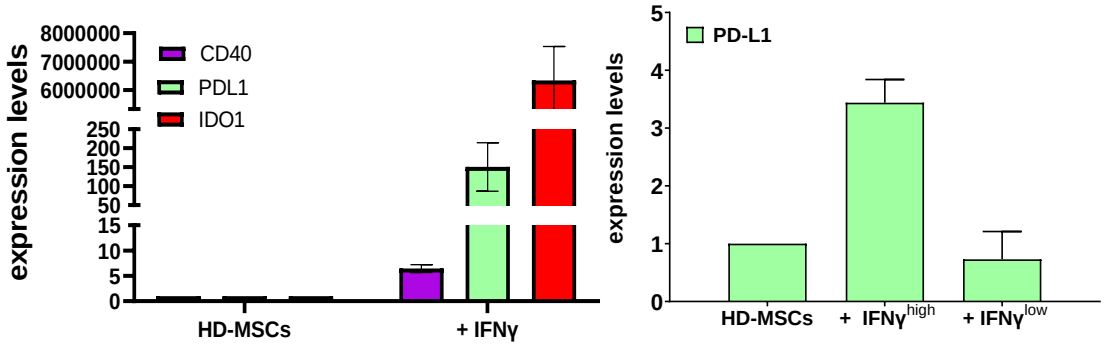
Inflammation and CKIs in the ME

In AML samples



Corradi et al., CCR 2022

in MSCs

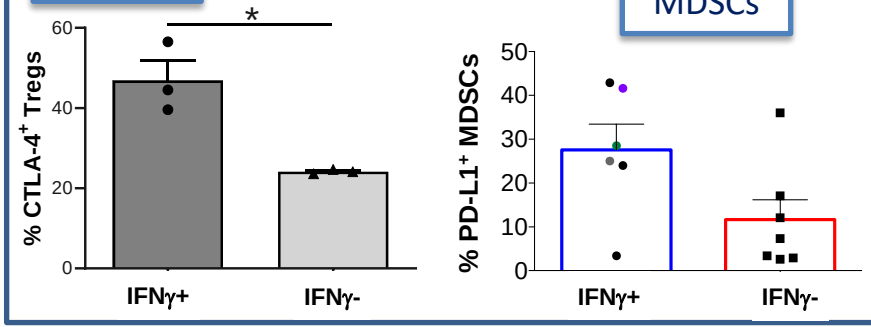


unpublished data

Tregs

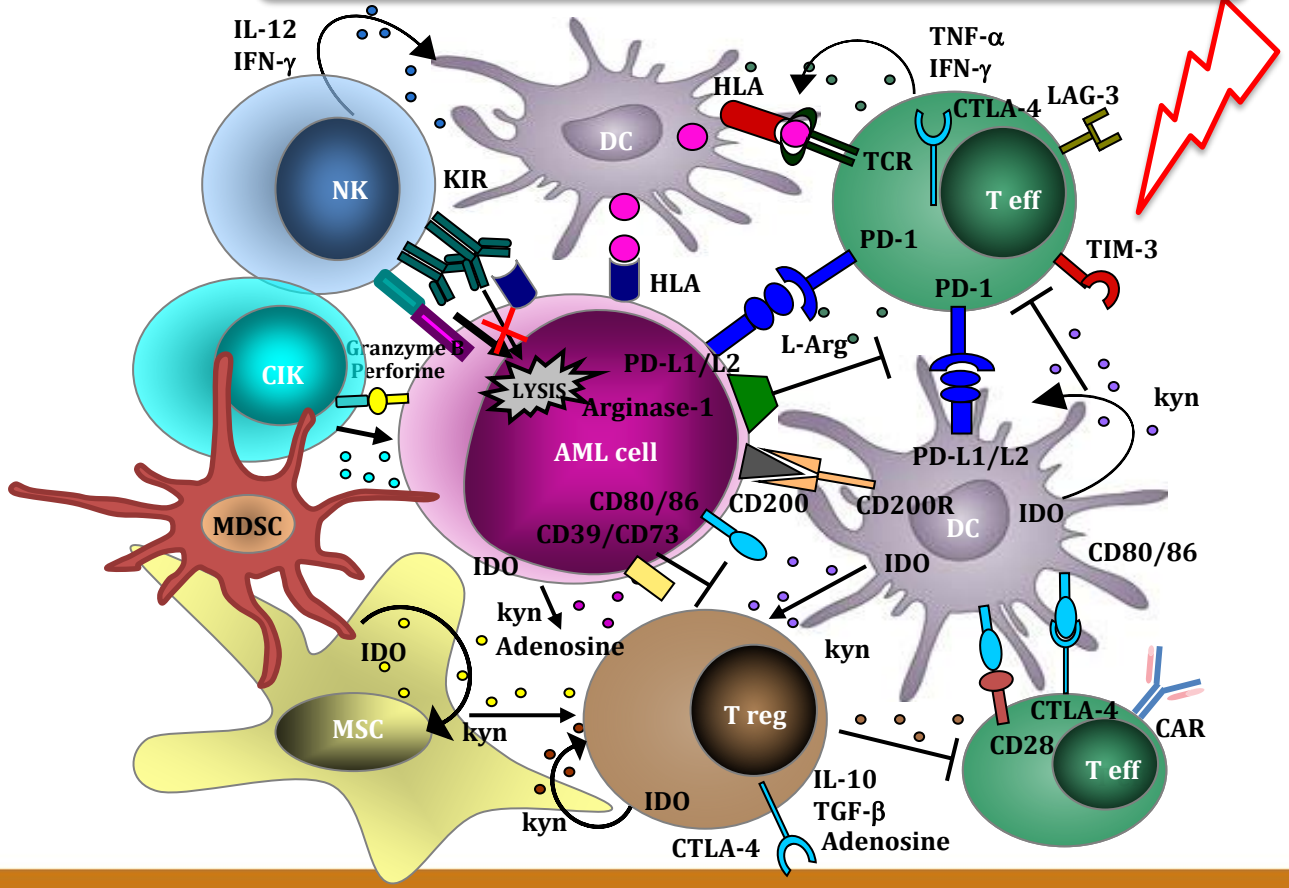
In mice

MDSCs



Corradi et al., CCR 2022
unpublished data

stromal/immune ME in AML



Therapy

Immune suppressive mechanisms

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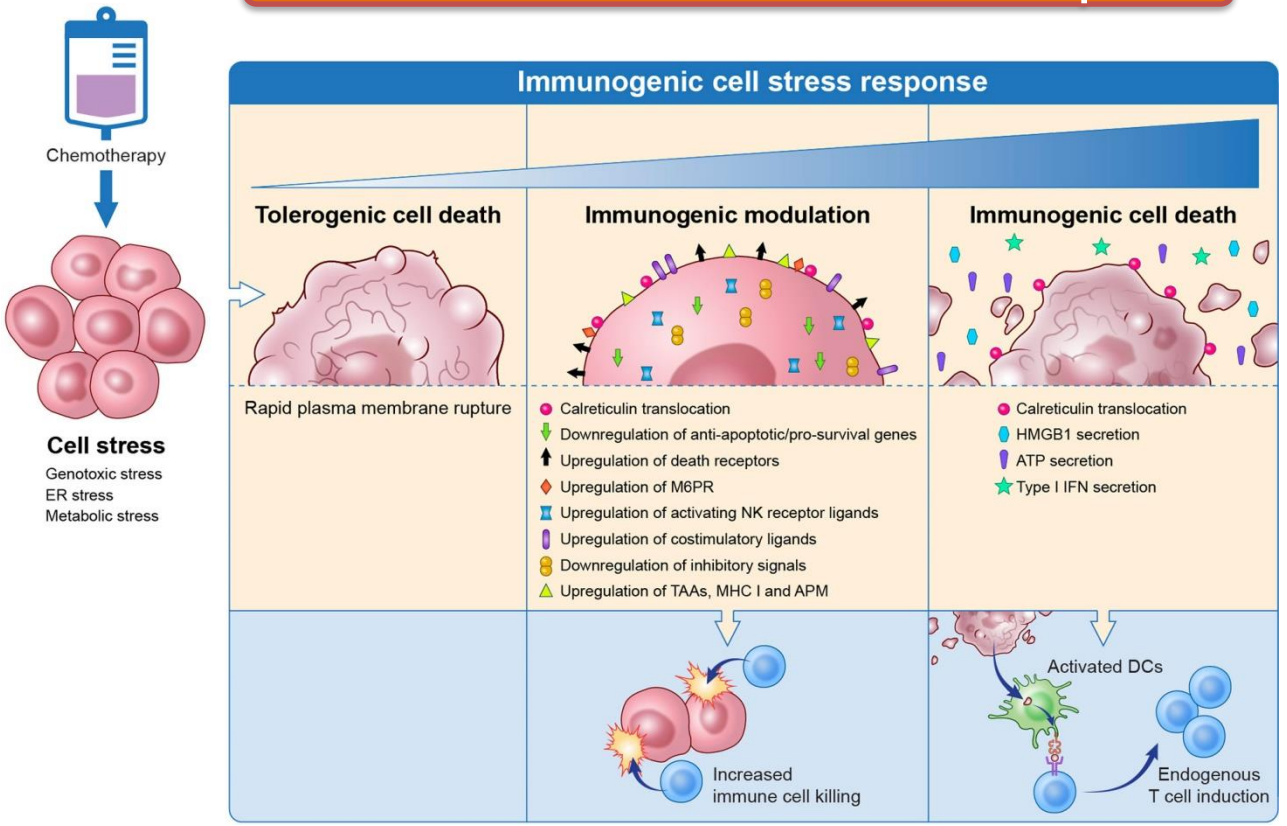
Adapted from D. Ocadlikova

Immune 'side-effect' of therapies



Immunetherapy synergistic strategies

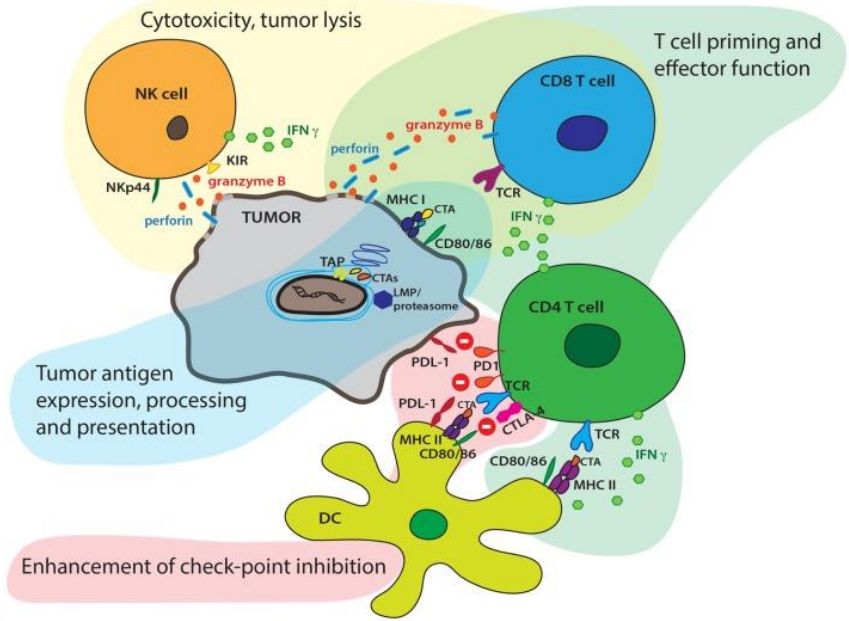
Leukemia (2004) 18, 1223–1230
& 2004 Nature Publishing Group All rights reserved 0887-6924/04 $30.00
www.nature.com/leu

Chemotherapy+ICIs

Cytosine arabinoside induces costimulatory molecule expression in acute myeloid leukemia cells

R Vereecque[1,2,4], A Saudemont[1,2,4] and B Quesnel[1,2,3]

EMAs enhance anti-tumor immune responses and tumor clearance



frontiers in IMMUNOLOGY
REVIEW ARTICLE
published: 04 February 2015
doi: 10.3389/fimmu.2015.00029

Augmenting antitumor immune responses with epigenetic modifying agents

*Erika Héninger[1], Timothy E. G. Krueger[1] and Joshua M. Lang[1,2]**

HMA+ICIs

Immunetherapy synergistic strategies

HMA+VEN+ICIs?

Triple combination targeting methyltransferase, BCL-2, and PD-1 facilitates antileukemia responses in acute myeloid leukemia

Zhihong Zeng MD | Abhishek Maiti MBBS | Shelley Herbrich PhD | Tianyu Cai PhD | Antonio Cavazos MS | Taylor Manzella BS | Helen Ma MS | Kala Hayes BS | Jairo Matthews BA | Courtney D. DiNardo MD | Naval G. Daver MD | Marina Y. Konopleva MD, PhD

Methods

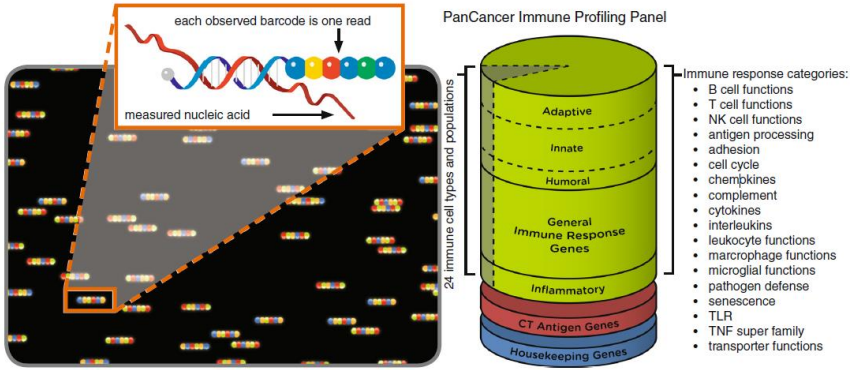
27 AML pts
AZA-VEN

- 6 Refractory
- 21 Responders → 7 Relapsed

BM samples

DIAGNOSIS → RESPONSE/REFRACTORY → RELAPSE

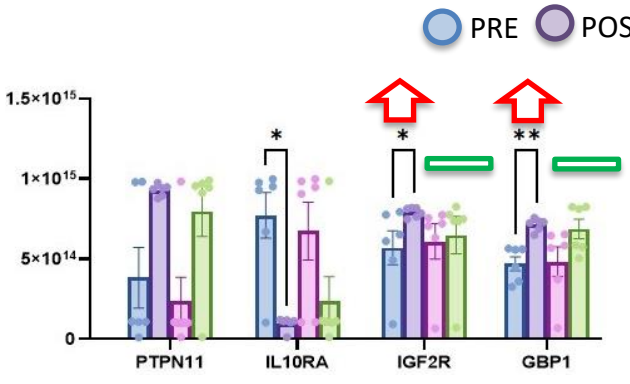
Gene expression analysis → NanoString PanCancerIO360



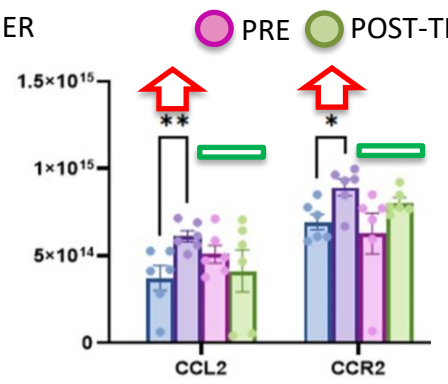
Zannoni et al., Unpublished data. Please do not share

RELAPSED

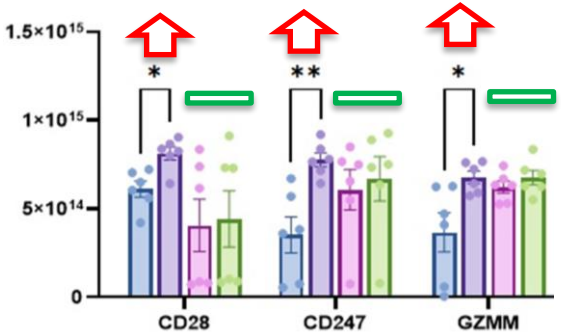
RESPONSIVE



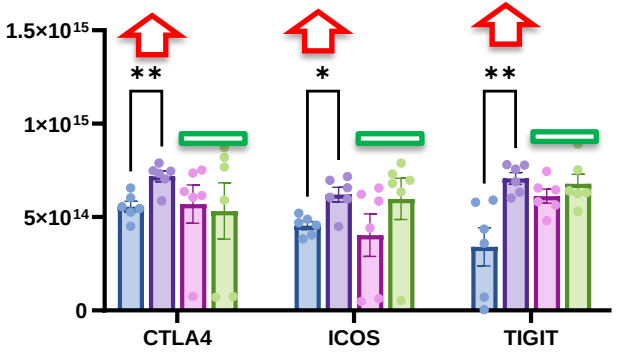
Interferons/Cytokines



Chemokines

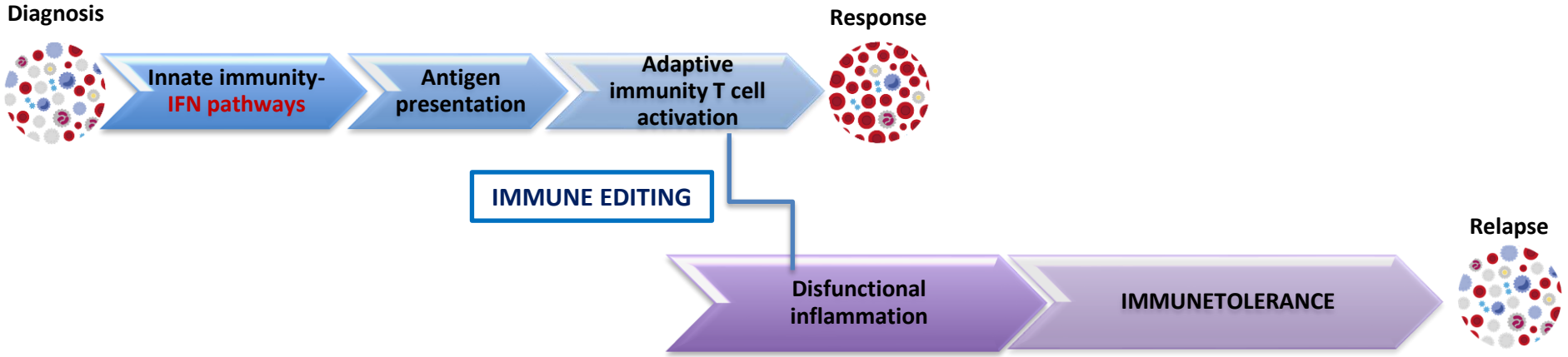


T cell activation and priming

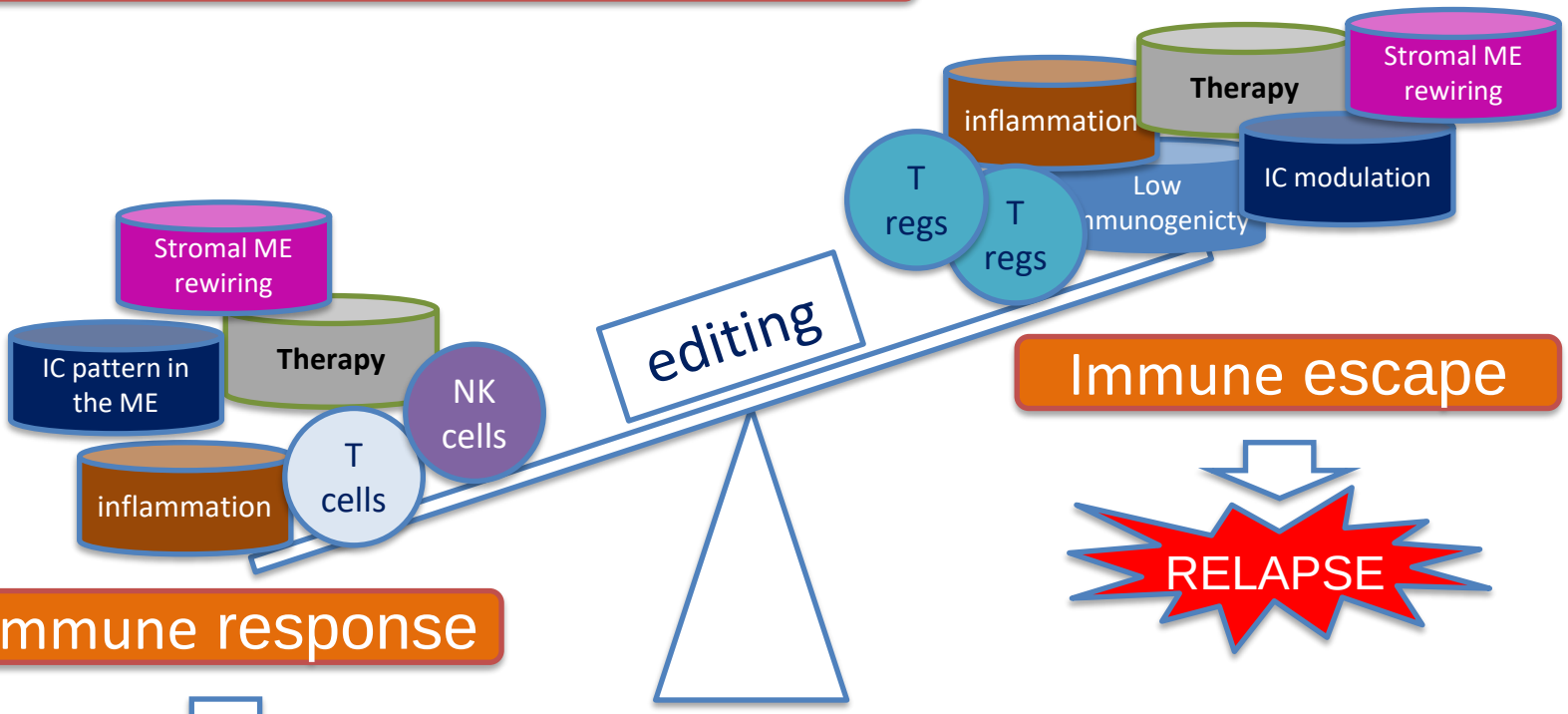


Checkpoint inhibitors

Zannoni et al., unpublished data.
Please do not share

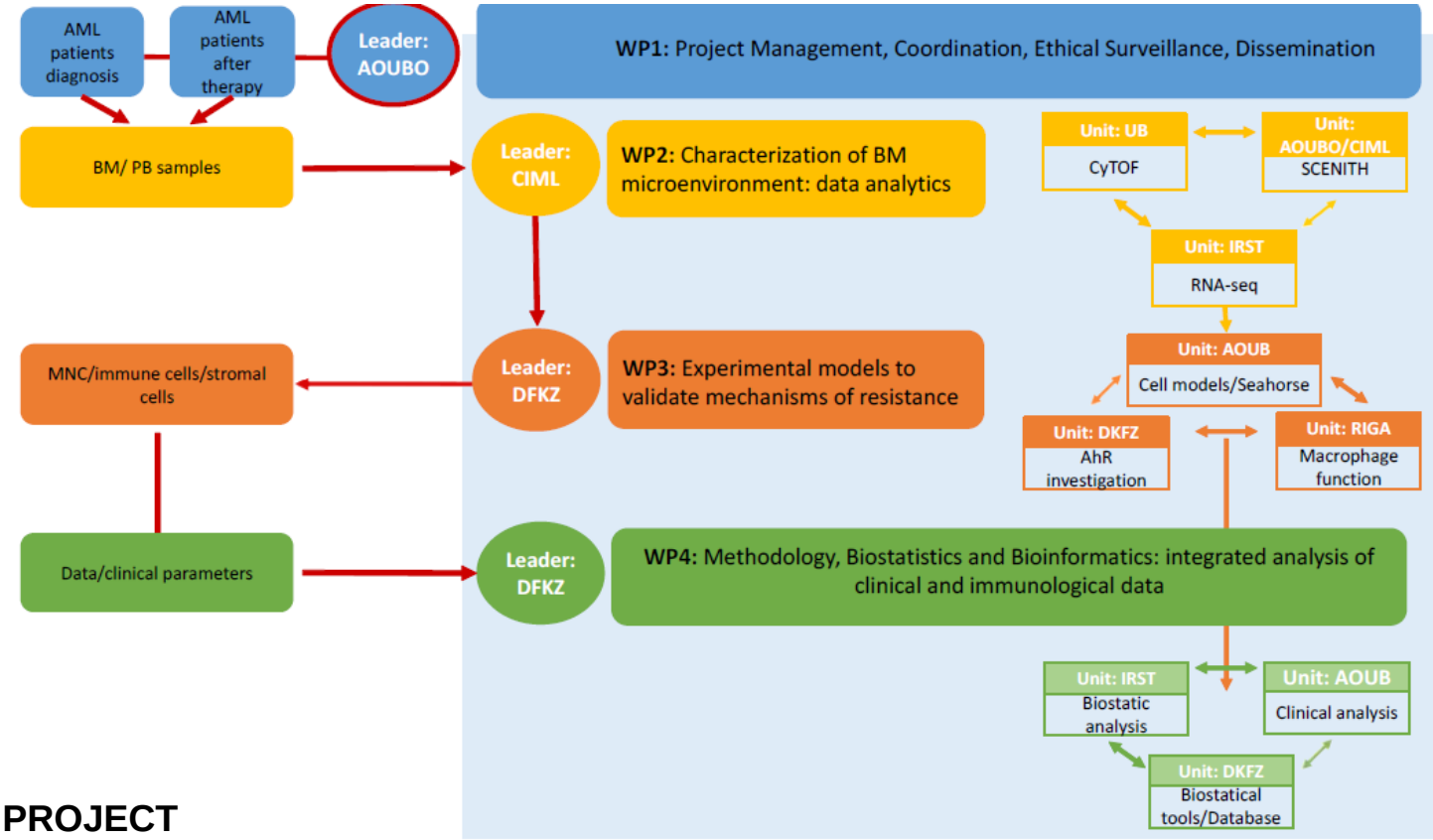

Diagnosis
Innate immunity-
IFN pathways
Antigen
presentation
Adaptive
immunity T cell
activation
Response
IMMUNE EDITING
Disfunctional
inflammation
IMMUNETOLERANCE
Relapse

IMMUNETHERAPY BALANCE



Transcan-3 JTC 2021

Aza+VEN



TALETE PROJECT

Thanks to:

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