Immune elements and cancer stemness

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Presenter disclosure information

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.

A. Balance, Key to life:

Immune imbalances and suppressive networks in the tumor microenvironment.

B. Immune impact, Key to cancer progression

Immune elements and oncogenesis model: MDSCs, Th22

A. Immune imbalances and suppressive networks in the human tumor microenvironment

I. Inhibitory and stimulatory B7 imbalance

II. T cell subset (Treg and effector T) imbalance

III. APC subset (DC and suppressive APC) imbalance

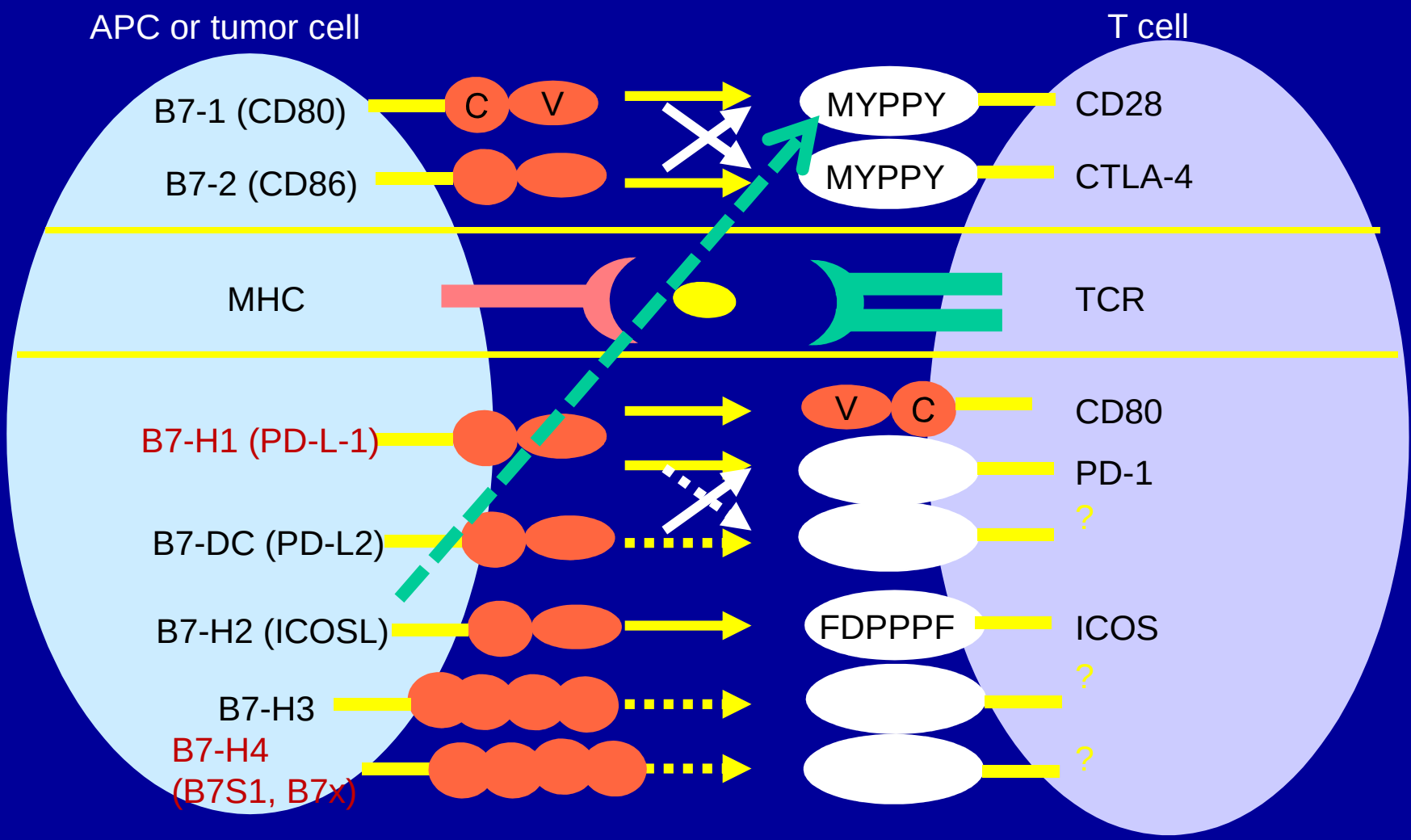
W Zou. Immunosuppressive networks in the tumor microenvironment and their therapeutic relevance. Nature Reviews Cancer, 5:263-274, 2005

W Zou. Regulatory T cells, tumor immunity and immunotherapy. Nature Reviews Immunology, 6:295-307, 2006

W Zou, L Chen. Inhibitory B7 family molecules in the tumor microenvironment. 8:467-477, Nature Reviews Immunology, 2008

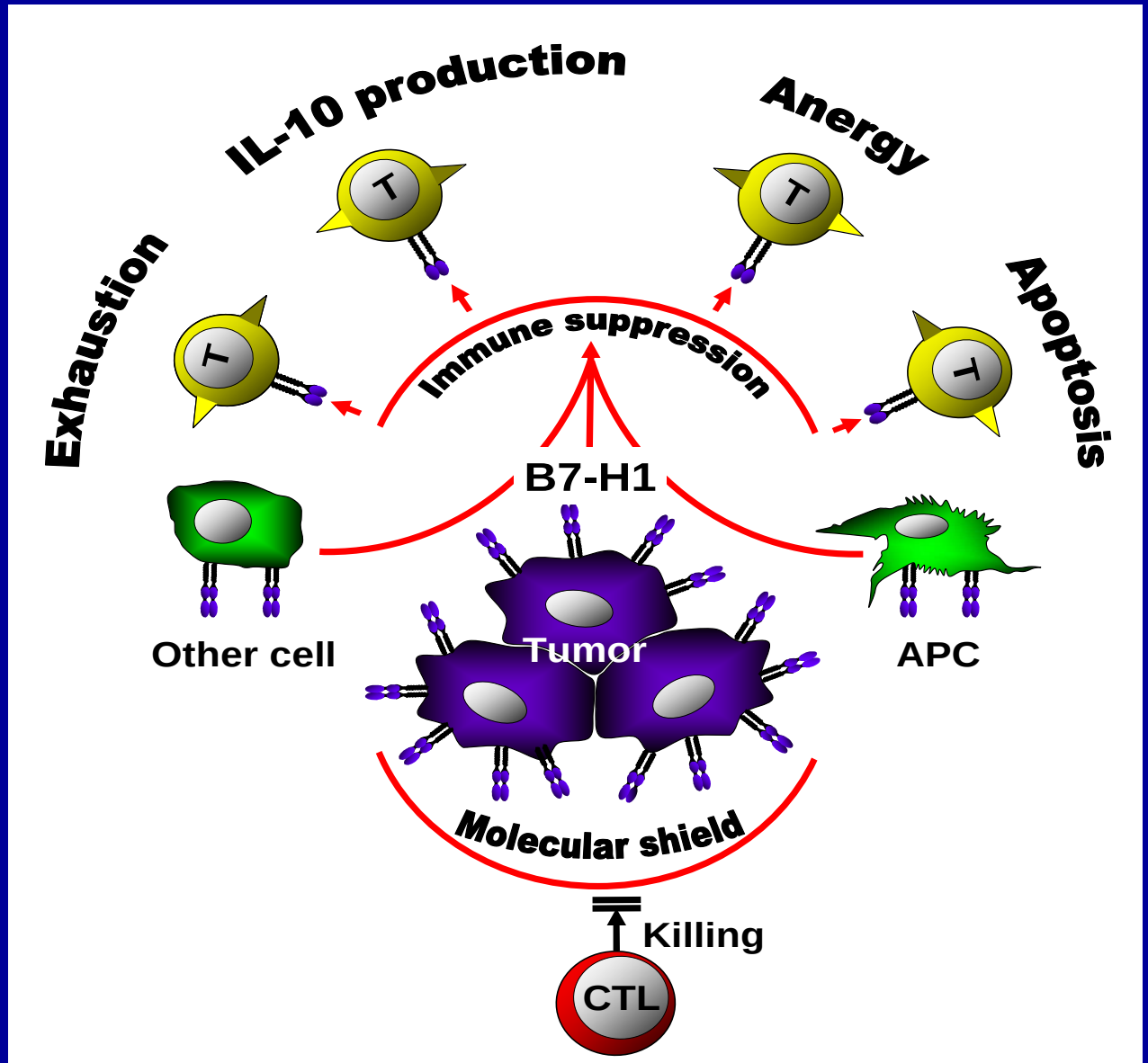
W Zou and N Restifo. Th17 cells, tumor immunity and immune therapy. 10:248-256, Nature Reviews Immunology, 2010

I. Inhibitory and stimulatory B7 imbalance



Nat Med, 2003, 2004; J Exp Med, 2006, Cancer Res, 2003-2011

Mechanisms of inhibitory B7-H1 (PD-L1) in the evasion of T cell-mediated immunity



Clinical response: it is REAL

2013 Science Breakthrough

June 2, 2012
New England Journal of Medicine

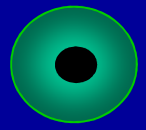
A. Topalian et al: anti-PD-1 treatment
18-36% patients with B7-H1^{+} tumors had an objective response.

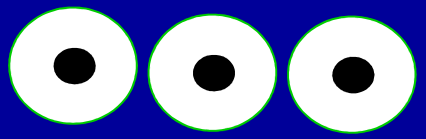
B. Brahmer et al: anti-PD-L1 (B7-H1) treatment
Anti- B7-H1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers

II. T cell subset imbalance

Effector T cells

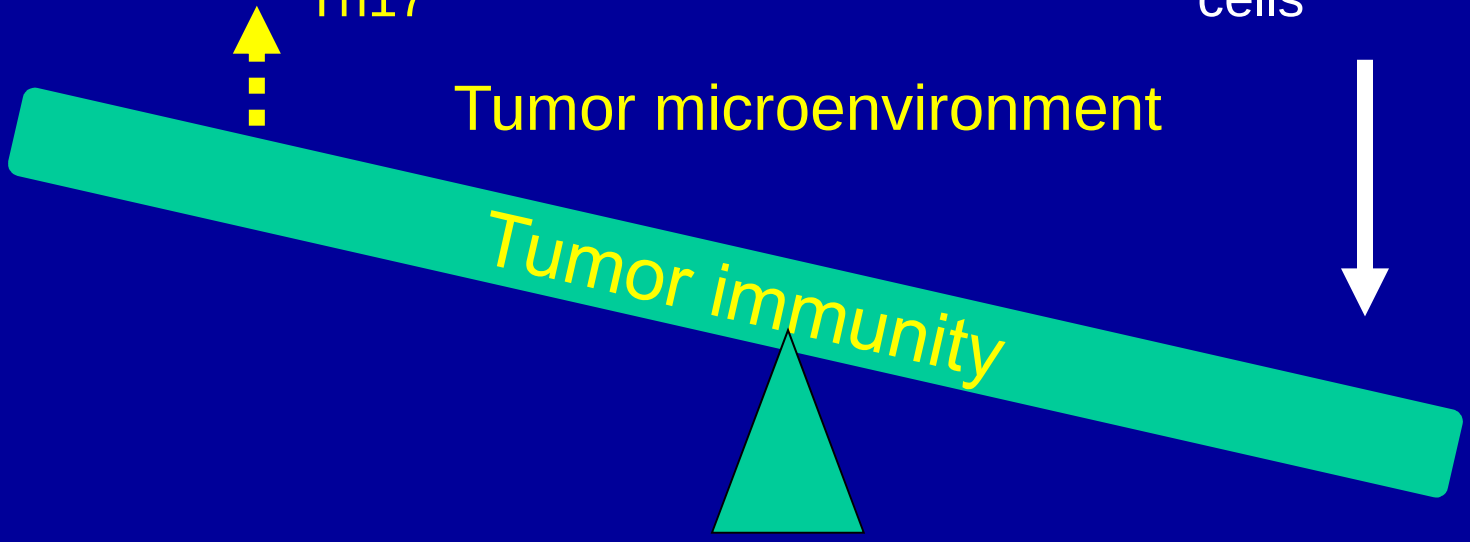
Regulatory T cells





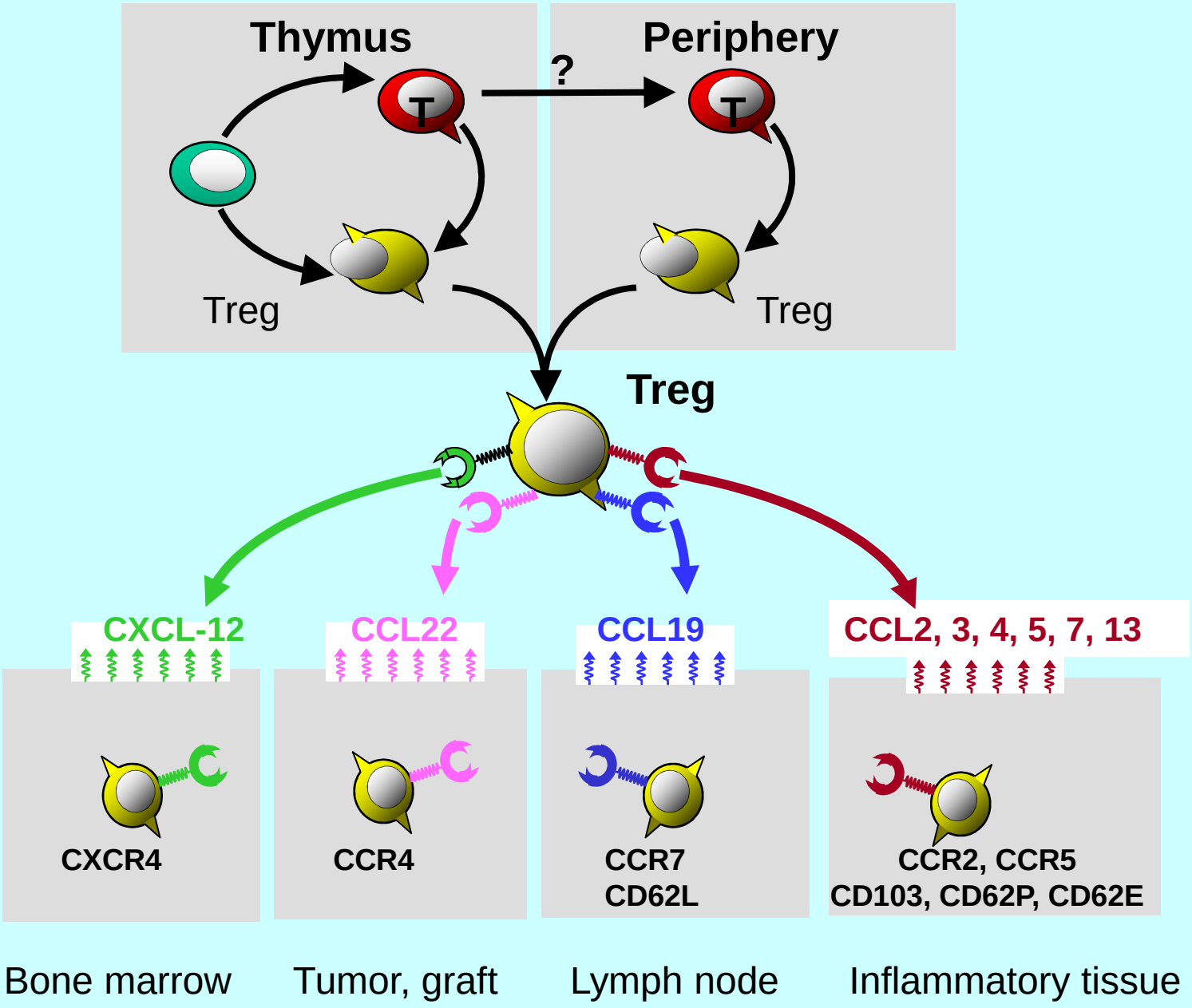
Effector CTL
Efector $CD4^+$ T cells including Th17

$IL10^+CD8^+$ suppressive T cells
$CD4^+CD25^+$ suppressive T cells



Nat Med, 2003, 2004, 2007, 2012; Science Translational Medicine, 2011; Blood, 2006, 2009, 2011; J Immunol, 2002-2011; Cancer Res, 2003-2012; Oncoimmunology, 2012; Immunity, 2014

Chemokines/receptors and Treg site/organ trafficking

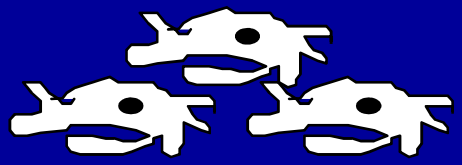


III. APC subset imbalance

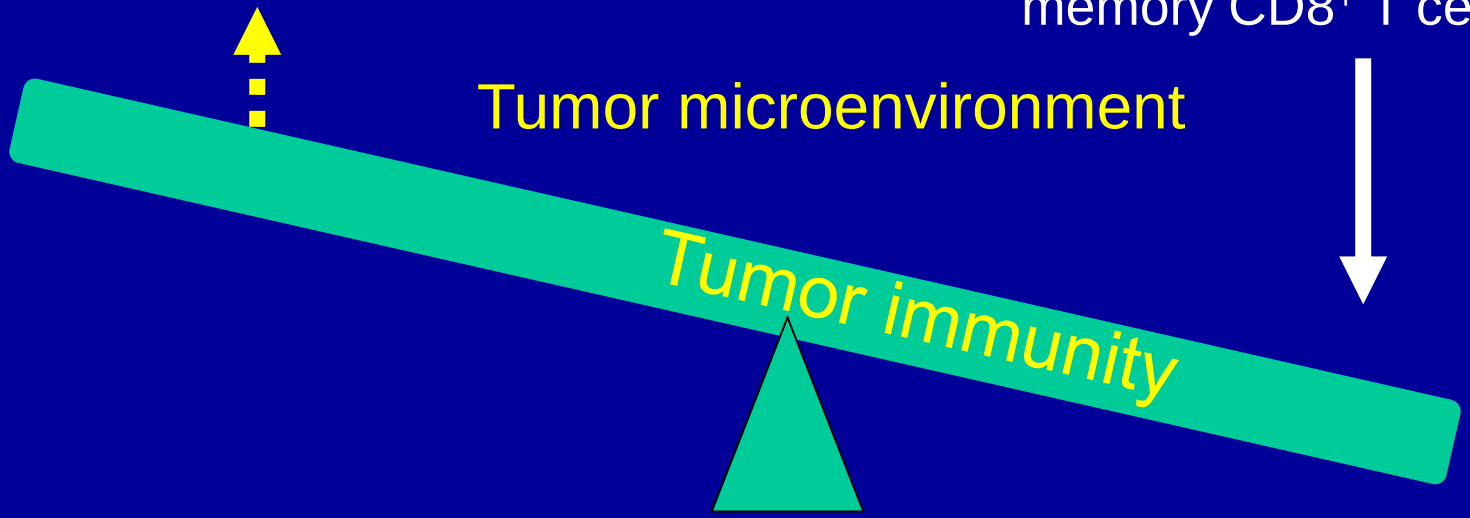
MDC

Potent IL-12, Th-1 polarization,
TAA-specific effector memory CTL

PDC, MDSC, immature DC



No IL-12, Th-2 polarization,
TAA-specific IL10^{+} central
memory CD8^{+} T cells?



Nat Med, 2001, 2003, 2004; J Exp Med, 2006, J Hepatol, 2012
J Immunol, 2002-2011; Cancer Res, 2003-2011; Immunity, 2013

Boost tumor immunity

Immune elements	Enhancing “enhancer”	Hypothesis: missing, insufficient
T cells	T cell therapy	Strategy: supplementation
Dendritic cells (DC)	DC vaccine	
NK cells	LAK cell injection	
Tumor antigen (TAA)	Peptide, TAA-Vectors	Purpose: boosting immunity
Cytokines	IL2, IFNα, IL12	

Recover tumor immunity

Target immune suppressive networks

Suppressive elements	Inhibiting “inhibitor”	Hypothesis: suppressive, dysfunctional
Regulatory T cells	Control Tregs	Strategy: subversion
Regulatory DC, MDSC	Blocking suppressive signal	
Self, Dominant Ag	Ag release and priming	
IL6, IL10, M-CSF, VEGF	Blocking common pathways	Purpose: recovering immunity

B. Immune impact, Key to cancer progression

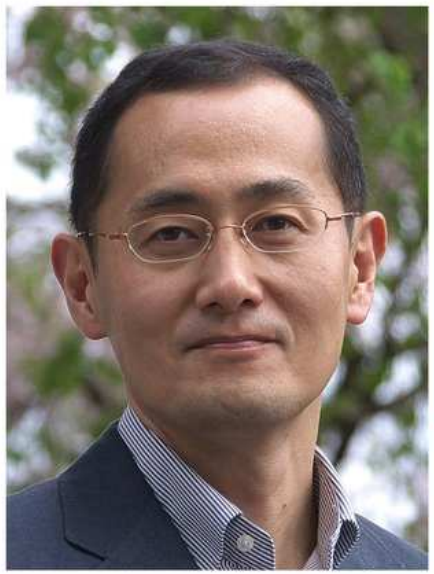
Immune elements and oncogenesis model

1. MDSCs and ovarian cancer stemness

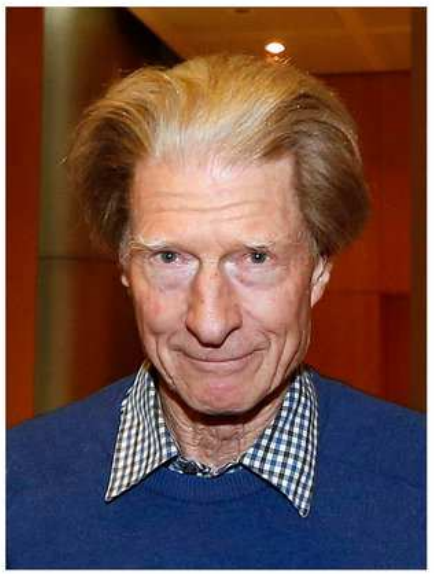
2. Th22 and colon cancer stemness

Important concepts:

Stem cells
Shinya Yamanaka
Kyoto University



John B. Gurdon
University of Cambridge



Cancer stem cells?

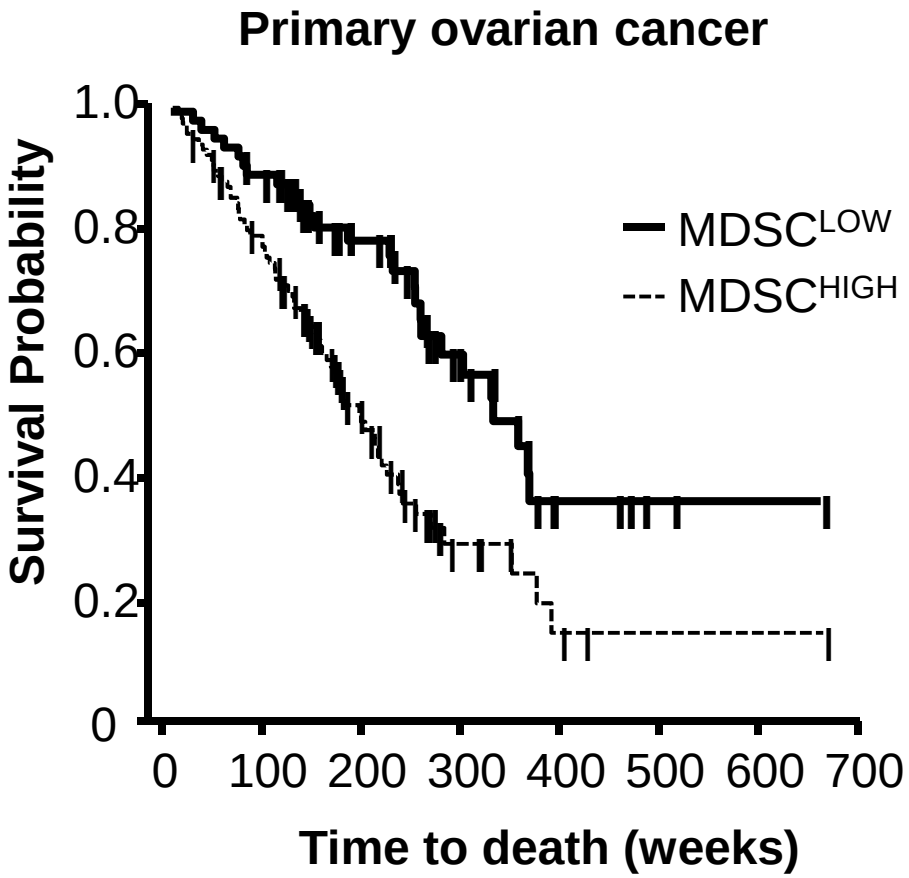
Oncogenesis model
Robert A. Weinberg
Massachusetts Institute of Technology

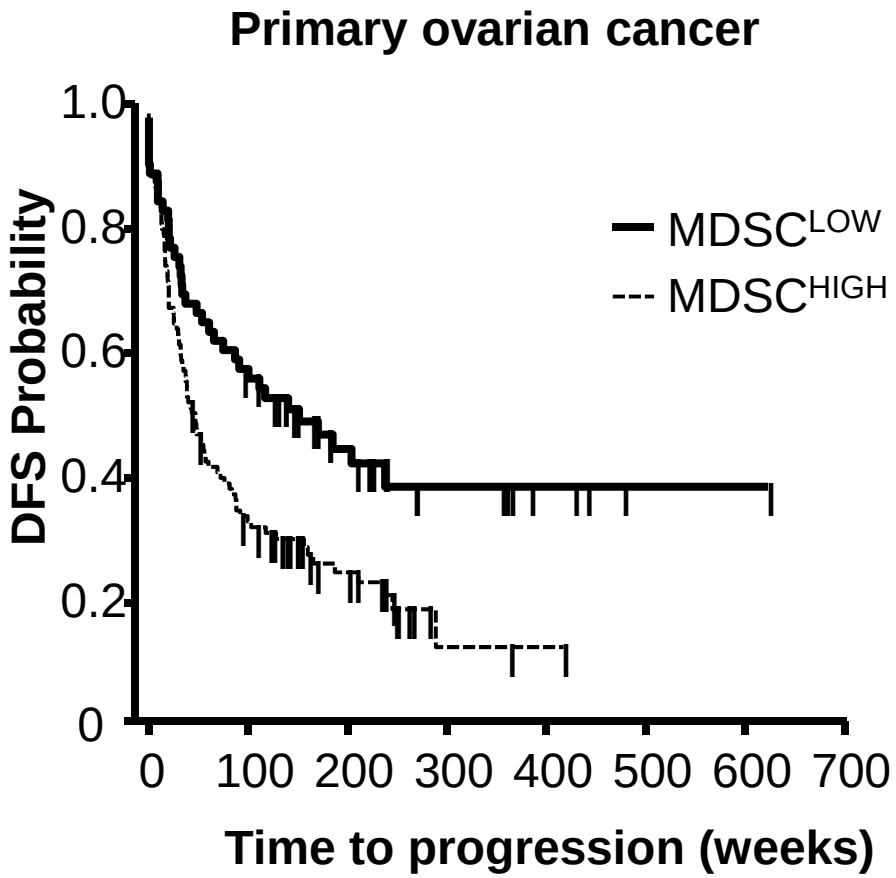
B. Immune impact, Key to cancer progression

Immune elements and oncogenesis model

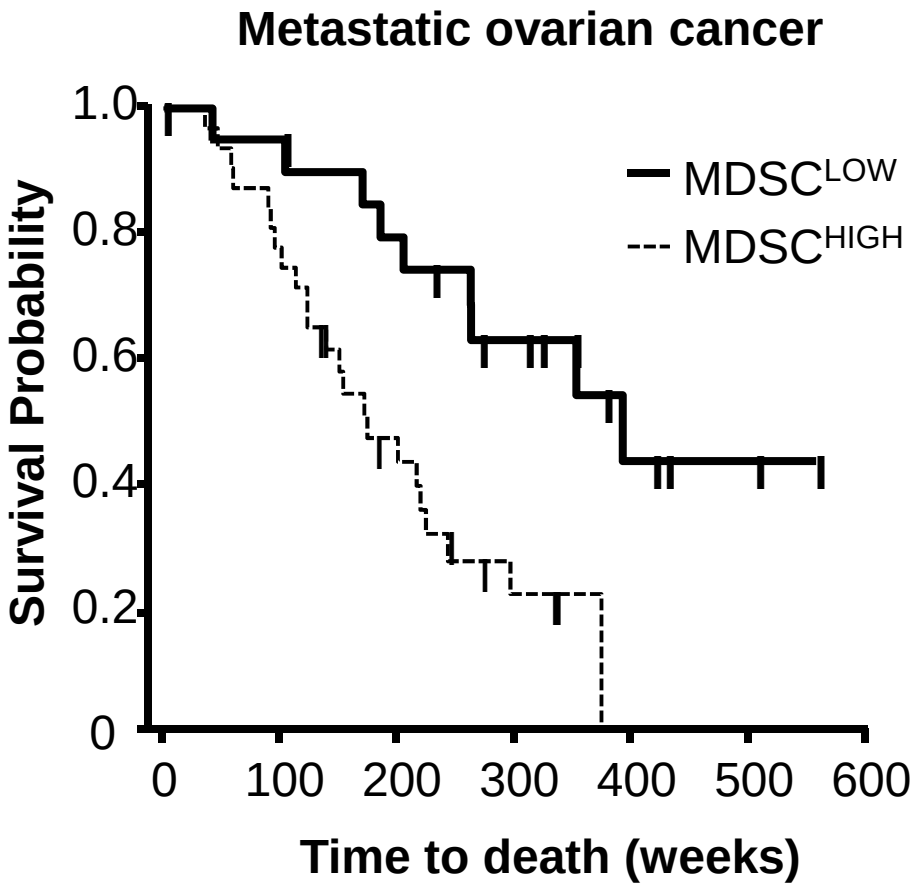
1. MDSCs and ovarian cancer stemness

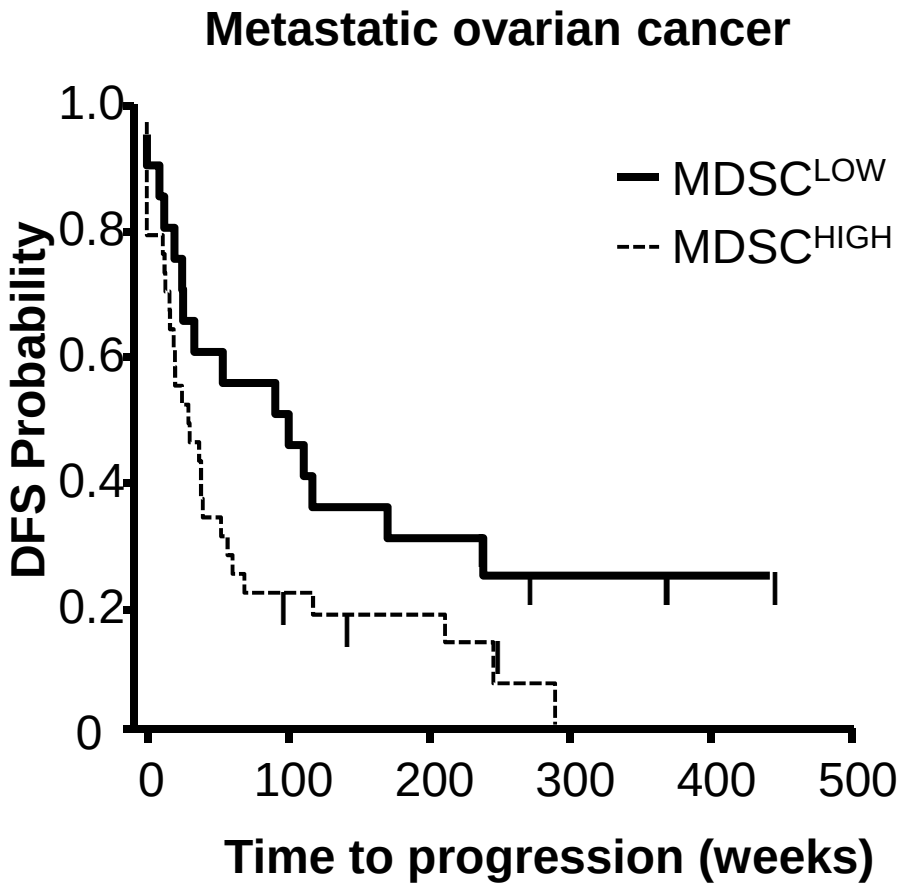
MDSCs and primary ovarian cancer progression



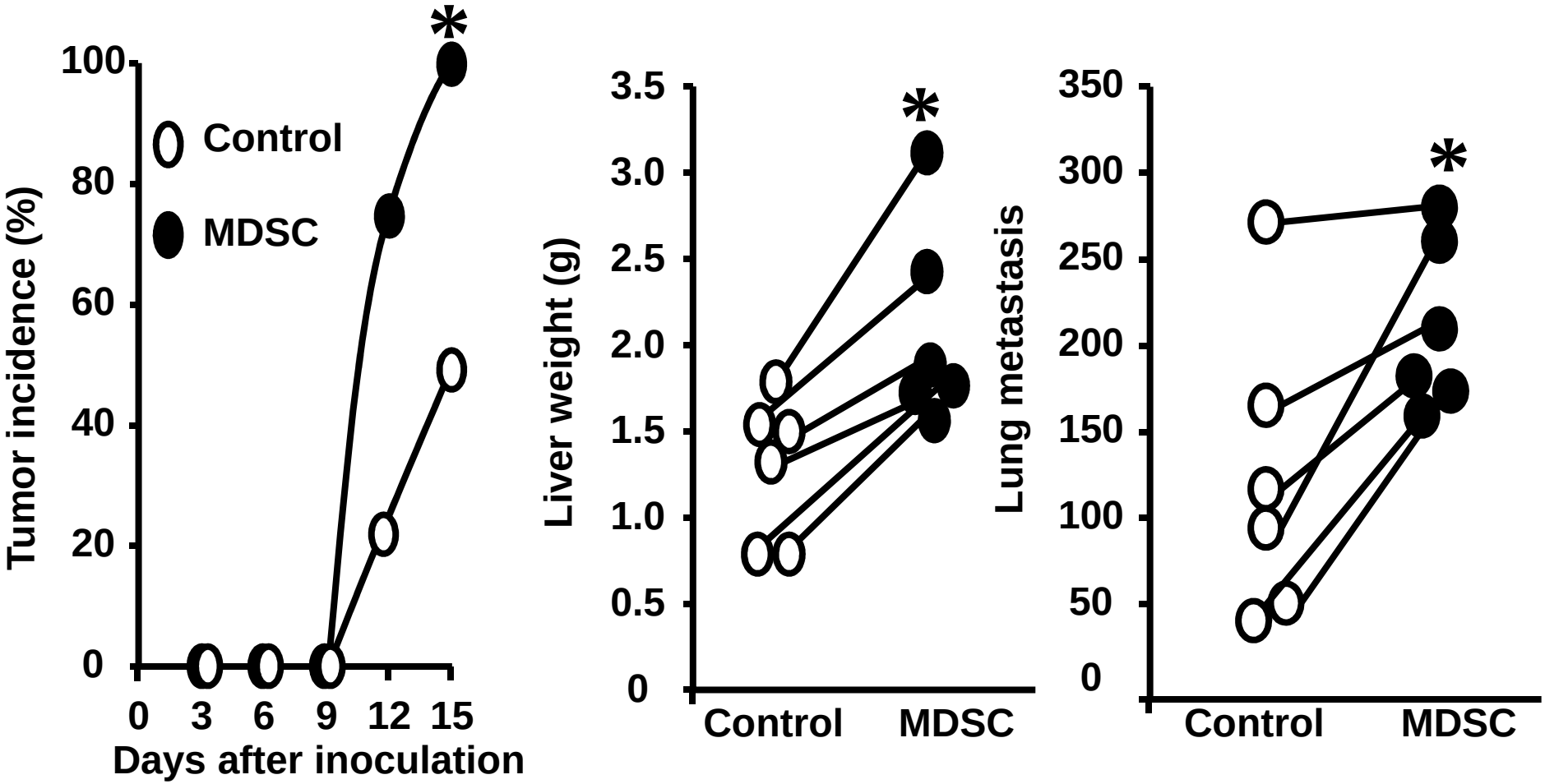


MDSCs and ovarian cancer metastasis

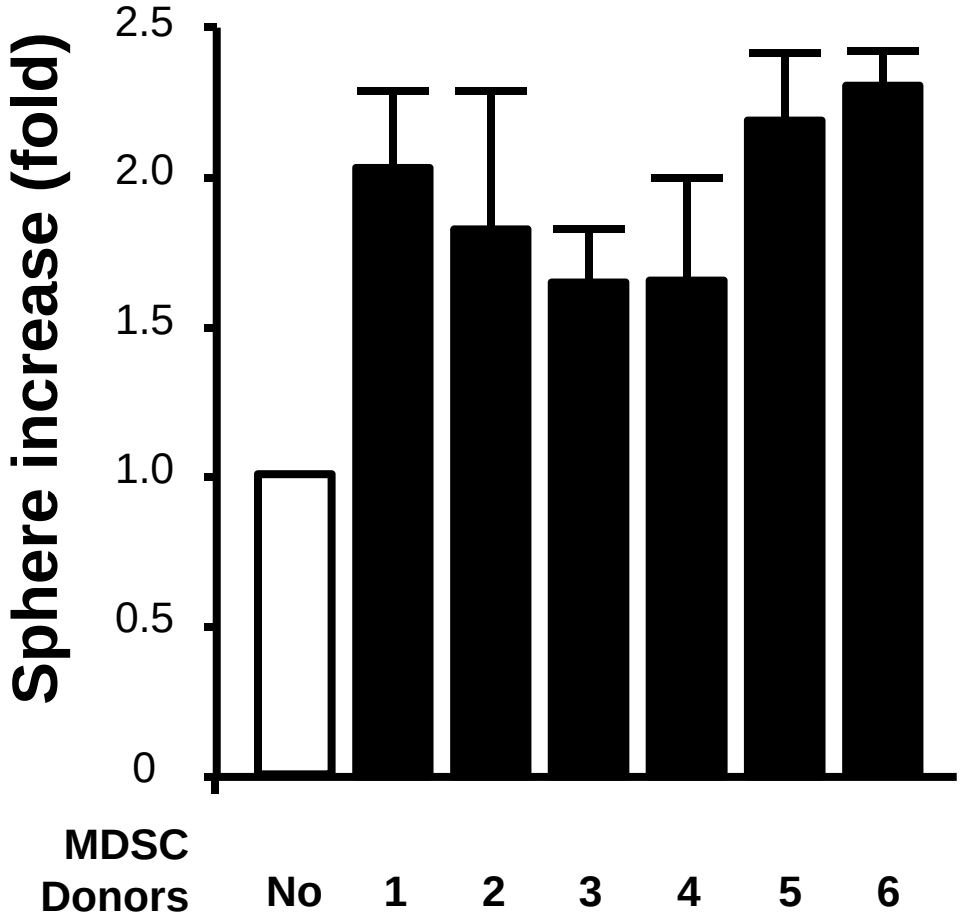


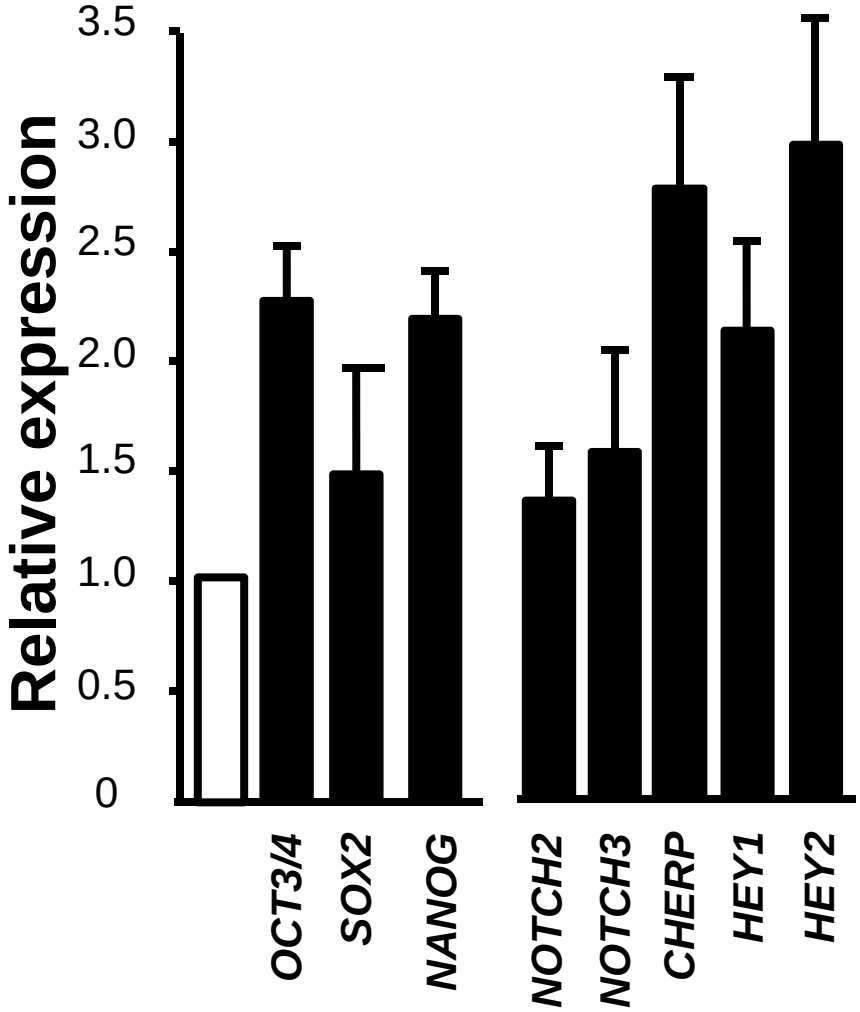


MDSCs promote ovarian cancer metastasis



MDSCs promote ovarian cancer stemness





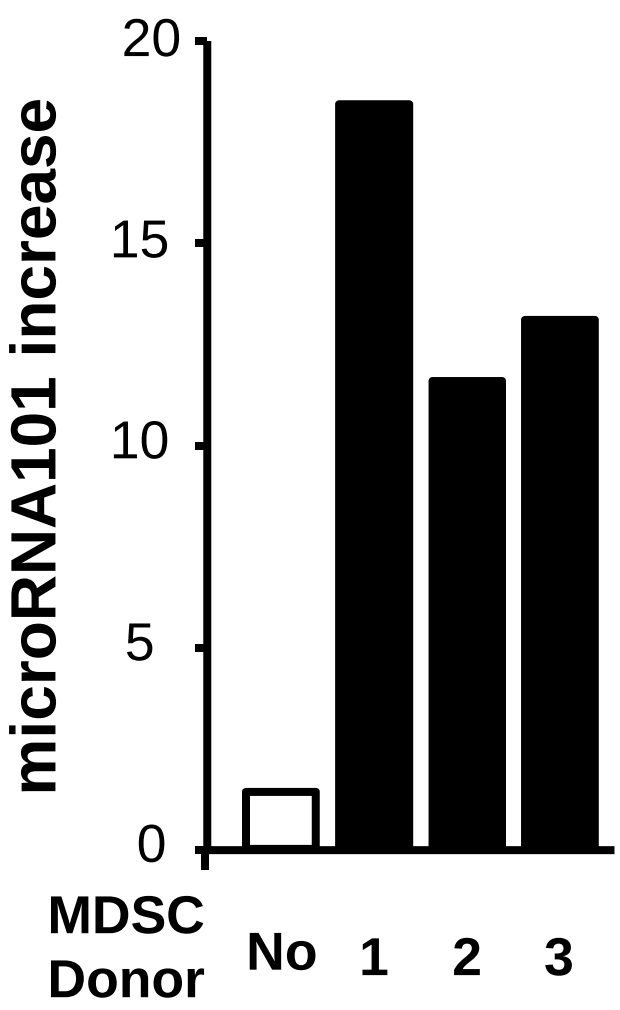
MDSCs promote ovarian cancer stemness

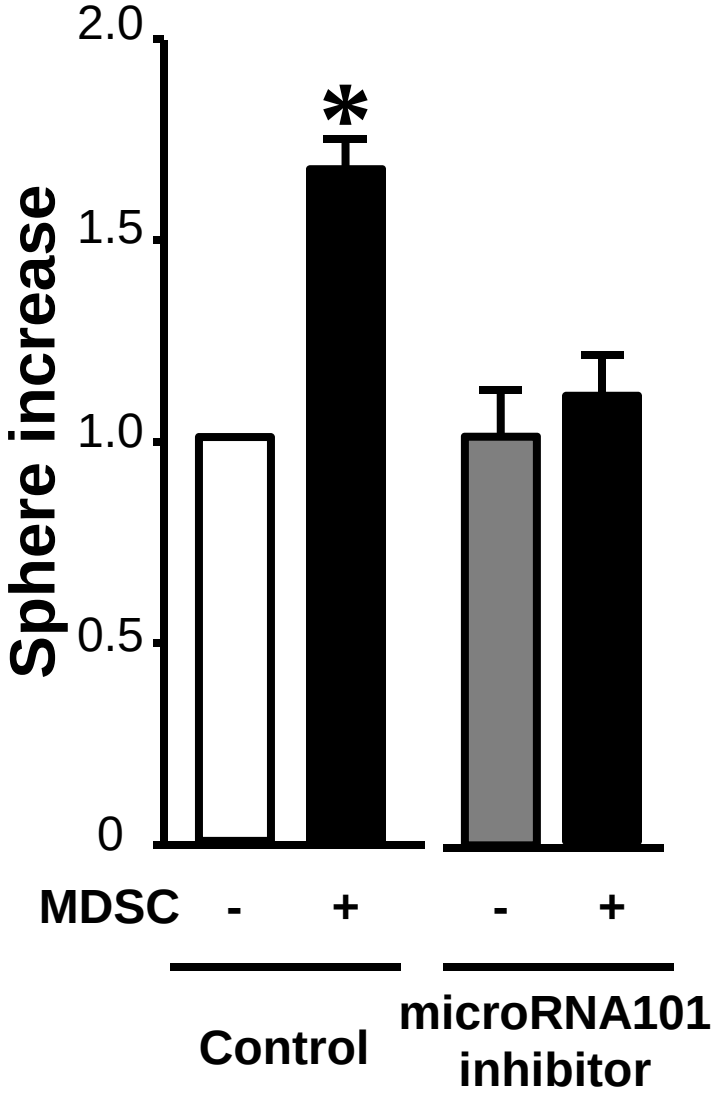
Mechanism?

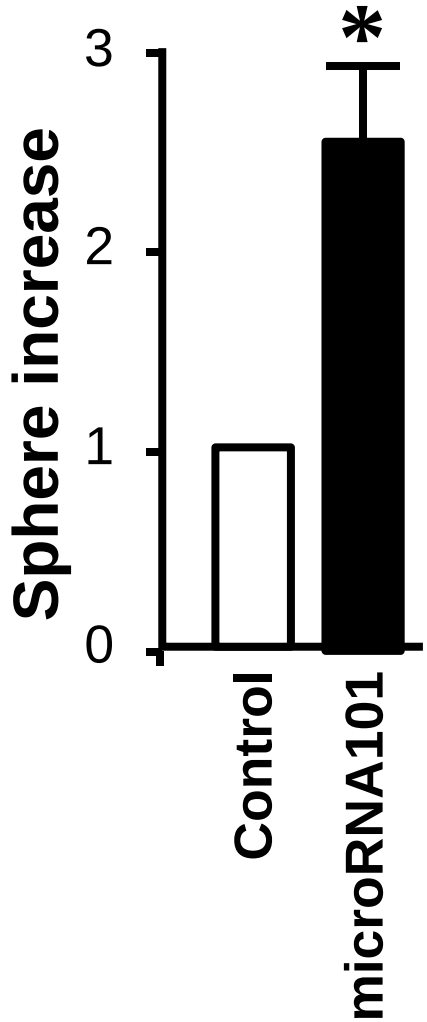
Genetics?

Epigenetics?

MDSCs stimulate microRNA101 and promote ovarian cancer stemness







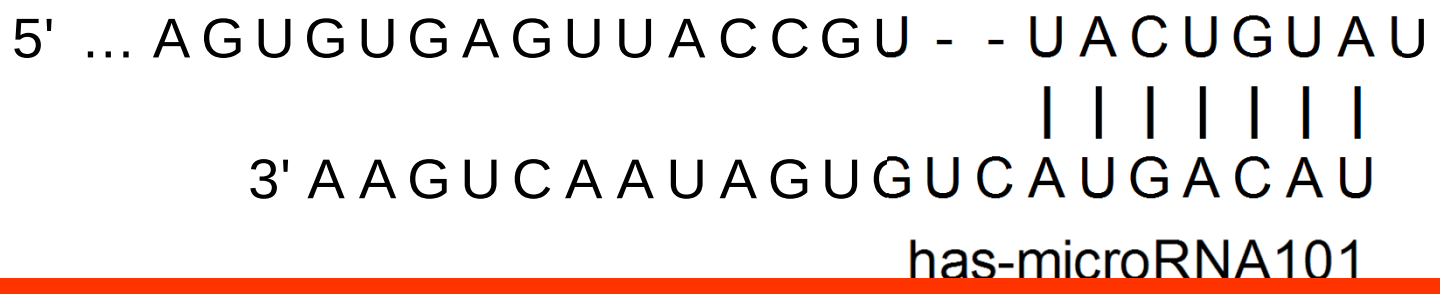
MDSCs stimulate microRNA101 and promote cancer stemness

Mechanism?

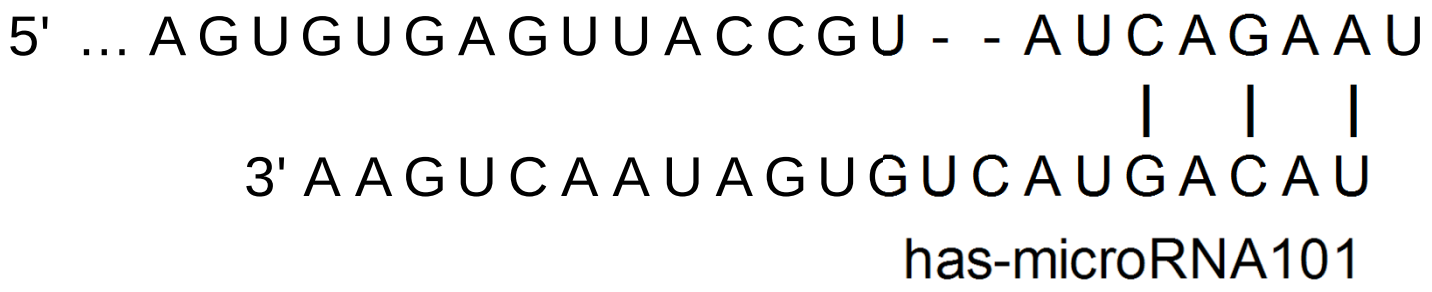
Eight repressor complexes:
SWI-SNF, PRC1, NURD,
CoREST (CtBP2), NCoR,
PRC2(EZH2), SIN3, TLE

MicroRNA101 targets CtBP2 and promotes ovarian cancer stemness

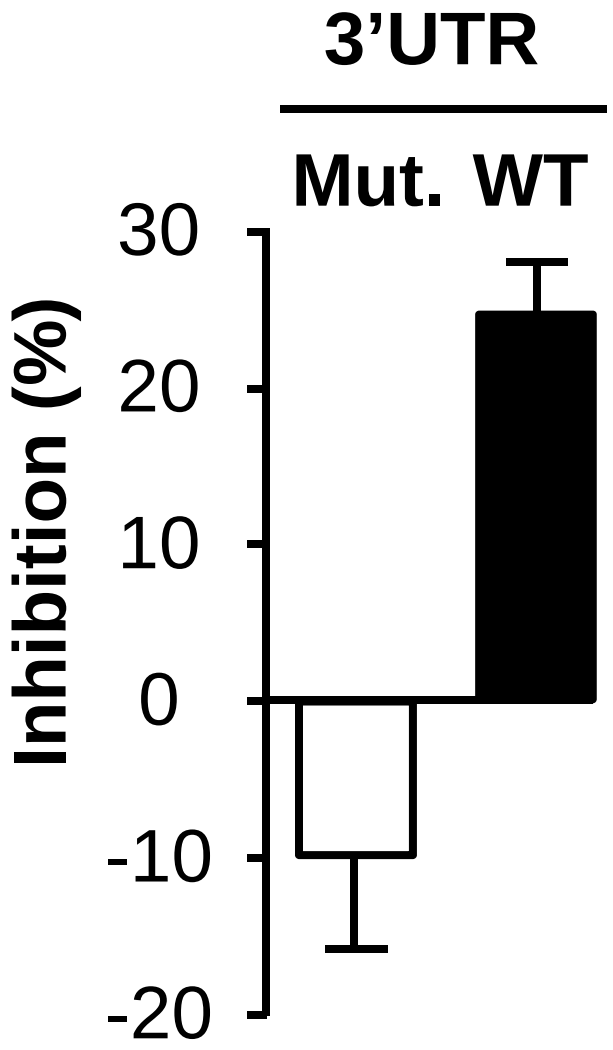
WT 3'UTR-CtBP2

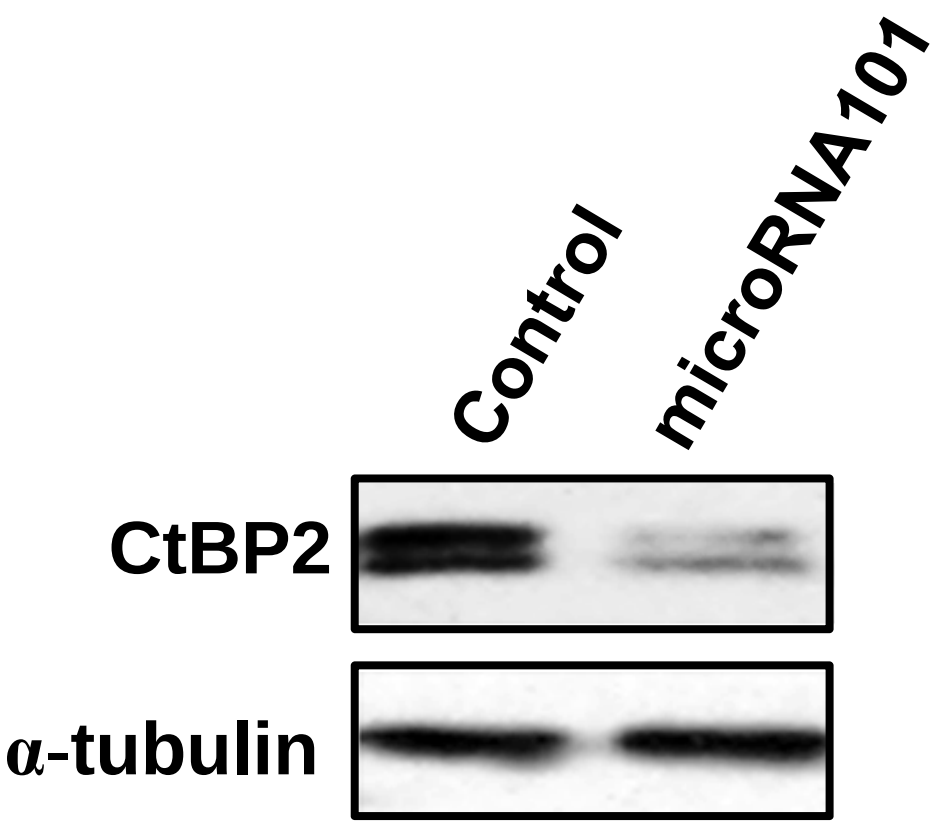


Mutant 3'UTR-CtBP2

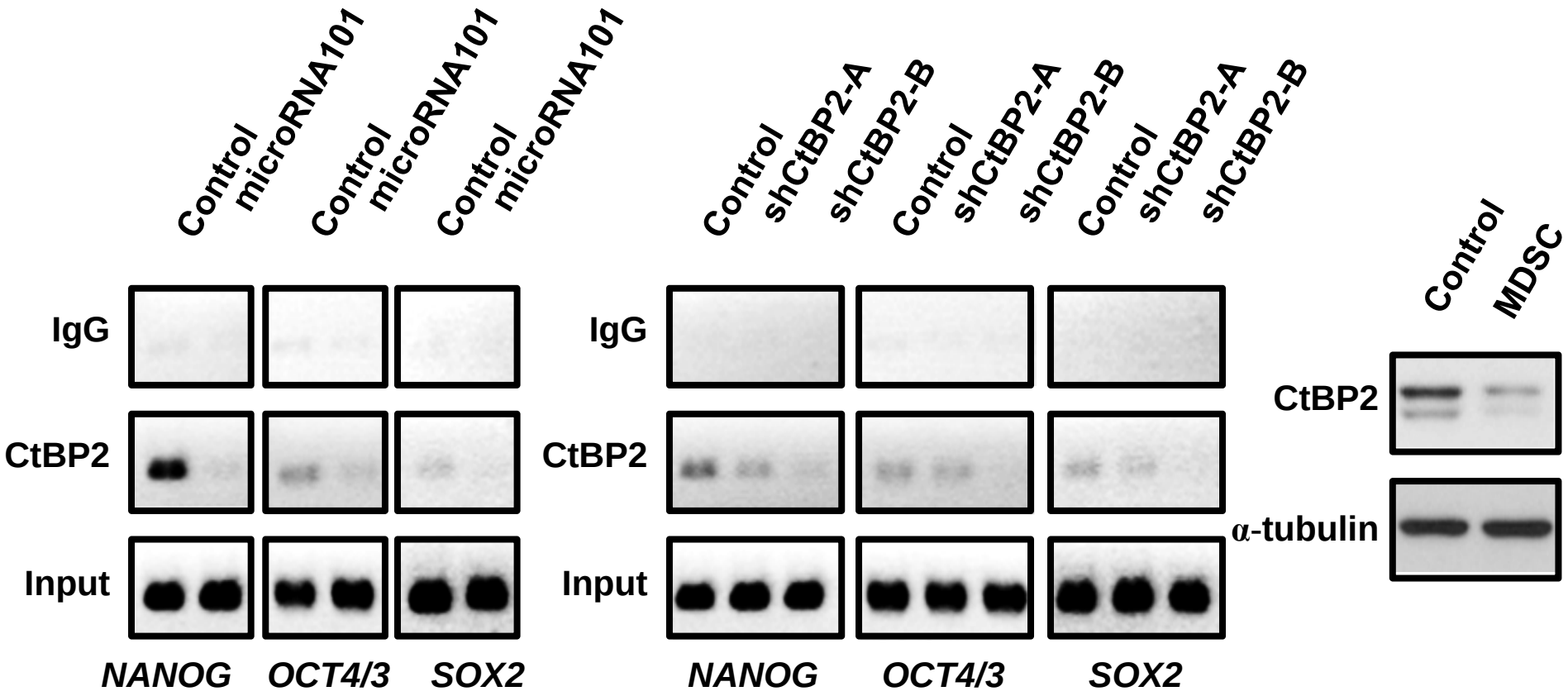


MicroRNA101 targets CtBP2 and promotes ovarian cancer stemness

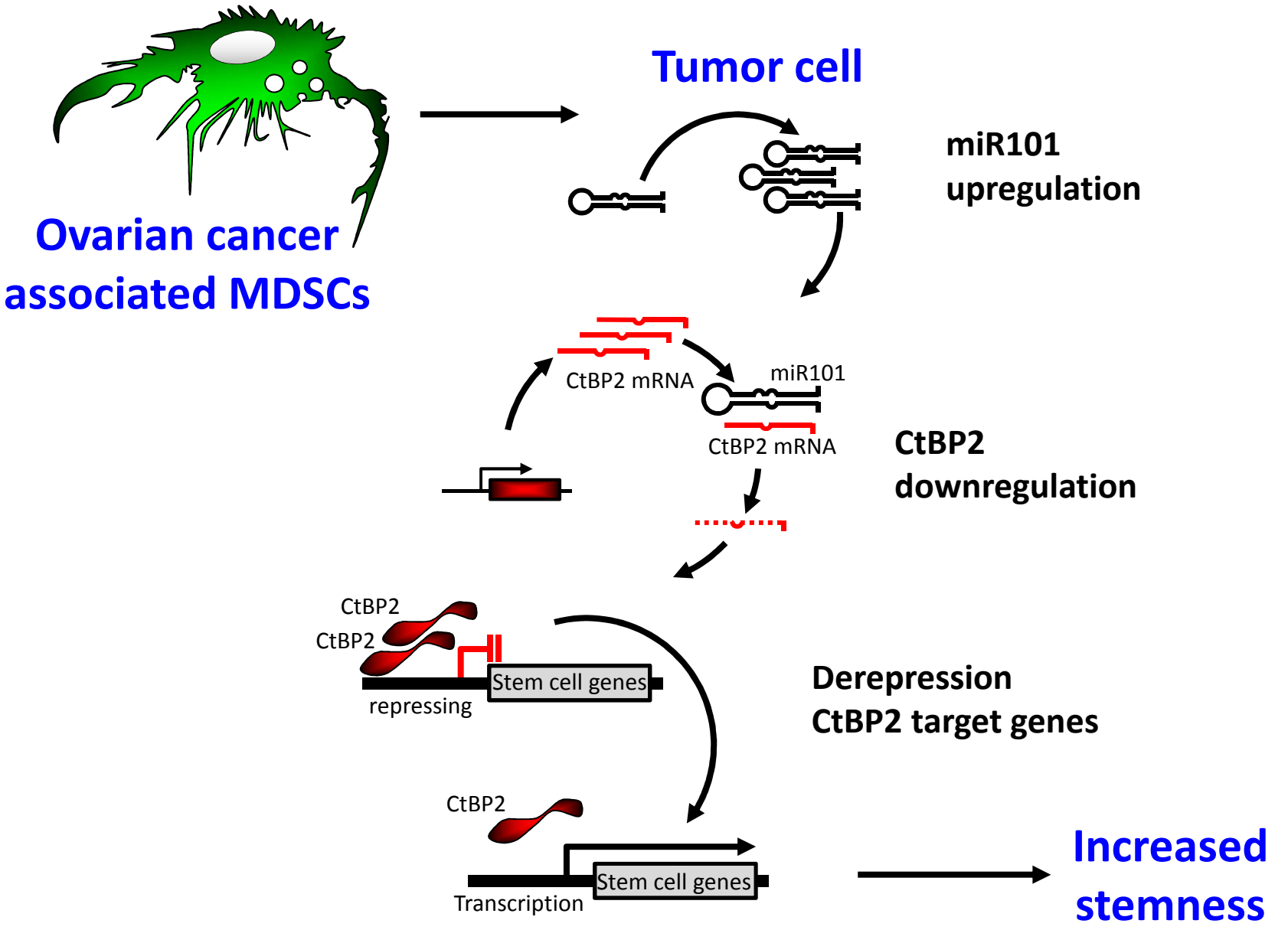




MicroRNA101 represses CtBP2 and targets core stemness genes



MDSCs support stemness via microRNA101/CtBP2



MDSCs, microRNA101 and cancer stemness

1. MDSCs: Immune suppression
Creating and maintaining immune suppressive environment

2. MDSCs: Stem niche
Promoting and sustaining cancer stem cell pool

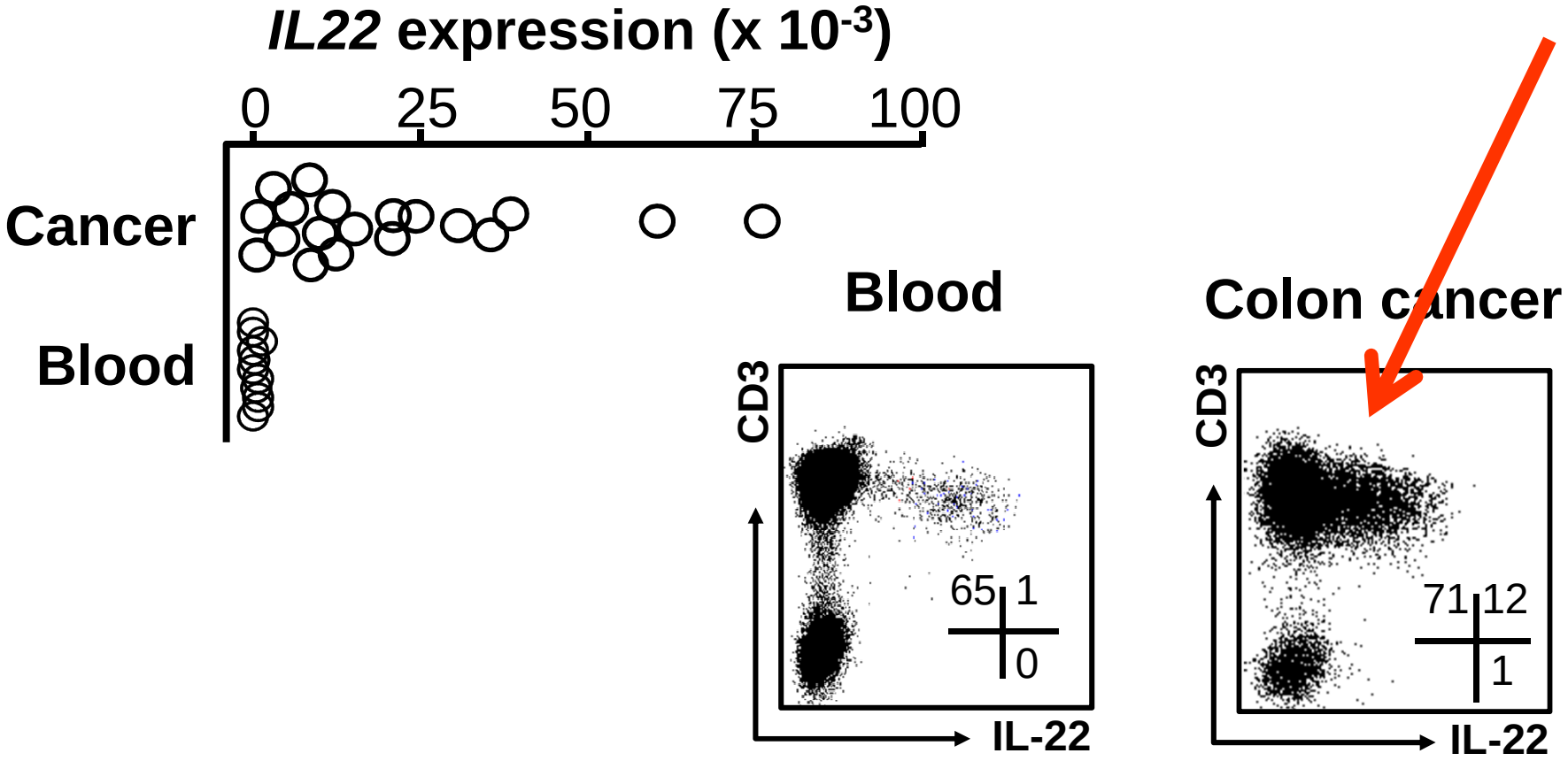
B. Immune impact, Key to cancer progression

Immune elements and oncogenesis model

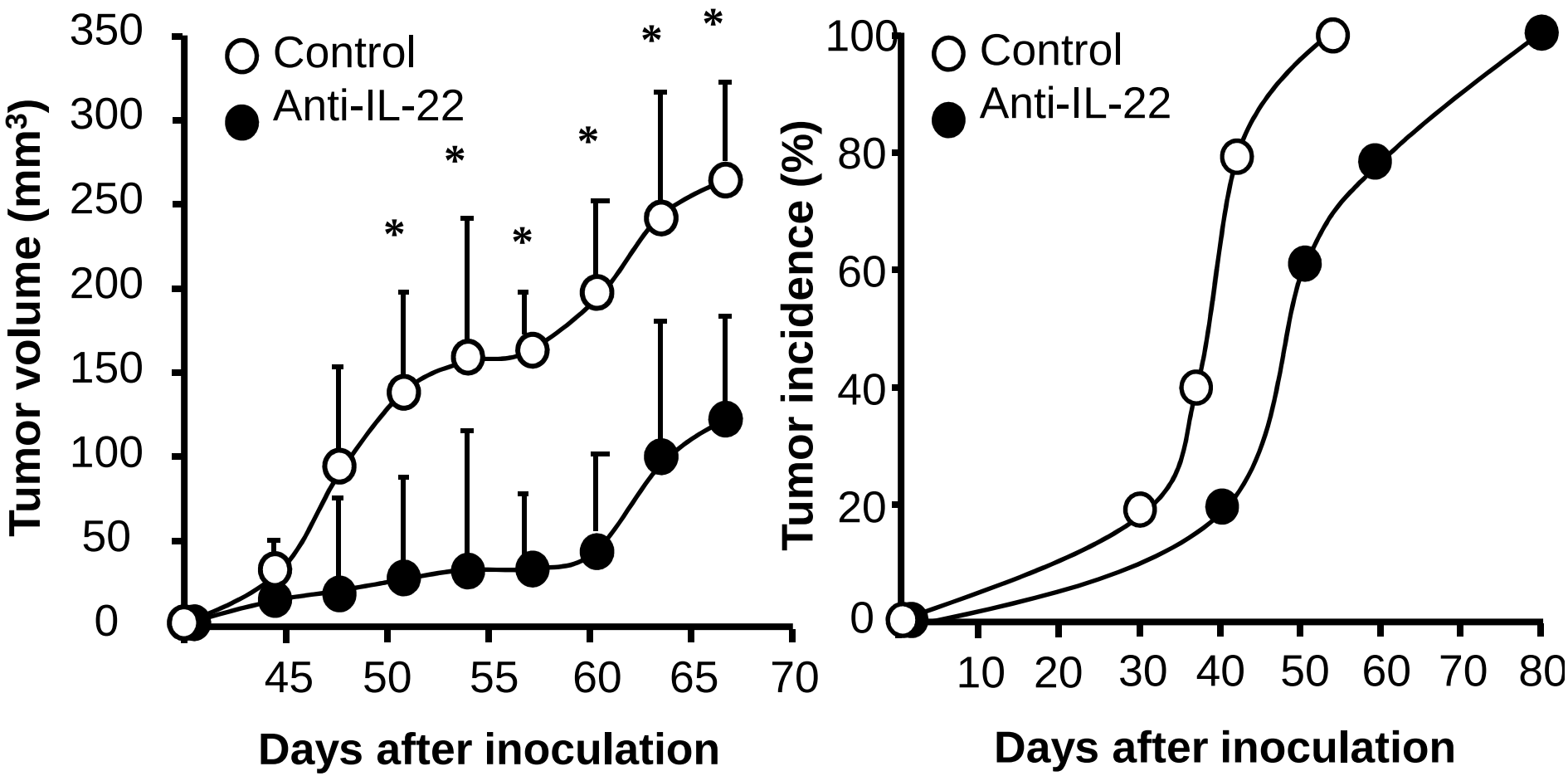
2. Th22 and colon cancer stemness

2. Th22 and human colon cancer stemnes

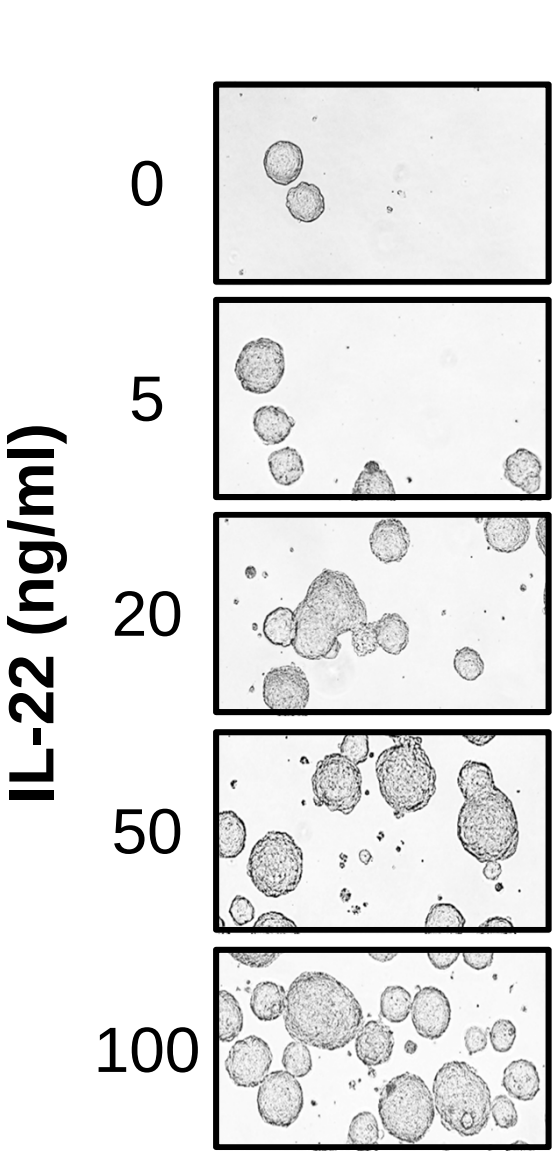
Th22 and IL-22 in the colon cancer environment

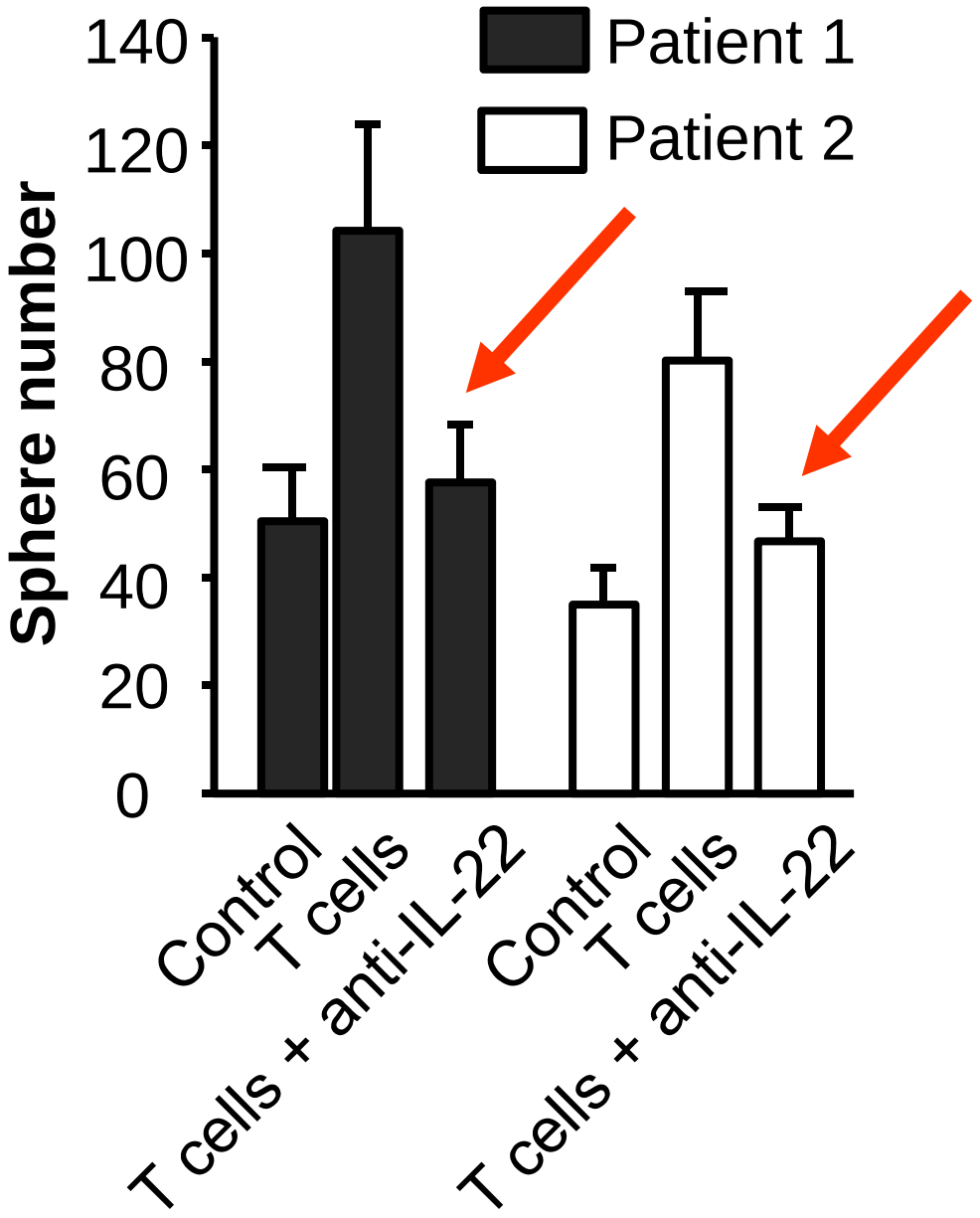


Th22-derived IL-22 promotes colon carcinogenesis

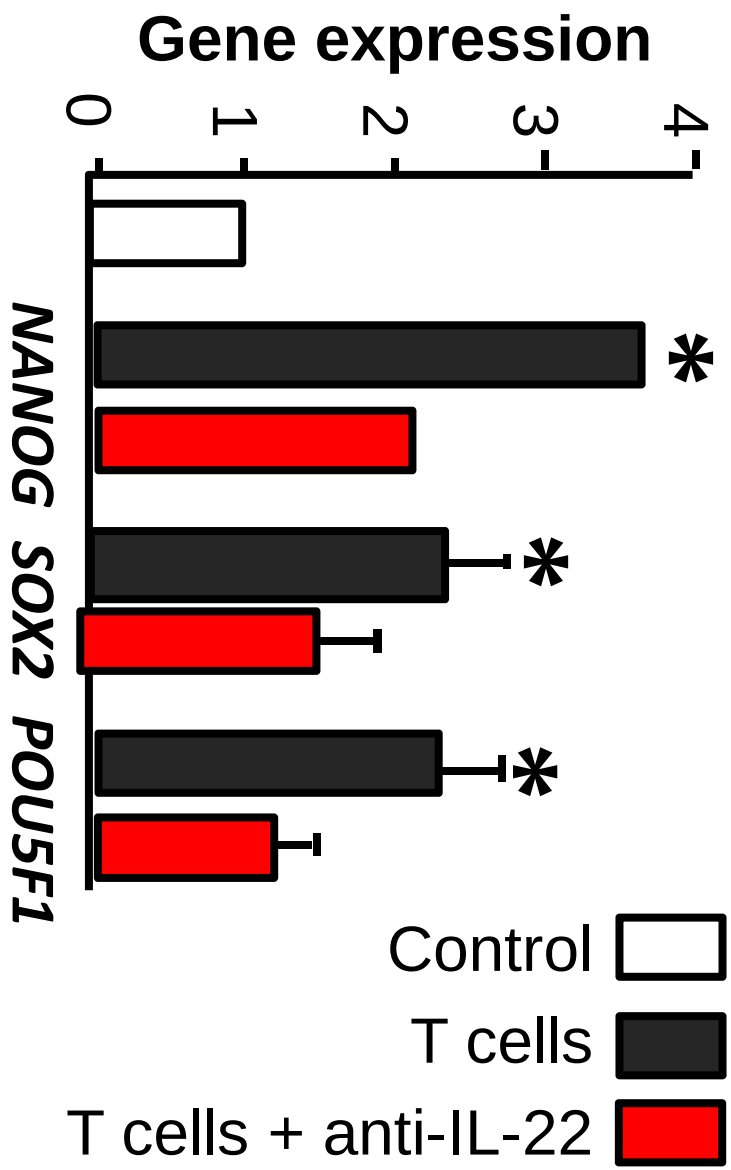


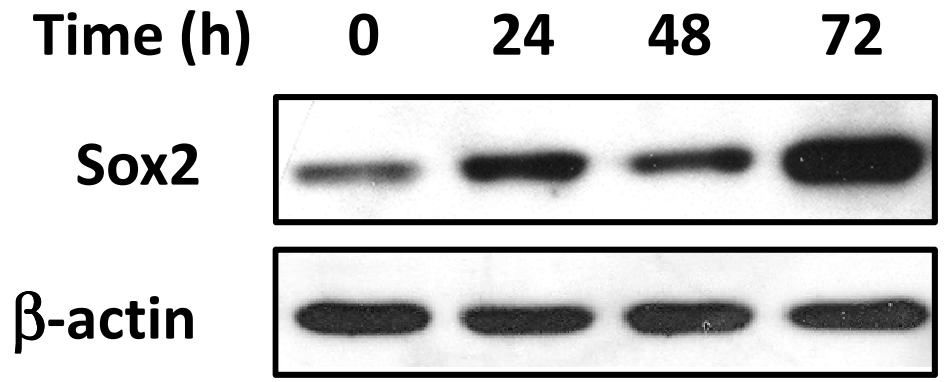
IL-22 promotes cancer spheres

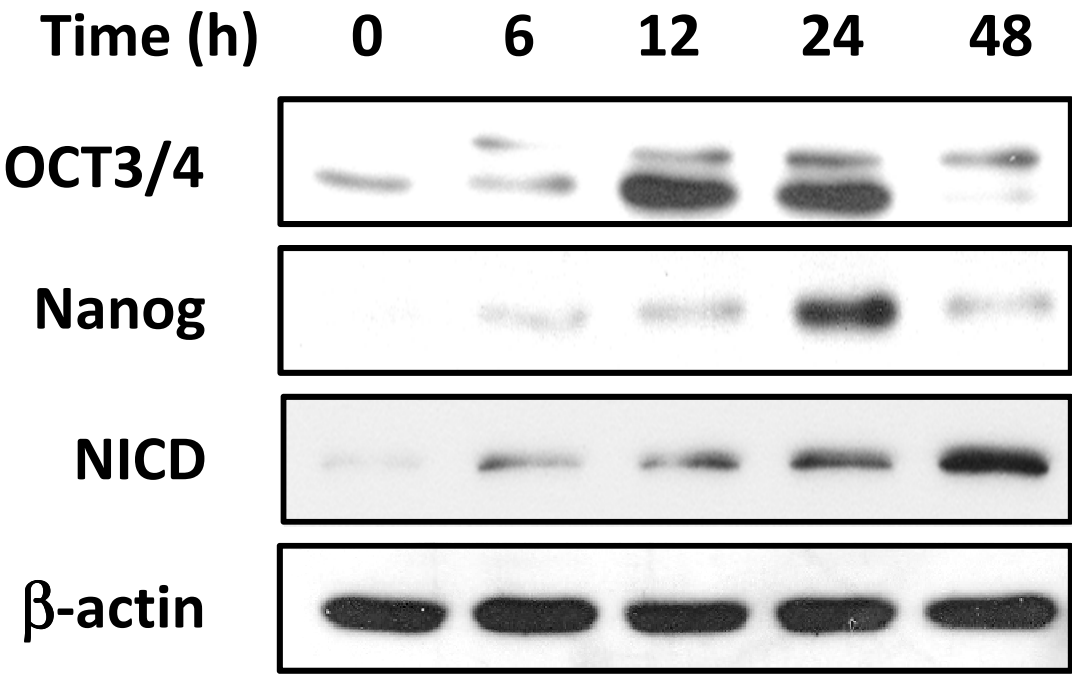




IL-22 targets core stem cell genes







Th22 cells stimulate core stem cell genes and promote cancer stemness

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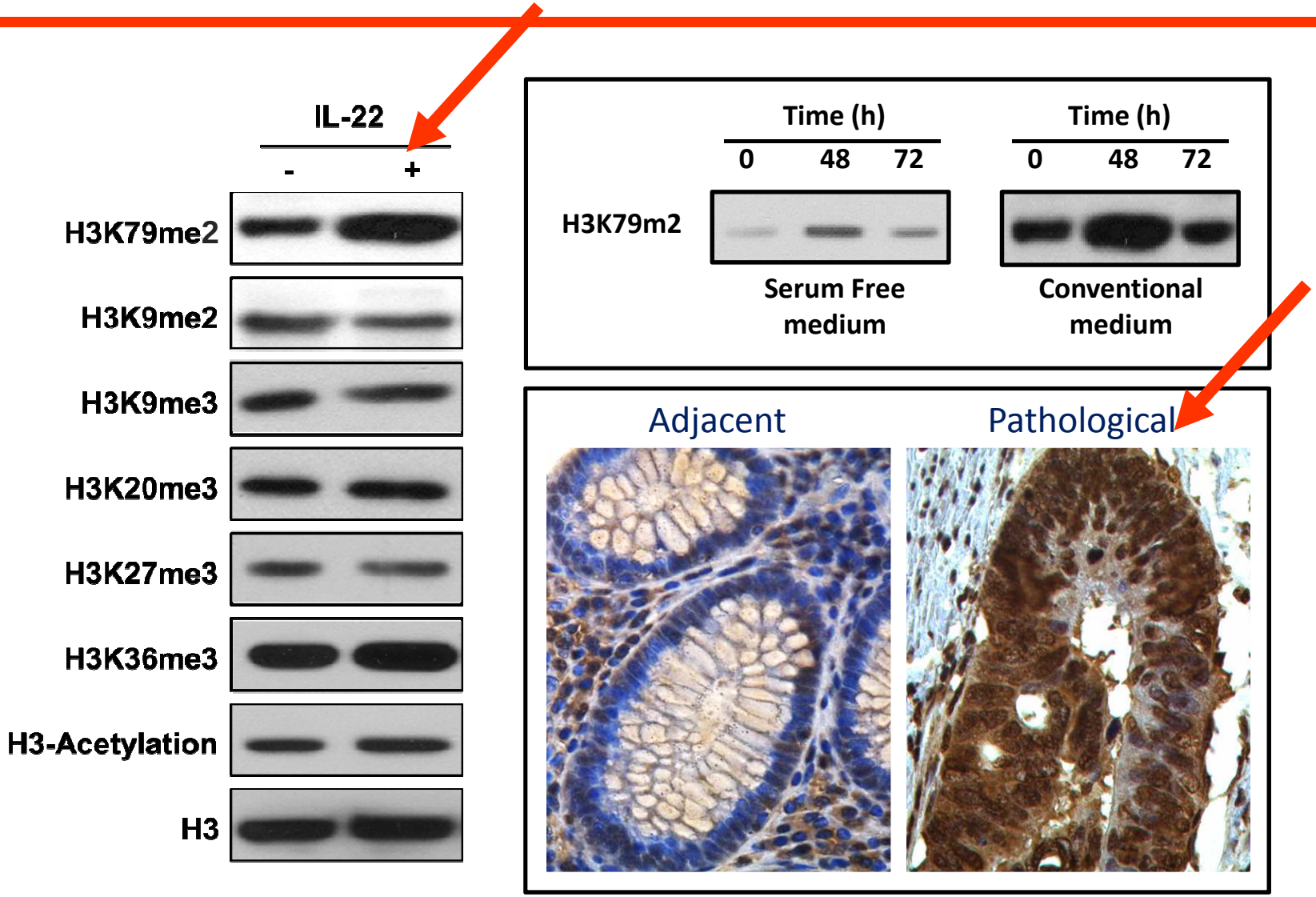
Mechanism?

Genetic?
Major transcription factor (STAT3)
Epigenetic?
Major histone marks

IL-22 induces global H3K79 di-methylation

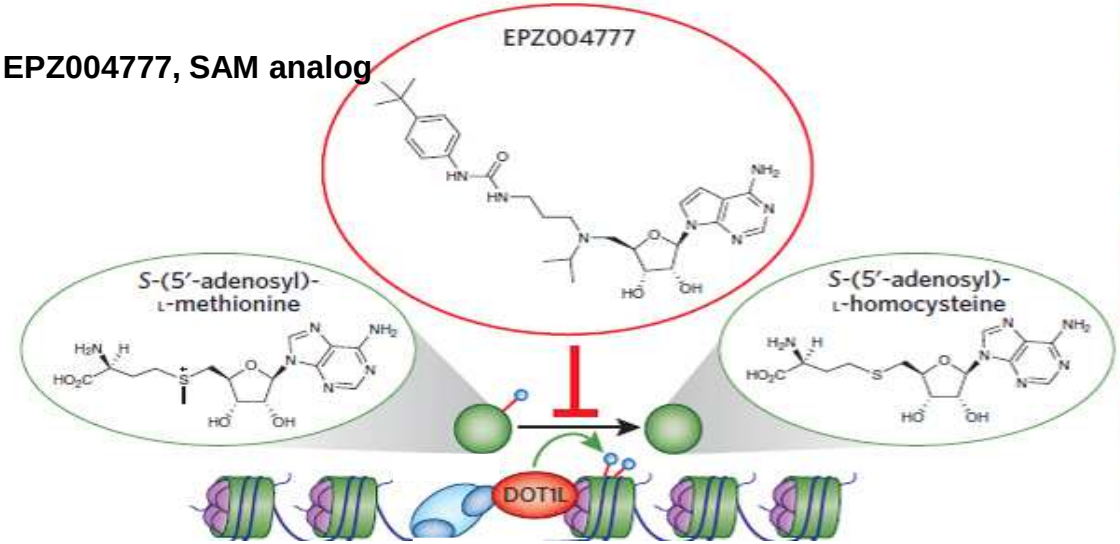


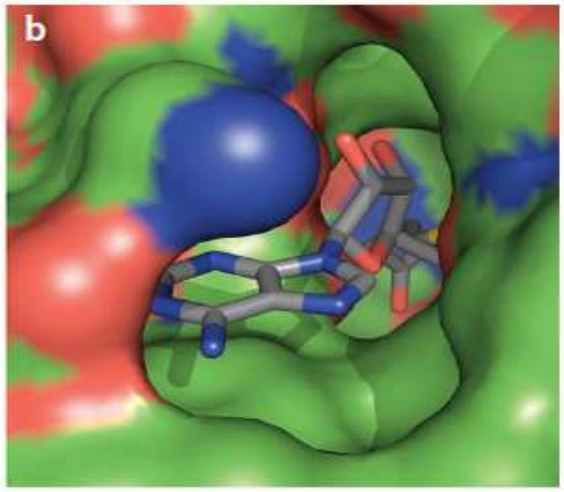
H3K79 methylation

Histone 3 Lysine 79 di-methylation (H3K79me2):

- DOT1L mediated methyltransferase
- Generally a mark for activation

EPZ004777, SAM analog

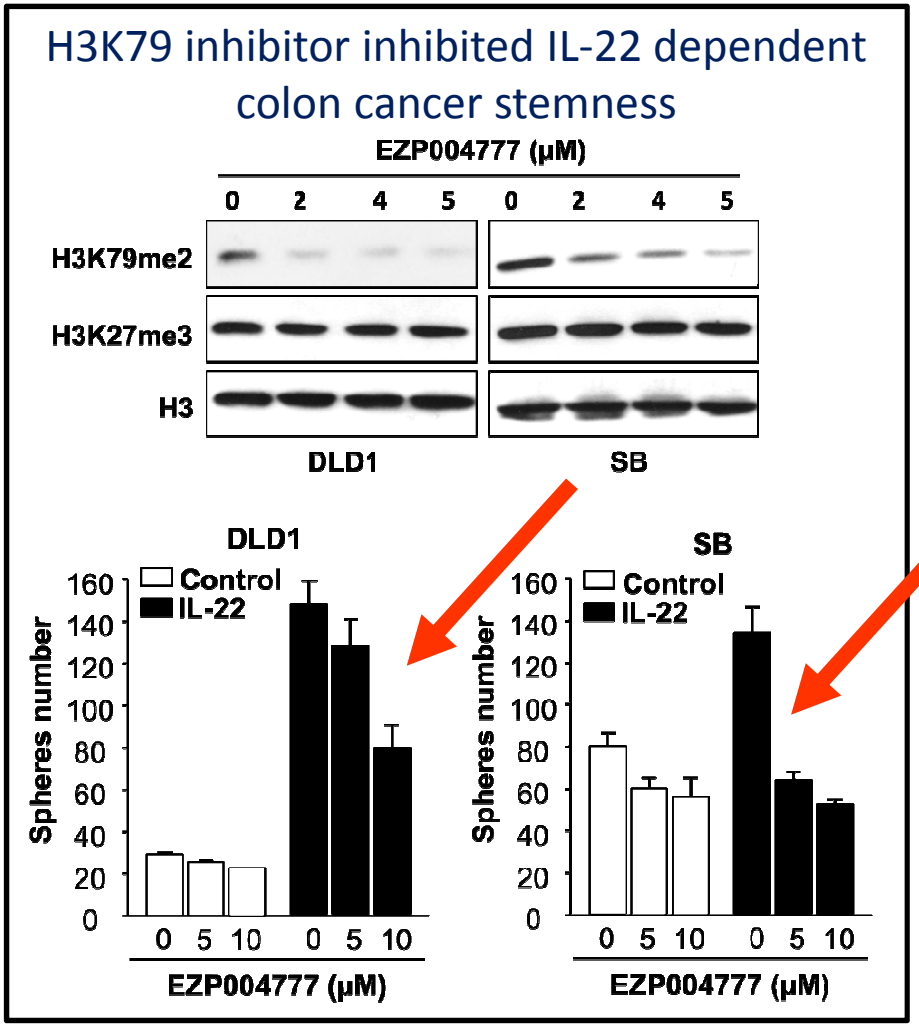


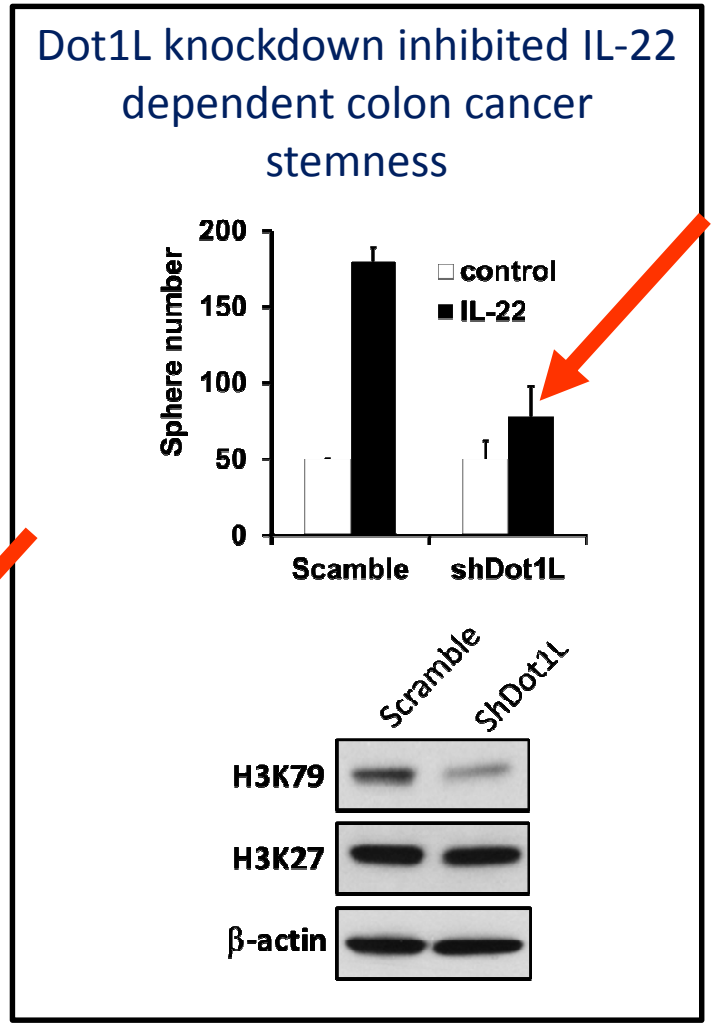


Space-filling representation of the SAM binding pocket from the DOT1L–SAM protein-ligand crystal structure

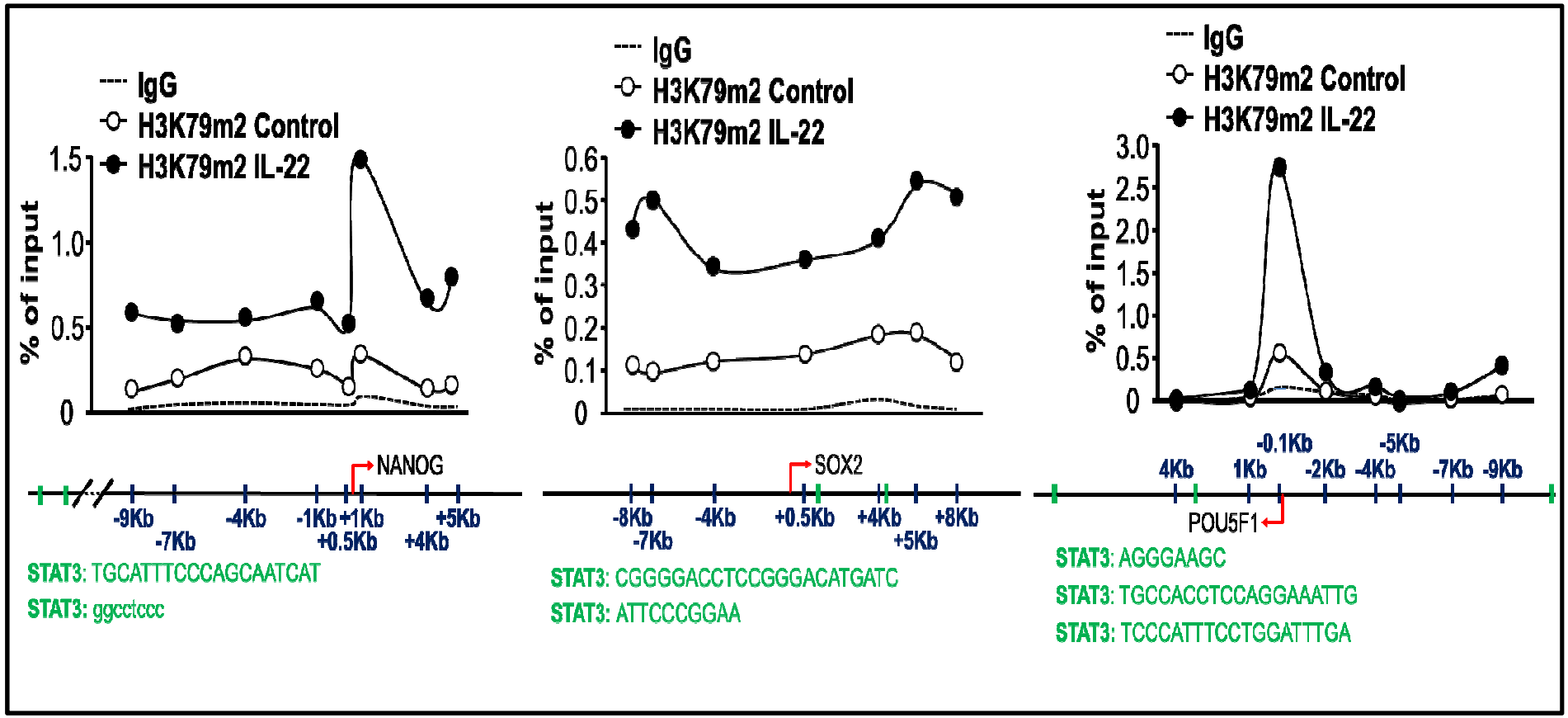
EPZ004777 is a specific DOT1L inhibitor

IL-22 induced-H3K79 di-methylation controls colon cancer stemness

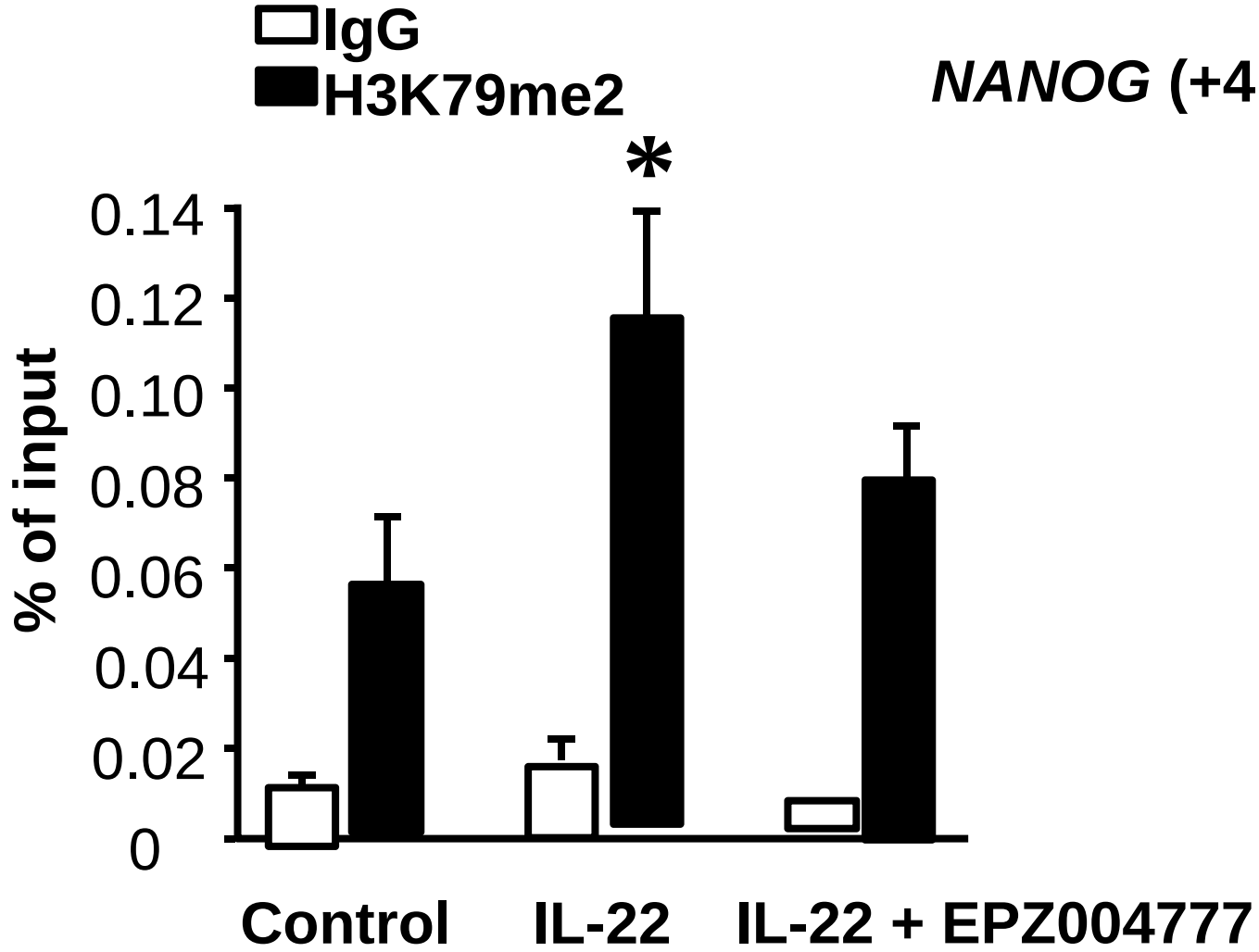




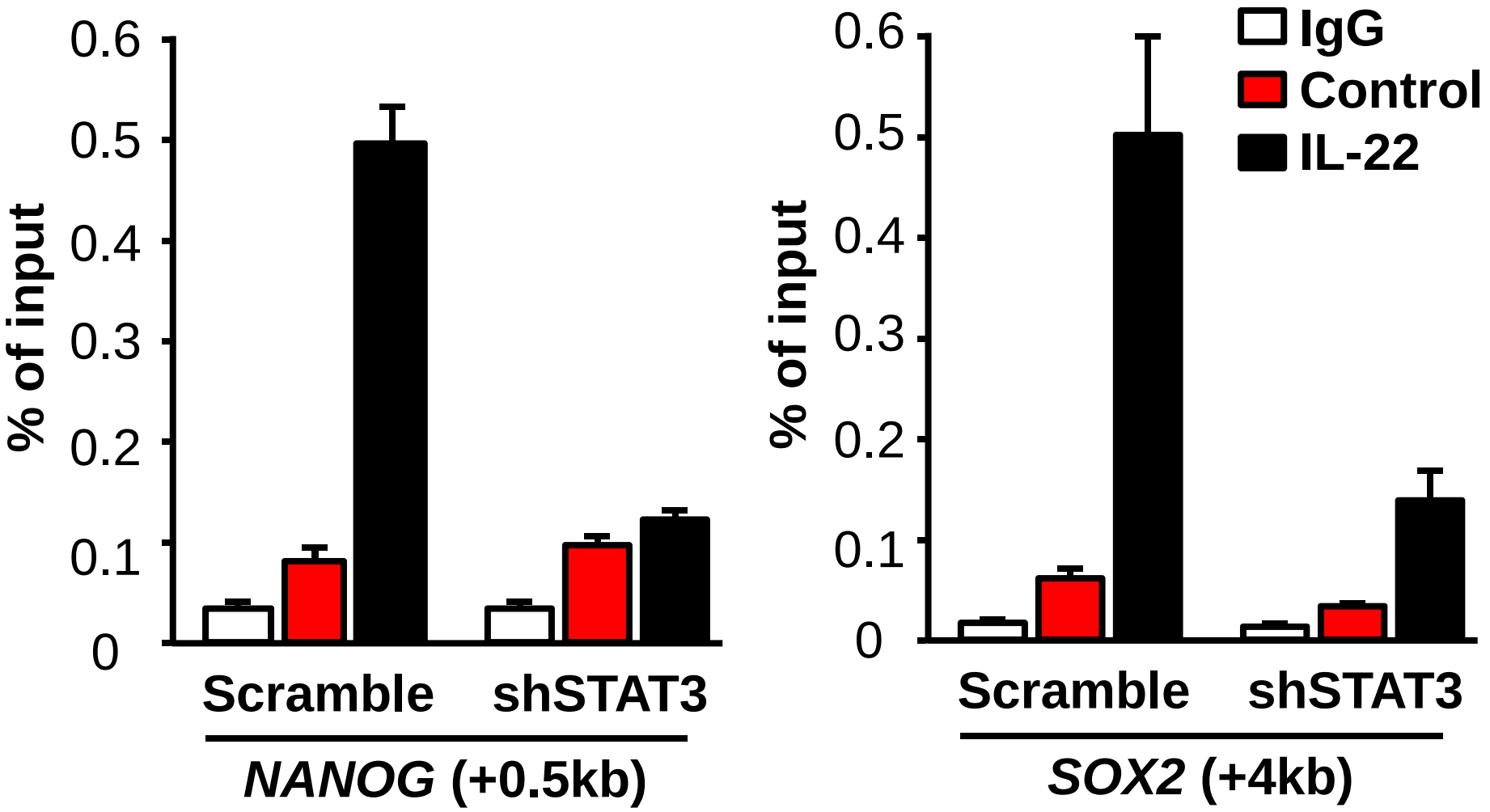
IL-22 induces H3K79 di-methylation on stem cell core gene promoters



IL-22 induces H3K79 di-methylation on stem cell core gene promoters



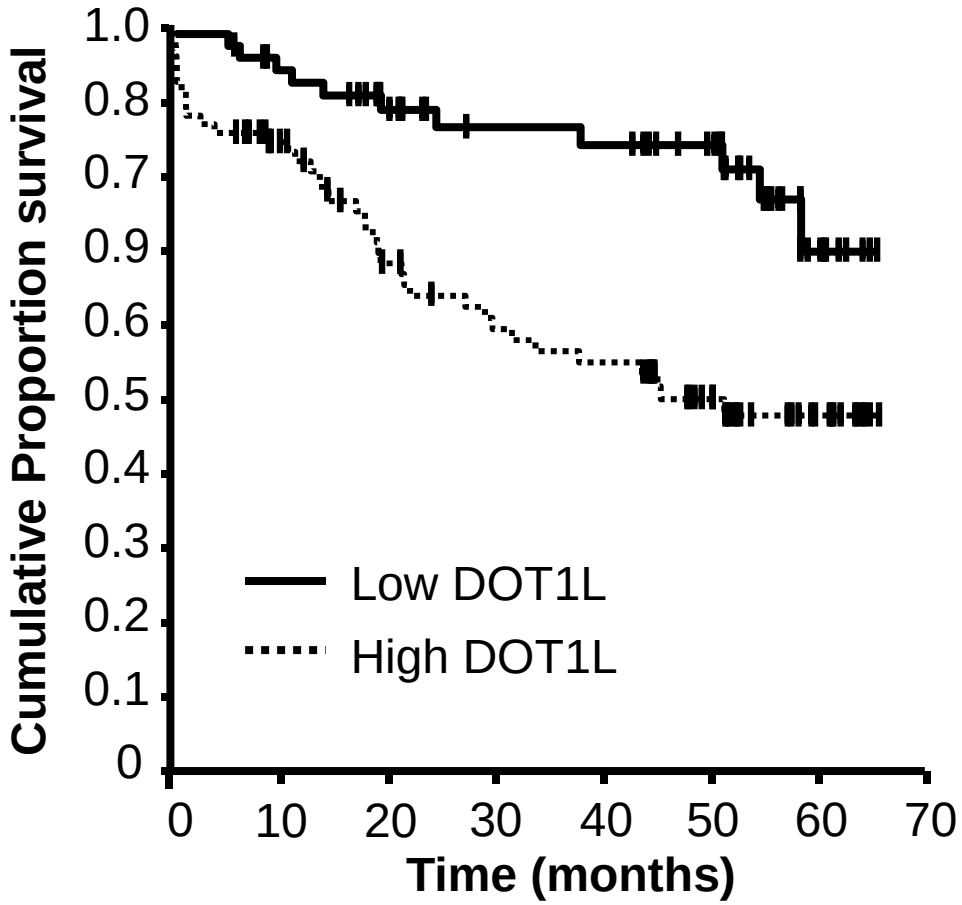
IL-22 induced-H3K79me2 on stem cell core gene promoters depends on STAT3

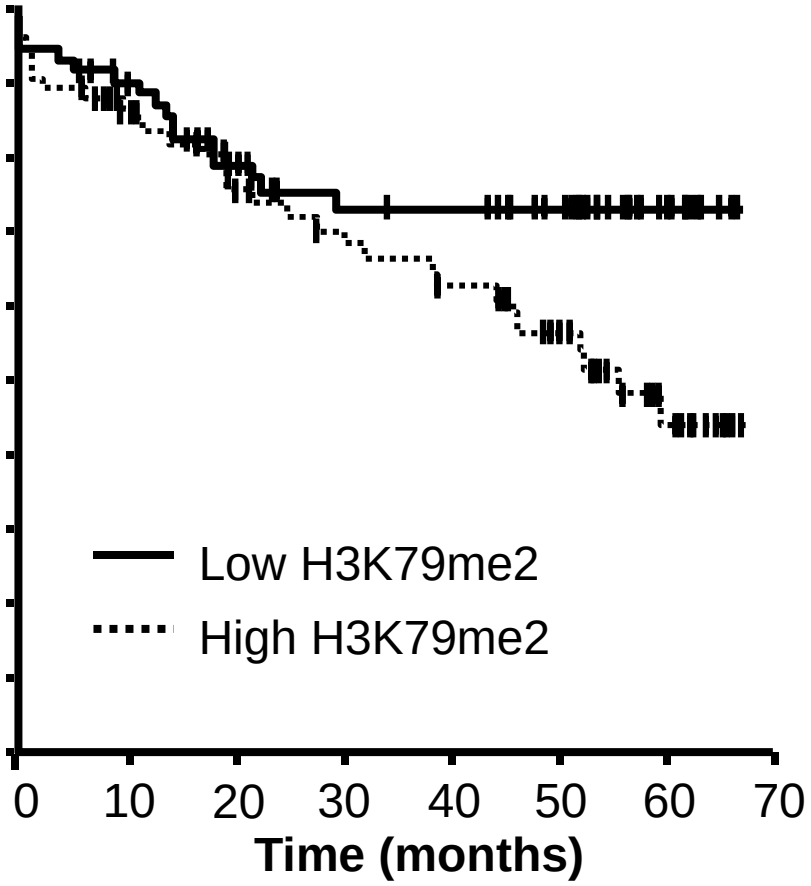


DOT1L and H3K79me2

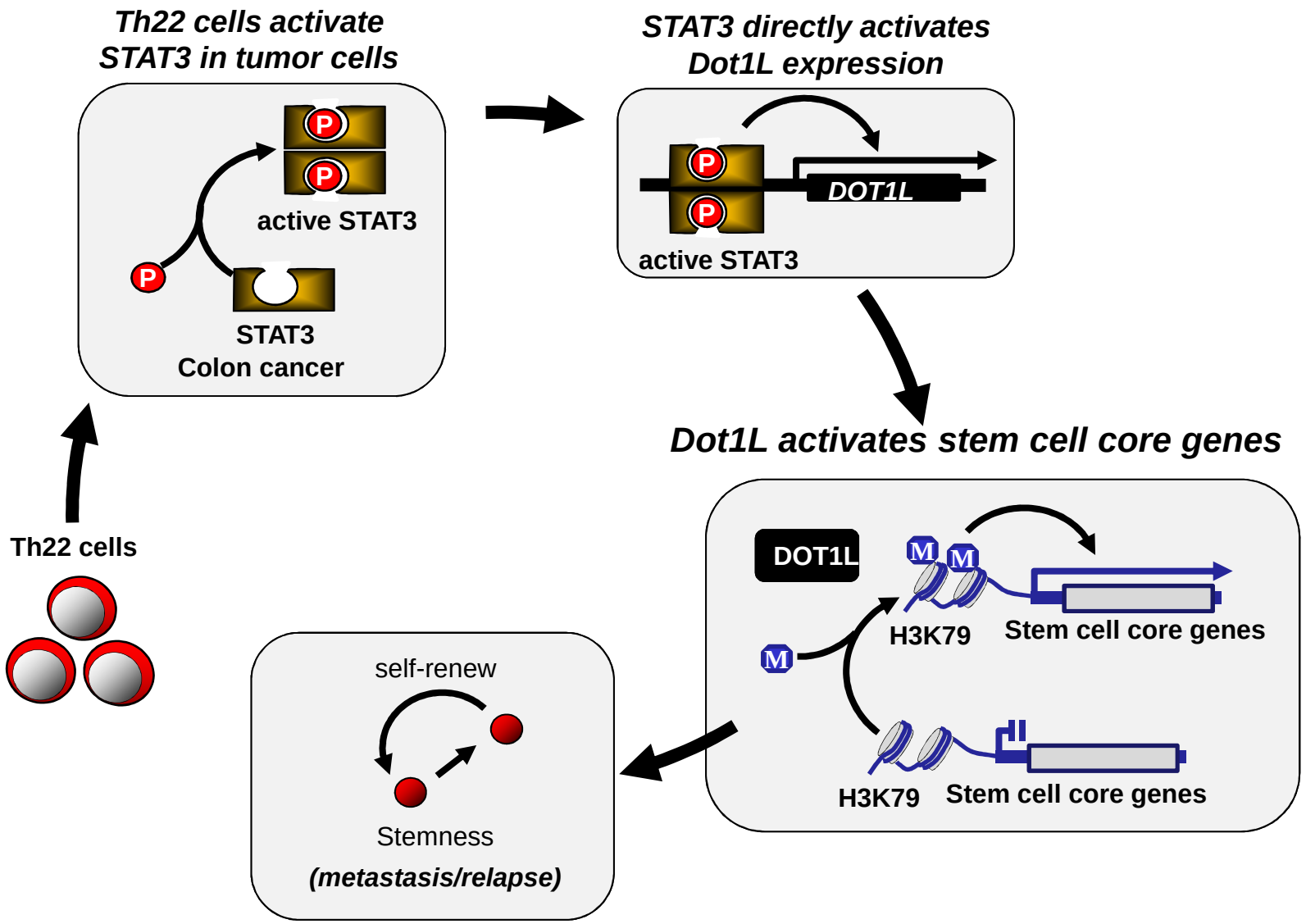
Clinical relevance?

Expression of DOT1L and H3K79me2 is associated with poor cancer survival





Th22 cells and cancer stemness: STAT3/DOT1L/H3K79me2/stem genes



Oncogenesis model

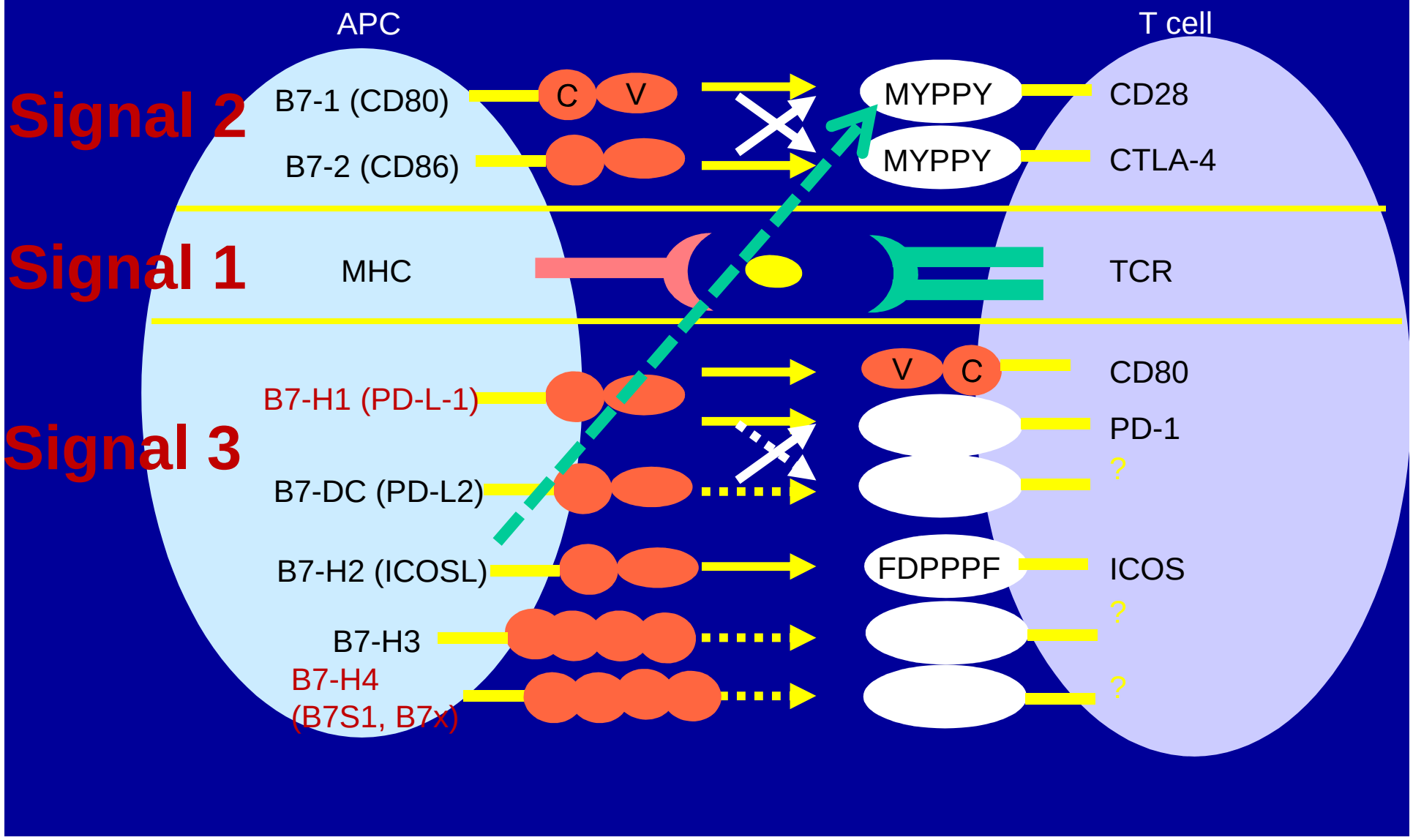
Potential cancer initiation: Genetic mutations/instability

Genetic signal, signal 1 (Knudson hypothesis):
Intraclonal genetic alternation: 10^{-8} x 10^{-8} = 10^{-16}
Interclonal genetic alternation: 10^{-8} + 10^{-8} = 2 x10^{-8}

Extrinsic stemness signal (MDSC, macrophage, Th22), signal 2:
Environmental inflammatory stimuli (Signals for stemness maintenance).
Mutation + extrinsic signals >10^{-8}

Immune suppressive signal (MDSCs, Tregs), signal 3:
Mutation + environmental stimuli + suppressed immunity >> 10^{-8}

Three signal T cell activation model



Take home message:

Three signal oncogenesis model

Oncogenesis: Cancer initiation, establishment and progression

Oncogenesis $\neq$ Initiation

Signal 1: Genetic signal
Signal 2: Stemness (inflammatory) signal
Signal 3: Immune suppressive signal

Ilona Kryczek
Wojciech Szeliga
Saleh Altuwaijri
Cailin Wilke
Linda Vatan
Ke Wu
Takashi Tanikawa
Joel Crespo
Nisha Nagarsheth
Tracy Cui
Dongjun Peng
Lili Zhao
Tyler Curiel
Theodore Welling
Yin Wang
Yan Liu
Shuang Wei
Rebecca Liu
Emily Finlayson
Emina Huang
Diane Simeone
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