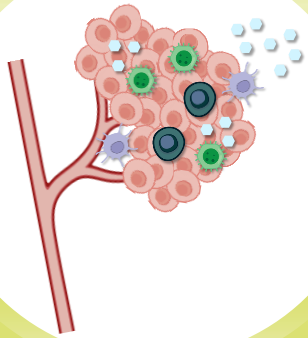
DOMAIN THERAPEUTICS

CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

PRECISION science
TRANSFORMING lives

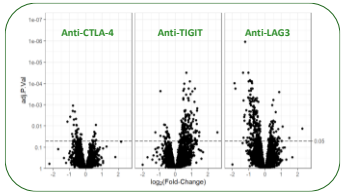
Domain Therapeutics : GPCRs as novel immuno-oncolgy targets

DOMAIN THERAPEUTICS IS A GLOBAL CLINICAL-STAGE BIOTECH COMPANY



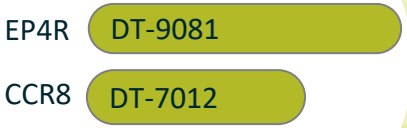
FOCUS

GPCR modulated immunology (cancer and inflammation)



PROVEN PLATFORM

Multiple candidates for development and partnerships.



PIPELINE

Drugs for targeted cancer patients with high unmet need.

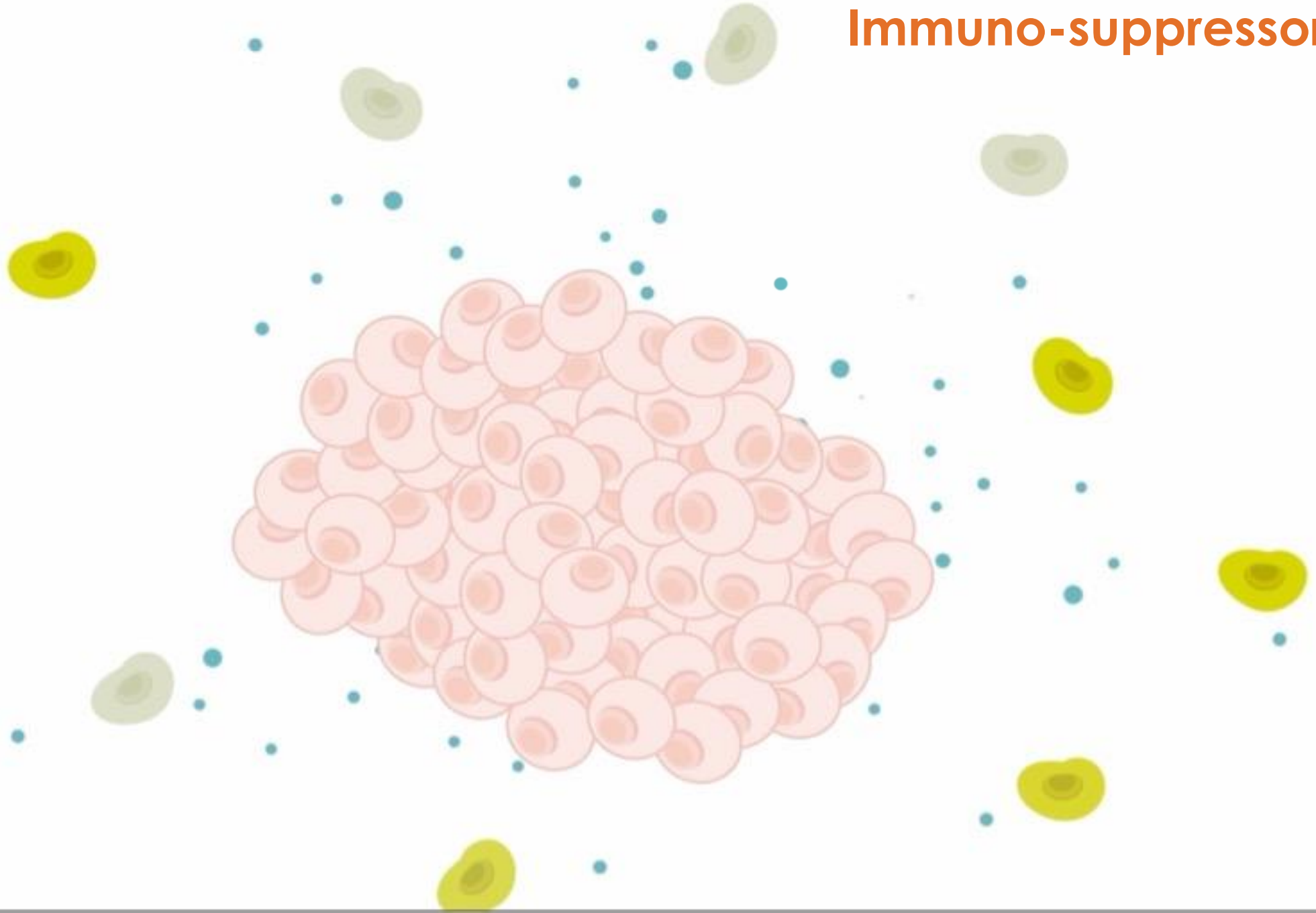
TEAM

Experienced team with established track record.

OUR MISSION: Unlock the full potential of GPCRs to target immunoresistance in the TME.

Immuno-suppressor mediators:

- *Adenosine*
- *PGE2*
- *CCL1*
- *H^+ / Lactate*
- *…*



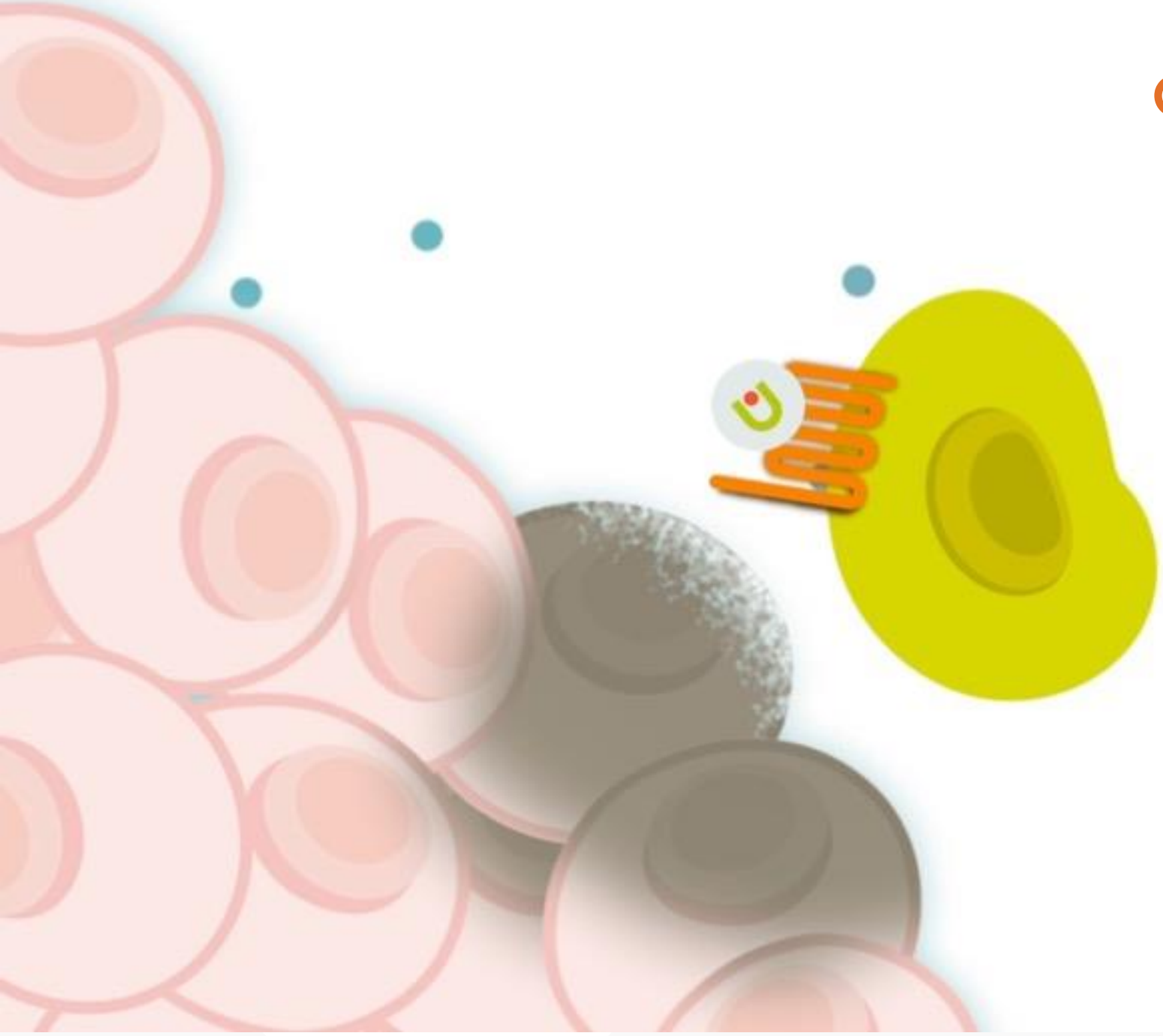
https://vimeo.com/649442780

- *Adenosine*
- *PGE2*
- *CCL1*
- *H^+ / Lactate*
- *...*

https://vimeo.com/649442780

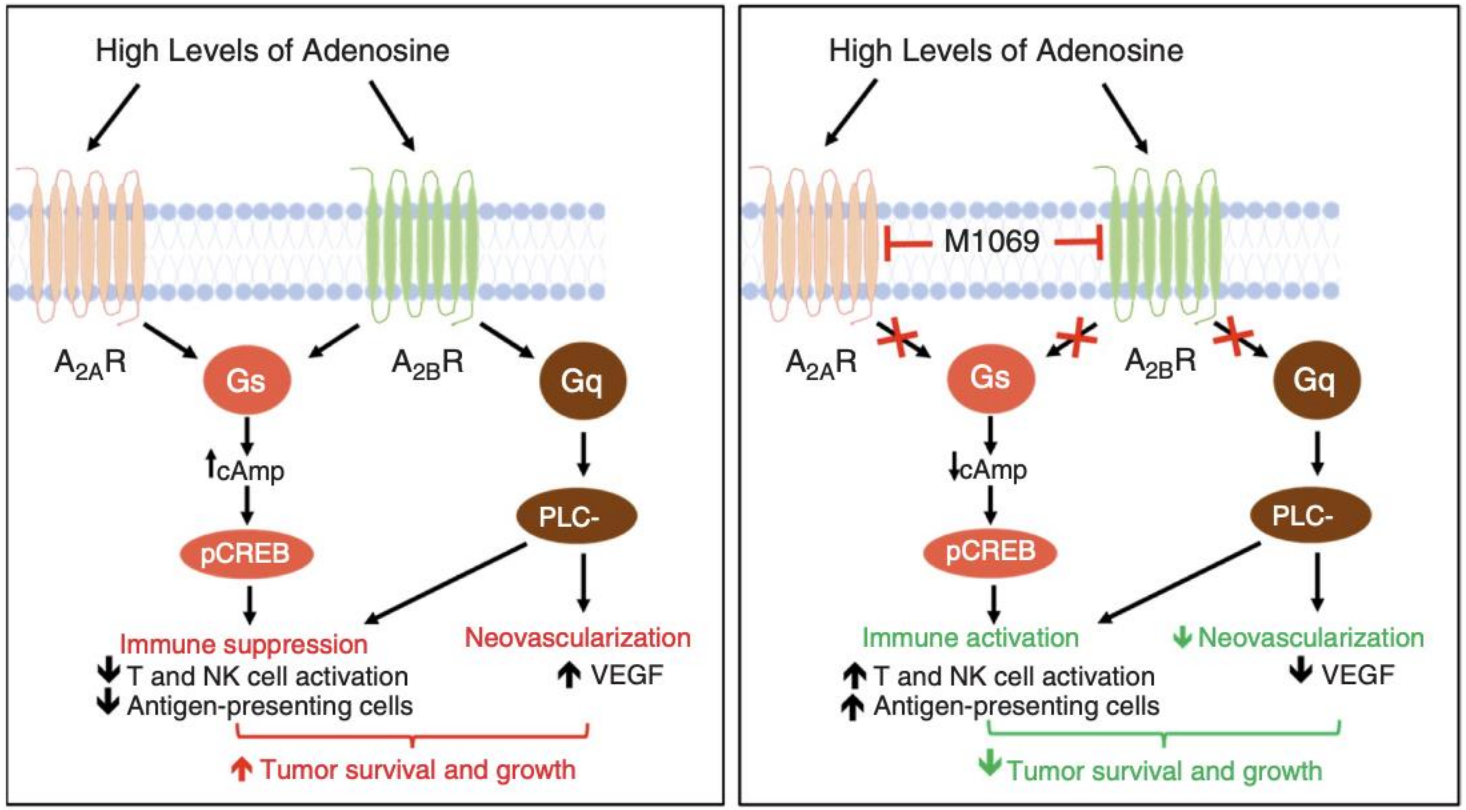
GPCR-based therapies

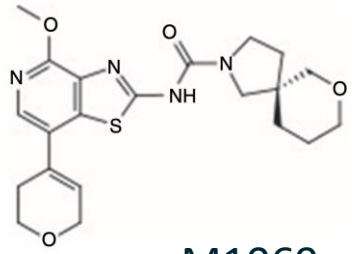
- *M-1069*
- *DT-9081*
- *DT-7012*



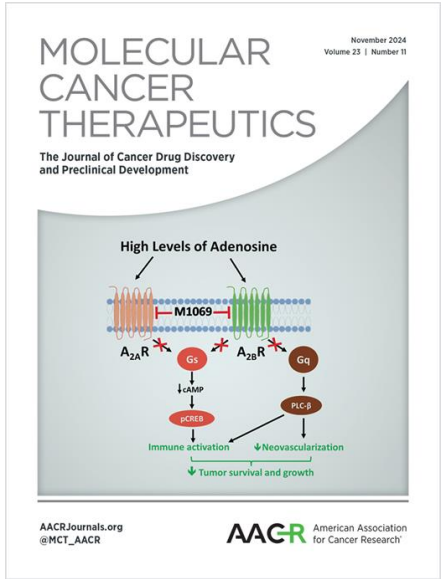
https://vimeo.com/649442780

DOUBLE ANTAGONISM OF IMMUNOSUPPRESSIVE ADENOSINE PATHWAY





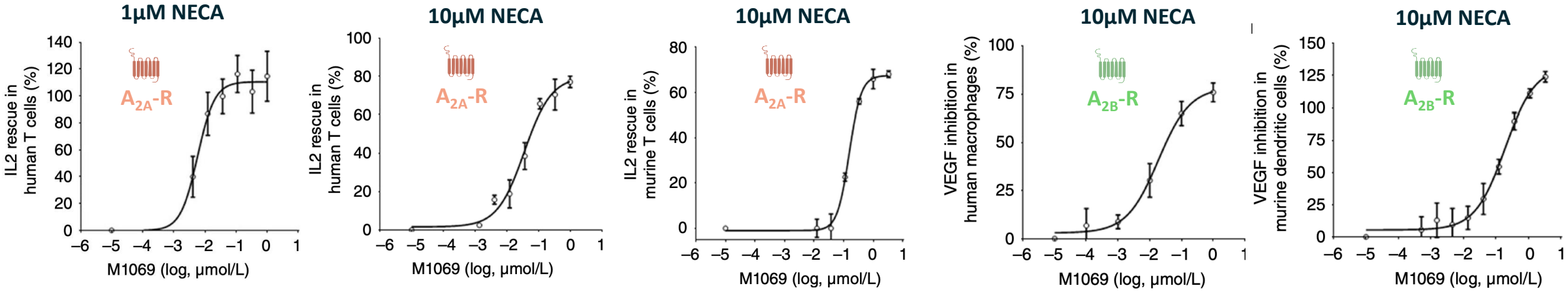
M1069



Schiemann K et al, Mol Cancer Ther 2024

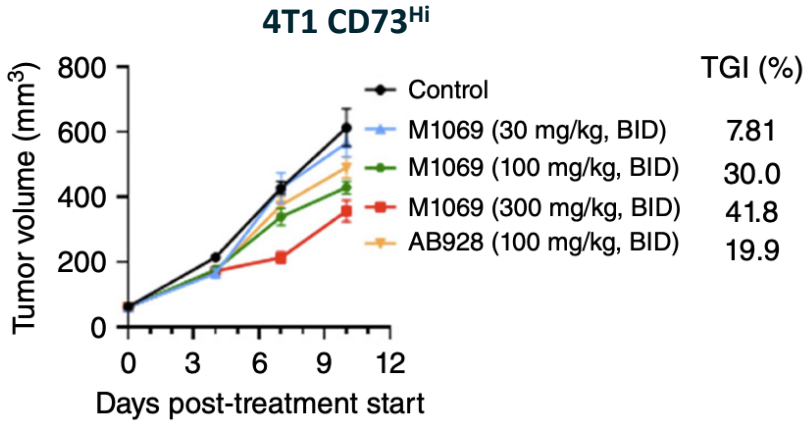
M1069: A DUAL A2A/A2B ANTAGONIST

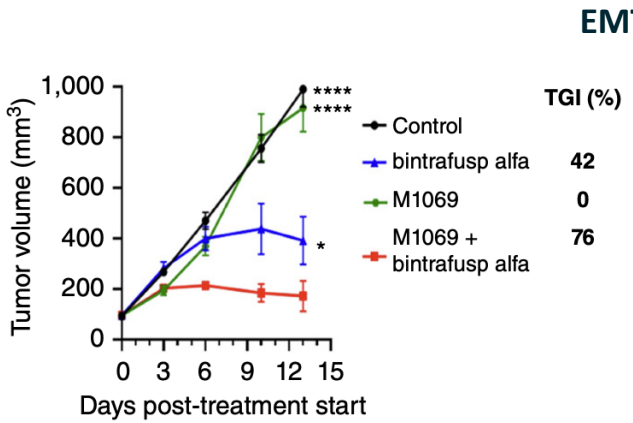
1 M1069 inhibits adenosine-mediated immuno-suppression

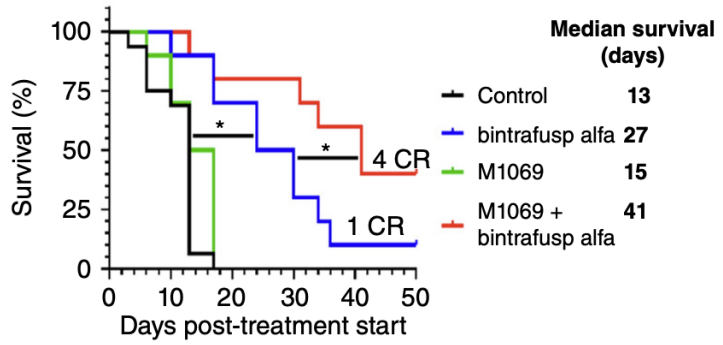


2 In vivo, M1069 shows antitumor efficacy in monotherapy and potentiates the activity of both chemotherapy and immunotherapy

Schiemann K et al, Mol Cancer Ther 2024





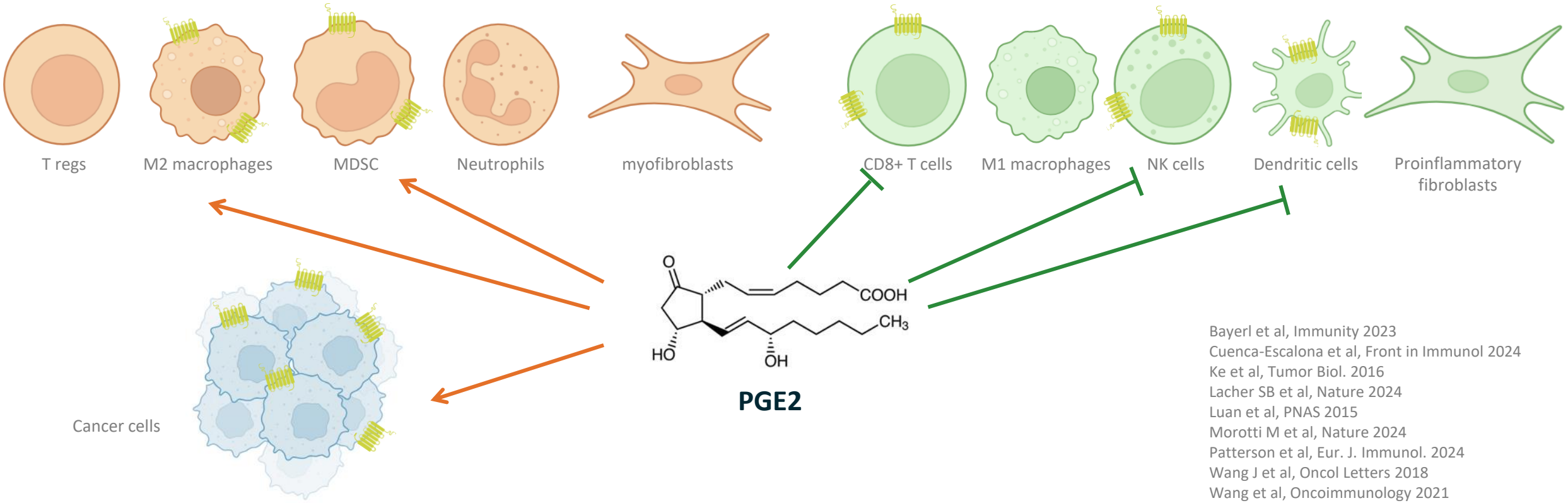


COX2 PRODUCES PGE2 INDUCING EP4R MEDIATED IMMUNE RESISTANCE IN THE TUMOR MICROENVIRONMENT

EP4 receptor

Immunosupressive cells

Immunocompetent cells

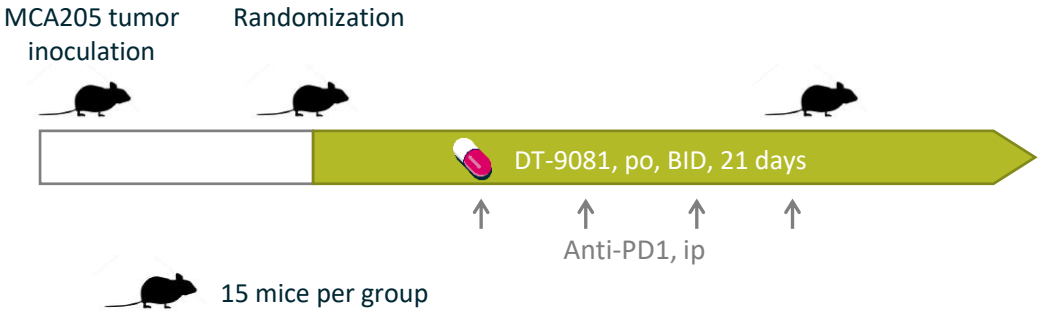


Bayerl et al, Immunity 2023
Cuenca-Escalona et al, Front in Immunol 2024
Ke et al, Tumor Biol. 2016
Lacher SB et al, Nature 2024
Luan et al, PNAS 2015
Morotti M et al, Nature 2024
Patterson et al, Eur. J. Immunol. 2024
Wang J et al, Oncol Letters 2018
Wang et al, Oncoimmunology 2021

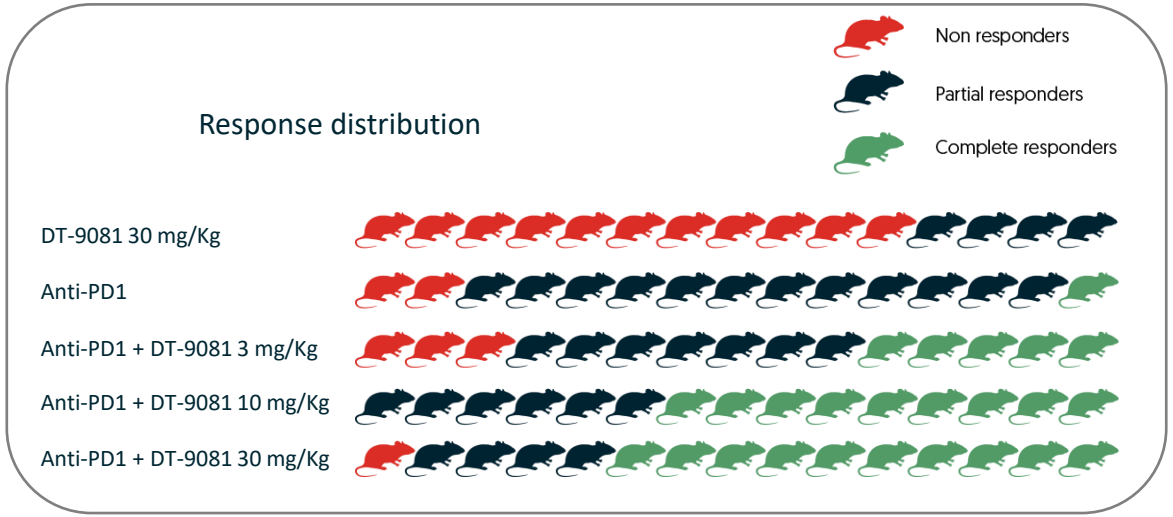
PGE2 promotes immunosuppressive cells (including cancer cells) and inhibits immunocompetent cells

EP4R ANTAGONIST: STRONG IMPROVEMENT OF ANTI-PD1 RESPONSE IN SARCOMA TUMOR MODEL

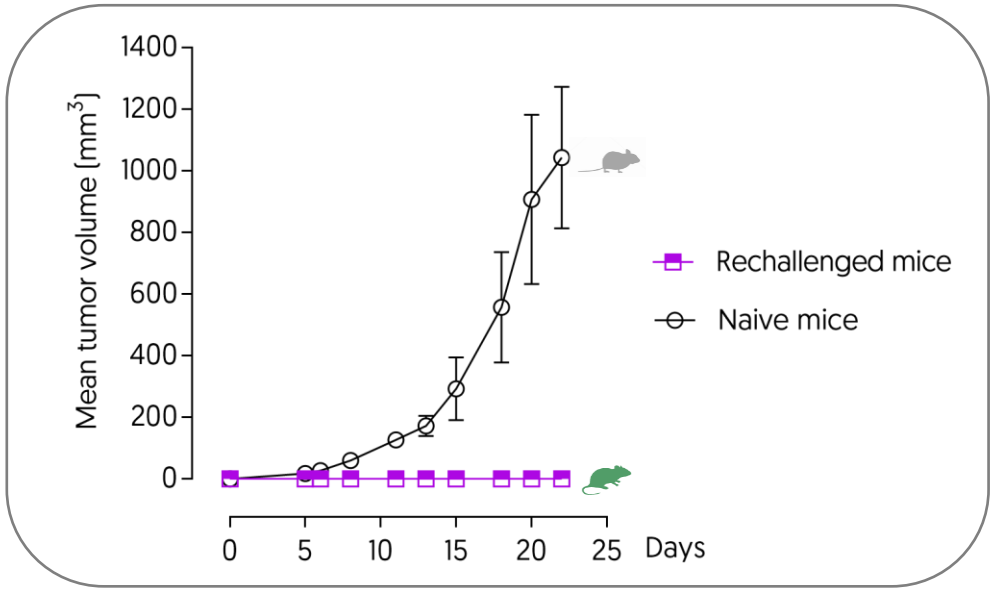
1 Experimental design



2 Results: response rate



3 Results: Rechallenge with MCA205 cells



- Dose-dependent massive potentiation of anti-PD1 effects
- Immune memory response conferred with anti-PD1 + DT-9081

DT-9081 in the CONDOR consortium

CONDOR
PRECISION MEDICINE AND IMMUNOTHERAPY OF SARCOMA

FRANCE 2030

- Domain joins the **CONDOR consortium** focused on revolutionizing soft-tissue sarcoma (STS) therapeutic management

https://condorprogram.com

- **CONDOR consortium** secured a French RHU grant of 10M€ and is led by Pr Antoine Italiano, Institut Bergonié

- A Phase II of DT-9081 in STS will be conducted as part of the **CONDOR consortium**. Principal Investigator will be Pr Antoine Italiano who previously tested immunotherapy in STS.

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-022-01821-3
Check for updates

Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort

A. Italiano[1,2,3,18] ✉, A. Bessede[4,18], M. Pulido[5,6,18], E. Bompas[7], S. Piperno-Neumann[8], C. Chevreau[9], N. Penel[10], F. Bertucci[11], M. Toulmonde[1], C. Bellera[5,6], J. P. Guegan[4], C. Rey[4], C. Sautès-Fridman[12,13], A. Bougoüin[12,13], C. Cantarel[5,6], M. Kind[14], M. Spalato[1], B. Dadone-Montaudie[15], F. Le Loarer[3,16], J. Y. Blay[17] and W. H. Fridman[12,13]

Pr Antoine Italiano
Institut Bergonié, Bordeaux, France
Member of Domain's SAB

CCR8 SPOTLIGHTED AS A “HOT” TARGET IN ONCOLOGY

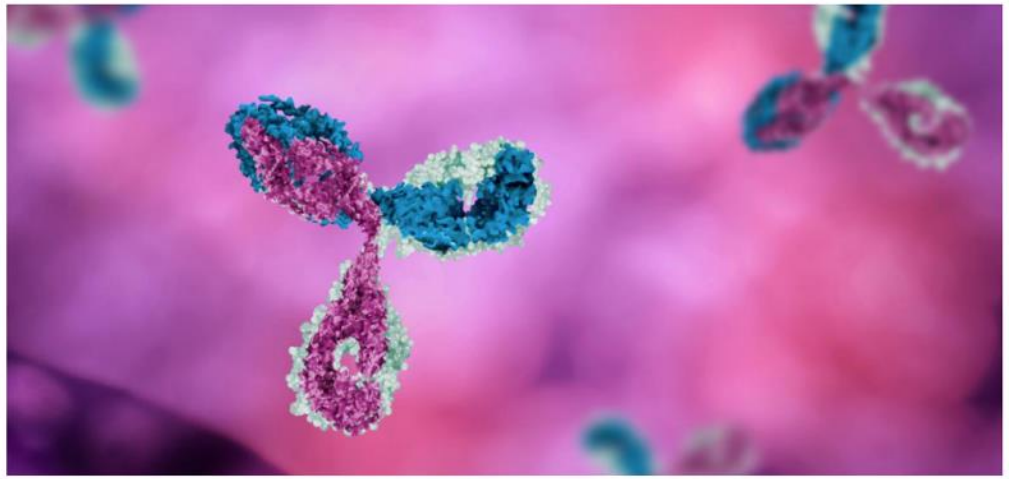
DATA INSIGHTS

CCR8 expectations

18 April 2024

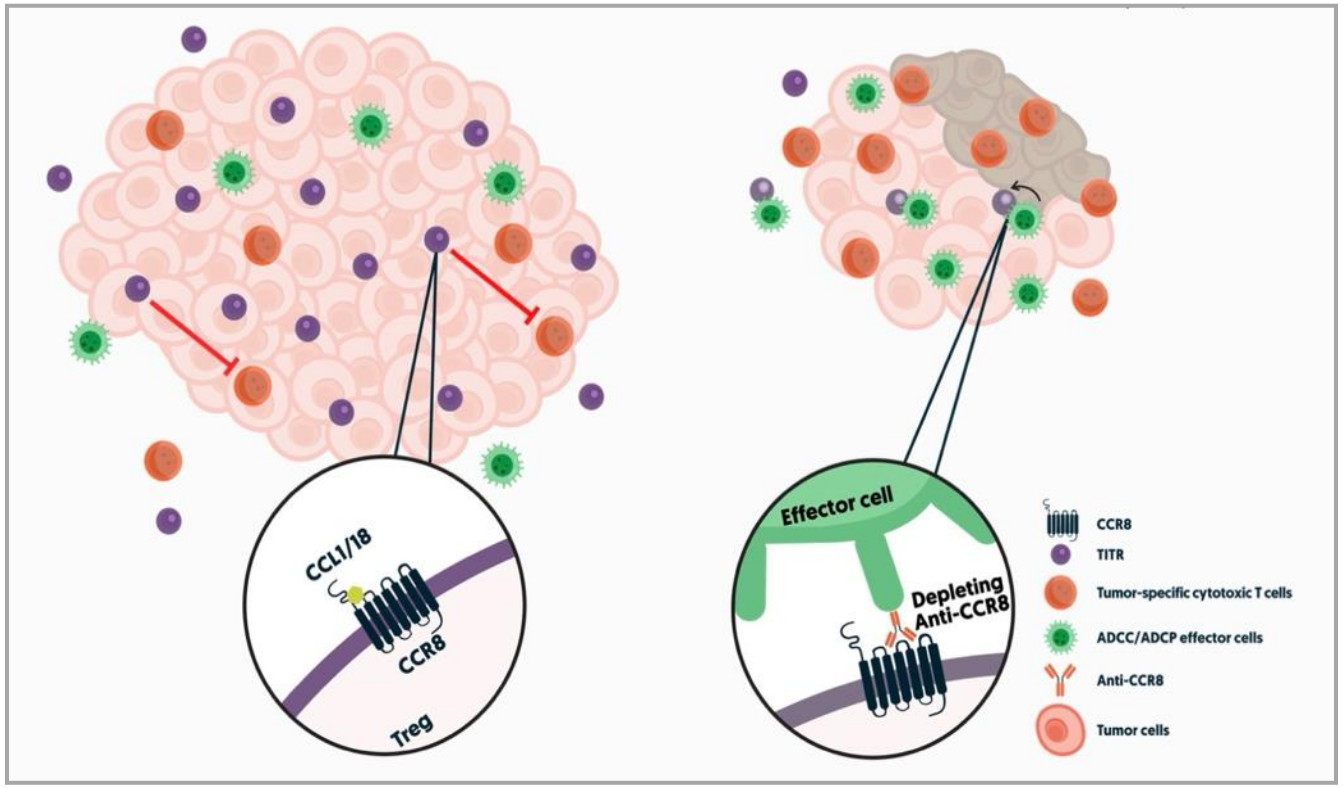
Jacob Plieth

Blockade of CCR8 has quietly emerged as a hot oncology target, especially for anti-PD-(L)1 MAb combinations.



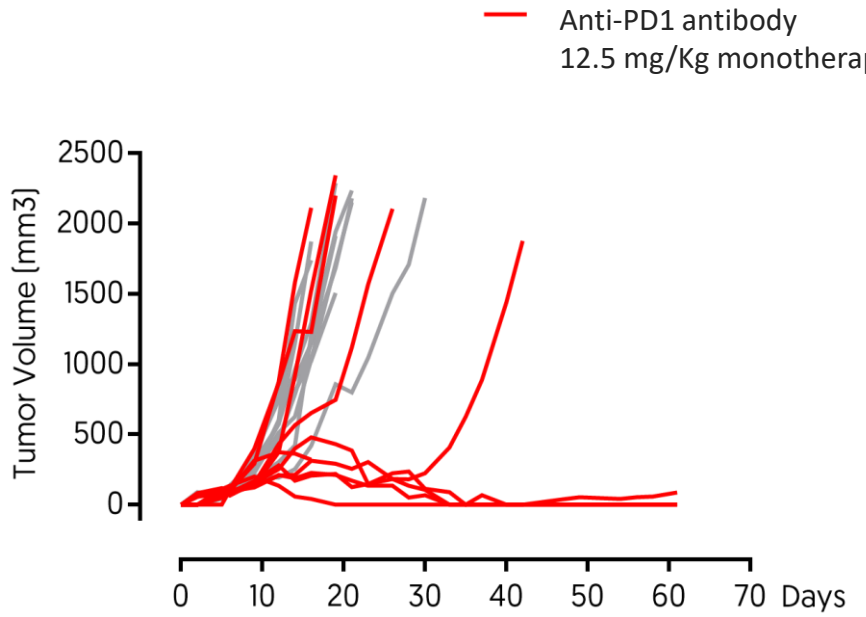
When last year Coherus acquired the distressed biotech Surface Oncology for $65m in stock few paid attention to the anti-CCR8 MAb SRF114, which came with the deal. Now a flurry of clinical activity in CCR8 antagonism, including the big hitters Roche and Amgen, suggests that Coherus might have been on to something.

https://www.oncologypipeline.com/apexonco/ccr8-expectations

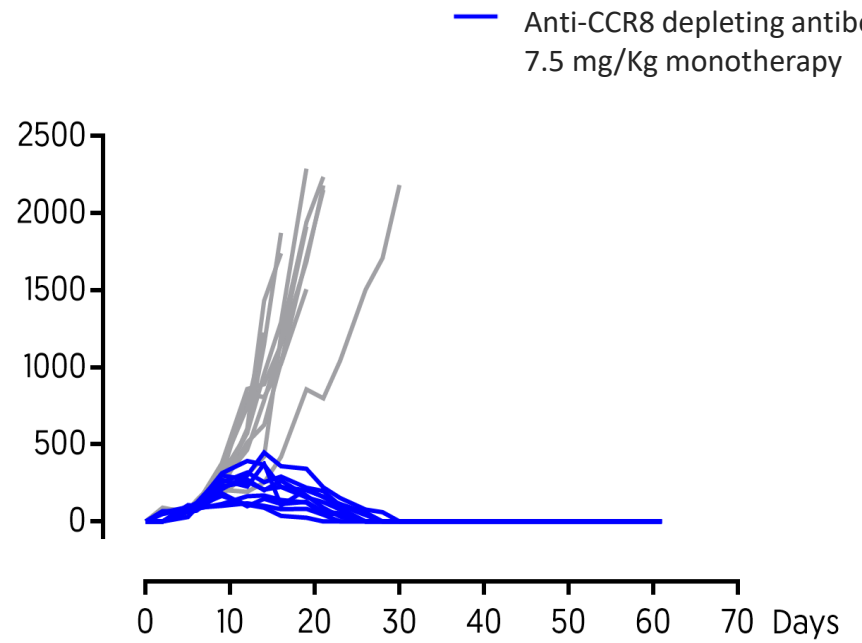


Treg depletion via CCR8 expressed on tumor infiltrating T-regulatory (TITR) cells is a promising new strategy for countering immunoresistance in the TME and improving outcomes for patients

ANTI-CCR8: 100% COMPLETE RESPONSE WITH MONOTHERAPY IN CT26 TUMOR MODEL



CR: 3/10



CR: 10/10

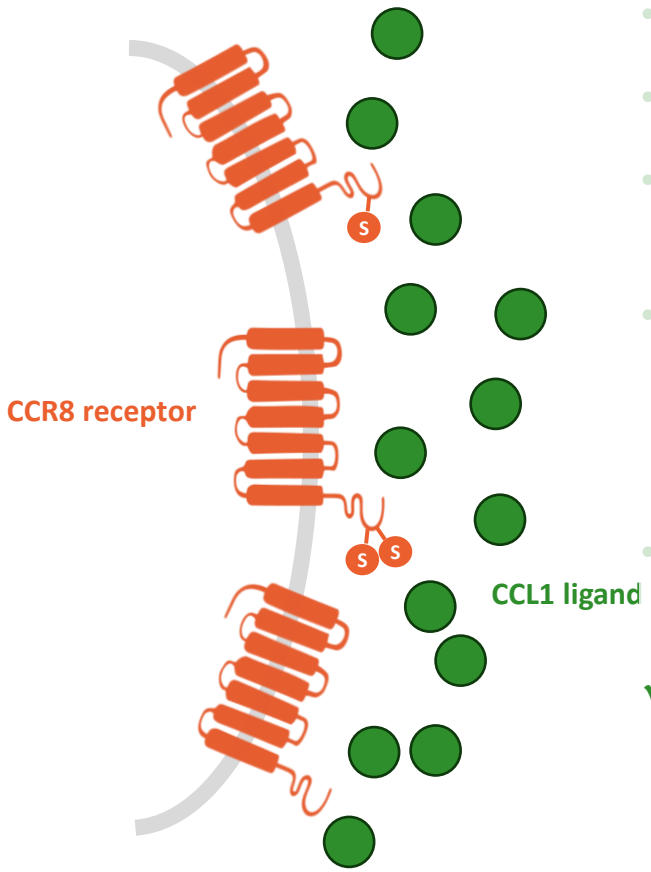
- Massive anti-tumor efficacy of anti-CCR8 in monotherapy
- Immune memory response conferred with anti-CCR8

DISCOVERY OF A HIGHLY DIFFERENTIATED ANTI-CCR8 MAB

- CCR8 is a chemokine receptor known to be post-translationally (PTM) sulfated by tyrosylprotein sulfotransferase TPST-1 and -2[(1-2)].
- This can lead to multiple forms of CCR8 and the exact PTM pattern in different cancer types or patient subpopulation is unknown.

✓ **The more ubiquitous pattern of CCR8 recognition is therefore preferable.**

[(1)] *Danan LM, 2006*
[(2)] *Gutiérrez J, 2004*



- CCL1 is the major ligand of CCR8
- CCL1 is involved in CCR8-mediated Treg migration.
- In tumor, CCL1 is secreted by cancer cells, CAF and TAM [(3)].
- CCL1 potentiates immunosuppressive activity of Tregs by inducing up-regulation of CCR8, FOXp3, CD39, IL-10, and granzyme B, resulting in enhanced suppressive activity of these cells [(4)].
- CCL1 concentration can reach single digit nM concentration in the TME[(5)].

✓ **Anti-CCR8 mAbs must be antagonist able to do the job in presence of high CCL1 concentrations.**

[(3)] *Korbecki 2020*
[(4)] *Barsheshet et al, PNAS 2017*
[(5)] *Shuna Liua, 2023*

DT-7012 in the SPRINT consortium

- Domain joins the **SPRINT consortium** focused on accelerating therapeutic innovation for CTCL
- **SPRINT consortium** secured a French RHU grant of approx. 10M€ and is led by Pr Adèle de Masson, APHP Paris
- A Phase I of DT-7012 in CTCL will be conducted as part of the **SPRINT consortium**. Principal Investigator will be Pr Adèle de Masson.

RESEARCH LETTER

blood advances

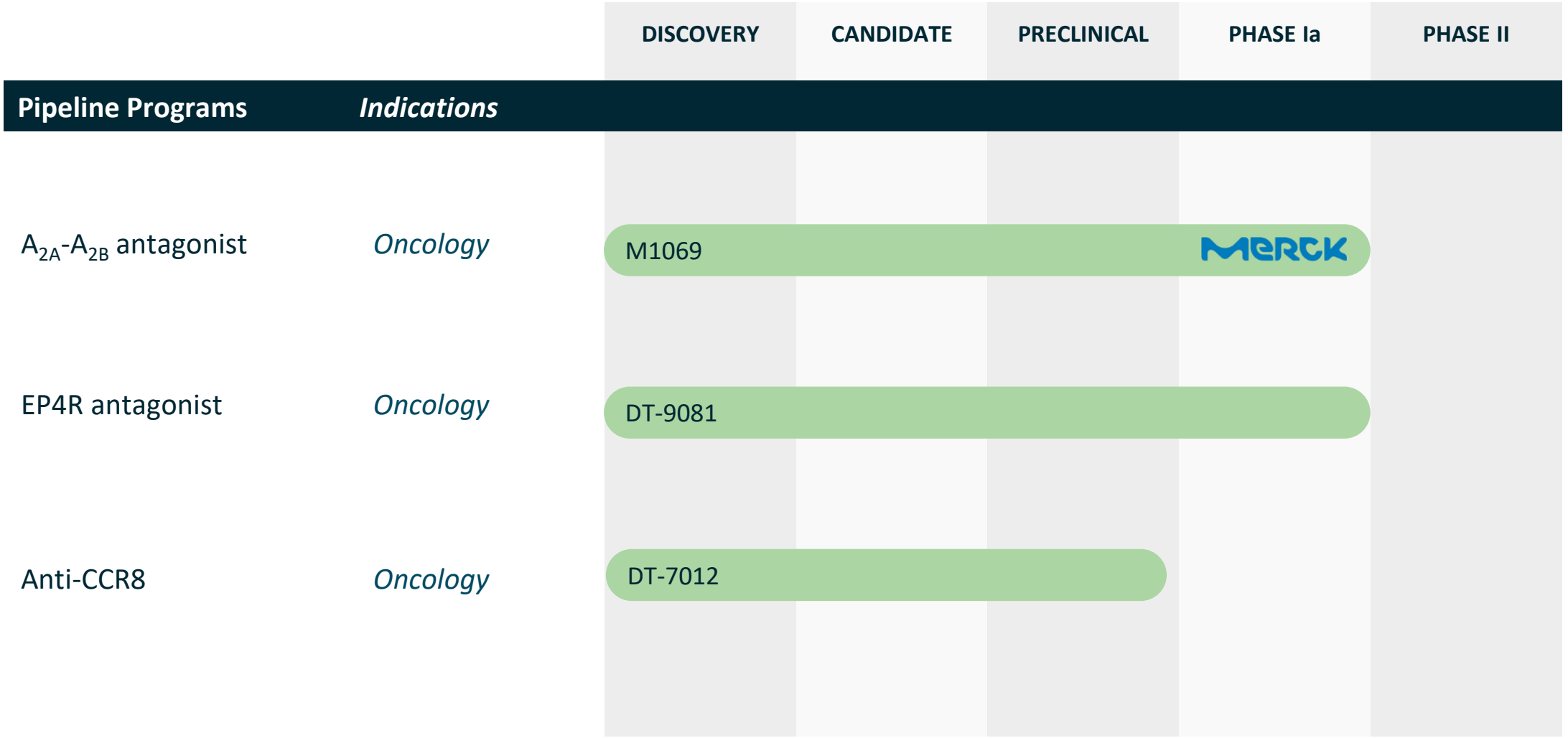
Check for updates

TO THE EDITOR:

CCR8 is a new therapeutic target in cutaneous T-cell lymphomas

Jérôme Giustiniani,[1] Gabor Dobos,[2-5] Hélène Moins-Teisserenc,[3,6,7] Tiago Eustaquio,[6] Maxime Battistella,[3,4,8] Nicolas Ortonne,[1,9] Caroline Ram-Wolff,[2] Jean-David Bouaziz,[2-4] Anne Marie-Cardine,[3,4] Samia Mourah,[3,4,10] Martine Bagot,[2-4] Thomas S. Kupper,[11] Rachael A. Clark,[11] Armand Bensussan,[3,4,*] and Adèle de Masson[3,4,*]

PROPRIETARY PIPELINE OF HIGHLY DIFFERENTIATED ASSETS



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CSO
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