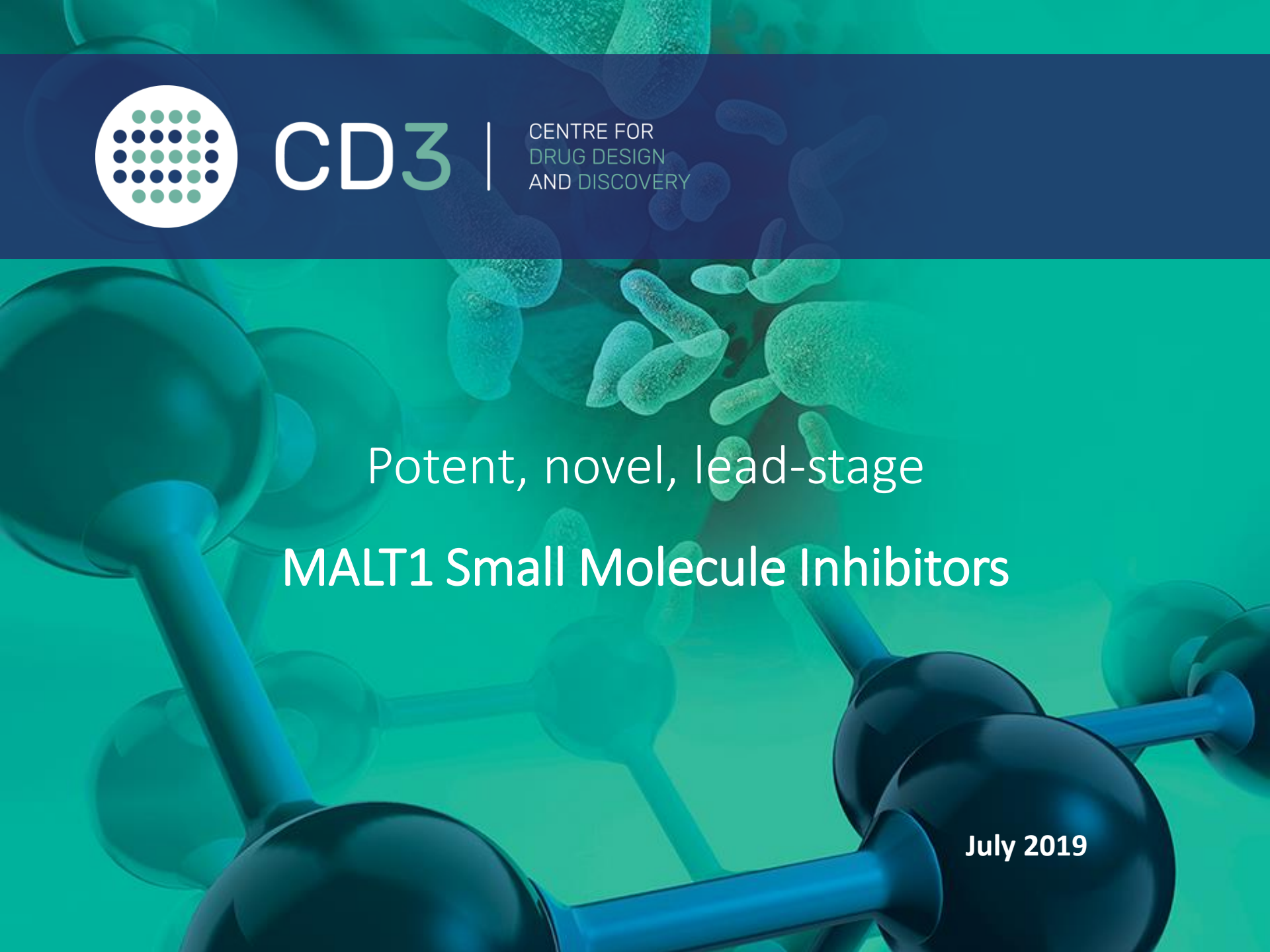


Potent, novel, lead-stage

MALT1 Small Molecule Inhibitors

July 2019

MALT1 inhibitors – Project overview

- **Allosteric MALT1 protease inhibitors at lead optimization stage**

- **Therapeutic applications:**

  1. Oncology:

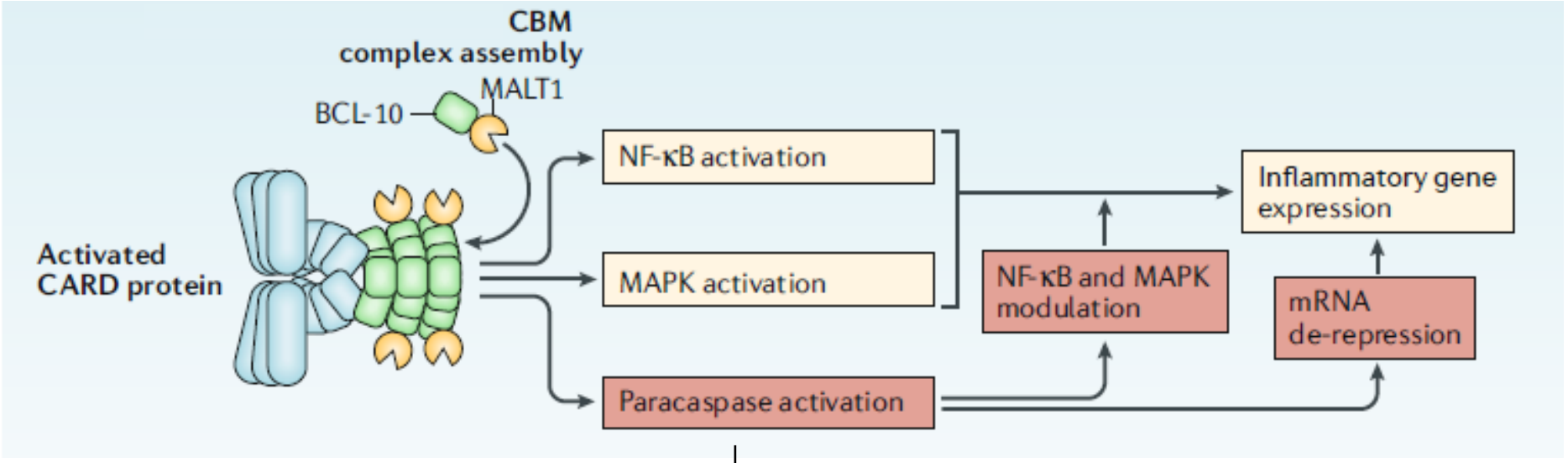
     I. MALT1-addicted B-cell malignancies (DLCBL, MCL, CLL, others)

     II. T_{reg} modulation in the tumor micro-environment to augment antitumor immunity (broadly applicable immune-oncology strategy across various tumor types)

  2. Several inflammatory disorders (e.g. psoriasis)

MALT1-mediated signaling pathways

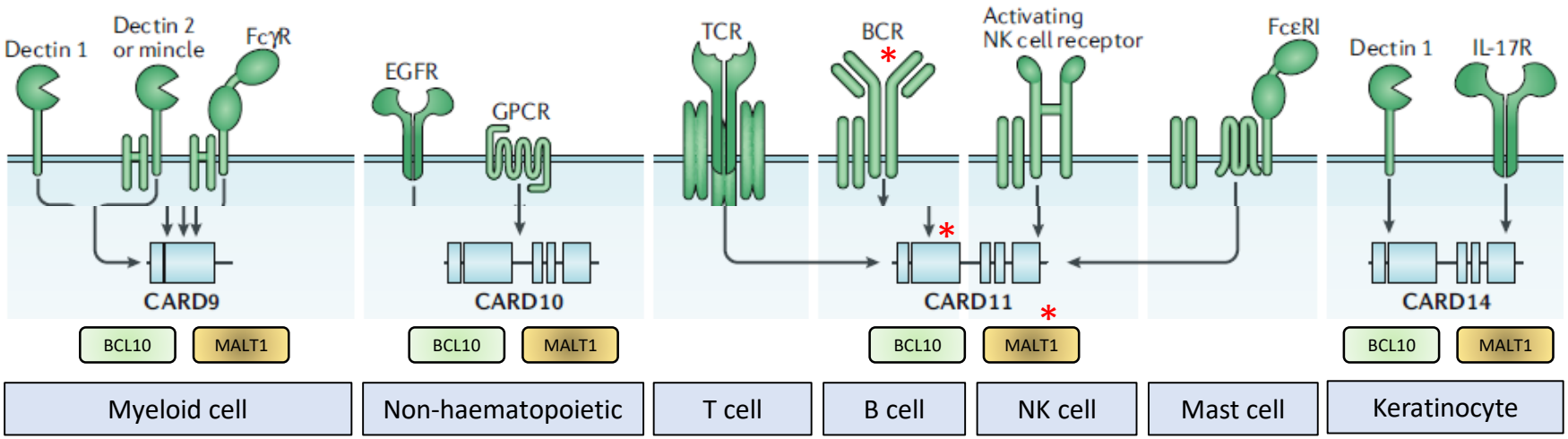
- Point of convergence: CARD-BCL10-MALT1 complex
  - **MALT1 as scaffold**: Initiation of T-cell (B-cell) receptor signalling to NFκB effect
  - **MALT1 as protease**: Enhancement & finetuning of the NFKB and MAPK signaling + termination of the signal



substrates → CYLD, A20, RelB, HOIL (ubiquitination)

Regnase1
Roquin1/2

MALT1-mediated proliferative disorders



Hyper-activated MALT1

Non-lymphoid cancers:
Breast (AGTR1 – HER2)
Lung (EGFR)
Melanoma
Glioblastoma

B-cell malignancies:
MALT lymphoma*,
ABC-DLBCL*,
MCL, CLL, PEL*,
BENTA*

T cell malignancies:
Cézary syndrome*,
CTCL, ATLL*, PTCL

* genetically driven

MALT1-mediated anti-tumor immunity

- Tumors with - high ratio $\frac{T_{eff}\ CD8^+}{T_{reg}\ FOXP3^+}$
  - better prognosis / increased overall survival

- high T_{reg} infitration
  - poor prognosis / shorter overall survival
  - limits efficacy of PD1 checkpoint blockade

- MALT1 as an **immunomodulator**:
  - ⇨ modulate T_{reg} phenotype
  - ⇨ reduce IL-2 production
  - ⇨ reduce T_{reg} numbers

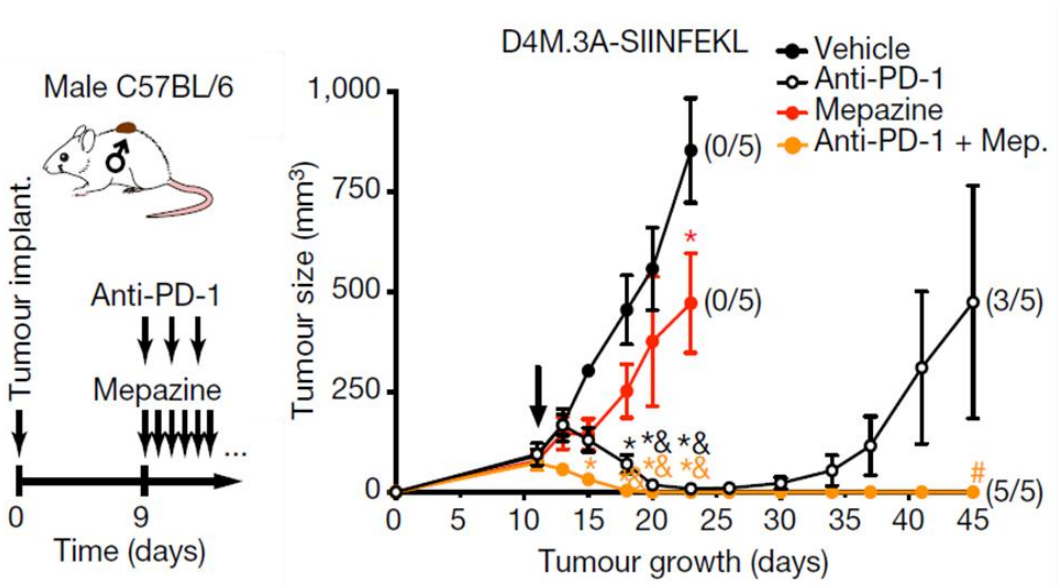
- **In vivo 'proof of principle':** pharmacologic and/or genetic models

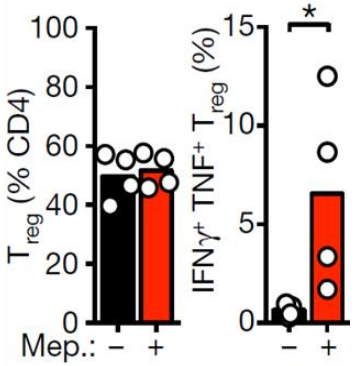
MALT1 is critical to suppress anti-tumor immunity

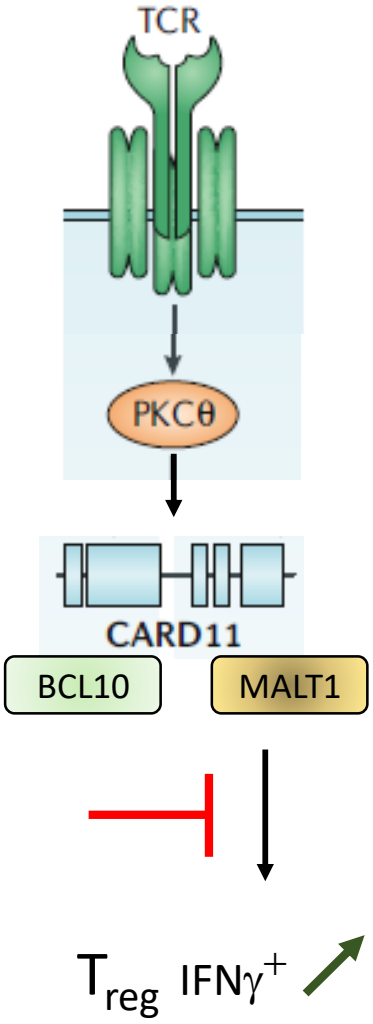
- MALT1 protease inhibition reverses the immune-suppressive Treg phenotype:
  - **Pharmacologic inhibition of MALT1 causes Treg cells to prime tumors for immune checkpoint therapy,** yet does not cause systemic auto-immunity (Di Pilato et al., Nature 2019)

MALT1i increases anti-tumor immunity

- *In vivo* "proof of concept" : pharmacologic (Mepazine)
  - Melanoma mouse model (high immunogenic)
  - Mepazine induces IFNγ production by T_{reg} in TME



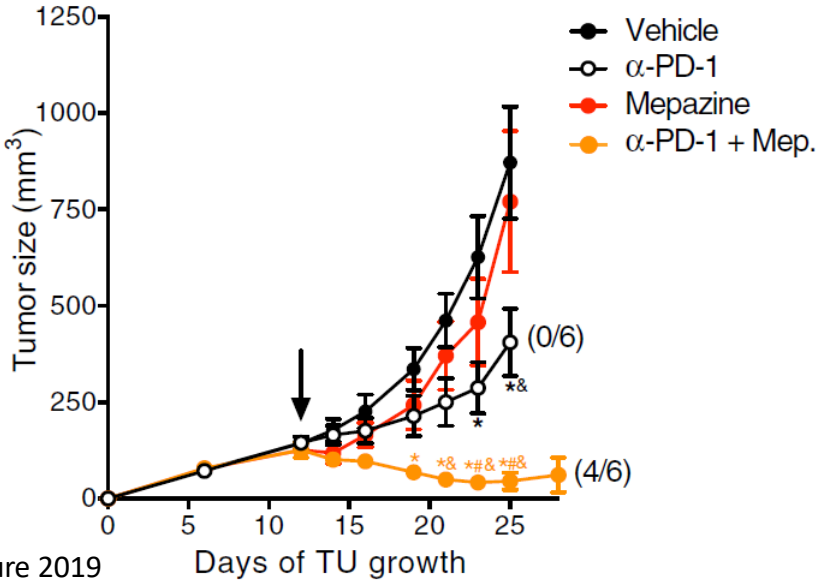




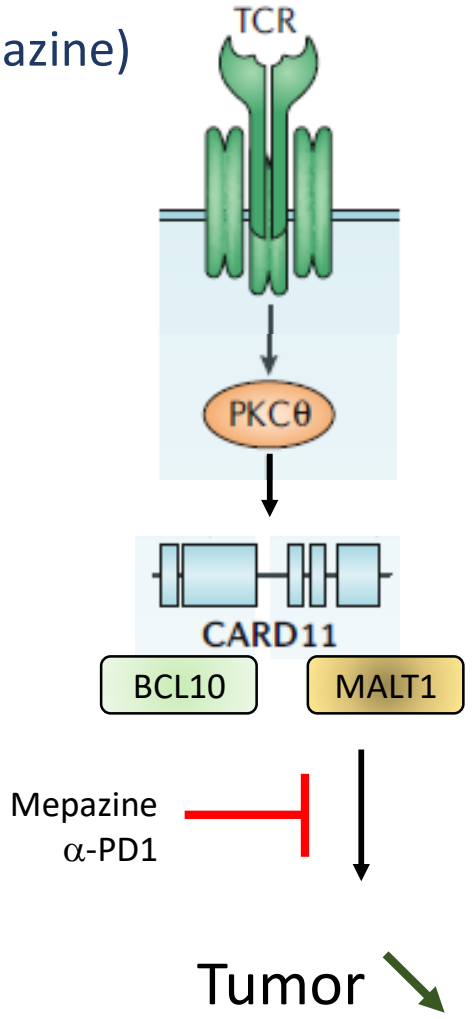
Di Pilato *et al.*, Nature 2019

MALT1i increases anti-tumor immunity

- *In vivo* "proof of concept" : pharmacologic (Mepazine)
  - **MC38 colon carcinoma** model (low immunogenic)
  - synergistic control through anti-PD-1 and mepazine combination treatment



Di Pilato *et al.*, Nature 2019



MALT1 is critical to suppress anti-tumor immunity

- MALT1 protease inhibition reverses the immune-suppressive Treg phenotype:
  - Pharmacologic inhibition of MALT1 causes Treg cells to prime tumors for **immune checkpoint therapy**, yet does not cause systemic auto-immunity (Di Pilato et al., Nature 2019)
  - **MALT1 protease is essential to mediate the immune-suppressive function of Tregs** in the tumor microenvironment and acute genetic blockade or pharmacologic inhibition enhances anti-tumor immunity (Rosenbaum et al., Nature Comm. 2019; Cheng et al., J. Immunol. 2019; Baens et al., Eur. J. Immunol. 2018)

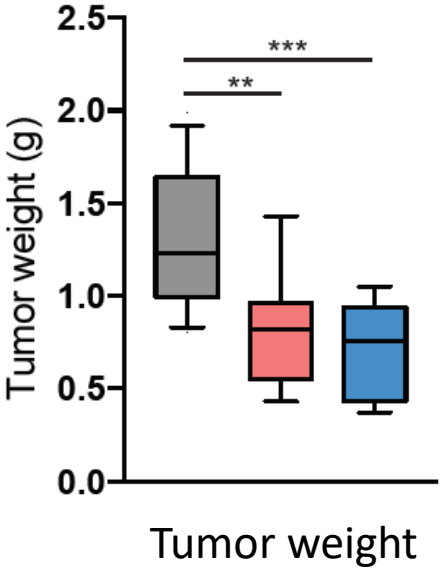
MALT1 protease is required to maintain T_{reg} levels

- *In vivo* "proof of concept" : genetic mouse models

MALT1-SR and MALT1-PD

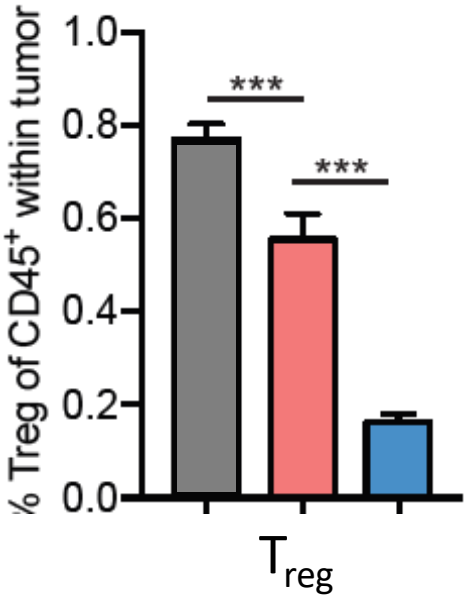
reduce

MC38 tumor growth



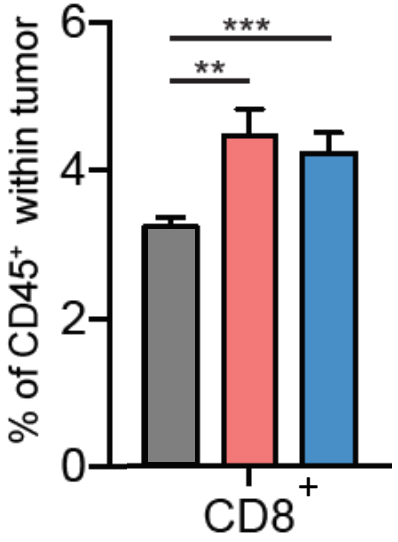
reduce

T_{reg} tumor infiltration



increase

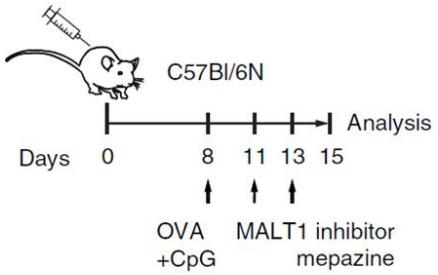
$CD8^+$ T cell tumor infiltration

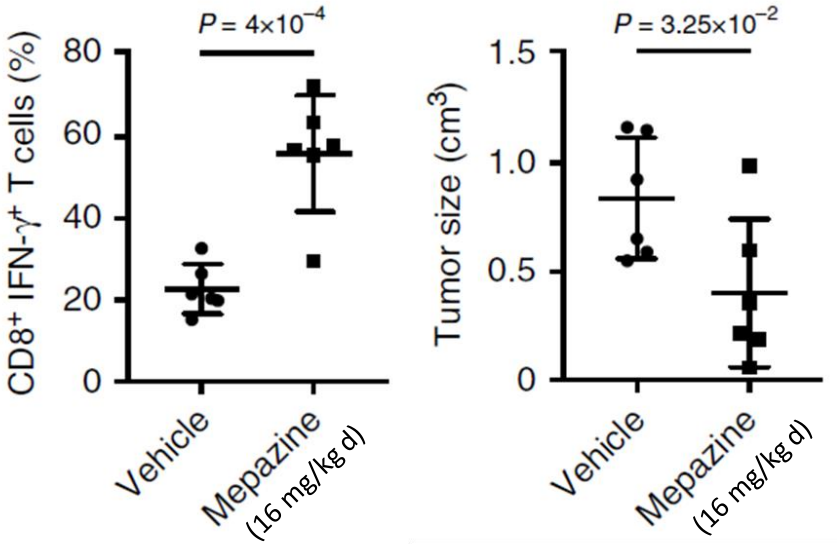


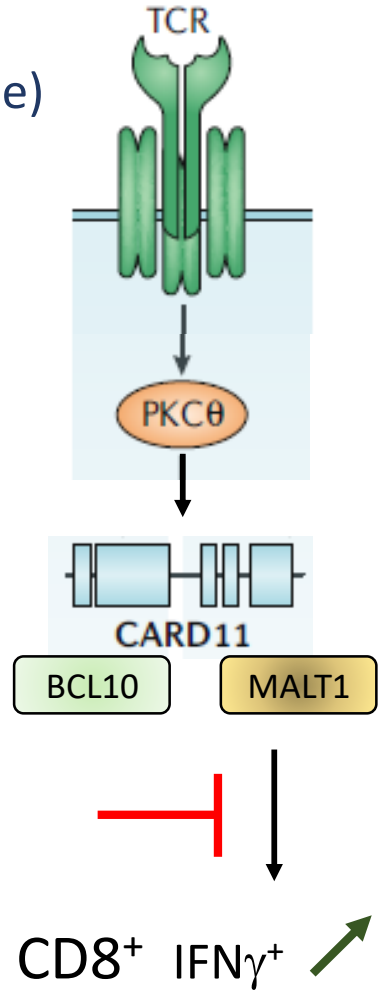
Baens et al., Eur J. Immunol. 2018

MALT1i increases anti-tumor immunity

- *In vivo* "proof of concept" : pharmacologic (Mepazine)
  - Melanoma mouse model
  - Mepazine: - increases CD8+ T cells (IFNγ+) in TME
    - reduces tumor size





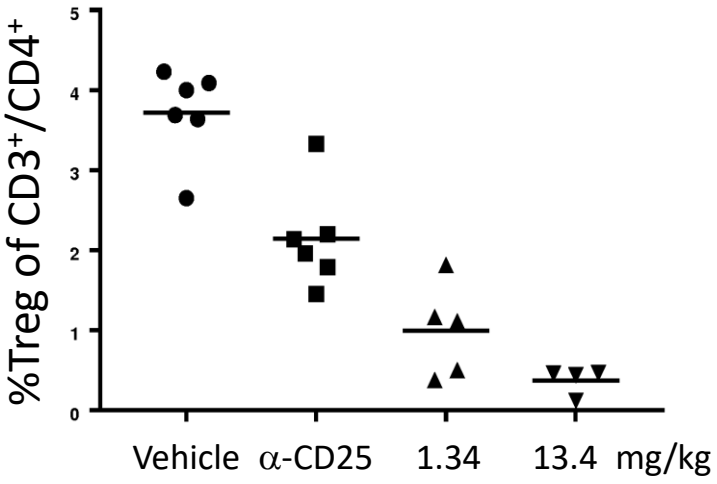


Rosenbaum *et al.*, Nat. Comm. 2019

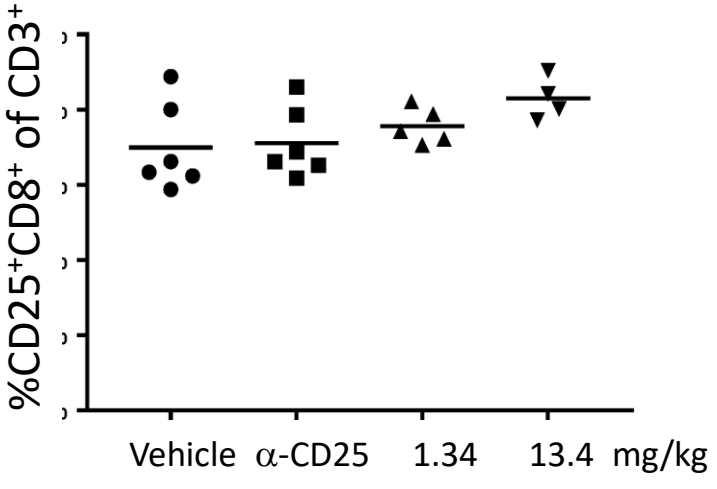
MALT1i depletes tumor T_{reg} levels

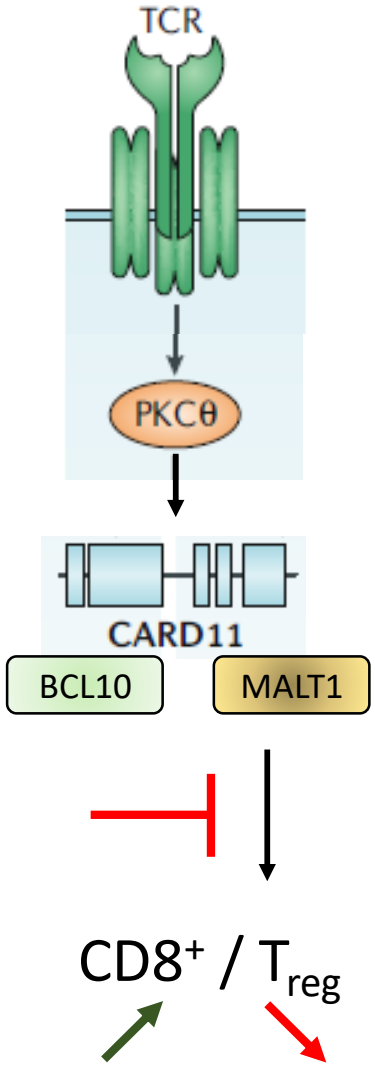
- *In vivo* "proof of concept" : pharmacologic (Medivir)
  - MB49 mouse bladder cancer model
  - MALT1i-#2 p.o. treatment (1.35 or 13,5 mg/kg day 8-9-10-11)

T_{reg} levels in TDLN



$CD8^+$ T_{eff} levels in TDLN





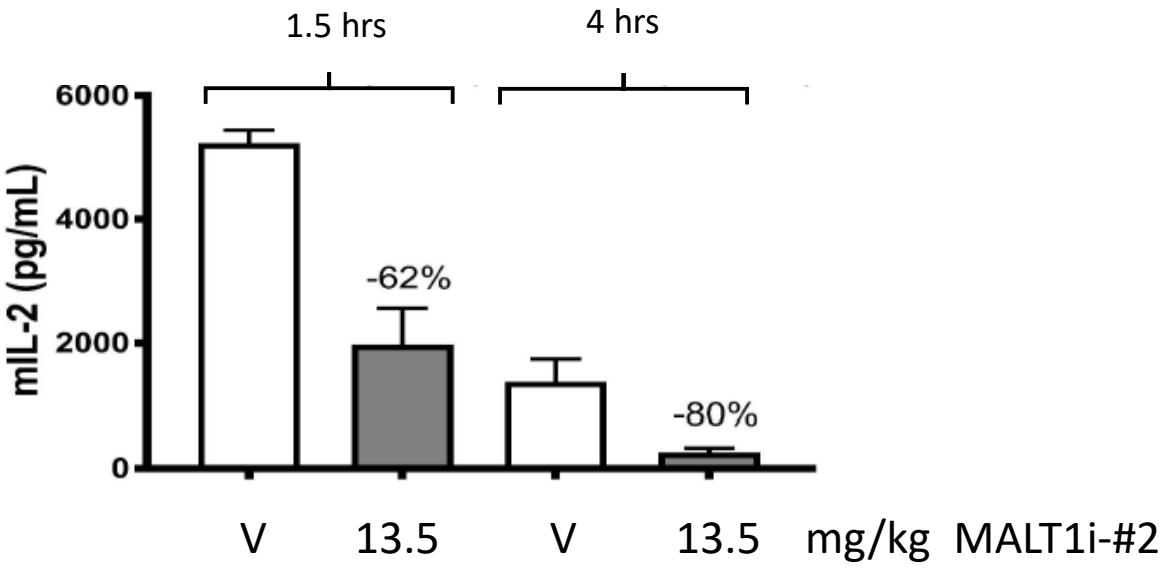
WO2018141749

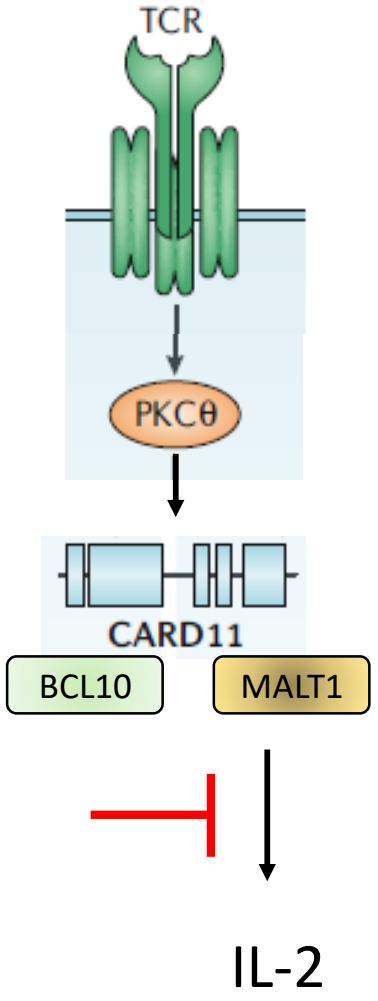
MALT1i reduces IL-2 levels

- *In vivo* "proof of concept" : pharmacologic (Medivir)

  MALT1 inhibition **reduces**: - IL-2 serum levels

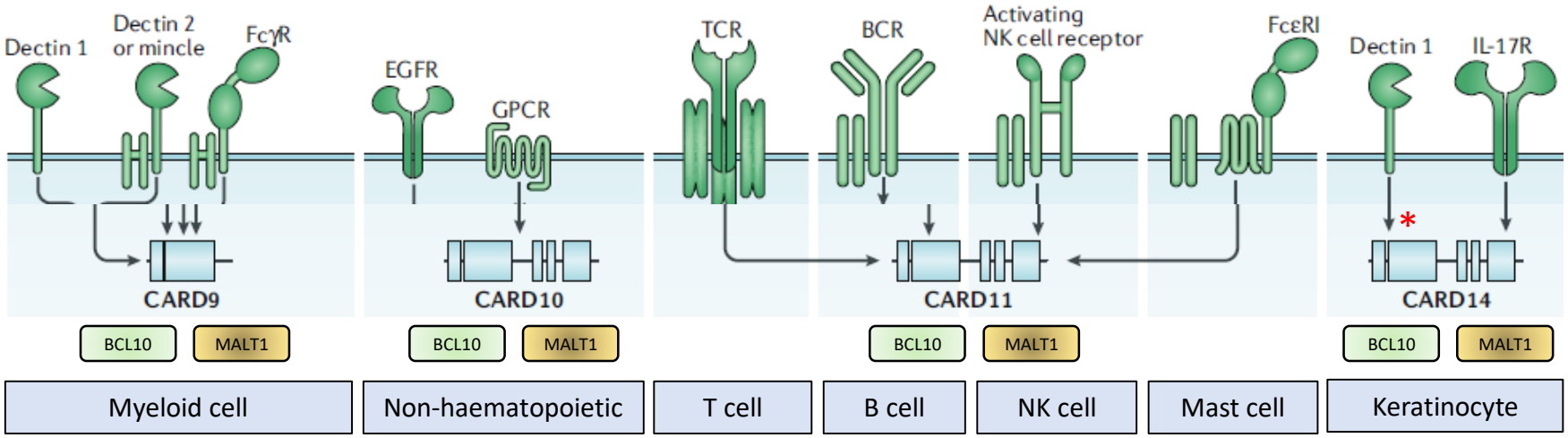
  (α-CD3 stimulation)





Finnberg et al., IO summit, Boston, 2018

MALT1-mediated inflammatory disorders



Hyper-activated MALT1

Rheumatoid Arthritis
Sjogren's Syndrome
Multiple Sclerosis
IBD, colitis
Lupus

Psoriasis

* genetically driven

Drug discovery tools and capabilities

Assay cascade: fully established/validated & up and running

- MALT1 enzyme assay
- Cell-based MALT1 substrate-cleavage assay (HEK293)
- IL2 reporter (Jurkat) & IL2 whole-blood assay (m/h)
- MALT1 dependent and independent lymphoma cell lines
- *In vivo* PD markers (MALT1 cleavage-specific Abs and downstream cytokines) validated (m/h)
- Short-term *in vivo* PD/efficacy mouse model (CARD14 mutant model, VIB) validated
- Whole-body and T-cell specific inducible protease-dead knock-in mice available, unpublished data up to 4 months PD
- VIB screening granted patent

Deep MALT1 biology expertise (from discoverers of MALT1 protease function)

- Mathijs Baens
- Rudy Beyaert Lab

Ongoing drug discovery and development program

- In depth MALT1 medchem know-how

MALT1 program – Status summary

- Allosteric MALT1 protease inhibitors at lead stage
- 2 compound subseries
  - Potent inhibition of MALT1 protease activity in vitro (IC_{50}'s up to 30 nM)
  - Inhibition of MALT1 protease activity in cells (EC_{50}'s up to 250 nM)
  - Inhibition of IL2 in Jurkat T cells (EC_{50}'s up to 200 nM)
  - Drug-like (Mw, cLogP, PSA…) properties
  - clear SAR available
  - Promising in vitro ADMET
  - Good oral bioavailability in mice
  - Proprietary and publicly available co-crystals for related allosteric inhibitors
- Composition of matter IP available – patent applications in preparation