Radio-immunotherapy of cancer

Therapeutic efficacy, underlying mechanisms and potential applications

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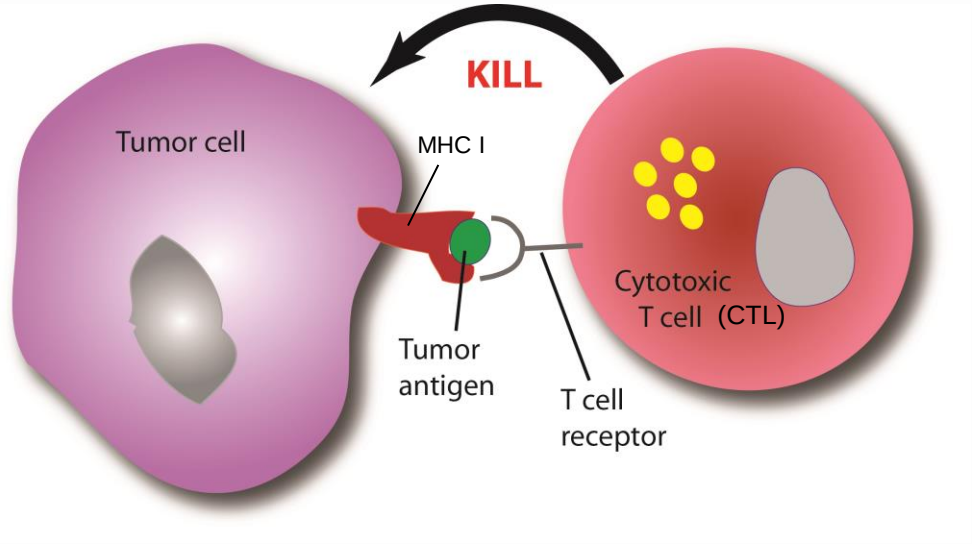
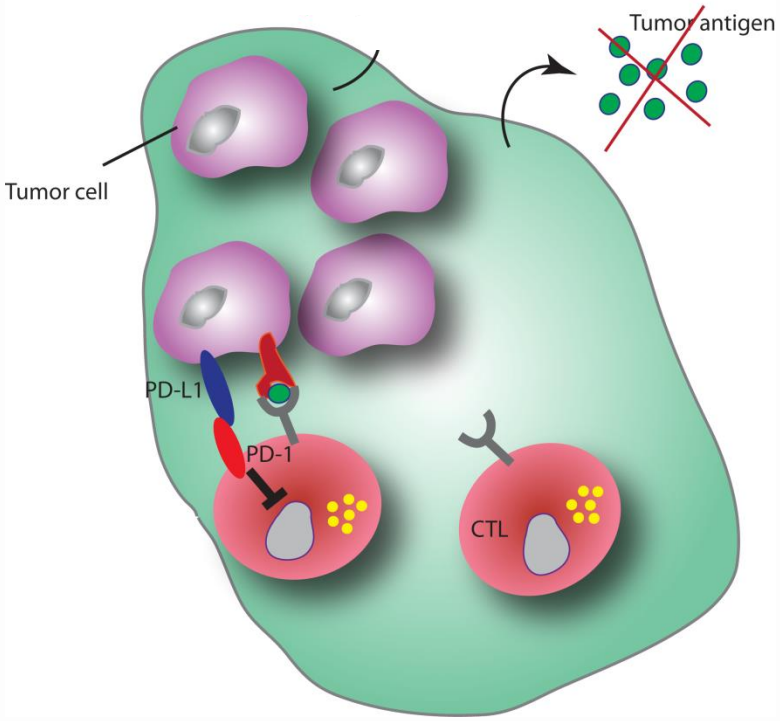
Curing metastatic cancer with systemic therapy

- Immunotherapy
  - Eliciting anti-tumor cytotoxic T cell responses



Established tumors are poorly immunogenic

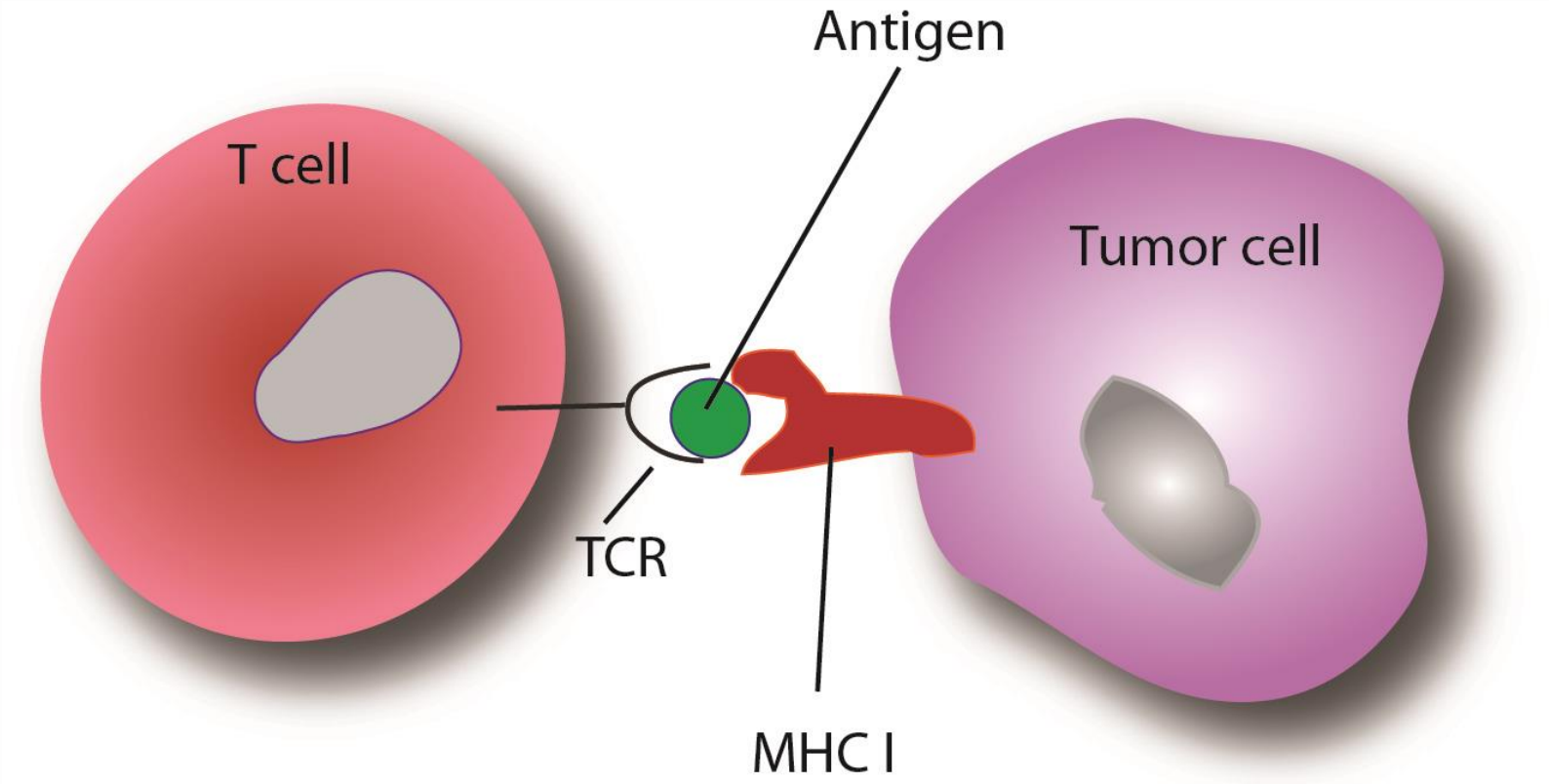


Bottlenecks

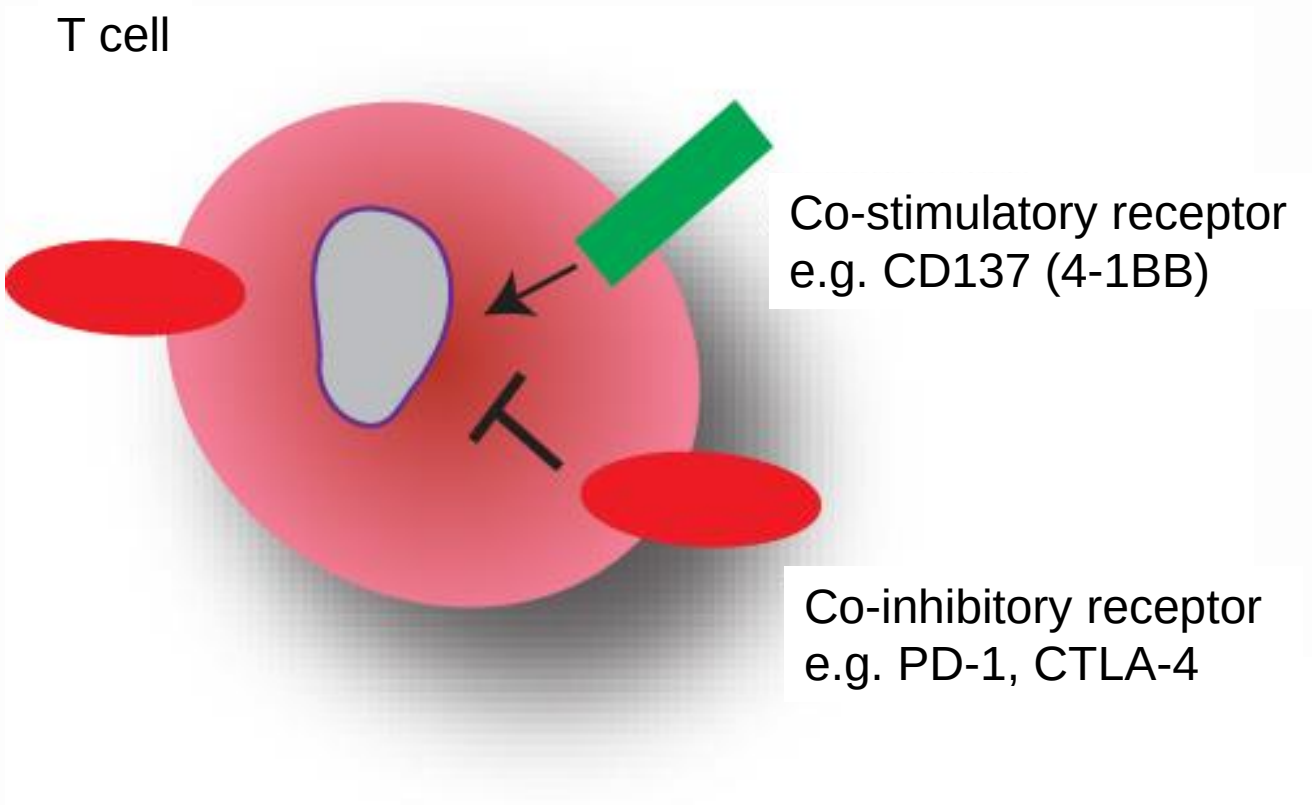
- Lack of ‘foreign’ antigens
  - T cells do not recognize tumor cells
- Inhibition CTL activity by tumor / tumor micro-environment
  - PD-1 signaling
  - MHC I downregulation tumor cells

Inspired by: Grosso JF et al. Can Immunity 2013;13:5-18

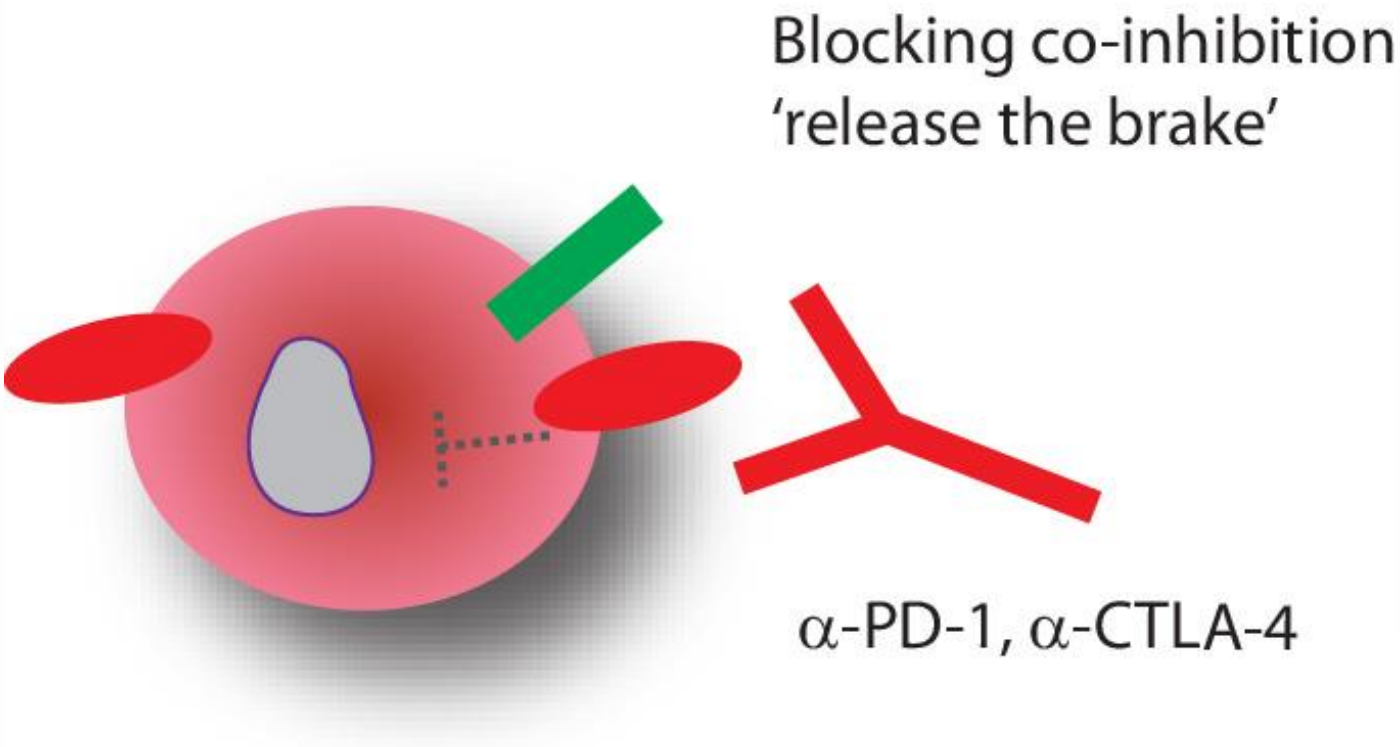
T cell-mediated immunotherapy; Signal (1) TCR triggering



T cell-mediated immunotherapy; Signal (2) co-stimulation



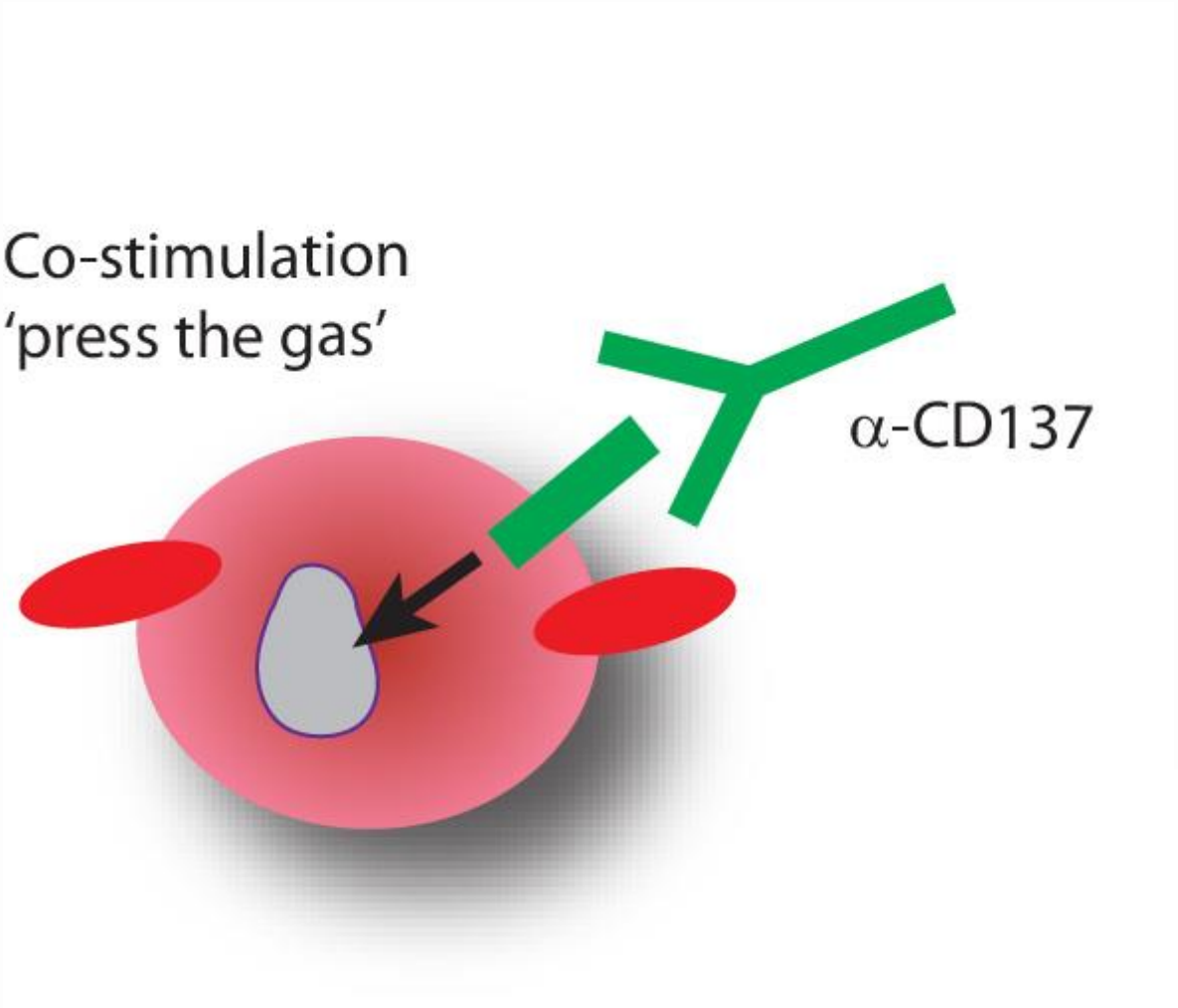
Antibody-based immune-modulation



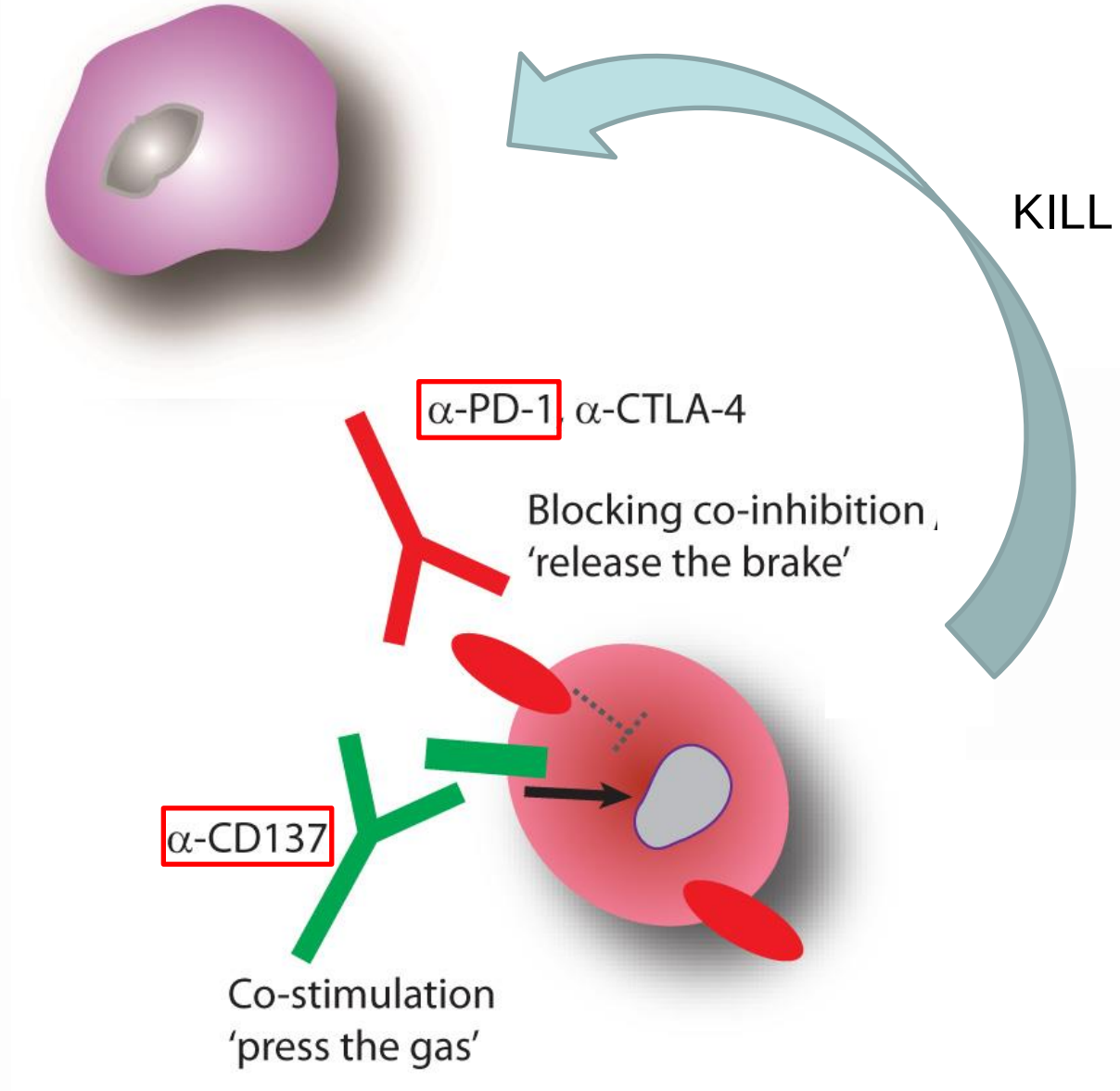
Pembrolizumab
Nivolumab

Ipilimumab

Antibody-based immune-modulation



Antibody-based immune-modulation



Problem:

Immunotherapy as single-agent promising, but sub-optimal

Solution:

Combine immunotherapy with radiotherapy

‘Radio-immunotherapy’

Radiotherapy

DNA damage

1. <u>Reducing tumor cell clonogenicity</u>

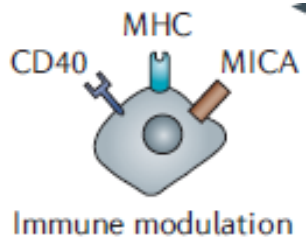
- (Irreversible) cell cycle arrest
- Mitotic catastrophe
- Apoptosis

Radiotherapy

DNA damage

1. Reducing tumor cell clonogenicity
   - (Irreversible) cell cycle arrest
   - Mitotic catastrophe
   - Apoptosis

2. Immunomodulatory effects
   - Induce anti-tumor immune responses through release of tumor Ags
   - Upregulate MHCI



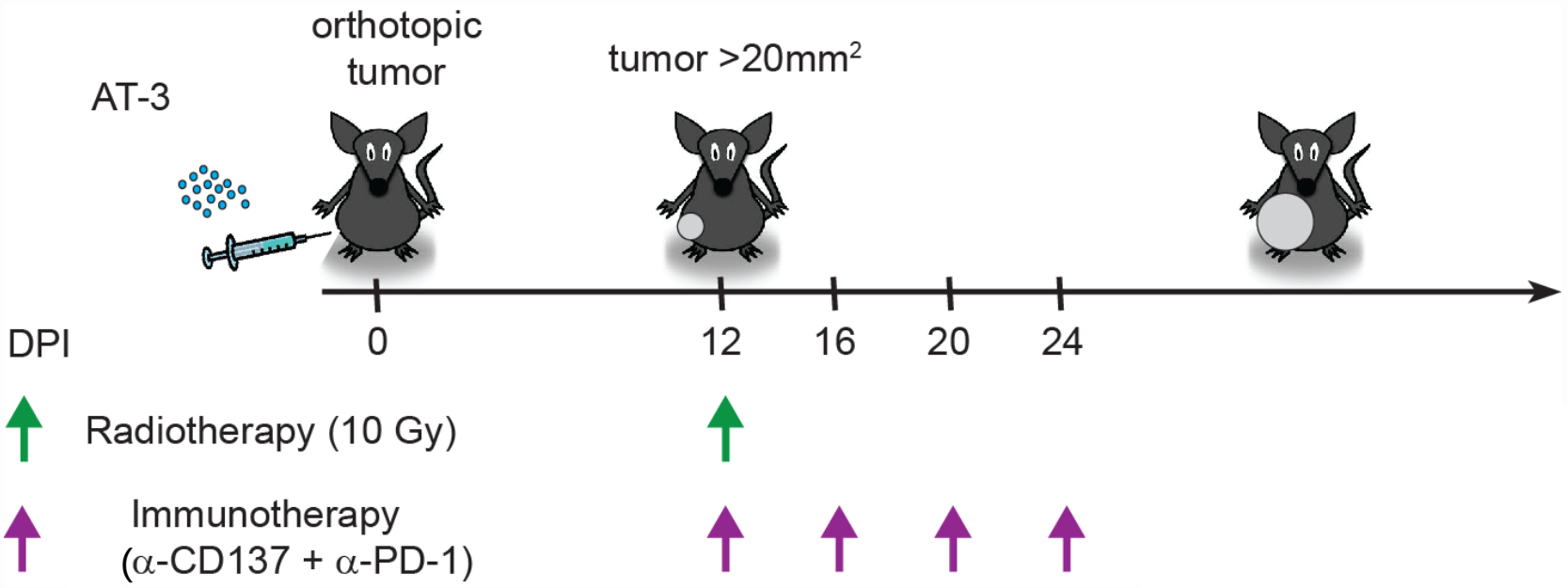
1) Efficacy?

2) Mechanism?

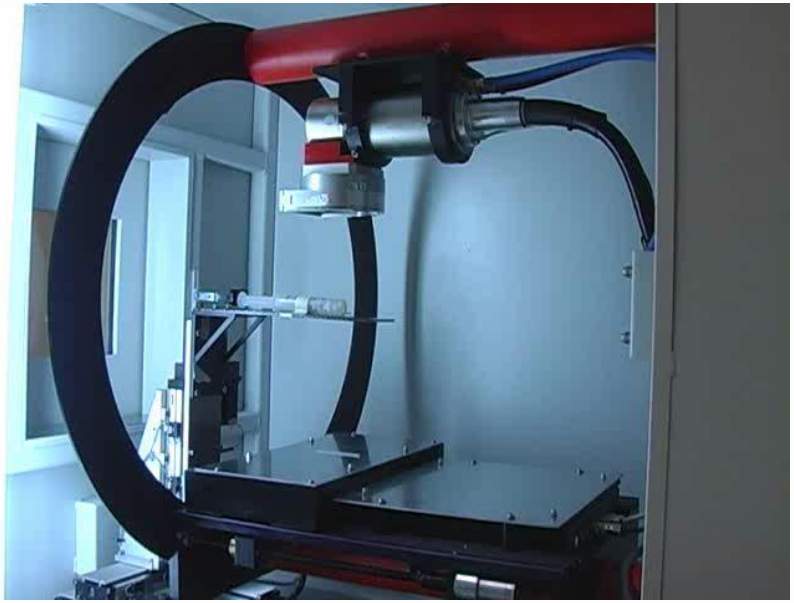
3) Potential applications?

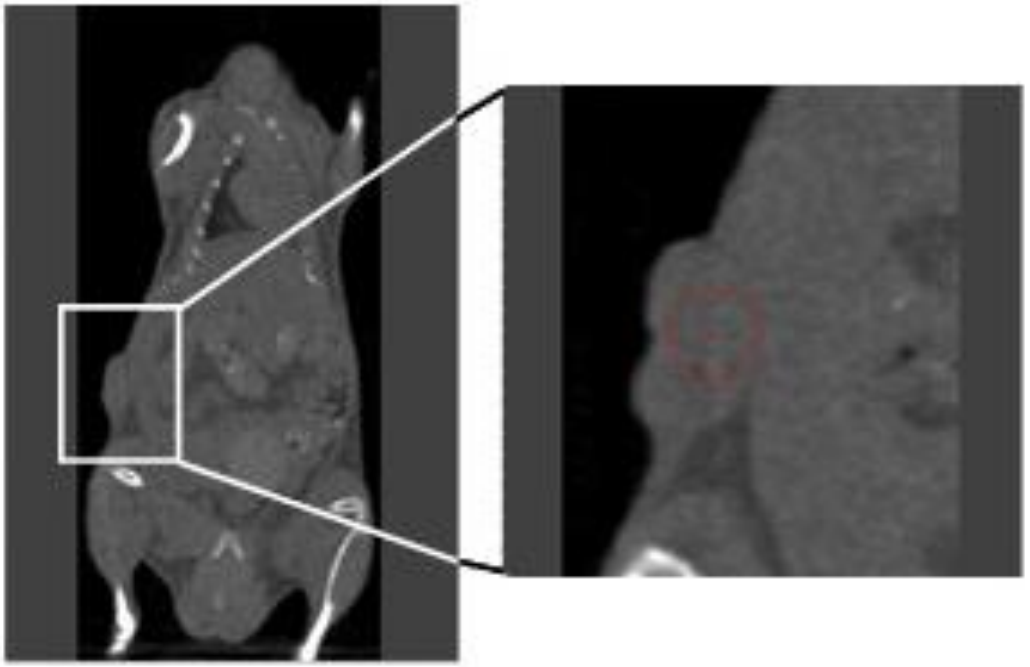
Transplantable AT-3 breast cancer model

- Triple-negative breast cancer cell line



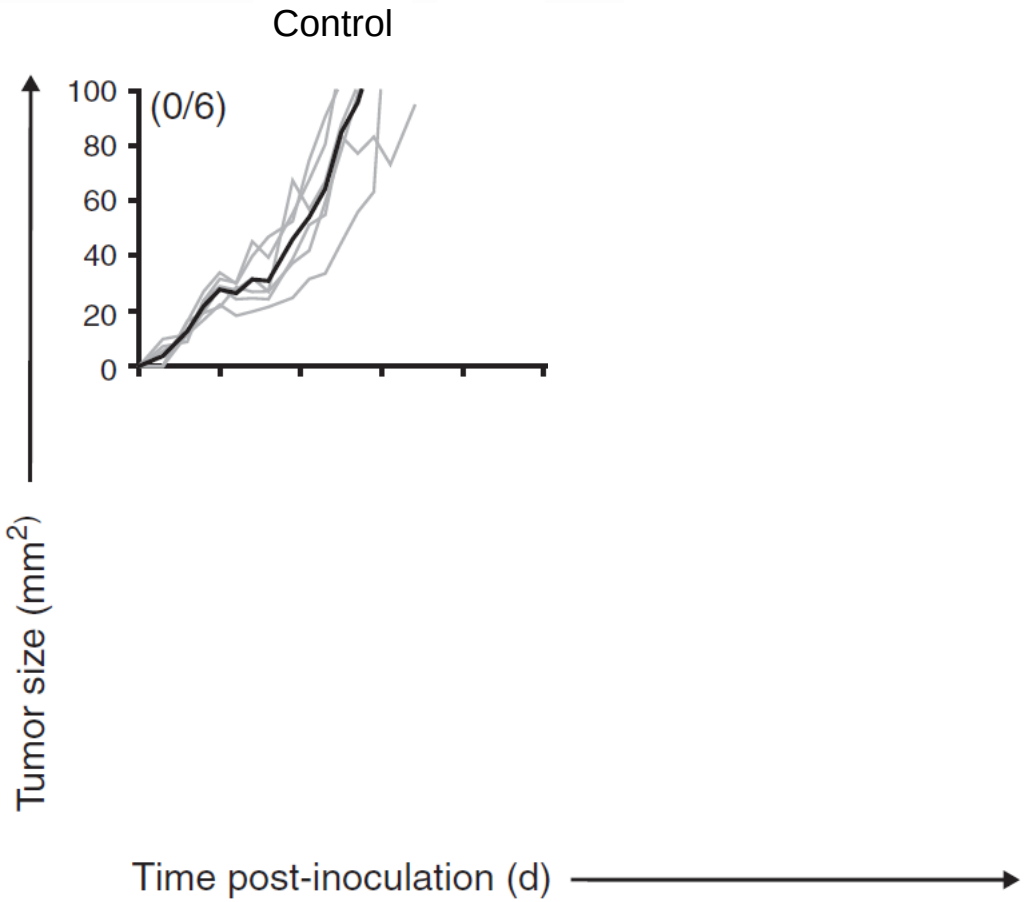
Small animal Image-Guided Radiotherapy





Movie: Jan-Jakob Sonke

Radiotherapy improves the response to immunotherapy



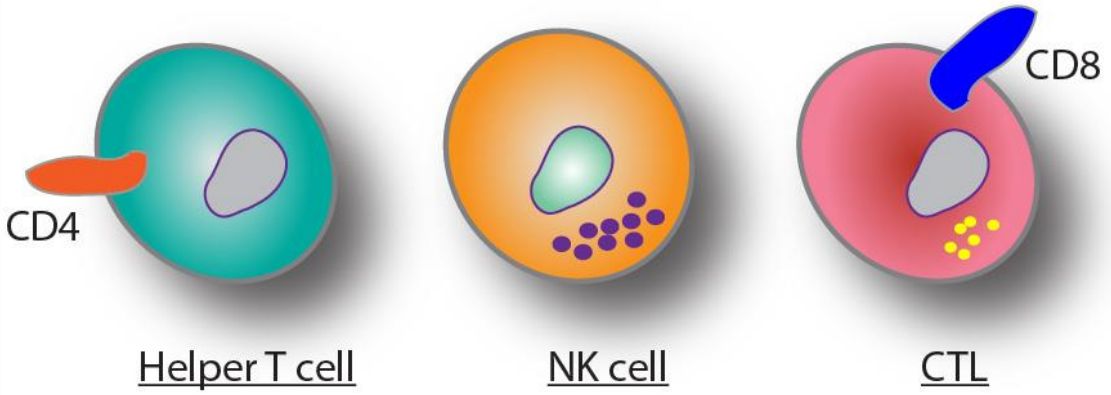
Verbrugge I et al. Cancer Res 2012;72:3163-3174

1) Efficacy?

2) Mechanism?

3) Potential applications?

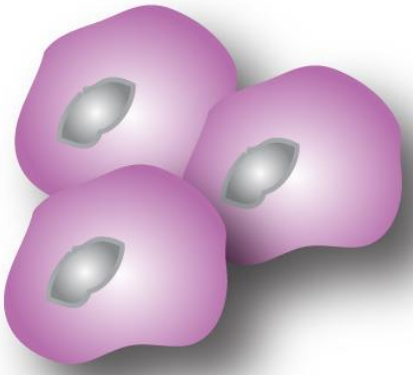
Immune cells



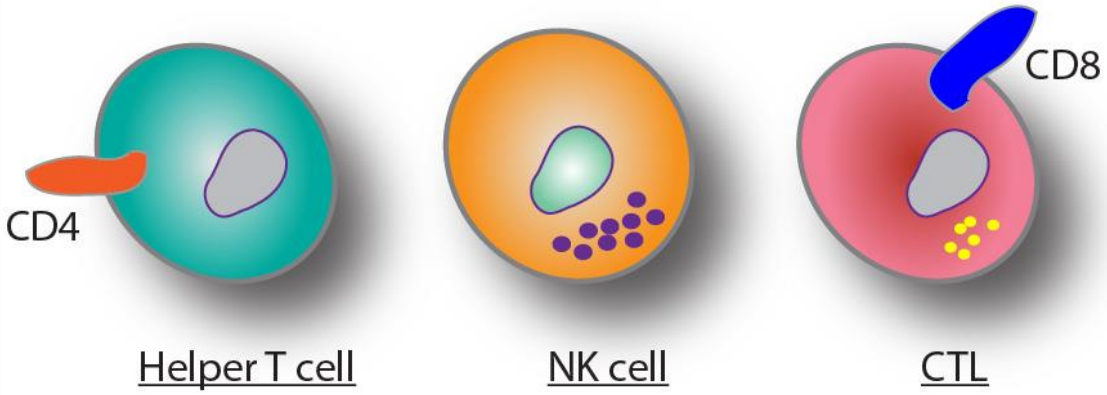
Helper T cell NK cell CTL

vs.

Tumor cells



Immune cells



Helper T cell NK cell CTL

vs.

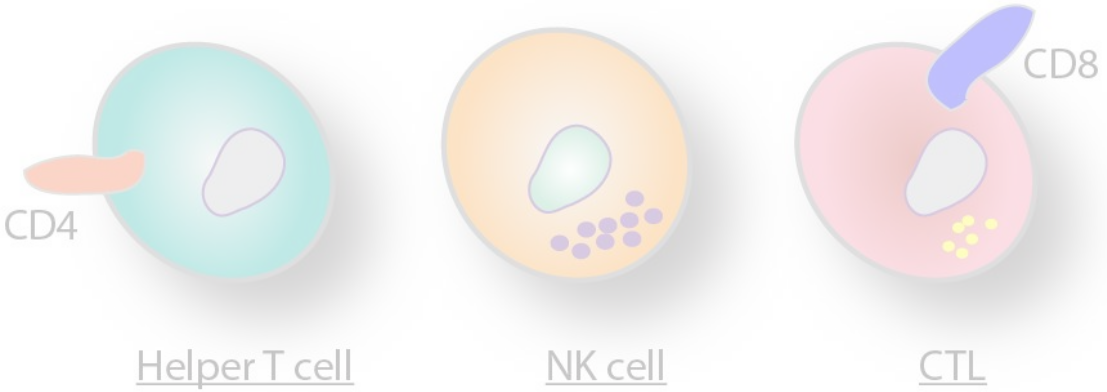
Tumor cells

CD8+ T cells crucial for radio-immunotherapy

IR+IT: radio-immunotherapy
Start Tx: Day 14
n = 6 mice /group

Verbrugge I et al. (2012) *Cancer Research*;72:3163-3174

Immune cells



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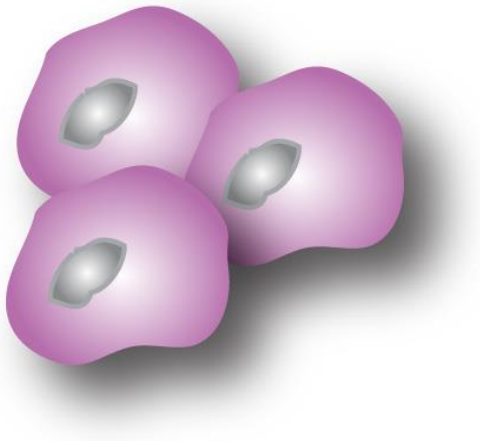
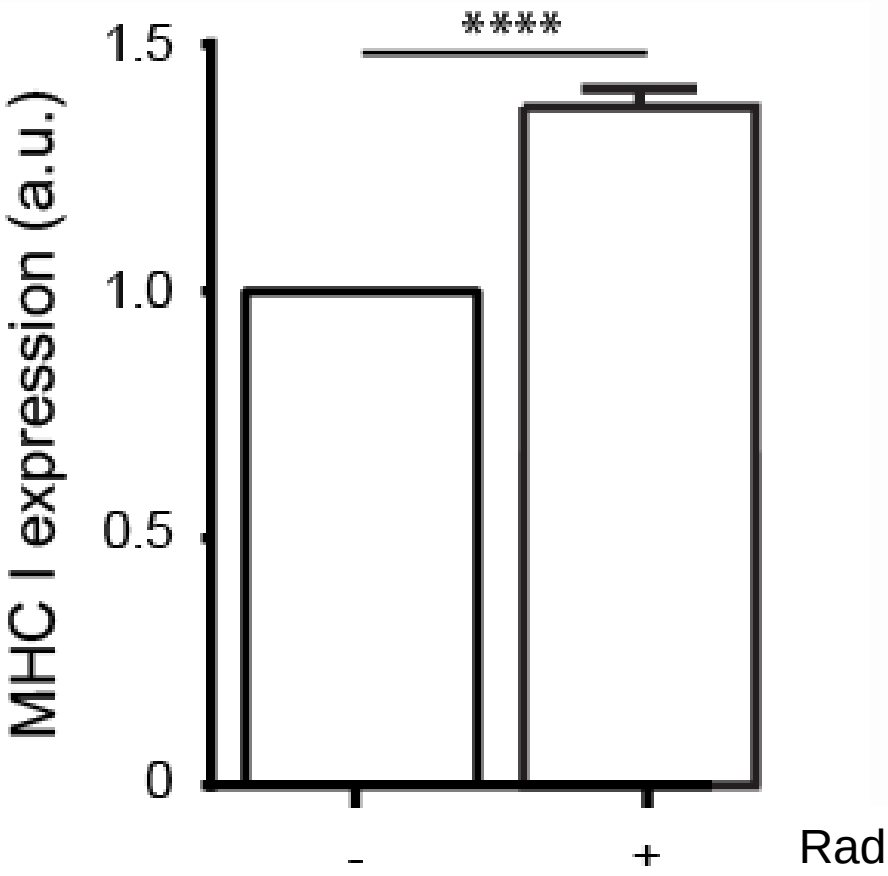
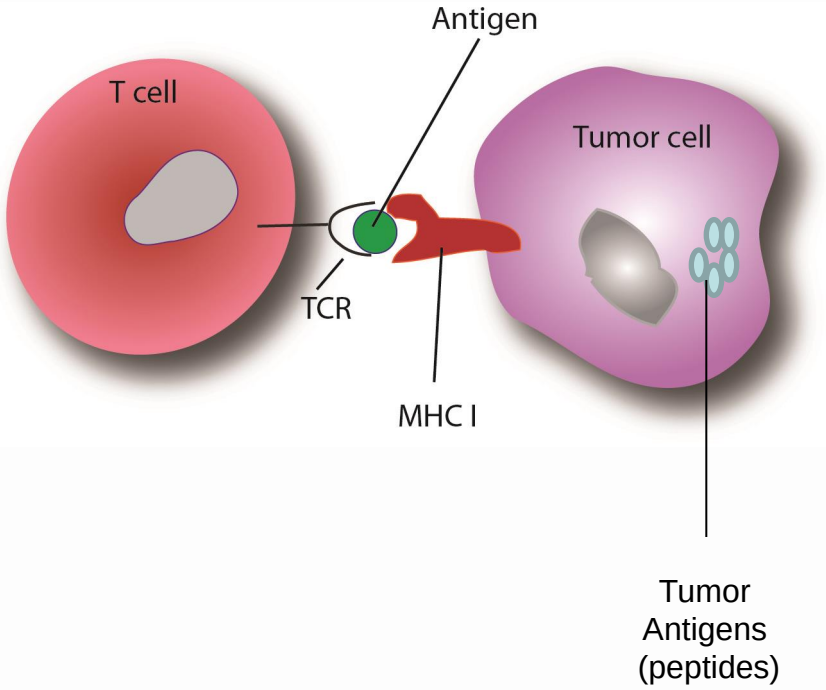
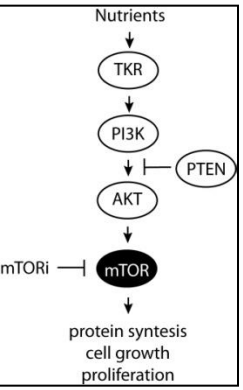


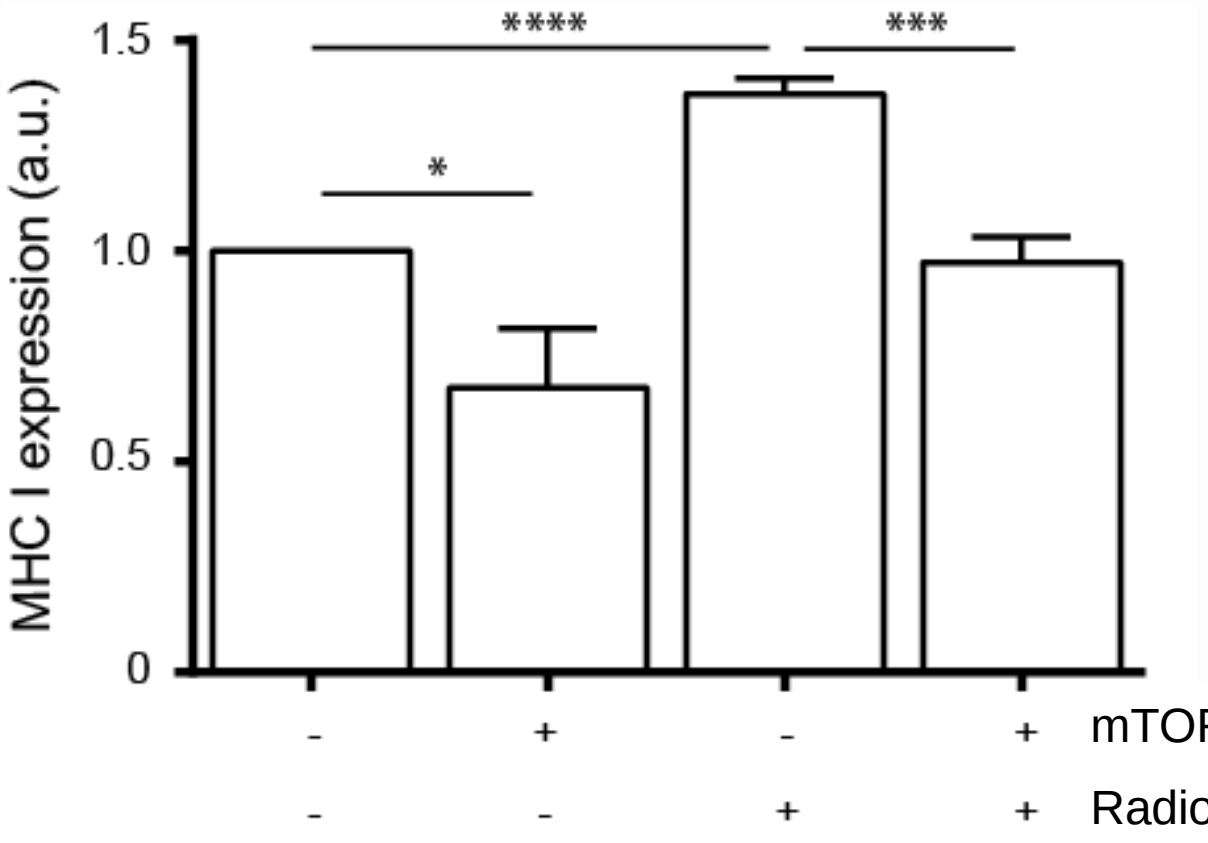
Radiotherapy upregulates surface MHC I on AT-3 tumor cells





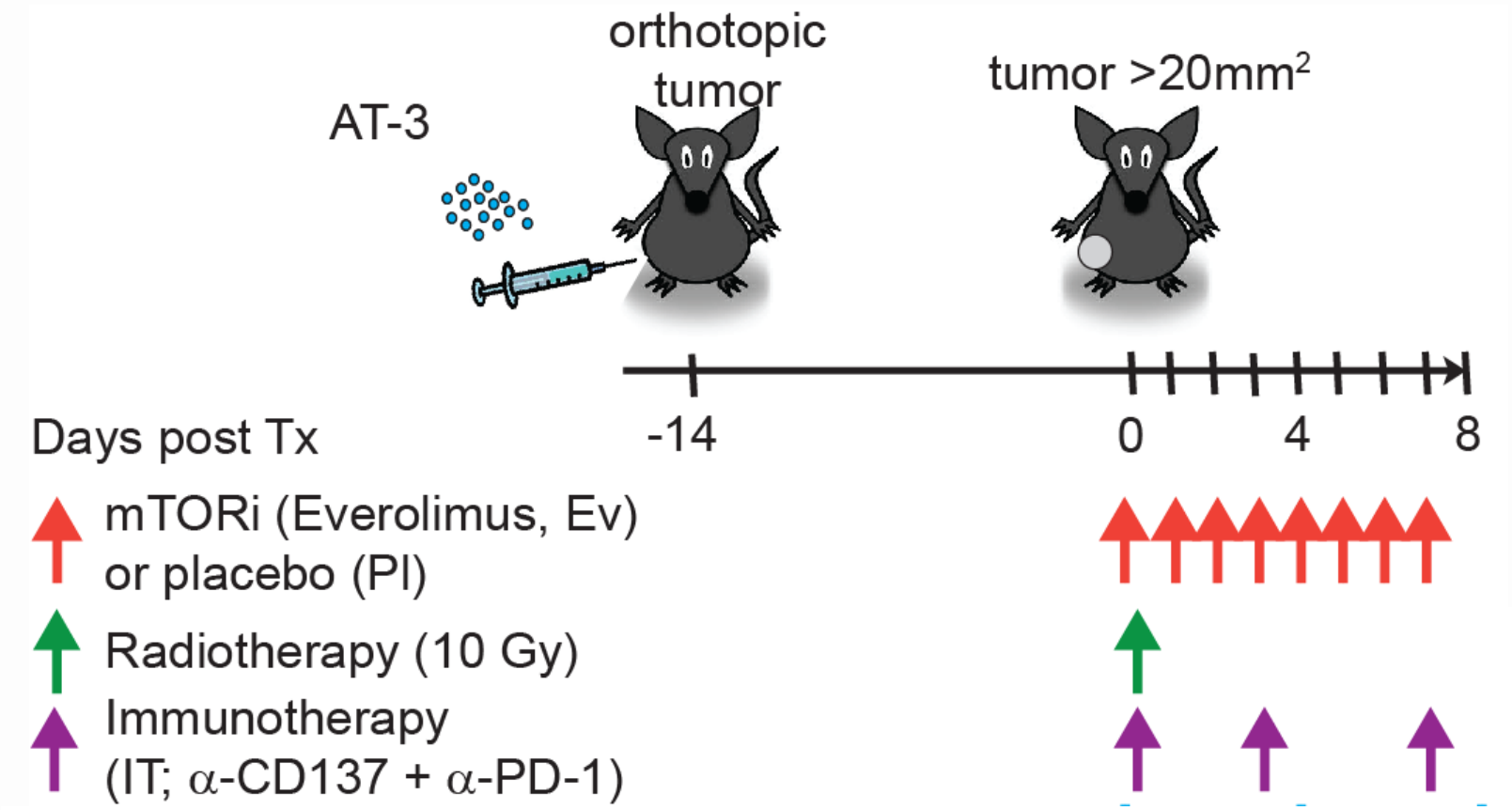
mTOR inhibition abrogates Radiotherapy-induced MHC I upregulation



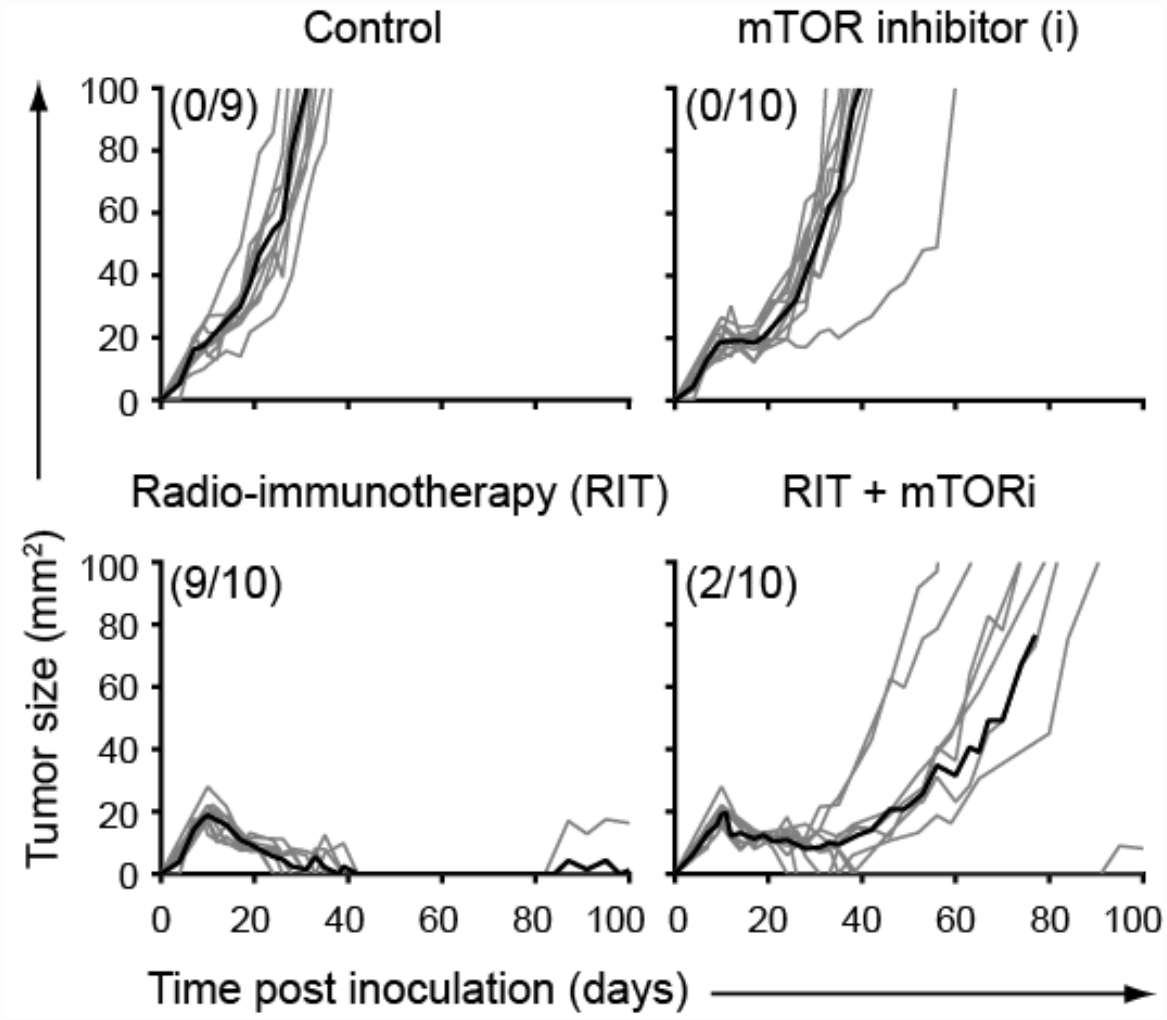


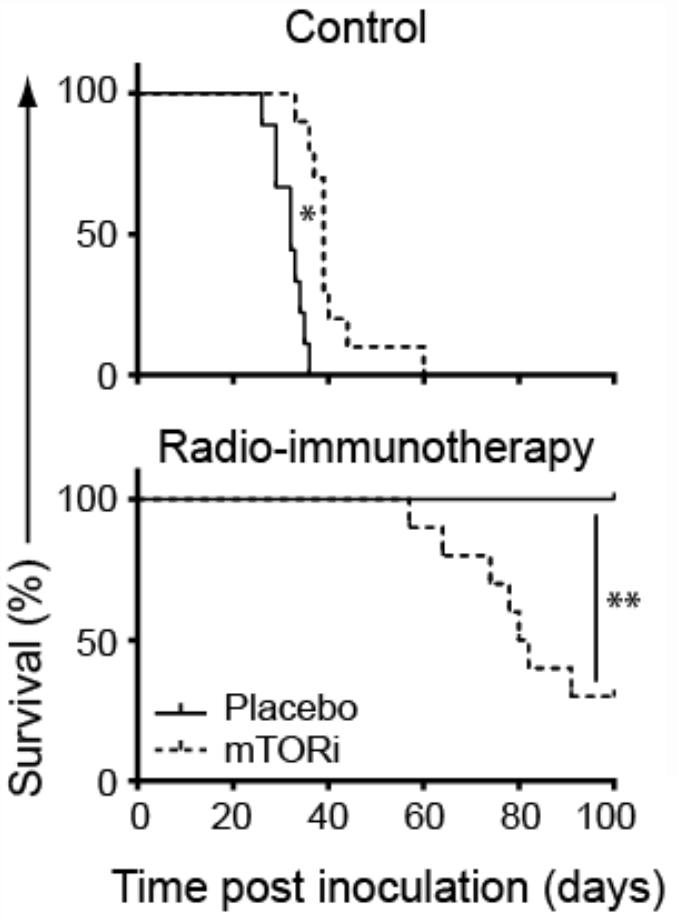
Verbrugge I et al. (2014) *Radiation Research*;182:219-229
Reits EA et al. (2006) *J Exp Med*; 203;1259-1271

Importance of mTOR signaling to the therapeutic effect of radio-immunotherapy



Inhibition of mTOR signaling abrogates the therapeutic response to radio-immunotherapy

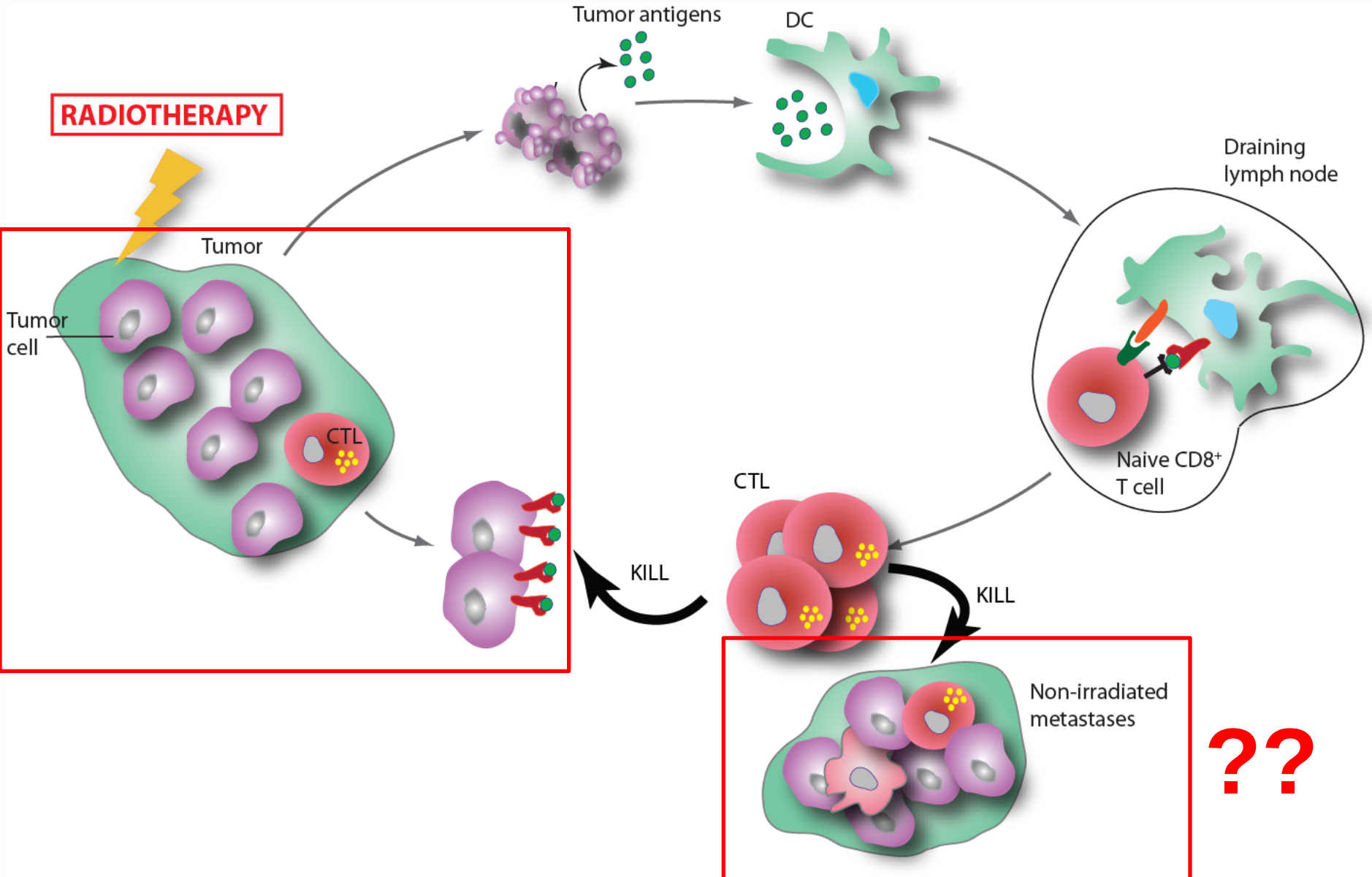




Parentheses: fraction tumor-free mice at day 100

Verbrugge I et al. (2014) *Radiation Research*;182: 219-229

Radio-immunotherapy: summary and potential applications



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