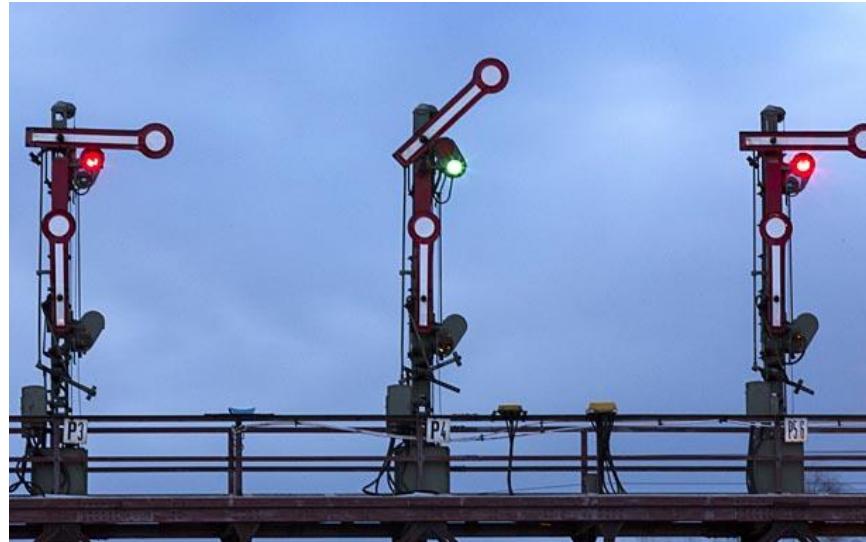


Immune Signalling



g. COMBATing Breast Cancer

CONFERENCE ON MOLECULAR BASIC AND THEAPEUTIC IMPLICATIONS IN BREAST CANCER

TraFo Symposium
10. - 11.11.2016
Tanja Fehm - Düsseldorf

„Improving Survival“
11. - 12. NOVEMBER 2016
DÜSSELDORF VAN DER VALK AIRPORTHOTEL

Thomas Karn

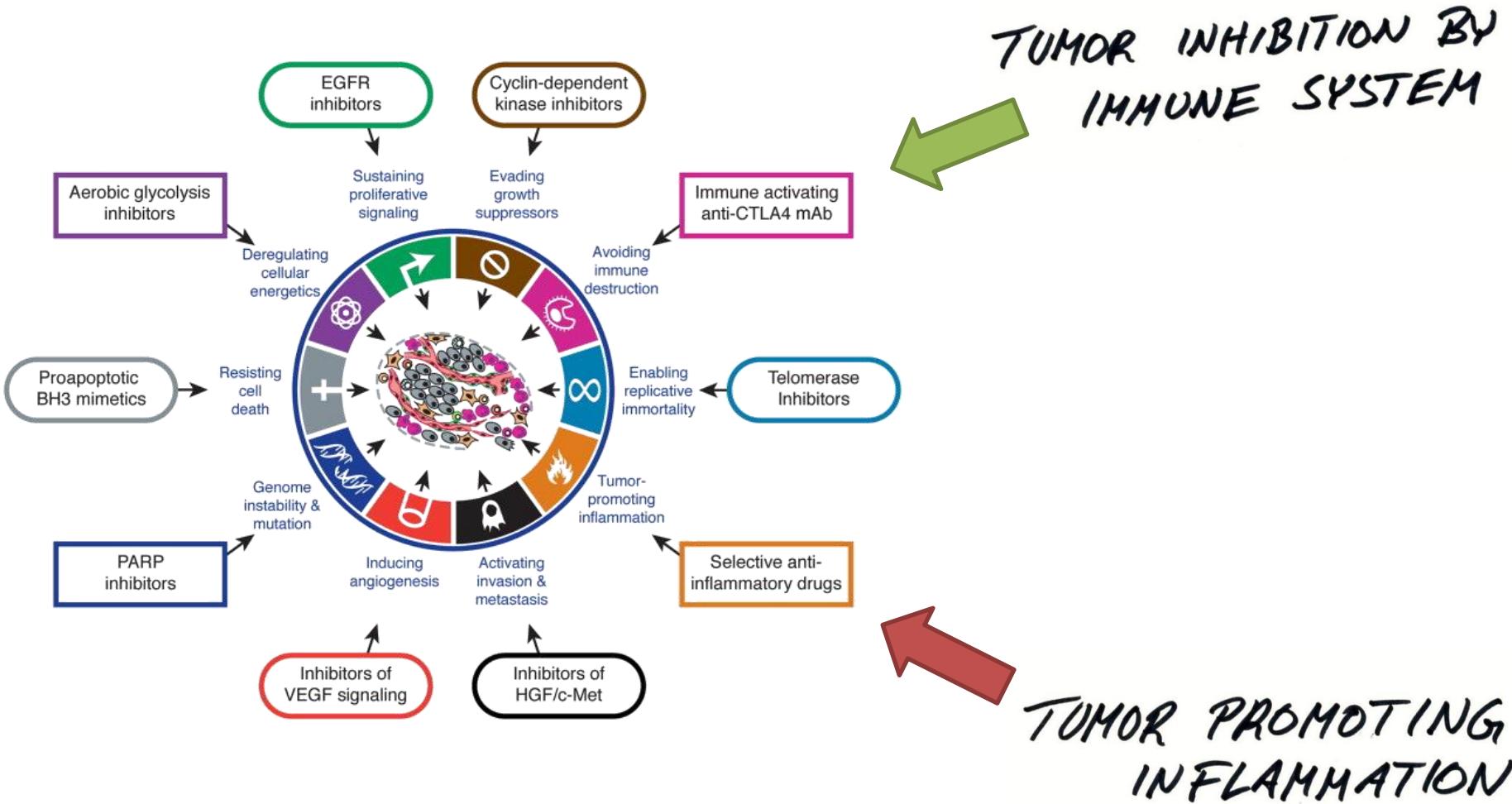
Klinik für Gynäkologie und Geburtshilfe
J.W. Goethe-Universität Frankfurt

Dept. Gynecology and Obstetrics / Breast Unit
Goethe-University
Frankfurt am Main

Thema

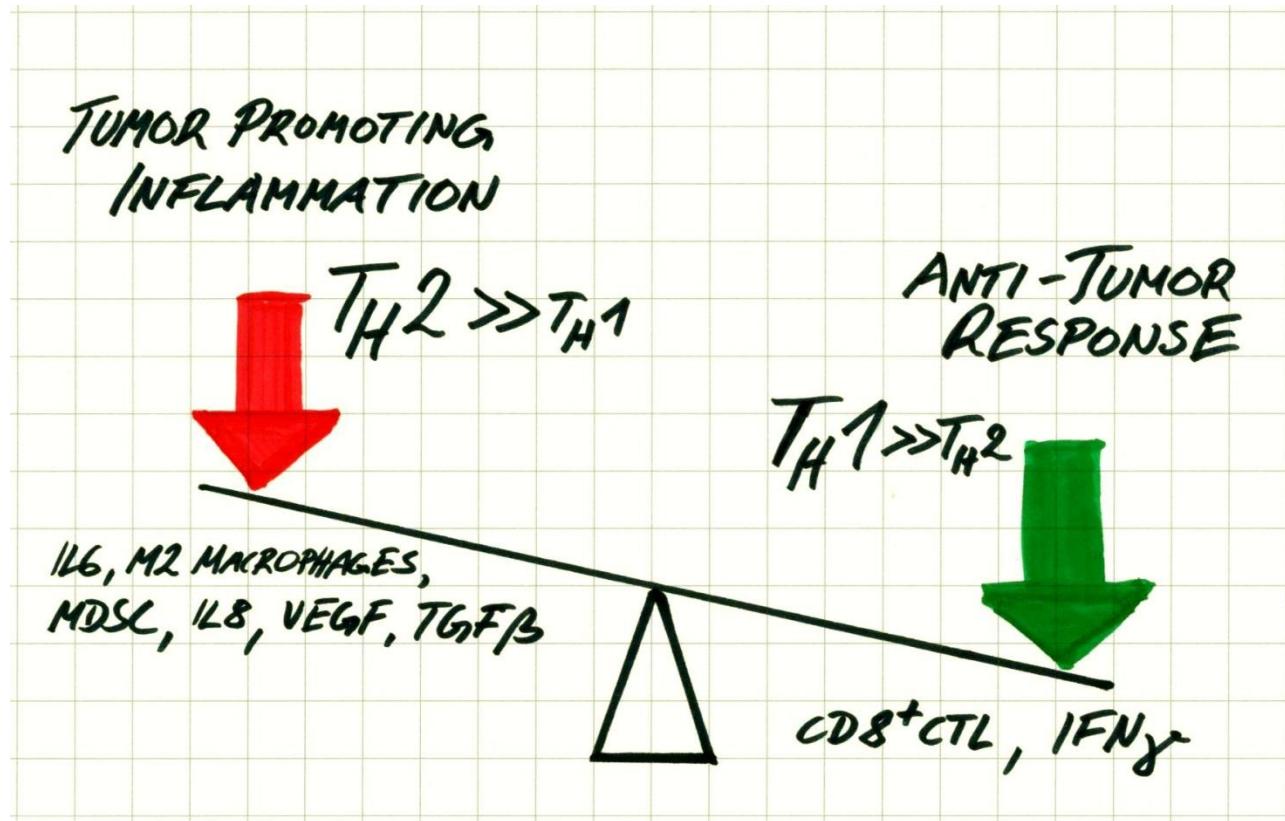
- Gleichgewicht der Tumorimmunität
- Die Rolle von Immune Checkpoints
- Prädiktive Faktoren
- Immune Editing und Escape

Immuno-oncology as a hallmark of cancer

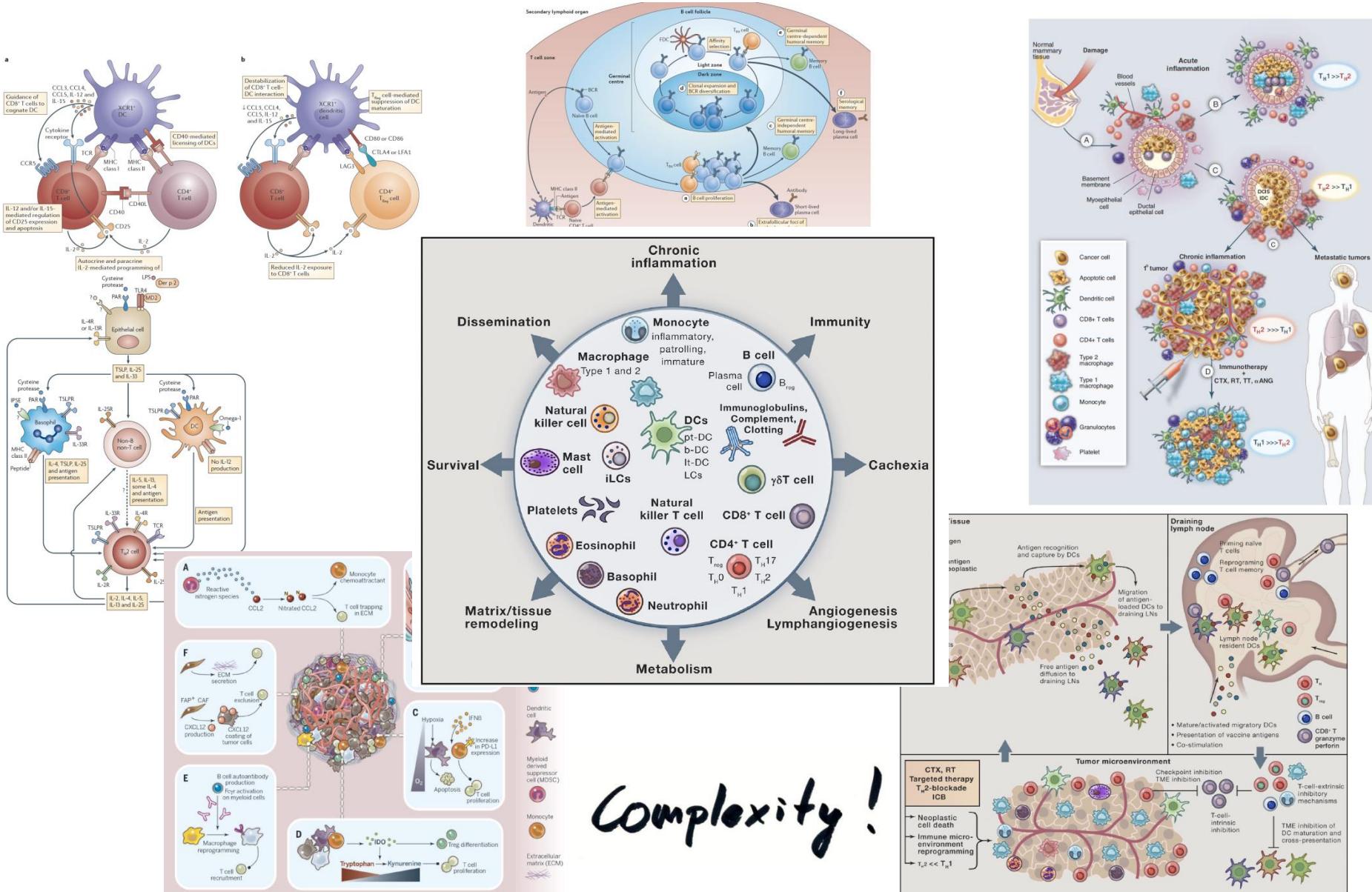


Hanahan and Weinberg 2011, Cell 144, 5, 646

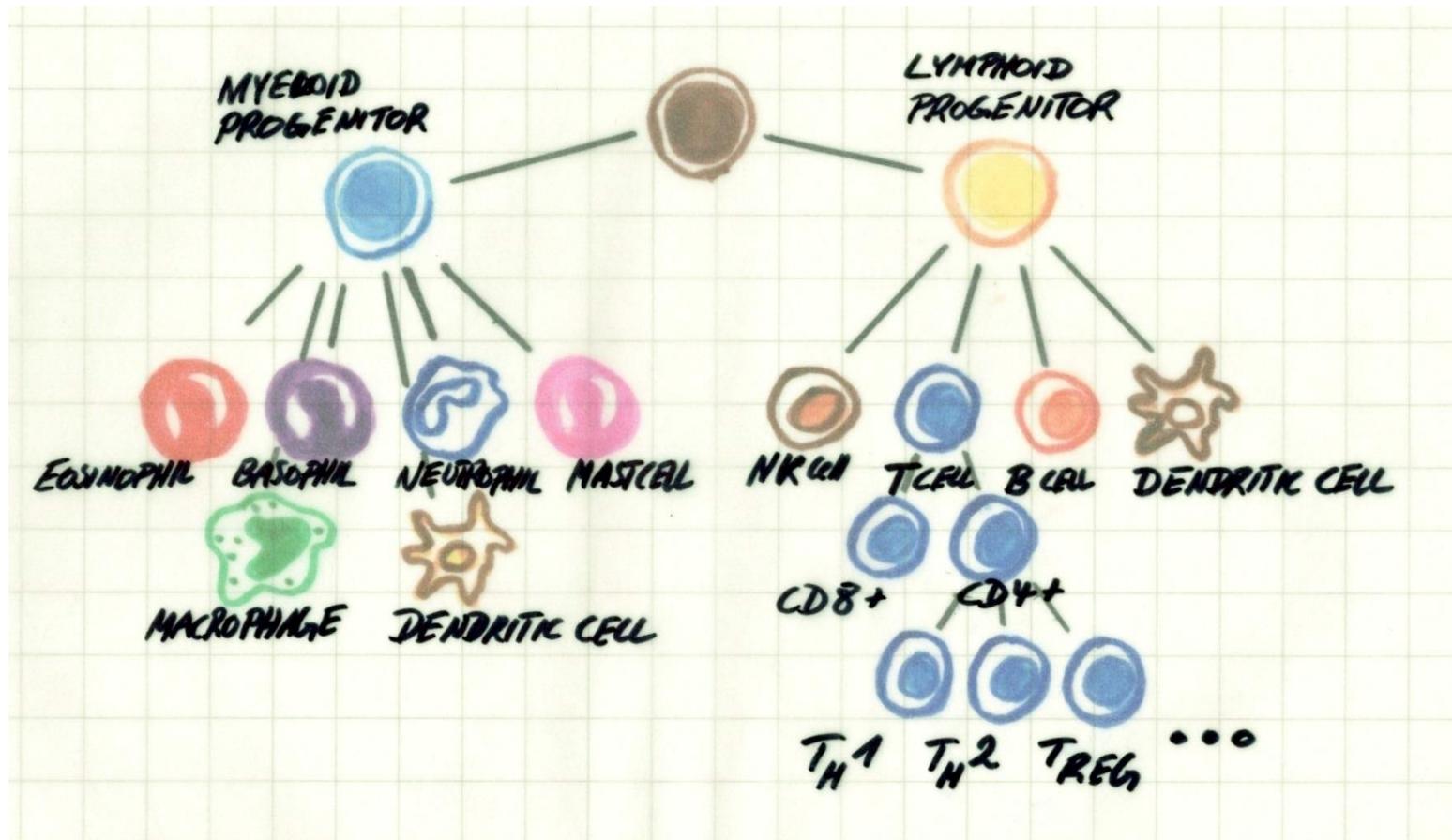
Balance of tumor immunity



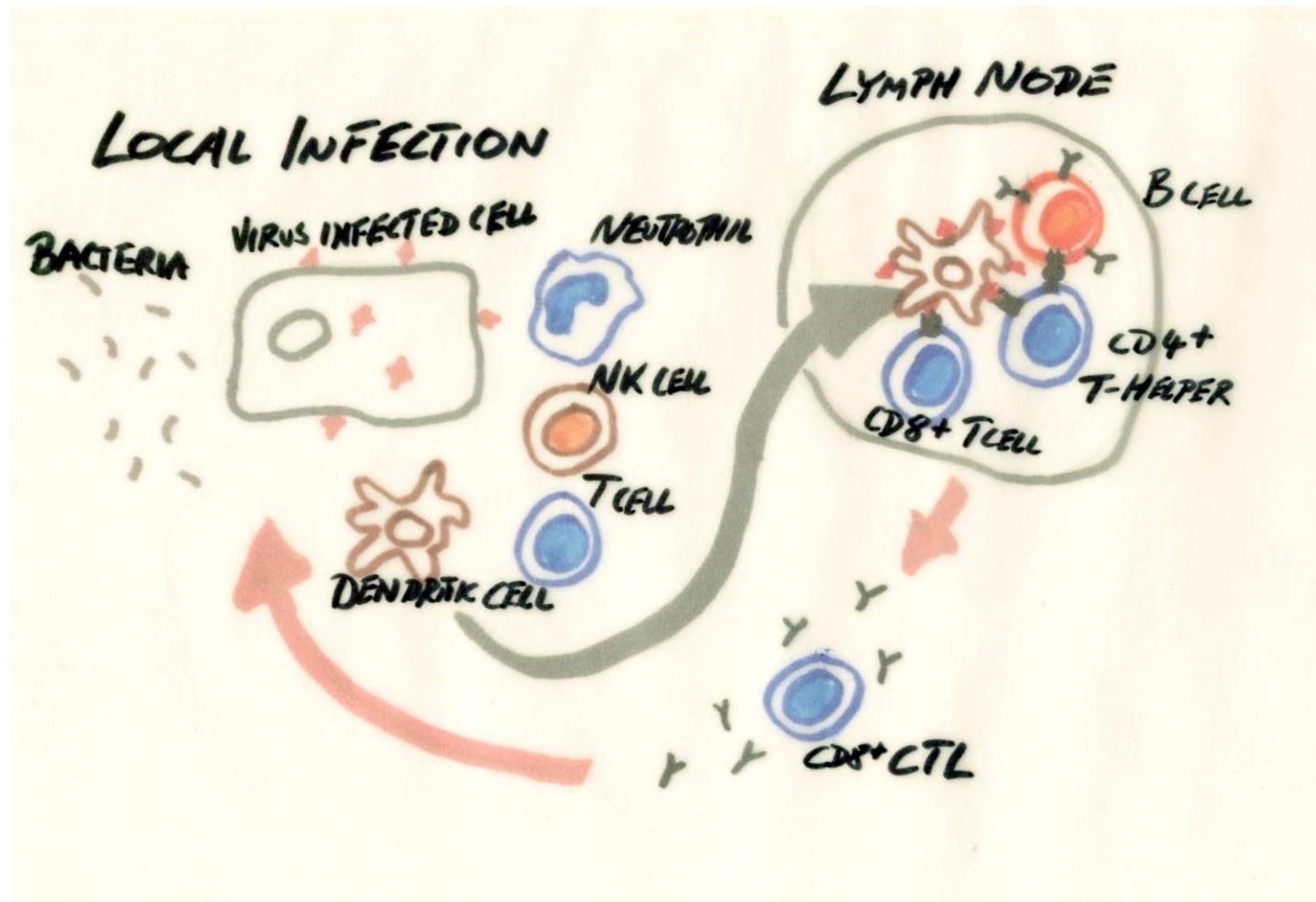
Tumor immunology is complex



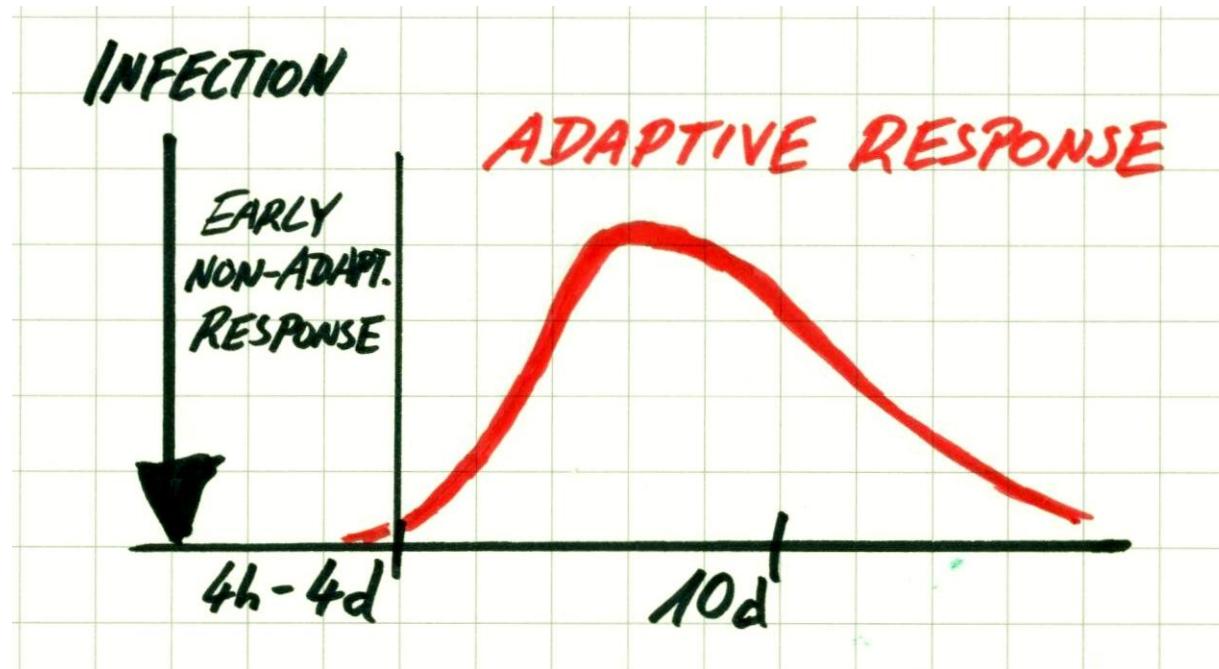
Immune cell types



Early and late adaptive response

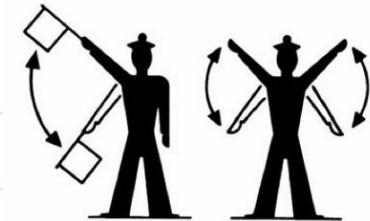


Timeline of immune response



Rapid on-/off-set of response

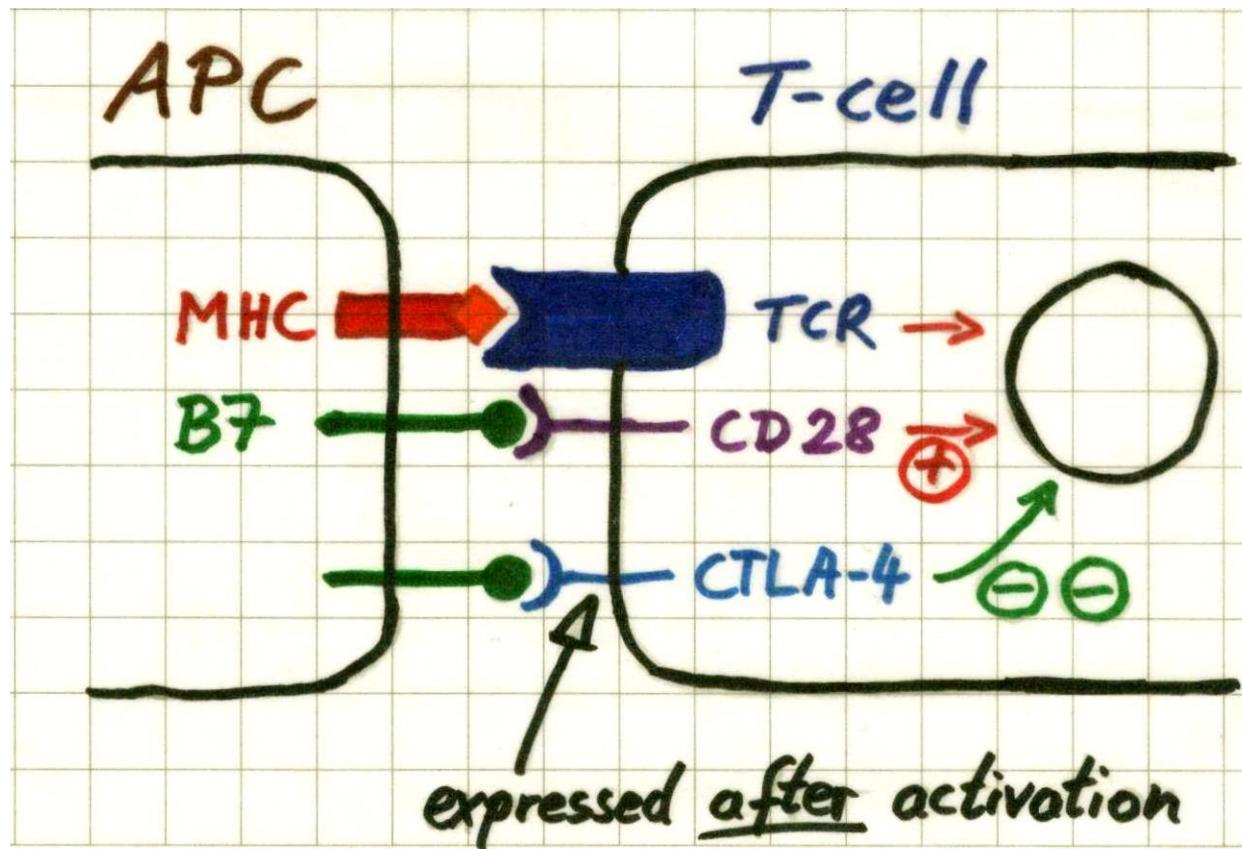
REGULAR INFECTION :



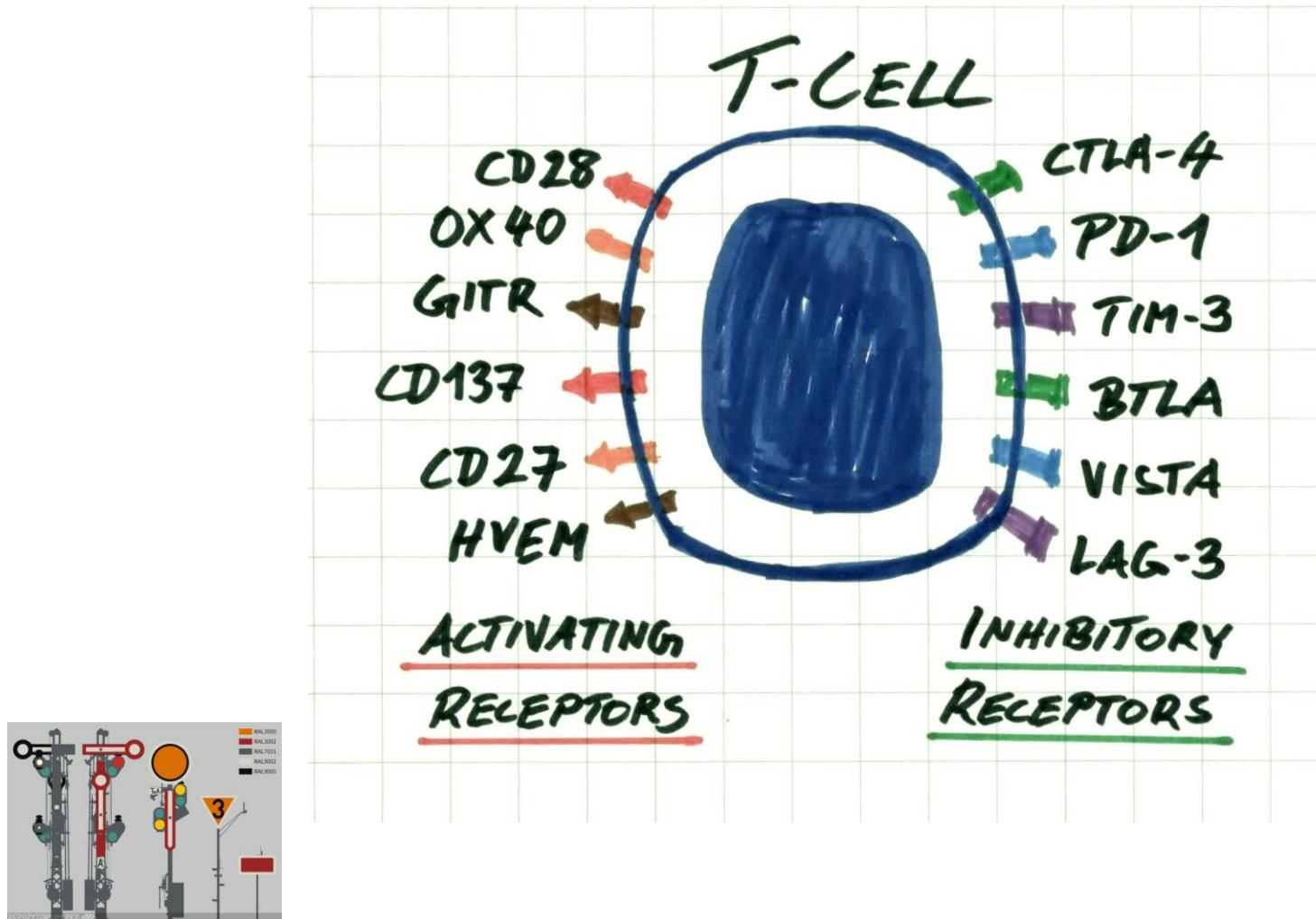
- POSITIVE SELECTION + RAPID ACTIVATION
- RESOLUTION OF INFECTION
- RAPID REPRESSION OF RESPONSE
- TIGHT FEEDBACK CONTROL
PREVENTS TISSUE DAMAGE

\Rightarrow POSITIVE + NEGATIVE REGULATION

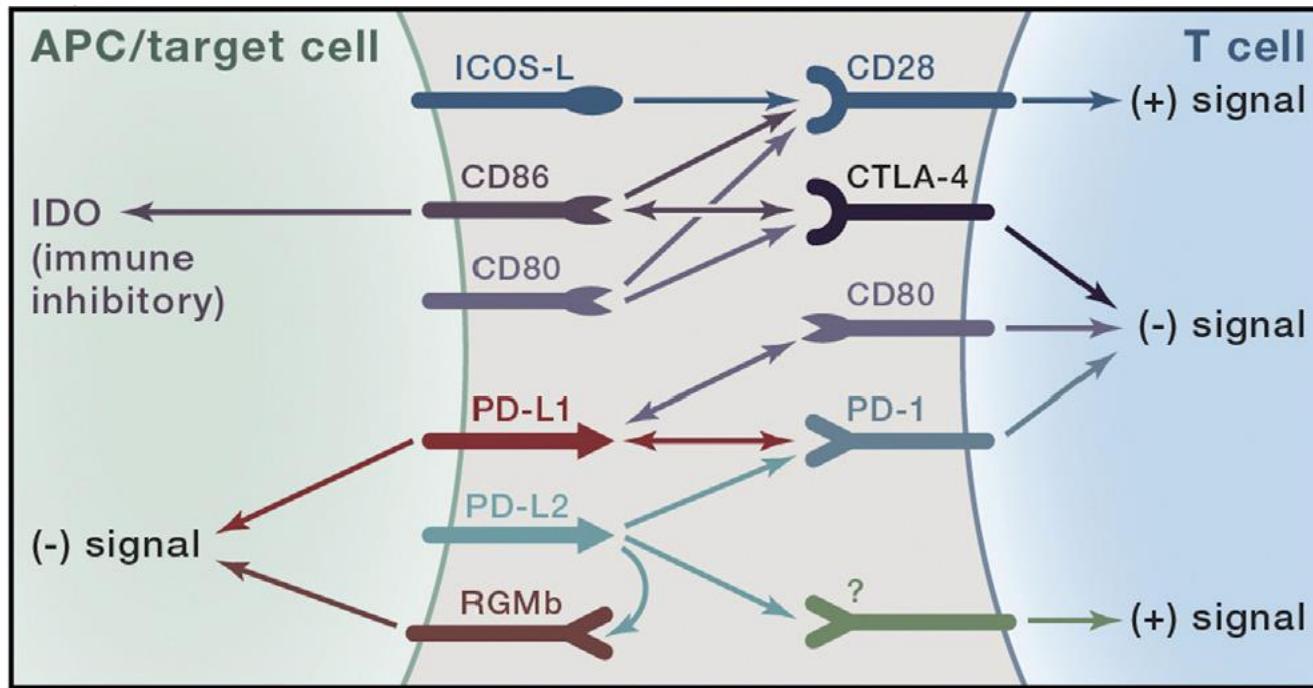
Co-stimulatory molecules



Co-stimulatory / co-inhibitory molecules

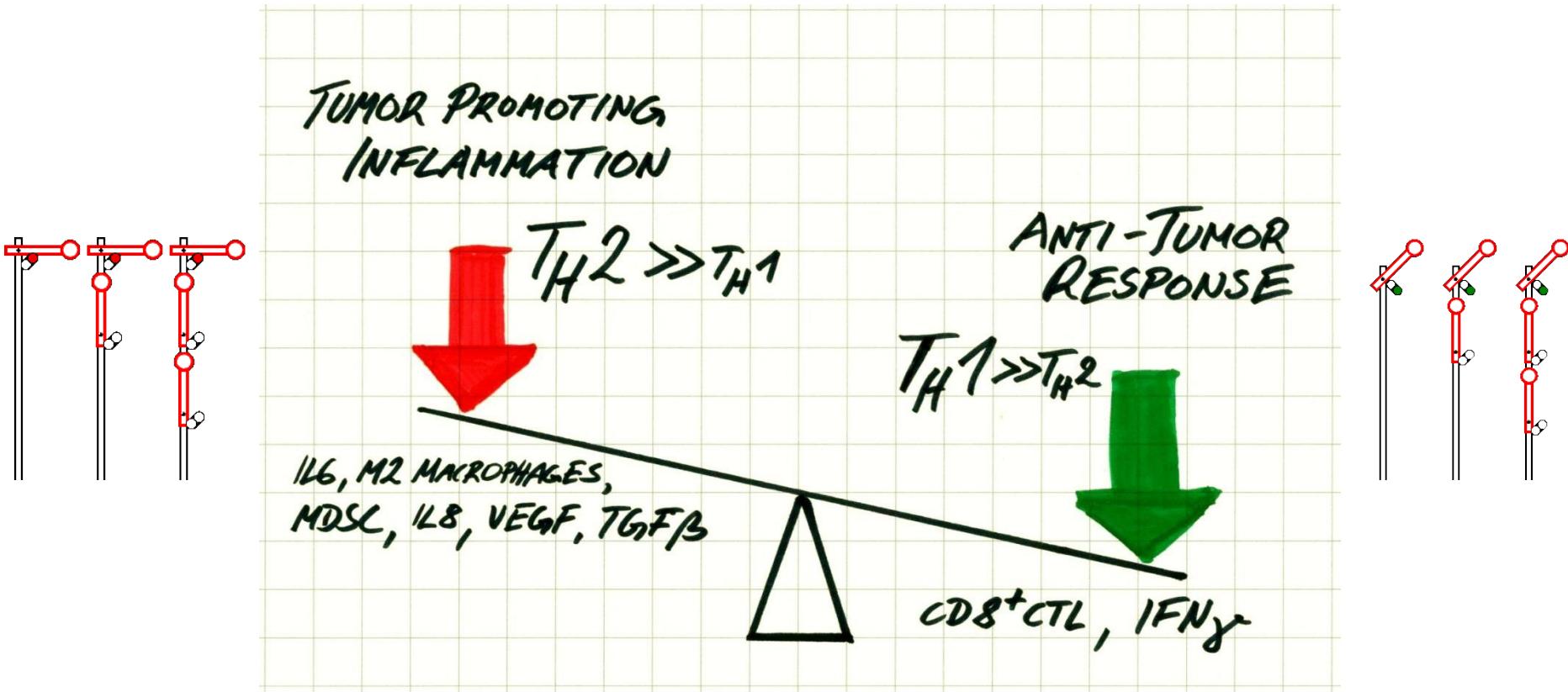


Complex interactions



Topalian et al. 2015 Cancer Cell, PMID 25858804

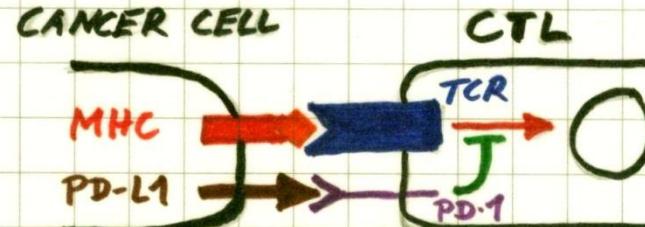
Chronic inflammation and cancer



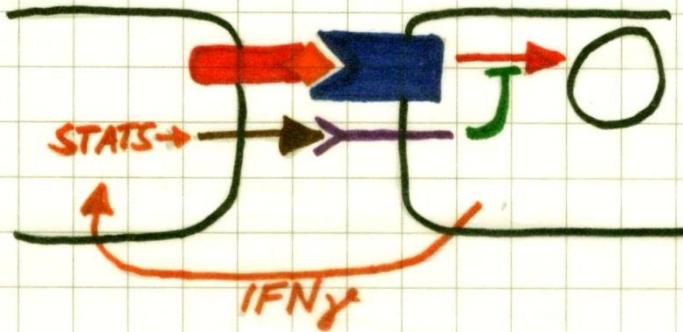
Tumor escape through PD-L1 expression



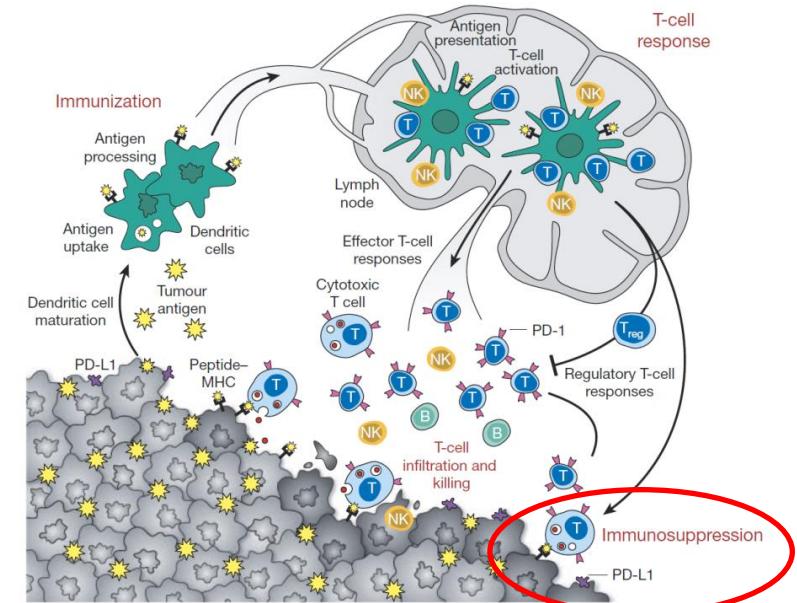
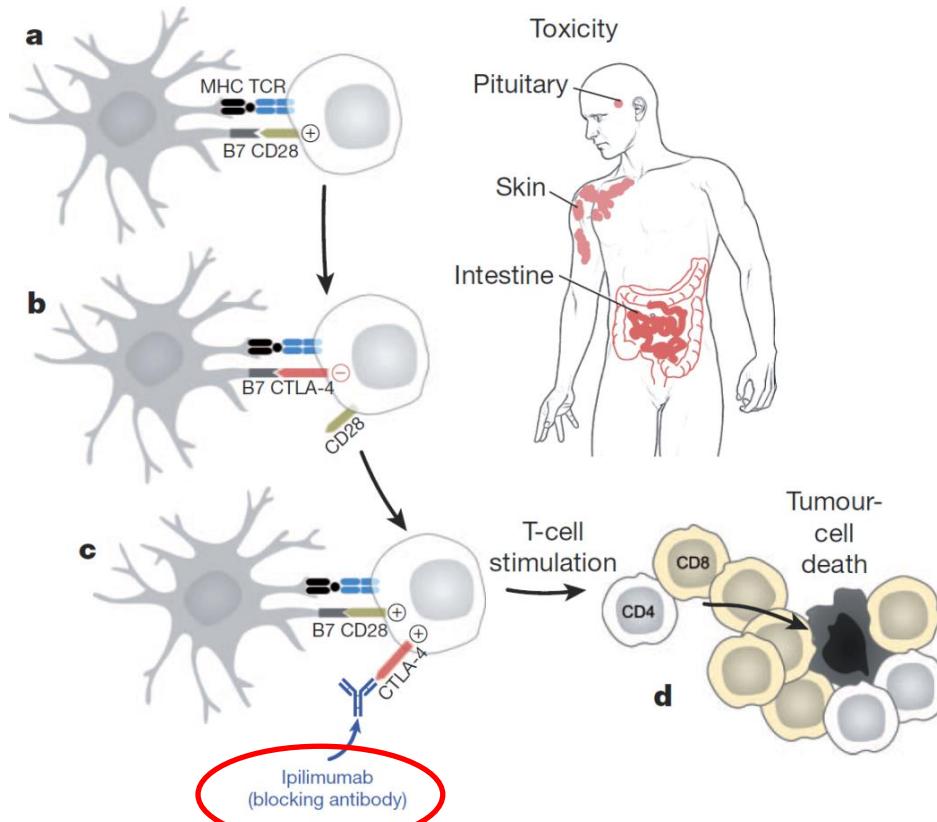
INTRINSIC RESISTANCE TO CTL



ADAPTIVE RESISTANCE TO CTL



The therapeutic potential of immunomodulation and immunotherapy



Mellman et al. 2011, Nature, PMID 22193102

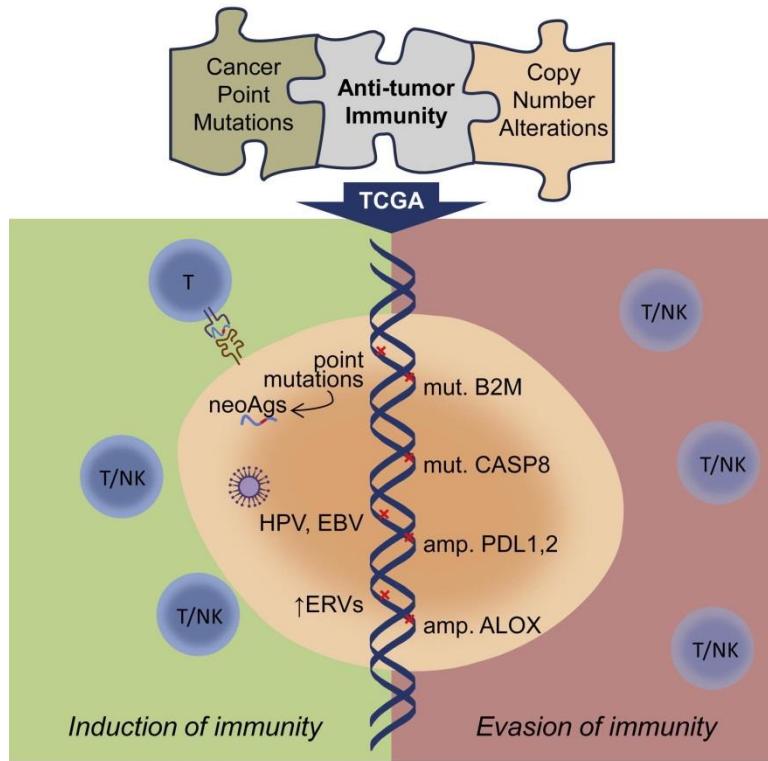
Predictive Factors for Immune Checkpoint Blockade

- Target expression (PD-1, PD-L1) problematic:
 - Antibodies & cutoffs (Kerr 2015 PMID 26134220, Patel 2015 PMID 25695955).
 - PD-L1 expression by infiltrating Lymphocytes (Herbst 2014 Nature PMID 25428504).
 - Negative cases may be strong responders (Postow 2015 JCO PMID 25605845, Topalian 2015 Cancer Cell PMID 25858804).
- Mutation/Neoantigen load:
 - Positive correlation with TIL in pan-cancer studies (Rooney 2015 Cell PMID 25594174).
 - Neoantigen load predictive for response (Snyder 2014 NEJM PMID 25409260, Rizvi 2015 Science PMID 25765070, Le 2015 NEJM PMID 26028255).
 - Clonal neoantigens associated with responders (McGranahan 2016 Science PMID 26940869).
- Signatures
 - BRCA2, IPRES (Hugo 2016 Cell PMID 26997480)
 - Immune signatures (Chen 2016 Cancer Discovery PMID 27301722)
- TCell-/BCell-clonality?

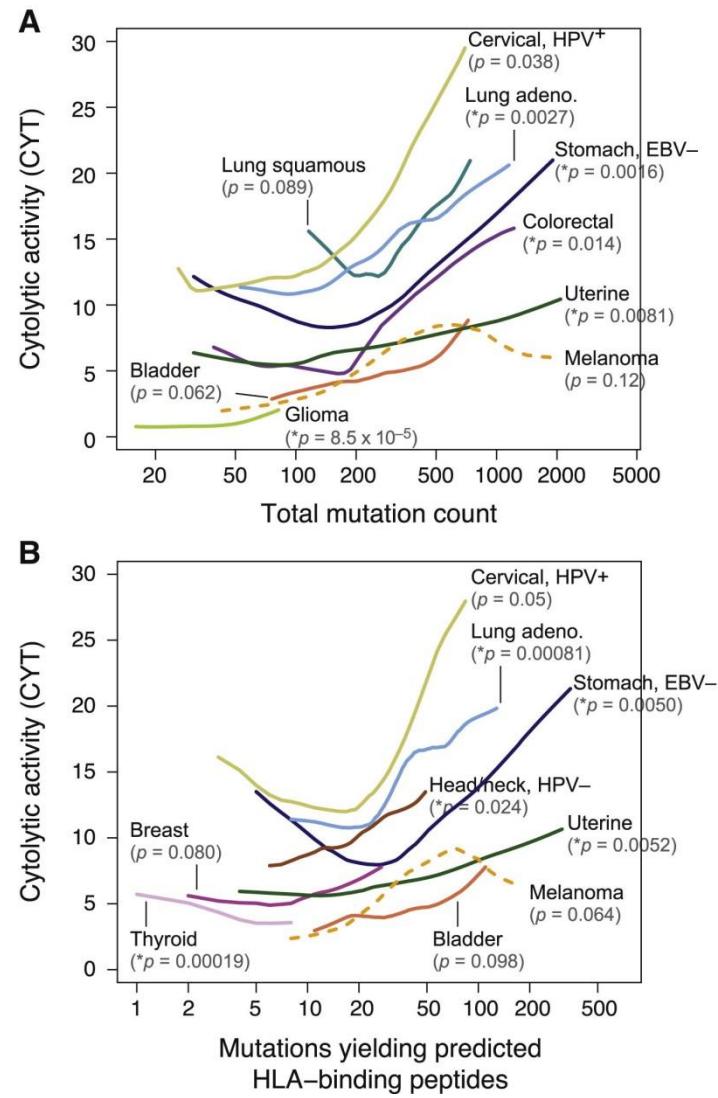


Genomics of TIL⁺ Cancer

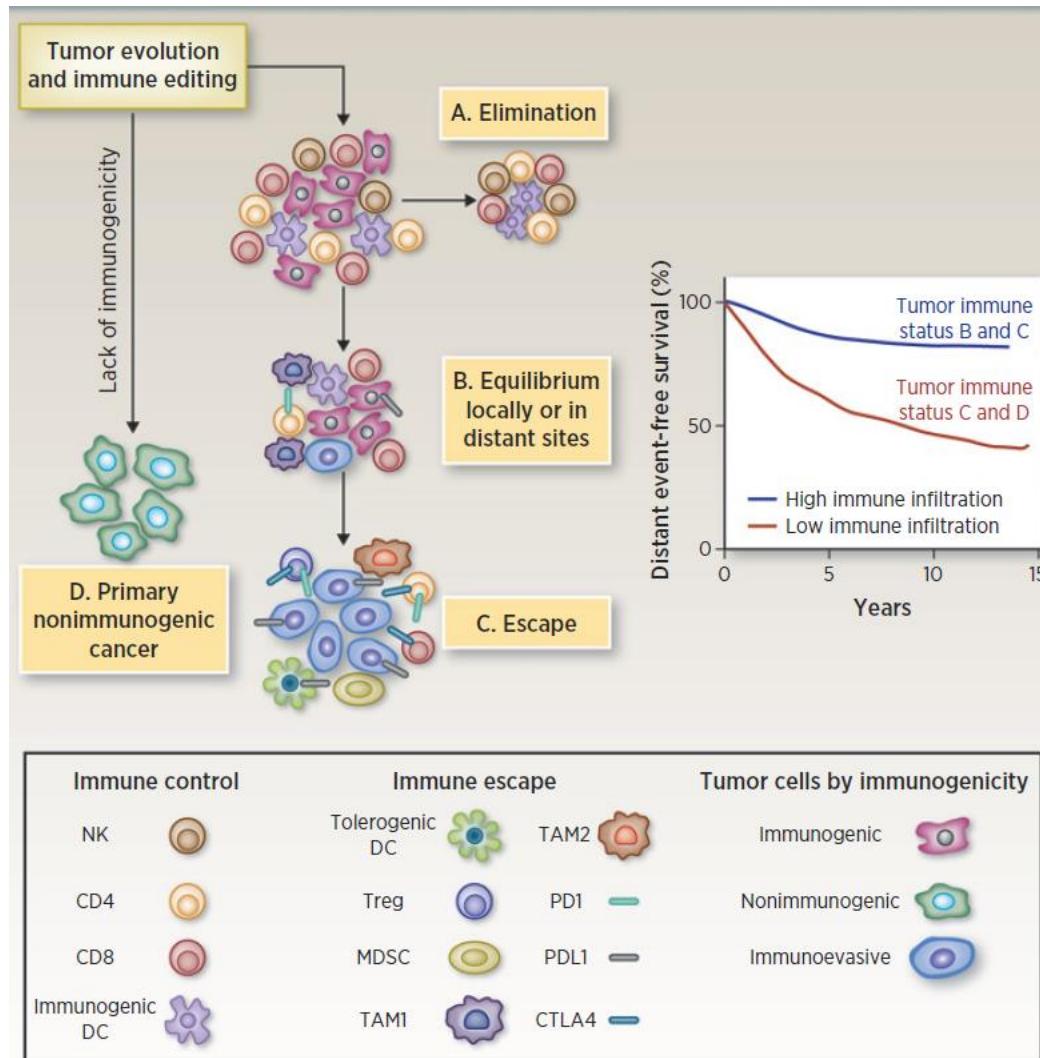
- 8462 TCGA samples
- “CYT” metric (GZMA & PRF1 expression)



Rooney et al. 2015 Cell, PMID 25594174



Cancer Immunoediting



Pusztai, Karn et al. 2016 Clin Cancer Res, PMID 26867935

Zusammenfassung

- Gleichgewicht zwischen gegenläufiger T_H1 - und T_H2 -Antwort des Immunsystems auf die Tumorerkrankung.
- Checkpoint-Blockade verschiebt das Gleichgewicht zur T_H1 -Antwort.
- Suche nach prädiktiven Faktoren
- Immunoediting kann wieder zu Escape und Relapse führen.

