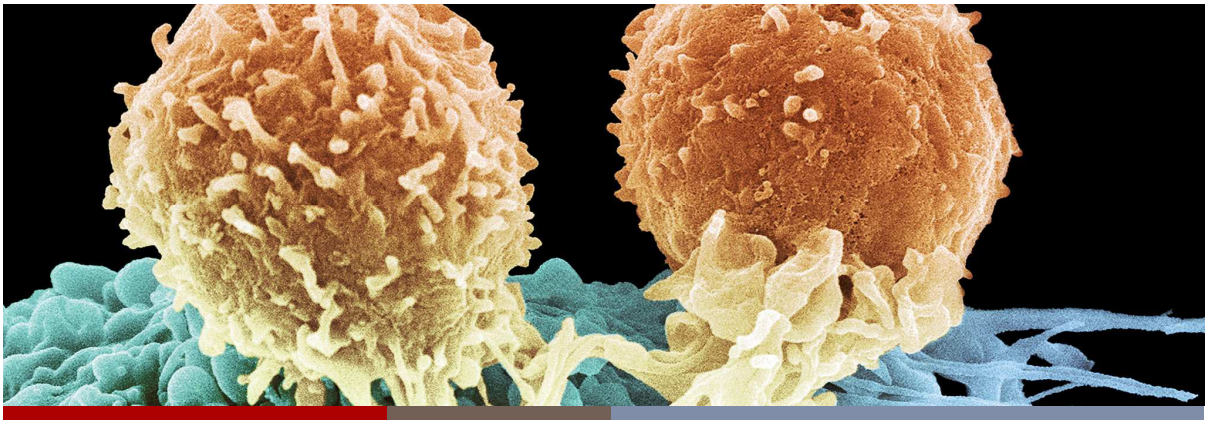

MUTATIONAL LOAD: IMPORTANCE IN IMMUNOTHERAPY

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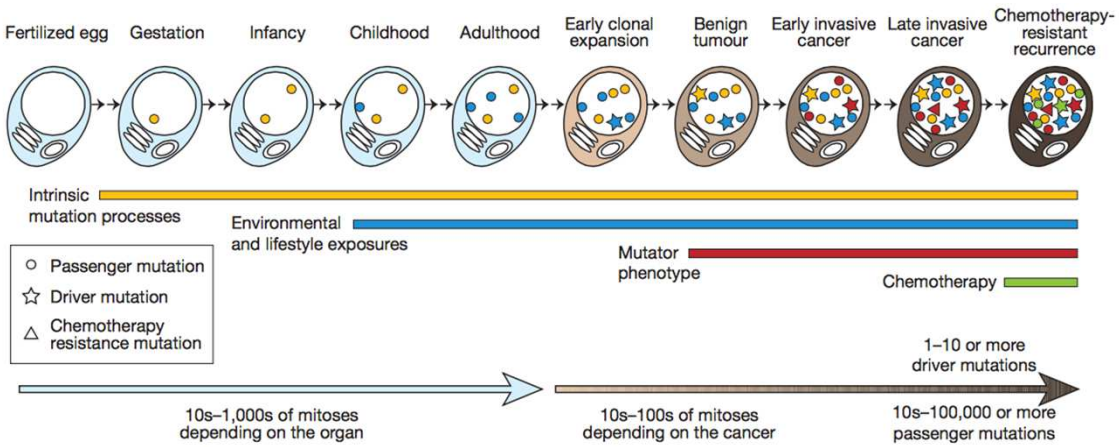
MUTATIONS EXPLAINED

- DNA is a **molecule** that carries the **genetic instructions** used in the growth, development, functioning and reproduction of all known living organisms
  - Genetic instructions are expressed as a stretch or sequence of 4 different nucleotides: adenine (A), cytosine (C), guanine (G), and thymine (T)
- Complete collection of all genetic instructions is called a **genome**
  - Human genome contains 3x10^9 nucleotides divided over 23 chromosome pairs in cell nuclei and small DNA molecules in mitochondria
- A **mutation** is the permanent alteration of the nucleotide sequence of the genome
  - Results from errors during **DNA replication** or other types of **damage to DNA** that have not or incompletely been repaired

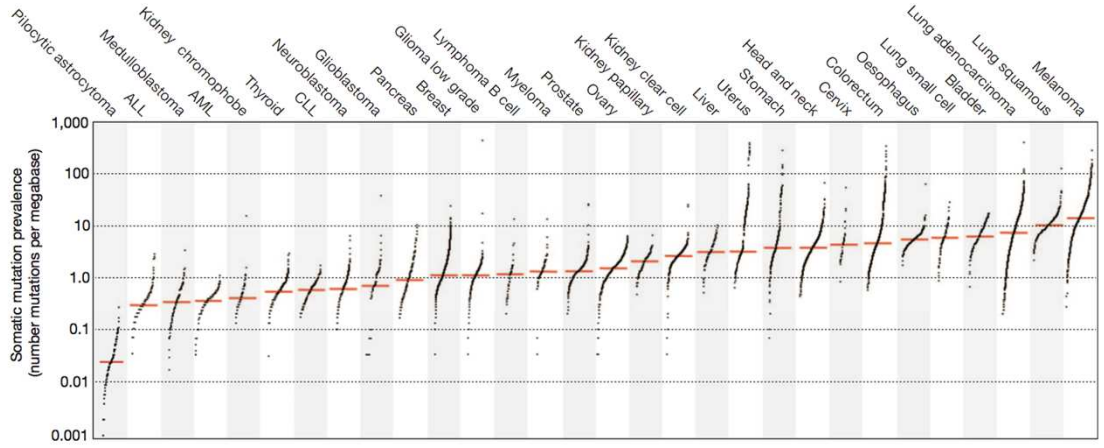
MUTATIONS EXPLAINED

- Classification of mutation types
  - By **origin**: germline *vs.* somatic mutation
  - By **structure**: small-scale mutations (e.g. substitutions or point mutations, insertions, deletions) *vs.* large-scale structural mutations (e.g. amplifications, deletions, translocations)
  - By **genomic location**: coding vs. non-coding
  - By effect on **function**: loss-of-function mutations, gain-of-function mutations, neutral mutations
  - By impact on **protein sequence**: frame-shift, nonsense, missense, neutral, silent
  - By effect on **fitness**: driver vs. passenger mutation
- In this talk: somatic, small-scale mutations that impact protein sequence

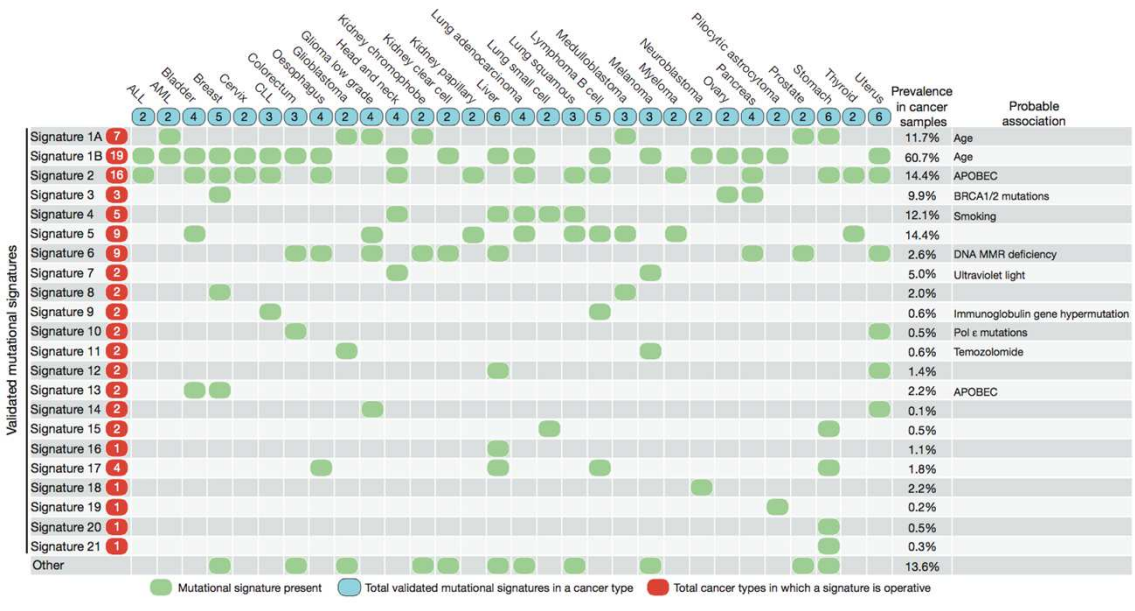
Lite history of a cancer cell - Stratton et al. Nature (2009)



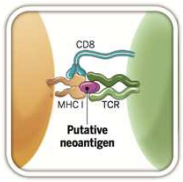
Mutational load across cancer types – Alexandrov et al, Nature, 2013



Mutational signatures across cancer types – Alexandrov et al, Nature, 2013

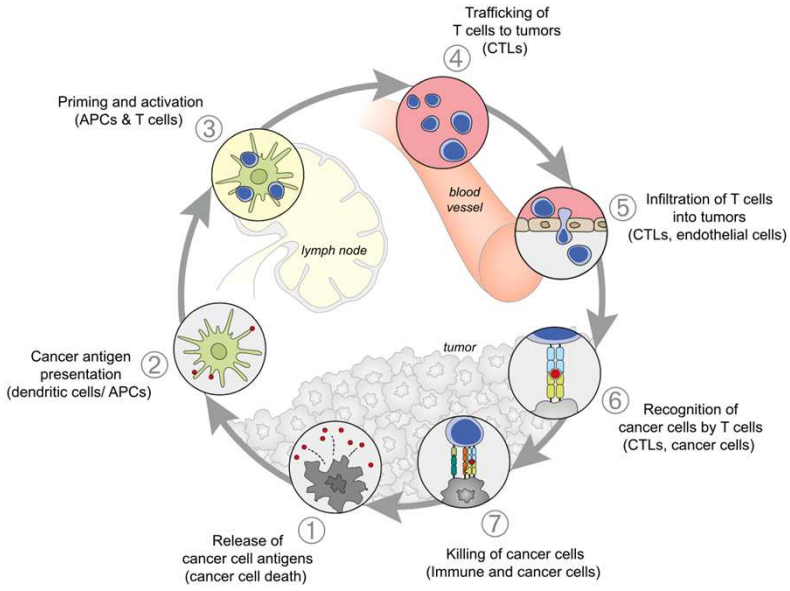


NEO-ANTIGENS

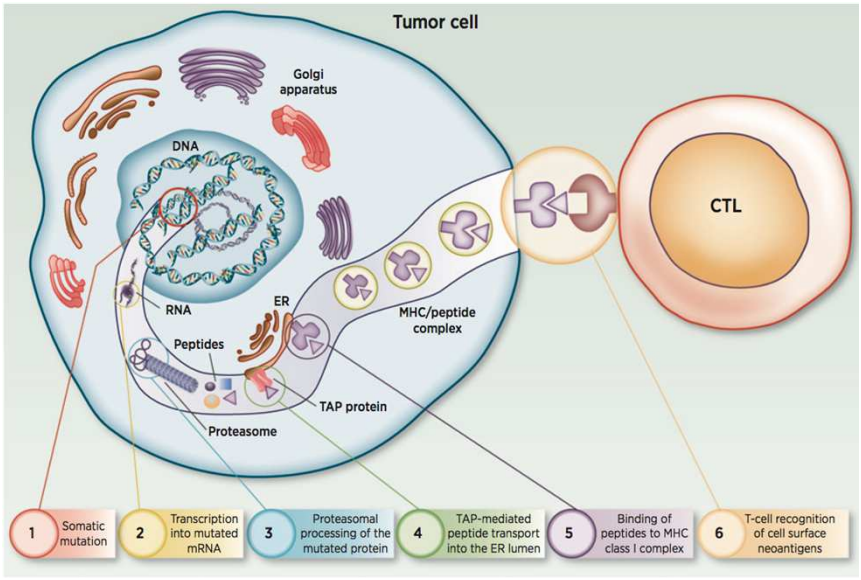


- Antigen: a molecule capable of inducing an **immune response**
  - Presented to immune cells by antigen presenting cells in the context of MHC molecules
  - Recognized by antigen receptors (B- or T-cell receptor) of the adaptive immune system
- Classification of antigens
  - **Exogenous** antigens: antigens that have entered the body from the outside
  - **Endogenous** antigens or self-antigens: generated in normal cells as a result of normal metabolism; Tolerated by the immune system (*cave* autoantigens)
  - **Neo-antigens**: entirely absent in normal cells and generated by somatic mutations that result in protein sequences changes
- Neo-antigen profiling: identification of neo-antigens using sequencing technology

The cancer-immunity cycle– Chen et al, Immunity, 2013



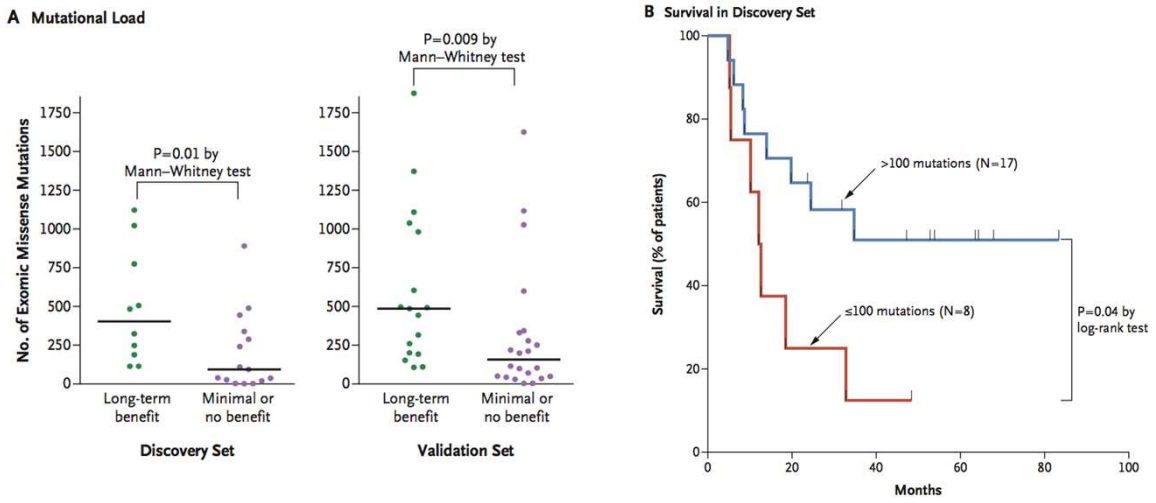
Identification of immune-relevant neo-antigens – Chabanon et al, Clin Cancer Res, 2016



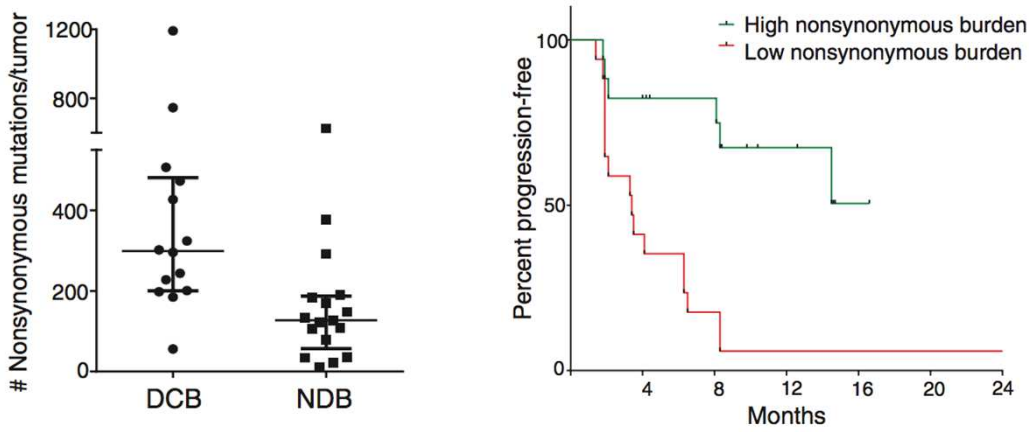
MUTATIONAL LOAD, NEO-ANTIGEN LOAD & IMMUNOTHERAPY

- Cancer immunotherapy: activate the immune system to target cancer cells
  - Directed against **self-antigens with incomplete T-cell tolerance** and **neo-antigens**
  - **Cancer vaccines**: immunization by e.g. antigens vaccines or adoptive transfer of antigen loaded dendritic cells
  - **Adoptive T-cell therapy**: T-cell are modified to specifically recognize a tumor antigen
  - **Check-point inhibition**: antibodies directed to CTLA4 (e.g. ipilimumab), PDL1 (e.g. atezolizumab) and PD1 (e.g. nivolumab)
- Biomarkers for personalized therapy?
  - Genes related to microsatellite instability and mismatch repair deficiency
  - Mutational load and neo-antigen load; Proof in melanoma and non-small cell lung cancer, bladder cancer, stomach cancer, renal cell cancer, head and neck cancer

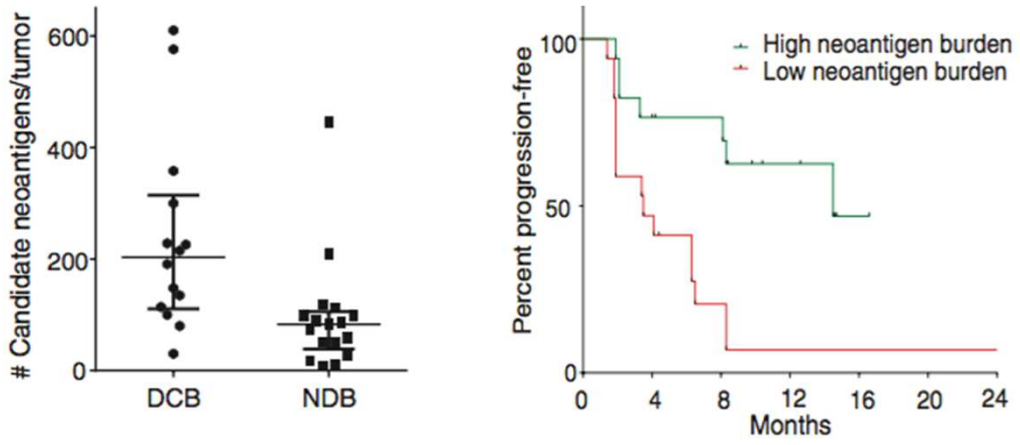
Mutational load and immunotherapy in melanoma – Snyder et al, New Engl J Med, 2014



Mutational load and immunotherapy in non-small cell lung cancer – Rizvi et al, Science, 2015



Neo-antigen load and immunotherapy in non-small cell lung cancer – Rizvi et al, Science, 2015



CHALLENGES

- Threshold "high" and "low" mutational load
- Mutational load or neo-antigen load?
  - Only a limited number of mutation result in the formation of neo-antigens
  - The formation of neo-antigens is a probabilistic process
- Neo-antigen profiling
  - Prediction of neo-antigen presentation and recognition is suboptimal and varies between algorithms (e.g. MHC1 *vs.* MHC2)
  - The process of neo-antigen presentation and recognition can be compromised in cancer biology (e.g. MHC mutations or downregulation)
  - Definition of optimal tumor purity and sequencing depth
- Resistance to immunotherapy: JAK-mutations

The cancer-immunity cycle and cancer therapy – Chen et al, Immunity, 2013