Bioinformatics for cancer immunology and immunotherapy

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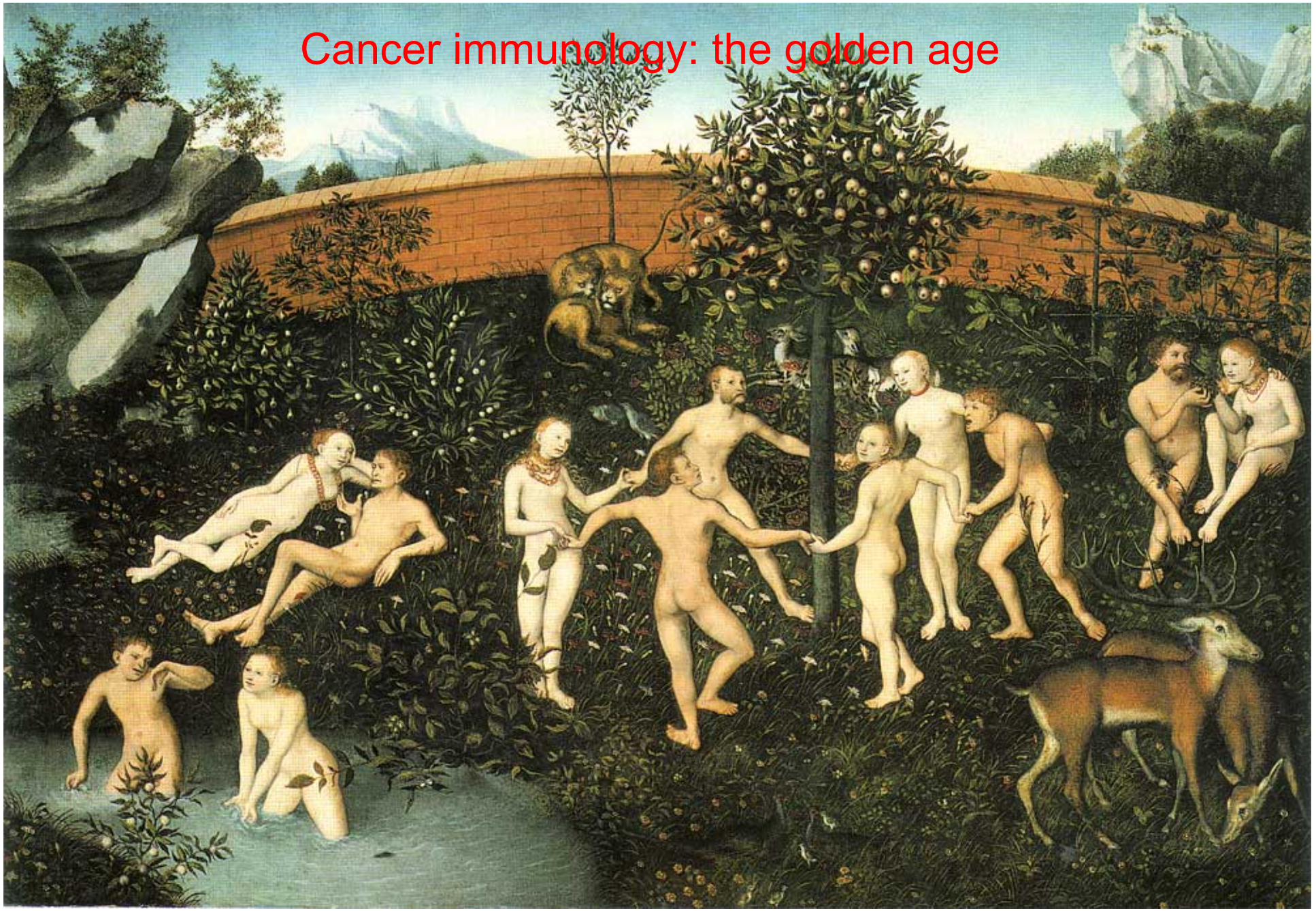


The Golden Age, 1530. Lucas Cranach the Elder

Cancer immunology

- 1906: Concomitant immunity-mammalian immune system is effective in eliminating cancer[1]

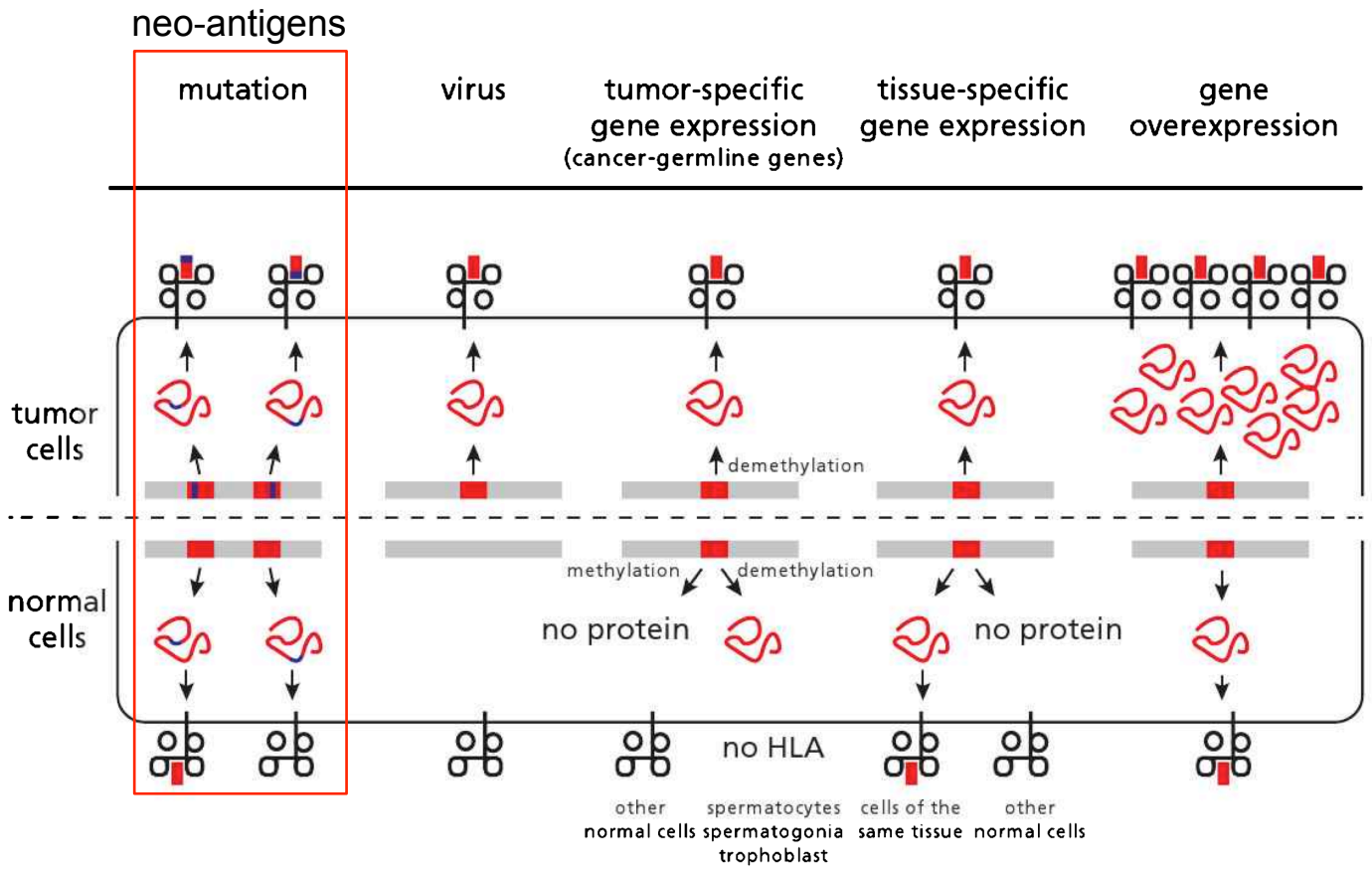
Paul Ehrlich, Frankfurt 1990

- 1970: Theory of cancer immunosurveillance[2]

- Past 10 years: renaissance of cancer immunology
  - Advances in immunology
  - Development of cancer immunotherapies
    Science 342: 1432, 2013: Breakthrough of the year

[1]Ehrlich P. Experimentelle Karzinom-Studien an Mäusen, *Arch Inst Exp Ther* **1906**;1:65
[2]Burnet FM. The concept of immunological surveillance, *Prog Exp Tumor Res*, **1970**; 13:1-27

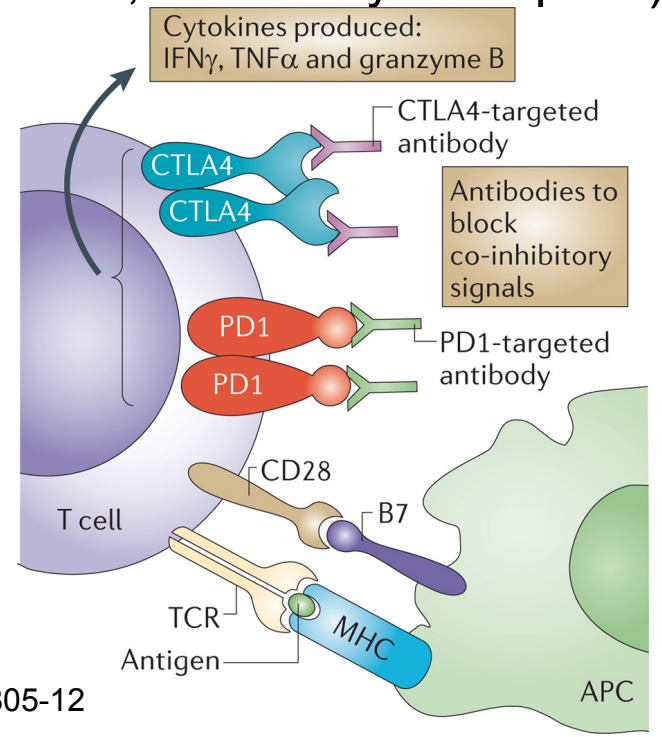
Classes of tumor antigens recognized by T-cells



Romero P, Coulie PG. Adaptive T-cell immunity and tumor antigen recognition. Tumor immunology and immunotherapy, Rees RC (Ed). Oxford University Press

Cancer immunotherapy

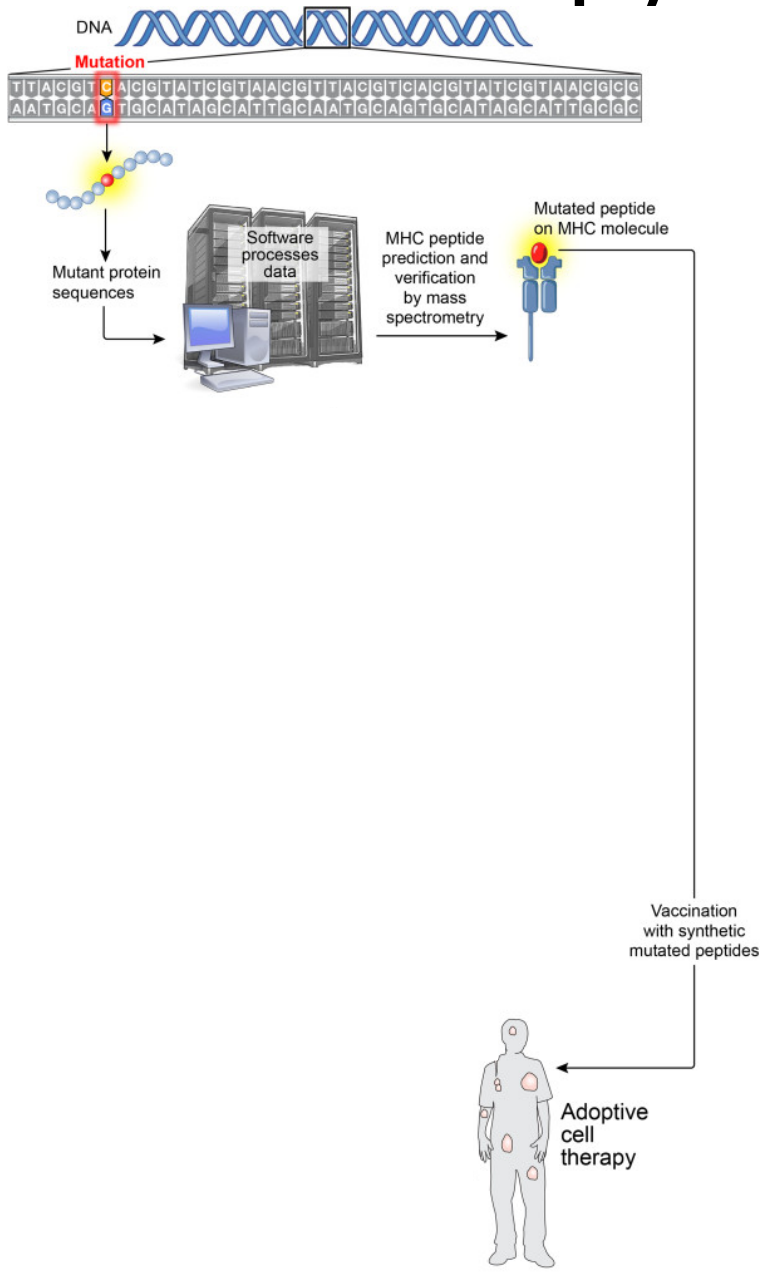
- Approved drugs:
  - Cellular immunotherapy: autologous antigen-presenting cells for treating metastatic, hormone-refractory prostate cancer (sipuleucel-T) , FDA approved in 2010
  - Monoclonal antibodies: anti-CTLA4 antibody, for treating late-stage melanoma (ipilimumab, Bristol-Myers Squibb), FDA approved in 2011



Sharma et al., *Nat Rev Cancer*, **2011**; 11:805-12

Personalized cancer immunotherapy

- Cancer vaccines
  - Castle *et a*l., *Cancer Res* 2012: Proof of concept
  - Van Rooij *et al*., *J Clin Oncol* 2013: Relevance in human cancer

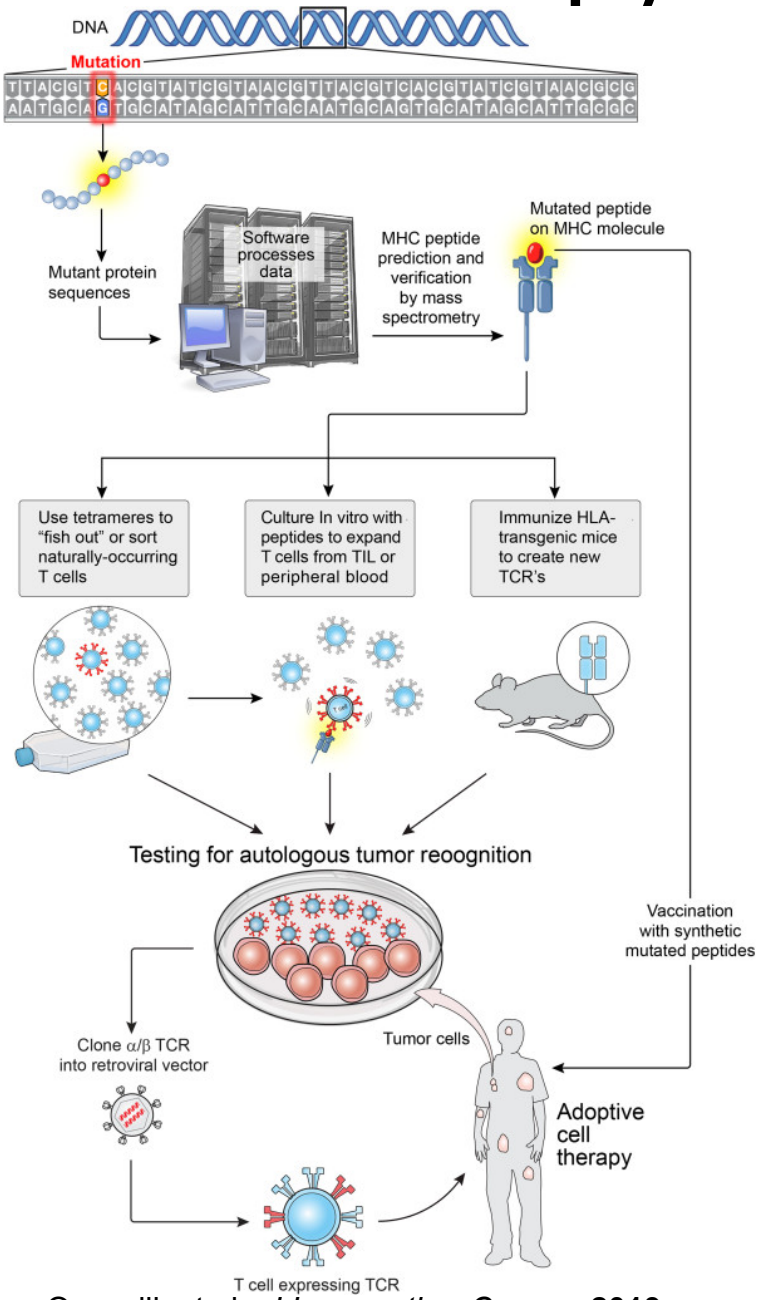


Overwijk et al., *J Immunother Cancer*, **2013**

Personalized cancer immunotherapy

- Cancer vaccines
  - Castle *et al*., *Cancer Res* 2012: Proof of concept
  - Van Rooij *et al*., *J Clin Oncol* 2013: Relevance in human cancer

- Adoptive T-cell therapy with engineered T-cells
  - Scholler *et al*., *Sci Transl Med* 2012
  - Tran *et al*., *Science* 2014



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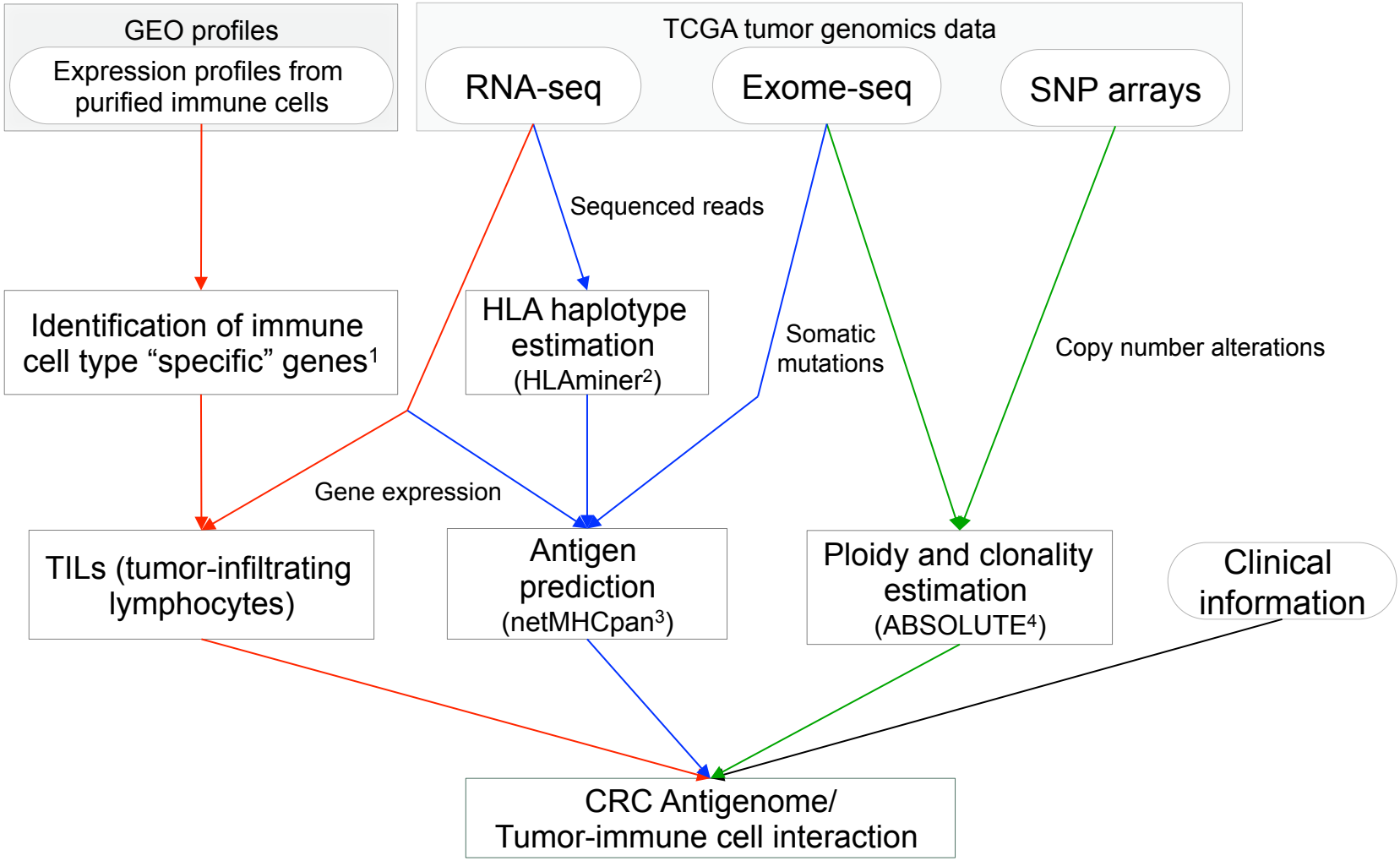
Bioinformatics requirements for cancer immunotherapy

- Publicly available data sets (GEO, TCGA)
  - Deep mining to extract relevant information
- Analytical pipeline for RNA-Seq data
  - Quantify tumor-infiltrating lymphocytes (TILs) for patient stratification
  - Estimate HLA-haplotypes
- Analytical pipeline for exome-Seq data
  - Derive somatic mutations
- Tools for predicting antigens from mutated peptides
  - Derive neo-antigens for vaccination

Bioinformatics for personalized cancer immunotherapy



Tools/Methods

1. Bindea G, *et al. Immunity* 2013; 39: 782-795
2. Warren R L *et al. Genome Medicine* 2012; 4**:** 95.
3. Nielsen M *et al. PLoS ONE* 2007; 2**:** e796
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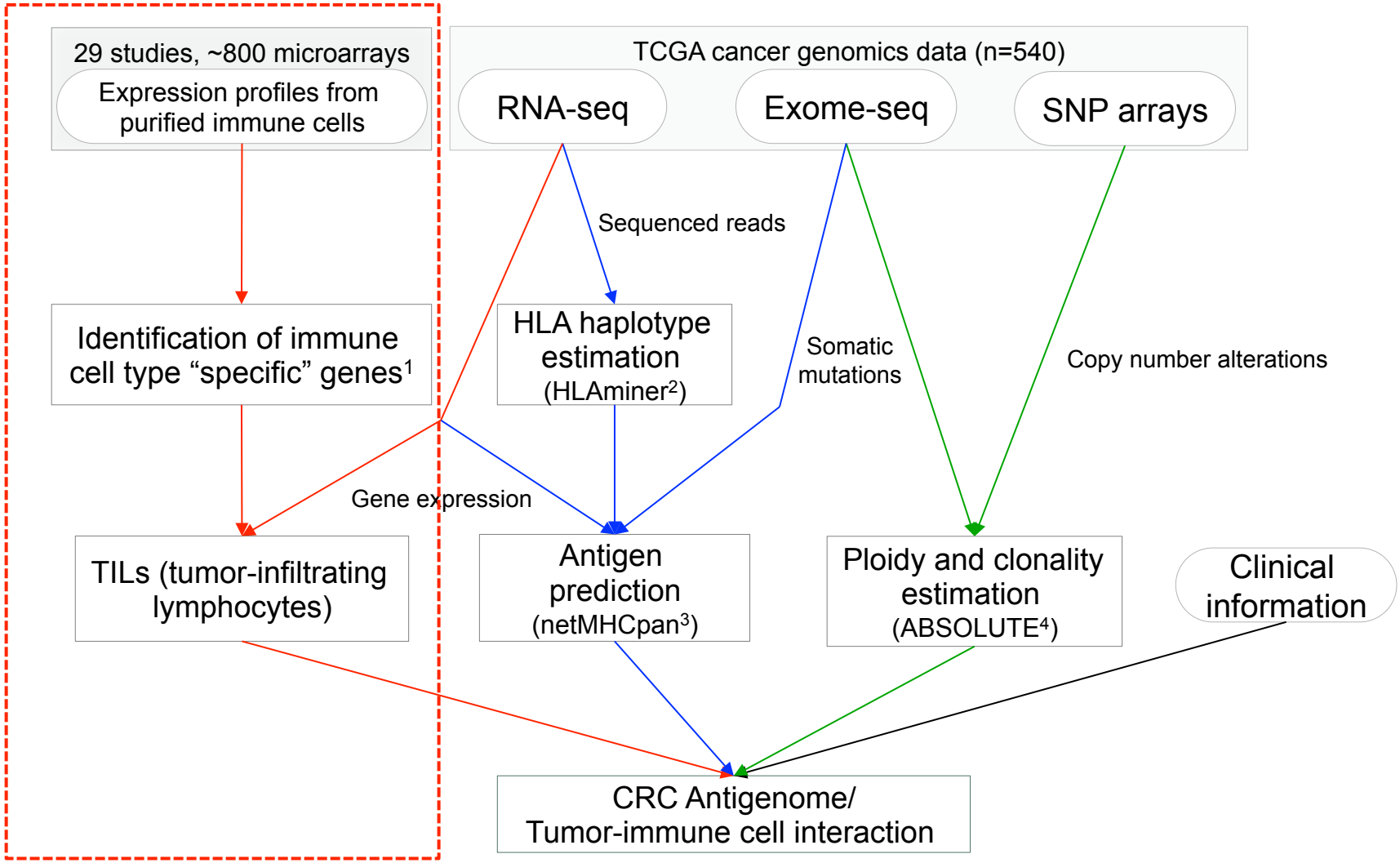
Characterizing tumor and immune landscape in CRC



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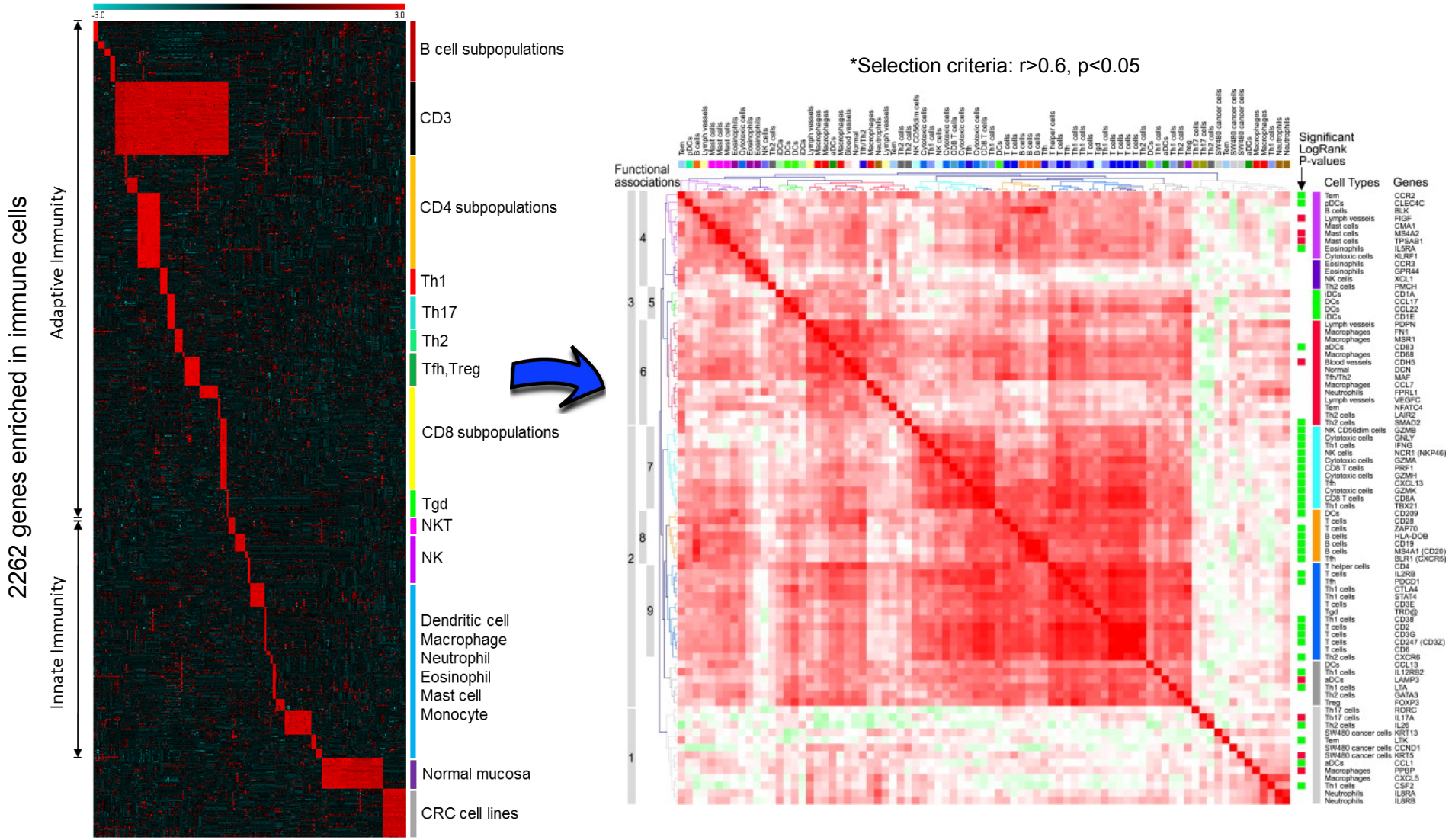
Data

The Cancer Genome Atlas Network. *Nature*; 2012; 487: 330-7

16.5 TB microarrays: 25 GB, SNP-arrays 250 GB, exome-Seq: 9 TB, RNA-seq: 7.2 TB

Compendium of genes enriched in immune cells



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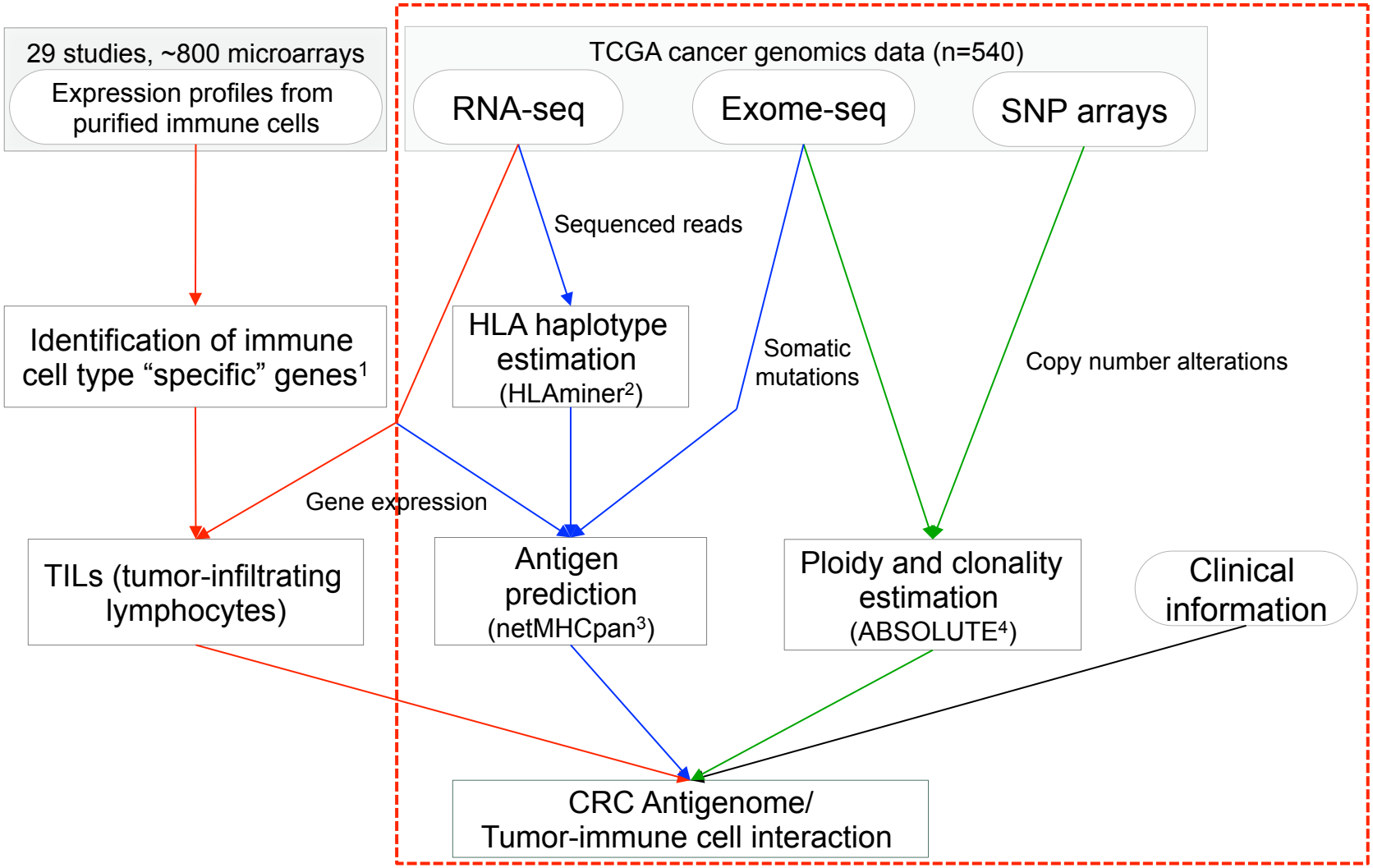

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Summary

- TILs enable precise classification of distinct molecular phenotypes in CRC

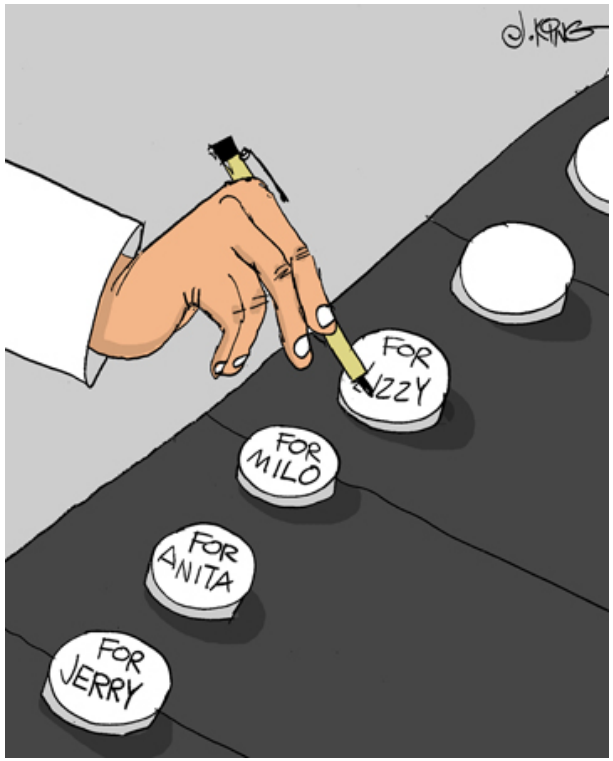
- CRC antigenome is sparse:
  - Small number of neo-antigens are shared between patients

Cancer vaccination strategy requires individualized multiepitope vaccines

Missing?

- Predictive markers for cancer immunotherapy with monoclonal antibodies
  - Only a subset of patients is responsive:
    - 18%-28% for single drug (anti-PD-1) (Topalian *et al*., *N Engl J Med* 2012)
    - 53% for combined anti-PD-1 and anti-CTLA 4 therapy (Wolchok *et al*., *N Engl J Med* 2013)
- Rationale for selecting candidates for vaccination
  - Large number of neo-antigens, small number of candidates (<12) for multiepitope vaccine

Personalized medicine



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