

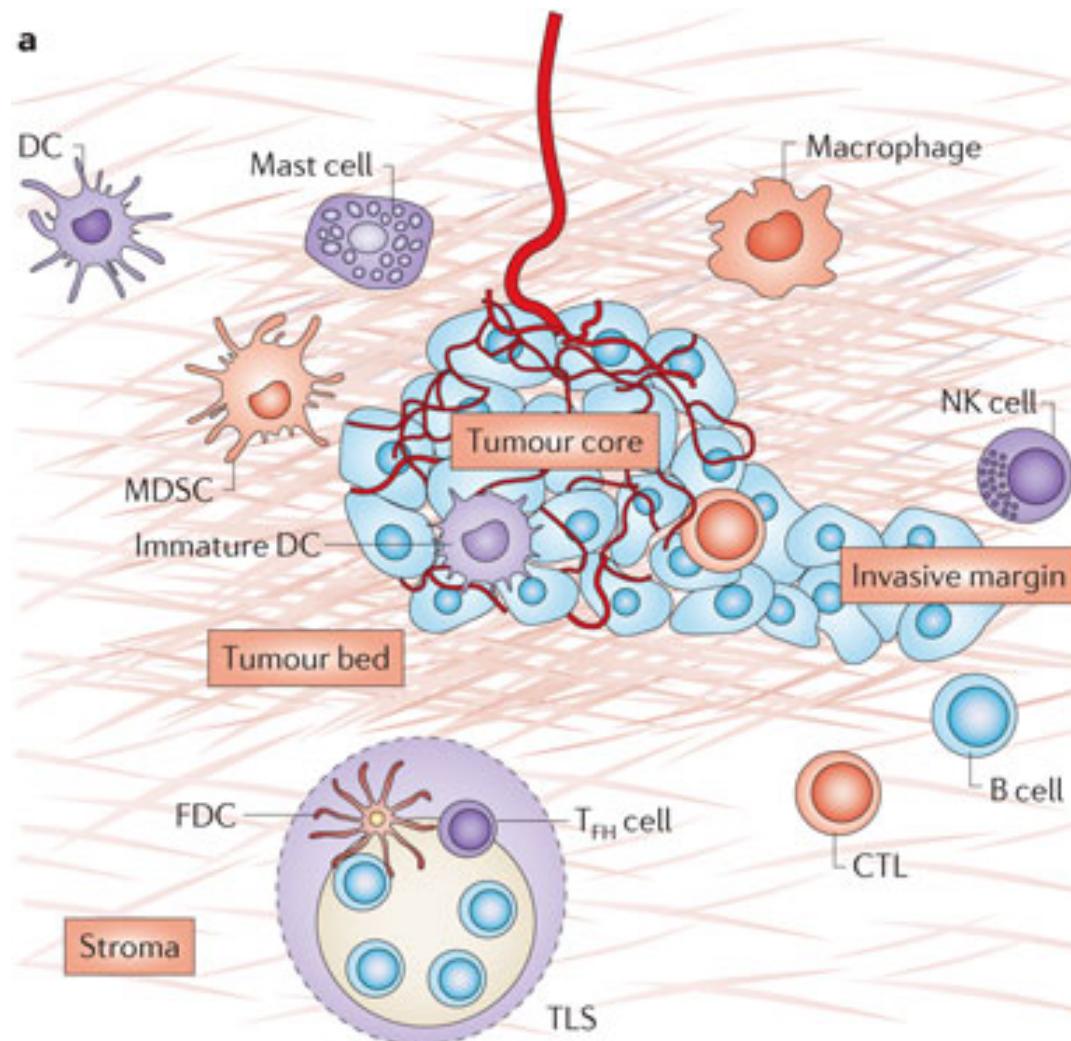
INTEGRATION OF MOLECULAR AND IMMUNE CLASSIFICATIONS TO GUIDE IMMUNOTHERAPIES

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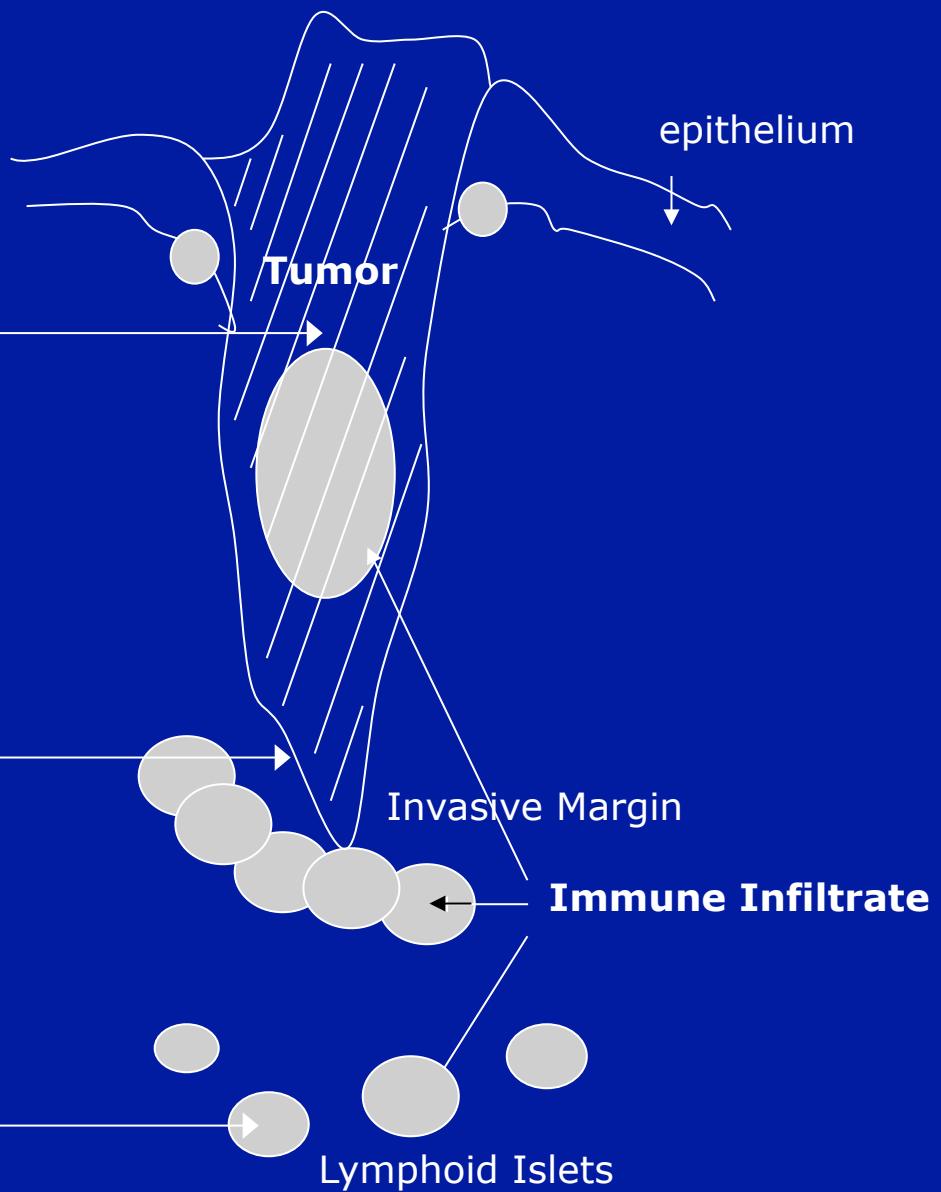
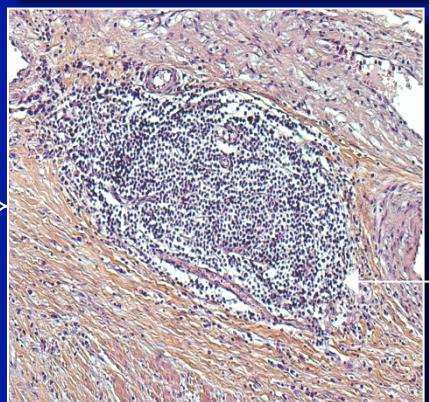
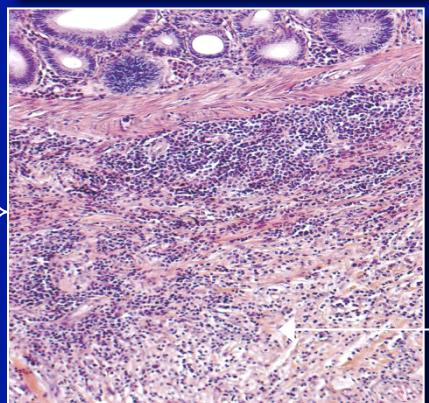
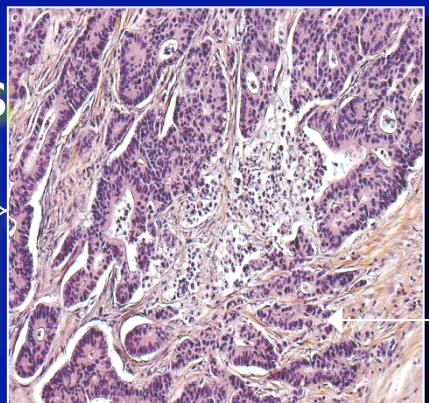
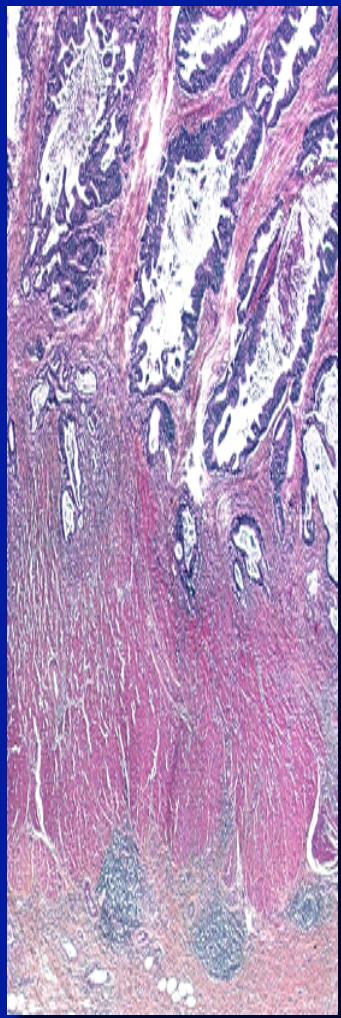
The immune microenvironment

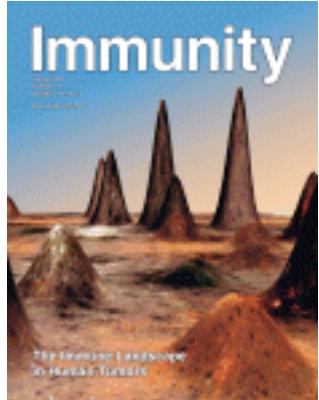


W H Fridman et al., Nature Rev. Cancer, 12, 298-306, 2012

Dissection of tumor regions

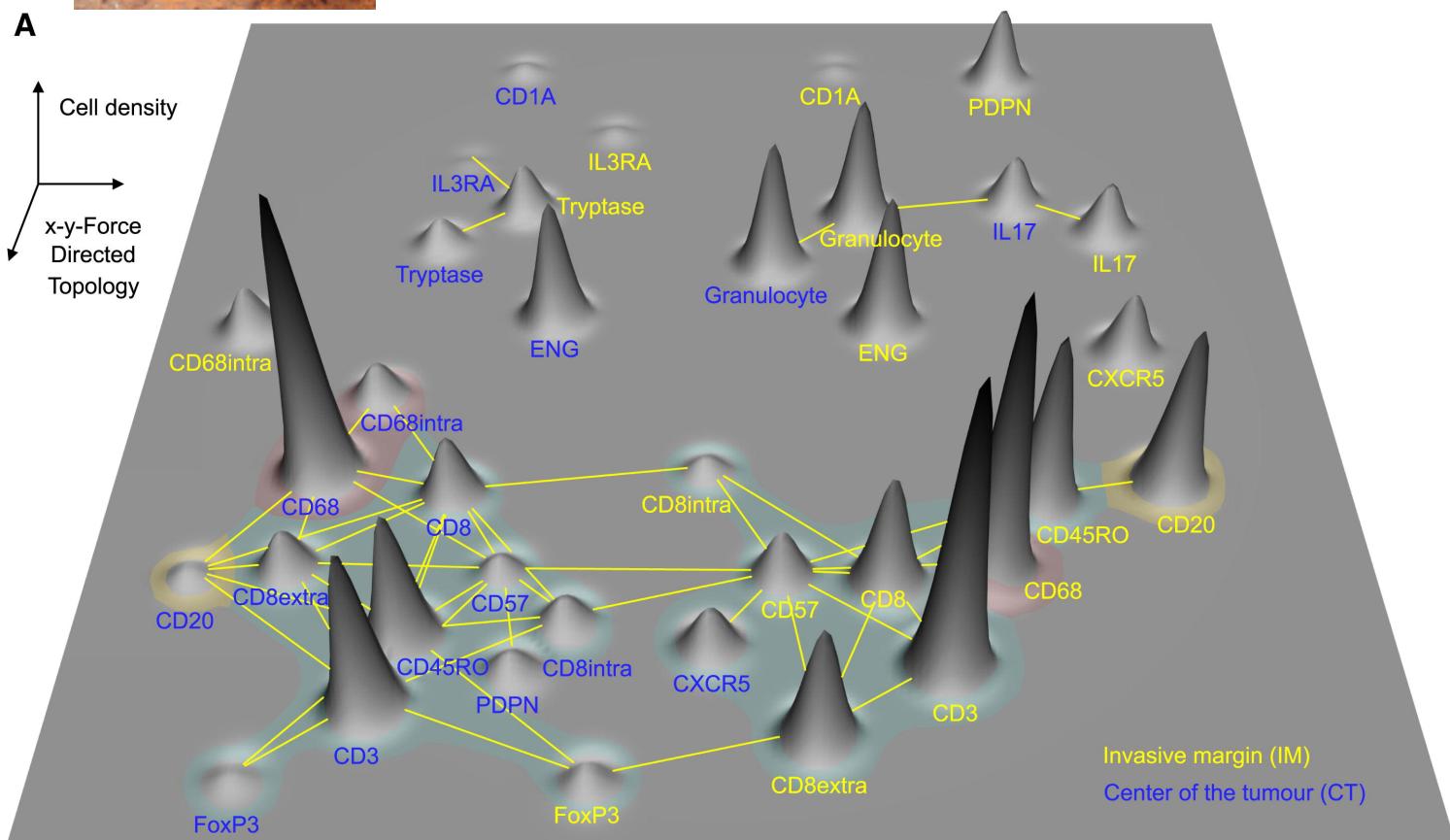
H&E sections





The immune landscape in Colorectal Cancer

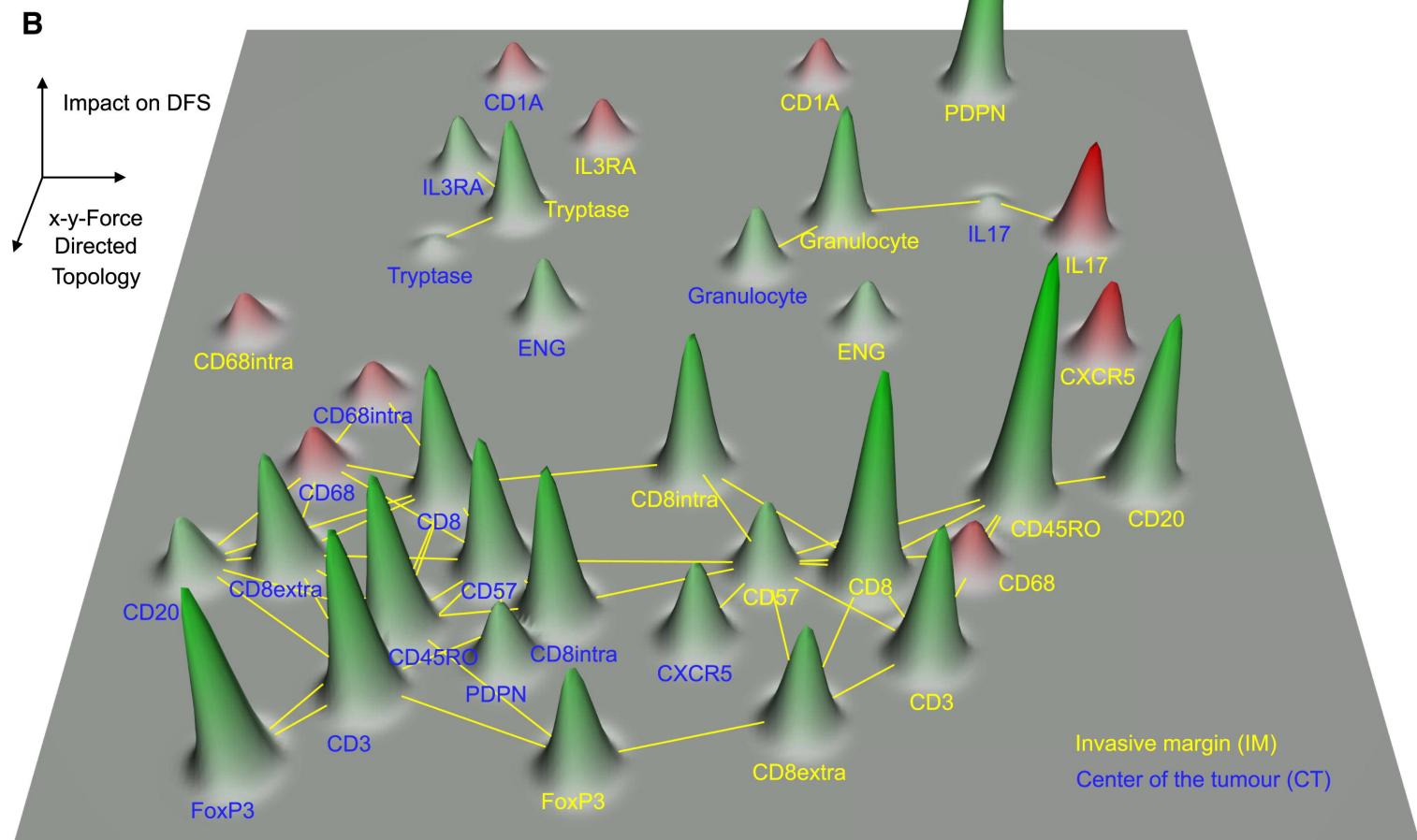
G. Bindea et al, *Immunity*, 39, 782-795, 2013





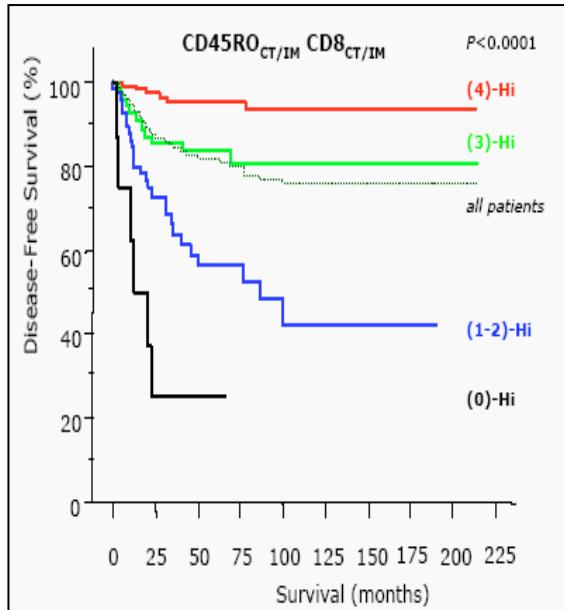
The immune landscape in Colorectal Cancer

G. Bindea et al, Immunity, 39, 782-795, 2013



The local immune score identifies a population of high-risk patients with non-metastatic cancer (stages I-III)

Stage I-II colorectal cancers (282 patients)



Stage I-III colorectal cancers

COX analysis for DFS	HR	Log Rank P-values
Tumour (T) stage	1.24	0.29
N Stage	1.31	0.17
Gender	1.47	0.18
Number of total lymph nodes	1.13	0.68
Histological grade	0.69	0.29
Mucinous colloid	1.29	0.47
Occlusion	1.03	0.94
Perforation	4.03	0.0084
Immune Score	0.65	0.0003

AJCC/UICC-TNM classification and the Immune score

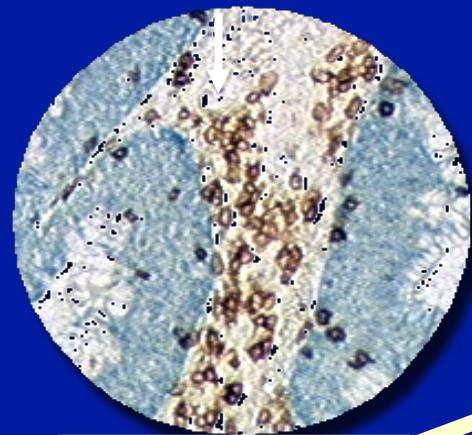
COX analysis	DFS		OS		DSS	
	HR	P-value	HR	P-value	HR	P-value
AJCC/UICC-TNM	1.38	0.09 ns	1.18	0.29 ns	1.43	0.10 ns
Immune Score	0.64	<0.0001	0.71	<0.0001	0.63	<0.0001

➤ Validation in 2 independent cohorts of colorectal cancer patients

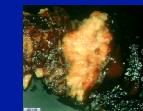
Pagès *et al.*, J. Clin. Oncol., 2009; Mlecnik *et al.*, J. Clin. Oncol., 2011

Cancers : Prognostic evaluation of patients

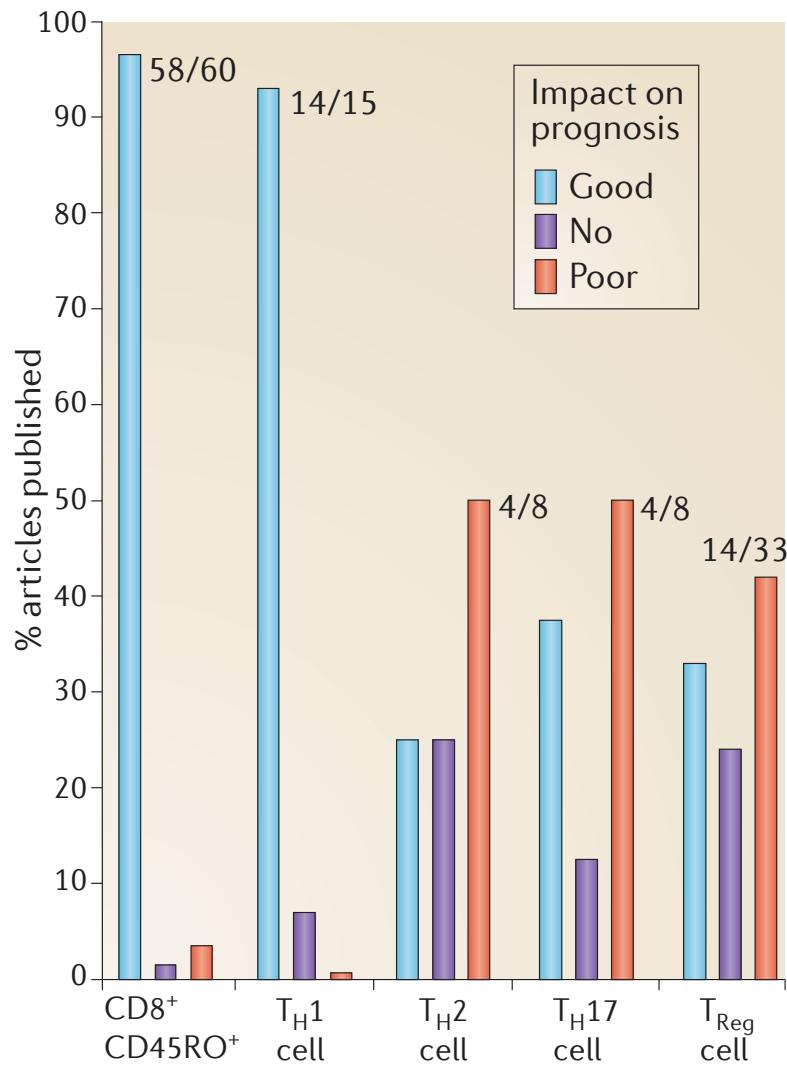
Immune reaction



Tumoral extension



Evaluation of the **Type**, the **Density**, and the **Location**, of the natural *in situ* **immune** reaction within distinct tumoral territories, predicts clinical outcome (Galon et al. Science,313,1960-4,2006)

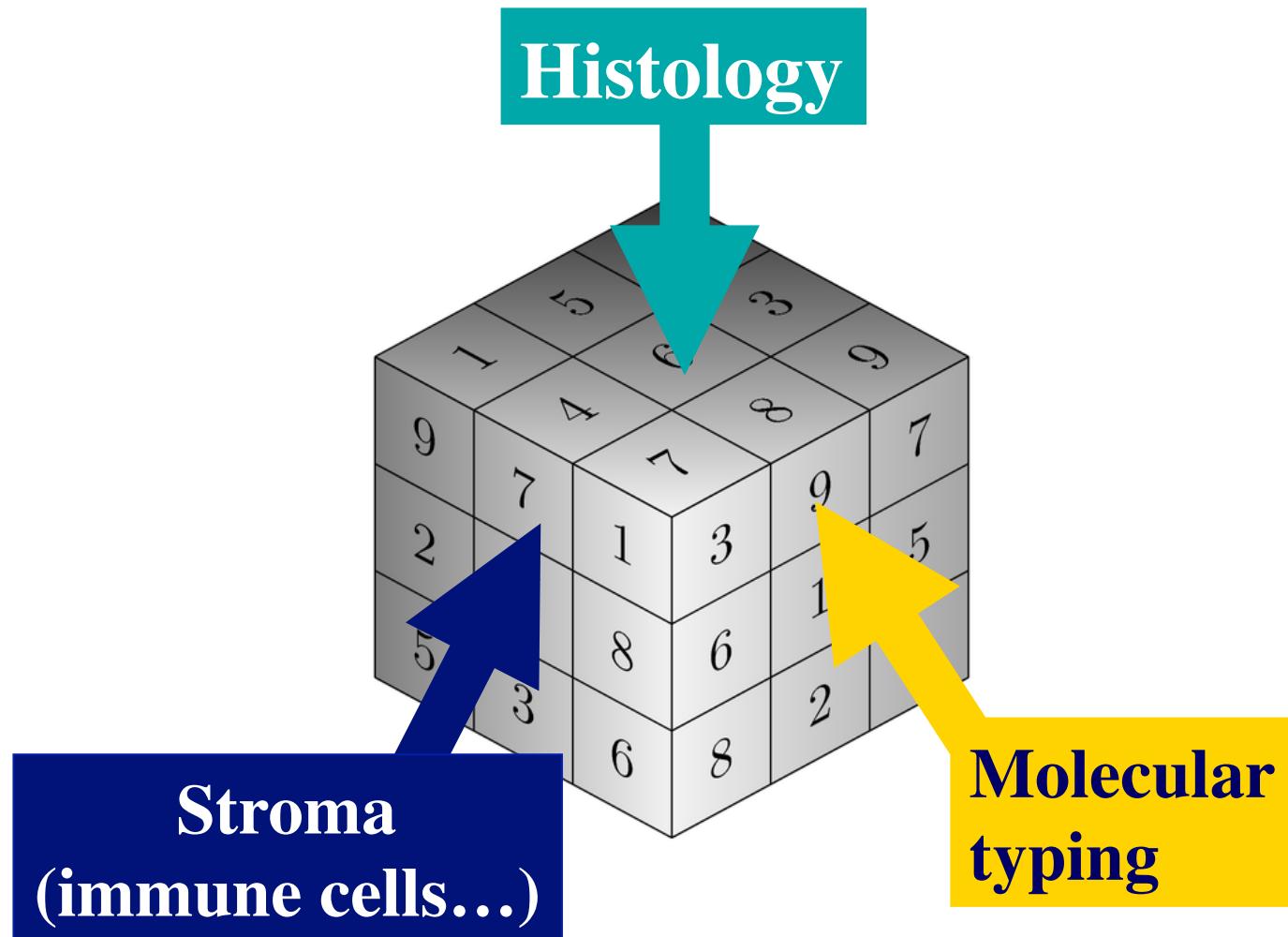


Nature Reviews | Cancer

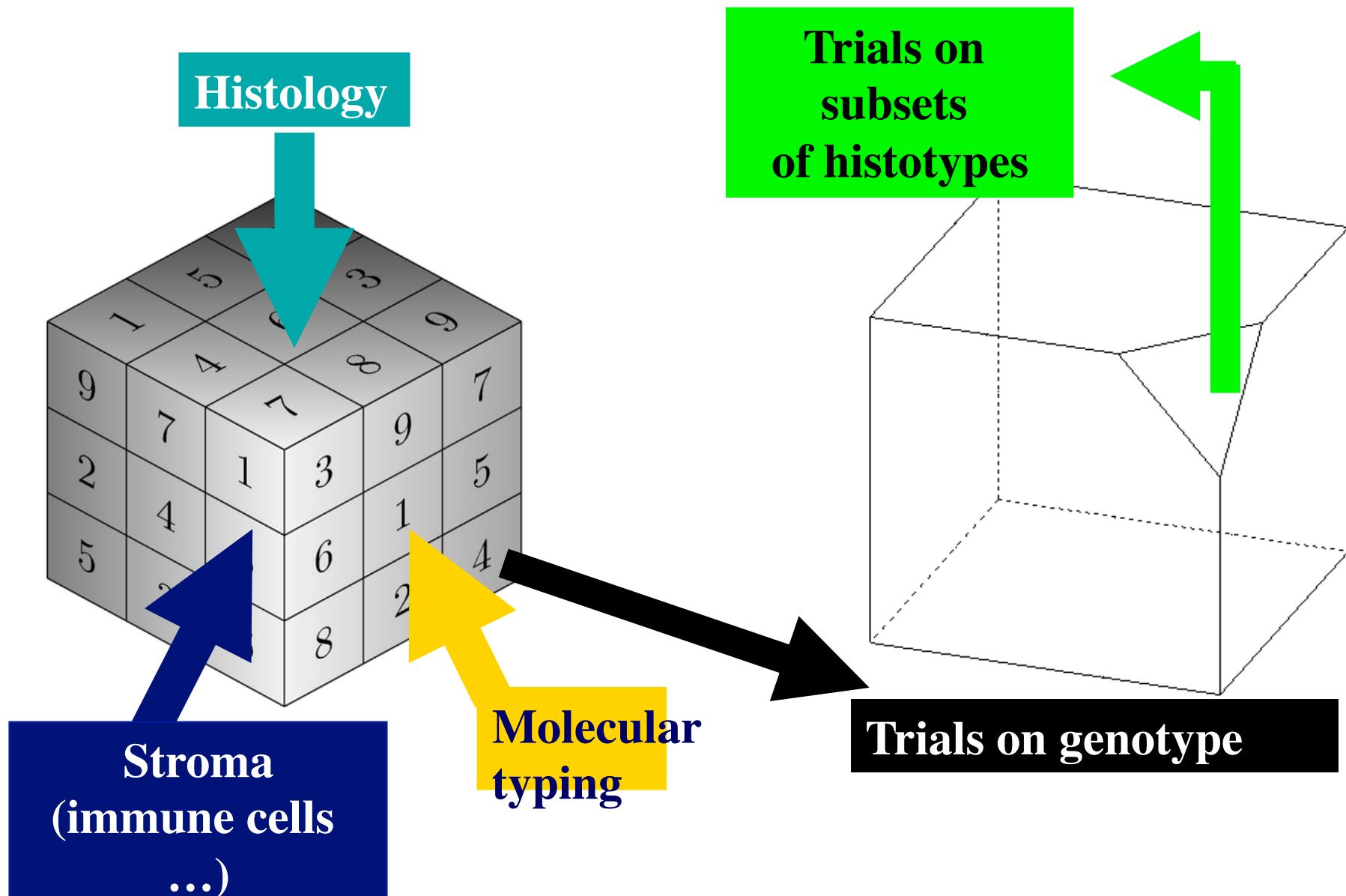
Meta-analysis of 124 published articles studying the impact of cytotoxic T cells, memory T cells, and T-helper subpopulations with regards to prognosis of patients with cancer (20 cancer types analyzed)

W H Fridman et al., Nature Rev Cancer, 2012

A new vision of the disease



A new vision of the disease



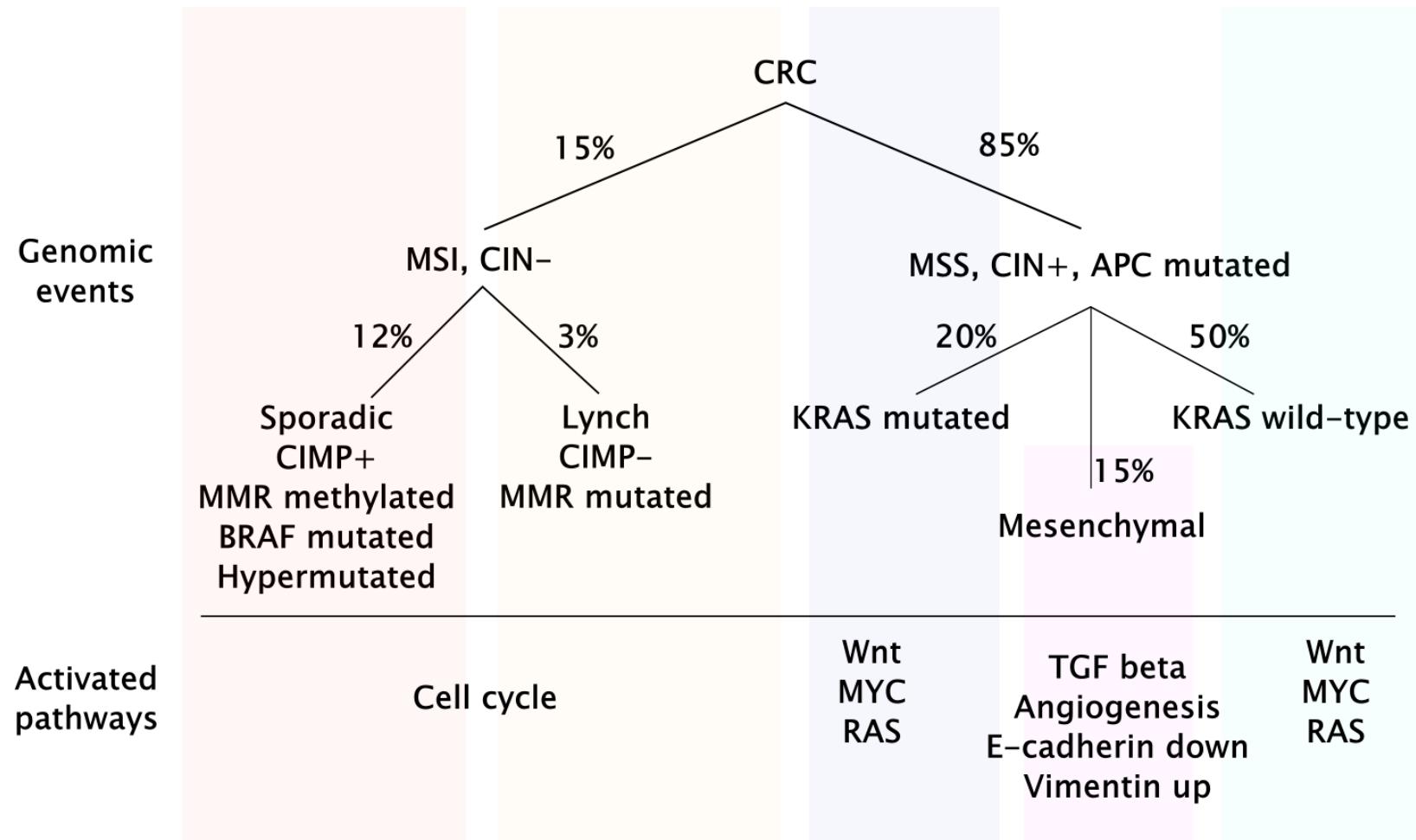
CLASSICAL AND IMMUNE CLASSIFICATIONS OF CANCERS

Cancers have been classified by histopathological , genomic and transcriptomic analyses into subgroups with different clinical outcomes and responses to therapy

Do these subgroups correlate with immune classifications which would support their different prognostic impacts and provide targets for immunotherapeutic approaches?

IMMUNOTHERAPY OF COLORECTAL CANCERS

Transcriptomics identifies a new subgroup of colorectal cancer



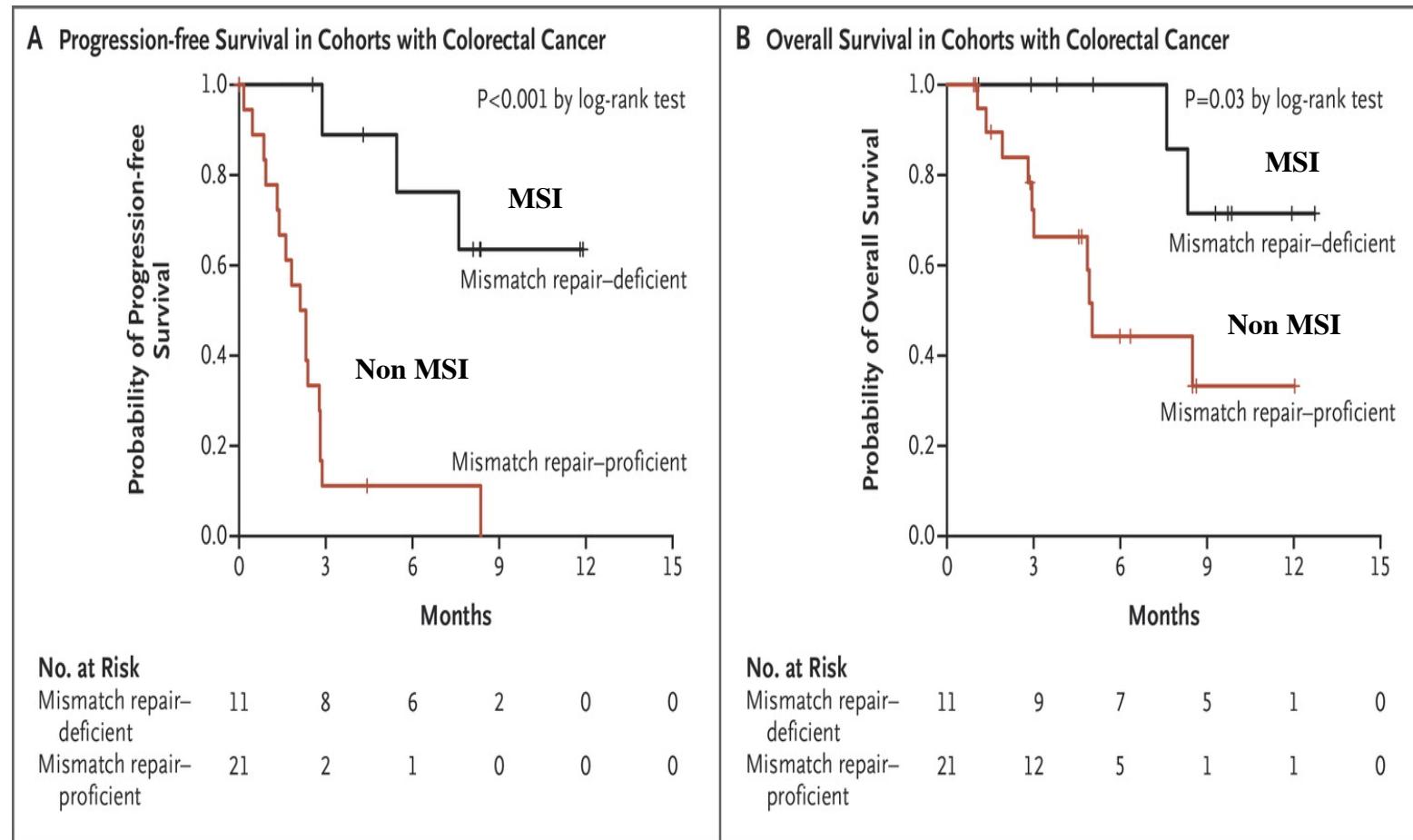
E.R. Fearon and B. Vogelstein, Cell, 61-759-767, 1990

J.R. Jass, Histopathology, 50-113-130, 2007

C. Richard Boland and A. Goel, Gastroenterology, 138-2073-2087, 2009

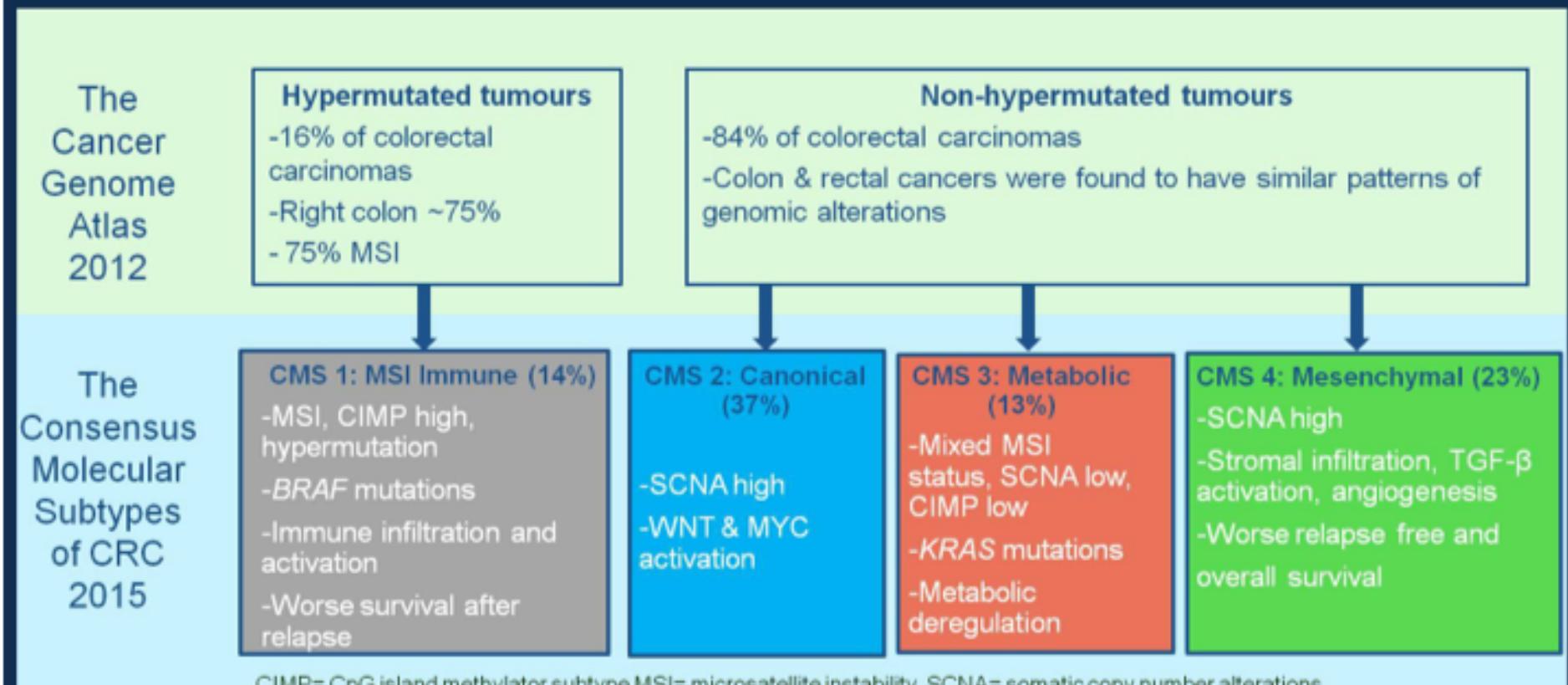
J.H. Tsay and J. Yang, Genes and development, 27-2192-2206, 2013

Clinical benefit of pembrolizumab treatment according to mismatch-repair status in patients with colorectal cancer



Identification of immune profiles in molecular groups of colorectal cancer

Progression in our understanding of CRC subtypes

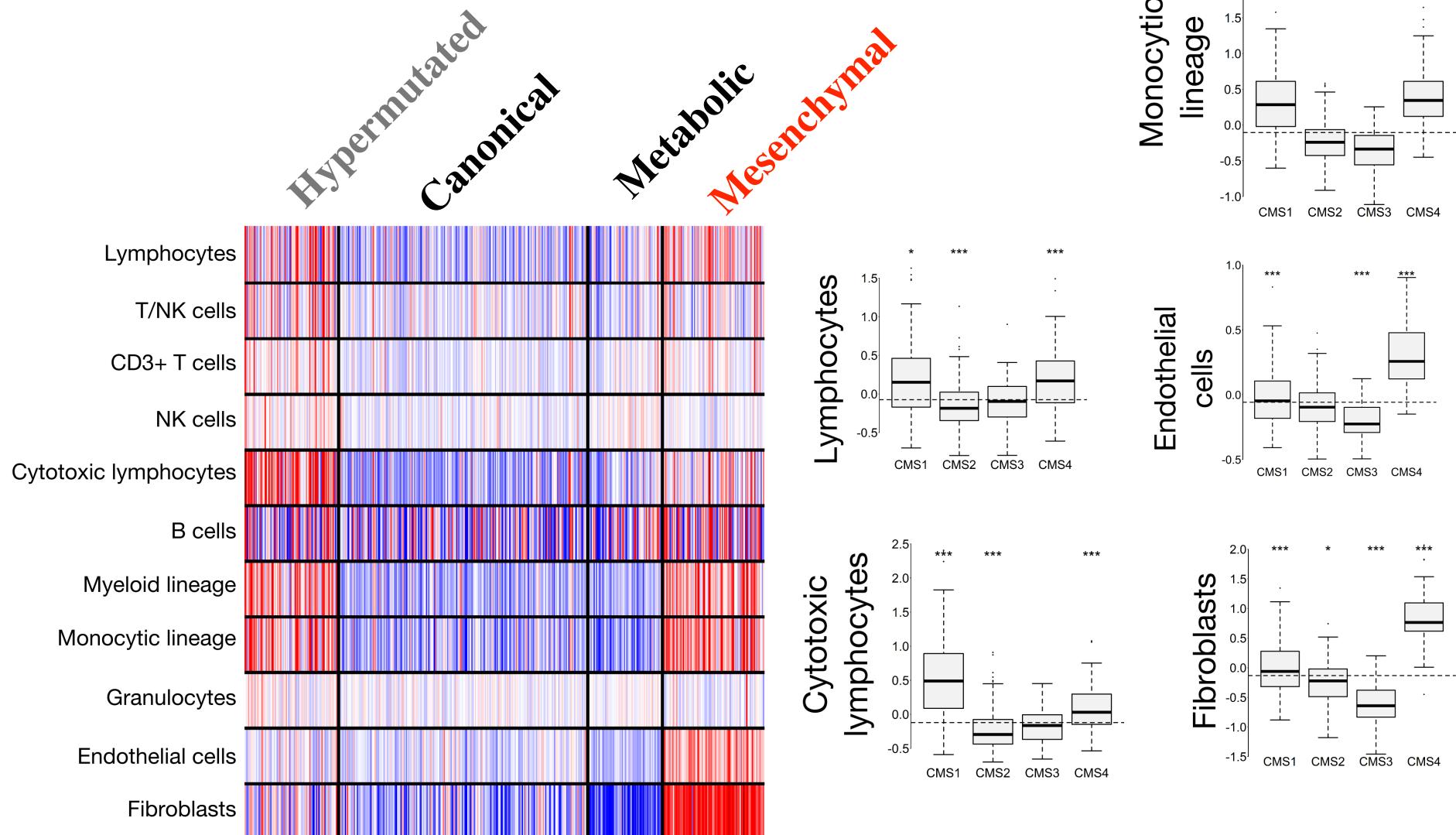


PRESENTED AT: **2016 Gastrointestinal Cancers Symposium**

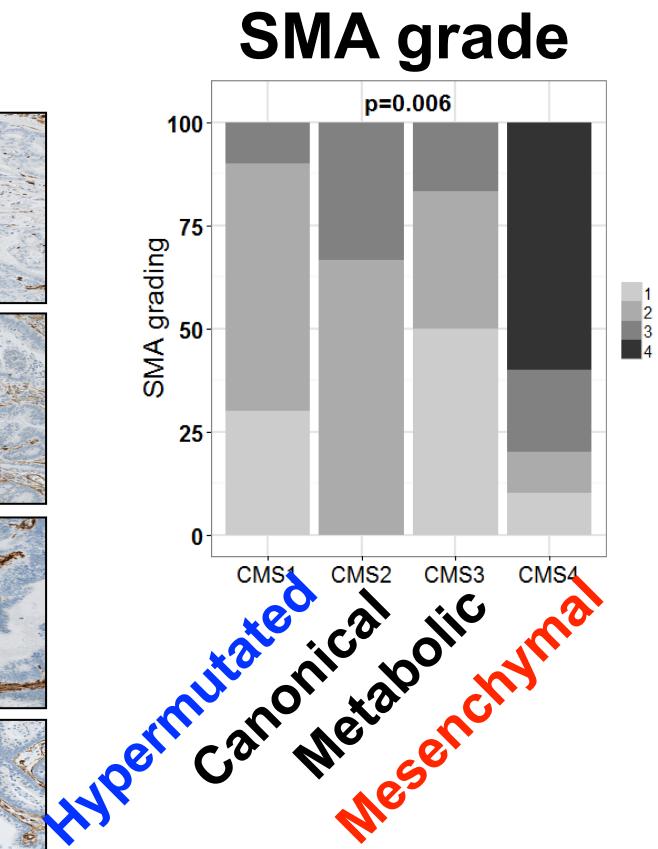
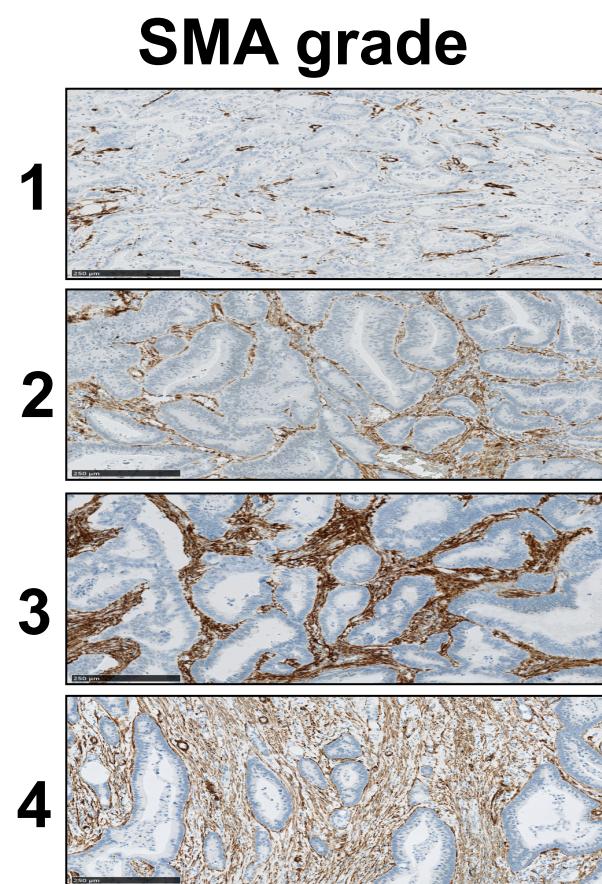
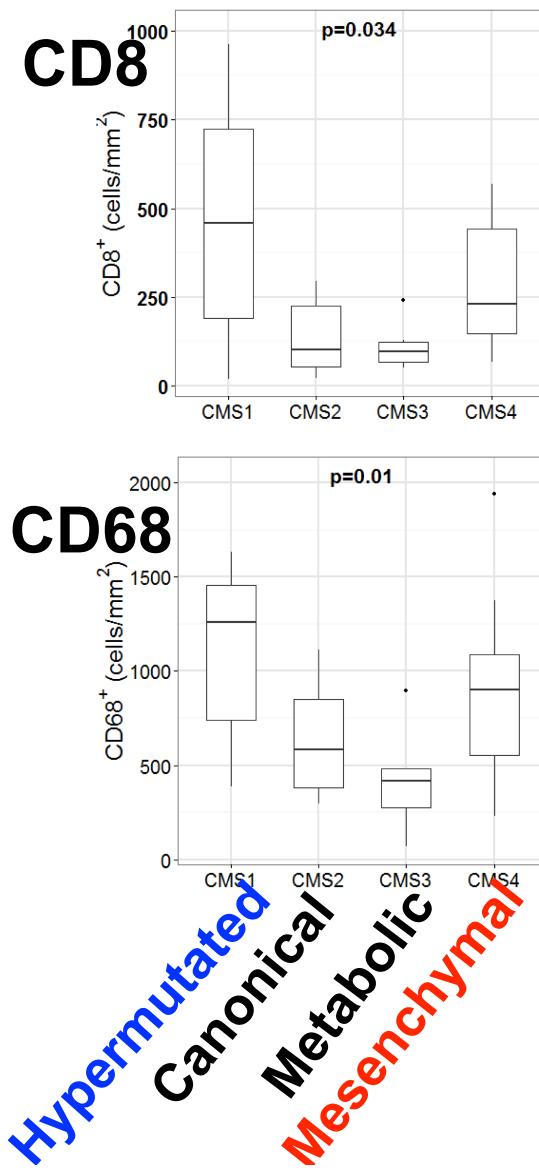
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Cancer Genome Atlas Network, Nature, 2012; 487(7407):330-7.
Guinney et al, Nat Med. 2015; 21(11): 1350-1356.

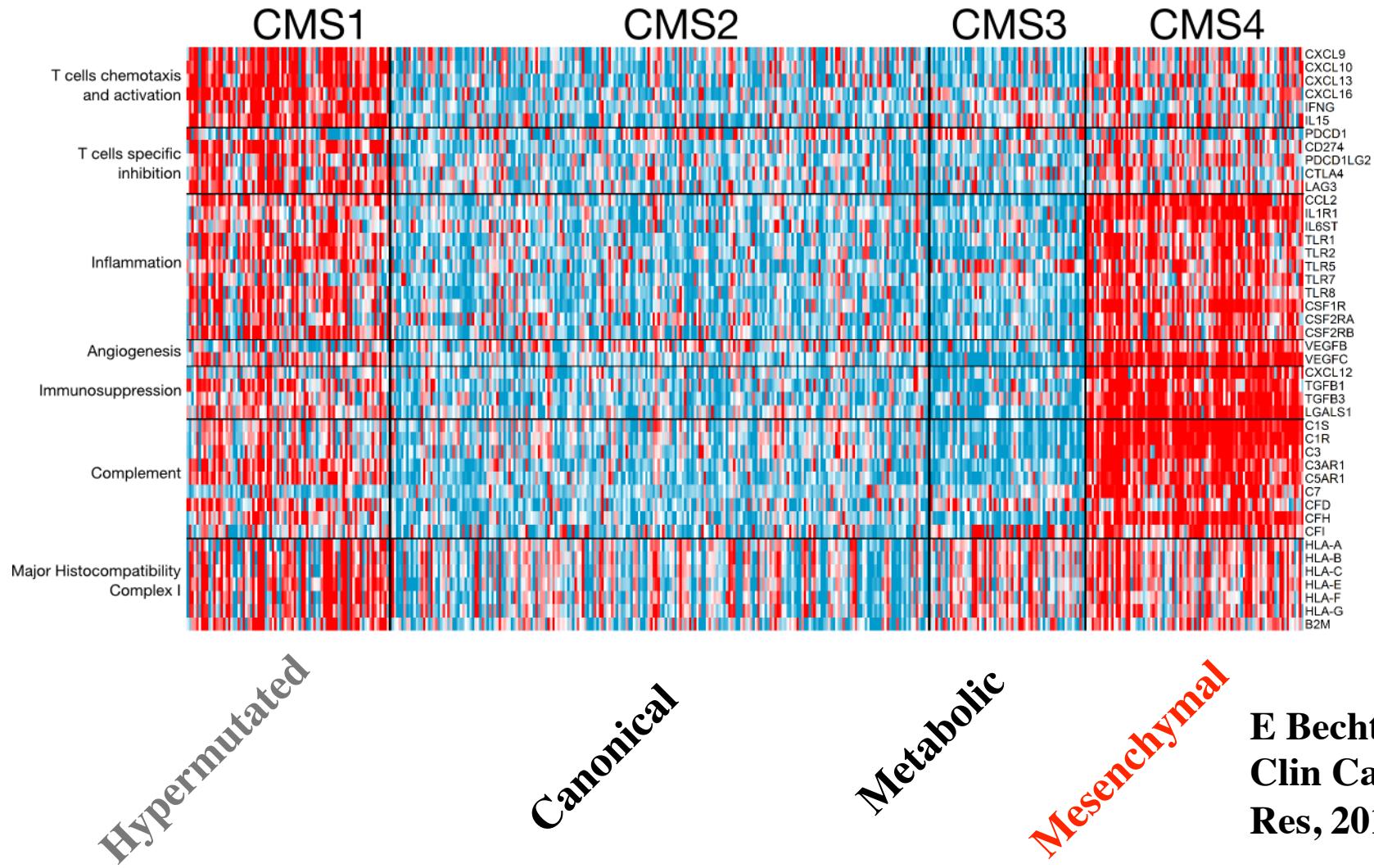
In CRC, immune signatures identify two « immune high » groups but with distinct profiles



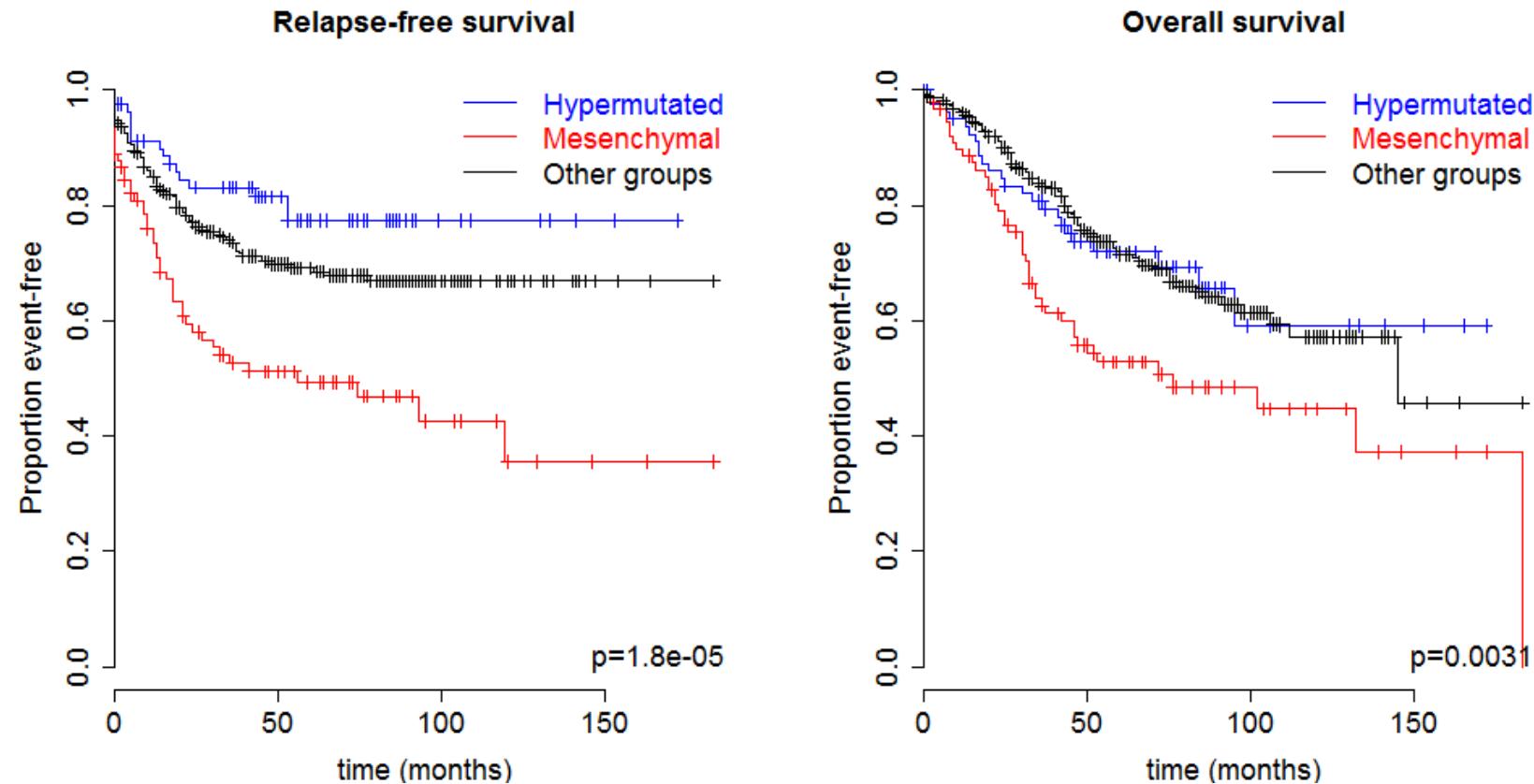
CD8 T cells, Macrophages and Fibroblasts infiltration in molecular subgroups of CRC



The CRC molecular subgroup CMS4 is characterized by an angiogenic, inflammatory and immunosuppressed profile

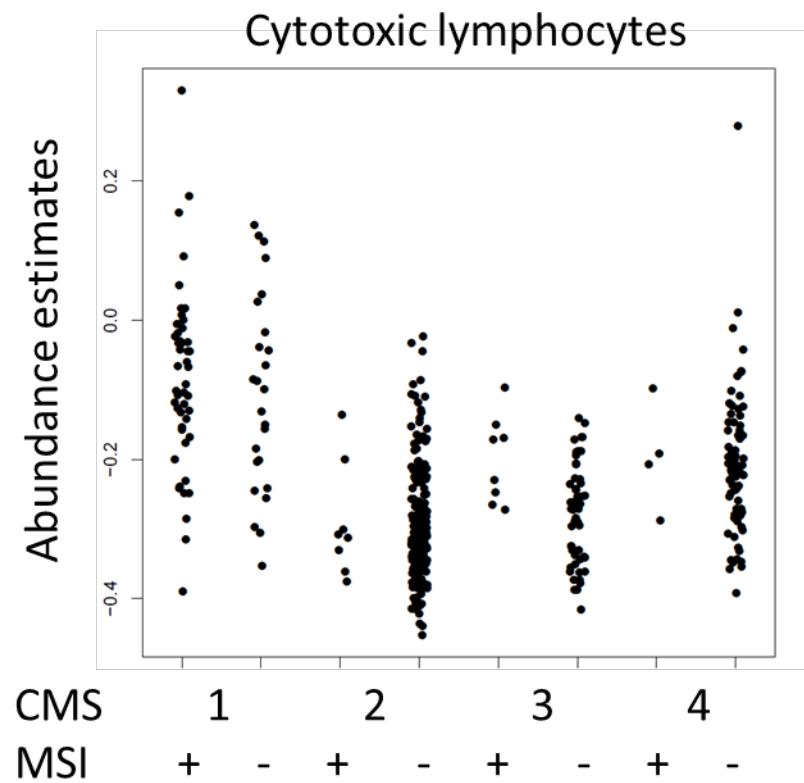
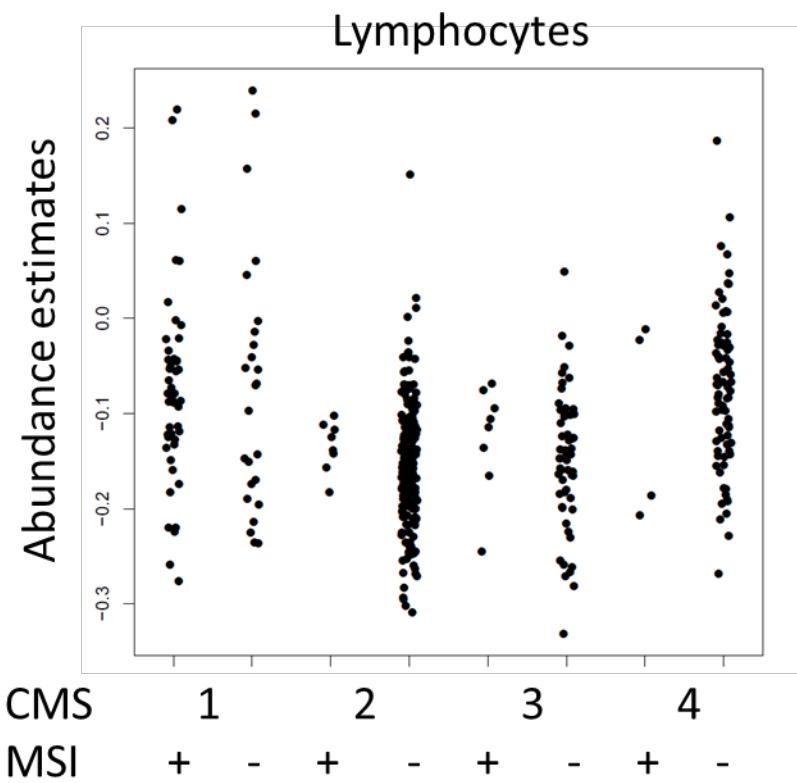


Opposite prognostic value associated with Hypermutated and Mesenchymal tumor phenotypes

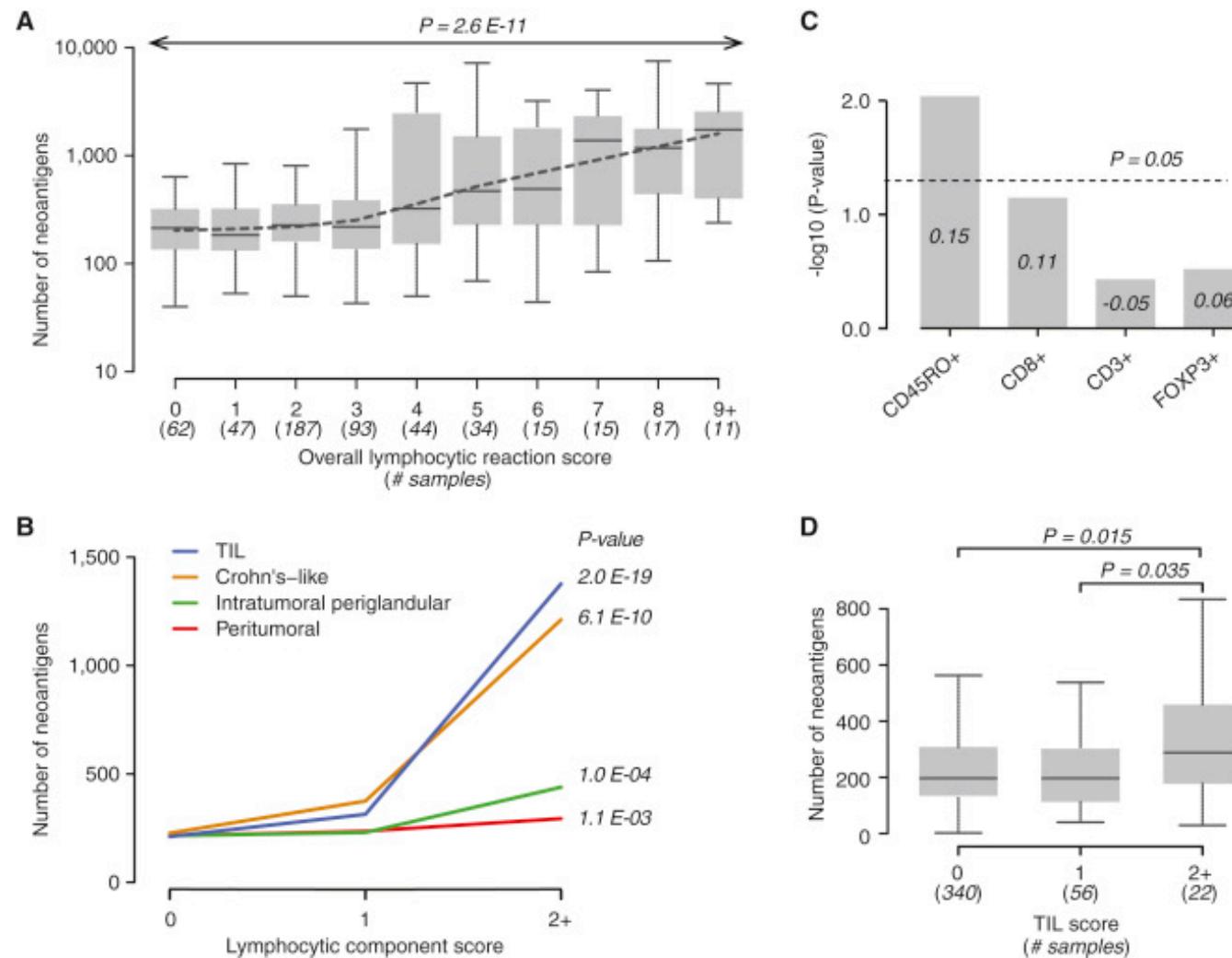


N=566

MSI distribution in CMS subtypes



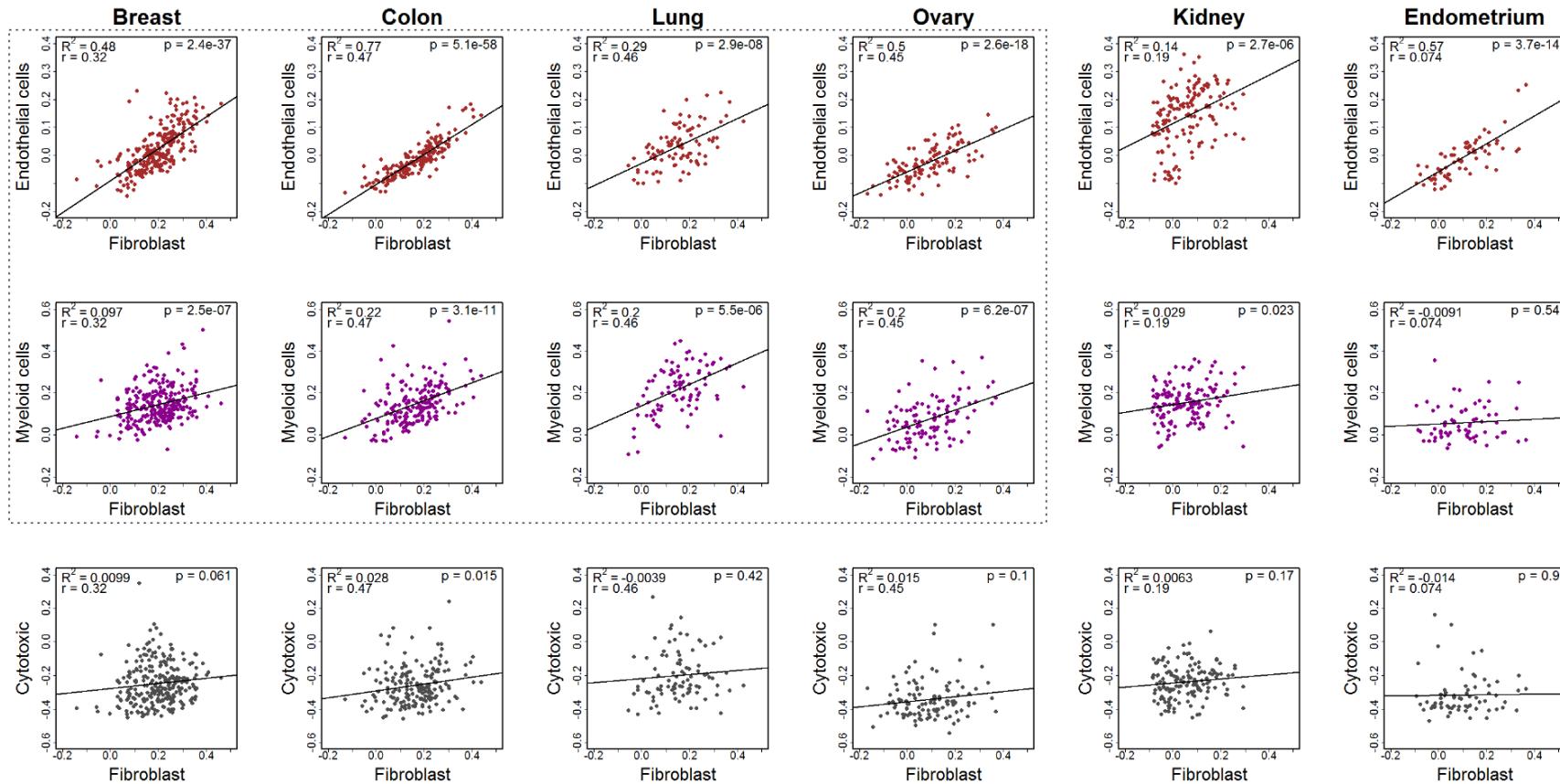
CORRELATION OF NEOANTIGEN LOAD WITH IMMUNE-CELL INFILTRATION IN CRC



Immunotherapeutic proposals for molecular and immune subtypes

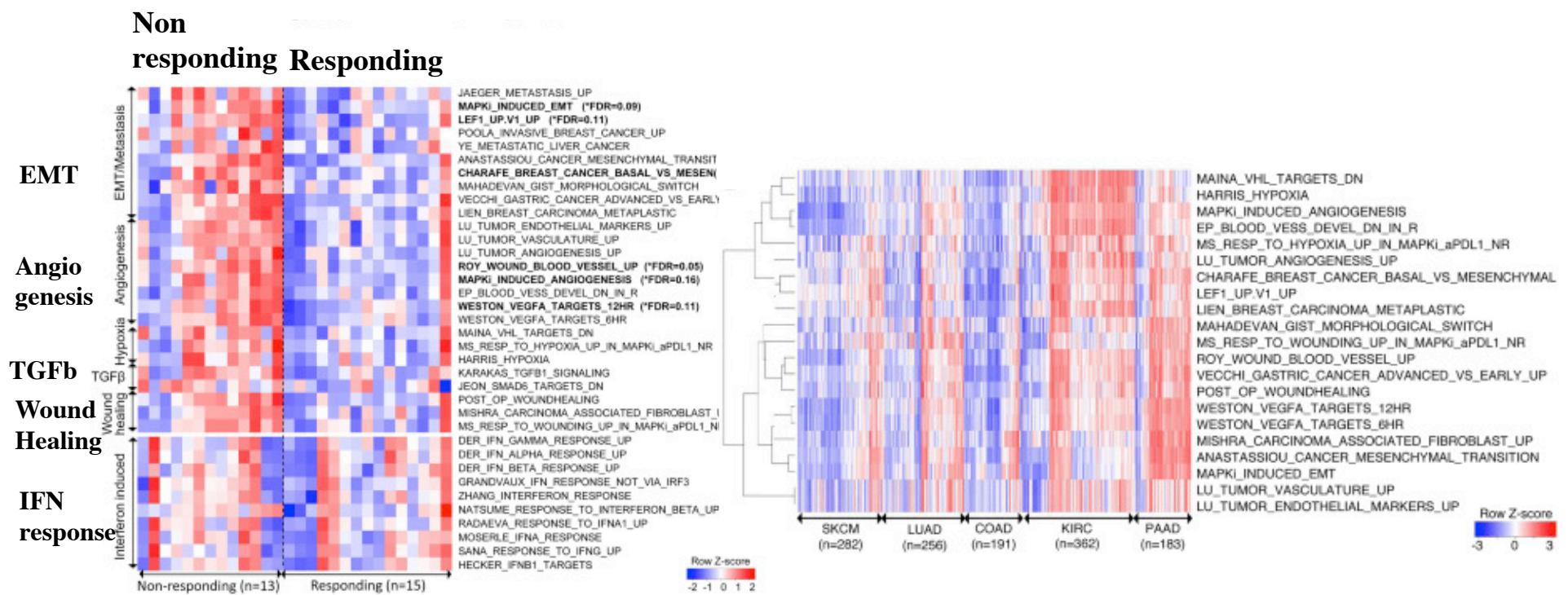
Molecular subgroups	Immunologic classification	Escape mechanisms	Potential immunotherapeutic approach
Hypermutated	High T cell infiltration with Th1 orientation and cytotoxic lymphocytes	Immune checkpoints: PD-1, LAG3	Checkpoint blockade
Mesenchymal	High lymphocyte and myeloid cell infiltration High angiogenesis Stromal mesenchymal cells	Hypoxia TGF beta PD-1 axis	Anti-angiogenic Anti-TGF- β Checkpoint blockade CAR T cells
Canonical & Metabolic	Low lymphocytic and myeloid cell infiltration	Low class I MHC expression	CAR T cells Bispecific antibodies

Inflammatory/Mesenchymal signature expands to other malignancies



TRANSCRIPTOMIC SIGNATURE OF INNATE RESISTANCE TO ANTI-PD1 THERAPY

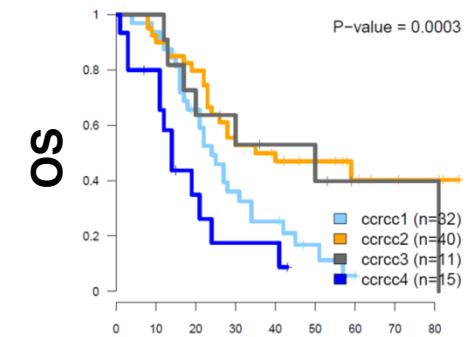
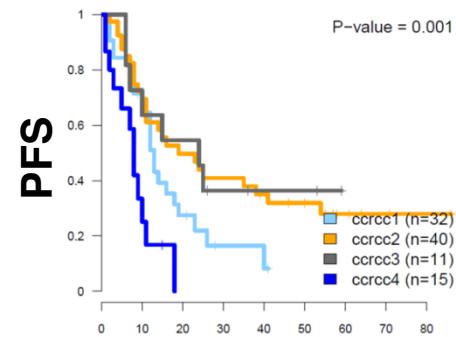
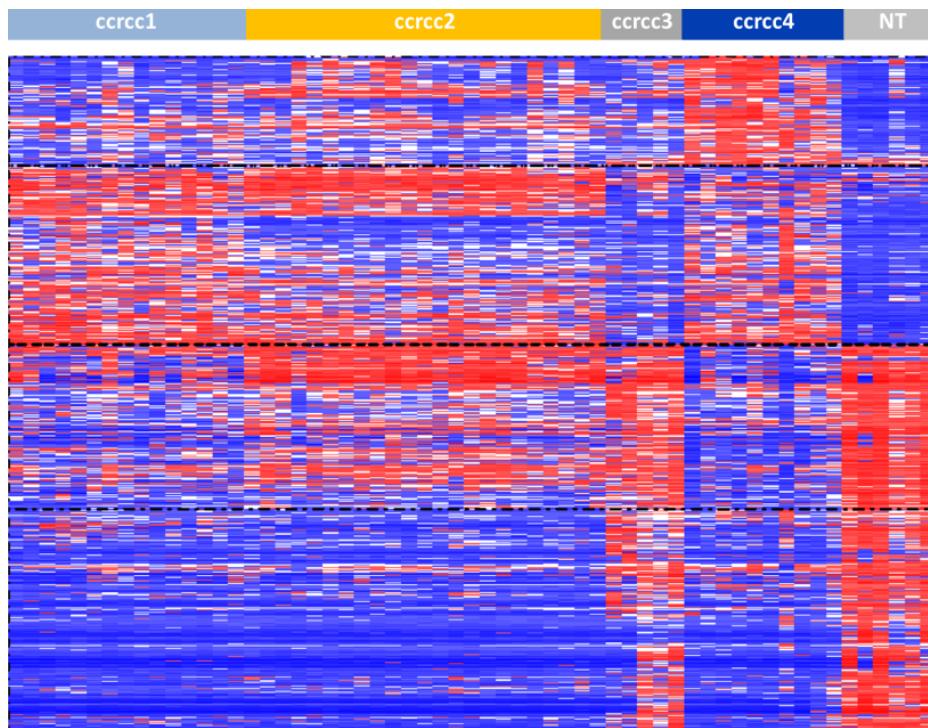
IN METASTATIC MELANOMA ACROSS CANCERS



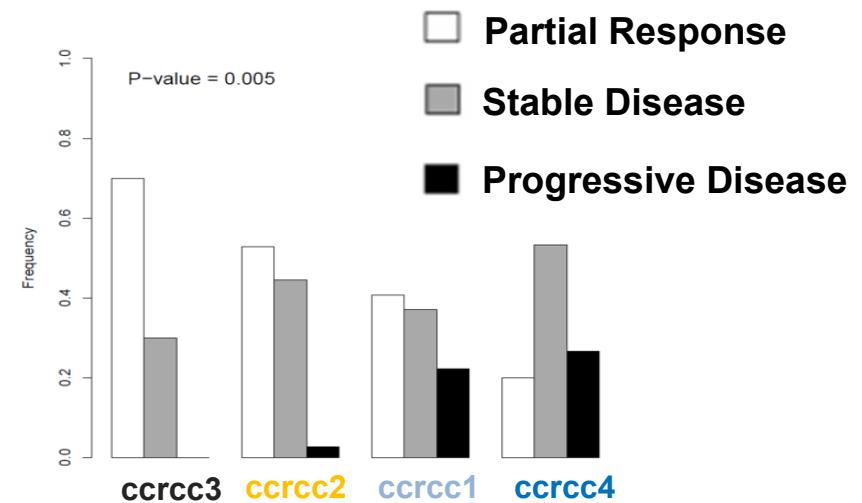
Molecular subgroups of clear cell Renal Cell Cancers

Unsupervised transcriptomic analysis identifies 4 robust ccRCC subtypes with different prognoses and response rates to Sunitinib treatment

Molecular subgroups of ccRCC



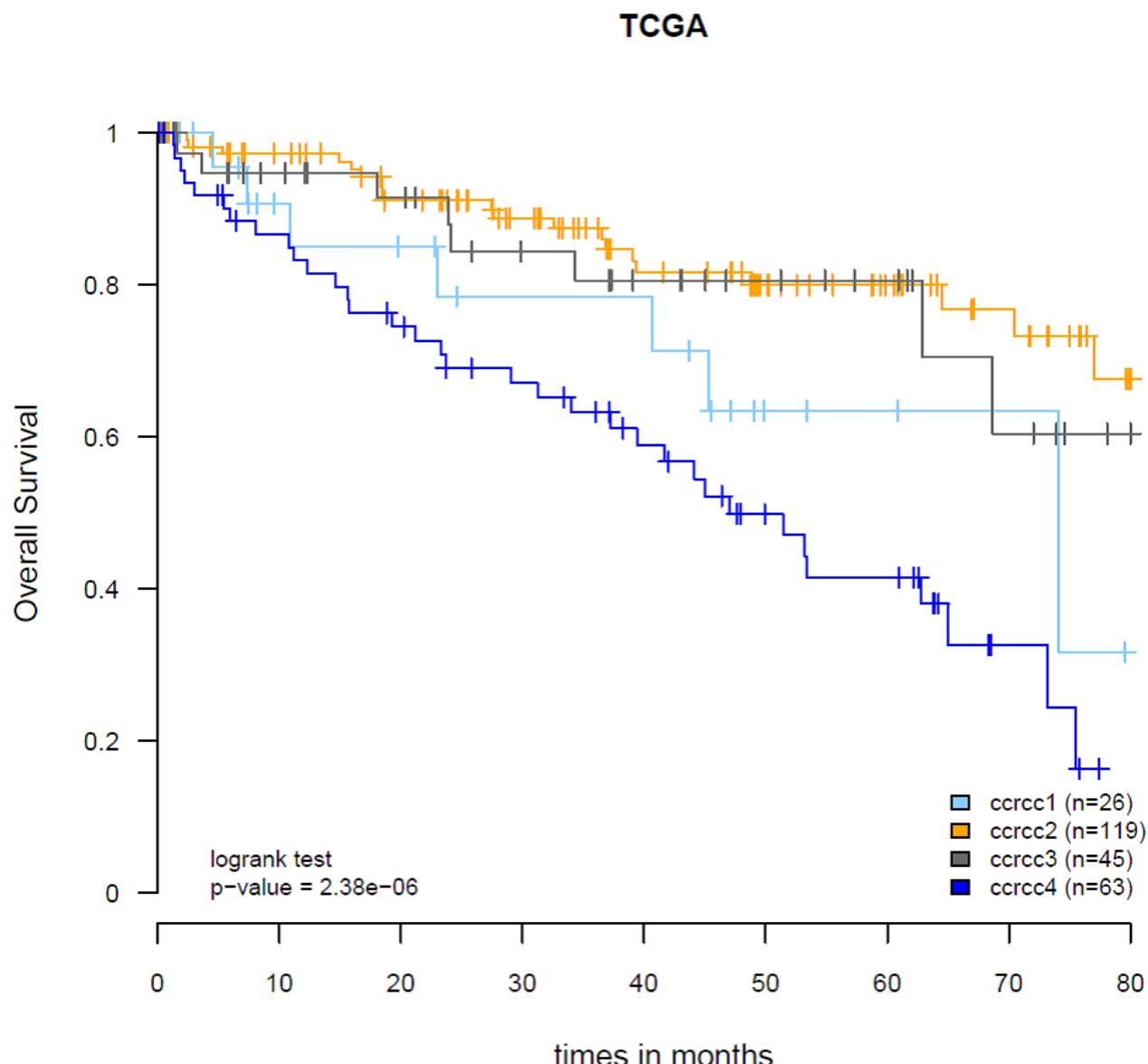
Response to Sunitinib



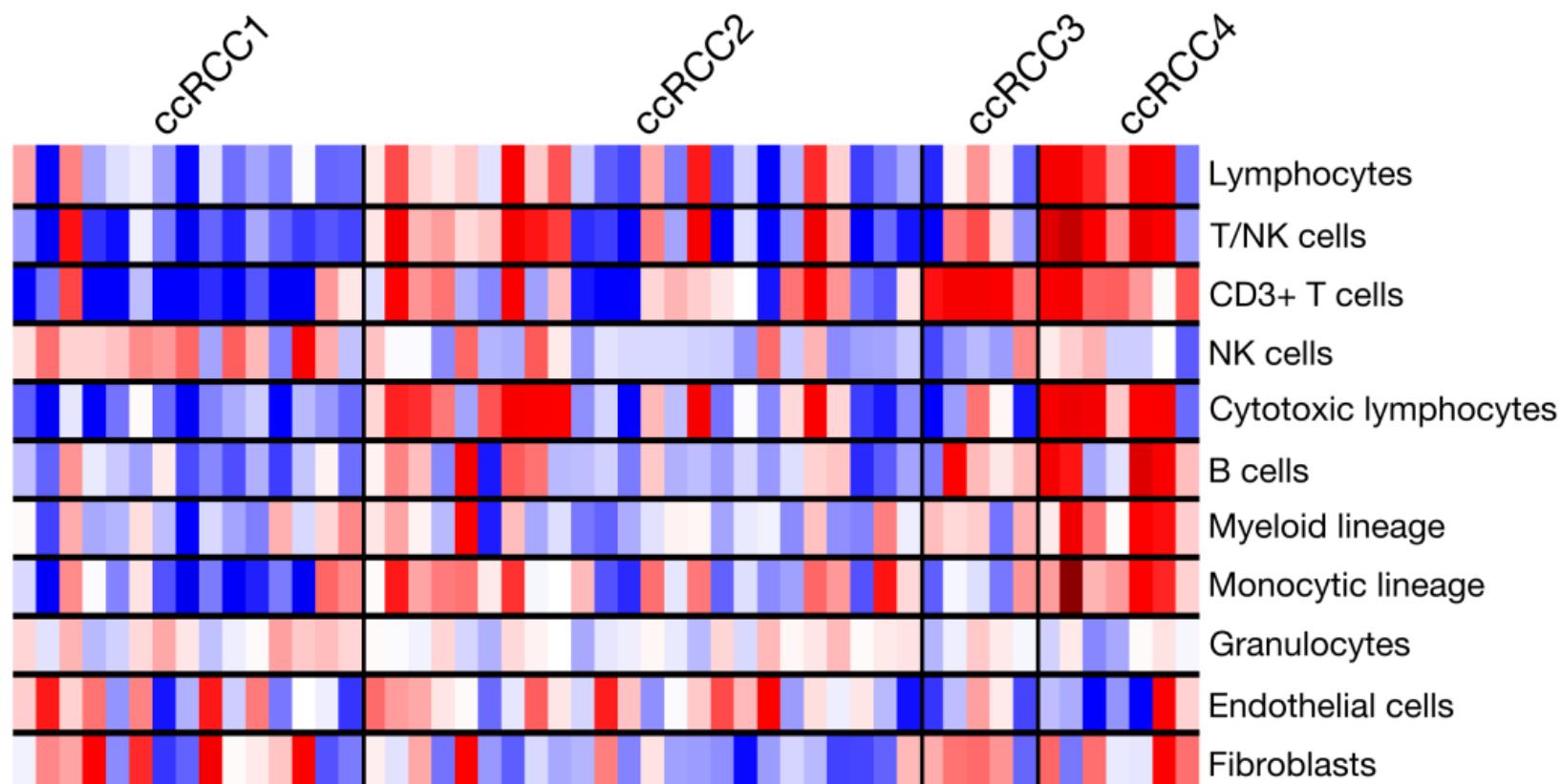
B Beuselinck, S Job, E Becht et al, CCR, 2015

Validation of the 4 ccRCC prognostic molecular subgroups in TCGA

B Beuselink et al, Clin Cancer Res, 21,1329-1339, 2015



The poor prognosis group ccRCC4 overexpresses CD8+ T cells, B cells and macrophages markers



ccrcc4 expresses genes related to inflammation, Th1 polarization and suppression and high MHC1

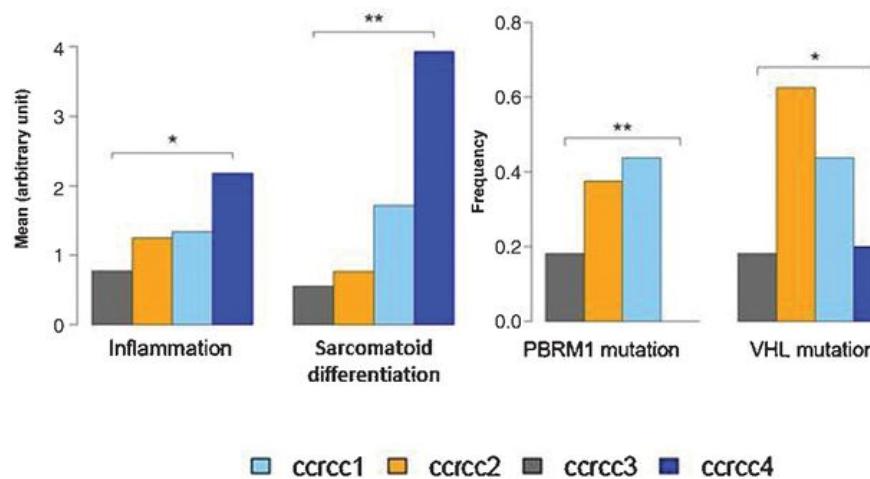
ccrcc1 has a low expression of immune genes including MHC1



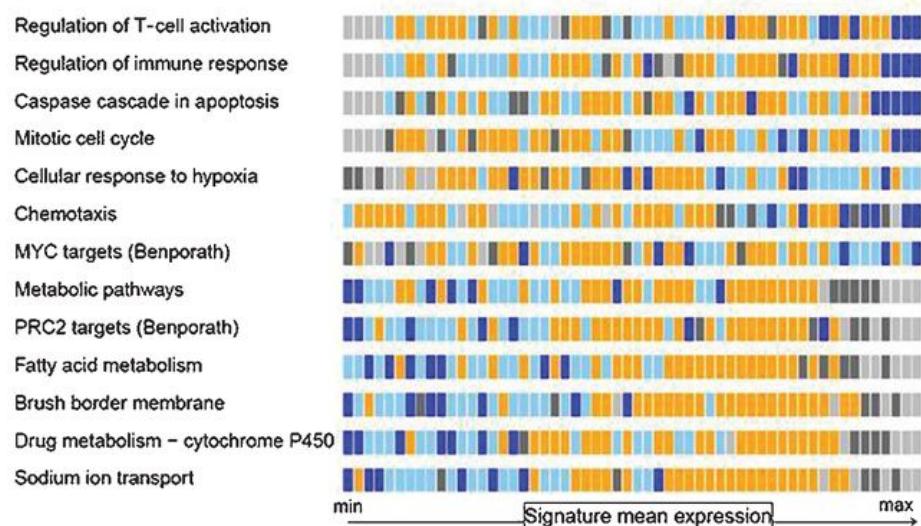
B Beuselinck, S Job et al, Clin Cancer Res, 2015

Characteristics of the four molecular subgroups of ccRCC

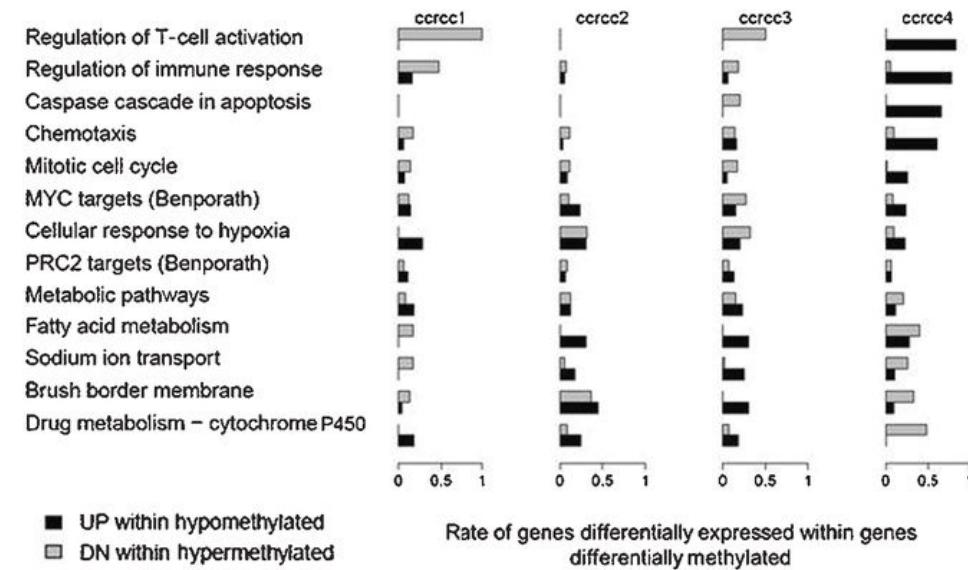
A



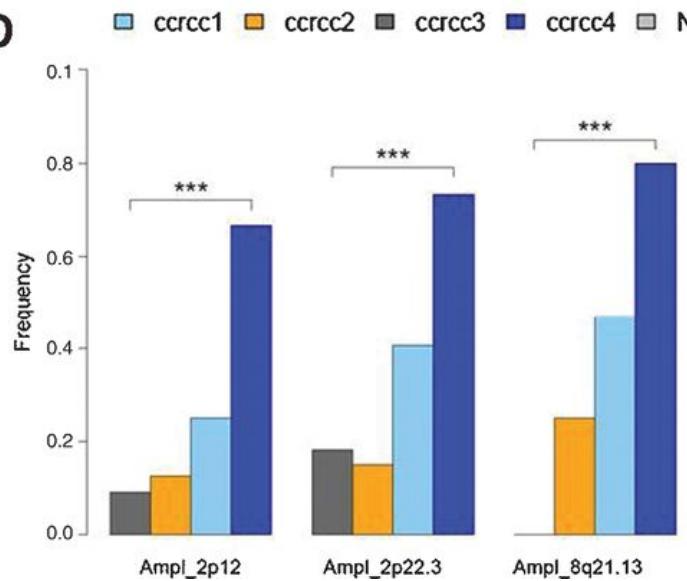
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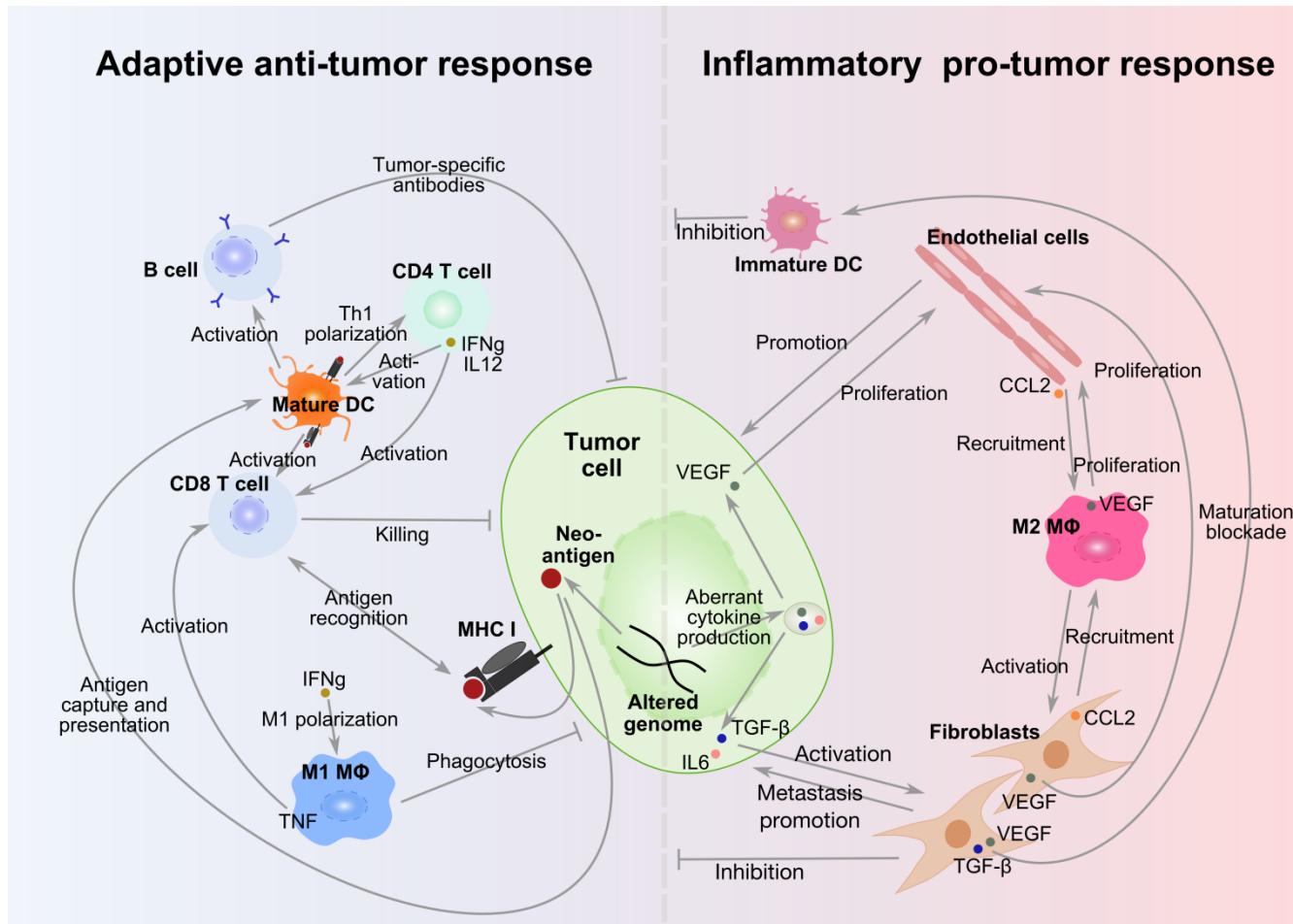
C



D

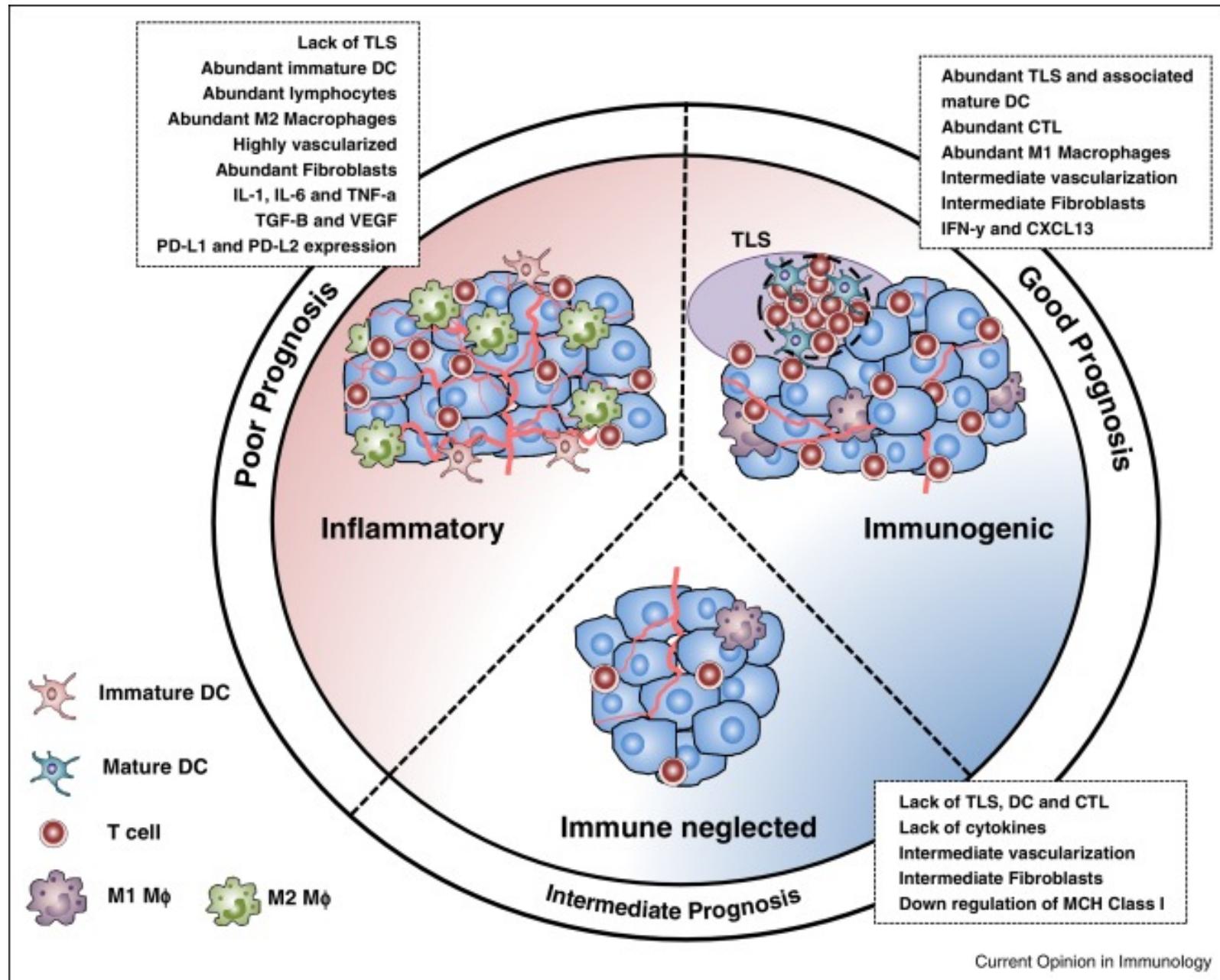


The complex interactions between malignant, stromal and immune cells of the tumor microenvironment

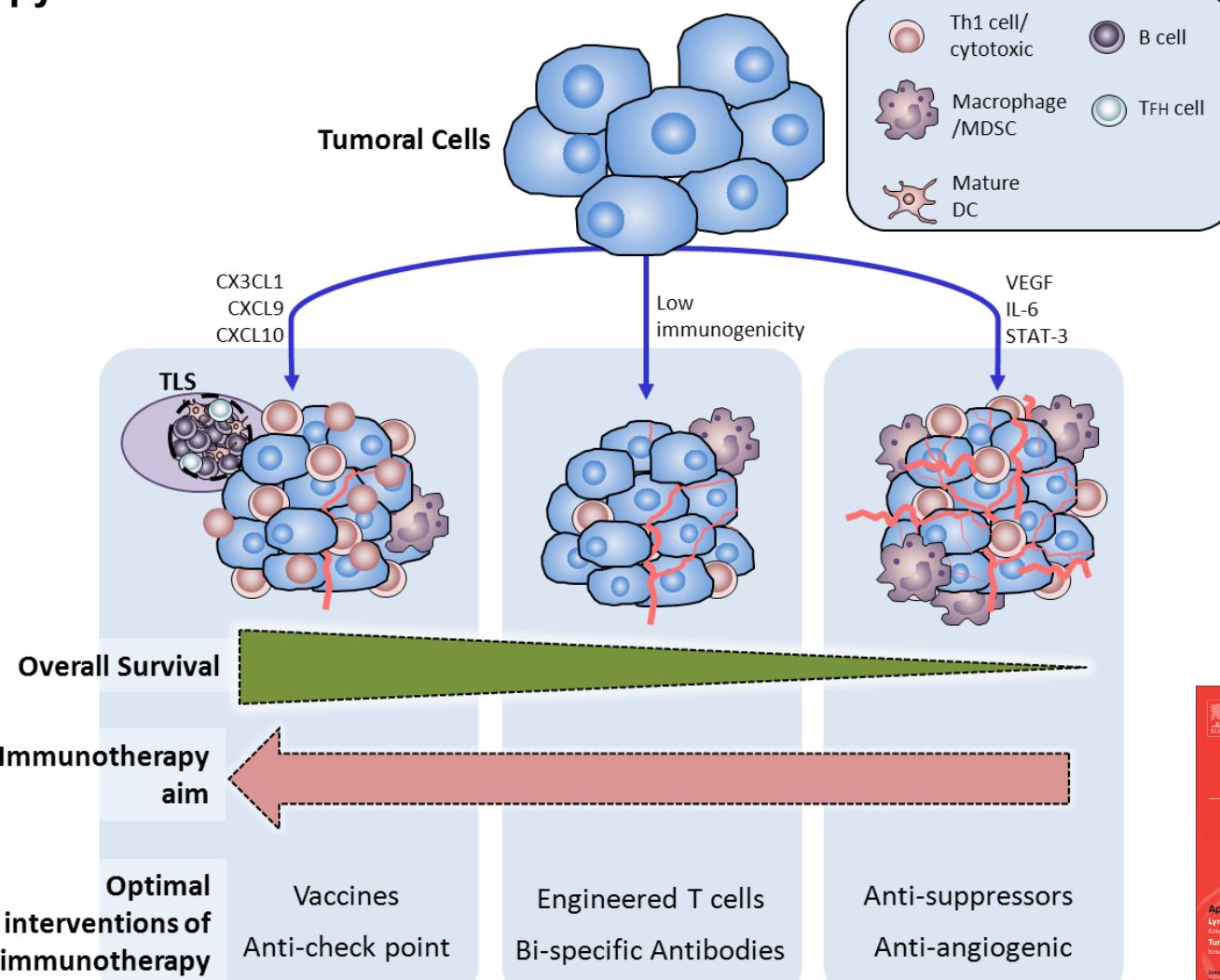


Becht E, Giraldo NA et al, Adv Immunol, 130, 95-190, 2016

THE IMMUNOLOGICAL WHEEL



Cancer immune contexture scenarios and personalized medicine for immunotherapy



N A Giraldo, E Becht et al, *Curr Opin Immunol.* 2014, 27, 8-15.

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