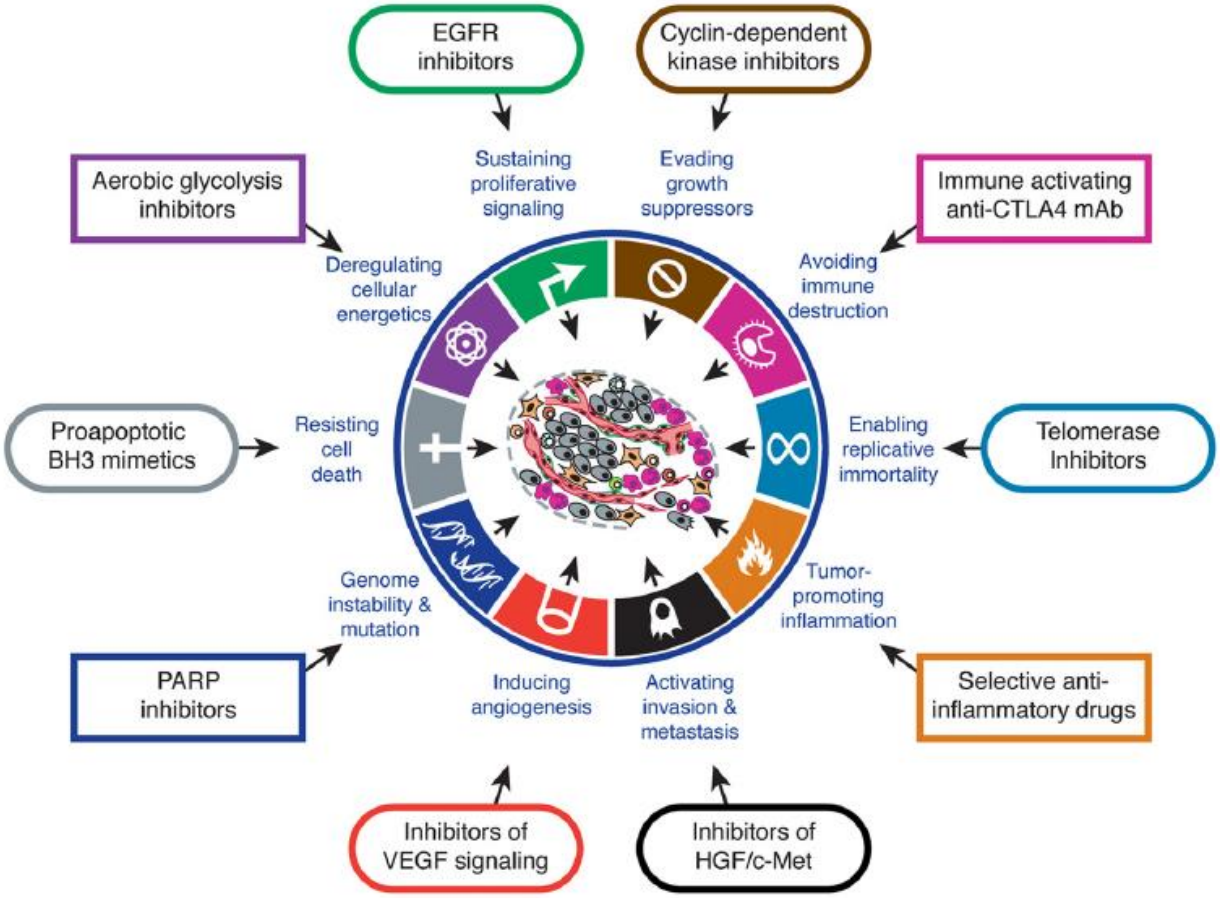
EMA - CDDF JOINT MEETING
CHALLENGES FOR THE APPROVAL OF ANTI-CANCER IMMUNOTHERAPEUTIC DRUGS
4th-5th February 2016
London, United Kingdom

The challenges of the different stakeholders

An academic perspective

Heinz Zwierzina, M.D.
CDDF
Early Clinical Trial Unit
Innsbruck Medical University

The challenge (level 1)



D. Hanahan and R. A. Weinberg, Cell 144:646-654, 2011

The challenge (level 2)

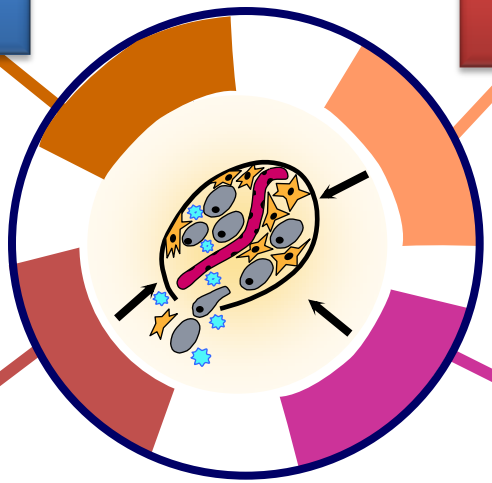
Evolving immunotherapy approaches

Enhancing adaptive immunity

- NK-cell activation*
- ADCC*
- CD137*
- IL-21
- IL-15
- CD40*
- Toll-like receptors*
- APC modulation

Immune priming

- Multiple vaccine approaches
- Use chemotherapy/ radiotherapy to prime
- Adoptive immunotherapy approaches
- Toll-like receptors*



Immunosuppressive microenvironment

- IDO*
- TGFβ*
- IL-10

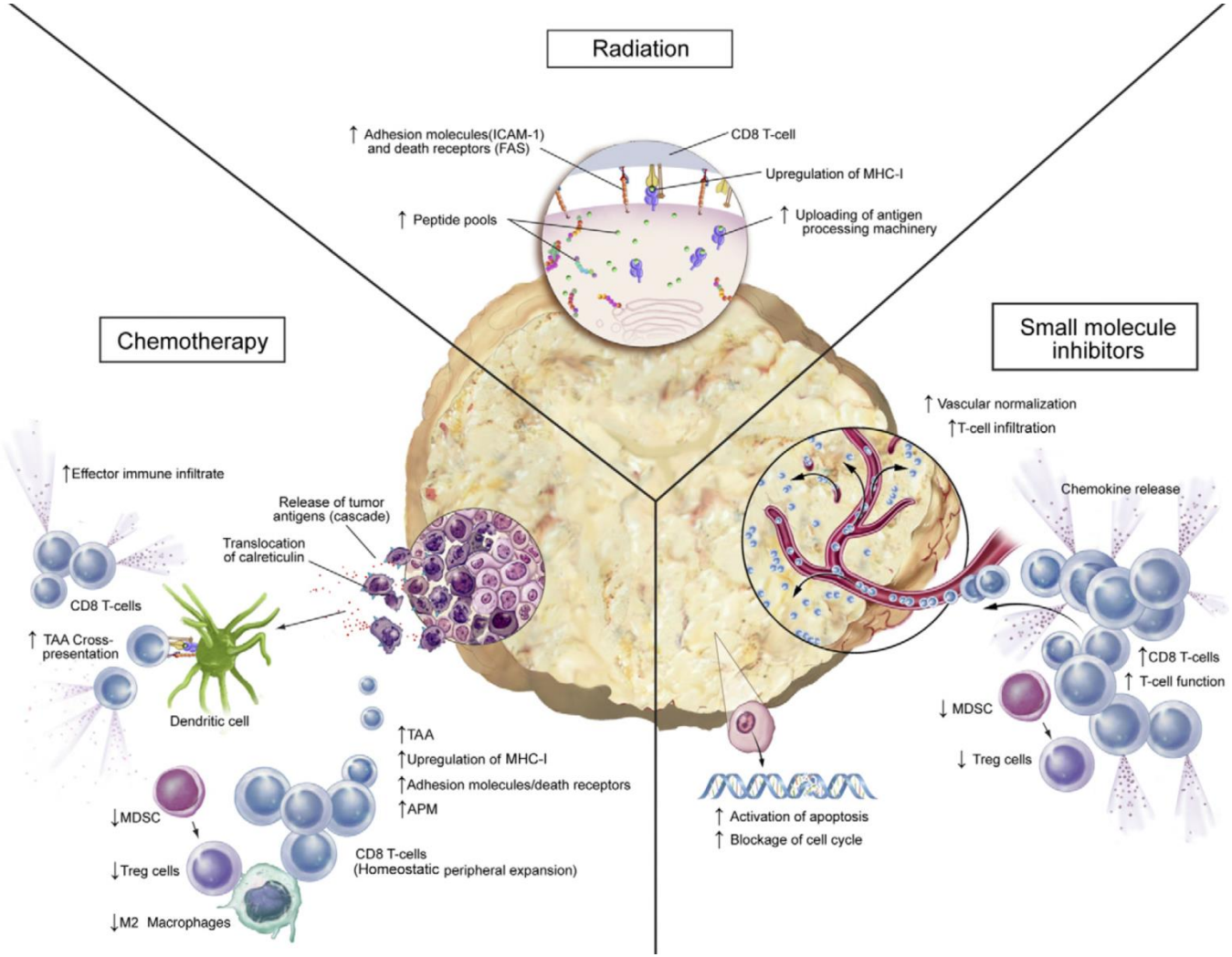
T-cell modulation

- CTLA-4*
- PD1 pathway*
- Lag 3*
- CD137*
- CD53/OX44*
- OX40/L*
- CD40/L
- Tregs*
- Adoptive immunotherapy approaches

*Target for therapeutic modulation

Finn OJ. N Engl J Med. 2008;358:2704-15
Spagnoli GC et al. Curr Opin Drug Dev 2010;13:184-192

The challenge (level 3): combination therapies



Hodge, Sem Oncology 2012

The challenges for the different stakeholders

- individualized approach ("molecular phenotyping")

no more blockbusters

versus

- subgroup analysis ("HER-2 expression")

(still) potential for blockbusters

Molecular phenotyping

Individualized therapy: We deal with a huge variety of malignant diseases

- each is less common than cancer defined by histology alone
- each likely to benefit from an individual approach

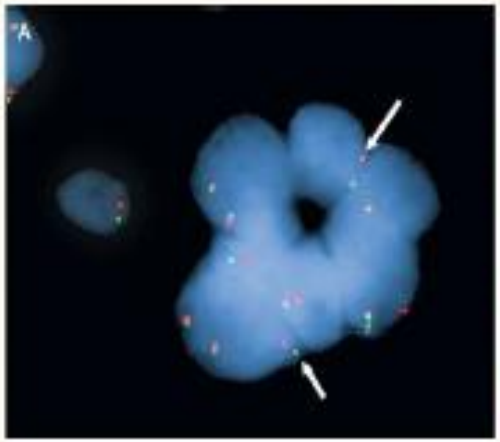
However:

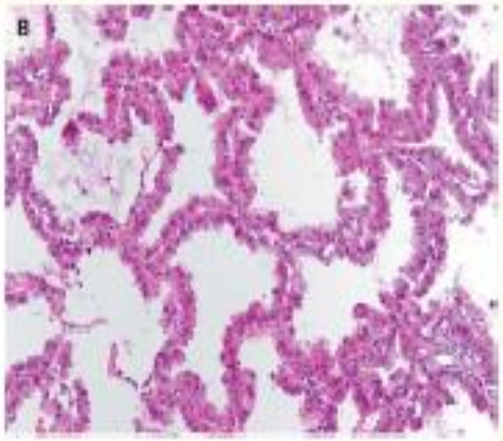
- redundancy of all biological networks
- resistance mechanisms
- tumor heterogeneity (intra- / intertumoral, over time)

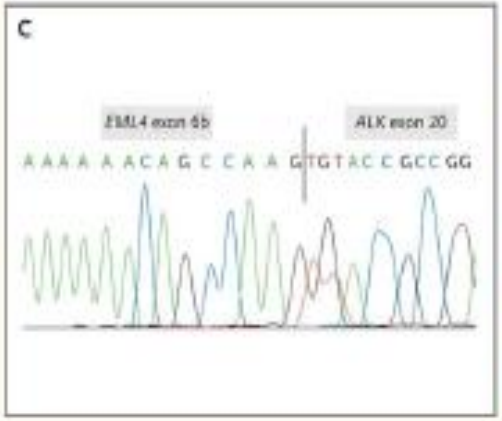
Will a completely tailored approach ever work?

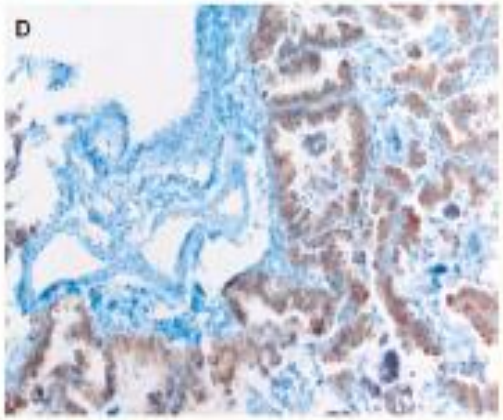
Crizotinib in metastatic NSCLC with ALK rearrangement

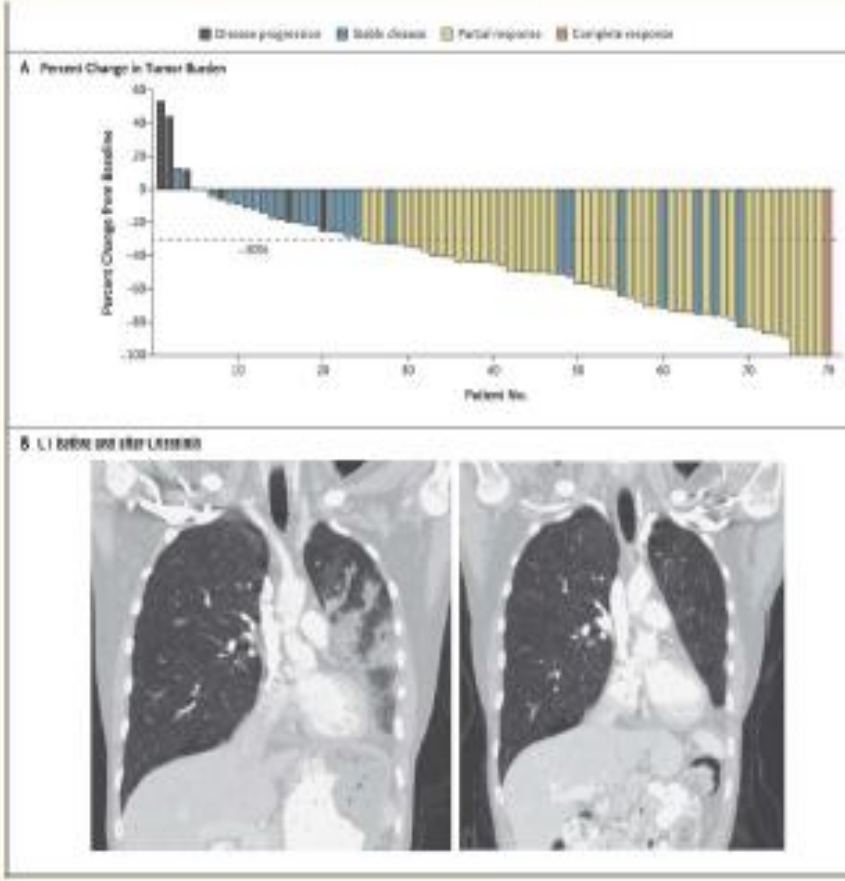
Incidence: 4-7% (mainly AdenoCa in nonsmokers)
n=82: RR 57% (1CR), SD 33%, 6-mths-PFS-Rate 72%











The NEW ENGLAND JOURNAL of MEDICINE

Kwak et., 201

tilak Universitätskliniken LKH Innsbruck

MEDIZINISCHE UNIVERSITÄT INNSBRUCK
UNIVERSITÄTSKLINIKEN
INNERE MEDIZIN
Hämatologie und Onkologie

CARIS LIFE SCIENCES

ONCO-T-PROFILING

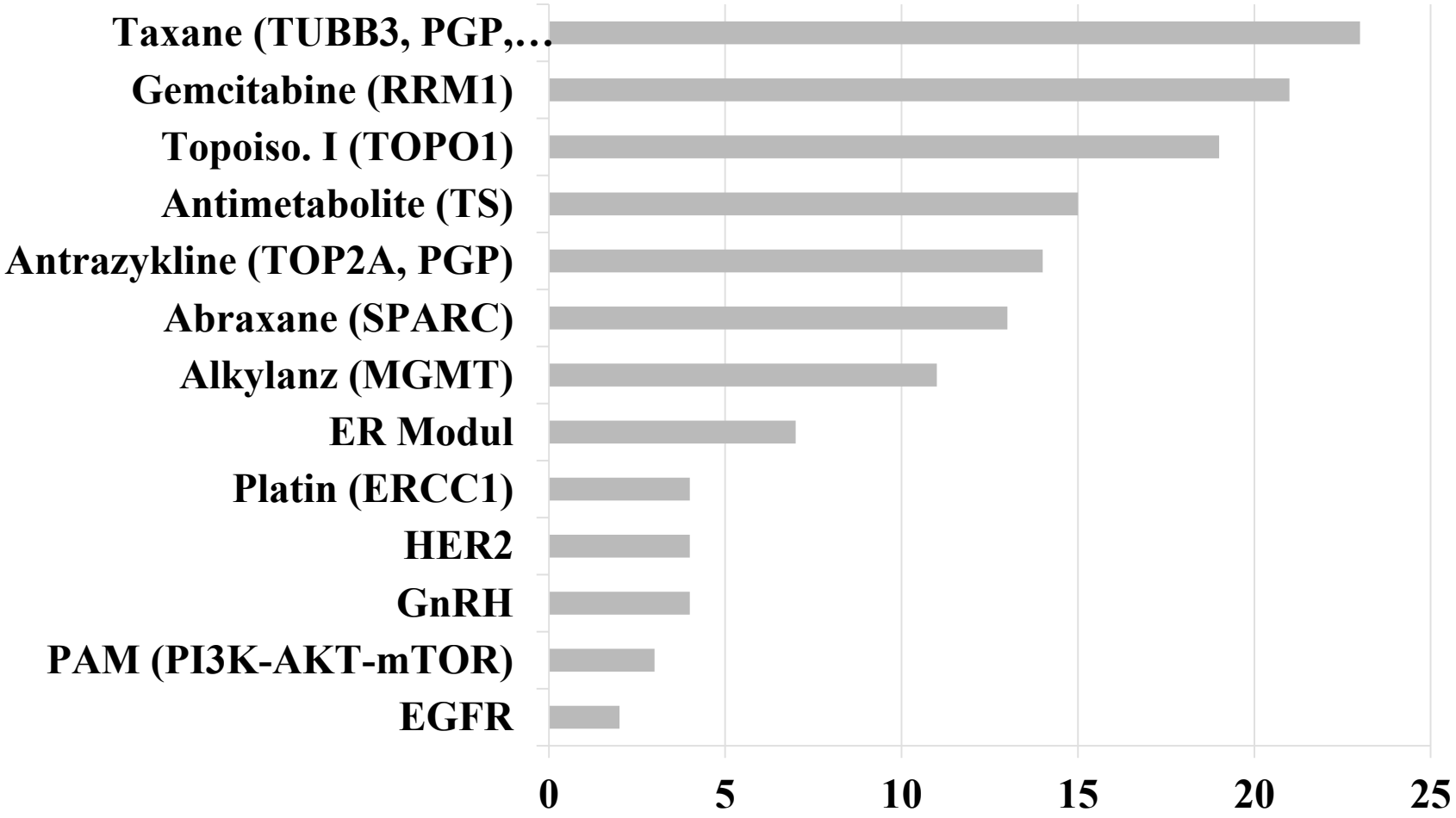
Status: Nov 27, 2014*

- **Collaborative project**
- **100 patients with solid tumours within 18 months**
  ECOG status 0-2, life expectancy > 3 months
  96 patients included after 14 months
- **Tumour tissue available at respective pathology department**
- **Informed consent**
- **Re-biopsy when possible**
- **Molecular profiling by Caris Life Sciences**

*A. Seeber, H. Zwierzina

Patient (Diagnosis)	Therapy according to typing	Marker
Patient 1 (CRC)	Nab-paclitaxel + gemcitabine	SPARC, RRM1
Patient 2 (CRC)	Doxorubicin	TOP2A
Patient 3 (breast)	Nab-paclitaxel	SPARC, PGP
Patient 4 (sarcoma)	Paclitaxel + gemcitabine	PGP, TOP2A, TUBB3
Patient 5 (sarcoma)	Gemcitabine	PGP, TUBB3, TL3
Patient 6 (endometrial)	Lip. doxorubicin	TOP2A, PGP
Patient 7 (pancreatic)	Regorafenib	c-myc
Patient 8 (SCLC)	Irinotecan	TOPO1
Patient 9 (NET)	Topotecan	TOPO1
Patient 10 (breast)	Exemestan + everolimus	PAM, ER
Patient 11 (NSCLC)	Gemcitabine	RRM1
Patient 12 (gastric)	Epirubicin + docetaxel	TOP2A, PGP, TLE3, TUBB3
Patient 13 (CRC)	Regorafenib	KRAS
Patient 14 (breast)	Exemestan + everolimus	PAM, ER
Patient 15 (breast)	Exemestan + everolimus	PAM, ER
Patient 16 (cervical)	Lip. doxorubicin	TOP2A, PGP

Potentially active drugs according to molecular typing



- **Male, 64a**
- **Soft tissue sarcoma (metastatic)**
- **Initial diagnosis 10/2009**
- **Previous therapies: doxorubicin, trabectidin, pazopanib, ifosfamide**

- **ONCO-T-Profiling: 04/15 → *TUBB3* +, *RRM1* -**
- **→ Start paclitaxel + gemcitabine: 22.05.2015**
- **Interim analysis 01/16: stable disease (SD)**

Molecular Typing – a word of caution

- Science behind is impressive
- We are learning a lot more about tumour biology
- We add a further level for complexity
- Challenge remains how to apply this technology in clinical trials (except for frequent genetic alterations)
- In most cases we come back to chemotherapy
- There are patients who profit
- Frequently the benefit for an individual patient is hard to prove

IMMUNOTHERAPY

- **First glance BIG difference**
  - **A potentially CURATIVE treatment in the metastatic setting (!)**

- **Second glance:**
  - **There are primary and secondary resistance mechanisms for ALL anticancer drugs!**
  - **Challenge is to define the (non-) responders**

Individualized therapy (molecular phenotyping) *versus* subgroup analysis (e.g. „PDL-1 expression“)

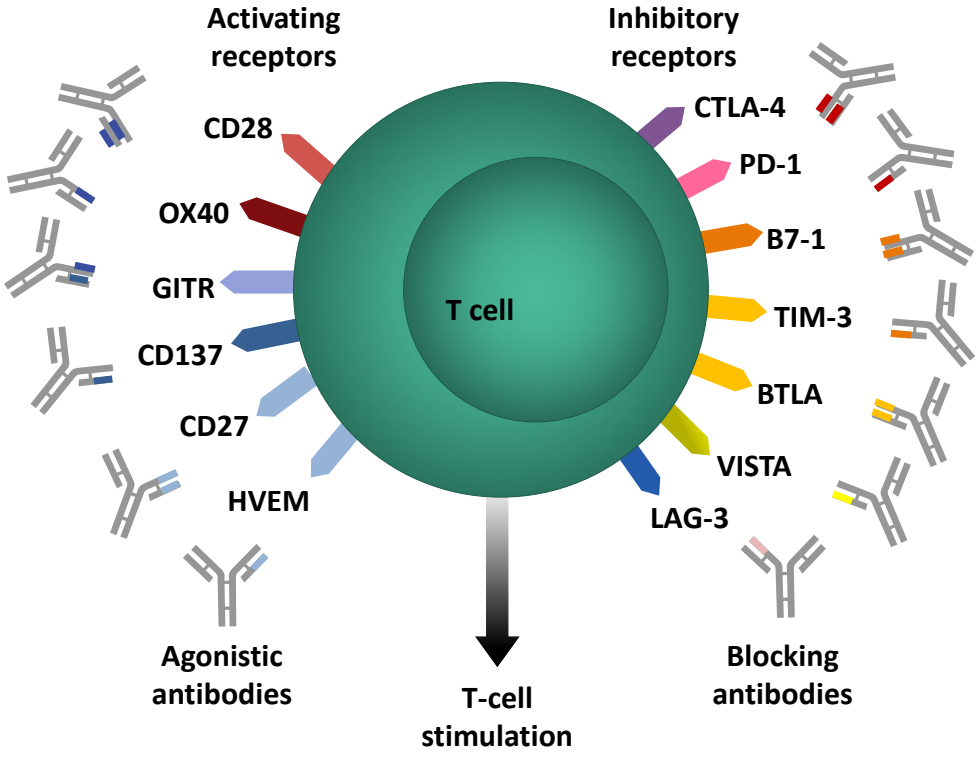
The heterogeneity issue

- **Fundamental question of personalized medicine**
- **Does the driver of lesion X really represent the driver of tissue Y?**
- **Is the immune system homogenous over the whole tumor load (e.g. PD L1 expression)**
- **Image guided biopsies from large tumors may not be representative for the entire tumor**

Peripheral blood markers may hold the potential to be the solution?

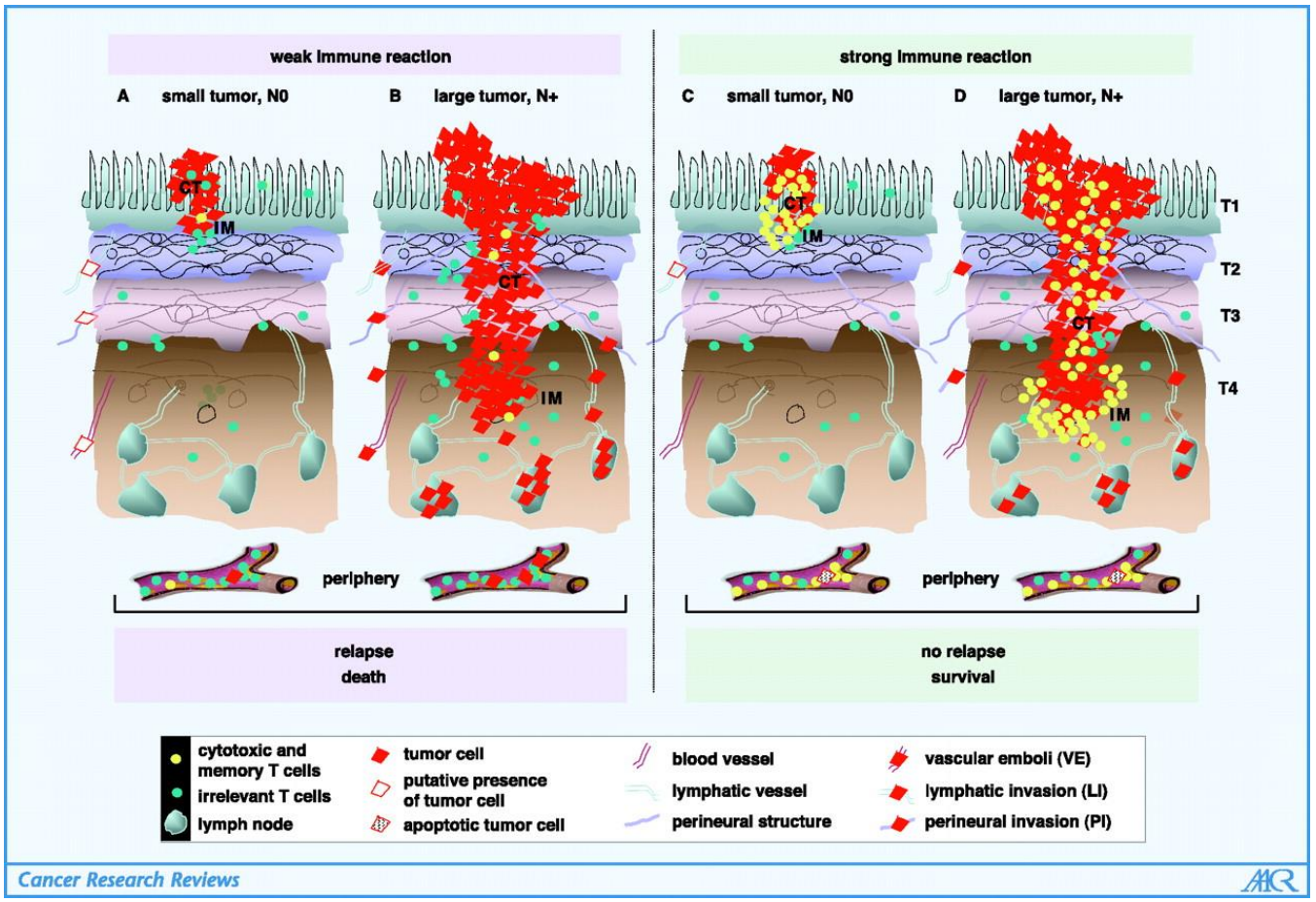
Subgroup analysis – search for biomarkers

The „checkpoint modifier“ pipeline is full!



adapted from Mellman I, et al. Nature. 2011:480;481–489; 2. Pardoll DM. Nat Rev Cancer. 2012;12:252–264.

Immune Control of Cancer T Cell Infiltration



Galon J et al. Cancer Res 2007;67:1883-1886

Tumor infiltrating immune cells after treatment with anti-CTLA-4 antibodies

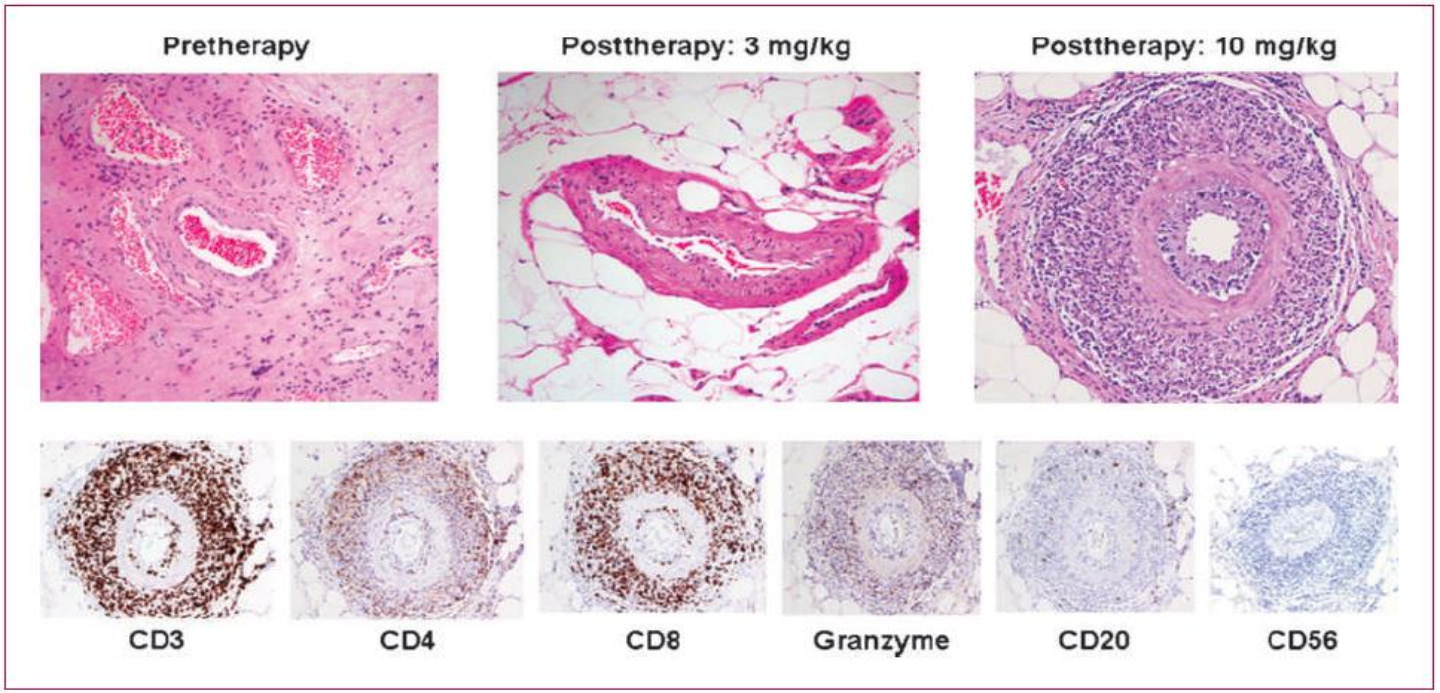


Fig. 2. Perivascular infiltration of cells into tumor tissues after treatment with 10 mg/kg/dose of anti–CTLA-4. Representative pictures showing an absence of perivascular infiltration of cells in untreated tumor tissues (0 of 11) and tumor tissues obtained from patients treated with 3 mg/kg/dose of anti–CTLA-4 (0 of 6) as compared with the presence of perivascular infiltration noted in tumor tissues obtained from patients treated with anti–CTLA-4 at 10 mg/kg/dose (2 of 5; top). Immunohistochemistry revealed that the infiltrating cells were positive for CD3, CD8, CD4, and granzyme, but were predominantly negative for CD20 and CD56 (bottom).

Carthon et al, Clin Cancer Res 2010

Increase in TILs at Week 4 from Baseline Associated with Clinical Activity of Ipilimumab

Biomarker	# with TILS increased from baseline (N=27)	P-value	Odds Ratio in favor of clinical benefit (95% CI)
Benefit group	4/7 (57%)	0.005	13.27 (1.09, 161.43)
Non-benefit group	2/20 (10%)		

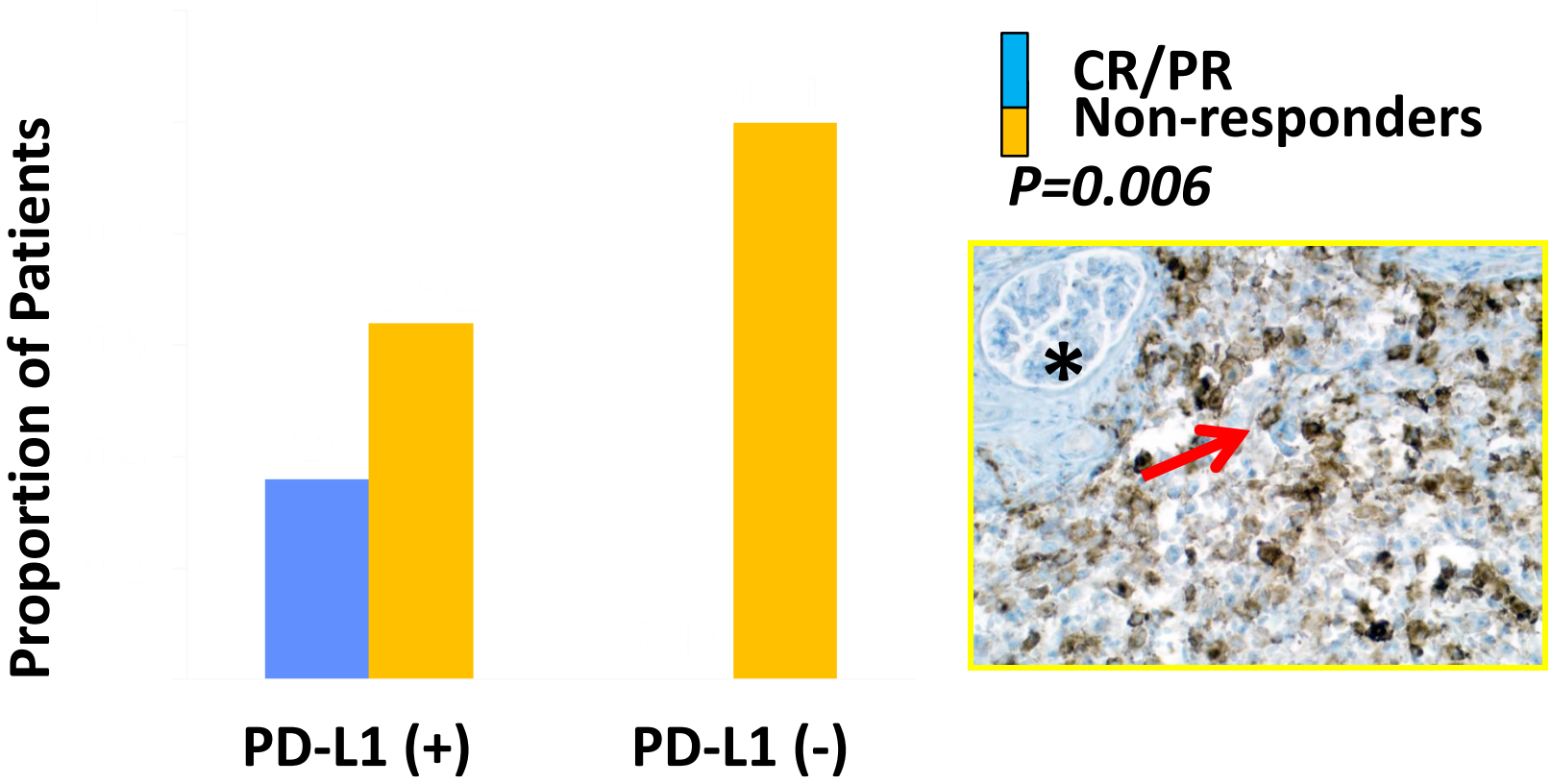
- Not all samples were evaluable for every parameter, and not all patients provided data for all time points
- *P* values uncorrected for multiple testing

TILs at baseline were not correlated with benefit

Hamid et al, J. Trans Med, 2011

Responsiveness was associated with PD-L1 on tumor cell surface

PD-L1 expression by IHC in 61 pretreatment tumor biopsies across tumor types from 42 pts



Patient samples: 18 MEL,10 NSCLC, 7 CRC, 5 RCC, 2 CRPC

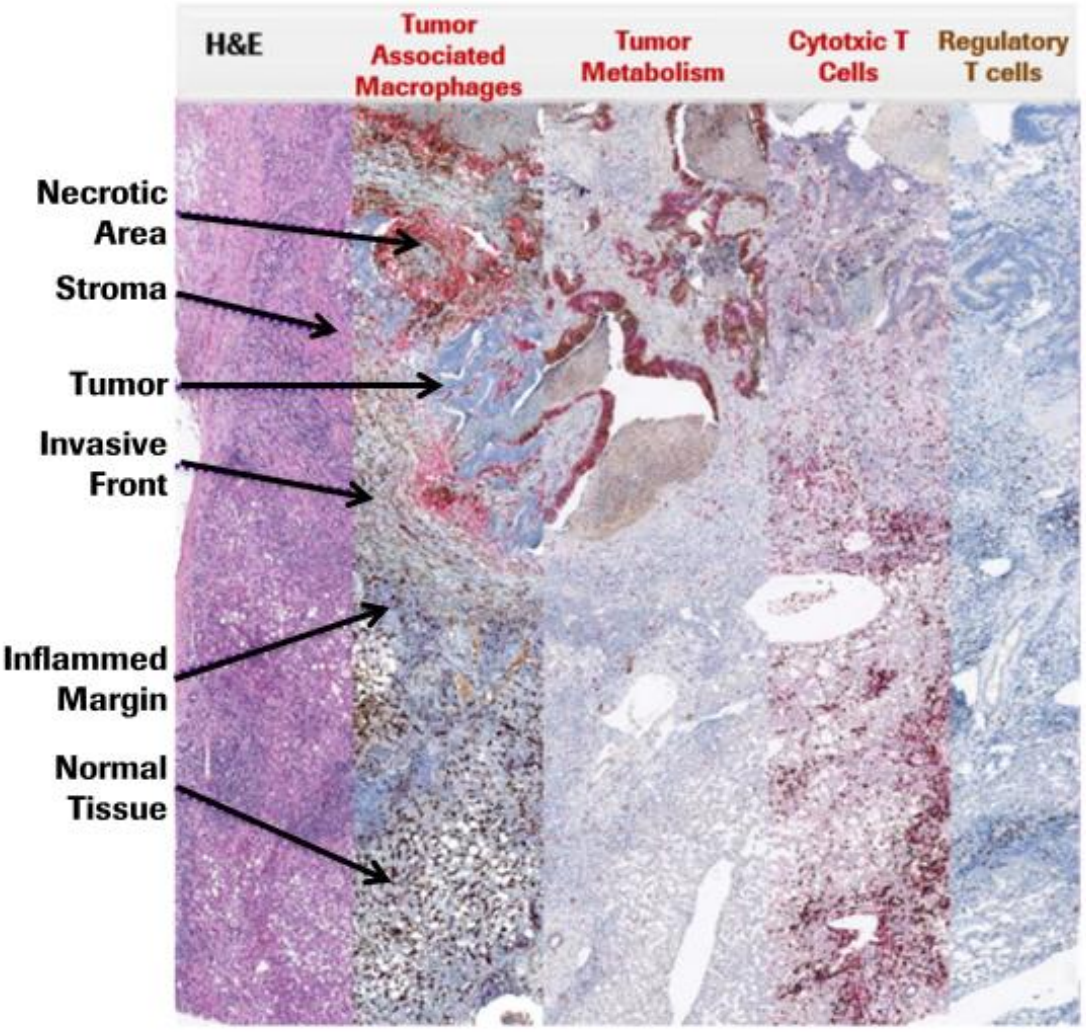
Topalian et al NEJM, 2012

Combining Durvalumab and Tremelimumab:
Clinical activity from Phase 1b dose escalation in NSCLC

PD-L1 status	D10–20 q4/2w T1	
	n/N	95% CI
All patients	11/39 (28%)	15–45
PD-L1^{+} ≥25%	3/9 (33%)	8–70
PD-L1^{-} <25%	6/23 (26%)	10–48
All 2L patients	7/16 (44%)	20–70

Rizvi N, et al. Oral presentation, SITC 2015; abstract 477

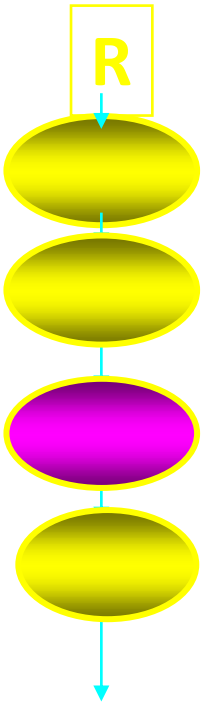
Tumor tissue analysis reveals a complex tumor micro-environment (TME) landscape



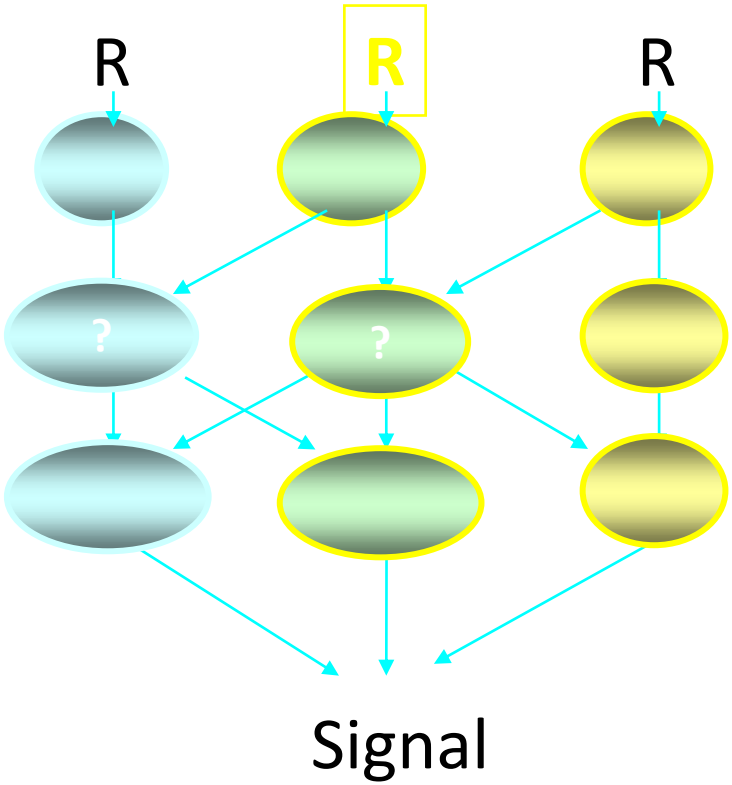
pRED Oncology, Translational Medicine Pathology, Roche Innovation Center Penzberg

How to Identify the “Relevant“ Biomarker?

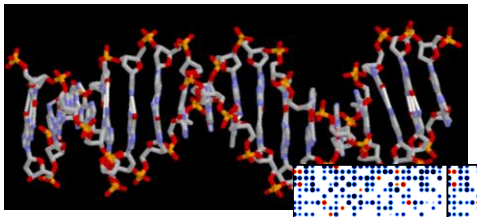
Dream: Single Signal Approach



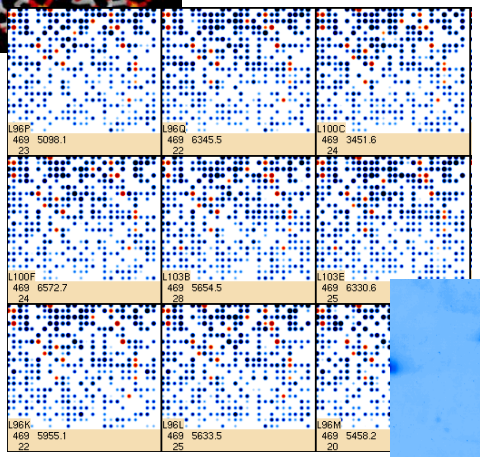
Reality: A lot of redundancy



Roles of Genome / Epigenome, Transcriptome, Proteome

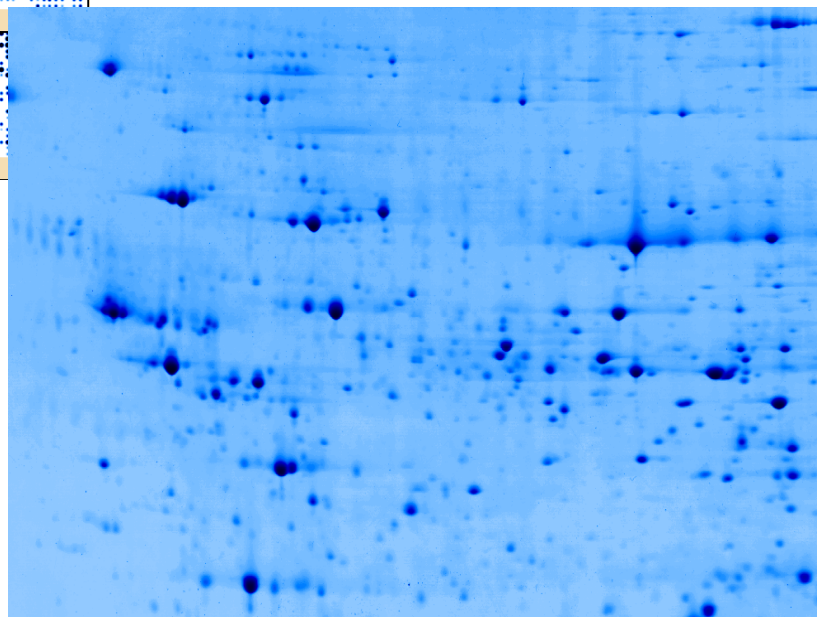


← Genome (all genes): What *could* happen

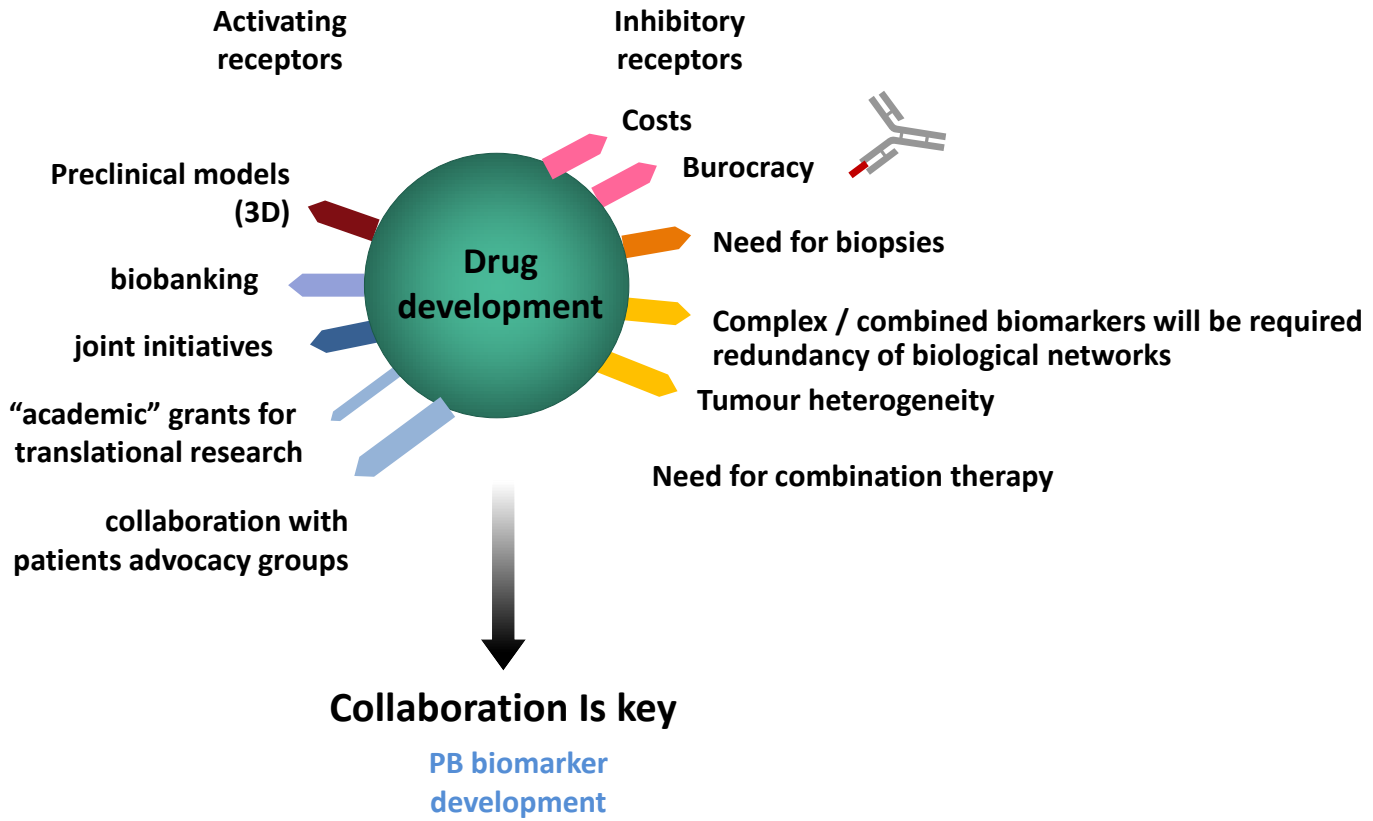


Transcriptome (all mRNA's): What *might be* happening

Proteome (all proteins): What *is* happening →



The „checkpoint modifier“ pipeline for drug development: Is the pipeline full?



“Adapted from Mellman I, et al. Nature. 2011:480;481–489”

Biomarkers - the future

- **Given the shortcomings of single biomarkers and the complexity of cancer biology, multiple / composite biomarkers will be increasingly relied on**
- **Peripheral blood markers may (only) be „surrogate markers“**
- **Serum / blood markers may help to overcome the logistic challenges of taking repeated biopsies**
- **Without the development of biomarkers that define subgroups of patients that may/may not respond**
  - **Treat „wrong“ patients and cause unneccessary side effects (ethical aspect)**
  - **our health care system will be in serious troubles (HTA issue)**

The way ahead

- Molecular phenotyping will play a role for well-defined patient population

- Biomarker development in the peripheral blood could be a joint project of all stakeholders

„collaboration is key“