4 Feb 2016

EMA – CDDF Joint Meeting, London

mRNA- and peptide-based anticancer immunotherapies

Michael Platten
Neurology Clinic, University Hospital Heidelberg
National Center for Tumor Diseases
CCU Neuroimmunology and Brain Tumor Immunology
German Cancer Research Center, Germany

dkfz.

NCT | NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

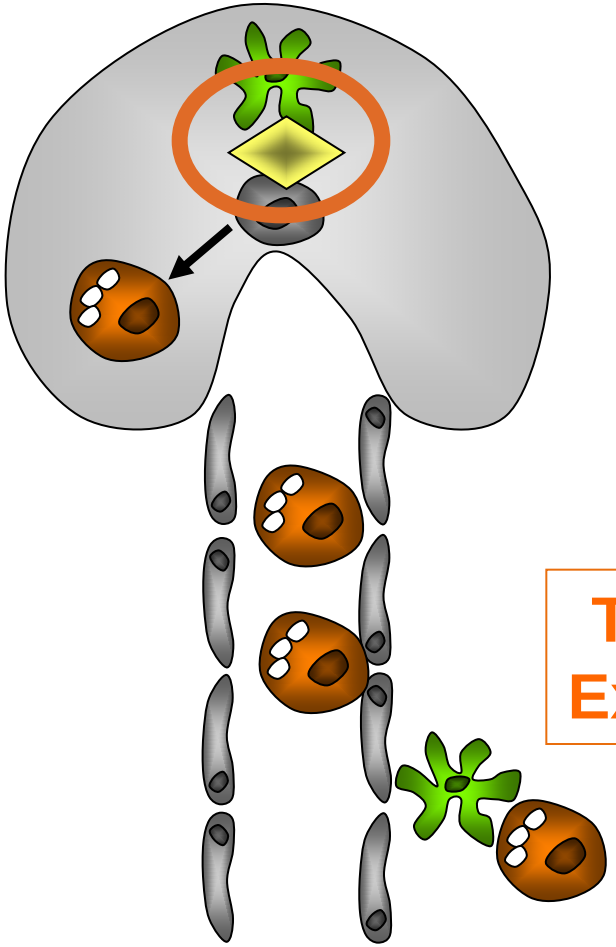
UniversitätsKlinikum Heidelberg

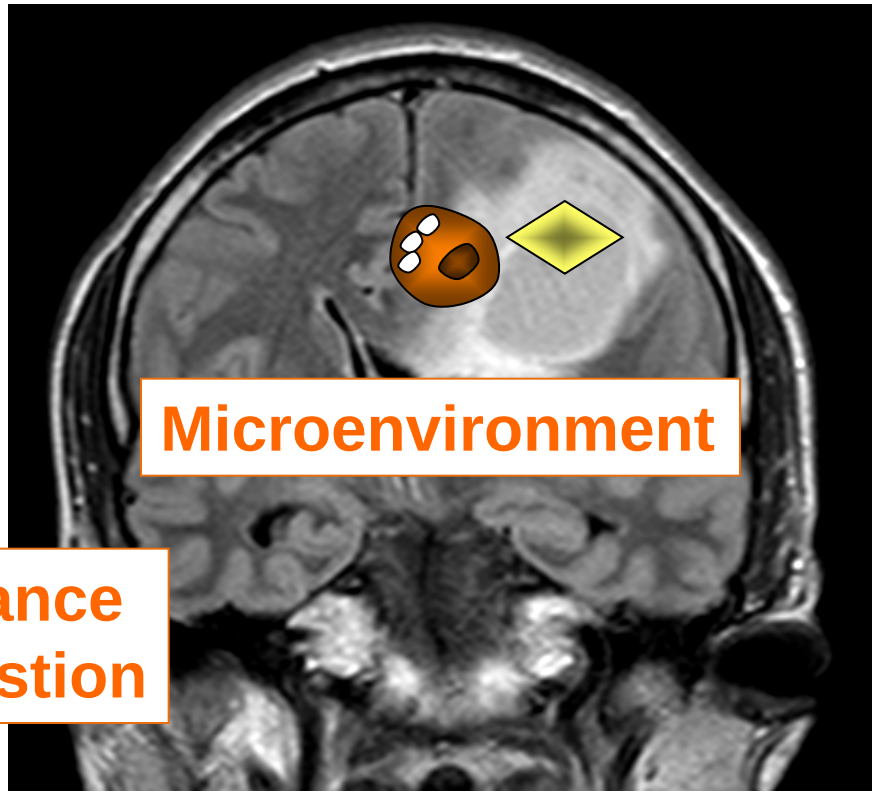
COI-disclosure

- **Patent „Means and methods for treating or diagnosing IDH1 R132H mutant-positive cancers“; WO 2013/102641 A1, PCT/EP2013/050048**

Challenges in anti-cancer vaccines

Target Antigen

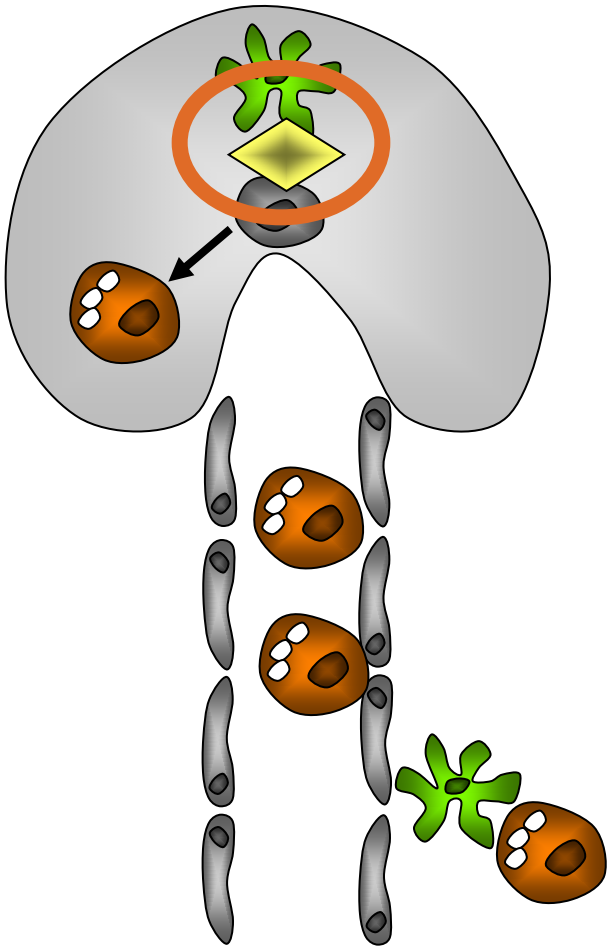




Tolerance
Exhaustion

Challenges in target selection

Target Antigen



TAA

- Shared Antigens
- Low immunogenicity
- Side effects
- Dependent on HLA-Type

➢ Classic trial concepts
➢ warehouse concepts

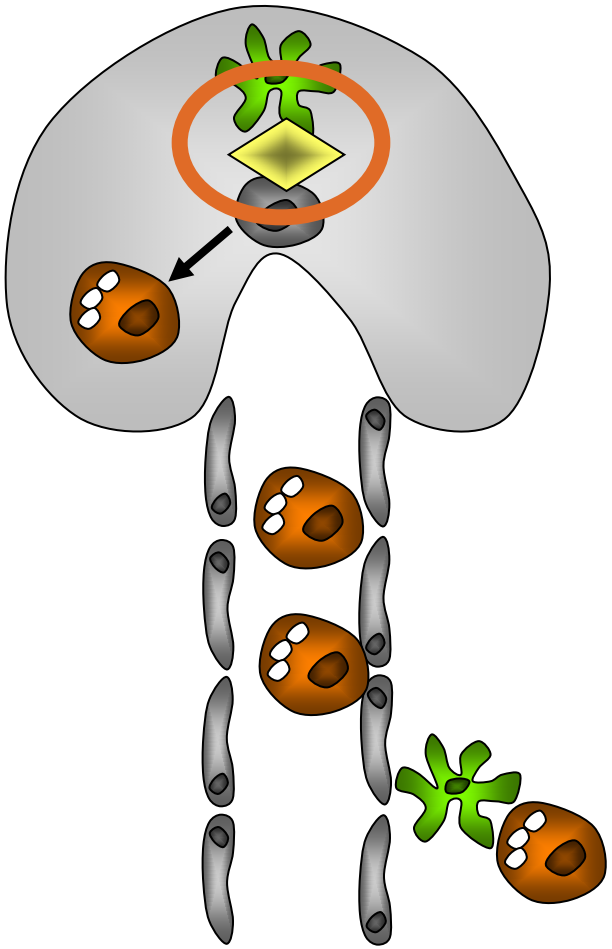
TA

- Specific immune responses
- Mostly mutated antigens
- Mostly private antigens
- Often minor antigens
- Mostly CD4 epitopes
- Often low expression

➢ Individualized concepts

Tumor-associated antigens

Target Antigen



TAA

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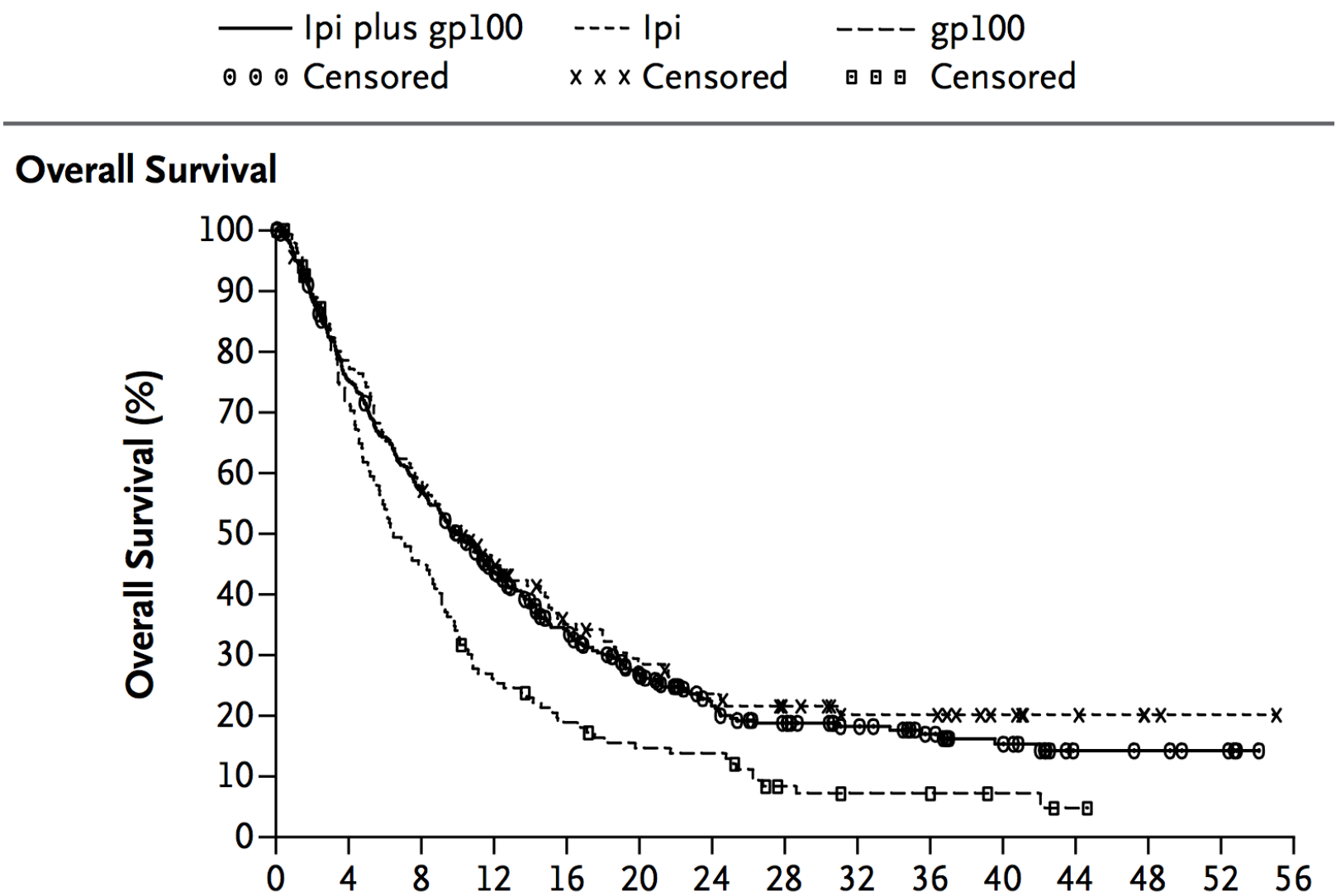
➢ Classic trial concepts
➢ warehouse concepts

Failure of classic vaccines targeting TAAs

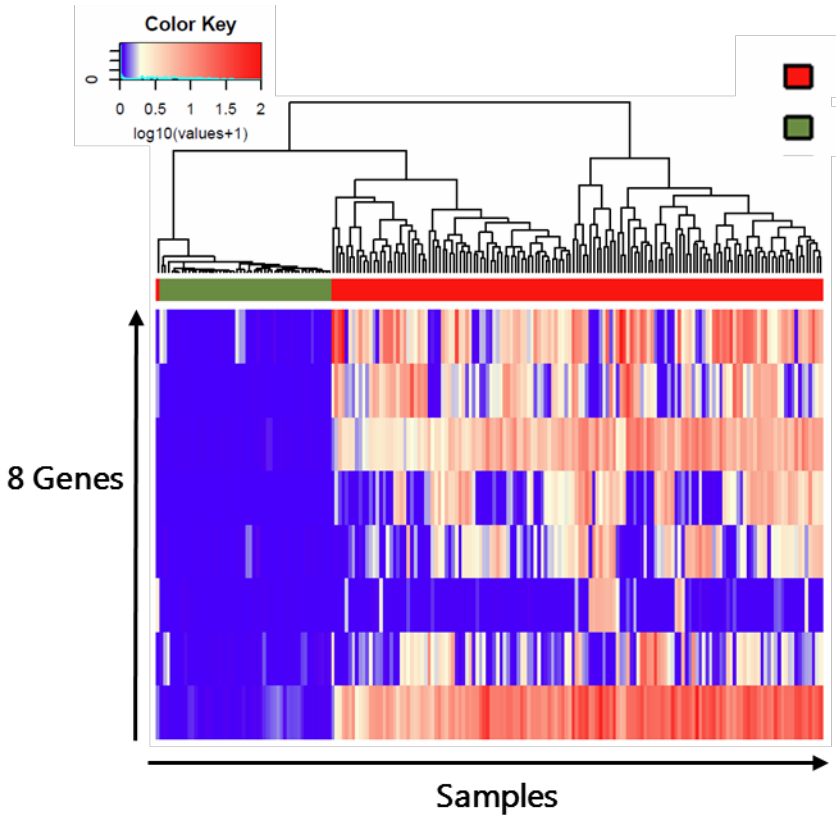


Hodi et al., NEJM 2009

Identification of shared antigens

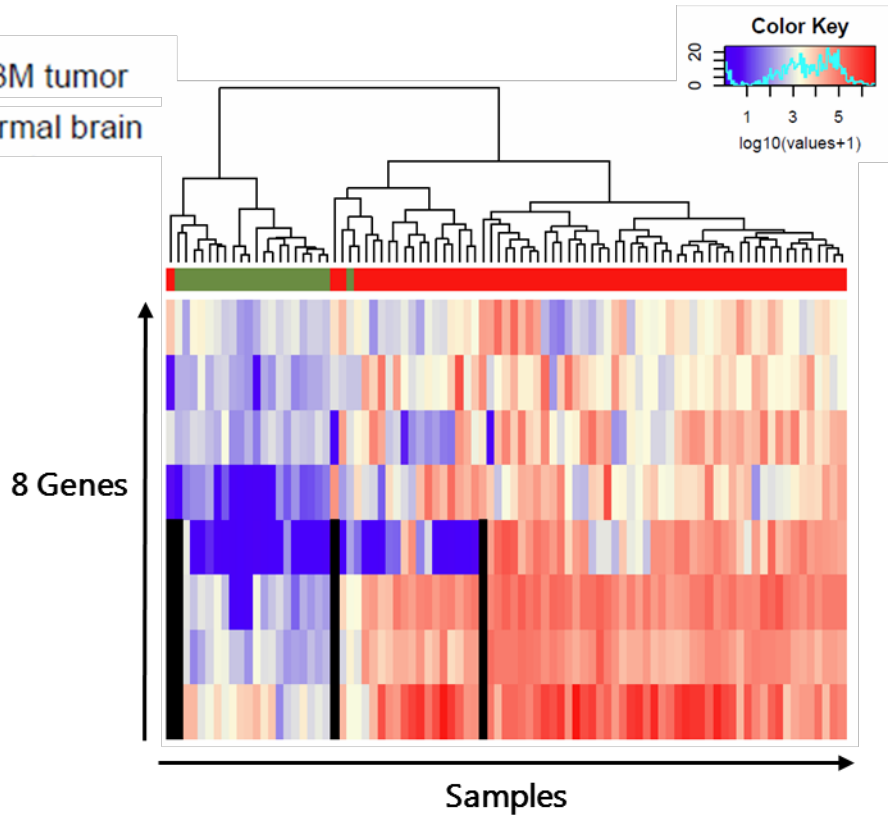
RNA sequencing data

Glioblastoma (n= 144)
Normal brain (n= 50)

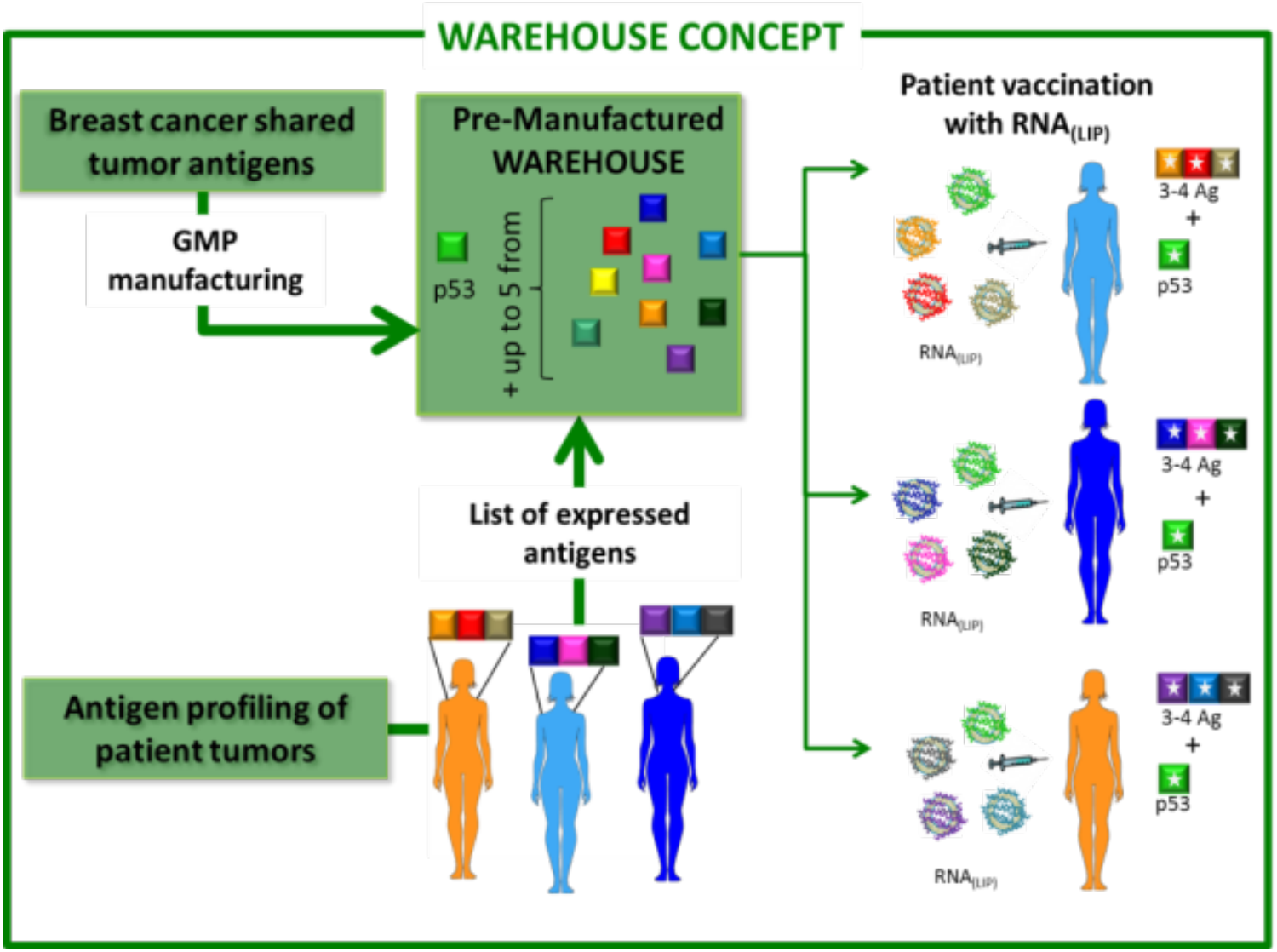


quantitative real-time PCR data

Glioblastoma (n= 66)
Normal brain (n= 21)

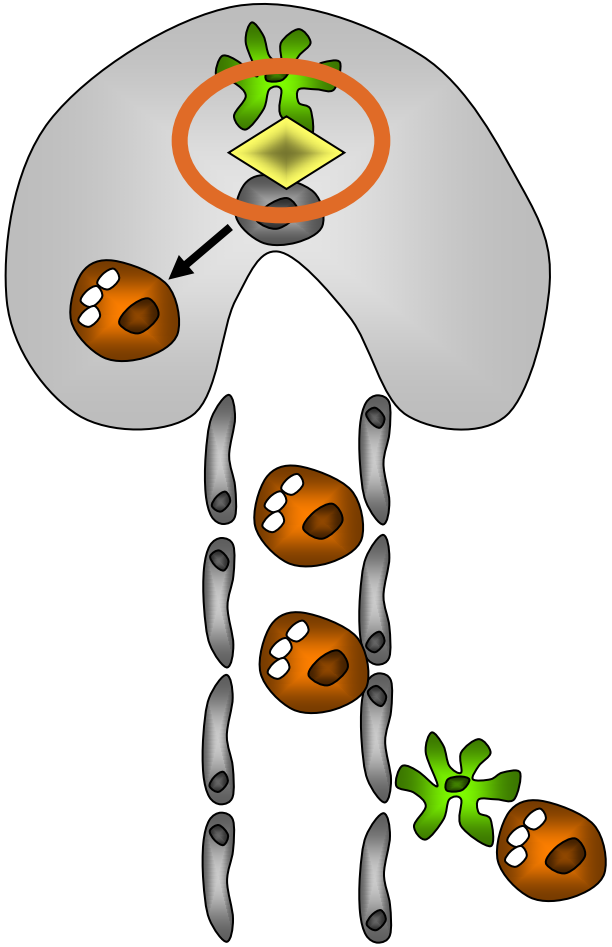


Vaccine warehouse targeting shared antigens



(Mutated) Tumor antigens

Target Antigen

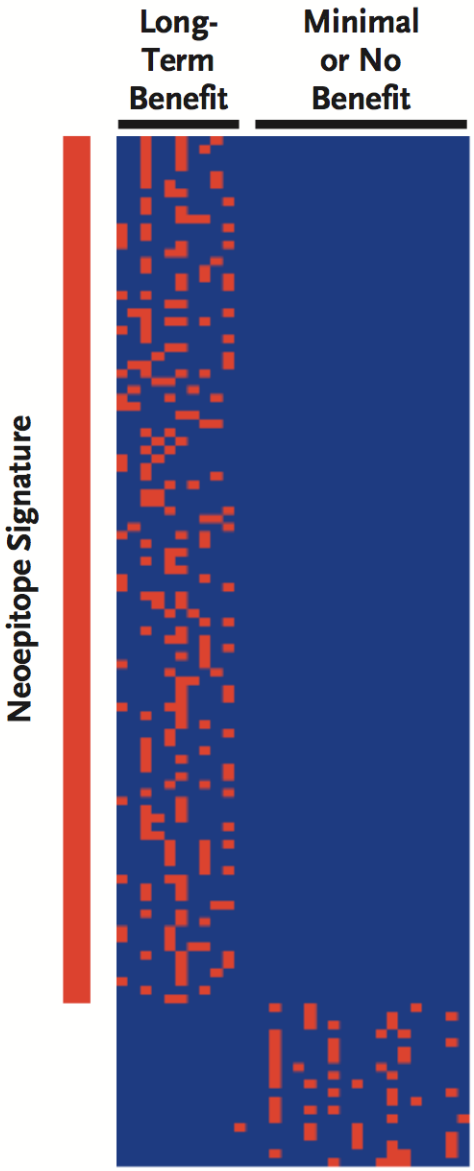


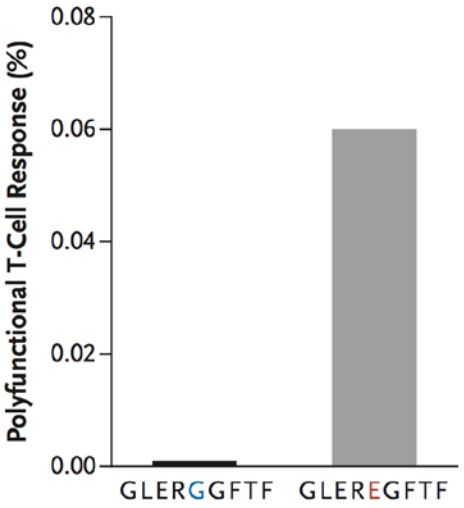
TA

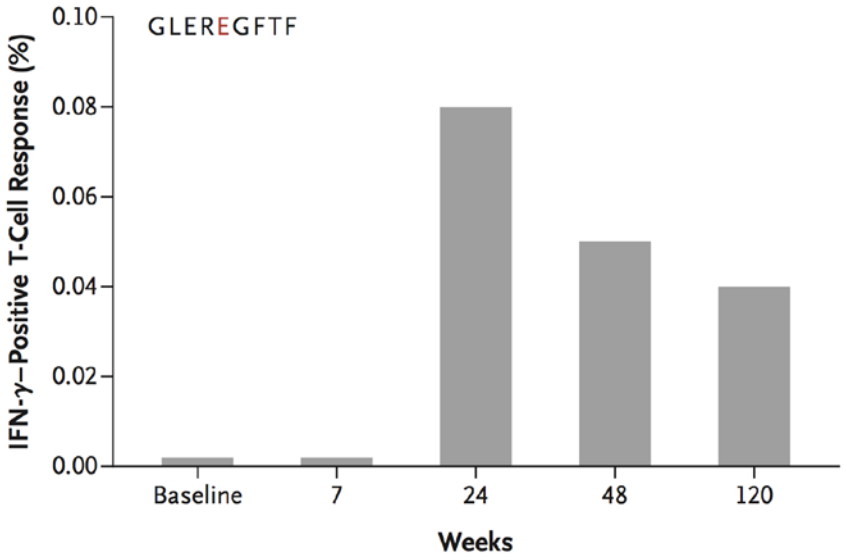
- Specific immune responses
- Mostly mutated antigens
- Mostly private antigens
- Often minor antigens
- Mostly CD4 epitopes
- Often low expression

➢ **Individualized concepts**

CI unmask T cell responses to mutated antigens

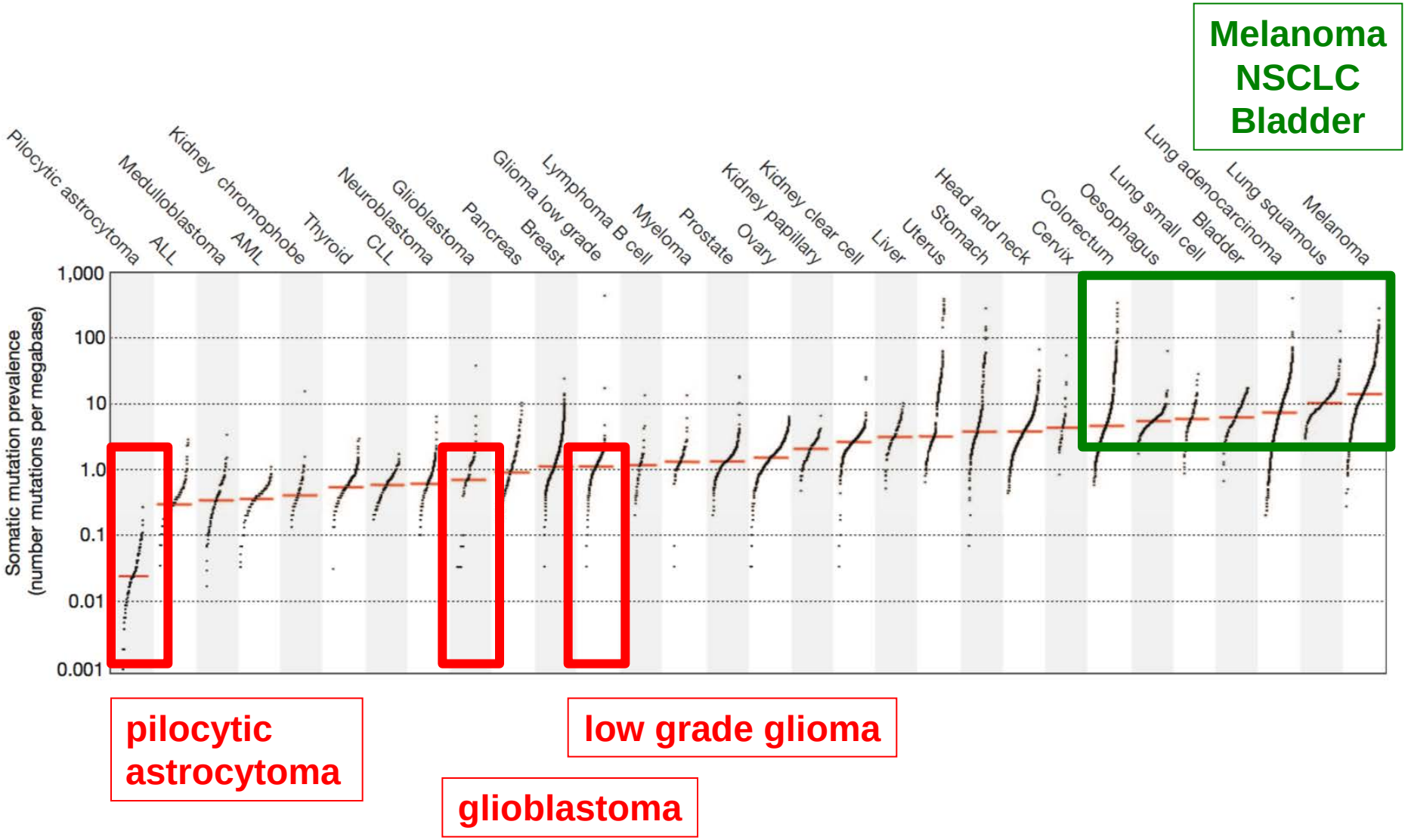






Snyder, NEJM 2014

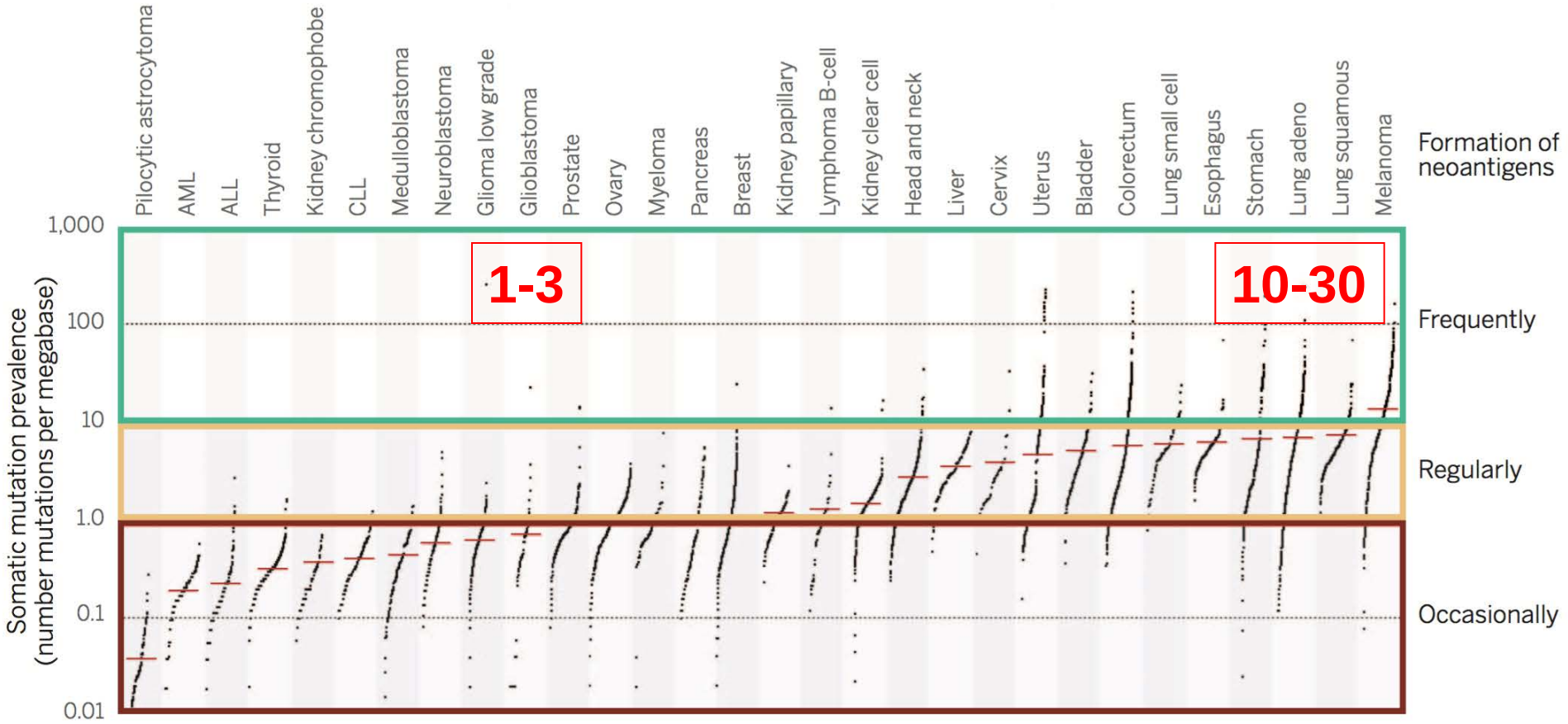
Mutational load predicts response to CI



TCGA, Nature 2013

The frequency of immunogenic neoepitopes is 1-5%

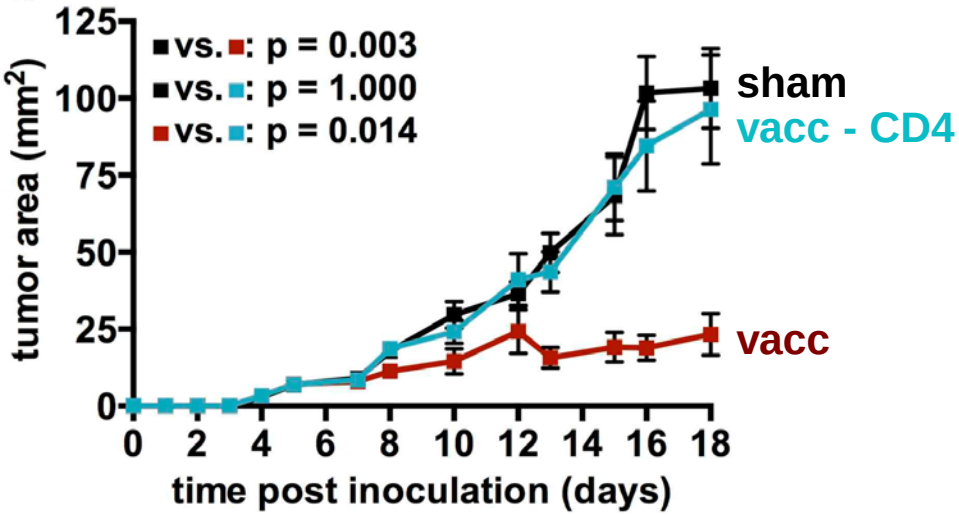
Immunogenic neoepitopes

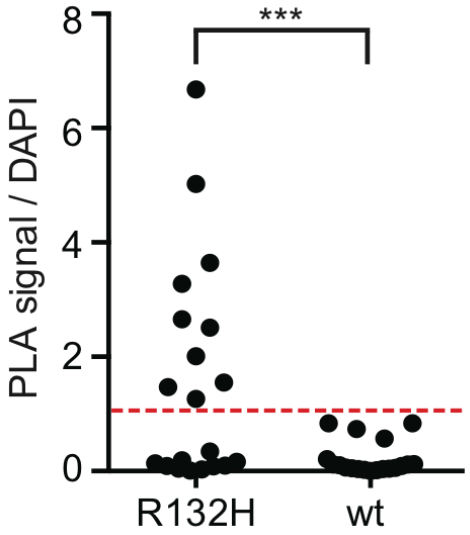


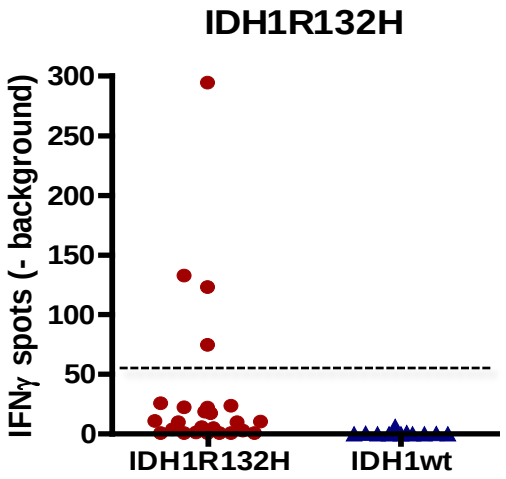
Schumacher and Schreiber, Science 2015; Tran et al, Science 2015

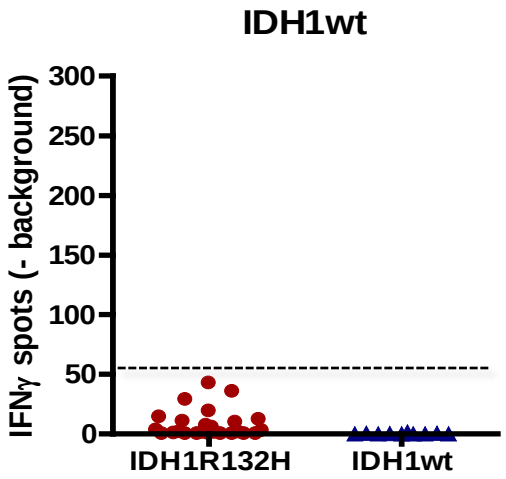
IDH1R132H – a shared mutated epitope

- uniform (R132H)
- specific (no tolerance)
- common (up to 80%)
- wide variety of tumors
- oncogenic
- early
- routine diagnostic marker





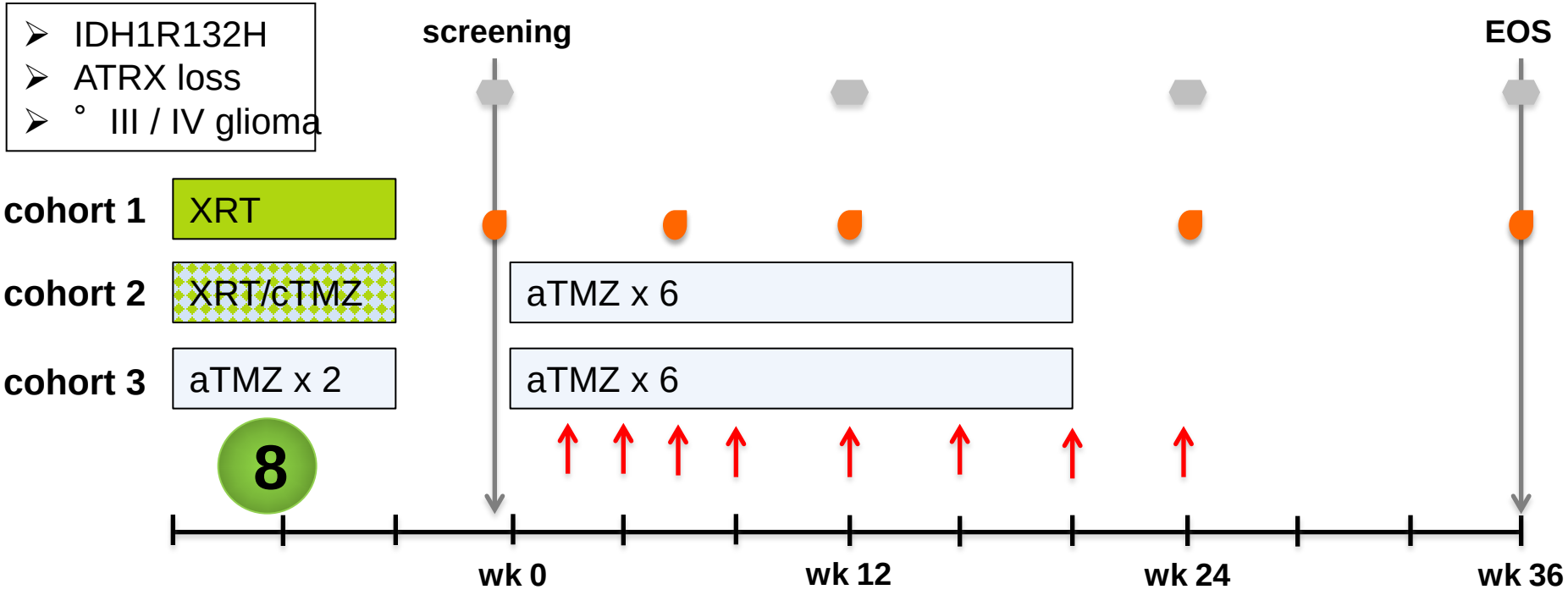




Schumacher et al., Nature 2014; Bunse et al., JCI 2015
WO 2013/102641 A1, PCT/EP2013/050048, EPA 14190538.0

NOA-16 trial (NCT02454634, EudraCT 2014-000503-27)

- IDH1R132H
- ATRX loss
- ° III / IV glioma



XRT: radiotherapy (30 x 2 Gy)

aTMZ: adjuvant temozolomide (200 mg/m2; d1-5 of 28-day cycles)

cTMZ: concomitant temozolomide (75 mg/m2 daily for 6 weeks)

↑ IDH1R132H vaccine with imiquimod wk 2,4,6,8,12,16,20,24)

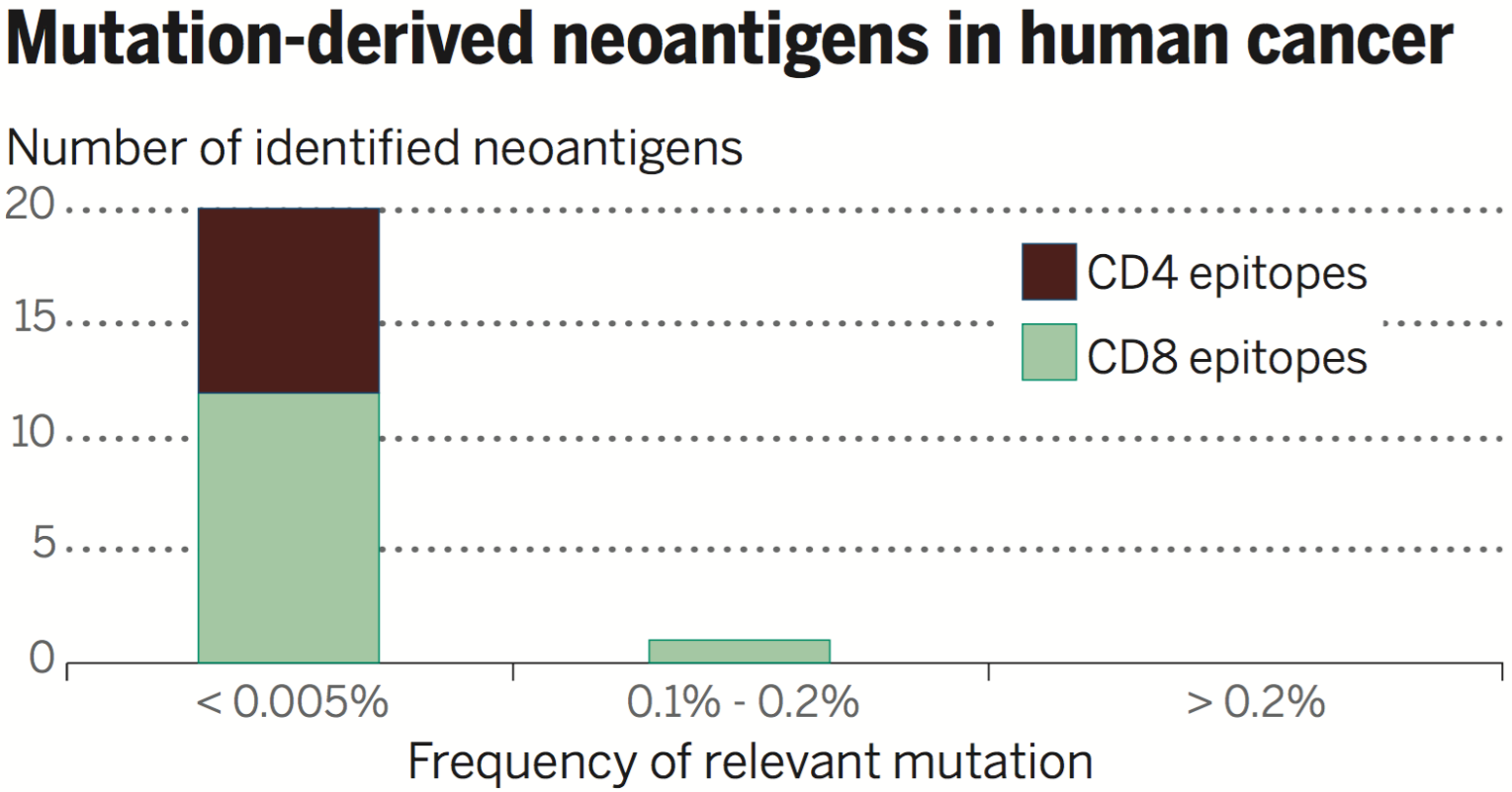
MRI + magnetic resonance spectroscopy (MRS)

Immune monitoring (IDH1R132H antibody ELISA, EliSpot)

3.0

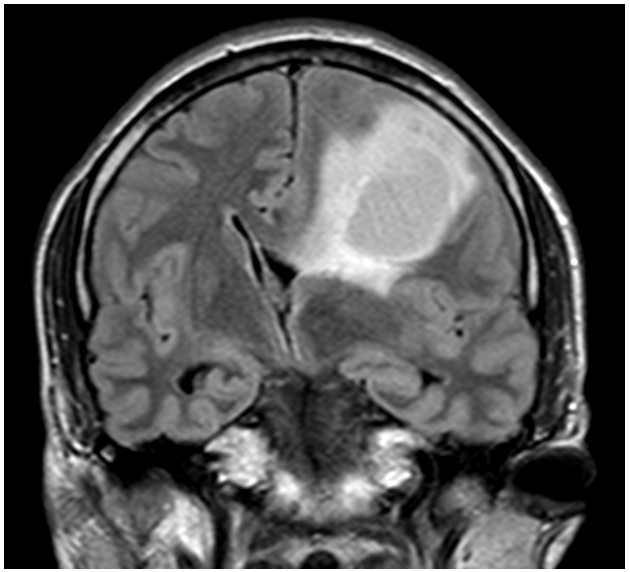
Deutsches Konsortium für Translationale Krebsforschung

Privacy of neoepitopes



Schumacher and Schreiber, Science 2015

Identification of immunogenic neoeptitopes



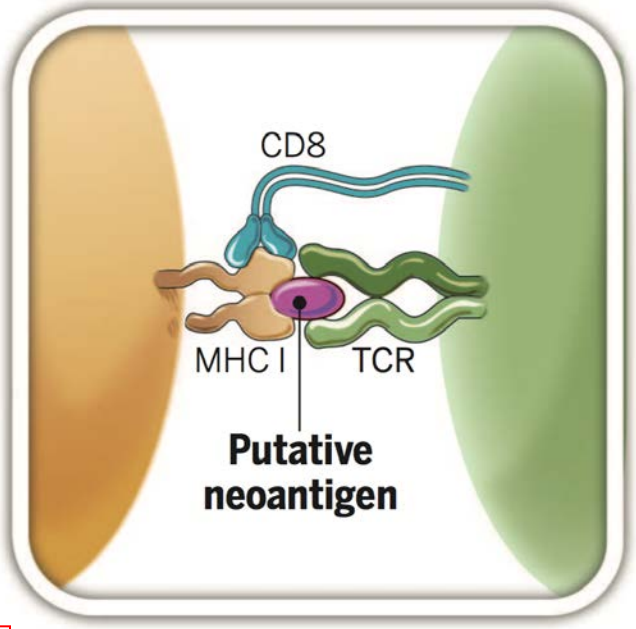
Mutated epitopes

HLA Binding

T cell recognition

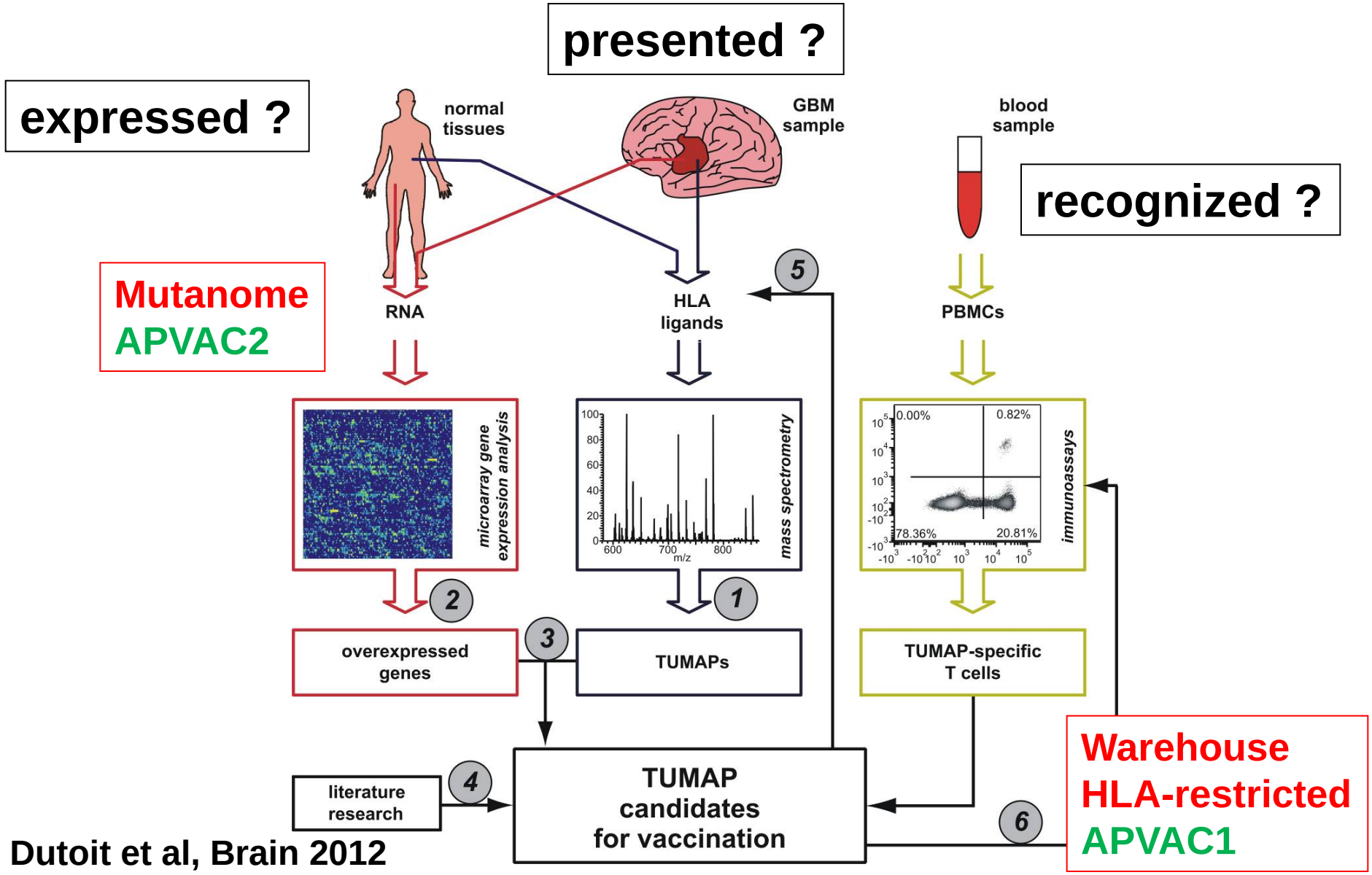
Target Antigen

Patient-specific



Schumacher and Schreiber, Science 2015

Identification of tumor-associated peptides



Dutoit et al, Brain 2012

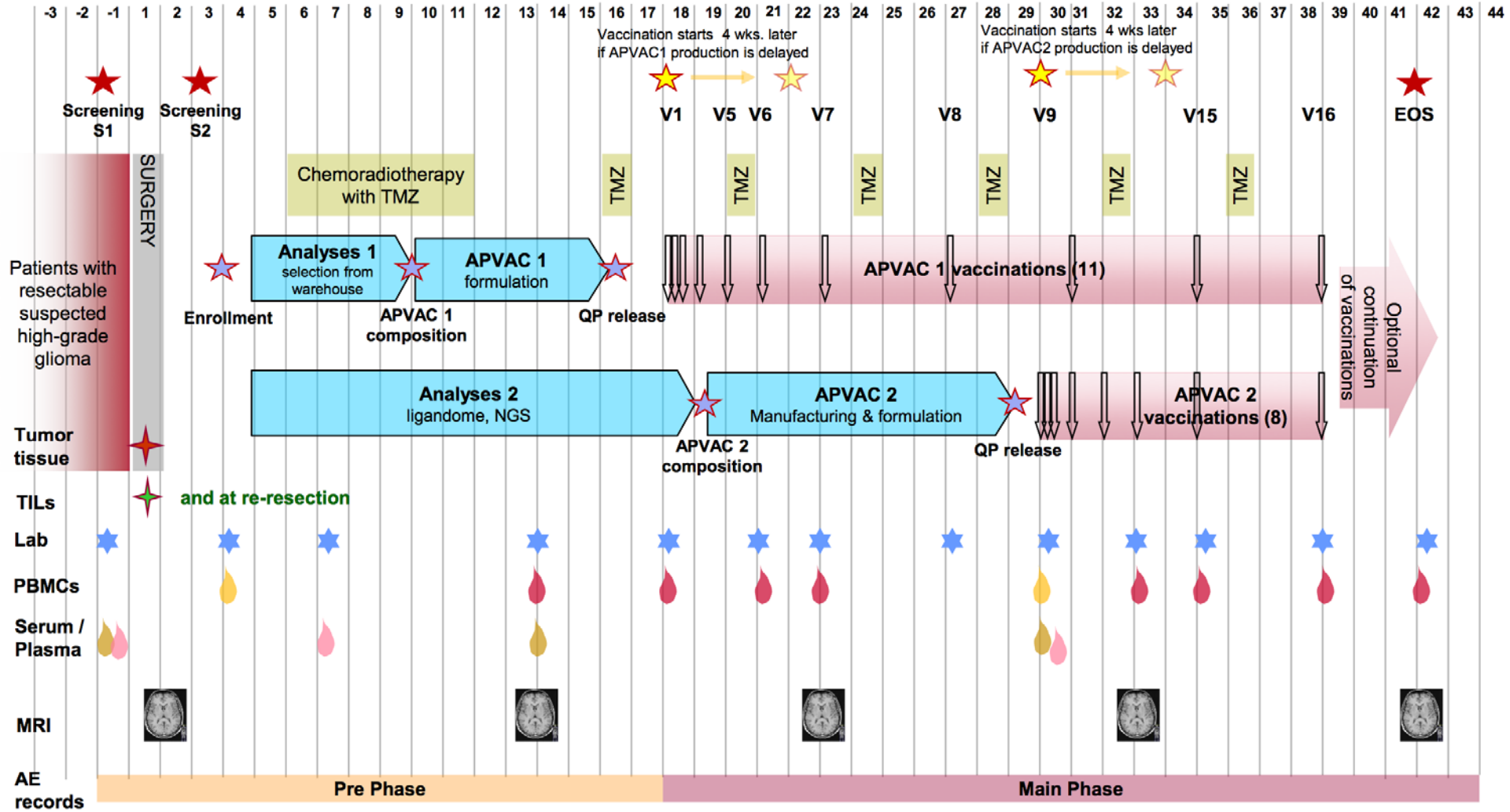
Individualized glioblastoma vaccine – the GAPVAC Trial

10

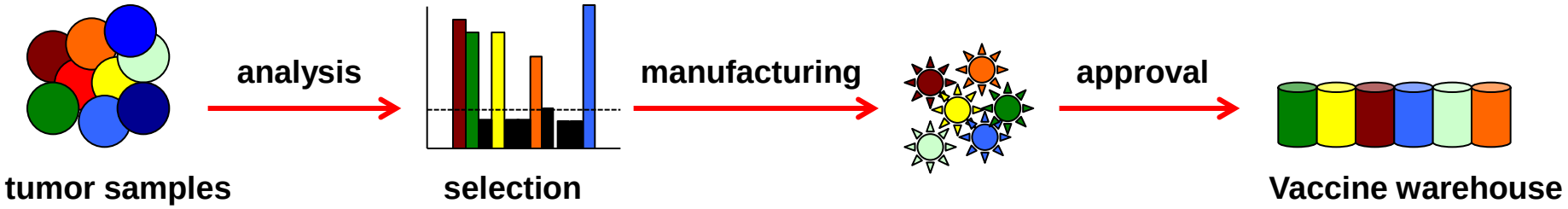
GAPVAC

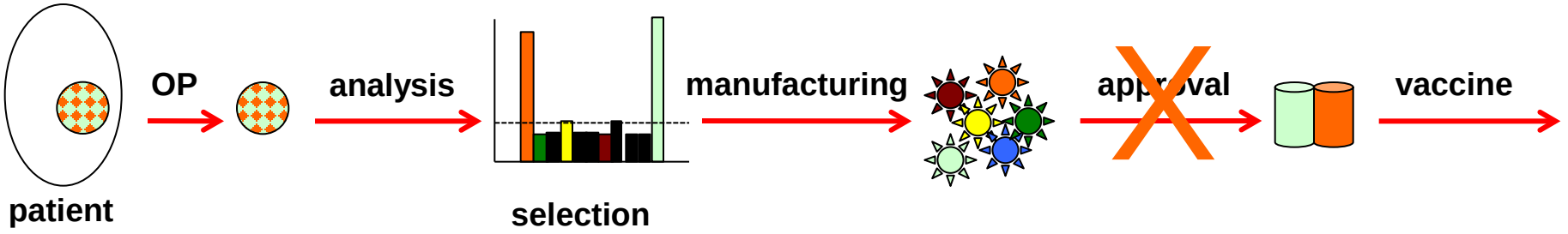
EU project 2012-2017
Clinical Study: 10/2014 -

PI: Wolfgang Wick



Regulatory challenges of individualized immunotherapy





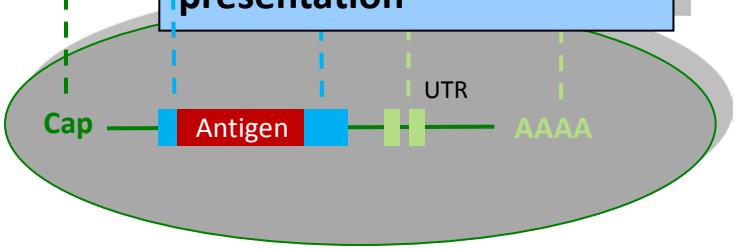
IMP-independent approval

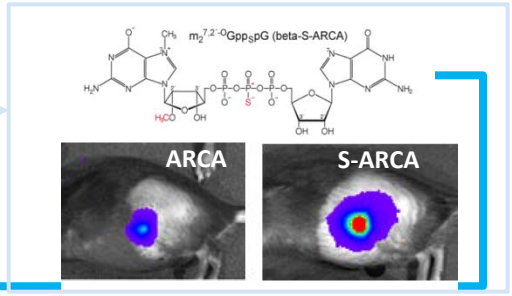
Pharmacologically optimized mRNA vaccines

Modified Cap-analogues to increase stability

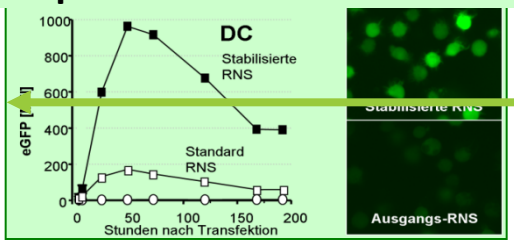
Regulatory sequences for stabilisation and increased translational efficacy

HLA-signal sequences for improved antigen presentation

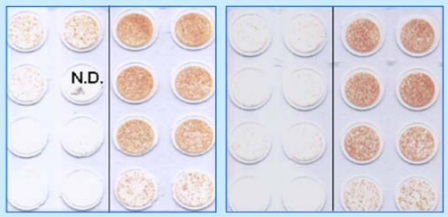




Improved Pharmacokinetics



Improved T-cell Expansion



Net Effect: 5000-fold Potency increase*

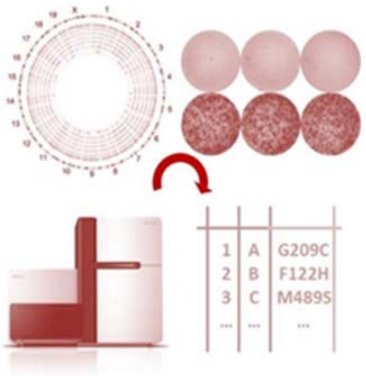
Ribological®, BioNTech

Pharmacologically optimized mRNA vaccines

Cancer mutation discovery & target prioritization

Synthetic vaccine design & Production

Diagnosis	Mutanome Analyses	IVAC® Vaccine Tailoring	Just-in-time tailored synthetic RNA drugs



Synthetic RNA

Individualized Cancer Immunotherapy

IVAC®, BioNTech

Concepts and challenges of cancer vaccines

- Multiepitope vaccines targeting TAA are increasingy used in warehouse trial concepts
- Vaccines targeting mutated epitopes offer conceptual advances over vaccines targeting TAA
- The rationale of neoepitope vaccines is supported by data from trials using checkpoint inhibitors
- Vaccines targeting mutated epitopes require patient-specific identification and manufacturing as most neoepitopes are private
- Combination of neoepitope vaccines with checkpoint blockade may increase efficacy
- mRNA vaccines may offer advantages over peptide vaccines in efficacy and manufacturing
- Current research addresses the mechanims of action (CD4 / CD8) and antigen spreading / escape machanisms

CCU Neuroimmunology and Brain Tumor Immunology

Simon Becker
Lukas Bunse
Theresa Bunse
Katrin Deumelandt
Edward Green
Melanie Keil
Katharina Ochs
Iris Oezen
Christiane Opitz
Martina Ott
Katharina Rauschenbach
Felix Sahm
Khwab Sanghvi
Jana Sonner

DKFZ
Heidelberg Cancer Immunotherapy Program

NCT

University Hospital Heidelberg and National Center for Tumor Diseases

Neurooncology
Neurology — **Wolfgang Wick**
Neuropathology

Andreas von Deimling
Felix Sahm
Neurosurgery
Neuroradiology
Immunology
Hematology — **Michael Schmitt**
Trial Center — **Daniela Schilling**
Immune Monitoring

University of Tübingen — **S. Stevanovic**
DKTK partner sites
TRON, BioNTech — **Ugur Sahin**
Immatics, Agios, Adaptive, CureVac

3.0

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