Using the Immune System for Brain Tumor Therapy

Michael Platten
Neurologische Klinik, Universität Heidelberg
Nationales Tumorzentrum
KKE Neuroimmunologie und Hirntumorimmunologie
DKFZ
Challenges in Brain Tumor Immunotherapy

Target Antigen

Microenvironment

Tolerance

Exhaustion
Important Presumptions for Glioma Immunotherapy

- The CNS is accessible for effective immune responses
- Antigens are presented in gliomas
- There is an endogenous immune response to gliomas
- Mutated antigens are superior targets
- Tumor-specific CD4 T cells may drive immunity
- Intratumoral heterogeneity results in antigen heterogeneity and immune escape
Immunotherapy of Gliomas – Current Approaches

• Phase III clinical trials (DCVax, ACT-IV)
• Multipeptide vaccines (ICT-107, SL-701, IMA-950)
• Checkpoint inhibitors
• Neoepitope vaccines (IDH1)
• CAR T/NK cells (EGFRvIII)
• Individualized concepts (GAPVAC, NeoVax)
• Integration into primary therapy
Checkpoint Inhibitors in Neurooncology

Mellmann, Nature 2011

Ipilimumab
Nivolumab
Pembrolizumab
Mutation Load Predicts Response to Checkpoint Blockade

TCGA, Nature 2013
Identifying Glioma Antigens

Atezolizumab

Nguyen, Nat Rev Immunol 2015
EGFRvIII

EGFR Mutation Variant III (EGFRvIII)

- Tumor-specific oncogene ideally suited for immune targeting
- Expressed in 31% of primary glioblastoma, but not in normal tissue
- In-frame deletion of exons 2-7 results in constitutively active protein with unique amino acid sequence at the fusion junction
- Epitope is in the extracellular domain; accessible to antibodies and highly immunogenic
EGFRvIII vaccine – Resistance

Sampson, Neuro-Oncol 2010; Fan, Cancer Cell 2013

prä

post

26/32 Vakzine
0/15 Kontrolle

Sampson, Neuro-Oncol 2010; Fan, Cancer Cell 2013
IDH1R132H – a Potential Tumor Antigen

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

Suzuki, Nat Genet 2015; Capper, Acta Neuropath 2010
IDH1R132H – Mutation-specific CD4+ T Cells

![Diagram showing IFN\(^\gamma\) spots for IDH1R132H and IDH1wt with MOG and vehicle treatments.](image)

**Bar Graph:**
- MOG (black), wt (white), R132H (blue), HLA-A (red), HLA-DR (red), HLA-A + DR (red), T cells only (red), APC only (red).

**Graphs:**
- IFN\(^\gamma\) spots vs. IDH1R132H and IDH1wt.
- Relative value vs. R132H, wt, healthy.

A2.DR1
The IDH1R132H-Peptide Vaccine is Therapeutic

Schumacher, Bunse et al., Nature 2014; Patent WO 2013/102641 A1
IDH1R132H Presentation *in situ* through PLA

Bunse, Schumacher, Sahm et al., JCI 2015
NOA-16-Trial (NCT02454634, EudraCT 2014-000503-27)

- III / IV Gliom
- IDH1R132H
- ATRX-Verlust

Kohorte 1: RT
Kohorte 2: RT/cTMZ
Kohorte 3: TMZ x 3

Screening

RT: Radiotherapy (30 x 2 Gy)
aTMZ: adjuvant Temozolomide-Therapy (200 mg/m2; d1-5 / 28)
cTMZ: concomitant Temozolomide-Therapy (75 mg/m2 daily for 6 weeks)

IDH1R132H-Vaccine / Montanide® with Imiquimod Wk 2,4,6,8,12,16,20,24)

MRT + 2-Hydroxyglutarate (2HG) Magnet Resonance Spectroscopy (MRS)

Immune Monitoring (IDH1R132H-ELISA, EliSpot, T-Zell-Phenotyping, TCR Discovery)
NOA-16 Trial Centers and Support

- Berlin
- Düsseldorf / Essen
- Dresden
- Frankfurt
- Heidelberg
- Tübingen
- Freiburg
- München

NOA
Neuroonkologische Arbeitsgemeinschaft

Wilhelm Sander-Stiftung

Hertie-Stiftung

Deutsches Konsortium für Translationale Krebsforschung
Personalized Immunotherapy – the GAPVAC Trial

PI: Wolfgang Wick
Future Concepts in Glioma Immunotherapy

- Peptide vaccination
- RNA vaccination
- T cell transfer

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- RNA vaccination
- T cell transfer

- Patient-specific epitopes / TCRs
  - TCR analysis
  - Immunogenicity
  - Neoepitopes
  - αTGF-β
  - TDO/AHR-I
  - αSTAT3
  - αCSF-1R
  - αPD-L1

- Microenvironment
  - Antigen spreading
  - Escape variants

- Warehouse
  - Selection
  - Recurrent tumor

- T cell tolerance / exhaustion
  - αCTLA-4
  - αPD-1
  - ...