Personalized Cancer Neoantigen Vaccines

Turning the Immune System Against Your own Unique Tumour-Specific Antigens

3rd Annual Advances in Immuno-Oncology Congress

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Agenda

1. Background Cancer Neoantigens

2. Vaccibody’s Cancer Vaccine Strategy

3. Neoantigen Prediction Tools
   Any general Principles?

4. Vaccibody’s Clinical Trial Experience
   and Future Plans
Immunotherapy: The next Wave of Cancer Therapy

Various Immuno-Therapy Modalities

Checkpoint Inhibitors

Vaccines

Cell Therapies

Others, e.g.
- Oncolytic viruses
- Cytokines
- Bi-specific antibodies
- Small molecules
- Adjuvants
CheckPoint Inhibitors – relationship to neoantigens

- Strong relationship between mutational burden and response to CPI
- Limits response to already existing neoantigen-specific T cell repertoire
- Reveals an important role of immune responses to neoantigens in cancer immunotherapy

Cancer neoantigen vaccines are the optimal tool to activate a truly specific, strong and broad neoantigen specific T cell responses

Yarchoan et al., 2017 NEJM
Neoantigens are strongly immunogenic Tumour Antigens

- Higher affinity TCR available for neoantigens than shared TAA
- IFN-γ T cell responses to neoantigens are stronger than to shared TAA
Proof of Concept published in Nature Letters July 2017

**LETTER**

**An immunogenic personal neoantigen vaccine for patients with melanoma**

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- 6 patients with melanoma (stage III/IV)
- 97 neoepitopes delivered as long-peptides with polyICLC (SC)
- CD4 dominated responses

**LETTER**

**Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer**

Ugur Sahin\(^1\);\(^2\);\(^3\), Evelyne Derbowski\(^1\);\(^2\);\(^3\), Matthias Müller\(^1\);\(^2\);\(^3\), Björn-Philipp Klok\(^1\), Petra Simon\(^1\), Martin Löwer\(^1\), Valeska Bukur\(^1\);\(^2\);\(^3\), Arbel D. Tadmor\(^1\), Ulrich Luxemburger\(^1\), Barbara Schröder\(^1\), Tana Ompokoko\(^1\), Mathias Vormehr\(^1\);\(^2\);\(^3\), Christian Albrecht\(^1\), Anna Parasyuk\(^1\), Andreas N. Kuhn\(^1\), Janina Buxi\(^1\), Sandra Hehr\(^1\), Katharina H. Schrevel\(^1\), Felicitas Müller\(^1\), Inga Ortez\(^1\), Isabel Vogler\(^1\), Eva Godehardt\(^1\), Sebastian Artig\(^1\), Richard Racz\(^1\), Andrea Breitkreuz\(^1\), Claudia Tolliver\(^1\), Martin Sachar\(^1\), Goran Martin\(^1\), Alexander Hoebberger\(^1\), Patrick Sorn\(^1\), Jan Hiebl\(^1\), Janka Ciesla\(^1\), Olga Wackenmuller\(^1\), Alexandra Kummer Brück\(^1\), Malte Wilt\(^1\), Martin Zilgen\(^1\), Andrei Borchet\(^1\), Barbara Kasemann\(^1\), David Langer\(^1\), Stefanie Böffel\(^1\), Mustafa Diken\(^1\);\(^2\);\(^3\), Sebastian Kreuter\(^1\);\(^2\);\(^3\), Romina Nemecek\(^1\), Christoph Gebhardt\(^1\);\(^2\);\(^3\), Stephan Grabber\(^1\), Christoph Höller\(^1\), Jochem Utikal\(^1\), Christoph Huber\(^1\);\(^2\);\(^3\), Carmen Loquai\(^1\) & Orien Tureci\(^1\)

- 13 patients with melanoma (stage III/IV)
- 125 neoepitopes delivered as ivt-RNA (intranodal)
- CD4 dominated responses

- Vaccinating with neoepitopes elicits a broad and strong tumour-specific immune response
- Both peptide and RNA neoantigen based vaccines elicit predominantly CD4 T cell responses

Ott et al., Nature Letters 2017
Sahin et al., Nature Letters 2017
The Workflow of Personalised Cancer Treatment

1. Tumour biopsy and sequencing
2. Neoepitope selection (TSNA)
3. Vaccine manufacturing (n=1)
4. Vaccine administration and immunogenicity

Time, cost, efficacy?
1. Background Cancer Neoantigens
2. Vaccibody’s Cancer Vaccine Strategy
3. Neoantigen Prediction Tools
   Any general Principles?
4. Vaccibody’s Clinical Trial Experience and Future Plans
# Vaccibody Product Pipeline

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- **VB C-01 (VB10.16)**
- **VB N-01 (VB10.NEO)**
The Vaccibody Technology Platform was developed based on the concept of targeting antigen to APC in order to create more efficacious vaccines.
Mechanism of Action – Intrinsic Adjuvant

Administration (i.m.) of DNA plasmid
In vivo protein expression and secretion

Chemokine MIP-1α
Target – Attract – Mature – Deliver – Cross-present

Tumour
Patient Friendly, simple Vaccine Delivery

- Needle free injection
- Small, handy, easy to use
- Minimal pain compared to electroporation
- Cost effective
- Applicable for multiple immunizations
- High patient compliance
Naked DNA plasmid as IMP

✓ Proven Safety
✓ Simple, Rapid and Generalized process
✓ Simple Formulation
✓ Versatile
✓ Easy i.m. Delivery
✓ Effective Homologous Boost
✓ CD8 prone

DNA plasmid is an ideal platform for bringing individualized neoantigen vaccines to the market as a viable product
VB10.NEO – A Robust Vaccine Format

>80 different VB10.NEO constructs with >250 neoepitopes constructed to date with up to 40 neoepitopes
VB10.NEO induces Rapid, Broad and Strong responses to multiple Neoepitopes by single Vaccination

- VB10.NEO induces a broader and stronger response than Peptide + Poly (I:C) Adjuvant vaccines after a single immunization.
- VB10.NEO vaccinated animals respond to all 10 neoepitopes after a single immunization.
- Immunodominant neoepitopes differ between delivery vehicles.
VB10.NEO generates a broader immune response profile dominated by CD8+ T cells than competing technologies

Peptide and RNA vaccines induces primarily CD4 T cell responses, while VB10.NEO induces strong, dominating CD8 responses to the identical neoepitope sequences

* Castle et al., 2012 and Kreiter et al., 2015
VB10.NEO leads to a unique CD8 dominated neoepitope response

VB10.NEO induces a strong, broad immune response dominated by CD8+ T cells

Peptide + poly I:C vaccination has been reported to induce dominantly CD4 T cell responses

VB10.NEO induces strong, dominantly CD8+ T cell response to identical neoepitopes that induces no or weak immune response if delivered as peptide vaccine

* Castle et al., 2012 and Kreiter et al., 2015-adapted figure based on B16 melanoma results
Confirmation of VB10.NEO’s unique ability to induce strong neoepitope-specific CD8 responses

VB10.NEO induction of strong CD8 T cell response, combined with a CD4 T cell response to all peptides tested for MC38 colon carcinoma.

-1/3 of these neoepitopes have been shown to be non-immunogenic delivered as peptide + adjuvant

-Confirmation of VB10.NEO’s ability to induce stronger CD8 responses to neoantigens
Vaccibody Induces Tumor Protection as Monotherapy

➢ Vaccibody vaccination induces strong CD8+ T cell responses and **tumor protection as Monotherapy**

➢ Combination with anti-PD-1 immunotherapy induced enhanced anti-tumour responses in mice involving **complete tumour regression** of large, established tumours

➢ **Long-term memory responses** ensure effective anti-tumour responses after a 2\textsuperscript{nd} tumour challenge in surviving mice with no sign of tumour growth
Agenda

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2. Vaccibody’s Cancer Vaccine Strategy
   Why the perfect fit for individualised Vaccines?
3. Neoantigen Prediction Tools
   Any general Principles?
4. Vaccibody’s Clinical Trial Experience and Future Plans
Developing VB10.NEO specific Neoepitope Selection

- Neoepitope prediction model
  - Trained on in vivo data

- Data to train algorithm

- Clinical data VB N-01

- Core tissue expression
- Proteome

- Neoepitope calling

- In vivo mouse experiments
  - IFNγ ELISpot (CD8/CD4) > 250 neoepitopes
  - Anti-tumour efficacy

- Anti-tumour efficacy
Verification of VB10.NEO neoepitope prediction tool-NeoSELECT™

NeoSELECT™ has a strong ability to select immunogenic neoepitopes
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**Legend:**
- VB C-01 (VB10.16)
- VB N-01 (VB10.NEO)
VB10.16 induces strong CD8 dominated T cell responses

Interim Phase I/IIa results

- No SAEs observed
- 96% of patients tested so far (n=24) elicit increased HPV16-specific T cell responses after vaccination with VB10.16
- A strong induction of CD8 T cells in patients is confirmed in a clinical setting
Clinical learnings – Vaccibody platform VB C-01 study

• HPV16-specific T cell response correlates with clinical responses
  • All patients with a strong (>650SFU/mill) T cell response experienced lesion size reduction

• VB10.16 induces high degree of CIN regression to CIN1 or less during the trial
  • Co-infection with other high-risk HPV and/or PD-L1 upregulation may inhibit CIN regression

VB10.16 induces a strong HPV16-specific T cell response and kills HPV16-infected precancerous cells if not inhibited by PD-1/PD-L1 checkpoint blockade
Clinical Trial VB N-01

**VB N-01**: An open labelled first human dose phase 1/2a study to evaluate safety, feasibility and efficacy of multiple dosing with individualised VB10.NEO immunotherapy in patients with locally advanced or metastatic melanoma, NSCLC, clear renal cell carcinoma, urothelial cancer or squamous cell carcinoma of head and neck, who did not reach complete responses with current standard of care immune checkpoint blockade

FPI April 2018

- Approved CPI as SOC
- Moderate to high mutational load
Study Design and Treatment Schedule VB N-01

Sequencing, Synthesis & Manufacturing → Vaccination Prime → Vaccination Maintenance → Follow Up

Week
0 3 6
Dose #
1 2 3

12 months

CPI treatment >12 weeks

Consent + Biopsy

Follow Up

24 months
Vaccibody’s Solution to Personalised Cancer Treatment

NeoSELECT™

1. Tumour biopsy and sequencing
2. Neoepitope selection (TSNA)
3. Vaccine manufacturing (n=1)
4. Vaccine administration and immunogenicity

-DNA vaccine:
  -Robust, rapid, cost-effective, stable, safe
  -up to 20 neoepitopes

-Needle-free
-Target, Attract, Mature, Deliver, Cross-present
-Rapid, strong, long-lasting
-CD8 dominated

Rapid, cost-effective, efficacious