Vaccibody’s approach to cost-effective personalized cancer neoantigen vaccines inducing a unique CD8-dominated T cell response

August 30, 2018
Agnete Fredriksen, PhD
President & CSO
Vaccibody AS
abfredriksen@vaccibody.com
Agenda

1. Background Cancer Neoantigens

2. Vaccibody’s Cancer Vaccine Strategy

3. Neoantigen Prediction Tools
   NeoSELECT™

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

Checkpoint Inhibitors

Vaccines

Cell Therapies

Others, e.g.
- Oncolytic viruses
- Cytokines
- Bi-specific antibodies
- Small molecules
- Adjuvants

Various Immuno-Therapy Modalities
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
An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott1,2,*, Zhaotong Hu1,*, Darin B. Kemkin1,2,8, Sachet A. Shukla3,4, Jing Sun1, David J. Boyn1, Wandi Zhang1, Adrienne Lucoma1, Anita Giobbie-Hurder1, Lauren Pettij3, Christina Cher1, Oriol Oliver1, Todd A. Carter1, Saujanya Li1, David I. Lieb7, Thomas Endresmaier8, Erika Gjini8, Jonathan Stevens8, Witham J. Lane10, Indu Jey10, Kati grillmair10, Riehards10, Andreas M. Saltz10, Heather Daley1, Michael Seaman9, Elizabeth H. Rochibrider2,3,4, Charles H. Yeold10, Maegyn Harder1, Niall Lennom1, Stacey Gabriel1, Scott I. Rodig1,9, Dan H. Barouch1,7,7, Jon C. Aster1,6, Gad Getz1,4, Yu Kucheremont1, Donna Neuberg1, Jerome Ritz1,2, Eric S. Lander1,19, Edward F. Fritz1,24, Nir Hacohen8,14,15 & Catherine J. Wu1,2

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

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

Ugur Sahin9,2,3, Evelyna Derhovanessary1, Matthias Miller1, Bjorn Philipp Klopke1, Petra Simon1, Martin Lowner2, Valesca Bulun1,2, Arbel D. Tadmor1, Ulrich Luxemburger1, Barbara Schreiner1, Tana Onokoko1, Mathias Vormehr1,2, Christian Albrecht1, Anna Paruszynski1, Andreas N. Kohlb, Janina Bick1, Sandra Heesch1, Katharina H. Schreede1, Felicitas Muller1, Inga Ottschoexter1, Isabel Vogler1, Eva Godehardt1, Sebastian Attip1,2, Richard Rae1, Andrea Breitkreuz1, Claudia Toller1, Martin Scharfe1, Gordan Maric1, Alexandre Hohberger1, Patrick Sorn1, Jan Bleikman1, Janko Cestra1, Olga Waksman1, Alexandra-Keenemo Bruck1, Meier Wirt1, Martina Zilgen1, Andre Rother1, Barbara Kaserberg1, David Lang1, Stefanie Boitel1, Mastafa Diken2,3, Sebastian Kreiter1,7,7, Romina Nemecek1, Christoffel Gebhardt1,2, Stephan Grabbe1, Christoph Hülter1, Focchut Utsch1,2, Christoph Huber1,2,3, Carmen Locqui1 & Othmar Türeci1

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 elicits predominantly CD4 T cell responses
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
   NeoSELECT™

4. Vaccibody’s Clinical Trial Experience and Future Plans
## Vaccibody Product Pipeline

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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

Deltoid

CD8+ T

CD8+ T

CD4+ T

CD4+ T

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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
DNA plasmid is an ideal platform for bringing individualized neoantigen vaccines to the market as a viable product.
>80 different VB10.NEO constructs with >250 neoepitopes constructed to date with up to 40 neoepitopes
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

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* Castle et al., 2012 and Kreiter et al., 2015

Peptide and RNA vaccines induces primarily CD4 T cell responses, while VB10.NEO induces strong, dominating CD8 responses to the identical neoepitope sequences.
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 induces a 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 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.
Neoepitope-specific CD8 T cells are crucial for tumour protection

Depletion of CD8 T cells prohibit tumour protection in VB10.NEO vaccinated mice, indicating a crucial role of neoepitope-specific CD8 T cells for anti-tumour efficacy.
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2. Vaccibody’s Cancer Vaccine Strategy
   Why the perfect fit for individualised Vaccines?

3. Neoantigen Prediction Tools
   NeoSELECT™

4. Vaccibody’s Clinical Trial Experience and Future Plans
Developing VB10.NEO specific Neoepitope Selection

- Neopitope calling
- Neopitope prediction model
  - Trained on in vivo data
- Core tissue expression
- Proteome
- Data to train algorithm
- Ranking
- VB10.NEO synthesis
- In vivo mouse experiments
  - IFNy ELISpot (CD8/CD4) > 250 neoepitopes
  - Anti-tumour efficacy
- Clinical data VB N-01

Synthesis of neoepitopes through in vivo mouse experiments.

- Anti-tumour efficacy
- IFNγ ELISpot (CD8/CD4) > 250 neoepitopes

Neoepitope calling and prediction model trained on in vivo data.
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- **VB C-01 (VB10.16)** for precancerous cervical lesions
- **VB N-01 (VB10.NEO)** for melanoma, lung (NSCLC), bladder, renal, head and neck
**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**

- **0, 3, 6 weeks**
- **10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50 weeks**
- **4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 weeks**

- **CPI treatment >12 weeks**
- **Consent + Biopsy**

- **Week**: 0, 3, 6
- **Dose #**: 1, 2, 3
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

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

DNA: Robust, rapid, cost-effective, stable, safe, up to 40 neoepitopes
- up to 40 neoepitopes

Vaccibody provide a Rapid, Cost-effective and Efficacious solution