Neoantigens – Novel Vaccine Strategies Against Cancer

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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Vaccibody AS

• Norwegian privately-held biopharmaceutical company

• Founded in 2007 on a technology platform developed at the University of Oslo and Oslo University Hospital

• Development of novel vaccines based on the Vaccibody Vaccine Technology Platform, designed to increase the immune system’s T-cell response

**First Product**

**VB10.16**

• HPV16 specific therapeutic DNA vaccine (against viral neoantigens E6 and E7)
• First indication precancerous cervical lesions (CIN 2/3), exploratory proof of concept clinical trial ongoing

**Product**

**VB10.NEO**

• Individualised therapeutic cancer DNA vaccines against tumour specific antigens (neoantigens)
• Preclinical stage
• Preparing for phase exploratory clinical trial(s) in 2017
Management Team and Board of Directors

Management Team

[Images of management team members]

- Martin Bonde, CEO
- Agnete B Fredriksen, CSO
- Mona Welschof, CCO
- Hans Petter Tjeldflaat, CFO

Board of Directors

- **Chairman**
  - Tom Pike
- **Directors**
  - Anders Tuv
  - Ingrid Alfhjem
  - Erlend Skagseth
  - Lars Lund Roland
  - Bernd Seizinger

Previous affiliations include:
- Roche
- Clavis Pharma
- NeoMed
- Affitech
- PCI Biotech
- Photocure
- Inovio
- EuroMed
- Axis-Shield
- BioMedical Innovation
- Ernst & Young
- Dako
- Torsana Biosensor
- Combio
- German Cancer Research Center
- Inovio
- EuroMed
- Axis-Shield
- Quintiles
- University of Oslo
- Oslo University Hospital
- Medinnova
- Inven2
- GPC Biotech
- Genome Therapeutics
- Bristol-Myers Squibb
- Harvard Medical School
- Princeton University
- Opsona
- MSD
- Ostemeter
- Natimmune
- Aros Pharma
- Epitherapeutics
Company

Neoantigens - Personalized Cancer Therapy

Vaccibody Vaccine Platform

VB10.16 – Viral Neoantigen Vaccine

VB10.NEO Cancer Neoantigen Vaccine
Why Personalized Cancer Therapy?

Aim:
- To provide the right treatment for an individual patient
- To predict which patients are more likely to respond to specific cancer therapies

Recent Advancements:
- Tumour biomarkers / tumour specific factors are associated with patient prognosis and tumour response to therapy
- Affordable whole genome sequencing of tumour DNA
- Better understanding of the complex interactions between tumour and the immune system (tumour microenvironment)

→ Identification and verification of targets in a patient's tumour
→ Tailor design a drug product for an individual patients

Hope that these treatments will be more efficacious and have fewer side effects
Neoantigens – Promising Targets for Individualized Cancer Vaccines

**Neoantigens**
- Non-self antigens, novel proteins and peptides generated by DNA mutations in tumour cells (also includes viral peptides in virally infected cells)
- Solely expressed on an individual patient’s tumour
- Are not subject to central tolerance

**Important role for anti-tumour immune responses documented in recent studies:**
- Patients with clinical benefit after checkpoint inhibitor and tumour infiltrating lymphocyte (TIL) therapy show strong T cell responses towards neoepitopes
- High mutational load correlates with improved survival in melanoma and NSCLC that benefit from checkpoint inhibitor therapy

Rizvi (2015) Science


Many Cancers Have High Mutational Load

- Immune response are too week to achieve tumour control
- Cancer vaccines are a promising modality to expand neoantigen specific T cells
- Combining vaccines against neoantigens with checkpoint inhibitor therapy may result in significant improved clinical outcome
Development of Individualized Vaccibody Cancer Vaccines

One medicinal product per patient
- Have to be fully individualized
- Will be produced on demand
- Have to be given to the patient as quickly as possible

Most things we do are have not done previously
- Limited information on quality, pre-clinical and clinical aspects of the development in regulatory guidelines on individualized drugs
- Important to seek interaction with Regulatory Authorities as early as possible
Company

Neoantigens - Personalized Cancer Therapy

Vaccibody Vaccine Platform

VB10.16 – Viral Neoantigen Vaccine

VB10.NEO Cancer Neoantigen Vaccine
VB10.16 Therapeutic Vaccine Targeting Viral (Neo)Antigens

Vaccibody DNA vaccines are designed to deliver antigens directly to Antigen Presenting Cells (APCs) and thereby induce a powerful cellular immune response against the given antigen.

**Human macrophage inflammatory protein-1 alpha (hMIP-1α)**
- Attraction and binding of APCs, APC maturation and processing, presentation of epitopes, T cell activation

**Upper and lower hinge regions and constant heavy chain 3 domain (CH3) from human IgG3**
- Bivalent and flexible binding of the receptor
- Improved uptake and signaling

**Disease specific vaccine component**
- Viral Neoantigens E7 and E6 from HPV16
- Patient Specific Neoepitopes

Modules are easily exchangeable
DNA Vaccines - Unique Mode of Action

Advantages of DNA Vaccines

- Use the body’s own cells to produce the protein vaccine
- Faster, simpler and cheaper production than most other vaccines
- High product stability
- So far not safety concerns observed
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Vaccine Targeting Viral Neoantigens – HPV16 Ongogenes E6 and E7 in CIN

Proof of Concept Indiation: Cervical Intraepithelial Neoplasia

- Not individualized, same product is given to all patients

Natural History of Cervical Cancer

- Healthy
- HPV Infection
- CIN 1
- CIN 2/3
- Cervical Cancer

Persistent Infection / Progression to pre-cancer

Clearance / Regression

2-5 years
4-5 years
9-15 years

Treatment

Preventive Vaccines*:
Gardasil, Cervarix

Continuous Observation
Local Surgery
Surgery
Radiotherapy
Chemotherapy

Barrier for Preventive Vaccines

Continuous Observation

Therapeutic Vaccine VB10.16
First-in-Human Study – Design

**Study Title**
An exploratory, safety and immunogenicity study of the human papillomavirus (HPV16) immunotherapy VB10.16 in women with high grade cervical intraepithelial neoplasia (HSIL; CIN 2/3).

**Primary Objective**
Assess the safety/tolerability

**Secondary Objective**
Assess immunogenicity and make a preliminary assessment of clinical efficacy

**Number of patients**
Up to 40 patients at 4 sites in Germany

- **Dosing Phase, Schedule 1**
  - CIN 2
  - 6-10 patients

- **Dosing phase, Schedule 2**
  - CIN 2
  - 6-10 patients

- **Expansion phase**
  - CIN 2/3
  - Best schedule
  - 15-20 patients

- **Interim Analysis**

- Design discussed with **German Regulatory Authorities** and developed with participating investigators
Study Results VB C-01
Summary of Interim Results

Safety
• The treatment with VB10.16 was well tolerated.
• No serious adverse advents (SAEs) have been reported.
• The most common AEs were transient mild to moderate local site reactions at the administration site.

Immunogenicity
• Immunological analyses of the peripheral blood demonstrated a strong induction of HPV16-specific T cell immune responses 86% of the patients evaluated to date against both antigens used in the vaccine (HPV16 E6 and E7) in all responding patients.
• The rapid immunization regimen in Cohort 1 induced a more rapid, stronger and longer-lasting T cell response than seen with the schedule with longer intervals used in Cohort 2.

Clinical Observations
• Early signs of clinical efficacy with histopathological regression to low grade neoplasia (CIN 1) or no disease in 50 % (4 of 8) of the patients already after 4 months.
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Structure of Vaccibody Vaccines

Generate individualised vaccines by exchanging the Antigenic Module

**VB10.16 Vaccine Protein**
- **Targeting Module**: hMIP-1α
- **Dimerization Module**: hIgG3
- **Antigenic Module**: hIgG3 - MIP-1α

**Neoepitope Antigenic Module**
- **Viral Neoantigens**: E7 and E6 from HPV16

**VB10.NEO Vaccine Protein**
- **Targeting Module**: hMIP-1α
- **Dimerization Module**: hIgG3
- **Antigenic Module**: hIgG3 - MIP-1α

**Patient-specific Neoepitopes**

- **Constant for VB10.16 and all VB10.NEO Vaccines**
- **Given to all patients**

- **VB10.NEO**: unique for each patient
- **Given to one patient only**
Non-Clinical Proof of Concept VB10.NEO Mouse Models

Documentation of the feasibility and immunogenicity of different vaccine formats

Two animal models:
→ B16.F10 Melanoma model
→ CT26 Colon Carcinoma model
Preparation of Clinical Testing

Selection of best indication for exploratory study(ies)

- High medical need / High mutational load
- Immunocompetent patients with sufficient life expectancy
- Possibility to demonstrate and follow efficacy within reasonable timeframe
- Incidence by stage / Feasibility
- Current/future standard of care
  - Window of opportunity for production
- Is it possible to take biopsies to follow impact on tumour microenvironment?
- Measurability of the tumour, Availability of tumour markers
- Heterogeneity of the tumours

- Work with clinical experts
- Seek regulatory advice
Thank you!