RNActive® – simple, cost effective and temperature stable mRNA vaccines

Ingmar Hoerr, CEO, CureVac
New Horizons for Vaccine Research and Innovation
Brussels, 12-13 March 2014
The RNA World
In the RNA world, RNA did it all...

Hey R, could you take this message over to -

Aw, come on, D! Give me something a little more challenging! I can multitask! I can do it all!

Ha. Where do you think we are? The RNA world?

(Source: http://evolution.berkeley.edu/evolibrary/article/ellington_03)
The variety of the RNAActive® technology
Discovery of the nucleic acids by Friedrich Miescher (1844 – 1895), physician and professor of physiology at the University of Basel. He found the nucleic acids in an extract of pus cells during his work in the laboratory of Felix Hoppe-Seyler in Tuebingen castle and called it "nuclein" – derived from Latin nucleus, nuclear.
Over 140 years later in Tübingen

CureVac’s GMP facility to produce large RNA molecules for medical purposes
CureVac – the RNA people®

CureVac – Development of mRNA-based Vaccines and Therapies

- Founded in 2000 as spin-off from University Tübingen, Germany
- Tübingen and Frankfurt, Germany
- ~ 120 FTEs
- Clinical trials in oncology (one Phase IIb) and infectious disease
- Key intellectual property with ~ 50 patent families

Major investor SAP co-founder Dietmar Hopp

- In total more than €145 million equity
The story: From the beginning until today

University of Tübingen
2000

CureVac, Tübingen
2013
CureVac – An integrated biopharmaceutical company

Platform from discovery to the patient

- Discovery & Research
- Preclinical development
- Production development & GMP Production
- Clinical Development

- Project Management
- Intellectual Property Management
- Quality Management
CureVac exploits its RNA technology for human protection and therapy

**RNAActive® Prophylactic Vaccines**
Use of RNAActive® for the development of prophylactic vaccines against infectious diseases

**RNAActive® Cancer Immunotherapy**
Development of cancer immunotherapies against oncologic diseases with current clinical focus on prostate cancer and non-small cell lung cancer

**RNAdjuvant®**
Development of non-coding immunostimulating RNA as potent adjuvant for prophylactic and therapeutic vaccines
CureVac’s R&D pipeline

<table>
<thead>
<tr>
<th>Product Line</th>
<th>Research</th>
<th>Non-clinical Development</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
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<tbody>
<tr>
<td><strong>Prostate Cancer (CV9103/9104)</strong></td>
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<td>Rabies</td>
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<td><strong>RNAAdjuvant®</strong></td>
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**RNAActive®**

Immunotherapy in Oncology

- Prostate Cancer (CV9103/9104)
- Prostate Cancer (Supportive)
- NSCLC (CV9202)
- NSCLC (Combination therapy)

**Prophylactic Vaccines**

- Rabies
- Influenza
- Undisclosed

**RNAAdjuvant®**

- Undisclosed
CureVac – Partnering

**RNActive® Tumor Immunotherapy**
Collaboration to enable clinical testing of novel immunotherapy treatment options for cancer

Others not disclosed

**RNActive® Prophylactic Vaccines**

- **SANOFI PASTEUR**
  - $33.1 million project volume over four years with additional option and license agreements with Sanofi Pasteur for several pathogens with up to €150.5 million plus royalties per pathogen

- **DARPA**

- **InCellart**

- **Janssen**
  - Collaboration and licensing agreement for the development of mRNA-based influenza vaccine

**RNAdjuvant®**
Not disclosed
RNActive® Technology
RNActive® – Mode-of-Action

Administration

mRNA uptake
Stimulation of innate immune system
Target expression and presentation

Skin

Antigen-presenting cell

Translation

Cytokine release

TLR

Lymph node

Activation of adaptive immune system
Expansion of antigen-specific T- and B-cells

Memory T-cell

CTLS

T-cell

B-cells

Plasma cells

Memory B-cell

Balanced cellular and humoral immune response

Blood

Target

Tumor

Virus
How to make mRNA work?

CureVac’s Screening Process

Protein Design (Selection, engineering, etc.)

Sequence Optimization (Expression level, time, etc.)

Format Optimization (Formulation, route, adjuvanticity, etc.)

Target Profile

Optimized RNA Product

[!] Identification of the optimal product candidate protected by composition-of-matter IP
RNActive® Prophylactic Vaccines
RNAActive® vaccines combine advantages of established vaccines

- Shown in various animal models and clinical trials.

- Live attenuated viruses
  - Broad activation of the immune system

- Subunit vaccines
  - Safety due to minimal vector

- Gene based approaches
  - Easy adaption of the gene sequence and stability
RNActive® storage and shipping without cold chain

Storage of RNA products
An improved formulation for storage and logistics at ambient conditions was developed.
Ongoing stability studies show stable products at
- 25°C at least 24 months
- 40°C at least 6 months
- 50°C at least 3 months
- 60°C at least 8 weeks
extended shelf live expected
Advanced and flexible In-House cGMP manufacturing facility for mRNA

Fast & flexible manufacturing process

- Standardized production process for all constructs (>800 different constructs)
- Multi-product production site (14 products in parallel)
- Production capacity up to 3.5 million doses at current site possible
- Scale-up for industrial size manufacturing feasible
- Rapid manufacturing within 6 weeks possible - Required in a pandemic setting

[!] One manufacturing process for all product candidates
RNAActive® Vaccines Against Influenza and Rabies
RNAActive® vaccines induce humoral responses comparable to inactivated viruses

**Anti-HA (IgG1)**

<table>
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<tr>
<th>Endpoint titer</th>
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<th>HA-RNAActive® mRNA</th>
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**Anti-HA (IgG2a)**

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Vaccination routes: RNAActive®: i.d., inact. virus: i.m.; H1N1pdm09: “swine Flu”
HA: Hemagglutinin
Line in graph: median; n=5 mice/group
RNAActive® vaccines protect against homologous lethal infection

Survival of H1N1pdm09 (swine flu) or H5N1 (bird flu) infected mice

Vaccination: HA RNAActive®: i.d.
HA: Hemagglutinin; n=5 mice/group

Experiments were conducted in cooperation with Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Tübingen
RNActive® vaccines induce long-term protection

**Kinetics of HI titers**

- **Buffer**
- **irrel. mRNA**
- **HA-RNActive® mRNA**

**Survival of PR8 infected mice**

HA: PR8 H1 Hemagglutinin
Survival cut off at 80% initial body weight
Experiments conducted in cooperation with Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Tübingen
RNActive® influenza vaccine protects against lethal challenge

- Cross protection
- Protection of different influenza strains by vaccine cocktail
- Protection via single administration of a combination of HA- and NA-RNActive® vaccine
- Long lasting immunity
- Induction of immune responses in mice, ferrets and pigs

Preclinical results of RNActive® vaccines against influenza
Protective efficacy of in vitro synthesized, specific mRNA vaccines against influenza A virus infection

Benjamin Petsch¹,⁵,⁶, Margit Schnee²,⁶, Annette B Vogel¹,⁵, Elke Lange³, Bernd Hoffmann⁴, Daniel Voss², Thomas Schlake², Andreas Thess², Karl-Josef Kallen², Lothar Stitz¹,⁵ & Thomas Kramps²*

Despite substantial improvements, influenza vaccine production—and availability—remain suboptimal. Influenza vaccines based on mRNA may offer a solution as sequence-matched, clinical-grade material could be produced reliably and rapidly in a scalable process, allowing quick response to the emergence of pandemic strains. Here we show that mRNA vaccines induce balanced, long-lived and protective immunity to influenza A virus infections in even very young and very old mice and that the vaccine remains protective upon thermal stress. This vaccine format elicits B and T cell–dependent protection and targets multiple antigens, including the highly conserved viral nucleoprotein, indicating its usefulness as a cross-protective vaccine. In ferrets and pigs, mRNA vaccines induce immunological correlates of protection and protective effects similar to those of a licensed influenza vaccine in pigs. Thus, mRNA vaccines could address substantial medical need in the area of influenza prophylaxis and the broader realm of anti-infective vaccinology.
RNActive® Vaccines Against Rabies
RNAActive® rabies vaccine protects against high dose i.c. challenge

- Protection in prophylactic and post-exposure prophylaxis regimen
- Induction of strong T cell responses in contrast to Rabipur®
- Long lasting titers of neutralizing antibodies
- Induction of significant VN titers in pigs
- Excellent robustness – still biologically active after storing at 40°C for 6 months

![Graph showing percent survival over time after infection for RNAActive® rabies vaccine, stored at 40°C for 6 months with buffer.]
RNActive® vaccines stored at high temperature are still biologically active

- **VNT**
  - IU/ml
  - Storage Temp [°C]
    - -80
    - +5
    - +25
    - +40
    - +60
  - Storage time [months]
    - Buffer
    - HDC

- **Survival of Rabies infected mice**
  - % survival
  - day after infection

RNActive® RAV G: rabies virus glycoprotein
Vaccination routes: RNActive®: i.d., licensed vaccine: i.m.; line in graph: median; n= 5 mice/group; Challenge with 40 LD_{50} i.c.;
Experiments conducted in cooperation with Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Tübingen
RNActive® Cancer Immunotherapy
Patient demographics
- 82% metastatic disease (bone 64%, lymph nodes 59%, visceral 11%)
- median age 67 years (51-84)
- 58% Gleason score ≥ 8

Design of the study
- Open, uncontrolled, multi-center, prospective

Study End points
- Primary endpoint: safety and tolerability
- Secondary endpoints: antigen specific immunogenicity

[!] RNAActive®: First in man mRNA vaccine with repeated vaccinations
RNActive® Cancer Vaccine CV9103
Summary of Phase I/IIa Clinical Study

Study Design

- Phase I: 12 patients – dose finding (256 µg, 640 µg, 1280 µg RNActive®)
- Phase IIa: 32 patients treated at highest dose to test immunogenicity

Immunoassays: ex vivo
Success criteria: according to CIMT (EU)/CIC (USA)
CV9103 is immunogenic in 79% of CRPC patients in a phase I/IIa trial

Patients treated at dose level III responding in different assays. Cellular response assays performed *ex vivo*

% responders

<table>
<thead>
<tr>
<th>Assay</th>
<th>Responders</th>
<th>Patients analyzed</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA ELISA*</td>
<td>4/33</td>
<td>33</td>
<td>12%</td>
</tr>
<tr>
<td>ELISpot</td>
<td>9/31</td>
<td>31</td>
<td>29%</td>
</tr>
<tr>
<td>ICS</td>
<td>12/26</td>
<td>26</td>
<td>46%</td>
</tr>
<tr>
<td>Tetramer</td>
<td>7/12</td>
<td>12</td>
<td>58%</td>
</tr>
<tr>
<td>Overall</td>
<td>26/33</td>
<td>33</td>
<td>79%</td>
</tr>
</tbody>
</table>

Patients responding/Patients analyzed

*Most patients showed pre-existing PSA antibody levels, an increase could be detected in 4 of those*
Overall survival of subgroup of patients with metastatic CRPC was 31.4 months

Kaplan Meier estimate of median overall survival*:

**31.4 months** [95% CI: 21.2-n.a.]

The median survival predicted by the Halabi prognostic nomogram** was **16.5 months

- 58% had a Gleason score ≥ 8
- 11% had visceral metastases

Encouraging survival in subgroup with unfavourable prognosis

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*Preliminary data from most recent follow-up- final data validation ongoing

Immune response is associated with improved survival (ongoing analysis)

Survival appears longer in immune responders despite the fact that the Halabi predicted survival is similar between responders and non-responders (HR=0.3)
Patients with multi-antigen response survive longer than single antigen responders (ongoing analysis)

Kaplan-Meier survival estimates
All immunologically evaluable metastatic patients (n=26)

- yellow: responders against 3 or all 4 antigens, n=5
- green: responders against 2 antigens, n=6
- brown: single responders, n=9
- blue: non-responders, n=6

multiple vs single responders: HR=0.41, 95%CI: [0.17-0.95], p=0.017
Executive summary of clinical data

CV9103

- Favorable safety profile
- Immune responses against all antigens, independent of cellular localization
- Good immune responses in the elderly,
- No restriction to certain HLA subtypes

Study Results

- Antigen specific immune responses in 79% of all patients
- 58% of responders reacted against multiple antigens
- Encouraging median overall survival of 31.4 months in subgroup with metastatic disease
- Immune response to multiple antigens associated with better survival
Conclusions
**RNActive® vaccines harbor eight distinct features**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>safe</td>
<td>Minimal vaccine</td>
</tr>
<tr>
<td>efficient</td>
<td>Balanced immune response with built-in adjuvant function</td>
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<tr>
<td>flexible</td>
<td>Any protein antigen can be encoded</td>
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<tr>
<td>fast</td>
<td>Rapid manufacturing within 6 weeks possible</td>
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<tr>
<td>versatile</td>
<td>One manufacturing facility for all vaccines is cost effective</td>
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<tr>
<td>robust</td>
<td>Stable at room temperature – no cold chain required</td>
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<td>convenient</td>
<td>Applicable via i.d., i.m. injection as well as needle free</td>
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<tr>
<td>validated</td>
<td>Safety and efficacy validated in clinical trials</td>
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Thank you for your attention!

Defining a new class of drugs

Visit us at www.curevac.com