mRNA-based Immunotherapies & Vaccines – A Novel Class of Drugs

European Business Development Conference 2013, Düsseldorf, Germany
CureVac – Development of mRNA-based Vaccines and Therapies
- Founded in 2000 as spin-off from University Tuebingen, Germany
- Headquarter in Tübingen, Germany; Clinical Development office in Frankfurt, Germany
- Hold key intellectual property with 40 patent families
- ~ 110 FTEs

Major investor Dietmar Hopp (SAP co-founder)
- Invested €80 million in September 2012
- In total more than €145 million equity raised

Research project with Sanofi Pasteur and In-Cell-Art: mRNA-based vaccines against infectious diseases
- $33.1 million project volume over four years, co-financed by DARPA (Defense Advanced Research Projects Agency)
- Additional option and license agreements with Sanofi Pasteur for several pathogens with up to €150.5 million plus royalties per pathogen
mRNA – an emerging new therapeutic class with unparalleled potential

Products based on our RNActive® technology can be developed in various disease areas

DNA → mRNA → Protein

CureVac focuses on cancer immunotherapies and vaccines in infectious disease
CureVac’s RNActive® technology platform transforms mRNA into a potent vaccine

**mRNA**
- Coding of almost any protein or antibody possible
- Unstable, rapid degradation

**CureVac’s mRNAOptimizer**
- Optimized for enhanced protein expression
- Increased mRNA stability

**RNActive® - CureVac’s proprietary mRNA**
- Immune stimulating
- Excellent robustness – no cold chain required
- Increases level and stability of protein expression up to several orders of magnitude
Achievements with immune stimulating RNA

**RNActive® Tumor Immunotherapy**
- Successfully completed Phase I/IIa studies in prostate cancer and non-small cell lung cancer (NSCLC)
- Recently initiated a Phase IIb clinical study in prostate cancer

**RNActive® Prophylactic Vaccines**
- Deal with Sanofi Pasteur and ICA co-funded by DARPA
- Broad external validation via the number 1 vaccine manufacturer

**RNAdjuvant®**
- Convincing preclinical data in infectiology and oncology
mRNA technology for molecular therapy

mRNA encoding EPO achieves biological effect *in vivo* as demonstrated in EPO model

Erythropoetin levels achieved by expression from CureVac’s mRNA *in vivo* match those of the therapeutic human Epo
In-house cGMP manufacturing facility for mRNA

**Fast & flexible manufacturing process**
- Standardized production process for all constructs (>1000 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

→ **Highly versatile – one manufacturing process for all vaccines**
Exploiting the full potential of the mRNA technology for tumor immunotherapy and prophylactic vaccines

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| **Prophylactic Vaccines** |   |
| Rabies |   |
| Undisclosed |   |

| **RNAdjuvant®** |   |
| Undisclosed |   |
RNActive® in Cancer Immunotherapy
Phase I/IIa clinical trials proved safety and high tolerability
- Induces antigen specific immune responses in 79% of patients
- Majority of immune responses are directed against multiple antigens (58%)
- Elicits immunological responses against all included antigens, independent of cellular localization
- Induces immune responses also in the elderly

Current Phase IIb clinical trial generates efficacy data in patients with castration-resistant prostate cancer
Encouraging survival data in the castrate resistant prostate carcinoma phase I/IIa study of CV9103

Survival follow-up of the subgroup of 36 patients with metastatic disease

Kaplan Meier estimate of median overall survival*:

**31.8 months** [95% CI: 22.9-na months]

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

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

- This was a less favorable prognostic subgroup than the population treated with Prostvac or Provenge in the phase II and III trials

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

The phase IIb trial with CV9104 is actively enrolling in 8 European countries

Phase IIb: Double blind, placebo controlled, n= 189
Chemonaive, asymptomatic or minimally symptomatic pts. with metastatic, castrate-resistant prostate cancer; ECOG 0,1
CV9104: Successor of CV9103 with two additional clinically validated antigens
Primary endpoint: Overall survival

Coordinating Investigator:
Arnulf Stenzl, Tübingen

For clinical trial sites see www.clinicaltrials.gov:
Trial CV9104-004
Promising data of the RNAactive® Vaccine CV9201

- Favorable safety profile
- Antigen specific and B-cell immune responses in 84% of all patients after chemotherapy
- 65% of responders reacted against multiple antigens
- Encouraging clinical course in some patients, need confirmation by further follow-up

Further clinical data on CV9202, the optimized successor of CV9201, will be generated
RNActive® for prophylactic vaccines
RNAVaccine® vaccines combine the advantages of established vaccines

- Broad activation of the immune system
- Easy adaption of the gene sequence and stability
- Safety due to minimal vector

Shown in various models
**RNAActive® prophylactic influenza vaccine**

An RNAActive® influenza vaccine does match most of the required differentiating product characteristics for game changing influenza vaccines (CIDRAP*):

- Superior efficacy across populations at increased risk for influenza related complications or death
- Broad protection against more than one strain of influenza
- Shorter production time
- Increased stability

**RNAActive® influenza vaccine fulfill high standards for vaccines**

Influenza as basis for the development of further vaccines

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* Center for Infectious Disease Research and Policy
**Infectious disease: Preclinical results of RNActive® in influenza**

**RNActive® vaccines tested in several preclinical studies**

- Crossprotection by NP-RNActive® of PR8 against lethal challenge with heterologous H5N1 virus
- Protection of different influenza strains by vaccine cocktail including different subtypes
- RNActive® vaccine induces immune responses in ferrets comparable to one human dose of an approved vaccine
- Protection through single administration of a combination of HA- and NA-RNActive®
- Induction of HI titers that persists for more than one year

![Survival of bird flu (H5N1) infected mice](image)

**HI titer in ferrets two weeks after boost vaccination**
RNAActive® vaccines: Proof-of-principle in flu preclinical data published in December 2012

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.
**RNAActive® prophylactic rabies vaccine**

**RNAActive® rabies vaccine protects against high dose i.c. challenge**
- RNAActive® performs similar to benchmark vaccine in a prophylactic and post-exposure prophylaxis regimen
- In contrast to Rabipur RNAActive® rabies vaccine induce strong T cell responses
- Encoded G protein protects against high dose i.c. challenge
- RNAActive® RAV G induced neutralizing antibody titers remains stable for at least 11 months
- Induces significant VN titers in pigs comparable to benchmark vaccine
- Excellent robustness – still biologically active after storing at 40°C for 6 months

The indication rabies proves the universal approach of the prophylactic RNAActive® vaccine
RNAdjuvant®
RNAAdjuvant® improves efficacy of approved influenza vaccines

**RNAAdjuvant® improves immunogenicity of different approved vaccines against infectious diseases**
- induces balanced immune response
- leads to memory response
- enhances immunogenicity of all tested approved infectious disease vaccines
- improves different antigenic formats (peptides, proteins, viruses)
- can be administered via different routes
- allows dose sparing
- is more active than PolyI:C with very favorable safety characteristics

**RNAAdjuvant® is a new, very promising adjuvant**
CureVac offers with its RNA technology platforms access to one of the most intriguing technologies in the market with un-paralleled potential.
Thank you for your attention!

Defining a new Class of Drugs

Visit us at www.curevac.com