Usage of an mRNA platform technology for “light speed” development of a vaccine against SARS-CoV-2

Dr. Andreas Kuhn – Senior Vice President RNA Biochemistry & Manufacturing

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BioNTech at a glance

Approach

Pioneering a range of next-generation immunotherapies for cancer and other diseases

Management

Prof. Ugur Sahin, M.D.
Sean Marett
Sierk Poetting, PhD
Ryan Richardson
Özlem Türeci, MD

Founded in 2008 in Mainz

Nasdaq-listed since October 2019

Diversity

Percentage women: 56%
Nationalities: >60
(as of Jan 2020)

11 ongoing clinical trials

10 product candidates in clinical development

> 25 product candidates across 4 drug classes

Strong investor base

More than USD 1.3bn raised

> 1,300 full-time employees

(as of Dec 2019)

4 in-house manufacturing facilities

World-leading corporate and scientific collaborators

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Agenda

- mRNA as a therapeutic platform technology
- Usage of our mRNA platform technology against COVID-19
- Next steps and challenges

mRNA as a therapeutic platform technology

Therapeutic messenger (m)RNAs are used
to introduce the genetic information for a protein,
encoded by the respective mRNA, into a cell of interest

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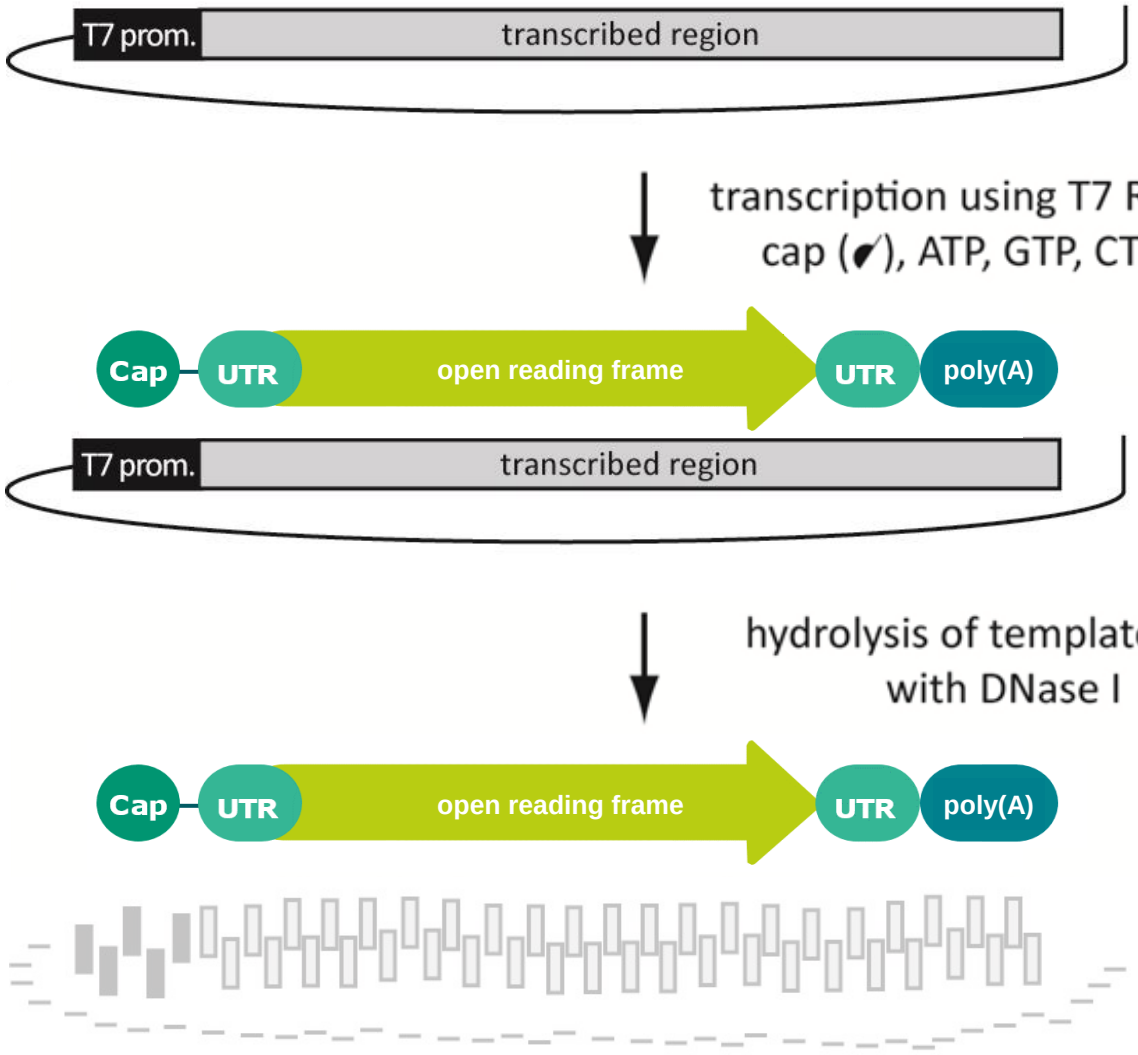
In vitro mRNA transcription



linear DNA template

in vitro transcribed mRNA
(> 500 copies per DNA template)

raw reaction mixture
with mRNA and impurities
(T7 RNA pol., remaining building blocks,
hydrolyzed DNA, …)

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“one process can be used to manufacture essentially any mRNA sequence”

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Advantages of mRNA therapeutics

- Lead candidate design starting from an amino acid sequence for expression can be done in hours
- Simple, fast, cell-free, and highly scalable manufacturing process essentially independent of the RNA sequence
- Allows expression of multiple proteins and thus targeting of multiple antigens on one RNA or using an RNA mixture
- mRNA can act as its own adjuvant (recognition by toll-like receptors, PKR and members of the RIG-I family) or can be made “immune-silent”
- Chemically stable molecule (just be aware of RNases)
- Needs to enter only the cytoplasm, not the nucleus of a target cell
- No risk of genomic integration
- Transient expression of the encoded protein/antigen
- Degraded into nucleotides, i.e. no toxic metabolites
- Possibility to introduce new functionalities through sequence modifications and by using chemically modified building blocks

Applications of mRNA therapeutics

Direct application of mRNA:

- Cancer immunotherapy
  - Induction of antigen-specific T cells by expression of corresponding tumor-associated antigens in dendritic cells
  - Expression of immune-modulating molecules (antibodies, cytokines, …)
- Vaccination against viral infections (induction of antigen-specific B and T cell responses)
- Transcript (or protein) replacement therapy

mRNA-transfected cells:

- Cancer immunotherapy
  - Induction of antigen-specific T cells by expression of corresponding tumor-associated antigens in dendritic cells
  - Expression of T cell receptors or so-called CARs (chimeric antigen receptors) in T cells
- mRNA-induced pluripotent stem cells
- Genetically engineered cells using mRNA coding for zinc-finger nucleases or CRISPR/CAS9

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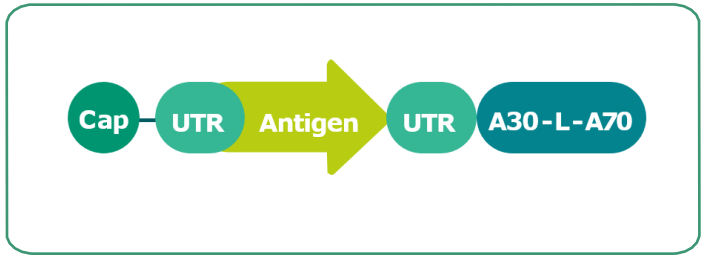
BioNTech’s strategy regarding COVID-19

- Usage of three available RNA types as part of our platform technology
- Design of multiple antigen variants using the SARS-CoV-19 S protein and their preclinical evaluation to bring the most active antigen into the clinic
- Generate preclinical data package for entry into clinic
- „Light speed“ manufacturing of small scale batches for fast entry into the clinic to demonstrate safety, tolerability (i.e. low reactogenicity), and immunogenicity
- In parallel, preparation of larger batch manufacturing for candidate with best output in the clinic
- Identify partners for collaboration to be able to develop and provide the vaccine worldwide

Rationale for testing three mRNA types in all Ph1/2 studies

Uridine mRNA (uRNA)



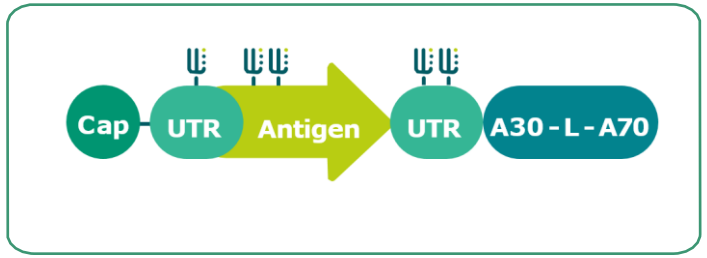
Clinical Stage RNA Technology

Manufacturing and CMC process in place

Rationale

- Intrinsic adjuvant effect
- Expected to have very good tolerability and safety
- Antibody & strong T-cell responses

Nucleoside-modified mRNA (modRNA)



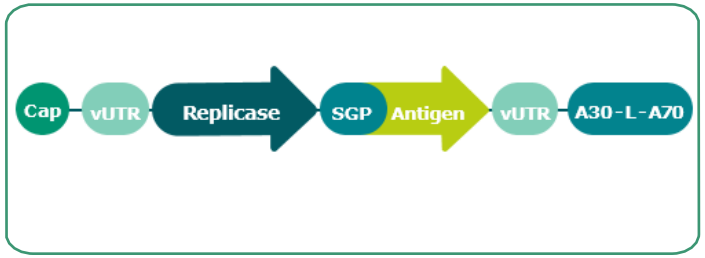
Clinical Stage RNA Technology

Manufacturing and CMC process in place

Rationale

- Less adjuvant effect
- Expected to have very good tolerability and safety
- Strong antibody responses & CD4 T-cell response

Self-amplifying mRNA (saRNA)



Preclinical Stage Technology

GLP tox. data available

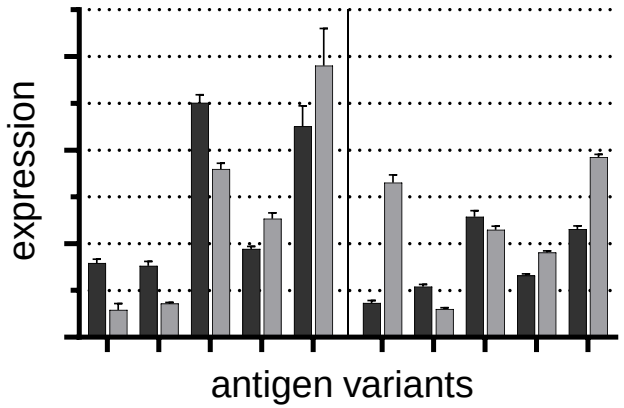
Manufacturing and CMC process in place

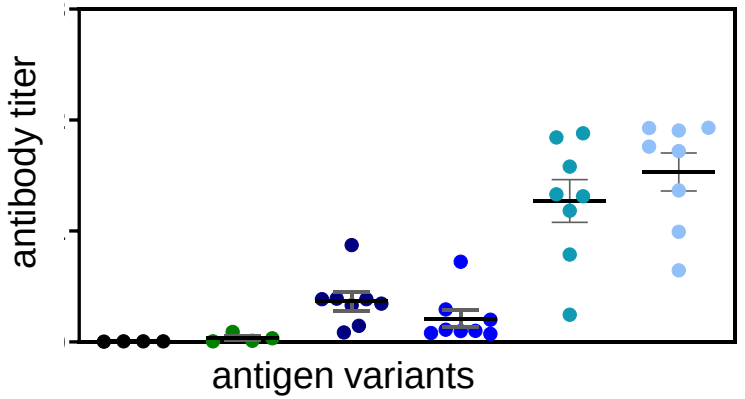
Rationale

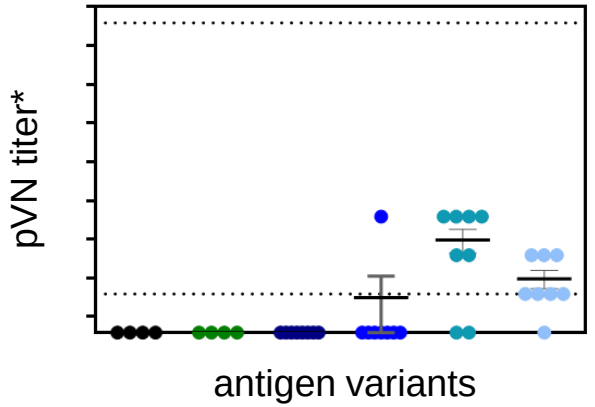
- Long duration of protein expression
- Expected to have good tolerability and safety
- Higher likelihood for good immune response with only 1× administration
- Higher likelihood for efficacy with very low vaccine dose

Selection of the best antigen

- Decision on spike protein based on experience with similar viruses
- Design of different variants (both on the amino acid and nucleotide – i.e. codon usage – level)
- Preclinical testing in multiple systems
  - In vitro expression data
  - Antibody titers in animal models
  - Pseudo-virus neutralization (pVN) assay in animal models







*: logarithmic scale

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What has made “light speed” possible?

- Upon availability of a target sequence (here the sequence of SARS-CoV-19), a lead candidate can be designed in just a few hours
- Using oligonucleotide synthesis, gene assembly and PCR amplification, a DNA template can be made within just a few days (dependent on scale and quality standard)
- Availability of **GMP-compliant RNA manufacturing process with clinical experience** for the technology
- Availability of **GMP-compliant LNP manufacturing process with clinical experience** for the technology
- Early and constant interaction with regulatory agencies

-> including pre-clinical screening of multiple antigen candidates, the first GMP batch was available (including CoA) within 84 days after first internal project meeting

If a new variant would be required (e.g. due to a mutated virus sequence), a new GMP batch could be available within half of the time

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Current status

- Manufacturing of seven GMP batches
- Approval of clinical study for all three RNA types as part of the COVID-19 BNT162 program
- First patient dosed on April 23rd
- Dosing of patients ongoing in both Germany and US

Next steps and challenges

- Upscaling of manufacturing for later stage clinical demand as well as pandemic and market supply (from 1 g of RNA to 1 kg)
    - Ensuring supply of starting materials
    - Required process changes and the corresponding comparability
    - Securing manufacturing capacity
- Start of phase 2/3 study as soon as possible

Acknowledgements

- Ugur Sahin
- RNA Biochemistry & Manufacturing team
- Preclinical, clinical and project management team
- Our partners

- All study participants