Comparability approach for an individualized product





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Agenda

- mRNA as a therapeutic platform technology
- The iNeST (individualized Neoantigen-Specific Therapy) concept
- Clinical testing of an mRNA-based iNeST
- Comparability for an individualized product

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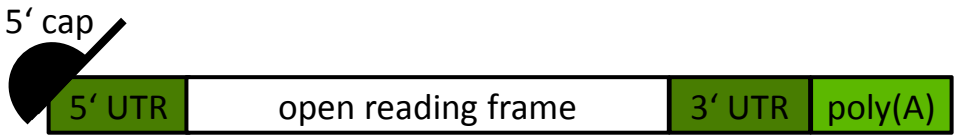
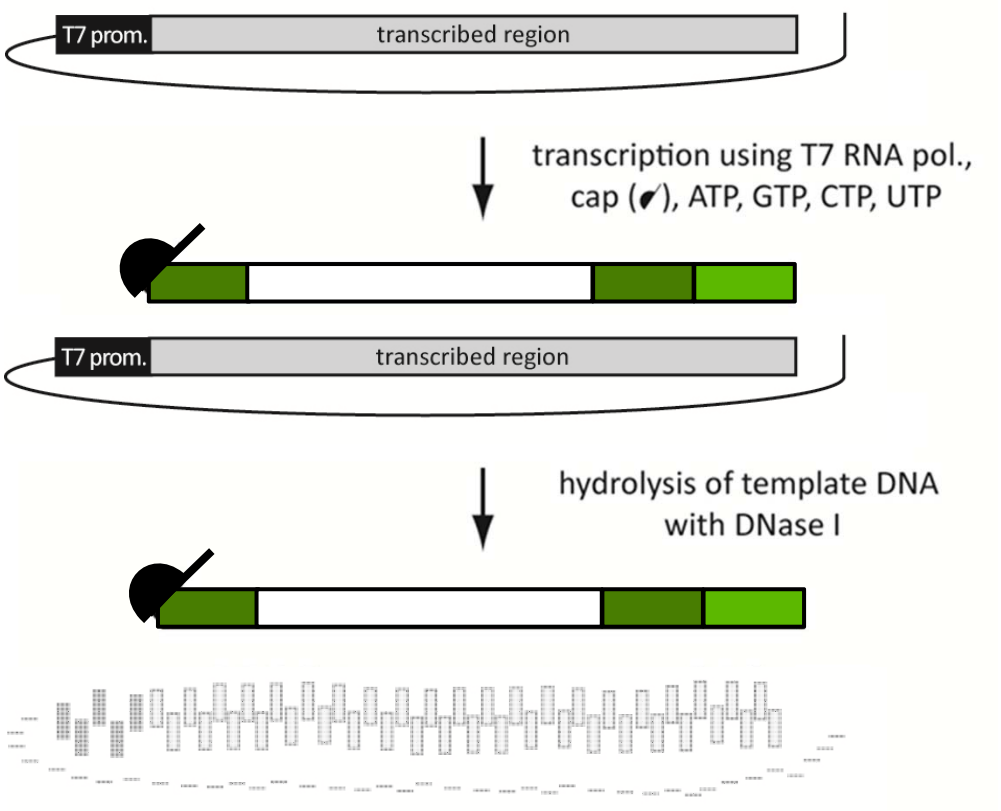
mRNA as a therapeutic platform technology

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



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, …)

one process can be used to manufacture essentially any mRNA sequence

Applications for 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
- 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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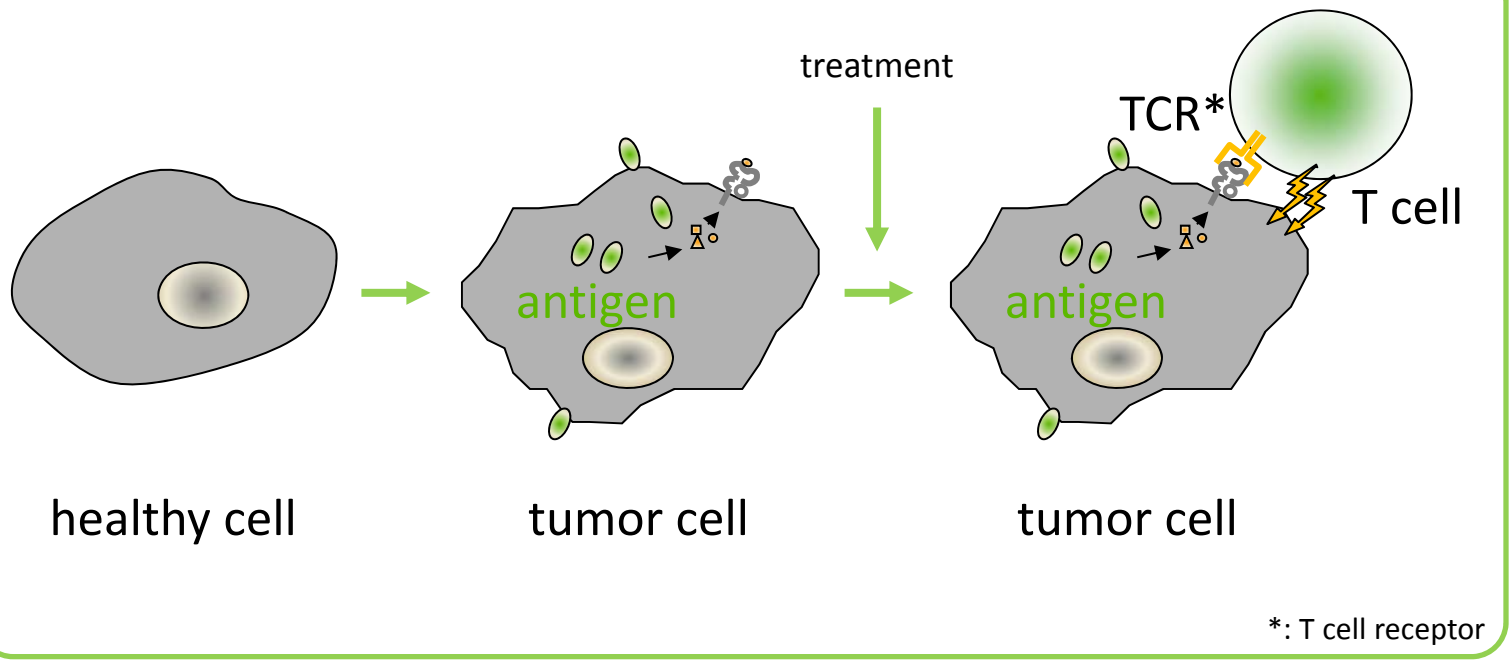
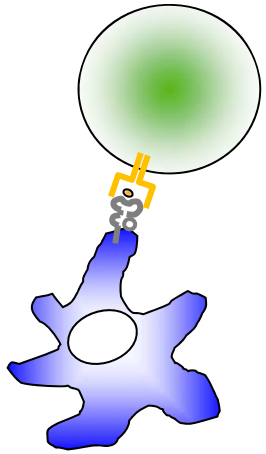
Cancer immunotherapy

Induction of tumor-associated antigen-specific T cells



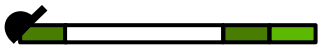


dendritic cell

Cancer immunotherapy

Induction of tumor-associated antigen-specific T cells

DNA → RNA → Protein → Epitope

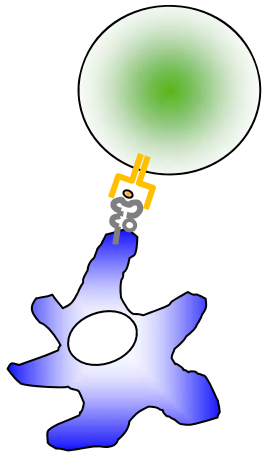


- Plasmid DNA
- Recombinant DNA-virus

- mRNA
- Recombinant RNA-virus

- Recombinant proteins
- Virus-like particles

- Synthetic peptides

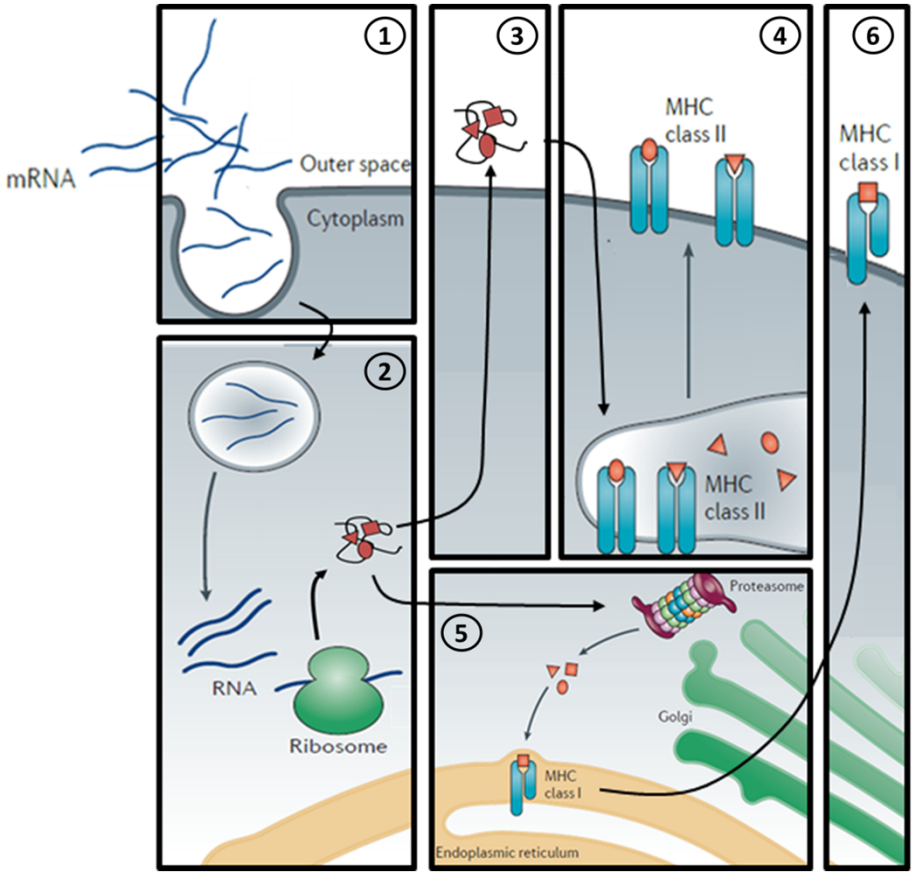


dendritic cell

Advantages of mRNA

- No integration into the genome
- Transient expression of the encoded antigen
- Needs only to reach the cytoplasm, not the nucleus
- Degraded into nucleotides, i.e. no toxic metabolites
- Antigen delivery independent of HLA-haplotype
- Induction of CD8+ and CD4+ T cell responses
- mRNA acts as its own adjuvant (recognition by toll-like receptors, PKR and members of the RIG-I family)
- Relatively simple production process independent of the sequence
- Possibility to introduce new functionalities through sequence modifications and chemically modified building blocks

Delivery and mechanism of action



dendritic cell

- Local injection of mRNA into lymph nodes leads to uptake by resident dendritic cells
- Induction and expansion of antigen-specific $CD8^+$ and $CD4^+$ T cells (via epitopes on MHC class I and II complexes, respectively)
- Systemic distribution
- Anti-tumoral effect

Neoepitopes as superior antigenic structures

A vaccine targeting mutant IDH1 induces antitumour immunity

Theresa Schumacher[1,2*], Lukas Bunse[1,2*], Stefan Pusch[3,4], Felix Sahm[3,4], Benedikt Wiestler[1,5], Jasmin Quandt[6], Oliver Menn[1], Matthias Osswald[1,5], Iris Oezen[1,2], Martina Ott[1,2], Melanie Keil[1,2], Jörg Balß[2,4], Katharina Rauschenbach[1,2], Agnieszka K. Grabowska[7], Isabel Vogler[8], Jan Diekmann[9], Nico Trautwein[10], Stefan B. Eichmüller[6], Jürgen Okun[11], Stefan Stevanović[10], Angelika B. Riemer[7], Ugur Sahin[9], Manuel A. Friese[12], Philipp Beckhove[6], Andreas von Deimling[3,4], Wolfgang Wick[1,5] & Michael Platten[1,2]

Mutant MHC class II epitopes drive therapeutic immune responses to cancer

Sebastian Kreiter[1], Mathias Vormehr[2*], Niels van de Roemer[2*], Mustafa Diken[1], Martin Löwer[1], Jan Diekmann[1,3], Sebastian Boegel[1], Barbara Schrörs[1], Fulvia Vascotto[1], John C. Castle[1], Arbel D. Tadmor[1], Stephen P. Schoenberger[4], Christoph Huber[2], Özlem Türeci[1§] & Ugur Sahin[1,2,3§]

Exploiting the Mutanome for Tumor Vaccination

John C. Castle[1], Sebastian Kreiter[1], Jan Diekmann[1], Martin Löwer[1], Niels van de Roemer[1,2], Jos de Graaf[1], Abderraouf Selmi[1], Mustafa Diken[1], Sebastian Boegel[1,2], Claudia Paret[1], Michael Koslowski[1], Andreas N. Kuhn[1,3], Cedrik M. Britten[2,3], Christoph Huber[1,3], Özlem Türeci[4], and Ugur Sahin[1,2,3]

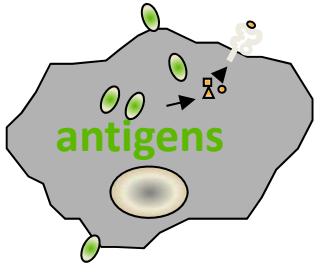
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2*] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5†]

VOLUME 31 · NUMBER 32 · NOVEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

Tumor Exome Analysis Reveals Neoantigen-Specific T-Cell Reactivity in an Ipilimumab-Responsive Melanoma



tumor cell

Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,[1] Simon Turcotte,[1*] Alena Gros,[1] Paul F. Robbins,[1] Yong-Chen Lu,[1] Mark E. Dudley,[1†] John R. Wunderlich,[1] Robert P. Somerville,[1] Katherine Hogan,[1] Christian S. Hinrichs,[1] Maria R. Parkhurst,[1] James C. Yang,[1] Steven A. Rosenberg[1‡]

Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade

Nicholas McGranahan,[1,2,3*] Andrew J. S. Furness,[3,4*] Rachel Rosenthal,[3*] Sofie Ramskov,[5] Rikke Lyngaa,[5] Sunil Kumar Saini,[5] Mariam Jamal-Hanjani,[3] Gareth A. Wilson,[1,3] Nicolai J. Birkbak,[1,3] Crispin T. Hiley,[1,3] Thomas B. K. Watkins,[1,3] Seema Shafi,[3] Nirupa Murugaesu,[3] Richard Mitter,[1] Ayse U. Akarca,[4,6] Joseph Linares,[4,6] Teresa

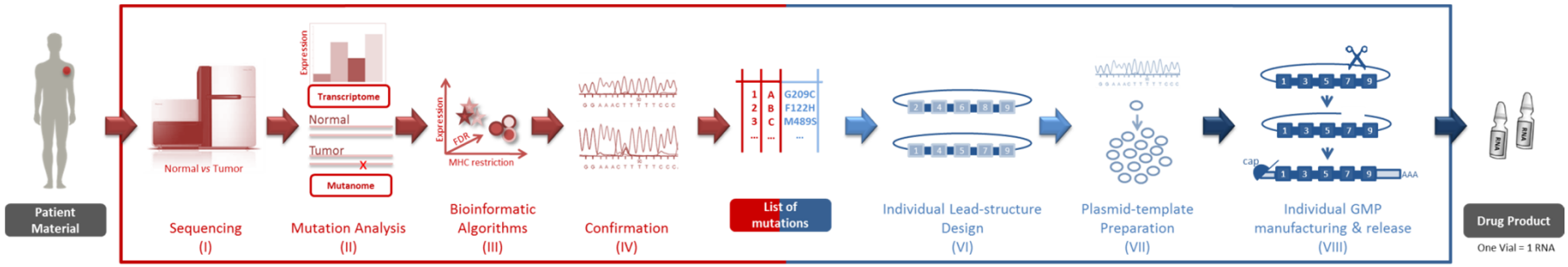
The response of autologous T cells to a human melanoma is dominated by mutated neoantigens

Volker Lennerz[†], Martina Fatho[†], Chiara Gentilini[‡], Roy A. Frye[§], Alexander Lifke[†], Dorothea Ferel[†], Catherine Wölfel[†], Christoph Huber[†], and Thomas Wölfel[†¶]

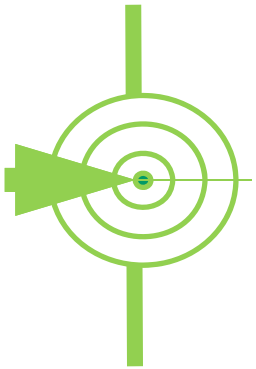
iNeST using mRNA

Patient- and tumor-specific mutations get utilized…

…to selectively activate the immune system with mRNA cancer vaccines tailored to the individual patient.



Of note: only transfer of data – no material



<u>mRNA-based iNeST</u>:

- On demand-manufacturing
- Suitable for potentially all tumor indications, also with low incidences
- No negative thymic selection of high-affinity TCRs against epitopes defined by patient- and tumor-specific mutations
- Induction of immune responses with high tumor specificity

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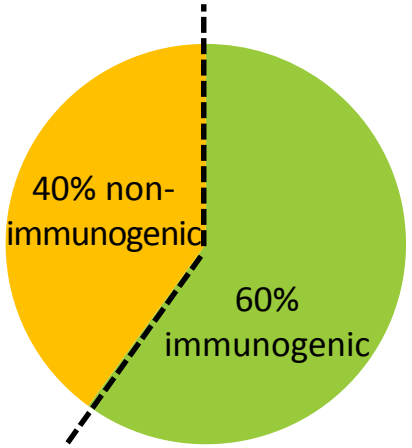
Translation into clinical testing

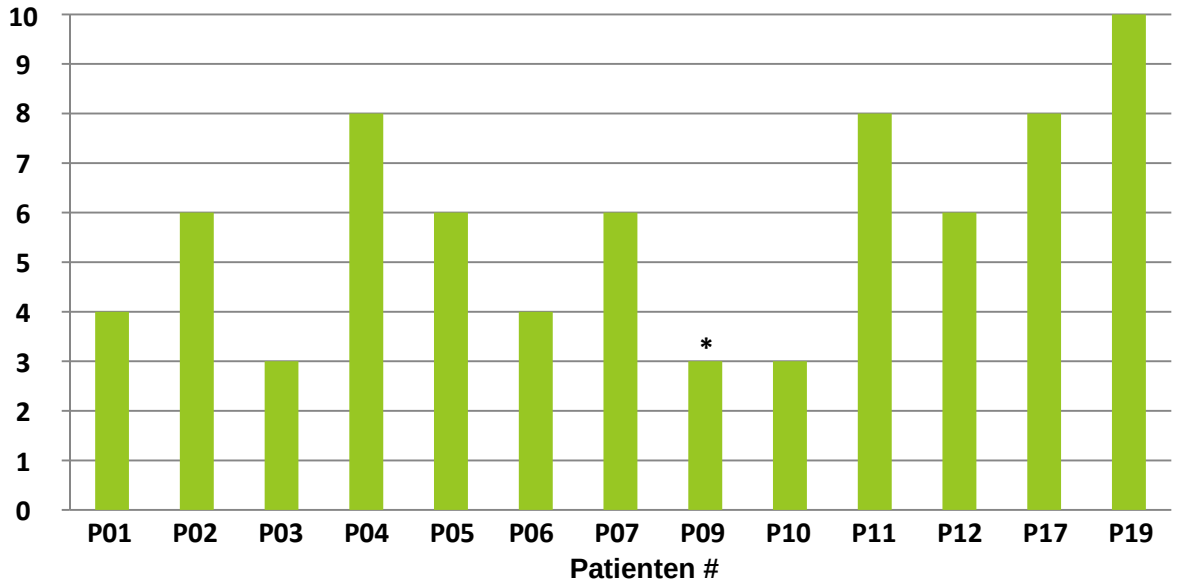
After verifying our mRNA-based iNeST platform preclinically, we started in 2013 the first clinical trial targeting neoepitopes defined by patient- and tumor-specific mutations using mRNA:

- Indication: malignant melanoma stage IIIa - IV
- Therapy: two mRNAs encoding in total ten neoepitopes locally injected into lymph nodes
- Dose: 0.5 or 1.0 mg of each RNA with eight applications within six weeks
- Number of patients: 13
- Primary endpoints: safety, adverse reactions and tolerability profile of multiple dosing with IVAC®
- Secondary endpoints: treatment-induced antigen-specific immune responses

Immunogenicity of neoepitopes

All 13 patients with a total of 125* neoepitopes selected for the manufacture of their mRNA-based iNeST have been analyzed:

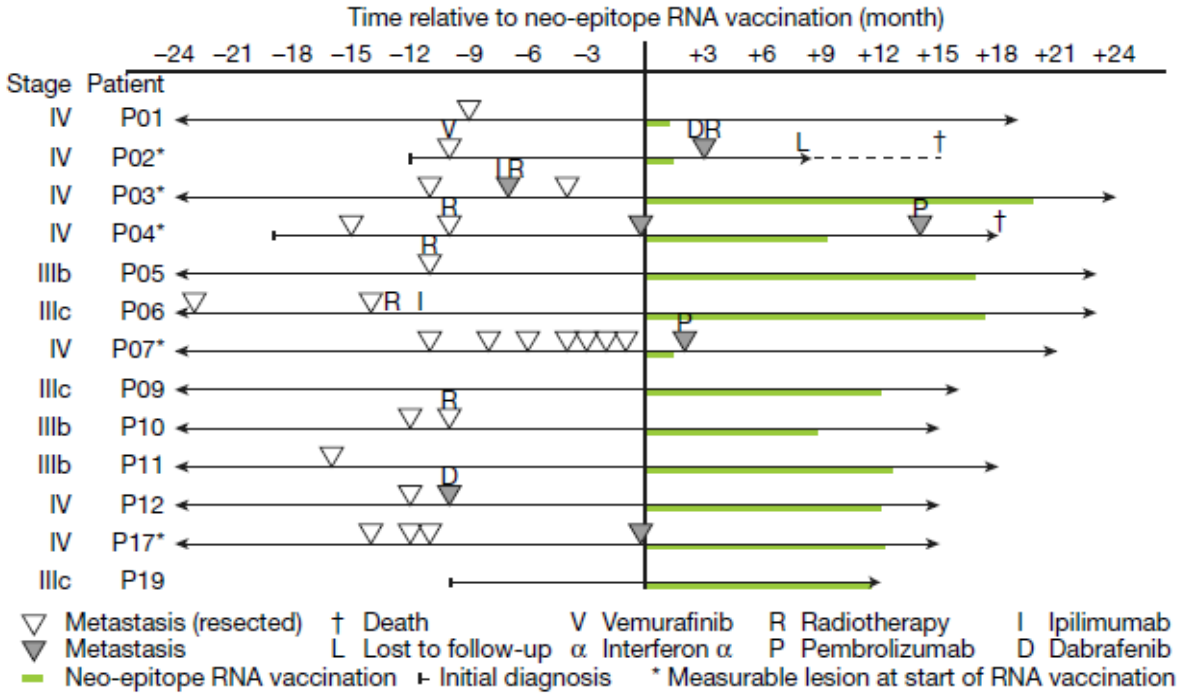




*: patient P09 was only treated with one RNA

Effect on tumor progression

The cumulative sum of metastatic events per month is significantly lower after treatment with our mRNA-based iNeST compared to the time before treatment:



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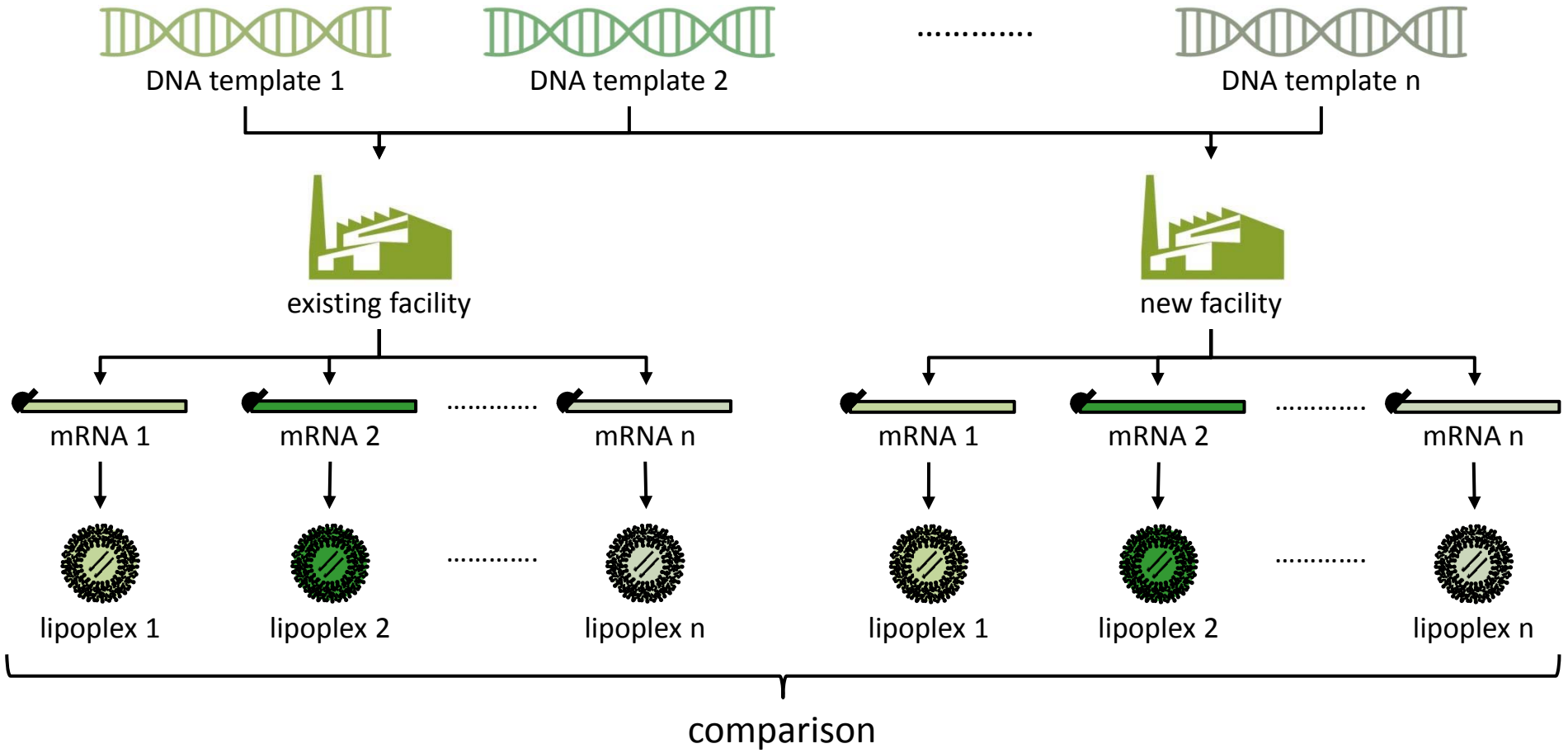
New facility for an individualized product

- As for any other transfer of a manufacturing process to a new facility (or actually for any change in the manufacturing process), it is required to demonstrate comparability between pre-change (here: existing facility) and post-change (here: new facility) as laid down e.g. in ICH Q5E
- This is especially challenging for an individualized product due to the fact that a product with a different mRNA sequence is manufactured for each batch
- To tackle this, we choose the following approach:
  - Definition of a set of “reference DNA templates” (i.e. the starting material that defines the individual sequence of each mRNA batch)
  - Manufacturing of mRNA drug substances and corresponding drug products from respective DNA template batches using a “split-stream” approach
  - Comparison of the drug substance and drug product batches manufactured at the two sites

„Split-stream“ approach for comparability



Considerations for the reference DNA templates

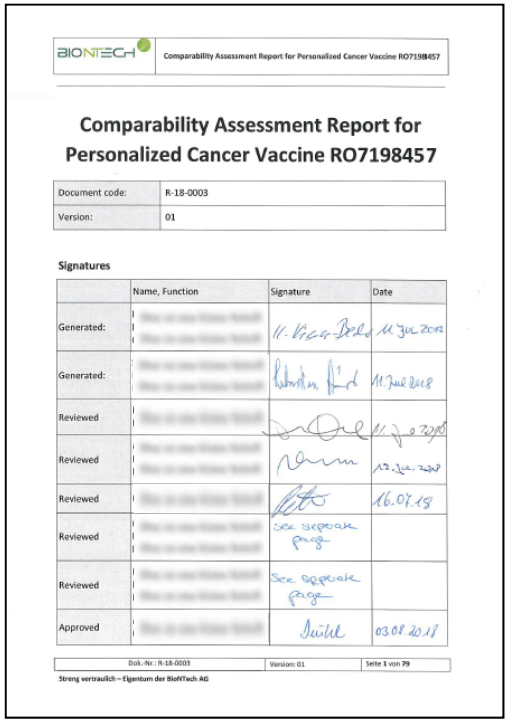
- Design of a set of sequences that bridge the sequence space of potential patient-specific sequences (including worst case and best case scenarios as well as typical sequences)
- Factors to take into considerations might include:
  - Sequence length (defined by number and length of individual neoepitopes)
  - GC-content (due to amino acid [and thus the corresponding codon triplet] distribution)

Approach for comparison

- Different levels, what to compare:
  - Drug substances (i.e. mRNAs) and drug products (i.e. lipoplexes)
  - Pair-wise comparison of mRNA and lipoplex batches from DNA templates 1, 2, …, and n
  - Comparison of all mRNA and lipoplex batches from existing and new facility
- Parameters to compare:
  - All parameters that are analyzed for release testing of drug substance and drug product (e.g. RNA content, RNA integrity, particle size, potency)
  - Further parameters that are part of the extended characterization (e.g. residuals not tested for every batch)
  - Stability (with initial read-out based on accelerated and stress conditions)

The result

- All drug substance and drug product batches within the specifications
- Comparable values for all parameters tested as part of extended characterization
- Similar behavior of batches in stability studies



BIONTECH | Comparability Assessment Report for Personalized Cancer Vaccine RO7198457

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Document code:	R-18-0003
Version:	01

Signatures

	Name, Function	Signature	Date
Generated:	[redacted]	[signature]	[date]
Generated:	[redacted]	[signature]	[date]
Reviewed	[redacted]	[signature]	[date]
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Approved	[redacted]	[signature]	03.08.2018

Dok.-Nr.: R-18-0003 | Version: 01 | Seite 1 von 79

Streng vertraulich – Eigentum der BioNTech AG

→ RNAs and lipoplexes manufactured at the two facilities are comparable

Summary

- mRNA is a promising therapeutic platform technology for multiple indications
- mRNA is ideally suited for individualized therapeutics
- A first-in-concept clinical study with our mRNA-based iNeST concept has demonstrated feasibility and signs of efficacy for a truly individualized treatment of patients
- In parallel, we have developed a liposome-based mRNA formulation that allows intravenous delivery with enhanced immune stimulation
- For further clinical development, a semi-automated manufacturing process and streamlined analytical testing, which allow a shortened “turn-around-time” from receiving the tumor sample to shipping the product back to the clinic, has been established
- As part of our efforts to increase capacity, a new facility has been set-up, for which comparability for manufacturing of our individualized, mRNA-based product has been verified

Acknowledgements

- Patients of the clinical studies
- The Genentech A Member of the Roche Group and BIONTECH iNeST teams