2nd International mRNA Health Conference

PROGRAM

November 11-12, 2014 • Cambridge, Massachusetts, U.S.A.

www.mrna-conference.com

CUREVAC the RNA people®

BIONTECH

moderna™ messenger therapeutics

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Greetings

Welcome to the 2nd International mRNA Health Conference!

We are delighted to have you join us for the next two days of educational presentations, discussions and personal connections built around the science of messenger RNA (mRNA).

Our belief in mRNA as an important new drug modality, combined with our passion for developing innovative medicines for patients in need, is what unites us in this rapidly evolving field.

As with any new major medical endeavor, the journey is more complicated than it looks. In all aspects- science, preclinical and clinical research, manufacturing and finance- we are venturing into new and unknown territory. This is why we believe strongly in scientific and business collaborations between key players in the mRNA field, as well as with pharmaceutical and biotech partners, suppliers and academic and clinical centers.

The effort we have undertaken to explore mRNA science is bigger than any one of our companies. It is bigger than any one of us. It can only be achieved through collaboration.

Last year, the 1st International mRNA Health Conference was hosted by CureVac in Germany. Based on the success of that conference, we are hosting the conference in Cambridge, and we plan to alternate the location each year. We are proud to represent the global desire to collaborate and bring pioneering mRNA medicines to patients.

We wish you a great conference and hope you will learn new things, discover new data, and that you will reconnect with old friends and make new ones.

Warmest Regards,

The Organizing Committee

Stephane Bancel
CEO Moderna

Ingmar Hoerr
CEO CureVac

Ugur Sahin
CEO BioNtech

Conference Program

Tuesday, November 11th

8:00 am **Breakfast, Opening Registration and Reception**

Introductory Session

9:00 am **Welcome remarks by the Organizing Committee**

9:30 am **Jack Szostak, *Massachusetts General Hospital, Nobel Laureate***

10:00 am **John Reynders, *Moderna Therapeutics***
Is mRNA like software?

10:30 am **Phil Sharp, *Massachusetts Institute of Technology, Nobel Laureate***

11:00 am ***Coffee Break***

11:30 am **Ingmar Hoerr, *CureVac***
Optimizing mRNA for versatile medical approaches

12:00 pm **Ugur Sahin, *BioNTech***
mRNA for personalized cancer immunotherapies

12:30 pm ***Lunch Break***

1:30 pm **Vaccines Session**

1:30 pm **Chair introduction by Ugur Sahin, BioNTech**

1:35 pm **Andrew Geall, *Novartis***

2:05 pm **Steve Pascolo, *University Hospital of Zurich***

2:35 pm **Ulrike Gnad-Vogt, *CureVac***

3:05 pm **Kris Thielemans, *University of Brussels***

3:35 pm ***Coffee Break***

3:55 pm **Therapeutics Session**

3:55 pm **Chair introduction by Rahul Kakkar, *AstraZeneca***

4:00 pm **Regina Fritsche-Danielson, *AstraZeneca***

4:30 pm **Ken Chien, *Karolinska University***

5:00 pm **Carsten Rudolph, *Ethris***

5:30 pm **Igor Splawski, *Novartis Institutes for BioMedical Research***

6:00 pm **Sessions End**

Networking Evening State Room Boston

6:15 pm **Bus to Reception Dinner**

7:00 pm **Reception Dinner with Scientific Poster Session**

Conference Program (continued)

Wednesday, November 12, 2014

8:00 am — *Breakfast*

9:00 am — **Panel Discussion: Vaccines**
Chaired by: Ugur Sahin, *BioNTech*
Panelists:
Andrew Geall, *Novartis*
Steve Pascolo, *University Hospital of Zurich*
Ulrike Gnad-Vogt, *CureVac*
Kris Thielemans, *University of Brussels*

10:00 am — *Coffee Break*

10:30 am — **Panel Discussion: Therapeutics**
Chaired by: Stephane Bancel, *Moderna Therapeutics*
Panelists:
Regina Fritsche-Danielson, *AstraZeneca*
Ken Chien, *Karolinska University*
Carsten Rudolph, *Ethris*
Igor Splawski, *Novartis Institutes for BioMedical Research*

11:30 am — **Panel Discussion: mRNA Products & Manufacturing**
Chaired by: Ingmar Hoerr, *CureVac*
Panelists:
Steve Harbin, *Moderna*
Peter Hutt, *Former FDA General Counsel*
Andreas Kuhn, *BioNTech*
Anton McCaffrey, *TriLink*
Florian von der Mülbe, *CureVac*

12:30 pm — *Lunch Break*

1:30 pm — **Peter Barton Hutt, *Former FDA General Counsel***
FDA Regulation of mRNA Biological Drugs

2:00 pm — **Dan Wattendorf, *DARPA***
Impact of mRNA on Global Health

2:30 pm — **Closing remarks by the Organizing Committee**

3:00 pm — **End of Conference**

Speakers & Abstracts

Tuesday, November 11, 2014

Introductory Session

9:30 AM

Jack Szostak, Ph.D., *Alex. A. Rich Distinguished Investigator, Department of Molecular Biology, Massachusetts General Hospital*

Dr. Szostak is an Investigator of the Howard Hughes Medical Institute, Professor of Genetics at Harvard Medical School, Professor of Chemistry and Chemical Biology at Harvard University and the Alex Rich Distinguished Investigator in the Department of Molecular Biology and the Center for Computational and Integrative Biology at Massachusetts General Hospital. Dr. Szostak's early research on telomere structure and function and the role of telomere maintenance in preventing cellular senescence was recognized by the 2006 Albert Lasker Basic Medical Research Award and the 2009 Nobel Prize in Physiology or Medicine, shared with Drs. Elizabeth Blackburn and Carol Greider. In the 1990s, Dr. Szostak and his colleagues developed in vitro selection as a tool for the isolation of functional RNA, DNA and protein molecules from large pools of random sequences. Dr. Szostak's current research interests are in the laboratory synthesis of self-replicating systems and the origin of life.

The Origins of the RNA World, and the Evolution of Translation and mRNA

RNA plays diverse roles in modern biology, many of which are thought to have emerged during the transition from the RNA world to the modern RNA-protein world. Ongoing work on the nonenzymatic replication of RNA is believed to be an essential step on the way from prebiotic chemistry to primitive cellular life. Recent findings suggest that the primordial version of RNA contained modified bases and non-standard backbone linkages. There exist possible pathways that lead to the emergence of mRNA-coded peptide translation and the evolution of protein enzymes.

10:00 AM

John Reynders, Ph.D., *Chief Information Officer, Moderna*

Prior to joining Moderna Therapeutics as Chief Information Officer in July 2013, Dr. Reynders served as the Vice President of Research and Development Information at AstraZeneca. As a member of the global R&D and IS leadership teams, he was responsible for R&D Informatics, Information, and IS capabilities across the R&D pipeline supporting discovery research, translational sciences, clinical operations, personalized healthcare, CMC, regulatory and payer functions. Previously, Dr. Reynders served as Vice President, Pharmaceutical R&D at Johnson & Johnson in multiple roles including Head of Integrative Neuroscience and Biomarkers, Head of the R&D Informatics Center of Excellence, Co-Founder of the Companion Diagnostic Center of Excellence and Head of Global R&D IT functions. Dr. Reynders received his Ph.D. in Applied and Computational Mathematics from Princeton University.

Is mRNA like software?

In software, it takes 333 bits to represent a google (10 to the hundredth power). And like software, the codons for a typical mRNA open reading frame can be combined into well over a google different permutations to code for the same protein. At Moderna, we are leveraging these degrees of freedom to create an mRNA compiler which combines multiple optimization techniques for a given protein to produce mRNA with desired expression, targeting, and synthesis properties. These optimizations are particularly challenging in modified mRNA where sequence/chemistry interdependence requires specialized and novel techniques.

10:30 AM

Phillip Sharp, Ph.D., *Institute Professor, Massachusetts Institute of Technology*

Dr. Sharp is Institute Professor (highest academic rank) at the Massachusetts Institute of Technology and a member of the Department of Biology and the Koch Institute for Integrative Cancer Research. He joined the Center for Cancer Research (now the Koch Institute) in 1974 and served as its director for six years from 1985 to 1991 before taking over as head of the Department of Biology, a position he held for the next eight years. His landmark work in 1977 provided the first indications of "discontinuous genes" in mammalian cells. The discovery fundamentally changed scientists' understanding of gene structure and earned Dr. Sharp the 1993 Nobel Prize in Physiology or Medicine. A native of Kentucky, Dr. Sharp earned a B.A. degree from Union College, Barbourville, KY, and a Ph.D. in chemistry from the University of Illinois, Champaign-Urbana. Dr. Sharp is a co-founder of Biogen (now Biogen Idec) and Alnylam Pharmaceuticals

Regulation of expression from mRNA

Processes controlling the expression of synthetic mRNA (S-mRNA) introduced by transfection methods have not been well characterized. The half-life of the S-mRNA is probably the major determinant and another is sequences influencing efficiency of initiation of translation. Factors controlling these two attributes of endogenous mRNA have been partially characterized and clearly vary between different cell types. Both of these steps are regulated by microRNAs and many RNA binding proteins. Some properties of miRNA regulation will be discussed.

11:30 AM

Ingmar Hoerr, Ph.D., *Chief Executive Officer, CureVac*

Dr. Hoerr, M.B.A., is a co-founder and CEO at CureVac in Tübingen/Germany. From their key discovery that the mRNA molecule is capable of generating a strong specific immune response in 2000, Dr. Hoerr and Dr. Florian von der Mülbe built up a company that is now a global leader in the research and development of mRNA-based drugs. Today, CureVac employs more than 140 individuals and has raised €145 million in capital investment. Current research and clinical development targets the development of cancer immunotherapies and prophylactic vaccines. CureVac has several strategic partnerships with international pharma companies and NGOs.

Optimizing mRNA for versatile medical approaches

When we saw our first preclinical data in the late '90s, we were already sure that mRNA is a very promising basis for therapeutics and vaccines. This exciting discovery led to the foundation of CureVac in 2000 and is still driving us forward.

Because of its physiological role in transferring genetic, protein-building information, mRNA has enormous potential as a basis for a revolutionary and very safe approach in medicine. Today we have found many ways of handling this fantastic molecule and are about to establish mRNA as a new class of drugs, together with our fellow colleagues. Continuous research has led to big leaps forward in optimizing mRNA for versatile medical approaches. The results are advanced platform technologies with highly increased productivity and composition-of-matter IP protection for the products.

12:00 PM

Ugur Sahin, M.D., *Chief Executive Officer, BioNTech*

Professor Ugur Sahin is a doctor of medicine and translational researcher with long-standing expertise in managing projects in the public-private interface. A pioneer in cancer target discovery using high throughput immunological methods and bioinformatics approaches, Professor Sahin holds more than 70 independent patent applications covering novel cancer biomarkers and targeted therapeutics platforms. His key focus is solving deeply rooted challenges in the multifaceted process of translating innovation from bench to bedside, an interest that was originally prompted by his experiences as a physician. Professor Sahin's publications have more than 6000 citations and he is the recipient of prestigious awards from the German Hemato-Oncology Association, German Association for Immunology, German Federal Ministry of Education and Research (BMBF) and American Society of Clinical Oncology.

mRNA for personalized cancer immunotherapies

1:30 PM Vaccines Section

1:35 PM

Andrew J. Geall, Ph.D., *RNA Vaccine Platform Leader, Novartis*

Dr. Geall is the RNA Vaccine Platform Leader at Novartis Vaccines (Cambridge, USA). Before joining Novartis in 2006, Dr. Geall was the manager of the Pharmaceutics Department at Vical (San Diego). There, he led the formulation development of the company's DNA vaccine program and was responsible for the production of the gene delivery systems for clinical trials. He has undergraduate degrees in Chemical Engineering and Pharmacy and completed his Ph.D. in gene delivery at the University of Bath U.K. in 1999.

Non-viral delivery of self-amplifying mRNA vaccines

Although the RNA vaccine field is in its infancy, the prospects are promising and recent advancements have demonstrated that vaccines based on mRNA have the potential to combine the positive attributes of other types of vaccines. Naturally transient and cytosolically-restricted mRNA can now be produced at sufficient quantity and quality from a cell-free enzymatic transcription reaction for human clinical trials. In addition, product stability, large-scale production, and purification are no longer perceived as barriers to the wide spread implementation of the technology. We have developed a self-amplifying mRNA vaccine platform and have utilized lipid nanoparticle (LNP) and cationic nanoemuslion (CNE) non-viral delivery systems, which substantially increases vaccine potency. The broad utility of this novel vaccine technology has been demonstrated with genes encoding vaccine candidate antigens from several pathogens and was found to elicit broad and potent protective immune responses in multiple animal models, including non-human primates. To demonstrate the speed at which synthetic self-amplifying mRNA vaccine can be produced, we responded to the recent H7N9 influenza outbreak in China as soon as the viral sequence was posted on a web-based data sharing system. Using rapid and accurate cell-free gene synthesis, the viral antigen was produced and incorporated into the self-amplifying mRNA vaccine, allowing the generation of a vaccine candidate within 8 days. If self-amplifying mRNA vaccines prove safe, potent, well-tolerated, and effective in humans, this novel nucleic acid vaccine technology will enable a new generation of vaccines able to address the health challenges of the 21st century.

2:05 PM

Steve Pascolo, Ph.D., *Senior Scientist, University Hospital of Zurich*

Dr. Pascolo began his study of mRNA-based vaccines in 1998 in the Department of Immunology, Tuebingen, Germany. He is a co-founder of CureVac and served as Chief Scientific Officer from 2000-2006, as well as a "Qualified Person" of the GMP facility within the company. Dr. Pascolo's work includes the implementation of the first clinical studies for the evaluation of immunotherapies based on direct injection of mRNA. He was a senior author on the first report on direct injection of mRNA in cancer patients (Weide et al. 2008). Since 2006, Dr. Pascolo has been at the University Hospital of Zurich working on immunotherapy of cancer. He is also the founder and CEO of Miescher Pharma, an organization dedicated to the development of immunomodulating RNA.

Immunotherapy of cancer using Protamine-mRNA nanoparticles

Injected synthetic unmodified mRNA has a dual activity: Immunostimulation through Toll Like Receptors and expression of the encoded protein. As shown through our pioneer clinical studies in cancer in patients, intra-dermal injections of naked or Protamine-condensed mRNA can generate an adaptive immune response against the encoded antigens. In order for this adaptive response to be highly efficacious against established tumors, type I interferon may be needed. Thus, intra-venous injections of mRNA may be preferred for therapy of cancer as it can induce systemic type I interferon and concomitant expression of the targeted antigen by professional antigen presenting cells (for example from blood phagocytes). To deliver mRNA intra-venous, we protect it with Protamine since this natural mixture of cationic peptide is available as a drug (used for neutralization of heparin). Depending on formulation conditions, we can generate Protamine-mRNA particles with different sizes ranging in average from 50 to over 900 nm. Depending on their size, the particles have differential immunostimulating activities and expression capacities. We will present our recent optimisation and pre-clinical evaluation studies using Protamine-mRNA nanoparticles for immunotherapy of tumor diseases. The potential of those formulations to treat or prevent cancer as well as for example infectious diseases will be discussed.

2:35 PM

Ulrike Gnad-Vogt, M.D., *Chief Medical Officer, CureVac*

Dr. Gnad-Vogt is Chief Medical Officer at CureVac in Tübingen/Germany. She is a board-certified medical oncologist and hematologist and worked at the National Center for Tumor Diseases in Heidelberg/Germany before joining CureVac in 2011. From 2005 – 2009 she was medical director at Merck Serono in Darmstadt/Germany, where she was responsible for the early clinical development of several cancer immunotherapeutic compounds. At CureVac, Dr. Gnad-Vogt and her team launched several phase I and II clinical trials with mRNA-based immunotherapies in oncology and for the prophylaxis of infectious diseases.

Clinical development of messenger RNA-based vaccines and adjuvants

Multivalent mRNA-based vaccines engineered by the RNActive® technology are being investigated as cancer immunotherapies and prophylactic vaccines. CureVac is currently conducting a number of clinical trials in patients with prostate cancer and non-small cell lung cancer. Results so far have shown that CureVac's mRNA-based products showed a favorable safety profile and induced humoral and cellular immune responses against a variety of encoded cancer antigens. Additionally, a phase I trial in healthy volunteers for the testing of a rabies vaccine as well as of an RNA-based vaccine adjuvant has been initiated, and encouraging preliminary results demonstrate the potential of mRNA for the prevention of infectious diseases.

3:05 PM

Kris Thielemans, M.D., Ph.D., *Professor, University of Brussels*

Dr. Thielemans was trained as an M.D. at the Vrije Universiteit Brussel (VUB), spent years in the Laboratory of Dr. R. Levy at the Department of Oncology at the Stanford University Medical School (CA, USA) and obtained a Ph.D. degree. Harnessing the immune system to combat cancer is the main focus of his work. He has managed the Laboratory of Molecular and Cellular Therapy (LMCT) at the VUB for more than 30 years with a main focus on immune-therapeutic translational research including clinical trials for the treatment of cancer and HIV. He is founder of the spin-off company eTheRNA.

DC-based vaccines: ex vivo and in vivo modification of DC with mRNA

Modification of dendritic cells (DC) with mRNA allows their loading with tumor antigens and their functional programming. To reprogram immature DC towards potent antigen (Ag) presenting cells, we provide 3 molecular adjuvants: mRNA coding for: caTLR4, mimicking TLR-4 activation; CD40L, mimicking 'licensing' of DCs and CD70 to provide an extra stimulus for the priming of CD8+ T cells. The mixture of these three mRNA's is referred to as 'TriMix.' The programming of DC with mRNA can be performed either in vitro, by electroporation, or in vivo after injection of mRNA into lymph nodes or at the tumor site.

We performed a DC-based clinical trial with DC electroporated with gp100, tyrosinase, MAGE-3, MAGE-C2 and TriMix mRNA combined with check-point blockade (ipilimumab). Thirty nine AJCC stage IIIc/IV melanoma pts were enrolled. Following DC-administration, gr2 skin injection site reactions were observed in all pts, post-infusion chills (< gr2) in 15 (38%), and transient flu-like symptoms (< gr2) in 33 pts (85%). Most frequent grade 3/4 adverse events were: dermatitis, diarrhea/colitis, hypophysitis, hepatitis, and pneumonitis. Systemic corticotherapy was used to treat irAE in 18 pts (46%). Best overall tumor response by irRC: 8 CR, and 7 PR (BORR 38%), 6 SD and 18 PD. All CR, and 3 PR are ongoing after a median duration of 19 mths (range 3-29 mths). The 6-mths DCR by irRC is 50% (95% CI 34-66). Median PFS and OS are respectively 6.2 (95% CI 3-9), and 14.4 mths (95%CI 10-18). These encouraging clinical responses indicate that further clinical development of TriMixDC-MEL in combination with immune checkpoint modulators is warranted.

Furthermore, pre-clinical studies indicate that DC can be modified in vivo. Upon intranodal (IN) and intratumoral (IT) delivery of mRNA in CD11c-DTR mice where DC can be ablated by administration of diphteria toxin, we could demonstrate the selective uptake and translation of mRNA by lymph node- and tumor-resident CD11c+ cells, respectively. Injection of TriMix mRNA induced a T-cell attracting and stimulatory environment. Enhanced induction of antigen-specific CD4+ and CD8+ T-cells was demonstrated using TriMix mRNA and mRNA's encoding several antigens upon IN immunization. Intranodal mRNA injection was shown to be as efficient in induction of CTLs and in therapy as vaccination with ex vivo mRNA electroporated DCs in several mouse tumor models. Upon IT injection of TriMix mRNA into P815 tumors, the tumor-resident DCs become activated, migrate to lymph nodes and activate CD8+ cytotoxic T-cell responses against several cancer Ag, including a cancer-testis Ag and a neo-epitope, indicating that in situ activation of DC results in auto-vaccination. Intratumoral injection of TriMix mRNA showed curative potential against disseminated tumors. In conclusion, IN injection of TAA + TriMix mRNA and IT administration of TriMix mRNA is a promising vaccination strategy that could evolve towards an off-the-shelf anti-cancer vaccine.

3:55 PM Therapeutics Section

4:00 PM

Regina Fritsche-Danielson, Ph.D., *Senior Director and Head of Heart Failure Bioscience, AstraZeneca*

Dr. Fritsche-Danielson is Senior Director and Head of Heart Failure Bioscience at AstraZeneca R&D, Sweden. She has a background in cardiovascular physiology and pharmacology and has over 13 years of experience in pharma. She is Strategy Area Lead for Cardiac Regeneration and Project Leader within Cardiovascular Diseases and in new modalities (modRNA) at AstraZeneca.

Modified mRNA – A new modality opening up novel treatments for patients with CardioMetabolic diseases

AstraZeneca's focus in the cardiovascular and metabolic disease area is on heart failure, diabetes and kidney disease. Development of new differentiated therapies within these areas faces several challenges. Treating chronic, non-immediately life-threatening disease requires well-tolerated, safe medicines. Due to the pressures on the health care system, not only the benefit/risk ratio of novel drugs needs to be proven but also cost effectiveness versus existing drugs.

On the research side, many interesting drug targets exist but are hampered by a lack of tractability so that even after decades of research no suitable pharmaceutical intervention is available. Our exclusive partnership with Moderna in the cardiometabolic space puts us in a leading position to explore the modified RNA technology platform for novel therapeutic targets, which are not amenable compared to standard drug discovery technologies and also allows for rapid validation of novel drug targets. Our investment in modified RNA technology has opened up the horizon for treatment with VEGF-A and similar key proteins in the cardiac regeneration/heart failure space. The VEGF-A modRNA project has pioneered the field in effective in vivo delivery of modRNA and driven an understanding of optimal chemical modification and formulation to reduce effective dose and toxicity thereby defining the next generation of novel disease modifying therapies for patients with huge unmet medical need.

4:30 PM

Kenneth Chien, M.D., Ph.D., *Professor, Karolinska Institutet*

Professor Chien received a Presidential appointment as a Professor to Karolinska Institutet in 2013. At Karolinska Institutet, Professor Chien leads a team of physicians and scientists on the pathways for human cardiogenesis, with a goal of finding new insights into congenital heart disease in children, as well as novel pathways and principles for regenerative medicine and the repair of damaged cardiac muscle cells. He previously served as the Charles and Elizabeth Ann Sanders Professor in the Department of Stem Cell and Regenerative Biology at Harvard University, Scientific Director of the Cardiovascular Research Center at Massachusetts General Hospital in Boston and Director of the UCSD Institute of Molecular Medicine. Professor Chien earned his M.D. in 1980 and his Ph.D. in 1983 from Temple University in Pennsylvania.

Synthetic Chemically modified mRNA (modRNA): Towards A New Technology Platform for Cardiovascular Biology and Medicine

Over the past two decades a host of new molecular pathways have been uncovered that guide mammalian heart development and disease. The ability to genetically manipulate these pathways in vivo have largely been

dependent on the generation of genetically engineered mouse model systems or the transfer of exogenous genes in a variety of DNA vectors (plasmid, adenoviral, adeno-associated viruses, anti-sense oligonucleotides, etc.). Recently, a new approach to manipulate the gene program of the adult mammalian heart has been reported that will quickly allow the high efficiency expression of virtually any protein in the intact heart of mouse, rat, porcine, non-human primate, and human heart cells via the generation of chemically modified mRNA (modRNA). The technology platform has important implications for delineating the specific paracrine cues that drive human cardiogenesis, and the pathways that might trigger heart regeneration via the rapid generation of modRNA libraries of paracrine factors for direct in vivo administration. In addition, the strategy can be extended to a variety of other cardiovascular tissues, and solid organs across multiple species, and recent improvements in the core technology have supported moving the first in human studies of modRNA in the next two years. These recent advances are reviewed along with examples of the utility of the approach into quickly delineating novel insights into new therapeutics for regenerative cardiology as well as projections of the potential impact of the technology for a host of other biomedical problems in the cardiovascular system.

5:00 PM

Carsten Rudolph, Ph.D., *Chief Executive Officer and President, Ethris*

Dr. Rudolph, CEO and President of Ethris, pharmacist by training, received his Ph.D. from the Department of Pharmacy of the FU Berlin. Since 2003 he has been group leader at the Dr. von Haunerschen Kinderspital of the Ludwig Maximilians University, Munich. He is lead inventor of the SNIM® RNA-Technology and co-inventor of numerous drug delivery patent applications. Dr. Rudolph received his post-doctoral lecture qualification at the Department of Pharmacy, FU Berlin in 2009. In 2005 Dr. Rudolph received the prestigious BioFuture Award of the BMBF which is the highest endowed young investigator award in Germany. He is supervising numerous research projects in the field of molecular medicine and gene therapy with a research focus on pulmonary diseases.

Stabilized non-immunogenic messenger RNA (SNIM® RNA) for transcript therapy

Ethris SNIM® RNA is an enabling platform for “Transcript Therapies” in a broad variety of medical indications, from hereditary or acquired metabolic diseases to regenerative medicine. SNIM® RNA circumvent TLR activation and thus enables repeated administration of mRNA. Because of its precursor function, SNIM® RNA yields sustained protein production within the body and overcomes short duration effects of recombinant proteins. Ethris has developed proprietary delivery systems for pulmonary, systemic and local SNIM® RNA administration and will present preclinical results from its activities. Efficient delivery systems and non-immunogenicity are the keys for making mRNA therapeutics reality beyond oncology applications.

5:30 PM

Igor Splawski, Ph.D., *Director, Biologics, Cardiovascular and Metabolic Disease Area, Novartis Institutes for BioMedical Research*

Dr. Splawski graduated from Sofia University (M.S., Biochemistry) and University of Utah (Ph.D., Human Genetics). He continued his work at Children’s Hospital, Boston, and Harvard Medical School, where he became an Assistant Professor. Dr. Splawski’s work showed that mutations in K+, Na+, and Ca2+ channels cause arrhythmias, including long QT syndrome associated with deafness - Jervell and Lange-Nielsen syndrome, and autism - Timothy syndrome. In 2005, Dr. Splawski joined Novartis. In Ophthalmology, he initiated and led three antibody programs. One has completed phase II clinical trials and two are in phase I. Since 2009, Dr. Splawski leads Biologics in the Cardiovascular and Metabolic Disease Area.

mRNA Therapy for Inherited Disorders

Recently, Novartis Institutes for BioMedical Research (NIBR) began exploring therapeutic mRNA. This technology is attractive for addressing several pressing medical needs, including: 1) Ex vivo cell

reprogramming for regeneration, immune modulation, and protein replacement; 2) replacement or expression of intracellular proteins in vivo; and 3) expression of secreted proteins, including therapeutic biologics, in vivo. Over the last two years, NIBR has demonstrated efficacy and tolerability in rodents with multiple targets, including ABC transporters, medium-chain acylcoenzyme A dehydrogenase, LDL receptor, LDLR adaptor protein 1, leptin, and erythropoietin. NIBR completed critical tolerability and toxicology experiments in rodents and non-human primates. By contrast with findings in cultured human dendritic cells and in rodents, experiments in cynomolgus monkeys revealed inflammation, including inflammatory response in the brain.

Wednesday, November 12, 2014

1:30 PM

Peter Barton Hutt, *Senior Counsel, Covington & Burling*

Mr. Hutt practices food and drug law as Senior Counsel at the Washington, D.C. law firm of Covington & Burling. Except for 1971-1975, when he served as Chief Counsel for the Food and Drug Administration, Mr. Hutt has spent his entire career specializing in food and drug law at Covington. He is the co-author of the casebook used to teach food and drug law throughout the United States, and beginning in 1994 he has taught a full course on this subject at Harvard Law School during the winter term. He became a member of the Institute of Medicine when it was first formed in 1971, and has served on a wide variety of scientific and medical organizations and on the board of directors of biotechnology companies.

FDA Regulation of mRNA Biological Drugs

Pharmaceutical products made through mRNA technology are regulated as biological products under the Biological Products Act of 1902 or as new drugs under the Federal Food, Drug, and Cosmetic Act of 1938, depending upon the method of manufacture. As with any pharmaceutical product, it is important to meet with FDA early and often in order to make certain that the company is following a development plan that will result in FDA regulatory approval. Attention must be given to applications for special designations that will provide increased FDA collaboration and advice, including fast track, breakthrough drug, priority review, and accelerated approval.

2:00 PM

Daniel J. Wattendorf, M.D., *Program Manager, Biological Technologies Office, DARPA*

Col Wattendorf, MC, USAF, joined DARPA as a Program Manager in the Defense Sciences Office (DSO) in 2010. In 2013 he joined the newly formed Biological Technologies Office (BTO). His interests focus on applying methodological advances in genomics and biotechnology to optimize health and prevent disease, including novel RNA vaccines to improve effectiveness and reduce production time.

Impact of mRNA on Global Health

DARPA is investing in RNA-based immunoprophylaxis technologies that include vaccines and passive gene transfer of antibodies. Compared to conventional vaccines, RNA-based vaccine platforms demonstrate increased effectiveness by encoding the antigen and enhancing the robustness of the immune response. The RNA antibody transfer platform encodes potent antibodies identified from humans, bypassing the adaptive immune response and establishing a near-immediate state of immunoprophylaxis. With regard to development and manufacturing hurdles, these approaches reduce risk, are undergoing preclinical and clinical proof-of-concept studies, represent new platforms for further pharmaceutical investment, and are amenable to rapid, inexpensive, and population-scale manufacturing.

The major advantages of nucleic acid-based immunoprophylaxis platforms include: (1) increased safety and stability of the drug due to its primarily synthetic rather than biological components and (2) reduced costs and timeline of production, manufacturing, and distribution due to modular design. With the successful development and commercialization of nucleic acid-based immunoprophylaxis platforms, candidates for future emerging outbreaks can be designed, produced, and distributed more rapidly than current methods, enabling highly effective and timely outbreak response.

The expected outcomes for this DARPA effort include:

- Novel platform(s) for in vivo gene transfer
- Direct pathogen sequence-to-vaccine production
- Increased prophylactic and therapeutic efficacy
- Streamlined path to clinic
- Rapid, scalable, inexpensive manufacture

2:30 PM

Stéphane Bancel, *Chief Executive Officer, Moderna*

Closing Remarks

Mr. Bancel has served as CEO of Moderna since its inception. He was previously CEO of bioMérieux, a world leader in the diagnostics industry. Prior to his time at bioMérieux, Stéphane was an executive at Eli Lilly. He holds a Master of Engineering from École Central Paris, a Master of Science in Chemical Engineering from the University of Minnesota and an M.B.A. from Harvard Business School.

Panels

Wednesday, November 12, 2014

9:00 AM

Panel Discussion: Vaccines

Chair:

Ugur Sahin, M.D., *Chief Executive Officer, BioNTech*

Professor Ugur Sahin is a doctor of medicine and translational researcher with long-standing expertise in managing projects in the public-private interface. A pioneer in cancer target discovery using high throughput immunological methods and bioinformatics approaches, Professor Sahin holds more than 70 independent patent applications covering novel cancer biomarkers and targeted therapeutics platforms. His key focus is solving deeply rooted challenges in the multifaceted process of translating innovation from bench to bedside, an interest that was originally prompted by his experiences as a physician. Professor Sahin's publications have more than 6000 citations and he is the recipient of prestigious awards from the German Hemato-Oncology Association, German Association for Immunology, German Federal Ministry of Education and Research (BMBF) and American Society of Clinical Oncology.

Panelists:

Andrew J. Geall, Ph.D., *RNA Vaccine Platform Leader, Novartis*

Dr. Geall is the RNA Vaccine Platform Leader at Novartis Vaccines (Cambridge, USA). Before joining Novartis in 2006, Dr. Geall was the manager of the Pharmaceutics Department at Vical (San Diego). There, he led the formulation development of the company's DNA vaccine program and was responsible for the production of the gene delivery systems for clinical trials. He has undergraduate degrees in Chemical Engineering and Pharmacy and completed his Ph.D. in gene delivery at the University of Bath U.K. in 1999.

Steve Pascolo, Ph.D., *Senior Scientist, University Hospital of Zurich*

Dr. Pascolo began his study of mRNA-based vaccines in 1998 in the Department of Immunology, Tuebingen, Germany. He is a co-founder of CureVac and served as Chief Scientific Officer from 2000-2006, as well as a "Qualified Person" of the GMP facility within the company. Dr. Pascolo's work includes the implementation of the first clinical studies for the evaluation of immunotherapies based on direct injection of mRNA. He was a senior author on the first report on direct injection of mRNA in cancer patients (Weide et al. 2008). Since 2006, Dr. Pascolo has been at the University Hospital of Zurich working on immunotherapy of cancer. He is also the founder and CEO of Miescher Pharma, an organization dedicated to the development of immunomodulating RNA.

Ulrike Gnad-Vogt, M.D., *Chief Medical Officer, CureVac*

Dr. Gnad-Vogt is Chief Medical Officer at CureVac in Tübingen/Germany. She is a board-certified medical oncologist and hematologist and worked at the National Center for Tumor Diseases in Heidelberg/Germany before joining CureVac in 2011. From 2005 – 2009 she was medical director at Merck Serono in Darmstadt/Germany, where she was responsible for the early clinical development of several cancer immunotherapeutic compounds. At CureVac, Dr. Gnad-Vogt and her team launched several phase I and II clinical trials with mRNA-based immunotherapies in oncology and for the prophylaxis of infectious diseases.

Kris Thielemans, M.D., Ph.D., *Professor, University of Brussels*

Dr. Thielemans was trained as an M.D. at the Vrije Universiteit Brussel (VUB), spent years in the Laboratory of Dr. R. Levy at the Department of Oncology at the Stanford University Medical School (CA, USA) and obtained a Ph.D. degree. Harnessing the immune system to combat cancer is the main focus of his work. He has managed the Laboratory of Molecular and Cellular Therapy (LMCT) at the VUB for more than 30 years with a main focus on immune-therapeutic translational research including clinical trials for the treatment of cancer and HIV. He is founder of the spin-off company eTheRNA.

10:30 AM

Panel Discussion: mRNA Therapeutics

The advancement of messenger RNA (mRNA) science holds vast potential for the development of new, innovative medicines across a wide range of diseases, many of which are not treatable through current approaches. This potential increases the level of responsibility for research and development teams seeking to leverage mRNA science to quickly and effectively deliver new medicines. Experts in this panel will explore all the facets of mRNA Therapeutics development, from discovery to preclinical and clinical testing phases. Panelists will also discuss the prior day's speaking presentations, including initial reactions and questions raised, and discuss the challenges of making mRNA Therapeutics.

Chair:

Stéphane Bancel, *Chief Executive Officer, Moderna Therapeutics*

Mr. Bancel has served as CEO of Moderna Therapeutics since its inception. He was previously CEO of bioMérieux, a world leader in the diagnostics industry. Prior to his time at bioMérieux, Mr. Bancel was an executive at Eli Lilly and Company. He holds a Master of Engineering from École Central Paris, a Master of Science in Chemical Engineering from the University of Minnesota and an M.B.A. from Harvard Business School.

Panelists:

Regina Fritsche-Danielson, Ph.D., *Senior Director and Head of Heart Failure Bioscience, AstraZeneca*

Dr. Fritsche-Danielson is Senior Director and Head of Heart Failure Bioscience at AstraZeneca R&D, Sweden. She has a background in cardiovascular physiology and pharmacology and has over 13 years of experience in pharma. She is Strategy Area Lead for Cardiac Regeneration and Project Leader within Cardiovascular Diseases and in new modalities (modRNA) at AstraZeneca.

Kenneth Chien, M.D., Ph.D., *Professor, Karolinska Institutet*

Professor Chien received a Presidential appointment as a Professor to Karolinska Institutet in 2013. At Karolinska Institutet, Professor Chien leads a team of physicians and scientists on the pathways for human cardiogenesis, with a goal of finding new insights into congenital heart disease in children, as well as novel pathways and principles for regenerative medicine and the repair of damaged cardiac muscle cells. He previously served as the Charles and Elizabeth Ann Sanders Professor in the Department of Stem Cell and Regenerative Biology at Harvard University, Scientific Director of the Cardiovascular Research Center at Massachusetts General Hospital in Boston and Director of the UCSD Institute of Molecular Medicine. Professor Chien earned his M.D. in 1980 and his Ph.D. in 1983 from Temple University in Pennsylvania.

Carsten Rudolph, Ph.D., *Chief Executive Officer and President, Ethris*

Dr. Rudolph, CEO and President of Ethris and pharmacist by training, received his Ph.D. from the Department of Pharmacy of the FU Berlin. Since 2003, he has been the group leader at the Dr. von Haunerschen

Kinderspital of the Ludwig Maximilians University, Munich. He is the lead inventor of the SNIM® RNA-Technology and co-inventor of numerous drug delivery patent applications. Dr. Rudolph received his post-doctoral lecture qualification at the Department of Pharmacy, FU Berlin in 2009. In 2005, Dr. Rudolph received the prestigious BioFuture Award of the BMBF which is the highest endowed young investigator award in Germany. He is supervising numerous research projects in the field of molecular medicine and gene therapy with a research focus on pulmonary diseases.

Igor Splawski, Ph.D., *Director, Biologics, Cardiovascular and Metabolic Disease Area, Novartis Institutes for BioMedical Research*

Dr. Splawski graduated from Sofia University (M.S., Biochemistry) and University of Utah (Ph.D., Human Genetics). He continued his work at Children's Hospital, Boston, and Harvard Medical School, where he became an Assistant Professor. Dr. Splawski's work showed that mutations in K+, Na+, and Ca2+ channels cause arrhythmias, including long QT syndrome associated with deafness - Jervell and Lange-Nielsen syndrome, and autism - Timothy syndrome. In 2005, Dr. Splawski joined Novartis. In their Ophthalmology Department, he initiated and led three antibody programs. One has completed phase II clinical trials and two are in phase I. Since 2009, Dr. Splawski leads Biologics in the Cardiovascular and Metabolic Disease Area.

11:30 AM

Panel Discussion: mRNA Products & Manufacturing

Finding the optimum formulation and manufacturing process is one of the biggest challenges in developing a completely new class of drugs. The experts in this discussion group will discuss and exchange interesting viewpoints on formulation and production of mRNA, as well as regulatory aspects.

Here are just some of the many questions about this interesting topic:

- What does the optimal mRNA product look like (existing/future)?
- What are the future challenges for mRNA products?
- What are the main characteristics of the manufacturing process of mRNA compared to other typical biopharmaceutical production processes?
- What are the challenges concerning application route and stability of mRNA products?
- What are the regulatory hurdles of mRNA products? Are there advantages that we can benefit from?

Chair:

Ingmar Hoerr, Ph.D., *Chief Executive Officer, CureVac*

Dr. Hoerr, M.B.A., is a co-founder and CEO at CureVac in Tübingen/Germany. From their key discovery that the mRNA molecule is capable of generating a strong specific immune response in 2000, Dr. Hoerr and Dr. Florian von der Mülbe built up a company that is now a global leader in the research and development of mRNA-based drugs. Today, CureVac employs more than 140 individuals and has raised €145 million in capital investment. Current research and clinical development targets the development of cancer immunotherapies and prophylactic vaccines. CureVac has several strategic partnerships with international pharma companies and NGOs.

Panelists:

Stephen Harbin, *Senior Vice President, Human Resources, Production, Global Facilities, Training & Development, Moderna Therapeutics*

Mr. Harbin brings more than 30 years of diverse operational experience in pharmaceuticals and in vitro diagnostics to his position at Moderna Therapeutics, having served in a variety of senior business and operational leadership roles both in Europe and the U.S. Prior to joining Moderna, he was the Corporate Vice President of Global Operations at bioMérieux. In his career, Mr. Harbin has held senior leadership positions driving strategic direction and performance in such areas as manufacturing, information systems, quality, regulatory affairs and compliance. Mr. Harbin has held leadership roles with Eli Lilly and Company, Shionogi Qualicaps (Spain), Elanco Qualicaps (U.K.) and Elanco Animal Health. He graduated in 1979 from Durham College of Agriculture in the U.K.

Peter Barton Hutt, *Senior Counsel, Covington & Burling*

Mr. Hutt practices food and drug law as Senior Counsel at the Washington, D.C. law firm of Covington & Burling. Except for 1971-1975, when he served as Chief Counsel for the Food and Drug Administration, Mr. Hutt has spent his entire career specializing in food and drug law at Covington. He is the co-author of the casebook used to teach food and drug law throughout the United States, and beginning in 1994 he has taught a full course on this subject at Harvard Law School during the winter term. He became a member of the Institute of Medicine when it was first formed in 1971, and has served on a wide variety of scientific and medical organizations and on the board of directors of biotechnology companies.

Andreas Kuhn, Ph.D., V*ice President RNA Biochemistry, BioNTech*

Dr. Kuhn has worked in the field of RNA biochemistry and molecular biology for more than twenty years. His work on RNA-based immunotherapies began in 2007 with Professor Ugur Sahin when Dr. Kuhn joined BioNTech RNA Pharmaceuticals GmbH (formerly Ribological GmbH) shortly after its founding. His main focus is expanding Ribological® proprietary technologies to increase the efficacy of RNA immunotherapies and to optimize GMP-compatible manufacturing processes for RNA. He has co-authored several publications and has patents ranging from basic research on RNA to its application as a diagnostic and therapeutic agent.

Anton McCaffrey, Ph.D., *Associate Director of Research & Development, TriLink*

Dr. McCaffrey is the Associate Director of Research & Development at TriLink Biotechnologies. and an Adjunct Assistant Professor of Internal Medicine at the University of Iowa School of Medicine, Division of Infectious Diseases. Dr. McCaffrey has specialized in the design, development and testing of nucleic acid based therapeutics for 25 years. He has worked with and published on antisense, ribozymes, RNA interference, microRNAs, aptamers and genome editing tools, focused both on in vitro models as well as in vivo models. Dr. McCaffrey currently heads a research group focused on scalable production of modified mRNAs and is the technical lead for the pharmaceutical GMP program at TriLink Biotechnologies.

Florian von der Mülbe, Ph.D., *Chief Operating Officer, CureVac*

Dr. von der Mülbe, M.B.A., is Chief Operating Officer at CureVac in Tübingen/Germany. He trained in biochemistry and business administration. Dr. von der Mülbe worked with Biotest GmbH and Roche AG before joining CureVac in 2000 - working with Dr. Ingmar Hoerr to build the business from the start. In his role as COO, he established the first GMP (good manufacturing practice) production for mRNA worldwide. Previously, he worked with Professor Jung at Tübingen University. He holds a Ph.D. in biochemistry from Tübingen University and an M.B.A. from the European School of Business in Reutlingen.

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AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: www.astrazeneca.com

BioNTech AG (Biopharmaceutical New Technologies) is developing entirely new and highly innovative immunotherapies and diagnostics for the tailored treatment of numerous cancers and other diseases with high medical need. BioNTech's platform technologies have been developed over the past 20 years originating from strong academic roots and leading to the foundation of BioNTech AG in 2008 with its headquarter in Mainz, Germany. We have assembled an international renowned team of more than 200 skilled and experienced scientists from almost 20 different countries. The unique combination of different techniques, unparalleled in-house scientific and management expertise, dedicated people and cutting edge technology offered through its subsidiaries allows the harnessing of unique synergies that result in faster development of novel diagnostics and therapies for human disease.

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CureVac, a clinical stage biopharmaceutical company from Tübingen, Germany, is pioneering the field of mRNA-based technology platforms for medical purposes with which mRNA is specifically optimized and formulated. Since 2000 the company develops novel mRNA-based cancer immuno-therapies and prophylactic vaccines against infectious diseases – both under the brand RNActive®. CureVac has successfully established the first GMP (good manufacturing practice) facility worldwide for the manufacture of RNA and mRNA and has pioneered mRNA-based drugs in clinical studies.

The company has successfully completed Phase I/IIa clinical studies with its RNActive® cancer vaccines in prostate cancer and non-small cell lung cancer (NSCLC). Results so far have shown that mRNA-based products showed a favorable safety profile and induced immune responses including humoral and cellular, helper (both Th1 and Th2) and effector and memory responses. CureVac is currently conducting a number of clinical trials with its RNActive® vaccines. A large randomized Phase IIb clinical trial in castrate resistant prostate cancer with CV9104 has been fully enrolled in December 2013. In the field of cancer immunotherapy CureVac is already collaborating with Boehringer Ingelheim and the Ludwig Cancer Research Institute to enable clinical testing of novel cancer immunotherapy treatment options e.g. the combination of CureVac's RNActive® with checkpoint inhibitors.

CureVac's RNActive® technology is also used to develop prophylactic vaccines for infectious diseases. In March 2014, CureVac received the EUR 2 million Vaccine Prize from the European Commission for its RNActive® vaccine technology. In particular, the jury acknowledged the fact that the RNActive® vaccines represent a novel technology enabling the production of safe, efficacious and cost-effective vaccines that are protected against elevated temperature as well as inadvertent freezing. In the field of prophylactic vaccines CureVac is amongst others collaborating with Sanofi Pasteur, In-Cell-Art, DARPA and Janssen Pharmaceuticals.

For more information please visit www.curevac.com.

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Moderna is pioneering messenger RNA therapeutics™, an entirely new *in vivo* drug modality that produces human proteins or antibodies inside patient cells, which are in turn secreted or active intracellularly. This breakthrough platform addresses currently undruggable targets and offers a superior alternative to existing drug modalities for a wide range of disease conditions.

Moderna has developed a broad intellectual property estate, including more than 355 patent applications covering novel nucleotide chemistries and drug compositions.The company plans to develop and commercialize its innovative mRNA drugs through a combination of strategic relationships as well as new formed ventures. Founded in late 2010 by Flagship VentureLabs, Cambridge-based Moderna is privately held and currently has strategic agreements with AstraZeneca and Alexion Pharmaceuticals.

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Ethris – Enabling Therapies develops innovative therapeutics based on proprietary platform technologies with high diversification potential that enable therapies for diseases with currently dissatisfying treatment options and high unmet need. SNIM® RNA is a first-in-class biopharmaceutical platform for therapies of rare diseases, alternative for recombinant proteins, and for “Transcript Therapies” in regenerative medicine. Ethris – Enabling Therapies provide access to highly profitable markets.

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