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Newsletter Issue No. 1

Editorial

This first electronic newsletter of EXPERT finds us in challenging times. As I write this, I am sitting behind the dinner table that has been my work spot for the past 10 weeks. I share it with my daughter, so my knowledge on the volume of a cylinder, climate in India, passé composé in French has in the meantime dramatically improved, but now that the initial excitement of dealing with the new situation is over, I yearn for a return to the lab.
Despite being out of the lab, this hasn't meant that the consortium was idle. Several labs could continue experimental work, albeit at reduced power.
We also held a first progress meeting via Webex and filled 3 GB with presentations and discussions and we have had our monthly consortium meetings. In addition, we added focus group meetings to address the critical path towards the clinical trial.
Everything is set to be quick off the mark, the moment we can resume our normal work.

I hope you and your loved ones stay safe.

Raymond Schiffelers
EXPERT Coordinator

About Expert

The EU research project EXPERT aims at developing a new off-the-shelf delivery system for RNA-based nanomedicines with a first clinical application in breast cancer and cardiovascular disease. In the long term, the platform technology could be used for improving therapeutic options for patients with several other diseases. The project will receive EUR 14.9 million funding from the European Union's Horizon 2020 Framework Programme over the next five years. The EXPERT consortium comprises 11 international partners from The Netherlands, Belgium, Norway, Sweden, Spain, Hungary, Ireland, France, Germany, and Israel.

Learn more about the project

Consortium

EXPERT is a public-private consortium. The complementary expertise of the partners spans the entire nanomedicine therapeutics development track from nanoparticle design and quality control, via Good Manufacturing Practice-based production to application in pre-clinical disease models and safety. Thereby the consortium spans also the entire value chain, from product design to pre-clinical product development and manufacture.

The University Medical Center Utrecht, Netherlands is coordinating the EXPERT project.

Our lab focuses on nanomedicine. We use natural and synthetic nanoparticles to improve diagnosis and therapy. We do translational research, where challenges in healthcare guide scientific research. We are based within the University Medical Center Utrecht. Key areas of expertise are extracellular vesicles (such as exosomes and microvesicles), non-coding RNA and synthetic drug delivery systems (such as liposomes and polymers). Our work spans the entire nanomedicine field from characterization of nanoparticles via in vitro study of their behavior to pre-clinical evaluation and measurements on clinical samples. To support these

broad activities, we collaborate with fundamental scientists, technological researchers, clinical chemists and medical doctors as well as with industry. We are an international multidisicplinary team with a diverse background in biomedical sciences. We are active in national, European and intercontinental collaborations and have successfully obtained personal grants and project grants.

Raymond Schiffelers

Raymond Schiffelers obtained his PhD in 2001 from Erasmus University Rotterdam, the Netherlands, on Liposomal targeting of antimicrobial agents in bacterial infections. In 2002-2003, he moved to Intradigm Co. (Washington DC) to work on siRNA delivery with nanoparticles. Here he developed the first intravenously administered siRNA nanoparticle for use in pre-clinical experiments.
After he returned, he built his own nanomedicine research group at Utrecht University. He received an NWO Vidi grant in 2007 on targeting inflammation to fight cancer and received an ERC Consolidator Grant in 2010 to explore extracellular vesicles as drug delivery systems. As a result of his ERC Proof of Concept grant in 2011 he founded Excytex bv, a company combining his liposome and extracellular vesicle expertise. He moved to the University Medical Center in Utrecht in 2012 and became professor of nanomedicine in 2015. Since 2016 he is coordinator of B-SMART and later EXPERT, two H2020 RIA projects. In addition, he currently coordinates five projects through national grants.

Pieter Vader

Pieter Vader graduated in Chemistry (B.Sc., 2005) and Drug Innovation (M.Sc., 2007) from the University of Utrecht. He earned his PhD degree in 2012 from the University of Utrecht on the subject of targeted delivery of siRNA to inhibit tumor angiogenesis.
From 2012 to 2014, Pieter was employed as a (senior) postdoctoral fellow at the University of Oxford, UK, in the lab of Prof. Matthew Wood, supported by a NWO Rubicon fellowship. The research topic was development of small RNA-loaded extracellular vesicles for targeted delivery.
In 2014 he moved back to The Netherlands to continue his work at the University Medical Center Utrecht. Currently, he is Assistant Professor at CDL Research and at the Department of Experimental Cardiology. His main research interests are in the field of therapeutic applications of extracellular vesicles, including unraveling the mechanisms underlying extracellular vesicle-mediated cargo transfer. His research has been supported by a NWO VENI fellowship (2014), ERC Starting Grant (2019) and Dutch Heart Foundation Dekker Senior Scientist Grant (2019).

Valentina Francia

Valentina has studied Molecular Biology at the University of Milan, Italy. She graduated cum laude in 2013 with a thesis on the cellular mechanisms of resistance to cancer drugs. In 2014 she was selected for a PhD program at the Groningen Research Institute of Pharmacy (Netherlands), where she studied the mechanisms involved in the uptake of nanomaterials. She defended her PhD in September 2018 and she continued her work at the University of Groningen as a postdoctoral fellow. Currently, Valentina is a joint postdoctoral fellow between the nanomedicine laboratory of Prof. Raymond Schiffelers, at the University Medical Center Utrecht (the Netherlands), and the laboratory of Prof. Pieter Cullis, at the University of British Columbia (Canada). Her project is part of the Horizon 2020 EXPERT consortium and it is focused on the investigation of the biomolecular corona of lipid-based nanomedicines for nucleic acid delivery. Apart from her work as a postdoctoral fellow, Valentina is Board Member, Chapter Liaison and Social Media Coordinator of the BeNeLux & France Local Chapter and of the Canada Chapter of the Controlled Release Society, and Social Media Manager of the Horizon 2020 EXPERT consortium.

Zhiyong Lei

Zhiyong Lei is an assistant professor at the University Medical Center Utrecht. He received his B.Sc. in biopharmaceutical engineering from Jilin University, M.S in Biochemistry in 2003, Molecular biology from Univeristy of science and Technology of China in 2006 and PhD in regenerative medicine from experimental cardiology labrarotary in University Medical Center Utrecht. In 2019, he joined the group of Prof. Raymond M. Schiffelers at the University Medical Centre Utrecht working on the delivery of modified mRNA. His research interests include the development of both lipid nanoparticles and extracellular-vesicle-inspired drug-delivery systems for biomolecules delivery including proteins and nucleic acids.

Mariona Estapé

My name is **Mariona Estapé** and I come from Barcelona. In 2016, I finished my bachelor in Biotechnology in the University of Barcelona. Afterwards, in 2017, I started a master in Drug Innovation in the University of Utrecht. During my master internship in the Laboratory of Translational Immunology (LTI) in the UMCU and the Pharmaceutics department from Utrecht University, I gained expertise and interest for drug delivery systems and their interactions with the complement system. Additionally, I pursued an internship on organ-on-a-chip devices. Since October 2018, I am working in the EXPERT project in the development of lipid nanoparticles for mRNA-based immunotherapies against cancer.

Omnia Elsharkasy

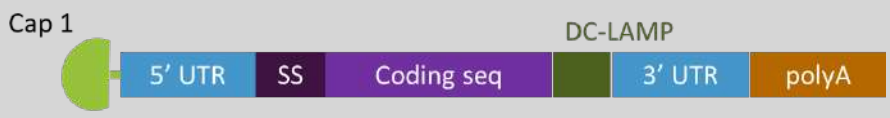
My name is **Omnia Elsharkasy**, and I am from Egypt. In 2016, I obtained my bachelor's degree from the faculty of Pharmacy. After that I started my masters at the University of Utrecht in drug innovation after being granted Utrecht Excellence Scholarship. During my masters, I was an intern at the Department of Pharmaceutics, during my internship I gained a lot of experience and grew fond of various drug delivery systems. Afterwards, I moved to the UMCU where I did my second internship at Schiffelers' lab on different ways of engineering extracellular vesicles for drug delivery. After finishing my masters, I happily continued to work at Schiffelers' lab as a PhD student in the EXPERT project where I am now exploring extracellular vesicles for the delivery of nucleic acids.

Related News

mRNA platform
(eTheRNA Immunotherapies)

eTheRNA Immunotherapies is developing first in class mRNA immunotherapies for the treatment of cancer and infectious diseases. We employ messenger RNA to unleash and boost a patient's immune response against tumors and infectious agents. We believe our mRNA platforms are broadly applicable across multiple diseases for which immunomodulation is key to therapeutic efficacy.

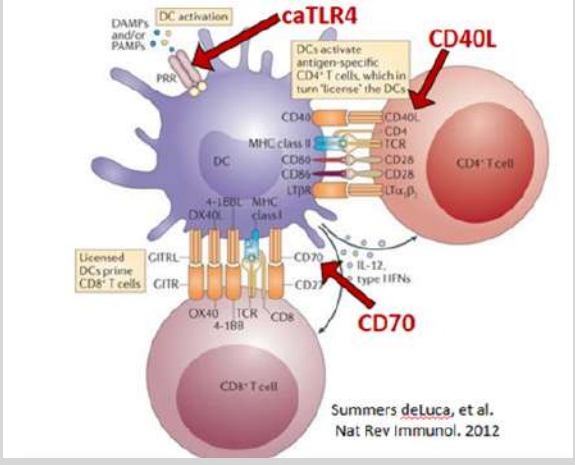
Our Technology
mRNA platform



- **Stabilized mRNA for maximum expression and antigen presentation**
- **Column purification for high purity mRNA**
- **In house GMP grade mRNA manufacturing**

Our mRNA platform has been optimized to maximize the expression of mRNA in antigen presenting cells. Antigen encoding mRNAs are endowed with a C-terminal DC-LAMP sequence to ensure optimal induction of CD4 and CD8 T cell responses. eTheRNA operates a cGMP accredited mRNA production facility in Niel to support its clinical development program.

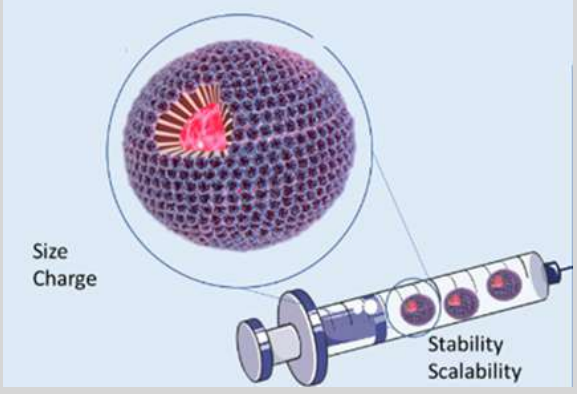
Proprietary mRNA APIs: TriMix and beyond



> Clinically validated TriMix platform
> Increased T cell responses when combined with tumor-associated antigen (melanoma), neo-antigens (RCC) or viral antigens (SARS-CoV2)
> Activation **of systemic T cell responses upon intratumoral administration**

TriMix mRNA is a mix of three mRNAs encoding caTLR4, CD40L and CD70. When delivered to dendritic cells alongside mRNA encoded antigens, TriMix mRNA dramatically enhances the generation of effector T cells. The potential of the TriMix technology to provide clinical benefit to cancer patients was first demonstrated using a personalized cell therapy approach, comprising injection of dendritic cells modified with TriMix and antigen mRNAs. eTheRNA is now turning this ex vivo approach into products that can be directly injected. TriMix mRNA is being explored as an immune enhancing agent in combination with tumor-associated antigens, cancer neo-epitopes and viral antigens. Besides TriMix mRNA, eTheRNA is exploring mRNAs encoding oncolytic and immunostimulatory proteins for in situ modulation of the tumor micro-environment.

mRNA delivery by lipid-based nanoparticles



> proprietary LNPs for the highly immunogenic delivery of mRNA
> Platform rapidly adaptable towards desired route of administration and application

To deliver our mRNA in vivo, we package the mRNA in lipid- based nanoparticles that have been optimized to target antigen presenting cells upon systemic administration. By modulating lipid chemistry, LNP size and charge, the LNPs can be tailored towards other routes of administration, such as the intratumoral route investigated within EXPERT.

Getting the body to make its own drugs (SINTEF)

In the EXPERT project we work with mRNA as therapeutic drugs. One thing that really sets mRNA drugs apart from all other medicines is that they are actually just instructions – for the body to make its own medicines. Every cell in our body uses mRNA as an intermediate to carry the information stored in our DNA over into proteins that perform and regulate the fundamental processes of life like nutrient uptake, tissue growth and removal of harmful substances. When proteins somehow fail at doing this properly, we get sick. A lot of 'traditional' small molecule drugs, like painkillers and antibiotics, work by changing the way our native proteins work. But they are rarely working only where they should; this leads to side effects that can be anything from mild to life threatening.

The beauty of mRNA drugs is that they can be extremely precise in their effect. They affect – in principle – only the exact protein they encode, and which the body needs. This could also be obtained by making permanent changes in the cells' DNA, but that process is more complex and complicated, and quickly leads to ethical challenges that are less problematic with the temporary mRNA. In a recent interview, Sven Even Borgos, who is PI of the SINTEF partner in EXPERT, talked to the popular science magazine Gemini about the EXPERT project and the promise and challenges of mRNA as therapeutics.

One application of medicinal mRNA that has recently gotten a lot of interest, is its use as vaccines against Covid-19. Many of the lead vaccine candidates, including that of Moderna due for Phase III clinical trials in July, is based on synthetic mRNA encoding virus proteins that can induce a suitable immune defence when they are produced in the body. The mRNA is delivered in lipid nanoparticles, similar to what we aim to do in EXPERT. The path to vaccine production and testing in the case of Covid-19 was extremely short; only 42 days after virus genome sequence was available, Moderna had a vaccine candidate ready for starting the first phase of clinical trials. This is extremely fast, and points to one of the most revolutionary aspects of mRNA therapeutics – the possibility to create delivery platforms that can quickly and easily be adapted to new mRNAs as the need arises. The EXPERT project aims at exactly such delivery platforms for mRNA.

Judging from experience with shorter RNA therapeutics, there is the risk that the drugs in development could be very expensive and thus only really available to certain groups of people. This has become a hot global topic also in the case of Covid-19 vaccines, as was pointed out already at an early stage (February) of the pandemic by Borgos in the Norwegian newspaper DN (reprint in English by sciencenorway.no).

The above dissemination towards the general public falls in line with important objectives of EXPERT, aiming to bring the attention of all stakeholders towards the revolution that mRNA drugs could be, maybe even surpassing that of therapeutic antibodies and immunotherapy.

Contact us

If you have any questions regarding the EXPERT project or suggestions for our newsletter, feel free to get in touch! We are looking forward to receiving your feedback.

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