



Editorial

Dear colleagues and followers of the B-SMART Newsletters,

The first 2 years of B-SMART are coming to an end and we would like to share our impressions of the last months.

The past months have been eventful for the B-SMART consortium: They successfully completed their first review meeting and prepared their first periodic report. Additionally, partners published first articles within the scope of B-SMART.

But the last weeks have been exciting for nanomedicine in general: Alnylam's ONPATTRO™ (patisiran) has first been approved by the U.S. Food and Drug Administration followed closely by the European Commission making in the first-ever RNA interference (RNAi) therapeutic to be approved for both the USA and the EU. This breakthrough is groundbreaking for the nanomedicine community as a whole: The approval of the first RNAi drug will pave the way for the next generation of RNA-based therapies, which aspire to reach the same level. Among them is the delivery system developed in B-SMART, but also the other initiatives funded by the European Commission under the same call as B-SMART. Read this newsletter to find out more about these "sister projects" of B-SMART.

The third edition of our Newsletter also includes news from our team as well as an

interview with members of the coordinating institution Universitair Medisch Centrum Utrecht. It also has received a new layout, which we hope you will enjoy.

Please do not hesitate to also share this newsletter with colleagues and friends who might be interested in this project.

Any feedback and suggestions to make this B-SMART newsletter a unique tool to present our activities are very welcome. We look forward to receiving your feedback.

Season's greetings and enjoy reading!

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www.b-smart-project.eu

or on twitter

[@BSMART_H2020](https://twitter.com/BSMART_H2020)

B-SMART Portraits

In each newsletter, we will portray individual B-SMART partners: the principal investigator and PhD students and Postdocs from their team. In this first issue, we are happy to introduce the team of the B-SMART coordinator and their views on the project.

Prof. Dr Raymond Schiffelers

Why do we need B-SMART?

Neurodegenerative diseases, such as Alzheimer's, affect over 7 million people in Europe – a figure which is expected to double every 20 years as the population ages. This poses a significant healthcare burden to European society. Despite this fact, few treatments for this group of diseases are available so far. Existing drugs only suppress symptoms or delay further deterioration but do not address the cause of the disease. For Alzheimer's disease, no drug has been approved in the past five years. Getting a drug into the brain in the first place, is a major challenge.

Nanomedicines can make a difference, providing new avenues for drugs to enter the brain. With B-SMART we have set out to provide an RNA-based therapy perspective for neurodegenerative diseases targeting the

direct cause of the disease instead of its symptoms. Transferring RNA therapeutics to the brain crossing the blood-cerebrospinal fluid barrier is a unique research endeavor. Finding a novel gateway to transport RNA to the brain will enable the development of causal therapies not only for Alzheimer's, but for other diseases as well.

What are the main outcomes expected from the consortium?

The consortium will work on specific nanocarriers protecting the RNA against enzymatic degradation while delivering it to the human brain. Crossing the brain-cerebrospinal fluid barrier requires specific targeting ligands, which will be based on nanobodies that are smaller and more stable than conventional antibodies. In fact, we have already succeeded in developing an effective first generation nanoparticle with customisable characteristics which is now being tested in a preclinical trial. The nanoparticle development marks a crucial step on the way towards the overall research objective where we aim to have a modular delivery system that is safe and efficacious and can be produced in an operator-independent and scalable way using microfluidics.

Raymond Schiffelers

Short CV

Raymond Schiffelers is a full professor of nanomedicine at the University Medical Center Utrecht, The Netherlands. He obtained his PhD degree from Erasmus University Medical Center Rotterdam, The Netherlands. His thesis focused on liposomal targeting of antimicrobial agents. He obtained a Vidi grant from NWO, to develop his own research line. In 2009 he received the Galenus Research Award for his drug delivery work and in 2010 was awarded an ERC Starting Grant (consolidator phase) to investigate extracellular vesicles for drug delivery. In 2011, he moved to University Medical Center Utrecht where he complemented his research lines on drug targeting with investigations on nanoparticles in diagnostic applications.



Dr Pieter Vader (PostDoc), Dan Murphy (PhD student) and Martijn Evers (PhD student)

What is your expertise and role in the consortium?

P. V.: I have a background in nanomedicine, focusing on both synthetic and biological vehicles for therapeutic RNA delivery. My main roles in the consortium are to provide daily supervision to two PhD students (Dan and Martijn) working in this project in Utrecht, and to coordinate collaborative efforts between the UMCU and other project partners.

D. M.: My role is to study the ways in which extracellular vesicles deliver their RNA cargo and to eventually compare the efficiency of

this delivery to LNPs. I am experienced with the production, isolation and characterisation of extracellular vesicles which is very helpful when studying extracellular vesicle-mediated RNA delivery.

M. E.: For the B-SMART consortium, my main role and expertise is the production (at a laboratory scale) and *in vitro* functional testing of lipid nanoparticles for the delivery of nucleic acids. In addition, I am also involved in the *in vitro* evaluation of other drug delivery vehicles from B-SMART consortium partners.

Pieter Vader

Short CV

Pieter Vader obtained his PhD degree from the University of Utrecht, The Netherlands. His doctoral research focused on the development of novel carrier systems for siRNA delivery to tumor vasculature. In 2012, he was awarded a Rubicon fellowship from the Netherlands Organization for Scientific Research (NWO) to study the use of extracellular vesicles for small RNA delivery to tumors at the University of Oxford, UK. In 2014, he moved back to Utrecht and was awarded a Veni fellowship from NWO to study the mechanisms involved in extracellular vesicle uptake and processing by target cells. Currently, his main research interests include the use of extracellular vesicles for drug delivery and regenerative medicine.



What aspects do you enjoy most working with this consortium?

P. V.: For me working within this consortium is a great opportunity to meet new people from different scientific backgrounds. This offers new possibilities for collaboration and ideas to approach scientific challenges from different angles.

D. M.: I enjoy the fact that my research as part of this consortium is directed towards the goal of improving the delivery of therapeutic RNA. I enjoy the fact that as well as contributing to

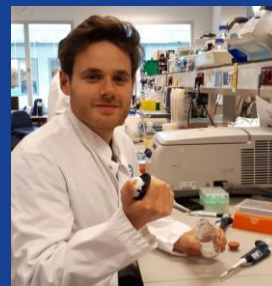
an improved understanding of extracellular vesicle biology, my work also aims to contribute to developing better methods of therapeutic RNA delivery.

M. E.: One of the aspects of the B-SMART project I like is that the consortium has set a clear goal of developing a new nucleic acid based therapy for Alzheimer's disease and that the right members are found to support this goal. Working together with these partners, which all have their own expertise, results in a working environment where we learn from each other and take the project to a next level.

Dan Murphy

Short CV

Dan Murphy graduated with a bachelor's degree in Biomedical Science from the University of Warwick in 2013. He then undertook a Master's programme in Drug Innovation at Utrecht University during which he became interested in extracellular vesicles. His research into extracellular vesicle mediated signaling began during internships at the Faculty of Veterinary medicine in Utrecht and at Massachusetts General Hospital in Boston. In 2017 he started work on his PhD, which focuses on extracellular vesicle-mediated RNA delivery, as part of the B-SMART consortium.



What impact do you expect will working in this project have on your professional life?

P. V.: The B-SMART project will provide a network of nanomedicine researchers with different expertise, which will provide opportunities for strengthening the interdisciplinary character of my work.

D. M.: I am very grateful to be working in such a consortium with people with a diverse range of professional backgrounds and skills. I am at an early stage of my career and the chance to

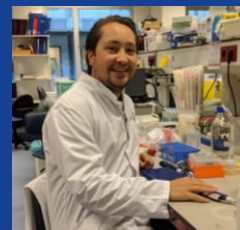
mix with such a diverse network will provide me with many ideas about what I could do after my PhD.

M. E.: Participating in this collaboration is a nice start of my professional life. Working together with scientists from different disciplines provides me with a sound basis for the future!

Martijn Evers

Short CV

Martijn Evers received his B.Sc. in pharmacy and his M.Sc. in pharmaceutical sciences both from the University of Utrecht. In February 2017, he joined the group of Prof. Raymond M. Schiffelers at the University Medical Centre Utrecht as a graduate student working on the delivery of nucleic acids. His research interests include the development of both lipid nanoparticles and extracellular-vesicle-inspired drug-delivery systems for nucleic acid delivery.



B-SMART News Corner

Important steps in the research of RNAi therapeutics

In May 2018, Alnylam Pharmaceuticals, the leading RNAi therapeutics company, announced that they have achieved delivery of novel small interfering RNA (siRNA) conjugates to the central nervous system

(CNS) and are planning to advance a pipeline of investigational RNAi therapeutics into clinical development. The conjugates achieved robust, durable, and broadly distributed silencing of CNS gene transcripts following a single intrathecal injection. Alnylam plans to complete selection of its first CNS-targeted development candidate in 2018, and then expects to file its first investigational new drug (IND) or IND equivalent in late 2019/early

2020, with the potential for one or more INDs per year thereafter.

Only a couple of weeks later, Alnylam also announced that they have received approval from the U.S. Food and Drug Administration and the European Commission for their patisiran for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis making ONPATTRO™ the first RNAi drug to receive this approval.

This progress confirms that the B-SMART consortium is on the right track with the development of effective nanoparticles that transport RNA therapeutics to the brain. The B-SMART strategy is designed to avoid the injection into the brain that was used by Alnylam for their proof of concept studies. It would avoid the obvious risks for side effects and a highly invasive procedure. The first B-SMART prototype is currently being tested in a preclinical study.

More on Alnylam's news can be found [here](#) and [here](#).

Honours for female B-SMART scientists

The Controlled Release Society (CRS) has announced the winners of their 2018 Awards. CRS was founded in 1978 as a non-profit organization devoted to the science and technology of controlled release.

The society grants their Founder Award since 1982, but 2018 marks the first year a woman is recognised for her outstanding contributions in the science and technology of controlled release: B-SMART partner Prof. María José Alonso ([Universidade de Santiago de Compostela \(USC\)](#)) is selected to receive this most prestigious award of CRS. She will also be inducted into the CRS College of Fellows, which recognizes CRS members who have made outstanding contributions to the

field of delivery science and technology over a minimum of 10 years.

B-SMART partner Ruth B. Schmid ([SINTEF AS](#)) receives the CRS Distinguished Service Award. Established in 1994, this award is presented to a CRS member who has exhibited exceptional commitment and service to the Society. The award is not automatically given each year, only in the years when there is an exceptional member who fits the criteria.

Awards were presented during the [2018 CRS Annual Meeting](#) award ceremony in New York City, USA, on July 22-24 2018.

Additional recognition for B-SMART member

The government of Galicia has awarded Prof. María José Alonso ([Universidade de Santiago de Compostela \(USC\)](#)) the Castela Medal 2018. With this distinction the government of the Spanish region highlights her successful professional career and her valuable contribution to research on application of nano-technology to pharmacy. María José Alonso will receive this medal in a ceremony presided by the president of Galicia on June 28.

Successful First Evaluation of B-SMART: 3rd Progress and 1st Review Meeting in Aprilia, Italy

From June 18-20, 2018, the B-SMART consortium came together for their longest meeting so far: Three days were scheduled to discuss the next steps ahead and the progress of the project, including the evaluation by the EC officer on the occasion of the 1st Review Meeting, a workshop dedicated to B-SMART dissemination activities at the University Hospital Tor Vergata in Rome as well as the liaison with the EU-funded project Starbios2. To counterbalance this heavy workload, it was

decided to hold the meeting in beautiful Italy on the premises of partner [Istituto Biochimico Italiano \(IBI\)](#) with most consortium partners staying in hotels close to the seaside. It was a special honour to be at IBI for this meeting, since 2018 marks the year of their centenary.

The first meeting day was reserved for internal discussions between the consortium members who were exchanging the latest news and the achievements since the last progress meeting. Coordinator Raymond Schiffelers was pleased with the overall advancement of the project. The consortium once again welcomed Dr Dorota Roberts for her second participation as external monitoring expert appointed by the European Commission as well as Richard Broadhead, who had also joined the previous meeting.

On the second day, the EC representative Mathias Lucas joined the B-SMART consortium for their 1st Review Meeting. The partners presented their progress over the first 18 project months. The officer was impressed with the presented achievements and the dissemination activities the consortium had already initiated. He stressed their importance

and encouraged the consortium to continue to pursue them and deepen their networking activities with other projects and initiatives.

On the last meeting day, the consortium took a tour around the IBI facilities. The highlight, however, was the workshop at the University Hospital Tor Vergata in Rome where the coordinator Raymond Schiffelers and Hannah Walgrave presented the B-SMART objectives and approach to nanomedicine in front of over 50 participants. Prof. Vittorio Colizzi (Tor Vergata) presented the EU-funded [Starbios2](#) project and Prof. Nicola Mercuri (Tor Vergata) gave a well-received presentation entitled “Alzheimer’s Disease: from bench to bed”.

The wonderful organisation and generous hospitality of partner IBI became particularly visible in the kind invitation of IBI’s CEO Dr Camilla Borghese Khevenhuller to her home: Dinner on her terrace overlooking the Mediterranean Sea and the surrounding gardens provided the perfect backdrop for a relaxing and balmy summer night. The whole consortium left the meeting excited and ready for the upcoming tasks.



The B-SMART Consortium at the 3rd Progress Meeting in Aprilia, Italy

The next Progress Meeting will take place in Utrecht, the Netherlands, on 6-7 February 2019.



Dr Camilla Borghese Khevenhuller (IBI) and B-SMART coordinator Prof. Raymond Schiffelers (UMCU) at the workshop at Tor Vergata

B-SMART – Other related Projects

B-SMART is happy to use this space to present two related projects that were funded by the European Commission under the same call as B-SMART: CUPIDO and NEW DEAL.



While B-SMART aims at the application of nanotechnologies to neurodegenerative diseases, CUPIDO addresses the cardiovascular field. CUPIDO aims to hit the core of the cardiovascular disease by developing inhalable nanoparticles that can deliver a therapy directly to the diseased heart. The consortium is composed of 12 partners: research groups, SMEs, pharma companies and industries alike. You can learn more about CUPIDO [here](#) and follow them on Twitter [@cupido_project](#).



NEW DEAL also tries to find new and innovative ways to transport medication directly to the affected organ. NEW DEAL strives to use nanotherapy to treat inflammatory bowel diseases. This innovative medicine will deliver a targeted and local siRNA therapy directly to the inflamed gut, through the gastrointestinal tract. The consortium consists of twelve partners in 5 countries. You can learn more about NEW DEAL [here](#) and follow them on Twitter [@NewDealEU](#).

B-SMART Publications

We are happy to present you to the latest B-SMART publications

Samaridou E., Alonso M. J., **Nose-to-brain peptide delivery – the potential of nanotechnology**, Bioorganic & Medicinal Chemistry.

doi: 10.1016/j.bmc.2017.11.001.

O'Loughlin A. J., Mäger I., de Jong O. G., Varela M. A., Schiffelers R. M., El Andaloussi S., Wood M. J. A., Vader P., **Functional Delivery of Lipid-Conjugated siRNA by Extracellular Vesicles**, Molecular Therapy.

doi: 10.1016/j.ymthe.2017.03.021.

Evers M. J. W., Kulkarni J. A., van der Meel R., Cullis P. R., Vader P., Schiffelers R. M., **State-of-the-Art Design and Rapid-Mixing Production Techniques of Lipid Nanoparticles for Nucleic Acid Delivery**, Small Methods.

doi: 10.1002/smtd.201700375.

Willms E., Cabañas C., Mäger I., Wood M. J. A., Vader P., **Extracellular Vesicle Heterogeneity: Subpopulations, Isolation Techniques, and Diverse Functions in Cancer Progression**, Front Immunol.
doi: 10.3389/fimmu.2018.00738.

Upcoming Events

[MedTech Forum 2019](#), Paris, France, 14-16 May 2019.

[Nanomed Europe 2019 – NME19](#), Braga, Portugal, 12-14 June 2019.

Facts

The B-SMART consortium unites internationally renowned experts in the field of innovative nanotechnological RNA delivery systems in Europe. The overall vision of B-SMART is to provide an RNA-based therapy perspective for neuro-degenerative diseases such as Alzheimer's. It was launched in January 2017 receiving support from the European Union's Horizon 2020 research and innovation programme. The participating experts are combining many years of experience in research of biological and synthetic nanoparticles for diagnosis and therapy such as nanogels, nanocapsules, extracellular vesicles and nanobodies.

Acronym:	B-SMART
Full title:	Brain-Specific, Modular and Active RNA Therapeutics
Call Topic:	H2020–NMBP-10-2016– Nanoformulation of biologicals
Contract N°:	721058
Duration:	60 months (01/01/2017 -31/12/2021)
Funding:	5,998,303.75 €
Partners:	9
Website:	www.b-smart-project.eu

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