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Revolutionising Human Medicine:

The Future of RNA Therapeutics

Opportunities & Priorities for Europe

B-SMART

EXPERT

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Context

Over the past few years, messenger RNA – mRNA – made headlines on a global scale as pharmaceutical companies used it to create COVID-19 vaccines at breakneck speed. Through this, RNA therapeutics have shown their truly revolutionary potential to radically improve human medicine. However, the scope and range of possibilities are much wider.

The consortia of the two EU Horizon2020 projects B-SMART and EXPERT have worked on the two major types of RNA-based nanomedicines for several years. In the future, their developments could serve as a starting point to help combat pervasive illnesses, such as neurodegenerative and cardiovascular diseases and non-communicable diseases such as cancer. While COVID-19 unlocked the power of RNA vaccines, much more research and funding are needed to tap into the huge potential and reap the benefits of RNA-based therapeutics.

In this policy brief, the B-SMART and EXPERT consortia will describe the opportunities, list the challenges, and recommend priorities to ensure that Europe remains at the forefront of the field to the benefit of people and patients all over the world.

1. What Is RNA and How Can It Be Used as Medicine?

The recipe of all life exists as a genetic code in the DNA of cells. Messenger RiboNucleic Acids (RNA) are short-lived conveyors transforming information from the DNA into proteins. This process is fine-tuned by small RNA species that can stimulate or inhibit protein production from mRNA. Together, mRNA and small RNAs offer the opportunity to start and stop protein production at will[1].

Almost all the actual functions in cells are performed by proteins. In fact, faulty protein production is found at the centre of most diseases. This makes RNA-based therapy very powerful. Without permanently altering the DNA, we can still precisely control protein production. The main challenge of RNA therapy is delivery into the target cells of the body. RNA molecules are naturally susceptible to degradation, may trigger the body's immune response and cannot spontaneously cross the cell membrane. For this, a coating needs to be developed. On the one hand, it needs to be large enough to accommodate, encapsulate and protect the RNAs, while on the other hand it still has to be small enough to be taken up by cells. This is the field of nanomedicine, the development of appropriate nanosized carriers to bring therapeutics to their destination.

The key of RNA nanomedicines lies in the code: simply changing the sequence in a string of four genetic 'letters' will make fundamentally different medicines. Interestingly, the remainder of these nanomedicines, and the way to make them, can be kept unchanged as the fundamental characteristics of RNA remain the same. This way, safe and efficacious medicines and vaccines can be developed and produced faster, cheaper, and more precise than ever before.

This brief will focus on what are currently the two biggest modalities of RNA medicine; mRNA and small interfering RNAs (siRNA), which have opposite (and thus complementary) functions in cells.

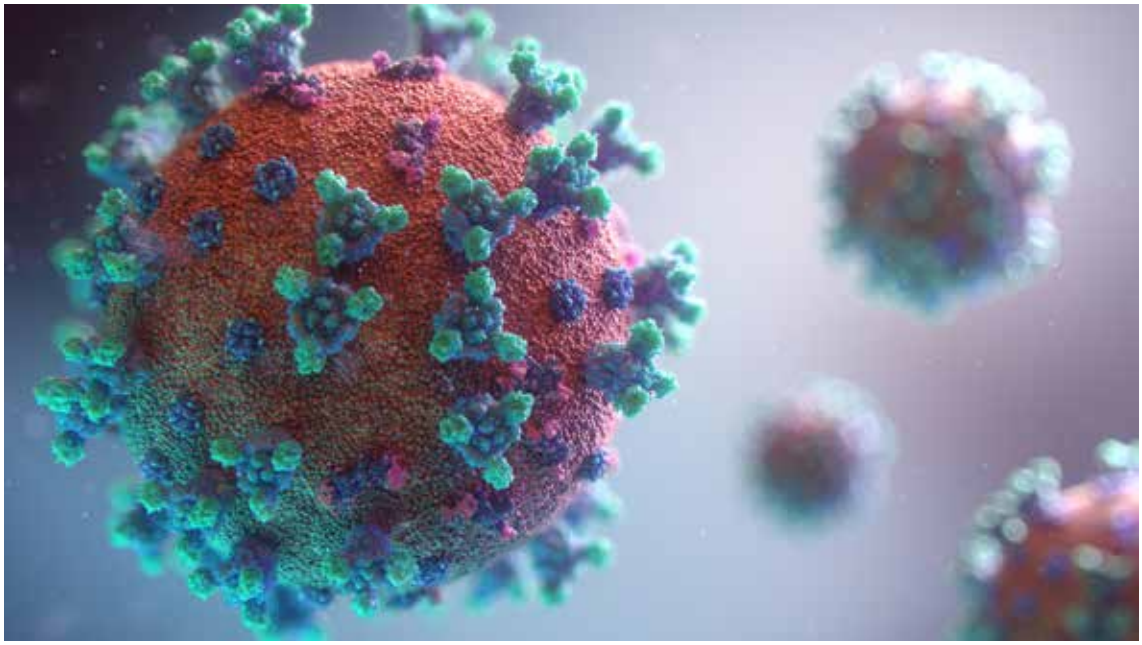
1 Zhu, Y., Zhu, L., Wang, X. et al. RNA-based therapeutics: an overview and prospectus. Cell Death Dis 13, 644 (2022).

mRNA

Messenger ribonucleic acids (mRNA) constitute the protein-encoding sequences in all cells. mRNA connects two cellular processes, namely transcription (i.e., copying a segment of DNA into RNA) and translation (i.e., synthesis of proteins). Interestingly, administering chemically modified mRNA to cells results in the corresponding protein being translated. This approach offers huge possibilities to treat a broad range of diseases, such as i) replacing a protein with errors in it; ii) providing a protein that is almost or completely missing in the body; iii) making proteins in tissues where it is missing; iv) making proteins that can train the immune system against infections or cancers (vaccines); v) making protein-based medicines that would be too unstable when produced outside the body. In summary, mRNA can be used to add a desired function to a cell. mRNA are very fragile molecules that are hard to deliver intact to their site of action inside cells.

siRNA

Only a very small part of the human genetic information encodes proteins, while the far greater part is non-coding. An important representative of such non-coding RNAs are small interfering RNAs (siRNAs) and microRNAs (miRNAs), which are characterised by their short length of 20-25 nucleotides. While they are much shorter than mRNA, they still pose many of the same challenges when it comes to delivery inside the body. siRNAs were the first regulatory RNAs to be discovered (preceding miRNA), and they are responsible for the now well-known phenomenon of RNA interference (RNAi). siRNA works by using the cell's own systems to selectively destroy specific mRNA produced by the cell. By doing this, the function of the corresponding protein is partially or fully removed. Blocking protein function is the mechanism of action of a lot of traditional, small-molecule medicines; the difference is that siRNA offers big improvements in precision and very few off-target effects.



2. B-SMART and EXPERT at the Forefront of Progress in RNA-based Therapeutics

Over the past few years, we have witnessed the approval and widespread use (over a billion doses) of lipid nanoparticles for the delivery of mRNA as COVID-19 vaccines. This shows that RNA-based nanomedicines have an enormous clinical impact. However, for other applications of RNA, i.e., beyond vaccination, much more research into novel nanosized delivery platforms is required.

In the finished B-SMART[2] project , we set out to provide siRNA-based therapeutics for the treatment of neurodegenerative diseases. Since RNA delivery to the central nervous system is not currently possible, we studied established (lipid nanoparticles), emerging (polymer/lipid nanostructures) and exploratory (extracellular vesicles) nanocarriers for this purpose. An important challenge in B-SMART was to design these nanocarriers in a way that they can transport RNA across important barriers, i.e., the nose-to-brain barrier and blood-cerebrospinal fluid barrier. To attempt this goal, we developed nanobody-based targeting ligands that are used to decorate the nanocarriers.

In the EXPERT[3] project, we develop off-the-shelf delivery systems for mRNA-based nanomedicines to treat cancer and cardiovascular disease. Besides the established lipid nanoparticles that we aim to develop and manufacture for application in clinical studies, we also develop cell-penetrating peptides as well as extracellular vesicles (EVs) as potential next-generation mRNA delivery systems. One main aim of EXPERT is to develop clinically-ready delivery platforms, which can be applied to a wide range of mRNA medicines.

2 The B-SMART project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 721058.

3 The EXPERT project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825828.

3. From Bench Side to Clinic: Seizing Opportunities and Solving Challenges

Opportunities – A New Wave of RNA Therapeutics

The success of the mRNA-based COVID-19 vaccines was stunning – in terms of safety, efficacy, development time, scale-up capacity, and the number of doses administered. Nucleic acid therapies, like RNA medicines, allow for a level of precision and absence of side effects that is almost never attainable with conventional therapeutics. This medical (and commercial) success has directed enormous research efforts and resources towards further development of RNA-based nanomedicines.

Looking at this global success story in more detail, it becomes clear that RNA has a huge and largely untapped therapeutic potential.

- With mRNA, we can make any protein, and with siRNA, we can block any protein we want. 85 % of all proteins involved in diseases cannot be targeted by conventional therapeutics. They are known as undruggable targets[4].

- Over 3,000 (orphan) diseases are caused by a mutation in a single protein making the protein less active or overactive[5]. mRNA or siRNA offer a direct therapeutic opportunity for these diseases.

- RNA therapeutics can activate the immune system against new infectious diseases, but also against non-communicable diseases like cancer and fibrosis.

- For conventional therapeutics, the mechanism of action can be challenging to understand and requires significant time and money to learn efficacy and toxicity profiles. For RNA therapeutics the mechanism of action is always the same for each class.

- Finally, new RNA species are continuously being discovered, such as long non-coding RNAs (lncRNA) or circular RNAs (circRNAs), that possess new regulatory roles in health and disease[6]. While many are in the early days of investigation, they could have significant potential in medicine if developed further.

4 Hopkins AL, Groom CR. The druggable genome. Nat Rev Drug Discov. 2002 Sep;1(9):727-30.
5 https://www.omim.org/
6 Sasso JM, Ambrose BJB, Tenchov R, Datta RS, Basel MT, DeLong RK, Zhou QA. The Progress and Promise of RNA Medicine – An Arsenal of Targeted Treatments. J Med Chem. 2022 May 26;65(10):6975-7015

4. Challenges

Despite their many potential advantages, today's RNA-based therapeutics leave room for improvement, and distinct avenues of development need to be explored further.

Within the B-SMART consortium, where we developed RNA nanomedicines for the central nervous system, we have witnessed that for applications beyond local intramuscular vaccination or liver targeting, delivery efficacy remains insufficient, and novel approaches to overcome these barriers are still needed.

We have experienced that optimisation of RNA nanomedicines is challenging due to the many parameters that affect activity. We went through production and manufacture cycles towards industrial exploitation which proved to be demanding. In EXPERT, we have begun working on possible ways to overcome these challenges but recognise that concerted efforts are required to address these. The main challenges are outlined below:

- Effective delivery of RNA nanomedicines cannot be achieved in many tissues and cells. For RNA-based medicines to unleash their full therapeutic and diagnostic power, it is very important to be able to efficiently target new tissues like the central nervous system or the heart and specific cell types like immune cells, using new compositions, and active targeting strategies. This also means actively preventing uptake in the liver.

- Comprehensive testing of all relevant parameters and their combinations of RNA nanomedicines, like nanoparticle composition, size, charge, choice of surface functionalities, etc., is complex. Design-of-Experiments combined with Quality-by-Design approaches are needed to rationally identify exploitable lead candidates.

- RNA nanomedicines need highly specialised methods and assays to test their quality, safety, and efficacy; existing pharmaceutical industry methods used for small molecules are mostly unsuitable. Characterisation methods need to be industrially robust and accepted by regulators. Certified reference materials to qualify the testing procedures need to be developed.

- RNA nanomedicines have a short clinical track record, which means very little modelling data is available. There is a need for improved in silico, in vitro and in vivo models that accurately predict the safety and efficacy of RNA nanomedicines.

- To date, there are only a few nanocarriers for RNA medicines which are mainly based on lipids. New generations of emerging and exploratory materials should be investigated that can provide unique functionalities to RNA nanomedicines.

- Scalable and reproducible manufacturing of delicate RNA nanomedicines requires a high-tech environment. Also, as observed in the COVID-19 vaccines, storage stability is a major challenge, in particular for mRNA nanomedicines. Open-access manufacturing and new compositions or methodologies to facilitate production and improve storage at ambient temperatures are required, also to make the technology available for underdeveloped areas.

- For many orphan or individualised applications, industrial exploitation is challenging. Alternative manufacturing, regulatory and reimbursement systems that enable local, small-batch preparations for dedicated patients could democratise access to RNA technology.

- Newly discovered RNA species could be important targets for therapeutic intervention. A better understanding of their role in the cell is required which in turn requires accessible low-cost small-batch RNA synthesis.

5. Recommendations

The Future of Nanomedicines: Policy Recommendations to Address Urgent Needs

We propose the following action points to meet urgent needs and to ensure that Europe fully participates in and benefits from the ongoing revolution in RNA therapeutics:

- Dedicate attention and resources to developing delivery solutions and technologies for specific cell types and tissue targeting beyond the liver, and including biocompatible biological and synthetic materials beyond lipid nanoparticles.
  Appropriate funding instruments: EIC Pathfinder, IHI

- Develop in silico predictive models, facilitated by AI or machine learning applied to Design-of-Experiments and Quality-by-Design, to accelerate the R&D product development towards faster clinical exploration.
  Appropriate funding instruments: EIC Pathfinder and Transition

- Prioritise to develop, standardise and validate characterisation assays and reference materials for quality, safety, and efficacy of RNA therapeutics to facilitate clinical translation.
  Appropriate funding instruments: Horizon Europe (Clusters 1 and/or 4), EURAMET, OITB-type funding, ERIC

- Develop new alternative methods (NAMS) to address the need for efficacy and safety investigation on human-relevant models in line with the European Commission directives on animal reduction refinement and replacement.
  Appropriate funding instruments: Horizon Europe (Clusters 1 and/or 4), EIC Pathfinder, OITB, ERIC

- Stimulate research into novel materials that can fill the pipeline for new RNA applications
  Appropriate funding instruments: Horizon Europe (Cluster 4), EIC Pathfinder

- Support GMP plant development and sustainability for RNA therapeutics in Europe to facilitate scale-up and clinical translation.
  Appropriate funding instrument: OITB-type funding, ERIC, EIC Transition

- Investigate and generate guidelines as to how far RNA medicines can be generalised, i.e., how much can the payload nucleic acid sequence be changed before new clinical testing and/or regulatory approval is needed. This should be seen in light of the developments in personalised medicine, local manufacturing, reimbursement frameworks, and needs to heavily involve regulatory considerations.
  Appropriate funding instruments: IHI, Horizon Europe (Clusters 1 and/or 4)

- Support basic research into novel therapeutic RNA modalities and mechanisms as well as fundamental knowledge on RNA chemistry and biology. Investigate ground-breaking developments in custom RNA synthesis that can be deployed in labs, to speed up and reduce the cost of developing new RNA therapies.
  Appropriate funding instruments: ERC, EIC Pathfinder Challenge and Open

We firmly believe that RNA therapies have a truly transformative potential to improve healthcare in Europe and globally. We therefore strongly encourage the authorities and agencies of the European Commission and the Member States to seize this opportunity to ensure that Europe takes a leading role in this field. Integrating RNA medicine with other advanced and highly successful therapies such as antibody drugs or cell- and immunotherapies carry big synergistic potential and should be encouraged and pursued on both scientific and political levels.

Ultimately, the work on RNA may pave the way for a safe and efficient cure of genetic diseases via permanent gene editing, alleviating the need for repeated treatment and reducing the burden on patients, their families as well as on the European healthcare systems. For this vision to be realised, all of the above points need to be addressed.

6. Partners

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Universidade de Santiago de Compostela, Spain
20 Med Therapeutics BV, The Netherlands
Vlaams Instituut voor Biotechnologie, Belgium
University of Oxford, United Kingdom
Istituto Biochimico Italiano, Italy
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