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The long-awaited solution for personalized medicine

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A Viewpoint on the Frontiers in Science Lead Article

NANOSPRESSO: toward personalized, locally produced nucleic acid nanomedicines

Key points

- The NANOSPRESSO project was created to promote the decentralized and personalized production of formulated nucleic acid-based therapeutics (NBTs) within hospital pharmacies (magistral production).
- The proposed magistral production methods include the encapsulation of NBTs in lipid nanoparticles using microfluidics technology.
- This project could help overcome obstacles to personalized medicine for rare diseases, such as the absence of suitable regulatory and inspection frameworks, patent laws, infrastructure availability, and long-term funding.

Introduction: unmet medical needs

The NANOSPRESSO project, described by Estapé Senti et al. in their lead article (1), aims to address the immense unmet medical needs in the rare disease and rare cancers communities, which are currently underserved by the pharmaceutical industry and healthcare providers. The current situation in rare diseases, with small patient numbers (sometimes with only a single case reported worldwide) and substantial drug development costs, makes it difficult for pharmaceutical companies to recoup their investments in this field.

These commercial disincentives, combined with an uncharted regulatory landscape, impede the translation to the clinic of the scientific advances made in recent years using nucleic acid-based therapeutics (NBTs) that could have already significantly improved the lives of many patients with rare diseases and some rare cancers (2, 3).

Although the exact proportion of genetic diseases treatable by formulated NBTs potentially produced by NANOSPRESSO is hard to calculate, a rough estimate based on the known types of pathogenic mutations and the proportions of genes amenable to

regulation by multiple endogenous mechanisms that can be engaged by NBTs shows that it could be significant. However, despite the plethora of known NBT-based approaches that can be used in the treatment of genetic diseases caused by point mutations or insertions/deletions, substantial practical challenges in this field could limit their impact (see Supplementary Material – Presentation 1).

Significant challenges

Although the first successful example of an "n=1" NBT (i.e., an NBT produced for a single individual) was published in 2019 (4), it has not been widely replicated, with only 26 other cases over 6 years (2). Currently available NBT treatments mostly focus on more common conditions (e.g., nusinersen for spinal muscular atrophy; SMA). The interdisciplinary team needed for the development of such personalized medicines would require members with expertise in diagnosing the diseases, sequencing the mutations, designing and manufacturing NBTs to pharmaceutical standards, resolving patent issues, ensuring regulatory compliance, and administering the treatment—with all of this provided in time to stop the progression of the disease. Assembling such a team for each individual case in the limited time available is practically impossible under current conditions. This process, however, could be facilitated if there were institutions to provide the necessary infrastructure, such as organizations capable of all the above functions.

Establishing and financing such institutions represents probably the biggest challenge in the translation of achievements in personalized medicine to the clinic. Other problems include the need for regulatory bodies to develop the appropriate framework for personalized drugs and maintain specialized personnel for inspections, as well as multiple other legal and societal implications, including treatment cost, patent issues, and ethical considerations.

NANOSPRESSO solutions and their feasibility

Estapé Senti et al. propose the NANOSPRESSO project as a solution to the challenges posed by the translation of personalized NBTs to the clinic (1). NANOSPRESSO promotes the decentralized and personalized production of formulated NBTs, construed as drugs for magistral preparation in hospital pharmacies. Magistral preparation is used for individual patients when no approved alternatives exist, which is the case in many rare diseases.

The authors outline a production protocol that includes encapsulation of NBTs in lipid nanoparticles (LNPs) using microfluidics technology on location in hospital pharmacies. The NBTs will have to be custom designed for individual patients or small groups of patients. This could represent the most labor-intensive, unpredictable, and expensive step in the production process. The designed NBTs will then be manufactured at pharmaceutical-grade nucleic acid synthesis facilities (such as CelluTx LLC, siTOOLs Biotech, or Anjarium Biosciences AG). The authors envision that the final step of NBT drug manufacture—its encapsulation in LNPs (potentially designed and manufactured by companies such as Lipoid or NanoVation Therapeutics)—will be accomplished at hospital pharmacies using a specialized piece of microfluidics equipment (potentially from Solstice Pharmaceuticals, University of Twente Mesa+ Institute, or Hogeschool Saxion). The necessary quality assessment testing of the final drug product could be supported by the Karolinska Institute, SINTEF (a research organization based in Trondheim, Norway), and University Medical Center (UMC) Utrecht, among others. The hospitals involved in delivering the resulting drug to patients could include the Val d'Hebron Hospital in Spain, the UMC Leids, UMC Utrecht, and the Princess Máxima Center in the Netherlands, the National University of Singapore, and other institutions with similar capacities. Currently, NBT and LNP synthesis and encapsulation technologies are well developed and have relatively low costs given the smaller amounts needed for drug quality control and single-patient treatment, which makes the proposed protocol feasible. As an additional benefit of the magistral preparation, encapsulating NBTs in LNPs locally in a hospital pharmacy may solve some of the technical problems of using NBTs, including the thermal lability of RNA drugs and the stability of nanoparticles (1).

One of the major obstacles in the development of personalized NBTs is the absence of an appropriate regulatory framework, addressed by NANOSPRESSO by involving regulators and public health researchers. Furthermore, magistral preparation itself could help solve some of the problems because it can be regulated at the individual member state level (1). Magistral preparation of personalized NBTs also falls under both the European Union's exemption for advanced therapy medicinal products (ATMPs) and the hospital exemption (1). In the United States, similar regulations concerning magistral preparation are enacted in the Section 503A of the Food, Drug, and Cosmetic Act (FDCA), which exempts pharmacy compounding performed for a specific patient from requirements such as compliance with current good manufacturing practices (5), appropriate labeling, and Food and Drug Administration (FDA) approval. However, due to the complex and innovative nature of NBTs, the regulatory bodies may need to develop the appropriate framework for personalized NBTs and maintain purpose-trained personnel for routine inspections of facilities in hospital pharmacies. Importantly, Estapé Senti et al. stress their ongoing communication with European and member state regulatory authorities (1).

The NANOSPRESSO project considers the implications of patent laws, ethical considerations around gene editing, and the implications for social equity and human diversity, all of which are essential for the wide adoption of personalized NBTs. Notably, the NANOSPRESSO project also plans to develop a unified platform for technology and data sharing with blockchain security and consistent data formats across the network. Such a platform could ensure patient privacy and intellectual property protection and provide an easy interface with artificial intelligence (AI) tools.

The current NANOSPRESSO-NL project is supported by the Netherlands Science Agenda grant from the Netherlands Organization for Scientific Research. However, it is only a 6-year

project, which does not allow sufficient time given the scope of the undertaking. Other financing sources may be available. Notably, the potential market for personalized drug technology is substantial, as more than 300 million people worldwide suffer from genetic disorders (6). Additionally, new genetic disease- and cancer-causing mutations are discovered every year. From the reimbursement point of view, treatment with NBTs could significantly decrease lifelong spending compared to the currently available treatments. For example, average inpatient admission costs over a 12-month period post treatment with nusinersen for SMA were reduced by 63% in pediatric patients and by 79% in adult patients as compared with the 12 months pre-nusinersen treatment with prior standard care (7). Treatment with the single-injection gene therapy drug for SMA, onasemnogene abeparvovec, further reduced the annual numbers of inpatient admissions (by 66%) and emergency department visits (by 50%) compared with nusinersen treatment (8). These numbers are especially significant given that direct non-healthcare informal costs for families of SMA patients can reach 63% of the total annual disease cost (9, 10). Experience gained in the NANOSPRESSO project may help obtain a more realistic estimate of the benefits afforded by personalized drugs.

Furthermore, data and expertise gained in the treatment of rare diseases could be instrumental in developing drugs for common diseases. The "intervention-outcome" type datasets in uniform format generated by NANOSPRESSO could be essential for training AI tools to discover novel gene-disease associations, determine structure-activity relationships, assess the delivery efficiency of the LNP formulations, and evaluate the toxicity of NBTs, among other tasks. Reports on drug preparation procedures and treatment outcomes provided by clinics utilizing the NANOSPRESSO approach are likely to be an important asset generated by the program. Licensing access to data and reports generated in the NANOSPRESSO project to pharmaceutical and biotechnology companies could provide revenue to extend the project beyond the current 6-year funding period. However, fundraising (and associated expenses) may be needed to engage these and other financing sources, including rare disease foundations, charitable organizations, and government programs.

At present, NBT treatments might not lead to a complete cure, due to issues such as late diagnoses, incomplete knowledge of disease biology, poor delivery to target tissues, suboptimal dosing regimens, toxicity, and immunogenicity. However, these issues can be resolved with more experience using NBTs in the clinic. Importantly, even in their current form, NBTs can bring significant improvements to patients' and caregivers' quality of life and offer financial relief (7, 8).

Conclusions

As significant as the challenges with magistral production of personalized formulated NBTs are, they are surmountable given the measures proposed by NANOSPRESSO. Furthermore, as Estapé Senti et al. point out, there are successful precedents of personalized technologies being used at the point of care, e.g., the Prodigy system (Miltenyi Biotec, Inc), which automated the entire process of chimeric antigen receptor (CAR)-T cell manufacturing from cell activation to reinfusion. The NANOSPRESSO project could also tap into a proactive network of rare disease foundations. Notably, NANOSPRESSO could enhance community participation by improving their website and posting frequent updates on the project plans, progress, crowdsourcing efforts, and citizen scientists' initiatives, making the website the project's major communication interface with patients and caregivers. It is the great hope of the rare disease community that NANOSPRESSO's plans will not perish due to bureaucratic hurdles and internal disagreements but will instead be successfully carried out.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsci.2025.1629021/full#supplementary-material

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