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A novel application of antisense oligonucleotide (ASO) technology, developed to treat a single patient, adds to the growing number of 'personalized' therapies for rare diseases; but pathways to implementation and access are urgently needed.

The term 'personalized medicine' has become a buzzword in healthcare, open to various interpretations and often used to describe the tailoring of interventions to subsets of patients rather than to single individuals. In this issue of *Nature Medicine*, however, Ziegler et al.[1] describe a truly personalized treatment developed for a girl with an ultra-rare neurological disorder, reporting safety and signals of efficacy. This is the first report on a treatment developed by n-Lorem, a foundation aiming to develop individualized antisense oligonucleotide (ASO) treatments for patients with ultra-rare mutations with unmet need[2], and it represents a new application of ASO technology.

ASOs are short, synthetic, chemically modified RNAs that can hybridize to gene transcripts in a sequence-specific manner. Notably, this is not the first report of an individualized ASO, which have previously been developed for the treatment of individual patients with *MFSD8*-related Batten's disease and ataxia telangiectasia[3,4]. However, in these earlier reports, ASOs were used to correct RNA mis-splicing and restore the production of missing proteins. Ziegler et al.[1], however, report on the clinical use of an individualized ASO to activate RNase H-mediated degradation of a target transcript, thus reducing the production of a toxic protein.

Specifically, the reported case involves a 9-year-old girl with *KIF1A*-associated neurological disorder (KAND), an ultra-rare disease affecting fewer than 1,000 individuals worldwide. KAND is associated with optic atrophy, epilepsy, cognitive impairment, spasticity and peripheral neuropathy. In this case, KAND was caused by a missense variant in the gene *KIF1A* that acts in a dominant negative way on protein function. As biallelic loss of function of the KIF1A protein is associated with a severe form of hereditary spastic paraplegia (HSP; MIM 620607), an allele-specific ASO – targeting the pathogenic but not the wild-type KIF1A transcript – was developed (Fig. 1). Notably, this is the first time an allele-specific ASO has been successfully used in a clinical setting.

As such, the report adds to the toolbox of ASO technologies, and the authors mention another 12 individualized ASOs for which n-Lorem has submitted Investigational New Drug (IND) applications to the US Food and Drug Administration (FDA), to treat additional patients with ultra-rare mutations in other genes[1]. Thus, the scale of individualized ASO development is growing; and although each ASO is applicable to only a single or a few cases, when combined, this will become a sizable group. Furthermore, the individualized treatment development does not limit itself to ASOs, as evidenced by a recent report of an individualized gene therapy treatment[5].

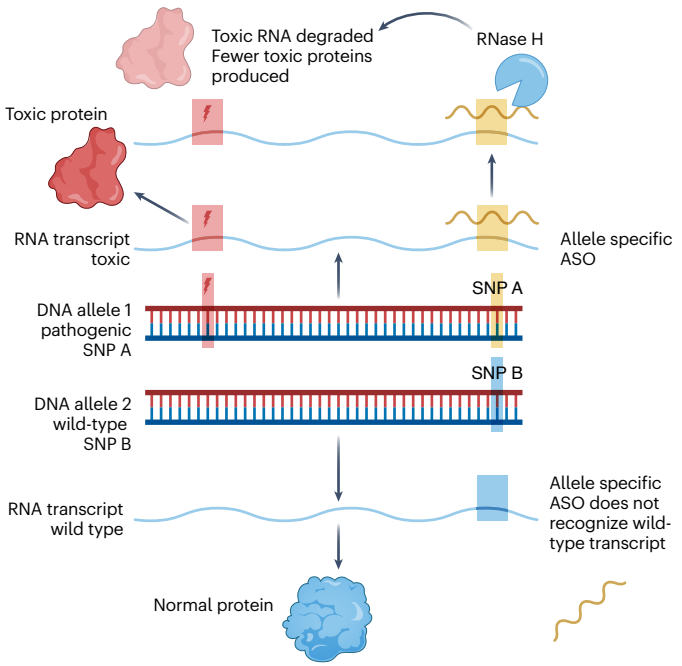

Fig. 1 | Mechanism of allele-specific RNase H ASOs. KAND is a dominant-negative disease caused by a missense variation (red shading) on one allele of the *KIF1A* gene. This allele will produce an RNA transcript that is translated into a protein with a toxic gain of function, whereas the wild-type allele produces RNA transcripts that are translated into normal protein. As loss of normal protein is not tolerated and is associated with human disease (severe hereditary spastic paraplegia), only the toxic transcript should be degraded by the ASOs, leaving the wild-type protein untouched. This is achieved using an allele-specific ASO that targets a single-nucleotide polymorphism (SNP) that differs between the wild-type and variant alleles of the treated patient (yellow and blue shading). The ASO will target only the SNP present in the mutated allele, causing it to be degraded by RNase H and thus reducing the abundance of the toxic KIF1A protein.

Individualized treatments are developed building on the premise of treatments approved for larger groups of individuals – using the data from a larger group with confirmed clinical benefit to support the approach per se and to guide dose selection for the individualized treatment. Furthermore, the pathological mechanism for each individual genetic variant needs to be elucidated to assess whether an individualized approach can be expected to benefit the patient and to estimate expected treatment effects. For the patient with KAND, Ziegler et al.[1] outline what the ASO treatment achieved: reductions in spells of behavioral arrest, qualitative improvements in gait, reduction of falls,

improvement of speech and attention. Assessment of treatment effects relied mostly on observer-reported measures, and quantitative scales largely failed to capture clear treatment benefits over the (too) short time span of 9 months. This emphasizes the need for quantitative and objective outcome measures to demonstrate treatment response with high sensitivity even for individualized treatments[6]. Notably, not all disease manifestations responded to treatment; cognition remained stable, and bothersome symptoms (such as pain, gastroesophageal reflux and behavioral problems) persisted. Haploinsufficiency for *KIF1A* leads to adult-onset progressive HSP, whereas biallelic loss of function causes severe, complicated HSP. Therefore, the allele-specific approach described here will, at best, convert KAND to a milder HSP phenotype — while any 'leaky' action of the ASO on the wild-type allele carries considerable risk of additional harm. This risk is only acceptable in the background of the even more severe and debilitating KAND that the patient would experience in the absence of treatment.

A challenge when treating a single individual is that the only available comparator is the disease state before treatment initiation in the same person[7]. Single baseline measurements, which are common in clinical trials, are suboptimal in this setting; instead, establishing a detailed disease trajectory in the period before the treatment will be more informative. Using this approach, Ziegler et al.[1] observed a strong reduction of behavioral arrests in the patient.

Developing individualized treatments involves more than simply producing the treatment itself. Well-selected, predefined outcome measures to assess safety and efficacy — in terms of both target engagement and quantifiable measurements of patient-relevant aspects of disease — are needed to assess whether treatment continuation is justified[6]. These outcomes need to be tailored to each individual's specific functional status and therapy goals, by means of a robust clinical, psychosocial and ethical assessment of each case[6,7]. Local infrastructure is also necessary — including psychological support for the patient and family, to facilitate decision making, and financial support for the clinician and/or hospital and the family, to facilitate clinical implementation of the treatment as well as close monitoring of the patient.

For individualized treatments, geographic differences currently affect who will absorb which costs. n-Lorem provides the ASO for free[2], but currently only in North America. A system needs to be set up whereby ASOs can be sent to the to a local expert center, so that patients can be treated there — rather than having patients move across continents to access treatments, which is not a scalable or equitable solution. Furthermore, n-Lorem only provides the ASO, but does not cover the additional costs (to the family and the hospital) of recurring treatment and monitoring.

In Europe, clinicians can request hospital approval to carry out individualized treatment on a named-patient basis, resulting in a lower administrative burden than in the USA (where an IND is required)[7,8]. However, the European strategy places the full responsibility with the treating clinician, for which availability of the specific preclinical toxicity and efficacy data is essential. The clinician is also responsible for establishing a strategy to quantify safety and efficacy and to define start and stop criteria and risk mitigation strategies. Responsibilities for the coverage of treatment- and monitoring-related costs are not clear.

For individualized treatment to reach its full potential worldwide, pathways to clinical implementation and access must be put in place; developing a drug is merely one step in the process. Globally, the N=1 Collaborative (N1C) and, within Europe, the 1 Mutation 1 Medicine (1M1M) initiatives are building the necessary infrastructure, tools and processes. This includes a data-sharing and communication platform that facilitates learning from each case to guide the development of additional individual treatments. Only with all of this in place will we be able to move from case-by-case individual treatment development to a standardized and scalable approach that is integrated into healthcare systems.

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References

1. Ziegler, A. *Nat. Med.* https://doi.org/10.1038/s41591-024-03197-y (2024).
2. Gleeson, J. G. et al. *Nat. Med.* **29**, 1302–1303 (2023).
3. Kim, J. et al. *N. Engl. J. Med.* **381**, 1644–1652 (2019).
4. Kim, J. et al. *Nature* **619**, 828–836 (2023).
5. Dowling, J. J. et al. *Nat. Med.* **30**, 1882–1887 (2024).
6. Synofzik, M. et al. *Nucleic Acid Ther.* **32**, 83–94 (2022).
7. Aartsma-Rus, A. et al. *RNA* **29**, 446–454 (2023).
8. Aartsma-Rus, A. *Nat. Med.* **27**, 939 (2021).

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Competing interests

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