Medicinal Chemistry and Chemical Biology Highlights

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The Evolving Landscape of Neuroscience Therapeutics: an Interplay of Multiple Modalities

Hendrik Knoetgen[a]*, Torsten Schindler[a], Felix F. Schumacher[a], Antonia F. Stepan[a]*, Alain C. Tissot[b]*, and Jaclyn I. Wamsteeker Cusulin[a]*

Correspondence: Dr. H. Knoetgen, E-mail: hendrik.knoetgen@roche.com, Dr. A. F. Stepan, E-mail: antonia.stepan@roche.com, Dr. A. C. Tissot, E-mail: alain.tissot@roche.com and Dr. J. I. Wamsteeker Cusulin, E-mail: jaclyn.wamsteeker_cusulin@roche.com.
[a]Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. HoffmannLa Roche AG, 4070 Basel, Switzerland
[b]Roche Pharma Research and Early Development, Roche Innovation Center Munich, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany

1. Introduction to General Principles of the Different Modalities

Today's therapeutics have become more diversified than ever and include modalities such as small molecules, biologics (proteins), nucleic acid-based medicines (NABM) and cell therapies. These different modalities can act on diseases by engaging signaling pathways through different modes of actions – a great benefit to patients, as it allows the development of multifaceted treatment plans important especially for the treatment of intricate conditions such as cancer and neurological disorders.[1,2]

Small molecules have historically dominated the number of new drug approvals.[3] Due to their low molecular weight, small molecules can be designed to have oral bioavailability, cell and brain penetration. The pharmacokinetic profile of small molecule drugs often allows for single day oral administration, a feature beneficial for patients' convenience and compliance. Small molecule drugs can target a plethora of mechanisms of actions, such as enzyme inhibition or activation, receptor antagonism or agonism, ion channel modulation, and – most recently also – modification of RNA splicing. The relatively simple structure of small molecules also makes their manufacturing processes and human pharmacokinetic properties largely predictable and scalable from preclinical investigations. In addition, small molecules typically do not require complex storage conditions, as they often come as solid formulations tolerating room temperature, thus allowing for widespread distribution of medications, also in nations with lower socioeconomic standards.[3] As a result, small molecules have considerably improved human health and several small molecule drugs can be found on the World Health Organization's (WHO) list of essential medicines.[4]

Advancements in gene and biotechnology have paved the way for biologic drugs like monoclonal antibodies to revolutionize modern medicine in diseases such as cancer or autoimmune diseases. Today, several biologics, like pembrolizumab (top selling drug), adalimumab, dupilumab or ustekinumab rank among the world's best-selling medications.[5] This success stems from the unique way protein-based drugs allow targeting protein-protein interactions with very high specificity. One limitation is that their biodistribution is restricted to the extracellular or endo-lysosomal compartment as they cannot enter into the cytosol or the nucleus of cells. A number of these drugs therefore inhibit or activate cell surface receptor interactions with their ligands. A distinguishing feature of this modality, as evident from the drug approvals, is that protein based biologics can mediate cell-cell interactions, leading to, for example, the elimination of target cells by phagocytes or lymphocytes. In addition, they can exploit mechanisms of phagocytic clearance to eliminate pathologic deposits such as amyloid in the brain. This is remarkable given that protein-based biologics only reach the parenchyma beyond the blood brain barrier to a very small extent so far. The route of administration is mainly parenteral and requires refrigeration in the distribution chain which can also limit access in countries with lower socioeconomic standards. Although there is an inherent risk of immunogenicity, which may or may not impact drug exposures or activity, this has not impeded the success of protein based biologics.

The youngest group of drug modalities are nucleic acid-based medicines (NABM), which include oligonucleotides [*e.g.* single stranded antisense oligonucleotides (ASOs) and double stranded small interfering RNA (siRNA)], guide RNAs (gRNA) and messenger RNAs (mRNA, *e.g.* RNA vaccines or RNA encoding CRISPR-Cas9 gene editing), gene therapies such as recombinant adeno-associated virus (AAV) and cell therapies.[6,7] The breakthroughs in this area of drug discovery can be seen with the recent approval of the world's first CRISPR-Cas9 gene-editing therapy exagamglogene autotemcel (Casgevy) for sickle cell disease, in which autologous, CRISPR-Cas9 engineered hematopoietic stem cells are transplanted back into patients to produce fetal hemoglobin, thus preventing the sickling of red blood cells.[8]

Major challenges have been overcome, others are actively pursued. Extensive chemical modifications have enabled the cellular uptake of oligonucleotides into the functional compartment of either the cell nucleus (for ASOs) or the cytosol (for siRNAs). Broad distribution after intravenous administration in particular to the central nervous system (CNS) remains a challenge though. AAV gene therapies face similar limitations, as natural serotypes of the AAV only poorly overcome the blood brain barrier to enter the CNS parenchyma. Direct injection into the CNS, mostly by intrathecal dosing, is the most straightforward alternative, but limits broad CNS distribution and remains a higher burden for the patient.

The therapeutic possibilities of NABM therapies have become much broader recently. Oligonucleotides enable target gene specific knockdown of mRNA or modification of mRNA splicing. AAV gene therapy can mediate diverse modes of actions as long as they can be encoded on the transgene within a size that can be encapsulated into the virus. Currently approved gene therapies are all gene replacements (*e.g.* Luxturna, Zolgensma, Roctavian, Hemgenix, Upstaza, and Elevidys) but various other modes of action are in development.

In this article, we will assess recent drug approvals per modality specifically for indications related to the central nervous system (CNS). While small molecule drugs remain a key modality in

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Department of Chemistry and Applied Biosciences (D-CHAB), ETH Zurich

this therapeutic area, biologics and NABMs make up close to half of the approvals for CNS indications, therefore clearly expanding patient therapy options.

2. Neuroscience Drug Approvals 2016–2023

Data used for the analysis was obtained from the FDA websites on New Molecular Entity and New Therapeutic Biological Product Approvals.[9] The data from both websites was collected for the years 2016–2023, merged and then filtered for prevalent neurological (Fig. 2) and neuromuscular and rare neurological conditions (Fig. 3). As such, neurological conditions included in this analysis are migraine (10 approvals), Multiple Sclerosis (MS, 5 approvals), Parkinson's Disease (PD, 4 approvals), sleep disorders (4 approvals), Attention Deficit Hyperactivity Disorder (AD-HD, 2 approvals), epilepsy (2 approvals), postpartum depression (PPD, 2 approvals), Depression (1 approval), Alzheimer's Disease (AD, 1 approval), addiction (1 approval), schizophrenia (1 approval), seizures (1 approval), hypoactive sexual desire disorder (HSDD, 1 approval) and tardive dyskinesias (1 approval). In addition, the following neuromuscular and rare neurological disease were included in this analysis: Duchenne Muscular Dystrophy (DMD, 5 approvals), Neurofibromatosis Type 1 (NF1, 4 approvals), Spinal Muscular Atrophy (SMA, 3 approvals), Amyotrophic Lateral Sclerosis (ALS, 3 approvals), Rett Syndrome (1 approval), Myasthenia Gravis (MG, 2 approvals), Friedreich's Ataxia (FR-DA, 1 approval), Cerebral Adrenoleukodystrophy (CALD, 1 approval), Dravet Syndrome (DS, 1 approval), Huntington's Disease (HD, 1 approval) and Neuronal Ceroid Lipofuscinosis or Batten Disease (CLN2, 1 approval). Approvals for both neurological and rare neurological conditions were then sorted according to three therapeutic modalities, namely 'small molecules' including peptides, 'biologics' comprising enzyme replacement therapies, proteins and monoclonal antibodies as well as 'NABM' consisting of antisense oligonucleotides, small interfering RNAs and AAV gene therapies.

In the period from 2016–2023, we assessed 61 drugs, *i.e.* new molecular entities and therapeutic biological products, that were approved by the FDA for CNS indications. As shown in the Fig. 1, each year these approvals consisted of a diverse set of modalities with a total of 39 small molecules, 13 biologics, and 9 NABM approvals. In the below section, we will further detail modality specific approvals, their innovative nature as well as future directions within a specific modality.
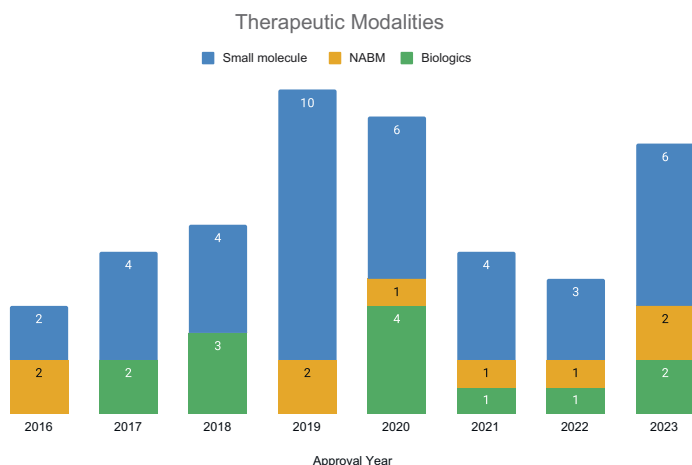

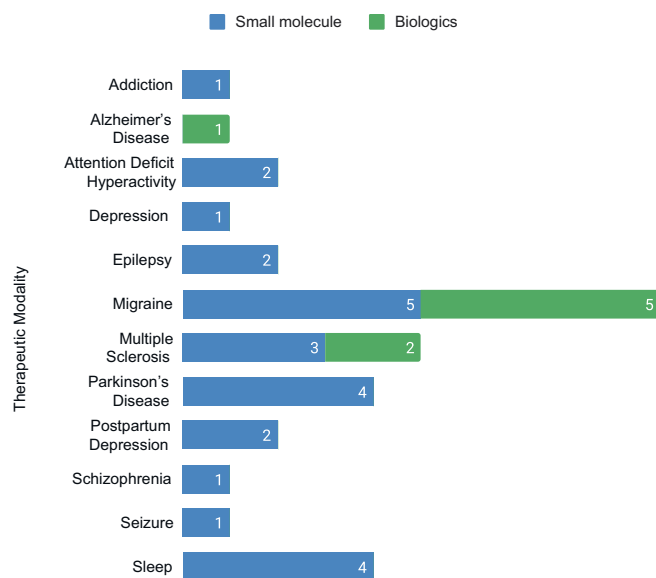Fig. 1. CNS Drug Approvals used in this analysis from 2016–2023, per year and modality.

Fig. 2. 2016-2023 drug approvals for the prevalent neurological disorders used in this analysis, per condition and modality.
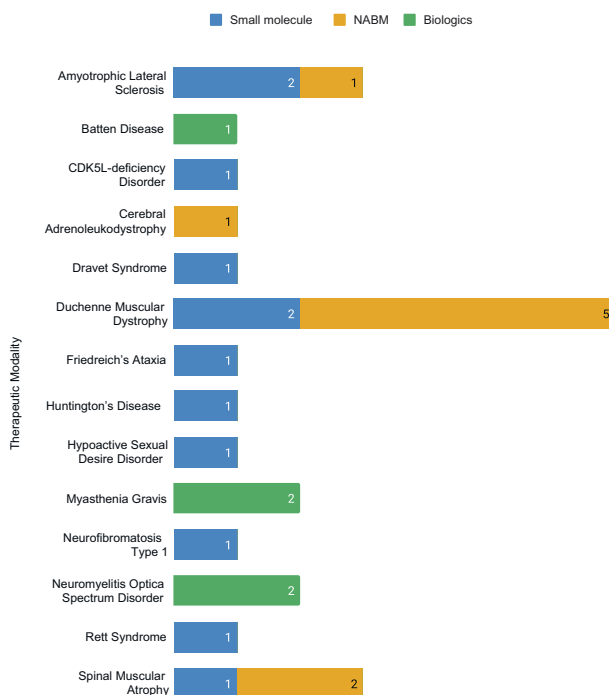

Fig. 3. 2016-2023 drug approvals for the neuromuscular and rare neurological disorders used in this analysis, per condition and modality.

2.1 *Trends in Small Molecule Approvals*

Since 2016, more than 35 small molecule drugs have been approved for neurological conditions, across a diverse array of specific indications. Notably, the most approvals (five) can be found for the treatment of migraine, four to alleviate symptoms in Parkinson's disease, four to address sleep disorders, with three additional approvals for the treatment of multiple sclerosis (MS). Moreover, two drugs have been approved for multiple indications, including attention-deficit/hyperactivity disorder (ADHD), postpartum depression (PPD), epilepsy, and amyotrophic lateral

sclerosis (ALS). Single approvals have been granted for over ten other indications within the neuroscience and rare disease space.

The largest portion of these small molecule drugs have been designed for oral administration. However, there are notable exceptions, such as bremelanotide (Vyleesi), a subcutaneously administered peptide targeting melanocortin receptors for hypoactive sexual desire disorder (HSDD) in premenopausal women; zavegepant (Zavzpret), an intranasal calcitonin gene-related peptide (CGRP) receptor antagonist for migraine; and brexanolone (Zulresso), a neurosteroid and positive allosteric modulator of the GABA receptor, administered *via* continuous intravenous infusion over 60 hours.

The period from 2016–2023 has witnessed the advent of a novel class of oral migraine therapeutics known as gepants [calcitonin gene-related peptide (CGRP) antagonists]. Ubrogepant (Ubrelvy), the first member of this class, was approved in 2019, followed by three additional approvals, including zavegepant (Zavzpret, intranasal application), oral atogepant (Qulipta), and rimegepant (Nurtec ODT). In addition, lasmiditan (Reyvow), a selective serotonin receptor agonist that targets the 5-HT1F receptor subtype, was also approved, offering a potentially reduced side effect profile compared to earlier triptans. For Parkinson's disease, three of the four approved medications serve as adjunctive treatments to address off periods, enhancing the efficacy of primary therapies such as levodopa. These include istradefylline (Nourianz), a selective adenosine A2A receptor antagonist; safinamide (Xadago), a monoamine oxidase B inhibitor with additional mechanisms of action; and opicapone (Ongentys), a catechol-O-methyltransferase (COMT) inhibitor. Additionally, pimavanserin (Nuplazid) was approved to manage psychosis-related hallucinations and delusions in Parkinson's disease, functioning as an inverse agonist/antagonist at the serotonin 5-HT2A receptor. The approval of additional orexin antagonists for insomnia, such as lemborexant (Dayvigo) and daridorexant (Quviviq), has expanded treatment options, despite not being first-in-class. Both drugs may offer different efficacy, safety, and tolerability profiles for individual patients over first-in-class suvorexant (Belsomra). The area of sleep disorders saw the approval of pitolisant (Wakix), a histamine H3 receptor antagonist/inverse agonist, and solriamfetol (Sunosi), a norepinephrine-dopamine reuptake inhibitor, both approved in 2019 for excessive daytime sleepiness (EDS) associated with narcolepsy. In the realm of MS, three sphingosine-1-phosphate (S1P) receptor modulators – ponesimod (Ponvory), ozanimod (Zeposia), and siponimod (Mayzent) – have been approved, offering enhanced selectivity for S1P receptor subtypes and improved safety profiles over earlier non-selective modulators.

Drug repurposing has also played a role in the reviewed period, with lofexidine hydrochloride (Lucemyra), an α2A adrenergic receptor agonist, transitioning from hypertension treatment to managing opioid withdrawal, and viloxazine hydrochloride (Qelbree), a selective norepinephrine reuptake inhibitor, shifting from an antidepressant to an ADHD therapy.

Examples of approvals in rare neurological diseases include the oral amyotrohic lateral sclerosis (ALS) medication sodium phenylbutyrate/ursodoxicoltaurine (Relyvrio), which inhibits mitochondrial cell death pathways, and edaravone (Radicava), an antioxidant, both offering novel therapeutic mechanisms. Deutetrabenazine (Austedo), a deuterated derivative of tetrabenazine for Huntington's disease chorea, represents the first deuterated drug approved by the FDA. Selumetinib (Koselugo), a kinase inhibitor targeting MEK1/2, has been a first-in-class medication for Neurofibromatosis Type 1. Risdiplam (Evrysdi), an oral small molecule splice modifier for spinal muscular atrophy, follows the antisense oligonucleotide nusinersen (Spinraza) and the gene therapy onasemnogene abeparvovec-xioi (Zolgensma), therefore expanding small molecules into novel target spaces and disease areas.

Despite the successful approvals of large molecules for the treatment of Alzheimer's disease, small molecule drugs have yet to achieve approval, reflecting several set-backs with safety and efficacy in clinical trials (*e.g.* semagacestat – a γ-secretase inhibitor; verubecestat – a beta-secretase inhibitor; intepirdine – a 5HT6 receptor antagonist). However, the successes of biologics and nucleic acid-based medicines (NABMs) in paving clinical pathways and advancing biology understanding inspire hope that small molecules will further improve patient lives. This excitement for novel small molecule drug discoveries is fueled by recent breakthroughs in novel modalities within the small molecule space, which not only includes small molecule splice modifiers, but also targeted protein degradation through, *e.g.* molecular glues, peptide macrocycles and peptidomimetics.[10]

2.2 *Trends in Biologics Approvals*

Three classes of monoclonal antibodies account for the large majority of approvals in the area of neuroscience: the calcitonin gene-related peptide (CGRP) inhibitors for prevention of episodic and chronic migraine (see above also for the small molecule CGRP approvals),[11] the anti-CD20 antibodies depleting memory B cells (including the pathologic ones) in multiple sclerosis (MS), and the neonatal Fc receptor (FcRn) inhibitors (it also includes a drug based on the soluble Fc fragment) which accelerate antibody clearance (including pathologic auto-antibodies) in myasthenia gravis. It is interesting that multiple drugs have emerged against the same targets. In some instances they came to market within a similar time frame (inhibitors of both the ligand CGRP, and its receptor), while in other cases the newer approvals have attempted to differentiate by various means (*e.g.* mode of action, route and frequency of administration) while the patient population addressed in the disease may differ as well.

The first anti-CD20 antibody approved for multiple sclerosis was ocrelizumab (Ocrevus) in 2017 for relapsing or primary progressive forms of MS, which has been followed since then in 2020 by ofatumumab (Kesimpta, relapsing forms of MS), initially approved for chronic lymphocytic leukemia, and by ublituximab (Briumvi, relapsing forms of MS) in 2022.

Anti-aquaporin-4 (AQP4) antibody positive neuromyelitis optica spectrum disorder (NMOSD) is an interesting case in which several mechanisms of action are targeting this auto-antibody mediated disease.[12] New drugs approved during this period include inebilizumab (Uplizna, depletion of CD19-positive B-cells and plasmablasts, 2022) and satralizumab (Enspryng, inhibition of the interleukin-6 receptor involved in T-cell, B-cell and other immune cell activation). A further agent, eculizumab (Soliris, complement component 5 [C5] inhibitor), inhibiting the complement pathway and initially approved in 2007 for paroxysmal nocturnal haemoglobinuria has added AQP4-seropositive NMOSD as an indication in 2019. These drugs differentiate mainly by their risk/benefit profile, frequency and the route of administration (maintenance regimen: inebilizumab intravenous (iv) every 6 months, satralizumab subcutaneous (sc) every 4 weeks, eculizumab (iv) every 2 weeks).

The largest part of the approvals for protein based biologics for neuroscience diseases has so far been based on a peripheral mode of action. However, there are remarkable recent exceptions. The first are anti-amyloid antibodies for treatment of Alzheimer's disease [accelerated approval for aducanumab (Aduhelm) in 2021 and full approval for lecanemab (Leqembi) in 2023] whose mode of action is by mediating removal of amyloid plaques by microglia through interaction with the Fc gamma receptors (FcgR). The other is pabinafusp alpha (Izcargo I.V.) for treatment of mucopolysaccharidosis II,[13] approved in Japan (not counted in our list of FDA approved drugs). It is a fusion of the iduronidase-2-sulfatase enzyme to an anti-transferrin receptor antibody, with the purpose of mediating increased transport of its enzyme cargo

across the blood brain barrier. The latter type of technology relying on antibodies binding to receptors mediating transcytosis at the blood brain barrier allows use of protein based biologics to interrupt protein-protein interactions in the brain, a modality which has led to many successes for example in oncology, immunology and ophthalmology. It could initiate a durable expansion of approvals for this class of drugs, as other molecules relying on this principle are in development with enzymes[14,16] or monoclonal antibodies as active principles (trontinemab[17] being the first and most advanced, RG6035, Grabody B[15]). Notably, some of these rely on bispecific antibody technology, which is now entering the neuroscience space after it has led to multiple approvals in oncology, ophthalmology and hematology. Finally, as will be detailed below, protein based biologics could be used as transport moieties to deliver other cargos to the brain.

2.3 Trends in NABM (Nucleic Acid-based Medicine) Approvals

Since 2016, the medical field has seen the approval of six single-stranded antisense oligonucleotide (ASO) treatments for neurological and neuromuscular conditions. Among these, four are phosphorodiamidate morpholino oligomers administered intravenously [casimersen (Amondys 45), eteplirsen (Exondys 51), golodirsen (Vyondys 53), viltolarsen (Viltepso)] with muscle as the target organ. In addition, two 2'-O-methoxyethyl ribose (MOE)-based ASOs delivered intrathecally for therapies effective in the brain and/or the spinal cord [nusinersen (Spinraza), tofersen (Qalsody)] have been approved.

In spite of clinical validation for CNS targeting ASOs, wider use of oligonucleotides in CNS indications remains elusive. Challenges to overcome include limited biodistribution – as oligonucleotides do not readily cross the blood brain barrier and must be administered *via* intrathecal or similarly invasive routes.[18] Furthermore, with intrathecal route, oligos may exhibit non-uniform distribution and efficacy in disease-relevant cells and brain areas (*e.g.* deeper brain structures) and may have acute/chronic safety liabilities. To address these challenges, the field is investing to increase mechanistic understanding and build screening strategies to earlier detect ASO-mediated neurotoxicity – as well as generating chemical approaches for improving the therapeutic index of newer generation drug candidates. Some of these approaches further aim at increasing the durability of oligo effects, *e.g.* by modifying stability[19] in order to enable less frequent dosing. Alternative modes of action and molecule formats may provide new avenues. For example promising clinical data is emerging for an approach that utilized double-stranded oligos – siRNA – in combination with fatty acid conjugation to achieve improved biodistribution and duration of action.[20]

While these research activities aim to improve the established route of intrathecal delivery, alternative efforts explore novel drug delivery systems which have been developed across the whole range of therapeutic modalities and may enable more convenient routes of administration.[21] Major work is aiming at the establishment of antibody-oligonucleotide conjugates as transport vehicles that utilize receptor-mediated transport mechanisms across the blood brain barrier and might enable intravenous or even subcutaneous dosing.[22,23] Interestingly similar strategies – combining the targeting properties of antibodies with the mode of action of oligonucleotide-based therapeutics – are also most advanced in the neuromuscular space[24] with alternative delivery vehicles such as peptides or small molecules having also made their clinical debut recently.

Three AAV gene therapies, onasemnogene abeparvovec (Zolgensma), eladocagene exuparvovec (Upstaza), and delandistrogene moxeparvovec (Elevidys), are currently approved for CNS and muscle diseases. For the CNS, the delivery to the brain remains a major challenge. AAV9 is a natural serotype with some, albeit limited, penetration into the brain after systemic administration. It is more effective in young children when the blood brain barrier is not completely developed. The AAV9 gene therapy Zolgensma is therefore approved for children only up to two years of age.[25] The second approved CNS gene therapy eladocagene exuparvovec circumvents that limitation by direct surgical injection into the relevant brain region (putamen).[26]

All three gene therapies are replacement therapies delivering healthy copies to compensate for a mutated, non-functional gene in the patient. As AAV delivered DNA remains mostly episomal,[27] it is only stable in non-dividing cells such as neurons. CNS and the eye remain therefore very attractive tissues for a durable potentially life-long effect of the transgene. The genome of the AAV is limited in size though. Therefore, also the recombinant transgene which is encapsulated into the therapeutic AAV can only have a maximal size of roughly 4700 nucleotides which includes the flanking sequences needed for encapsulation (inverted terminal repeats, ITR) but also the regulatory elements needed for protein expression. Therefore, the coding gene cannot be much longer than 3500 nucleotides. For gene replacement therapies such as for Duchenne Muscular Dystrophy this is a challenge as the dystrophin gene is the largest known human gene encoding isoform of 427-kDa proteins translated from 14000 nucleotide mRNAs. Therefore only truncated versions, micro-dystrophins, can be encoded by an AAV gene therapy.[28]

Capsid engineering is currently explored to identify capsid variants which can overcome the fully established blood brain barrier and reach the brain after intravenous administration. Recent animal data indicates that AAVs can be engineered to accomplish that goal.[29]

Additional challenges are the safety in particular of high dose systemic treatments which seem to be mostly dose-dependent and require more potent, lower dose treatments as well as more advanced immunosuppressive pre- and co-treatments.[30] Pre-existing immunity against AAV is common in the human population and limits the patient number depending on the serotype to 20 to 40%.[31] High cost of goods are currently another challenge even for a one time treatment which is an intense focus of the technical development in the pharma industry.

In the future new modes of actions are likely to be pursued beyond the most straightforward gene replacement in monogenic diseases. In principle every mode of action that can be encoded on a 4700 nucleotide transgene can be considered. Non-human proteins may remain a challenge as they are potentially immunogenic and may not be tolerized. Optogenetics, RNA editing, durable gene knockdown by shRNA/miRNA, and vectorized therapeutics are some of the opportunities and most of them cannot be achieved with other therapeutic modalities.

3. Looking Forward: Modality Interplay for Neuroscience

The development of drugs based on different therapeutic modalities has opened new horizons in the treatment of complex neurological disorders. Small molecule drugs continue to improve patient quality of life with several first-in-class medications for neurological and rare neurological disorders in the period reviewed. Biologics offer new dimensions of specificity and potency and move beyond the small molecule druggable space while enabling new modes-of-action. The innovation of nucleic acid-based medicines is redefining the boundaries of what is therapeutically possible, offering hope for genetic modulation and correction at the most fundamental level. The synergy of these modalities holds the potential not only to ameliorate symptoms but also to alter the course of diseases that have long challenged the medical community.

We therefore believe that the interplay of modalities is particularly important in the space of neurological conditions. Preclinical and clinical outcomes of one modality can lead to informed

decisions for another. This is particularly true in diseases with a genetically defined background, as shown with the example of treatments for spinal muscular atrophy: Nusinersen (brand name Spinraza), an antisense oligonucleotide, was approved first in 2016, followed by the gene therapy Onasemnogene abeparvovec-xioi (brand name Zolgensma), approved in 2019, and finally the oral small molecule treatment risdiplam (Evrysdi) approved in 2020. This gives hope that the specific strength of each particular modality, including the ones not reviewed in the article (*e.g.* cell therapy), can be used to fight the many to date incurable diseases in the field of neuroscience and that the interplay of modalities will help to do so in accelerated timelines and greater probabilities of success.

Acknowledgements

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