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Case Report

mRNA: a Physiological Multipurpose Tool for Hitherto Hard-to-treat Neurological and Neuro-Ophthalmological Diseases

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Abstract

Interdisciplinary translational research between physiologists and clinicians based on mRNA technology has opened and shall open treatment perspectives for a broad range of diseases, many of them hitherto hard to treat or not treatable at all. In this overview, various options for applications of mRNA technology are presented for the treatment of quite different neurological and neuro-ophthalmological disease categories such as metabolic and neurodegenerative diseases, infectious diseases, and tumors, illustrated by a few selected examples of current clinical trials and experimental approaches. mRNA technology allows for developing tailor-made individualized therapies by which the body may even produce the remedies itself according to the physiological recipe of the mRNA assembly instructions.

Key Words: organ-specific malfunctioning proteins; mrna-technology; mrna-vaccination for infectious diseases; mrna cancer therapy

Introduction

Aim of this overview is to interest ophthalmologists and clinical neuroscientists in the immense therapeutic novelties brought forth by mRNA-technology.

Malfunctioning proteins play a role in a broad spectrum of diseases. When our immune system sends antibodies into the battle against pathogens, it commands nothing more than an army of protein fabrics. From birth through all of life, everyone carries a potential multipurpose tool in the cell nuclei of our body: the messenger ribonucleic acid (mRNA). mRNA as a kind of physiological multipurpose tool to develop tailor-made therapies. In principle, mRNA is an optimal tool for multipurpose approaches in medicine because it holds the physiological blueprint, a kind of software program, for the realm of proteins.

In 2023, the World Health Organization (WHO) Science Council took an initial step towards assessing the potential of mRNA technology for improving global health by conducting an independent review of its role in the development of vaccines for the prevention of infectious diseases and virus-induced cancers. This report summarizes the advantages and limitations of the technology and provides recommendations to focus research efforts [1].

Physiological principles for mRNA as a tool in the manufacture of proteins

The double-helical structure of DNA is the carrier of genetic information and the basis for heritability. That a gene expresses itself and a protein can be produced, transcription, splicing and translation are necessary, the underlying physiology is shortly summarized as follows:

Within the cell nucleus, in DNA, the nucleobases adenine (A), cytosine (C), guanine (G), and thymine (T) are found. The sequence of the four bases of DNA encodes the genetic information, which is why the four letters A, C, G, and T can be regarded as the “alphabet of life”. The nucleobases A-C and G-T form complementary base pairs in the two strands of DNA. The human genome is made up of approximately 3.2 billion base pairs.

First, the double-stranded DNA is split into two single strands. One DNA strand serving as a template for complementary base pairing is transcribed to a ribonucleic acid (RNA) molecule, the precursor-messenger RNA (pre-mRNA) molecule. In RNA, the nucleobase uracil (U) replaces thymine (T), distinguished from thymine only by one methyl group.

Second, during RNA exon splicing the pre-mRNA transcript is transformed into messenger mRNA. All the non-coding regions of RNA, the introns, are removed and the coding regions, the exons, are spliced together. Splicing is necessary, so that, during translation, an mRNA molecule can be translated into a protein.

Third, the RNA-adapted G-C/A-U message of the genetic code is messaged by mRNA from the nucleus to the cytoplasm. The single-stranded mRNA is translated from the "nucleotide language" into the "amino acid language". Such as words in a book, the mRNA is read in one direction, thereby, translating the genetic code of the DNA sequence to the amino acid sequence in proteins. Triplets are composed of three nucleobases, deoxyribose or ribose and a phosphate group forming together a nucleotide ("the word in the nucleotide language"), thus, a codon for a codon-specific different amino acid ("the word in the amino acid language") in the cytoplasm. Therefore, ribosomes in the cytoplasm are needed. Ribosomes consist of two subunits: one subunit decodes the mRNA, reading the nucleotide that corresponds to a specific amino acid; the other subunit forms the peptide bonds. The sequence of nucleotides ("the sentence in the nucleotide language") is translated into a sequence of amino acids which form in that way a chain of amino acids, the specific protein ("the sentence of the amino acid language"), thus, the structure of DNA determines the structure of proteins. mRNA is decoded with the help of transfer ribonucleic acid (tRNA). tRNA transfers one after the other corresponding amino acid to the end of the amino acid chain until the entire sequence is translated into the specific protein.

Methodological remarks on mRNA technology

Initially, the inflammatory nature of the mRNAs limited the in vivo use. Robert W. Malone for transfection modalities for delivery of mRNA [2], and Katalin Karikó and Drew Weissman deserve special recognition for the development of the mRNA technology. The latter could show that naturally occurring nucleoside modifications suppress the immunostimulatory activity of RNA [3]. Replacing uridine with pseudo-uridine made the mRNA non-immunogenic, with increased translational capacity and biological stability [4]. It was not unexpected that the 2023 Nobel Prize in Physiology or Medicine was awarded jointly to Katalin Karikó and Drew Weissman.

The labile nature of the mRNA is ideal for a transient production of a viral antigen, to trigger an effective antibody and cellular immune response. mRNA transcribed in vitro can serve as a template for specific proteins of infectious agents such as viruses and, thereby, allow for a novel approach for vaccination. Inherent challenges are related to controlling the translational efficacy and immunogenicity.

mRNA transcribed in vitro can also be engineered to transiently express proteins and, thereby, replace or supplement proteins that are impaired due to gene mutations. Because insufficiently functioning proteins can be produced in specific cells, there is a critical need to develop organ/cell-specific delivery strategies to reach the full potential of genomic medicines. The development of CRISPR/Cas-based gene editing [5] and mRNA-based gene replacement technologies opened the way towards new therapies for currently untreatable genetic diseases. Novel approaches included in vitro-transcribed mRNA-based generation of pluripotent stem cells and genome engineering using in vitro transcribed mRNA-encoded designer nucleases [6].

A major challenge of gene sequence delivery is to achieve the most complete transfection of the target structure while avoiding leakage into neighboring regions or perivascular spaces. In vivo vector-mediated delivery encompasses different viral and non-viral (particle-mediated gene delivery, plasmid transfection) strategies, none of them universally applicable, e.g., lentiviral vectors bear a mutagenic risk, adeno-associated virus vectors possess a specific tropism for different cell types, including neurotropism. RNA interference may reversibly silence any gene. Delivery systems, including particle-mediated gene delivery through lipid nanoparticles and small interfering RNA (siRNA) conjugates, are required to transport siRNA to the site of action in the cells of target tissues [7].

A novel experimental approach applicable to various nanoparticle systems is termed Selective ORgan Targeting (SORT) and allows nanoparticles to be systematically engineered for accurate delivery of diverse cargoes, including mRNA and Cas9 mRNA complexes, to the lungs, spleens, and livers of mice following intravenous administration. The addition of the supplemental "SORT molecule" precisely alters the in vivo RNA delivery profile and mediates tissue-specific gene delivery and editing [8].

Another novel approach is to process and pack mRNAs into mature ribonucleoprotein complexes (mRNPs), recognized by the essential transcription–export complex (TREX) for nuclear export. mRNPs are recognized through multivalent interactions between the TREX subunit ALYREF and mRNP-bound exon junction complexes. Exon junction complexes can multimerize through ALYREF, which suggests a mechanism for mRNP organization. Endogenous mRNPs form compact globules that are coated by multiple TREX complexes [9].

mRNA treatment for malfunctioning proteins

Brain: Huntingtin protein

Huntington's disease is an autosomal-dominant neurodegenerative disease caused by a CAG trinucleotide repeat expansion in the exon 1 of the huntingtin (HTT) gene. If a child inherits the mutated gene, the disease usually does not occur until adulthood, and then leads to progressing involuntary, sporadic jerking or spasmodic movements (chorea and athetosis), and mental deterioration. So, for children in Huntington-families an early mRNA-therapy could prevent the severe course.

The caudate nucleus of the striatum of the brain is dramatically affected prior to symptom onset, eventually leading to massive bilateral atrophic degeneration of both caudate nuclei (figure 1).

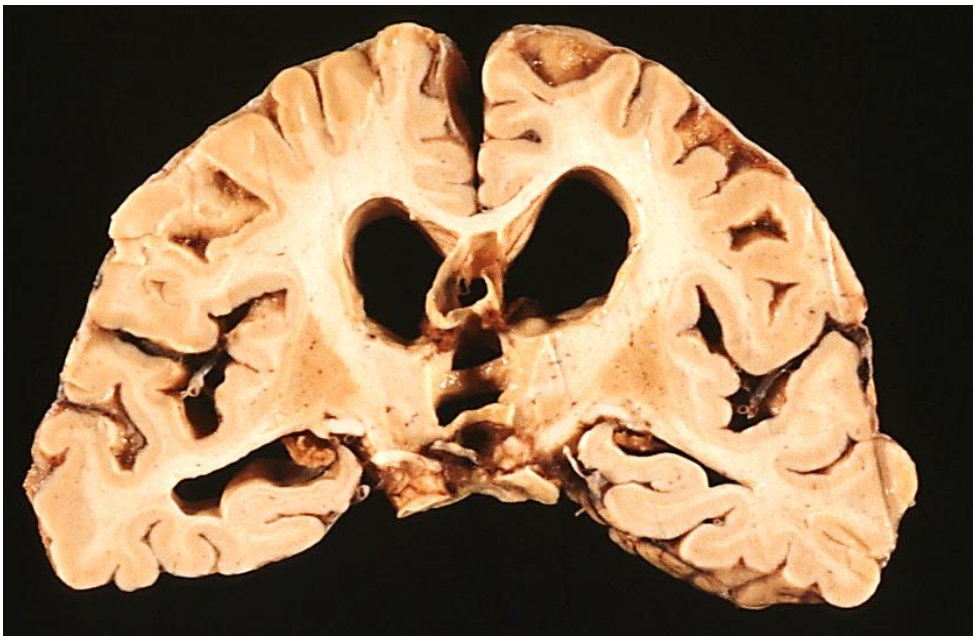

Figure 1: Bilateral atrophic degeneration of the caudate nuclei in Huntington's disease.

Since mutant huntingtin protein is the root cause of Huntington's disease, huntingtin protein-lowering strategies are a focus of therapeutic approaches. Oligonucleotide-based therapeutic approaches using siRNAs and antisense oligonucleotides designed to specifically silence mutant huntingtin may be a novel therapeutic strategy. A clinical trial (ClinicalTrials.gov Identifier: NCT02519036.) used IONIS-HTTRx (Ionis Pharmaceuticals and F. Hoffmann-La Roche), an antisense oligonucleotide designed to inhibit HTT mRNA and thereby reduce concentrations of mutant huntingtin protein. Intrathecal administration of IONIS-HTTRx to patients with early Huntington's disease induce a dose-dependent reduction in concentrations of mutant huntingtin protein [10]. Further, a synthetic physiological strategy was proposed that integrates the naturally existing exosome-circulating system with artificial genetic circuits for self-assembly and delivery of mutant huntingtin-silencing siRNA to the brain cortex and striatum [11].

These approaches target full-length HTT alone and would not be expected to reduce pathogenic exon 1 HTT levels. It could be shown in knock-in mouse models that HTT mRNA carrying an expanded CAG repeat was incompletely spliced to generate HTT1a, an exon 1-only transcript, which was translated to produce the highly aggregation-prone and pathogenic exon 1 HTT protein. This could also be detected in patient cell lines and post-mortem brains. To extend these findings to a model system expressing human HTT, a model was established with YAC128 mice that are transgenic for a yeast artificial chromosome carrying human HTT with an expanded CAG repeat. The HTT1a transcript could be detected throughout the brains of YAC128 mice. Homogeneous time-resolved fluorescence analysis demonstrated that the HTT1a transcript had been translated to produce the exon 1 HTT protein. The levels of exon 1 HTT in YAC128 mice correlated with HTT aggregation, supportive of the hypothesis that exon 1 HTT may initiate the aggregation process [12]. Therefore, it is important that the effects of HTT-lowering strategies on the subcellular levels of all HTT transcripts and their various HTT protein isoforms are understood.

Nerve cells of the retina: All-trans retinyl ester isomerase

The visual cycle operates via an isomerase acting on all-trans retinol in the pigment epithelium [13]. The sight-threatening autosomal recessive genetic disorder RPE65-associated inherited retinal disease is caused by biallelic mutations in the RPE65 gene, which encodes the all-trans retinyl ester isomerase, an enzyme critical to the visual cycle. This severe form of rod cone-mediated retinal disease eventually progresses to complete blindness, so early treatment – which should be possible in inherited cases – may be especially helpful (figure 2).

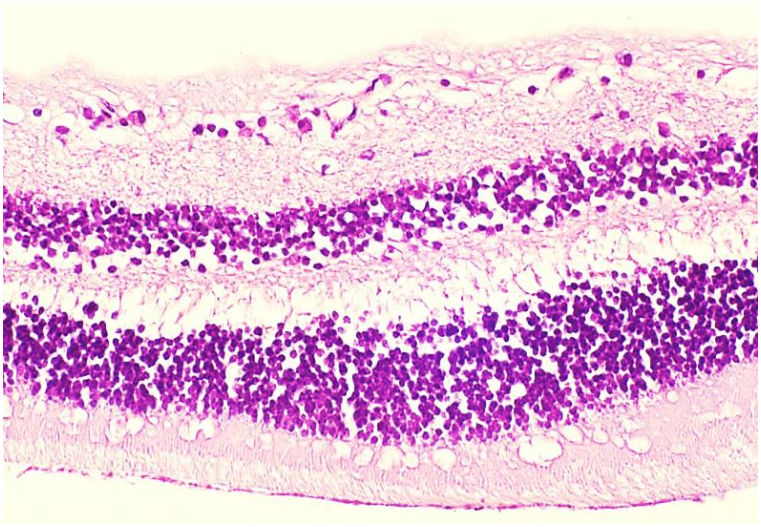

Figure 2: Mild damage retinal degeneration, stage B [14], with a favorable benefit-to-risk profile for treatment (hematoxylin-eosin),

Ocular gene therapy has become an option for treatment, in which a recombinant adeno-associated viral vector serotype 2 (AAV2) gene replacement therapy produces an encouraging outcome. Clinical trials (Study of efficacy and safety of Voretigene Neparvovec in Japanese patients with biallelic RPE65 mutation-associated retinal dystrophy; ClinicalTrials.gov Identifier: NCT04516369) confirmed the safety, durable efficacy, and favorable benefit-to-risk profile of Voretigene Neparvovec (LUXTURNA™; Spark Therapeutics Inc, Philadelphia, PA, USA, Novartis, Basel, Switzerland), administered as a one-time subretinal injection, in improving retinal and visual function. Voretigene Neparvovec received marketing authorization from the US and the European Union in 2018 for the treatment of adult and pediatric patients with vision loss due to inherited retinal disease related to confirmed RPE65 biallelic mutations and who still have sufficient viable retinal cells [15-17].

mRNA technology for the development of vaccines against infectious diseases

Herpes zoster (varicella-zoster virus)

Herpes zoster affects millions of people around the world each year and may sometimes take a severe course (figure 3).

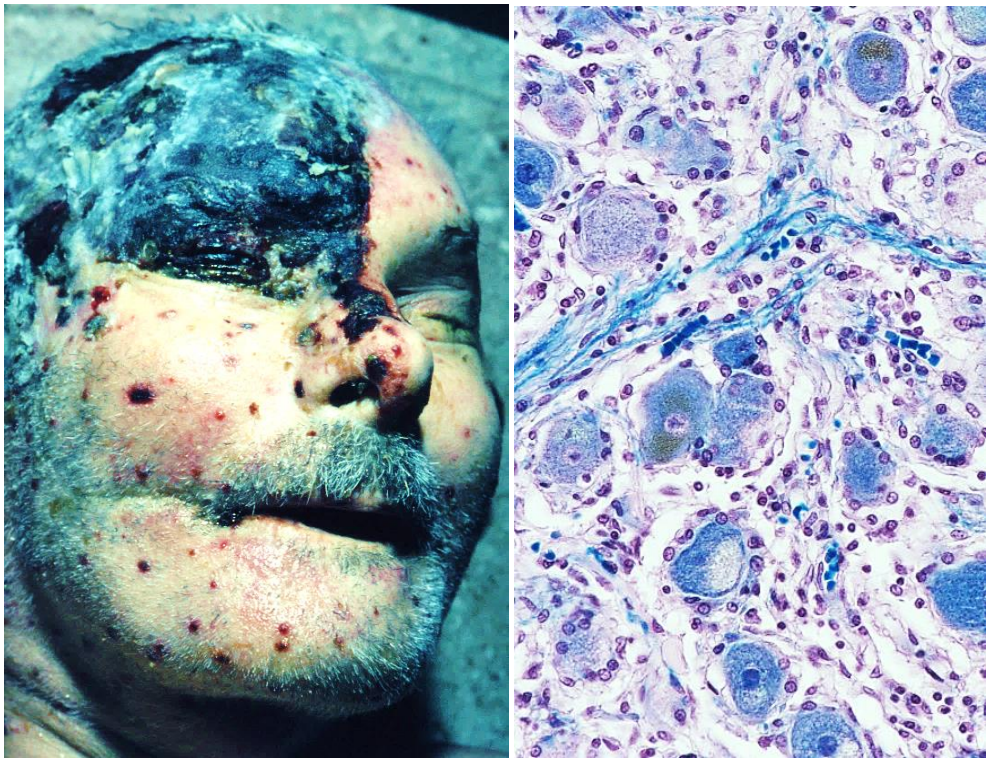

Figure 3: Fatal supraorbital zoster ophthalmicus (left) caused by varicella-zoster-virus infection of the ganglion Gasseri of the trigeminal nerve with lymphocytic infiltration (right; Masson-trichrome)

Recent developments are reported by the pharmaceutical industry, e.g., by Pfizer Inc. and BionTechSE announcing the start of a Phase 1/2 multicenter, randomized, controlled, dose-selection study (ClinicalTrials.gov Identifier: NCT05703607) enrolling up to 900 healthy volunteers 50 through 69 years of age for exploring the safety, tolerability, and immunogenicity of mRNA vaccine candidates against herpes zoster [18]

Rabies (lyssaviruses, including the rabies virus)

Rabies remains a lethal zoonotic disease. The rabies virus produces ribonuclear proteins in the form of intracellular Negri bodies (figure 4). Results of the first-in-human proof-of-concept clinical trial in healthy adults of a prophylactic mRNA-based vaccine encoding the rabies virus glycoprotein (CV7201) are reported (ClinicalTrials.gov Identifier: NCT02241135) and show that this candidate vaccine can induce functional antibodies [19]. Another mRNA vaccine construct (LVRNA001) expressing the rabies virus glycoprotein (RABV-G) provided protection against rabies infection in both mice and dogs [20].

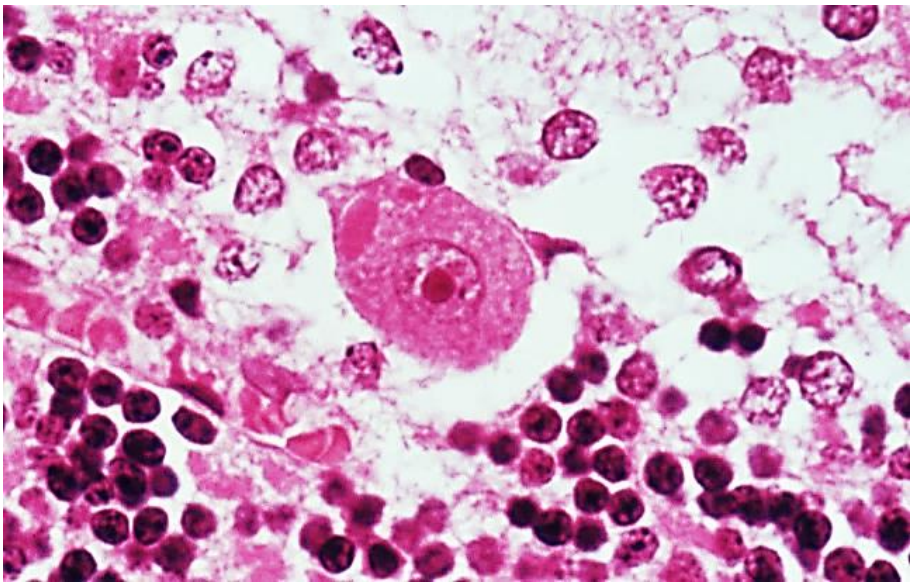

Figure 4: Eosinophilic Negri body (arrow) in a Purkinje cell of the cerebellar cortex, typical for rabies infection of the brain (hematoxylin-eosin).

Malaria

The World Health Organization estimated that there were over 247 million cases of malaria (figure 5) and 619,000 associated deaths in 2021 [21].

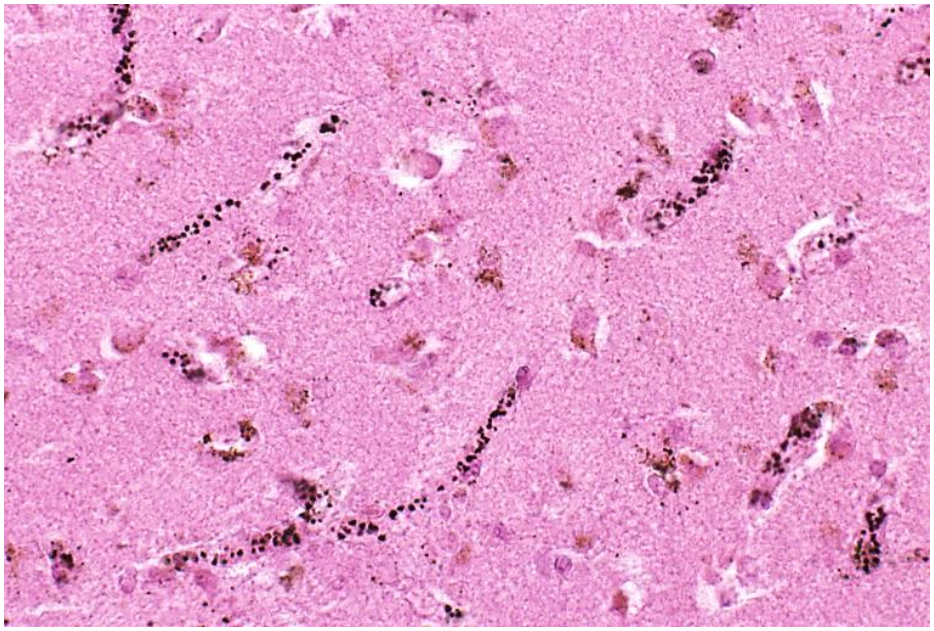

Figure 5. Malaria pigment (black) in capillaries of the brain (hematoxylin-eosin). Malaria pigment or hemozoin is an iron–porphyrin–proteinoid complex formed by the parasite Plasmodium sp. from the breakdown of hemoglobin.

The different approaches to provide more effective malaria vaccines – "from the past towards the mRNA vaccine era" – were recently summarized [22]. The circumsporozoite protein (CSP), expressed at the surface of sporozoites of different Plasmodium species, has been identified as a major immunogen. For example, in a double-blind, randomized, controlled, phase 2b trial (ClinicalTrials.gov Identifier: NCT03896724), the circumsporozoite protein-based vaccine R21, with two different doses of adjuvant Matrix-M (MM), was given to children in Burkina Faso [23]. At its regular biannual meeting held in September 2023, the World Health Organization has recommended R21/Matrix-M vaccine for the prevention of malaria in children [24]. The R21 vaccine is the second malaria vaccine recommended by WHO, following the RTS,S/AS01 vaccine, which received a WHO recommendation in 2021.

mRNA technology for new therapies against cancer

Tumor cell-specific protein expression patterns that could serve as a starting point for mRNA treatments. These treatments ought to alert the patient's immune system to proteins that are carrying the cancer-typical alterations.

After decoding the genetic code of a surgical or bioptic tumor sample, an mRNA working copy of it is introduced into the patient's cell plasma, and eventually, the body now produces exactly those proteins that allow the immune system to recognize and attack the actual tumor cells. In a personalized form of immunotherapy, mRNA is immediately inserted into the patient's own dendritic cells. which initiate immune responses and give the correct instructions on which proteins should be targeted [25].

Glioblastoma

Notwithstanding various treatment approaches in the last decades, glioblastoma multiforme still has a catastrophic survival rate (figure 6). mRNA-technology may open a way to develop special vaccines for glioblastoma and other hard-to-treat gliomas.

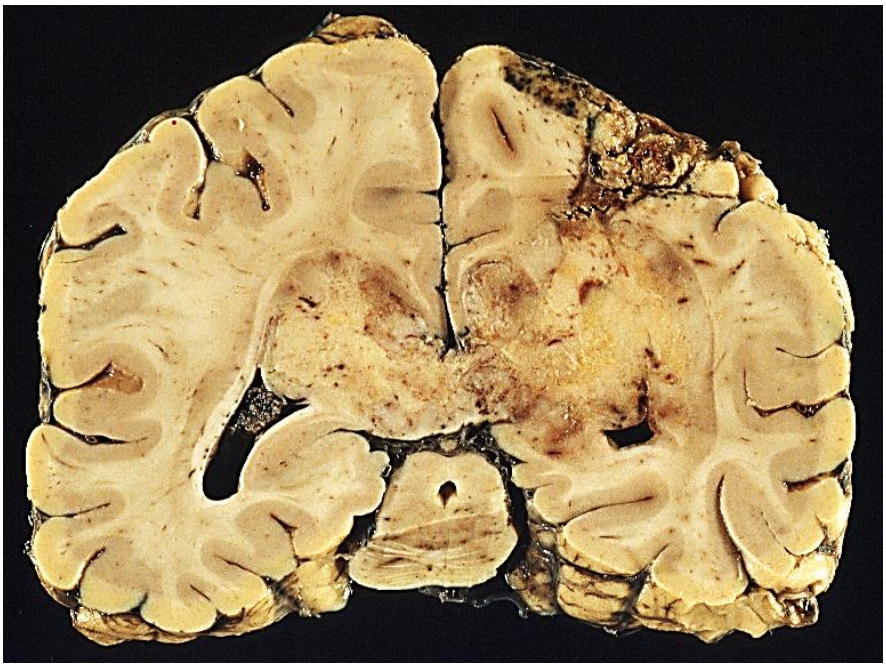

Figure 6: Fatal "butterfly" glioblastoma multiforme with diffuse growth via the corpus callosum and large tumor necroses.

In an experimental study, mouse and human mRNA-based multifunctional T cells were generated co-expressing a multitargeting chimeric antigen receptor (CAR) based on the natural killer group 2D (NKG2D) receptor and the proinflammatory cytokines IL12 and IFNα2. Multifunctional CAR T cells demonstrated increased activity of attacking in vitro and in vivo in three orthotopic immunocompetent mouse glioma models without signs of toxicity [26]. Gene expression profiles can identify effective antigens. There exist several immune subtypes of glioma, each one linked to unique prognoses and genetic/immune-modulatory changes. Patients with immune-active and immune-suppressive phenotypes were found to respond better to mRNA vaccines [27].

By using a microfluidic electroporation in which a combination of nano- and milli-second pulses produces IFN-γ mRNA-loaded small extracellular vesicles (sEVs) with CD64 overexpressed on their surface. These immunogenic sEVs preferentially target glioblastoma cells and generate potent anti-tumor activities in vivo, including against tumors intrinsically resistant to immunotherapy [28].

Uveal melanoma

Melanoma is one of the most aggressive and therapy-resistant cancers, primarily found in the Caucasian population with susceptibility factors including fair skin, light eye color, and inability to tan. Ocular melanoma is the most common primary eye tumor in adults (figure 7) metastasizing in up to 50% of cases.

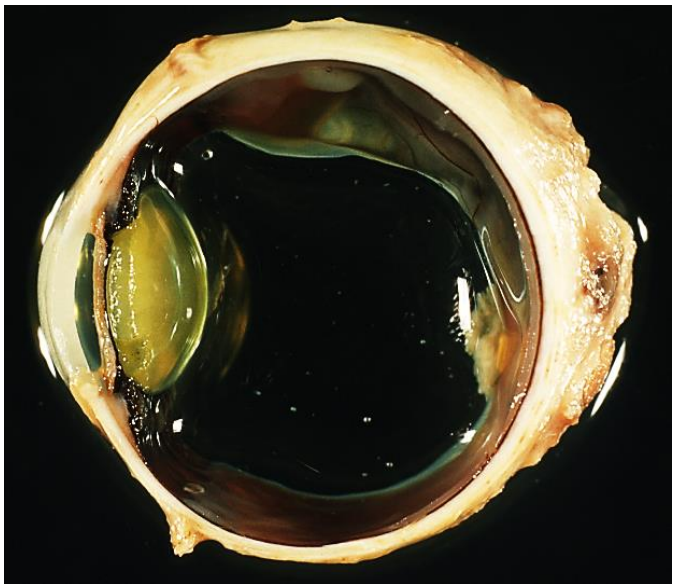

Figure 7: Intraocular uveal melanoma (arrow) located in the choroid.

The efficacy of an mRNA vaccine was tested in an aggressive B16F10 melanoma model of the mouse. A strong CD 8 T cell activation was observed after a single immunization. Treatment of B16F10 melanoma tumors with lipid nanoparticles containing mRNA coding for the tumor-associated antigens gp100 and TRP2 resulted in tumor shrinkage and extended the overall survival of the treated mice [29].

In patients with high-risk melanoma, an efficacy study – KEYNOTE-942 (ClinicalTrials.gov Identifier: NCT03897881) – of adjuvant treatment with the personalized cancer vaccine mRNA-4157 and Pembrolizumab was performed, and specific immune responses have been observed. The KEYNOTE-942 trial may establish the incorporation of the mRNA-4157/V940 vaccine into the melanoma treatment [30].

Discussion

Gene therapy and in particular mRNA therapy are at an inflection point [31]. If it becomes more and more possible to intervene in a targeted manner in the realm of proteins, therapeutic options for disease in the broadest sense can be envisaged, and it does not seem exaggerated to assume that a physiological principle opens the door for a new form of medicine to target a multitude of diseases. mRNA represents an almost universal tool for developing tailor-made therapies.

Conflict of interest

The authors declare that they have no conflict of interests.

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