WHY NO TREATMENT FOR MYOTONIC DYSTROPHY WHEN WE HAVE A VACCINE FOR COVID-19?

by

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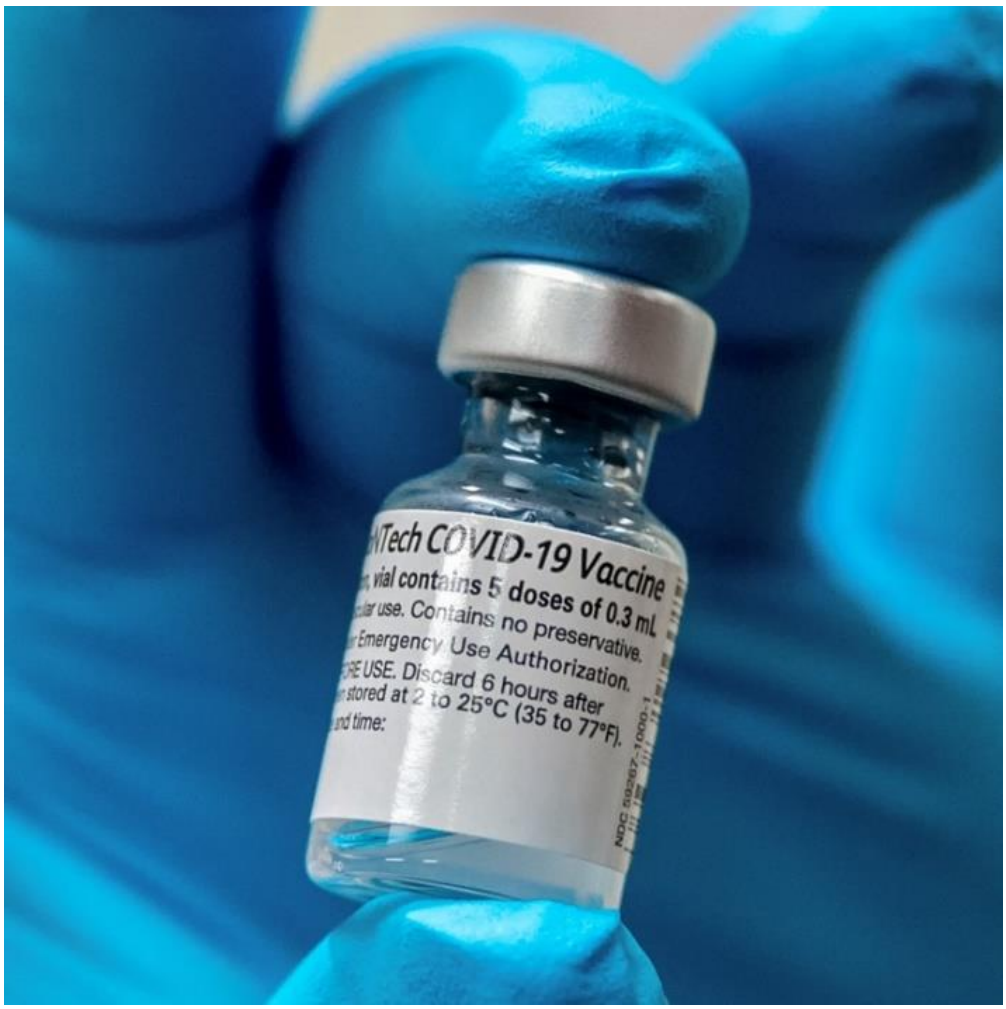
If it was possible to create a vaccine to prevent COVID-19 in a year, how come we still have not cured myotonic dystrophy?

The above question is one that many people are asking. It is an excellent question, and it is perfectly reasonable to ask why the amazing progress in developing vaccines to prevent COVID-19 cannot be replicated in developing treatments for myotonic dystrophy, or indeed, any of the many other rare, and not so rare, diseases that still afflict us. First, it is worth considering whether the rapid development of COVID-19 vaccines has been really that remarkable? The simple answer to this is a definite yes. There are several reasons why the process of developing a vaccine to prevent COVID-19 was always likely to proceed faster than developing treatments for myotonic dystrophy. Nonetheless, progress was exceptionally rapid and facilitated by a number of factors. Most obviously, is the fact that COVID-19 was rapidly recognised as a very serious condition with significant mortality that could spread rapidly in the population of the entire planet with the potential to overwhelm health care systems and mediate a devastating impact on every aspect of society, not least of which was the potential economic impact of the lockdown measures required to contain the spread of the virus. Not surprisingly, given the scale of the problem, its potential to escalate out of control, and its potential to have long term societal impacts, governments, research funders, regulators, the pharmaceutical industry, and the scientific community, worldwide, all acted to facilitate as rapid a development of a vaccine as could physically be achieved. Clearly, a major driver in this regard was money. Science and drug development is an expensive endeavour, and governments were quick to fund work in this area with the expectation that money spent now on research could potentially save hundreds of thousands of lives and mitigate against trillions of pounds worth of economic damage. Similarly, the pharmaceutical industry needed no convincing that there would be a ready market for any vaccine once generated with the potential to sell billions of doses. Money talks. However, it would be overly simplistic to suggest that money is the only driver in treatment development and there is good reason to believe that, even with unlimited cash resources, such a rapid development of new treatments for myotonic dystrophy could not be achieved in under a year from a standing start. There are a number of additional key factors that facilitated vaccine development to prevent COVID-19 and mitigate against such rapid progress in myotonic dystrophy.



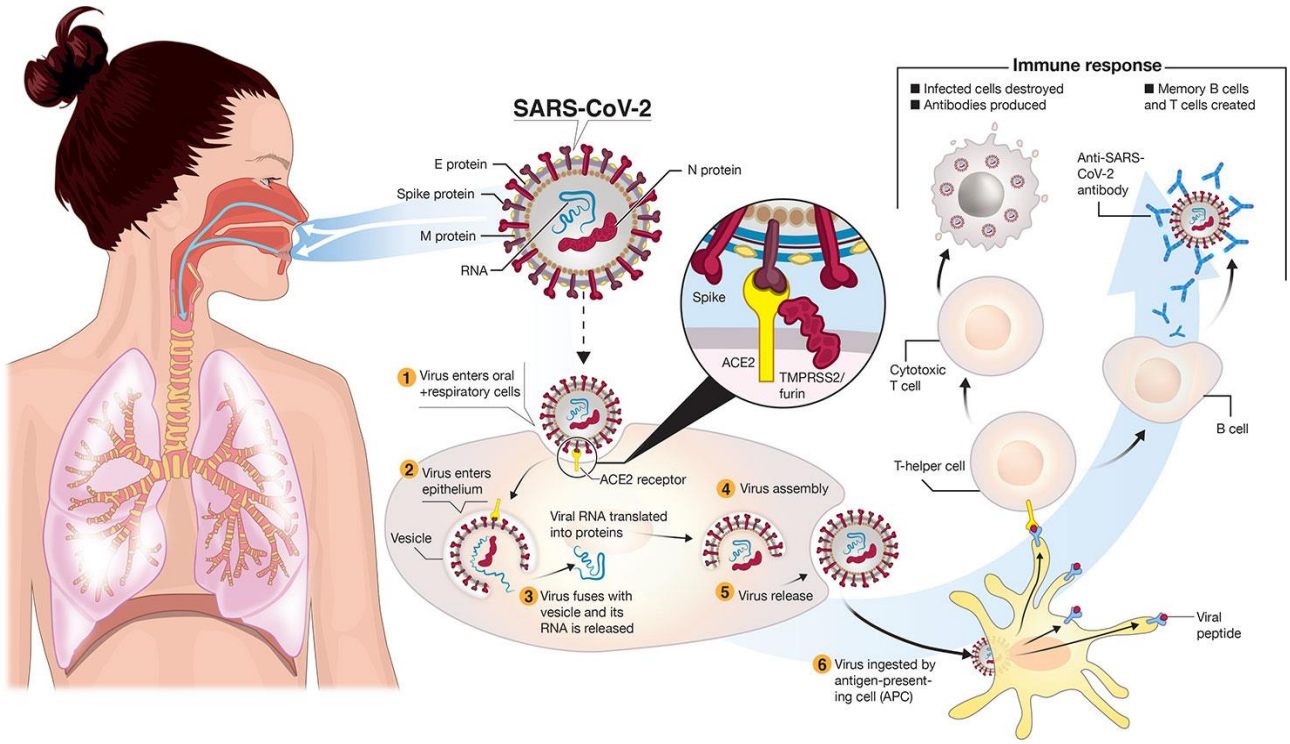
The generation of a COVID-19 vaccine in under a year was a remarkable scientific achievement that was facilitated by many factors.
Image obtained from:
https://commons.wikimedia.org/wiki/File:Pfizer-BioNTech_COVID-19_vaccine_(2020)_C-beschnitten.jpg

Firstly, was the ability to very quickly identify the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the causative agent within a matter of weeks of the recognition that a new respiratory disease was circulating in the Wuhan region of China. In the past, it was necessary to try and physically identify and isolate the causative agent of a new infectious disorder. However, recent advances in the ability to sequence the genetic material, DNA, has now made it possible to circumvent this process by simply extracting the DNA present in the tissue of an infected individual, sequence all the DNA present, subtract from this all the DNA sequences that are from the human host and known commensal microbes (non-harmful microbes that are naturally present). The DNA sequences that are left are then likely to be from the causative infectious agent. This was essentially the case for identifying the COVID-19 causing SARS-CoV-2 virus, with additional support provided by the observation that the DNA sequence detected was found in multiple patients and was very similar to other corona viruses known to cause similar previous disease outbreaks such as SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome). In contrast, it took over twenty years to map and determine the nature of the inherited mutation that causes myotonic dystrophy type 1

from early efforts in the 1960s, when we had no mechanism for sequencing or manipulating DNA, until the early 1990s, by which time we could manipulate DNA in the laboratory and sequence short stretches of DNA, albeit very slowly. At the time the myotonic dystrophy type 1 mutation was identified in 1992 there was no human genome sequence that we could use as a detailed map to guide us, and relatively few other human disease-causing mutations known that could provide insights into how go about it. However, it's worth noting that the final step toward identification of the myotonic dystrophy type 1 mutation as the expansion of a genetically unstable CTG repeat in the DNA, was facilitated by the determination, a few months earlier, that fragile X syndrome was caused by a similarly unstable repeated DNA sequence that appeared to explain the unusual inheritance patterns observed in that disorder and appeared to be analogous to the anticipation, earlier age at onset observed in successive generations, that characterises myotonic dystrophy type 1. Nowadays, identification of the mutation causing myotonic dystrophy could be achieved in matter of months, if not weeks, by sequencing the entire genomes of a dozen or so affected individuals from a few families. The genome sequence of affected individuals could then be compared to not only the known human genome sequence, but also our present knowledge of the millions of non-disease-causing genetic differences that are naturally present in our genomes, to narrow in on the precise changes that cause myotonic dystrophy. Whilst the massive increases in speed and associated plummeting costs of DNA sequencing came too late to help in the initial identification of the myotonic dystrophy mutations, these methods are nonetheless proving useful to better understand the more subtle DNA sequence variation within, and the dynamics of, the genetically unstable CTG repeat that causes myotonic dystrophy type 1. Coupled with analysis of natural genetic variation in thousands of other genes throughout the genome, these types of approaches are increasing our understanding of why myotonic dystrophy is so incredibly variable and revealing new insights into how we might treat the disease.

The second key factor that allowed repaid vaccine development for preventing COVID-19 is the relatively simple life cycle and biology of a virus. Viruses are the simplest form of life. Indeed, there are some arguments as to whether viruses are even alive as they are 100% reliant on other more complex cells to carry out most of the functions necessary for them to survive and propagate. The genome of a virus is very simple and needs to fulfil only a limited number of functions: the virus needs to gain entry to the host cell, usually by binding to a receptor protein on the surface of the host cell; subvert the host cellular machinery to make copies of the viral genome and the proteins necessary to make the viral particle; and then package the viral genome into and assemble, and release multiple new viral particles that can then go and infect new cells. Because the virus uses nearly all of the host cells natural machinery to replicate its genome and make the viral proteins, this can all be achieved with just a handful of genes. Most viruses have also evolved to also contain a few extra genes that counteract the host cells and host bodies response to viral infection. The small number of genes that viruses need to survive is well illustrated by the observation that the SARS-CoV-2 genome encodes only about a dozen genes. Whilst we still don't know exactly how all of the genes function, particularly with respect as to how they subvert normal cellular functions and mitigate against host cell defences, the nature and function of a few critical structural genes were readily established. Most important amongst these for understanding how the virus spreads, and how we might develop a vaccine against it, is the so-called spike protein. This protein sits on the outer surface of the viral particle and is the protein that binds to the ACE2 protein that is present on the surface of human cells and facilitates entry of the virus into human cells. From our long-established understanding of how viruses work, it was obvious that making antibodies

against this one protein on the surface of the virus would likely block the virus from entering cells and mark infected cells for destruction by the immune system. The spike gene of SARS-CoV-2 was so similar to the spike genes of other related viruses, that as soon as the viral genome was sequenced this gene was immediately identified, and work toward developing a vaccine could begin. In contrast of course, human physiology is orders of magnitude more complex than that of a virus, as illustrated by the fact that the human genome encodes more than 20,000 genes. Whilst we know what quite a lot of these genes do, there are still many thousands for which we know very little, or have only a minimal insight. It's probably fair to say that the *DMPK* gene in which the myotonic dystrophy type 1 mutation lies, is one of the genes for which we have some idea of what it does, but we still don't know exactly what its function is precisely. Much early effort was thus directed at understanding what the *DMPK* gene does. However, it slowly became apparent that myotonic dystrophy type 1 was more complicated than most other inherited human disorders. In the majority of inherited human disorders, a mutation in the DNA sequence changes the sequence of the protein encoded such that the mutant protein usually no long carries out its usual function. More rarely, the mutant protein becomes more active, or even more rarely adopts a new activity. Most puzzlingly, the myotonic dystrophy type 1 mutation does not change the protein coding potential of the *DMPK* gene at all. Thus, quite reasonably, it was assumed myotonic dystrophy type 1 must be caused by a more indirect effect on how the *DMPK* gene was activated producing either too much or too little of the DMPK protein. It took several years to generate the mouse models necessary to test these hypotheses, with the surprising upshot that neither too much nor too little DMPK seemed to cause the primary myotonic dystrophy type 1 symptoms. Attention then switched to the *SIX5* gene that, as the human genome sequence was filled in, was determined to be immediately downstream in the genome from *DMPK*, very close to the CTG repeat expansion. Data from myotonic dystrophy type 1 patient cells suggested that when the CTG repeat expanded, the *SIX5* gene was turned off. Disappointingly, several more years generating more mouse models again revealed that too little *SIX5* does not cause the primary myotonic dystrophy type 1 symptoms either. Finally, after nearly 10 years of hard work and many dead ends, it was determined that unlike every other inherited human disorder characterised up until that point, the primary myotonic dystrophy type 1 symptoms were not caused by a change in the activity of any of the proteins encoded by genes near the mutation, but by an abnormal new toxic property of the *DMPK* RNA molecule. RNA is the chemical intermediate that carries the information contained in the DNA sequence to be translated into protein. Whilst not in the protein coding region of the *DMPK* gene, the CTG repeat is contained within the *DMPK* RNA. Up until that point it was believed that RNA couldn't mediate a cellular defect on its own. However, data from cell and animal models of myotonic dystrophy type 1 established that an RNA could be toxic completely independently of the protein it encoded. This finding broke new ground in human genetics, and it has since been established that the CCTG repeat expansion that causes myotonic dystrophy type 2 acts in a similar manner, and subsequent to that, at least 10 other inherited human disorders are now thought to be similarly caused by toxic RNA molecules.



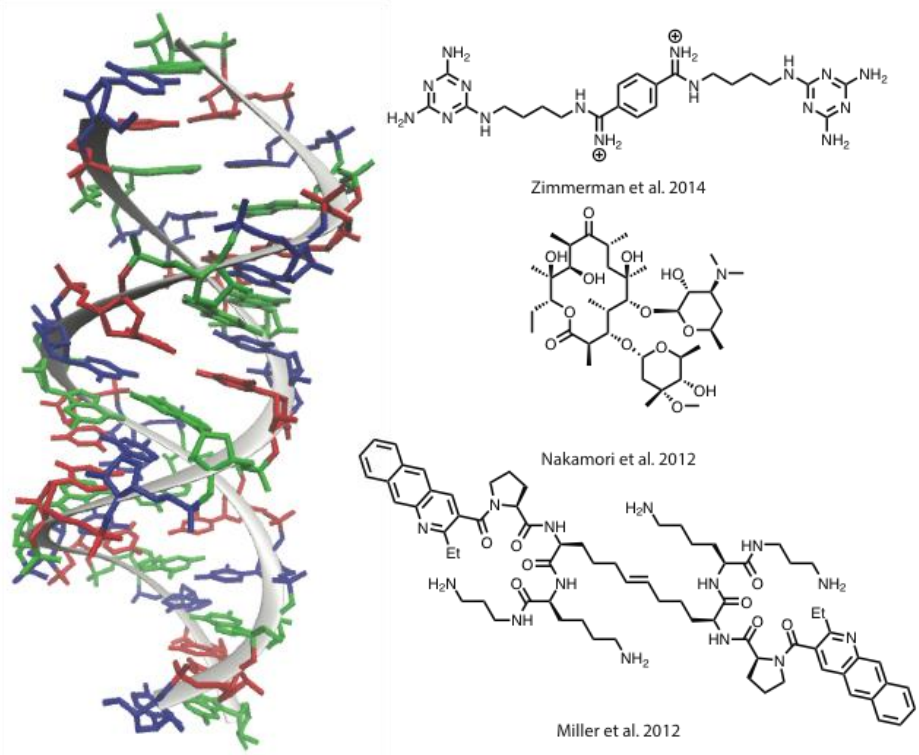
The SARS-CoV-2 virus uses its spike protein to bind to the ACE2 protein to enter human cells. White blood cells from the immune system (T-cells and B-cells) mediate an immune response that results in the production of infection blocking antibodies and the destruction of infected cells. Image obtained from: https://commons.wikimedia.org/wiki/File:Fphar-11-00937-g001.jpg

This insight into the toxic nature of the *DMPK* RNA was obviously a tremendous breakthrough and at last allowed the field to think about how to develop treatments for myotonic dystrophy type 1. However, as this was essentially a brand-new area of biology, there were no “off the shelf” treatment strategies or established drug development pipelines that could be applied to generating new therapies for myotonic dystrophy type 1. Again, this is in stark contrast to the situation with tackling an infectious disease using vaccine technology. Vaccines are based upon harnessing the body’s natural immune response to infection, that is to create antibodies against the infectious agent (either a virus, bacteria, fungus, or parasite). Antibodies are proteins that bind very specifically to a protein from the infectious agent, and either physically interfere with other protein-protein interactions that limit the ability of the infectious agent to infect cells and/or function, target the infectious agent itself, or cells infected by it, for destruction by white blood cells. Antibodies are encoded by unusual genes; in that we do not inherit intact antibody genes from our parents. Rather we inherit an array of short sections of antibody genes that are genetically patched together in specialised white blood cells. Each such cell randomly patches together sections of antibody genes form the repertoire to create a unique antibody in each cell, such that there are millions of cells each expressing their own unique antibody. Any antibody producing cells that produce antibodies that recognise the body’s own “self” proteins are eliminated during early development, a process that sometimes goes wrong and can result in autoimmune disorders where the body attacks its own proteins and cells. Those cells that remain, producing millions of different antibodies, essentially remain dormant until an infection occurs. Then, when an infection occurs, any of these cells that produce an antibody that recognises the infectious “foreign” agent are

activated and start to divide producing more of the cells with that antibody, and releasing more of that antibody, with the hope that enough antibody is produced to allow the body to combat the infection. In the usual situation though, the body is playing catchup as it takes time to activate the correct antibody producing cell to amplify itself and produce effective amounts of the antibody. As such, an infectious agent may get a hold and persist for some time, or in the worse-case scenario cause death, before an effective immune response can be mounted. If the individual does survive though, the cells producing antibodies effective against that infectious agent remain at a much higher level and are ready and primed for any possible reinfection with the same infectious agent. In that case the individual may become "immune" to that particular infectious agent by virtue of being able to produce enough antibody against the infectious agent quickly enough to prevent the infection from taking hold at all, or at least limiting the severity and length of an infection. The concept that humans are capable of acquiring immunity to repeat infections has been around for more than a millennium, and the concept of vaccines since the pioneering work of Edward Jenner and others in the late 1700s. Jenner's vaccine against smallpox was based on infecting people with cowpox. The cowpox virus causes a relatively mild disease in humans, but activates the immune system to produce antibodies that are also capable of neutralising the much more serious, but highly genetically related, smallpox virus. Over the next few hundred years, vaccines for many infectious agents were developed including against anthrax, yellow fever, diphtheria, measles, mumps, and rubella. Many of these vaccines were made by growing the infectious agent in the lab and then inactivating it, usually using heat, so that it could no longer infect a person, but could still illicit an immune response. With the advent of recombinant DNA technology in the 1980s, it became possible to use harmless bacteria to synthesise in the lab individual proteins from the genome of the infectious agent and use purified proteins as vaccines. Recently, it has become possible to insert parts of the DNA from one infectious agent into harmless non-replicating viral particles that can be injected into the recipient where the hosts own cells then express the immune system activating pathogen protein. Even more recently, technology has been developed whereby the RNA molecules encoding immunogenic proteins from the infectious agent are synthesised in the lab, injected into the host, and again the hosts own cells are used to produce the actual immune response inducing foreign protein. As such, once the genome sequence of SARS-CoV-2 was determined, and the spike protein on the surface of the virus particle identified, established procedures could be immediately implemented to produce a new vaccine. Indeed, this process is so relatively straightforward that the first batches of vaccines were actually produced within a matter of weeks of the significance of COVID-19 being recognised in early 2020. As alluded to, the situation in myotonic dystrophy is so much more complicated, and even more critically, so different from other human disorders for which effective treatments already exist(ed) that there was no obvious route to treatment, equivalent to the vaccine pathway, that could be easily followed. Thus, much of the research in the myotonic dystrophy field has concentrated on understanding exactly how the toxic RNA causes disruption within the cells, and how this in turn relates to defects at the levels of tissues and organs, and how this in turn relates to the symptoms experienced. There's still lots of this that we don't understand, but enough is known, and has been known now for a number of years, that we can imagine how myotonic dystrophy could theoretically be treated. Indeed, many different approaches to mitigating the effects of the toxic RNA have been developed and shown to be highly effective in treating cells grown in the laboratory. Many of these approaches use cutting edge genetic technologies for manipulating RNA and DNA, which to an extent can be relatively simply "designed" using our knowledge of the genetic code and the sequence of the *DMPK* gene. Most

promisingly, this includes trying to harness some of the body's natural responses to combating RNA viruses (some viruses use RNA as their primary genetic material rather than DNA), using so called "antisense" technology. Using this method, it is possible to trick human cells into destroying the toxic *DMPK* RNA. This has worked tremendously well in cells grown in the lab, and in mouse models of myotonic dystrophy. Very disappointingly though, the first clinical trials of this approach in myotonic dystrophy patients failed to yield any evidence for a meaningful effect on symptoms. The primary reason for this failure appeared to be that despite injecting relatively large amounts of the drug into the body, not enough of the drug got inside the muscle cells. In myotonic dystrophy, the mutation is present in every cell, and every cell needs to be treated, and thus every cell needs to receive a sufficient quantity of the drug. Again, this contrasts to vaccine delivery, where the primary target is the circulating white blood cells that are naturally moving around the body and actively seeking out pathogens and foreign proteins against which to mount an immune response. Once the immune system has been activated antibodies are released into the blood stream and circulating white blood cells move around the body actively seeking out infectious agents. Unfortunately, the antisense oligonucleotides that constitute the actual drug used to try and treat myotonic dystrophy were relatively large molecules, and they simply don't naturally distribute themselves about the body and penetrate into cells in the same way that a classic so called "small molecule" drug like aspirin does. So, in this case it was not that the drug didn't work *per se*, rather it was just not possible to get enough of the drug into enough cells to be effective. Much work is proceeding to modify the antisense oligonucleotides so that they can better penetrate into tissues and cells. Intriguingly, one approach that looks very promising is to attach the antisense oligonucleotides to an artificial antibody that recognises a protein on the outside of muscle cells and mediates entry of the antibody, and its attached antisense oligonucleotide cargo, into the muscle cells, in a manner which is analogous to the way that SARS-CoV-2 uses its spike protein to bind to the ACE2 protein and gain entry into human cells in the respiratory tract. Delivery of a new drug to all the cells necessary across the whole body remains one of the major challenges in translating therapies that work great in cells in the lab, to being able to actually treat patients with myotonic dystrophy. Thus, as well as using antisense oligonucleotides, and other even larger "macromolecules" and gene therapy and editing approaches, that work great in the laboratory, but are difficult to deliver effectively in humans, much effort is also going into identifying small molecule drugs that are capable of reversing some of the cellular defects observed in myotonic dystrophy. Although such small molecules drugs have the promise of easier and more effective delivery, potentially in the form of a simple pill, they are much harder to identify. The traditional route to developing them is to take millions of essentially random chemical compounds and test them using some sort of high-throughput laboratory assay in the hope of finding something that works. Once a lead compound is found that works at least partially, much more work is then needed to find out how it works, and modify it to make it work more efficiently at lower doses, and ensure that as well as doing the good thing, it doesn't also cause any bad things to happen to cells that could result in deleterious side-effects in humans later down the line. This approach thus tends to be slower and more laborious than drugs designed using genetic approaches but have the promise of greater efficacy and ease of use once they are developed. Several groups, including MDSG's own patron, David Brook, are using this approach with substantial progress having already been made. Thus, although it has taken a lot longer than anyone might have hoped, major progress developing new treatments in the lab has taken place. Critically, despite the rarity of the disease, the opportunities to exploit the scientific advances made in the myotonic dystrophy field to develop new therapies is now widely

recognised by the pharmaceutical industry. As a rare disease, for many years myotonic dystrophy was of little interest to the pharmaceutical industry, as the market for any new drugs was deemed likely too small to allow for a company to recoup the considerable upfront investment required to develop a new drug and bring it to market. However, following considerable pressure from many different patient organisations, the government regulators of drug approval, have introduced changes to the drug approval process that make it slightly easier and cheaper for companies to test new drugs for so called “orphan” diseases (rare diseases without effective therapies) and granted them a longer patent period. These changes alter the economics of drug development for rare disease such that it is now deemed much less of a risk to invest in these areas than it once was. That’s not to say that drug development and testing for rare disease is cheap, just not as prohibitively expensive as it once was. The involvement of the pharmaceutical industrial is absolutely crucial, not just for the funding they provide, but also for the essential expertise they bring in conducting trials. Clinical trials are hideously expensive and incredibly complicated, but that is what pharma do, and by and large, drug development programmes and trials of new therapies cannot go ahead with industrial support. Fortunately, building on the scientific success of understanding what causes myotonic dystrophy, many companies are now investing heavily in myotonic dystrophy drug development, and several are expected to initiate clinical trials of new myotonic dystrophy therapies in the next few years.



Some prototype small molecules have been developed that are at least partially capable of treating myotonic dystrophy in cells in the laboratory. More work will be needed to optimise these and other small molecules so that they can be used safely and effectively to treat myotonic dystrophy, ideally in the form of a simple pill. Image obtained from: https://commons.wikimedia.org/wiki/File:Small_Molecule_Drugs_for_the_Treatment_of_Myotonic_Dystrophy_Type_1_(DM1).png

Having developed a vaccine or a drug in the laboratory that appears to be effective, the next step is to conduct a clinical trial, firstly to establish that the vaccine/drug is safe, and secondly that it actually helps in preventing an infection/treating the symptoms of a disease. Despite the absolutely critical need for a vaccine to prevent COVID-19 to be available as soon as possible, human clinical trials still had to be conducted and these took place very rapidly over the summer of 2020. The trials were then quickly followed in the autumn of 2020 by the first approvals from the regulatory authorities for the widespread use of the vaccines following the success of the clinical trials. These studies were accelerated much in advance of what would otherwise have occurred not least of course, by the tremendous hard work of the investigators, but lubricated by the availability of substantive funding, and the cooperation of the regulatory authorities to prioritise COVID-19 research, trials and approvals ahead of other work. The clinical trials were also greatly facilitated by the relative ease with which large numbers of unaffected individuals could be recruited from the general population, and the large numbers of cases of COVID-19 in the population, that meant that the efficacy of the vaccine in preventing infection could be quickly determined. It's critical to note though that, although they occurred faster than would be achieved under normal circumstances, the necessary safety studies and trials of efficacy were completed. Similarly for myotonic dystrophy, despite the huge unmet need, we must be sure that any new potential treatments are both safe and effective. Inevitably though, clinical trials of new therapies in myotonic dystrophy will take longer. Not because of any lack of urgency from the investigators, and not even in many cases because of insufficient funding (although that will inevitably be a rate limiting step in some programmes). Trials of new myotonic dystrophy treatments will be slower because myotonic dystrophy is a rare disease. Very willing as the patient community is to participate in new trials, the relative rarity of the disease is such that trials will need to be conducted at multiple centres, likely in multiple countries. This makes them more complicated to set up, slower to initiate, and longer to complete, and therefore more expensive too. Additionally, myotonic dystrophy is a complex and highly variable disease, and also relatively slowly progressive. This raises questions about what do we measure to determine whether a new drug has actually worked or not? With a new vaccine, working out whether it worked or not is relatively straight forward; did the people who got the real vaccine get the infection less often than those who received the placebo version? With myotonic dystrophy it is less obvious. Even if we ignore the complex constellation of other symptoms and focus only on muscle, we are then challenged with questions as to which muscle, and how to actually measure strength in that muscle in a meaningful, sensitive, and quantitative way. This is especially challenging when we consider that myotonic dystrophy is a relatively slowly progressive disorder. Whilst long term changes are obviously highly debilitating, and whilst we hope that some new treatments might be highly effective in actually reversing symptoms in a readily detectable way, we should recognise that a new treatment that halted, or even only slowed disease progression, would nonetheless be highly desirable relative to the status quo. Designing a clinical trial capable of detecting such relatively subtle effects will not be easy. These questions are though under active consideration and the field is narrowing in on a set of outcome measures that can be utilised in myotonic dystrophy trials. Of course, as we know from bitter experience, not all of these trials will be successful and some of what looked like great potential treatments for myotonic dystrophy in the lab will fail, as did several of the SARS-CoV-2 vaccines. Indeed, we know that whilst successful vaccines have been created for many infectious diseases, vaccines for others such as against the human immunodeficiency virus (HIV) that causes acquired immune deficiency syndrome (AIDS), have proven much less successful. HIV has proved particularly challenging because the

virus directly targets and kills the white blood cells that would normally mount an immune response, and the virus has a very high mutation rate that means that its protein coat keeps changing, helping it to keep one step ahead of the immune system. Fortunately, SARS-CoV-2 is evolving much more slowly such that vaccines that were developed against the initial strain of the virus are still effective against the more recently evolved strains, such as the delta variant. Thus far, we have been lucky vaccine resistant strains do not appear to have arisen, and we should all keep our fingers crossed that they don't! Similarly, we need to remain positive and expect that some of the trials of new therapies that are expected to be conducted over the next few years for myotonic dystrophy will also be successful. Some extra luck in hitting the right answer sooner than later wouldn't go amiss too.

The COVID-19 vaccine can be effectively delivered by a simple injection into the arm. Delivering drugs effectively to individually treat all of the cells in the body in a person with myotonic dystrophy is much more challenging. Image obtained from: https://commons.wikimedia.org/wiki/File:Sinopharm_COVID-19_vaccine_(2021)_H.jpeg

We can thus see that the development of vaccines against SARS-CoV-2, was greatly facilitated by a number of different factors that unfortunately do not apply in myotonic dystrophy, and to be fair, to many other disorders likewise. Myotonic dystrophy is simply a much more complex biological problem than COVID-19. Nonetheless, substantive progress has been made in understanding and working toward new treatments for myotonic dystrophy. What the last 18-months have taught us though, is that science works.

Science has led to our understanding of COVID-19, the identification of SARS-CoV-2, has driven the testing regime, informed government policy, and has led to the development of effective vaccines that have already saved tens of thousands of lives. The same scientific approach will work for myotonic dystrophy. It will take longer than any of us hoped, but we will get there. We are nearer now than we ever have been, and there is a genuine expectation that at least one of the new therapeutic approaches being explored and trialled over the next few years will prove effective.

Now is not the time to lose hope.

All of us in the myotonic dystrophy community must continue to push forward, to continue raising awareness of the disease, to continue to support research by fund-raising and participating in it, and to continue to campaign for and on behalf the patients and families that continue to be affected by myotonic dystrophy such that when new treatments are approved, they are rapidly made available to all those that need them.

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