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The Needs of the Few

Star Trek fans will remember the iconic moment when Leonard Nimoy as Spock says, “The needs of the many outweigh the needs of the few,” but would he have said the same had he been speaking of the emergence of personalized medicine and the treatment of extremely rare diseases? The advent of fields such as bioinformatics and the invention of DNA sequencing technology have opened the doors to personalized medicine and made possible the treatment of rare genetic diseases which were previously completely untreatable. However, this approach to medicine is still very young, and the development of treatments tailored to an individual’s genome is still costly. One may ask, what is the greater benefit of developing treatments for extremely rare diseases which affect a scarce few or even only a single individual? This is a fair question to ask, as it’s easy to see the social benefit of treatments that benefit the many compared to those that benefit the few, or even the one. That said, personalized medicine has the potential to make a profound impact on how disease is treated and how health is managed, ultimately providing benefit to a huge number of people. Through developing treatments for rare diseases, researchers and doctors are able to develop new insights into health and disease, pioneer new techniques, and push the limits of what’s possible in modern medicine. In this light, developing treatments for rare genetic diseases provides immense social value, as it’s helping bring to fruition a new era of medicine which will benefit everyone.

To explore this topic further, we’ll consider the case of Mila, a 7 year old girl who was born with a rare, perhaps unique, mutation which inflicted her with Batten disease, and she received an experimental treatment tailored to her own genome[1]. Batten disease is a neurodegenerative genetic disorder which causes seizures, vision loss, cognitive impairment, and is ultimately fatal. The mutation prevents the production of a protein required for the normal degradation of proteins and lipids, leading to a buildup which impacts normal brain function. Mila received the recessive mutation from both mother and father, and thus developed the disease. However, the copy she received from her

[1] https://www.statnews.com/2018/10/22/a-tailor-made-therapy-may-have-halted-a-rare-disease

mother was mutated in an interesting way; a retrotransposon had copied another segment of DNA within the transcription unit which coded the protein Mila needed.

To fully diagnose Mila's disease, her genome had to be sequenced so her mutations from both mother and father could be identified. After analyzing her mutations, her doctor, Dr. Timothy Yu, developed an antisense oligonucleotide[2] drug, named milasen, which bound to the faulty section of mRNA and allowed it to splice correctly and ultimately go on to be translated into the protein Mila needed. The approach of using an antisense oligonucleotide drug therapy was heavily inspired by the newly developed drug, Spinraza, but unlike Spinraza, milasen was tailored to Mila's specific genome. Indeed, the treatment Mila received serves as an excellent example of personalized medicine, and it thwarted an extremely rare and fatal disease for which no other treatment existed.

Because Mila's treatment was so unique, its development came at considerable cost. Mila's mother established a philanthropy[3] for Mila's cause and raised millions[4] to pay for the steep monetary cost of her treatment. The development of milasen took over a year, and it required a team of doctors and researchers, led by Dr. Timothy Yu. The result of this effort, the drug milasen, is an antisense oligonucleotide, a short synthetic RNA fragment which binds very specifically to a section of Mila's mutated mRNA. Mila's mutation is so rare that milasen might never be of use to anyone other than Mila. It's a high cost to pay in money, time, and skill to develop a drug for a single person. However the act of developing such a drug may benefit a far broader audience by pushing the boundaries of what's possible in personalized medicine and establishing techniques which may be replicated for others with rare genetic diseases.

As mentioned, Spinraza (also known as nusinersen) is another antisense oligonucleotide drug, which was developed before milasen and served as the inspiration for its development. Spinraza's development[5] started in 2003 and was finally approved for use in 2016 as a treatment for spinal muscular atrophy, another rare and devastating genetic disease. That's 13 years in the making. In contrast, milasen was developed in just over a year. Of course, milasen's development had the benefit of following a model that Spinraza had already pioneered. Milasen was also able to bypass the same

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[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5909143/
[3] https://www.stopbatten.org/
[4] http://kdvr.com/2017/02/04/charity-steps-up-to-help-family-raise-4-million-to-find-cure-for-daughters-deadly-disease/
[5] http://www.curesma.org/research/our-strategy/drug-discovery/therapeutic-approaches/

regulatory scrutiny, being developed under the FDA's Compassionate Use pathway[6]. Still, even with with these advantages, milasen's development took 1 year, versus the 13 needed for Spinraza. By following the same process as milasen, hopefully future antisense oligonucleotide drugs will be able to be developed at the same speed or even faster.

Cost to consumers is another big hurdle with this kind of treatment. Spinraza's high cost to consumers is a controversy in itself as treatment can cost upwards of $750,000 in the first year plus an annual cost of $350,000, lasting for life[7]. Biogen, the company which developed Spinraza, hasn't disclosed their own development costs, but considering Spinraza is the only treatment for spinal muscular atrophy, Biogen would be able to demand a high price tag regardless how much the drug cost to develop. However as the techniques and technology used to develop drugs like Spinraza become more common, there would likely be more competition leading to market pressure which would, hopefully, drive down costs for consumers. The work that Yu and his team did to replicate the process of creating a drug like Spinraza are a step in that direction.

An interesting aspect when thinking about the market forces involved in precision medicine and treating extremely rare diseases is that the drug itself, an oligonucleotide drug tailored to an individual's own genome, very likely won't exist before it's needed. This means that as soon as the drug is made, it will have cornered the market, but that market might be only a single individual. As in the case of milasen, the cost to the consumer isn't so much the drug itself, but the cost of the technology and the people involved. As the technology and techniques involved become more common, perhaps many labs would offer personalized oligonucleotide drug development as a commoditized service, and consumers would simply pick a doctor with this specialty or be referred to one.

Another point of interest is that of intellectual property. While traditionally drugs are patented, a patent may not be useful for a drug that only has a target audience of one. Also, an oligonucleotide drug may not even be patentable, as human genes are not patentable in the United States[8], and an oligonucleotide drug is a synthetic complement to a person's mRNA. This can be both good and bad for consumers. While these factors may prevent a company from monopolizing a new drug and thus demand a higher price, it may also discourage a company from developing such drugs or providing the services to create them, thus creating scarcity. However if we consider generic medications as

[6] https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm
[7] https://www.npr.org/sections/health-shots/2017/08/01/540100976/drug-puts-a-750-000-price-tag-on-life
[8] https://ghr.nlm.nih.gov/primer/testing/genepatents

an example, consumers have typically benefited from lower costs of generics which have fallen out of patent. Likewise, if treating rare diseases with oligonucleotide drugs paves the way for treatments which emphasize commoditized tools and services rather than patented drugs, this will likely lead to a benefit to the consumer. The consumer would no longer be “locked-in” to a pill they need, and they would benefit from having more choice.

It’s clear that the treatment of rare diseases, like Mila’s, has become a vehicle for the advancement of modern medicine. Such extremely rare mutations provide a model for applying DNA sequencing and synthesizing technology, and for testing our understanding of the human genome and molecular biology. In pursuing new treatments for rare genetic diseases, not only are lives of those in desperate need being saved, but also the boundaries of what’s possible are being pushed further, and a new approach to medicine is emerging. The accessibility of DNA sequencing and synthesizing technologies along with the ingenuity of people like Dr. Timothy Yu are making the goal of personalized medicine possible. The development of milasen is something concrete which embodies and realizes a solid step forward towards that goal. Indeed, Dr. Yu and his organization hope their work can serve as a template of end-to-end personalized medicine for the treatment of rare diseases[9], and is paving the way for treating other genetic diseases, like Mila’s or perhaps more common ones too. In pursuing the needs of the few, we are changing the way medicine is done for the better, which benefits us all.

About the author

Alexander Smith is pursuing a Masters degree in Bioinformatics and Computational Biology from George Mason University’s School of Systems Biology. This essay was written as part of his studies in Molecular Cell Biology, taught by Professor Donald Seto, Ph. D.

[9] https://eventpilot.us/web/page.php?page=IntHtml&project=ASHG18&id=180124037