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Novel Antivirals against SARS-CoV-2: Tools for Future Viral Pandemics

by Eric Jiang

In the realm of antimicrobials, antiviral drug development remains a stronghold against emerging pandemic threats. The primary methods of slowing viral transmission involve excellent disease vector management, patient tracking, and fundamentally, drug intervention[1]. A modern demonstration of those pandemic management techniques involves the SARS-CoV-2 emergence from Wuhan, China in late 2019. Mimicking the rapid repeat of the SARS-CoV epidemic in 2003, SARS-CoV-2 is characterized by its use of angiotensin converting enzyme-2 (ACE2) to mediate cell entry[2]. Learning from the use of glucocorticoid and interferon treatment from the 2003 SARS outbreak where patients experienced a myriad of adverse effects[4] following prolonged supraphysiological dosage[5], the use of exogenous immune enhancers are not a viable solution long-term for patients[6]. Almost immediately, the SARS-CoV-2 genome was sequenced and released. Promising research towards existing classes of antivirals such as nucleoside analogues, polymerase inhibitors, and potentially interfering with the ACE2-mediated host entry mechanism has shown success in preliminary testing as a result of quick collaboration and intervention. Full-force in an era of globalization and a gradually more interconnected world, the COVID-19 outbreak shows both the weaknesses within out healthcare structures but also demonstrates the progress made within the last two decades in drug development and pharmacy.

Following the research output burst during the 2003 SARS outbreak, the mechanism for SARS-CoV replication was elucidated. Binding to the transmembrane ACE2 receptor allows for viral docking and its positive-sense single-strand RNA release into the cell, which is subsequently translated and replicated into negative-sense RNA to under transcription into mRNA. The viral membrane is formed in the Golgi, which then is transported towards outwards to mature and engulf viral RNA. When the envelop completely forms, the virus is exocytosed out. Likewise, SARS-CoV-2 has shown to exhibit identical pathways of entry[7] and similar replication mechanisms. While the sequencing of membrane spike proteins has allowed for immediate analyses of receptor usage, drug development against specific ACE2-binding has not yet produced significant results. One potential treatment against ACE-2 transmembrane binding would be the use of soluble ACE2 or ACE2 analogues to opsonize the virus to prevent binding to host cells. Additionally, both β-coronavirus genomes are cleaved by the same replicase complex in host cells (polyprotein 1a), which in turn is cleaved by two viral proteases (papain-like and 3C-like proteases)[8] during the replication process. This mechanism can be targeted by PL protease inhibitors[9] and 3CL protease inhibitors such as lopinavir and ritonavir, two of the most promising agents currently used to treat COVID-19 cases. Despite their inhibitory potential at the cellular level, no definitive cure was derived from the use of combination lopinavir/ritonavir.

Similarly, another replication targeting drug GS-441524, or remdesivir, shows clinical promise in treatment against cases of COVID-19. As a nucleoside analogue prodrug, remdesivir interrupts RNA polymerase by either forcing mutations or terminating the RNA chain, the exact mechanism of which is unknown[9]. In one notable case, the first US patient for COVID-19 was treated successfully with remdesivir with no immediate adverse effects, as well as rapid recovery the following day since starting treatment. It is noted that multiple drugs were in use at that time, and no conclusive evidence supports the causal effect of remdesivir against SARS-CoV-2[10].

Currently*(*This was true at time of submission),* remdesivir seems to be the most likely candidate for inclusion into COVID-19 therapies, undergoing clinical trials in China. Derived from lessons in 2003 SARS treatment and HIV antiretrovirals, remdesivir promises to be free from longer-term adverse effects.

Antiviral development against SARS-CoV-2 in China has yielded another promising drug, chloroquine (or hydroxychloroquine, a less toxic metabolite of chloroquine), an old malaria drug that prevents heme formation in red blood cells[2,11]. How can an anti-parasitic and anti-inflammatory drug combat viral infection? Research has shown evidence of increased basicity of viral endosomes as one of its off-target effects, which inhibits viral survivability[12]. It exerts antiviral effects even at low concentrations in vitro, around 1-5μM. Since the SARS in 2003, its antiviral effects were known and as such, was repurposed for potential use in viral pandemics. Notably, it played a role in the treatment of avian influenza H5N1 during its pandemic. Chloroquine phosphate has shown efficacy in treatment of COVID-19 associated pneumonia in clinical studies as a last-ditch effort to save lives during severe presentations of the disease. Unfortunately, as most of the patients with the highest mortality risk are the elderly, chloroquine has not yet been tested in that age group for adverse effects. Having been in use for 70 years, *in vivo* pharmacokinetics and pathologies have been well characterized Retinal and gastrointestinal damage may occur and require careful monitoring and dosing changes. Despite the small risk, it has shown great potential for future use in viral pandemics as a common drug used to prevent the contraction of malaria for travellers.

However, it is impossible to determine the course of future pandemics, as it was impossible to determine the explosive spread of COVID-19. Having built up research background into SARS-CoV and potential antivirals, we are able to immediately identify compounds that may show efficacy against SARS-CoV-2 based on years of previous research on SARS-CoV. Nonetheless, a pandemic with dissimilar viral genomes to previous pandemics may present a large challenge as there is a lack of underlying research against a novel cell-entry mechanism. Treatment options may revert to treating symptomology or innate immune enhancers such as using NSAIDs or serum interferons respectively. Yet, current advancements in machine learning and protein simulations have allowed researchers to algorithmically determine yet another compound with potential against SARS-CoV-2. A Korean-American research collaboration suggested that atazanavir, an antiretroviral treating HIV infections, show higher 3CL binding than both efavirenz and ritonavir, both of which are potent 3CL protease inhibitors and are used to treat patients in Wuhan, China[13]. Even more, it showed high binding kinetics and "inhibition of all the subunits of the [SARS-CoV-2] replication complex," which allows for decreased likelihoods for individual mutations to induce resistance. However, real-world research into atazanavir has not materialized compared to the quick response of lopinavir/ritonavir treatments. As AI platforms identify optimal compounds for use as repurposed drugs, it is imperative that researchers take advantage of the use of machine learning to augment, and even substitute years of prior research on similar viruses. With the use of artificial intelligence and machine learning, we may react with as much success when a significantly unique viral pandemic occurs as we would have with more genetically similar viruses.

As such, our toolbox for future novel viral infections relies on the quick reactions and well-established collaborations between research bodies, as has been shown through the many efforts to identify drugs and treatment regimens for the immediate threat. The characterization of multiple drugs against SARS-CoV-2 exemplifies the solid foundation of research against a novel viral outbreak. Nevertheless, improvements in implementation of the uncovered research could be applied to more rapidly improve patient conditions and reduce hospital load.

A more immediate response by healthcare professionals to published research would allow drugs such as atazanavir or (hydroxy)chloroquine to become a cornerstone in preventing new infections before the onset of a pandemic. Regardless of the threat of an incoming viral outbreak, antiviral drug discovery remains a cornerstone in the defense against our microbial foes.

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Nanomedicine: How science on a smaller scale is making large strides in tackling challenges in drug delivery

by Chinmayi Yathiraju

Over 100 years ago, Paul Erlich first proposed the notion of the "magic bullet", envisioning a future of drug development where compounds were precisely targeted to their intended sites, eliminating off-target adverse effects [1] . Today, despite being armed with a much-expanded and vast pharmaceutical arsenal, conventional drug delivery methods are a far cry from such a profile. The rapidly growing landscape of nanotechnology has gained traction in the past two decades however, and drug-delivery methods designed using nanotechnology are offering renewed promise to revive Erlich's vision on a grand or rather, nano-scale.

Pharmacokinetics and challenges

The journey of a drug from administration to its target site is arduous and riddled with several biological obstacles. Pharmacokinetics describes a drug's journey in the body, and is an umbrella term encompassing the study of the absorption, distribution, metabolism, and excretion (ADME) of compounds [2]. A persistent goal in drug development is to optimize the ADME parameters, an endeavor that can be limited by conventional drug delivery methods. Oral delivery for instance, is by far the most common and preferred route method of drug administration. However, a drug's journey from mouth to its target is long and precarious, with multiple opportunities for metabolism and thus drug loss in the acidic stomach environment, blood circulation, and liver as all blood leaving the gastrointestinal tract is first filtered through the liver before being sent out into the rest of the body (a phenomenon called the first-pass effect). Thus, only a small fraction of an orally delivered dose often reaches the intended target, resulting in poor bioavailability, or low concentration of drug that is available to exert its actions [3] . Topical formulations, or those that do not reach the bloodstream can mitigate this problem, but are limited to external application such as the skin or to local areas that can easily be accessed. Thus, there exists a pressing clinical need to deliver drugs in a targeted and precise manner, while minimizing the concentration of drug lost in the delivery process.

Nanotechnology and benefits

Nano-technology based drug delivery systems offer several advantages over conventional methods and may be an effective strategy to enhance the pharmacokinetic profile of drugs. Simply put, nanotechnology is the development of materials at the nanometer scale. These materials are often between 1 – 100nm in size, dimensions that reflect the scale of atoms and molecules [4]. Development at this atomic or molecular level can confer distinctive advantages as nano-scaled materials exhibit unique chemical and physical properties that differ from larger counterparts that are designed at the micrometer level [4,5].

Firstly, the reduced size of nanomaterials results in increased surface area to volume ratio, resulting in enhanced absorption through capillaries and increased uptake into cells. It has been suggested that 100 nm particles may be taken into cells 15–250x more efficiently than particles 1 to 10 μm in size [6]. Upon cellular uptake, these materials can establish a cytoplasmic concentration, acting as intracellular drug reservoirs 6 . The small size of nanomaterials also confers increased ease in crossing biological membranes and may permit delivery across barriers such as the blood brain barrier that prevents passage of larger compounds 7 . Encapsulating drug molecules in nano- carriers can also be an effective strategy to increase drug stability by offering protection from degradation, and consequently increase bioavailability and half-life [7].

Nano-based systems also offer a promising approach for targeted drug delivery, and are being used in cancer to specifically target cancer cells. The tumor environment is characterized by increased angiogenesis or blood vessel formation, and these vessels are often "leaky", a phenomenon termed the "enhanced permeation and retention"(EPR) effect. The increased permeability of blood vessels surrounding tumours can be exploited clinically by delivering drugs in nanocarriers, which on account of their small size, can easily diffuse across and accumulate in tumor cells. Vessels surrounding tumours also have impaired lymphatic drainage in tumours, allowing the nanocarriers to be retained in tumour cells and locally release drugs into the tumor environment [8].

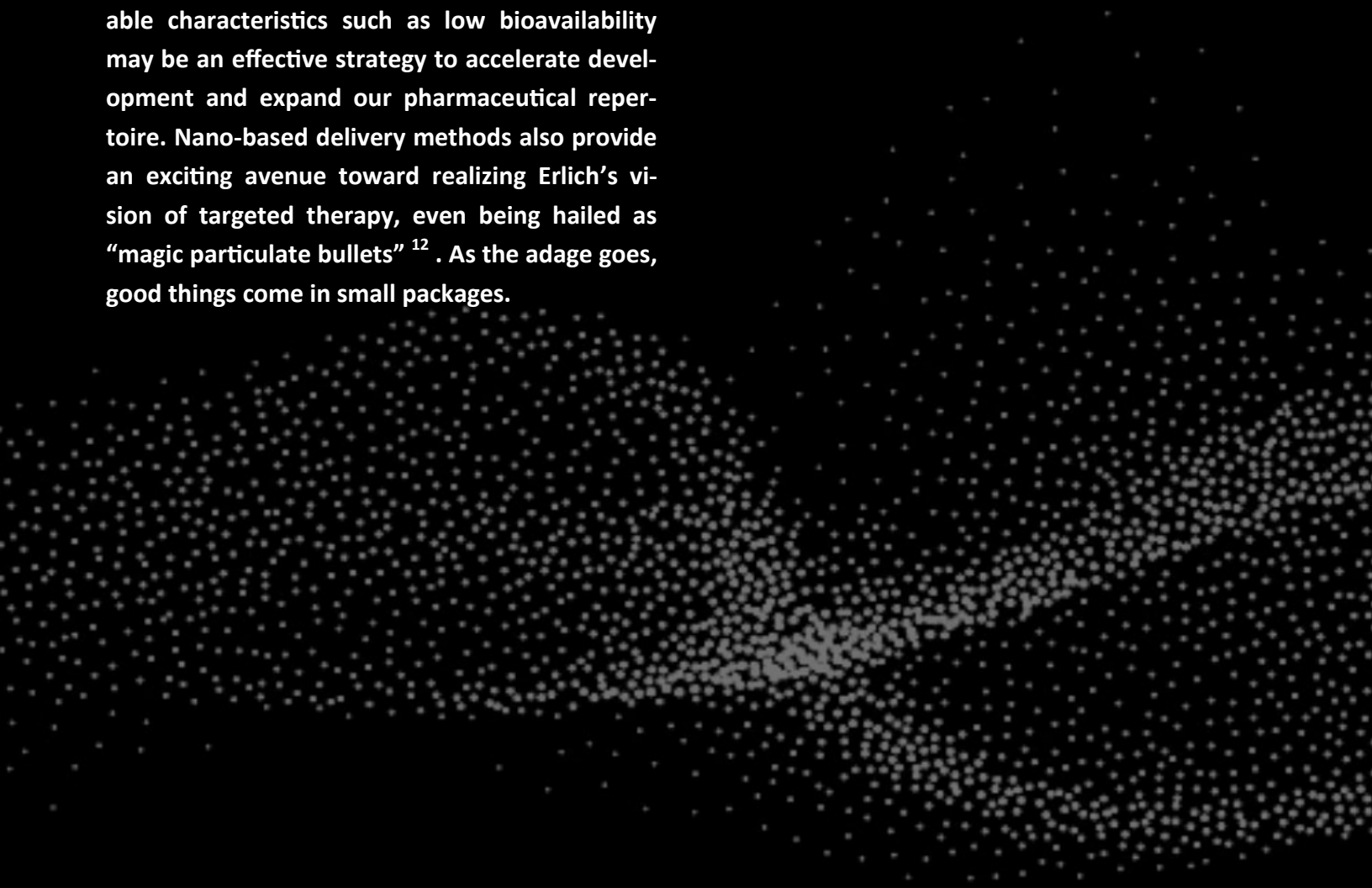
Types of nanomaterials used for drug delivery

Numerous nanomaterials developed from inorganic as well as organic materials are being used in drug-delivery systems. The following discussion will briefly describe two commonly used methods, liposomes and nanogels, in more detail.

Liposomes are capsule-like compartments created from lipid bilayers, and are among the most commonly used vehicles for controlled drug delivery [7]. Consisting of one or more lipid bilayers, liposomes are versatile structures that can carry both hydrophilic drugs in their central aqueous core, or hydrophobic drugs, which can be embedded within the membrane [9]. Due to their amphipathic nature, liposomal drug delivery systems can be particularly useful for delivering hydrophobic or drugs with poor aqueous solubility. Estimates suggest that up to 70% of new drug candidates and 40% orally delivered drugs currently on the market exhibit inadequate solubility in aqueous media [7]. Liposomes can be used to transport hydrophobic drugs in the circulation and also act as a shell to protect drug molecules from degradation. Interestingly, the first FDA-approved nano-based drug system, Doxil®, consists of the chemotherapy drug doxorubicin delivered in nanoliposomes. This method of doxorubicin delivery has been shown to result in increased half-life and 300x greater bioavailability compared to free drug delivered at the same dose [7].

A nanogel is a polymerized non-fluid substance developed from nanoparticles 100 – 200nm in diameter [4]. Nanogels can be created from various synthetic or natural polymers, and are used as carriers for drug delivery. An example of a biodegradable polymer used for developing nanogels is Pullulan, a polysaccharide product of the fermentation of the yeast species Aureobasidium pullulans [10]. Transporting drugs in nanogels is an attractive option as they have high inner surface areas and can hold a high drug load. Nanogels are also particularly useful in creating controlled release or "smart" delivery systems in which the physiochemical properties of the nanogel can be exploited to induce drug release in response to particular stimuli such as pH or temperature that may be altered in disease conditions [11].

Nano-based drug delivery systems are offering powerful ways to overcome limitations of conventional drug delivery methods and are broadening the current paradigm of drug development. Using nano-based delivery methods to repurpose existing drugs and drug candidates that may have been overlooked due to unfavourable characteristics such as low bioavailability may be an effective strategy to accelerate development and expand our pharmaceutical repertoire. Nano-based delivery methods also provide an exciting avenue toward realizing Erlich's vision of targeted therapy, even being hailed as "magic particulate bullets" [12] . As the adage goes, good things come in small packages.



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Orphan Drugs: Canadian Government Oversight Creates Nightmare for Rare Disease Patients

by Maja Soltysiak

Just for a minute, I want you to imagine that you are a new and excited parent; enraptured by your little bundle of joy and dreaming of the life that you are going to share together. Now, imagine after just a few short weeks, you bring your child to the doctor and they are diagnosed with a rare and incurable disease. A nightmare, right? Now, imagine the only treatment option for your child's disorder has been deemed the "most expensive drug in the world" and is inaccessible where you live. This is the heart-breaking reality of the parents of Eva Batista, a Canadian baby with spinal muscular atrophy, and is a story of struggle shared by many rare disease patients and their families[1]. Canada is one of the most developed countries in the world and our universal healthcare system is a prized achievement. However, it fails in one large respect, the lack of an orphan drug framework.

Orphan diseases are diseases that have either been neglected by doctors or only affect a very small population[2]. The prescription treatments for these disorders are referred to as orphan drugs, and though these are potentially life-saving treatments, they are often highly inaccessible in Canada due to their hefty price tags and difficulty faced in the rise to market approval. Without an orphan drug framework in Canada to coordinate drug coverage and negotiate prices, rare disease patients are left to face this great barrier to treatment on their own, suffering and desperate to improve their quality of life, and sometimes to even save it.

Spinal muscular atrophy (SMA) is one orphan disease that has garnered a lot of media attention. SMA is a rare, genetic, neuromuscular disorder that causes the muscles of patients to waste away and currently has no cure[3]. The only available treatment options for SMA patients are astronomically high-cost drugs such as nusinersen (trade name: Spinraza), approved in Canada in June of 2017 and the first drug approved to treat SMA[3]. According to an article in the *Globe and Mail,* the average cost of Spinraza runs extremely high, at $708,000 for the first year of injection treatment and $354,000 in each subsequent year of life[4]. In December 2017, the Canadian Agency for Drugs and Technologies (CADTH), responsible for advising provinces and territories on the coverage of emerging drugs, recommended for drug plans in Canada to reimburse the cost of Spinraza for Type I SMA patients[3]. Spinal muscular atrophy is a spectrum disorder, with Type I SMA onset at less than six months of age and having an average patient life expectancy of less than two years[3]. This initial coverage recommendation was extremely limited, excluding Type 0, II, III, and IV SMA patients and leaving them to suffer, with the knowledge of a possible treatment just out of their reach (see Table 1[3] outlining the SMA spectrum). In March 2019, however, the CADTH extended their recommendation to SMA patients 12 years old or younger who had never walked[4]. Although a tremendous improvement from the previous recommendation, recommendations by the CADTH are not binding, and Saskatchewan and Ontario extended their provinces' eligibility for coverage even further. Ontario's government now covers Spinraza for patients 18 years old or younger who have never walked, and patients above this age may apply for coverage and be considered on a case-by-case basis[4].

Great progress, even still, one might say. But, as wonderful as these changes might be for some patients, the revisions create a discrepancy between the eligibility for coverage between patients of different provinces. Some will fail to meet the requirement in their home province but would be covered in another. This heartbreaking situation is a prime example of how the lack of an orphan drug framework in Canada and instead, a mix of private and public drug plans, results in unequal coverage and medical treatment of Canadian patients[4].

Furthermore, with the lack of an orphan drug framework, less drugs are approved for the Canadian market, therefore adding to the problem of orphan drug inaccessibility. Orphan drugs in Canada follow the same approval process as other drugs[5]. This means a challenging and long process for orphan drugs to make it to the market due to their high cost and small number of users, and therefore, puts companies off from even applying for Canadian market approval[6]. Data provided in an article in the *National Post* shows an immense difference in the number of drugs being approved for the market in Canada compared to the United States - Canada approved 85 orphan drugs between 2013 and 2017, while 30-45 orphan drugs were being approved in the US every year between 2013 and 2016[6]. With this comparison, it must be taken into consideration that the US has a much greater population than Canada and therefore, has more people who require prescription drugs. However, this higher production rate is enabled by the United States' orphan drug framework, an efficient system that Canada lacks. So, not only is there a discrepancy in the coverage of orphan drugs throughout different parts of Canada, there is also a notable lack of approval of orphan drugs for the market in Canada when compared to countries that have orphan drug frameworks in place, such as the US.

Table 1. Phenotype of SMA at different stages (adapted from Table 1 from Vukovic et al. 2018[3])

SMA Type	Age of onset	Signs and Symptoms	Life expectancy
Type 0	At birth	Severe muscle and respiratory weakness	Few weeks after birth
Type I	0-6 months	Muscle weakness, difficulty breathing and swallowing	Less than 2 years without respiratory support
Type II	6–12 months	Muscle weakness, difficulty breathing and swallowing, joint and bone issues	Generally, less than 20 years
Type III	≥18 months	Progressive muscle weakness, swallowing difficulties, scoliosis, joint and bone issues	Normal
Type IV	>30 years	Progressive and gradual muscle weakness, tremors	Normal

The lack of approval of orphan drugs in the Canadian system is also affecting a second treatment for spinal muscular atrophy, Onasemnogene abeparvovec (trade name: Zolgensma). Zolgensma is a single prescription gene therapy, with hopes of becoming a more successful treatment than Spinraza. Zolgensma has been deemed the "most expensive drug in the world", with the single-dose treatment running for $2.1 million per patient[1]. Because it has yet to be approved in Canada and runs at such an astronomical price, Canadian SMA patients are turning to fundraising websites and entering into treatment lotteries offered by drug companies to access Zolgensma[1]. The firm that owns the drug, Novartis, is giving out up to 100 free doses throughout 2020 using a blind lottery system[1]. There is debate between ethicists and parents of patients about ethical concerns of the lottery system. Some argue that a lottery is the best solution, pointing to the fact that lottery systems are accepted ways to give out limited resources and that it creates an equal chance for all entered into the draw to receive treatment[9]; a slim chance of treatment is better than no chance, right? Others say that Novartis has not done enough to improve the scarcity of the drug and that a better solution would be to treat the sickest patients first[9]. As unique and ethically debatable as this "compassion lottery" situation is, it is still an attempt, however, to try and help these suffering patients; an effort not even being made by the Canadian government.

Spinal musical atrophy is a key example of the suffering taking place due to the Canadian government's neglect of orphan diseases and orphan drugs. Plans for a rare disease drug framework were proposed by Stephen Harper's government back in 2012, but in 2017, references to the framework mysteriously disappeared from the Health Canada website[6]. While orphan disease patients were left hopeless for the past couple years, both the Liberal and NDP parties promised new drug frameworks as part of their campaigns for the federal election in 2019[7]. The Government of Canada website currently contains a implementation plan for national Pharmacare, focusing on three main elements: The Canadian Drug Agency, a national formulary, and a national strategy for high-cost drugs for rare diseases[8]. The Canadian Drug Agency will work in cooperation with provinces and territories to evaluate the effectiveness of drugs and help negotiate drug prices, coordinating efforts into a singular entity. The Budget 2019 also proposes to invest over a billion dollars to help improve rare disease drug access in the coming years[8]. This will include the creation of a national strategy for orphan drugs, an effort to improve consistency of decision-making across Canada, and will aim to improve the negotiation of prices with drug manufacturers[8]. Will this proposed national strategy be the end of Canada's orphan drug nightmare, or will the government healthcare system once again disappoint rare disease patients, like those with SMA, and leave them to continue to search independently for medical care to save their lives? Orphan disease patients are already isolated in many respects, with their diseases often lacking attention and understanding in the medical field and pharmaceutical industry, and their experiences unrelatable to the vast majority of people. They do not deserve to feel abandoned by their government, as well.

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How Incentivizing Scientific Evidence Standards Can Legitimize Natural Health Products

by Emily Saso

How would you define a drug? Do you consider "natural" products to be drugs? What about the fact that morphine is natural[1]? When searching the internet for what a "drug" means, the search for a distinct definition becomes quickly blurred with many subjectivities. Drugs are "especially narcotics"[2] — does this mean that non-narcotic drugs are less qualified to be a drug? Synonyms involve "cure" and "remedy"[3] — confusingly, these words are not synonymous with one another[4]. At Health Canada, there are divisions that distinguish between "drugs" and "non-prescriptive and natural health products"[5]. One might assume that Health Canada, the governmental regulatory body for drugs in our country, would be able to distinctly define a drug from other substances we consume. As follows:

A drug is *"any substance or mixture of substances manufactured, sold or represented for the use in:*

1. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals, or

2. restoring, correcting or modifying organic functions in human beings or animals, or

3. disinfection in premises in which food is manufactured, prepared or kept [2, FDA]."[6]

A natural health product (NHP) is *"a substance […] or a combination of substances in which all the medicinal ingredients are substances set out in Schedule 1, a homeopathic medicine or a traditional medicine, that is manufactured, sold or represented for use in:*

1. the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans;

2. restoring or correcting organic functions in humans; or

3. modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health."[6]

When comparing a drug to a NHP with respect to intended use in human administration, they almost appear convincingly identical. They both are used for diagnosis, treatment, prevention and mitigation of diseases and symptoms. They are also both involved in the restoration, modification, and correction of organic functions. In order for a drug-claim to be approved, the product must have an effect on the body that is beyond what is associated with food — that is, it must be involved in the "the treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms"[6]. A NHP does such, yet it does not qualify as a "drug". Frankly, it is confusing and frustrating for two compounds to be regulated so differently at Health Canada despite their own definition of the two compounds being so similar. Approval for a drug at Health Canada is a two-year process, let alone all of the additional years spent preparing the drug for market — approval for a NHP can take as little as 60 days[7,8].

In 2012, a 19-month-old boy in Alberta died from meningitis when his parents opted for the use of natural remedies instead of seeking conventional Western medical approaches[9]. Dr. David Juurlink, a professor at the University of Toronto in the Department of Medicine, claimed that Health Canada essentially "legitimizes this nonsense" — referring to NHPs[9]. He states that Health Canada can make money by pushing products towards uneducated consumers who are enticed by the philosophy of natural medicine without realizing that, "what they're being sold is just absolute garbage"[9]. On the same topic, Dr. Heather Boon, a faculty member at the Leslie Dan Faculty of Pharmacy, believes that the extreme dichotomy between natural products and conventional medical treatments aren't necessary, and that educating the public on what Health Canada's approval for NHPs accurately means[9]. She continued by pointing out examples of patients taking both a combination of conventional medicine and natural, "alternative" medicine to treat illnesses such as cancer[9]. However, Boon points out that there is no approved NHP to treat meningitis, and as such, conventional medicine is more suited for the treatment of acute illnesses[9].

It is clear that in the medical community, NHPs are not taken in a serious light, as displayed by Dr. Jurrlink claiming them to be "nonsense"[9]. If NHPs are defined to be substances that treat and prevent disease while correcting, modifying and restoring organic functions in humans, why is it then that most NHPs cannot scientifically prove so? This is where Health Canada's regulatory standards become the root problem of this concept with NHPs in the medical community; it is not the fact that all NHPs are illegitimate, but rather the fact that an absent incentive to provide scientific evidence leads to the approval of illegitimate products within the class of NHPs.

Where drug-approval requires rigorous data from multi-phase clinical trials, NHPs can apply solely for "traditional claims"[10]. In order for a substance to make a traditional claim, two sources of evidence are needed, including at least two generations of use. It is stated that traditional claims are "claims based on the sum total of knowledge, skills, and practices based on theories, beliefs, and experiences indigenous to a specific culture, used in the maintenance of health, as well as prevention, diagnosis, improvement, or treatment of physical and mental illness." One of these sources can be based on belief, and the other can be any article about the substance — peer reviewed or not[11]. NHPs also have the option to make "modern claims," but it is not a necessity for NPH labelling standards[12]. A modern claim is "based on evidence from a range of sources, including (but not limited to) clinical studies, animal and in vitro studies, pharmacopoeias, textbooks, peer-reviewed published articles, and regulatory authority reports"[12]. The scientific rigour that is required in order to meet the standards of modern claims far exceeds what is needed to make a traditional claim. This is not to say that traditional claims need less "tradition" and more "science," or that traditional claims should be discarded altogether — minimizing tradition by smothering it with science is not the argument being made, nor is it necessary. Rather, modern claims should be mandatory for the approval of NHPs, not optional. Maintaining traditional integrity and values of natural products while increasing scientific standards is essential. By doing so, the class of NHPs will become more refined in terms of approved products and more robust in terms of knowledge within databases and in the medical community. If this is not possible with the way that current NHPs are pooled together, then further segregating the NHP branch into more subsections would needed. This can ensure proper usage of NHPs, especially when taken in conjunction with conventional Western medicine. To emphasize the harm of NHP misconceptions and the lack of thorough regulations, consider the following (hypothetical) scenario:

A patient has kidney failure — they are constantly going to the hospital for dialysis, which is emotionally, physically and financially draining. Unfortunately, dialysis is no longer sufficient, and the patient needs to have a kidney transplant. In order to cope with the mental toll this has taken on the patient, they decide to go to a NHP store to purchase St. John's Wort.

They heard from their friends that this NHP can help with feeling moderately depressed, which is what the patient is looking for as they cannot afford psychiatric therapy in addition to other medical bills[13]. With the current perception and knowledge on NHPs being "fake medicine," this patient thinks that St. John's Wort will at best provide a placebo effect, and so they begin to take the product. A few months down the road, the patient is relieved of some of their depressive symptoms. They feel more confident about their kidney transplant procedure and successfully come out of the surgery with no complications. While they are healing, the doctor prescribes the patient immunosuppressants in order to prevent organ rejection. However, the patient does not notify them of any medications they are taking, because they do not see St. John's Wort as a "drug". The patient while in recovery becomes ill and their body starts to reject the kidney despite taking immunosuppressants — the patient's immune response to the transplanted organ quickly becomes severe and fatal.

St. John's Wort is a chemical substance with legitimate medical implications — it is not "nonsense" just because it is classified as a NHP. St. John's Wort has active constituents, hypericin and hyperforin. These substances interact with an enzyme in our liver that metabolizes roughly 60% of prescribed drugs, known as cytochrome P450 3A4 (CYP3A4)[14]. CYP3A4 is induced by the active constituents in St. John's Wort — enhancing metabolic activity, therefore increasing the metabolism of other drugs that interact with this enzyme[15]. In the given scenario, the patient experienced a fatal immune response to the transplanted organ post-surgery as the immunosuppressants were metabolized by CYP3A4 and rendered inactive at a faster rate due to this enzyme induction. The majority of consumers are under the influence that NHPs are "safe" and do not have serious medical implications on our health like Western medication. However, any administered chemical substance to a human can be toxic depending on its dose and the accumulated concentration of the substance. NHPs are not always safe just because they are natural, and can pose serious medical consequences, as seen with St. John's Wort.

This is the heart of why NHPs need more credibility for their medical effects on the human body, and why the regulations at Health Canada need to incentivize stronger scientific standards in order to legitimize the entire class of substances. There are thousands of compounds in the Non prescription and Natural Health Product Directorate[16]. Due to the lack of scientific evidence required for the approval of such products, substances that have no scientific validity end up being approved, and the NHPs that do have medical implications have no incentive to produce research that displays their accurate effects on humans. This makes for a very dangerous guessing-game and overall illegitimacy to the class of NHPs. If scientific standards required for NHPs incentivized additional, more rigorous scientific evidence proving drug efficacy and health implications, the class of NHPs would become more legitimate and the public would know more on how to safely use such products. It would kill two birds with one stone — a class of products that are efficacious and also have medical information to keep the public safe. With this legitimization of NHPs, the medical community would acknowledge such products as more than just "garbage" and would in turn encourage the public to communicate these types of products to their health care provider(s) to ensure optimal treatment.

Beyond this — regardless of Health Canada changing their regulations — a step that should be taken is the education of the public on NHPs. Awareness of the medical implications of products that aren't necessarily classified as "drugs" is crucial to maintaining the safety of the public's health. This is a step we can control, and with that it can significantly influence our health and therefore our lives. Doing research, attending educational classes on NHPs and communicating with pharmacists, physicians and other health care providers about taking over-the-counter products is essential to improving the health care system. In science, we don't know something until it is proven — or disproven. Just because there is no scientific evidence on an NHP's efficacy does not mean that is not efficacious. Better yet, and seen throughout this article, perhaps the dismissal of product efficacy is due to the fact that there is no incentive to prove it. What would you now consider a drug compared to when you first opened this article?

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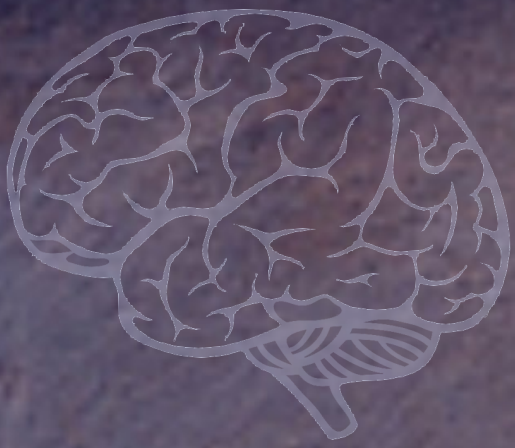
An insightful conversation with

Dr. Kirk Nylen, PhD

"...Sometimes our view...



...isn't alway

the only

approach.

Can you tell us a little bit about yourself?

To start off, I originally wanted to be a police officer, but my mom told me I needed an undergrad before I could go to police academy! In undergrad I went to the University of Saskatchewan. I took a neuroscience class for fun, and I really enjoyed it., I published my first paper in that class actually, and that's when I realized I wanted to do research. Of course, this meant that I needed to take more classes and really apply myself. Later on, I came to UofT for my Masters and PhD in neuroscience and pharmacology. My plan was to be an academic, to run my own lab. As I was writing my thesis, I realized this was no longer what I wanted, instead I wanted to find a job and start working. Most of my friends have been working many years already, and I was still in school. I felt pretty unprepared, and it was a painful few months while I was looking for work. I learned a lot in that process, and ultimately, I networked with some people in the field, they introduced me to some other people, and eventually I was offered a 6 month contract at Cancer Care Ontario. Eventually I came to the Ontario Brain Institute (OBI), where I have worked for nearly 9 years.

At the Ontario Brain Institute, what's your day to day role?

I oversee many of the research programs that we fund. There are six major programs that span neurodevelopmental pediatric conditions through to neurodegenerative conditions, and everything in between. We bring these networks together to collaborate, share data, work with public and policy makers, patients, clinicians, and industry. Our day job is to manage these outputs of science, where we make sure science happens by providing funding. Once people have funding, we make sure collaboration happens, and they have what they need so they can get the job done. I meet with lots of different people to discuss funding and facilitate these partnerships. We talk about timelines, what needs to be done, and many other logistic topics. We also need to ask them a lot of questions about the nature of their research, their contracts, and how we can support each other. Meeting with collaborators is a huge part of my job, and we need to facilitate communications between groups.

What skills do you think help you in school as you do in work?

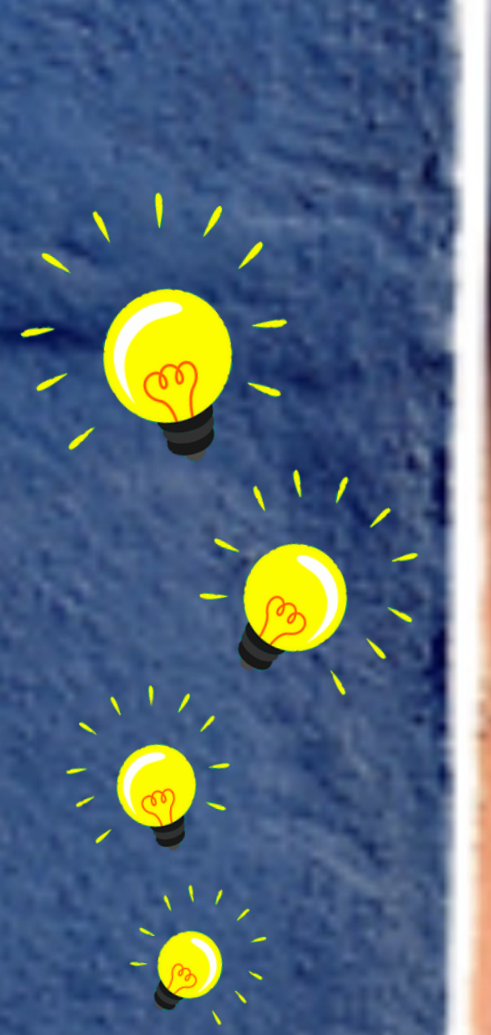
Communication is a big one. Being able to communicate to colleagues, to external stakeholders, and laypeople is foundational. In this environment, you really need to be a good communicator. Also the ability to work by yourself. Often you work in teams, but you need to be driven. No one is starting things for you, you need to be a self-starter. There's also the analytical aspect: it's easy to find problems, but proposing solutions to that problem can be challenging.. If you don't propose solutions, someone else will do it, and their solution might not be the one you like.

What inspired you to go into neurosciences?

There is a family connection for me in epilepsy, so that was one thing. Also, I was fascinated byy epilepsy because it really got me curious about how the brain works. When I was doing early research, we were doing electrophysiology, and we were finding that creating the same stimulation over time can cause a full blown seizure. You're creating plasticity in the brain, a network that is very unique. Different parts of the brain can be more or less plastic, and they're all very different. During my PhD, I studied this at the cellular level - figuring out what's causing the brain to make connections in some areas but not others. After these years of hard work, I still feel like there is still so much to learn. It's quite challenging! Will we ever understand our own brains?

So after all these years of working on projects in academia and in the industry, what would you say is the most rewarding project?

That's a good question, to me the most rewarding activities involve the communities. That's what we ultimately want to impact, we want to see people living healthier and better care for the people they love. You want them to have access to resources, so one of our programs called GEEK funds community organizations. They specifically support people with brain disorders at the community level and we aim to help them increase their reach to other communities. An evaluator will come in to measure the effectiveness of their program as they spread the scale of their activities as well as understand the value of the program. That stuff is meaningful because you get to go to the communities and see the good work that people do, you see people that can't do things now able to do these said things due to the support that they can get. We've done work with indigenous groups which was an amazing learning opportunity for me, because I was able to learn about their world views towards diseases. For many of us, we see diseases as where you are healthy or not, and if you're not we need to help you to become healthy again. In other cultures, they view it as a different phase in life, where it has its own virtues and drawbacks. Where the need isn't to fix it, but to embrace and accept it with a different approach. There is very powerful learning there, where we realise that sometimes our view isn't always the only approach. Communities are where I am rattled and able to see the impact we have. In the research world, it is hard to see this since you are so far removed from target. For example, if you are studying a cancer drug, it's unlikely you get to see people that have cancer telling you the issues they are having or how the drug is working directly. You are often far removed from it. One thing that we do is be part of the community and see what's happening first hand.



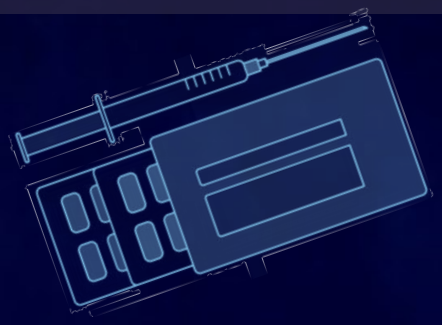
Many students now are looking for jobs potentially for the summer or after they graduate, perhaps having trouble writing resumes or cover letters, or how they approach emailing companies. Do you have any tips on how to improve these skills?

The department is very well connected with the industry and as I say often, you don't want to be totally anonymous. If you send an anonymous email, your odds are lower than you are known somehow. If you send a note about an internship to a drug company and they have no idea who you are, it is treated very differently than if a member of thefaculty says "I know so and so, I can put you in touch and you can email them about their internship program". Totally different response, first of all you will get a reply. Secondly, there is built-in trust since this person may not personally know you, but someone they trust knows you meaning you are more highly recommended than coming anonymously. So networking is really important. Not being anonymous as someone who knows someone that can maybe make an introduction may be better than no introduction at all. There's little tricks you can do, like if you are applying for a job. I need to go from 200 applicants to 6 or 5 applicants I want to talk to. How do I do that? Most people that have similar applications. Usually things that distinguish them I find interesting, versus someone else that may not. If I know you, it goes to the short pile. If i have any reason to think you are good, then you get into the short pile. If I don't have a method like that, then I look for keywords. Often big companies have keyword search. They have a document with several keywords for that position. So in your cover letter, you need to hit them. They just do a word matching exercise. So what are the things that this company/role really want and how do I convey this. Hence the purpose of the cover letter is to get into the short pile and also receive an interview. It's not to get the job itself. So understanding and trying to be known and address the key things directly in the cover letter. You never use the same application for two jobs. If you do, you've not done the word mapping, and every job is slightly different. You need to tailor the side that you want to show for that job.

"Healthcare doesn't only happen in hospitals and drug companies, healthcare is something that is led by the government, and implemented by the healthcare community and furthermore informed by the community."

A lot of students have the mindset of not wanting to do research and perhaps want to do industry. What are some of the challenges being in industry?

That's a good question, I think there are challenges no matter where you go, especially in Ontario, there are many big companies. With these big companies it is harder to stand out, but there is more opportunity as well. I guess for me it's very personal: if you want to feel you are making a difference and having an impact, it's harder to feel that in a larger company. And what you're doing is very far removed from what is happening on the ground. Not many people are interested in policy or government, but if you want to impact 14 million people right away, then policy can have that effect. It may be a bit unfair to say, but I think that in pharmacology, people get a very singular view on how we can help people. Obviously pharmaceuticals are a cornerstone of healthcare, but there are other areas that you can get into that may also allow you to do things that can have the same positive Impacts.



What advice would you give to an undergrad student in pharmacology right now?

The thing that I wish I had known back then is what is happening right now (during that time) in the health area. You can get really drilled into your field, but it's important to remember you are in a health field. Healthcare doesn't only happen in hospitals and drug companies, healthcare is something that is led by the government, and implemented by the healthcare community and furthermore informed by the community. You need to know what is going on in those spaces to operate in them. When I was in a research lab I was very invested in that research, but when I decided that I no longer wanted to do that, I felt lost. I had no idea on how policies were made, how research shaped any of that stuff, how clinicians gain knowledge outside of medschool and grow their learning. Not knowing that stuff left me at a disadvantage. I was probably quite naive, even though I had a PhD in pharmacology, compared to individuals with a Masters in Health Policy who are much more "worldly". So I had to learn those things on the job. Hence, I would've tried to understand policies and how these work, what their key priorities are, and how my research may have benefited these said policies. Also perhaps meet people outside of academia. Academia is quite insular, government is insular, healthcare is also insular where they all have their own communities. Hence these things need to be heavily connected and networked, where I don't find that they are such that you should do this as early as possible.

STUDENT PERSPECTIVES: ACAD

Phrom Pharmacology & Toxicology to PharmD

The PharmD program offers an opportunity to integrate some contents acquired from the Pharmtox program and applying that on a clinical level. It brings you closer to the aspect of patient-care and healthcare beyond just theories and the physical science environments. Personally, I find it valuable going through the Pharmtox program during my undergraduate years because it provided an extensive amount of knowledge to drug mechanism and toxicology. Although this plays a minor role for the PharmD program, it allows a chance to connect the "why" and "how" drugs are being studied and applied for therapeutic management. The PharmD program allows me practice my knowledge of drugs in medicine while working alongside other professions to benefit the healthcare system.

- Khoa Vu, 1st year PharmD

A Winding Road for Toxicolo

In the first 6 months of r experienced many ups and dow all) grad students go through. I to be in a lab that has a great su through all the downsides of sc grounded when things are goin

My advice to undergrad pursuing a graduate degree is t three things: the PI, the researc ronment. Because your PI will b graduate studies, it's important your PI. It is equally important what you are looking for. In adc that you will be taking on must joy and find interesting - this w couple of years.

Lastly, your lab mates w will be seeing everyday for the they will become part of your s need to be able to get along wi good working relationship. Goi won't be an easy endeavour; if it. I decided to pursue graduate ested in pursuing a career in sci part of research and graduate s tially be the first person ever to thing. I strongly encourage any ence to apply to and pursue a g

- Jonathan Chow, 1st

EMIC LIFE AFTER UNDERGRAD

a Pharmacology & gy PhD

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Master's Degrees in Applied Clinical Pharmacology: Same Title, Different Paths

Graduate school does not necessarily always entail research – those who wish to delve further into pharmacology, but are uninterested in academia may choose to pursue a course-based Master's program instead. Applied Clinical Pharmacology (ACP) is a coursework-based program offered by this department that combines the theoretical aspects of pharmacology with practical applications in the real world. ACP offers the same standing (MSc) as any other Master's degree, while granting much more flexibility – while courses can be challenging, students have enough freedom to pursue other interests, allowing for them to develop into more well-rounded individuals.

Many students wish to pursue graduate school but are hesitant to do so because they may not be interested in research. ACP serves as a compromise, a best of both worlds, where students can continue to gain knowledge of pharmacology and pursue an advanced degree, but at the same time are exposed to the world of industry. And as such, most ACP students eventually pursue a successful career in industry, such as pharmaceutical consulting, working for a governing agency, or managing clinical trials.

- Daniel Li, 1st year ACP


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