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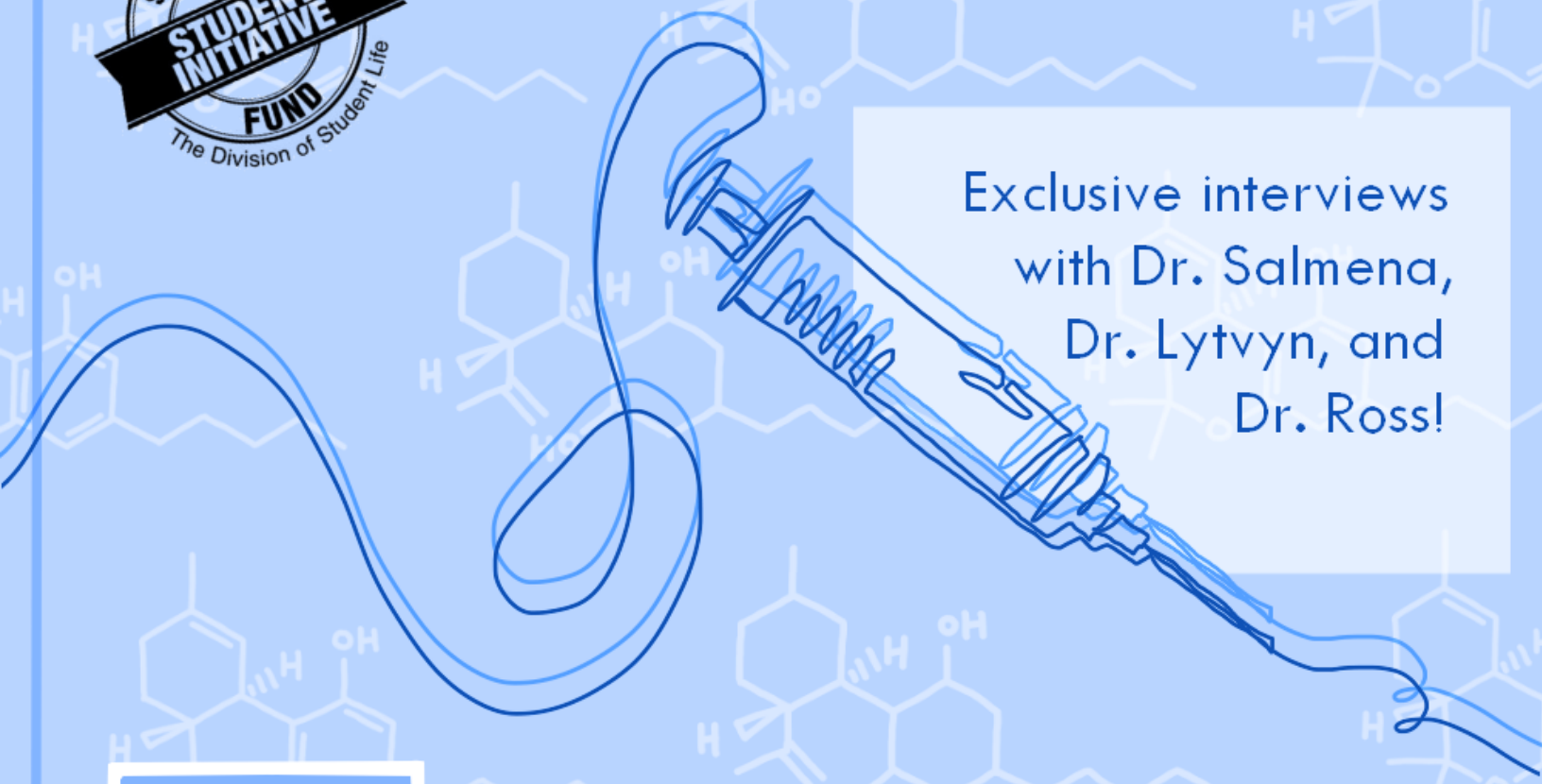

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Pharma Chronicle

January 2020

welcome to the 4th volume of the Pharmachronicle!

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L-DOPA: Restoring Coordination and Qwelling the Tremors of Parkinson's Disease

by Cathy Zhang

For centuries, many individuals in the elderly population have been afflicted by the neurodegenerative disorder known as Parkinson's disease – or 'PD' for short. Characterised by physiological changes in various motor and non-motor functions, Parkinson's disease is the deterioration of neurons in the brain, and typically impacts those who are around 60 years of age or older. When certain neurons break down, the amount of dopamine decreases, thus impacting brain activity and consequently motor function (Zafar & Yaddanapudi, 2019). Those with PD mainly exhibit motor symptoms such as bradykinesia, which is characterised by the slowing of bodily movements. Other attributes include rigidity of limbs and resting tremors. The latter is observed as shaky limbs when the muscles are relaxed or limbs are stiff (Zafar & Yaddanapudi, 2019). In addition, those with PD can also potentially develop sleep and mood disorders (Massano & Bhatia, 2012). Although there currently exists groundbreaking therapeutic medications – such as L-DOPA (Figure 1) – that effective ly treat PD, the exact cause of the disease remains undetermined. It is postulated that a combination of various environmental and genetic factors plays a significant role in increasing the risk of PD. Environmental factors include lifestyle (such as exercise and choice of diet), exposure to agricultural chemicals, and a history of head/brain injury ("Environmental Factors," 2018); genetic factors include mutations on the genes SNCA, EIF4G1, GBA, LRRK2, PINK1, SOD2, and VPS35 (DeMaagd & Philip, 2015). Overall, the risk of PD in the population is largely associated with age, with an increase in occurences of PD in older individuals (Massano & Bhatia, 2012).

People with PD typically have little to no dopamine in their brain, and consequently exhibit changes and irregularities in motor control. Deficiencies in dopamine play a crucial role in Parkinson's disease. Dopamine relays signals between neurons, and these signals act as messages that coordinate and manage movement (Figure 2). The neurotransmitter is produced by nerve cells in the substantia nigra section of the basal ganglia (Massano & Bhatia, 2012), and in the case of Parkinson's disease, these dopaminergic neurons deteriorate and die, resulting in substantially lower dopamine levels in the brain, and consequently changes in motor control (Brazier, 2018) which are observed as motor symptoms.

In the late 1960s, levodopa, or L-DOPA, was identified as a potential drug therapy to treat the symptoms that accompanied PD. The drug was further developed in the 1970s to reduce side effects and improve efficacy, by administering it in combination with the drug carbidopa (Tolosa, Martí, Valldeoriola, & Molinuevo, 1998); the levodopa-carbidopa combination medication was FDA-approved in 1975, under the name *Sinemet ("Levodopa," 2019). Levodopa continues to be the most promising drug used in standard dopaminergic therapy to treat PD (Salat & Tolosa, 2013).*

L-DOPA works as a prodrug, meaning that it is a precursor molecule that is metabolised to the desired drug, dopamine. It is used instead of directly administering dopamine, as L-DOPA can pass through the blood-brain barrier ("Levodopa," 2019) whereas dopamine cannot. During therapeutic treatments, L-DOPA is administered together with carbidopa, which prevents early metabolism of L-DOPA into dopamine prior to crossing the blood-brain barrier. Thus, a higher concentration of L-DOPA is able to cross the barrier into the brain, where it is subsequently metabolised through decarboxylation, to yield dopamine ("Levodopa," 2019). Now present the brain, the dopamine derived from L-DOPA supplements the deficient dopamine levels in those with PD, and can thus stimulate dopaminergic receptors to help control body movement.

The treatment of Parkinson's disease using L-DOPA comes with many benefits. L-DOPA can be used as a treatment at any stage of the disease, and it remains the most effective drug therapy to alleviate the debilitating symptoms that arise from PD, especially rigidity and stiffness of limbs ("Levodopa," 2015). In terms of treating Parkinson's disease, L-DOPA can be administered intravenously (IV) or orally, with the former method historically being used first, and the latter quickly gaining popularity as an alternative means of treatment (Siddiqi et al., 2016). In addition, L-DOPA can be taken through enteral and respiratory methods; the former is performed using a pump for enteral infusion, to directly introduce a levodopa/carbidopa dose – in gel form – to the intestines. Studies regarding oral and IV L-DOPA have shown similarities in the safety and efficacy of both methods in humans. Moreover, IV administration of the drug does come with its own merits – it has shown comparatively consistent pharmacokinetic properties across various patients, and allows for further studies regarding related pharmacological and pathophysiological properties, even after approval (Siddiqi et al., 2016). When taken orally, the drug can take effect in as early as 30 minutes, and persist for approximately 3 to 5 hours. However, it should be noted that the actual duration of drug effectiveness might vary between individuals ("Parkinson's Disease Medications," 2014).

Like the vast majority of drugs, however, L-DOPA has side effects. As substantiated by data from a paper by neurologist Barbeau (1969), common side effects include gastrointestinal complications such as nausea and vomiting (clinically problematic in 43.7% of patients in the documented study), and neuropsychiatric effects such as dyskinesias (50.0% of patients) – this is when the patient exhibits unusual, involuntary body movements (Siddiqi et al., 2016). It has been observed that switching to lower doses of L-DOPA can lessen the occurrences of Dyskinesias (Barbeau, 1969). Vomiting can serve as a significant challenge for those who take L-DOPA orally, especially if the patient experiences the side effect even in small doses. Hypotension is another commonly observed effect in PD patients using L-DOPA (31.2% of patients); furthermore, changes in mood and behaviour were also noted (Barbeau, 1969). Overall, these side effects act as limitations in the prolonged use of L-DOPA to treat Parkinson's disease.

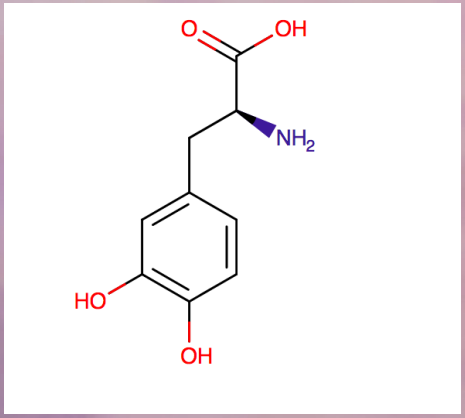

Figure 1: Chemical structure of levodopa (L-DOPA), a therapeutic prodrug used to treat Parkinson's disease, where there is a deficiency in dopamine. L-DOPA can be metabolised to dopamine, and is useful in therapy for Parkinson's disease as it can cross the blood-brain barrier. Figure source from "Levodopa," 2019.

Some long-term users of L-DOPA may experience the 'wearing off' effect, where the therapeutic effects of the drug fade before the next scheduled dose (Jankovic & Aguilar, 2008). This is characterised by the return of PD symptoms, and is potentially alleviated through extending the rate at which L-DOPA is administered. *Sinemet CR (controlled release) is a form of the levodopa-carbidopa combination drug, where L-DOPA is slowly released over a period of time to mitigate the wearing off effect (Jankovic & Aguilar, 2008). However, in comparison to the standard Sinemet medication, the controlled release preparations may see a weaker response after the initial morning dose, and can furthermore intensify dyskinesia (Jankovic & Aguilar, 2008). It is also imperative to note that the effectiveness of L-DOPA only lasts for around 5 years, and the ability for the drug to work after then begins to diminish shortly after. Thus, there is still the problem of providing long-term L-DOPA treatment to patients, beyond the 5 years for which it is effective.*

The discovery of levodopa in connection with Parkinson's disease serves as a key milestone in medical history with regards to treating the symptoms of Parkinson's disease. It reflects the prominence of neuroscience in clinical trials and drug development, and has dramatically improved the lives of many individuals diagnosed with PD (Jankovic & Aguilar, 2008). Given its exceptional, unparalleled effectiveness in treating the symptoms of PD, L-DOPA currently remains the standard therapeutic drug for the disease. However, although it is presently the most effective and commonly used drug used to treat Parkinson's disease, L-DOPA still carries various complications and side effects which hinder its ability to provide long-term relief for the symptoms of PD.

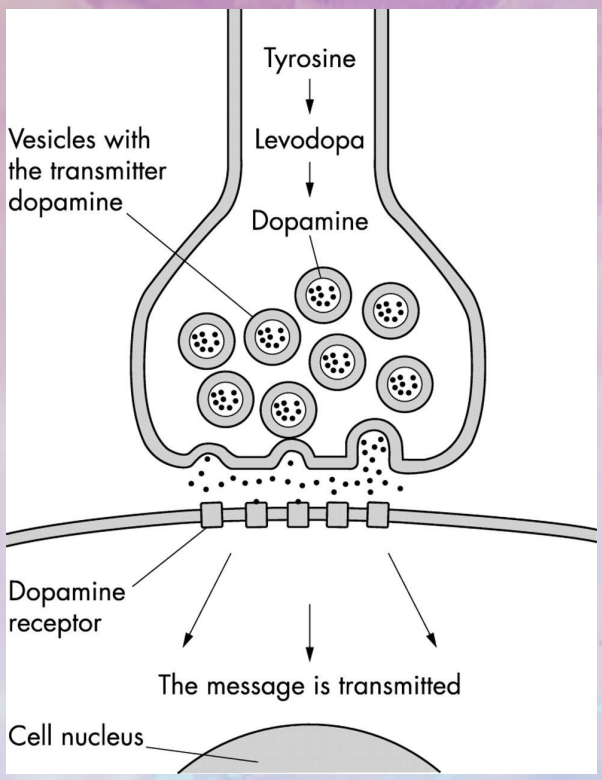

Figure 2: Mechanism of action of levodopa (L-DOPA). Tyrosine, an amino acid, can react with the enzyme tyrosine hydroxylase to yield L-DOPA, which can in turn be decarboxylated by the enzyme aromatic amino acid decarboxylase (AADC), thus producing dopamine. The neurotransmitter can then be transported via vesicles, from the presynaptic neuron to the synaptic cleft, and subsequently interacts with dopamine receptors on the postsynaptic neuron. This allows ion channels on the neuron to open, eventually leading to an action potential; a nerve impulse, which acts as a message, passes through, and movement is controlled. Figure source from Thanvi & Lo, 2004.

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Sertraline: The Therapeutic to Treat Depression and Obsessive Compulsive Disorder

by Brian Chan

Mental health disorders - such as depression, obsessive-compulsive disorder and panic disorder - are found in individuals of all ages, where a wide range of symptoms can be experienced. For depression, this includes and is not limited to feelings of unhappiness, losing interest in hobbies, and/or symptoms of anxiety. Physical symptoms can also be experienced, such as inconsistent sleep patterns, aches or pains, etc. The mechanism of depression is very complicated, such that multiple neurotransmitters are involved in the development of the disorder. These include serotonin, dopamine, norepinephrine and many others, where these neurotransmitters have been known to regulate mood.

For an accurate diagnosis, symptoms for mental disorders must follow a strict manual such as the Diagnostic and Statistical Manual (DSM). The DSM is a widely accepted and used diagnostic manual for mental disorders, where for depression, five of the ten stated symptoms must be experienced by the patient. The symptoms must be experienced for at least two weeks and affect the individual's daily life to be considered according to the manual. However, this manual is not the only available one, such as "The Chinese Classification of Mental Disorders" (CCMD). However, the reliability of these diagnostic manuals has been criticized for many years, since most of the symptoms are self-reported by the patient, which can result in different treatments for the disorder. One of these treatments is the administration of sertraline, which will be further discussed below.

1. (https://www.nhs.uk/conditions/clinical-depression/)
2. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6065213/)
3. (The most complete account of sertraline discovery, targeted at chemists, see: Welch WM (1995). Discovery and Development of Sertraline. Advances in Medicinal Chemistry. 3. pp. 113–148. doi:10.1016/S1067-5698(06)80005-2. ISBN 978-1-55938-798-9.)
4. (Hilal-Dandan R, Brunton L, Goodman LS (30 December 2013). *Goodman and Gilman Manual of Pharmacology and Therapeutics* (Second ed.). McGraw Hill Professional. p. 247. ISBN 978-0-07-176917-4.)

In the past few years, the prevalence of depression and other psychiatric disorders have increased to unimaginable levels. The main causes of these disorders are unfamiliar, yet there are still methods in which are applied to treat individuals suffering from them, such as the drug Sertraline. The start of sertraline goes back all the way to the early 1970s, where the invention of a novel psychoactive compound derived from the structure chlorprothixene was performed by the a chemist at Pfizer, Reinhard Sarges. Through this process, he was able to create lometraline and tametraline. The development of tametraline was quickly halted due to its stimulant effects found in animals that was not the desired outcome. However, in 1977, Kenneth Koe – a pharmacologist – became interested in tametraline's structure. He requested Pfizer chemist William Welch to help synthesize unexplored tametraline derivatives for testing. One of the many derivatives was found to have a serotonin reuptake inhibitor action. Stereoisomers of this compound were produced and tested in animal model by behavioural scientist Albert Weissman. The most potent isomer was further developed into the drug we know as Sertraline.

Sertraline is a type of selective serotonin reuptake inhibitor (SSRI),; hence it a class of drugs that targets sodium dependent serotonin transporters by inhibiting its ability to retake serotonin back into neurons. This thereby increases serotonin concentrations in synapses, meaning there is increased activation at the post synaptic neuron. It also has a relatively high affinity for the dopamine transporter. Hence, at high dosages, it is possible that it can be inhibited by sertraline. This mechanism is also highly beneficial for the treatment of depression as it increases dopamine concentrations in synapses, hence aiding depression therapy. Sertraline, when ingested orally, is slowly absorbed. Maximal concentration of the drug is observed ~4 to 6 hours after ingestion, where it has a volume of distribution of >20 L/Kg. It is then later metabolized in the liver via demethylation to produce an inactive metabolite by multiple types of cytochrome 450 enzymes.

Sertraline can be used for multiple mental health disorders, such as depression, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder. The development of these disorders is not as simple as an imbalance of neurotransmitters; hence it is hard to pinpoint and find an effect therapeutic for each patient. However, the administration of this drug can result in some side effects. Sertraline can cause undesired sexual affects, much like other SSRI's. This includes sexual arousal disorder and difficulty obtaining orgasm. As stated by Ferguson (2001), after receiving treatment, around 67% of men had difficulty ejaculating. However, overall patient mood improved over time, as the positive effects of the drug counteracted their sexual discomfort. The drug can also have an effect on pregnancy, where there is an average decrease in duration of pregnancy by three days. There is also the chance of lower birth weight in babies. As seen on the packaging of sertraline pills, there is a warning for increased suicide rate in individuals younger than 25. This is based on the statistical analysis performed by the FDA that showed that individuals under the age of 25 that are given this drug have an increased risk of suicide ideation and suicidal behavior. Finally, there is the possibility of experiencing discontinuation syndrome, where dose reduction or discontinuation of the drug will cause side effects. These include flu-like symptoms, disturbances in sleep, movement, mood, etc.

Sertraline has had a profound effect on many individuals with mental disorder, improving the quality of life for many. Having been the most prescribed psychiatric drug in United States in 2016, it is not hard to say that it is a crucial drug in mental health history.

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The Opioid Crisis

by Ersi Zabzuni

Dilated pupils. Unconsciousness. Respiratory depression. This is the opioid overdose triad, which occurs from the immense respiratory depression opioids are responsible for. The opioid crisis can be observed around the world. According to the WHO, the extensive use of opioids lead to 118,000 people subsequently dying from overdose in 2015 alone (2019). This population is equivalent to that of the entirety of Aruba being annihilated. Common examples of intentionally used opioids that may cause overdose include morphine and heroin, however overdose can also occur by lacing other drugs with trace amounts of opioids such as fentanyl and carfentanil. The increasing prevalence of opioid overdose has made it a current hot topic that is being intricately researched and devoted attention to.

Some background information

Opiates, opioids or analgesics, can be natural or synthetic compounds, which are derived from the opium poppy. They produce a response by binding to mu, kappa and delta opioid receptors and reducing the ability of neurons to excite and elicit action potentials.Normally, GABA neurons release GABA to inhibits the dopamine neuron from releasing dopamine. When opioids are present, they bind to the mu opioid receptors on the GABA neuron and block the release of GABA. With the lack of inhibition from GABA, dopamine neurons are unable to hyperpolarize and therefore releases dopamine into the nucleus accumbens. The pharmacological profiles of the various opioids are similar, however have distinct characteristics. For example, heroin is a semi-synthetic opioid that exerts similar effects as morphine, however is 3X more potent. It is also more lipid soluble than morphine, which allows for the immediate onset of it. Dependence and tolerance are significant effects that can occur while using opioids because of the drugs' highly addictive profiles. Chronic administration may result in the need for a higher dose each time to achieve the same effects, otherwise known as tolerance. Homeostasis is an offset when tolerance occurs and a new benchmark of "normal" is achieved. The local inhibition of the preBotzinger Complex by opioids are responsible for causing respiratory depression, which can be lethal. Montandon et al discovered that this area of the brain is especially sensitive during sleep (2011). Symptoms include low rate of breathing and low tidal volume, sleep apneas and cardiac arrhythmias.

Identifying the problem

A good place to start when tackling the crisis would be determining the possible causes and patterns of impact. Every year, over 250 million prescriptions for painkillers, most of which involve some type of opioid, are written in the United States (Ghertner, 2018). A positive correlation between prescription sales and deaths can be observed according to data collected by the Drug Enforcement Agency (DEA). SpecGx is among the many pharmaceutical companies that have contributed to the increased production of opioids. They were ranked first in the ARCOS data that allows for drug companies to report their controlled substances transactions to the DEA.

In 2009, email conversations between Borelli, a former SpecGx account manager, and a client showed Borelli stating that the drugs being shipped are "Just like Doritos keep eating. We'll make more. '' (Higham, 2019).

Another scandalous incident occurred with the Sackler family who owns the company responsible for the marketization of OxyContin, Purdue Pharma. The family is being sued for many purposes, those of which includes lying about the potential addictiveness of OxyContin, pushing it aggressively on doctors to prescribe it, and asking staff "what they were doing to fight back to convince doctors and patients to keep using the drug" (Walters, 2019). Perhaps the increase in opioid overuse can be partially attributed to the dishonest actions of the employees and owners of pharmaceutical companies. An alternate yet connected cause may be the prevalence of opioids being sold as street drugs. Professor Arnot says that possible reasons for the crisis could be attributed to "using in isolation, not at a safe injection site or with peers" and "the fact that some continue to use despite recent OD/treatment". She additionally mentions that "likely the biggest reason [of opioid overuse] is ease and access." Adding on that opioid use is very present in poverty stricken areas and those with lower economic prospects, it becomes evident that opioids could be a form of easy relief from reality (Ghertner et al, 2018). The eagerness of pharmaceutical companies to sell the opioids they are manufacturing, coupled with the need of lower income individuals to find compensation gives leeway to the crisis. The individuals that purchase opioids from local dealers may be unaware of the features of the drug they are using and therefore may not realize the possible catastrophic outcomes. Similarly, the disregard for the health of clients some dealers possess may cause them to lace the drug they are selling with a higher potency drug, such as fentanyl, to maximize profit. What they fail to realize is that fentanyl is approximately 100 times stronger than morphine and simply 0.25 mg of it is enough to kill an average person. Suppose a heroin user didn't take a dose large enough to cause death and has decided to stop using their opioid of choice. As a result of the body adjusting to the drug, symptoms of withdrawal arise and are often quite severe. Chief of substance use disorder at the California Department of Health Care Services estimated that detox is a realistic option for simply 15 out of 100 people.

Taking Initiative

Although the opioid crisis is a developing issue around the globe, there have been efforts to decrease overdose rates. A prime example is naloxone, which is a direct competitive antagonist of the mu receptor. In Canada, naloxone is available at most pharmacies for free if you are an opioid user or someone in a position to aid an opioid overdose. Naloxone may need to be administered 2-3 times, as it has a short half life of about 30 minutes. There are also government plans set out to stop the overuse of opioids. For example, most states in the United States are implementing Prescription Monitoring in order to reduce the liberality of opioid prescriptions by doctors (Schiller et al, 2018). The DEA, along with new online databases have allowed for easier methods to determine who is at high risk for opioid addiction or overdose (Schiller et al, 2018). Despite the initiatives that have been taken, opioid overuse and overdose is still on the rise. Creative solutions must be established to educate potential or current users of the harmful effects, put a halt to the illegal spreading of opioids, and to rehabilitate users that may be in withdrawal.

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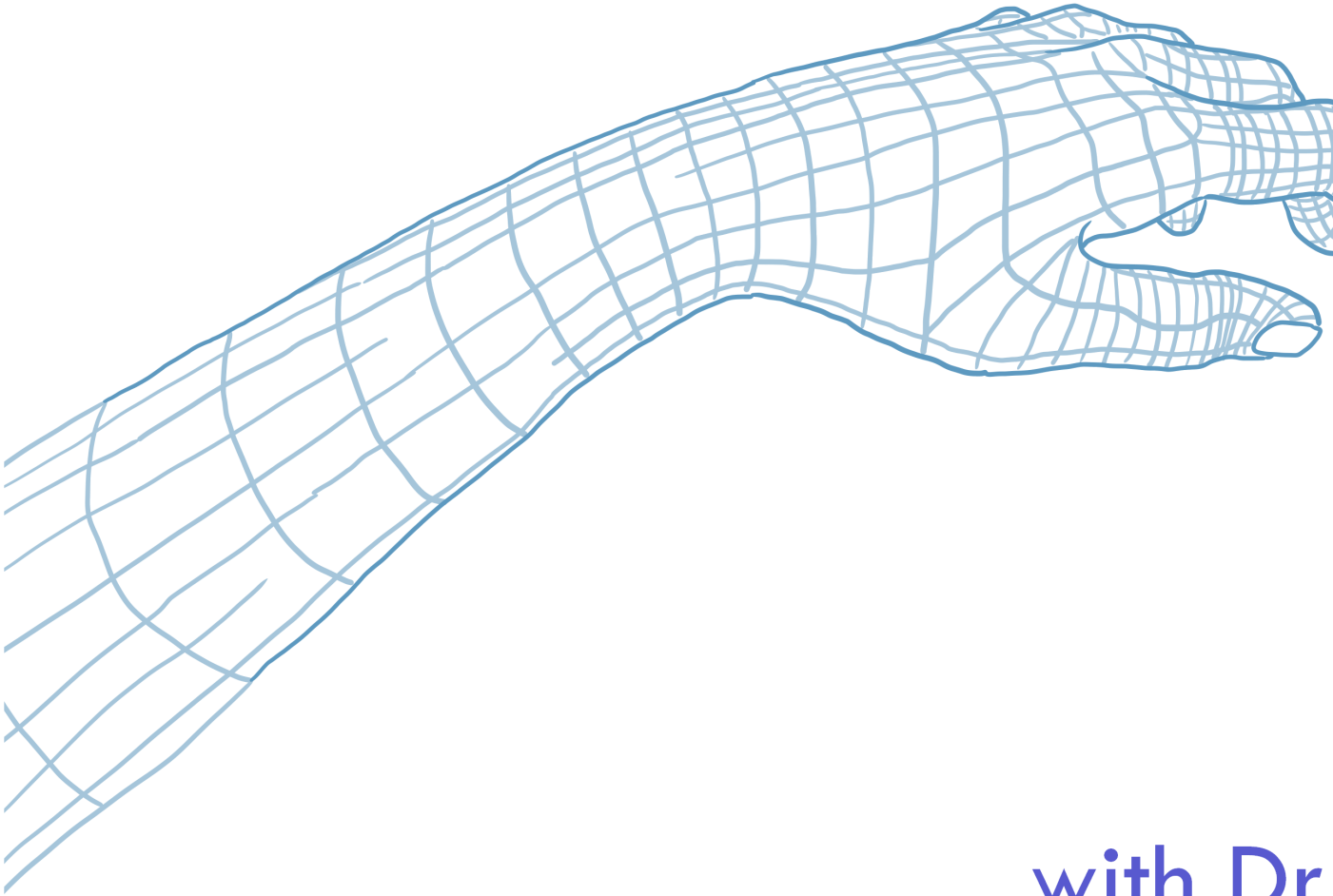

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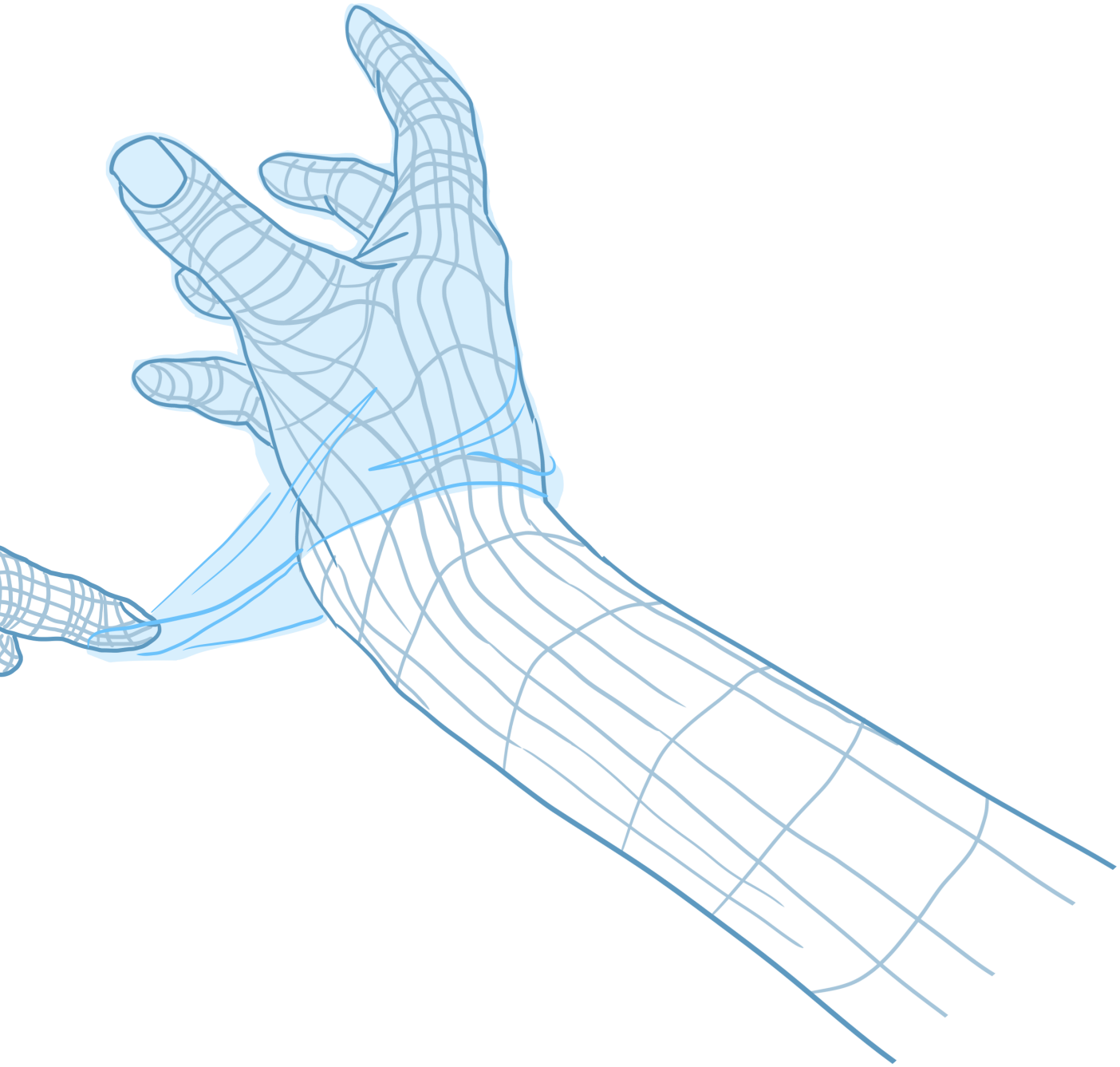

. Ross, Dr. Lytvyn, and Dr. Salmena

An educational talk with

Dr. Ruth Ross

conducted by Emily Mathers

Professor Ruth Ross is currently an active researcher, Pharmacology & Toxicology professor, and the chair of the Department of Pharmacology & Toxicology at the University of Toronto. She obtained her PhD from the University of Edinburgh and became a professor at the University of Aberdeen before coming to the University of Toronto in 2013. Professor Ross currently studies cannabinoid receptor type 1 (CB1) allosteric modulation, with the hope that therapies may be created one day to allow CB1 to exert its anxiolytic effects without the side effects of psychosis.

Background on Prof. Ruth Ross's Research:

Professor Ross has studied G protein-coupled receptors (GPCRs) throughout her academic journey. CB1 receptors are the most common type of GPCR found in the brain, and when activated, has been found to reduce anxiety. CB1 receptors are activated by many compounds, the most common endogenous compounds being anandamide and 2-AG.

Recently, cannabis has been heavily researched due to the CB1 stimulation caused by the exogenous compound THC and the effects of cannabidiol (CBD). It is unknown if CBD is a CB1 ligand; however, researchers are working on finding out the mechanism of CBD since it is a main component of cannabis. THC side effects such as psychosis have been observed, causing researchers to delve deeper into the mechanism of CB1 receptors and how the negative side effects such as psychosis can be managed.

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ade you decide to go into cannabis research?

career was a bit strange. I did my undergrad in pharmacology, and then I spent one year at Pfizer. I then decided , and I did it in researching prostaglandin receptors — a type of GPCR receptor. They're in the same class as can- but way back then we didn't know about cannabinoid receptors. I did a few post-docs afterwards, both in the es and Scotland, then I took a 5 year career break because I had 2 kids — pretty unusual for an academic!

rward, I decided I wanted to go back to work. I thought my CV was so out of date and didn't publish, so I applied hnician job. I didn't get that job, but they gave me a position as a TA. I did a PhD and they made me a TA again! I r a year and then I found the option to do a special fellowship called a "career re-entry fellowship", which was for had a career break of some sort. I needed a sponsor, and it turned out my sponsor was a world expert in canna- macology. I felt it was really good because it was still a GPCR related field, but it was a new type. So I did a fellow- ab, and that's how I ended up in cannabinoid research. I did 6 years of that fellowship and then I got my first facul-

What made you decide to come to UofT?

I was in Scotland for most of my career, but UofT is a great university and I love pharmacology. In Britain, there isn't much of a pharmacology specialty anymore since they mostly do biomedical science. To be chair of pharmacology here is amazing. I was reaching the age at which if I don't do it now, I'll never do it.

What made you decide that research was what you wanted to do?

Back in undergrad, we did a lot of lab work as part of our degree, and I suppose that was my first lab experience as an undergrad in pharmacology. My real experience that made me want to do research was my job at a drug company. It was a basic level job, and I remember thinking that I loved the research, but I wanted to be more independent in my own work. Rather than just doing technical stuff, I wanted to run my own projects. At that point, I realized I needed to do a PhD so that I can really start doing my own things. Honestly, only until you've started to do a project of your own, can you start to realize what you want to do. Lots of times things don't work out, and a lot of people get discouraged by that. But a lot of people really love to do that.

have an experience that you consider the most memorable or most valua- ou?

thing that's valuable to me now... it's not what I would've thought of before. I studied cannabis for 25 years, and ed it wasn't a very "fashionable" topic. Cannabis wasn't considered a serious topic until recently. People often do use they find it really interesting, and I find it really rewarding that all these 25 years have stayed very relevant ing on today.

ally nice to feel that something I spent a lot of my life researching is now very important and relevant to current being asked my expert opinion on all sorts of things in cannabis since there are lots of people brand new to this industry and research. Over the years you accumulate all sorts of weird and wonderful bits and pieces of info, der if they will be relevant to society as a whole. And here for me, it turns out it is. So that's quite rewarding!

ou got really lucky in that way?

urse! Years ago I didn't know this would happen, and now that it is, it's a wonderful feeling.

What would negative allosteric modulators do to cannabinoid receptors and why is this beneficial?

When we're looking at CB1-selective drugs, we're looking at any situation where any endocannabinoid system may be... say... overactive, and where it may be a good idea to switch the system off. For example, in non-alcoholic fatty liver disease, it's been shown that CB1 blockers cause significant improvement in the liver. This is quite a common problem, and so negative allosteric modulators can be something used to treat that.

Another one is schizophrenia and psychosis. We found some evidence that some parts of the compounds, especially in animal models, help to normalize some of the signs of psychosis in mice. So that's somewhere we can potentially use negative allosteric modulators.

Your research focuses primarily on CB1, is there a reason why not a lot of research is looking at CB2?

Ever since I've been working on this, we knew that CB2 is expressed in immune cells, but there's really no disease related to CB2. CB2-selective molecules didn't seem to do all that much. They might have some anti-inflammatory effects, but nothing spectacular. But, that might change as time goes on.

CB1 is the most highly expressed protein receptor in the brain, and so it's a really interesting target. It modulates many things like memory, emotions, appetite, stress response. But, on the other hand, it's hard to make a drug for this receptor because it's everywhere and does so many things. So, there's a huge risk of side effects. CB1 is interesting because people take THC, which is a CB1 agonist. THC also works on CB2, but the effects mostly come from CB1. That's why we focus on it, although we've worked on CB2 in the past.

Have you done any research in regulating those side effects?

This is the idea of the allosteric modulator, that it should be free of some of the side effects. The positive allosteric modulators don't produce some of the side effects when tested in animals. They don't create a "high" effect, but they are an analgesic. So allosteric modulators can help produce a therapeutic effect but not the side effects.

Do you know anything about the mechanism of allosteric modulators in the case of mediating side effects?

The endogenous cannabinoids bind to a binding pocket on the receptor, called the orthosteric binding site, and they produce many different effects. The allosteric compound binds to a separate pocket, which doesn't do anything on its own. For example, we know that in chronic pain, the endocannabinoid levels go up. Because they've gone up in pain pathways to produce pain relief, if you give the positive modulator it makes the relief bigger but has no effect on direct-activating CB1 in other places. In other words, it does not cause you to feel high, it just magnifies the effect of the endocannabinoids that are already causing a pain relief effect.

"Ultimately health is much more important than grades or academic success."

What therapies are being focused on with allosteric modulation? Are any currently feasible for drug development?

We do have molecules that may possibly become new drugs as they work in the animal models, but obviously there are many steps between animal testing and clinical trials. We must know much more about the safety of the molecules.

I think we still need to make molecules that are better than the ones we've got, so we're working with medicinal chemists to make compounds that might be better for things like oral bioavailability, pKa, or solubility. So, we're working on making the molecules better, but obviously the goal would be to try and get something clinically applicable. But, even if we don't, we're learning a lot, using the molecules to study the endocannabinoid system and how it works. You can use them to tune the system down or up to see what hap-

Is there maybe one molecule that interests you the most in terms of what you've been looking at so far?

It's hard to tell, really. It's too early to suggest just one, but there are definitely allosteric binding pockets that make an interesting target for both positive and negative allosteric modulators. So, we'll keep moving forward that way.

Are there other endocannabinoid therapies that you may know of being researched, or could you think of some therapies that should be given more focus?

I think looking at the molecules affecting endocannabinoid metabolism is a really interesting way to approach modifying the system, and it will be interesting to see these more in the future. For example, compounds that inhibit fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) modify 2-AG metabolism. Drug companies do have select FAAH inhibitors, and they are actually working through clinical trials relating to social anxiety disorder, so it's going to be interesting to see how the research shapes up and what kind of data comes out.

Another thing that's important for us to research is CBD, because it's being heavily marketed at the moment and people are taking it. But, we do not know what the molecular target is. We know that THC acts on CB1, but for CBD, the major component of cannabis, we are unsure about the molecular target. So, it is a really important area of research to focus on right now. Many people are selling it, but we don't know how it works, meaning we don't know the potential side effects could be, which is why going forward I would like to see more research into that.

Is there a side effect of cannabinoids that concern you the most, possibly one that researchers would generally want to eradicate?

I think it's not so much one side effect, but one thing that people are trying to find out is if there is one group of people that are more at-risk than others, and if you can identify the risk factor. For example, some people may be more at risk for mental health problems and some people have no problems with it. So, it is a good idea to identify populations that are more at risk, and I think this is an important question. Hopefully data will emerge within the next few years.

If you could give any pharmacology or toxicology student advice, what would it be?

To anyone doing any kind of university program, I would say try to enjoy it! I've been at university, doing research, and it can be really fun. You get to do interesting things relevant to society, cool things that are going to make a difference. Rather than focusing on grades and numbers...um...this sounds really weird coming from the department chair haha...try not to worry too much about achievement and actually find enjoyment, since you will be more likely to do better at it instead of getting stressed about grades and thinking about how interesting it is. I'd also encourage students to really focus on health and wellness; supporting one another and building community. Ultimately health is much more important than grades or academic success.

Hahaha we've all been definitely been guilty of that...

Well, it's understandable; obviously people sometimes become so concerned about grades they are no longer interested excited by the in the subject anymore, which is a shame because you're missing out on the opportunity to enjoy it. Sometimes when you lose interest it also works against you in performance, so enjoyment

An insightful conversation with

Dr. Leonard Salmena

Could you please tell us a bit about yourself?

I'm a University of Toronto pharmacology and toxicology graduate, and I did my masters in this department as well. Feels like I'm home grown and it's great to be back here in the department. I did do some training away from the department for my PhD and abroad in the US, where I completed a post doc in two excellent cities and research institutes including glamorous New York and Harvard medical school in Boston. Apart from my academics, I'm a Toronto native, a dad, a husband and my life revolves around family and children. I have two young boys who are growing up quickly. And when I'm not doing science, I'm taking care of my two young boys. That's a little bit about my life.

"...I really fell in l
with science, canc
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cided my career to

What experience made you Science?

I discovered science as a topic of interest in High Sch teachers there which were inspiring and that's a part science. Why I'm in academic science and specifically in have an amazing story. I don't have a long history of ca lucky. The reason why I'm in cancer is because it's the t my interest in my undergraduate studies. Since I did tox tumorigenesis and cancer, where that to me was fascina learned in my university career. It was the first inspirat cer. During my masters, I dabbled in graduate schoo where to go with my career. It went well but I didn't f experience or fulfillment for my thirst for science, thus I made a deal with myself that I'm going to dive into it and most ambitious lab in the city, hence I ended up ambitious and that's where my passion came out. Par and the project worked out well but that's where I reall cancer biology and where I decided my career to be. I'm today since I found my dream job!

What are some of the big hurdles you have encountered during your university career?

This is going to be specific to University of Toronto undergraduate program. It's large and I was lost as an undergraduate here, especially in the first year. If I didn't pull my socks up and worked hard, I probably wouldn't be here. University of Toronto is huge, and I did get lost in the shuffle of first year, especially. As you probably know, or might have excelled from the get-go, once I started learning how to study to specific type of courses, multiple choice or written courses, then I was able to work within the system. Didn't love 1st and 2nd year but come 3rd and 4th year where classes were smaller and less of multiple choice, more discussion, thinking, using imagination, its where I felt more comfortable and where I was able to express myself scientifically and find where I want to be in science. It took a while to get there but those were the important former years. Graduate school in Toronto is the most amazing experience I have, where the graduate school is the top institute in this department. Finally, Post graduate studies was another amazing experience that shaped me. It got me out of Toronto which was important for me growing up as a person and in my training as a scientist. Mainly because of the institute, I was lucky to stay in cities, such as Boston and New York. Since these places are full of scientists, Nobel prize winners and ambitious people, you could really see the passion and drive. You can fit into the framework which we called it science today and see what it takes to make it, to see what the upper echelon is made of – see what it takes to be a scientist and the dedication required. Meeting people who want to make a difference in whatever discipline, and it was one of the best experiences I had in the cities. One story particularly in Boston, since it's a small city, you can be in a subway and listen to small conversation about medicine or science. I found that inspiring and it's a great place to be!

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with a young PI who was
tially because I was lucky
y fell in love with science,
n lucky enough to be here

Was there a project you did that you find interesting and unique?

When I graduated from my masters and made the decision to go into science, one of the fields that was flourishing and emerging was the field of apoptosis or cell death and the importance of cell death in cancer. At the time, a Nobel prize had been awarded for the mechanism of cell death and apoptosis. I remember the moment when I first saw that paper and said that this field is super cool and wanted to enter this field. In fact, my PhD was focused in apoptosis and understanding its role in cancer where I was lucky enough to get a position at the Prince Margaret cancer center. Within the group of individuals who were influential in developing new mouse models in cancer and immunology, my project was specifically on knocking out a caspase in mice. All In all, it's the apoptosis that was the emerging field at that time and that was what really inspired me. Now I'm out of apoptosis and I'm doing other things but that was one project that really inspired me.

Your studies highlight how cross talking interaction between RNAse and how they may play an important role in diseases like cancer. Do you know what would happen if that interaction was disrupted and changed in a way?

In our studies of studying an important tumour processor in cancer, we found that it was regulated through this RNA biology and some of the things we study now is how RNAse interference is altered in cancer cells, which is something I teach now. Effectively, this small RNAse controls the regulation of other genes, like tumour suppressor oncogene or important cancer genes, they are selected for or selected against in a specific cancer and you often see mutations in these RNA genes. I'm talking about miRNA but lncRNA is a really hot field that is emerging now as well. We have a great understanding that RNAase are important. This wasn't really appreciated previously as they were thought as messenger molecules but the so called RNA evolution which occurred within the late 2000s told us that RNA biology is more than a messenger but play an important role in all processes which ultimately means they are important in all kinds of processes. They can be altered, and they will lead to diseases. Just like other genes which are lost or gained in diseases such as cancer. Not only limited to just cancer but cancer is the one I understand the most.

Based on your research, would corresponding approaches to combating diseases like cancer be mostly preventative, responsive, or both?

Prevention research is still tough, and that's reflected in how much prevention research is going on. Currently, most of cancer research is studying cancers that have already developed. So, we're trying to cure a disease that has already ravaged the individual with cancer. It's important to be able to cure cancers that have already emerged, but prevention is more tough because you have to have an understanding of a specific individual's risk.

I'm lucky enough to have a wife who wo
search, and we work together. She's worki
examples of how prevention research sho
cally with a gene called BRCA1 - a breast
these individuals that are born with one
breast cancer gene, they know that these
risk of developing cancer later on in life, c
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women, they're conducting a lot of preve
some of the ways they can prevent is by
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women that develop cancer, and having ac
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vegetables, did they smoke. Information
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correlate their life experiences with their
can start saying that this woman drank 3
had a slightly decreased risk in cancer, or
menopause much earlier and her risk is alt
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to be healthier. That's the first step in pre
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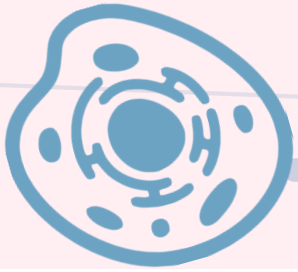

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Do you have any tips/qualities to a younger student who wants to join your lab or someone else's lab?

I think the scientists of the future will have a good understanding of biology and biological process. However, the best thing we have today is access to large datasets. I am not a computational biologist, and I don't think computational biology is enough to answer important biological questions, but in my opinion scientists of the future will harness all this data with a basic but functional bioinformatic understanding. An ability to mine the data in an effective way. To inform the biology we do. I encourage many of my graduate students to obtain a minimal level of bioinformatics/statistics so they can use all the data out there and apply it to the biology that they are doing. To inform as well as to form new hypothesis and find supporting data for it. However, I mention biology a lot, as you ultimately need to really understand the mechanisms of a cell. Bioinformatics is amazing, but it is never real until you validate it with the happenings within a cell. Computational biologist would say this is the truth and we have so much data show that this is the way it is, I still think we need to do experiments to understand the mechanisms. Any experiment we use a drug to generate its going to be targeting one protein/rna/process/receptor but you need to have the mechanistic understanding. Take that statistics or bioinformatics course. I do that with my graduate courses as well. Also a word of warning for you, I encouraged one of my students to do computation biology and now it's been a struggle to bring him back to do experiments.

An inspirational conversation with

Dr. Yuliya Lytvyn

Prepared by Daniel Li, Brian Chan, Dinie Syahmi

Dr. Yuliya Lytvyn is a first-year medical student at the University of Toronto, who previously completed her PhD in the Department of Pharmacology and Toxicology, University of Toronto and a post-doctoral fellowship at the Toronto General Hospital Research Institute. During her graduate studies, her research focused on pharmacologic prevention of cardiorenal complications in conditions such as diabetes. While conducting clinical research studies to answer her research questions at the Toronto General Hospital, she was fascinated by how clinician scientists can observe a knowledge gap in their clinics, address the gap in their research and apply it right back to patients in their clinic. Inspired by interactions with participants in clinical trials and her mentors, Yuliya is now also pursuing an education in medicine. The PharmaChronicle team had chance to discuss with her about her academic career, as well as aspects of her research on diabetes.

Can you tell us a bit about yourself; your career path from undergrad until now?

I started my undergraduate degree at the University of Toronto Mississauga in forensic science. I thought the program would be like CSI, but I quickly figured out that although the detective skills are important for forensic scientists, I will not actually graduate as a detective. After first year, I switched to a program with a broader application, molecular biology and chemistry. I did a lot of research but mostly looked at insect models, and hardly anything that's mammal-related, so I felt very removed from practical application. I was interested in trying clinical research where I could observe the translation of the knowledge to application sooner. I learned about the pharmacology program at the St. George campus and thought that was a very applicable and translational field. I found a researcher who did clinical trials and asked to join the lab as a graduate student. Right away I enjoyed speaking to clinicians and patients to identify the current needs and knowledge gaps, which if addressed would influence patients' well being. It was like a puzzle, in which I needed to figure out how to solve it by designing studies, carrying out the clinical trials, and analyzing data. It was detective work after all, so perhaps my forensic scientist skills from first year were worthwhile. It was very satisfying to then present my work to physicians at conferences and listen to their ideas on how our research findings could translate to clinical practice. I found clinical research to be a very rewarding career path that allowed me to interact with both, patients and physicians. I also enjoy teaching: I was a teaching assistant during my graduate studies and I really enjoyed interacting with and mentoring stu-

What made you interested in researching diabetes in particular?

Diabetes is a disease with increasing prevalence and is a major cause of blindness, kidney failure, heart attacks, strokes and lower limb amputations. It is a very complex disease where many different systems are affected and inter-related, such as the kidneys, heart, eyes and the nervous system. Interindividual differences affect the complexity. I find it fun to tease out how these systems are affected separately, and how they interrelate together. I also enjoy that this particular field of research allows me to interact with physicians from a number of disciplines: cardiologists, nephrologists, neurologists, and ophthalmolo-

As someone who finished their grad studies recently, how did your perspective of science and academia change throughout your undergrad, grad school, and post-doc?

Well, I used to look at my professors and think that the more you learn with the years of education, the more you know and the more questions you can answer. During my graduate degree however, I realized that the more you know, the more you understand how much you actually don't know. And this is when I understood that it is more important to develop critical thinking skills in order to be able to solve scientific puzzles. In terms of academia, I always thought during my undergrad that once you are done graduate or professional school, that the uncertainty of what to do next stops. But it never really does! Your interests and opportunities available are constantly evolving and changing, and I never thought about that as a student. I think it's important to keep an open mind and embrace the things that come your way.

If someone wants to become a PI in the future, that person has to take into account factors such as managing students working for you, as well as grant applications and such. How would they develop the skills for this task?

When you do your graduate studies, especially during the final years, you can ask your supervisor or the people you work with to let you take on mentoring responsibilities for junior trainees in the lab. You also get experience helping with grant writing or even putting together your own ideas into a grant. This is the time to learn those skills, as once you are a PI there is more pressure on you to get the funding for your lab and to provide the environment for your graduate students to successfully finish their degree.

It seems that statistics is becoming more and more important. do you think that learning statistics is important for the future?

I think it's extremely important as it not only helps you analyze your own data, but also to critically evaluate other published literature. I can do basic stats myself, but if I need to do something more advanced, I would

consult a statistician. It's actually becoming common to have a statistician shared by physicians and researchers in a department or a medical unit. There's also the emerging and constantly evolving field of big data. We will definitely need experts in computer science and statisticians to help us understand and use such complex and powerful methods.

Are there skills you learned in undergrad that you are still using now?

Of course there are, even though the molecular biology and chemistry I studied in undergrad are very different fields than the clinical trials I work on now. First, I still use the knowledge from my undergrad to read basic science papers to critically validate the findings and to see how they can be applied to my clinical research. Second, I learned how to work hard, organize myself and communicate scientifically in during my undergraduate training. It is a great time to explore and develop interests and work ethic. Knowledge itself can be learned on your own if you are self-directed or found on the internet, you can learn anything really. Thus, it's not so much about the knowledge, but about you developing interests and skills.

A lot of diabetes drugs today involves just preventing symptoms, and patients usually have to be on the drugs for a lifetime. Do you think we might be able to find a cure for diabetes in the future?

That's a good question! It's difficult because diabetes involves so many different variables. I'm not sure if we can cure it, but I think we can reduce the comorbidities that come with it. For example, the big topic right now is SGLT2 inhibitors. There are sodium/glucose co-transporters in your kidney that makes you re-absorb salts and sugars. These receptors are upregulated in people with diabetes, so they re-absorb even more sugars and salts leading to greater blood glucose levels. We can use SGLT2 inhibitors to inhibit these receptors to increase excretion of sugars and salts and lower blood glucose levels. In the last 4 years, large clinical outcome trials showed that these drugs also decrease hospitalization for heart failure and kidney problems by about 30%, and that kind of response hasn't been seen in about 30years, since the RAAS inhibitors were introduced. In fact, recently the use of SGLT2i has been added to guidelines as an indication for patients with diabetes and cardiovascular risk.

"The more you know, the more you understand how much you don't know."

PharmTox Professional Experience Year (PEY)

The Professional Experience Year (PEY) Co-Op program is an opportunity for speciali Department of Pharmacology and Toxicology to gain real-world insight into ca knowledge acquired during coursework, and be better prepared for careers after g name implies, the primary goal of the PEY program is to gain *experience.*

Between 3rd and 4th year, students can work at a jobsite for 12-1 opportunity is the preparation ahead of time. For this reason, in occurs during early September of 3rd year. The PEY Co-op progra the Engineering Career Centre, which runs the PEY Co-op program related disciplines. Mandatory preparation workshops include t shop, followed by multiple offerings of training sessions about re torically, PEY Co-op employers have been pharmaceutical comp hospital research sites, biotech companies and government labo posted each year for PharmTox students, and many of these pos multiple universities. Most years, 15-18 PharmTox students partici

Information sessions about PEY are generally held and in early September of 3rd year. During the su ist students are invited into the Quercus site for P the program and instructions and timelines to ap

For students who participate in place have a major impact on th are right for you, before gradua plete their studies, and bring the member in the Department of P dents. Further questions about t

ist students in the reer paths, apply graduation. As the

16 months. A big part of the PEY take into the PEY applicant pool am is offered in partnership with n for students in Engineering and he "Pathway to Success" work- esumes and interview skills. His- panies (eg. Sanofi), academic or ratories. About 50 positions are sitions are advertised broadly at pate in the PEY Co-op year.

d in PCL201 during Spring of 2nd year, mmer between 2nd and 3rd year, special- EY Co-op, which has information about ply.

PEY Co-op, their insights about the professional world and the environment of the work- heir futures. It's a way to make an informed choice about whether particular career paths tion. Our Department is enriched by PEY Co-op students who return to 4th year to com- eir work-integrated learning experience into our 4th year classrooms. Dr. Laposa, a faculty harmacology and Toxicology, is the current faculty liaison for PEY Co-op for PharmTox stu- he PEY Co-op program can be addressed to pey.pharmtox@utoronto.ca.