An interview with Dr. Murtaza S. Nagree, the 2023 Drew Lyall Awardee: HSC-directed gene therapies, predictions for stem cell advances, and a love of cooking

Drew Lyall Awardee Q&A
Murtaza S. Nagree, Ph.D., University Health Network

Murtaza S. Nagree, Ph.D., is a Postdoctoral Fellow in the John Dick Lab at the University Health Network. Murtaza completed his doctoral studies at the University of Toronto where his thesis explored alternative gene therapy methods to treat lysosomal storage disorders, the outcomes of which provide novel gene therapy platforms and tools for efficacy testing.

Murtaza has won the 2023 Drew Lyall Award of Excellence as the lead author of the highest ranked abstract in the TMM2023 abstract competition for his work on *A hematopoietic stem cell subset that retains memory of prior inflammatory stress accumulates in aging and clonal hematopoiesis.*

SCN's Joanna Valsamis, Director of Knowledge Mobilization, had the chance to chat with Murtaza, who spoke about his work, his career path, and some personal anecdotes.

Congratulations, Murtaza on your Drew Lyall Award and thanks for taking the time to chat with us! To start us off, tell us a little bit about your area of research.

During my Ph.D. I focused on trying to improve hematopoietic stem cell (HSC)-directed gene therapies. I was interested in following that work up with understanding how an HSC works and joined the Dick Lab. Stephanie Xie, Andy Zeng, and I have been able to start unravelling how HSCs are able to withstand a lifetime of demand that results from insults in the form of infections and inflammation. With the ability to generate a graft of human blood in mice, we created a model that allowed us to observe that human HSCs directly respond to inflammatory cues, which then result in a programmed epigenetic and transcriptional change in a portion of the most primitive blood stem cells.

We observed this phenomenon when, using state-of-the-art single cell Multiomics, a whole separate population of what we then referred to as “weird HSCs” showed up.

Surprisingly, this new population has molecular properties that align well with memory T cells. We can find the gene program governing this HSC with inflammatory memory (HSC-iM) more enriched in individuals as they age, and more so when the donor has clonal hematopoiesis. We’re now trying to sift through cell surface markers to prospectively separate HSC-iM from conventional HSCs so we can evaluate their biological properties and confirm some of what we suspect from our in silico findings. We could leverage a marker like this and our knowledge of HSC-iM to help refine clinical transplantation practices and improve outcomes in HSC-directed ex vivo gene therapies.

In the lab or in another aspect of life, what is the best piece of advice you have ever been given?

Never give up, keep pushing, persevere and variations thereof. I have been very fortunate to have an amazing support system, including my parents, my teachers and mentors, my wife, my parents-in-law, and my community at large. Now, my children inspire me to be patient and keep moving even when I can’t see the light, and I hope I’m passing along the same virtues to the students with whom I have the fortune of working alongside. Also, “Don’t forget to have lunch!” – said often by my dear wife, without whom I’d be very unhealthy.

In your opinion, what is the single most important life science or biomedical breakthrough in the last decade?

I would say genome manipulation, because of the increased focus recently placed on it after our forebearers brought to light its possibilities and conceptual applications. The strides made by a combination of industrial/academic competition, healthcare needs and advocacy, and even push from patients and their organizations are just astounding. I remember at the beginning of my scientific career I was trying to wrap my head around how to use homologous recombination to maybe solve medical problems. Now, reputable groups have shown the ability to correct genomic alterations in a specific, rare cell type using an injectable particle!

There might be many scientists who inspire you. It could be someone you know personally or a famous scientist from history. If you had to pick one, who is your favourite scientist and why?

I have always answered this question with Dr. Jonas Salk, the inventor of the Polio vaccine. While I can certainly understand (and maybe empathize) why his outlook on patenting biotechnology is not widely appreciated in current times, his actions have saved innumerable lives, especially in impoverished countries. I admire his dedication to his patients and his science. There are a few others with similar ideologies, some of whom are near and dear to the stem cell field. Also, Dr. John Dick – I do not take the privilege of working in his lab lightly.

What was your biggest mistake (personally or professionally) that ultimately turned into a positive?

Two stories come to mind, one during my Ph.D. studies and one that is more recent. I made the decision to skip some steps/testing when generating a mouse model, which at the time made me panic as I had lost the phenotype present in the original strain. With a bit of patience and a measure of stubbornness, I managed to figure out the phenotype had simply changed to another. Turns out I had accidentally created a mouse model of another ultra-rare disease and had to spend a few more years generating my original controls to prove why this had happened.

More recently, a combined lack of bioinformatic diligence and eagerness to start wet lab work led to the investigation of a cell surface protein that we thought was the most promising candidate for marking HSC-iM. Turns out it likely has a whole other role in sensing and maybe modulating how HSCs respond to inflammation during mitogenic activation. We would have missed the opportunity to investigate that protein had we been overly careful!

Innovations are always around to corner. For the sake of speculation, what are your predictions for stem cell advances in the next 5, 10, 20 years?

In 5 years: the possibility of in vivo stem cell compartment editing for correction of tissues that can regenerate and/or transient manipulation of these cells to stimulate them to aid in tissue repair, where possible. At least one product in a clinical trial.

In 10 years: transplantable off-the-shelf or custom-made organs! Hopefully at least one, though I imagined 10 years ago we'd already have this…

In 20 years: unprecedented cooperation between academia and biotech sectors, followed by achieving healthy immortality (or as close to that as possible; by choice, of course) :) But in all seriousness, the trend observable to someone from the outside is that many new technologies are applied to more unique problems, to avoid direct competition of interests. Most headway is made by the biotech sector, for maybe obvious reasons. Eventually, we will have to take a step back as a field, have our governments invest in us, demand comparisons between technologies, find a way to all work together, pick the best ones and focus on those. But that is a wishful (and perhaps naïve) thought.

Tell us about one thing you do outside of the lab in your free time. Is there anything you are watching or reading that you recommend, or another hobby that keeps you busy?

I absolutely love cooking. I often like to make things with very layered flavours, and usually spend substantial time perfecting specific dishes to my own liking. Nowadays I've been playing a lot with the sous vide technique, which can lead to some fun flavours and textures!
This may be an unusual suggestion, but I love the fanfiction Harry Potter and the Methods of Rationality. It has its own little fandom and encompasses a contextual description of the most fundamental scientific principles, of which many are simply never taught.