[Interview] Hacking Metabolomics With AI To Improve Clinical Research

May 12, 2020 by Andrii Buvailo

Personalized medicine has become a paradigm-shifting trend in healthcare - the hegemony of “one-size-fits-all” drugs is increasingly challenged by novel innovative modalities and therapies, laser-sharped for a specific group of patients, or even a single patient in some cases. This is a complex story, and the progress in personalized medicine will take time and tectonic shifts in the pharmaceutical research workflow.

On the other hand, the advent of personalized medicine is only possible with a more personalized system for health assessment, new robust biomarkers, and novel approaches to run and monitor clinical trials. This will require diagnostics that can provide sufficient insight into the metabolic status of individuals, and relatively new science of metabolomics is now taking off in the biotech industry.

To get first-hand insights into an exciting area of metabolomics, and how it can revolutionize clinical research, I asked several questions to Dr. Elizabeth O'Day, CEO, and Founder of Olaris, Inc - a precision medicine company that uses a pioneering metabolomics platform and proprietary machine learning algorithms to fundamentally improve how diseases are diagnosed and treated.

Dr. O'Day is also the co-chair of the World Economic Forum's Global Future Council on Biotechnology, the advisory

board member for the Precision Medicine Initiative, and was also a "nominated changemaker" and invited to attend the first United State of Women Summit convened by the White House in 2016. She participated in Vice President Joe Biden's Cancer Moonshot Summit to discuss collaborative ways “to end cancer as we know it.”

Andrii: Can you briefly outline your journey with Olaris? Why did you decide to start the company, what was that key realization that led you to become a biotech entrepreneur?

Elizabeth: My journey started in the first grade when my older brother was diagnosed with neuroblastoma, a rare form of cancer. It was an extremely difficult time for our family - we essentially lived in Boston Children’s Hospital for two years. My brother survived, and from that moment on I was inspired to help find a better way to treat cancer.

Over the next two decades, as a student, I spent the vast majority of my waking hours doing everything I could to contribute to the field of cancer research. Along the way, I was fortunate to be recognized for my work. As an undergraduate at Boston College, I received many of the nation’s top undergraduate awards such as the Beckman Scholarship, Goldwater Fellowship, National Institute of Chemistry Excellence award and Finnegan award. I then received a Churchill Fellowship to pursue a MPhil in Chemistry at the University of Cambridge in the UK, and a National Science Foundation Fellowship to support my PhD at Harvard University.

After I finished my PhD, a mentor asked me, “If you could do anything in the world, what would it be?” I wanted to cure cancer, and believed that the metabolomics platform I developed during my graduate work could help accomplish that.

Andrii: Why metabolomics? Most of the biotech startups are traditionally targeting proteins, while there is a relatively new wave of genomics and transcriptomics companies. What special insight can you get from analyzing metabolites on a systems level?

Elizabeth: Metabolomics is the study of metabolites - all the small molecules that swim around in you and I that provide energy and biomass for life to exist. Metabolite levels are influenced by your genetics but also by your environment, and that's what makes them such a powerful reservoir of biomarkers.

A long-standing goal of precision medicine is to uncover biomarkers that differentiate drug responsiveness. To date most efforts have focused on genomics or transcriptomics, looking at DNA or RNA respectively. This is important information but only tells you "what could happen" - it's like a risk factor. There are many other factors such as age, diet, environment and the microbiome that influence whether a drug will work in a patient.

Fortunately, all of these elements get captured in the metabolome. Thus, metabolites relay "what is actually happening" in a patient. Olaris uses that comprehensive measurement to help get the right drug to the right patient at the right time.

Andrii: Let's talk about technology stack, how do you do all that? Do you run wet-lab experiments? How do you do computation? What is your competitive edge?

Elizabeth: Olaris has a wet lab and dry lab component. We are unique in that our primary method to measure metabolites uses multidimensional nuclear magnetic resonance (NMR) spectroscopy. NMR spectroscopy is extremely reproducible. A metabolite, say lactate, will always be in the same position on the spectra. This enables us to monitor changes in lactate or other metabolites from patient to patient and at different time points. We can also use the spectral features to uncover unknown metabolites that could be important to predict drug response. Traditionally, multidimensional NMR lacks sensitivity and requires extremely lengthy run times. However, Olaris has developed custom "non-uniform sampling" (NUS) techniques that allow us to dramatically increase the sensitivity, resolution and reduce the time required to collect the data. Olaris' team includes the world's NUS NMR leaders and inventors. Through our collective expertise, we are pushing the limit of what others thought possible.

We also have a leading data analysis and machine learning platform. Metabolomics data is incredibly complex and cumbersome to analyze. We have developed a fully automated platform to streamline and

optimize the entire process. We feed our NMR data into the platform, first passing the data through basic statistical tools and then through advanced and proprietary machine learning algorithms. Using our approach we have demonstrated the ability to identify drug-responsive metabolic signatures across patient groups. The technology has been patented and presented at numerous conferences, including at the World Economic Forum's Annual Meeting in Davos, the American Society of Clinical Oncology Annual Meeting, the San Antonio Breast Cancer Symposium, World Clinical Biomarkers and Companion Diagnostics Conference, Practical Applications in NMR Industry Conference and the Experimental NMR Conference.

Andrii: What pain of your customers are you helping solve? What is your company's offering and what kind of customers and partners you are looking for?

Elizabeth: Olaris is creating a scalable solution for determining which patients will benefit from a specific drug. As mentioned above, Olaris has developed a platform that measures each patient's metabolome, providing a fingerprint for what is actually happening in that specific patient and deducing which drugs will help that individual.

Our first product is aimed to help metastatic breast cancer patients, the overwhelming majority of whom receive a CDK4/6 inhibitor as their first-line therapy. Unfortunately, 1 in 5 women will have no response to the drug, and because their cancer is not being treated, their chances of overall survival plummet. For these patients, survival depends on choosing the optimal therapy first. At present, because physicians have no way of knowing who those non-responders will be, it's a roll of the dice when prescribing.

In 2019, Olaris completed a series of retrospective studies wherein from a blood test prior to and during treatment we could predict which patients would benefit and those that would not benefit for the CDK4/6 inhibitors with over 90% predictive accuracy. This level of accuracy indicates that our diagnostic test could revolutionize how metastatic breast cancer patients are treated. In addition to CDK4/6 inhibitors, Olaris is developing diagnostic tests for other breast cancer drugs including anti-HER2 drugs like Herceptin.

This year, we also announced a grant from The Michael J. Fox Foundation for Parkinson's Research. Our initial project is focused on uncovering metabolic signatures associated with the neurodegenerative disease to provide deeper insight into the mechanisms involved in Parkinson's and its progression. We plan on announcing findings from our initial research later this year.

Andrii: You have been an active biotech leader and frequent contributor to some of the world's top events, including a forum in Davos. Can you share some of your thoughts about the future of biomedical research in general? And how does it relate to COVID-19?

Elizabeth: My work as a co-chair and task force lead on numerous projects with the World Economic Forum has provided me an amazing opportunity to work with organizations across the globe committed to improving the state of the world, and in particular the health of the world. Biotechnological innovation has enabled society to identify an unmet need and then build solutions (diagnostics, treatments, wearables, devices, etc.) that can be deployed to those in need. When this works correctly, biotechnology and precision medicine have the potential to dramatically improve health and even cure many diseases.

As you can imagine, however, there are scenarios where biotechnological innovation won't always have a positive outcome. How can we prevent that or at least mitigate against it? In part, we need to have consensus that just because science enables us to do something, doesn't always mean we should. Furthermore, safeguards to ensure that new innovation doesn't widen health disparities need to be implemented. The good news is that these conversations are happening and in many cases have gone from thought exercises to active initiatives engaging stakeholders from all sectors of society. More work remains to be done but through these efforts I believe biotechnology solutions have the potential to leapfrog towards a healthier and hopefully more equitable future.

The COVID-19 crisis is exemplifying the role of biotechnology to solve problems, as well as the need for more inclusivity. To combat COVID-19 we need diagnostics and we need treatments. Existing and new biotechnology solutions will, eventually, be available to solve these needs. However, it won't be enough that these tools are available we need to make sure they are accessible to all. Part of the tragedy of the pandemic is the disproportionate effects across socio-economic and regional lines. I'm encouraged to see the "we're all in this together" messaging because truly through science and solidarity we will eradicate COVID-19.

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