At the Congress, you will explore how we can use mRNA technology to develop next-generation therapeutics. mRNA has already revolutionized vaccine technology—what do you feel are the greatest challenges associated with using mRNA for therapeutic interventions?

This is a great question—because I think the comparison to mRNA vaccines highlights a number of the challenges faced by mRNA therapeutics.

If you think about vaccines, a core idea is to harness the body's adaptive immune system for both signal amplification and memory. So, a relatively small vaccine dose can, in principle, confer immunity for years—although, of course, that hasn't yet been the outcome for COVID-19 vaccines.

The barrier faced by mRNA therapeutics is that, unlike vaccines, they cannot leverage the body's adaptive immune system for amplification and persistence. As a result, you often need to administer far higher therapeutic doses—a recent review noted that mRNA doses are often *100 to 1000-fold* higher for therapeutics vs. vaccines. And you often may to administer those doses repeatedly—because current RNA technologies can degrade in hours to days.

And there's another barrier: current RNAs, including those delivered in lipid nanoparticles, lead to substantial immunogenicity. This may provide an adjuvant advantage for vaccines, but it's unfortunately an additional way to accelerate the loss of therapeutic RNA.

These challenges sound daunting—and they are—but it's worth noting that they were previously overcome for siRNA therapeutics. The drug that comes to mind is Alnylam's Onpattro. So, there's a clear precedent for believing that we'll find solutions for mRNA therapeutics, too.

I will ask the reverse question. What are the greatest opportunities for mRNA therapeutics, and why do you feel a next-generation approach will enable us to mine those opportunities?

At a first level, the greatest opportunities for mRNA therapeutics would seem to be in novel technologies that can tackle the above 3 barriers. And there are a number of these next-generation mRNA technologies that are already quite evolved in development—we're seeing some of them at the conference. For example, self-amplifying RNAs are being developed to directly amplify RNA *in vivo*, circular RNAs are being developed to enhance RNA persistence, and novel transcription and purification strategies are being developed to minimize inherent RNA immunogenicity.

But some of the greatest opportunities of mRNA technologies may be paradigmatically different. If you think about it, current mRNA therapies are often focused on producing proteins *in vivo*. I think a fair question is: "why don't we just deliver the protein directly'? We may not like asking that question in the mRNA field, but we clearly have to—since some of our competitors are in the protein field.

But there's an additional question we should ask—what can we do with mRNA therapeutics that we can't do with proteins? If we can answer that question, we have a potential path to developing next-generation drugs that weren't previously possible.

Here are some examples. I think about proteins that are extremely difficult to produce, purify or effectively deliver—for example, transmembrane proteins. Or therapeutic proteins that you don't want to express constitutively and systemically, but that are life-saving in certain contexts. Ultimately, I think about how mRNA could be used as a circuit board to precisely control therapeutic protein production both temporally and spatially.

So, to me, mRNA 2.0 moves from plug-and-play production to plug-and-play control. There are a few companies already thinking about this in the cancer context—imagine if we could localize chemotherapies or immunotherapies—and I think there will be more from cancers to autoimmune diseases.

Autonomous' website refers to developing countermeasures before the next pandemic. How does your technology enable protection against variants we likely haven't encountered before?

Great question. I'll start by saying that we don't take the approach of trying to predict the future.

Before I started Autonomous, I spent years mathematically modeling the evolution and spread of pandemic viruses. And the lesson I kept learning is that you can't predict a stochastic process with scores of unmeasurable parameters and "heavy" tails to the level of detail that you need to develop an effective precision therapy in advance. And even if we could know the random genotype of a future viral variant, we wouldn't have a way to map its pandemic potential. Some have proposed using new AI approaches to solve these problems—but the pandemic prediction problem is likely a lot less tractable (and deterministic) than problems in, say, computer vision where AI has changed the world.

So what can we do? I think the solution is to develop broad-spectrum or variant-proof countermeasures that can control whatever viral variant ultimately emerges—even if the precise genomic confirmation of that variant is frankly unpredictable months to years in advance.

How can we develop these broad-spectrums? To me, there are two options. One option is to target the part of the system that doesn't change from virus to virus: the host. And we've seen a ton of recent interest in host-directed therapeutics; I think it's an extremely promising avenue. The concern has always been that *targeting the host means targeting the host*, and raises the specter of toxicity.

The other approach is to find the kernels of viral genomes or proteins that don't change from virus to virus. These conserved viral elements are not likely to be in the Spike or receptor-binding proteins of a virus that vaccines generally target—those proteins are under too much diversifying selection from the immune system. In fact, the conserved regions that we want to target are often the regions that are the least well-suited for vaccine and antibody approaches. But these regions can be targeted using RNA technologies.

Admittedly, I don't think there is enough conservation across entirely different viral species to be able to develop a single virus-targeted drug that works equally well across all viruses. There's just too much viral genomic diversity.

But what we can do is find elements that are conserved within a viral genus or species. For example, we can find targets that are conserved across all the variants of SARS-CoV-2 or across all influenza variants. And then we have the possibility of developing countermeasures that don't lose efficacy every 6 months—and that can be effectively administered for lifetimes.

More broadly, we have the possibility of pre-developing an armamentarium of pan-variant countermeasures for each major viral family. That's what Autonomous uses RNA to do.

Historically, antivirals and vaccines have been less well-funded by private investors. Do you feel that the pandemic has changed the funding landscape for early-stage companies, or do you worry that the landscape will revert?

I think substantial funding will remain in the space, at least in the near term.

There's always some reversion, since some funding will likely jump to the next hottest thing. But, on the whole, I think the financial incentives are hard to ignore for an investor. You're talking about $75B that's likely to be grossed for COVID this year alone by just two companies (and we keep hearing that the pandemic is over).

At the same time, these numbers were clear before the pandemic. The market sizes for viral pathogens with pandemic potential are (unfortunately) massive. And there were already blockbuster returns for earlier antivirals and vaccines—from HIV and HCV to HPV.

I think that some of the historical shortfalls for antiviral and vaccine funding have also been on us: the companies. We haven't always been developing new classes of approaches that offer major benefits over state-of-the-art strategies. How many similar monoclonal antibody or Spike vaccine approaches can we keep funding? More fundamentally, some of the issues have been at the Government and academic level. If we keep funding the same sorts of basic science studies, we'll get more of the same translational products, and *less* of the same investment funding.

My view is that new classes of drugs and vaccines for major market indications will always have substantial investor interest—and that'll especially be the case in the ID space after COVID. It's just that you have established biopharma companies that have already developed and clinically tested existing products. The bar is high: you have to disrupt and supplant these existing approaches to enable the kinds of potential returns that would really excite investors.

What do you think presents the biggest health threat for the future?

A lot of my work is on viruses—so I believe (I think for good reason) that these are the critical global health threats.

Earlier on, I argued that we can't predict the next outcome of a random process. So we can't know if the next viral pandemic will be another flu, COVID, or an entirely different pathogen.

But I think that we can fairly assume that there are going to be more viral pandemics—we're still in one. And many of the pandemic strains that emerge will likely be close relatives (i.e. variants) of viruses that have previously infected large numbers of humans. After all, these viruses have already crossed the major evolutionary barrier: transmission across humans.

To me, the critical threat is that the next pandemic variant is again untreatable or is resistant to all approved therapeutics and vaccines. In other words, after years of COVID and millions of deaths, we could be back in March 2020 all over again.

Sure, new platform technologies (including mRNA) could speed up response times—so maybe we'll have an authorized vaccine or monoclonal antibody in 6 months. But we know that's six months too late and that it's fundamentally impossible to develop, clinically test, and manufacture a *new* countermeasure faster than a pandemic virus can spread.

We were based in New York City in March 2020. Being in that environment is something that you never forget. People felt helpless and knew that there were few medical countermeasures for them or their families if an infection took a turn for the worse. It's incumbent on us to do everything possible to make sure that doesn't happen again.