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Hey, everyone. Welcome to FYI, which is the four-year innovation podcast. We're very excited today because we have an amazing distinguished guest today, which is Dr. Jonathan Wiseman. Just a few good things to say. I mean, we could spend hours talking about Jonathan's accomplishments, but we'll keep it rather brief here and we'll talk about it a little bit more within the podcast. Dr. Wiseman is really focused on how cells ensure that proteins fold into the correct shape. We'll get into that a lot. If anyone's listened to our podcast or our brainstorms, they know we talk a lot about alpha fold and other neural network-based algorithms that can predict protein folding. A lot to talk about there. Dr. Wiseman also looks at the role of protein misfolding in disease, normal physiology as well, widely recognized for building these innovative tools, broadly exploring different principles of different biological systems.
We'll get into all of that too. This includes many things. If you don't know what these things are, we'll dig into that as well, but ribosome profiling, also CRISPR-i and CRISPR-a, which I would love to talk about, something I'm really passionate about. We have the creator here, so very exciting. That's going to control the expression of human genes. Dr. Wiseman is also part of the Whitehead Institute for Biomedical Research, a land and T-cell clay professor for biology at MIT. We could go on and on and on. We will have a bio printed here, also numerous awards. Let's get right into the heart of the discussion. First of all, I did a very, very brief unfair representation of all the amazing things you've done. Maybe can you just tell us a little bit about your background, how you got interested in the field, what brought you to this point? My background actually was trained in mathematics and physics. Somewhere around my first year in graduate school, I had that sort of road to Damascus moment and decided that, as fun as it was to study the quantitative sciences, that I was much more interested in biological questions. What's been really satisfying is over the course of my career, is that the sort of computational approaches that were used in things like math and physics became just a central component of biomedical research, as biology has become an information rich science. A big theme in sort of what we tried to do is we sort of live in two worlds. We're interested in specific biological questions. I'm particularly interested in, how does the cell maintain its integrity in an organism? Maintain its integrity? There's some questions of homeostasis despite a harsh world that we live in that you're able to, cells and people are able to function for the most part with a high degree of quality and efficiency. That has led to a number of rich discoveries in biological processes. That's on the one hand where we have these questions that we're interested in, but I'm also very interested in how we ask the questions. We always hear that science is about testing hypotheses. You have hypotheses, you try to

disprove it, and if you can't disprove it and you try harder, you start to believe that that hypothesis has some validity. Equally important to me is where do new hypotheses come from? How do we understand what questions to ask? That to me has been a real change in how biology is done and one that CRISPR has had a huge impact on. It's allowed us to go from this sort of follow-your-nose qualitative gut sense of what might be important and what things I should study to systematic data-driven principled approaches to understand what are the important biological functions to be testing and generating hypotheses for. That's a really helpful overview and you said a few things that I'd love to kind of circle back on in a minute, but I think maybe switching gears just slightly right now, I think it'd be helpful if we sort of framed the podcast. So I know we've talked a little bit about this, but I'd love to just, if I could, maybe we can segment the podcast into sort of thirds. So we can talk about programmable medicines or genetic medicines as sort of the overarching purpose of this podcast and one that you've contributed greatly to and one, obviously, if anyone's listened before that I have a specific real strong interest in. It's my coverage universe, but it's also something that I'm really passionate about and I think from that you can imagine sort of three branches. One would be sort of the drug, one would be efficient delivery and the other sort of just basic functional genomics and so I think how we can start if I may and that works for you. Maybe let's spend a little bit of time talking about the drug and drug discoveries. So it seems like reading about your incredible work and journey that you're always trying to develop and research these new therapies and it sort of goes back to what you said, which is where do these new hypotheses come from and how do we generate them and do so in the most efficient and hopefully efficacious way possible. So one such initiative that you developed with colleagues from UCSF was this technique called CRISPR-I, which can allow researchers to regulate gene expression, but it can also be used for other things like drug discovery. So I think this is an important place to start because obviously when you're talking about drugs, it can happen without, as you say, generating these hypotheses and also generating these important and potentially life-saving drugs. So I think one thing that we're focused on here at ARC is the idea CRISPR-I and some of these other tools that we're seeing come out for drug discovery. A lot of people that we find investors, et cetera, science aficionados and people just kind of trying to learn about the space, I think when they hear CRISPR, they think gene editing and they think drug and they think potential cure. But I don't know if there are so many people who know about its role in drug development and we've done some work on sort of pricing, et cetera. And if you look at drug development costs, including sort of the cost of failures, the average is about $2 billion and it takes about 10 years to create a drug and that's before any commercialization costs. So we've seen from scientists like yourself estimate that preclinical costs could account for about 40% of costs in clinical development. And so lowering these costs will substantially help with getting to the market cheaper and being able to provide potentially more affordable drugs to patients, which is what we all want. So maybe we can separate these two a little bit further even and that is how is CRISPR helpful in the first bucket in disease biology and target identification? And then maybe in the second one, you know, sort of more in the development and drug segment. If those work for you, otherwise you can bucket it any way you want. That's just how my brain came to it. Absolutely. So I maybe restate a little bit what you said is because to help frame it, this idea of programmable medicine and the notion is that we would understand the mechanism of the disease. So for example, that you inherited

a mutated protein from your parents and know that what we would like to do is to change that, is to correct that mutation, basically bring you back to people who are not going to develop the disease. That's sort of the vision. And the beauty of this would be that once you've identified what you want to do, if you, when you've worked out tools like CRISPR and gene editing, gene therapy, you could immediately design the drug. And that may seem like, and that's really the idea of programmable medicine. And that may seem like science fiction, but that's essentially what happened
with the mRNA vaccines for SARS-CoV-2. Once the sequence of the SARS-CoV-2 virus was put on the internet within something like seven days or something, Moderna had designed the vaccine and then it was a matter of producing it and testing it. And so that shows you the promise of being able to shorten with programmable medicines like CRISPR therapies or RNAs, the promise of shortening this
development time really dramatically. So there's two sides to this. There's what is the programmable drug we're going to use? Is it an RNA as it was in the vaccine? Or is it going to be CRISPR editing to change the sequence of your DNA or a CRISPR-I or CRISPR-A to turn on or off a disease-causing gene?
That's one side. And there's been really great progress on this. So we have tools like CRISPR cutting for knocking out genes, but now base editors are prime editors for changing the sequence of DNA
or some of the tools that my lab has focused more on, so-called epigenetic editors that let us turn on or off or on or off existing genes. So that's sort of the one bucket, what are the drugs going to be? And that's really starting to, we really have very nice tools. Not that we can't do it better once, but we can do a lot with the ones that we have. And maybe later I'll talk about CRISPR off as one of our sort of favorites of this. So those tools are in pretty good shape. We're really limited by delivery, but so which organs, which tissues we can deliver these tools to? So for deliver, we really are able to, with things like LMP technology, really able to deliver these tools very effectively. And other tissues are coming on board with AAVs. We can start to get to the CNS, and there's a lot of activity, a lot of interest in this question of delivery.
But then the final and ultimate thing that's going to determine how the impact of programmable medicines is which genes, what changes do we want to make to end to what tissue? Which genes do we
want to turn on and off that will modulate a gene, or which genes we want to change that was going to modulate a disease. And this is this broad discovery that sort of the whole edifice of modern molecular biology is trying to understand what genes we can change that will ameliorate disease. And that's where, in my view, CRISPR has had an equal impact in revolutionizing biology and
medicine. And so that I'll switch to and start talking about. And that's where I was talking about this sort of hypothesis generating systematic principled way of doing discovery, both basic biological discovery and disease mechanism discovery. Because as you said, if you're talking about spending billions of dollars and years of work to develop a therapy, you want to accelerate that process, we also want to be really sure that the therapies you're developing are the best ones. Yeah. And I think the way you framed it, I really liked. So we talked about the Cas9 or the traditional cutting, which I think we've talked a lot about on this podcast.

And we've also talked about basin prime editors. And then you mentioned sort of your lab is more focused on the more sort of epigenetic editing and that your favorite is CRISPR off. So I kind of want to circle back to that and maybe for listeners, give sort of like a practical example. So for example, for Cas9, we obviously know CRISPR therapeutics and Vertex are partnered on a sickle cell beta thalassemia program, which hopefully may get approved soon. It's with the FDA for review. But I would love to know if you sort of can talk about maybe some practical examples and then also what sort of you see as the benefits and maybe some of the drawbacks to some of these tools? For a therapeutic, and I'll talk in a moment about this application to discovery of what changes we want to make. But now I'm talking directly using CRISPR tools as a therapeutic. So the CRISPR cutting, prime editing, base editing, these are editing the genome. They're changing the sequence of the gene of the genes. But we know that there's a critical role for epigenetics as controlling the expression of the genes in both normal biology and in disease processes. So every cell in our body has exactly the same DNA. And yet the photoreceptors in your eye are very different than muscle cells are different than T cells and B cells, etc. And the reason they're different is because of the epigenetics, because of the control of which genes are being expressed and when. And we also know that misregulation of the genes plays a critical role in a wide variety of disease processes. So for some things, for some changes, like if you have a stop codon in your cystic fibrosis transmembrane regulator, your CFTR gene, and that's causing cystic fibrosis, what you'd like to do is correct that stop codon, so you have the wild type sequence. And for that, things like base editors are prime editors are really sort of ideal. But for other things where you have a disease, a gene that's contributing to disease. So for example, the one that's very popular now, for good reason is PCSK9, a protein that's expressed predominantly from your liver. And we know that the expression, normal expression of this disease of this gene rather contributes to hyperlipidemia and coronary artery disease. We know that because there are people naturally walking around who have mutated versions of PCSK9 and are not expressing this protein. And those people have a dramatically lower risk of getting heart disease. So the human genetics has done this experiment for us, identified what change we want to make. And here's something like CRISPR-OV, which is a tool for epigenetic editing, where we can permanently silence a gene by without changing its sequence, is in my view sort of the ideal route for silencing that gene. And it's sort of the perfect solution. If you don't want PCSK9 to be expressed, rather than mutating PCSK9, so it's in the damaged form, so that for the rest of, and permanently changing your DNA, so that you will then express continuously a damaged version of the message and a damaged version of the protein, we can, we can silence that gene and have none of the transcripts being expressed. And this becomes particularly important if you want to do multiplexed silencing of genes. So if you want to turn down multiple genes. Now, the tools that I, with my UCSF colleagues developed for shutting off genes initially, the so-called CRISPR-I or CRISPR interference, where you could, in a programmable way, bring in CAS9 to shut off a neighboring gene, were very effective if you want to study the function of the gene. But they weren't great therapies, and the reason they weren't great therapies is

as soon as you stopped expressing your CRISPR-I, your gene would turn back on. And so you solved one problem, which is the expression of your, a silencing expression of a disease gene, but then you created the second one, which is, how do I keep the continued expression of my CRISPR-I? And also, what's going to happen when you continuously express this foreign bacterial protein? It really did not seem to me realistic therapy. So the beauty of things like CRISPR-cutting is that it was once and done. Once you, once you cut the gene, it was never going to be functional again. And what CRISPR-off does is it uses the body's natural mechanisms for epigenetically, permanently, heritably silencing genes through DNA methylation. And so now we can, in a once and done way, methylate the promoter of a gene. That gene will be turned off, and it will remain off as we found in, in vitro for months or years, and essentially we can expect, at least in some cases, permanently off. So this gives us way of shutting down disease genes in a permanent way without changing underlying DNA sequence, sequence of your genome.

I think that's really helpful context, and it kind of gives us a roadmap for, for which types of technologies we should look to for which potential indications. And maybe just staying on, on the theme of, of these tools and how they become somewhat developed as therapeutics. I'm thinking about also, CRISPR is also pretty important for when we're looking at a drug or potentially developing a drug, and we want to use things like high throughput drug screening. That's a pretty critical step in sort of the whole drug discovery process. So, you know, CRISPR technology can be integrated into that process, which I'm not sure how many people are familiar with. I'm sure all the scientists who may or may not be listening know about this, but maybe some of the other people who are just getting into the space, this may be surprising. And one of the things it can do is it can enhance, you know, efficiency. It can also potentially enhance accuracy. So by using CRISPR to create sort of human and maybe animal cell lines, what it can propel is it having specific genetic alterations that then, you know, people like you can study the effects of potential drugs on these various disease relevant cellular models. So this really allows for these more precise evaluation of drug candidates, and it could potentially significantly reduce the number of false positives in the drug screening process. You know, I've been reading quite a few papers about different people. I recently read one from the College of Life Sciences in China that used this method to find a treatment for acute myeloid leukemia. They did a CRISPR-Cas9 screen, as we call it. So, you know, we at ARC and scientists and people we've collaborated with are really excited about the promise that this can generate. And, you know, I think we can expect to see a growing number of CRISPR-based therapies entering into the clinic. And then that will help for ultimately reaching to sort of patients that are in need. So I'm just curious sort of, you know, in the spirit of continuing the conversation on sort of this discovery and development piece of using CRISPR, how you sort of have been implementing this in your lab and sort of how you feel this is an important development? Yes. So that's this really brings us to the second major use of CRISPR and discovery, which is try to understand how our genes, which genes are contributing to either a normal biological process or to a disease process. And really, I think the backdrop for this is over two decades ago, we've had the first draft of the human genome, and we knew that there's 20,000 plus or minus different proteins that are different classes of proteins that our body can express. And all that we do all going from a fertilized egg to an adult person and all that happens in disease is really comes down to which of these proteins are expressed. And

we've for a while known how to measure which proteins have been expressed through different technologies that people might be aware of like micro rays and RNA seek. And the way I, the analogy
I like to say is this is like a listening to a composition. You hear the music, you get to
you get to see which notes, which of these 20,000 notes are being expressed and when. Not let you, you know, understand a lot about how diseases happen. But it's not very satisfying.
At some point, you'd like to be able to compose. You'd like to be able to change the notes and change which notes are expressed and when and see which ones are reable and which ones are disagreeable. And what CRISPR has allowed us to do is turn off any gene or any or on any gene or any combination of genes. And so now rather than just looking at which genes are expressed, listening to the music of this expression, we can compose new, new scores and see how that affects different biological processes. I like the, the musical analogy. Did you have any musical training or is that a side hobby? Just as a, just as a consumer. And to make that a little more concrete an area where this is probably most mature is this idea of cancer, synthetic lethality, especially synthetic lethality in the context of cancer. So we know that cancer is driven by genetic and epigenetic changes and especially either oncogenes like mutated forms of K-RAS that are so common in many cancers like pancreatic and lung cancer or loss of tumor suppressor genes. And so the one people may be familiar with would be things like Brock, the Brock mutations that you inherit. You can inherit from your parents that make you much more prone to a number of types of cancers like breast cancer and ovarian and pancreatic cancer. So when you lose these tumor suppressor genes, they make cells prone to getting developing tumors, but they also create vulnerabilities. And we want to exploit these vulnerabilities to be able to specifically kill cells that have lost both copies of the Brock gene and not the ones that haven't. So be able to distinguish between normal and cancer-causing genes, cancer's prone cells, sorry. And the analogy I have is it's a little bit like losing Brock as a little bit like losing one of the legs of a four-legged chair. The chair is unstable, but it won't fall down. If you then can remove the second leg, now that chair is not going to stand, is not going to be stable. And this is exactly what was done actually before CRISPR, but using the predecessors to CRISPR, is that they found that
Brock was a critical gene in repairing mistakes in your DNA. But the reason that cells could live without Brock is because there are other mechanisms, other DNA repair mechanisms. And one of them involves
something called PARP. And so it's found that if you made small molecule inhibitors of PARP, so PARP inhibitors, that these were then particularly effective at treating Brocka or Brocka-like tumors, tumors that involved loss of the Brock gene. And this is now one of the
very successful therapies for treating Brocka-like mutant forms of cancer. But this can now be applied to, with CRISPR technology, we can very effectively search for each tumor based on its genetic lesions, which oncogenes it has, or which tumor suppressor it's lost. Look for specifics, vulnerabilities. Look for what is that second leg to pull out from underneath it.
And so this is done now in a number of different contexts, and giving us
really true promise for true precision measurement, medicine and tumors. But this model can be now
extended to a number of different disease processes. And I can talk about those in a second,

how we've extended beyond cancer. Yeah. So just to note, for anyone who doesn't know, the predecessors to CRISPR, you meant Zincfinger Nucleus is entailed. Actually, this was RNAi technology. So functional genomics was usually relied a lot on the RNAi, this sort of being able to screen through many genes and see what their effects are, how they modulated the disease process.
RNAi was really the precursor. And the reason why, from a therapy point of view, Zincfingers and tails were great. From functional genomics where you really wanted to change notes at will, they weren't because it was too hard. Every gene you wanted to change, you had to develop a new tool.
And so it didn't let us test all 20,000 genes at once. So RNAi did, the problem is it was less effective, it had more off targets, and it just got much noisier results. So I want to give you the opportunity. Do you want to maybe highlight how we've evolved even beyond cancer? Oh, yeah. So
examples are one of the challenges. I know you've covered CAR-T, so immunotherapies, cell-based therapies. One of the challenges with using engineered T cells against tumors is that T cells have this period where they're very active, and then they have the built-in mechanism of basically going into an energetic state of basically no longer being effective as the killer T cells.
And that makes a lot of sense, because the immune system, when it's overactive, or unregulated, can lead to forms of autoimmunity. But that's great when you're talking about the natural immune system, and it stops us from having a preventing autoimmunity. But when you're trying
to do manufactured T cells, it really limits their efficacy. So one of some of the first CRISPR screens outside of cancer were in T cells to really try to identify targets that when you knock down prevented these cell-based therapies, the T cells from sort of going into these energetic, non-functional states. So I think something that we should also just maybe touch upon. I mentioned it briefly in the beginning, but I would love to get your thoughts a little bit more. When talking about drug discovery and all of these different tools and drugs, I know you've done a lot of work on protein folding. We've definitely talked about it a lot. We've done several blogs and others, and we're really fascinated on how sort of these neural network-based algorithms, I think I mentioned alpha fold, there are others obviously like rosetta fold and others. But we think that that could really accelerate drug discovery, and that's really going to be helped by this prediction of the protein folding. So would love to hear a little bit more about why you see this as an important issue, and a little bit more about sort of the solutions that you've potentially come up with. So alpha fold, first of all, in the various forms like other forms like ESM fold and the new flavors that are coming out are really transforming biology, accelerating it dramatically. But what they rely on is the fact that the sequence of amino acids, the sequence of a protein determines its structure. So that's in theory, it does. In practice in a cell, proteins often misfold, and they misfold, they form aggregates, and these aggregates can be in some cases highly toxic. So we now know a common theme
in many neurodegenerative diseases is that you get protein aggregates or protein misfolding. And it's a different flavor of protein depending on the disease. So in Huntington's, the Huntington proteins, and Alzheimer's, it's A beta peptide or tau, and Parkinson's seems to

involve a protein called alpha-synuclein. But it's this common theme that you end up getting proteins which never make it to their native state and instead sort of aggregate like a scrambled egg.
And in some cases, it's even worse that these aggregates can propagate or grow. So once you have a cell that has it, it can actually spread in the cell and maybe even spread between cells. So where our interest has been on the machinery that allows proteins in this complex environment in the cell to reach their native state, the states predicted by alpha-fold.
Great. And one of the things, obviously, that we've seen as maybe not a criticism, but one of the limitations that we've seen with some of these algorithms is the protein-to-protein interactions maybe are difficult to predict and also just sort of the environment. So the environment obviously changes within the body. And so those have been challenges and limitations that we've seen. So perhaps there's more room for your work to kind of grow there as well.
I think there's clearly going to be a role for these AI approaches for an understanding, not just the final state, but the multiplicity of states the protein can go into and how it can breathe within this type of breathing that can promote aggregation and misfunction and lead to disease. So I'm very up. The first, it was extraordinary that they were able to largely solve the protein folding problem and get us to predict the fold of the protein. But I think the next, one major next frontier is to solve the protein misfolding problem, understand when this process, when and where this process is most likely to fail.
And I think that could have correct implications for treating diseases like neurogenetic diseases that involve protein misfolding. Because if we understood how this process went wrong, we could then start to design small molecules to prevent that. And this is not so hypothetical. There's actually the major drugs for cystic fibrosis, a major class of them developed by vertex are in fact preventing the mutant forms of CFTR from misfolding or for Transcyritan TTR, a protein that accumulates these sort of amyloid aggregates. My friend colleague Jeff Kelly developed
a small molecule that prevents this misfolding. That's a very successful and therapeutically important treatment for these types of misfolding diseases.
Definitely. I think it may be time. I mean, I think we've spent a long time talking about sort of the drug discovery piece and how CRISPR is really being used both in drug discovery, but also as a drug as a therapy itself. But I think it may be helpful now if we shift gears a little bit and go on to sort of our delivery process. And I think if we have a good and potential therapeutic, if we can't get it to the proper tissue or organ, it is less helpful. So I know you touched a little bit on this before when we were talking about the different CRISPR applications, but maybe it would be helpful just to touch upon the different types of deliveries that we have and maybe where they can go within the body and sort of where you see the future kind of going in that vertical. What the excitement to me about the sort of functional genomics is ability to change expression of genes, one every gene and in combination of gene and to understand how it impacts a disease process, whether it's killing of a cancer or keeping a CAR-TE functional or ameliorating the effects of a genetic disease, is that we use CRISPR as a tool to discover what changes impact a disease process. And then we can immediately switch gears and turn that discovery tool into the therapy itself, because with CRISPR we can test all the different possibilities of genes to change in which ones are best at impacting a disease and then implement

those changes as a therapy, whether it's through base editing or prime editing or things like CRISPR off to make those changes. The key thing, the key missing thing though is we have to be able
to deliver these gene editing tools or these epigenome editing tools to the right cell and to do it effectively. So in the liver, lipid nanoparticle LMP technology is incredibly effective. We can really, realistically in an adult and probably even with redosing, hit every one of the major cell types of hepatocytes in your liver. And that means as soon as we have a change that we want to make, so for example you have mutations in the gene that causes phenylketonuria or PKU, you would then be able, if you have the editor, you design an editor that can edit cells in vitro in a test tube and then deliver it through LMPs to deliver to make that correction. So we've really sort of come full circle on this idea of programmable medicines. So being able to accelerate the discovery and the development from years to potentially months or even weeks.
But that delivers really at the moment unique in our ability to deliver. So a big limitation now is how do we get to other organs and other tissues? And here we need a delivery vehicle. So people are developing new LMPs that are targeted more effectively to different tissue. So I just to sort of give you a sense of how important, how much of a change that could make. We have CRISPR therapies, some of the first CRISPR therapies were to treat sickle cell trait. We've known it was actually the first gene where we understood how mutation led to disease. We understood that mutations in hemoglobin, the hemoglobin gene, caused sickle cell anemia, that caused people to inherit sickle cell anemia. We can develop editors that allow us to get around these mutations or to correct those mutations. But the way we have to do it as a therapy is to give the patient essentially a bone marrow transplant. So you take out their so-called hematopretic stem cells, the stem cells that we can populate your blood system, edit them in vitro in the test tube, create a niche so that we can now transplant them back to the patient and so replace the existing HSEs with the edited HSEs that will then go on to perform, to produce a normal variant of the hemoglobin. And that can cure people and it has. And it's remarkable to miracle, but it's a very expensive and very debilitating process. So this process of getting a bone marrow transplant can itself cause a lot of morbidity, the mortality. So you would love to instead of having to take out your bone marrow and essentially replace it and go through this long expensive process. If we could edit our HSEs inside, if we had, for example, an LMP, like the ones that you use for the mRNA vaccines, that could instead of going in that case, the muscle went to the HSEs and edited them. Now you would have a therapy that you could administer very broadly, including in Sub-Saharan Africa where sickle cell trade is most common.
So that's a very discreet technical engineering challenge. And it's a hard one, but whenever you have these sorts of engineering challenges, I'm much more optimistic that will make rapid progress because you know exactly what you're supposed to do, what you have to do. It's a very well-defined technical problem, as opposed to sort of the conceptual problems of like, how do we, you know, how do we treat cancer? We had to first understand what cancer was and had to
took, we had a war on cancer from Nixon in the early 70s and it took decades and decades to have that impact to how we treat the disease because we didn't know what cancer was or what changes we want to make. So all of this is a long-winded way of saying the delivery problem is a hard one, but a wonderful engineering problem where there's a lot of create a lot of

different approaches. And we didn't even talk about the preconditioning regimen for sickle cells, so there's so many benefits, you know, to be a crew there. So yeah, that would be a fantastic initiative and I know there are a lot of labs really focused on delivery. So, you know, I think there's been some interesting papers this year, you know, I was very interested in EVLP specifically, but I think there, yeah, I don't know if you want to say a few words on EVLPs or...
So I'll talk about that. There's the LMP technology which now has been demonstrated that can be done at an enormous scale. It went from a hypothetical it had been done to a very few people had treated it to something that's been, you know, a billion people have received more than a billion that have received LMP vaccines. So that is sort of a gold standard, but I don't think it's going to be the best solution for all tissues and all deliveries. So the other approach has been to use viruses because viruses are naturally good, they're basically vehicles for delivering DNA and RNA to our cells and they're very good at, that's how they make their living. So a favorite is adeno-associated virus or AAB and there's different flavors of these and these have been used natural ones and engineered ones that are better at, for example, delivering to the central nervous system or to different tissues. And that's AAB, that's a real therapy. There are a number of therapies based on AAB, some quite successful. And so, for example, for delivering to the central nervous system, there's been a lot of work and a lot of success in AABs.
The other approach, though, has been to take the best of what viruses do, which is deliver either proteins or RNAs to cells, but to do this in a truly engineered way. So either use natural viral-like particles or variants of viral-like particles that don't actually aren't capable of replicating or aren't viruses unknown, but you can manufacture and use them as a delivery approach. So there's a number of different strategies out there that I think are quite exciting. Definitely. It's definitely a field that will continue to evolve and the idea of going to more tissues is the most important and giving really what patients need. But because this is ARC and our focus is on disruptive innovation, I wanted to ask if you had any thoughts on, we talked a lot about drug discovery and about creating better and more efficacious therapies. So my thought is, how can we further reduce time to market for new therapies and get even better technologies? Do you think we need better sequencing technology?
Is it a matter of better neural network algorithms? Is it we need to be able to create better predictions for more viable drugs? We've talked about, through our research, that looking at AI CRISPR and next generation sequencing, we could improve the time to market and trial phase reductions by about 25% each with these new technological advances. So I'd just love to hear from you. What will get us to better, faster to the market with cheaper and better therapies? Do you have a sense or is it all of the things we just talked about?
So ultimately, we have to speed up the efficiency of clinical trials. It's not my area of my research at all, but I have some thoughts on that. But I think it is sort of all the above, and I also think that machine learning has potential of impacting all of these. It's such a broad and ubiquitous tool. It's actually sort of an umbrella term for very rather different algorithms and different approaches. So the key thing is you want to understand what changes you need to make. The biggest failure of drugs in the expensive one in late stage is on efficacy. That is, you succeeded in making a change, turning alpha gene, preventing

a data aggregation in the brain, and you make a therapy that does this, you make the drug, you give it, try it in people, and it either causes some toxicity that we didn't anticipate, or it just doesn't treat the disease as you would hope. And these kind of late stage failures are enormously expensive and sort of also heartbreaking because you can do 100 things right. And if your hypothesis that you started with was wrong, if your hypothesis that if I do X to the body, if I turn on this protein or change this protein, that it's going to ameliorate the disease, if that hypothesis was wrong, then all the work and all the years you poured into it are for naught. So increasing, understanding better what changes are going to impact a disease process is going to be central to making better therapies. And here I think a combination of the CRISPR type tools that let us make these changes, either in cells or increasingly in animal models and mice, but even in more sophisticated models like non-human primates, to be able to make these changes and to test many, many possibilities so that we get to choose the one that is truly most promising, not just the one that you have, is important part. The second part of the equation, so that lets you make changes and see which ones impact the disease and to do this on scale. So it gets back to this generating hypothesis as I talked about. The second aspect of this is to use the natural experiment of human genetics. And in the end, it's the human drug targets that are validated by human genetics have an enormous advantage over ones that are just based on work we do in a dish or in an animal model. And so I talked about PCSK9 because it's such a paradigm. Here, you knew people had mutations, naturally occurring mutations in PCSK9 that either got rid of half or all of the function, that those people not only were they healthy, not only did they not develop a disease because of missing this protein, but they lived longer. They didn't have heart attacks. So you're really confident that this was both a safe and efficacious target. So this combination of testing and generating hypotheses with things like CRISPR and functional genomics on the one hand, and then going into human genetics to see whether those impact human health and lifespan is a powerful approach for understanding which changes we want to make to affect a disease. Then when you validated those, the programmable medicine could be a terrific way forward, but even if it's a tissue you can't get to, for example, by delivery, then you can try to replicate that with small molecules or drugs or with antibodies. So it's this discovery of functional genomics plus human genetics to validate targets is modality independent. It's of course most elegant when you can use the same tool, the same CRISPR tool that discovered what therapy you should, what changes you make as the therapy itself. And I think increasingly that's going to be the case, but for the time being there's going to be an important role for other modalities, small molecules and protein drugs. Yeah, I think that's all really good context. In addition to being such a prolific researcher, you're also really involved in the science outreach and the education. So I guess from your perspective, what do you think is really important for younger scientists to engage with the public and what are some of the challenges
involved in doing so? And maybe sort of just if you could speak a little bit about your outreach and maybe any advice you'd want to give to young scientists as well. So the advice to young science is a career now, I think it's a wonderful time to go into biology. And actually this is what I would say also as outreach is that it's an incredibly exciting time. Our understanding of

fundamental understanding of biology, of who we are and where we came from is changing dramatically
after a long time of sort of getting better tools. I think we really have sort of a tipping point where we are our ability to understand human biology and to impact it rapidly is changing.
And I think that one thing that I think doesn't get enough, it's almost taken for granted is like what a remarkable miracle was that we could get mRNA vaccines so quickly. And a couple decades before that, how we were able to identify HIV and make the blood supply safe. And then within another decade develop therapies that turned into a chronic disease. And where did these come from?
They came from a lot of basic research, a lot of understanding. If we had not had all this understanding in RNA biology, which seemed like to the outside world probably the most esoteric thing or things like LMP technology, if they had not already been in place, we would not have had a vaccine anywhere near the same time. So you have to do this basic research ahead of time so that you're prepared for the next pandemic or the next disease process.
That's incredible. So I think, unfortunately, our time is up. So I just want to thank you so much for joining the podcast today. I've certainly learned a lot and I know that everyone on the listening end will really appreciate the comments and sort of all of the contributions as well. So thank you very much. Well, thank you so much for having this conversation, as we really enjoyed it. ARC believes that the information presented is accurate and was obtained from sources that ARC believes to be reliable. However, ARC does not guarantee the accuracy or completeness of any information and such information may be subject to change without notice from ARC. Historical results are not indications of future results.
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