[Transcript] FYI - For Your Innovation / Gene Therapy Could Cure Cancer with Professor Waseem Qasim

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Hello. Welcome to FYI for your innovation podcast put on by Arc Invest. I'm Kathy Wood, Arc's founder and CIO. Well, I wanted to set this podcast up because I found it fascinating, first of all, but also I wanted to tell the story about how I found out about what now seems to be a miracle and how little attention it attracted at the time. And I have a hypothesis for that. I was in Asia in December on a roadshow and listening to BBC, which was the only English language show. I think I was in Malaysia at the time. And I heard a story about a young girl, Alyssa, 11, 12 years old, who really last May was on her deathbed. And she had leukemia, a certain kind of leukemia that resisted treatment. And she had tried dozens of therapies. And she was on her deathbed. And so her parents were willing to let her go into a research study. The research was being done at the Great Ormond Street Institute of Child Health in the UK. And Professor Wasim Kasim was the lead in this research. And she went through it last May, May of 22. And by November, she was cancer-free. This news came out, I guess it was in a publication
called Blood in November. Not very many people read blood. But it was a poster at ASH, which is the American Society of Hematology Conference, which took place from December 10th to the 13th. I was in Asia at the time. So I called Aly Ehrman, who's our Therapeutics Analyst. And I asked her, she was at ASH. I asked her, was it making a big splash? I wanted more details. And she said, it wasn't making a buzz at all. It was a poster, but there was very little buzz about it. And I thought about this for actually a month. And we were in a terrible bear market at the time. And on January 4th, I tweeted, just to help people understand what miracles are taking place out there, how much innovation is taking place, and how fearful the world is about everything, including everything, including bank crises now, and how it was missing some of the biggest breakthroughs in our lifetimes. So I just wanted to... There was no publicity in the US. It was just the UK and wherever the BBC was, which was in Asia, obviously. So in this podcast, I know Aly's going to set it up now and introduce you to Professor Wasim Kassim. But I also wanted to highlight that Charlie Roberts, who is an advisor to ARC and who is also one of the co-founders of Freenome, he's the chief growth officer now. He and Aly interviewed Professor Kassim. So I hope you enjoy it.
Professor Wasim Kassim is a professor of cell engine therapy at the Institute of Child Health, UCL, and a consultant in pediatric immunology, BMT, at Great Ormond Street Hospital in London. Professor Kassim's lab focuses on developing new treatments for inherited diseases and exploring how the immune system can be used to fight cancer. In the lab, they draw an extensive experience in bone marrow and stem cell transplantation. They use special clean room laboratories to manipulate

the cells where they do their research. They're also very interested in the power of the T-cell and how they can work with pharmaceutical companies and other biotech firms to develop these new next-gen approaches of these molecular tools. They've also done research including things like tail proteins and CRISPR-Cas9 for targeted gene editing. Their groundbreaking work has already led to very interesting development of universal T-cells and base editing technology for childhood diseases. There will be much more to come and we look forward to the conversation.
Hi and welcome to FYI, the For Your Innovation podcast. We're very excited today because we are joined by Professor Wasim Kassim. Really exciting data that came out on a patient while we were at the ASH conference this year. Just really excited to dig in to learn more about this particular patient and about the field in general, immunology, CAR-T, etc. Also really excited to have Charlie Roberts on the line who was our former NHS clinician. Also the co-founder of Freenome, an entrepreneur, really focuses on the intersection of AI and biotech and is also an advisor to ARC. So welcome to you both and really excited to have you both on. Hello. Thank you Ali. Hello Professor.
Awesome. So let's just start and dig in. So firstly one thing that we're really interested in is just about what led you to focus on sort of developing these gene therapies for immune and other genetic disorders, but also particularly in children. Well, I'm a pediatric trained clinician. So I'm actually a specialist in pediatric immunology, which is the study of in particular children who grow up without a properly functioning immune system. Often they present early in life and need bone marrow transplantation. So I become an expert in transplanting children and as part of that, perhaps 20 years or so, we've been developing genetic therapies, gene therapies, to try and correct some of those conditions around which we've learned a lot about how to engineer immune cells, repair immune cells, give them new properties
and directly as a result of that, we've learned how to develop what we call chimeric antigen receptor immune cells, which have got special properties and are being used to treat various forms of leukemia. So some years ago, I took a step back from clinical work directly in the hospital with face-to-face day-to-day work and pursued and advanced some of the new technologies that we could see would be useful for the kind of patients that we have in front of us who otherwise don't really have any treatment options. And that over a period of, well, 15 or 20 years almost now has led to a number of early-phase clinical trials and we're beginning to see the successful fruits of some of the early development work that's gone on over a long period of time, actually.
So one thing you just mentioned was the successful fruits and there are two patients, I think, that have been somewhat publicized. Obviously, you've probably had many more successes than aren't as publicized, so maybe we can start there. So there was one patient, the earliest patient that I've seen kind of mentioned in the media, I think was around 2015, a patient named Layla Richards, who was treated with CAR-T cell therapy. As you mentioned, she was diagnosed with a very aggressive form of leukemia called acute lymphobelastic leukemia and she was diagnosed, I think, at about three months old. So we'd just love to hear sort of your experience and how that was. If that was one of sort of your earlier successes. You're absolutely right. One or two of these patients have become publicized in the media, really because they were the first ones entering a particular phase of new technologies being applied as therapies. So in 2015, we were in the laboratories working on developing what we call off-the-shelf CAR-T cells, meaning could we

come up with ways of making immune cells target leukemia that could then be generated from a single donor or a small number of volunteer donors and be given to larger numbers of patients. So you'll be aware at the moment, most CAR-T cells are generated from a patient's own blood cells and given back to them. So we wanted to see if we could get an advance on that to make the technology more usable and more applicable. And we'd actually just finished manufacturing one of the first full sized banks of CAR-T cells using a technology called talons, which is a precursor to CRISPR, really. It allows us to cut genes in a very precise way. And one of the advantages of working in a university setting, which is directly linked to a hospital and people sit in and out of each other's meetings and you kind of know what's going on, is one of my clinician colleagues and in fact head of transplant unit, Paul Veys, almost jokingly said to me, you know what, if you had those cells ready, we could use them right now because we have a patient who's run out of treatment options. And from that half joke and suggestion came the first application with this under what's called a specials license. The hospital has a special license to allow you to use treatments as a one off on a compassionate basis if there's no other usable option for that patient. And the family were incredibly supportive of that, realizing that, you know, this young infant, not even one year old was facing, otherwise was facing palliation really. So we treated that young girl back in 2050 and were really impressed by the strength of the response that she had. And she is now, well, she's nine years old or eight years down the line and is, you know, living a normal school child, schoolage child lifestyle going to school and doing all the normal things that you would normally do. So yes, at the time, that was the first application of a genome edited cell therapy that had a successful outcome for a patient. And so there was quite a bit of publicity at the time. And I think it did galvanize people to try other versions and other applications of that particular technology. You manufactured the T cells from Selectus. Is that right? Well, University College was collaborating with a French company called Selectus, who own the intellectual property around talent technology. So they had brought something to the table, which was the ability to deliver talent mRNA at high efficiency into cells and deliver very efficient knockout of genes. And we had expertise in lentiviral vectors and combining the two together resulted in a very fruitful collaboration. And we like those type of collaborations where the commercial partner is bringing something that accelerates developments and perhaps some funding and development support, and we can offer something in return. And the synergy there was very useful. And in fact, I think accelerated deployment of those kind of technologies into early phase trials, not just in the UK, but also in the US at the time. Yeah. And obviously, this was an incredibly complicated story and patient having received many therapies before, but also even before this therapy. And I think she just received one single dose. I think at the time it was called UCART 19 T cells. And I think relatively little toxicity. So pretty incredible story.
Yeah. It's important to point out that the technologies was applied in a very specific context, knowing that you were going to use it to try and clear out leukemia and a young patient, get them disease free. And then we follow through with a bone marrow transplant. So it's not a small or easy procedure. It's a complex procedure over many, many weeks and months. And she was fortunate in not developing serious toxicities, but these type of treatments do carry various risks and so on. So in their first iterations, they are being applied probably in some quite complex, difficult patients, but have the potential to be applied more widely as we learn how to use them and understand how to improve them over time. And you mentioned that talents were sort of the

precursor for CRISPR. So really interested in obviously talking about the next patient that's been quite widely publicized. But we were at Ash at the time, the American Society of Humanitology Conference. This was around January of this year. And a BBC story came out and it covered a patient that you treated, Alyssa, who's a 12 year old girl. She received base edited CAR T cells with CRISPR. And this really showed the promise of base editing, which is obviously an innovative form of gene editing that can make these precise changes to the genetic code and then corrects mutations that can cause diseases. And this example obviously is within cancer. So I just love to hear about sort of the whole premise, you know, we had a call last time and talked a little bit about it. But I think it's so interesting because the story of how it's evolved and, you know, how you were a clinician and really went into research, it's, yeah, it's incredible.
I'll give you the stepping stone in between the two patients. There's a third patient there, or a patient in between, a young girl who was treated in the middle of the COVID pandemic. In fact, at the start of the COVID pandemic, with a technology which is kind of in between. So CRISPR Cas9, which as an academic center, our job is to move on and pick out things that we think are coming through and going to be useful. So the UCAR program was taken off and developed by
Serbia and Pfizer and Allergy. Our job, in the meantime, was to pick up CRISPR and try and apply that in a more flexible way. And the first CRISPR Car19 T-cells in the UK, certainly, were applied for a younger age two at the start of 2020 for a type of leukemia that had come back after a bone marrow transplant. And in fact, this story isn't publicized really because the family didn't want as much exposure. At some point, she may well be presented more formally, but it's a very interesting story because this poor family, the girl that relapsed after her bone marrow transplant, and because of COVID, and she caught COVID, because of COVID, she and her mom were basically restricted to a single cubicle in the hospital, perhaps for a period of, I don't know, it must have been close to six months where they were not allowed family visitors. The mom wasn't allowed to go home and see the other children. And it was a very emotional and stressful time for the whole family. But that child was treated with a CRISPR Car19 product. And as with the first patient we described, she did go into a remission and was then eligible to have a follow-on transplant. And again, even up to date, is managing really quite well without any additional treatments. So that just tells you that even in the face of some very difficult situations, and at the time, it's before we had vaccination for COVID, so there was a lot of anxiety about whether she'd be able to manage it or whether she'd spread around the virus if she hadn't cleared it and so on. But it turned out okay. And then you mentioned our jump from CRISPR to base editing, but the two are linked because if you can manufacture cells using CRISPR Cas9 technology, the jump to using CRISPR and base editing versions of CRISPR for engineering is actually turned out, was actually relatively straightforward because it involves the same manipulation steps of collecting cells, activating them in a particular way. We developed automated machinery that handles them and cleans them and washes them and cultures them. So all those steps were in place for the pre-existing technologies. And what we managed to do was pick up David Lou's publication in Nature from around 2017 describing how base editors work and full credit to the MIT team that they published that paper in such a way that they provided the full recipe of how they'd done all the work and how they got those reagents to work, that we were able to pick them up in developer version that went fast into a clinical use.

In fact, that's probably the fastest development we've certainly done and it's probably the most complicated cell therapy that we've made so far. And I think in those, you edited those healthy T cells that came from the donor and there were, I think there were three edits, is that right? There's three simultaneous gene disruptions by creating what we call stop signals or stop codons in the genes for those cells. But the technology is being used and it's very clever in the way that it allows us to change single letters of the DNA code inside the cells at very high efficiency, not quite 100% efficiency, but very high efficiency. And the ability to do that now on cells that we, we collect the cells and we engineer them in the laboratory. So it's something that's done ex vivo and then the cells have pooled together into doses that can be given back to multiple patients. Now again, the advantage of being able to do that over CRISPR, a normal existing CRISPR is that the likelihood of other changes in the cells drops off and because we're not breaking the DNA, we're just kind of using chemicals to change the letters. It's a much gentler process compared to the previous one. So two advantages and I have to say the technology that we've put into that first product is the first iteration and since then there's been dozens, I've lost count of how many versions have appeared since then that let you change various letters between the various combinations of letters that you can change them to and the efficiencies are all looking very high. So credit to the chemists and the basic molecular scientists that have developed those technologies and shared how they can be applied. We actually did a blog recently where we looked at CRISPR. So I don't know if you've ever used it and Oh, you do. We did a CRISPR, a base and a prime just to see the difference in outcomes and unintended outcomes. So it's very interesting in our analysis sort of proved exactly what you said, which in a base edit because of those chemical conversions, it's sort of a cleaner process typically. But of course, every technology has its own challenges. It'd be interesting to hear Prof Kasim about the quality assurance process that happens before the cells go back to the human. Is there a lot of work still to be done there? Is that something you're very comfortable with? Well, again, we had some expertise because it's built up over a period of time. It's a dynamic situation. So as the technology evolves and comes out, we have to get agreements hand in hand in the
UK. It's the MHRA. And so it's an evolving situation. But I think we've got a very good relationship and a trusting relationship that we propose how we're going to do it. And it goes backwards and forwards with them and generally accept a rational, well thought out package of testing that we can do, acknowledging that we might not have all the answers, but we've got enough answers or enough contingencies to understand what's going on. And so we've gone from some years ago
using gamma retro rail vectors to using lengthy rail vectors to now using vectors combined with mRNA technology and guide technology that even a few years ago didn't really exist.
And another important COVID phenomenon that occurred was we ordered, we contracted BioNTech German company to manufacture mRNA for us to deliver the base editor. And we were fortunate in managing to do that just before the emergence of COVID, because since then their main work has been obviously manufacturing vaccines. And luckily, we've managed to manufacture before or at least
order the manufacturing before that. And that then did allow us to continue production through the lockdown period. But yes, the analysis we do, there's obviously analysing the raw materials that

we've
produced, often custom manufactured. And then there's analysing the cells that have been produced at the end of our manipulations, and having enough data on those to understand what's happened to them,
how they're going to work, and what the possible side effects and expected or unexpected might be when they go back into patients. It's interesting to hear about you mentioning sort of the challenges that happen, you know, with BioNTech, with supplies, with the ex vivo and Charlie's question about sort
of GMP and what testing is needed. Because I think one important shift also is going to be from autologous to allogeneic cell therapies. And I think that's sort of an underlying theme of what we're talking about here as well. And so obviously, there would be a lot of benefit to having an allogeneic cell therapy because it's off the shelf, or it's donated. So it's more simple, it's less time. And obviously, autologous cell therapies have a lot of benefit to them, obviously the biggest one being no risk of real cell rejection, and obviously allogeneic having its own challenges with graft versus host disease, etc. But despite the risk, you know, obviously allogeneic cells can really help patients, and they can maybe get into even earlier stages of cancer and really reduce the cost by an organ of magnitude. So just curious sort of on your thoughts there in terms of the differences, what you're seeing in terms of shifts, and obviously for solid tumors, autologous has been really the only one that's shown real results to date. So just curious if you have any thoughts there. It's an important area of development. And you're right, when we first started, we were talking about autologous cells from the patient themselves. Now there's obvious advantages to doing that in terms of the chances of side effects are reduced in terms of GVHD and not likely to get rejected. There is a quality issue, of course, if you've had a lot of chemotherapy or treatments, but how good those cells might be. But there's no doubt that the products that have been made and put into patients have had some quite dynamic and strong
effects for those patients. But of course, again, as you mentioned, there's a lot of logistics and infrastructure required around collecting cells from individuals, getting them engineered and back to those individuals. And that probably is limiting in terms of what the size of the market for those can be. And there'd be a much larger application if you can get around some of the hurdles of using cells from an otherwise not matched individual. I think removing the T-cell receptors is what we've been doing. And that has, I think, more or less addressed the risk of GVHD. The more problematic issue is how long the cells might persist or if they get rejected too quickly by the recipient. Even a small amount of immunity or even patients have had quite a lot of chemotherapy
still have reduced immunity will reject cells over a period of days or weeks or months. And so that needs to be addressed. But there are steps that one by one will be put into, I'm sure, overcome that. And then you'll be looking at versions that are available in a ready made format and can be shipped around or be shipped around with a cold chain. So they're shipped around frozen and used in larger numbers of patients, perhaps earlier in their disease course, instead of some of the heavy chemotherapy that's being used at the moment. And you're also right that most of the successes
so far are in the context of blood cancers, what we call soluble tumor. So leukemia is an infirmary.

They're exactly the same conditions that are amenable to treatment or have been targeted by bone marrow transplantation in the past, because you're dealing with the blood immune marrow system.
And there's a good handle on how the immune system can or can't treat those type of cancers. It's much more challenging when you're talking about a complex cancer or tumor involving one of the solid organs that's had no prostate or breast cancer, where there's an architecture around it, it's got its blood supply, there's an environment. So they're no longer what we call simple cancers. So I think at the moment, the car therapies are heading towards the simple types of malignancy. The more complex ones, I suspect will need more engineering steps and all combination treatments with some of the checkpoint pathway inhibitors or antibodies or other things that can help them get over the line to give you a more potent targeted response. So that's a work in progress. Thanks, Prof Christine. That's fascinating. And it'll be great to return to some of these topics in a moment to actually about just where this sort of technology could go. I just wanted to say, I mean, you know, having been a clinician and only for a few years and not taking it nearly as far as you, one of my enduring frustrations and just upset was just seeing how much of the therapies we give and gave were really just symptom alleviation and really sort of moving deck chairs around on the Titanic and really not getting at the heart of the problem and being disease modifying. I think in cancer, to use a provocative word, the C word, the other C word, cure, I think we can only safely say really in cancer, we see cures in early stage resection, where you often do see an enduring benefit. And more recently in PD1, PDL1, CTLA4 and these other immune checkpoint approaches. Outside of that, very scant examples of people really doing very well consistently. And I think, you know, these things come around once in a generation maybe and hopefully the pace of acceleration is such that that will happen more. But one could, I know we approach this as clinicians with real trepidation because we're always worried about recurrence and
we've seen so many false dawns. But this does appear on the face of it to be a new generation technology that has the potential certainly in certain settings, certain patients, certain populations of being a cure. And is one of very, very few. How do you feel about that? Do you feel that that's that's excess hype? Or is that real? How does that make you feel as a topic and a concept? As you said, we avoid the use of the word cure, because that's something you'll only know in the rear view mirror. So looking forwards, I can't say cure, although the length of time that goes on, so you talk about disease free survival over a period of time, let's say at nine, ten years, cure is a difficult one. And it may be that you will only know about it afterwards. But I think you're absolutely right that there will be specific conditions and circumstances where these technologies will give you a deep clearance and a possible completely eradication where the problem just doesn't come back. There may be other situations where, and this is a generic issue, where your malignancy is perhaps controlled or debolked in some way. And you may live with it. And it's not going to be the cause of demise. There'll be something else that you'll live with it for a long period of time. And something else will be the complicating factor in a circulatory thing or something else will be the final event. So there's no one size fits all. It's a complex picture and it's a question of picking out as we go along. And of course, what's going to happen and what is happening is there's more and more data being generated through genome sequencing, RNA profiling, and so on. So what we think of as homogeneous cancers

with a particular label may turn out to be lots of different things with different susceptibilities to particular drugs or treatments, which then need to be tailored to that signature that you as an individual have. And that, again, is a moving target and things are changing as more and more data accumulates. Absolutely. Thank you. And whether we call it a cure or just a very compelling, durable response, how do you think about even the societal and the health system implications of that kind of a change? Because it is a fairly radical change. I mean, we've seen it in some cases with melanoma and lung and bladder and other places that IO works very well. And this begins to speak to your point about where else could this technology go and be very interested to hear how you think about that. And maybe even in 10 years time, as we look back, whether it's impact on individual patients or patient populations or society and health systems more generally, how do you think this type of technology will have changed things in a really radical way? Or do you think it is going to be more incremental and we won't have seen that tidal wave of change? I think there's a lot of incremental steps underway. And if you add up all the little increments, you'll see changes in the disease-free survival and the swiable curves over, for example, a 10-year period, you'll start seeing those. So from a practical or logistical point of view, in the UK, in North America, the autologous car therapies have become authorized licensed products, the health services or insurance services are paying for them, they've become standard of care for some circumstances, and there'll be more of those applications. At the same time, the example I can really only focus on is the UK example with the NHS, which has taken on those treatments. But there are wider issues about bed capacity, logistical capacity of harvesting and so on, which may turn out to be the rate limiting parts of this. So the technology might be moving quicker. We still have to deliver it and get it to patients and then follow those patients up. Absolutely. And building off that thread, I mean, how do you think about the future of access here both within underserved communities and indeed across the world? Because obviously some of these technologies require quite a lot of infrastructure and indeed cost to get them to people. And yeah, any thoughts there would be fascinating. So there's a lot of infrastructure already in place for the ones that are managed around the context of cells and transplant and so on. So the infrastructure and the expertise is there to do that. There's extra infrastructure that has to be built for manufacturing cells and testing them and quality control and so on. So there are some obvious jumps in the costs involved. There's obviously debates going on in the background about where the pricing should be for some of the newer agents that are brought out and marketed. I mean, we're still dealing with relatively small numbers of patients. So it's not become a critical issue. But there's arguments about whether the health services would be able to manage the costs involved if there were high price tags for large numbers of patients over a larger period of time. And then there's a longer term question about, well, for example, at the moment, we're obliged to monitor patients for 15 years for possible side effects of genetic therapies. And how that's done and who makes sure it happens and who pays for it is in the mix of how you do the pricing and absorb the costs of having to do that. So there's a strong debate going on in, well, you'll know more about this than me, I guess, in the investment communities and the pharmaceutical communities about where the price points should be and what prices are too high and what's affordable and not affordable. Okay, I cannot help the pickup on this conversation, obviously. We're doing a lot of work currently on

how do you cost and we'll use the word cure very lightly, but we can say a potentially one-dose therapy. How do you cost that appropriately so that the researchers and scientists are adequately incentivized, they're incentivized by many different reasons, but financially incentivized and then also that the investors recruit their investment, that pharma companies continue to bolster their R&D with new capital coming in, and then obviously that the patients who need these therapies are able to get them. And I think this has been a prominent discussion. There are new therapies that keep coming on the market and the pricing, I think sometimes is unclear why certain medications are priced in certain ways. We can have a very long conversation about all of this, but I think when we're talking about these new innovative modalities like gene editing, like gene therapy, we can just think of the example of hemophilia, which is obviously the blood clotting disorder. And we estimated in our Big Ideas deck this year that hemophilia direct cost, the lifetime direct cost for treatment for a patient with hemophilia would be over $28 million. And then a recent drug came out that was approved for hemophilia B that was about 3.5 million per dose. And now this could be because hemophilia is quite prevalent and that could have lowered the cost. And of course, hearing 3.5 million is obviously a shocking number, but if you think about it sort of in the idea of someone's entire lifetime of cost to the healthcare system, in addition to the patient's own mental health of continuing to go through chronic treatments all the time and their quality of life and also their indirect costs, it's quite staggering. We also did some kind of gene editing revenue projections where we did a base and a high, but we estimated that by 2030, we could get to about $60 billion in revenue for gene editing companies. And this is obviously if things happen like type one diabetes approvals where there's substantial patient markets. But I think the question really is that it's going to be challenging to create pricing transparency and correct drug pricing in whatever way correct means for these drugs to actually get to the patients that need them. So I don't know if you've thought about how that would work with CAR-T and other therapies that you're working on or what you see from sort of the patient's perspective and how they're struggling with the cost, but it'd be very interesting to hear more about that. Yeah, I know there's no straightforward answer to all of this and it's an incredibly complex picture. We do see those numbers of lifetime costs of treatments and so on. I suspect they're generated in such a way as to give a particular pitch value in terms of where you think your product, your total product value lies. I'm not sure they're directly fair comparisons. A good comparison might be, for example, in the setting I work in where we do transplants. We know quite accurately what a bone marrow transplant might cost. It's different in the UK and the US, or you could go to the Far East and have it done and be costing less there, but we know roughly what it would cost. And if you have a comparable treatment that delivers the same kind of outcome over the same kind of time period, well, that might not be an unreasonable pitch point for therapy. And that's kind of where I think, I don't know the exact numbers, but I think that's kind of where some of the car treatment costs have landed. There may be a bit less, but the very high numbers I've seen around the hemophilia and some of the other metabolic conditions, I personally think they're a bit odd because they're relatively small markets and the treatments,

you haven't got lifelong cure, you've got treatment for a period of time, so you're looking forward looking and claiming the advantage over a long period of time. And I actually suspect that what will happen is there'll be other versions that come along that might well be better and more effective because the technology is moving so fast. So you probably don't want to commit to saying that is the version that's going to give you the 25 or 30 or lifetime output that you want. So it's a dynamic moving field. It's not sitting still. And also it's going to be a global market. So at the moment, a lot of these things are in the hands of United States companies or European companies, perhaps, but we shouldn't discount that there's a lot of work going on in the Far East and the speed and the rapidity at which the technology is developing means it's going to be a global outlook, not just a Western one, I think. Yeah, I think that's definitely true. We also looked specifically more sort of at immunotherapies as opposed to gene editing, gene therapy, like in 2021. And I think the other thing that is important to note is that currently a lot of these therapies are done in late stages. So obviously that will change the TAM as well and potentially the cost as we move more and more into the earlier stages. And as we also kind of alluded to you before, we're typically focused on the liquid tumors right now. That's where we seem to be having the most traction. And so again, the TAM sort of evolves as we move into the solid tumors. And then that TAM, as it increases, could also really add additional revenue, which could potentially drive costs down. But do you think there's anything else that could be a driver for reducing cost or causing like some kind of cost decline for these therapies?
I think that the driver for the cost coming down will be the treatments that work the best and get adopted most widely. At the moment, there's a whole spread of things that may turn out to be
useful or not. And we'll only know over a period of time which one of those come good or maybe something that we haven't even tried yet comes good very quickly. But the analogies are all there from every other. Again, this is your field, not mine. But if you look at anything else, cars, phones, everything, there'll be some high price points at the beginning. And then as people get better at doing it, it's going to come down pretty fast. Very interesting to hear. Maybe what's been the biggest surprise of your career, whether good or bad, or maybe both?
I still can't get over reading David Lu's paper and spitting out my conflicts where he's base edited at such high frequency and converted a C to a T in those first descriptions of how a base editor works. It was science fiction. And it's gone from science fiction to science real super fast. And we've been very pleased to be able to pick it up and run with it.
Great. Thank you. Agreed. And we're obviously very excited about David's work and the associated things coming from that. Another sort of related question to career wise, you've done really an incredible job of balancing advances in basic science and foundational research and having real world impact in applications that directly benefit patients. And that's actually still unfortunately quite rare, I think, and actually not often where clinicians and clinician scientists are guided. It feels like there's still an either or kind of philosophy around. And if you've got any advice or thoughts for, especially up and coming young researchers looking at their own forward career path, and in some cases actually being told by very senior people that they really need to make a choice between doing foundational research and having applications and any thoughts about that. You're absolutely right. The career pathways are not straight forward. For medics, I think there's more structure these days than there used to be. And it's probably easier

for medics than straight forward science postdocs, easier for medics to go into science and then balance the two than the other way. The structures are there. For example, I picked up a couple of fellowships along the way. And then the NIHR, which is the National Institute of Health Research in the UK, the research arm of the NHS, paid a large fellowship, allowed some of this work to jump from lab into clinic. But I do remember some words ringing in my ears from a long time ago. There's a group of quite animated and angry people all arguing about career pathways and so on. And somebody wise in the background just stood up and said, look, if you're excellent, just go off and be excellent. Go off and do things. And if it's good and it works, people will fund it and it will find its own way. And I think that's still true. So the good things will find their way through. It's a harder slog with things that if they're not going to work, if there's a dead end, then you have to turn around and go and do something else. Yeah. And have you seen any, obviously, there's a great
research hub in and around UCL and with the welcome and companies like Syncona, which are very involved in helping co-found even very early stage. What do you see as the role for industry in supporting some of this very foundational research and really building? Absolutely critical now, because this cannot just be done, certainly can't be done just academically. All the academic developers have to partner and find a way to develop and advance on to the next phase of application. It's really good to work with companies that come, as I mentioned, with some technology or expertise that synergizes with what's going on in the universities. And the universities and the hospitals, NHS in particular, is full, is a massive resource. And it's well, I mean, there's lots of criticisms about the way it runs particular things. It's well organized in terms of the resource, in terms of the patient and the data available, the samples available in that environment. And it's an ideal environment to get some of the things through into early phase testing. And early phase testing used to be all about testing the safety of a product. And that's no longer the case, certainly no longer the case in the pediatric trials we're doing. So we would no longer do a study or bring something into study that was just testing, is this safe for a phase one? Everything that goes in now has to have a reasonable chance or reasonable expectation of having a useful biological outcome, even in the early phase studies. And I think in that environment, we could probably put quite a lot of new technologies and new techniques through with all the framework around about how you're checking and testing what's going on in the patients. So that's all there. As I said before, the rate-limited things about the day-to-day management in the health service and how things run is probably going to slow things down more than the technology is. Thank you. Absolutely. I was just going to pick up on something you said that got me to thinking about some of the research we've done where, you know, we've looked at how
AI has accelerated drug discovery and potentially caused assets to go through the pipeline quicker, more efficiently and cheaper with things, you know, like AlphaFold and other sort of machine learning techniques. So just with the idea of what you're saying about these new technologies, these new modalities, have you guys thought about, or are you implementing any sort of artificial intelligence into the pathway of looking for new drugs or new techniques?
I would love to be able to implement some of the AI technologies coming through.
We haven't had the expertise. If we could partner with people with the expertise,
there's a whole bunch of things that would be plugged into those development pathways.

There is a shortage of people with the bioinformatics and the computing expertise to set those things up. So that, again, is one of the rate-limiting things in the wider environment, the numbers of people, the intensity of the technology up and moving with it.
I'm chairman, professor of a company, Relation Therapeutics. Only five minutes walk from UCL, that you'd be very welcome to come. And the CTO is the former head or one of the heads of AI, VP of AI at GSK and AstraZeneca. And I'm sure the company is using a lot of CRISPR as well. So it'd be very interesting and very happy to set up that conversation.
We should definitely do that, yeah.
Convergences between and among technologies, even on a podcast.
Yeah, there's no stopping.
Professor, thank you so much for your time. I don't want to take up too much more of your time just because we know you're busy and actually seeing patients. But we really, really appreciate the time that you were here with us today. You've obviously done an incredible job sort of looking at both the basic sciences, the real world implications of that work as well. And obviously that's going to only benefit patients. So we're just happy to be able to have contact, to have the conversation. And we think a lot of people will really benefit from hearing the words of wisdom that you imparted. So we appreciate it.
Thanks very much. It's been actually quite fun. I've quite enjoyed that.
So and I'll pick up with Charlie on the AI thing. Thanks very much.
Absolutely.
Please.
Thank you so much.
Thank you so much.