Hello, everyone. I hope you're well. I'm Charlotte Kilpatrick, reporting for VaccineNation and I'm pleased to be hosting another one of our exclusive interviews in preparation for the World Vaccine Congress in Washington this April. Today, I'm delighted to be speaking to Doctor Niranjan Sardesai, CEO of Geneos, sorry, founder, President, and CEO of Geneos Therapeutics! It's wonderful to have this opportunity to speak to you, so thank you so much for your time.

It's a pleasure being here, Charlotte; good morning, good afternoon, and really delighted to be chatting with you.

Thank you! So just to give us a little bit of context to kick us off, would you kindly tell us about your current role?

Certainly, so as you introduced me, I'm President, CEO, and founder of Geneos Therapeutics. We are a clinical stage immuno-oncology company focused on the development of exquisitely personalised cancer vaccines based on our GT-Epic platform. So, we're developing individualised patient treatments based on the concept of personalised cancer vaccines and I'm excited to share our thoughts and our findings with you.

Fantastic. So, at the Congress you will be exploring efforts towards these cancer vaccines, and you've used the lovely phrase "exquisitely personalised". Could you tell us a little more about your team's approach to these vaccines?

Yeah, certainly Charlotte. These are really exciting times for the cancer vaccines field. You know the idea of the immune system being able to recognise tumours and mounted immune system immune response against those tumours is not a new finding; we've always known that the immune systems capable of driving antitumour immunity.

The challenge has always been how do we get that to happen in more patients? Why is it that only some patients are able to drive an antitumour response but not all? So, the biology has always been, you know we've always known that the biology is sound, the immunology is sound, and now the exciting data that's coming out of not only our work but also a number of our peers in the field is showing that, you know, we are finally able to understand what drives the immune system, what drives antitumour immune responses and then more crucially, what are the critical factors for successful outcomes for patients who have been treated with their personalised cancer vaccines.

So, the way Geneos is approaching this very important question is that to make a successful cancer vaccine, for cancer vaccines to be effective, you know certainly the antigens matter. So, what you target makes a difference. Platforms matter. How you target those antigens makes a difference, and also clinical development settings matter. So which indications, what lines of treatment that you develop your products for, can make all the difference between success and failure, not only in the cancer vaccine field, but in in clinical development in general.

So, as we thought about Geneos and our approach for addressing this, you know this big challenge in the cancer vaccine space, we sort of took a holistic view of the cancer vaccines field. How can we identify the right antigens; how can we develop the right immunity to those antigens, and what would be the ideal clinical settings?

We designed these; we call these exquisitely personalised because these are truly N-of-1 treatment. So, they are truly tumour derived from each patient and the product is developed exclusively for that patient and that patient only.

And so, you know we are developing our vaccines based on the idea of targeting tumour neoantigens. So just a little, you know, comment on neoantigens. As tumours progress, they start developing somatic changes and these somatic changes make the cancers different from the normal within the same patient. Now the cancer does this because as the cancer cells divide, the replication machinery is imperfect. So, there are these stochastic changes that show up in the tumours.

Those changes helped the cancer in some ways to avoid the immune system to also, you know, avoid cell death. So, the cancer benefits from those mutations, but the cancer also turns out that those mutations are the Achilles heel of the tumour.

So they also end up marking those cancer cells with flags to the host immune system saying that "hey, this is a cell that's different from the rest of the, you know, of the person". So what we're trying to do is exploit those differences in the cancer cell and because these differences are idiosyncratic, they're different from each patient to patient. The products that are designed based on these differences necessarily have to be personalised. So that in a sense is what Geneos does, how do we identify the changes, how do we make the product, and then how do we treat the patients becomes the core of all the essence of the GT-Epic platform that we have developed.

That's, that's fascinating. Thank you. And it sounds like you've gone to real lengths to tailor your approach to, as you mentioned the individual in question. So, you have the most specialised response which is great. I imagine that comes with a host of sort of challenges. What are some of the main challenges that you, and as you mentioned your peers in the community, face when trying to target personalised cancer?

So that's a, that's a really fundamental question for the field. I think what's known through biology is that we can, as tumours progress, they start accumulating changes. The technology exists for us to identify those changes through the tremendous improvements in sequencing capabilities, both in terms of accuracy, because we want to make sure that the somatic changes are accurately identified, but just as crucially in terms of time: speed of identification, as well as cost of identification.

So, you know sequencing the genome has had exponential improvements both in terms of time and cost over the years. So, we are truly in this sort of golden age of genomics and bioinformatics and in that sense, we are relying on the external developments that are happening in the space beyond us to provide solutions for the sequencing component for identification of somatic changes and we are truly grateful for making it feasible.

So, I feel like this is the right time and the right place for cancer vaccines, personalised cancer vaccines because some of the key technological hurdles around identification have been addressed by the field as a whole. So, we're certainly grateful for that.

The next challenge becomes, a patient may have hundreds of somatic changes. How do you identify which ones are, you know, the ones to target? And here, you know a number of peers we all have our different methods for identifying what we like to call targetable neoantigens and these targetable neoantigens certainly, we all agree have to have certain features that they have to be expressed.

They have to be non-synonymous, meaning that the mutation has to lead to a change in amino acid or an encoded protein. That protein has to be expressed in the tumour. And then there's a few other features that you know that we look for in deciding whether an antigen is targetable or, it's irrelevant.

But beyond that, I think that what we've learnt through our work is targeting more neoantigens is going to be preferable compared to less and what I mean by that is, so Geneos is taking the approach that we identify all targetable mutations, and we incorporate all of them into our tumour vaccines and let nature make the call, in terms of which new antigens are not only immunogenic but can also lead to clinical efficacy.

So, our view is the immune system is capable of driving a response to a large number of antigenic targets and we know this because, you know, through our learnings from natural immunity; every day the immune system is assaulted with hundreds of thousands of pathogens. So we know the immune system is capable of driving responses to a large range of immunogens and we want to take away the decision-making process and leave the decision-making process in the hands of the patient's own immune system. So, we are taking the approach that we're going to target all targetable neoantigens and let nature make the call.

So that's one aspect. The second aspect is that, you know, these are typically, we are treating patients, clinical development paradigms are such that we treat patients with advanced cancer first and show proof of efficacy in advanced cancer settings. And what that means is that these are patients with bulky tumours that are progressing. So, patients and the tumours are certainly not waiting around for the personalised cancer vaccine to be developed. So, speed is of the essence.

So, the one of the challenges is how can we not only identify the neoantigens, design it and manufacture it in a reasonable frame of time for those treatments to be meaningful to that patient. So, so numbers matter, time of, turnaround times matter. And with our DNA based platform, we've been able to already shrink the timeline from biopsy to treatment down to 6-8 weeks today for our clinical trials. But simply by integrating the entire process under one roof, we know we can do this in 3-4 weeks.

So, this is an important distinction because 3-4 weeks is a good, a perfect time that allows us to not only go treat advanced tumours in later stage, you know, lines of treatment, but we can also go into first line treatment of cancer patients. We can also go into adjuvant therapy or neoadjuvant therapy.

And Charlotte this is, this is one of the interesting, you know elements, where sometimes clinical development decisions are made based on the capabilities of the platform. What I mean by that is if you if you have a platform that has a long turnaround time 12-16 weeks, then it constrains the kinds of patients that you're going to be able to treat. So, so some of our peers have, there's been an increased focus, recent focus around treating patients with adjuvant, in an adjuvant setting.

So, these are patients who had surgically debulked tumours, they're essentially tumour, cancer free but have higher rates, high probability, higher likelihoods of recurrence. And so, the idea there is you can treat if you treat patients with no tumour to drive an immune response against the tumour you can prevent the tumour from recurring and that's a really creative way of solving a technological challenge by identifying a patient population where the platform is best suited to serve and we are very excited by the data that's being reported in that setting.

What Geneos has done is we've shown that we are treating patients with bulky tumours. We're looking for objective responses that is showing that patient that begins with a large tumour, progressing tumour gets vaccinated and then we can see by radiological imaging the tumour starts decreasing in real time.

Right? So, so that's so, so we're quite excited about the results we're seeing showing that a successful cancer vaccine approach can work not only in earlier stage cancers where you're driving immunity to prevent recurrence, but also in late-stage cancers where you're using a cancer vaccine like a like a therapy, so you look at as an immunotherapy to treat patients with cancers.

That that does sound like a really promising opportunity. And like you say it, I get the sense from you that this is the sort of the right time for these things to be happening and it certainly sounds like you're rising to all the challenges that you've mentioned.

On the theme of, sort of challenges and technological developments. What bearing do infectious diseases have on your research? Because obviously we have the recent example of possible distractions or, something in the way of your research with COVID-19. Or have there been technological advancements that have been really helpful in your research from infectious disease areas?

So, I think we so speaking for me personally, I come into the cancer vaccines field certainly from the infectious disease side and I think the infectious disease vaccine developments have had a phenomenal impact on how we, how we approach cancer vaccines and in particular this idea of personalised cancer vaccines and let me point out a couple of the parallels over there.

So, one of the key issues with cancer vaccines has been around the idea of central tolerance. So, the immune system through you know thousands of years and millions of years of evolution has developed the capability of identifying what is self from foreign. And if the immune system was not able to do that successfully then then we would have a lot of autoimmune diseases. I mean autoimmune diseases do exist as phenomena but for the most part the immune system is pretty efficient at identifying what is self from what is non self.

And that has been exploited fundamentally in the infectious disease vaccine development because by definition infectious diseases are against, the pathogen or virus or a bacteria, those sequences are different in some way from human sequences. And so, we we've learnt through the infectious disease development, vaccine development, what is it that drives immunity and then how do we tailor the immunity to that pathogen?

So, in the personalised cancer vaccine space, I think the one direct parallel is that these tumour neoantigens that we are targeting as a field, these are these are somatic changes in proteins that exist in humans, but these are changes, so as immunogens these neoantigens are non-self, so to the extent that the mutation sides or the insertions or deletions or whatever the changes may be are likely not subject to central tolerance mechanisms, giving us a better chance of driving an immune response to those antigens.

So, we think of these antigens as foreign just as we think of viral antigens and bacterial antigens as foreign. So that's one direct convergence of ideas. The place where the two diverge is that you know, usually you're looking at infectious disease vaccines as preventative vaccines, prophylactic vaccines, prevention of infection. And in those settings, you're trying to drive an antibody response, a

neutralising antibody response, to prevent infection, or if an infection takes hold, to clear that before it, you know it becomes persistent.

Whereas for cancer you're typically only treating the cancer patient after the patient has already got cancer. So, now you're looking at it from a therapeutic setting and so the challenge or the question for us as vaccinologists is how do we drive a T cell response and more specifically a CD8 T cell response to allow for the clearance of the cancer cells which in many ways you can can resemble an infected cell.

So, what we have learnt from infectious diseases is what are the parameters that drive effective immunity, what we need to do, and what we're giving back to the infectious disease community is how, how do those rules apply in a cancer setting to allow for induction of effective T cell responses in addition to antibody responses?

And then what we learnt from cancer can now get applied to infectious diseases because now we are looking at, and that's been one of the challenges with the COVID vaccines, very, very effective in in sort of prevention of infection because of the antibody responses, but it's been challenging to do clearance because of lack of T cell immunity and those contexts. So what we love about the idea is that I think we started out from the infectious disease we all learnt a lot what we learnt through developing cancer vaccines is what drives effective cellular immunity which can then go back into developing better infectious disease vaccines.

That's great. And it's lovely to think of the idea of learning but then giving back some lessons. And I think that's really important to view the whole vaccine community as connected and able to share progress wherever possible.

So, my final question is, after everything we've discussed so far, I'm sure that everyone who's watching this will be really excited about the Congress. But what are you excited about at the Congress? What is bringing you there? And what do you hope to sort of take away from it?

Yeah, Charlotte, what I love about the you know the World Vaccine Congress is the way it's been set up is that you know, I see it as a Congress has been organised to talk, you know, topics essentially all things vaccines!

So you've got you know there's certainly specialised conferences and meetings and a number of them you know that we that we go to which might be focused on the science side, the clinical development side, or the immunology side, or manufacturing, or also only regulatory, but what I what really brings me to the World Vaccine Congress is the idea that you know, we've got sessions, concurrent sessions going on, not only on the antigen side - how do we identify what are the good targets?

There's discussion on platforms, there's discussion on manufacturing, there's CMC is such a crucial topic in especially in the personalised cancer vaccine stage because if you don't solve for manufacturing, you can have a perfectly good idea, a scientific concept, but it can't be translated into a meaningful into a meaningful therapy.

But beyond that you know the clinical tracks and then I'm also very excited about the regulatory tracks that that are in here because some of these developments that are going on are happening real time. The regulatory frameworks are catching up or are being are being built in parallel with keeping pace with the technology and keeping pace with the development schedules.

So that's what I'm looking forward to at the meeting, being able to interact with colleagues across different silos. We all like to think of ourselves as being in silos, to be able to interact with colleagues across, you know, across silos and you know learn from them but also share and what we're finding in you know in a separate but related space that of therapeutic vaccines.

We are so grateful to Dr Sardesai for his time and enthusiasm in creating this for us. We look forward to hearing more at the World Vaccine Congress in Washington this April. To join us, make sure you get your tickets soon!