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Predicting Patients' Immune Response to Viral Infections with AI

Dr. Turck:
Artificial intelligence, or AI for short, is rapidly changing how we practice medicine in a variety of ways. So, in the midst of the COVID-19 pandemic, could AI also help us predict the disease course of patients infected with the virus? Coming to you from the ReachMD studies, this is *COVID-19 on the Frontlines*. I'm Dr. Charles Turck, and here to talk about her research on this exact topic is Dr. Pradipta Ghosh, Professor of Cellular and Molecular Medicine at UC San Diego. Dr. Ghosh, welcome to the program.

Dr. Ghosh:
Thanks, Charles. Great to be here.

Dr. Turck:
Well before we dive into your study, Dr. Ghosh, let's start with some background. Would you tell us what made you first consider using AI to assess the immune response for patients with COVID-19 and other viral infections?

Dr. Ghosh:
Well artificial intelligence, or AI and machine learning approaches, which are a big part of AI, have really revolutionized our ability to handle and process huge amounts of data.

Now findings patterns within huge amounts of data is something that the human brain just cannot process, at least not the way machines can. And that is because of three limitations. One is speed, or lack thereof. And second is when we are looking at any data, humans tend to get biased; machines can remain unbiased. And the third things is human beings have a tough time distinguishing what is noise and what is signal. What I mean by that is what is unnecessary randomness in the data versus what is truth; what is consistently presenting as a pattern. Therefore, it was absolutely a slam dunk choice to go for.

Dr. Turck:
So how did you go about determining whether AI could be used to assess the human immune response? What strategies did you use to test your hypotheses?

Dr. Ghosh:
So there was a bit of a lag period for data to really be released that belonged to COVID-19 patients. So this posed a unique situation for us. No data, and yet we wanted to go ahead and use AI ML approaches to build a model.

So in that setting we decided, why don't we build a model, train it on pandemics of the past? There was no dearth of datasets there. There was 45, 46,000 datasets. So we thought we will go ahead and train the model in pandemics of the past because that would be a better approach and take us closer to the truth, if there is a shared fundamental host response signature for any viral pandemic. There was a distinct advantage to doing it this way because in some of the pandemics of the past, you can right away see a hepatitis B and C and HIV, they would be mostly seen in liver and immune cells and brain. Then you have Zika, which is mostly the brain, and then you

have all the respiratory pandemics, which should be lung samples. So our model was trained to identify the signature no matter the sample type. It could extract that shared fundamental signature from these diverse viral illnesses, diverse tissue types, and that made it actually a stronger model. And then when the new datasets emerged, we prospectively tested it. What that means is as new datasets emerged each morning, we would go in and check on PubMed, NCBI, we would immediately throw it on the model and it would work. We have not come across a COVID-19 dataset where the model did not stand true. And that is how we tested our theory because a model that was trained on everything of the past worked in the current pandemic.

Dr. Turck:
For those just tuning in, you're listening to *COVID-19 on the Frontlines* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Pradipta Ghosh about her study on patients with viral infections and how artificial intelligence may help us understand and possibly predict a patient's response to viral illness.

So Dr. Ghosh, now that we have some background on your research, let's dive into the results. You mentioned some of them before, but would you share the key findings from your study with us?

Dr. Ghosh:
I told you moments ago that we built the model on pandemics of the past, and we allowed ourselves to take a journey through this COVID-19 uncharted territory of this current pandemic using this model as a guardrail. And we asked several questions.

One of the first things we asked is what does the nature of this host response look like? And when I say nature of the host response, we're looking for these small molecules called cytokines that our body releases whenever it sees an infectious threat such as a virus. And the reason why we always ask this question is because many of these cytokine pathways have drugs on the shelf that could be rapidly repurposed to go ahead and use it in the current pandemic. So we knew we were looking for these very high-value therapeutic targets. Now what we found is the algorithms pinpointed not ten, not five, one, one single cytokine pathway that had to be the most fundamental at the heart of the cytokine storm and that was interluken 15. It's one of those key cytokines that end up causing an exhaustion.]A key cell type in our immune system gives up and that is the natural killer cells. And without these natural killer cells, what happens is our body tends to give up the urge to fight this virus. And so that was an insight into the biology. But then we could ask a second question. Using numerous cell types of the lung as datasets, we could pinpoint which cell type in our lung is actually contributing to this cytokine storm. And we could very easily pinpoint that one of the primary sites for releasing these cytokines happen to be at the alveolar pneumocytes. Basically, these are cells that line the gas exchange chambers in our lungs, and these cells are absolutely vital for our body to really exchange oxygen and carbon dioxide. And these are the cells which are destroyed during severe infection, causing us to get what we call ARDS, respiratory distress syndrome, that leads us to really think of putting the patient on a ventilator and so on and so forth.

Now so far I told you we found out what is the type of post-immune response that's killing us, which cell types release it, but that's for academic interest. We wanted to have a translational impact, meaning a quick insight into what can we do to change management of patients. So in that regard, we had three other findings, which is we could demonstrate that the severe gene signatures that emerge out of this COVID model They could identify which patients as soon as they're admitted to the hospital, let's say by just testing the blood, we could tell which of those patients actually had a poorer outcome and who did better. And this is something that really hasn't been able to be done before.

Second, we could actually put objective definition for what is our therapeutic goal, what is that we want to achieve with any new treatment we would like to consider? And that would be if the ViP signatures are up in disease, we knew that we simply wanted to test and screen for drugs that can bring those signatures down. And that is essentially what we did. Golden Syrian hamsters are now widely used as modeling of COVID infection, and we could go ahead and test the efficacy of two treatment measures, one of them actually was approved for therapy, which is antibody cocktails against the spike protein of the virus. We administered this in the hamsters and we could demonstrate that the hamsters that did very well with this treatment had absolutely no up-regulation of those signatures at all whereas those who did poorly and were left untreated, they reacted to the infectious agent that we challenged them with, which is SARS-CoV-2, and their lungs filled up with infiltrates, they lost weight, and they induced very high amounts of this ViP signature. And we tested a second agent, which is actually in phase 2 trials right now, and it's a compound that can actually reduce the viral replication specifically tested for SARS-CoV-2. And in that case as well we could demonstrate that both these therapeutic measures were widely successful and that gave us really good hope that each of these therapies would be beneficial when they get to the clinic.

Dr. Turck:
Now before we close, Dr. Ghosh, let's look ahead to the future for just a moment. How might this research help, should another pandemic emerge?

Dr. Ghosh:
Everything that we have seen so far tells us that the next pandemic, it's not a matter of if but as we all have recognized, it's a matter of when. The next pandemic must follow this fundamental shared host response and the rules of gene regulation that we have uncovered here. By that token, we can see that these signatures will be up in the next pandemic and the drugs that are being followed up right now including the specific one to go ahead and target the cytokine, we think that the drug that is found in the current pandemic will be ready to go for the next one. We should be able to use the signatures to go ahead and risk stratify right at the time of hospital admission who is likely to do better and who is likely to need additional support including mechanical ventilation so that the level of care can be adjusted. So these are things that we think will be easily translatable and learned aspects here should apply to the next pandemic.

Dr. Turck:
That's such interesting information Dr. Ghosh. And as that brings us to the end of today's program, I want to thank you for joining me and for sharing those compelling findings. It was great having you on the program.

Dr. Ghosh:
Well thank you, Charles.

Dr. Turck:
I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/COVID-19, where you can Be Part of the Knowledge. Thanks for listening.