Yale Talk: Conversations with Peter Salovey
Episode 45: Harnessing the Immune System to Detect and Eradicate Disease
Guest: John Tsang, professor of immunobiology and biomedical engineering; director, Yale Center for Systems and Engineering Immunology; advisory committee member, Chan Zuckerberg Biohub New York
Description: Professor John Tsang and President Peter Salovey discuss the vast possibilities of the Yale-backed Chan Zuckerberg Biohub New York and its ambition to engineer immune cells for early disease prevention, detection, and treatment.
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FULL TRANSCRIPT

Peter: Hello everyone. I'm Peter Salovey and welcome to Yale Talk. At Yale, we are connected by a need to improve the world for this and future generations. And to realize Yale's mission, we must push forward the frontiers of knowledge. And this includes advancing our understanding of and increasing our impact in science and engineering. Last semester, we took a bold step toward this priority as a founding partner of the Chan Zuckerberg Initiative's new biomedical research hub. CZ Biohub New York will leverage the intellectual resources of three leading institutions to engineer immune cells for early disease prevention, detection, and treatment. To discuss this exciting project, I am pleased to welcome Professor John Tsang, who serves on its executive committee. John is a professor of immunobiology and of biomedical engineering at the Yale School of Medicine. He is also the founding director of the Yale Center for Systems and Engineering Immunology, a cross-departmental home and center of collaboration for systems, quantitative, and synthetic immunology. John, I'm delighted to have you on today's program.

John: Thank you for having me, Peter.

Peter: Thank you for joining us. It's great to see you. So the CZ Biohub New York is the fourth and newest research institute in the Chan Zuckerberg Biohub network. It's a collaboration between three complementary research institutions: Columbia University, The Rockefeller University, and, of course, Yale. Although based in Manhattan, we're pleased the hub will maintain a satellite location on Yale's campus. So before we delve deeper into the science, maybe you could tell us a little bit more about Chan Zuckerberg Biohub network and this particular part of it?

John: Sure. For those of you who may not know, so Chan Zuckerberg Initiative was founded as a philanthropic foundation with funding from the Facebook founders, Mark Zuckerberg and Priscilla Chan, his wife. So back about six, seven years ago, they conceived of this idea of funding biomedical research hubs with the idea of bringing leading research institutions locally together to facilitate interactions and, more importantly, collaborations to tackle major challenges in biomedical sciences. The idea is that with a physical hub, they can provide the foundational resources and infrastructure to help facilitate those interactions, and also to pursue long term ideas. So that was founded initially in San Francisco.

Peter: Right. When I go to San Francisco and I'm on 101 going into the city from the south,

John: Yeah,

Peter: It's all on the right side on the highway.

John: Right.

Peter: All of that new construction.

John: Yeah, they're very close to the UCSF new campus. So they brought in UCSF, UC Berkeley, Stanford, three Bay area local institutions, and they come together to pursue ambitious ideas in cell science as well as infectious diseases. So that was its beginning. And about two years ago, they decided that was a success. And they wanted to expand this idea to other regions in the country. So they decided to form this network of Biohub. So they call it the Chan Zuckerberg Biohub network. So that's when they had a national call for ideas and institutions to come together and say, can you guys propose something to form these bio hubs in different locations across the country?

Peter: So what inspired Yale to join on? How did we become a part of it?

John: So the call about two years ago from the CZI, they called for wildly ambitious, technology- driven ideas to better understand human biology and tackle all human diseases. So very ambitious. So this sort of led to our proposal of harnessing the immune system, which has been implicated in basically all human diseases, because it has this capacity to constantly surveys and fixes both internal and external threats of our body, and beyond even the well-known infectious diseases and autoimmunity and cancer. So there's also already the precedent of engineering immune cells in the form of CAR-T therapy for cancer that some of you may know, that's been a groundbreaking advance in terms of using cells as a modality to detect and treat cancer. So that really provided us with a proof of principle that this ambitious of idea of developing these immune cell sensors may really be allowing us to extend to other diseases and conditions.

Peter: Right, so this node in the Biohub network will be focused on immune cells and immune cells as sensors. And it'll be researchers from Yale, from Columbia, and from Rockefeller all working together on this particular issue.

John: Exactly.

Peter: Let's stay with the science a little bit. You use this phrase 'using immune cells as sensors.' And I think that's going to be new to a lot of people who are listening. And I know that typically

we use lab tests and blood work, maybe even try to look at actual organs and tissue, but that's hard to do, right? Sometimes the actual diagnostic work is invasive, sometimes it's inaccessible. So tell us a little more about using immune cells as sensors.

John: Right, yes. It's this notion that the immune cells as sensors really stems from our observations in immunology. So our understanding of the immune system often comes from seeing how it combats infectious diseases. And if you think about an infection, there's various sensing going on at the site of the infection. For example, you have local immune cells and other cells that will detect the infection and send out alarms and calling for other cells to come in and try to deal with the infection. And that's also happening in, for example, tumors, when there's growth and when there's mutation, those signals are also being detected by immune cells. And one unique aspect about the immune system is that it's got this army of cells that basically it's circulating around your body. So it surveils and try to detect issues. And often that's sort of happening in the background. The reason why, for example, we're typically, on average, relatively free of cancer until fairly old age when the risk gets higher, it's partly because of our immune system. It's checking and it's helping us to detect and removing these threats, basically. So it's kind of already naturally doing that. And one of the major challenges is to understand how, how it does it. And can we now start to customize and tailor it to do what we wanted to do, which is what you refer to as can we actually start to detect that way before something happens? And current existing technologies, like imaging and other approaches, often can only access information in the blood. And we may actually have that information in the blood sometimes, but we actually don't fully understand whether it's telling us something in the liver or something in the gut. So therefore we don't fully understand that language yet in terms of what the cells are telling us. And the second aspect, it's the invasiveness. So you can do a tissue biopsy currently and then look at that. And so that's what pathologist would do. But imagine the future where you could send a tiny cell and these cells can actually go in, in a non-invasive manner. We think that's possible because they are already doing it for us, but we just don't fully understand how it does it in the background.

Peter: You've been using the example of cancer in this conversation so far, but I understand that you might be able to use immune cells as sensors for Parkinson's, or Alzheimer's, or other kinds of neurodegenerative conditions. Can you say a little more about that?

John: Sure. So the diseases you mentioned, including cancer, they often have a long sort of developmental window of time scale and other diseases that we thought about was autoimmunity, for example. So it takes years for these to develop. And we don't fully understand, especially some of these early processes that drive the system out of so-called homeostasis. So typically when we're healthy and things are going well, our tissues and organs, they are functioning in this homeostatic mode, so to speak. But sometimes certain things happen. For example, we may have a severe infection that may damage certain tissues, and that starts to change the status of the tissue. And the system may start to go outside of its comfort zone. So that's typically when the immune cells can come in and start to detect some of these signals and start to revert them back. So for all of these diseases that you mentioned, we believe that there's a

large window through which we can understand some of these early signals. And then we can send immune cells in and detect those signals and report back to us what may be going on. So Alzheimer's and autoimmune diseases, some of these signals are already beginning to be unraveling, broadly speaking, in the scientific research fields.

Peter: It sounds great. And I've heard the phrase cellular endoscope, using the cell to look inside. And as you say, detecting the disease well before there's any symptoms of that disease. And as a psychologist, I think now you have that information as a human. Essentially these are biomarkers, right?

John: At the tissue level,

Peter: At the tissue level, that you may have a vulnerability to a certain disease or maybe that you're going to have this disease, but it might be years away.

John: That's right. That's right.

Peter: And so now what do you do with that information? That's kind of an interesting question.

John: That's a great question. So we thought of multiple possibilities. One of the most exciting and dear to my heart is you also program these cells to actuate and respond. One reason for disease development and progression is that the natural system sort of fail to respond to certain changes and deviations, and that's why we may have these markers going up and down. And we're hoping to detect those signals. But imagine the same cell that can detect that signal can also now respond and say, well, I can move the system back to the comfort zone. And I can either secrete a molecule, I can secrete a drug, or I can, again, utilizing the natural capacity, the system has evolved these kinds of feedback mechanisms to get it back. But maybe something has gone wrong, like I said. So therefore, if we can synthetically put in something to detect the issue and respond, that would be a natural, again, non-invasive, and very local way of potentially solving the problem.

Peter: Yeah. So it sounds like it's what our friends in public health call secondary prevention, right? You see the marker. And then you do something to prevent things getting worse. That's a very efficient way to do prevention.

John: Exactly. And the hope will be no more diseases.

Peter: So you were able to learn some things from Covid19 and the pandemic. Tell us a little bit more about the long-term influences of infection on the immune system, and variation in immune responses that revealed themselves during research that you were trying to get done during the Covid period.

John: Sure. Well, I'm glad you asked that, Peter. Actually, that also was a good example showcasing why we wanted to pursue what we proposed for the Biohub. So in my own lab, we've been long studying the basis of immune variation in the human population. For example, why do two individuals, seemingly very similar age and sex, and even from the same region, when they receive a vaccine or when they see an infection like SARS-CoV-2 and Covid 19, can have very divergent different responses? And why is that? So, obviously genetics can play a role, but the immune system is also very environmentally driven, so it remembers our exposure over time to infections and other types of stresses. And so therefore, when you look at an individual in adulthood and ask, why is it that two individuals may have different types of responses? Often you find that genetics actually play relatively small roles in those situations. Measuring and understanding the status of the immune system of that person at that moment in time, it's very important. So advances in technology in the past decade or so has allowed us to comprehensively measure a lot about their immune cells and their state and so on. But it's often still limited to blood. We can draw blood from individuals and look at all sorts of immune cells from that tissue. But as we discussed before, often the immune system also has cells in different tissues of the body, and cells in the blood may have gone to a tissue and send certain things and come back out. And right now, at this moment, we don't yet have a lot of predictive understanding to see, well, this cell maybe has gone to the liver, this cell may be telling us this and that, right? So that's what led to this notion of, wow, wouldn't it be nice if we don't just relying on observing nature, but be able to engineer cells and say, can you go to these tissues and measure things for us, and come back? So that would provide a fuller picture of the immune status of the individual. Now back to your question about how Covid 19 and an infection has taught us. It's been a long-standing question on how when you measure two individuals, they may look very different in terms of their current immune states and status. But where does that difference come from? Is it through some past exposure, or some other perturbations they've had again, beyond genetics, right? So this opportunity to ask this question came up at the early phase of the pandemic, when, if you recall back in March 2020, we had this very big wave, and then many people were exposed in the given community. So then we thought, wow, that's a very nice natural experiment to look at individuals who got infected. But many of them still recover nicely and they look healthy again.

Peter: This was all before we had vaccines.

John: Before we had a vaccine. You may also recall back in 2020, because of all the public health measures, there were just Covid 19. There's no flu, not much RSV. So it was one of the cleanest human experiments you could imagine. Natural experiments. So you got a group of people who got Covid recover and became healthy again, but you can still find a set of individuals who are matching in age and coming from the same region. And then you can ask the question, did that exposure change the immune system in ways that we didn't expect? And more importantly, if you now probe them again, I will explain in a bit what I mean by probing them. Would they have changed their responses? So this probe I mentioned, it's basically utilizing the influenza vaccine that we often get during the fall season. We and others have been using the vaccine as a probe to perturb the immune system and basically ask if you see some differences

across individuals, and now you stimulate them to get a systemic response, do you see a difference? So one of the functional differences would be, for example, antibodies that you elicit by the vaccine to get this response. When we did that experiment comparing these two groups of people, they're all healthy. But one group, they had Covid once and they recovered. The other one, they never had Covid, and we gave all of them an influenza seasonal vaccine. And to our surprise, we found that only the males had elevated antibody responses to the vaccine. So, almost a good thing because you imagine,

Peter: That means the vaccine is working better,

John: Better,

Peter: For the men,

John: For the men who recover,

Peter: For the men who previously had Covid.

John: Exactly.

Peter: A flu vaccine is working better.

John: Flu vaccine. Right.

John: We learned two things from that experiment. One, it's the fact that the immune system can have one exposure to something totally different, in this case Covid. But yet their immune system didn't return fully back to the baseline original status. And now, especially the Covid-recovered males, they have a more intense response to something different in this case than the influenza vaccine. And the second interesting thing is the sex dimorphic nature of the immune response and how males and females, they may have been exposed to the same things, but their responses were different, and their long-term impacts are also different. And now we can extrapolate and say, well, the immune system is constantly being calibrated. It's changing. So we learned quite a bit about the molecular and cellular nature as to how such an exposure event may change the immune system, and under what timescale they may change again.

Peter: Very, very interesting. And so you could see this a little bit as a silver lining of Covid. I hate to ever talk about silver linings of Covid. I mean, people died, people were very sick. But it's not just that we now know how to teach through technology in ways that we didn't before, we were able to actually conduct immunology research that we might not have been able to do otherwise and learn something quite interesting. One of the things I always ask anyone on our faculty who speaks with me, particularly when the program is about their research, is to also talk

about their role as an educator on our campus. Could you talk a little bit about the teaching you do, and to whom, and in what context?

John: Yeah, so most recently this semester I'm helping to teach an advanced immunology class. So it's a second in a series of immunology courses for PhD students, medical students, and advanced undergrads interested in delving deeper into the immune system.

Peter: And so undergrads are sitting side by side with medical students.

John: Yeah, I've had some brilliant, great questions from advanced undergrads coming up to me afterwards telling me how excited they are about some of the concepts we discussed, and also the fact that they are thinking about MD PhD programs in the future. And my focus in the teaching is really to delve into this notion of how to think about the immune system as a system. So often biomedical research, especially with the revolution of molecular biology, has gone deep into reductionism. We've been delving into molecules and how individual genes and proteins it's regulating, for example, the immune response. We can understand the function of a single molecule. But if we zoom out a little bit and ask questions about how does the overall immune response work, what determines the level of the response? And if I change this and that, how would it impact the system's output? I emphasize the importance of zooming in and out and cutting across the scales, and how to think about the system as a system, and how to think about the immune system being an interface and its interaction with all physiology as an important element of understanding the immune system, and also how to use quantitative, computational, and data science approaches.

Peter: So you're doing both, right. Your lab, which is located in our new facility at 100 College Street, which is also where the psychology department is and where my faculty office is, you're using both experimental approaches. You have a traditional-looking lab, but you're also integrating them with computational approaches. And you must have a computer cluster there, too. Are there many labs that are kind of a double threat in that way or are you kind of different?

John: We are relatively unique, but it's being recognized as more common. Grad student and postdoc fellows, they're learning and being trained into thinking across these approaches, both on the experimental side and thinking about the design of experiments. That kind of natural human experiment that I mentioned. It's actually also one type of experiment that we think about and also technologies. It's very important because measurement technologies and how to measure to obtain the necessary information. And then finally, when you have all of this data that now you get from these advanced technologies, how do you transform the data into biological insights? So that's where a lot of the computational advances in AI would come in. We can now infer things based on the data. But then back to understanding. We also need to now build back up what we call mechanistic models. So these are more detailed dynamical equation models, for example, about how the immune system and how various molecules and cells and tissues interact. Back to the Chan Zuckerberg Initiative, our hope is that those models would allow us to build these predictive models and toolkits to allow us to say, well, given a cell, if we put in XYZ and modify

it this way, how would it behave? Where would it go in the body? What kind of molecules can it detect? And we want to be able to do that way before we do any experiment. So the other hard quantitative sciences like physics, our predictive capacity is fairly high before we do an experiment. The immune system is complex. We're not quite there yet, but that's where we're pushing towards.

Peter: That's so great.

John: When you face with a problem as complex as understanding human health and the immune response to these threats, all of the disciplines and various approaches and ways of thinking would come in. So that's one of the reason why we're also building up the Center for Systems and Engineering Immunology, to be able to draw physicians and folks with different expertise and perspectives, working together, hand-in-hand, to tackle these problems that none of us individually can tackle.

Peter: So this kind of work, from basic cell biology to immunology to engineering to data science and computer science and artificial intelligence and the applied math that drives all of that, it really involves investigators from all parts of campus. Is that fair?

John: Yeah, you're absolutely right, Peter. And for the problems that we just discussed to tackle in human health, it really does require the coming together of all of these disciplines. And to be honest, we are all sometimes too busy working within the deep problems within each discipline. But when you zoom out a little bit and look at the challenges, all of them can contribute in significant and meaningful ways by coming together. And that's why I'm so glad that Yale it's supporting the scientific initiatives across campus to really help us to bring researchers and students all coming together to tackle these major challenges.

Peter: That's so good to hear. You know, more than eleven years ago, when I was announced as Yale's 23rd president, I gave a little speech and talked about a more unified Yale. And among the things that I meant by that phrase, a more unified Yale, was investigators, scholars across disciplines coming together to tackle problems that might not be addressable just by focusing in on, as you call them, the deep problems within one's discipline. But by stepping back and looking at ways in which we can work together across traditional boundaries.

John: That's awesome, and thanks for that. I think we're seeing the fruit.

Peter: Yeah. I think it's really happening. It's great. In other parts of campus, we're building up biomedical engineering. Those are going to be collaborators. And we have data science, not just in Kline Tower, where many of the data science investigators are, but also in the medical school. So, you know, it's going to be a rich environment, I think, for collaboration across fields and your lab and center, not to mention the Biohub, exemplify. So let's finish by returning to the Biohub. Are Columbia and Rockefeller and Yale already collaborating, or is that coming soon?

John: There's already collaborations. There's a lot of planning going on since the announcement about getting things up and running. And what should some of the initial scientific priorities be and what kind of talent do we want to recruit? And so there's already a lot of discussion. There's also been some informal meetings among potential investigators and colleagues. To prepare for this application, the three institutions have been coming together for almost two years, so there's a lot of synergy and rapport as we move forward.

Peter: So the new node in the network will be in New York, but they'll also be this mini node at Yale. Do we know where that's going to be yet?

John: Not quite. We're still trying to figure out the details, but potentially in 101 College, which would be convenient for both of us.

Peter: Directly across the street from 100 College, there's a new building going up that will also house Yale Ventures. So if anything comes about from this research that is commercializable, the people who do that work would be in the same building.

John: Same building. That's another area of collaboration and cross disciplines. Yeah, absolutely.

Peter: That's so great. Well thank you, John. The science is so interesting. And the larger implications for humans and for the university are so interesting to me. And thank you for the work you're doing on the CZ Biohub New York, to expand our understanding of the immune system and how we can harness it, essentially to monitor health and detect, and then eradicate disease. You know, with some of the world's leading minds and academic departments and centers and institutes dedicated to immunobiology, engineering, biomedical engineering, data science, technology development, Yale is uniquely positioned to accelerate the ambitions around disease eradication. And our potential to shape the future of biology and medicine seems boundless to me, and it's invigorating to consider where we can have world-altering impact. Thank you again, John, and to our friends and members of the Yale community, thank you for joining me for Yale Talk. Until our next conversation, best wishes and take care.

Peter: The theme music Butterflies and Bees is composed by Yale professor of music and director of university bands Thomas C. Duffy and is performed by the Yale Concert Band.

Chan Zuckerberg Biohub New York

Yale Center for Systems & Engineering Immunobiology