New Possibilities in Infectious Disease and Cancer Vaccine Development

Enhancing T cell Responses for Advanced Vaccine Development Strategies



Interview with Moriya Tsuji, MD, PhD
December 2024

Luna Labs recently talked with Dr. Moriya Tsuji, a leading researcher at Columbia University's Aaron Diamond AIDS Research Center (ADARC), one of the world's top HIV research centers. Dr. Tsuji is a renowned T cell expert with extensive experience in malaria and HIV vaccine development, having worked in the Department of Medical and Molecular Parasitology at NYU School of Medicine, a leader in malaria vaccine development.

Tsuji's major research interests are the development of a glycolipid-based adjuvant for vaccines against infectious diseases and cancers, exploration of natural Killer T cell-mediated protection against infectious diseases and cancers, and generation of a "humanized mice" model mounting human immune system.

LL: Your focus is on understanding the immune system for the development of effective vaccines against infectious diseases and cancer. What are the current gaps or barriers to creating more effective vaccines?

MT: Well, let me explain why I think we're at a critical juncture in vaccine development. You see, the traditional approach has always focused heavily on generating neutralizing antibodies. This worked well for many vaccines - just look at COVID-19 vaccines - but we now understand there are limitations. The main issue is that these antibodies target epitopes, essentially recognition sites, on the surface of pathogens. The problem is that due to constant immune pressure, these surface epitopes are like moving targets - they keep mutating. Each mutation can potentially reduce vaccine effectiveness.

But this is where T cell research becomes really fascinating. What we've discovered is that T cells recognize different types of epitopes, which are mostly hidden inside the pathogen rather than on the surface. These internal epitopes are what we call 'highly conserved' - they don't change nearly as much as the surface ones. They're processed through what we call MHC class I and II molecules. It's a bit like having a more reliable target that doesn't keep shifting.

In my research, we're seeing tremendous potential for this approach, not just for infectious diseases like malaria and HIV, but also for cancer vaccines - both preventative and therapeutic. We've even identified some specialized T cells, what we call Natural Killer T cells or NKT cells, that have particularly interesting properties.

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What makes me particularly excited is how we can combine this understanding with new technologies. For instance, we've developed novel adjuvants - substances that enhance the immune response - specifically designed for T cell-based vaccines. When paired with modern delivery platforms like Luna Labs' carbon nanotubes, you're looking at potentially much more effective and durable vaccines.

This represents a fundamental shift in how we approach vaccine development. Instead of just focusing on antibody responses, we're developing a more comprehensive strategy that leverages the stability and effectiveness of T cell responses. This could be game-changing for diseases that have historically been difficult to target with conventional vaccines.

LL: At Luna Labs, we're developing a carbon nanotube delivery platform – NanoVac - with high potential for multiple clinical applications, including respiratory vaccines, cancer therapeutics, and more. Could you explain how carbon nanotubes and T cell vaccine development work together?

MT: The relationship between carbon nanotubes and T cell vaccine development is really quite fascinating, addressing fundamental challenges in current vaccine technologies. Let me explain why this is so important.

Current delivery systems, like mRNA vaccines, have a significant limitation: they tend to express antigens for only a short period. This results in what we call 'transient expression,' leading to relatively short-lasting T cell responses. But this is where carbon nanotube delivery systems show remarkable promise.

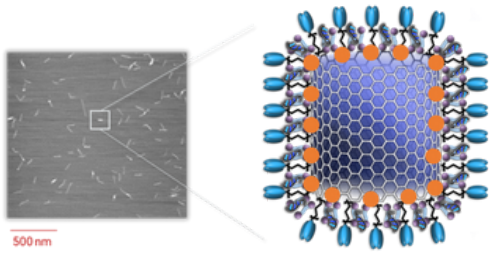
The key advantage of carbon nanotube vaccines is their ability to express antigens for a much longer period. This extended expression is crucial for developing strong, long-lasting T cell responses. Think of it as giving the immune system more time to 'learn' and develop a robust response.

These carbon nanotube platforms are exciting because they can serve as a versatile delivery system that can carry multiple components. We can incorporate not just the T cell antigens or cancer antigens, but also specialized adjuvants like the 7DW8-5 adjuvant I discovered several years ago. This combination approach is showing remarkable results – in non-human primate studies, we've seen a 5 to 10-fold enhancement in T cell response compared to vaccines without the adjuvant.

When you consider the challenges we face with HLA polymorphism – the variety in how different people's immune systems present antigens – having a delivery system that can maintain antigen expression longer and incorporate

About NanoVac

- Controls payload presentation and enhances cellular uptake
- Stabilizes mRNA/proteins, enabling cold storage flexibility
- Compatible with intramuscular and intranasal administration
- *In vivo* studies of the vehicle indicate wide distribution, rapid clearance, and no signs of toxicity

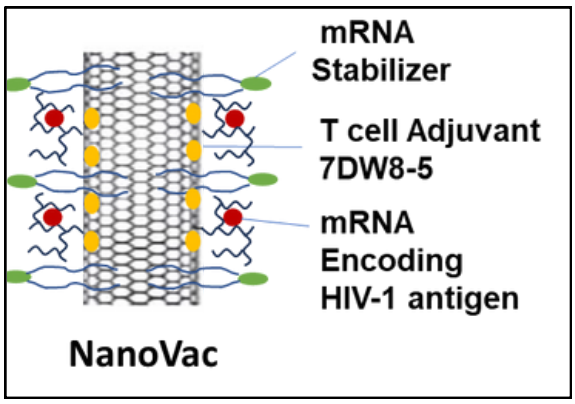


SEM image shows the 150 nm long NanoVac delivery vehicle; schematic illustrates surface chemistry that enables loading and stabilization of nucleic acid and protein payloads

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powerful adjuvants becomes even more valuable. It's not just about delivering the vaccine; it's about optimizing how long and how effectively it can train the immune system.

I'm particularly optimistic about combining carbon nanotube delivery systems with advanced T cell vaccine approaches. This combination could enhance the duration and strength of immune responses, which are critical factors in developing effective vaccines against infectious diseases and cancer.



LL: You are well-known for your work with humanized mice models. Tell us more about their significance.

MT: One of our most significant breakthroughs came from developing humanized mice models, which arose from a fundamental challenge in immunology research. We faced a persistent gap between mouse studies and human applications. The traditional solution was to use non-human primates, but this approach faced several serious obstacles - ethical concerns, prohibitive costs, and a crucial biological limitation: monkeys have different biomarkers than both mice and humans.

This difference creates a real bottleneck in translating research findings between species. That's what led me to develop a human immune system mouse model - essentially, mice that mimic human immune responses.

What makes this particularly exciting is how it bridges the gap between basic research and clinical applications. We can now test vaccine candidates in a system that much more closely mimics human immune responses, potentially reducing the need for extensive non-human primate testing and accelerating vaccine development.

LL: Tell us more about the potential you see for cancer vaccines.

MT: Let me explain our vision for cancer vaccine development, particularly its integration with our humanized mice model. We've already published a paper on human breast cancer using our humanized mice model, and we're expanding into other cancer types.

What makes our work unique is how we've established human immune system mice with functional CD4 and CD8 T cells, and then we engraft them with HLA-matched human cancer cell lines. For instance, with ovarian cancer, we've demonstrated protection against HLA-matched human ovarian cancer through CD8 T cell and NKT cell responses.

> *This is groundbreaking work - nobody else has done this kind of HLA-matched cancer modeling in humanized mice.*
> Dr. Moriya Tsuji

This is where I see exciting potential for Luna Labs' carbon nanotube platform. To move forward, we need to be very strategic about selecting the right neoantigens and matching them with specific HLA types. Whether we're working with ovarian cancer, breast cancer, pancreatic cancer, or other tumor cell lines, we need to carefully type the HLA and create matching immune system

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mice. This allows us to manipulate and study CD8 or CD4 T cell responses under HLA-matched conditions using Luna Labs' carbon nanotube technology.

The combination of our humanized mice platform with Luna Labs' carbon nanotube delivery system could create some really exciting opportunities for cancer vaccine development.

LL: You have a long-standing relationship with the biotech team at Luna Labs, including working together on malaria, COVID-19, and HIV-1. Can you tell us more about this collaboration?

MT: It started back around 2015 at the American Society of Tropical Medicine Meeting, which focuses on malaria vaccine development and immunology. I saw Dr. Yang Xu, Luna Labs' principal investigator for the carbon nanotube delivery platform, presenting on malaria vaccines using Luna Lab's platform, with a particular focus on T cells. I approached her thinking we could enhance their T cell response using my research on adjuvants.

Dr. Xu was already familiar with my work through my publications on T cell-based malaria vaccines, and she suggested we collaborate. We began working together on NIH and DOD grant applications, achieving an impressive success rate of over 50% funded.

Our collaboration evolved into a highly productive partnership. Dr. Xu directs the research priorities with specific requests for different mouse models or vaccine testing, while I contribute my expertise, particularly regarding the glycolipid adjuvant I developed.

This has turned out to be quite significant - Dr. Xu has confirmed that our glycolipid adjuvant is one of the better adjuvants for Luna Labs' carbon nanotube vaccines. What's particularly exciting is that in our collaborations with other particle companies, we've found that our adjuvant has a better safety profile compared to alternatives like poly-IC and other adjuvants.

The timing couldn't be better, as we're approaching Phase 1 trials for our adjuvant. This could create an excellent opportunity for Luna Labs to incorporate this adjuvant into their carbon nanotube vaccine platform.

> *It's been a mutually beneficial relationship. We get access to Dr. Tsuji's expertise in immunology and novel adjuvant technology, while he gets to see his research applied in innovative ways through our NanoVac delivery platform.*
> Christopher Tison, PhD
> Director of Biotech, Luna Labs

LL: What does it look like to bring this new approach to actual clinical use?

MT: The ultimate goal here is clear - we need to move this technology from the bench to the bedside. We have to push toward clinical trials because, ultimately, this work is about making a real difference in human health.

The principles we're establishing could be applied to Luna Labs' carbon nanotube platform. This is particularly relevant given current priorities - consider H5N1 (Bird Flu) for example. We could potentially develop a carbon nanotube-based vaccine combined with our glycolipid adjuvant. Luna Labs could design the vaccine, and we could collaborate to advance it through preclinical and clinical stages as efficiently as possible.

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But there's that other exciting direction we're exploring - cancer vaccines. In cancer immunology, T cell responses are crucial, and this is where I see Luna Labs' carbon nanotube platform having unique potential. The carbon nanotubes have shown remarkable capabilities in terms of enhancing T cell response induction.

We need to secure funding for these initiatives, of course, but I believe the potential impact justifies pursuing them. The combination of Luna Labs' delivery technology with our immunological expertise will open up new possibilities in both infectious disease and cancer vaccine development.

Related Publications

1) Microfluidic Synthesis of Scalable Layer-by-Layer Multiple Antigen Nano-Delivery Platform for SARS-CoV-2 Vaccines, *Vaccines* (2024)

2) A pancreatic cancer mouse model with human immunity, *bioRxiv* (2023)

3) Short Carbon Nanotube-Based Delivery of mRNA for HIV-1 Vaccines, *Biomolecules* (2023)

4) Mucosal Delivery of HIV-1 Glycoprotein Vaccine Candidate Enabled by Short Carbon Nanotubes, *Particle and Particle Systems Characterization* (2022)

5) Layer-by-Layer Delivery of Multiple Antigens Using Trimethyl Chitosan Nanoparticles as a Malaria Vaccine Candidate, *Frontiers in Immunology* (2022)

6) Targeted Co-delivery of Tumor Antigen and α-Galactosylceramide to CD141+ Dendritic Cells Induces a Potent Tumor Antigen-Specific Human CD8+ T Cell Response in Human Immune System Mice, *Frontiers in Immunology* (2020)

7) A Potent CD1d-binding Glycolipid for iNKT-Cell-based Therapy Against Human Breast Cancer, *Anticancer Research* (2019)

8) An AAV vector-mediated gene delivery approach facilitates reconstitution of functional human CD8+ T cells in mice, *PLOS One* (2014)

Contact
Chris Tison, Director of Biotech at Luna Labs
chris.tison@lunalabs.us

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