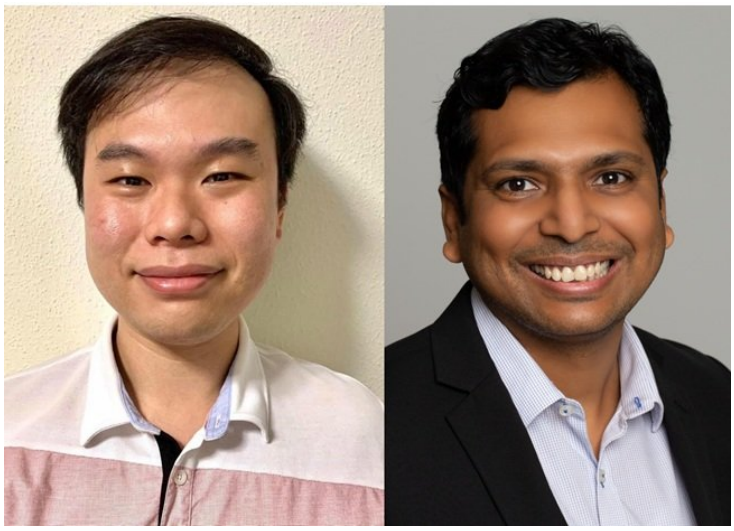
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Asia-Pacific's Nanomedicine Potential: Achieving optimum conquest over therapeutic bioavailability

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Quantum leap in healthcare modalities as a potential game changer An expert opinion by Dr. Shaun Lim Wen Zheng, the Field Application Scientist (APAC) at Cytiva and Krishna Karnati, the General Manager for Genomic Medicine (APAC) at Cytiva



- **Dr. Shaun Lim Wen Zheng, the Field Application Scientist (APAC) at Cytiva** *(Left)*;
- **Krishna Karnati, the General Manager for Genomic Medicine (APAC) at Cytiva** *(Right)*

In recent years, several innovations have emerged around long-acting formulations and therapeutic models to enhance patient compliance. A combination of controlled drug release and technological advancements in pharmacology is driving the adoption of novel drug delivery systems (NDDS). The NDDS facilitate the delivery of medicine to cells or tissues (organ, cellular, or subcellular level of specific tissues) in a regulated or coordinated manner. This enhances the performance efficacy ratio of medications through the efficient management of therapeutic assets. Asian drug formulation companies are exploring these advanced therapeutic modalities to maintain their competitive edge in the global market in terms of bioavailability, dosage, and absorption.

Drug Delivery Systems (DDS) offer a wide range of matrices and formulation approaches to increase kinetics and delivery. For complex parenteral drug molecules such as vaccines, nucleic acids (mRNA, DNA, siRNA), and ligand-targeted formulations, microencapsulation is a preferred method of encapsulation. Several types of 'micro molecular vehicles' can be used to carry medicine or genetic material in capsule form by using nano-sized vesicular carriers.

Among established DDS formulations, some of the most widely adopted nanoparticles are Lipid Nanoparticles (LNPs), exhibiting a wide range of drug-delivery potentials and preventing API degradation in acidic and alkaline body fluids. Nanomedicine offers promising novel approaches to treating autoimmune diseases, cancer, and rare inherited diseases, including early disease detection and molecularly tailored therapies for diverse diseases. In recent years, LNPs have gained resurgence due to their well-established track record and versatile therapeutic properties.

Cytiva is a leading solution provider to biopharmaceutical companies manufacturing therapeutics and vaccines involving complex biomolecules and enables researchers to optimize and analyze nanomedicine formulations. In addition to developing analytical assays to analyze nanomedicines, Cytiva is assisting with advanced technologies for the preclinical and clinical development of LNPs. Biospectrum Asia spoke to **Dr. Shaun Lim Wen Zheng, the Field Application Scientist (APAC) at Cytiva** and **Krishna Karnati, the General Manager for Genomic Medicine (APAC) at Cytiva** about nanomedicine's prospects in the Asia-Pacific region and the potential it holds.

- **How can lipid nanoparticles and nanomedicine formulation technologies be explored for application in RNA-based therapeutics and vaccines?**

Dr. Shaun Lim: Lipid nanoparticles (LNP) encapsulating messenger RNA (mRNA) have shown to be efficacious in reducing morbidity and mortality through the COVID-19 pandemic as a vaccine. With a unique ionizable lipid as part of its lipid formulation, it is primed to interact favorably with the nucleic acid, providing extensive protection to the payload before its destined release in the organ of interest. However teething problems trouble this technology, such as inefficient endosomal escape, degradation of mRNA and niche application area, mainly the liver. As such, current exploration on lipids formulations include:

- Synthesis of unique ionizable lipids for the specific application/organ of interest
- Replacing cholesterol with other forms of sterol to investigate effects on cellular uptake
- Replacement of PEGylated lipids to other forms or lengths to prevent anaphylaxis to the greatest degree.
- Investigation of structural lipids for better endosomal escape

There are also efforts in the overall lipid composition, to better perfect the delivery system with the nucleic acid payload.

- **How do precise nanomedicines formulations contribute to achieving optimal precision therapies? What are the latest noteworthy advancements in nanomedicine impacting medical care?**

Dr. Shaun Lim: Realizing that the mRNA synthesis post COVID is no longer a bottleneck as before, treatments involving mutation of a specific gene in a human body can be better looked at. The evolution of this need pivoted to a specific cancer treatment, or what is better known as Personalized Cancer Vaccine (PCV). Whenever there is a cancer patient with a specific gene mutation on the tumor, the mRNA will be tailored specifically to that mutated gene to train the immune system on recognizing and fighting that cancer cell. On the lipid formulation front, one should also choose lipid components that tend to accumulate out of the liver, into the spleen where more immune cells are located. This helps enrich the amount of immune activity that can destroy the cancer cells.

Moderna published successful phase 2b results with mRNA-LNPs combination therapy with Keytruda, to reduce risk of recurrence or death of melanoma by 44%. This mRNA codes for 34 neoantigens based on the unique mutational signature of the patient’s DNA.

Another medical care advancement would be the first FDA approved non-COVID mRNA-LNP drug product, also by Moderna. This is jointly achieved with GSK, for the treatment of Respiratory syncytial virus (RSV). These developments suggest that mRNA-LNPs treatment are still at its infancy, but it will eventually move towards clinically impactful drug products soon. This is attributed to its fully synthetic nature, from both the payload and the delivery system.

- **How can the clinical evaluation of novel nanomedicines be accelerated? What is the potential of nanomedicine platforms for accelerating drug delivery? How can it enhance cost-effectiveness, reduce timelines, and increase efficiency?**

Dr. Shaun Lim: Specifically with novel nanomedicines such as mRNA-LNPs, there have not been extensive clinical products owing to its infancy in the market. Therefore, acceleration of such novel clinical products stem from experience in producing such LNPs. On the manufacturing end, it should also be straightforward and scalable. Another aspect of drug development is regulatory clearance. It has to be adjusted between population medicines and such novel treatments. Using PCVs as an example, the patients that will enroll in the clinical trials will not be high in numbers. Requesting multiple large GMP batches of drug product for a single patient will incur unwarranted loss of resources. Understanding and streamlining this pathway through fast-track programs including FDA’s Platform Designation program (currently in public consultation) will certainly

reduce the financial/time burden on this budding technology.

One particular benefit for LNPs would be its ‘plug and play’ model, where various mRNA targets complement with its lipids counterpart. This allows companies to have a platform of LNPs, and encapsulate multiple mRNA targets for diverse indications. We also live in a time where manufacturing of such LNPs can be reproducible, straightforward and easy.

If all this can be achieved this will result in a lower cost in terms of manpower, resources and time. While it is awaiting results from Moderna’s phase II trial, if PCV treatment proves to be efficacious towards a certain indication, a reduction in trial patients can be achieved. This could be very exciting since off-target effects would be minimized and potency of the drug can be increased.

- **How is Cytiva addressing LNP formulation complexities while advancing RNA nanomedicine drug delivery approaches?**

Dr. Shaun Lim: At Cytiva, we aim to advance and accelerate therapeutics. We know that drug development is multi-pronged, from scientific, technical, manufacturing, regulatory and even legality, so reducing the number of investigations needed from the researchers helps to lower the barrier to a clinical drug product.

In terms of LNP formulation complexities, 3 main aspects are well taken care of by Cytiva. The first would be the delivery system, or the lipid formulation. Ensuring fit-for-purpose lipid mixes for a specific indication reduces laborious screening studies, freeing up manpower and time towards optimization of the nucleic acids.

The second aspect would be the manufacturing technology, in which reproducibility, scalability and ease of use are some of the most crucial. Cytiva's mixing technology ensures remarkably consistent results across various manufacturing scales, reassuring regulators that controls are in place for the final drug product.

Finally, the last aspect taken would be helping nanomedicine developers jumpstart the capabilities by providing state of the art services in terms of process development, analytics and regulatory support. We understand that not many budding researchers or investigators have the total solution towards developing the next blockbuster drug product; instead many are concerned about their own payload technologies. In this aspect we are able to leverage 100 years of combined experience in various forms, from clinical manufacturing, analytical method development and hand-holding regulatory support towards Investigational New Drug (IND). Cytiva is prepared to address all complexities associated with LNP formulation, whether they be scientific, technical, or regulatory.

- **How is Cytiva leveraging its bioprocessing expertise to achieve robust LNP characterization and optimize nanomedicine production scalability?**

Dr. Shaun Lim: Cytiva has been in the bioprocessing space for a wide array of drug modalities, from monoclonal antibodies to newer drug modalities cell therapy, nucleic acids and viral vectors. In the LNP world, encapsulation of the mRNA into the lipids is just one piece of the puzzle. We leverage critical bioprocessing steps, ensuring quality mRNA is produced in the IVT stage, through purification and chromatography. It is also critical to ensure that post processing of the LNPs is done in a controlled manner through Tangential Flow Filtration (TFF). All capabilities are then put through the rigors of scaling up, even embarking on new product initiation aimed to fill up some of the process gaps.

When it comes to characterization of the LNPs, we would leverage the expertise of various Danaher Corporation’s operating companies. These examples are familiar names such as Beckman Coulter, SCIEX and IDT. We have worked extensively in developing analytical methods to better characterize LNPs, the integrity of the payload, stability of the particles and catch off-quality products with the same analytical suite of instruments.

- **What role does Cytiva serve in the global nanomedicine market, and how does it maintain a competitive edge?**

Krishna Karnati: Cytiva's technologies have positively impacted the lives of patients, and we are helping many patients through clinical trials. With our lipid nanoparticle formulations, manufacturing on the NxGen platform, and bioprocessing steps such as chromatography, purification and TFF, we play a critical role as a technology enabler. We strive to maintain our competitive edge by investing in analytical development, improving quality control of materials, and fit-for-purpose equipment

or consumables.

For example, in analytical development for CRISPR technologies, trying to analyze multiple nucleic acid payloads have presented challenges to researchers for quite some time. A robust way to quantify each strand of RNA in the LNPs was required, for Cas9 mRNA and the guide RNA. Through the collaborative efforts of various stakeholders at Cytiva, we have developed an orthogonal method for analyzing guide RNAs without compromising resolution or sensitivity.

- **How has Cytiva advanced nanomedicines through collaborations and partnerships?**

Krishna Karnati: As an innovator, we are actively collaborating with research institutes, novel tech firms, and even CDMOs to help address future challenges. To better understand the needs of the current research landscape, through the collaborative efforts of various stakeholders at Cytiva, we have developed an orthogonal method for analyzing guide RNAs without compromising resolution or sensitivity often partner with translational institutes to develop the next lipid formulation suitable for that specific application. This could be helping scientists whose progress may be hindered by subpar delivery systems and helping to accelerate their studies towards clinical progress.

An example of a hugely successful collaboration would be through Replicate Bioscience's rabies virus vaccine. Just recently in January, they published their successful phase 1 clinical trial results using their saRNA platform, showing efficacy at 1/100 dose compared to a linear mRNA and its first generation of snRNA. As a result of the novel RNA design, enabled by Cytiva's LNP formulation and drug manufacturing expertise, they were able to move to clinic in a much shorter time frame, enabling drug product commercialization to be one step faster.

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