Lucas Chan – Scientific Founder & CSO, CellVec

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Lucas Chan, Scientific Founder and CSO of CellVec, a Singapore-based CDMO that specializes in the development and manufacture of viral vectors for clinical gene therapy, discusses how his company is helping companies with mature preclinical gene therapy projects wanting to progress into the clinic. Moreover, he discusses why Singapore is a good strategic place to launch regenerative therapy projects, and how CellVec can help reduce manufacturing and development costs in an area that so badly needs it.

Can you begin by discussing your scientific background, your years-long work with gene therapy and the decisions that led you to Singapore?

My fascination with gene therapy came during my time as a PhD student in London, where our department was conducting the first trial treatment for cystic fibrosis (CF) using liposomes to deliver a functional copy of the CFTR gene into CF sufferers. This was not very effective, and I was part of an initiative to develop alternative viral vector based strategies, including generating stable suspension cell lines that produces retroviral vectors. However, it was during my post-doctoral years where I saw first-hand the potential of genetically reprogrammed cells as therapy using re-engineered viruses. We were developing a first-in-man gene-modified cellular therapy for Acute Myeloid Leukaemia, where the normally immune evading leukaemia cells are genetically re-programmed by a viral vector to express immune modulatory factors and hence being turned into effective immune stimulating antigen presenting cells. This eventually led to the first regulatory

approved clinical study of its kind using lentiviral vectors.

The ensuing process of regulatory filing meant we had to put in place processes and pharmaceutical quality systems necessary to comply with Good Manufacturing Practices (GMP) as followed in the pharmaceutical industry. This included developing the first manufacturing process for lentiviral vectors under GMP in Europe and unintentionally, led us down a path that would result in the establishment of a GMP vector core in the UK.

The GMP vector core became a centre of supply for clinical grade lenti/ retro viral vectors for a multitude of first-in-man clinical studies ranging from rare genetic conditions to haematological malignancies. Some of these studies would eventually progress towards advance commercial development. The process in establishing the vector core as a multi-batch vector manufacturing centre was an invaluable experience to see first-hand the critical role and potential roadblock viral vectors play in facilitating clinical development of cell and gene therapy. The tremendous pressure to deliver vector batches which differ in transgene nature had to be balanced by maintaining quality of the product, GMP compliance, patient safety and of course at the highest possible titre and yield to enable sufficient study enrolment. The demand for vector batches from both academic and commercial clients soon outstripped our manufacturing supply capability. This is when it became apparent that the demand for viral vectors would rapidly become a holdup to keep pace with cell and gene therapy development and required urgent attention for improvement.

Viral vector manufacture in particular those requiring transient transfection involve a complex process that is labile and mostly comprised of technologies repurposed from more traditional biologics manufacture. Therefore, a logical area of focus is on how to make the manufacturing process more fit for purpose for viral vectors, particular in consistency and overall yields. This requires breaking down the current process to redefine critical parameters using principles of Quality by Design and would apply to the entire process down to the molecular level. A small incremental improvement upstream of 2-fold could well result in a significant gain in reduction of scale as well as a reduction in cost of goods.

An opportunity came in 2018 to establish the first clinical viral vector supply capability in South East Asia based in Singapore. This encompasses the building of a new state of the art GMP manufacture facility and a process development laboratory to address much needed deficiencies in viral vector manufacture, all of which in a location with an established logistics infrastructure for biologics manufacture and a world class biomedical research hub within the island state’s vicinity. These served as the backdrop in the creation of CellVec.

Can you explain in layman's terms what the technology is behind viral vectors and the role they play in gene therapy?

The concept itself is actually not very complex. Take the example of CAR-T cell therapy, which is often referred to as a "living drug" for the treatment of several types of leukaemia, the critical new function of these T cells, which were ordinarily benign, is provided by way of genetic modification by inserting new DNA into the T cell genome. The new DNA expression cassette provides instructions to the T cells to produce new cancer hunting and killing properties and are delivered into the cells using a vehicle called vector, created from re-engineered viruses that have been made safe and non-pathogenic. Viruses are chosen for this task because they have evolved over time to be extremely efficient in doing one thing – to deliver its own genes into human cells in order to hijack them as a host for virus reproduction. We made safe these normally pathogenic and disease causing agents by removing all of its DNA that encodes viral proteins and substitute in its place the new functional transgene – chimeric antigen receptor coding DNA in the example for CAR-T cell therapy, or a new correct copy of a mutated gene in the case for inborn genetic conditions. These new viral vector vehicles are produced using a cell line in a not too dissimilar way as traditional biologics manufacture and controlled under the same Pharmaceutical Quality principles used in established regulatory requirements that govern industrial Good Manufacturing Practice to ensure safety. Depending on regulatory jurisdiction, viral vectors in pharmaceutical manufacture setting are classified either as Active Pharmaceutical Ingredients (API) or critical starting materials when used for genetic modification of cells outside the human body in a laboratory or as a medicinal product itself when infused directly in humans. There are now several approved therapies that utilize viral vectors.

Can you introduce CellVec, your capabilities, structure, and the part you are playing as a CDMO that specialized in viral vectors for gene therapy?

CellVec was established and registered in 2018 in Singapore as the first CDMO in the region dedicated to viral vector development and clinical manufacture and it has two main objectives:

- To conduct in-house innovation and development on viral vectors including molecular system design and manufacturing process development
- As a contract process development and manufacturing entity to supply clinical grade viral vectors produced under GMP for human gene therapy applications

The founding principle and mission of CellVec is to enable and accelerate human gene therapy development by advancing gene transfer technologies through innovation and manufacturing development of viral vectors. We felt that we can only function competently as a viral vector CDMO and to begin addressing some of the bottlenecks in viral vector supply discussed earlier by beginning with the science of viral vectors to establish in-house know-hows including viral vector construct system design, novel cell line development, manufacturing process development and analytical development, with our manufacturing activities conducted under a certified Pharmaceutical Quality System. By establishing these in-house capabilities, CellVec is in a position to offer an assured collaborative hand to our partners in innovation, clients in contract development and manufacture, as well as other service providers, who all form indispensable parts of an ecosystem necessary for gene therapy implementation.

With a clear focus in direction and founding principles, in a little over 2.5 years, CellVec has successfully completed the construction, commission, qualification and GMP certification of our new state of the art manufacturing facility dedicated to viral vectors, the first of its kind in both Singapore and South East Asia to current requirements and expectations. CellVec’s GMP certificate, issued under the compliance principles of PIC/S annexes for medicinal products permits us to manufacture Retro and Lenti viral vectors as Active Pharmaceutical Ingredients for human gene therapy.

To date, CellVec has successfully completed several clinical manufacturing runs with class leading titres and yields. On innovation, CellVec has generated novel molecular expression systems that are significantly more efficacious.

All of the above are achieved by building a family of dedicated personnel in innovation and development, GMP manufacture, quality control and assurance and warehousing. External facing are CellVec’s marketing and project management personnel to ensure our collaborator’s voice and needs are carefully communicated and attended to.

Cell and gene therapy is a highly collaborative field and its successful deployment necessitates CellVec to build close working partnerships with others across the entire ecosystem. CellVec hope to continue to play a contributive role in developing Singapore’s base as a hub for gene therapy development and manufacturing.

Stephen Hendricks, Global Head of Novartis Oncology’s Cell & Gene division, told PharmaBoardroom that they are they are working on a “next-generation manufacturing

platform that has the potential for higher efficiencies, shorter turnaround times and hopefully better outcomes." With that mindset, how can they benefit from your manufacturing capacities and expertise?

CellVec is currently focused on early and mid-phase clinical gene therapy development with future plans for commercial manufacturing. CellVec is particularly interested in this space because our experience tells us that it is this phase that has the greatest impact on whether it become successful in its product development cycle. Hence CellVec has been dedicating its resources in optimizing its manufacturing platform. As an example, CellVec has created a set of DNA helper expression constructs that provides up to 5-fold improvement in viral vector titres compared to parallel commercial systems. Each of CellVec's viral vector batch manufacturing run is completed in a relatively short time frame of 15 days. Each of CellVec's contract projects are bespoke depending on needs and with an end-to-end mindset so that our clients can focus on therapeutic development whilst CellVec ensures that the vector products are manufactured optimally and at the highest quality.

CellVec and its peers in industry are all endeavouring to improve efficiencies and reducing cost of goods so that access to these live changing therapies can be enabled more widely.

How significantly can a CDMO like CellVec reduce manufacturing and development costs while maintaining the high-quality and safety profile required for gene therapies?

Reducing the cost of goods in manufacturing is a key focus within the cell and gene therapy industry. CellVec has clients across the globe, but we have started working with projects based in South Asia, a less mature market when it comes to gene therapy, where the cost of viral vectors can be as much as half of the total cost of the therapy.

This is where CellVec has been working closely with collaborators. The first approach CellVec has taken is to develop a manufacturing process that is highly efficacious to generate class leading yields, such that in the economy of scale, the more that can be produced per batch, the lower the costs are for testing and more product could therefore be made available for clinical use. But all of this still under the clear guidance and robust governance in Quality without compromise. For example, CellVec has recently formed a strategic partnership to supply lentiviral vectors to the first Indian based CAR-T company with a remit of treating cancer patients at affordable costs.

In-house, we are continuing in technological innovation in areas including stable producer cell line development and novel process development with the aim to continually improve process efficiencies and yields. CellVec engages with key stakeholders from industry, academia and regulatory agencies, to ensure CellVec is both at the forefront of technological advancement and up to date with current regulatory guidance. CellVec also keeps pace on characterisation development through our collaboration with industrial partners and continues to review risks and make improvements in our manufacturing activities.

Why did you decide to establish the company in Singapore in particular?

Singapore is known for its high quality medical services. Patients visit from both within the region and further afield globally. As a result, there exists well established infrastructure as an international treatment centre, potentially serving the needs for a south east Asian population of over 300 million. With increased access to patients, there is a potential to establish a base for clinical development in cell and gene therapy, and we are already seeing biotech industry establishing regional headquarters here. In addition, there is a mature biomedical research hub with world class academic institutions such as A*Star, NUS, NTU and others. But the main driving factor is a mature biomanufacturing industry with established logistics infrastructure and this has not been a recent development but Singapore has been a regional centre for manufacturing of biologics for a number of years. These all form important parts of an ecosystem that has taken years in strategic planning to build. The regulatory agency of Singapore – HSA has recently released the Cell and Gene Therapy product registration guidance, again demonstrating a cohesive approach in developing Singapore as an advance therapy manufacturing hub.

CellVec has stated that it seeks to collaborate with local and international academic institutions on one side and commercial organizations on the other for development and manufacturing in Singapore. What does the perfect partner look like for you at the moment?

Viral vector development and manufacture is a highly collaborative field, and it involves an entire spectrum of stake holders within the ecosystem from academic researchers to commercial development partners to raw material and equipment suppliers to assay characterization expertise and regulatory agencies.

To advance technological innovations in viral vectors, CellVec has formed collaborations with both academic and commercial organisations. For commercial clients, CellVec forms close partnerships to address their process development and manufacturing needs from molecular construct design to GMP production. CellVec's experienced personnel provide quality and regulatory advice to help steer client projects through their product development cycle. CellVec is developing close links with characterisation assay service providers who have regional headquarters here to build further capabilities.

As a notable example, we were approached by a client who were developing a CAR-T cell therapy for haematological malignancies but had a specific problem in achieving safe and efficacious transduction efficiencies using their existing non-viral platform technology. We successfully generated a functional expression construct using our proprietary viral vector system. We then produced a small scale batch of lentiviral vectors using a process that has been specifically designed and demonstrated to simulate our full scale GMP process in both quality and yield, but at a smaller scale to reduce cost. This allowed us to test the new construct's compatibility with our manufacturing process as well as to provide an estimation on titre and yield at full GMP scale. The small scale product is produced with >90% materials alignment with the GMP process, thereby allowing functional assessment on downstream T cell transduction with confidence on scalability. The test product was shown to be both efficacious and achieving a low copy number integration profile on primary T cells. The project is now advancing rapidly towards clinical development.

Another example is with one of CellVec's commercial clients who are entering their first clinical trial for advanced cell therapy using clinical grade vector supplied by CellVec and where CellVec helped them navigate the regulatory landscape by providing advice on regulatory expectations of clinical viral vector products particularly in viral vector characterisation.

CellVec seeks to provide end to end solutions and vertical integration with our partners to ensure a smooth pathway from pre-clinical, clinical development and a successful regulatory and clinical outcome for developer and patients.

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