Gurutz Linazasoro – CEO, VIVEbiotech

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VIVEbiotech is a Spanish CDMO specialised in the production of lentiviral vectors used in gene therapy. Its CEO, Dr Gurutz Linazasoro, tells the story of the company's creation, comments on the unique properties of lentiviral vectors, and analyses the main trends shaping the future of the gene therapy industry. In addition, Dr Linazasoro, a renowned neurologist, outlines the company's grand ambitions and the role it aims to play in making the province of Gipuzkoa in the Basque Country an advanced therapy European hub.

VIVEbiotech operates as a CDMO fully dedicated to lentiviral vector production and does not have its own pipeline. Can you share the story of the company and explain in detail the services it offers to the industry?

The story began in 2009 with Fundación Inbiomed, a private foundation dedicated to research in regenerative medicine, where I collaborated as a neurologist doing stem cell research for Parkinson's disease. After being offered the possibility to lead the foundation, we established several platforms, one of which was centred on viral vector production to be used in research and development (R&D); we distributed the vectors to almost all research centres in northern Spain.

At a certain point, we realised that it could serve as the bedrock of a new company that could produce under GMP conditions; Juan Carlos Ramirez, VIVEbiotech's scientific director's deep expertise in lentiviral vectors, and more than 30 years of experience in the field, made the

launching of this company successful. This is how VIVEbiotech was created in 2015.

The company's philosophy is to accompany clients from the moment they give us the gene until the end. That accompanying process includes the design of the viral vector and the use of adequate plasmids; in other words, we help clients across all development phases. Once the first stages of development are completed, which carry an intense R&D effort, we start producing first under experimental conditions to understand how the binding of the viral vector with the specific gene works, and then move to GMP production. This is our great virtue; all our clients appreciate the complicity established from the beginning. The company's greatest asset as a CDMO is its broad expertise in virology and the opportunity to work hand-in-hand with clients from the start.

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As we understand it, most lentiviral vectors are based on human immunodeficiency virus (HIV). Can you explain what lentiviral vectors are generally used for and the role they play in the production of gene therapies?

The viruses we use, in general, are artificial constructs. Lentiviruses are RNA-based and replicate thanks to a retro transcription process, leading the genetic integration into a DNA host genome. The transformation of lentiviruses into viral vectors consists of separating the sequences needed for packaging and production from those encoding unnecessary viral proteins, meaning that they are deprived of their pathogenicity conditions and only keep their ability to reach human cells. They essentially serve as transportation devices that ensure that new healthy genetic material is produced in large enough quantities, which is why the production platform is constantly being improved.

VIVEbiotech dedicates one third of its budget to R&D, which can be divided in two: one is oriented to improve the production process and the other is client specific.

A 2020 paper on lentiviral vector production revealed that, at the time, there were around 200 ongoing clinical trials and two approved therapies (Novartis' Kymriah and bluebird bio's Zynteglo) that used lentiviral vectors. With those numbers in mind, what can you reveal about the nature of your clients?

Our clients are both biotech or pharma companies working mostly on immuno-oncology and ultra-rare diseases. Lentiviral vectors are particularly good at treating haematological diseases such as leukaemias, lymphomas, and myelomas, as well as solid tumours. Moreover, VIVEbiotech is also developing and manufacturing lentiviral vectors to be administered in vivo.

Last year VIVEbiotech completed the construction of new facilities that would increase the company's manufacturing capacity. What can you tell us about the investment and the impact it has had on your GMP production?

We invested around EUR ten million to build seven cleanrooms specifically set up for lentiviral-vector manufacturing and to install the largest bioreactor currently available on the global market, new R&D laboratories, and engineering spaces. Versatility in the design has resulted in a more flexible configuration enabling the possibility of further cleanrooms in the future as well as making it feasible to accommodate a much larger number of batches.

However, the processes and systems are not yet standardised. The platform and production methodology we are using is standardised but remains subject to change depending on the size of bioreactors and production quantity. The company has been working with bioreactors to cover clinical trial requirements, and now is scaling up to bioreactors that could be used to make commercial size batches. Moreover, we are designing a new 10,000 m^2 facility that will be located nearby.

The only way to ensure high quality production is through comprehensive quality control processes. To give an example, for every three weeks of production, we do three months of quality control assessing all purity, potency, and safety. The process is time consuming and expensive but necessary when working with gene therapies. There are no shortcuts which is why the FDA and EMA have raised the bar while a comprehensive regulation is completed as strong regulatory requirements are in the best interest of everyone.

Key opinion leaders in the gene therapy field have spoken about the importance of having the manufacturing process as close to the patient as possible as to avoid contamination or a loss of efficacy. How is the company looking at this challenge considering that it is located in the Basque Country, the north of Spain?

This is a fantastic opportunity to speak about the local ecosystem in San Sebastian and Gipuzkoa more broadly. The region is betting on advanced therapies and has shared a proposal with the authorities in charge of the European Union recovery funds that are being sent to Spain.

There is great institutional support for a project called GANTT (Gipuzkoa Advanced New Therapies Territory) which is centred around gene therapy. For the ecosystem – which is being built by companies, hospitals, research centres and institutions – to succeed, we must establish a large clinical trials hub for gene therapy. The hub is already underway, and onco-haematology will play an important role. VIVEbiotech is a strong supporter of the initiative since it will be good for its ambitions and those of its clients. We believe that the region is set to succeed.

Regarding contamination and loss of efficacy, we have not had any issues whatsoever when sending products around the world. Cold chain solutions, among other things, make our business possible.

How do you assess the strategic importance of viral vector manufacturing for today's gene therapy industry?

The manufacturing of viral vectors is the true bottleneck for the gene therapy industry due to the lack of large-scale producers and skyrocketing demand. According to recent data, there are almost 2,000 gene therapies in development. This includes gene-modified cell therapies, some of which are close to commercial stages and require steady production of viral vectors. While few of them are approved today, the US FDA has said that their objective is to approve ten to 20 new cell and gene therapy products per year starting in 2025.

We are very positive about the future of the industry. The recent news about the two patients free of tumour cells after ten years of receiving the first CAR T cell therapy has provided the proof of concept that we have been waiting for, that the therapy works and saves lives. I am confident that new indications will be added, increasing demand for viral vectors.

You just mentioned the US FDA plans to approve 10 to 20 new cell and gene therapy products each year. How different is their approach from that of the EMA?

Both agencies have the same vision, the difference is that most companies working in the area are based in the United States, making the FDA the first agency to receive applications. There is a

long-standing effort to unify the criteria from the FDA and EMA to facilitate the development of new treatments. VIVEbiotech’s production plant is designed with both FDA and EMA requirements in mind.

How do you see the company and the Gipuzkoan ecosystem evolving in the next five years?

The next five years are not difficult to imagine. I foresee a fully digitalised VIVEbiotech with an operational new plant. Regarding the ecosystem, I believe that the clinical trials centre will be in place and way more breakthrough research being performed by new companies, institutions, and world-class talent. For its part, the company is working closely with the Basque Government to boost the detection and professional development of local talent, which has historically enjoyed a great reputation compared to any Spanish region.

We have signed an agreement to receive between 16 to 20 people with a biotech background so they can complete their vocational education and training (VET) with the company, inspired by the model used by Germany’s automotive industry. The Basque Country’s VET programs are a point of reference in the continent and the region has been looking for new industries to invest in for a long time.

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