SME of the Month – ZeClinics

ZeClinics, a young innovative Biotech Contract Research Organization (CRO) and early-phase biopharmaceutical company from Barcelona, is using zebrafish (Danio rerio) for safety and efficacy screenings of novel chemical molecules. The EuropaBio SME member aims to challenge the traditional drug discovery pipeline in a novel and highly innovative way. Read our interview with Ignasi Sahún, ZeClinics co-founder and CMO.

How did ZeClinics start out?

ZeClinics began as a reaction to a market that was in full transformation and that required new actors to continue working correctly. The market that required that new effort was the Drug Discovery, and in 2013, when ZeClinics was founded, it was more than clear that there was a funnel between the drugs that were being discovered and the drugs whose patents expired. The pharmaceutical industry needed to introduce changes in its processes to be more efficient, and that was to open its mind to new alternative models that allowed them to refine its decisions better. The zebrafish was the emperor of those models. So, we decided to start a company between four partners, all doctors, and friends, and test our market hypothesis, which is the core of our business: is zebrafish a necessary model in the drug discovery pipeline?. We do not reject the null hypothesis. It worked because drug discovery relies on costly, time-consuming, and not always translational research with mammals to advance a molecule toward clinical phases.

For this reason, a bunch of new research models is emerging to streamline drug discovery and allow better correspondence between preclinical and clinical data. Among them, zebrafish stands as a powerful model for disease target validation and drug discovery. 35,000 articles on zebrafish research have been published during the last 20 years; over 10,000 related to the validation of the model for understanding human disease and its use for discovering new drugs, both from a safety and efficacy standpoints. Relevantly, 200 drug discovery pipelines have been reported using zebrafish; from them, around 60 drugs are in clinical phases. The increasing use of zebrafish in drug discovery is due to its significant experimental and translational advantages.

Introduction Video of ZeClinics

ZeClinics is using zebrafish for safety and efficacy screenings of novel chemical molecules. Why do you think it is necessary to challenge the traditional drug discovery pipeline?

The truth is that the classic drug development model is no longer sustainable. The development process of any drug, from early target identification to clinical tests, registration and market approval, takes at least a decade and is extremely costly. Moreover, the industry faces increasing pressure from global regulatory agencies. Our clients realize it is challenging to have internal know-how at every step of the process, and by specializing in particular therapeutic areas and stages of compound development, CROs can provide quality services and operational flexibility at more competitive prices. Speaking about CROs, last year, Nature published a paper about the current trend towards pharma outsourcing. We are not merely replacing in-house development with external expertise, this is about risk management and early predictability. Withdrawal of potential drug candidates due to toxicity or efficacy issues remains a significant source of losses for the pharma industry, particularly late-phase attrition at clinical and post-market stages. Preclinical assays allow us to funnel down large compound libraries by scrapping unsuitable candidates before reaching more costly regulatory *in vivo* studies and clinical phases. The trick is to generate enough biologically-relevant data early on to improve the predictability of drug targets and decrease the risk of late-phase attrition, bringing our clients much-needed certainty as they move forward and ultimately contributing to the sustainability of their projects. And zebrafish allows us to do precisely that.

What makes ZeClinics unique as a company?

It is complicated to talk about ourselves and try to be objective. But if I had to tell you what makes us unique, I would say to you that we are a combination of very

prepared, united young people, with a shared vision and strongly well-aligned. Plus, our business model works, and we put all the illusion of the world in the project. But if we have to speak in more prosaic terms, it is quite remarkable that a small SME/CRO like ZeClinics can offer preclinical services ranging across so many therapeutic areas: Cardiovascular, CNS, CRISPR/Cas9, atherosclerosis, hearing loss, retinal degeneration, muscular dystrophia, etc. Likewise, ZeClinics' track record of partnerships and awards is also impressive. We achieved a Horizon2020 SME Instrument Phase 2 grant worth €2M. We have a CRISPR/Cas9 license from the Broad Institute of MIT and Harvard, and we made several collaborations with key players like the University of California, San Francisco or the University of Bern in Switzerland. More recently we established a cooperation with the SEAZIT from NIH (USA) to perform a critical inter-laboratory study to generate data for public use so that researchers can optimize their chemicals in drug development. I imagine it may seem like we are juggling too many balls, but actually our diverse portfolio and multidisciplinary disposition are critical to the company's adaptability.

Can you give more details on your product, ZeC*ardio* which is funded under Horizon 2020?

ZeCardio® screening platform is the jewel of our crown. This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement N° 755988. This is what makes it exciting. The rate of achievement of this type of European aid is meager, and we get it at first attempt, presenting ourselves as mono-beneficiaries and completing the project successfully, as you can see on CORDIS website. That fact fills us with pride. It is the result of the effort of a team of people dedicated to increasing knowledge and developing powerful tools that bring innovation to the market. More in deep, ZeCardio® allows quantification of cardiovascular parameters obtained from in vivo high-resolution video imaging. The platform is optimized for fluorescent imaging, and transgenic larvae are used in the multiple applications derived from this platform: assessment of drug-induced cardiovascular safety, gene target validation/discovery in the cardiovascular field and discovery of novel cardiovascular therapies. The hardware conforming the screening platform consists of LP Sampler/VAST BioImager, an advanced image acquisition equipment integrated by a microfluidics system that allows zebrafish larvae sampling from multiwell plates, and their positioning and automatic orientation in a glass capillary under a microscope. Sampling, imaging, and dispensing of larvae are fully automated. This is an important factor, given manual adjustment might stress larvae and, therefore, impact on their cardiovascular performance. The other component of the screening platform is ZeCardioTM software, a video imaging analysis software developed by ZeClinics. Alternative analysis tools measure heart rate but do not give quantitative readouts of heart rhythm disturbance, heart features or blood flow related irregularities. In that sense, ZeCardioTM software is designed to quantify a plethora of different cardiovascular phenotypes besides heart rate: distribution of individual beats and beating regularity, QTc interval, length of the longest period without beating (i.e. cardiac arrest), atrioventricular coupling defects (Bigeminy, Trigeminy), ejection fraction, heart size and atrial and ventricular blood flow speeds.

Learn about ZeCardio

As an innovative SME in Europe – where do you see the main barriers starting a successful biotech business in the EU?

When one delves into the most significant pitfalls, one concludes that the problem is probably not the lack of ideas. There are hundreds of start-ups and spinoffs with innovative ideas that could potentially revolutionize various aspects of the biomedical field. The problem is redundant and is the MAIN barrier: the search for financing or funds to grow these ideas and make them a reality. And that search for funding is arduous and complicated. It represents an intense effort in time and money, for small companies (such as most European biotech) that is not always rewarded. European aid policy is excellent, no doubt, in fact, it should be a mirror to reflect for foreigner agencies, but surely the problem is of a more profound nature. Strong policies should be established aimed at generating a significant change in the business models of EU countries, focused on science as an engine of wealth. It has been shown that investing in science in the medium and long term is not only profitable, but it is also that it represents investing in the society of the future. And, of that we are entirely sure, there is no future without research. ZeClinics is living proof of that.

On the contrary, are there any key points in the development of the company where the biotech ecosystem in the EU was (or still is) benefitting your company?

Absolutely, there are many points in favour. For example, the fact that we can easily hire personnel with an international profile allows us to generate synergies with research centers throughout Europe. The possibility of establishing consortia to be able to request aid for more ambitious projects is also a direct benefit. On the other hand, there are many state agencies with European funding that give aids in the form of organization of subsidized missions to attend to international congresses and meetings, they also provide us with access to specific training courses and other networking activities vital to our environment.

You have a strong team of experts with a multidisciplinary background – how do you and your team foresee the future of health biotech, especially with the development in the area of genome edition and new techniques such as CRISPR Cas-9?

From our point of view, the future is shining. The life and health sciences sector generates € 31,087 M per year just in Catalonia and represents 7.2% of gross domestic product (GDP), with companies in the industry and health services. Overall, more than 223,000 people work, about 7% of people employed in Catalonia. On average, every week, a new company is created in Catalonia in the sector. By the end of 2018, the biotech industry had 1,060 companies that occupy near 58,000 workers and invoice € 17,802 million, with an average annual growth of 2.4% between 2000 and 2016. Between 2015 and 2017, the Catalan health sector start-ups attracted 340 million euros of investment, tripling it over the period 2013-2015, through 214 investment operations. In 2018, between January and October, it had risen to 100.2 million). So, biotech environment, here in Catalonia, is wealthy and growing, as in other places of the world. We can't do anything but be optimistic.

Regarding CRISPR future, last year the European Court of Justice (ECJ) ruled that gene-editing techniques such as CRISPR/Cas9 would be regulated as GMs. ZeClinics is as much a zebrafish CRO as it is a CRISPR authority, and we have a sincere opinion about the ECJ's decision. This recent ruling concerns other sectors more than healthcare, and in any case, it will not affect us directly. Our gene-edited lines are employed as part of in-house preclinical assays under controlled and contained conditions which do not fall under Directive 2001/18/EC, the piece of European legislation on the deliberate release of GMOs into the environment that is also the primary source of controversy in some circles. ZeClinics does not believe the ECJ ruling could potentially undermine the use of gene editing in healthcare because in his words high-precision targeted mutagenesis with CRISPR/Cas9 will remain an irreplaceable tool for the study of life-threatening diseases, the understanding at the molecular level of drug/target interactions and ultimately speeding up personalized medicine development.

What are the aspirations for ZeClinics in 2019 and beyond?

This may be the riskiest question to answer. The truth is that as much as we work in our annual Business Plan, we observe with satisfaction that we are fulfilling them quite accurately. We decided that at the beginning of the year we would have our own modern zebrafish facility with space for more than 5,000 fish and we made it. We decided that in 2019 we would reach 25 workers and we made it. We decided that in 2019 we would achieve greater penetration in the Asian market and we achieved it. We decided that in 2019 we would have our first spin-out, ZeCardio Therapeutics ready, and we have it available. What do we have left for this year? We have three critical objectives, the first one is to successfully complete collaborative studies with the U.S. National Institutes of Health (NIH), the Environmental Protection Agency (EPA), the National Toxicology Program (NTP) and other corporations and academic groups in a global project aimed to broaden the adoption of the zebrafish model and harmonize protocols for preclinical toxicological screenings. This is the first step for zebrafish studies regulation and an open door for the future of ZeClinics. Second, at the end of this year, we want to finish our GLP certification to have access to different markets as agrochemicals or cosmetics. And finally, the third one, probably for the beginning of next year, we will open our first office in the USA. We never get tired of getting challenges. As a joke,

we always say that, if you have any questions about a compound, "Better call ZeClinics."

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About EuropaBio

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a biobased and zero-waste economy. EuropaBio represents 75 corporate members and 17 national biotechnology associations and bioregions.

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