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What Does It Take To Launch And Lead An Oncology Biotech Today?

An Interview With Theolytics CEO Charlotte Casebourne

by Lucie Ellis-Taitt

Oncolytic virus company Theolytics has emerged ready to raise a series A round and get its preclinical assets into human trials by 2021. CEO Charlotte Casebourne talks to *In Vivo* about the challenge of standing out from the crowd in oncology, how viruses have evolved as a treatment approach in cancer, and how oncolytic viruses might be able to answer the cancer drug pricing conundrum.

- Founded in 2017, Theolytics is a preclinical-stage biotech using oncolytic viruses to combat cancer. The Oxford, UK-based company is pioneering a "Darwinian" selection approach that leverages the fact that – by their very nature – the fittest viruses in a pool will out-compete when exposed to a given niche.

- As the company comes out of "stealth mode," CEO Charlotte Casebourne talks to *In Vivo* about its platform technology, the importance of differentiating its pipeline as a new biotech on the scene, and the skills required for a biotech leader today.

- She also discusses the concerning issue of access, as novel personalized cancer treatments are reaching "eye-watering" prices on the market.

To date the oncolytic virus field has focussed on the slow, careful design of therapeutic viruses – an approach dependent on the human mind creating the best possible virus from thousands of base pairs. However, Theolytics is leveraging a convergence of emerging technologies within the viral therapy field – long-read sequencing, sophisticated bioinformatics and advanced genetic engineering – to accelerate discovery and development.

The company launched with £2.5m in seed investment from Oxford Sciences Innovation (OSI), a £600m fund focused on commercializing ideas originating from the University of Oxford. Lansdowne Partners, Wellcome Trust, Invesco, Google Ventures and IP Group – as well as sovereign wealth investors – are among OSI's shareholders.

Theolytics CEO Charlotte Casebourne

The company is now preparing to raise further funds through a series A financing round. And later this year, it expects to announce the selection of a lead virus, as well as the target cancers that will be an initial focus for clinical trials.

In an exclusive interview, Casebourne speaks to *In Vivo* about Theolytics' approach and the big issue of differentiation that faces all companies entering the oncology development space. She also discusses management challenges for emerging biotechs and the leadership qualities that will make today's CEOs fit for business in the 2020s.

As well as being CEO and co-founder of Theolytics, Casebourne, aged 26, is also a board member of the UK Bioindustry Association. Previously, she was a co-founder and director of the strategic consultancy group New Medicine Partners and she has held leadership roles within a number of organizations, including: curator of the World Economic Forum Global Shapers network; managing director of HealthTech Women London; and Hello Tomorrow's London chair for health care and medical technologies.

Theolytics is built around core technology developed by Margaret Duffy, who is also the company's chief scientific officer. The small biotech has 11 employees, primarily R&D focused, and has recently made additions to its board of directors. In June 2019, Ken Powell was appointed chair of the board – bringing significant virology and commercial expertise into the group, as a founder of Arrow Therapeutics and ReViral. Powell has led the development of multiple products including antiviral compounds against herpes viruses, HIV, hepatitis C and respiratory syncytial virus (RSV).

Q **In Vivo: Theolytics is sticking its head above the water, so to speak, and preparing for a series A financing round. Why should people pay attention now?**

A Charlotte Casebourne: It is an interesting situation when you are an early-stage company: how do you balance making sure the right people know that you exist, with not giving away your competitive advantage while you're still emerging? After a period of rapid development, we are now establishing the systems that we need to build sustainability through to the next phase. We have not publicly disclosed the target amount for the series A round, but I can confirm that we are currently raising the resource that will enable us to clinically validate our core technology platform. We want to ensure that we are moving fast and using our capital efficiently in order to quickly prove the potential of what we are working on.

Q **What do you see as the biggest challenge in cancer drug development today?**

A Differentiation. It is a busy space. More drugs have been approved in oncology than any other therapy area since the 2000s, and the number of active compounds in oncology R&D has doubled since 2008 representing around 40% of the global clinical pipeline.

A We are experiencing an exciting new wave of therapies coming through, including potential cures such as *Merck & Co. Inc.*'s PD-1 inhibitor Keytruda (pembrolizumab). Working on incremental technologies that are going to have marginal improvements for patients is not going to stand-up anymore in what is an incredibly busy space. Differentiation – significant differentiation – is important.

A Another challenge – which is also representative of progress in the field, though perhaps a double-edged sword – is the increasingly sophisticated stratification of patients. Over a third of clinical trials are now using biomarkers to stratify patients; this is unprecedented. Chimeric antigen receptor T-cell (CAR-T) therapy, for example, is exquisitely personalized to a single patient. This represents a challenge when it comes to the health economics of some of these drugs.

A When price points rise to the level that they become a serious barrier to patient accessibility, this is a critically important challenge. Within the immunotherapy space we are seeing eye-watering prices, which is just one of the reasons viral therapies for cancer represent an attractive approach. We are not quite talking the same price as a vaccine, but oncolytic viral therapies have the potential to be much closer to the cost of a vaccine than that of a CAR-T treatment. This is important when we are working towards ensuring that patients all over the world have access to effective drugs for cancer.

Q **Thinking about differentiation, what sets Theolytics apart in oncology?**

A Oncolytic viruses are particularly interesting within the immuno-oncology space; they represent a unique therapeutic paradigm. First, oncolytic viruses can selectively infect even very heterogeneous tumor types. Unlike an antibody or a CAR-T therapy,

these viruses are not dependent on a single surface marker to infect. Their ability to be effective even in heterogeneous tumors is an important differentiator. If one looks at the market today, there are either these exquisitely targeted options or something like chemotherapy, which just kills rapidly dividing cells in an undifferentiated manner; there aren't many options in the middle.

A Second, oncolytic viruses are interesting because the dose is amplified *in situ*. These are one of the only types of therapy where you can amplify the dose that you want to expose the patient to in an exquisitely selective way, exactly where you want your dose to increase.

A Third, the viruses can even activate the immune system in "cold" tumors. There has already been some nice early data from oncolytic viruses in combination with checkpoint inhibitors like Keytruda and *Bristol-Myers Squibb Co.*'s Opdivo (nivolumab). Checkpoint inhibitors are not effective in patients who have cold tumors, where the immune cells are not present. So, viruses are able to pull immune cells into the tumors. Therefore, we are seeing some synergistic effects for oncolytic viruses in combination with treatments that are already available but are otherwise ineffective for many patients. We are in a strong position now to start thinking about combination approaches.

A Theolytics works with adenovirus. We can arm that virus with almost any genes. This ability to potentially deliver additional therapies by arming our viruses means that there is a useful niche within the oncology space.

A Furthermore, viral manufacture is significantly less expensive and the product is easier to distribute than most immunotherapy products. This opens up global markets to us that might otherwise be inaccessible.

Q **You mentioned biomarkers and there use in clinical trials today, but how else have you seen the R&D sector change in recent years?**

A It's interesting to look at the dramatic changes in the industry over the last five years. My role on the BIA board has provided valuable visibility over both historical trends,

and how the sector is evolving. For example, it is evident that over the last five years major pharma companies are increasingly outsourcing R&D activities to smaller, more nimble biotechs with successful results. An example here would be Gilead Sciences; most of their lead products are the result of external licensing deals, and have not come through from internal R&D pipelines.

A When we look at how innovative some of these big pharmas are, one of the reasons Gilead stands out is because over 60% of its 2018 revenues came from products launched over the last five years. To put this into context, that is six times higher than the average of the top 30 companies in some comparisons and is an interesting surrogate for how "fresh" (or stagnant) some of the incumbent big pharma pipelines are.

A There is a disparity between the percentage revenue coming into these companies from new products versus old. When we look at those companies doing well in terms of the 'freshness' of their pipelines, a lot of those products are coming from licensing deals and acquisitions. It goes some way towards demonstrating how the different stakeholders within the R&D sector can capitalize on what they're good at. For some of the bigger players, that might not necessarily be doing innovative R&D in-house.

Q **What excites you in the oncology space when you are looking at development trends and innovation?**

A There are multiple converging technological advances that are enabling us to develop better therapies – that are more selective and more potent – and to do that faster. At Theolytics, our core technology platform is powered by three enabling technologies. Each of those technologies has really emerged over the last three to five years.

A The first of which is long-read sequencing technologies. The reason the long-read sequences are important for us, is because the viral genome is genomically diverse. We had to find a way to characterize the viruses that we are working with, both as drug candidates, and in the form of pooled virus libraries. We wouldn't be able to do that if we didn't have access to these advances in technology.

A The second enabling advance is within genetic engineering technologies. These technologies allow us to exquisitely manipulate the genome in a way that we have never been able to do before. We can pull drug candidates out of our libraries using a "Darwinian" selection approach, as opposed to what the field has historically done, which is to use human brain power to rationally work through what the best virus sequence for a given indication might be. Our approach speeds up timelines from what historically might have been five to 10 years, to six to 12 months for us to pull out a good drug candidate.

A The third technology that's accelerating development for us is advances in bioinformatics. These have improved our ability to work in a sophisticated way with the sequencing data that we generate. We are building rapid feedback loops into the drug development process so that we can start to apply a tech company mind-set within the life sciences. The data points that we are generating improve our ability to be responsive and iterate quickly.

Q **Was the goal always to be a "platform technology" company?**

A We were never interested in being a single-asset company. With Theolytics, we are working towards revolutionizing the way in which oncolytic viruses are discovered and developed, and are building what we need within the company to ensure that we are best placed to lead that shift in the field. What our platform enables us to do is to identify highly efficacious, selective drug candidates within diverse virus libraries, and we can do that rapidly, across a broad range of indications.

Q **What are the big milestones coming up for Theolytics?**

A We're working toward regulatory enablement with IND submissions for two lead assets, with the aim of instigating clinical trials in 2021. These are the big milestones. We will be building out our team over the next 12 months to enable us to successfully achieve these goals.

Q **What was your first role in the life sciences industry and how did that lead you toward being a CEO today?**

A I was exposed to patients first, and I think that has shaped a lot of my perspective of the life science industry. I lost my grandmother when I was a child, and that was my first exposure to the challenges within the health system. I went on to volunteer in Denmark Hill Hospital in South London while I was studying through my undergraduate degree, primarily working in geriatric and oncology wards. I realized that in many instances the clinicians did not have the tools that they needed to support patients, and decided that that was the problem that I wanted to work on.

A As an industry it is critical that we do not forget the people that we are serving. Keeping patients front-of-mind has driven Theolytics to establish a network of exceptional key opinion leaders within the clinical setting to ensure that we are accessing the breadth of expertise and perspective that we will need to deliver life-changing therapies.

Q What skills are required to be a biotech CEO today?

A Stamina, energy and commitment. It is a long game. We are setting audacious goals and intend to see them through. One thing that is critically important is the ability to learn quickly. It is a complex environment to be operating in; no one person knows everything. You have to learn enough to be able to ask the right questions and also have the humility to seek out individuals who know more than you do. The last thing I'd add would be perspective - the ability to zoom out. To develop and deliver great products to the market in a changing landscape you need to have a finger on the pulse of the sector. This is an additional way in which my involvement with the BIA has been invaluable: access to the information that enables us to zoom out and take stock of the international environment that we are operating in. This is an important contribution that the organization makes to the UK Biotech sector.

Q What is one of the most difficult parts of your job?

A Finding brilliant people is one of the hardest but most important challenges as Theolytics grows, and we are increasingly seeing Oxford companies attract talented individuals from all over the world. I am fiercely proud of our team at Theolytics;

there are few things less important than finding great people to work alongside. Finding the right people, building that high-performing team is challenging but critically important. It takes time.

Q **Do you have any concerns around accessing talent, considering external issues such as the unstable situation around Brexit?**

A We're not coming up against issues yet. However, there is a concern that the situation might change, especially with some of the more senior roles that we are looking to recruit for. Whatever change does happen, for the right person we will always go above and beyond to make sure that we can find a way to enable them to join the team. The right person is the most important factor.

Q **What is the one myth or misconception about the biopharma industry that you would like to set straight?**

A The myth within the industry that I would like to set straight … it is that drug prices can keep getting higher and it will not affect access because payers will cover the costs. Extortionate drug prices do contribute to decisions by payers to restrict or ration treatments. It is not about undermining our ability as companies to be commercially successful, to generate revenue that will allow us to sustain growth and to continue to invest in developing great therapies. But the balance is important; the balance between greed, sustainability and fairness.