Interview: Michael Leek – CEO, TC BioPharm, UK

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After 30 years in the cell therapy space, Dr Michael Leek founded TC BioPharm in Scotland. Within four years the company has forged major partnership deals and advanced its CAR T therapies towards the clinic. Developing allogeneic variants of Gamma Delta T Cells, TC BioPharm aims to become a global company, taking the next step of its international expansion with opening of an office in continental Europe.

Can you outline for us your personal journey and what led you to found TC BioPharm (TCB) in 2014?

Although TCB is a young company, I have been active in the cell therapy space for 30 years. My dedication to this field comes from a profound love of the science I have nurtured since I was young.

In the 90's, I worked for Smith & Nephew. They developed high technology bandages and advanced orthopaedic implants. At the time we were pursuing the idea of re-engineering damaged skin and bone with living tissues – dressing a wound with new skin instead of a band-aid for instance. I was recruited to develop their regenerative medicine programme and in the mid-1990's we were developing the first cell therapies to regenerate skin and cartilage with our US partner Advanced Tissue Sciences.

In 2000, I co-founded a company called Intercytex (Manchester, UK), we took several products into the clinic over an 8 year stretch. Whilst at Intercytex I realised how different the regenerative medicine manufacturing process is to conventional (small molecule) therapies. Conventional drugs can be mass-produced, placed on a shelf and won't change significantly if left there for two years

or even more. Live cells are far less compliant, if stored at room temperature their shelf-life can only be measured in days. Moreover they are ‘independent’, often behaving unpredictably, like cats – you want them to go left they go right. Stick a load of chondrocytes (cartilage cells) on a shelf for a day or two, turn off the light, when you come back they’ve spontaneously differentiated into fibroblasts (skin cells). It became obvious that advanced therapies need to be considered in a completely different manner, from manufacture to shipping and of course pricing.

Also, at Intercytex we decided to control the manufacturing process by investing heavily in GMP-compliant clean rooms – however the VC’s hated that we had our own bricks and mortar! We were convinced about the requirement to optimise cell therapy manufacturing in-house as a product matured from phase I to phase III clinical studies. It was considered extravagant to build your own facilities as a small and young company – however we grew quickly by going against the mainstream model of contracting-out manufacture to CMO’s.

Learning lessons from the past when doing it all over again with TCB, we immediately decided to build our own cleanroom and clinical infrastructure. I founded TCB after working alongside a Japanese IO company who were using autologous, unmodified Gamma Delta T Cells to treat small numbers of patients in Tokyo-area hospitals. Having decided the therapeutic approach had enormous potential, we filed several patents around use of CAR Gamma Delta T’s, and so the next journey began.

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How has TCB developed since its inception?

When we first transferred cell-processing technology from Japan, it was very much a bespoke manufacturing system. At TCB we modified and optimised the process, not just to be UK, EU and US regulatory compliant, but also to increase cell-product yield (we can routinely grow over 500 billion cells from a healthy donor). We then took unmodified cells and generated an innovative platform by genetically modifying Gamma Delta T Cells with a chimeric antigen receptor (CAR) and thus – TCB was born.

Since the beginning, we have been strongly supported by the Scottish Investment Bank who provided several million (UK) in equity-based investment. More recently a couple of large Scottish Enterprise (SE) grants provided additional research and clinical support. As a regional development agency SE have proven to be our guardian angel on more than one occasion.

Today we employ over 70 staff, a number we expect will increase to over 100 by the end of 2018. This headcount is not surprising – not only do we manufacture our own therapies, we design our own clinical trials, compile our own regulatory submissions, initiate trial sites and monitor patient progress.

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grant by Horizon2020. This was instrumental in taking a decision to roll out the move from autologous to allogeneic therapies.

Basically, there are two ways of treating patients – autologous and allogeneic.

Autolgous therapy means you are taking the cells of one specific patient to treat the tumour from that same individual. This is logistically and technically complicated, you have to ship patient cells (the starting material) from clinic to GMP facility, grow the treatment then ship it back to the patient/clinic – a long and expensive process.

An allogeneic product uses cells from one (healthy) individual to treat many different patients. This kind of therapy can be produced in a much more cost-effective manner as it allows reproducible cell banks to be engineered to treat thousands of people. It also provides an efficacy benefit as healthy allogeneic-donor cells are not affected by underlying pathology seen in cells from autologous therapies.

We are advancing towards our allogeneic treatment goals at a remarkable pace. So much that we will commence our first allogeneic trial within the next two or three months. In Prague we have just submitted regulatory documents for a trial in acute myeloid leukaemia (AML) where we will treat patients with allogeneic cells from related donors. This trial allows us to start on a very small scale and monitor/control key safety parameters. The next step will be to treat larger numbers of patients with banked cells from non-related donors.

What is the added-value of TCB's science?

While most companies in the CAR-T field work with Alpha Beta Cells, we started with Gamma Delta's.

Alpha Beta's constitute part of the adaptive (or memory-driven) immune system, while Gamma Delta's are more innate, and programmed to 'always be ready for a fight'. Historically, they have been considered hard to expand in culture, so many CAR-T companies focussed on Alpha Beta Cells. At TCB however, we developed a system to routinely produce Gamma Delta's by the billion. The advantage of working with Gamma Delta's is they are already programmed to attack cancer and cells infected with a virus. Moreover, they only become activated to kill in presence of cells which have become 'stressed' by transformation or infection – these stressed cells produce a unique signal isopentenyl pyrophosphate (IPP) not expressed on healthy cells. CAR T therapies based on Alpha Beta technology are controversial as they may provoke adverse responses by destroying healthy cells. Gamma Delta's CAR-T's can't target healthy cells as the IPP 'killing switch' is not triggered – so we have a healthy, next generation CAR-T approach.

What are the next steps you will be taking in TCB's development?

The move into allogeneic therapy will accelerate expansion into Europe, the Prague AML trial is very exciting, the Czech Republic providing a supportive environment for clinical trials.

We very much consider TCB a Scotland-based global company. Our mandate is very clear – we need to treat patients in Europe, the US and Asia. We are fortunate enough to have several high-value pharma partnerships developing new CAR-T products -in the US through our collaboration with bluebird bio (a leading CAR T company), and in Japan where we work with the Nipro Corporation in Osaka.

In 2014 we built our GMP cell processing facility, in 2015 we developed our CAR-T platform. 2016 and 2017 saw TCB become a phase I/II clinical company and establish credible pharma collaborations. These collaborations are transformational for TCB – if we meet our milestones potential revenues in excess of USD 3bn may be realised.

We have grown rapidly from myself and a couple of co-conspirators over the last four years to a mid-size biotech company – this is largely because of our driving ambition to treat patients and improve quality of life. With our current pharma collaborations (we are always looking for more) TCB has achieved sustained funding which provides great stability moving forward.

We are moving our CAR-T programmes into the clinic one step at a time to learn more about how these therapies behave in a real-life patient-centric environment. For now, we focussing on leukaemia – blood cancers, but with reduced potential for toxicity TCB plans to treat solid tumours in the near future.

Our next two steps include transition to treatment of solid tumours, followed by a move into treatment of infectious disease – specifically hepatitis, HIV and sever influenza.

What will business model be moving forward?

We are great at producing clinical-grade efficacious cell therapies and treating patients with these products. We don’t have sales and marketing infrastructure at the momen and will continue to partner with companies such as bluebird bio and Nipro with much of our CAR-T platform. Nonetheless, when it comes to certain orphan indications, we may consider commercialising treatments ourselves in-house.

Do you consider with CAR T and regenerative therapies there is a race around being first to market – or is there space for everyone?

In cutting-edge business, there is always a kind of race, we are all competing for similar cash and clinical resources. However, the IO field we operate in is very broad, I consider that if you have developed an efficacious, cost-effective therapy, there will be market space for it.

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Where do you see regenerative medicine heading?

The Scottish demographic presents us with a long, distinguished history in cell therapy. Angela Scott who contributed to creation of Dolly the Sheep in 1996 is our co-founder and COO. Cell therapies were just starting back then – right now I suspect every company in the space will be

developing an allogeneic ‘pharmaceuticalised’ treatment – for sure this is the future of cell therapy

What are your thoughts on Brexit, and its influence on the life sciences industry?

I think it is a shame that we talk about a majority decision when such a small percentile were responsible for the final outcome? For our industry there will be complications arising, but I hope we will also witness opportunities. TCB for instance has decided to accelerate entry into Europe after the vote and establish a presence in the next six months.

It’s possible for biotech companies to be pragmatic about upheavals such as Brexit, by our very nature we are constantly going through change. In order to survive, we have to embrace such change. Whilst a surprising outcome, Brexit is not terminal for us. We see the opportunity for TCB to introduce our oncology products into other European markets and take bigger steps in our anti-infectives business. We are concerned about a lack of clarity surrounding Brexit, but the mists should clear within the coming year.

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