Interview: James Noble â?? CEO, Adaptimmune, UK

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Adaptimmune, a British-based biotech company born out of the University of Oxford has a solid research base in the UK and manufactures its T-Cells in the US. Its CEO, James Noble, shares Adaptimmuneâ??s story and explains why regulatory support is essential in a field as complex and novel as T-Cell therapies.

James, what was your passion for cell therapy and the biotech industry at large born out of?

I actually studied Medieval Studies and Russian before becoming an accountant and later on an investment banker. Subsequently, I became the CFO of a British biotech company and this is how I first came in contact with the field of biotechnology. Now, being the financial director of a biotech company is very different from being the CFO at a more conventional company. Margins, sales and revenues are not your primary worries, your interests revolve around cash flow and how to raise money.
This necessity to raise funds is what got me into T-Cells after starting in biotech. At the time, I worked with John Gordon and he asked me to participate in the funding of a T-Cell company, and I did. It was an entirely new field at the time, and I was intrigued by the fact that there are only two ways to reach the immune system of a human: through monoclonal antibodies and T-Cells. The first one had already been well explored, but there had not to date been a company focusing on T-Cells.

What makes T-Cell therapies so complex and has prevented them to be the new go-to therapy since their discovery?
When I first invested in T-Cells, no one had yet been able to make a stable T-Cell receptor. In 1993, Professor Sir John Bell, the author of the Life Sciences Industrial Strategy for the UK, hired Dr Bent

Jakobsen to the Institute of Molecular Medicine in Oxford to focus his research on the development of a stable T-Cell receptor, which he achieved by 1998. On a side note, this is just one fact highlighting the visionary capacity of Professor Sir John Bell.
However, even with a stable receptor, T-Cells continue to pose challenges. The receptor guides the T-Cell in the process of identifying whether the cell it encounters is good or not. The T-Cell destroys the cells the receptor identifies as bad, but if it makes a mistake and destroys healthy cells, this creates an autoimmune disease, such as Multiple Sclerosis. Cancer cells appear just as healthy cells to the receptors and this is why they escape regulation by the T-Cell. At Adaptimmune, we are today very advanced on solving this problem, and have created receptors that can be taught to target cancer cells specifically.

Can you tell us a bit more about Adaptimmuneâ??s story that lead to where the company is today?
It all started with a company called Avidex, in 1999, which later became two sister companies, Immunocore and Adaptimmune, one concentrating on technology with ultra-high affinity soluble TCRs, the other one focused on very modest increased affinity cell therapy. Both companies are today entirely separate. In 2008, I formed Adaptimmune as a virtual company with a group of likeminded people and an investment of GBP 2.5 million.
Our first steps revolved around collaborations with academia, mainly in the USA, such as the University of Pennsylvania. Although we employ scientists in the UK, the regulatory and clinical side of business has been carried out in the US from the very beginning, because we were unable to find someone that could produce the required cells or run trials here.
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Our first clinical trial involved HIV patients, and later we went on to expand to cancer. Here we moved from myeloma to ovarian cancer and finally sarcoma. The research and pre-clinical work are exclusively carried out in the UK.
Adaptimmune was forced to become self-sufficient. Although challenging, this is what made us into the success we are more and more today, as we had to change our initial business model to set up our own T-cell manufacturing and our own vector supply. The manufacturing process of T-Cells is extremely complex, and many companies developing T-Cell products have to rely on their own facilities. Of course, this is bound to change within the next decade, just as there was a time when molecular antibody companies would build their own factories. Today, no biotech in molecular antibodies would build its own factory.
Most exciting to us however remains the future. As we speak we are discovering new targets to investigate. We are currently working on 60 pre-clinical programmes. And the T-Cell field is still very open patent-wise because it is so novel. This holds even more true when it comes to SPEAR T-Cells that we develop.

Moving forward, where do you see most challenges coming from?
Our main challenge currently lies in the science itself. Ensuring safety in T-Cell therapies is challenging, because the T-Cells kill every cell they recognise as threatening. The thing is, they can also recognise cells that should be left alone and are healthy. This is why we are further working on pre-clinical processes to develop safe therapies.
We are also developing second and third generation programmes for more durable and deeper responses than our first-generation programmes. In order to achieve these goals, we need scale of science, but also scale of financing if we do not want to be royalty slaves.

Can you share with us the current status of the various treatments in your pipeline?
We have shared good results with one of our products, which we have recently transitioned to GSK, called NY-ESO. With NY-ESO, we have shown responses in two solid tumors, synovial sarcoma and myxoid round cell liposarcoma (MRCLS). In MRCLS, of the seven patients treated, we have had three confirmed responses, one unconfirmed and three stable.

We have two wholly owned products for which we should have further results by the end of the year. Our Safety review Committee (SRC) has recently endorsed the decision to start dosing patients in our MAGE-A10 trials with cell doses ranging from 1 to 6 billion, after a positive safety review of three patients who received 1 billion cell doses. The SRC had agreed, a few weeks prior, a dose escalation in the MAGE-A4 trial to billion cells, after positive safety review of three patients who received 100 million cells. We have a third wholly owned product called AFP, currently dosing patients with 100 million cells.
This is important because the first dose used in therapy is not actually therapeutic, it just checks cross reactivity. In order to treat, it has to be augmented, and the second dose is tenfold the first one administrated. Only then will we be able to see response to treatment, as below a billion injected T-Cells this is unlikely. This is why these decisions to dose escalate are so encouraging for us.

How have you found collaboration with public stakeholders in a therapy field that is still so novel?
The regulatory environment we encountered has been unbelievably helpful. In the US, we obtained breakthrough status after only 12 patients and prime designation in Europe for NY-ESO. To us, a good relationship with authorities, based on dialogue and understanding is essential, because it is the guarantee for a continuous discussion.
The feedback we receive is incredibly helpful to us, and we could not collaborate with regulators that do not fully understand what we do. For instance, because not even chimpanzees have the same T-Cell receptors as humans, our safety tests have to be carried out in human patients, not animals. Moreover, we cannot perform a placebo-controlled study because in order to be injected with a T-Cell therapy, your endogenous T-Cell population has first to be reduced. This is achieved through chemotherapy, which has to be followed by treatment, and a placebo is unimaginable after such an aggressive prior treatment. Therefore, even our pivotal studies have a single arm. Also, our success possibly will not be measured in conventional survival rate but upon response rates alone. Without regulatory support, we could not carry out any studies and would not have the chance to develop our treatmentsâ?? efficacy.

We often hear that the UK sets the standards on an international stage. Does this also hold truth in the field of biotech?
The UK has always been a big pioneer in adapting, and been flexible in pre-approving treatments, even reimbursing them. NICE is an international reference body. Through the NHS, it has the potential to continue on this path, leveraging on the immense data basis available in the system. Finally, it has historically been a great environment for clinical trials and used to dominate Phase I trials. Today, only one percent of the worldâ??s Phase I trials are carried out in the UK.
I think that overall, the regulatory environment in the UK is very supportive. The Life Sciences Industrial Strategy and its goals to grow a certain number of companies up to critical mass is but one illustration of the willingness to mov forward.
However, the fundamental issue biotechnology companies encounter time and again in the UK and Europe at large is in raising capital. In the end, the UK and Europe are as good at setting up companies, but those making money out of them are always the US. The vision regarding venture capital in Europe is very limited, so much so that it equals to a self-inflicted handicap. We are just as clever in the UK as on the other side of the Ocean, but we have difficulties putting the available capital to use.
We create the four or five hundred million pounds capital companies, but rarely the four or five billion one. I reckon that the biggest destructive force for the whole of the European biotech field lies in venture capital scaling. This is complemented by a general aversion to repeat funding amongst institutional investors.
We observe a willingness to change that. In the UK the Wellcome Trust and Woodford Patient Capital Trust are two examples of this change. Nevertheless, it remains true that institutions in the

UK are overall very risk-adverse and prevent growth of small businesses into scalable companies.

How do you see the company evolving over the next 24 months?
We are currently active in 11 different cancers with three different programmes, and will be investigating second generation and new HLAs, we currently have more targets pushing through. For some aspects, we will be able to do our own Phase III trials on a small scale. We can manage those 50-people studies in cell therapy, because without a substantial response rate cell therapy is not viable.
However, for the bulk of the required larger scale studies, we will be partnering, with Big Pharma or large biotechnology companies. We are currently debating whether we can build up our own capacity for the European market, and are expanding our infrastructure here in the UK, but we are not interested in spreading ourselves too thin by controlling it all.
In a nutshell?
We started with a technology that is incredibly broad, T-Cell receptors have a multitude of targets. We started also from an ownership position: we own a lot of our products and technologies. I think that based on those points linked with a strong ambition, you can build a substantial company in Europe, but with American funding.

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