INTERVIEW

# Commercial Business Models for Immunotherapies

**HELEN TAYTON-MARTIN** has over 25 years of experience working within the pharma, biotech and consulting environment in disciplines across preclinical and clinical development, outsourcing, strategic planning, due diligence and business development. She co-founded Adaptimmune from the former company, Avidex Limited, where she had been responsible for commercial development of the soluble TCR program in cancer and HIV from 2005 to 2008. Dr Tayton-Martin transitioned to become Adaptimmune's Chief Business Officer in March 2017, having served as its Chief Operating Officer since 2008, a role in which she oversaw the transition of all operations in the company from 5 to 300 staff, through transatlantic growth, multiple clinical, academic and commercial collaborations and private and public financing through to its NASDAQ IPO. Today, she is responsible for optimizing the strategic and commercial opportunity for Adaptimmune's assets, leading on business development and commercial activities. Her role encompasses all aspects of pipeline and technology assessment, strategic portfolio analysis, integrated program management and commercial planning and partnerships, including the company's strategic partnership with GSK. Dr Tayton-Martin also serves as a non-executive director of Trillium Therapeutics Inc. She holds a Ph.D. in molecular immunology from the University of Bristol, U.K. and an M.B.A. from London Business School.

**Q** What factors will influence the business model(s) for immunotherapies?

**HT-M:** Fundamentally you have to start with what works, and that approach needs to have a game changing impact for patients, for it to be a viable therapeutic option to bring to commercialization.

In our experience, that's the autologous approach. It's the therapy we've been developing right from the foundation of the company back in 2008

and our early academic collaborations where we saw signs of clinical response. Some of those responses have been durable with an autologous TCR-directed T-cell product.

The approach needs to show significant clinical benefit. Our data using autologous engineered T-cell therapy particularly in synovial sarcoma, and more recently in myxoid/round cell liposarcoma, indicate significant benefits. We believe that they are the therapies that are going to have an impact in patients with high unmet need and few options.

We start with a view that you need a product that does work and then everything flows from there in terms of how we think about developing the business. You know the business model options from that point.

What does that mean? That means we then focus on delivery - control of supply, and steadily moving in that direction. We have to control GMP manufacturing and at Adaptimmune, we're also looking to manufacture our own lentiviral vector which is how we get the TCRs into the patients' T-cells.

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As we start to control the supply we can then focus on how to make that more efficient, it becomes engineering solution-oriented. Enclosing the system, reducing the number of handling steps, strategies to expediting the process, release testing etc., are all elements to focus on. In parallel, we engage with clinical sites, to focus on what's important to them in terms of scheduling patients, preparing patients, persistently getting the product back within a certain timeframe.

As we go from pilot studies with a clinical signal, we can plan for pivotal interactions with the FDA and EMA etc, and plan for a pivotal program, and then look ahead commercially. Its' really about how we make that manufacturing process even more robust, how we get the cost of goods down, and how we manage these elements and plan to scale up when moving from pivotal to commercial.

Further down the line, ultimately like others, we would like to have an off-the-shelf approach to this therapy; where it's possible to treat any patient with a particular target, a particular HLA type which is relevant for us. That would mean that you have a cell product you can thaw, grow up and give to that patient. You can schedule that very easily, quickly and reproducibly.

The reality is that it is scientifically very challenging to have an off-the-shelf product. We have to start with a stem cell, edit that stem cell to develop uniform T-cell from that stem cell, and then drop in the T-cell receptor for that particular target antigen. But it is possible, and we've been working on creating universal SPEAR T-cells for 2-3 years now. That's our vision for the future, but fundamentally we believe we have a viable business model with an autologous TCR based T-cell therapy today.


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**Q** What factors come into play when assessing whether to build the manufacturing capabilities within a company or to outsource to CMOs/partners?

**HT-M:** When we started out with our initial pilot studies, we relied on our academic collaborator at the University of Pennsylvania (UPenn) and cells were produced in their GMP environment.

As we gained more data, the company grew, signed the partnership with GSK and raised more money, it was important to have contract organizations and we started working with the best-known ones in the field. There were very few organizations at that point that had experience of autologous T-cell production.

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Although we have now built our own facility, we still work with HCAT, formerly PCT prior to the Hitachi acquisition. We also work with CMOs to manufacture our lentiviral vectors. However, we believe that a fully-integrated approach is the best option for us to deliver for patients in the long term.

I think early on when you need to establish the product platform and want to get clinical proof of concept data, you need to work with contract organizations because you don't have the financial resources at hand. It's a significant effort to build a facility, but to do that you have to get to a certain stage, raise a certain amount of capital and have data to support a future vision. You can't do that when you're just starting out. I think we had around 20-25 people when we first took the programs away from UPenn, took on the IND sponsorship and had to find CROs and CMOs to work with. We started out with 1 program in the clinic with 2 or 3 indications, and now we have 3 of our own programs on top of that in the clinic for multiple indications. That's a significantly increased portfolio, and at a time when the competition and therefore demand for contract supply is increasing. Because the field has really taken off in the last 2-3 years, there's a lot more competition for cell manufacture and lentiviral production.

For a number of reasons, partly the scale, partly our ambition and scope of our pipeline, and partly the need to control those elements so we can optimize them and know we have a robust and consistent supply, and plan for the future, it's important to build our own facilities, which we have done and are currently doing with the vector.

**Q** Can you share a bit more about Adaptimmune's strategy in terms of pipeline development and the challenges you're navigating as therapies move towards commercialization?

**HT-M:** It's obviously still early for us. We are currently conducting clinical trials with SPEAR T-cells targeting MAGE-A4, MAGE-A10, and AFP across several solid tumor indications.

We're at the safety evaluation stages of these initial programs. The MAGE-A10 program has passed through the first safety stage earlier this year. We follow a dose escalation design, whereby we give a low dose of cells initially to the first few patients and then escalate the dose to what we think is the therapeutic dose. We're moving or about to move into that stage now, depending on which program we are talking about.

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In terms of what we would take forward down a registration path, it really depends on where we see the best clinical signals. And it's a bit early to predict that. We are working on 8 different indications, we've got 2 programs that overlap, with common targets in multiple solid tumors. We've got MAGE-A10 in non-small cell lung cancer, bladder, melanoma and head and neck cancers and MAGE A4 in those tumors plus ovarian, esophageal and gastric cancers. The AFP study is slightly unique because the alpha fetoprotein is specific to hepatocellular carcinoma, so that's a different type of target and different criteria altogether for that study.

There are a couple of things about how you then decide what to take forward as a product into registration studies and think about commercializing; firstly, when you see responses in patients we see them reasonably quickly and that's something novel to T-cell therapy. In a cohort of 10 patients, you might see them in all 10, half of them, or 3 out of 10, and depending on the indication that can be extremely relevant and meaningful in terms of thinking whether you plan now to expand the cohort for that indication.

From there you've almost got enough information to go into a registration study. It depends on the indication, and prior to GSK exercising the option over the NY-ESO T-cell therapy program we had been granted breakthrough and prime designation for synovial sarcoma, based on the response from the first study cohort where 6 out of 10 patients had confirmed responses. We were discussing the registration study and had actually got an agreed registration study mapped out with both agencies at the point when GSK decided they wanted to opt in on the program. GSK


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## TABLE 1: ADAPTIMMUNE PIPELINE OVERVIEW

| Candidate | Indication | Partner | Development stage: Research | Pre-IND | Phase 1/2 |
|---|---|---|---|---|---|
| MAGE-A4 TCR | Multiple Cancer Types | Wholly owned | | | |
| MAGE-A10 TCR | NSCLC | Wholly owned | | Cohort 1: Study initiated in Q4 2015 | |
| | Bladder Melanoma Head and Neck cancer | Wholly owned | | | |
| AFP TCR | Hepatocellular Cancer | Wholly owned | | | |

now holds the exclusive licence to research, develop, and commercialize our NY-ESO SPEAR T-cell therapy program and transition of this program to GSK is ongoing.

In a rare indication, if you see a signal in a small number of patients you can start planning the pivotal trial. In a bigger indication you can probably also start planning, but then you need to think about additional factors like, which patients you're going into, which line of therapy, and how you're going to scale, whether you're going to do a randomized trial, how you do the controls etc. How you plan to do the control study for a pivotal registration study might be quite different in a larger indication where the benchmarks are different, for example in lung cancer. You need to see it in enough patients to be convinced that it's real. And then you can expand that up to a slightly larger cohort, and from there you can move very rapidly forward to think about what a registration pathway would look like, taking on board standards of care, particularly if there are checkpoint inhibitors that are standard of care and whether you might need to do a combination study.

**Q** When targeting niche disease areas, how challenging is it to recruit patients for clinical trials?

**HT-M:** It is often easier working on niche disease indications because rare indications often have fewer alternatives to more conventional chemotherapy, radiation and surgery.

It's more competitive potentially for more common disease indications. If you're trying to develop a therapy for lung cancer, there is a lot of competition for patients. A lot of patients have also been through several lines of therapy before they may go into something investigational like this.

That makes it challenging in terms of fitness of patients. Whereas in niche indications, because there are fewer options, although rarer they may actually be fitter and more likely to be eligible for treatment.

I would also say it depends on whether you have data that is convincing to the clinicians in that community. For example, we have talked about this publicly before, in the context of our first cohort of sarcoma patients. I think it took the best part of 2-3 years to recruit that initial cohort of 10 patients. Once we published the initial response data, we recruited the most recent cohort of patients in around 3 months.

That's a rare indication, but I think that speaks volumes. When you see meaningful responses in a clinical community where there are few options, often those groups are more tightly knit in terms of the clinicians interested in developing the therapies in that area. They all then know this is something that looks like it works, and they want patients to have access to it. Patients themselves are also much more proactive in terms of researching what's available.

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Therefore, if you're starting from a more crowded level playing field, and nobody knows if your therapy works versus the next one, you are facing competition. But where there's precedent you've got something that might actually be significantly better and the clinicians are protagonists of that and can see the potential value for their patients, then I think it's not as challenging as you might think.

**Q** What are the key considerations when assessing whether to enter into partnerships or collaboration with Pharma/Biotech companies?

**HT-M:** Certainly from our experience, the GSK collaboration has been hugely positive for Adaptimmune. We struck that deal in 2014, a year after Novartis had signed up with UPenn for what is now a registered product, the CD19-focused CAR-T, Kymriah.

Endorsement by a large pharma company was a great deal for us at that time when the world was just beginning to even understand what a CAR-T therapy was, let alone an engineered TCR T-cell therapy. At that stage we were around 35 people, we had a US office as well as a UK research base, and we were running everything through contract organizations. What was important was that it was an option-based deal primarily focused around the lead clinical program, NY-ESO.


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The reason that the partnership was incredibly valuable and a good structure for us is because we ran everything: we continued to expand the programs to enrol the patients, to have the relationships with investigators, to manage regulatory interactions, to manufacture the cell product, to optimize and centralize the screening technologies. We were able to optimize the platform clinically. We also agreed with GSK how we wanted to explore certain questions clinically. We started with 1 cohort and added another 3 to the sarcoma program, to specifically look at some key questions, namely, whether the amount of target antigen was important, whether the conditioning regimen was important. We learned about any safety issues and we built our translational capabilities. GSK worked alongside us and learned about the therapy while they recreated their oncology development capabilities for this type of therapy.

They were funding everything through milestones, so we kept the knowledge, built the clinical capability, regulatory capability, manufacturing capability of the organization, learning a great deal from that program, but we also structured it so that the other targets for GSK were not the ones immediately behind it in the clinic, or indeed anything on which Adaptimmune was already working.

What we have in the clinic today: MAGE-A10, MAGE-A4, and AFP, weren't part of the deal. GSK has nominated another target, PRAME, currently in preclinical development. GSK will get access to 2 more targets from the discovery pipeline once they complete the NY-ESO option exercise, which is basically when the program is fully transferred and they hold the IND.

That was a really good way to structure a deal. Because of the option, it meant we kept control of the program and gained all that knowledge to build our capability and knowledge of how these things work. We've been the leader in every sense in the collaboration, but working collaboratively alongside them.

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We also did a cross-over round to position the company for a subsequent IPO immediately after our GSK deal which enabled us to raise a substantial sum to bring our own pipeline forward and build the manufacturing capabilities we talked about earlier.

Strategically I think that GSK deal triggered all of that and we wouldn't have been able to build the company without having that in place.

Having said all that, it is challenging for two reasons mainly when you're a small biotech and working with a large pharma. Firstly, we want

to move more rapidly. But we've always got to have a healthy respect for and work alongside a development partner that's got different layers of governance.

Secondly, the turnover of staff in large pharma is often greater. On the one hand, as a biotech company we have been moving forward and continuing to make steady progress (and we've been fortunate to continue to attract and retain exceptional people). On the other hand, even going through the transition of the program to GSK more recently, now they've optioned, we're dealing with completely different people to the team we dealt with at the outset of the collaboration. That generates its own challenges. They've had a change in CEO, change in R&D director, so quite a lot of change going on in the other side. Notwithstanding that they've strengthened their commitment to cell and gene therapy and in oncology specifically, they're really building out other areas of what they're doing in T-cell therapy, leveraging this is a core collaboration.

My advice would be; it's important to keep hold of assets where you can which we were able to do. If you can structure things appropriately, it can be transformative, and you can try and make sure it doesn't completely bog down your own development activities. It's a challenge to do but if you can get that right it can have a transformative effect as you grow the company.

**Q** How does the TCR-based approach address some of the challenges we're seeing in the CAR-T space?

**HT-M:** The CAR-T successes with the approval of 2 products have been phenomenal, and the recent approval in a second indication for one of the two products. Both of these therapies are for cell malignancies where the CAR-T is targeting antigens on all B cells. Phenomenal success in hematological malignancy, and potentially further approvals in other hematological malignancies are following from that. I think everyone is probably on the same page in the view that the next likely product to be approved will be a BMCA CAR for multiple myeloma, so again hematological malignancy.

But I think absolutely the holy-grail in this field, is having similar impactful responses in solid tumors. That's absolutely the key for the next stage of growth and innovation in T-cell therapy and we've focused almost entirely in solid tumors with a TCR-based approach from day 1. We fundamentally think that T-cell receptor-based targeting is essential for solid tumors for a number of reasons. One is the vast majority of targets for T-cell receptors are based on intracellular proteins, proteins inside the tumor cell. Whereas in a CAR-T based approach, the recognition molecule


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is on the cell surface. That's extremely powerful for B-cell malignancies where the CD19 marker is expressed on a particular cell, and the B-cell delineates the development opportunities. But you're wiping out healthy B-cells with a CD19-based approach and you have to accept the fact that there's collateral damage. That's the case for lymphomas and leukemias where the CD19 CAR-T products are indicated; patients require intravenous immunoglobulin. There are also some longer-term effects and relapses that happen in some cases but that's an acceptable risk/benefit trade off in those indications.

It's completely different in solid tumors, you can't have a powerful T-cell therapy attacking normal tissue. We're very safety conscious and to get those kinds of targets you really have to look at tumor-specific cancer proteins. These proteins are generally inside the cells, and the only way you can see them on the surface and attack them is through peptides on HLA molecules which the T-cell receptor will detect. That's been fundamentally part of our safety screening package, to make sure what we generate is T-cell receptor that will only detect peptides from targets on cancer cells.

The other thing that's really important in terms of response in solid tumor is, you see responses quite quickly and these responses are generally durable and evolve over time. In our experience, there seem to be 2 elements to that. One is the initial expansion of T-cells you see when you give the T-cells to the patients, where you get a rapid expansion in the patient early on, and those patients tend to go on to respond. And also those T-cells tend to persist over time. This does seem to link to an evolving control and gradual decrease in solid tumor we're measuring in these patients.

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Having T-cells that can see something on a solid tumor, having those T-cells expand, having them persist over time, is important. And that's a feature of our platform, and I think that will be important in terms of having solid tumor responses that are meaningful for the patient over time.

There will be several other elements that will be added over time. We have a whole host of second generation products coming through which will add additional features into the T-cell, apart from the T-cell receptor, that will help deal with the hostile tumor microenvironment, and or to test in combinations with other drugs too. The initial response is what we start with, and then we build on that.

**Q** What are your thoughts on the manufacturing strategies that we're seeing within this sector?

**HT-M:** If you're shipping products into a central manufacturing facility, logistically we can freeze that product. If we can freeze the apheresis that's sent in, and freeze the manufactured product we send back, you have a lot more control over scheduling of those patients, and managing production of the product in relation to the patient's disease progression and location.

Because of the freezing capability, it is possible to treat patients in Europe, US, Asia or anywhere in the world. With an autologous product, although it is feasible to ship product backwards and forwards across manufacturing sites, ultimately you may want manufacturing sites in each major territory.

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Developing an infrastructure to enable robust control of the supply chain is going to be very important moving forward. It will guide our thinking in terms of how we optimize manufacturing for the current autologous product, and what would be necessary for an off-the-shelf product down the line.

As you move towards an off-the-shelf product, looking further out to the future, you could have banks of cells, again closer to the sites of patients in the US, Europe, Asia, Japan etc.

**Q** How do you anticipate the immuno-oncology sector evolving over the next 5 years?

**HT-M:** There's a huge amount of innovation going on in the immuno-oncology sector, basically triggered by clinical responses, and the realization that engaging the immune system is incredibly powerful in how we think about treating cancer.

T-cell therapies have been at the forefront of driving that. There are a huge number of combination studies going on, and many innovative T-cell therapy companies coming forward. There are companies working on the variations of CAR-T cells, NK cells, neo-epitopes etc. But I think there will be increasing fall-out as certain combinations do or don't work. There will be convergence of a lot of these and I think there may be quite a lot of consolidation as things do look as if they work. There will be attrition


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as we work through the complexity of the combinations that work and the therapeutic modalities that work from the cell therapy side.

There's an awful lot of manufacturing innovation - automation, closing systems, etc., that's actually going on to make autologous production far more cost-effective. There are a lot of engineering companies also kicking off, which will transform how our particular type of autologous therapy will become more commercial going forward as well.

We're also going to see new pricing and reimbursement models emerging based on value demonstration over time. There's going to be quite a revolution in innovation in terms of combining therapies and thinking about how they generate value that the payers can agree to, and then clinical sites have a path through in terms of enabling access and reimbursement.

Finally, I think we will get there with the off-the-shelf approaches, but that's further away than people may be indicating right now. But ultimately that will bear fruit down the line.

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## AFFILIATION

**Helen Tayton-Martin, PhD MBA**
Chief Business Officer
Adaptimmune.
Helen.tayton-martin@adaptimmune.com