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Stick To The Plan – But Be Ready To Change

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By ASHLEY YEO

KNOW YOUR STRENGTHS, SURROUND YOURSELF with experts and ensure your solution "does what it says on the tin." These are among the guiding principles of Christophe Bancel, co-founder of France's biopolymer innovator TISSIUM, a health cares to help companies manage the situation.

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Without a vision, unmet clinical needs do not get turned into products. But without the right support for original concepts that can be turned into solutions, the vision often dies before it has had time to take root. Importantly, before any of that happens, the unmet need must be defined.

That was the thought process that led Christophe Bancel and colleague Jeff Karp, from the Brigham and Women's Hospital, to form TISSIUM (formerly Gecko Biomedical) in 2013. Their remit was to tackle one of the biggest medical challenges since the inception of surgical procedures: the reconstruction of damaged tissue and the restoration of natural function.

The technology they used was created jointly by Karp and Massachusetts Institute of Technology (MIT) professor, Robert Langer. TISSIUM has developed the technology to the point where, in April 2020, the company received CE marking for its first sterile biodegradable sealant in a pre-filled syringe for use in vascular reconstruction. Before this, it gained a CE marking in 2017 for the vascular sealant, Setalium.

The Market

There are many potential applications for the company's polymer. This has made for complexities when explaining the solution to different stakeholders, said Bancel. Four applications are underway, each with its own sub-market:

- the first, in the vascular/cardiovascular space (Setalium Vascular Sealant), addresses a $300m market;
- the second application, for peripheral nerve repair, is in a$1.2-1.3bn market;
- the third market that will be addressed, hernia mesh repair, is valued at $2bn; and
- the fourth – but not to be the last – is in the ENT submarket of chronic sinusitis, a $3.95bn market.

These four markets represent a target opportunity of some $7bn. TISSIUM is expected to follow its CE marking for Setalium some 2.5 years ago with the filing later this year for an IDE with the US FDA.

Need For User Case

Getting momentum behind the concept and growing users' awareness called for a user case. This became the basis for building the company. The user case was selected to be around vascular/cardiovascular applications. This established with stakeholders that TISSIUM's core technology is the polymer. But surgeons buy final surgical solutions, not substances. "We had to demonstrate that our polymer from MIT could be developed for clinical use," said Bancel. "We also had to show that it could be assembled into a product with the right accessories."

The challenges at the beginning were that the polymer was a completely new concept, and it was targeting the market share of established technologies. There was also lot of uncertainty on the regulatory and clinical fronts, Bancel admitted. "Taken altogether, that was too much uncertainty at once, so we said we should balance the risk, and pick an indication where we knew that, if we were successful, we would have an approved product."

It was not the biggest market, but having settled on the cardiovascular indication as the user case, TISSIUM saw that it could use all the work that was derisked at

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this first stage of product development and redeploy it very quickly for second, third and fourth products, etc.

So while it had taken four to five years to bring one product to market readiness, the ensuing 18 months yielded another two or three. "It was a snowball effect, and to have that, you need to invest from the get-go in your platform," said Bancel. "We were very fortunate to have investors who believed in our strategy and were able to give us the financial resources and the time," he said, alluding to a key entrepreneurial quality common in leaders – the ability to attract funding.

CHRISTOPHE BANCEL

Seen in another way, two years of the company (2014-2015) were spent on scaling the product and making it a "safe version" of what had been developed in the academic phase. The next two years were a period of validation from a clinical and regulatory point of view of the first use case. "But in parallel, we were starting to expand already and deep dive into new indications," said Bancel. "Now we have reached the stage where we are capable of running projects one after another."

Clinical trials of the peripheral nerve repair product are expected to launch in summer 2020, however the company isstill finalizing this schedule in light of the COVID-19 pandemic. The hernia repair product will enter clinical trials in early 2021; and the ENT product, for chronic sinusitis, which is a mix of a drug and a device, is being prepared for a Phase I clinical trial in late 2021/early 2022. "With a new trial every six to nine months, we are at the stage where the platform is going at full pace," said Bancel.

Manufacturing – A Trump Card

Not so common among medtech start-ups, TISSIUM, a company of 55 staff, owns its manufacturing facilities, in Roncq, northern France. Bancel's logic is clear. "If you don't have your own manufacturing capabilities, with such a technology, you are not able to produce technical batches for regulatory purposes or clinical batches for clinical indications. You're simply stuck."

The strategy at TISSIUM was always to plan for leveraging the effort on the first product for ensuing solutions. A proprietary manufacturing plant is key to Bancel's strategy. "If I had to rely on subcontractors or suppliers for my polymers, I would be extremely dependent on others." The way TISSIUM has set itself up, it can expand programs when it needs to, and focus on the priorities it identifies.

"It's a huge leverage," Bancel said, adding that the crucial element for the company was getting investment from day one. One of its investor partners is Sofinnova, whose Antoine Papiernik sits on the TISSIUM board. "They believed in our vision and have been supporting us." Bpifrance Investissement's Jean-François Morin and CM-CIC Capital Innovation's Karine Lignel are other investors on the board.

"The challenge has always been: how to do work for tomorrow, but prepare for what comes after tomorrow at the same time." It was a balancing act, said Bancel, who added that the company needed to be fully hands on. "I always keep in mind thoughts around, 'If we are successful, how do we move this forward in an accelerated manner?'"

Efficient business planning has provided breathing space. "From idea to first-in-human, we can now do things in 12-18 months; what we didn't want was to take three years to get to the first product, and the same for each product thereafter.

TISSIUM is now churning its R&D activities to develop new applications. Three years ago, the company restructured internal R&D into two parts. One led to the formation of an Innovation Hub, to devise ideas inspired by unmet needs and develop them to prototype. That division is led by CIO Pereira. The second was the Group Development Factory, where products are industrialized and prototypes are rapidly made into commercial products.

"From top to bottom, the processes are all fully integrated. It's one of the reasons we did a pretty decent

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job," said Bancel, allowing himself a rare moment of self-congratulation. "I am convinced we will be successful moving forward because of just that – we have integrated and can control everything."

Market Focus

TISSIUM chose to focus on the US and EU markets first, and later bring China and other parts of Asia into the business plan. In the EU, the change of regulation from the Medical Device Directive (93/42/EC) to the Medical Device Regulation (EU 2017/745), recently delayed by COVID-19 to 26 May 2021, has led to a lot of uncertainty in the air.

"We made a decision not to be dependent on those changes," said Bancel. "At the end of the day we can have limited impact on those changes, so we decided to leverage certain geographies where first in human could be done in an effective manner. For instance, in the US for early feasibility studies, and in Australia, where we can get those early data, and then go on to do pivotal trials in the US."

He added, "Until we have visibility back in Europe, which won't be the case for the next few years, we cannot put ourselves in uncertain situations. We may set up centers in Europe, but the design of studies would in future be aimed towards FDA approvals first."

Thus the pivotal trial for an expanded indication of the already CE-marked vascular sealant (Class III) will be in the US. In the US, it will be expanded into a cardiovascular product, with a change in the polymer formulation to tap the broad $300m market. But the plan here is to be able to partner on the product. "This cardiovascular asset is, we believe, something that should belong to a portfolio within a large medical device company that targets a broad audience."

Bancel explained that the original polymer formulation used as a vascular filler has been evolved into a resin that can be used for 3D printing. It has an enhanced design in terms of adhesion, allowing more pressure to be withstood and greater medical application. "We now have polymers for adhesion and fixation, and for use as a resin for 3D printing, both from the same family."

TISSIUM's ongoing products in development will all be based on the resin, PGSAA, with all of the finished product polymers provided sterile and pre-filled. "We tailor the kits to the surgical procedure – this is something quite unique to us; we don't sell polymers, we sell surgical solutions," said Bancel. "What we do is provide the full solution."

This was a function of the company's capacity to internalize all its programs and processes, Bancel maintained. "My team wants to define both the unmet need, and the right accessories," he said. "This makes for simplified surgery for doctors, more consistent for outcomes for patients, and greater efficiencies for the health care system, as there is not much variability in how the product is used and costed."

This is where TISSIUM offers elements of personalization, tailoring products to individual fields for better surgical solutions for the patient, including the right accessories. "Whatever we bring to the market is better and simpler for the surgeon we tailor it for the surgical approach, rather than the individual patient."

In peripheral nerve repair, the technology should allow TISSIUM to make two to four products, with options of either designing the first product and commercializing it within a subspecialty field; or building the portfolio to become a leader in the peripheral nerve repair area.

It is an example of the flexible business ethos Bancel is overseeing. If a product is more "standalone," the idea is to partner it with a company that has an existing portfolio, as in the example of the cardiovascular product. But if it can be expanded into a portfolio, Bancel wants to develop the position internally and build standalone business area leaders.

The vehicle for these decisions will be a new body, Tissium Ventures. "We have plans for single asset companies and multiple assets in a field. For some, we will partner, for others, we will provide finance or go direct in the field."

Funding Needs

Bancel said he was fortunate to have investors, co-founders and team members around him who understood that TISSIUM had a unique product, and that realizing its full potential meant taking a somewhat

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longer view. Other key elements are the right supply of materials and a total understanding of where the product can create the most value.

In late 2019, TISSIUM announced the completion of a series B funding round of €38.75m, which has given the company the means to develop all four of its programs currently underway. Later, it will go back to the market for funding for full commercialization operations.

Alongside these programs, TISSIUM has been doing other development work away from the public view. These projects are appraised by the group of experts who review the clinical needs, market potential and the ability and suitability of TISSIUM's technologies to provide clinical solutions. "When all these intersect, we define a program, create a new business plan, and, if it is robust enough, we invest internally. We already have the top four, but the list is quite long."

And the pipeline is flowing. In February, the company announced an early collaboration with the Crohn's and Colitis Foundation's IBD Ventures funding mechanism, to accelerate the discovery and development of novel research-based products targeting perianal disease, including anal fistulas. What is certain is that any design proposition must bring value to the multiple stakeholders involved: the patient, the person who benefits; the surgeon, who implements it and is accountable for execution; and the payer, either through tax or insurance, who funds it. "Design propositions need to factor in the integration of all three," he noted.

But the emphasis differs, depending on the product type. In the more generic product areas, payers are more central; in chronic care delivery, the patient has more of an influence in the use of one product over another; and in acute care cases, the surgeon and payer are central in decisions of which solutions are used, and why. For the company's cardiovascular and nerve repair solutions, a lot of decisions are driven by the surgeon.

Value Of Clinician And Provider Partners

Using the skills and expertise of clinicians and providers is an important element in TISSIUM's design-for-innovation processes. "It is hard to be an expert in everything. We are experts in our own material and how to develop it into products," said Bancel.

TISSIUM does not always know all the clinical subtleties, he admits, so once an idea is identified, a team of experts and practising surgeons is assembled. They create a scientific and surgical report for that specific field, after which the company identifies the R&D experts to use. "We share the vision with them, and they work with us to validate and innovate products until we are ready."

Later, in clinical trials, the decision-making moves to focus on geographies and regulatory issues – seeking the routes that are faster and/or most favorable. It requires a mix of clinical knowledge and regulatory awareness. "Essentially, it's about surrounding ourselves with the best surgeons for the innovation in question." Bancel described it as a co-innovation effort: "It's us in the lab when it comes to chemistry, but it's not us in the lab when it comes to making a product." At the root of it all, if you want to make the right product, you need to spend time with people who know the unmet need and who the surgeons are.

R&D-based health care companies have long since not designed products that are country specific unless it is a very big market. TISSIUM has its operations in France, is headquartered in Paris, and has stronger connections in Europe than in the US. But the technology on which its products are based originated in the US, where it has a subsidiary (Boston), and the industry is global.

"Our strategy at the start was to develop the business with both the US and Europe the core markets – in mind. Later, when entering the stage of commercialization, we would look to prioritize locally," said Bancel. That includes factoring in the complexities of national reimbursement, where solutions are all viewed differently, depending on the product. "It is hard to make a general rule, which means we are really looking at every single case individually."

But as a general rule, from the earliest stages of an innovation, the company has already assessed its reimbursement dynamics – whether existing codes can be used, or if a new code must be created. The latter points to a major slow down on entering commercialization.

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China is also on the TISSIUM road map. It is not a key market yet, but will be in two to three years. "We are still at the business case design stage there, educating ourselves and how we can make a difference."

Going Public?

TISSIUM has not sought to go public through the IPO route, but it has completed funding rounds. "It's a balance," said Bancel. "Financing at the end of the day for the entrepreneur is a means to an end, not the goal in itself." The need is both to finance the project in advance and ensure the right return for investors will be delivered down the line.

Going public as a single asset company was extremely risky, said Bancel. That is because the market seeks motion. "It needs news flow, information and a dynamic picture. If a company is at a stage where it is delivering its key milestones at certain stages, then it is probably not ready," he explained. But if a company has scale, production and innovation, it is more in tune with what the market seeks. "In that case, the market can judge you in a fair manner. Whether you are successful or not is a different matter, but at least you are compatible with those requirements."

TISSIUM seems to tick those boxes, but Bancel is cautious. "My core belief is that going public too early can be very dangerous. TISSIUM has been trying to remain private to achieve the right breadth. Eventually, when we are ready to fit that kind of dynamic, we will do it."

Bancel anticipates that the company will be generating revenues in 2021, but at present it is content to pick up the plaudits for its innovation. La French Tech picked TISSIUM as one of its 120 French innovators to watch in 2020, labelling it as a fast-mover and interesting innovator. This kind of validation is humbling, in Bancel's view, but it shows that the company is going in the right direction. "We were proud to be selected last year in a competition to identify 'future potential unicorns' in France." TISSIUM was in fact selected two years in a row.

"Designing solutions for health care is a very long road, but we aim to be proactive and we are getting the right traction," said Bancel. "We tend to do what we say we'll do, and there is growing confidence in and around the team now." Back at the company's origins, the leaders made a commitment to expand what it saw was a great material in multiple directions for the benefit of patients. "We have recently begun to deliver on that."

That is due in no small part to the realistic take on business success and failure that the TISSIUM CEO brings to bear. His guiding principles include being honest from the start and be ready to change tack. "It's a combination of bold options, strong pragmatism, and a twist of paranoia," as Bancel puts it. "And you have to deal with all three. The pragmatism is there for when you have a bad day: you have a plan B, so you can come back strongly the next day."

Useful Advice For Start-Ups

Elsewhere, Bancel has advice for fellow start-ups: the highs are indeed high, but the lows are very low, and companies need to be prepared for that. Is TISSIUM a role model in this respect? If so, Bancel would not say as much, but he does make himself available. "I am open to sharing my experience; I don't need keep it all to myself. I am always happy to talk with peers, but I ensure they know that mine is just one opinion. And they need to start from somewhere."

Bancel, also a founder and venture partner at the Paris-based iBionext health care technologies growth platform, has three top tips for fellow start-ups who are in the early stages of their journey:

1. In your technology-based company, the technology is key, but think about the team that you need. It is impossible to make it on your own. Once you are sure you have a good technology, it is all about the people. The journey will be very hard in some cases, so surround yourself with people who can complement you.

2. If you have the good fortune of being able to select your investors, work with people who believe in you, and who are there not just to make money. In fact, they will anyway, but the point is that you want them to be part of the journey.

3. Enjoy what you do, as you'll be doing it a lot! Don't turn it into a prison; have fun along the way.

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