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09 Apr 2018 |

Meeting Growth Challenges Roundtable Panel Part 3: Pursuing Growth Without Overreaching

Thought Leadership In Association with Freyeur & Trogue, Impactiv BioConsult, and rbb Communications

by Mike Ward

Three decades ago when biotech was in its infancy many of the pioneers had ambitions to create fully integrated pharmaceutical companies (FIPCOs). Picking low hanging fruit – recombinant versions of therapeutically relevant human proteins, such as insulin, human growth hormone, erythropoietin and tissue plasminogen activator – a number of the first movers prospered but many withered on the vine. The FIPCO model fell out of fashion and subsequent start-ups pursued strategies that took assets to proof of concept before licensing to established commercial organizations. The advent of personalized medicines and initiatives to incentivize development of therapeutics to treat orphan diseases has underpinned a renaissance of the FIPCO model. However, challenges still exist.

Developing products that are clinically meaningful requires more than a novel approach to an unmet medical need. A panel of biotech executives and venture investors discuss how to meet the challenges of building a sustainable business from day one.

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proof of concept before licensing to established commercial organizations. The advent of personalized medicines and initiatives to incentivize development of therapeutics to treat orphan diseases has underpinned a renaissance of the FIPCO model. However, challenges still exist.

Scrip spoke with Gil Van Bokkelen, chairman and CEO of Athersys, Inc., Daniel R. Orlando, chief operating officer of Vericel Corporation, Robert McNeil, general partner and managing director of Sanderling Ventures and CEO of Dalcor Therapeutics, Ali Fattaey president and CEO of Curis, Inc., Mei Mei Hu, co-founder and CEO of United Neuroscience, Inc., Gregory Hanson, CFO of MabVax Therapeutics Holdings, Inc., and Dennis Podlesak, partner at Domain Associates LLC, in a roundtable interview about the challenges company executives face as they try to build their business. Sponsored by Freyeur & Trogue, Impactiv and rbb Communications, the roundtable took place during the J.P. Morgan Healthcare Conference in San Francisco.

Growth strategies are dependent on several factors. First, the founders and initial investors need to think about their ambitions for the assets they have: Are they looking to develop programs to proof of concept to then license or sell to other companies to commercialize asset by asset? Are they wanting to pursue a build-to-buy business model which usually involves early involvement with a potential purchaser? Or is the plan to create a standalone commercial scale company? Second, to achieve their ambitions they need access to clinically meaningful assets, capital and teams with relevant experience.

While a number of companies have demonstrated that it is possible to evolve from research intensive start-ups to fully functioning commercial organizations with critical mass to become large cap biotechs, they are still pretty rare and more often than not are subsequently acquired by big pharma. Access to capital is probably the major determinant for successful evolution of that model and while tapping the capital markets is an option, the most common source of financial support comes through partnering deals with big pharma.

“Most companies end up partnering their main programs or lead portfolio assets with a big company, which sometimes leads to complete acquisition. Big pharma has been preying on biotechs for the past 10-15 years and increasingly we are now seeing big biotechs taking the

same route," noted Athersys' Van Bokkelen.

Companies with platforms that can generate multiple therapeutic opportunities can buy the time they need to transform into commercial standalone entities. "We acquired our core regenerative medicine technology from the University of Minnesota and recognized that putting it into a platform that yields a number of clinical programs was the best route. It is our intention to take that all the way to the finish line but I understand that it is a long hard road. We have been at it for more than 20 years and not all organizations are going to be able to maintain consistent leadership, have consistency of vision or frankly have patient enough investors to be able to do that," he added.

Platforms As Springboards

During the 1990s, the biotech sector shifted from the FIPCO model where companies attempted to develop and commercialize therapeutics on their own – many crashed and burned following failures in their lead programs - to the less risky platform model that allowed biotechs to create a plethora of products that would be sold onto companies with established commercial infrastructures. The challenge of the platform model in the early days was that it was often a proxy for a fee-for-service approach that constrained the ability for companies to gain critical mass as they sold off the family silver. This gave rise to a hybrid model which saw companies generate license fees and milestones from the platform that were recycled into proprietary programs.

"What is important is to how to retain as much value as possible," added Curis' Fattaey.

In 2003, Curis signed a collaborative research, development and license agreement with Genentech that gave the Roche company an exclusive, global, royalty-bearing license to make, use, sell and import small molecule and antibody Hedgehog pathway inhibitors for human therapeutic applications, including cancer therapy. Genentech subsequently granted a sublicense to Roche for non-U.S. rights to Erivedge (vismodegib), which was the first FDA approved medicine for the treatment of metastatic or locally advanced basal cell carcinoma.

"It was a different time and the company did give away commercial rights. At that time, I was at Onyx and it took a different route and retained all the commercial rights we could, and obviously it did very well," he noted.

Onyx Pharmaceuticals was the company behind Nexavar (sorafenib), co-developed and co-marketed with Bayer approved for renal cell carcinoma and currently the only targeted treatment available for first-line hepatocellular carcinoma patients, Stivarga (regorafenib), a tyrosine kinase inhibit approved for the treatment of metastatic colorectal cancer, and Kyprolis (carfilzomib), the proteasome inhibiting multiple myeloma treatment. Onyx was acquired by Amgen for $10.4bn in 2013.

While royalties from Eviredge – the company pulled in just over $9m in 2017 – have been important to Curis, the company is now looking to leverage as much as it can from the multiple partnering opportunities it platform offers, while retaining an ambition to become a profitably sustainable commercial organization.

In order to grow, Fattaey believes companies need to retain as much as they can and keep a close grip on development and marketing plans. "Mathematically, it is fairly simple. With one drug, you have four opportunities to access capital. One is equity and the other three are the commercial rights associated with the US, European and Asian markets. If you have two assets then you have seven options. The choices become a little easier – we don't have to choose one drug to give away in order to try and finance another one. By licensing commercial rights to markets we are never going to address -- we are not going to try and commercialize in Asia – we can hang onto assets and focus where we can target discrete disease populations. So we look at them and ask ourselves as a management team, board and company what do we strategically want to do about it? We are not interested in Asia so those commercial rights create a financial opportunity for us," he explained.

However, partners have to be able to offer more than just hard cash. "You have to ask yourself, are they willing to put in more commitment than just dollars? Are they willing to put their expertise into your drugs? That is what is important to us. In the case of Eviredge, Roche and Genentech continue to market it phenomenally across the globe," he added.

Having a broad platform creates the additional challenge for small biotechs of knowing what to focus on. Noting that her company is developing a technology that has potential in many areas, United Neuroscience's Hu asked: "We know we can go broad but do we want to do so all the way? Our constraint is whether we have the finances to take all the programs forward. It is a question of which ones we de-prioritize and maybe partner off?"

Adopting Orphans

Homing in on discrete disease populations in specific markets offers biotechs an opportunity to cut their commercial teeth without over-reaching. Orphan diseases provide such a sweet spot. Although United Neuroscience's lead program is an Alzheimer's vaccine, Hu has no expectation that her company will try and take that all the way. "We are a small translational company and that is where our core is right now. We don't see ourselves commercializing an Alzheimer's vaccine as that would be a big leap for is. Our priority is to find a partner to do that," she noted.

Hu, like many biotechs, prefers orphan indications because she thinks she can handle them. "Many companies are being built to focus on rare diseases. They have a single focus, know the regulatory path and can commercialize them. For smaller companies like us that is a much more feasible option," she added.

Admitting that she started off with a pursuing a philosophy of being vertically integrated and doing everything, United Neuroscience's Hu has shifted her focus on what her company is good at and finding partners to supplement those areas where it is less accomplished. "That means you don't have to acquire them," she argued. If anything, she is awash with technology and rather than looking for technologies to acquire she is looking for partners that would use the platform in other areas.

"We have figured out a way to get the body to respond to endogenous proteins - no other vaccine can do that safely – and there are many that involved in chronic diseases. So if another company came to us and said they would like our technology to help them out we would look to figure out how it would also work for us. Even if you are outlicensing you are still committing to that relationship and dedicating resources. This is a constant calculus – for us right now we are approached by number of companies for different programs. Our primary focus, however, is to build our own pipeline," added Hu.

Funding Growth

Access to capital is a rate-determining step in the growth of early stage companies, for companies generating revenues, the task is less challenging. Describing his company as a different animal from others represented in the roundtable, Vericel's Orlando noted that its rapid growth in the past four years has been underpinned by the assets bought from Genzyme following its acquisition by Sanofi.

"We just launched our replacement product last year and have expanded the number of sales representatives from 21 to 28 and expect to increase that this year. We are in a rapid organic growth phase," he noted.

Indeed, Vericel reported its third straight quarter of 30% or higher revenue growth compared to the same quarter of the prior year for the fourth quarter of 2017 driven by both the accelerating uptake of MACI as well as substantial growth for Epicel. Total net revenues for the year ended December 31, 2017 were $63.9m, including $43.9m of Carticel and MACI net revenues, $18.9m of Epicel net revenue and $1.2m in license revenue. Total net revenues for the year ended December 31, 2017 increased 18% over 2016.

In guidance released at its full year results meeting, the company expects total net product revenues for the full year 2018, excluding additional license revenue, to be in the range of $73m to $78m. "We will continue on this path. With a strong balance sheet and an expanded sales force in 2018, have positioned the company for continued strong revenue growth that will take us to profitability," he added.

Access to sustainable revenues provides businesses with more flexibility. "Once you are a revenue generating company, your access to capital changes – you find you can be more creative

accessing a debt and equity mix. Armed with such financial firepower, the company can now look at other options to fuel its growth. "For us, the interesting thing would be to make an acquisition of a product or company. That would require significant investment but it is the kind of thing we are discussing," explained Orlando.

If Vericel were to embark on the acquisition path, Orlando added, it is currently most likely to buy something that fits well with its existing business. "We are in essence an orphan company and so have to be cautious. We don't do a lot of basic R&D and so would be looking at something like a cell therapy that is in the latter stages of development," he explained.

As it starts to replace Carticel with MACI, Vericel has freed up a lot of its manufacturing capacity. "We are a fairly rare entity in that we are a commercial manufacturer of cell therapies and there are many small companies that are inching their way to the market. Manufacturing quality product can be very difficult for some companies so there may be some opportunities there for us," he noted.

Indeed, with its strong revenue growth and improving balance sheet, Vericel is not short of opportunities. "We have people coming to us with companies that we might buy and sometimes they have financing support as well. We are, however, busy preparing ourselves for the growth we are experiencing right now – it is important not to get distracted. We have been a very disciplined company to date," he added.

Keeping A Lid On Costs

As capital preservation is essential for keeping biotechs on course, companies need to keep a tight rein on costs, not get over-leveraged, nor run out of cash. That means the executives with financial responsibilities will view growth strategies through a different lens.

As a CFO, MabVax's Hanson, who has had experience of building businesses both organically and through acquisition, agrees that he sees things differently. "At Avanir Pharmaceuticals, we took the organic growth route and intended to take our lead compound, the cold sore product Abreva, all the way. We ended up having to license the product to GSK because it went over the counter immediately and we didn't have a salesforce for that kind of product. If we could have detailed it, we would have kept it," he noted.

Avanir had previously licensed North American and other ex-European rights for Abreva (docosanol 10%) to Bristol Myers Squibb in 1996, a deal which was terminated a year later. The company then filed an NDA in 1998, licensed the US and Canadian rights to GSK in 2000. A few months later the product was approved by the FDA as an OTC treatment of oral herpes. Avanir subsequently sold a portion of its North American royalty stream to Drug Royalty, while licensing some European country rights to a number of regional pharma companies.

"In that way, we financed ourselves organically with license agreements with companies that

would fund our R&D people – we had about 20 people who were funded at the time by various big pharma," he recalled.

The challenge for CFOs is when programs disappoint and decisions need to be taken to not continue as that can leave a company exposed to fixed costs. "As a CFO, I am a believer that when you have uncertainty you want to have variable costs because if you hire people you can have a pyramid of costs. You have to have more buildings, more chemistry labs, biology labs and, at that time, that worked out at about $50k per person in overheads. It is probably a higher number these days," he added. At the point when Avanir decided it needed to start a salesforce, the management team chose not to hire one but instead get a commercial capability through acquisition.

Having flirted with a monoclonal antibody platform, Avanir built a presence in the CNS space, ultimately succeeding with the approval of Nuedexta, a combination of the NMDA receptor antagonist dextromethorphan with quinidine sulfate, a cytochrome P450 enzyme inhibitor, in pseudobulbar affect.

Dextromethorphan with quinidine sulfate is also in Phase II studies in other indications including: agitation in Alzheimer's disease; amyotrophic lateral sclerosis; autism in adults; treatment resistant depression; central neuropathic pain in multiple sclerosis patients; diabetic peripheral neuropathic pain; and Parkinson's disease levodopa induced dyskinesia. Japan's Otsuka Pharmaceutical acquired Avanir at the end of 2014 for $3.5bn.

Although MabVax is a smaller company, Hanson is staying true to his philosophy of keeping costs variable. "It allows you to adjust if you have a delay. In my experience, clinical trials never get completed in the timeline you really want – things happen – it could be some regulatory issue or it takes longer than expected to bring on another clinical site," he explained.

"Organically, you can grow if you have massive amounts of funds, you have an investor that believes in you, will stay with you. If $150M came into our company that would be outstanding for us. We have backers who have invested time and time again but you have to be in line with your investors, your management, your board, know your markets and your assets to grow organically," he added.

Thinking about technologies that MabVax might bring in-house, a good fit, according to Hanson, would be antibody-drug conjugate (ADC) expertise. "We don't have ADC experience so finding a company that can provide that would be good. We are aware of companies like Seattle Genetics but they would be more likely to acquire us. We do look at technologies we don't have and look to acquire them and have had some discussions on that front to try and find the right fit. Figuring out the valuations of activities is usually the biggest challenge," he added.

This is the third and final installment of a multi-part coverage of the Meeting Growth Challenges Roundtable, sponsored by Freyeur & Trogue, Impactiv and rbb Communications, conducted during

the J.P. Morgan Healthcare Conference in San Francisco.

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