

Meeting Growth Challenges Roundtable

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INTRODUCTION

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.

Starting up life science companies has probably never been easier. Our understanding of disease biology continues to grow, the pool of experienced biotech executives with the battle scars of entrepreneurship has never been deeper, and the cash pile to bankroll their development continues to grow. The challenge these days is what do company executives have to do to ensure they can translate their ground breaking ideas into sustainable businesses that develop products that make a meaningful difference to patients.

Scrip and *In Vivo* 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 Pharmaceuticals, 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, COO at Domain Associates LLC, in a roundtable moderated by Mike Ward, Head of Pharma Content at Informa 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.

ROUNDTABLE PANEL



Gil Van Bokkelen has been chairman and CEO of Athersys, Inc. since 2000 having being one of the company's co-founders in 1995. Athersys is a clinical stage Cleveland, Ohio-based company developing its MultiStem cell therapy product, a patented, adult-derived "off-the-shelf" stem cell product, initially for disease indications in the neurological, cardiovascular, and inflammatory and immune disease areas.



Daniel R. Orlando is chief operating officer of Vericel Corporation, a Cambridge, Mass.-based company which develops, manufactures, and markets autologous cell-based therapies for patients with serious diseases and conditions, with two cell therapy products on the US market. Joining Vericel in August of 2012, Dan is responsible for manufacturing, operations and commercialization of the company's products.



Robert McNeil, is a general partner and managing director of Sanderling Ventures and CEO of DALCOR Pharmaceuticals, a cardiovascular-focused precision medicine company currently in the middle of a 5,000 patient Phase III clinical trial. Bob founded Sanderling Ventures in 1979 and has served since then as a managing director of Sanderling's seven investment partnerships.



Ali Fattaey has been president and CEO of Curis, Inc. a Lexington, Mass.-based development stage oncology company since 2013. Curis currently has two drug candidates in the clinic – an orally-available, small molecule inhibitor of HDAC and PI3 kinase enzymes in Phase II, an oral small molecule dual antagonist of PD1 and VISTA in Phase I and an orally available small molecule inhibitor of the IRAK4 kinase in Phase I.



Mei Mei Hu is a co-founder and CEO of United Neuroscience, Inc., a clinical-stage biotech company, headquartered in Dublin, Ireland focused on developing immunotherapeutics for the brain. With operations in the US and Taiwan, United Neuroscience's lead program is UB-311, an anti-amyloid endobody vaccine for Alzheimer's Disease currently in Phase II trials.



Gregory Hanson, is CFO of MabVax Therapeutics Holdings, Inc., a San Diego, California-based a clinical-stage biotech company with a human antibody discovery platform. Gregory has more than 30 years of experience in the industry including being a former CFO at Avanir Pharmaceuticals and Mast Therapeutics and investment banking at Brinson Patrick Securities. MabVax has programs targeting pancreatic cancer and CA19-9 malignancies including lung and gastrointestinal cancers in Phase I studies.



Dennis Podlesak, is a partner at Domain Associates LLC, which, having been founded in 1985, was one of the first venture capital firms to invest exclusively in the life sciences sector. Since then, Domain has been involved in the formation of more than 260 companies and has raised more than \$2.8bn to invest. Dennis joined Domain as a partner in 2007 and has served as an active investor, a company founder and as the chief executive officer or executive chairman for a number of portfolio investments.

LAYING THE FOUNDATION FOR A SUSTAINABLE BUSINESS

One of the strongest foundation stones life science entrepreneurs can lay when starting to build a company around an idea they have is a thorough understanding of the indication they are targeting and develop a way to dramatically change the treatment paradigm.

“Until 10 years ago, if a drug was approved, the general sense was it could have an important role in treating patients and that would be seen as a success. If you look at how the landscape has changed over time, no entrepreneurs or business leaders would invest either time or money unless the treatment has the potential to be truly differentiated,” warned Domain’s Podlesak.

“Venture firms and companies both look at how to grow the business. Unless they can dramatically change the treatment paradigm they tend not to be able to attract capital,” he added.

An example of a paradigm-shifting approach in the Domain portfolio is Adynxx, a San Francisco-based biotech that is testing brivolidide, a molecule that inhibits EGR1, a transcription factor that plays a critical role in establishing and maintaining pain following injury or trauma, as a potential non-opioid, disease-modifying therapeutic for post-operative pain. The drug is in a second Phase II trial. If it works it would be the first drug to actively prevent chronic pain.

“Given the prevalence and severity of chronic pain following surgery, combined with the lack of safe, effective and non-addictive treatment options, we believe it can fundamentally transform the treatment paradigm for post-surgical pain. It is an example of how the bar can be raised,” added Podlesak.

The challenge comes when the indication has historically been intractable or the endpoints for the clinical trial are not obvious.

“Stroke is a perfect example. Everyone is aware that it is one of those areas where there has been a lot of disappointments – outright failures. Current

practice is to either give the patient a thrombolytic like tissue plasminogen activator or take one of the recently developed surgical procedures. Both require treating the patient in the first few hours of the stroke and the clinical reality of that is only a small percentage of patients – roughly 8% – will benefit,” noted Athersys’ Van Bokkelen.

Athersys is developing an approach



that will buy clinicians and patients more time testing MultiStem, a proprietary stem cell product manufactured from human stem cells obtained from adult bone marrow or other non-embryonic tissue sources, in the treatment of multiple distinct diseases. The company is currently evaluating in a Phase II study the administration of MultiStem therapy to patients who have suffered a heart attack, or acute myocardial infarction.

“Our clinical data show that we can effectively treat patients up to 36 hours after a stroke has occurred. It’s a very simple procedure that involves an intravenous drip. We believe it will dramatically improve clinical outcomes,” added Van Bokkelen.

A lack of meaningful endpoints has been a major stumbling block for companies in the neuroscience space.

“That is what has been holding back neuroscience for so long – it’s a chicken and egg situation – we needed to figure out the outcomes that we could measure against. It is also a regulatory challenge as the endpoints we have are a bit fuzzy,” explained United Neuroscience’s Hu. As neurodegeneration takes place over years it is difficult to identify objective and clean endpoints.

United Neuroscience’s lead program is UB-311, its novel synthetic peptide vaccine targeting beta amyloid in the treatment of Alzheimer’s disease. So far, the company has reported from an ongoing Phase I study that UB-311 was able to generate antibodies to specific beta amyloid oligomers and fibrils with no decrease in antibody levels in patients of advanced age. Moreover, amyloid PET imaging and genetic screening for APOE4 status demonstrated an efficient method to identify subjects with mild Alzheimer’s for disease modification trials in early-to-mild Alzheimer’s.

PREDICTABILITY AS A VALUABLE AS CLINICAL OUTCOME

Oncology is one of the areas where the outcomes are more clearly defined and

standard clinical trial endpoints are already well established. Emerging oncology companies, however, have to look beyond those endpoints – which normally revolve around durability of the clinical benefit. “It is more important that you can enhance the predictability of choosing the right patients – knowing who may or may not benefit,” noted Curis’ Fattaey.

Being able to identify the best patients for a particular treatment clearly not only benefits patients, it helps payers, investors and the companies too. “For us, it impacts our way of thinking about how we grow. Do we have enough infrastructure and technologies to be able to tell who is going to benefit or not,” Fattaey added.

Curis’ lead program, CUDC-907, an orally-available, small molecule inhibitor of HDAC and PI3 kinase enzymes, is currently in a Phase II, open-label, multicenter trial designed to evaluate its efficacy and safety in subjects 18 years and older with relapsed/refractory (RR) MYC-altered diffuse large B-cell lymphoma (DLBCL). Patients with RR DLBCL are eligible for treatment with CUDC-907, as long as they have tumor tissue available that can be tested for MYC-altered disease.

Marrying assets that help improve the predictability of outcome, according to MabVax Therapeutics’ Hanson, are probably more important for building a business than the market opportunities or intellectual property.

“We are in pancreatic cancer, an area that many companies have failed when trying to come up with effective treatments. Why would we want to go after it? It just so happens our antibody targets a particular antigen that is expressed on more than 90% of pancreatic tumors and so has a high probability of success,” he added.

MabVax Therapeutics’ approach was to develop the HuMab-5B1 antibody, which was discovered from the immune response of cancer patients vaccinated with an antigen-specific vaccine during a Phase I trial at Memorial Sloan Kettering Cancer Center and subsequently in-licensed, as a therapeutic. Moreover, noting that the

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HuMab-5B1 antibody has excellent tumor targeting capabilities, as well as being internalized by pancreatic cancer cells, the company created a tumor-targeting platform.

The company conjugated the antibody, MVT-5873, with the radiolabel zirconium 89, to create MVT-2163, a PET agent, as an important tool to aid in the diagnosis, monitoring and assessment of pancreatic cancer patients as well as an attractive companion diagnostic for the MVT-5873 therapeutic product.

“The problem with pancreatic cancer is by the time it is discovered it’s too late. Your life expectancy is such that you would be lucky to get beyond a year. So by being able to identify the metastatic sites you can know whether the patient is suitable for surgery or

not. This is a new paradigm because many surgeons find out after that surgery was not a good decision. We feel that we are going to do something that has not been possible before,” he added.

MabVax Therapeutics is testing both MVT-5873 as a monotherapy or in combination with the current standard of care chemotherapy regimen in subjects with metastatic pancreatic cancer and MVT-2163 in the diagnosis, monitoring and assessment of pancreatic cancer patients and as a potential companion diagnostic for the MVT-5873.

Investors are particularly keen on sifting out the probable from possible. “One way of thinking about it – a lot of our job becomes sorting out what is more probable. You are looking for things that are disproportionately more likely to succeed,” noted Podlesak.

One way of increasing the probability of success is to take under-appreciated and underperforming assets and revive them. In 2014, Vericel, created when Ann Arbor, Mich.-based Aastrom Biosciences, bought Sanofi’s cell therapy and regenerative medicine business, a holdover from Sanofi’s 2011 acquisition of Genzyme Corp. Vericel paid \$4m in cash plus a \$2.5m promissory note to get access to Carticel and MACI cell therapy products for the treatment of cartilage defects in the knee and Epicel (cultured epidermal autografts) a permanent skin replacement for the treatment of patients with severe deep-dermal or full-thickness burns, a business with about \$44m in annual revenue. In the first nine months of the current year, these products posted net revenues of just under \$41m.

At the time Aastrom was a struggling company but the acquisition of the cell therapy portfolio, the name change the shift of its headquarters to Cambridge were, according to Vericel’s Orlando crucial steps in the transformation of the business from a clinical-stage company to a fully integrated, commercial-stage specialty biologics company. “We believed with the right attention we could get leverage more of the potential of the products we had acquired,” he added.

ALIGNING SCIENCE, TALENT AND EXPERTISE

Translating a promising discovery into a product that helps patients requires input from various stakeholders, many of whom are not part of the original research and more often than not are actually outside the company. The challenge for investors and management teams is to ensure that the nascent business has access to the right expertise at the appropriate time.

development plan – what are the studies you are going to have to do preclinically? What are your clinical plans? How many drugs fail because they don't get the dose right? Because they didn't have a great clinical plan to get the endpoint for approval?" questioned United Neuroscience's Hu.

"There is the raw drive to get the idea, then there is the task of translating it into a drug and then there is the executive decision of assessing which

those big ideas that is hard to get your head around. We actually studied the company for almost two years before we invested. We took all that work that he had done and sent it to Stanford where we replicated all of the clinical work, including a lot of the preclinical work, to validate the model. And while we were figuring out whether it was something we wanted to invest in we started surrounding the company with key opinion leaders and experts in the area of pain – some of whom eventually became part of the management team," noted Podlesak.

The challenge is how investors convince the scientists with great ideas that they may not be the right people to advance a program. "Our job is to make sure that it is something worthwhile. We then have to put together a team that can grow cost effectively and develop the compound into something that you can submit an IND and take it into the clinic and do all the studies," added Sanderling's McNeil.

DALCOR was created in such a way. In 2012 he had discussions with investigators at the Montreal Heart Institute led by Jean-Claude Tardif and Marie Pierre Dubé who had made an interesting observation about dalcetrapib, a CETP inhibitor that was being developed by Roche and Japan Tobacco. The companies had conducted a large, double blind cardiovascular study, dal-Outcomes, randomized over 15,000 patients already taking statins for cholesterol control but the study results were equivocal. While the drug was well tolerated, there was no significant reduction in CV events in the dalcetrapib group, and the dalcetrapib development program was terminated.

The Montreal team, however, found a significant association between the effects of dalcetrapib in altering CV events and the allelic polymorphism at the rs1967309 location in the adenylate cyclase type 9 (ADCY9) gene. When comparing dalcetrapib with placebo, patients with an AA polymorphism had a 39% decline in cardiovascular events, while GG had a 27% increase, and GA



"It is about marrying promising technology with great talent. One doesn't do well long term without the other. Great technology without the right management team probably won't get very far or funded or succeed. Conversely, great talent without really valuable technology tends not to go far either," noted Domain's Podlesak.

For entrepreneurs, CEOs and companies, he added, it is about accessing the right experience. "In some cases it is the formation of the early management, in others its augmented by great key opinion leaders."

Indeed, scientific founders may have great ideas and science but that is different from developing a drug. "That requires a much more comprehensive

programs to pursue based on unmet clinical need and/or good payer coverage. That takes different skills and why it is a team effort. I don't know a single person who can do all of that," she added.

Often that means having different people at the helm as the company evolves from research idea to discovery program, development plans and finally product delivery either to a pharma partner or to patients directly. That decision is often made by experienced executives in venture capital syndicated.

"Before Adennyx was created I met with the French founder in Paris and he had this idea about how we can prevent chronic pain and it was one of

had a neutral effect, in the cohort of dal-Outcomes patients.

“They described what they had seen having conducted a GWAS on dalcetrapib. It was a compelling argument right there so I said OK here is \$50M let’s go. We put together a \$150M round because we were going to go directly into a Phase III study. We know now we have, retrospectively, a gene – ADCY9 – and we know prospectively that it reduces atherosclerosis the same amount as statins. The scientist stayed in his lab and the rest of us went out and figured how to put together all you need to have: a board, an executive steering committee to run a 5,000 patient trial,” he noted.

DALCOR in-licensed dalcetrapib from Roche in 2015 and raised \$50M in a series round in the same year and \$100M in a series B round in 2016. The company is conducting a double-blind, randomized, placebo-controlled, multicenter Phase III clinical trial that will enroll 5,000 patients recently hospitalized with ACS and who express the AA genotype at variant rs1967309 in the ADCY9 gene, determined by an investigational companion diagnostic test developed by Roche Molecular Systems (RMS). The primary endpoint of the study, which started in 2016, is the time to first occurrence of any component of the composite of cardiovascular death, myocardial infarction and stroke. The trial will be conducted at 880 sites in 33 countries.

Advice offered by both McNeil and Podlesak to biotech boards is find the right marriage of both science and talent. “One of the great things about our space is it is so rich in talent that you don’t always have to have it residing inside the company. In fact, a lot of companies that grow up very nicely start out using the right external resource to help them navigate their path forwards,” added Podlesak.

ALIGNING WITH KEY EXTERNAL STAKEHOLDERS

One key group that biotechs need to engage with as they pursue the development path to market and even sustainability are the regulators. And

the advice is to get in early as they are more receptive and helpful than some may think.

“It wasn’t too long ago that we were talking about how tough it was to work with the FDA – and why isn’t anything getting out? You are now seeing guidance and breakthrough designations and different approaches that make it easier to develop drugs that both the FDA and companies think have the potential to be really advantaged treatments,” noted Domain’s Podlesak.

Indeed, the metrics bear this out. In recent years there has been a significant increase in the number of new chemical entities being approved year on year by the FDA and other regulatory bodies. In 2017, the FDA approved 46 new molecular entities, while the European Medicines Agency gave the green light to 28 new products containing 29 new active substances.

Regulators are taking a more pragmatic view around approvals to get to help patients as quickly as possible and biotechs are being encouraged to open communication as early as possible.

“The first thing start-ups should do is develop a very firm understanding of the indication they are addressing and the status of existing treatments. Second, they have to meet with regulators to get their perspective on what they find acceptable in terms of different development approaches. I would argue that we have never been in a better time with respect to the transition and evolution of the way that the FDA and other regulators are actually viewing highly innovative therapies,” added Athersys’ Van Bokkelen.

During the J.P. Morgan meeting, the Alliance for Regenerative Medicine revealed in its state of the industry report some of the dramatic progress taking place. “These are all reflections of an evolution in thinking at the FDA, EMA, Japan’s MHW and other regulatory bodies that has been occurring in the past four to five years. That has been underpinned by the efforts of a lot of stakeholders including advocacy groups such as ARM and BIO that have met with FDA leadership in Washington DC,” noted Van Bokkelen. “I think the

regulatory environment has changed dramatically. Under Dr Gottlieb’s leadership it is going to continue to evolve in very important and effective ways.”

Companies should see the regulators as potential allies and not antagonists. “We have got to stop punishing the FDA every time something bad happens, making the FDA the scapegoat when the unexpected happens. It is not productive – it may be good political theatre but it does not help new medicines get developed,” he added.

The interaction with regulators should be both as early as possible and open-minded. “You know the one thing the FDA and other regulators hate most? It is coming to them with the mentality that you want to cut as many corners as possible, spend less, and take less time to do what needs to be done. They hate that,” he cautioned.

“If you approach them with a rational intelligent model then the FDA will work with you in a very productive way. I think more and more companies are learning that there is a right way to do it and a wrong way to do it – come at them with a pitchfork or an adversarial mindset – that you want to cut as many corners as fast as you can – then they are going to resist,” he warned.

Interestingly, there was a consensus among the panellists that biotechs might find it easier to work pragmatically with the regulators than the multinationals. Progress with CAR-T has been achieved without the need for enormous studies being conducted. Regulators have been willing to draw on a lot of relevant data from real clinical experience.

TAPPING REAL WORLD DATA & EVIDENCE

One of the ways in which the FDA has demonstrated its willingness to being open-minded is the conversations it is having around how companies might utilize real world data and evidence. The challenge, however, is that real world data can mean different things to different people.

“The FDA expects you to be very clear about the type of real world data you are going to utilize. How did you

obtain it? How are you prospectively going to use it and gather trial data in the context of enabling them to make an objective decision about whether your therapy is safe and effective. Unfortunately, a lot of people talk about real world data and they don't know what that are talking about because they have never had to make the case and present it to regulators and explain to them how they are going to use it," argued Van Bokkelen.

While it sounds like a relatively simple thing -- accessing the data in electronic medical records or health records from clinics around the world -- the reality is that data are not collected or created in a way that is universally acknowledged. But there are ways that companies can use real world evidence, benchmarked against standard of care, that can move the needle and speed things up.

Real world data and evidence, however, are mostly collated to inform pricing and reimbursement discussions. "I have a commercial background and have for more than a decade used real world outcomes sourced through the many payers to leverage for better contracts. That is the traditional use -- use in clinical studies has not really changed. When you go to the FDA now they still want the placebo-controlled demonstration and clear differentiation and safety and efficacy," he added.

That is a view that Vericel's Orlando concurs with. "If you ask me where I really want to see RWE is for getting expanded use and expanded indications. Why would we not all pursue the real clinical data to support the payers -- its expensive for payers, physicians and everybody loses. Instead of us pursuing that next clinical study, if we were allowed to use real world data we would be able to expand that authorization of products appropriately and reduce costs in general," he noted.

With his commercial background Orlando has been using real world outcomes to leverage for better contracts with payers and while acknowledging that the FDA has been very helpful to Vericel with its pediatric indication for Epicel, Orlando believes that the FDA's

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appetite to allow real world data to expand labels is still not in place.

"Use in clinical studies has not really changed. When you go to the FDA now they still want the placebo-controlled demonstration and clear differentiation and safety and efficacy. They want you to go back and make huge investment and do placebo-controlled trials. Some of the markets are a bit smaller so it is not realistic for small companies to do that," he added.

The FDA still has a very strong orientation towards wanting data from double blind randomized placebo-controlled studies. Companies can

augment that with real world clinical experience and patient testimonials but the regulators are still reluctant to make arbitrary decisions about only one treatment group, that by definition is open label, and compare that to ad hoc datasets that companies may have constructed without giving them full transparency about where the data came from or the limitations associated with it. A position that the roundtable participants recognised is perfectly rational.

RECOGNISING THE VALUE PROPOSITION

Where real world data and evidence is gaining traction is in the pricing and reimbursement arena, so companies, irrespective of their maturity or the development stage of their programs need to lay the foundations for payer discussions. That is something VCs consider when evaluating potential investments.

"I think that it has to be both early and through the entire process -- although the way through to post-approval -- that the ability to validate these around empirical data becomes critically important because it helps fine tune and refine the decision making. If a drug can get approved in Europe but it can't be sold at a price where it has to compete favourably with generic drugs -- even if it is better -- it will probably never end up being a drug there," warned Domain's Podlesak.

To be investable, companies need to understand the therapeutic area, its market dynamics and the competitive environment. Not only today but what will it look like at the time of approval for the decade plus post-approval. Consequently, managements need to understand how payers will perceive value throughout the entire drug development, approval and post-marketing process.

"It has now become more a part of the investment thesis. So when we see things that are really well presented -- it is not about providing \$10M to run a clinical study but is \$20M needed to show how it would be attractive to pharma and payers in the therapeutic area," he added.

PURSuing GROWTH WITHOUT OVERREACHING

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

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

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



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.

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

with relevant experience.

“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

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 inhibitor approved for the treatment of metastatic colorectal cancer, and Kyprolis (carfilzomib), the proteasome inhibiting multiple myeloma drug. 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 its 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 overreaching. 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 us. 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 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 an-

tibody 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.



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