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"In this boundaryless organization, we can ... take people with skillsets in one area and apply them correctly to the ... problems in other areas."

Dr. Michael Thien, **SVP of Global Science, Technology and Commercialization**

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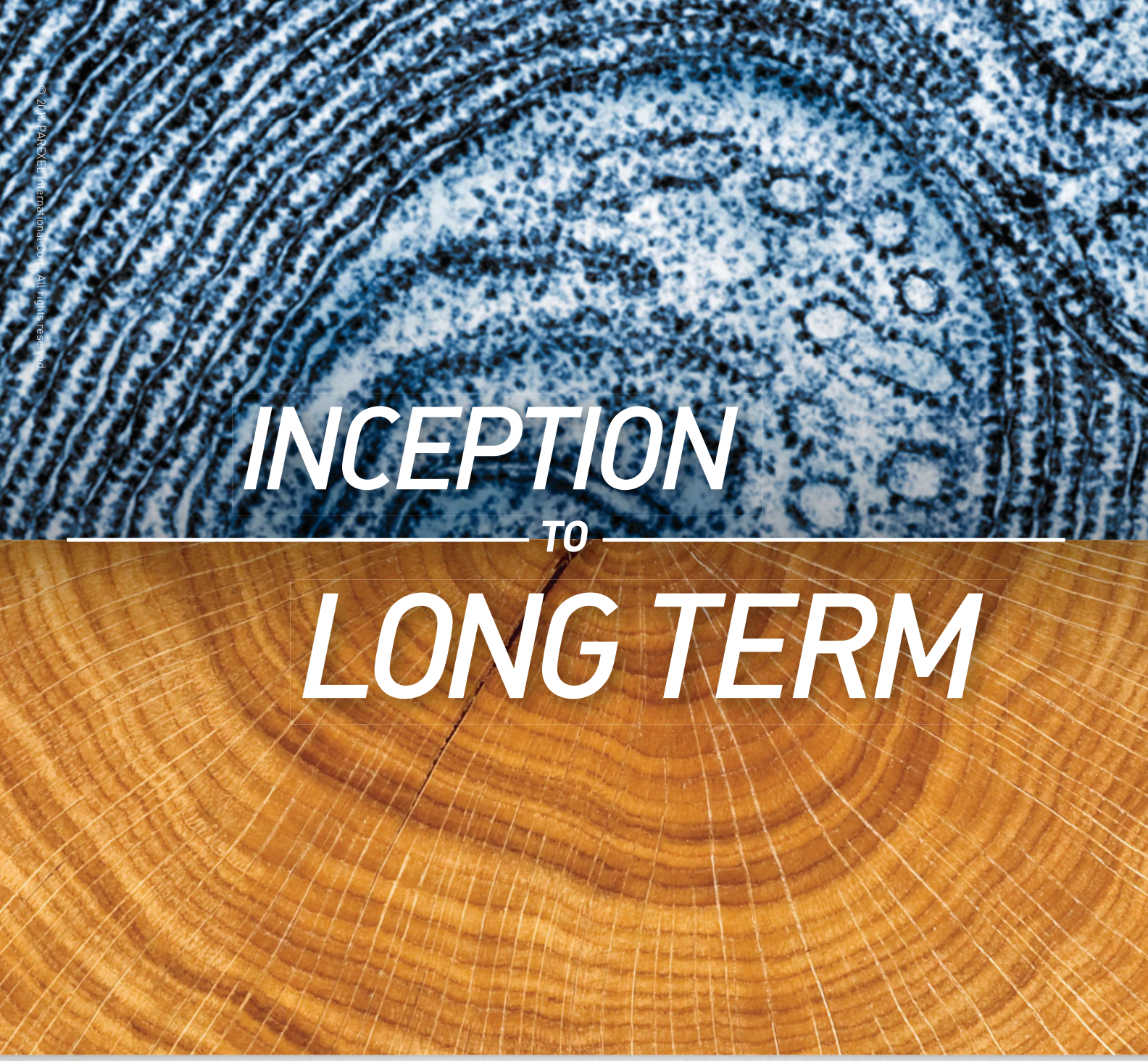

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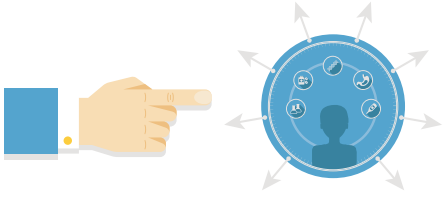

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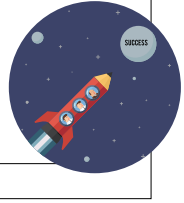

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Will Missing Out On Personalized Medicine Be Your Legacy?

ROB WRIGHT Chief Editor

"Not to mince words, Mr. Epstein, but we don't like your boys' sound." This phrase uttered by Decca Records talent evaluation executive Dick Rowe left him a lasting legacy — the man who *did not* sign the Beatles. There are numerous examples of even the most successful of executives failing to recognize business opportunities placed before them. In Rowe's case, this gaffe led to him being known not as the man who signed The Rolling Stones (which he did), but instead the one who *spectacularly* missed an *incredible* opportunity. Will personalized medicine (PM) be a lasting legacy of opportunity lost for life sciences industry executives? Time will tell. But, if you would rather position yourself as that visionary life science executive who not only recognized the opportunity PM promises, but captured it, start by gaining a deep understanding of what PM really is. And perhaps I can help with that understanding.

In October I attended a PM dinner discussion hosted by the *National Journal Group* (a division of the Atlantic Media Company) and underwritten by AstraZeneca. Prior to attending, I sought PM insights from a variety of stakeholders to help me prepare for the dinner. (Those insights are included in my blog, *Can Personalized Medicine Ever Truly Become A Reality?*) The dinner discussion provided additional knowledge from an impressive group of PM stakeholders (see page 31). However, as I was soon to find out, my PM education — and enlightenment — was about to continue.

Two days after returning from the PM event, I was offered the opportunity to preview a not-yet-published book on the subject, *The Personalized Medicine Revolution: How Diagnosing and Treating Disease Are About to Change Forever*, by Pieter Cullis, Ph.D., professor of biochemistry and molecular biology at the University of British Columbia. Cullis provides clarity on the links between the various components constituting PM. We will soon be able to create a fairly complete digital version of ourselves that includes so much more information beyond the genome (e.g., metabolome, microbiome, pharmacogenomics, proteome), and it will be complemented by other information (e.g., vital signs), so that, for the first time ever, we will have access to a comprehensive "operator's manual" for our unique bodies. The impact of this information on how we live will be greater than any other technological advance *ever* experienced.

To avoid a PM legacy akin to Rowe's and the Beatles, seek to understand components beyond your area of expertise so you will have a clearer picture of how the disciplines fit together. But more importantly, seek to find the technologies and companies that are finding the answers to PM questions you think unanswerable, or worse, have not even thought to ask (e.g., How or where are we going to store all of this data?). In other words, find the PM *enablers*, for they hold the keys to pharma realizing a PM legacy worth remembering. L

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Q What game-changing technology/technique is not being utilized within the clinical space, and what can be done to change this?

A THERE ARE THREE THAT COME TO MIND: 1. Business intelligence tools geared at giving insight to key performance indicators and compliance; **2.** Central statistical monitoring (CSM) software used to target sites that can be identified "at risk" (By identifying discrepancies early we can implement timely corrective actions to ensure the quality and integrity of the data. Industry groups need to collaborate on testing these systems to gain insight into the pros and cons of these systems.); **3.** Electronic monitoring devices to capture subject information (e.g., vital signs, ECGs) wirelessly and seamlessly to the vendor and sponsor EDC systems. This technology, to some extent, can reduce or eliminate redundant data entry and reconciliation time while also improving quality and timeliness of data. In addition, it would make centralized remote monitoring a reality, reducing costs and improving detection of adverse events.

DR. MITCHELL KATZ
Dr. Mitchell Katz has 26 years' experience in the pharmaceutical and biotech industries, including preclinical research, pharmaceutical operations, and regulatory affairs. In his position at Purdue Pharma L.P., he is the executive director of medical research operations.

Q What's the most valuable insight gained from working with local government officials during expansion projects, and how would you suggest to prepare for these types of interactions?

A I LEARNED THAT THERE ARE AS MANY INTERESTS AT PLAY as there are government agencies and officials. You shouldn't expect that it is a simple bilateral interaction. As with most interactions with government officials, you need to be familiar with the remit and perspective of the various agencies and political bodies. There are a lot of local nuances in how these groups interact with businesses and each other, and you should spend time getting good intelligence from people who have experience in dealing with them on projects of similar scope. It helps to understand the constituencies and "hot" issues for the various groups so that when negotiating on particular points you know who are the likely allies and who are likely to be in opposition.

WILLIAM CIAMBRONE
William Ciambrone is the executive VP of global technical operations at Shire. He has more than 20 years of experience in the pharmaceutical, device, and biopharmaceutical industry.

Q What supply chain practices need to be updated, and how would you do so?

A SUPPLY CHAINS ARE TYPICALLY MODELED around the core processes of plan, source, make, and deliver. Upstream in the supply chain are forecasting processes that have inherent variability and lead to (amongst other things) high inventory levels, wrong product mix, and product shortages. More progressive companies see their supply chains as an integrated, collaborative, end-to-end process that delivers a competitive advantage and enhances total value. Shifting from being a reactive, forecast-driven supply chain to a demand-sensing one allows for better alignment between functions. A pull-replenishment model receives demand signals from downstream in the supply chain, helping to reduce inventory levels while providing greater total value and service. All of this drives an enhanced customer experience.

ANU HANS
Anu Hans is the VP and chief procurement officer, enterprise supply chain at Johnson & Johnson. She also serves as a board member for the Drug, Chemical, and Associated Technology Association (DCAT).

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New Congress: Bipartisan Opportunity To Spur Innovation

JOHN McMANUS The McManus Group

While the concluding 113th Congress will be remembered more for ideological warfare than notable healthcare policy achievements, the upcoming 114th Congress holds promise for advancing several bipartisan bills that can have a material impact in promoting innovation to address unmet medical needs.

Energy & Commerce Committee Chairman Fred Upton (R-MI) along with Rep. Diana DeGette (D-CO) have spearheaded a bipartisan effort known as the *21st Century Cures Initiative*. This workstream has included eight hearings and four roundtables on Capitol Hill and over a dozen more across the country and is meant to solicit ideas expediting the lengthy and costly process of bringing drugs and devices from discovery to treatment delivery as well as retrofitting important arenas like health information technology. The committee is expected to unveil a comprehensive package early next year, but the dialogue has already resulted in the production of concrete proposals and legislation from some unusual quarters.

For example, the National Health Council (NHC) — a coalition of over 100 patient advocacy groups, provider associations, nonprofit groups, and industry, focused on assisting patients with chronic health problems — has led the charge in advocating for legislation that they believe will spur research and development on medicines for unmet medical needs. The MODDERN (Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network) Cures Act (H.R. 3616) would address two barriers to product development: 1) complete lack of patent protection for dormant products (those discovered but never brought to market) and 2) predictable post-approval patent protection.

In testimony to the Energy & Commerce Committee this summer, Marc Boutin of the NHC explained that, "A drug cannot be patented if it was previously disclosed to the public; no exception is made for when the disclosed drug has not yet been tested in clinical trials and thus has not been approved by the FDA." Thus, a company has no incentive to undertake costly clinical trials of a dormant product because it would have no effective intellectual property protection upon FDA approval.

Secondly, Boutin explained, "The unfortunate reality is that manufacturers stop developing a drug when they believe that its patent protection will not extend long enough after it enters the market and allows the company to recoup the investment. Because the drug manufacturers must apply for patents early in the development process, there can be little or no patent life left when the drug finally enters the market, even with patent extensions granted under Hatch-Waxman … . This uncertainty discourages companies from pursuing medicines with long development time lines in favor of those with shorter development time lines."

The MODDERN Cures Act is championed by Rep. Leonard Lance (R-NJ) and a whopping 78 cosponsors equally divided by both political parties. It would address the aforementioned challenges by permitting companies to apply for a fixed 15-year period of combined data package and patent protection from date of NDA (new drug application)/BLA (biologic license application) approval for qualifying medicines that the FDA designates as being investigated for an unmet medical need. At the end of the 15-year period, generic and biosimilar drugs are assured immediate abbreviated approval where the sponsor would waive the ability to litigate patents that would delay market entry beyond the 15-year protection period.

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"Can such legislative incentives spur innovation? History shows that the emphatic answer is 'Yes'!"

The creation of an aligned period of patent and data protection commencing upon FDA approval provides incentives to pursue R&D for products that require longer development time lines — often those that treat a disease with no existing treatments, a drug with a new mechanism of action, or drugs to treat chronic diseases. It also eliminates gaming between innovator and generic companies that mutually benefit from delayed market entry of a generic drug, but leaves patients picking up the higher costs during that period. The bipartisan breadth of support as well as the patient groups' leadership in spearheading the legislation's advocacy make this a viable product that could move toward enactment.

ADDRESSING THE ANTIBIOTIC PIPELINE CRISIS

In the case of antibiotics, spurring innovation has had more to do with addressing market failures than securing sufficient intellectual property protection. But here, too, legislative progress has been made to address the immediate public health concern that sparked Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, to proclaim that, "We are facing a huge crisis worldwide not having an antibiotics pipeline."

Novel antimicrobial products, especially those targeting multidrug-resistant Gram-positive and Gram-negative bacteria, face significant commercialization barriers that run counter to typical pharmaceutical market dynamics, including:

- administration in acute care settings, where reimbursement is largely controlled by predetermined payment bundles with a relatively small pharmaceutical cost component
- use as short (6-10 days) and/or episodic courses
- reserved for third/fourth-line use to control resistance, used in conjunction with stewardship policies.

Without a steady development of new products that keep pace with pathogens increasingly resistant to existing therapies, patients will face a world without effective treatments for even commonplace infections. Leaders in infectious disease, including the Infectious Disease Society of America, Antimicrobial Innovation Alliance, and the President's Council of Advisors on Science and Technology, encourage greater market-based reimbursement for these innovative products.

In response, representatives from Illinois on both sides of the aisle — Peter Roskam and Danny Davis — recently introduced the DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms) Act (HR 4187) with strong bipartisan support, to better incent the development and commercialization of antibiotics that address unmet medical needs. Medicare's current bundled payment does not adequately reimburse antibiotic drugs and gives hospitals little incentive to utilize innovative antibiotics. The bill would provide more appropriate payments to hospitals when they treat dangerous pathogens with more expensive and novel antimicrobials.

Can such legislative incentives spur innovation? History shows that the emphatic answer is "Yes"!

In 1983, Congress passed the Orphan Drug Act, which was the first step toward creating economic incentives for orphan drug development by awarding grants, tax credits, and seven-year market exclusivity for orphan-designated products. During the decade before the Orphan Drug Act was signed into law, only 10 treatments were developed for rare diseases, but since passage, 450 orphan drugs have been approved by the FDA and over 3,000 orphan products are in development.

In addition to benefiting from the development of new medicines, the American public can gain from substantially lower drug costs when the intellectual property protection period expires. The Hatch-Waxman Act, a great example of bipartisan compromise which recently celebrated its 30th birthday, created the modern generic drug industry. The Government Accountability Office has found that between 1999 and 2010 generic drug substitution achieved more than *$1.2 trillion* in cost savings for American consumers.

In assessing the positive impact of 30 years of the Hatch-Waxman Act, Senator Orrin Hatch (R-UT) expressed a hope that this success might "inspire(s) ideas on how to improve the effects of the Act through additional legislation."

The incoming 114th Congress can certainly relitigate Obamacare. But a more productive endeavor would be to move bipartisan legislation such as the MODDERN Cures Act and the DISARM Act, which can actually make a material difference for patients waiting for a cure.

JOHN MCMANUS is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University.

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ORGANEXT

A European enterprise, started by pharma veterans, champions a product for age-related muscle wasting – an overlooked but critical medical need.

WAYNE KOBERSTEIN Executive Editor

SNAPSHOT

OrgaNext is developing the low-dose, short-term Recovery Booster therapy, a combination of nandrolone decanoate and Vitamin D3 (NDD), for age-related muscle-wasting conditions with the initial indication of recovery after hip fracture. The therapy's objective is to reverse the catabolic state in muscle wasting, activate the endogenous muscle stem cells, and improve functional outcomes. It consists of a weekly injection for a maximum of six months. The next milestones will be pivotal Phase 2b and Phase 3 studies, as well as scaling up for commercial-size batches of the product.

WHAT'S AT STAKE

One night, when I was a very young man living in a third-floor flat in San Francisco, I answered the doorbell, and a maid grabbed me and led me into the landlady's first-floor apartment, where the 91-year-old woman lay on the floor next to her bed with a broken hip. Holding my hand while the maid called an ambulance, the woman was alternately lucid and incoherent. One moment she spoke to me as a stranger, showing her fear and certain knowledge that she was done for; the next, I was her son, her grandfather, her father, comforting a frightened little girl. I stayed with her until the ambulance arrived and carried her away forever.

Back then, a broken hip in the elderly was a death sentence, and this woman knew it. Guess what? The common mishap of falling and breaking a hip still carries a stiff, though no longer fatal penalty for most seniors. Care has improved, but not nearly enough. "Half of women older than 65 years who break a hip in a fall never walk again," says Marjanne Prins, the founder and CEO of the Dutch company OrgaNext.

That is what's at stake in OrgaNext's quest to go beyond better care for patients who have broken bones or otherwise injured themselves in accidents where muscle wasting and weakness may impede recovery or even increase injury risk. After Schering Plough bought Organon in 2007, Prins — a nutritionist long interested in the aging health issues, specifically muscle wasting —assembled a small team of fellow Organon alumni to form OrgaNext, which ultimately focused on treating the condition in elderly patients with the combination of a critical vitamin for muscles and an existing anabolic steroid labeled for anemia in severe renal insufficiency.

The company steered away from nonsteroidal compounds such as SARMS (selective androgen receptor modulators) because they fell short of OrgaNext's goals for functional improvement and posed safety concerns in the elderly, Prins says. She cites clinical studies showing treatment with nandrolone decanoate resulted in a significant increase in muscle mass and muscle strength associated with functional improvement. "Nandrolone, a naturally occurring steroid — albeit in very, very low quantities — with a well-documented safety profile in older patients, is known to reverse the catabolic state." She says the company incorporated vitamin D in the product because older patients at risk typically have low vitamin D levels, which she says contributes to the risk of falls, muscle weakness, loss of muscle mass, and hip fracture.

It has been a somewhat hard slog raising money for the company, according to Prins, because of what she sees as a large gap between the perceptions of investors and medical experts. "We found both the EMA (European Medicines Agency) and the FDA very constructive, and geriatric, orthopedic, and endocrinology experts (on vitamin D and androgens) all immediately grasping the concept and eager to use the Recovery Booster therapy. But we found the attitude of the European VC community more wait-and-see." Now that OrgaNext is confident it has confirmed the product's scientific feasibility and commercial attractiveness, it is preparing a Series A financing. Many, like me, know what could be at stake in the company's success.

MARJANNE PRINS
Founder and CEO

Vital Statistics

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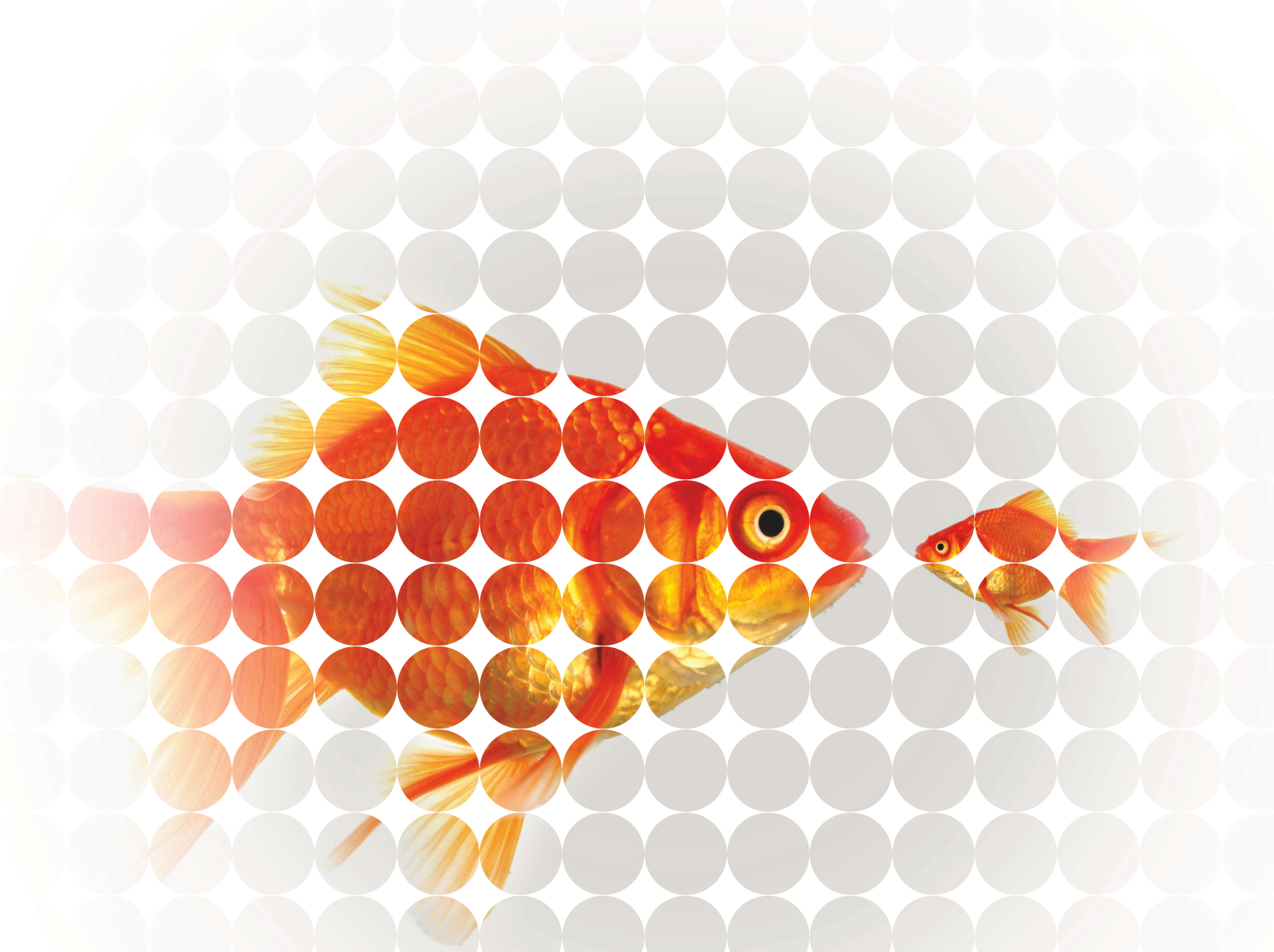

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A Recap On 2014 Outsourcing Trends And What To Expect In 2015

2014 was an exciting year in outsourcing. Several high profile mergers and acquisitions in both the CRO and CMO world will mean some familiar names will go through big changes — Huntingdon acquired Harlan, and PRA acquired RPS in the CRO world; Patheon acquired both DSM and Gallus Biopharma, and AMRI acquired Cedarburg and OsoBio in the CMO world.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

Consolidation is nothing new to the industry, but as CROs and CMOs move toward functioning as strategic partners, is consolidation best for the relationship? Sure, it enables a more end-to-end service offering from a single provider, but the advantages of the "one-stop-shop" sometimes come with a host of disadvantages, too. Nice Insight data has shown how M&A activity can impact buyers' perception of CRO/CMO performance postmerger, so it will be interesting to see whether these businesses are able to fully integrate the company while maintaining the strengths of its acquisitions.

A continued increase in expenditure compared to the prior two years was another exciting factor in 2014 outsourcing. This rise in spending coincided with a decrease in the prioritization of affordability when selecting an outsourcing partner. Biopharma companies boosting their budgets and the number of services they entrust to CROs and CMOs follows a new pattern in outsourcing — engaging contract businesses for access to scientific expertise that is not possessed in-house. Shifting priorities in partner selection and rethinking the big picture regarding the long-term strategy for time and cost savings show that the dynamic of these relationships is still evolving toward a true partnership.

Nice Insight research data shows that interest levels in strategic partnerships vary by the type of business. Not surprisingly, emerging biotechs showed the greatest interest in forming partnerships with three-quarters of emerging biotech respondents expressing interest. Biotechs also showed strong interest, with more than half (53 percent) stating their company is interested in forming long-term, win-win relationships with CROs/CMOs. Biotechs are likely interested in forming partnerships for different reasons than pharma companies, as these businesses have limited in-house staff, a more focused pipeline, and are often cost-driven. Biotechs may also lack internal expertise and seek specific skillsets through contract partners.

Pharma companies showed more indifference to forming new strategic partnerships, with a near-even split between the percentage who are interested and those who are not interested. This tepid interest could be influenced by the high number of

> *"Pharma companies showed more indifference to forming new strategic partnerships."*

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FIGURE 1 Rank of Industry Drivers

	2011 - 2012	2012 - 2013	2013 - 2014
Quality	1	1	1
Reliability	2	2	2
Affordability	3	4	5
Productivity	4	5	4
Regulatory	5	3	3

FIGURE 2 Annual Outsourcing Expenditure (%)

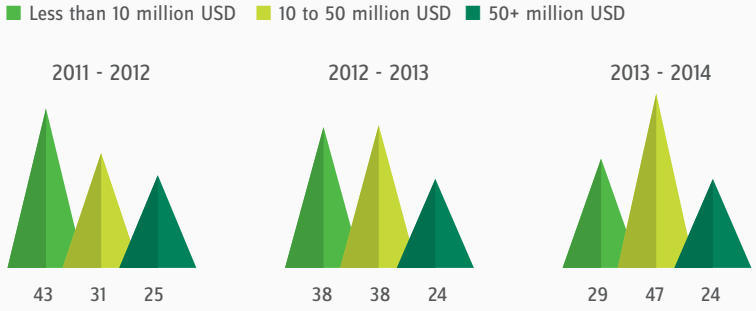
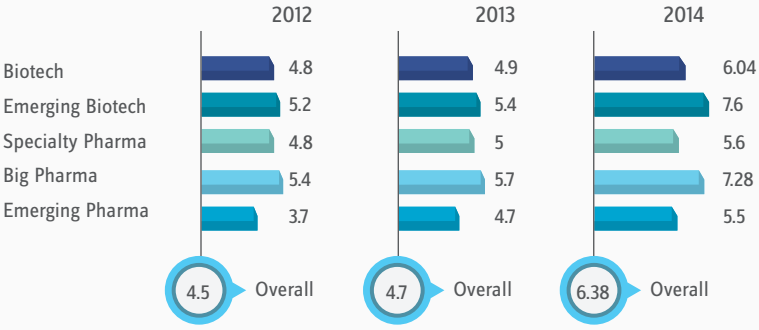


FIGURE 3 Average Number of Services Outsourced by Company Type



Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2013-2014 report includes responses from 2,337 participants. The survey comprises of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 100+ CMOs and top 50+ CROs servicing the drug development cycle. Five levels of awareness from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

existing partnerships among pharma companies, considering these respondents noted they are currently allocating a larger portion of work to strategic partners than to biotechs. It may also be influenced by the corporate culture at long-established pharma companies where there is a significant amount of expertise available in-house, a standard set of internal procedures, and a more rigid structure for a contract business to fit into.

The results from Nice Insight's 2015 Outsourcing survey are currently being tabulated and analyzed to identify any behavioral changes to the way buyers engage contract suppliers, as well as how these companies are perceived by the industry they serve. The 2015 data will include industry feedback on nearly 200 companies and 44 services.

N. WALKER

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, or Kate Hammeke, director of marketing intelligence, at Nice Insight by sending an email to nigel@thatsnice.com or kate.h@thatsnice.com.

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Biomanufacturing Industry Not Providing Employees
The Tools To Succeed

ERIC LANGER
President and Managing Partner
BioPlan Associates, Inc.

Biopharmaceutical manufacturing is almost always viewed as a technical discipline. But the industry is surprisingly dependent on the creativity of people who stoke its energy and direction. Indeed, as with many scientific sectors, the effectiveness of the bioprocessing industry is very much reliant on the hiring, training, and retention of high-quality staff. But with all the focus on new technologies and systems, it seems those very employees may be getting the short end of the stick.

IN-DEPTH TRAINING IS DECLINING

There's a relentless push for efficiency in the biopharma industry, which requires companies to constantly reinvent leaner versions of themselves. Sometimes this reinventing can cut across several areas — and job training may be one of them.

As part of our *11th Annual Report and Survey of Biopharmaceutical Manufacturers*, in which we surveyed 238 qualified biomanufacturers from around the world, we asked respondents how much training their organization provides to new staff or manufacturing employees.

We found that the majority of respondents (61 percent) provide 1 to 10 days of training, with this fairly evenly split between those providing 1 to 5 days (29 percent) and 6 to 10 days (30 percent). Although just 2 percent of companies provide less than a single day, in-depth training of more than 20 days is offered only by about one-quarter of respondents.

Surprisingly, just during the past five years, we have seen a marked decrease in the percentage of respondents who offer in-depth training. Back in 2009 and earlier, employees were receiving more than 20 staff days of training per year. Now, new hires are receiving somewhere between 6 and 10 days of training. That's essentially a half-day per month. One conclusion is that the industry is now hiring from a larger pool of pretrained operators and managers. But to the contrary, the hiring data from our study indicates that the pool of eligible, trained employees is actually shrinking.

So the issue is whether a few hours of training per month is sufficient to ensure high-level performance and productivity from new staff.

IS THIS CAUSE FOR CONCERN?

The difference between university education and training in bioprocessing is the direct applicability of that education or training. Certainly in commercial manufacturing, the need for trained, experienced bioprocessing operators has been growing. This expertise has traditionally been learned while on the job, often taking years to reach the desired level of expertise. The drop in training days for new hires is a problem area in need of addressing to assure availability of future, skilled operators.

However, there are several mitigating factors. The decline in training days may be the result of budget cuts, but might also reflect the evolution of standardized and simplified manufacturing processes. In addition, many companies and suppliers are developing more-effective online training programs and webinars. These tend to be cost-effective and time-efficient ways to deliver training on highly targeted topics. Even YouTube videos are now being offered to provide specific unit-operations training.

Separately, many governments — particularly those at the state level — are now finding it beneficial to have local universities and community colleges offer industry-targeted bioprocessing training at all levels. These programs provide a larger pool of trained workers which, in turn, improve the attraction of biotechnology companies to their areas. As a result, there are a host of bioprocessing training programs being initiated, funded, and managed by state-run or other taxpayer-supported programs.

WHO'S INVOLVED IN TRAINING

Educational efforts also include industry-academic partnerships such as internships, apprenticeships, and industry-oriented, collaboratively developed training and certification programs. State and local educational institutions also may be offering training for new hires and current workers, with these programs directed at providing industry-needed expertise rather than the usual academic/research orientation.

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Moreover, many college- and university-based programs are providing industry-oriented certification courses rather than purely academic programs. In other words, they are beginning to teach biotechnology — ultimately an industrial and production-oriented activity — rather than molecular biology or other disciplines that have a bias towards research rather than product development and manufacture. As a result, declines in the number of training days may actually be a reflection of improvements in the workforce's education, such that the industry is finding there is less training needed.

Efforts by some states such as North Carolina to improve the industrial-hiring readiness of the workforce are often specifically targeted at supporting the local biotechnology industry and may be paying off. The Johns Hopkins University in Maryland has been offering its M.S. in Biotechnology for more than 15 years and provides basic, applied, and lab science, with an industry focus. The Zurich University for Applied Science (ZHAW) in Switzerland offers continuing education that is both scientifically and practice-oriented.

Additionally, practical hands-on training for biotechnology and bioprocessing is no longer college-based; many high schools (particularly in biotechnology-intensive regions) are starting to offer students lab and other hands-on training and even local company, cooperative, and apprentice programs.

GOOD BIOPROCESSING HIRES HARD TO FIND

While these are all encouraging signs, our report reveals that these efforts have yet to reduce the difficulties of hiring process-development staff. When we asked industry participants in our study about the positions most difficult to fill, they were most likely to cite:

- process-development staff, upstream (42 percent)
- process-development staff, downstream (35 percent)
- process engineers (27 percent).

Compared to last year, more respondents are finding it more difficult to hire downstream process development staff and process engineers. Over the past few years the problems appear to be gradually worsening.

The pain in hiring is even more acute in Western Europe:

- process development staff, upstream (53 percent of Western European respondents citing difficulties versus 32 percent in the U.S.)
- process development staff, downstream (47 percent in Western Europe; 29 percent in the U.S.).

Differences between the U.S. and Western Europe may reflect the varying stages of development in different regions. For example, one can expect hiring status and patterns to differ when comparing a near-mature biotechnology cluster (with marketed products) to a region with many start-ups.

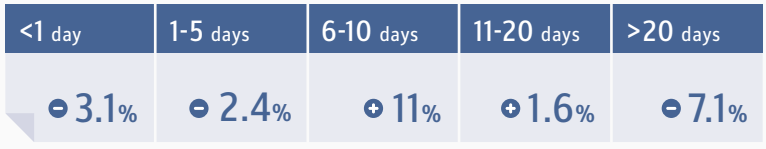
WHERE TO GO FROM HERE

Companies continue to make their processes more efficient, productive, and less expensive. This is often done by implementing new initiatives such as PAT (process analytical technology) and QbD (quality by design), which require specialized and experienced staff. As a result, it is not surprising to see the data continue to show that the most difficult positions to fill involve process improvement specialists for upstream and downstream processing. These employees appear to continue to be difficult to find, recruit, and retain.

Things are not likely to change soon. Skilled employees are produced primarily through internal training, a process that frequently leads to "poaching" from one company to another. Anecdotally, industry observers feel this cycle will only be broken by stronger relationships between employers and top universities that result in more qualified candidates being available who have some industry exposure. Encouragingly, those partnerships seem to be increasing.

In the end, whether or not training programs are conducted in-house by biopharmaceutical manufacturers or in educational institutions, it's important that these programs provide broad knowledge and ensure students are capable of problem-solving and independent thinking. As seen elsewhere in our report, the human side of things also must not be overlooked. Bioprocessing professionals require many "soft" and less-defined skills, such as the ability to communicate well, to write coherently, to learn to lead teams, and to work effectively in a team environment.

FIGURE 1 Change in Training Days: Percentage Point Difference, from 2009 to 2014



Source: 11th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2014, www.bioplanassociates.com/11th

Survey Methodology: The 2014 Eleventh Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 238 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also included over 173 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the world's major markets in the U.S. and Europe.

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MERCK – MAKING IT, NO BOUNDARIES | By W. Koberstein

DR. MICHAEL THIEN Senior Vice President of Global Science, Technology and Commercialization in the Merck Manufacturing Division

MERCK —
MAKING IT, NO BOUNDARIES

WAYNE KOBERSTEIN
Executive Editor

WHAT DOES IT MEAN TO "MAKE" A DRUG? Most people would think first of manufacturing — big facilities with huge tanks, pipes, and valves all strung together with other strange equipment, taking in raw materials on one end and spitting out capsules or tablets on the other. Such things exist; I've seen them! But I know whatever I saw in the production plant is itself the end link in the long chain of activities that contribute to making a drug.

From a small amount of the molecular entity compounded by the medicinal chemist, scientists and engineers must formulate an end product and plot a process pathway that will produce clinical and commercial quantities that satisfy a battery of requirements such as dissolution, stability, and purity. And beyond those basics, making the drug continues with fill and finishing, delivery forms, packaging, distribution, and a host of other compartmental tasks. If you can visualize that chain from beginning to end, you will have a picture of the functions headed by Dr. Michael Thien, senior vice president of Global Science, Technology and Commercialization in the Merck Manufacturing Division.

"My responsibilities have three aspects: product development for manufacturing, technical support for our in-line products, and the conceptualization, construction, and start-up of the company's capital assets — laboratories, manufacturing plants, and offices — overseeing about 1,500 people in support of $44 billion in annual revenue," Thien says. In other companies, and by traditional pharma ways, he would likely be describing his role in narrower terms, perhaps covering only one of the "aspects" rather than all three, and fewer product forms than the full set of therapeutic proteins, vaccines, and small molecules his responsibilities now include.

Thien's overarching purview has a unifying purpose. His primary task has been and is implementing a global program to restructure Merck's far-flung manufacturing technical operations as a "boundaryless" organization, where workers of all disciplines interact constantly in ways that quickly solve problems, while capturing the knowledge accumulated from all of the individual and collaborative work.

His own team works with all of the company's facilities and contractors around the world, confronting and diligently disassembling the physical, mental, and cultural barriers, or "boundaries," between them. If plans succeed for this relatively young organization launched in November 2013, Merck will be among a select few Big Pharmas to break free of their legacy systems and traditions and to embrace new technologies and operating methods. (See also the sidebar, "No Boundaries for New Technology.")

THE WAYS WE WERE

Thien describes the line of thinking company management took from operating the "old way" to the new way, with a global, "interconnected, interdependent" manufacturing organization uniting operations worldwide. "It had become abundantly clear we had been working in silos. The small molecule people worked on small molecules, the vaccine people worked on vaccines, therapeutic protein people worked on therapeutic proteins — you didn't mix or match." Management recognized, in some of the disciplines, people in different areas often shared the need for the same skillsets. Thien cites an example: Chemistry development, traditionally employed with small molecules, also applies to the new area of conjugate vaccines and antibodies. The next logical step was finding ways to encourage and optimize sharing of skills and knowledge among all three areas and hence, the idea of removing boundaries of all kinds between them.

NO BOUNDARIES FOR NEW TECHNOLOGY

Under Merck Manufacturing's new "boundaryless" structure, the company is beginning to move into more advanced manufacturing technologies and methods — and in a deliberate fashion. Dr. Michael Thien, senior vice president of Global Science, Technology and Commercialization (GSTC), says his area has created a "picture of our future state," compared it to the current state, and developed five "challenges" for the current year in categories that reflect his new organization:

NEW TECHNOLOGY ADOPTION. "We are looking at new technologies in every single area of what we do. We're looking at new types of biocatalysis in our drug substance area, continuous processing for our drug production, new platforms in vaccines and therapeutic proteins, single-use technology for formulation and filling, and so on. We have technical projects going on in each of those areas. That's our first big challenge."

RIGHT FIRST TIME (RFT) IN NEW PRODUCT LAUNCH. "100 percent right first time for all of our new-product introductions. We have a team working on implementing RFT activities for product validations across vaccines, therapeutic proteins, and small molecules."

CONTINUOUS IMPROVEMENT AND STABILIZATION. "We have a team totally focused on this for all of our in-line products." (See "Merck's Continuous Process Improvement," *Life Science Leader*, July 2014.)

BOUNDARY BUSTING. "Another team is working on boundarylessness itself, harmonizing processes, creating the open sourcing work, looking at how we can align all of this with career development opportunities, and so on."

PRIORITIZATION. "How do we come up with a prioritization and resourcing mechanism for this new organization? All of those challenges have come out of the creation of this new organization that covers all of Merck's major businesses and modalities."

The GSTC area has also laid down some principles for adoption of new tools and methods. "We want new product introductions without drama," Thien says. "We know that when you introduce new products and there are new processes, things may go wrong. But we want to make sure we have mitigated our risks and followed our timelines, so, when something does happen, it is not a dramatic disruption."

"In this boundaryless organization, we can, with much greater alacrity, take people with skillsets in one area and apply them correctly to the technical or scientific problems in other areas," Thien says. "Doing so allows us to get a much better picture of the science and engineering that underlies our processes and products and of the challenges we may face with a particular process or product."

Boundaries can consist of many elements, tangible and intangible. But they are all institutionalized in the form of an organization as it has evolved over a long time. As Thien describes it, the solution was to perform an evolutionary leap.

"We had to overcome the organizational boundaries, but they were largely overcome by putting the new organization together," he says. "We had to also overcome the business process issues. Vaccines did investigations differently than small molecules. We have now harmonized all that, taken those barriers out, so again, we can apply the right scientific expertise to the right work. And we have realized the creation of a boundaryless condition is, in itself, critical to accelerating the transition to a boundaryless state. We wanted people to be able to directly reach out to one another."

The scenario Thien describes as the "before" state will be familiar to most readers. "In the past, if you wanted to get help from somebody in the network, you had to go up to your boss, who went up to another level with your request, which then went back down and over into another area for consideration while you waited for the response."

To turn such crooked lines into straight ones, Merck created its own social media hub called the Virtual Technical Network (VTN), which can connect any member with any other, regardless of function or rank. "We set up about 25 online communities, so people can blog to any or all of them. If you belong to, say, the sterile processing community and have an issue in our sterile plant in France, you can just pop your query into that worldwide community, and anyone in the community can now respond to your email. Generally, we have found about 50 to 60 percent of the responders are people whom the questioner didn't know or had never met before. But now, here it is — you get an answer from anywhere in the world within 24 hours, and you have access to a hugely rich set of information to help you solve your problem."

Thien says one of the VTN's advantages is it encourages responses from people who not only have the requisite expertise but also the essential motivation and interest in addressing the issue at hand. "That discretionary effort along with their expertise makes a huge difference."

TOOLS OF THE TRADE

Beyond the structural barriers to instituting a "boundaryless" organization, Thien says, subtler walls presented the greatest hurdles. "We come across the personal biases of people in one area against those in other areas: 'They can't possibly have the right knowledge or expertise to help me with my problem.' We had worked hard to get rid of the organizational lines that prevented people from moving around and communicating. We had worked hard to harmonize the business processes. But to really eliminate all the boundaries, you have to change the culture."

Teaching people how to communicate their issues in the proper context, and to define or identify what kinds of expertise they needed to tap, helped in one way. Another solution was to increase the bandwidth — to broaden the access to embrace the full set of expertise areas that might apply. "In a boundaryless organization, I may have to ask the broader question to help me with my issue. I may not even know what I don't know. How can I appeal to the broader community? How can I move knowledge or technical processes or people to the work to get a better answer?"

The organization recently put up its own "open source" or, as Thien clarifies, "open posting" board to broaden such lateral communications, with the added motivation that employees can also appeal for help with temporary work surges. "Let's say I have two weeks' worth of bio assays backed up in some development work. I can post a request, such as, 'Does someone in small molecules want to get experience in bio assays?' If someone has the interest and the time, and provided they get their boss' agreement, we can let that resource flow to the task."

> "To really eliminate all the boundaries, you have to change the culture."
>
> **DR. MICHAEL THIEN**
> Senior Vice President of Global Science, Technology and Commercialization
> Merck Manufacturing Division

Thien says the organization is now extending the boundaryless idea to other parts of the company and outside entities. It is reaching out to Merck's manufacturing partners, along with its sister groups in the company's research labs, to create a flow of resources between those areas and the commercialization, science, and technology area.

ROGUE WAVE RESPONSES

With every reformation, the unexpected occurs. Asked if any "rogue waves," or unanticipated disruptions, had crashed upon his shores in implementing the boundaryless mission, Thien laughed.

"Yes, there are times when our little boat was toppled. When we put our Virtual Technical Network together, one of the things we didn't expect was the hesitancy of people to post their problems, despite the obvious appeal of having access to all of the organization's expertise. When we asked them why, the responses were

varied, but amounted to 'I don't want to look dumb.' We had to take on a cultural battle to get everyone to understand the importance of making their problems visible. We created an expectation that the group leader would ask whether a person had posted the problem or question on the VTN. We also gathered many success stories of how people had used the network, and the success stories were typically from early adopters. We distributed those stories everywhere. We put them out in email bulletins, we had them in our newsletter, we talked about them in our town halls, and we let people know they are the stories of what the future should look like."

It took about a year and a half to turn the tide so people routinely posted their issues on the network, says Thien. But just as the first challenge receded, the second rogue wave splashed ashore: fear of *answering* questions replaced the fear of *posting* them. "People were concerned that, if they posted an answer and the answer tuned out to be wrong, they would look like idiots."

It took another educational campaign of new expectations and success stories to get people to understand that "nobody will advance if everyone doesn't offer up their expertise," he says. "The world is self-correcting. If you post an answer, someone may say, 'Actually it's not X, it's Y.' And people will move along. There's no embarrassment. In fact, isn't it better that you know the truth rather than continue in the falsity you've been living with?" Once again, 18 months of effort changed the culture, and posting answers became the new normal.

"We very successfully brought everyone around, and now we have a thriving Virtual Technical Network with over 2,000 members," Thien says. "Every day there are dozens of questions being asked on the network and people getting answers within 24 hours."

HARVEST OF KNOW-HOW

Solving problems in making products is only one facet of the organization without boundaries, however, as the company views it. If that were all, each solution would be an ephemeral insight. Even beyond problem-solving, all activities in the line of production constantly inject a more lasting and valuable asset into the organization: what it learns at every step. Thien explains.

"In our new product development area, for example, we make two things. We make the kilos for clinical trials, and we make knowledge — knowledge about the product, about the process, and about the methods. We believe it is critically important to capture the knowledge we create in an explicit way so it is easy to reuse it." Thus, he says, the organization created a "knowledge management strategy" with four parts: capture and categorize product knowledge, continuously build on technology-platform knowledge, share implicit knowledge through the VTN, and record critical knowledge from company experts in transition to another job or retirement.

Capturing, categorizing, storing, and retrieving knowledge, from all of the operations falls to an IT infrastructure built to handle the job. Such computing power helps handle the capture of so-called implicit knowledge as Thien explains. "We know that 70 to 80 percent of all knowledge is implicit or tacit; it is not written down anywhere; it consists of what people carry in their head. That was one of the purposes of the Virtual Technical Network: capture that knowledge in the form of conversation strings so we can use it again."

For the fourth part of the strategy, recording critical knowledge, the group borrowed a concept from Shell Oil for a program called R.O.C.K. (Recording Of Critical Knowledge), which uses a programmed interviewing technique for people in transition to capture what they know on various topics, then put the knowledge in a reusable form, and make it available to the entire community.

Thien says one major lesson gleaned from implementing the knowledge management strategy is that all of the associated activities must transpire in the normal flow of work. "People should not see the recording of knowledge as something extra to their job, but as critical to their job. They are knowledge workers, and knowledge management has to be an integral part of their job."

More recently, Thien's group has added a fifth part to the strategy: implementation of a formal after-action review process. "We had a lot of lessons learned where nobody learned the new lessons. You might create a deck of PowerPoint slides that went up to the highest person possible in the company, but nothing really changed because we didn't get the right information to the right people and change the right things. Now we are putting in a very disciplined after-action review process, modeled after a Navy Seals program, so we can have effective lessons learned where people truly do learn the lessons."

Another lesson was to take instructive

> "Now we are putting in a very disciplined after-action review process, modeled after a Navy Seals program."

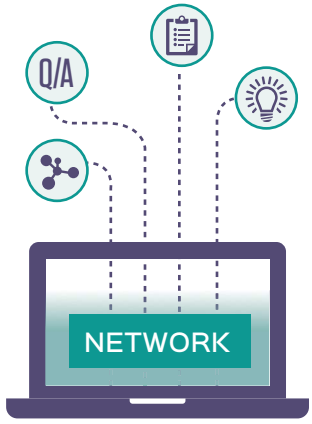
DR. MICHAEL THIEN
Senior Vice President of Global Science, Technology and Commercialization
Merck Manufacturing Division

examples from other industries. Thien says the company looked for good models in the manufacturing and new-product development spaces of the pharmaceutical industry and came up empty-handed. So it went outside of the industry to work with some of the giants, such as IBM and NASA, for which knowledge management is absolutely critical. "We just attended the annual knowledge management conference that NASA holds just for its knowledge stewards, as one of the only two external companies to be invited this year to speak about our knowledge management efforts to the NASA knowledge team."

Harvesting, organizing, and applying knowledge in the boundaryless organization has already produced some significant results, according to Thien. Merck made headlines in October when the FDA approved its cancer immunotherapy product Keytruda (pembrolizumab), the first FDA-approved anti-PD-1 (programmed cell death protein) therapy for metastatic melanoma. (See the series, "Combination Cancer Immunotherapy — A Virtual Roundtable," beginning in our September 2014 issue.)

Thien describes the Keytruda mobilization: "We recognized it was going to be a significant undertaking to get this monoclonal antibody out and into the public. We used our boundaryless organization to essentially funnel resources from all over the Global Science, Technology, and Commercialization (GSTC) areas to the Keytruda team, so the team could be fully staffed and work at an extremely rapid pace. That was a huge benefit because we were able to accomplish the deployment very quickly and continue to pull those resources almost at will as the needs occurred, while we moved this product rapidly through the pipeline and through manufacturing readiness. We are now working to do the same in other areas of the business."

The no-boundaries approach applies to all three areas of Thien's responsibility: product development, in-line product technical support, and capital assets. As an example of support for in-line products, an expert from the material science lab for small molecule drugs could come



in to help solve a problem with particulates in a vaccine.

Another, more general example of no-boundary support is in the supply of clinical-trials material. Thien mentions the unit has not missed a clinical delivery since the new organization has been in place.

"We have a certain sense of confidence that comes from knowing that our processes are as robust as they can be, and the people developing those processes know they can tap into any discipline required to help them characterize and understand the processes. If we are working on a biocatalytic chemistry step, we know we can bring in people from the therapeutic-protein area to help us understand a particular behavior of the biocatalyst or enzyme we are using. This has made us a stronger organization with more robust processes even in the clinical supplies area, so we are better equipped to make every clinical delivery in the right quantity, with the right quality, and at the right time."

OUTSIDE THE BOX

Reorganizations of any kind tend to be inward-looking. But how does the boundaryless organization — using knowledge management and open sourcing internally — translate into benefits for customers, however they may be defined?

"We have internal and external customers," says Thien. "A plant manager at one of our sites knows the power of the entire network is available to work on any problem at the site. The problem will get a significant and completely deterministic response from our technical network worldwide. But one of the other areas where this boundaryless approach has paid off is in our support of external suppliers. We provide technical support as necessary to our CMOs when we have issues with products and processes. It may not be apparent to our external partners, but we are using the entire network to solve their problems, just as we do with our internal partners."

Thien says the advantages of the network extend to "customers" outside the industry, such as regulators. A simple case in point is the availability of the network's expertise to help sites appropriately prepare for, or respond to, pre-approval inspections (PAIs). More generally, the company can make its pan-modal teams — encompassing small molecules, vaccines, and therapeutic proteins — available to speak with regulators about issues that affect them all, such as statistical sampling.

The network can also produce some leverage with payers. Thien offers an example of sending a technical team along with a commercial team to visit some of Merck's biggest clients and discuss their problems and challenges — in one case, resulting in a packaging improvement for a particular product.

"The areas we work in are not typically of the highest concern for payers. But we do ask them to tell us about any problems they encounter in using our products, and we try to find ways to address those problems."

Looking outside also means looking at the future. Thien says his group conducts an annual strategic review for that purpose. "Let's look at the world around us and ask the question, Has anything changed? And if things have changed, what do we need to do to modify our picture of the future state to better serve the manufacturing division, the company, and our patients?" And, as with all new or renewed organizations such as the Merck Manufacturing Division, the future will be the ultimate judge of whether, in Thien's analogy, the steps it takes over time are the right steps, in the right direction. L

ARE YOU PREPARED FOR THE PENDING

PERSONALIZED MEDICINE REVOLUTION?

ROB WRIGHT Chief Editor

Arriving at 600 New Hampshire Avenue NW in Washington, D.C., I stride through the lobby of The Watergate toward the elevator. I am on my way to what promises to be a "lively" and "on-the-record" personalized medicine discussion hosted by the *National Journal* (a division of the Atlantic Media Company). Joining me this October evening are members of the medical community, media, a variety of healthcare experts, and three executives from the event's underwriter, AstraZeneca.

Although my invitation provides a list of planned exploratory questions as well as a brief primer on personalized medicine, it is not until Dave Fredrickson, VP of specialty care for AstraZeneca, shares his opening remarks that I discern the desired outcome from the discussion. "Each of you represents different [personalized medicine] stakeholders," he says. "We are keen on hearing your perspectives so we [AstraZeneca] know where to focus, so we are leaders in the field, not followers."

The personalized medicine discussion is the third in a series of four involving topics on which AstraZeneca desires to have a leadership role. As the fourth has yet to take place, I am not at liberty to divulge the topic. However, the previous discussions focused on patient-centricity and value. And while there has been some media coverage, as well as blog postings on AstraZeneca's Health Connections website of the previous discussions, these provided a somewhat surface-level understanding of the subjects. Given the enormous potential personalized medicine promises for patients, payers, providers, and pharma alike, there seems to be an opportunity to provide a much deeper understanding beyond the issues impeding progress. What follows are insights gained from diving deep into the world of personalized medicine — which will be nothing short of revolutionary.

PANELISTS LIST

Ⓐ **Moderator Marilyn Werber Serafini** Vice President, Policy, Alliance for Health Reform
Ⓑ **Julie Appleby** Senior Reporter, Kaiser Health News
Ⓒ **Rich Buckley** Vice President, North America Corporate Affairs, AstraZeneca, and President, AstraZeneca Healthcare Foundation
Ⓓ **Andrea Califano, Ph.D.** Clyde and Helen Wu Professor of Chemical Systems Biology; Chair, Department of Systems Biology; Director, JP Sulzberger Columbia Genome Center; Associate Director, Herbert Irving Comprehensive Cancer Center, Columbia University
Ⓔ **Dave Fredrickson** Vice President, Specialty Care, AstraZeneca
Ⓕ **Yuval Itan, Ph.D.** Postdoctoral Associate, The Rockefeller University
Ⓖ **J. Leonard Lichtenfeld, M.D.** Deputy Chief Medical Officer, American Cancer Society
Ⓗ **Daryl Pritchard, Ph.D.** Vice President, Science Policy, Personalized Medicine Coalition
Ⓘ **William Mongan** Vice President, Business Development, New Product Planning and Foundations Portfolio, AstraZeneca
Ⓙ **Aris Persidis, Ph.D.** President and Co-Founder, Biovista
Ⓚ **James Salwitz, M.D.** Clinical Professor, Robert Wood Johnson Medical School
Ⓛ **Wendy Selig** President and Chief Executive Officer, Melanoma Research Alliance
Ⓜ **Paul Sheives, J.D.** Director, Diagnostics and Personalized Medicine Policy, Biotechnology Industry Organization
Ⓝ **J. Russell Teagarden, DMH, RPh** Senior Vice President, Medical and Scientific Affairs, National Organization for Rare Disorders
Ⓞ **Sheila Walcoff, J.D.** Chief Executive Officer and Founder, Goldbug Strategies, LLC

IS PERSONALIZED MEDICINE PRECISION MEDICINE?

Prior to attending this discussion, attendees were provided the following definition for personalized medicine — "Getting the right targeted treatment to the right patient at the right time." While somewhat accurate, according to dinner discussion attendee, Andrea Califano, Ph.D., professor of chemical systems biology at Columbia University, this definition, along with the term itself — personalized medicine — creates a common misunderstanding. "We talked to people on the street," says Califano. "They tell you that personalized medicine is getting a drug that is 'personalized' to your particular type of disease." Califano shares that Columbia has been doing a lot of "N-of-One" studies. "N of something means how many patients you need to have in a study for it to be statistically powerful," he explains. "We're doing studies that consist of a single patient. Of course you have to do a lot of these [studies] in order to have statistical power, but each patient is treated individually." At Columbia they are finding that personalized medicine doesn't necessarily require personalized *medicines*. "We find that the drugs that would work in patients are very much the same across a large number of patients," he says. "It's just that we don't know which patient should get which drug." This is why Califano says you are seeing a shift away from the traditional research approach which views cancer tumors as padlocks, biomarkers as the keyholes, and the drugs which fit and open the lock as the cure. "We've come to realize that cancer is not a disease of the organ," he shares. "It's a disease induced by the genetic pathway." As a result, researchers have been approaching cancer with a repertoire of drugs. "In very many cases, what we find is drugs that were never even thought to be used for cancer, let alone a particular type of cancer, are putting the patient-derived xenograft in regression, especially when used in combination with others," Califano states. For example, thalidomide, originally developed and prescribed as a sedative (1957), is Celgene's branded treatment (Thalomid) for multiple myeloma. Imatinib, first approved by the FDA in 2001 to treat patients with advanced Philadelphia chromosome positive chronic myeloid leukemia, today has 10 indications generating $4.6 billion+ in annual sales for Novartis under the brand names of Gleevec and Glivec.

These are just a few of the reasons why Columbia University is using the term "precision medicine" when referring to the concept of personalized medicine, and why the school has also created an interdisciplinary precision medicine task force. Consisting of nearly 40 faculty members located throughout the institution, the task force is taking a university-wide approach to precision medicine, rather than just a medical one owned by a single department. Daryl Pritchard, Ph.D., VP of science policy at the Personalized Medicine Coalition (PMC), feels that getting caught up in the semantic debate over which term is better (i.e., precision

or personalized) will only further confuse patients. From the practicing clinician perspective of James C. Salwitz, M.D., clinical professor at Robert Wood Johnson Medical School, the belief is, "The bedside clinician doesn't believe that personalized medicine is anything different than what they've been practicing for a long time. We need to start thinking of this at a much higher level, with the medical community having a holistic image of the patient, because what we are talking about is game changing." Personally, I prefer the term personalized medicine. Here's why.

WHO IS GOING TO PAY FOR OR REIMBURSE FOR PERSONALIZED MEDICINE?

One of the personalized medicine debates that elicited some strongly held opinions during the evening revolved around the question of who is going to pay for personalized medicine initiatives (e.g., genome sequencing, diagnostic testing) — with the patient being notably absent from the conversation regarding financial responsibility. J. Russell Teagarden, DMH, RPh, SVP medical and scientific affairs at the National Organization for Rare Disorders (NORD), commented, "They [patients] won't pay for anything. They won't pay for penicillin." It is hard to argue with Teagarden, who spent 19 years developing policy coverage at Medco Health Solutions prior to joining NORD. He believes that patients have become so accustomed to having healthcare coverage that they don't expect to ever have to pay much, if anything at all, and actually have to put forth effort into thinking that they may, should, or have to, on occasion, pay for healthcare. J. Leonard Lichtenfeld, M.D., the deputy chief medical officer for the American Cancer Society, referenced the experience of his spouse, a practicing OB/Gyn in Thomasville, GA, and her dealings with a Medicaid and uninsured patient population that is either unwilling or unable to pay for their healthcare.

> "If I were in the drug development sector, I would invest in medical informatics."
>
> **JAMES SALWITZ, M.D.**
> Clinical Professor
> Robert Wood Johnson Medical School

I find it unfortunate that we as a society have allowed the slow evolution of a healthcare insurance reimbursement system to devalue the products and services of payers, providers, and pharma alike to items of entitlement. Personalized medicine is what its name implies — personal — personal data and personal treatments. As such, there should be a *reasonable*

portion of *personal financial responsibility*. While we can all probably point to some examples of individuals not wanting to pay for products or medical services, defining *all* patients in this way is a mindset in need of change — starting with all the stakeholders other than the patient.

There are numerous examples to dispute the notion of patients being unwilling to pay. For example, *U.S. News & World Report* notes the growing number of physicians moving away from accepting insurance to concierge care — cash-only and membership-based retainer models, even among primary care practices. During the discussion, Aris Persidis, Ph.D., president and co-founder of Biovista, a drug repositioning company, shared an example of patients being willing to pay. "There's a company in Richmond, VA that is the eastern seaboard's largest recipient of FedEx packages," he states. "It's called HDL – Health Diagnostic Laboratory." According to Persidis, using technology to reduce the cost of the wet lab, combined with touting the ability to test for cardiovascular disease risk factors and some very simplistic correlations, HDL has grown into an enormous enterprise worth studying. While Lichtenfeld was quick to point out that HDL is under investigation for Medicare fraud, Persidis' point wasn't advocating the questionable behavior of HDL but the fact that many patients willingly paid for healthcare in the form of $120 diagnostic tests. Another example is the 23andMe direct-to-consumer personal genome test. While Paul Sheives, J.D., director of diagnostics and personalized medicine policy at BIO, stressed the limited viability of the do-it-yourself test, Wendy Selig, president and CEO of the Melanoma Research Alliance, questioned the ethics of such tests that give patients information about their susceptibility for getting a disease when a viable treatment does not presently exist. Nonetheless, Sheila Walcoff, J.D., CEO and Founder, Goldbug Strategies, a biomedical consulting firm, pointed out that over 700,000 people have already had their genome typed via the 23andMe retail DNA test. What makes this particularly interesting is when you consider 23andMe is just one company in a market expected to reach $19 billion globally by 2020. Despite 23andMe sales being slowed by FDA-imposed marketing restrictions, the impact of the product recognized by *Time* magazine as the best invention of 2008 in driving down diagnostic test prices is almost as glaring as the revelation that not only are people willing to pay out-of-pocket for such tests but also share private medical information willingly and openly. Early in the personalized medicine discussion, Califano expressed one of his biggest concerns, saying, "We've actually been performing personalized medicine for maybe 100 years. Why is personalized medicine becoming such a hot topic at this point?" While Califano believes the cause to be the result of genome sequencing transforming scientific understanding of biology, Persidis, sees the consumer, not industry or the FDA, as being the driver that will tip personalized medicine from concept to reality. "I'm going to use the democratization of music as an example," says Persidis. Though you may think this a silly comparison because healthcare is highly regulated, he reminded the group that music is regulated because it is considered intellectual property. "The consumer led the charge to change the rules," he affirms. "What happened when music was democratized is that technology made it so darn easy and cheap, that the producers, along with everyone else, had to adapt." Continuing he asks the group, "Can you imagine a world where it is so easy to have these [personalized medicine type] tests conducted, interpreted, and matched up with a person's electronic medical record information, and then you extract the differential effect of drugs, possible benefits and risks, and a whole bunch of other things? This is possible today. If you stack all of the technologies we currently have together, you end up with a really cheap point-of-care solution that is good for the patient and the doctor." If the cost can be brought down to a reasonable price point, patients most certainly will pay.

> "I think we're at a crossroads for the two key pieces that could prevent the promise of personalized medicine — reimbursement and regulation."
>
> **SHEILA WALCOFF, J.D.**
> Chief Executive Officer and Founder
> Goldbug Strategies, LLC

CAN PERSONALIZED MEDICINE BECOME A REALITY?

When the evening's moderator, Marilyn Werber Serafini, VP of policy at the Alliance for Health Reform, asked the group what incentives and payments are necessary to make personalized medicine happen, James Salwitz, M.D., responded, "As medicine is currently practiced, it can't be done." There is a variety of reasons for his well-placed skepticism. For the realization of personalized medicine, a plethora of interfaces needs to be developed to facilitate the linking and sharing of all your personal health data (e.g., electronic medical health record, genome, medical history, metabolome, microbiome, pharmacogenomics, proteome, vitals), so it can be properly analyzed. "If I were in the drug development sector," Salwitz advises, "I would invest in medical informatics." Teagarden adds, "We don't have a uniform payment system, but gazillions of different payment systems, each having different reasons for what they are willing to pay for and why." The lack of uniformity across insurances is one of the challenges he sees to personalized medicine becoming a reality. "Different payers from different segments are willing to accept different levels of evidence," he says. Sheila Walcoff sees another obstacle, stating, "I think we're at a crossroads for the two key pieces that could prevent the promise of personalized medicine — reimbursement and regulation." Her concern is that if these two areas aren't able to find an appropriate balance, it will result in stagnation of innovation, investment, and quality. Selig affirms, "The incentives have to exist for people to invest." Referring to the preclinical space, she analogizes how the incentives

are misaligned. "Industry is not investing in preclinical because it's expensive and hard to convince your shareholders it's worth doing. Academia is doing it, but under great duress due to funding constraints and misaligned incentives which emphasize publishing, not collaboration." Yuval Itan, Ph.D., postdoctoral associate at The Rockefeller University, agrees. "In rare Mendelian [one gene] diseases, we are becoming more efficient in actually identifying the disease-causing gene," he states. According to Itan, once they have proven in the lab that a gene causes a disease, and then they publish that finding, that's where it typically ends. "For an academic researcher there is usually no follow-up as to the benefit of the discovery for the patient," he laments.

All of these barriers considered, the personalized medicine revolution is coming, and probably sooner than you think. In an ironic stroke of luck, two days after attending the *National Journal* dinner discussion, I was invited to review *The Personalized Medicine Revolution*, a not-yet-released book by Pieter Cullis, Ph.D., professor of biochemistry and molecular biology at the University of British Columbia. He anticipates the impact of personalized medicine on you and how you live your life to be *greater than any other technological advance you have ever experienced.* While this may seem far-fetched, for those of us who experienced the world before the existence of the Internet, I am sure many of us would admit ever having envisioned how this once neat curiosity would absolutely change *everything.* But it took innovators and inventors to change the Internet from a cool interconnected computer tool used by researchers into something people could use as easily as any other home appliance. Cullis writes, "If you want to take advantage of the benefits of personalized medicine, you are going to have to start to assemble your digital self as best you can and use your doctor as a sounding board to help interpret what you find." This is the best business-practice actionable information you have been waiting for. Because, though Persidis stated during the dinner that consumers will drive the personalized medicine revolution just as they did in music, it took the visionary leadership of Steve Jobs to bring all of the stakeholders together. If you want to be in the position of creating and shaping the iTunes of personalized medicine, you better figure out who are the leaders among key stakeholders and start bringing them together — now, before the likes of Google, Netflix, or some other revolutionary company does it for you. Rewards are not reaped by visionaries who lack the will to execute.

COMBINATION CANCER IMMUNOTHERAPY — A VIRTUAL ROUNDTABLE

A SERIES ON THE CHALLENGES AND OPPORTUNITIES OF USING NEW AGENTS TO RALLY THE IMMUNE SYSTEM AGAINST CANCER

WAYNE KOBERSTEIN Executive Editor
LLEW KELTNER, M.D., Ph.D. Roundtable Moderator

Why have some of the biggest companies in cancer immunotherapy shied away from this roundtable discussion? Why have others joined in? And why do so many companies, small to large, want to take part in this forum? In addition to a dozen key opinion leaders (KOLs) featured in the first two parts of this series which began in September, twice as many companies responded to our call. Now, after publishing Part Four here, we will still have at least ten more company responses to run in the coming months, with even more responders wanting to jump on board before the end — having seen their peers and rivals speaking through this report.

There is a parallel explanation for the number of responses the roundtable has attracted: KOLs and companies have many ideas about cancer immunotherapies and how they may be used in combinations. In certain cases, someone's definition of immunotherapy excludes another's approach; for example, those who champion the new checkpoint-inhibitor or co-stimulation therapies which target the immune system, not the cancer, may refuse to acknowledge any form of tumor-targeting strategy as immunotherapy. Moreover, many believe tumor heterogeneity and adaptability doom tumor-targeting to an ultimate dead end. But others consider traditional chemo, hormone therapies, and tumor-targeting drugs as ready candidates for immunotherapy combinations. This roundtable encompasses both sides of that debate and more.

PART FOUR: COMPANIES AT STAKE, CATCHING UP, AND COMPETING

QUESTIONS VERBATIM

This month's installment of the Combination Cancer Immunotherapy roundtable continues the presentation of responses to questions we sent to the leaders of companies that aspire to play a role in this exciting field. We did our best to invite and include all of the companies now developing cancer immunotherapies, chiefly in the new areas generating the most excitement in the oncology community: checkpoint inhibitors and co-stimulators and complementary immunostimulators such as cancer vaccines and ablative modalities that promote immune-cell production. We also heard from a few companies that believe other approaches deserve a place among the possible cancer immunotherapy combinations the roundtable addresses.

The questions we asked the panelists were as follows:

Why combinations?
Do you believe cancer immunotherapies should be used in combinations rather than as single agents or is it possible to envision a single effective immunotherapeutic agent?

Essential components?
In your opinion, if cancer immunotherapy combinations are essential, what are the essential constituents of any combination therapy?

Backbone therapy?
Will a particular approach such as PD-1/PD-L1 be the "backbone" of cancer immunotherapy combinations? Or will consensus on a hierarchy of therapies continue to evolve with the growth of scientific understanding in ongoing research?

Combo criteria?
By what criteria will physicians select specific immunotherapy combinations for individual patients or patient groups? Or will regulatory and reimbursement realities dictate the combinations?

Narrow or wide applications?
Will the most effective immunotherapy combinations be specific to traditional cancer indications (NSCLC [Nonsmall cell lung cancer], HCC [Hepatocellular carcinoma], etc.) or tend to have general effectiveness against all or a wide range of cancers?

Personal or broad?
Do you see limits on the practice model for cancer immunotherapies; i.e., will cell-based approaches remain restricted to a small number of patients in intensive-care or salvage settings?

Commercialization challenges?
What are some of the major hurdles you face in commercializing your cancer immunotherapy product or products, especially considering that the science, regulatory pathway, and market are still evolving?

General comment?
Is there anything else that you believe is critical to understanding how combination immunotherapy or another immunotherapeutic approach will move into use as the backbone of cancer therapy?

At this point, reading the previous installments in this series is essential to understanding its mission, organization, and context. (See also "Questions Verbatim.") So, in the interest of using this space efficiently, we hereby continue our companies' responses in this, Part Four of "Combination Cancer Immunotherapy — A Virtual Roundtable."

(MORE) COMPANY LEADERS RESPOND

The following are the responses:

DAIICHI SANKYO

Currently developing nonimmunotherapeutic agents of potential use in combination with immunotherapies.

FRANCIS G. KERN, PH.D.
Senior Director
External Scientific Affairs

Why combinations?
The promise of PD-1 (programmed cell death protein 1) and PD-L1 (programmed death-ligand 1) antibodies in demonstrating the ability to elicit deep and durable responses as monotherapies in a number of indications suggests that, in many instances, a single agent may be sufficient. However, the combination of ipilimumab (Yervoy) and nivolumab tested in clinical trials for melanoma also demonstrated that the same type of benefit may be extended if the right agents are utilized. At present, though, we have little understanding of biomarkers that can be efficiently utilized to determine when a combination will be needed and when it will not. With the added toxicity that is likely to result from some of these combinations, it will be important to begin to sort this out.

Essential components?
The increased rate of grade 3 and grade 4 toxicities seen with the ipilimumab and nivolumab combination in melanoma was balanced by the greatly increased

response rate and the clinical experience developed in effectively managing these toxicities. In the near future, we are likely to hear about how applicable this particular combination is in other settings. We should also soon learn about the initial results of other combinations that companies with PD-1 and PD-L1 antibodies are trying with other immunotherapy assets in their own armamentarium or in collaboration with other pharmas and biotechs. Obviously, any increase in toxicity or autoimmune-related adverse events with these new combinations must also be sufficiently balanced by increased efficacy and clinical understanding of how to manage these events.

Backbone therapy?

Certainly the relative safety and extent of efficacy seen with the PD-1 and PD-L1 antibodies in early clinical trials warrants the major ongoing effort to identify the most appropriate combination partners. The increased efficacy seen in clinical studies with the addition of ipilimumab to treat melanoma demonstrates the endeavor is likely to succeed in at least some cases. However, it is still unclear if the lack of efficacy in some nonresponding patients is due to the absence of this particular checkpoint inhibitor system functioning in those particular patients. We know that there is a large number of related molecules postulated to have similar inhibitory effects on T-cell function. It would not be too surprising to eventually find that some of these may be working where the PD-1/PD-L1 antibodies are not.

Combo criteria?

In the near term at least, the old standbys of efficacy and safety will likely dictate which combinations physicians will choose to use. If deep and durable responses occur with these combinations, it should be apparent to payers that they may obviate the need for subsequent second and third lines of therapy and their accompanying supportive care costs. Therefore, the expense associated with two biologics may be justified by the curative potential.

Personal or broad?

Clinical studies have shown remarkably deep and durable responses with CAR (chimeric antigen receptor) T-cell approaches in relapsed and refractory leukemias and in some lymphomas. But cell-based approaches also require intensive, supportive clinical care and are presently associated with a very high cost of goods and may not be compatible with a pharma's business model. The same factors also currently apply to other engineered T-cell receptor approaches that might be able to show more utility for solid tumors. The large numbers of engineered T cells currently required for both CAR T- and exogenous TCR (T cell receptor)-based approaches remain an obstacle to the expanded use of these cell-based therapies. However, progress is being made in identifying and selecting the most appropriate T-cell subtypes for use as recipients for the vectors, which could significantly reduce the cost of goods. Lack of identification and validation of cancer-specific targets also impedes the safe extension of these approaches to solid tumors.

Off-the-shelf immunotherapy agents may still require predictive biomarkers and can therefore still be considered as "personalized medicines" but not to the same extent as the current cell-based therapies. In contrast, off-the-shelf cancer vaccines have not delivered the same type of response rates as the antibodies but could eventually prove their utility in combination with immune checkpoint inhibitors, co-stimulators, or other immunomodulatory agents. In fact, some sort of vaccination-type approach may be required for the other immunotherapies to exert their full effects. There is also data that indicate that an immune response to the tumor needs to pre-exist in the patient for checkpoint inhibitors to be effective. It doesn't matter if you remove your foot from the brake or step on the gas if the car isn't running.

Commercialization challenges?

Daiichi Sankyo is not currently running clinical trials with immunotherapy agents, but we believe we have some agents in our pipeline that might be active as a part of an immunotherapy combination. Because it seems there are so many combinations that would make sense to try, we need to generate sufficient interest among potential partners for using our pipeline agents in combination with theirs. We are now making good progress on that front as we generate more preclinical and clinical data supporting the rationale.

When we start getting into three or four agents and an aging population seeking these combinations in greater numbers, something will have to give. It is unlikely that a single company will have exclusive rights to all of the combination partners, and the market value of their particular agent may in many cases be coming exclusively from the synergy seen from use in combination. It seems likely then that pricing will be affected and reimbursement for use will be less than the sum of prices seen with current biologics used as single agents. Partnering companies should be willing to accept this as a price for having a piece of the action.

General comment?

Better preclinical models need to be developed to allow us to predict the efficacy and safety of the various possible combinations. There are already too many combinations to test efficiently in the clinic, and this number is likely to grow to an even greater extent as we get a better understanding of the role of some of the emerging targets and identify new targets.

CURETECH

Antibodies and peptide therapeutics designed to modulate the immune response, allowing it to exert its anticancer activity in an effective manner.

RINAT ROTEM-YEHUDAR, PH.D.
Vice President
Research and Development

Why combinations?

We support a combination approach for the obvious reason that single-agent immune therapeutics still do cure cancer

> "A combination approach has already been proven more efficacious in several advanced-stage clinical studies."

RINAT ROTEM-YEHUDAR, PH.D.
Vice President, Research and Development
Curetech

for the majority of the treated patients. A combination approach has already been proven more efficacious in several advanced-stage clinical studies (e.g., ipilimumab and nivolumab for melanoma; pidilizumab and rituximab for lymphoma). Further support for this rationale is widely provided in experimental tumor models.

Essential components?

Essential constituents would be immune-enhancing reagents and/or tumor-targeting reagents (ADCC [antibody-dependent cell-mediated cytotoxicity] or direct cytotoxic conjugates) and checkpoint inhibitors.

Backbone therapy?

With a level of ORR (overall response rate) of 30 to 40 percent using the PD-1/PD-L1 blockade, this approach could be considered at this time a backbone of cancer immunotherapy combinations, yet once more data is generated in the clinic, we estimate that a hierarchy of therapies will continue to evolve with the growth of scientific understanding.

Combo criteria?

Will physicians select specific immunotherapy combinations for individual patients or patient groups based on medical evidence and judgment? Or will regulatory, formulary, and reimbursement realities dictate the combinations? It's a combination of both, I'm afraid. In an ideal world, the criteria would consider the specific indication, the subject's genomic/protein profile, and off-the-shelf SOC (standard-of-care) approved for this subject population. The SOC would probably be constituted of multireagent protocols — immune-enhancing reagents, tumor-specific vaccines, tumor-targeting reagents (mAbs using ADCC or direct cytotoxic conjugates), and checkpoint inhibitors, as well as other approaches such as mutation-targeting small molecules.

Personal or broad?

We do not see the two options as mutually exclusive; namely, we do not exclude the possibility of using a combination of patient cell-based approaches with checkpoint inhibitors. Obviously, the limits on customized cell-based therapy may render this approach less practical or cost-effective.

Commercialization challenges?

Collaboration/cooperation among companies and between companies and regulators should be better facilitated to bring optimal combo protocols to the market and maximize patient benefit.

General comment?

We need a governmental budget and regulatory path to support and expedite a global effort to map and optimize multireagent combo protocols with existing and investigational therapeutics.

JANSSEN

Immunotherapeutics in the preclinical and IND stage, plus hemo-oncology candidates in late-stage clinical development for potential use in immunotherapy combinations.

CRAIG L. TENDLER, M.D.
Vice President
Late Development and Global
Medical Affairs, Oncology

Why combinations?

We agree that immunotherapy is certainly going to be a cornerstone of cancer treatment. Initially, of course, most of the data is for solid tumors, but we believe there is also an excellent opportunity in the hematologic malignancy space. We have specific immunotherapy strategies for each of our three major disease areas of interest — prostate cancer, heme malignancies, and lung cancer — where we're looking for the best targets that could synergize with other drugs we have in those spaces. Some of the single immunotherapy agents can deliver durable remissions in a small subset of patients, whereas targeted agents may be active in a larger proportion of patients but have short durations of remission. This would provide a strong rationale to combine immunotherapy and targeted therapies in the hope that we can substantially increase the percentage of patients achieving durable remissions and prolong survival without a substantial increase in toxicity. We are also looking at strategies to block multiple negative immune checkpoint pathways on T cells or agonize stimulatory checkpoint pathways in parallel, as some of these checkpoint pathways may become more active and mediate resistance when a PD-1 inhibitor is used as monotherapy.

Essential components?

The essential components include exceptional biologics expertise, synergy with internal (small molecules) and external platforms, and disease area-focused strategies with potential for cancer interception. We also need a lot of comparative studies to test add-on study designs, and many of the companies that have drugs in this space are already doing them. Also, who are the patients most likely to respond to immunotherapy? Do they have high levels of PD-1 and infiltrating T cells in their tumors? A personalized medicine approach to immunotherapy is also likely to be a key success factor. Finally, it will be very important to study the responding patients over time to see what happens when they relapse. Is it that some of the other proteins become activated and they are not blocking them? What drives rational combinations is understanding what happens during disease progression.

Backbone therapy?

There are 10 checkpoint proteins at least, so it would be short-sighted to believe that a single therapy would dominate. We need to understand what happens to the other proteins when you inhibit one and to learn from that in building rational combinations. We are also trying to look at immunotherapy beyond what we call the T-reg space and prime antitumor immunity using bispecific monoclonal antibodies optimized for T-cell recruitment to tumor antigens. Such bispecific antibodies can mediate highly potent, but selective, immune cell killing of tumors.

TOCAGEN

In clinical trials with selective immunotherapeutic products based on gene therapy technology (selective cancer immunotherapy).

HARRY GRUBER, M.D.
Chief Executive Officer

Why combinations?

It is likely any effective immunotherapy will require several diverse mechanisms of action (MOAs). Whether that will be through what is considered a single agent or a combinatorial approach remains to be determined.

Essential components?

MOAs must break tumor tolerance — boosting the immune system, tumor killing, antigen presentation, expansion of TAA-reactive immune cells, reduction of immuno-suppressive cells in the tumor, or other approaches, depending on the potency and mechanism included in a particular therapy. Selecting the right combination of mechanisms will depend on how the cancer has evolved to evade the immune system and how a particular patient's immune system is structured. Selective killing of cancer while sparing normal tissue and avoiding autoimmunity is the goal of immunotherapies, single or in combination. Our product candidates are designed to activate the immune system selectively to kill cancer cells.

Backbone therapy?

Immune checkpoint inhibitors are likely to play an important role in the hierarchy of combinations, but it remains to be seen how effective and durable they will be across the whole cancer landscape. Also, it should be noted that immunotherapies including PD-1/PD-L1 approaches may face challenges with autoimmunity, which could limit their use. Systemic delivery of PD-1 inhibitors will affect both normal cells and cancer cells and therefore disrupt normal T-cell regulation, resulting in potential autoimmunity.

Combo criteria?

Today we accept efficacy as the most important outcome of cancer treatment. As cancer begins to be conquered, but with a cost of very serious side effects or meaningful inconveniences, safety and tolerability along with efficacy will become the dominant requirements for the most commercially successful treatments.

Narrow or wide applications?

Patient-specific cancer therapy is being routinely used today, and now matching proper immunotherapies to the patient's immune status as well as tumor environment will be key to the success of each therapy. Platforms that are amenable to surgical, chemo-, radio-, and immunotherapeutic combinations have the potential for multiple routes of administrations, are well-tolerated, and will lead to cancer immunotherapeutic drugs with the greatest chance of success across multiple indications.

Personal or broad?

Both approaches, personalized and broad spectrum, should be explored. The armamentarium oncologists will need to outwit the cancer must be larger and more powerful than those the cancer has developed to attack the immune system. The most successful products will activate the immune system selectively against the cancer, ideally tricking the tumor into becoming a factory that generates immune-related components and destroys itself.

Commercialization challenges?

Companies that want to be relevant in this extremely fast-moving industry need to be completely dedicated to leveraging this amazingly unique opportunity in the history of the war on cancer. Staying focused on the battle at hand is the most important and difficult task. Recruiting and motivating a moderate-sized team of highly passionate and driven individuals is always hard but typically the path to success.

GALENA BIOPHARMA

Immunotherapy program led by NeuVax (nelipepimut-S) currently in an international, Phase 3 clinical trial.

BRIAN L. HAMILTON, M.D., PH.D.
Executive Vice President & Chief Medical Officer

Why combinations?

It is possible for a single immunotherapeutic antigen to elicit a robust and effective immune response, depending on the intrinsic immunogenicity of the antigen and the related sensitivity of the target tumor cells. Combining a peptide antigen with the addition of immunoadjuvants, immunomodulators, or checkpoint inhibitors may boost the immune response of most antigens.

The effectiveness of a cancer immunotherapy depends on multiple factors. The immune response is a function of the immunogenicity of the antigen, the route of antigen administration, and the relative responses of cytotoxic T cells, T helper, and T regulatory cells to the antigen. The ability of the immune response to destroy tumor cells is a function of the density of antigens on the target tumor, the sensitivity of the target tumor cells to immune destruction, and the patient's tumor burden. The stage of the patient's disease, including the level of tumor burden, also has a big impact on the effectiveness of the immunotherapy, as tumor micro-environments are known to have a significant effect on immunogenicity of the mass.

Essential components?

The specific adjuvants and modulators added in combination with the antigen will likely be antigen-specific and identified empirically for each antigen. The selection of the approach to take and the specific adjuvants or immunomodulators used may be guided by an assessment of the initial immune response. Antigen processing may be enhanced by the addition of GM-CSF (granulocyte-macrophage colony-stimulating factor) to mature dendritic and other antigen-processing cells. An excessive T-regulatory cell response could be decreased by adding checkpoint inhibitors or low-dose cyclophosphamide.

Backbone therapy?

The immunogenicity of each specific antigen, the repertoire of immune responses elicited, and the range of sensitivity among the target tumors suggest there will not be a "one size fits all" approach. The requirement for additional adjuvants, checkpoint inhibitors, or other immunomodulators must be determined empirically for each immunotherapy and possibility for each stage of disease. Immunotherapy may be more effective in specific settings when combined with targeted chemotherapeutic agents. Improvements in the immunotherapy of cancers will depend on the ever-increasing scientific understanding of the immune response from ongoing basic and clinical research.

Combo criteria?

The selection of immunotherapy for patients will depend primarily on the evidence that this approach will benefit patients and their side-effect profile, along with the cost of the therapy and the reimbursement of the treatment by third-party payers. The specific choice of the immunotherapy, including the patient populations and the addition of immunoadjuvants and/or immunomodulators, will be guided by the combination's scientific rationale and by regulatory input. With NeuVax, an HER2 (human epidermal growth factor receptor 2) immunodominant peptide vaccine, the addition of the monoclonal HER2 antibody, trastuzumab, may facilitate the antigen processing of the vaccine peptide and provide a second effector mechanism to potentiate the killing of HER2-expressing tumor cells by cytolytic T cells. Checkpoint inhibitors tend to have significant side-effects, and the use of these agents in minimal disease settings, such as the adjuvant setting, may not be appropriate for this class.

Personal or broad?

Although cell-based immunotherapy has the advantage of boosting the immune response to the patient's individual tumor-associated antigens, the technical complexities and cost will limit the number of patients who will be treated and receive benefit from this approach. The relative simplicity of more general immunotherapy approaches such as peptide-based vaccines would apply to a larger number of patients who could be treated and receive benefits and would be less expensive than the cell-based approaches.

The complexity of cell-based immunotherapeutic approaches will continue to restrict their use to a small number of patients. As with any immunotherapy, cell-based approaches would best be used in minimal residual disease settings such as neoadjuvant and adjuvant treatments. Conversely, late-stage, bulky tumors in the salvage setting would be more aggressive and less sensitive to destruction by the immune response.

Commercialization challenges?

The major hurdles to developing and commercializing cancer immunotherapies include the prolonged development times; the complexities of optimizing the combinations of antigens, adjuvants, and immunomodulators; and the immunization schedules to optimize the effectiveness of this approach (cancer immunotherapy) to cancer therapy.

Preventing disease recurrence is an ideal setting for cancer immunotherapy and attractive for patients and payers. Galena Biopharma is developing innovative peptide vaccine cancer immunotherapies that address major patient populations of cancer survivors to prevent recurrence. These therapies work by harnessing the patient's own immune system to seek out and attack any residual cancer cells. The approach of using peptide immunogens has many clinical advantages, such as a well-tolerated safety profile, long-lasting protection through immune system activation, and convenient delivery. NeuVax is easy to administer because it is given as an intradermal injection once a month for six months, followed by a booster injection once every six months.

PELICAN THERAPEUTICS

Developing co-stimulatory antibody therapy to TNFRSF25 (tumor necrosis factor receptor superfamily member 25) to expand "memory" CD8+ T cells in immuno-oncology.

TAYLOR H. SCHREIBER, M.D., PH.D.
Cofounder and SAB Chair VP of Research & Development

Why combinations?

For some patients, single-agent therapeutic blockade of CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) or PD-1 appears to be an effective approach that can facilitate long-term survival even in late-stage disease. For both strategies, however, clinical benefit is unfortunately observed only in a minority of patients, even in a highly immunogenic tumor such as melanoma. Thus, it is highly likely that combinations among several immunotherapeutic and/or conventional modalities will provide synergistic benefit for patients.

Essential components?

The essential constituent of any combination therapy is a solid understanding of the mechanism of action of each individual agent. Short term, most combinations will likely include a CTLA-4 or PD-1/L1 blocking antibody. To expand the base of patients responding to checkpoint-blockade monotherapy, there are three obvious choices for combination: other checkpoint-blocking antibodies, vaccines,

and T-cell co-stimulatory antibodies. Combinations with other checkpoint-blocking antibodies may extend responses to include patients where PD-1 or CTLA-4 are either not the dominant or are a co-dominant source of tumor-mediated immunosuppression. Combinations with vaccines are likely to expand the repertoire of tumor-specific T cells that may more effectively proliferate and kill tumor cells when a checkpoint inhibitor is on board. Finally, combinations with T-cell co-stimulatory antibodies will likely provide enhanced proliferation and effector function of pre-existing, tumor-specific T cells to overcome resistance to other sources of immunosuppression.

Backbone therapy?

For the next several years, checkpoint-blocking antibody therapies are likely to remain the backbone of combination therapies. These therapies have had the earliest FDA approvals and will continue to have approvals with other agents and in new indications for several years. Approved agents are more readily available as combinations in new clinical protocols and, if effective, will remain on the label for subsequent approved combination modalities. Other indications may become the testing ground for noncheckpoint inhibitor-based combinations.

Combo criteria?

Physicians will likely opt to participate in clinical trials where combination modalities are based on solid preclinical data supportive of mechanistic synergy. Combination treatments using approved indications can, and should, be based upon superior efficacy of certain regimens over others on the basis of randomized controlled trials. It remains to be seen how the pricing of specific combinations will be set by the drug providers and how physicians (vis-à-vis insurers) will respond.

Personal or broad?

Allogeneic cell-based vaccine approaches have an outstanding safety record, and there is no reason to believe that their implementation should be limited to patients with late-stage disease. Indeed, this is the setting where vaccines are most likely to succeed only in combination with other modalities. Vaccine monotherapy is a very attractive approach for patients with minimal residual disease to "mop-up" microscopic lesions and prevent recurrence.

CAR T-cell therapies will likely remain a strategy for hospitalized patients. Even in the limited numbers of patients treated so far, severe side effects were common and required patient management in the intensive care setting, mainly due to tumor lysis syndrome but also other inflammatory sequellae. Other long-term concerns will eventually surface, due mainly to the risk for off-target T-cell activation.

Patient-derived autologous vaccines have always held the promise of being an effective strategy because the final vaccine composition is more likely than an off-the-shelf vaccine to contain a repertoire of antigens matching the patient's tumor. Unfortunately, commercialization of such vaccines has stalled because manufacturing cost and complexity have not been scalable.

The more recent development of autologous chimeric antigen-receptor transfected T-cell therapies and tumor-infiltrating lymphocyte therapies offers new hope for autologous-based therapies. Although they have not yet been successful in solid tumors, their early record in some hematologic malignancies is impressive and likely to reach broader utility in the near future.

Commercialization challenges?

Current excitement over cancer immunotherapy has driven significant investment in promising new treatments. The FDA has demonstrated a willingness to consider novel-novel drug combinations provided that the early safety monitoring of treated patients is rigorous. In many immunotherapy trials, there seem to be responders and nonresponders for specific agents. Developing prognostic markers for responders is a complicated task, but markers may ultimately identify patient-specific treatment regimens without the need for patient-specific therapeutics. This will not only facilitate the approval of new combinations but also may link combinations to patient subsets for maximum safety and efficacy.

> "We agree that immunotherapy is certainly going to be a cornerstone of cancer treatment."
>
> **CRAIG L. TENDLER, M.D.**
> Vice President, Late Development and Global Medical Affairs, Oncology
> Janssen

General comments?

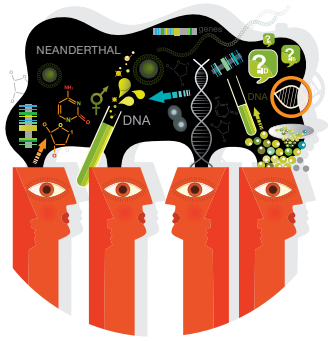
There are three "elephants in the room" for the emerging field of cancer immunotherapy: 1) What combinations make sense? 2) What combinations have an acceptable toxicity/benefit profile? 3) Who will pay for expensive combinations? Some extremely innovative work is taking place to address each of these questions, and the results are likely to shape the eventual cancer immunotherapy market in currently unpredictable ways. It is relatively straightforward to design experiments that decide what the right combinations might be, but developing methods to merge combinations into single-drug compositions or to limit the activity of those agents to specific anatomical sites will be an interesting story to follow.

As in Part Three last month, we have run as many company responses as space allows this month and will follow with the remainder next month and beyond if needed to explore this rich vein of lessons in translational R&D, business development, scale-up, and commercialization of breakthrough medicines. We are still open to hearing from companies that either missed our first invitation or believe they belong in the conversation. Also, join the discussion on Twitter at #CCIRLSL.

Biotech CEOs Express An (All-Too-Human) Risk-Taking Gene

LOUIS GARGUILO Executive Editor
@Louis_Garguilo

Anthropologists have confirmed that most Homo sapiens today carry one to four percent Neanderthal DNA. (My wife is convinced I received a larger contribution.) Potentially more damaging to our egos, Svante Paabo of the Max Planck Institute for Evolutionary Anthropology theorizes that we out-survived other Homo sapiens because of a gene mutation that makes us insanely explorative and major risk-takers.



In *The Best American Science and Nature Writing 2012*, Paabo mentions a "sort of Faustian restlessness," and adds, somewhat less eloquently, "We are crazy in some way."

Who might express this risk-taking gene in our industry if not the leaders of biotechs? Why else would a highly intelligent individual start a drug discovery company, despite possessing full knowledge of the odds for failure in an industry requiring over $1 billion and a decade to get a drug developed and approved?

Whether the three biotech CEOs I interviewed for this article are crazy or not, their risk-taking gene benefits society and increases the chances for individuals in the fight against diseases. But to continue this quasi-scientific investigation (if it rises to that level) and discern motives and behaviors, we must understand these Ph.D.-CEOs as they understand themselves. During separate interviews with Robert Gould (Epizyme), Hank Safferstein (Cognition Therapeutics), and Joe Payne (Arcturus Therapeutics), four main areas of commonality emerged:

1) A wait to set sail
2) A profound belief in success
3) Risk is relative
4) Drive not defined by dollars.

1) A WAIT TO SET SAIL

All three entrepreneurs immediately embrace our anthropological theme. At first mention of Neanderthals and a human "crazy gene," Robert Gould of Epizyme smiles wryly and thinks for a brief moment. "Certainly drug discovery is not for the faint of heart, nor for those who don't want to take a long-term perspective," he says.

Epizyme, founded in 2007, is a clinical-stage biopharmaceutical company based on the science of epigenetics. The company aspires to discover, develop, and commercialize personalized therapeutics for patients with genetically defined cancers. Gould was an early board member who became CEO in 2008. Previously, he was at the Broad Institute, and before that a VP at Merck Research Laboratories.

"I clearly understood the risks [of joining a start-up biotech], having spent 23 years at Merck," he says, "but during my whole career I hoped and expected to apply myself to discovering drugs that make a difference in people's lives. If you stay true to that motivation, you have to embrace a certain amount of risk-taking. For me, like many things in life, it comes back to having a north star to continue to guide you."

Like modern-day Vasco da Gamas, our CEOs focus on a far-off horizon and patiently prepare for the long journey. Their steady-as-you-go outlook, though, is antithetical to that of the get-rich-quick ideal we often attach to modern entrepreneurs, particularly those in other industries.

While day-to-day fund-raising demands that these science-executives live a here-and-now existence, if that detracts from long-term goals, our CEOs say the potential for ultimate success is diminished. Patience is a virtue in our start-up world; in many cases, it is born of long experience.

This is a significant difference between bio and, for example, IT start-ups. IT is known for youthful entrepreneurship; our industry is led by those armed with Ph.D.s

and often long years of industry experience. We're more mature and steeped in the industry when we, to change the metaphor, grab the helm and head out to sea. For example, Safferstein became the CEO of Cognitive at the age of 43 after a career path through the NIH, BMS, and Acorda Therapeutics. Payne adds, "My whole life I've wanted to set up a company. I've been entrepreneurial since I was 5 years old. I've always been interested in science, and I would have pulled the trigger earlier if I could have gotten the right people and the right idea at the right time. But all the right things weren't in place until years into my career."

Therefore, in our knowledge-based industry dealing with human health, the entrepreneurial gene often needs to be kept in check for years. But once the timing is right, there is no holding back.

2) A PROFOUND BELIEF IN SUCCESS

Belief in ultimate success is so profound in these CEOs that at times during our conversations I interrupt to ensure we are talking about drugs and technology still in the clinic or about to get there. Their certainty slips them into the past tense, as if "their drugs" and "their delivery systems" were already approved, or at the least, a sure bet to be.

I actually feel guilty at points. I want to believe as they do that they have the next drug, synthesis of technologies, or delivery system to significantly better human existence. But the cynicism, if you will, about the awaiting clinic and its resultant data, looms large in the path of full acceptance.

Arcturus Therapeutics describes itself on its website as "poised to become an industry leader in the application of RNAi technologies for the treatment of disease and improved quality of life." Payne, cofounder and CEO, says confidently, "We will prove our technologies next year, which will be a value inflection for our company," affirming his drug and delivery platform will be in humans for the first time in 2015.

There should be a degree of confidence. Arcturus has developed a chemistry called UNA oligomers, a more flexible version of DNA and RNA. This chemistry is paired with a delivery system dubbed LUNAR™, which involves the application of a nanoparticle. The packaged technology is initially targeted at patients suffering from transthyretin-mediated familial amyloid cardiomyopathy (TTR-FAC), a serious, rare disease that leads to the formation of plaques that damage the heart, leading to death.

When I ask Safferstein of Cognition Therapeutics what phase his compound is in, he quickens his speech: "We discovered a novel target for Alzheimer's disease, and we are hopeful we will be published on this soon. We are doing formulation, pulling the trigger on IND-enabling studies and deep into CMC. We are there." To be clear, "there" is also a candidate moving towards the clinic in 2015.

The point here is that a clarity of vision — a near messianic message and belief of better things to come — is part of the make-up of biotech executives. That assuredness stems in large part from a philosophic approach to the risk factors inherent in their long-term endeavors.

3) RISK IS RELATIVE

Arcturus' Payne puts risk in perspective — and its place. He is an Alberta-born, East-Coast-U.S.-trained, and now San Diego-based CEO. His career includes years at DuPont, Merck, and Japan's Nitto Denko, as a scientist and manager.

"Sure, risk-taking is a part of my personality," he says, still retaining a bit of his Canadian-English accent. "When I think of people who jump out of planes, I don't know if they are crazy. I think they like the energy in that activity. The point is they recognize the risks and have done everything possible to mitigate them."

"It gets to a point where you believe in your experience and capabilities and feel ready to jump from a corporate path to setting up a new company," he continues. "It is risky, but there is still a high level of comfort."

That comfort can be challenged quickly. The second day into his venture, and with a total initial investment of $50,000, the Arcturus business plan fell apart. "Our strategy was to license a certain technology, but we suddenly heard that it was not going to happen. We were sitting there going, 'Oh crap, now it gets interesting.'"

"Certainly drug discovery is not for the faint of heart, nor for those who don't want to take a long-term perspective."

ROBERT GOULD
CEO of Epizyme

Payne explains that in situations like these, you calmly reevaluate your options and strengths. "We knew it was an edgy strategy, but we also knew we could create and execute; we had enough education and career experience. Plan A didn't work out, and I'm glad. Now we have this novel opportunity and expanded horizons because of what happened in the early days," he says.

Gould from Epizyme says risk is mitigated by your strategy and the very technology and science you are bringing to the challenge. Epizyme is discovering first-in-class small molecules applied to new understanding of the cancer genome for personalized therapeutics in genetically defined patients. "You have to embrace a certain amount of risk-taking, particularly if you want to do it in a novel area combining a number of fields and sciences. In trying to bring all these together, we know there is a chance of failure, because that is what the history points to."

However, says Gould, countering that risk is the fundamental understanding that cancer is a genetically identified disease. "If we can identify the patient population with the genetic changes that drive those cancers," he explains, "we challenge that high-risk endeavor and make it less so. To say it in business terms, we improve our probabilities of success."

"We thought strategically and drew analogies from the kinase inhibitors

self-signaling world," he says about the beginning of Epizyme. "In summary, we were looking at a panel of 20 enzymes that had the potential to be effective drug targets. If we are right only 25 percent of the time — just to pick a random number — those are still five very important targets."

For Safferstein of Cognition Therapeutics, the risk is actually reversed. It is in not setting up his company and allowing the industry to continue on an unchallenged path, one he believes is not adequately serving patients. "The industry won't take the real risks," he says. "It's as though Big Pharma companies have sort of stepped away from diseases like Alzheimer's and ALS, and they are waiting for the science to advance."

We hear more on how this drives Safferstein and the motivations of our other CEOs in our final section.

4) DRIVE NOT DEFINED BY DOLLARS

Business is business, and as such, is driven mostly by the bottom line. Mostly, not always. Our CEOs desire to do well (financially) by doing good (for society), but they are intently focused on the "good" side of the equation — none more convincingly than Safferstein.

"Twenty-eight years ago my dad was diagnosed with Lou Gehrig's disease," he says evenly. "At the time, I was astounded, we had no idea what to do, no way to treat ALS. And today we still struggle with this disease. This suggests to me the approaches in the industry may be misplaced.

"For diseases like Lou Gehrig's, Alzheimer's, Parkinson's, and Huntington's, we need to step back and remember how some of the most important drugs in our time were discovered," Safferstein continues. "It was by looking at phenotypic changes in specific cells or systems and using those as a measure for finding new drugs."

Safferstein lauds the power of the "fine-tuned approach" of genetics, epigenetics, and proteomics, but says, "We have focused on them too much." He believes it is better to try to create the disease system to capture therapeutic approaches that work on multiple pathways in multiple ways. Placing this approach back in the mainstream is a goal for him.

"Companies must manage returns for investors and focus on share price, but at the end of the day, none of that exists unless we improve public health," concludes Safferstein. "That really drives me to get up every day and keep doing what we're doing."

Of the three companies, only Epizyme has completed an IPO. But when I ask Gould about that successful financial market entry, he becomes intent upon my understanding what the IPO is "really all about."

"It is important to understand why we did the IPO, and within that context, address what still motivates me on a day-to-day basis," he says. "In my mind Epizyme is a unique juxtaposition of modern genome science, drug discovery, and the ability to focus on therapies for oncology patients. Presented with this unique opportunity, I wanted to make sure we were building a company that had the upside to be able to realize all of that potential.

"That means two things," he explains. "We need to ensure adequate funding for the long haul, and that we are able to apply the kind of focus necessary to bring new medicines forward. We built the company in the context of early partnerships to get the platform off the ground, but always with the view of a potential IPO as a fund-raising enterprise. We will finish this year with more than $174 million in the bank, which enables us to continue to grow.

"So the IPO, to me, is very much another tool: You use drug discovery, robust clinical development, modern science and technologies, and financing." Gould concludes, "It is in this context that I view the IPO."

Let's be clear, though, for those readers looking to express their risk-taking gene someday as a biotech CEO: You will be focused relentlessly on funding.

Payne doesn't hesitate when I ask his most important daily activity: "Right now, my most important day-to-day task is raising money and educating institutional investors about Arcturus. I have been traveling to New York, Boston, San Francisco, etc. drumming up interest from institutional investors."

Safferstein concurs without hesitation: "Primarily fund-raising and expanding our investor network. I need to make sure our nonscientific operations are up-to-snuff, and we are managing the budget."

Perhaps because he's had the "luxury" of a successful IPO, Gould of Epizyme takes a second to collect his thoughts, but then he, too, says, "The most important thing that I have to do during the day is ensure that all of the stakeholders in the company are staying aligned on the mission of the company."

To end on a personal note, all three of our CEOs are married, have children, and say that although work-family balance is tilted a bit too much to the work side, they most enjoy spending time with their family. And Gould thinks he's passed down the gene for risk-taking. "I have a son who lives in Alaska and studies earth science. He does ice climbing, ski patrol, and avalanche control. He recently sent us a picture of himself under a glacier. I guess getting back to our discussion of risk-taking genes, it runs in the family."

"Right now, my most important day-to-day task is raising money and educating institutional investors."

JOE PAYNE
CEO of Arcturus Therapeutics

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VERSARTIS:

Extending Action & Going It Alone

WAYNE KOBERSTEIN Executive Editor

Jeff Cleland, CEO of Versartis, got into the biopharma industry early. Cleland grew up in the San Francisco Bay Area, and his parents bought him his first biotech-company stock when he was still in high school in the early 1980s.

The stock was Genentech's, right after its first IPO. He caught the typical triple-whammy bio-industry fever — characterized by scientific wonderment, humanitarian motivation, and career attraction. He first earned a degree in chemical engineering, which was, he says, "an intermediate step, doing more of the process side of the biotech, not the hardcore molecular biology." After a short time interning at Genentech, he went back to school at MIT and earned his Ph.D. in 1991, then returned to a job at Genentech.

It was a different time in biotech back then. It was back in the days when they had food fights in the Building One cafeteria and [CEO] Bob Swanson would run around in a hoola skirt to get people to go to a Hawaiian Ho Ho. It was a lot of fun."

At the same time, Genentech was also "a great place to be creative and collaborative with all different levels and different departments and at the same time, still advance really important products. The scientific rigor and the process I learned at Genentech was even more advanced than what I learned in grad school at MIT."

Cleland went on at Genentech to help launch Herceptin and Nutropin Depot, among others. Even before Roche's second, majority acquisition of Genentech in 2009, however, the company had become too large and bureaucratic for Cleland's taste, and he launched himself into the entrepreneurial space to work in several smaller companies before applying everything he learned to founding Versartis in 2009. His most important lesson at Genentech?

"I had mentors like Andy Jones, a staff scientist who had been there from the beginning, and he taught me to do the 'killer experiment' early in the evaluation of a new drug candidate. Too much time and money is often wasted in later development because companies don't do the killer experiment for an early go/no-go decision." The killer experiment figures prominently in the story of how Versartis came into its present form.

COMPANY FACTS

Focus

New Long-Acting Recombinant Human Growth Hormone

Startup Date

Early
2009

25
Employees

Finances

Market Cap
$469M
11/6/14

Cash
$181.6M
9/30/14

FINDING A PURPOSE

Versartis is developing a "long-acting" form of recombinant human growth hormone (rhGH) for growth hormone deficiency (GHD), using the XTEN technology developed by Amunix. XTEN is essentially a type of molecular scaffold that Cleland says has enormous flexibility compared to older drug-carrying molecules. The founding concept for Versartis was to find and fill the first, most appropriate need for an XTEN-based therapeutic. Ultimately, the company selected rhGH, which patients must now inject daily; the Versartis product, coded for development as VRS-317, is for a single semi-monthly or monthly injection.

The first big challenge for developing the product was also the most fundamental one for establishing the company: raising the money to pay for it. To make matters worse than usual, Cleland and his partners were attempting the founding in the depths of the Great Recession. But sticking with a tiny staff, virtual operations, and careful cash management brought them through the darkest times to the present day, with a number of international Phase 2 and 3 trials set for the coming year, clinical/commercial-scale manufacturing in place, and more ambitious plans for the future. All that — and a product with a purpose and modality investors found appealing.

Cleland neatly summarizes the company's achievement: "We built a virtual, capital-efficient organization, but we hit every milestone, created value, and were able to raise enough financing to achieve the next key milestone in our plan. We had the insight to take the right molecule forward with a truly novel approach. We figured out how to address the key issues with growth hormone, which no one had done before, and we were amazingly efficient. We had an IND for GHD within eight months of cloning the first VRS-317 molecule, using the killer experiment to show, first preclinically and then in adults with GHD, that the molecule was a monthly product with the same biology as daily growth hormone — another big milestone. But to really convince people, we also did a pediatric study, just completed recently, showing we are the first company able to achieve monthly dosing in children with no trade-offs on safety and efficacy compared to daily growth hormone."

A monthly dosing of rhGH is much more than a convenience; poor compliance and other problems with daily injections create major safety concerns and poorer outcomes. Even with all of the problems, however, current rhGH drugs constitute a $3 billion market worldwide.

"The long-acting form is what really resonated when we went out and talked to public investors, in particular," he says. Versartis raised $129 million pre-IPO, then went public in March 2014 after a lightning-fast filing period of four months in which it added only five employees to the nine it already had, according to Cleland. In total, the company raised about $200 million in 2014.

I had assumed the company began with the idea of a long-acting rhGH and then found a technology to create one, but it was really the other way around. Cleland met a pioneer researcher in drug delivery, the late Dr. Willem "Pim" Stemmer, who had previously started several successful companies before founding Amunix with Volker Schellenberger. Cleland ultimately agreed to help start a company to commercialize the initial application for the technology.

"But Pim didn't want to take any outside money from venture capitalists for the new company," says Cleland. "So we came up with a plan to create Versartis, getting a venture capitalist to invest in Versartis, with Amunix owning part of Versartis, to develop products. We essentially became the 'product development arm' of Amunix for rhGH, to validate the technology." (See also the sidebar, "Technology Close-Up.")

"What investors liked about us was that, even with our private equity, we could take the product into Phase 3 because it was an orphan drug and did not need a large trial to get approved. Even now, as we talk to investors through the IPO process, we could launch and sell this asset ourselves as a commercial company with a small specialty sales force."

Versartis also has a second product in the pipeline going through its own killer experiments. Cleland says the company will likely have data on the product and be free to speak with investors about it in 2015. Meanwhile, he says, with the company having more than 100 years of growth hormone experience among its two medical directors, the manufacturing team, and himself, there was "nothing to

Technology Close-Up: XTEN

The key to the long-action of Versartis' long-acting recombinant human growth hormone (rhGH) is the XTEN technology licensed from Amunix. Some aspects of the technology make it ideal for the product, and for future ones, according to Versartis CEO Jeff Cleland:

"XTEN is extremely tunable. Normally, with pegylation or something similar, you cannot easily change the length of the endogenous proteins and move them around within another protein. XTEN can be controlled or 'tuned' anywhere from very small sequences of maybe a dozen amino acids, all the way up to ones with more than 900 amino acids, which allows you a lot of flexibility. You can put them all over the molecule in different locations and separate domains or put a small amount on the C terminus and a large amount on the N terminus, as we did with rhGH.

"XTEN was first designed with the thought of replacing pegylation, so initially we had our growth hormone taking a similar path, where we added a long hydrophilic tail of over 900 amino acids to the N terminus, and we dramatically increased the size so that didn't clear through the kidney. But the unique thing we did was to end up tuning the receptor binding of the molecule by adding the small sequence of XTEN to the C terminus that sterically interferes with the receptor binding. By doing that, we reduced receptor binding by tenfold, while increasing the half-life by thirtyfold. We were all taught in school that you don't want to reduce receptor binding, you want to maximize receptor binding, but in this case it actually hurts you because you have more safety issues and a shorter half-life. Anyone given a month's worth of rhGH in a single bolus would have severe side effects. Reducing the receptor binding made it possible to dose VRS-317 only once a month."

be gained" from partnering at this stage of development. "Once we've gotten through the Phase 3, we can win a much better agreement with a partner for some marketing outside the United States, particularly in a territory such as Japan where it would be difficult to build a sales force."

SCALE-UP SOLUTIONS

Versartis is also ready to manufacture its first product at the commercial scale. Like many companies in early development, it went through a couple of other suppliers before establishing a relationship with Boehringer Ingelheim as its CMO. Again, however, it was its own internal expertise that helped the company navigate all the challenges of process scale-up and commercialization. It is now making GMP lots and will be ready to launch its Phase 3 trials next year, according to Cleland.

Most of the process for making the rhGH product is straightforward and familiar biotechnology using E. coli, he says. But one aspect of the product and its long-acting technology presented an initial challenge. XTEN dramatically increases the solubility of proteins because the hormone-carrying molecule is hydrophilic and typically negatively charged.

"Growth hormone normally forms an insoluble inclusion body in E. coli. But in our case we form soluble proteins. That made that initial extraction step a bit challenging, but we figured out a way to overcome it early on, and we now have that part of the process, as well as the downstream process, well-scaled."

Cleland says the company also initially used some uncommon resins that were unavailable in the sizes and quantities needed for commercial scale, but it found alternative sources of better resins. "It looks now like the costs of goods will be less than it would cost for an equivalent daily growth hormone dose."

THINKING AHEAD

Pre-commercial development in any industry never means closing one's eyes to the commercial realm. A start-up company must project not only the size and potential of its market but also its conditions as key factors in the business model. Cleland and his team applied that principle to elements they knew would determine the commercial fate of their long-acting rhGH as a specialty product — pricing and reimbursement.

"Even before the IPO, we did quantitative market research with the U.S. prescribers, 68 pediatric endocrinologists, and with payers, about 14 different pharmacy directors and medical directors, managing formularies for about 250 million lives. What the research told us — which will be highly valuable for us when we reach commercialization — was that there will be really strong demand for this product, if it continues to perform as hoped. But payers also told us that we should not 'premium-price' the product if we want to be considered preferred or health-preferred. 'Just try to price it close to parity with the daily growth hormones already approved and access will not be a problem,' they said."

Cleland calls the situation with VRS-317 "a real opportunity to disrupt and consolidate the market, which is really fragmented right now." There are more than a half-dozen daily growth hormones now on the market, with none having a majority share.

At the same time, Versartis is not alone in the long-acting rhGH development space. But, Cleland says, of the several competing companies in the space, all are working on weekly dosing. Versartis is also ahead of the pack in developing the pediatric GHD indication, for which it hopes to be first-to-market. "Entering the market first with the longest-acting product should be an advantage for us if we can stay ahead of them. But that is the challenge, obviously — you need to stay ahead of the competition, and you need to prove your differentiation as you go forth."

PARTING ADVICE

Cleland has a few thoughts for startups gleaned from his own experience. "One important principle we learned early on was staying lean, staying virtual. Don't add staff, and outsource as much as you can. Try to get to the next inflection point and do the next important experiment without spending a lot of capital. We are seeing a trend in our industry with more startups turning to a virtual model, and I believe it has really served us well. We are also fortunate to have talented people managing outside resources to achieve our goals, so make sure you get the right people with the right experience, to run your virtual operations."

"Payers also told us that we should not 'premium-price' the product if we want to be considered preferred or health-preferred."

JEFF CLELAND
CEO of Versartis

As for Versartis, Cleland says the company will go the distance with its now lone product but will continue to invest in additional products for its pipeline. It will also continue to add people — those who meet a high standard.

"We are planning to launch three registration trials next year — in the United States, Canada, Western Europe, and Japan — so we really need more resources. The biggest near-term challenge is finding the right talented people to come in and help us build the organization. Companies often underestimate the importance of culture, so we are being proactive and interviewing not just for talent but also for a cultural fit. We want people with the spirit we had at Genentech in the 1990s."

Thus, Cleland supplies another reason Versartis belongs in The Enterprisers. May this industry never forget its roots — they were not about style, but enterprise.

Engaging Investor Interest in Biotechs: A Professional Perspective

GUR ROSHWALB, M.D.

What can executives of biotech companies working on novel treatments do to attract investors? With a professional background that has spanned the worlds of finance and biotech, I believe I have a valuable perspective on this question.

In my view, the lessons can be boiled down to a few key insights that could be useful for biotech company executives who wish to attract investor interest and potential new sources of funding.

Before I share these insights, let me briefly detail my own experience. Prior to assuming my current position as CEO at Celsus Therapeutics, a NASDAQ-listed biotech company developing a new class of anti-inflammatory drugs, I served as a VP at Venrock, a leading venture capital firm. At Venrock, I was an investment professional on the healthcare team, investing in both private and public healthcare companies and becoming intimately involved in the valuation and diligence of numerous pharma and biotech firms. Prior to Venrock, I was a VP and senior research analyst at Piper Jaffray & Co., where I focused on specialty pharmaceuticals and small cap biotech companies. In this role, I was responsible for analyzing, valuing, and publishing research on both private and public biotech/pharma companies.

"Be familiar with the investment style and return objectives of the funds you are speaking to."

SO WHAT INSIGHTS HAVE I GAINED WORKING IN THESE AREAS?

As an investor, there were several specific qualities I looked for in a biotech company. The first of these was a management team with relevant experience. A company is much more likely to inspire confidence if its CEO, chief medical officer, and/or other top-level executives have a background that involves working in the particular therapeutic area being presently addressed, or a closely related area, and a history of successful execution. This lets an investor know that management is likely to be intimately familiar with the specific challenges involved in treatment, as well as the competitive landscape. Overall, it increases the chances the company is well-run and will remain on track.

Second, a careful investor will seek to ensure that a company's treatment is based on sound biology. Does the company's description of the drug and its proposed method of action make sense? Good investors will be able to sniff out dubious claims or those that are radically inconsistent with the current state of medicine in the field. Just as important, an investor will ask if the data obtained to date is consistent with the claims being made.

Also, investors will be sure to assess if the return potential offered by a company fits in with their current portfolio needs. Given that every investor has a specific investment profile they are seeking to maintain, a company whose promise does not seem like a good match is much less likely to be pursued as a viable investment.

As an investor myself, companies I passed up were often those where I did not believe the data demonstrated sufficient proof of concept or where I and company management disagreed about the real market potential — and hence return profile — of the company. A prototypical example would be an oncology company; often, it will present with open-label, early data with "interesting" responses versus historical response rates. It is very difficult to invest in such a company with confidence as the comparability to historical response rates is rife with too many questionable assumptions.

I worked at a long-only, micro/small-cap fund, where returns are generally driven either by being contrarian or "early to story" (e.g., recognizing the value of a company early in its development). Among the companies I liked to invest in were those that had data from an unsuccessful later-stage trial, where the company resolved to redo the trial "correctly." This type of company allows an investor to assess all three of the considerations I outlined above. Did management recognize the issues that led to the first failure, and can they successfully carry out the new trial? Does the data from the failed trial demonstrate a failure in the biology of the drug or more in trial design and execution? These companies are often written off, but can come back with a roar if successful.

Based on the above, what advice can I offer to companies going forward? First, it is wise for management teams to be intimately familiar with their data and their competitive landscape. If management can convey to potential investors that they really understand what they have and who they are up against, the more secure investors will be in taking a position. Second, remember that a good management team is one that is open to outside viewpoints. If an investor comes away from a conversation with management with the impression that they have blinders on, this lack of flexibility will serve to deter them. It's important to conduct the right trials — i.e., trials that really get to the heart of the science behind your drug and answer real questions about what treatments might do. Finally, be familiar with the investment style and return objectives of the funds you are speaking to — often, you can shape your story to speak more directly to satisfy these points.

In my view, executives at biotech companies wishing to attract investor interest should be aware of the insights I've outlined above, as these are likely to motivate investors focusing on this space.

Gur Roshwalb, M.D., is CEO of Celsus Therapeutics, a biotech company focused on the development of a new class of non-steroidal, synthetic anti-inflammatory drugs termed Multi-Functional Anti-Inflammatory Drugs or MFAIDs.

A 7-Step Guide
To Finding The Right Strategic Investor For Your Start-Up

EMILY WELSCH

While institutional VC has been the traditional funding route for many start-ups, entrepreneurs are now more often turning to life sciences industry corporate venture capital (CVC) partners for financial and development support.

This source of strategic partnership offers a synergistic relationship that combines monetary and functional resources, capabilities, and core competencies for the purpose of technology commercialization. Entrepreneurs who are looking to accelerate the growth of their businesses often realize they can capture a greater bang for their buck when they collaborate with CVCs who offer value beyond the dollar.

As a life science management consultant who aids in facilitating these types of relationships, I am frequently asked by entrepreneurs how they can find these strategic partners. I discussed this topic with Marian Nakada, VP of pharmaceutical venture investments at Johnson & Johnson Development Corp., and Jason Hafler, director of investments at Sanofi-Genzyme Bioventures, and they provided some valuable insight from a CVC perspective.

Life sciences start-ups considering a strategic investment can benefit from checking their progress and development against a series of partnership measures laid out in the steps that follow.

STEP 1: KNOW YOUR COMPANY

The first step in this process is to conduct an internal assessment of your start-up. Please note that these criteria are subjective to the individual investor; however, every entrepreneur should be prepared to provide justifications for each.

- Significant Market Need: Does the technology apply to an indication for which there is a significant unmet need?
- Transformational vs. Incremental Technology Advantage: Does the technology demonstrate a clear differentiation from the competition and the standard of care by providing efficacy where there is none today, rather than a modification to a current treatment option?
- Patent Ownership: Does the start-up own the IP rights to the technology, or does the start-up have a clear path to strong IP?
- Strong Team: Do the start-up team members have proven capabilities in their areas of expertise? Keep in mind that a first-time entrepreneur can compensate for a lack of experience in a particular area by building a strong advisory board.
- Product Development And Commercialization Strategy: Does the start-up have a realistic product development plan? Does the start-up understand how much capital will be necessary to reach the development milestones?
- Regulatory Environment: Does the start-up understand how to navigate the regulatory environment?

STEP 2: ESTABLISH DEVELOPMENT PLAN AND SHARED PARTNERSHIP GOALS

While the industry partner may be interested in financial returns or strategic growth opportunities from equity investments in the start-up, the start-up may be looking to gain access to capital, in-house development resources, vendor connections, market validation, exposure to and expertise with international markets, and assistance with manufacturing, distribution, pricing, and/or reimbursement. Regardless of what the goals of the partnership are, there must be an established and fair balance that is agreed upon by all parties involved. Put simply, every partnership should be mutually beneficial.

Not every investor is the right fit for every start-up. Identifying the appropriate strategic partner and evaluating the potential relationship prior to engagement is a critical component in becoming partnership-ready. The start-up should begin by identifying what it is aiming to gain from the collaboration and which partners would be able to meet these needs.

- Required Resources: What resources are needed? What kind and how much support will the start-up require to reach its development goals? What are the major milestones? How will the support be used to reach each milestone? This information can be extracted from a refined product development plan.
- Capital Efficiency: How will the start-up illustrate its ability to be capital-efficient? How has the start-up proven its capital-efficiency in the past?
- Time Efficiency: How has the start-up proven that it is able to meet milestone deadlines on time? Proving that the start-up can stick to deadlines also helps

illustrate capital efficiency because, after all, time is money.

- Identification Of Partners: Who is strategically investing in the start-up's therapeutic area? Information on strategic interests of partners can be found on most of the CVC firm websites.
- Identification of Capabilities: Does the partner have the level and quality of resources that the start-up requires to reach its development goals?

STEP 3: PREPARE FOR ENGAGEMENT WITH INVESTORS

As the saying goes, you never get a second chance at making a good first impression. Therefore, it is crucial to fully prepare for engagement with potential investors. Preparation should include the development of an executive summary and a nonconfidential pitch deck presentation consisting of 8-12 slides that concisely covers a broad overview of investment criteria from steps 1 and 2. The intent of the presentation is not to necessarily explain every aspect of the technology, but rather to explain the value of the technology and how the technology will change the therapeutic landscape. Incorporating the start-up's product development plan and anticipated budget into these slides can be a great tool to show the partner that the start-up not only understands what needs to be accomplished but also recognizes that the timely completion of the product development milestones builds company value and enhances the potential upside for investors.

STEP 4: GET THE INVESTOR MEETING AND BUILD YOUR BRAND

The number-one way to make contact with a strategic partner is to be introduced through a mutual connection that can vouch for the legitimacy of the start-up team. While not every entrepreneur has direct connections to potential partners, there are ways to develop new relationships with these individuals and with others who can offer introductions.

Using social media, such as LinkedIn, to identify network connections to the partnership companies of interest is a great first step. Cold LinkedIn messages or emails will likely not garner a positive response, so instead of using this approach, consider asking shared connections to make introductions to the decision makers or partners of interest. The start-up can also participate in publicity activities including publications (articles, social media or blog posts, white papers, newsletters, scientific literature, and press releases), courses, webinars, angel group events, venture café events, and networking panels.

The start-up should build its brand through speaking opportunities, conferences, and networking events. There are many ways to publicize your company without providing any confidential information, and generating buzz can open the doors for partners to engage with the start-up. Partners will not seek out the start-up if they haven't had the opportunity to get excited about what the company is doing.

STEP 5: EVALUATE THE PARTNER'S INVESTMENT STRATEGY

At this stage, it is important to assess whether or not the goals of the start-up are aligned with the corporate venture fund of interest. When both parties are working toward synergistic goals, they can easily operate in a mutually beneficial partnership. The following questions are provided to assist the start-up in assessing the appropriateness of the partner prior to final selection.

- What value will the partner add beyond the dollars?
- What are the partner's development capabilities in the indicated therapeutic area?
- Does the partner have marketing and commercialization capabilities?
- What is the start-up's expectation for the scope of involvement?
- If the partner syndicates its investments, does it co-invest with top-tier investors?
- What level of interaction will be expected between the partner and the portfolio company? Will the strategic partner interact between board meetings, or are they hands-off in their approach?
- What other investments has the CVC made, and does its investment strategy fit the start-up's technology and core therapeutic area?
- At what stage does the partner invest?

STEP 6: NEGOTIATING THE PARTNERSHIP AGREEMENT

If the investor is interested in partnering with the start-up, a term sheet will be generated that outlines the goals, milestones, responsible parties, and general terms for the partnership. A lawyer may assist the start-up in negotiating these terms.

Once the terms of the partnership are established, the start-up and partner need to devise strategies to achieve these goals together. The development of these strategies requires input and action by all participants in the partnership. Often a partnership agreement may be drafted to define roles and responsibilities based on the agreed-upon goals and milestones from the term sheet.

STEP 7: MAINTAIN A WORKING PARTNERSHIP

A healthy partnership takes hard work to keep it working smoothly, frequent and effective communication, and a strong personal commitment from both parties. According to Nakada and Hafler, when it comes to functioning partnerships, it's essential that start-ups stay focused on delivering milestones and are proactive about communicating and confronting any problems immediately.

Finding the right strategic investor can be daunting for life sciences start-ups, but successfully navigating this partnership process can be a beneficial step toward ensuring the start-up's long-term success. Life sciences start-ups pursuing a partnership with a CVC can find a higher likelihood of success if they follow the measures laid out here, including assessing the start-up's assets and deficiencies, establishing mutual partnership goals and milestones, and maintaining expectations. Developing a start-up beyond the seed stage is challenging. Establishing strategic partnerships with the right partners benefits not only the start-up, which gains access to capital and commercialization expertise, but also the CVC and consumers by bringing transformational new products to market.

Emily Welsch is a consultant at Halloran Consulting Group specializing in assisting entrepreneurs to reach their commercialization goals. She has more than nine years of experience in pharmaceuticals, medical devices, and early-stage new ventures.

Making The Decision To Implement Adaptive Trials Across A Portfolio

PHIL BIRCH

Dr. Phil Birch is VP of innovation strategy, alliance partnerships at ICON plc. In the industry for more than 28 years, he's held senior positions in corporate development and R&D in consulting, biotech, and top 10 pharma companies.

The Phase 3 failure rate is hovering near 50 percent. One in five drugs requires a dose change within the first five years of marketing. The cause of these dismal statistics is rooted in the inaccuracy of the assumptions upon which trials are designed, particularly during dose selection in Phase 2.

Adaptive designs can significantly improve early-phase development decision making by allowing sponsors to correct assumptions made at the outset of the study. In the same way a football coach adapts his strategy at half-time if his team is losing, an adaptive design allows alteration of a trial's "game plan" based on accumulating data at defined interim analysis steps.

In the case of adaptive dose-finding, this can mean economical testing of a wider range and number of doses and adapting the patient allocation by adding or dropping doses at the interim analysis point. The flexibility of adaptive designs allows for a more accurate estimation of the minimum effective dose and increases confidence that the right dose is moving into Phase 3.

Design assumptions are not flawed in every trial, and errant assumptions do not always lead to complete failures, but the only way to prevent these risks from draining resources is to institute a process that reduces the probability of error across an entire portfolio.

ADAPTIVE DESIGNS CONSERVE RESOURCES AND IMPROVE DECISION MAKING

Simple adaptive designs, which include re-estimating the sample size to prevent an underpowered trial from failing or stopping early for futility or efficacy, can provide substantial benefits. The Tufts CSDD (Center for the Study of Drug Development) estimates that simple designs could save $100 to $200 million annually when applied across a portfolio. Most of these cost savings are driven by futility stops, which means products are failing.

The real value of adaptive design lies not in accelerating failure, but driving success. Sophisticated designs deployed in exploratory development increase the probability of products completing pivotal trials — and the identification of the most favorable dosing and safety profiles for maximum commercial return. Sophisticated adaptive designs are central to the value proposition that "getting it right" at Phase 2 drives enterprise value.

ADAPTIVE DESIGNS ARE NOT NEW, AND REGULATORY AGENCIES UNDERSTAND THEIR VALUE

Adaptive designs are not new; Pfizer, for example, ran its first adaptive trial in 1984. While adaptive trial adoption grew at a rate of 38 percent from 2011 to 2013 to reach 20 percent of ongoing trials, further adoption is essential to realize benefits only possible at the portfolio level. Several top pharmaceutical companies are expanding the application of adaptive design as evidenced by widespread interest in Novartis' adaptive dose-finding methodology and Janssen's heavy investment in quantitative sciences for the design of adaptive trials. Furthermore, Novartis, Janssen, Eli Lilly, Pfizer, and Roche have recently partnered in the ADDPLAN DF Consortium to improve existing technologies for the design and execution of adaptive dose-finding trials.

Regulatory agencies understand the value of adaptive designs and encourage their use. The EMA (European Medicines Agency) recently qualified an adaptive analysis method called MCP-Mod as an improved procedure for dose-finding designs. The qualification indicates the organization's desire to see more innovative trials. The FDA has issued several adaptive guidances and in 2013, began granting potential priority review status to IND (investigational new drug) applications that utilize adaptive design. In July 2014, CDER director Janet Woodcock testified to Congress that the FDA encourages adaptive designs, when appropriate, to increase trial efficiency.

INVEST IN RESOURCES UP FRONT TO IMPROVE RETURN LATER

Implementing an adaptive strategy across a portfolio requires input from experts in adaptive design, translational sciences, clinical development, and regulations in order to identify where, when, and how an adaptive design approach will add value for each indication and phase of development. For each asset selected, the choice of an adaptive design should be thoroughly reviewed on an ongoing basis during the life cycle of the asset.

Adaptive trials require additional upfront planning to simulate and select the optimal design before the trial begins. This has to become an integral part of the protocol development process. In an environment where the costs of drug development are still increasing and the Phase 3 failure rate remains high, optimal decision making has never been so critical. Taking time to set the stage for success instead of rushing to get to market will pay off. L

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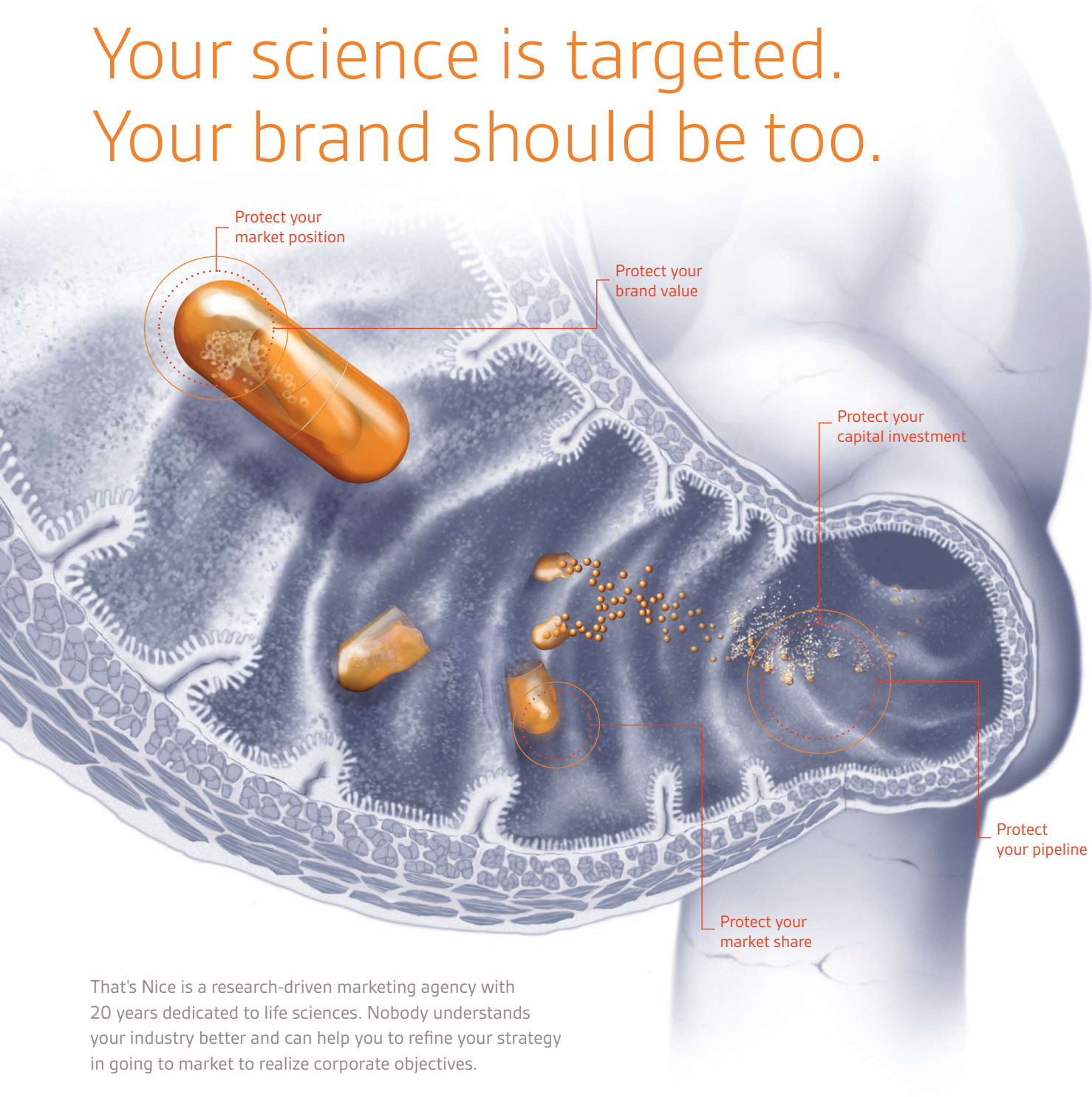

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Choosing To Be A Transformational Leader

DR. STEVE BROE

Life is vibration. Galaxies and asteroids, oceans and continents, electrons and protons all vibrate. Managers and leaders also bring a kind of vibration to their workplace. When a leader works with their team, activities follow a predictable orbit of behavior. It is comforting to see that work and motion remain stable within known patterns and ranges.

Occasionally, a quantum shift happens to the way people work. Leaders often initiate change; however, not all leaders change the nature of work. When a shift happens in the way people work, the cause is often due to a transformational leader. These people are game changers.

You have known leaders in your career, but few, if any, leaders are transformational. However, a transformational leader does not have to create world-shaking changes. Any leader who changes the vibration pattern with the way people work or live can be considered a transformational leader.

Do you want to be a transformational leader? Here are four behaviors that experts (McGregor, 1978, *Leadership*; Bass, 1985, *Leadership And Performance Beyond Expectation*) agree mark the work of a transformational leader:

1 CONCERN FOR THE INDIVIDUAL

The transformational leader regards every person on a team as a unique contributor. Each person has fears, needs, and motivation priorities. The leader pays attention to every colleague and responds to them with individualized consideration.

2 INTELLECTUAL STIMULATION

Presenting a vision of a possible and better future, the transformational leader encourages all followers to participate in making the vision work. A leader will encourage others to be innovative and develop their creative talents. New ideas are encouraged by a transformational leader, and instead of attacking new ideas, people find ways to make these ideas work.

Dr. Steve Broe is an executive coach who lives in Scottsdale, AZ. His book, *Leaders in Transition*, answers the question, "How do people change careers and become a leader in the new field?"

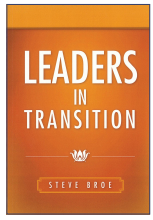
3 PROVIDER OF INSPIRATION

People want to have reasons to hope. A great leader will challenge followers to do work because it means something important to them. An inspirational leader finds a way of connecting each person's efforts with the mission of the team. A transformational leader can change the vibrational level of the team, and followers share the inspirational message with the leader.

4 LEADS THROUGH INFLUENCE

Great leaders don't need to command. They have learned the skill of influence: encouraging others to work with them because they want to do so. Transformational leaders are usually role models in the work, helping others to do their best work. The skill of influence builds on emotional intelligence and the power of conviction. Leaders offer the following to others: "Work with me, and I will help you become a stronger leader, too."

Aim high. Look for ways to improve your work and your world. With deep conviction and a vision of a better way to work, you might succeed as a transformational leader. L



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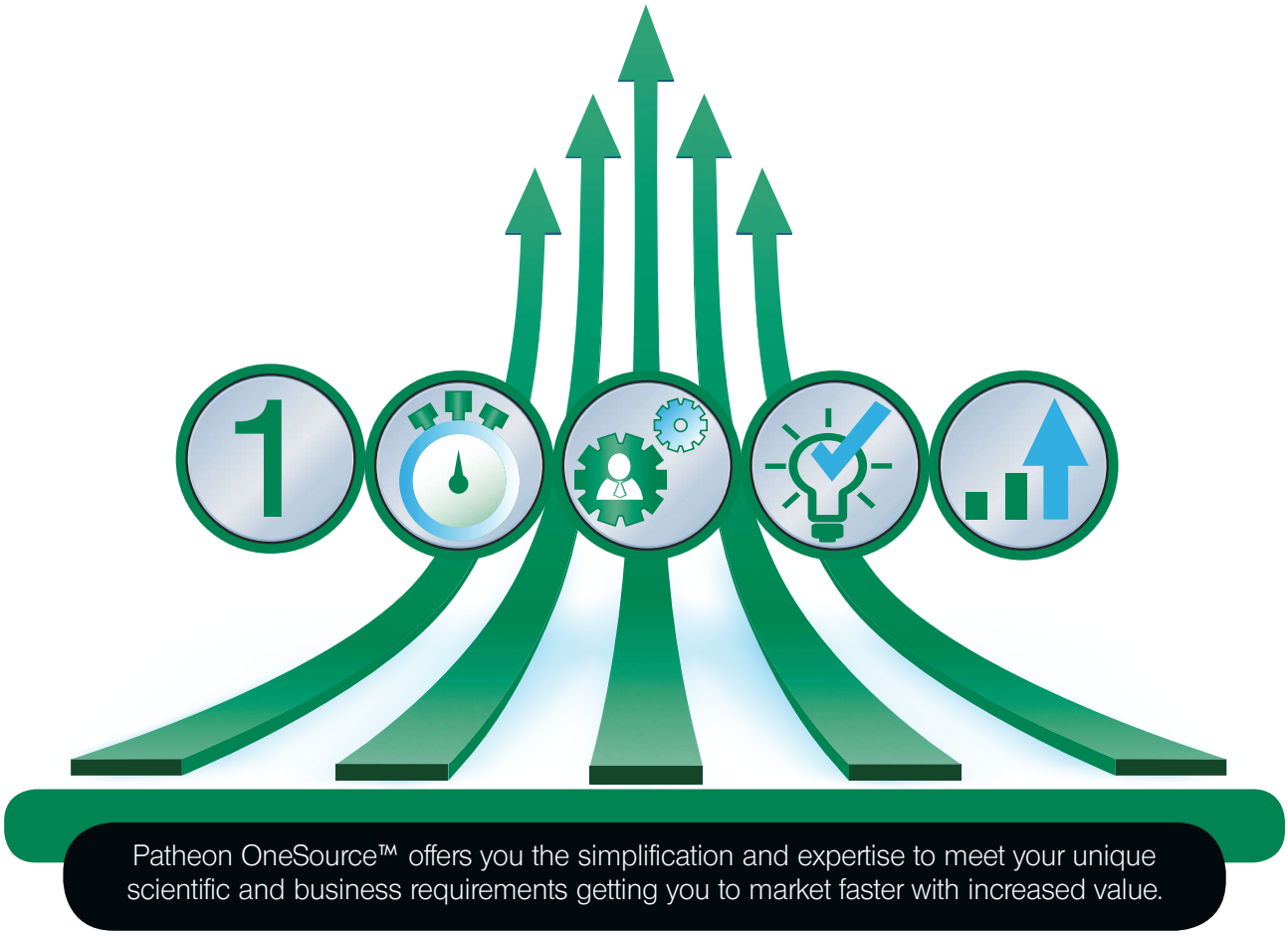

Patheon OneSource™ offers you the simplification and expertise to meet your unique scientific and business requirements getting you to market faster with increased value.

- One partner for collaborative drug substance and drug product development
- Single point program management for clear and direct communications
- Simple and flexible contracts to match business needs and rapid project starts
- Parallel processing and activities for time savings of 8-12 weeks or more
- Experienced and responsive experts to ensure project success
- Reliability and trust with Right First Time and On-Time-Delivery proven with an industry leading quality track record

Patheon OneSource™– delivering a simplified development solution with expertise in **drug substance and drug product development** – getting you to market faster.

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