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Biotechnology

Cytokinetics Stays the Course

Is it crazy for a discovery company to create a ten-year plan and follow it? Cytokinetics thinks not.

By Jeffrey Dvorin

The vast majority of biotechnology companies to-day have abandoned the traditional discovery model—determining that it's simply too expensive and time-consuming to first create novel compounds, demonstrate their biological relevance and then advance through clinical trials. Instead, almost everyone has tried to shortcut the discovery process, for example, by in-licensing, repositioning, reformulating or delivering existing products.

Cytokinetics Inc. is thus a rare bird in the biotech world: a well-funded public company relying on its own R&D to generate the products it hopes to commercialize. Moreover, unlike so many of its peers, it has, for the most part, stuck with the original scientific and commercial vision of its founders; eschewed in-licensing to accelerate its R&D program; moved into development without retrenching discovery; and, despite its significant cash position, done but one deal—with **GlaxoSmithKline PLC** in oncology—in the seven years since it was founded.

Cytokinetics isn't the only company based on discovering and, at least to some extent, developing its own products. **Exelixis Inc.** and **Theravance Inc.** have both been successful in advancing their own products into the clinic, as has **Rigel Pharmaceuticals Inc.** Along with individual differences (Exelixis, for example, in-licensed its leading candidate; Theravance doesn't plan on commercializing its own products), Cytokinetics claims to have distinguished itself by a far more methodical approach to strategic planning than is typical in the biotech industry—the kind of apparently bureaucratic process small companies are famous for avoiding. But it is precisely this process that, its executives maintain, has allowed the company to exploit the synergy between its scientific and commercial approach, while maintaining focus and financial discipline.

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CYTOKINETICS
STAYS THE
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Zeroing in on the Cytoskeletal Highway

Perhaps as much as any company, Cytokinetic's scientific approach is inextricably linked to its business model. It's an approach largely pioneered by Cytokinetics, which is now the leader—indeed, one of the few players—in the field.

The scientific core of the company remains, as when it was founded by a group of cell biologists in 1998, the biology of the cytoskeleton. The founders, including Cytokinetics' president and CEO James H. Sabry, MD, PhD, were inspired by recent discoveries regarding the crucial role that the cytoskeleton plays in many cellular processes. Once thought to be an internal scaffolding that provides architectural support for the cell, it is now known to serve as a framework for organizing many cellular processes, including signal transduction, cell division, intracellular transport, cell motility and muscle contraction.

The cytoskeleton is a sort of cellular urban planning system for getting the right proteins to the right place at the right time. The major structural proteins of the cytoskeleton that act as highways in this plan are tubulin, actin and intermediate filament proteins. These proteins join to form polymers of variable length known as microtubules, actin microfilaments and intermediate filaments, which mediate nearly all aspects of intracellular transport and cellular movement. Most importantly, these filaments interact with a group of important and function-specific motor proteins, including kinesins, dyneins and myosins which transport various forms of cellular cargo along filaments. The cytoskeleton also contains groups of non-motor filament binding proteins that regulate it and its motors so that the system can carry out particular cellular functions.

Several then-existing cancer therapies—paclitaxel (*Taxol*), vincristine and estramustine—attack cancer by targeting microtubules, the major highway protein involved in cell division. But because microtubules are also implicated in a variety of other important cellular activities, interfering with its activities in cancer cells inevitably results in serious side effects. “The mechanisms of action of drugs like *Taxol*,” says Sabry, “may involve the cytoskeleton, but were discovered essentially by happenstance and not as the result of any systematic understanding of the cytoskeleton.” Cytokinetics thus set out to go after molecular targets possessing highly specific functions and expression patterns.

To that end, the company initially concentrated its efforts on mitotic kinesins, a group of motor proteins that appear to be expressed only during cell division and which seem to be upregulated in cancers—thus offering the possibility of cleaner side-effect profiles for drugs that target them.

An Early Commercial Vision

The company's founders believed that the biology of the cytoskeleton provided a unique opportunity for building a scaleable business—in contrast to the enabling technologies much in vogue with biotech start-ups at the time. Cytoskeletal targets had already been validated by the various approved drugs with mechanisms of action directed at such targets. But Cytokinetics could lay claim to being the first company to specifically focus on the cytoskeleton, and to this day continues to have very little competition in the area. Indeed, maintains Robert Blum, EVP, corporate development & commercial operations and CBO, the company has so far been able to keep expenses down and early-stage productivity up—to create a congestive heart failure (CHF) program while being paid only for the GSK oncology work—largely because of the scalability of the cytoskeleton platform.

Still, the novelty of the field also meant that the company's bet on the cytoskeleton as the sole basis for a business had its risks. The success of drugs like *Taxol* notwithstanding, it was not at all clear that the cytoskeleton would yield a sufficient number of drugable targets to sustain the company.

On the other hand, says Blum, a cell biology approach avoids the risks faced by the many biotechs that narrowly focus on a single compound against a single target. Rather than looking at proteins acting in isolation, Cytokinetics' cell biology-based drug discovery examines proteins acting in concert, either in multi-protein complexes or in cohesive pathways. As a consequence, says Blum, Cytokinetics can pursue “multiple ways of inhibiting a pathway or a biology” and thus manage risk by generating multiple compounds against each target.

And concentrating on the cytoskeleton has allowed Cytokinetics to dig deeply into the structure for potential targets. Advances in genomics enabled researchers to very quickly identify every mitotic kinesin involved in mitosis, thereby providing the basis for building an oncology program around multiple targets and an understanding of a whole biological pathway.

Sabry contends that focusing on biology, and the cytoskeleton in particular, provided an opportunity to create a scaleable business that could leverage its cell biology approach across technologies and therapeutic categories. “In a genomics-based company you have to build it from the ground up every time” for each gene target, says Sabry.

In contrast, Cytokinetics' other programs—in CHF, fungal diseases, inflammation, hypertension and asthma—will benefit from infrastructures created for the oncology/mitotic kinesin research, according to Sabry. Focusing on biology, allows “us to leverage certain technologies across programs, certain insights into chemistries and pharmacophores that extend from one target space to another and risk-manage our business so that we are building programs at a marginal economic spend altogether, not having to then recreate the drug discovery infrastructure.”

The one major deviation from the original vision for the company was its abandonment of an application service provider (ASP) business in cellular bioinformatics based on *Cytometrix* technologies for automating cell biology. The plan was to provide funding for the company's drug discovery programs by offering compound profiling services for pharmaceutical companies, and eventually selling subscriptions to a line of predictive databases. But because the *Cytometrix* technologies had to be customized for each biological application, it was not a scaleable business; and thanks to its successful fundraising, Cytokinetics felt free to abandon it.

Thinking Long-Term

Despite the *Cytometrix* ASP diversion, Blum says the company has been “ruthlessly consistent” in pursuing its original goals. “Most biotech companies,” observes Blum, “including those that have been led astray by venture investors looking for early returns and shortcuts, have not had the resolve to bet on a biology and build a company on that framework.” Doing so, Blum continues, requires “a certain discipline and focus that allows you to be sure that every incremental investment you make is consistent with the company's mission.”

When Cytokinetics was about three years old, its leadership began a formal long-term planning process, forming a group—consisting mostly of scientists—to evaluate the company's strengths and weaknesses and examine such things as the ways in which they could leverage their technology across therapeutic areas and research projects, the areas in which they'd need a partner, and the funding that they'd need to raise to achieve their goals. In addition to helping to chart a future course for the company, Blum says that the exercise created “collective buy-in” from the R&D side for what the company needed to do build a sustainable enterprise.

That qualitative self-examination was followed by a quantitative evaluation of what it would take to advance the company's long-term goals. Roughly 40 people, including most senior staff, participated in this process. The group drawn from across research, development, IT, commercial planning, and facilities—created a profile of what the company should look like in ten years, in terms of revenue, number of employees and number of programs. This allowed the team to determine the appropriate cost structure and approach to accessing capital at various stages of evolution. They then developed a roadmap to take them to their long-term objective of moving from a company with no commercialization infrastructure, and only early-stage development capabilities, to one that commercializes its own cardiovascular and oncology products in specialty markets and that has strong development in those and other acute therapeutic areas. In effect, Cytokinetics wanted to make sure it didn't continue to merely do what its scientists knew how to do. It's the type of planning, observes Blum that a lot of Big Pharmas do, but that “biotechs, for some strange reason, ignore.”

Or perhaps not so strange. The notion of a start-up creating a detailed ten-year strategic, operational and financial plan, as Blum and a small team he hired actually did, seems absurd, given the vagaries of discovery and development science. Nonetheless, Blum's team started by identifying successful companies against which to benchmark themselves to see how they managed the growth of their portfolio of programs through risk and attrition, as well as how they accessed capital and leveraged in-licensing and M&A. These data were used to create a strategic plan that goes “all the way from lab bench to marketplace with detailed revenue and costs, including such things as product forecasts and launch costs,” says Scott Jordan, a former Wilkerson Group consultant and one of the Cytokinetics business development team members who has spearheaded this process.

The team projected, for each of the company's programs, the number of FTEs required for target identification, target validation, assay development, lead optimization, preclinical and clinical—as well as the number of programs that would be needed at each stage in light of industry standard attrition rates and the ways in which Cytokinetics technology might allow it to improve upon those rates. The plan projected the costs associated with the various stages of the process, along with the points at which the company would need to raise additional capital.

Planning for the Best and Worst of Times

Each program plan came with a variety of outcomes: best-, worst-, and base-case scenarios. These scenarios are plotted with what the company calls “pipeline rulers” that identify risk factors and

requisite project resource allocations for the ten-year periods they cover. The pipeline rulers are built around a variety of assumptions—for example, how long a program will be at each R&D stage, the costs associated with each stage, and what the company's cash position will look like in light of all of all of its programs. The planners then created variations on a set of base assumptions to account for possible deviations. The company's leadership can thus anticipate points at which it may need to raise capital, also building into its projections possible fluctuations in financial market conditions

The idea, according to Blum is to “ensure that if we hit an air pocket, we can react to it rapidly,” for instance, by anticipating a clinical or regulatory setback and laying out the company's options—shifting resources to another program, cutting a program entirely or in-licensing (specifying the criteria to be used in selecting compounds from the outside). “You can't decide once you have a failure to go out and in-license ... or you'll delay 12-18 months,” says Blum. To that end, the plan contemplates a possible failure to establish proof-of-concept with the lead oncology compound, factoring in when such data might be expected to hit and projecting the impact that those results would have on the ability to raise capital and on the pipeline as a whole. Thus, although the company's lead oncology candidate appears to be on track, it is already talking to potential partners about compounds that would fit its pipeline should clinical/regulatory problems arise.

Blum says it's equally necessary to plan for unexpected successes, so that if a product progresses through the clinic faster than anticipated and is approved, there are contingency plans to address the need for additional capital to cover increased development and commercialization costs. And, more fundamentally, the plan tries to ensure that the company doesn't become so development oriented that it starves research.

Drawing up strategic plans is a very inexact science. In fact, Jordan maintains that the most important benefit from the plan are the internal discussions it triggers each time the plan is revisited (in annual cycles and whenever events dictate a change in the assumptions) to assess the company's current state and consider what adjustments are needed looking ahead.

How Far to Look Ahead

Thinking ahead ten years is entirely appropriate for a biotech at Cytokinetics' stage of development, according to Vaughn Kailian, Blum's former boss as CEO of Cor Therapeutics (where Blum served as director, business development and then director, marketing) and more recently vice chairman of Millennium Pharmaceuticals Inc. In fact, anything short of ten years, he says, doesn't make sense. “If a product is in the clinic, you need to go out ten years just to get cash flow from the programs; if it's in Phase II, you're probably only capturing the first five years of sales.”

Failing to plan long term has been the downfall of many a company. “In the mid-90s, there were a bunch of companies” that made foolish capital bets when they took down convertible debt,” but “didn't have the cash flow to pay it back and couldn't survive a downturn,” recalls Kailian. “If they'd really done a good strategic plan, they would've realized that they were totally betting on the upside scenario and that if that didn't work” the company couldn't survive.

Cytokinetics' board member Grant Heidrich, a partner with Mayfield, one of the company's original investors, says that he urges all of the companies with which he works to engage in the sort of long-time planning undertaken by Cytokinetics—just so long as they “don't get so caught up in the plan that they.... miss the train that's coming right at them.”

Still—ten years? Steve James, now president and CEO of **KAI Pharmaceuticals Inc.**, but who's had senior business development and operations stints at several other discovery companies, including **Sunesis Pharmaceuticals Inc.** and **Exelixis Inc.**, says that the detailed plans with which he's been involved have covered a three- to five-year range. “The only time I've ever used or seen a ten-year plan is what I would call a vision plan to get the team and the Board to think about what we'd call success in ten years.” But “it's uncommon to go out ten years and try to plan every step of the way, anticipating all of your portfolio programs, and which will succeed and what you do if one fails.” Instead, such detail should typically go into a three, possibly five-year financial plan—“because that's pretty much the product and financing horizon for every biotech.” Beyond years three or five years, the world may look completely different: it's just not worth “anguishing over unpredictable details many years out.”

And besides—just when does one start a ten-year plan? Cytokinetics didn't have it in 2001, for example, when it created one of the most important determinants of its business future: its alliance with GSK. As far as it goes, the deal is certainly a rich one for an ambitious biotech—including \$30 million to \$50 million in R&D milestones for each of the collaboration's ten-plus targets. It can buy in to any development program and thereby increase its royalty rate up to the high teens and also opt-in for North American co-promotion rights. And should Cytokinetics exercise its option, GSK will cover all marketing costs and provide an undisclosed amount of funding for sales force expenses incurred by Cytokinetics. That option, Blum notes, affords Cytokinetics the opportunity to advance towards its long-term goal of building a sales and marketing infrastructure—at least in part on GSK's dime.

In most basic ways, however, the deal is typical—the large partner gets most of the value. Cytokinetics can build some infrastructure through the alliance, and goose up its share of the proceeds—up to what Blum argues could be 50% of the profits, factoring in the time-value of money—but it’s still not the kind of deal that will ensure its long-term popularity with investors because it doesn’t leave Cytokinetics in control of its project’s destiny. For example, while Cytokinetics has the right to pick certain GSK-optionable targets and develop compounds around them, GSK has a buyback right for each such project, which means Cytokinetics can’t sell it to another partner.

The Deal That Wasn’t

In short, the GSK deal was a step in the right strategic direction—but only a step. “There are cheaper sources of capital,” Blum says. “The aftercare of deals and overhead associated with those relationships is a strong deterrent” to doing many of them. Now partnerships will only be struck, says Blum, “with specific objectives in mind—leveraging resources at Pharma companies where they can help further our business ambitions.” That’s why it abandoned, at the eleventh hour, a deal in congestive heart failure: they would have benefited from sharing development risk and cost, but no longer needed the partner’s early-stage development capabilities.

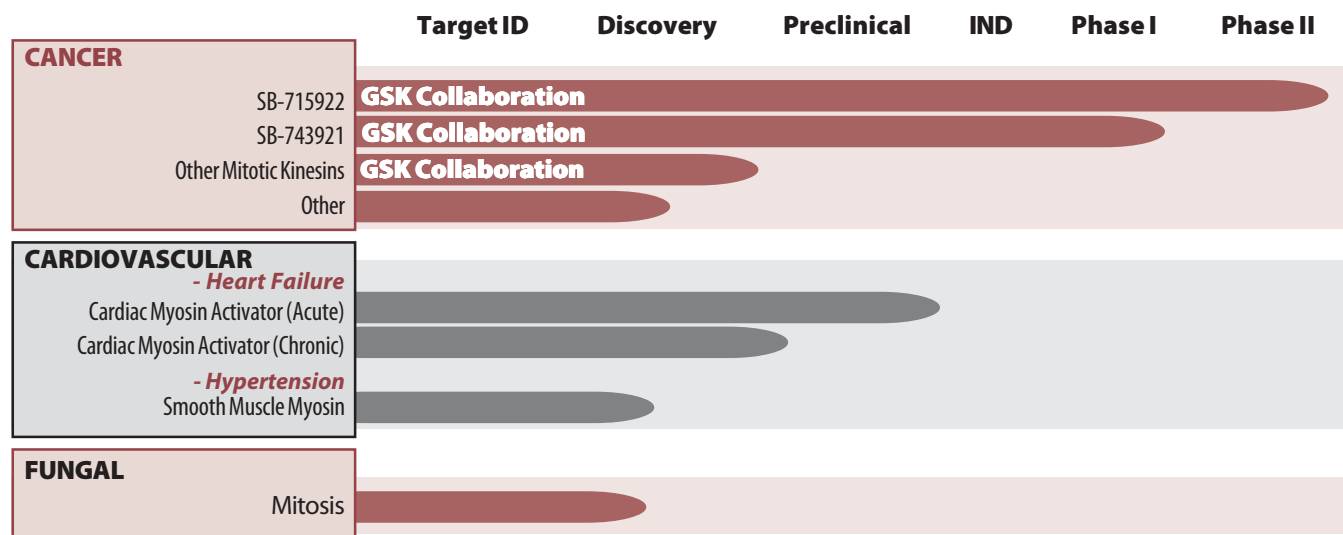
The CHF program targets cardiac myosin, the cytoskeletal protein responsible for converting chemical energy into the mechanical force that results in contraction of the heart muscle. Cytokinetics researchers reckoned that, by directly activating cardiac myosin, they could increase contractility while avoiding the unwanted effects of existing therapeutics.

By late 2003, the company had a preclinical CHF candidate (CK-1213296) for intravenous administration in an acute care setting and was also conducting research on orally available cardiac myosin-activating compounds for chronic care treatment. Cytokinetics initially planned to retain all commercial rights to its acute care CHF program, figuring that it could manage the late-stage development and commercialization of a product that would be marketed to institutions, but that it would need a partner to move into the chronic care market with an orally available treatment.

But it became increasingly apparent, says Blum, that the acute and chronic care programs

Cytokinetics Pipeline

EXHIBIT 1



SOURCE: Cytokinetics Inc.

needed to be handled under a single umbrella: CHF treatment involves a continuum of care that often begins in the hospital setting and is then managed on an out-patient basis. Thus, in late 2003 the company began looking to make a deal that would encompass both the acute and chronic care products.

With the company on sounder financial footing and having established stronger development capabilities, it could drive a considerably harder bargain than it had with GSK in 2001. According to Blum, any deal would have to give Cytokinetics the lead in developing and commercializing the acute care therapy—which the GSK deal specifically did not—and allow it to share the responsibilities and upside potential of products for the chronic market.

In September of last year, company officials said that a CHF deal was imminent. Then, on the brink of signing a contract, Cytokinetics pulled out of negotiations and decided to continue the program on its own, at least for the time being. They had the near-term money they needed, thanks to the IPO. They had a project team “with more acute cardiology experience than any other company—bar none,” says Blum. That group includes researchers—brought in both as consultants and employees—who worked on nesiritide (*NatreCor*) at **Scios Inc.** (acquired by **Johnson & Johnson** in 2003), eptifibatid (*Integrilin*) at Cor and tissue plasminogen activator (tPA) at **Genentech Inc.**

One key to abandoning the deal was the hiring of CHF specialist Andrew A. Wolff, MD as CMO and SVP clinical research and development. Before joining Cyto-kinetics, Wolff spent ten years at **CV Therapeutics Inc.** One of the rationales for partnering the CHF program was that that the company would need help in identifying and developing an orally available compound. But just around the time that Wolff came on board, according to Sabry, it became apparent that Cytokinetics might have generated just such a compound on its own. And Wolff helped confirm the viability of continuing work on the chronic care indication in-house. Sabry thinks Phase I will commence some time this year.

But another important factor in ditching the partnership, says Blum, was the strategic plan. According to Blum, it helped determine that Cytokinetics no longer needed the development capabilities it initially sought from the partner. In particular, the timeline projections for scenarios with and without a partner indicated no difference in time to market. And, from a financial standpoint, the company’s leadership determined that, with the IPO, Cytokinetics could afford to handle the programs internally through at least proof-of-concept and would get a better return on investment by waiting to do a deal.

Going Solo in Development

But before Cytokinetics reaches its new dealmaking stage, Blum and his colleagues will need to find the funding that that the aborted deal would have provided. As of December 31, 2004, Cytokinetics had \$116.2 million in cash, anticipating a net burn for 2005 of about \$55 million, up from about \$40 million in 2004—that leaves it with about two years worth of capital, less than it needs to get the CHF compound through proof-of-concept.

Blum notes that the company has raised over \$134 million in private financings, \$96 million through the IPO, and has never had a down round. But past is not necessarily prologue. There’s still the option of partnering its CHF program. The company, however, would be getting, at best, the same value for the project that it probably was given in the abandoned alliance and would thus be doing something it has assiduously worked to avoid: using dealmaking to raise capital. Another possibility—though one that Cytokinetics also wants to avoid—would be cutting back on discovery.

A Contrast in Approaches

The strategy pursued by Exelixis, which began as a genetics-based technology platform company, provides an interesting contrast—as well some similarities—to the course taken by Cytokinetics.

Exelixis and Cytokinetics (which until recently had a combinatorial chemistry collaboration) have both largely relied on internal R&D. And major deals with GSK represent defining partnerships for both. But the structures of those partnerships also say a lot about the differences between the two companies.

In its original deal with GSK, Exelixis was to deliver a set of molecules that met certain criteria, including validation through proof-of-concept (Phase IIa). GSK agreed to fund the program with a minimum of \$90 million, as well as an \$85 million loan facility. At proof-of-concept, GSK could then exercise an option to take over development, paying roughly \$90 million for the privilege, along with additional milestones as the product progresses and low double-digit royalties. Exelixis also received a \$30 million up-front payment, a \$14 million equity investment and has certain North American co-promotion rights.

The Cytokinetics agreement with GSK is, in some ways, a mirror image of the Exelixis/GSK alliance. Exelixis received considerably more cash and retained control over development through Phase II. Cytokinetics’ deal is arguably weighted more downstream: it hands over development to GSK, but keeps some later stage and commercialization rights, including funding to support any co-promotion efforts that it might undertake. Of course, at its stage of development, Cytokinetics couldn’t offer a partner the sorts of development capabilities that GSK sought from Exelixis.

To some extent, though, Exelixis was limited by the GSK alliance. The more productive it was, the more it would have to find the money to prosecute its programs—but since GSK owned rights to them all it would need some innovative financing structure to push them forward, without signing up another partner. That’s one reason Exelixis bought **X-Ceptor Therapeutics Inc.**—to get a

new set of preclinical programs it could turn into licensable material to which GSK did not have rights. (See "Feeding the Machine: Exelixis Buys X-Ceptor," IN VIVO, November 2004.) It's also what led to the amendment to the GSK deal, which advances some of the GSK milestones while permitting Exelixis to pursue expensive project financing with GSK potentially funding part of the additional capital cost. (See "Exelixis/GSK: Using Project Financing to Accelerate R&D," IN VIVO, February 2005.)

Challenges On The Horizon

While Exelixis' president and CEO, George Scangos, PhD acknowledges that it had to focus all of its attention on the GSK relationship for a while (especially since the milestone payments increase substantially depending on how quickly Exelixis delivers compounds), he says that's no longer the case. And, Scangos emphasizes, there is substantial upside potential from the GSK programs. The amendment limits the partnership to 12 programs, from which GSK can choose two or three compounds. According to Scangos, should GSK choose three compounds, the proof-of-concept milestones could reach \$275 million, with additional milestones—as well as a minimum of double-digit royalties—depending on how the compounds progress. Moreover, Scangos points out that GSK must make its pick of two to three compounds per program as the compounds are delivered (i.e. GSK doesn't get to look at them all at once before choosing) and that Exelixis is likely to retain some promising candidates as a result. Thus, he says, the resources devoted to the GSK programs are also being invested in compounds that will belong solely to Exelixis.

To the extent that Exelixis did have to set aside work on its own programs because of the GSK deal, it faced some of the same sorts of decisions that Cytokinetics will confront as its CHF program proceeds. Cytokinetics has already been forced to sharply prioritize its R&D efforts. In addition to oncology and CHF, Cytokinetics has programs in fungal disease, inflammation, hypertension and asthma. But all of that research is in the early discovery stage and Cytokinetics leadership makes clear that the current focus is on CHF and oncology.

As Cytokinetics moves into clinical development of its acute CHF compound, it will be entering a new and critical stage. Until now, the company has relied on a partner to shoulder the burden of developing its drug candidates. Now it will have to do that heavy lifting, at least for a while, on its own. At the same time it plans to maximize the value of the GSK deal by co-funding later stage development. Should the company be unable to raise sufficient capital from the financial markets, it will have to make some difficult choices—e.g. partnering in CHF, downsizing discovery, or reducing the development co-funding in oncology.

Whatever tough decisions may lie ahead, it's safe to assume that the company's leadership will have already thought long and hard about them. And though it may face turbulent waters ahead, at least they won't be uncharted.



Comments? Send an e-mail message to the
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