

LILLY'S CHORUS EXPERIMENT

A skunkworks at Lilly has been trying to dramatically increase likely-to-succeed shots on goal. If it works, will Lilly embrace the program—or will its venture partner reap the rewards?

BY ROGER LONGMAN

- Lilly set up Chorus as an independent division to get compounds to proof-of-concept far faster and cheaper than its internal research organization.
- To do so, Chorus pursues only what it needs to answer its POC question—skipping many of the activities required for beginning pivotal trials but which also increase costs and time to POC.
- Chorus hasn't yet proven that its ideas work—and within Lilly's R&D group, there's plenty of skepticism that it will, and maybe some anxiety.
- Chorus is also working with Versant Ventures to test some of the compounds sourced by the venture group—giving Lilly an early look at molecules it otherwise wouldn't see and Versant an opportunity to access de-prioritized Lilly assets.

In the race for biotech's most interesting projects, **Eli Lilly & Co.** looks like an also-ran. Maybe even a bystander.

One can understand Lilly's reluctance to pay the racing fees regularly anted-up by more aggressive in-licensors like **Roche**, **Merck & Co. Inc.**, **Pfizer Inc.**, and **Astra-Zeneca PLC**. Not too long ago, Lilly was considered the leading alliance-builder in the industry—when deals were far cheaper than today's mega-transactions. Now though, given the group's confidence in its near-term pipeline and commercial prospects, executives want to avoid adding the sky-high cost of external R&D to Lilly's internal expenses.

But there's still some creative dealmaking life in the venerable Indianapolis dowager. Several important groups at Lilly are very much interested in external innovation—

granted it can come relatively cheap. Thus, in January, Lilly signed, but didn't announce, a deal between early-stage investor Versant Ventures and Lilly's experimental early-stage development division, Chorus. Lilly would get a look-see at the potential of compounds Versant has uncovered through its EuroVentures in-licensing operation; Versant would get some preferential access to Lilly compounds flowing through Chorus that Lilly doesn't want.

The secret to this deal is how Chorus works: it gets compounds to proof-of-concept (POC)—clear evidence in human beings that a drug works—fast and cheap. Far faster and far cheaper than Lilly's internal research organization—and probably faster and cheaper than biotech, too. Thus, Chorus can give Lilly's development organization a choice of more compounds to put

into registration trials—and, theoretically, can give Versant a similar advantage.

Chorus accomplishes this trick by running a very lean organization, located outside of Lilly's labs, managing the process using a proprietary software package that gives all the key players instant access to all key information, and by taking shortcuts most Big Pharma development organizations won't. Those shortcuts mean that Lilly can't just put a Chorus-proven drug immediately into registration trials: it needs to spend extra time doing the work Chorus didn't do in its single-minded rush to POC. With any luck, however, that should be less time than it has saved in getting the product rapidly to POC. And more important, it should have many more post-POC programs to choose from.

For Versant, the additional time required post-POC is less important than the savings up to POC. That's because there's a huge valuation jump for compounds that reach positive POC, a jump on which many of its companies are actually built to capitalize.

To a certain extent, Lilly can capitalize on the same thing: it can also sell assets that have reached positive POC for a lot more money than it could get pre-POC, unlocking value otherwise trapped in its R&D organization. But although out-licensing has been an important side-business to Lilly (one it pioneered and has used effectively, among other purposes, to manage earnings over a

number of quarters), its real goal is marketing its own products, particularly novel products. Theoretically, Chorus is a way of managing the risk of novel research, providing more shots on goal—both in terms of internal programs brought forward and external ones acquired and validated inexpensively.

So far, the data is still out on whether the Chorus program actually works as intended: will its positive POC programs actually succeed at the same rate as those done in more traditional fashion? Will their development take longer because of the shortcuts? But if it does work, there's a second question: will Lilly's organization, cautious in face of the approach's novelty and, perhaps, the possibility that fewer of its people will be required, accept the answer?

STARTING CHORUS

In 2002, Lilly was experimenting with a number of alternative R&D approaches, largely through its now defunct e-Lilly initiative. (See "Lilly's Web-Based Research Marketplace," *START-UP*, September 2001.) One was InnoCentive, an electronic marketplace for soliciting solutions to scientific problems Lilly needed solved. Chorus was another, originally set up to improve the company's use of positron emission tomography testing to accelerate compounds toward POC. The concept's author, Lilly development scientist Neil Bodick, MD, PhD, led the consolidation of Lilly's PET activities into

Chorus, and he began designing software to advance projects much more efficiently. When the PET activities were folded back into Lilly, Bodick's concept for Chorus expanded way beyond it, into real clinical development, with the management software taking a central place in the program.

By 2003, Michael Clayman, MD, had joined the organization as its general manager. For family reasons, the former VP of global regulatory and safety had had to move from Indianapolis to Boston and—with neither side anxious to part from the other—had gotten the job running Chorus, which Bodick had designed from the beginning as a largely virtual organization.

Chorus' central goal was to get more innovation into Lilly's pipeline. "We know that our ability to predict whether an early-stage compound will get to the market is very small, except in infectious diseases," says Clayman. That means that any preclinical project is a crapshoot—and that choosing those that Lilly should work on is largely a matter of chance. "And it's getting worse," says Steven Paul, MD, EVP science and technology and president of the company's R&D organization, **Lilly Research Laboratories (LRL)**. "Only 25% of our compounds in Phase II now get to Phase III—probably because so many of them are novel mechanisms." But there are plenty of data, says Clayman, to show a big increase in predictability once a drug had demonstrated efficacy in humans—

proof-of-concept. "And at that point, the compound's value increases dramatically," he says. So Chorus' goal was to get as many early-stage compounds to POC as quickly and cheaply as possible—to let Lilly developers choose their projects when choosing was still risky, but less risky than the roulette most of Lilly's programs represented.

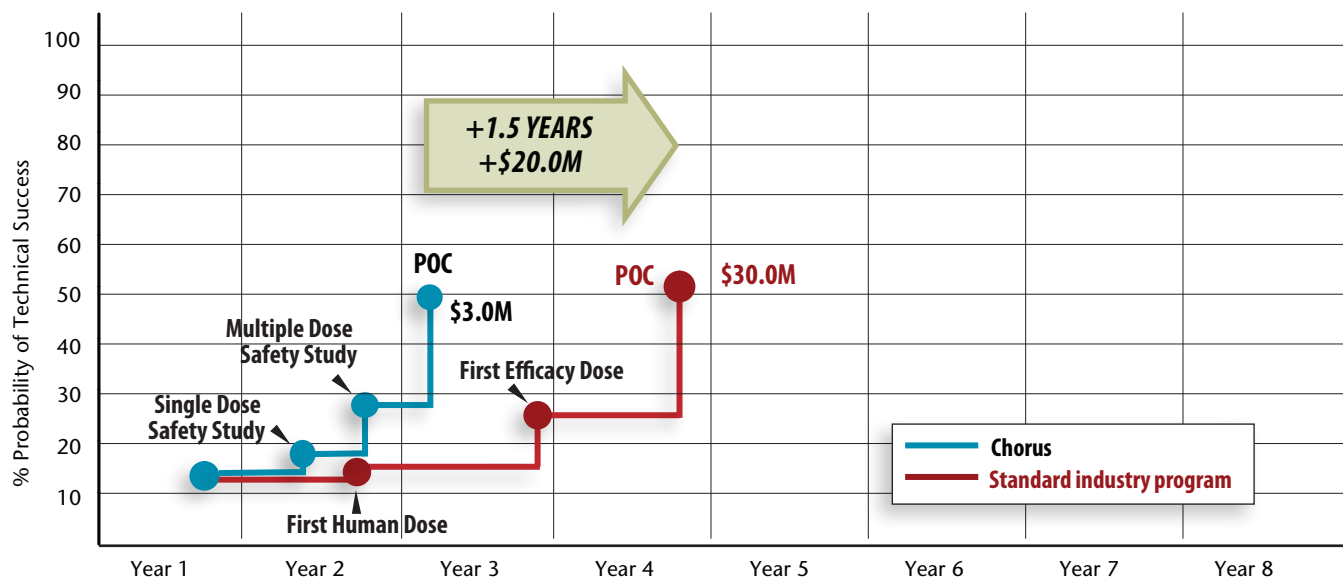
The Chorus experiment started with four preclinical compounds, all of which Lilly had shelved for one reason or another. Three of them failed Chorus's rapid-fire POC testing, two so convincingly that the larger organization, says Bodick, began to realize the power of short-circuiting likely failures. Even with its scaled-down, cheap POC testing, the answers were so definitive that "we got some real recognition in the larger organization—and a willingness to give us some more assets," says Bodick.

Meanwhile, a fourth compound, an analgesic, had been originally sidelined because it belonged to the same chemical class as another molecule that had proven toxic; its developers presumed the toxicity was part of a class effect.

It wasn't. Under Chorus's management, it reached positive proof-of-concept in a total of 29 months (Lilly's corporate average is 40) at a cost of \$3.2 million (it's not clear what Lilly usually spends to get a compound to POC, but Clayman quotes Tufts data that Phase I costs about \$15 million—without getting to POC). The drug is now back in

Exhibit 1

Chorus Beats Standard Time & Cost to Proof-of-Concept



SOURCE: Chorus/Eli Lilly

Lilly's pipeline (see Exhibit 1).

But the numbers are misleading. LRL takes more time and spends more money getting to POC in part because it's doing more—"success-based behavior," as Bodick calls it. LRL teams assume, says Bodick, that a drug they're testing will work and therefore they should do everything they can to speed its entry into registration trials—working out all the formulation problems, for example, or the production challenges, in parallel with early clinical testing. "The mindset at most companies," he continues, "is that 'we'll hit POC on the way to market.' They think they're doing POC—but they're not. They're planning on success without any evidence for it."

PLANNING FOR FAILURE

Chorus, instead, assumes that most of its compounds will fail—it figures when it first gets hold of a compound it has a 10% chance of making it to market—and the trick is to determine, as cheaply and quickly as possible, which ones are likely to fail and which to succeed. That's called "truth-seeking behavior," says Bodick. For truth-seekers to find the maximum amount of truth, they need to do the maximum number of programs—which, on a fixed budget, requires a developer to do the absolute minimum necessary to figure out whether or not each compound is likely to work.

But doing the minimum means deferring work that normally gets done in parallel. "If the goal is to get to POC, why do anything that delays that—things like figuring out the manufacturing process or the right formulation? You do that because you have confidence that the product will need to be manufactured because it's going to get approved. But there's no evidence that it will—and in fact by doing the work on manufacturing you're creating opportunity costs," says Bodick.

And the main opportunity cost is in not developing other compounds because you don't have the money or staff. Chorus instead reduces the money and staff required to get many compounds to POC. It does almost nothing that interferes with its ability to get a POC answer. No two-year carcinogenicity studies; no exploratory trials that might explain hypotheses not directly related to basic POC; it will start, but not finish, extended toxicology tests. It has put several large molecules into the program—but only because it can rely on LRL's in-house manufacturing. Otherwise the expense

and time of finding bulk material would destroy Chorus' advantages in getting to POC. "We're not going to reduce the attrition rate" of early-stage compounds, says Clayman. "We're going to increase shots on goal" for late-stage developers.

Take the centrally acting pain drug, Chorus' first big success. It did almost no formulation work—developers created a suspension version they gave to patients

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every half hour over six hours, simulating sustained release, and doing just enough preparatory testing to make sure the mimicry was clinically and chemically reasonable. And they tried it in just 35 healthy volunteers, using a mildly painful local stimulus and then testing the drug's ability to limit the surrounding area of increased sensitivity to pain. Result: the new drug was equal in pain reduction to gabapentin and wholly separable from placebo.

Like all Chorus's tests, the pain drug's was designed to add a minimum of 15 percentage points of confidence (for a total of 25%), so that Lilly's corporate drug developers would have enough evidence of efficacy to recommend it for further development work, including the additional work needed to prepare it for registration trials.

The 25% figure is a minimum: Clayman believes that most of the compounds Chorus gets to positive POC are at a 30 to 40% probability of success. Such percentages are less mathematically derived than they appear: to determine the probabilities, says Clayman, "we use our best judgment guided by, in my case, over 10 years of experience in portfolio management at Lilly where all projects are accorded probabilities of launch and all clinical experiments are assessed in terms of their impact on probability of launch."

But whatever the validity of its probability statistics, Chorus' economic statistics are compelling. Chorus is currently managing eight assets (with a capacity for 10). This

work is handled by 24 employees who oversee all aspects of development including manufacturing, toxicology, regulatory affairs, quality, and clinical studies. "These 24 employees replace many times that number in traditional R&D organizations," says Bodick. "In essence Chorus' compact infrastructure frees money to go into the variable costs of running clinical studies." Chorus outsources 75 to 80% of the work—about 75% of the total expenditure. "That's exactly the opposite of what most drug companies have," says Clayman—75% fixed, 25% variable. The average time to POC is now well below 29 months.

THE LIMITS TO CHORUS

The Chorus approach isn't right for all programs. Its sweet spot is novelty—but the program won't work, for example, for novel compounds that don't have relatively predictive biomarkers, notes Steve Paul. A drug for congestive heart failure probably wouldn't fly: too many candidates with promising surrogate data fail to work in survival trials, which are likely required for approval. Meanwhile, for drug programs pursuing well-validated mechanisms, or where time to submission is crucial and confidence is high, Chorus' approach probably slows things down. And because Chorus works autonomously, without tapping into key groups in LRL, it can't work on molecules with challenges that require more substantial work—like complex CMC or manufacturing problems.

Not surprisingly, Chorus hasn't yet become central to LRL's strategy. In the first place, there's the simple human reaction to having to do things differently. "When a positive POC goes back [from Chorus] to Lilly, teams have to do all the work we didn't—which is what they've done with our pain drug," says Bodick. "Any time an asset moves from one management team to another it can be challenging—which is compounded when the teams are operating with different expectations."

Natural human reactions aside, many R&D executives, note Bodick and Clayman, are not unreasonably concerned that a Chorus program will actually take longer to get a product to first registration dose than Lilly's current system. "The question is: will winners get delayed?" asks Clayman. "My hypothesis is that they won't, that we'll save more time getting to POC than we'll spend getting from POC to first registration dose. But we don't have the data yet."

Nor has Chorus proven that its stripped-

down POC tests really do increase, as much as it says, the likelihood that a compound will successfully get through pivotal trials. No Chorus compound has yet been submitted to the FDA for approval; only two have actually gotten accepted by LRL for full-scale development. The jury, in short, is still out on whether discounted POC is worth—probability-wise—what Clayman calls “full Monty” POC.

ORGANIZATIONAL ANXIETY?

And then there is the unspoken concern about job security. If Lilly adopted the Chorus model, it could choose to shrink its R&D organization. Even granted that Chorus’s 24 people don’t do much of the work a successful compound will need to have done, the virtual model they are pioneering inevitably raises the question: is LRL significantly overstaffed?

LRL development efforts that require more heavy lifting for their success.”

But Armstrong’s advocacy aside, LRL will only accept Chorus if the organization is firmly told to do so—or if they believe they need to. And there is no obvious near-term crisis that would compel such a belief. Lilly’s near-term prospects are reasonably good. A new anxiety indication for duloxetine (*Cymbalta*) should boost sales of that drug; so would an approval in fibromyalgia. Diabetes drug exanatide (*Byetta*) is doing well on the US market and will soon launch in the much more profitable territory of Europe (in its deal with **Amylin Pharmaceuticals Inc.** it keeps 80% of European profits, not 50% as in the US); an extended-release formulation should help even more. And most importantly, Lilly’s confidence in platelet-inhibitor prasugrel is growing—its

definitive: “Will Lilly accept Chorus if the experiment works? The answer is yes.”

THE IN- AND OUT-LICENSING OPPORTUNITY

Lilly isn’t the only company that has tried rapid POC experiments. Roche implemented such a model in its Palo Alto site in the late 1990s—and it ultimately abandoned the experiment. A top **Wyeth** research executive says his company studied what it could about the Chorus model and rejected it, in favor of what it calls Early Clinical Development Centers. It’s got 10 set up so far. Better known is a strategy at **Novartis Institutes for Biomedical Research Inc.** (NIBR), pursuing POC in larger-indication drugs with early testing in rare diseases that are seen as models of the broader conditions—although it only works in those diseases for which clear models can be found. (See “*Novartis’s Research Experiment*,” *IN VIVO*, May 2006.) But there are now increasingly open conflicts between NIBR and the Basel-based pharma division about the research group’s ability to fill the pipeline. In part as a result, the pharma division has set up a competitive venture-based in-licensing effort. (See “*Novartis’ Competing Venture Funds Pursue Lower-Cost Innovation*,” *START-UP*, May 2007.) Pfizer is mulling a Chorus-like plan—named Project Fisher (after the British admiral who pioneered the big-gun battleships that rendered obsolete most of the older warships). It’s not likely to get much traction, says one source; it may indeed get spun out.

But if rapid-POC strategies haven’t yet gotten much traction, Chorus does at least promise another route to value creation: efficient out-licensing. Drugs that don’t meet LRL’s criteria for full-development, or even positive POC, might be perfectly well suited to another company. At least one of the Chorus compounds, a cognition enhancer, did achieve positive POC—but LRL didn’t think it was positive enough to justify a registration program. The compound’s on the out-licensing block. Another drug, an anti-coagulant, didn’t achieve Chorus’s definition of positive POC—but LRL is now deciding whether or not it’s worth out-licensing.

One big advantage for Lilly: Chorus makes out-licensing relatively cheap and easy. For most companies, simply gathering all the relevant data on a compound is a time sink—with relevant files scattered over any number of divisions and geographies. But Chorus’ software maintains everything about the drug in a single database. And

LILLY’S FIP-NETS

Chorus is in fact just one of a variety of external programs that report to Rob Armstrong, who, two years ago, began working on a number of experiments for tapping external sources of R&D and R&D processes. In 2005, for example, Lilly connected with faculty members from the **Shanghai Institute of Organic Chemistry** to create a group that would work with Lilly; now a separate company, the group provides organic chemistry services to Lilly. Another handful of companies in Asia, like India’s **Nicholas Piramal India Ltd.**, are taking preclinical Lilly assets, and—usually at their own risk—developing them through POC, at which point Lilly has the chance to opt back in to the program.

But Armstrong’s vision goes beyond creating merely a set of independent programs. He wants to set up a network of interdependent programs that, linked together, create virtual pharmaceutical R&D organizations, potentially capable of completing an entire R&D program—not just pieces of it. Steve Paul, at the PureTech Ventures meeting, called such loosely connected organizations FIPNets (fully integrated pharmaceutical networks), in contrast with FIPCOs (fully integrated pharmaceutical companies).

For Armstrong, Chorus fits philosophically into this set of R&D experiments, all of which generally provide both additional R&D capacity, at relatively low initial cost, as well as new thinking and approaches. The challenge is that external programs can’t be fully tied to Lilly—particularly if the Lilly organization doesn’t embrace their very different ways of doing things. Indeed, to thrive, the external programs need to start working with other drug businesses.

Clayman’s boss, Robert Armstrong, PhD, VP, external R&D, dismisses the idea entirely. He sees Chorus as having the potential to extend LRL’s development reach—to work alongside, not replace, LRL. “As we triage the innovation coming from the discovery organization, Chorus was designed to pilot programs with specific proof-of-concept end points. By utilizing Chorus to capture a subset of programs, this provides an opportunity for additional

head-to-head trial looking for superiority against the blockbuster clopidogrel (*Plavix*) could report out as early as November. Meanwhile, like every other company, it continues to express confidence in its Phase II programs—for whatever that confidence is worth.

“Like all experiments, people want to see the data” from Chorus, says Rob Armstrong. “But I think there’s a lot of support to see if it will work.” Steve Paul is more

“the data packages are substantially more robust” than the normal out-licensing file, says Clayman, given not merely its organization but its POC information. Lilly should be able to “monetize these compounds at much better rates,” he argues.

ENTER VCS

That’s exactly what the venture world thinks, too—and it was apparently more than willing to listen when, about two years ago, Clayman and Bodick started talking with a number of VCs both about bringing on venture-sourced compounds and about spinning out the division. “The larger organization [at Lilly] sees that for every Chorus compound that gets to positive POC, they’ll need to spend another 6 to 12 months getting it ready for its first registration dose,” says Clayman. “That could be problematic. But a VC is much more focused on POC, which is frequently his or her exit.”

Lilly CEO Sidney Taurel and other senior executives pulled the plug on the spin-off idea, at least in part intrigued by the venture groups’ interest. Notes one of those senior executives: “We felt that if Chorus were done right, we could influence LRL over time to do things faster and cheaper...Rather than spin off Chorus, it would be far better to incubate it with gusto. We wanted to use it to cause change in the organization as well as to make money.”

That change is slow in coming. And so Chorus has modified its spin-off ambitions into its deal with Versant. The collaboration aims to give LRL low-cost access to interesting external compounds as well as an avenue to monetize assets Lilly won’t pursue on its own. Meanwhile, Versant gets a way to relatively quickly determine the value of compounds flowing from its EuroVentures in-licensing organization. Notes Brad Bolzon, PhD, a Versant partner: “The biggest challenge [in creating an in-licensing start-up] isn’t acquiring the compounds. Through EuroVentures, we find plenty of opportunities. It’s development capability and capacity.”

Neither Versant nor Lilly would give much detail on their arrangement, but the outlines seem to allow Versant to finance the development, within Chorus, of early-stage compounds that EuroVentures sources from academics and entrepreneurs. Versant funds the work and Lilly gets some sort of access at POC—sometimes a right of first negotiation, sometimes a right to license the compound at a predetermined price; a first look in any event.

Given that Chorus has a limited capacity, Chorus gets to choose which Versant molecules it works on, through its 50% representation on the alliance’s six-person joint steering committee. “We’ll only look at compounds that would be of interest to LRL,” says Clayman. “We will always ask the heads of the therapeutic areas: ‘If we demonstrate these kinds of POC data, would you support bringing in this molecule?’ If they do, we’ll go ahead with it.”

In short, through the Versant-Chorus arrangement, Lilly gets to look at molecules its R&D executives would see too early, before they could make reasonable licensing decisions, or not at all—with Versant taking the capital risk. Says Clayman: Lilly is paying nothing until POC and then it gets the chance to in-license an asset rigorously studied by its development affiliate.

There’s a flip side to the deal: Versant also gets some preferred access to Lilly compounds that Chorus is developing and that Lilly decides not to pursue. “That’s the real upside for them,” says Clayman.

AN EXPERIMENT FOR VERSANT, TOO

For Versant, the deal is a twofold experiment. First, for a VC industry fascinated by the opportunities to exploit Big Pharma’s shelved compounds, Chorus is a route to preferred access—to seeing a stream of innovation, not a piece at a time. Very few start-ups have managed to establish any kind of private route to in-licensable material from Big Pharmas, notes Bolzon, a former Lilly executive who also ran business development at Roche before joining Versant in 2004. Versant, through its Chorus deal, he notes, at least has begun to build a path. (See “*The New Out-Licensing Start-Ups: Securing Product Supply*,” START-UP, December 2005.)

The second experiment is the same one Lilly is running: can the Chorus method get Versant compounds to a POC value-inflection point recognized by the marketplace—other investors and, as importantly, Big Pharma partners.

If the experiment works, the Versant-Chorus deal will almost certainly be only a first step. To really exploit the opportunity of fast POC, Versant will have to create its own Chorus, free of Lilly, whose presence would likely freeze any talks with Big Pharmas interested in out-licensing to a Versant portfolio company. Take **Synosia Therapeutics Inc.** (the former Synosis). The recent Versant start-up began life with eight

compounds from Roche, **Novartis AG**, and **Syngenta International AG**, few of which would have done the deal with Synosia if they’d figure that Synosia would be turning over their assets right away to Lilly inspection (See “*Synosis: the Financial Leverage of Translational Medicine*,” Start-Up, January 2007.) Nor is it likely that Versant’s current portfolio companies are going to use Chorus, given the complexities of crafting specific deals for each compound.

Instead, most of the material Versant will provide to Chorus will probably come through its EuroVentures subsidiary and consist of compounds from entrepreneurs and academics that might form the basis for a company, but that don’t yet have the clinical evidence to justify Versant’s full investment attention.

THE HEART OF THE INDUSTRY’S DILEMMA

If the Versant deal has some clear theoretical advantages for Lilly, it also raises questions about Lilly’s confidence in the program. Chorus has no plans to grow beyond its current 24 employees and 10-compound capacity—which implies that it doesn’t think LRL will supply enough compounds to keep Chorus busy. Lilly’s representatives on the collaboration’s joint steering committee can govern the flow of Versant compounds into Chorus, reserving space when necessary for LRL molecules—but the deal itself argues that there likely won’t be an overflow of them.

And yet there’s no question that the Chorus experiment goes right to the heart of the industry dilemma. At a PureTech Ventures panel held during the BIO annual meeting, **Amgen Inc.** SVP, R&D Joseph Miletich, MD, PhD, noted that his company’s basic research productivity problem wasn’t ideas, molecules, or tools: it’s “how we go about seeing whether a compound works. We just don’t have a good skill-set for it.”

Chorus, says Steve Paul, is a major experiment to develop just that skill-set. The issue is whether large companies such as Lilly will take it seriously enough or whether, as with recombinant technologies and monoclonal antibodies, they’ll be out-raced by smaller companies. What’s particularly intriguing about the Chorus-Versant partnership is that it frames this issue so starkly. Both Lilly and Versant are poised to reap the benefits; the drama to play out is whether both will be equally committed to doing so.



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