

How Licensing Helps Small Bio-Tech Firm

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Partnership concept has been a big success; company learns from mistakes

How important is outside technology to Sphix? I can say that access to outside technology and compounds has been and remains important to Sphix.

Sphix was born, in effect, with its first license agreement with Duke University in October 1987. The agreement was a simple one that did two things for Sphix:

- It provided Sphix with an exclusive worldwide license to a group of molecules that inhibit Protein Kinase C.
- It established, perhaps more importantly, a relationship for Sphix with Duke that consisted of a right of first refusal on certain future licenses in the field of lipid regulated signal transduction discovered in a founder's lab at Duke.

A little more than two years elapsed before Sphix entered into its next agreement involving technology transfer, and then we began signing agreements frequently. Why the two-year lag?

Let's go back to 1987. Duke and Sphix signed the agreement in October. Duke got about six Sphix, and Sphix got the rights to some potential lead compounds of undetermined worth since no similar compound had ever been got into the clinic. Sphix also established a relationship with Bob Bell's lab at Duke. It thereby gained access to the technology, most of which had been published but was difficult to reproduce, by which these potential lead molecules had been discovered.

Sphix's founders spent the next 18 months finding the money necessary to get the company started on adding value to these important pieces of technology — the

compounds and the know-how from the Duke lab. In August 1988, Sphix got its initial venture financing, and the company, which had a research plan as to how to go about discovering new compounds, needed a business strategy for how to turn the research insights of its founders into an attractive commercial venture.

- What Sphix had was:
 - Technology from Duke.
 - A couple of million dollars out of the 100-200 million needed to develop a product in our industry.
 - And two employees.
- What we needed was:
 - More research funding to support research to lead to revenues.
 - To get more money, we needed to demonstrate to potential investors and to potential corporate partners that the technology from Duke could either produce revenues from its first discoveries — the compounds — or produce additional future products that would be successful in producing significant revenues.

We set about adding value to the actual technology transferred from Duke on two fronts. We put a program in place to test a number of analogues of the compounds from Duke in as many animal models as possible, hoping to find some therapeutic utility for these prototypical first generation protein Kinase C inhibitors.

• Talking Begins •

We also set about the process of building an ongoing, fully commercial program of practical drug discovery. The program began with the original insights of our founders, but because of the enhancements to their original work added at Sphix, a program was developed that is unparalleled in its field in either

academia or industry.

By the end of 1989, after spending approximately \$5 million in 18 to 20 months, we felt the drug discovery program was ready to talk about with potential corporate partners. We began talking with large corporations about research funding, and we began talking with small companies and universities about using our technology to uncover value in their compound and natural product collections. It was easier to enter into agreements where we provided other services or in some cases money for research support than it was to get an agreement that provided Sphix with substantial funding. (See Figure 1)

The Lilly agreement provided Sphix with \$4 million of much needed equity and research funding of \$0.2 million per year for four years. By the time we signed the Lilly agreement, we had spent almost four years and approximately \$10 million dollars. We had built a mini-pharmaceutical company with capabilities in drug discovery, medicinal chemistry and drug development — all centered around the original technology insights of our Duke University founders. Without the original technology from Duke, Sphix would have had nothing to differentiate itself from other companies. Without the enhancements Sphix added to, and the infrastructure Sphix built, the technology had no value in the marketplace.

Bob Bell, our founder, had spent several years trying to interest major pharmaceutical companies in his technology, and while many found it interesting and several offered him a

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a job, none was willing to start a major drug discovery program around his insights at the time. Without the proof of principle achieved by Sphing's efforts, no drug company was willing to take the leap of faith required for such a major direction of research.

The major drug companies also were not interested in the compounds we got in the original licensing agreement with Duke. In our hands, they showed promise in two therapeutic areas — in the treatment of psoriasis and as a chemopreventive for the treatment of solid tumors with standard anticancer drugs.

We will just test two of those compounds in the clinic during 1992. The potential for these compounds ranges from \$20-200 million for the protein agent and up to \$1 billion for the chemopreventive agent. In order to find the true value of these compounds, we'll spend \$1-5 million on them this year for additional pre-clinical work, with the real money, around \$25-40 million, to be spent on the clinical trials over the next 4 years.

We are committed to fulfilling our founders' vision of moving novel lipid second messenger regulators of important cellular functions into the clinic to meet unmet medical needs as soon as possible. We're committed to providing as large a return as possible to our shareholders and technology transfer partners — in Duke's case one and the same — as soon as possible.

► Market Objectives ►

We're also looking forward to moving compounds we've uncovered from other technology transfer partners in to toward the market, hopefully into the clinic, as soon as possible. Sphing intends to put two compounds per year into the clinic every year for the next five years, if at all possible. In order to do so, we have adopted an aggressive drug development policy as is consistent with a high standard of regulatory quality. We believe a start-up pharmaceutical company must manage the risk associated with an early-stage company by developing a portfolio of

products with a variety of novel mechanisms toward the market. To that end we are aggressively and actively seeking both new technology in our field to drive new discovery programs and new compounds to license and fill our development pipeline.

I hope I've given you an idea of how important technology transfer and licensing are to Sphing. We spend a lot of effort to enter into licensing arrangements and we spend a lot of time and money at this stage of our company while trying to turn licensed technology into revenue generating products. We take our technology at a very early stage in its development and commit resources and our own technology to move the licensed technology along to the market. We look for similar commitments from companies with which we enter into licensing arrangements as licensees. We won't license technology in unless it is important to us and we won't license technology out unless it is important to its licensee.

The technology transfer process has worked extremely well for Sphing. I'd like to be able to say that it has worked well because we've been smart, that we've designed extremely clever agreements and contracts. But since there are at least a few of you in the room who have had dealings with Sphing, you would know that I was lying if I made those claims. Technology transfer has worked well for Sphing so far because we've chosen the right technology transfer partners. We've chosen partners who recognize that the technology transfer process is a living partnership arrangement where the spirit of cooperation is as important as the original agreements.

Duke gets the credit for the original structure in which, by taking an equity position in Sphing in return for technology, the interests of Sphing and the university were aligned in probably the only way that makes sense for an unproven technology and an unproven start-up company. In exchange for equity, Duke assigned patent rights to Sphing without traditional due diligence-developer clauses that

would have been inappropriate for a young company with no drug development infrastructure. Duke took a chance on Sphing and thereby facilitated our financing efforts over the coming years.

Duke was also the first technology transfer partner to renegotiate its agreement with Sphing. The original agreement provided Duke's original equity stake from ever being diluted. Duke negotiated that provision would prohibit the company from raising venture capital, and Duke allowed it to be renegotiated away for reasonable consideration.

Duke and other technology transfer partners of Sphing have been cooperative in granting other, less fundamental, but very important provisions in our licensing and research agreements. In talking about the kinds of changes we have made in our agreements, I'll cover the subject of what we could have done to make the technology transfer process work better.

► Improvements ►

Most of our research relationships are targeted toward using our technology to uncover potential lead compounds others have used their technology to create or invent. It is difficult to collect. Because we had research relationships with individuals at many of the institutions with whom we have entered into technology transfer relationships, we often failed to define the consideration to be received for joint discoveries at the front-end of the agreement.

The thought was, let's get on with the research, let's discover something before we start worrying about what it is worth. We have had to renegotiate a number of these ill-defined agreements, and we are in the process of renegotiating others. The problem for us, and I think for our partners in these relationships, is that once we uncover an active compound at Sphing, we are anxious to get resources behind it to define its potential.

We want to put it into our early discovery project team to define its worth — we need to make or obtain more of the compound, and others

we need to do some formulation work on the compound before we can test it in animal models of disease. We then want to test it in relevant animal models. We also often want to dedicate some resources to developing an analytical assay for the compound in order to determine its bioavailability.

What we don't want to do is to spend the resources necessary to do all this without knowing whether we can obtain the rights to the compound on a commercially reasonable basis. So essentially the development process stops until we can negotiate a well-defined agreement. A delay that is not in either our or our partner's interest results. The good news is that, to date, because we have been fortunate enough to enter into agreements with the right sort of partners, the delays have been reasonable and we've been able to reach agreement in every case we've dealt with. I wouldn't want to count on that kind of cooperation, so today we only enter into agreements in which the economics are well defined on the front end.

Another way in which we could have improved our licensing contracts is to have anticipated the fact that in many cases, in an emerging pharmaceutical company, it was likely that we would have a large corporate partner. Most of our agreements with other small companies and with universities contained confidentiality provisions that did not contemplate our entering into a collaborative research relationship with another company. We paid attention to the right to sublicense, but we failed to cover the right to disclose research results to a corporate partner who agreed to be covered by the confidentiality provisions, which we had entered into with the first partner. In several instances, we have had to go back and get permission from a partner to release information that might result in a royalty stream to

that partner. Our current agreements try to anticipate likely future agreements that would be in the interests of both original parties to the first agreement.

Splitting technology agreements have been somewhat favored, and yet overall the technology transfer process has worked extremely well for us. Throughout my paper I have used the word partner over and over again. Technology transfer agreements attempt to define the economic terms and to protect the licensor from a failure to perform by the licensee. Yes, as licensing restrictions could perhaps tell us how often the protection provisions of these agreements actually work. I believe viewing the agreements as a partnership arrangement probably provides more protection. You choose partners carefully, you often have to depend on them, their actions reflect on your institution or company, and your future on the investment you have made in your discovery depends on both their capabilities and their need to commercialize them.

I shall close by putting in a plug for the emerging pharmaceutical company as a potential licensor of technology transfer partner. Every potential partner has its advantages and disadvantages. Large pharmaceutical companies have lots of money and expertise but they also have lots of things they need to do with it.

Your technology could be very important to and actually receive more resources from an emerging pharmaceutical company if it is in the company's field of expertise. The need to get products on the market or add value to technology in order to survive works well to focus the attention. After I joined Upjohn in 1989, we held a meeting once a week to ask ourselves what else we could do to prove the concept that lipid regulated signal transduction was a valid drug discovery target.

We asked ourselves constantly where we could spend money to accelerate the drug development process. I think if you asked our technology subcontractors about the pain we expect and our willingness to spend money to accelerate necessary steps in the drug discovery process, they probably would tell you we were slightly mad. We like to think of ourselves as being possessed of an appropriate sense of urgency, as highly focused on commercializing our technology and that of our licensing partners.

LICENSE & COLLABORATIVE AGREEMENTS

- Lipid Agreement with Dale - 8/1991
- Collaborative Research Agreement with Myriad - 11/89
- Confidential Exchange Agreement with Duke - 1/25/90 (in execution)
- Biological Testing Letter Agreement with UPIC - 3/7/90
- Agreement with Texas A&M - 4/7/90
- Agreement with Research Triangle Institute - 5/27/90
- UPIC Agreement with Dale - 11/89 (in execution)
- Agreement with Southern Research Institute - 6/25/90
- Biological Testing Letter Agreement with Maryland University - 12/14/90
- Grant Letter to UPIC - 12/21/90
- Biological Testing Letter Agreement with YCU - 1/28/91
- Agreement with Stone Mountain - 5/17/91
- Biological Testing Letter Agreement with Kean College - 12/91
- Biological Testing Letter Agreement with Upjohn - 1/25/91
- Collaborative Research Agreement with Yale - 4/9/91
- Collaborative Research Agreement with Myriad - 5/1/91
- Biological Testing Letter Agreement with Upjohn - 6/10/91
- Biological Testing Letter Agreement with Cornell - 6/24/91
- Agreement with YCU - 7/1/91
- Letter of Option with Duke - 10/91
- Agreement with Rockefeller University - 12/15/91
- Agreement with Univ. of Rochester - 12/17/91
- Agreement with Eli Lilly - 11/17/91
- Agreement with Pfizer - 11/27/91

Figure 1