

Decisions, decisions, decisions
A Case Study by Dr. Richard Hamilton, CEO, Ceres, Inc.

Sitting at the kitchen table of his Cambridge, MA apartment, Joshua Crane cradled his 6-month old daughter Samantha and her bottle of formula in the crook of one arm while opening up the Sunday NY Times with the other. There on the front page was an article entitled “Celera and National Institute of Health Announce Completion of Human Genome Project”. Joshua was well aware of the existence of the Genome Project and the announcement came as no small surprise to him. He settled back in his chair to ponder the implications of the Genome project for himself and the decisions he had made over the past several months.

Six months ago Joshua was a senior post-doctoral fellow at the Whitehead Institute, working in the laboratory of Arthur Landoin. His area of expertise was the biochemistry of nucleotides, the chemical building blocks of DNA and RNA. He had a solid publication record and had recently made a breakthrough discovery on a new class of synthetic nucleotides. He had been invited to several interviews for assistant professor positions at various universities but he felt uneasy that the jobs were somehow not for him.

Joshua had seen two potential commercial applications of his work in nucleotide biochemistry. The first was in automated DNA sequencing which relies on the use of fluorescently-labeled synthetic nucleotides. Automated DNA sequencing takes advantage of the double helix nature of DNA where one strand can be used as a template for the other. A single strand of template is mixed with a polymerase enzyme along with free nucleotides or building blocks so that a new, second strand can be synthesized. Incorporated into the mixture are small concentrations of labeled synthetic nucleotides which prevent the strand from being further extended, resulting in the synthesis of a series of DNA strands of various lengths, each ending with a specific nucleotide. By separating these strands via capillary electrophoresis and concomitant fluorescence spectroscopy, one can infer the DNA sequence of the template strand.

The novel chemistry that Joshua had discovered could lead to the development of inexpensive “desk-top” automated sequencing. With the Genome Project completed, many were predicting the development of a new generation of DNA-based diagnostic tests and an explosive demand for personalized DNA sequencing in doctor’s offices and hospitals.

The second application for the nucleotide chemistry that Joshua had developed was in the area of cancer chemotherapeutics. For decades cancer chemotherapy had taken advantage of the fact that rapidly dividing cancer cells needed to replicate their DNA faster than those of normal cells. By giving cancer cells synthetic nucleotides that would “stall” DNA replication, their unregulated proliferation could be slowed or halted. While there were many classes of nucleotide chemistry that were able to stall DNA synthesis, there were very few which had the right combination of pharmacological characteristics;

absorption, distribution, metabolism, toxicology, therapeutic index, pharmacokinetics, etc., to stand a chance of becoming effective drugs.

Joshua had thought about the commercial applications of his work and his lack of enthusiasm for continuing his scientific career in an academic setting. His uncle, Ernest Crane, was a successful software entrepreneur having founded and sold a small software security company and was in the process of starting a second. Over a dinner of tandoori chicken and beer at one of Joshua's favorite Cambridge restaurants, his uncle had encouraged him to explore the idea of starting a biotechnology company.

At first intimidated by the idea, Joshua had thrown himself into the endeavor with enthusiasm. He still had nine months of fellowship funding left and the support of Dr. Landoi to pursue the idea of creating an entity to commercialize his discoveries. His first stop had been the Technology Licensing office of MIT which was responsible for administering the intellectual property assets of the Whitehead Institute. Faced with the practicalities of needing to incorporate a company, draft, review and execute licensing documents and to file additional patents, Joshua knew that his own meager savings would be seriously depleted by the rapidly mounting legal bills. Fortunately, Uncle Ernest had come through with \$100,000 of seed funding to get Joshua's enterprise on the way.

Joshua knew that in order to attract additional funding for his enterprise he would need to present his ideas to some of the many venture capital firms that dotted the Route 128 high-tech "corridor" around Boston. While Uncle Ernest knew a few venture capitalists, they specialized in high-tech not in biotech and could not be much help to Joshua, other than to encourage him to write a business plan as most potential investors would want to review such a document before agreeing to meet with him.

Joshua spent the next three months perfecting his business plan, including an executive summary, an overview of the market opportunity, the technology, the commercialization plan and a series of financial projections. He read in the MIT newspaper, "The Tech" that the University was sponsoring an annual business plan competition next month and the judges would be three general partners from local venture capital firms. Joshua submitted his plan and began to put together a twenty minute Powerpoint presentation that would be presented orally as part of the competition.

At the same time as putting together his business plan and perfecting his "pitch" presentation, Joshua knew he had to move the development of his technology beyond the "proof of principle" he had achieved at his academic lab bench. With regard to the chemotherapeutic applications of his work, he needed to initiate some of the basic animal testing work that would be necessary before beginning clinical testing in humans. There were plenty of pre-clinical testing laboratories in the area who were well-equipped to conduct the studies that the FDA would require and while the tests would eat up a significant portion of Uncle Ernest's seed capital; Joshua knew that the results would be professionally compiled and presented. He bit the bullet and wrote the checks. He also gave some compound samples to another post-doctoral fellow at the Whitehead, Robert Green, who was investigating some animal models of carcinogenesis and who promised

that he could easily test Josh's compounds in some immune-deficient mice that had been injected with human lung carcinoma cells.

Joshua did not want to ignore the DNA sequencing applications of his work and knew that the next steps would be to have his compounds evaluated in the latest high-speed capillary electrophoresis machines. While there were several automated DNA sequencers at the Whitehead, all were being utilized at full capacity by other researchers and none were being used to test new methodology, only to sequence new genes as fast as possible. Dr. Landoiu had a former post-doc, Thomas Telling, who now worked as a Senior Scientist at Applied Biosystems, a manufacturer of DNA sequencers out in Wakefield, and after a quick email exchange with Josh, Thomas agreed to a lunch meeting to discuss Josh's interest in automated DNA sequencing technology.

Applied Biosystems was housed in one of the typical modern three story metal and glass technology buildings that populate the Route 128 expressway that rings the Boston/Cambridge area. Josh waited for Thomas at the receptionist desk and then together they went to the company cafeteria. After grabbing something to eat and making some small talk about life as an MIT post-doc, the talk turned technical and a discussion ensued about projected developments in sequencing technology. Josh started to describe some the characteristics of his compounds but Thomas held up his hand to stop him. "Hey Josh, this sounds interesting, and I know you're a bit new to this game, but we should really have a non-disclosure agreement (NDA) in place before we take this conversation further. Why don't you send me a draft NDA and a draft materials transfer agreement (MTA) which we would need before we could have a detailed discussion about your technology and agree to test it in some of our next-generation machines?" Embarrassed, Josh readily agreed and mentally calculated the additional legal bills that his nascent enterprise would incur in order to generate the requested agreements. Thomas agreed to set up a next meeting with some of his colleagues as well as Applied Biosystem's Manager of Technology Acquisition.

Soon the day of the business plan competition was at hand. Joshua felt that his presentation had gone well, as he had practiced it several times in front of the mirror, and certainly he was a better public speaker than most of the other "would be" entrepreneurs. The panel of venture capitalist judges was present and asked polite but pointed questions about each entrepreneur's plans for the commercialization of their technology. The companies that presented covered the full gambit of technologies one would expect to come out of a top notch university like MIT. Unfortunately, the venture capitalist that specialized in biotechnology had a last minute conflict and could not be part of the panel of judges.

Joshua was crestfallen when he read the grade that his business plan had received, a B-. Some of the comments included were; "lacks focus" and "unclear what business this company intends to be in." Josh knew that the development of novel automated DNA sequencing technology and the development of cancer drugs were two different endeavors, but there was a common biochemistry and intellectual property estate that

under lied both of them and wouldn't investors want to have more than one possible product to make the company successful?

Determined that the panel of venture capital judges simply did not have enough biotech experience, Joshua carefully numbered a stack of his business plans and set them out to thirty different venture capital firms that he knew specialized in biotechnology. That had been three weeks ago and all he had received were some form letter rejections and several polite refusals from the executive secretaries that he reached when following up by telephone.

In the meantime, he had a follow-up meeting with Tom Telling and his colleagues at Applied Biosystems. The NDA and MTA had been executed and Joshua was able to provide them with enough samples of his compounds to run through several trial runs of their new sequencers. The results had been compelling. "Joshua, we'd really like to talk to you about in-licensing this work" said Peter Find, the Manager of Technology Acquisition for Applied Biosystems. Joshua stalled politely, saying he would need to think about it. After all his idea was to use his enabling chemistry to start a new company that open new markets of automated sequencing, not to simply supply Applied Biosystems with a new set of reagents.

That meeting had been last week and now here Joshua was, sitting at his kitchen table on a Sunday morning. Uncle Ernest's seed funding had been nearly exhausted by legal bills, and the preclinical testing services. Joshua had three months of NIH funding left for his post-doctoral fellowship and his wife Lisa was beginning to get nervous about being able to make the rent payment on their apartment. "Maybe you should take the job at Northeastern" she had gently chided him last night. Josh didn't tell her that he knew that the Northeastern job had been filled and that his immediate job prospects were bleak as he had thrown all his energies into his new business and not into interviewing for academic positions.

Joshua had shifted Samantha onto his shoulder and was gently burping her when the phone rang. It was Uncle Ernest. "Hey Josh, how are you this morning?" he inquired. "Heard anything back from the vc firms you sent your b-plan out to?" "Nothing much so far Uncle E." he replied. "I think the vc's are getting turned off by the idea of a company trying to go after two different commercial opportunities simultaneously. Perhaps I need to focus on one application or the other" said Josh. "Look," said Uncle Ernest, "I spoke with Jack Stevens, the technology partner at Seed Ventures that backed my last company. He said they just hired a new general partner to do biotechnology investing and as a favor to me they are willing to meet you next week. I agree with your comments on focusing the company, Josh. It's hard enough to do one thing well, so you're just going to have to pick one of the applications and go after it. I would amend your presentation and business plan to reflect that and then go knock them dead" said Uncle Ernest encouragingly. Josh nodded in agreement and said "Thanks Uncle Ernest, I'll do just that." Josh hung up the phone and headed for Samantha's bedroom. He had a diaper to change... and decisions to make.

Concept Questions

1. How should Joshua commercialize his technology?
2. What obstacles does he face?
3. How should Joshua protect his technology?
4. How would Joshua go about starting a Company? What steps will he need to take and what resources and personnel will he require?
5. What potential conflicts does he face, if any, in using his academic research results in a company?
6. How will Joshua fund his commercial venture? What will he have to give up, if anything?

Questions

How much should Joshua pay MIT for the rights to his discoveries?

- How much of Joshua's company should MIT own?
- How much of Joshua's company should Uncle Ernest own?
- What is missing from Joshua's business plan – competitive analysis, management team.
- Who will own the results of the experiments to test Joshua's compound in immunodeficient mice?
- What application of his technology should Josh choose to commercialize and why?
- What are the commercialization challenges that face the sequencing company approach?
 - Who will develop diagnostic tests that link sequence information with disease?
 - Even if this happens, does it change the clinical decision tree?
 - What about the additional automation required to make desktop sequencers? Is this a core competency of Josh's company?
- What are the challenges with commercializing the chemotherapeutic option?
- What should Josh do if Seed Ventures does not fund his company?