Bio-business in brief: The case of Cytokinetics Inc.

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One of the best ways to build a discovery biopharma company is to have a unique class of molecular targets, a good patent portfolio, venture capital to power growth, experienced and wise advisors and, in due course, strategic collaborations with big pharma companies. The more these conditions are met, the more likely the success of the venture. The company Cytokinetics – built around its academic expertise in the area of the cytoskeleton and motor proteins – fulfilled all these criteria and serves as a good case study for future entrepreneurs of this sort.

Keywords: Biopharma companies, cytoskeleton, molecular targets, motor proteins.

CYTOKINETICS Inc. was co-founded by cell-biology pioneers Lawrence Goldstein (University of California, San Diego), James Spudich (Stanford University School of Medicine), Ronald Vale (University of California, Berkeley) and James Sabry (then a postdoctoral fellow with Spudich) in 1998. It is located in South San Francisco, California. The goal of the company is to discover, develop and commercialize novel small-molecule drugs that target the cytoskeleton for the treatment of cancer and cardiovascular diseases.

Target identification and technology development

The cytoskeleton is a complex framework of proteins and is indispensable for many aspects of cell function, including cell division, cell motility, intracellular transport, muscle contractility and regulation of cellular organization. The major structural proteins that make up the cytoskeleton are actin, tubulin and several proteins comprising the intermediate filaments. The anticancer drug taxane acts on the protein tubulin that makes up the mitotic spindle but is also present elsewhere. Cytokinetics, however, is targetting the mitotic kinesins. These enzymes are responsible for mitotic spindle formation, but are expressed only in proliferating cells and play no role outside mitosis, thereby improving the specificity in terms of cell-type targetting. And for the treatment of acute and chronic heart failure, the company is developing small molecules that directly target the contractile proteins of muscle.

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In order to discover novel small molecules, the company is using combinatorial chemistry to generate a range of molecules. To identify the best modulators of kinesin molecular motors, it has developed its own PUMA high-throughput screening system, a series of assays to determine biological specificity. Separately, it has developed an automated imaging-based cellular phenotyping and analysis system, Cytometrix™, described in a prominent publication[1].

Investments and alliances

So how does a start-up company afford to do such sophisticated things, involving so much money? Besides individual investors, Roy Vagelos (former CEO of Merck), Bob Swanson (Founder and former CEO of Genentech) and Bill Rutter (former Chairman of Chiron), the initial funding came from venture capital firms, Mayfield Fund and Sevin Rosen Funds. Over the years, the company received several rounds of funding from individual investors and venture capitalists, as represented in Table 1.

The company's product pipeline is represented in Table 2. It includes ispinesib (SB-715992), SB-743921, GSK-923295 and CK-1827452. The first three compounds are drug candidates to treat multiple tumour types. Between them, they are being considered for breast, ovarian, renal cell, prostate, hepatocellular, melanoma, head and neck, colorectal and non small-cell lung cancer, and non-Hodgkins lymphoma. To be noted is that in the area of cancer, one molecule is often the subject of clinical trials related to several forms of the disease. The fourth drug candidate is for the treatment of heart failure.

Aside from venture capitalists, there is a culture of strategic collaborations between biotech companies and large pharmaceutical companies in novel drug development. The biotech company may do the initial R&D for a novel compound, and the large pharma company (with deeper

Table 1. Major milestones of Cytokinetics Inc. based on information available at http://www.cytokinetics.com/press_releases

Year	Fundings	Venture capital firms (and revenue from company deals)	Individual investors	Strategic alliances	Clinical trials*	Technology developed	Granted US patents	Other develop-ments
1998	US$ 3.5 million (Series A)	Mayfield Fund and Sevin Rosen Funds	Roy Vagelos, former Chairman and CEO of Merck; Bob Swanson, former CEO of Genentech, Inc					Establishment of Cytokinetics, Inc.
1999	US$ 20 million (Series B)	International Biomedicine Holdings, Paul Allen's Vulcan Ventures, Mayfield Fund and Sevin Rosen Funds, Duke University and New Medical Technologies	William J. Rutter, former Chairman of Chiron Corporation					
2000	US$ 55 million (Series C)	CSFB Private Equity, Alta Partners and Lombard Odier & Cie, Mayfield and Sevin Rosen Funds, Vulcan Ventures, Inc.						
2001	US$ 50 million (Series D)	(GlaxoSmithKline)		GSK			5	
2002 small-				Exelixis	Inhibitors of KSP	Cytometrix™	42	Designed and generated molecule compounds
2003	US$ 40 million (Series E)	General American Investors, HBM BioVentures, PRM Ventures and Mizuho Capital Sevin Rosen, CSFB Private Equity, Alta Partners, Mayfield Fund, Vulcan Ventures (and GlaxoSmithKline)		Astra-Zeneca		Predictive hepatotoxicity	24	
2004					Phase II for SB-715992, phase I SB-743921		12	IPO launched
2005					Phase I for CK-1827452		8	
2006	US$ 33 million	Federated Kaufmann and Red Abbey Venture Partners			Phase I/II for SB-743921, phase I for oral admini-stration of CK-1827452		11	
2007	US$ 75 million committed equity financing			Amgen	Phase II for CK-1827452, phase I for GSK-923295		15	
	US$ 273 million						117	

*Clinical trials are listed according to the year of initiation, unless otherwise mentioned.

Table 2. Product pipeline and conditions for which clinical trials are going on (based on information available at http://www.cytokinetics.com/pipeline)

Candidate drug	Number of ongoing clinical trials	Organization conducting the clinical trial	Condition
Ispinesib (SB-715992)	15	GSK, National Cancer Institute	Breast, ovarian, colorectal, head and neck cancer, non small-cell lung cancer, prostate, hepatocellular, renal cell, pediatric solid tumour, haematological and solid tumour cancer Three trials involve combinations of ispenisib with capecitabine, docetaxel and carboplatin
SB-743921	2	GSK, Cytokinetics	Multiple tumour types, including non-Hodgkins lymphoma
GSK-923295	1	GSK	Multiple tumour types
CK-1827452	3	Cytokinetics	Heart failure patients
	21		

pockets and more experience in the subsequent steps) carries out the clinical trials, regulatory submissions and marketing of the drug. This path was followed by Cytokinetics as well. It now has collaborations with several big companies such as Amgen, GlaxoSmithKine (GSK), AstraZeneca and Exelixis. These kinds of alliances distribute the financial burden, and by utilizing each company's expertise, helps to bring drugs to market relatively cost-effectively and efficiently.

The first collaboration was with GSK in 2001 for validating the novel anti-cancer molecules. The lead candidate, ispinesib, is undergoing clinical trials in association with the National Cancer Institute (NCI) (http://www.marketwire.com/mw/release.do?id=806443). Although GSK could have performed the clinical trials itself, NCI has access to certain patient groups that neither GSK nor Cytokinetics has. Also, it did the studies at no cost (James Sabry, pers. commun.). Further collaborative research with GSK is also being done on GSK-923295, an inhibitor of mitotic kinesin, CENP-E (centromere-associated protein E). In 2007, together with Amgen, Cytokinetics developed novel small-molecule therapeutics that activate cardiac muscle contractility. The candidate drug in trials is CK-1827452 (http://www.fiercebiotech.com/node/5078). Separately, in 2003, Cytokinetics entered into an exclusive collaboration with AstraZeneca to further develop CytoMetrix™ for *in vitro* prediction of hepatotoxicity using an imaging-based analysis technique. The system shows good reliability in predicting toxic and non-toxic pharmacophores.

Since biotech companies with strengths in R&D often license their molecules to 'big pharma' companies (such as Pfizer, Merck, GSK) for further development, a common impression is that the latter companies in-license most of their molecules and do very little R&D themselves. However, a 2002 study (reported in Pisano[2]) found that 'big pharma' in-license less than 50% of the molecules in development. The percentage varied from 47 to 41 for the top ten versus the top 50 pharma companies. Regardless, it was less than 50%. Thus, whereas Cytokinetics licensing its molecules to 'big pharma' for further development is normal for a biotech firm, we cannot assume that all of GSK or Amgen's molecules in development come from companies such as Cytokinetics.

Two asides concerning the dealings of a small, unproven company with two large pharma companies[3]: (a) Well before Cytokinetics was formed, Spudich was on the Scientific Advisory Board of GSK and advised them to think of motor proteins as drug targets. However, the company was not very receptive to the idea at the time, and did not initiate work in this area. Later, after Cytokinetics was formed and had made progress, GSK revised its thinking: the subsequent deal with Cytokinetics cost it millions of dollars. (b) When Cytokinetics initially sought a big pharma partner, it approached Merck. At the time Merck offered less than what they expected, and the Cytokinetics team therefore turned down the offer. They were quite impressed with the fact that as a small company, they had had the gumption to turn down the large Merck! In subsequent conversations with Cytokinetics, Merck has regretted not entering a partnership. The moral of the two stories is that if a company – no matter how small – has the right science, it can be right and the multi-billion dollar companies wrong.

Why should a large pharma company or a venture capitalist invest such large amounts in a small, unknown biotech company? Amongst other things such as the scientific credibility of the founders, patents (in the company's name) are one of the signs of 'credit-worthiness' of a company, even though there is a great range in the number of patents that biotech companies own[4].

Patents

We carried out an analysis of the patent portfolio of Cytokinetics and found that it has filed 652 applications worldwide (http://patinfo.nic.in/). However, since there is

Table 3. US patents of Cytokinetics categorized on the basis of subject matter protected

Category	US patent number									
Motor proteins	7,247,473	6,974,688	6,794,178	6,743,897	6,680,369	6,638,754	6,582,958	6,562,610	6,551,787	6,544,766
	6,534,309	6,514,738	6,492,158	6,461,855	6,458,930	6,455,293	6,440,731	6,437,115	6,436,686	6,429,005
	6,426,207	6,420,162	6,414,121	6,403,372	6,399,346	6,395,540	6,395,527	6,391,613	6,391,601	6,387,679
	6,383,796	6,379,941	6,368,841	6,361,993	6,355,471	6,355,466	6,355,447	6,346,410	6,335,189	6,333,184
	6,331,430	6,331,424	6,294,371							
Inhibitors of mitotic kinesins	7,271,167	7,230,000	7,214,800	7,211,580	7,208,487	7,176,222	7,166,595	7,161,002	7,119,089	7,105,668
	7,053,094	7,041,676	7,038,048	7,009,049	6,992,082	6,956,961	6,949,538	6,924,376	6,908,923	6,831,085
	6,753,428	6,630,479	6,562,831	6,545,004						
Bioinformatics	7,269,278	7,246,012	7,235,353	7,218,764	7,151,847	7,016,787	6,999,607	6,876,760	6,743,576	6,738,716
	6,651,008	6,631,331	6,615,141	6,599,694						
Screening methods	7,214,503	7,202,051	7,005,272	6,939,684	6,905,840	6,797,484	6,762,043	6,759,240	6,743,599	6,706,489
	6,664,072	6,649,363	6,627,408	6,617,144	6,617,115	6,613,540	6,610,525	6,573,061	6,548,267	6,509,167
	6,495,337	6,492,151	6,468,760	6,448,026	6,440,686	6,440,685	6,440,684	6,432,660	6,432,659	6,426,193
	6,416,966	6,410,254	6,391,573	6,387,644	6,379,912	6,284,480				

likely to be a heavy overlap in the protections sought in different territories, we have considered in greater detail only those patents granted in the United States. In order to determine the US patent holdings, we looked up the 'Issued Patents' section of the USPTO database, under 'Quick Search' (http://patft.uspto.gov/netahtml/PTO/search-bool.html). The search was done for 'Cytokinetics' as 'Assignee name'. As of early November 2007, there were 117 issued patents. The patents falling in each category are listed in Table 3, and the type of protection is summarized below.

Novel motor proteins

Cytokinetics has identified and isolated many novel kinesin motor protein sequences using BLAST. Most of the patents deal with new motor proteins, the polynucleotide sequences encoding them, and their uses in diagnosis, prevention and treatment of many diseases, including cancer. Besides isolating these proteins from humans, the company has also isolated motor proteins such as actin (commonly known as profilin) from *Aspergillus fumigatus* and bacterial systems.

Inhibitors of mitotic kinesins

Mitotic kinesins such as kinesin spindle protein (KSP) are ATP-dependent motor proteins essential for functioning of the mitotic spindle and are targets for the discovery and development of novel mitotic chemotherapeutics. The compounds that have been protected are derivatives of quinazolinones, phenothiazine, urea, pyridinone and benzamide.

Bioinformatics

A large number of compounds have been identified that have the ability to modulate the kinesins. However, for reasons of time and cost, it is not easy to test all of them for biological activity and Cytokinetics has automated the biological study of such compounds. This is done to identify lead molecules and only those compounds deemed promising are then tested in animals. This group of patents particularly deals with hardware, computer code and databases. The techniques protected are of image analysis, characterizing biological stimuli by response curves, cell imaging to determine ploidy, and predicting hepatotoxicity using imaging of cells, including cell–cell interactions.

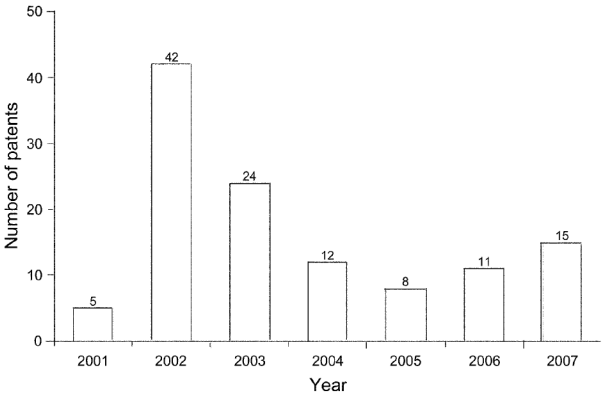

Figure 1. Year-on-year tracking of US patents granted to Cytokinetics, as of 8 November 2007.

Screening methods

Patents in this category protect the methods and kits for identification of candidate compounds that have the ability to modulate the activity of target proteins. Also protected are assays to identify antifungal agents. The company has not pursued its anti-fungal work, although it has a related publication[5].

The year-wise patenting profile of the company is represented in Figure 1. We have restricted our analysis to

issued patents. With a start in 2001, there was a surge in the number of granted patents in 2002, after which the numbers gradually declined till 2005. For the last couple of years, it has slowly been rising again. This is expected of an R&D-driven start up biotech company. The initial discoveries generate many patents, but with time as these initial discoveries move into development, fewer numbers of patents are generated.

In 2002 alone, the company received 42 patents, the maximum number of patents assigned to it in a single year. Most of them deal with the kinesin superfamily. These patents cover novel human kinesin motor proteins, the related polynucleotides and the use of these proteins in the diagnosis, treatment or prevention of cancer, neurological disorders, and disorders of vesicular transport. Some patents cover methods of screening modulators of these motor proteins.

The most comprehensive patent is US patent number 6,876,760 with 108 claims. The patent, which protects the Cytometrix™ system, is a good example of comprehensive protection of every aspect of such sophisticated instrumentation, including the collection of cell images and their automated classification based on the cell-cycle stage, whether G_1, S, G_2 or M. It also protects the computer program, the code and the apparatus that does image analysis. However, we should point out that a recent law in the US places a limit of 25 claims per patent and one cannot have 108 claims in one US patent any more.

Patentability of software is still a topic of debate in terms of what is or is not patentable. Although in many countries software is only granted copyright protection, in the US both copyright and patent protection is allowed if the software is embedded in hardware. This option is exploited by Cytokinetics. It has several patents that specifically protect bioinformatics software.

Another point we would like to highlight is that each granted patent does not necessarily denote a radically unique invention that is very different from any other invention patented hithertofore. Multiple patents exist that embody concepts that are broadly similar and yet different in certain detail. In the case of Cytokinetics, more than 40 patents have been granted that relate to novel motor proteins. Although the protection is similar – from isolating the novel sequence to making the antibodies and the kits – a separate patent is granted for each protein. For instance, claims of patent number 7,247,473 are very similar to those of 6,294,371. The separation of similar matter into multiple patent applications is due to the concept of 'unity of invention', which requires that only one invention be the subject of a single patent application. In fact, often, when one prepares a patent application, the patent attorney (or, subsequently, the patent office) will recommend creating two or three applications out of the single application, since it does not exhibit unity of invention.

Another example of less closely but still broadly similar patents is that provided by 7,246,012, which is related to many other granted patents as shown in Figure 2. These patents relate to cell image acquisition and classification of cells on the basis of their DNA content or stage of cell cycle.

There are two ways to start a company

We end by considering the two strategies for starting a company, one of which Cytokinetics illustrates well. Amarnath Bhide is Glaubinger Professor of Business at Columbia University. In 2003, he collaborated with a team at the Indian Institute of Management, Bangalore, to study companies (in diverse fields of activity) in Bangalore, which involved interviewing over 100 entrepreneurs. Their report[6] identifies systematic differences between what Indian and US entrepreneurs do and includes issues like how government regulations favour companies staying small; how companies have to 'make' services (such as electricity) that they would 'buy' in the US; how for the same starting capital the number of employees in the US is five times greater and the revenue is 20 times what they are for a company in Bangalore; how small companies in India tend to compete with large companies head-on, rather than identify separate niches, and so on. What Bhide has found is interesting and throws light on our entrepreneurial ecosystem.

Equally interesting is a 33-page memo[7] that he prepared as a supplement to a course that he taught at Harvard University in 1996. He says that there are two ways of setting up a company. The first is a capital intensive one and can be likened to the invasion of Normandy, where everything is planned to a T. An example of this type is Compaq Computer, which was able to play the game just right from start. Elements that enabled their starting advantage included high-quality market research, a top notch experienced founding team, a wise board and backing from the right kind of venture capitalists. The company was able to achieve sales exceeding US $100 million within its first year of operation.

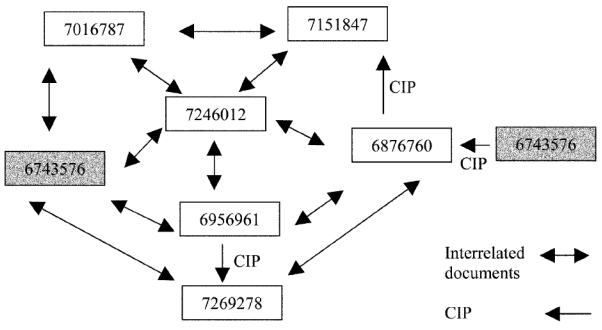

Figure 2. The interrelationship of granted US patents to Cytokinetics Inc. that broadly relate to cell-imaging. CIP is continuation-in-part. The direction of the arrow is from 'parent' patent to continuation patent. Shaded boxes represent a repeated patent number.

The second strategy is a boot-strapped one, and is like jumping on successive rocks to cross a stream. Most companies follow this path, and of course come close to tipping into the water every now and then. It is reported that when Hewlett and Packard started their now-famous company, they did 'anything to bring in a dime'. The philosophy, as expressed by Seshadri[8] can also be stated as 'win small, win early and win often'. That most companies, even in the US, are of this type is a consolation to those of us who work with young companies, since this is the pattern we see. Successful entrepreneurs in India acknowledge in conversation that this was the strategy that they adopted and that worked for them.

In the area of drug discovery, a company like Cytokinetics shows us that although the intersection of biology and chemistry cannot be accurately predicted or planned, Normandy-type planning is required in the sense that the long and expensive process of original drug discovery should be undertaken only when several pieces of the puzzle are in place (as it exists in pockets of the US today).

Conclusion

The case of Cytokinetics illustrates what San Francisco (and certain other academic–industrial 'clusters' in the US) has, that the Indian entrepreneurial ecosystem does not yet have in adequate abundance. Currently, we do not have the density of high-quality academic research that increases the probability of science suitable for commercialization; we do not yet have a culture that encourages a postdoctoral fellow to go off and start a company; we do not have experience in drug discovery and so one cannot pick up the phone and get good advice. Perhaps as a reinforcing result of all this, there is no venture capitalist willing to take a long-term bet on drug discovery in India, although some, like Nexus India Capital – originally from the Bay Area – are looking around for backable ideas.

In California, the fact that neither the professors concerned, nor the postdoc who became the CEO, had any experience with drug discovery was not considered a major stumbling block. The financial community in Silicon Valley – unlike in perhaps any other spot in the world, including other entrepreneurial 'hotspots' in the US – has an attitude that first-timers out of the best universities can create wonderfully innovative companies even without knowing much about business. The venture capitalists know business and help such pioneers build the business part. They are also comfortable with the long time horizon for a return on their investment. The value of a company created in this manner is often much higher compared to companies which start their revenue streams within, say, six months (although there are exceptions, such as the internet-based company Facebook). This has been seen with other engineering-based companies such as Apple and Intel as well.

Thus, the environment was enabling, and good science was considered financially backable. Ten years and US$ 273 million dollars (over Rs 1000 crores) on, the company is yet to have a product on the market, but this is not considered unusual in the area of drug discovery, and money continues to be available. We will watch with interest as to how and when such a venture is undertaken in India.

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ACKNOWLEDGEMENT. We thank Dr James Sabry, Executive Chairman of the Board of Directors, Cytokinetics, for his time and for several clarifications. All of the authors were part of IBAB during the course of this work.

Received 9 April 2008; accepted 21 May 2008