Commercialisation Processes in Converging Technologies: Case Study of Bioinformatics

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Definitions of Bioinformatics[1]

There is no single universally agreed definition of bioinformatics. At its broadest, bioinformatics is the application of information technologies and sciences to the organization, management, mining and use of life-sciences information. A narrower and typically undisputed definition of bioinformatics is the application of information technologies to the processing of molecular biology datasets (Bilateral and the Bioinformatics Industry Opportunity Taskforce 2002).

Bioinformatics is a product of the explosion in data and data management requirements arising from the genomics revolution and in particular the Human Genome Project.

> The efforts of genomics [ ] yielded thousands of genes and millions of single nucleotide polymorphisms (SNPs), not to mention the millions of potential proteins coded by those genes'. (Hoffman 2001)

Further Tollerman et al. have suggested that:

> The genomics wave is technology-driven, formed by the integration of new high throughput techniques with powerful new computing capabilities. … We characterize genomics… as the confluence of two interdependent trends that are fundamentally changing the way R&D is conducted: industrialization (creating vastly higher throughputs, and hence a huge increase in data), and informatics (computerized techniques for managing and analyzing those data). The surge of data – generated by the former, and processed by the latter – is of a different order from the data yields of the pre-genomics era. (Tollerman et al. 2001)

In this way bioinformatics is at the convergence of IT and biotechnology, combining the two technologies to produce solutions mainly for the biomedical sector, but also in agribusiness and environmental management. While most of the firms that provide bioinformatics services are in the software business, there are also firms that design specialist instruments and those that have designed specialist high-powered computers for the sector.

Thus the convergence has produced a range of types of companies, some starting with a predominately IT background and others bringing a biotechnology specialisation. Integrating these different skills has been one of the great challenges of bioinformatics. Much of this integration has been undertaken through partnerships - some between small specialist companies and others between small and large companies. This has had important implications for the commercialisation process. While most of the new technologies have emerged through small specialist companies, large companies have had an important role in integrating the disparate

[1] Much of this early section is taken from Houghton and Rasmussen (2002).

product offerings. This has been particularly true in the biomedical sector, which is the focus of this paper.

Bioinformatics in the Biomedical Sector

In the biomedical sector the early focus has been in the drug *discovery* aspects of the drug development business and in particular on disease target identification and validation. In identifying genes and related proteins that provide the keys to particular diseases it has appeared to be the area of greatest opportunity for bioinformatics. The conventional drug discovery methodologies were experiencing declining productivity and as a consequence a declining number of new drugs were being approved at the end of the pipeline. Genomics appeared to offer a methodical way of generating disease targets and therefore of rapidly improving the productivity of the drug pipeline. Although some of the initial optimism of rapid drug discovery and development now seems overdone, such remains valid. More recently some firms have moved into lead identification and optimisation as they have attempted to apply the same techniques to identifying lead compounds.

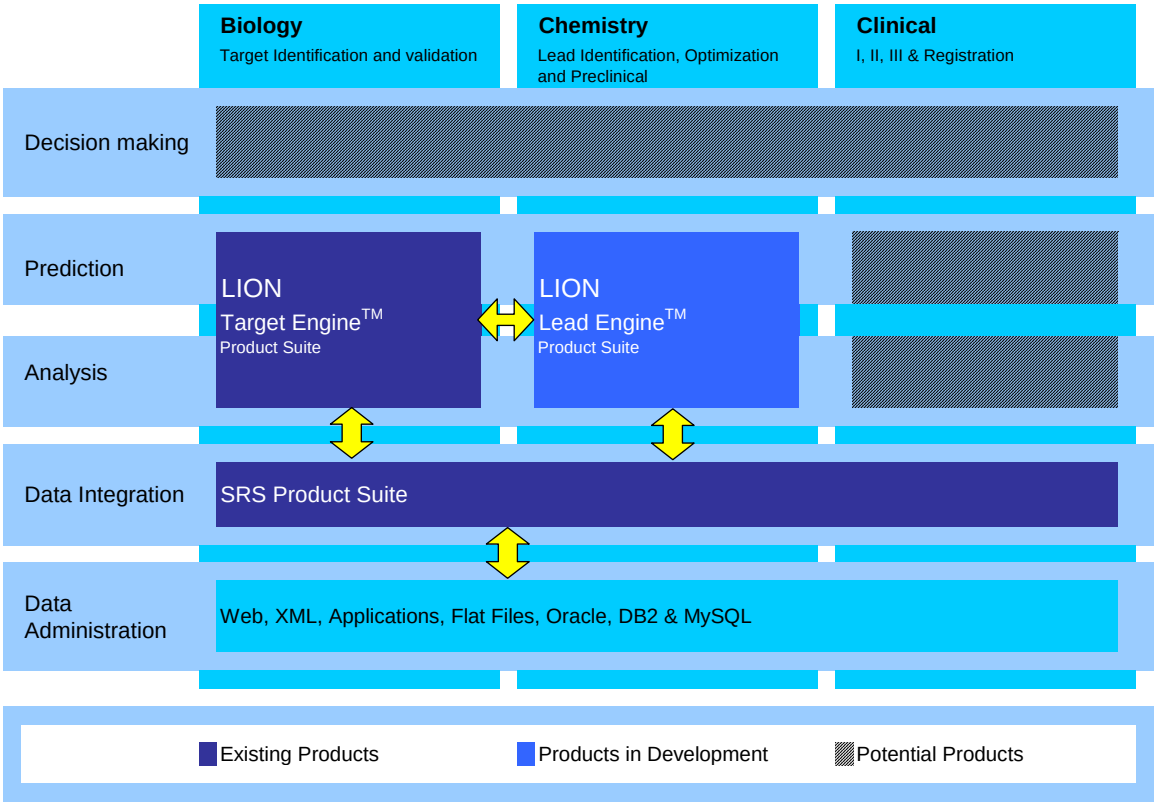
Bioinformatics business models and company strategy

The business model for specialist bioinformatics companies has depended on the profitable sales of specialised data and data management systems. Their largest customers, the large fully integrated pharmaceutical companies, while requiring the latest, specialised bioinformatics product, also have a strong interest in integrating the disparate systems within and across their value chain. These two somewhat competing requirements are evident in the business strategy of LION Bioscience, one of the leading bioinformatics companies.

Figure 1, extracted from The Business Model and Strategy section of the 2004 LION Bioscience *Annual Report,* illustrates both the early focus of a leading bioinformatics company and the intended direction of product development (LION Bioscience 2004). To date LION Bioscience has focussed on target identification, but has under development a product suite designed to assist with lead compound identification.

It is noteworthy that LION Bioscience has also earmarked products in clinical trials and decision making as having potential for product development. Most bioinformatics companies offer specialised services in one of more of these areas but few have developed integrated solutions for the whole value chain. LION Bioscience with its SRS product suite is one of very small number to provide a service that integrates the outputs of many specialised products across the whole value chain from early stage discovery to clinical trials. This failure by the majority of bioinformatics companies has left an opening for the large IT companies such as IBM, which initially became involved in the sector more as a hardware supplier, particularly of super computers. Increasingly these companies have moved to provide pharmaceutical companies with integrated bioinformatics solutions across the whole value chain.

Figure 1. Product Development at LION Bioscience



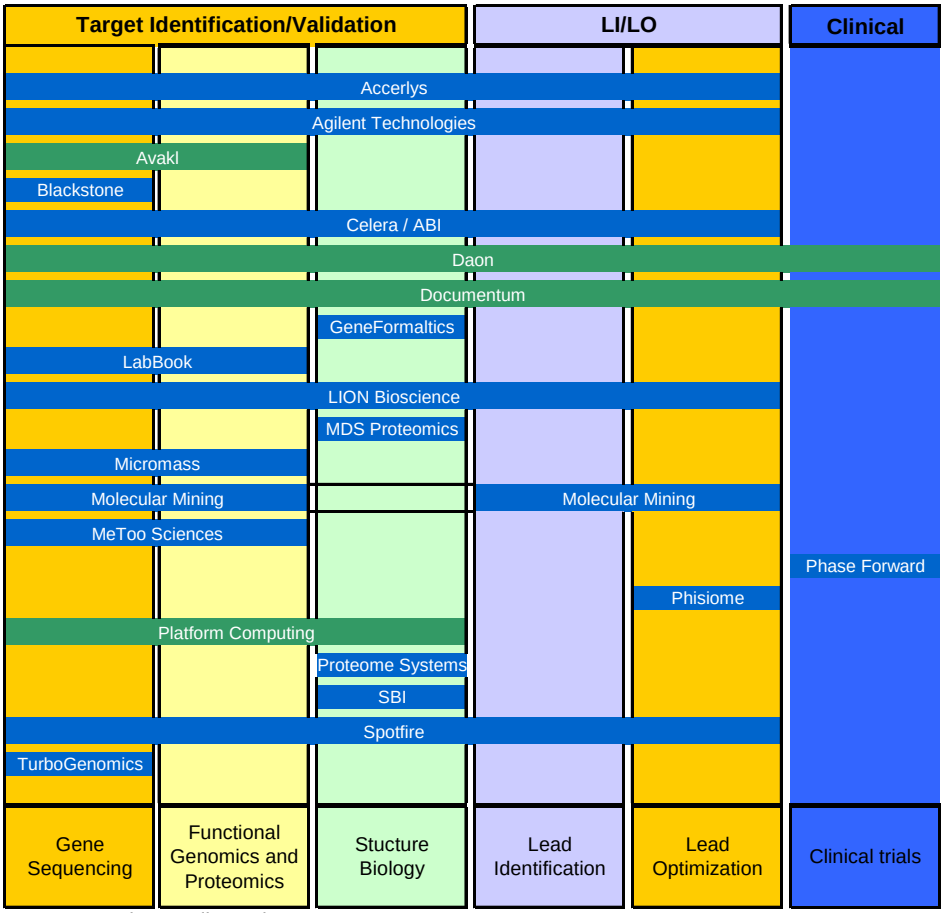
Source: LION Bioscience.

IBM is an interesting case study. IBM turned to bioinformatics in 2000 when it established IBM Life Sciences. In a sector dominated by a large number of small companies with limited distribution capabilities, it was in a relatively unique position of being able to leverage off the industry's requirements for large main frame computers. With its considerable distribution power but lacking the specialist software skills, it formed partnerships with a large number of small, 'best of breed'[2] specialist firms so as to offer the end customer, typically a major pharmaceutical company or large biotech, an integrated solution employing industry leaders in specialist roles. This is illustrated in Figure 2 extracted from an IDC report by Hall (2002), which shows some of the main alliances formed by IBM with specialist bioinformatics and other IT companies. These alliances have enabled it to offer bioinformatics services across the functional areas from target identification and validation, lead identification and optimisation to clinical trials.

Doubtless this offers advantages to pharmaceutical companies unwilling or unable to perform this integration function themselves. As noted by LION Bioscience however, 'LION's main competition comes from other scientific software suppliers and the *IT departments of major drug manufacturers*' [author's emphasis] (2004, p. 3). Another model of bioinformatics integration is for the major pharmaceutical companies to form these alliances directly with the specialist bioinformatics companies themselves, using the expertise of in house IT and other specialists to select their alliance partners and integrate the output of the various specialists.

[2] Interview with Sal Causi IBM Life Sciences by Y. Friedman, available at: http://biotech.about.com/interviews/1/aa_ibmbiotech.htm?terms=compsci

Figure 2. IBM Partner Functional Area Coverage



Source: IDC (see Hall 2002).

The table below illustrates the extent of this practice by the larger pharmaceutical companies. The table shows the bioinformatics alliances with the top 10 global pharmaceutical companies listed by Recombinant Capital on its alliance database. Where relevant, or the information is available, alliances listed on Recap are classified by 'technology'. Bioinformatics is one of the technology classifications on Recap.[3]

The table below also shows the relatively large number of companies (68) involved in bioinformatics alliances with the major pharmaceutical companies. Fewer than 30 have multiple alliances with these companies, while 8 leading companies have 3-4 alliances with this group of 10 companies. About half of the companies shown in the earlier chart of IBM partners also have direct relationships with the major pharmaceutical companies. On the basis that IBM has most of the major pharmas as clients, these specialist companies may have more than one way of delivering their expertise to the large pharmaceutical companies.

[3] Established in 1988, ReCap attempts to collect comprehensive, worldwide biotechnology alliance information from press releases, United States Securities Exchange Commission filings and industry presentations. The information is limited to those alliances that are announced publicly. Sometimes this means that commercially sensitive information is withheld. On other occasions information is not reported until there are some positive results. For these reasons the information must be regarded as indicative and not necessarily comprehensive. However, public disclosure rules generally require listed firms to announce information that is price sensitive. In other cases firms find it in their interests to release information about alliances as a sign of progress towards their strategic goals. For these reasons it can be expected that information about most significant alliances is released, and therefore available to ReCap. See www.recap.com.

	Pfizer	AstraZeneca	GSK	Merck	Aventis	Novartis	BMS	Roche	Lilly	Wyeth	Total
Gene Logic	✔		✔		✔			✔			4
Inpharmatica	✔		✔		✔	✔					4
LeadScope	✔	✔			✔				✔		4
Lexicon Genetics	✔		✔	✔			✔				4
LION bioscience	✔	✔	✔						✔		4
Ingenuity Systems			✔	✔						✔	3
Morphochem AG		✔			✔	✔					3
SurroMed				✔					✔	✔	3
accelrys		✔							✔		2
Ardais					✔		✔				2
Beyond Genomics		✔	✔								2
BioVisioN		✔						✔			2
Caprion Pharma		✔								✔	2
Cell Signaling Tech	✔	✔									2
Compugen	✔					✔					2
deCODE Genetics				✔				✔			2
Genaissance Pharm	✔	✔									2
GeneData AG		✔				✔					2
GeneGo			✔				✔				2
Genomics Collab	✔		✔								2
Jubilant Biosys			✔			✔					2
ParAllele Bioscience				✔				✔			2
Pharsight					✔					✔	2
Phase Forward			✔						✔		2
Rosetta Inpharmatics			✔		✔						2
Spotfire	✔				✔						2
Tripos	✔						✔				2
ACLARA BioSciences	✔										1
Ambit Biosciences		✔									1
ArQule	✔										1
Astex Technology		✔									1
Athersys	✔										1
Aureus Pharma								✔			1
Celera Diagnostics							✔				1
Celera Genomics										✔	1
Cellomics		✔									1
ChemNavigator		✔									1
Chondrogene	✔										1
Deltagen				✔							1
DoubleTwist				✔							1
EraGen Biosciences					✔						1
GeneFormatics							✔				1
Gene-IT					✔						1
GeneTrove			✔								1
Genomica					✔						1
Genstruct	✔										1
GPC Biotech					✔						1
InforSense			✔								1
LifeSpan Biosciences							✔				1
Lynx Therapeutics	✔										1
Molecular Staging									✔		1
Neurion Pharmas	✔										1
Odyssey Thera								✔			1
OSI Pharmaceuticals				✔							1
Pharmacopeia						✔					1
PharmaDesign				✔							
PPGx							✔				1
Protein Mechanics					✔						1
Protein Pathways				✔							1
Proteome				✔							1
Scynexis				✔							1
Serenex			✔								1
Sertanty					✔						1
Structural GenomiX									✔		1
Summit Pharma				✔							1
Symyx Technologies	✔										1
Third Wave Tech						✔					1
TransForm Pharma								✔			1
VistaGen						✔					1
Total	19	14	14	12	14	8	8	7	7	5	108

There is a high correlation between the size of the pharmaceutical company and the number of alliances formed. The largest, Pfizer has 19 listed on Recap, while four others have between twelve and fourteen. One of the smallest of the group has just 5 bioinformatics alliances listed. The number may also reflect the relative interest by the companies in pursuing genomics based drugs.

The interaction between the small specialist company and the large company, either pharmaceutical or IT, appears to be central to the commercialisation process of bioinformatics. As with other new sub technologies entering the biotechnology sector, bioinformatics started in small companies, by entrepreneurs who had a new addition to the range of technologies and services on offer and who had identified a gap in the existing range of offerings. Early in this commercialisation process they formed alliances with other small companies offering complementary technologies as well as the larger companies which provided money and support.

This tendency is apparent from the bioinformatics alliance data extracted from Recap. It shows the number of bioinformatics alliances listed on the database from 1992 by alliance party. In the table below, bio means a biotech, generally a bioinformatics specialist company. Drug means a pharmaceutical company and uni is a university or research institute. Non-medical includes IT companies and other non medical, e.g. agribusiness companies, seeking bioinformatics solutions.

Number of Bioinformatics Alliances by Party, 1992 to 2004

Year	Bio_Bio	Drug_Bio	Drug_Drug	Non-medical	Uni_Bio	Uni_Drug	Grand total
1992	4	2					6
1993	2	2					4
1994	6						6
1995	2	1		1			4
1996	4	6			3		13
1997	5	8		1	1		15
1998	7	15		3	4	1	30
1999	20	14	1	4	7		46
2000	30	32		8	18		88
2001	99	46		13	34	1	193
2002	80	47	3	3	20	2	155
2003	55	43		5	11	1	115
2004	36	51	1	2	8	1	99
Grand total	350	267	5	40	106	6	774

Source: Recap February 2005.

The table shows that from very small numbers, 4-6 in the early 1990s, the number of alliances grew rapidly over the five year period from 1997 to peak in 2001at 193. A high component of this number, 133 of the total of 193 in 2001 were alliances formed between bioinformatics companies and by universities and bioinformatics companies - the former by those seeking complementary specialist technologies and the later for a range of reasons, most notably by universities as part of new start ups, but also by research institutes seeking access to the new genomics based data bases. But by 2003,

these alliances had fallen rapidly to only 66 and perhaps further, to 44 in 2004[4] In contrast, the number of alliances with pharmaceutical companies continued to trend upwards from 8 in 1997, to 43 in 2003 and 51 in 2004.

One of the reasons for this divergent trend is the poor performance of the independent bioinformatics companies. Doubts about the viability of the bioinformatics business model began to emerge in 2001 (see for instance Hoffman 2001). In the late 1990s investors thought that GPT companies such as bioinformatics companies offered a low risk but profitable means of sharing in the gains from biotechnology. The stock price of GPT companies, especially those with an exposure to genomics, increased rapidly and new listings attracted significant capital.

However from 2001 this view was completely revised. The prospect of making money from selling data was undercut by much of it being transferred to the public domain. The pace of innovation and the difficulty of maintaining market leadership against competing firms with new and improved products meant that recently launched products quickly became obsolete and suffered declining sales. One of the market leaders, Double Twist simply closed its doors in 2002. Other companies such as Celera Genomics, which had undertaken much of the work on the human genome, transferred its genomics database product to an associated company so as to focus entirely on drug discovery.

Listed in the table below is the current status of ten leading bioinformatics companies ranked by number of bioinformatics alliances.

Current Status of Bioinformatics Companies Ranked by Number of Alliances*

Bioinformatics Company	Alliances*	Current status
Celera Genomics	27	Exit to focus on drug discovery
LION bioscience	23	Falling revenues, significant losses
Gene Logic	19	Increasing revenues but significant losses
Tripos	18	Increasing revenues but continuing losses
DoubleTwist	18	Closed
MDL Information Systems	16	Purchased by Elsievier
Third Wave Technologies	14	Increasing revenues but continuing losses
Inpharmatica	14	Private, unknown
Genomica	14	Purchased by Exelixis
Compugen	14	Falling revenues, significant losses

Note: *Number of bioinformatics alliances formed since 1995 listed on Recap.

Of these10 high profile bioinformatics companies, only three have increasing revenues. None are known to be making a profit, two have exited the industry, and two have been taken over. Several are attempting to build revenue streams based on their own drug discovery programs.

[4] There are delays in alliances being listed on the Recap database, which is sourced from public documents and in particular, SEC filings made in the second quarter each year. For this reason the alliances listed for 2004 are likely to be incomplete.

In contrast to the lack of viability of the independent bioinformatics company, the pace of innovation in the sector appears to be if anything increasing. Patents issued by the USPTO in selected bioinformatics related classes are shown in the table below.

Patents Issued: Selected Bioinformatics Related Classes USPTO

Year	703/11	702/19	702/20	702/27
1996	4	8	3	7
1997	10	6	2	18
1998	7	16	5	17
1999	12	20	9	14
2000	12	27	15	15
2001	17	49	23	26
2002	11	70	42	34
2003	11	94	25	37
2004	17	106	39	56
CAGR 1996 to 2004	17.4%	33.3%	33.0%	26.0%

Notes: Classes:

703/11	Data Processing: Structural Design, Modeling, Simulation, and Emulation; Biological or Biochemical
702/19	Data Processing: Measuring, Calibrating or Testing Measurement System in a Specific Environment Biological or Biochemical
702/20	Data Processing: Measuring, Calibrating or Testing Measurement System in a Specific Environment; Gene sequence determination
702/27	Data Processing: Measuring, Calibrating or Testing Measurement System in a Specific Environment; Molecular structure or composition determination

Source: USPTO March 05. For discussion of relevant classes see Gatto (2001).

Following Gatto (2001), who identified a number of bioinformatics related patent classes, those shown above have been selected for their particular relevance to the biomedical sector. They cover a range of activities relating to data processing: structural design and measuring and calibrating, applied to molecular structure, biological and genetic environments. For these classes the number of patents issued has rapidly increased over the period since 1996 at CAGRs of up to 33%. This would suggest that the pace of innovation is now independent of the viability of the business model of the independent bioinformatics companies. More research would be required of the assignees of the recently issued patents to better understand this aspect of the innovation and commercialisation process.

Implications for Australia

The Littlejohn Report (Biolateral et al. 2002) observed about the Australian bioinformatics industry that:

> The small local commercial customer base is a serious barrier to the growth of the bioinformatics industry. Investment strategies that grow domestic biotechnology and other bioindustry firms would help reverse this situation. (p. 22)

It recommended a program of government sponsored partnerships between local and overseas firms, to accelerate Australian product development, provide commercialisation channels for Australian data banks and link Australian firms to end markets such as large biotechnology and pharmaceutical firms.

Proteome Systems, arguably Australia's leading proteomics/bioinformatics company and recipient of the 2003 Frost & Sullivan Award for Technology Innovation for its novel technologies and unique proteomics automation products,[5] appears to be following this script. It was established as a company in 1999, with the founders

[5] http://www.separationsnow.com/basehtml/SepH/1,1353,6-1-4-1-0-news_detail-0-803,00.html

emerging from the Advanced Proteome Analysis Facility at Macquarie University. (see Mathews and Carmen 2002). The company has formed a range of alliances with leading international firms to assist with the development, marketing and distribution of its product range. For instance, Proteome Systems and IBM have established a global strategic alliance, under which IBM has worldwide co-marketing rights to one of its key products, ProteomIQ, a suite of proteomics technologies integrated through an information management and analysis system. ProteomIQ capabilities are impressive. It:

> …provides an end to end solution which allows a researcher to take a raw biological sample (e.g. blood or a tumour biopsy), separate it into its constituent parts, simultaneously process these parts and identify and characterise the proteins of interest present in that sample. (Proteome Systems 2004a, p. 27)

The components of the system are also sold individually. For instance, one instrument that automates the separation of proteins, a critical step in identifying disease targets was developed in partnership with Shimadzu, a Japanese scientific instrument manufacturer (Protome Systems 2004a).

Despite the strength of these alliances, the company confronts significant challenges for its survival. Its revenues in 2003/04 ($8.3m) were less than 40% of their level in 2002/03, for which the company blamed 'lumpiness' in its product sales. It posted a loss of $15.7m in 2003/04 on reduced R&D expenditure of $9.2m and finished the financial year with just $213,684 in cash and few other realizable assets (Proteome Systems 2004b). It listed on the ASX in September 2004, raising $20m at an issue price of $1.20 (Proteome Systems 2004a). Its share price has fallen steadily, despite the generally favorable market conditions and is currently at just $0.40, having lost two thirds of its value since listing. As at 31 December about half of the money raised in the IPO had been spent and no further significant sales achieved.

The experience of overseas bioinformatics companies emphasizes the difficulties faced by Proteomic Systems. The need to retain the confidence and funding from investors, while sales are insufficient to cover costs and perhaps trending down.

Conclusion

The evidence presented in this paper suggests that the initial optimism of the early commercialisation process through small specialist companies has had only limited success and that the commercialisation process has become more dependent on the activities of large companies, both major pharmaceutical and IT. These large companies have become increasingly important, as alliance partners to specialist bioinformatics companies, in supporting the transfer and use of knowledge generated in these specialist companies into the drug discovery and development processes of major pharmaceutical companies. This has occurred either directly with the integration role undertaken by internal IT departments or indirectly through the integrating functions performed by large IT companies, such as IBM. There is also evidence that some bioinformatics companies have transformed themselves into R&D drug discovery and development companies seeking to leverage their greater bioinformatics expertise to discover and develop their own drugs.

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