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Downstream and into deep biology: Evolving business models in 'top tier' genomics companies

Harry Rothman and Alison Kraft

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Professor Harry Rothman has worked on biotechnology policy issues for over 20 years. His most recent book, authored with P. Glasner, is 'Splicing Life?: The New Genetics and Society'. He is Special Professor at Nottingham University Institute for Enterprise & Innovation, and edits the journals *Technology Analysis & Strategic Management* and *New Genetics & Society*.

Dr Alison Kraft has recently been working on the commercialisation of the life sciences, with particular reference to the impact of genomics on pharmaceutical innovation. She is Research Fellow on an ESRC-funded project which is analysing the clinical and commercial development of haematopoietic stem cells (HSC), including HSC transplantation, umbilical cord blood banking and the use of HSCs in regenerative medicine.

Keywords: *biotechnology sector, business models, commercial strategy, drug innovation, drug pipeline, genomics, pharmaceutical industry*

Abstract

Genomics companies are changing their business models and some have moved beyond drug discovery into drug development. The authors' analysis of genomics companies' business models yields further insights into the widening role of genomics firms within drug innovation and on the evolving dynamics between the genomics sector and the wider pharmaceutical industry. Business models within the sector have included that of the FIPCO (Fully Integrated Pharmaceutical Company), technology and information platforms, and, more recently, a new 'dual' business model that combines established platform capabilities with drug development. The study identifies a cohort of 22 leading genomics companies and takes as its focus those companies following the dual and platform business strategies. The paper describes how, over the past five years, leading genomics companies have, typically, refocused their interests downstream within drug innovation, a move that brings new commercial opportunities but also threats. New and evolving business models are enabling these companies to leverage their commercial positions and capture value in the later stages of drug development. These shifts are characterised and the possibility that this 'downstream' trend could exert a major effect on the future relations between genomics companies and pharma/large biotechnology firms, and on drug innovation, is explored.

INTRODUCTION

The failure of genomics to provide the anticipated, and much hyped, novel drugs over the short term has been much commented upon, especially following the collapse of the genomics bubble in 2000.[1] Less attention has been paid to the manner in which genomics firms have been willing and able to change their business models in light of the fact that the development of genomics-based drugs is proving more difficult and taking far longer than was initially envisaged. Changing business models have been crucial not only to the commercial viability of individual start-up companies and the genomics sector as whole, but also to sustaining the vision of genomics-based drugs.[2] With big pharma and big biotech typically viewing genomics per se as one option within their discovery enterprise – 'another arrow in (our) quiver' – genomics companies continue to be a major driver of and key institutional focus for the development of genomics-based drugs.[3] The genomics sector is characterised by rapid technological change and obsolescence, and remains acutely sensitive to the vagaries of the financial markets and wider economic cycles. 'Strategic versatility' – the ability of management to both anticipate and respond to scientific, technological and regulatory change, as well as competitive threats, is a critical determinant of company success or failure. As a result, commercial strategy and business models within the sector have changed markedly since the halcyon days of the early 1990s.

Changing business strategy has become a hallmark of the sector

As part of recently completed research into the impact of genomics on pharmaceutical innovation, funded under

Alison Kraft
Senior Research Fellow,
Institute for the Study of Genetics, Biorisks & Society (IGBiS),
The University of Nottingham,
Nottingham NG7 2RD, UK

Tel: +44 (0)115 846 7169
E-mail:
Alison.kraft@nottingham.ac.uk

the ESRC-IHT programme, we have studied the evolving commercial dynamics within the genomics sector since the mid-1990s.[3] This paper takes as its focus the development of business models within leading genomics firms and draws together some of our broader research findings.[4] Particularly striking is the fairly recent and widespread trend for genomics companies to refocus their research efforts and commercial interests 'downstream' within the drug innovation cycle. Since 2000, some companies have moved beyond drug discovery into drug development and there is a sector-wide trend to reorient proprietary assets (technologies and/or databases) to downstream applications. We describe and analyse the range of factors – technical, competitive, financial – that are driving this trend. At the same time, the development of the genomics sector remains inextricably coupled to, and is both reliant upon and shaped by, the pharmaceutical and biotechnology industries.

Genomics companies beginning to move downstream in drug innovation cycle

Historically, genomics companies sought to meet needs of big pharma

That said, in moving beyond drug discovery, genomics companies are laying claim to a much wider role in drug innovation. In extending their reach into the clinical phases of drug development, genomics companies are, of necessity, both changing and expanding the range of their scientific expertise and technical skills, the corollary of which is qualitative change in the content and direction of research. Not only does this 'downstream migration' bring genomics companies nearer to the market and, potentially, bring the much-vaunted vision of genomics-based drugs a step closer, we argue that it may also be reshaping the contours of drug innovation in a number of important respects. That vision, however, is taking much longer to realise than was initially envisaged; for all the investment in genomics, it remains a paradigm in search of a drug product. Currently, a great deal of research within the sector is focused on unravelling pathophysiological processes (disease, deep or systems biology) in order to fully validate targets. This vast and complex scientific enterprise is proving costly and time-consuming.[5] We emphasise the central importance of business strategy within the sector in sustaining – in the absence of drug products – the quest to develop genomics-based drugs.[6] In order to provide a context in which to situate our analysis of contemporary commercial dynamics and business models we begin by reviewing broad trends within the genomics sector.

How can genomics firms survive commercially?

THE GENOMICS SECTOR: REVIEW AND CONTEXT

The pharmaceutical industry's search for new sources of innovation has provided fertile terrain for start-up companies. Genomics companies do not – could not – act alone. Historically, the landscape of success and failure for genomics companies has been framed in terms of meeting big pharma's needs, which, first and foremost, centre on reinvigorating its product pipelines. From the outset, the emergence and growth of the genomics sector have, in large part, reflected the ability to meet the needs of and been reliant on the wider pharmaceutical industry.

The principal strategy of all genomics start-ups centred immediately on the development of proprietary technology or knowledge-based assets, protected by patent. 'Intellectual property' was critical to business and competitive position, and formed the cornerstone of commercial development. Proprietary assets came to form the basis of alliances with pharmaceutical/biotechnology partners: in the early to mid-1990s, proprietary assets, typically a database, or enabling ('platform') technology, became the subject of multiple alliances with different partners. In this period, alliances chiefly involved licences and/or subscription fees: access could be either on a non-exclusive or exclusive basis.[7] 'Proprietary assets' not only provided revenue via alliances but also, crucially, allowed companies to carve out a business niche and build a distinctive commercial identity within the nascent genomics

market. Genomics companies have, for strategic reasons, consistently sought to leverage their position by 'adding value' into proprietary assets: for example, a database can be annotated, a microchip can be engineered to measure a wider range of parameters more sensitively and/or with greater accuracy and some types of asset can be customised to meet the needs of a particular partner.[8] In providing vital near-term revenue streams to young, cash-strapped genomics start-ups, alliances have been, and remain, the financial lifeblood of the sector. The ability to attract and form alliances also confers credibility on a company and on its proprietary assets. Alliances are both a source of commercial kudos and generate cash income for genomics companies which, typically, have large 'cash burn' deficits which result, primarily, from heavy R&D expenditure.

Top 22 genomics start-ups formed over a thousand alliances in last decade

Commercial survival for start-up companies is fundamentally a question of cash flow. Revenue flows only when the utility of a particular asset has been proved; the market value of an asset at any one time has been governed largely by the needs of the pharmaceutical industry. Initially these needs centred on new drug targets, a need that reflected the deepening 'productivity crisis' against which the industry has, since the 1990s, struggled.[9] Incumbent firms looked to genomics companies to bolster their pipelines with validated targets and/or lead compounds. Throughout the 1990s the vast majority of genomics companies therefore operated in the very early 'upstream' stages of the drug innovation cycle, that is, in target identification and later extending into target validation, lead validation and lead optimisation. This dynamic led to the relationship between genomics companies and their more powerful, established pharmaceutical partners being framed in terms of a supply chain. Through this supply chain framework, alliances came, in effect, to sustain a vast research enterprise aimed at developing genomics-based drugs and provide a solution to pharma's ailing pipelines.[10] Put simply, the genomics sector comprises niche players in a supply chain that leads to big pharma and/or big biotech, a relationship both symbolised and sustained by a complex and diffuse network of alliances. The 22 leading genomics start-ups profiled in this study have, collectively in the last ten years, formed over a thousand alliances.[11]

Survival strategies of leading cohort of genomics companies

The rapid pace of scientific and technical change underpins the equally rapidly evolving commercial landscape within the genomics sector. This quickly came to be characterised by high turnover, as companies struggled on the one hand to commercialise their proprietary assets and, on the other, against the vagaries of investment trends within the venture capital sector. The reasons for company failure are manifold: many flounder because they fail to commercialise scientific and/or technical advances quickly enough, others respond to changing competitive conditions too slowly, especially the dangers of technical obsolescence and commodification, while others were acquired by incumbent firms. For some the death knell was sounded by the investment preferences/strategies of the venture capital industry, the influence of which intensified amid the worsening financial climate of 2000 and beyond. These circumstances have imposed on companies the need for excellent management and a regime of 'survival decisions' whereby commercial strategy and business models are adjusted in anticipation of, or response to, prevailing conditions. This can involve new types of alliances, and may influence merger and acquisition activity within both the genomics sector and the pharmaceutical/biotechnology industries.

For most of the 1990s, genomics companies remained, for the large part, clustered within the drug discovery stage of the drug innovation cycle (DIC).[12] While target identification formed a vital initial market for genomics companies, it was to have short-lived commercial viability. The reasons for this were three-fold: firstly, the widened availability of

DNA sequencing technologies and sequence databases had, by the late 1990s, reduced them – and their use – to commodities. Second, target generation and screening technologies, especially combinatorial chemistry (CC) and high-throughput screening (HTS), which were developed to automate and thereby accelerate the speed with which the genome could be searched and targets identified, were readily adopted by and *integrated within* big pharma. These early 'target generation' technologies shared sufficient similarities, in terms, for example, of expertise in medicinal chemistry and rational drug design, with the screening tradition in 'front end' drug discovery within big pharma. Many CC companies were acquired by large pharmaceutical firms, including, for example, Sphinx (by Lilly for US$80m in 1995), Selectide (by Hoechst for US$58m in 1996) and Affymax (by Glaxo for US US$533m in 1996).[13] Absorbed within the R&D function of pharma, CC and HTS had, by the late-1990s, become 'generic' technologies; their diminished market value wholly undercut their commercial viability. More recently, the commercial ramifications of such commodification has again been demonstrated in companies centred on DNA sequence data.[14] The marked decline in value of raw sequence data has, since the late-1990s, created serious difficulties for sequencing companies such as Incyte and Sequenom, and evidenced more emphatically by the fate of Double Twist and Genset.[15] Third, by 2000 the industry was awash with new targets about which little was known: value came to lie in knowledge about targets. This shift in scientific focus was accompanied by a downstream reorientation of commercial strategy.

Only Millennium and HGS pursued FIPCO strategy from outset

In response to the risks, uncertainty and prevailing commercial dynamics within the sector, genomics companies have, over time, developed a number of means through which they are able to differentiate their products, add value to the chain and thus leverage their position in commercial negotiations. The recent trend to 'move downstream' can be seen as one more strategic turn in the evolving trajectory of the genomics sector. It might also be understood as the latest, perhaps most ambitious but also risk-laden 'survival decision', which nonetheless has been taken by a substantial number of larger, older and publicly held genomics companies. It is within this context that we now return to our analysis of current commercial strategy and trends among leading genomics companies.

THE GENOMICS SECTOR, 2005: STRATEGY IN LEADING COHORT OF COMPANIES

Our analysis centres on a 'core set' of 22 leading genomics companies[16] (Table 1). We have assembled in-depth profiles of these companies and have tracked the evolution of commercial strategy and business models within them. Membership of this cohort has, since 2000, remained fairly stable, however, as is clear from Table 1, within the group there is considerable variation with regard, for example, to size and financial position. The constituent companies also display wide-ranging scientific and technological competencies. That said, members of the cohort share a number of characteristics: all are US-based public companies, all but one were formed between 1991 and 1997, most continue to operate at a loss and all remain reliant on alliances with pharmaceutical and/or biotechnology partners for near/mid-term revenue. While emphasis within all companies remains strongly oriented to therapeutics, it is noteworthy that some companies are also turning their attention to the diagnostics market.

Within the cohort, a clear distinction can be drawn between Millennium and HGS, both of which from the outset pursued the Fully Integrated Pharmaceutical Company (FIPCO) strategy, and the other 20 companies. FIPCO genomics companies are the exception rather than the rule; if some

Table 1: Key data for genomics company cohort (as of end 2004)

Company	Location (headquarters)	Year founded	1st initial public offering (IPO)	No. staff (full time)	IP estate* (held/pending)	Total revenue (US$m)	R&D expenditure (US$m)	Business model
Affymetrix	Santa Clara, CA	1993	June 96	907	303/405	346	73.4	Tech. platform
Celera Genomics	Rockville, MD	1998	March 2000	530	n/d	n/d	10.82	Dual
HGS	**Rockville, MD**	**1992**	**Dec. 93**	**840**	**432**	**3.8**	**219.6**	**FIPCO****
Incyte	Palo Alto, CA	1991	Nov. 93	186	n/d	14.2	88.3	Dual
Millennium	**Cambridge, MA**	**1993**	**Jan. 96**	**1477**	**n/d**	**448**	**402.6**	**FIPCO****
Aclara Biosciences†	Mountain View, CA	1995	March 2000	60	285	1.5	15.6	Tech platform
Arena	San Diego, CA	1997	July 2000	291	40/273	13.7	57.7	Dual
Ariad	Cambridge, MA	1991	May 94	72	32/97	7.4	27.7	Dual
Caliper Life Sciences	San Jose, CA	1995	Dec. 99	414	250/174	80.1	22.7	Tech platform
Ciphergen	Fremont, CA	1995	Sept. 2000	255	21/124	40.2	19.3	Tech platform
Curagen	New Haven, CT	1993	March 98	242	79	6.3	72.7	Dual
Exelixis	San Francisco, CA	1994	April 2000	517	86/306	52.9	137.8	Dual
Gene Logic	Gaithersburg, MD	1994	Jan. 2000	446	54/105	75.9	2.3	Info. platform
Lexicon Genetics	Texas	1995	April 2000	704	150/600	61.7	90.6	Dual
Large Scale Biology Corp	Vacaville, CA	1987	Aug. 2000	76	80/94	3.6	11.5	Dual
Lynx Therapeutics‡	Hayward, CA	1992	March 2001	75	84/98	12.9	15.5	Tech. platform
Maxygen	Redwood, CA	1997	Dec. 99	230	70/50	16.3	53.3	Dual
Nanogen	San Diego, CA	1993	March 2000	78	111	5.4	18.1	Tech. platform
Icoria§	Research Park Triangle, NC	1997	May 2000	188	17/107	24.6	26.7	Tech. platform
Rigel	San Francisco, CA	1996	Nov. 2000	144	50/150	4.7	48.5	Dual
Sangamo Biosciences	Richmond, CA	1995	April 2000	54	55/69	1.3	11.1	Dual
Sequenom	San Diego, CA	1994	Feb. 2000	148	72/70	22.5	18.6	Info. platform

n/d = not disclosed
*As of December 2004. (Figures refer to US patents only/exclude co-owned IP. Some companies do not disclose information on patents pending. Single figures refer to patents already held.)
**Fully Integrated Pharmaceutical Company (FIPCO)
†Now ViroLogic (merger June 2004).
‡Now Solexa (acquisition August 2004).
§Formerly Paradigm Genetics (name change August 2004).
Note: IP data for Aclara, Lynx and Paradigm Genetics relate to period ending December 2003.
Source of data: SEC 10K Filings, end-2004/2005

Why the current trend for 'downstream migration'?

genomics start-ups harboured aspirations to become FIPCOs, this was precluded by many factors, not least financial considerations and a lack of expertise in drug development, marketing and distribution. It is the 20 smaller (though publicly held) genomics companies that form the analytical focus of this study. Most members of this company cohort started out as 'platform' companies, developing and commercialising particular technologies or DNA databases (informatics providers). Proprietary technologies and databases were initially geared towards target identification and validation: the current trend for 'downstream migration' reflects how value has come increasingly to reside in 'the molecule', that is, a validated target, a lead compound or a candidate drug. The reorientation of commercial interest downstream is reshaping commercial opportunities and providing fertile terrain for the formation of new relationships within drug innovation.

Figure 1 captures the 'downstream' trend within the genomics sector. Eleven genomics companies – nine former technology platforms and two former informatics providers – have, since 2000, repositioned themselves within drug innovation by moving into drug development. This has been achieved by establishing internal drug development programmes (IDDPs); in effect, this has provided a means by which companies are able both to leverage their biological expertise and further integrate discovery

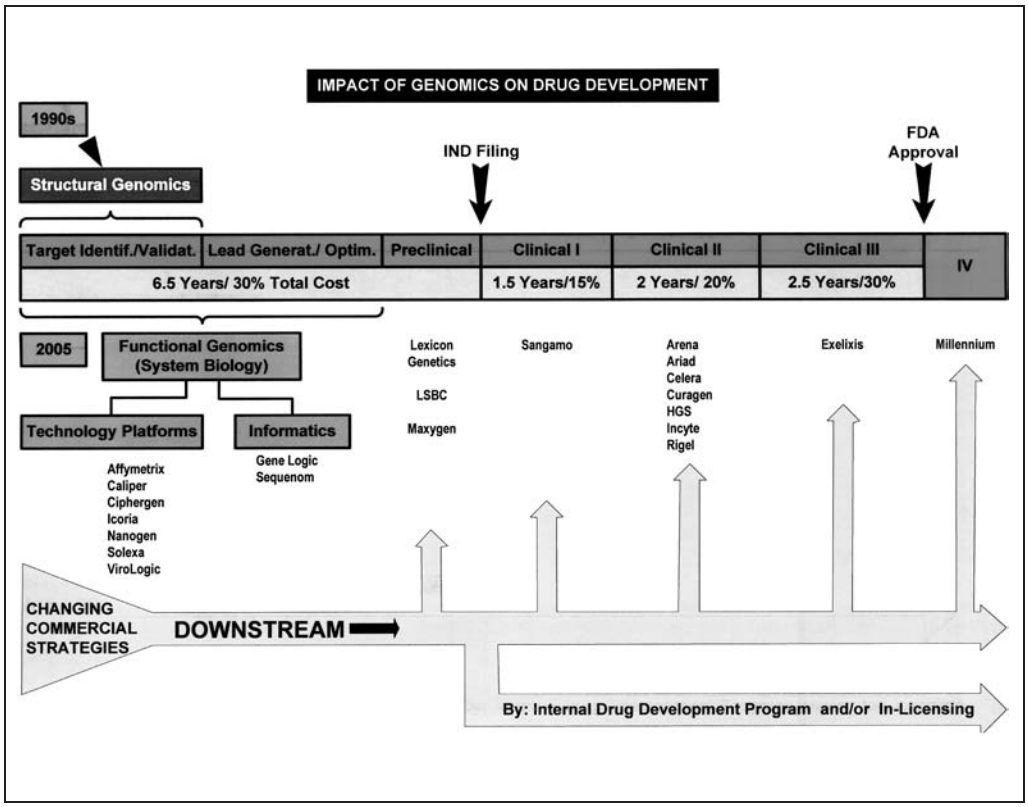

Figure 1: Impact of genomics on drug development

capabilities. Some companies have established IDDPs using in-licensed compounds from pharmaceutical or biotechnology companies, thereby accelerating the creation of a pipeline. Others have combined in-licensing with the use of internally generated compounds, affording greater control over the drug development programme. Significantly, those companies moving into drug development have, typically, continued to develop their IP estates and innovate their 'core' proprietary assets, which remain a valuable source of near-term revenue.[17] The 'dual' business model therefore accommodates both near- and (new) longer-term commercial objectives. At the same time, the emergence of the 'dual' model is also, in part, a response to changing priorities within the investment sector which, since 2000, has shown a strong preference for companies to be engaged in the development of clinical products.

The dual business model

The move into drug development marks something of a watershed in the overall trajectory of the genomics sector. Moreover, that a substantial number of genomics companies have been prepared and able to undertake the hugely expensive and risk-laden move is not only testimony to their strength, but might also be interpreted as an indication of the sector's growing maturity. In one sense, the new drug pipelines of genomics companies can be seen as lending material reality to the genomics paradigm; however, any affirmation must be tempered by the caveat that a great deal of research, both scientific and clinical, remains to be done before genomics-based drugs reach the market. The data in Table 1 cast into sharp relief the research intensive culture and financial trends characteristic of the genomics sector. Only 5 companies (one FIPCO/four platforms) have revenues that exceed R&D expenditure; for all 11 companies adopting the 'dual' business model, R&D costs far exceed revenue and these costs rose markedly with the creation of IDDPs.[18]

For companies adopting the dual business model, the move into drug

development makes both strategic and financial sense in the longer term. The regulatory and structural framework of the drug innovation cycle is such that value increases downstream. A drug candidate that has passed through preclinical trials has much higher commercial value than a lead compound. Likewise, candidates gain additional and increasingly substantial value as they pass successively through clinical Phases I, II and III. In moving downstream, genomics companies are not only creating value, they are also advancing closer to the market: both are extremely attractive to investors. The trend to downstream migration apparent since 2000 reflects both internal and external factors; the former includes the FIPCO ambitions of the individual company, the latter reflects changes in the wider business environment/financial climate. Among the external factors are challenges to the continued viability of the 'platform' business model, the changing needs of both pharmaceutical and biotechnology companies and, perhaps most influentially, the growing preference amongst investors for drug products (rather than, or alongside, genomics technologies and databases). As one genomics company adopting the 'dual' business model recently commented:

> potential partners are now more interested in drug candidates for a specific therapeutic area, and particularly drug candidates with clinical data, rather than just the technologies that could be used to find such candidates.[19]

The downstream trend due to combination of internal and external forces

Thus, the downstream trend has been spurred by a powerful combination of strategic and commercial considerations. Table 2 highlights the development of drug pipelines since 2000 within those companies switching to the dual business model. Data for the FIPCOs, Millennium

Table 2: Genomics companies switching to dual business model, 2000–2005

Company	Pre-2000 (Pipeline?)	Year IDDP established	Pipeline as of April 2005 (#/position of most advanced candidate)
Dual business model			
(i) Technology platforms			
Arena			
Ariad			
Curagen	x	2002	9 (Phase II)
Exelixis	x	2003	5 (Phase II)
Lexicon Genetics	x	2000	5 (Phase II)
Large Scale Biology Corp	x	2000	8 (Phase III)
Maxygen	x	2003	2 (Preclinical)
Rigel	x	2001	6 (Preclinical)
Sangamo Biosciences	x	2000	4 (Preclinical)
(ii) Informatics Providers	x	2002	5 (Phase II)
Celera Genomics*	x	2000	4 (Phase I)
Incyte			
	x	2001	
	x	2001	9 (Phase II)
			3 (Phase II)
FIPCO			
Millennium	√	–	15 (2 products on market/7 in Phase II)
HGS	√	–	18 (Phase II)

Most companies also have extensive 'early' discovery programmes comprising numerous 'lead' compounds. Typically scheduled for entry into the official 'pipeline' in the near future, little is disclosed about these candidates prior to entering into preclinical trials.
Some candidates which are being developed for use in more than one indication are included here as a single candidate.
Sources of data: SEC 10K Filings end-2004/*2003; Company websites accessed on 14th April, 2005.

and HGS, have been included for comparison: the contrast between the FIPCOs and former 'platform' companies gives some sense of the magnitude of change within these companies in the past five years. The adoption of the dual business model is not undertaken lightly: drug development is hugely costly, drug pipelines require massive investment and the risks are inherently high. Given finite resources, the interplay between biological diversity (scope of pharmaceutical intervention) and drug specificity (depth of knowledge required to develop a drug) sets limits both on a company's ability to develop a drug pipeline and on pipeline size. Thus, there are limits on pipeline size within the genomics sector – yet risk is amplified in smaller pipelines. Nevertheless, those companies embarking on IDDPs clearly view the strategic benefits and the potential longer-term commercial rewards as offsetting the risks inherent in drug development.[20]

The move into drug development requires a different set of skills and organisational capabilities

It must be emphasised that there is considerable variation between companies. The specific characteristics of each company unavoidably reflect to some extent the expertise and research strengths established during their previous incarnation as technology or informatics 'platforms'. Most, for example, are focused in specific disease areas, typically complex but prevalent diseases with vast market potential – oncology, cardiovascular disease (CVD) and immune/inflammatory disorders. Companies may be concerned exclusively with biopharmaceuticals (protein therapeutics/monoclonal antibodies (MAbs)), others with small molecule drugs. Some, such as Curagen, are building pipelines that include candidates targeted to a broad spectrum of indications, which also range across peptide, MAbs and small molecule drugs. Ariad, Celera and Exelixis focus exclusively on small molecule drugs for cancer, while at Arena and Lexicon Genetics emphasis lies on small molecule drugs for a range of chronic prevalent disorders, including CVD, obesity and diabetes, immune/inflammatory disease. In a further variation, LSBC's strategy is focused on improved, or 'follow-on', protein therapeutics and vaccines for drugs coming 'off patent'. From their inception, Arena and Sangamo have specialised in particular areas of biology with proven relevance for drug innovation – G-Protein Coupled Receptors (GPCRs) and 'zinc fingers' respectively – and this expertise is reflected in their drug pipelines.

There is, however, considerable variation between companies

The move into drug development requires vastly different scientific, technical and organisational capabilities since it calls for deep understanding of the biological context within which all drugs work and requires the wherewithal to undertake clinical trials. In order to reposition themselves as drug development companies, genomics companies have, of necessity, had to broaden both their science and technical base. This has, typically, been achieved through a combination of alliances (with pharmaceutical and/or biotechnology partners), and via acquisition and merger activity *within* the sector. At Curagen, for example, alliances with Abgenix (1999) and with Bayer (2001) were crucial to the development of the company's MAbs and small molecule drug programmes respectively – programmes based on Curagen-generated drug targets.[21] Alliances and acquisition paved the way for Exelixis to move into drug development. Key acquisitions included that of MetaXen in July 1999, which strengthened Exelixis's lead optimisation, drug profiling and predictive modelling capabilities and of Genomica in November 2001, which augmented its bioinformatics base, specifically its ability to manage data from clinical trials. Alliances have been equally important, most notably perhaps that agreed with GSK in October 2002 and valued at US$439m, whilst the company's lead drug candidate – the small molecule anti-cancer compound, Becatecarin, currently in Phase III trials – was in-licensed from

BMS, another key alliance partner (US$235m/2001). Thus, the requisite skills, capabilities and financial resources have been steadily assembled through strategic alliances and acquisitions by genomics companies in order to realise changing commercial goals centred on extending the sector's reach within the innovation process. The adoption of the dual business model and IDDPs has therefore been accompanied by far-reaching structural change within the genomics sector.

New strategic possibilities are created by IDDPs

The establishment of IDDPs creates a number of strategic possibilities: first, big pharma remains hungry for validated targets and leads, and especially for candidate drugs that have passed through preclinical testing. In the short term therefore, in creating these molecules, IDDPs offer a high-margin revenue stream from the sale of lead compounds and candidate drugs to pharmaceutical firms. Royalties may also accrue to the genomics partner in relation to subsequent downstream development and market launch. Secondly, genomics companies and pharmaceutical firms may form alliances centred on collaborative agreements to 'progress' a validated molecule together. Indeed, collaborative alliances, in which genomics companies and big pharma undertake co-development of drugs, are becoming more frequent. A third scenario, considered unlikely by many and which at the very least remains a distant prospect, is for genomics firms to take a drug to market *wholly independently*.[22]

Biological diversity is giving rise to commercial diversity

From positions further downstream in the innovation cycle, genomics companies are better able to command more favourable financial and contractual terms within alliances from pharmaceutical firms still searching for the means to invigorate their pipelines. As some genomics companies attempt to make the transition into drug development, the dynamics of the supply chain may change in light of increasingly complex, and perhaps long-standing, relations between genomics companies and their partners.[23] This complexity reflects the changing point – the 'biting point' – within the innovation process at which genomics companies 'interface' with their pharmaceutical/biotechnology partners. It is also a reflection of the highly specialised and integrated character of downstream activities and the move into deep biology. The extent to which the commercial rationale for the dual business model was motivated by the desire on the part of genomics companies for emancipation from the supply chain dynamic that has, historically, governed their commercial horizon and business options, is open to speculation. Whether it turns out to be sustainable or successful in the longer term remains to be seen; certainly, as we have indicated, the structural barriers to radical changes in the supply chain dynamic are formidable. Although moving downstream may create new opportunities, it also opens up new and serious risks for genomics companies. Since many companies have nonetheless made this move, it seems that the potential benefits must offset these risks – and any risks that arise from *not* changing business focus and commercial strategy. Pharmaceutical companies too are rethinking strategy in light of shifts within the genomics sector. In particular, should genomics companies turn to pharma for assistance in order to progress candidates through Phase III trials, pharmaceutical companies will, in all likelihood, consider whether to 'buy or ally'.[24] This underscores the way in which genomics and pharma are locked together within a constantly changing innovation landscape.

In one sense, by engendering new opportunities for innovation, biological diversity is giving rise to commercial diversity, which has become the hallmark of the genomics sector. While overall the genomics sector is diversifying, it is clear that individual companies are becoming more highly specialised, a trend amplified by the creation of IDDPs. Indeed, moving downstream within drug innovation requires – is predicated on – specialisation. Specialisation and its

corollary, 'niche creation', provides one means to build value and establish competitive advantage in a fiercely competitive environment: specialising in a disease area, or a specific biological pathway, moiety or mechanism, is seen as a primary means of realising broader commercial goals. In one sense, specialisation might also be seen as a pragmatic response to the limits that biology sets on the industrialisation of drug discovery; once a target has been validated, its role in physiology/pathophysiology must be fully understood.[25] Genomics companies have, of necessity, extended their reach into disease or systems biology, research which is expensive and highly specialised. It seems a logical step to capitalize on the value thus created; hence the shift in which value has come to reside in the molecule and further downstream. By establishing IDDPs, genomics companies retain greater control over the fruits of their research and over the integration of that knowledge within drug innovation. Careful choice of markets may offer strategic benefit to genomics companies: for example, many genomics companies are focused in oncology; moreover, they are willing to cater to smaller markets which, by virtue of their size, are unattractive to pharma.[26] Several genomics companies have abandoned more speculative drug development projects in favour of those lying within their perceived 'core' areas of established strength and/or projects that have progressed further downstream. IDDPs are becoming tightly focused and are drawing closer to the market.

Genetics companies now having to research disease and systems biology

A growing trend for mergers between companies that have complementary skills and capabilities

Equally importantly, as is clear from Table 1 and Figure 1, nine companies within the cohort have chosen to remain as technology or informatics platforms. Strategy among platform companies has also evolved rapidly since 2000 in response to changing market conditions and competitive threats, especially technological obsolescence and the acquisition and internalisation of genomics technologies/databases by incumbent firms. Typically, platform companies have created value by three strategies: developing increasingly specialized products, customising products to the specifications of individual customers and/or devising modifications which extend the uses of their proprietary products. (Many, including Affymetrix, Caliper and Ciphergen, have also moved into diagnostics.) Here too, however, emphasis has come to be placed on 'downstream' applications, for example, assay technologies for use in preclinical or clinical testing. Of the platform companies, several have established market leadership within a particular domain, exemplified by Affymetrix, which has risen to dominance in microarray technology/applications. Of the technology-platform companies, Affymetrix holds by far the largest patent estate, a circumstance central to its commercial success.[27] In business jargon, success for companies such as Affymetrix lies in the creation of a 'unique selling point' that 'hits the market' at the 'right' time, enabling the company to build market share and establish market leadership. Elsewhere among platform companies there is evidence that strategic change is bringing about structural shifts. There is, for example, a growing trend for mergers between companies that have complementary skills and capabilities. Consolidation can yield competitive advantages which may secure or strengthen the market position of the resulting company. Sequenom's merger with Gemini Genomics in May 2001 and valued at US$238m, sought to exploit business synergies between Sequenom's population genotyping database collection and Gemini Genomics's genetic/clinical association knowledge.[28] Other recent high-profile mergers include those between Hyseq and Variagenics (Novelo, 2002), Biogen and IDEC (BiogenIDEC, 2003) and COR Therapeutics and Millennium (2001). These dynamics point to the constant need for companies to innovate with respect to strategy. The demise of Deltagen, which filed for

bankruptcy in June 2003, serves as a stark reminder – if a reminder were needed – of the vulnerable position of platform companies and of the risks endemic to the wider genomics sector.

CONCLUSIONS

Our analysis of 'top tier' companies provides fresh insights into the place of genomics within drug innovation and aids understanding of the evolving commercial dynamics within this economically and scientifically important sector. Strategic change within individual companies has, historically, been contingent on scientific and technological developments, as well as changing financial and competitive conditions, and has engendered structural change within the sector. The extent to which the current trends for downstream migration and consolidation will reshape the sector and the contours of drug innovation in the longer term remains to be seen. It is clear that these trends, realised through the emergence of new business models, are impacting the relationships between genomics and pharmaceutical companies in ways that might, over time, affect the supply chain dynamic between them.

The new business models could change the supply chain dynamics between genomics firms and big pharma

The question as to whether genomics-FIPCOs, HGS and Millennium, will be able in the longer term to emulate the success of biotechnology forerunners such as Amgen, remains to be seen. Within the genomics sector, the FIPCO strategy has not been widely adopted, and, as we have shown, the other 20 'top tier' genomics companies profiled in this study are following one of two business models. Although the 'dual' business model may create new opportunities for genomics companies, the outcome of IDDPs and the future viability of this business model remain uncertain. Likewise, platform companies are also evolving, in terms of both strategy and products, in order to remain competitive and commercially viable. The contingent nature of change within the genomics market and the speed with which change takes place mean that the survival and success of individual companies are, to a large extent, determined by management, a point emphasised by industry insiders.[29] In the course of its 15 year existence the genomics sector has undergone marked change, the scientific focus of companies has, for example, advanced ever deeper into biology, allowing the sector to remain a key site in contemporary pharmaceutical innovation. The co-evolution of business models and drug innovation within 'top tier' genomics companies may have profound implications for the types of drugs available in the future. However, the place of genomics companies in that future, and their role in bringing drugs onto the market, remain to be seen.

Current dynamic is an 'ecology' of expertise diffused through a network of heterogeneous companies

The evolving preferences and strategies of both pharma and the investment community continue to exercise decisive influence over the genomics sector. Operating between the needs of big pharma, the expectations of investors and the vagaries of prevailing financial conditions, genomics companies have always been niche players. Over time, structural constraints have continued to shape the strategic opportunities open to genomics companies whose response, typically, has been to become increasingly specialised. Unsurprisingly, perhaps, regardless of the business model adopted by genomics companies, the relationship between them and their pharmaceutical partners continues to conform to a 'supply chain' model. That said, the character of this chain has evolved and continues to do so: current dynamics can perhaps be described in terms of an 'ecology' of expertise diffused within a network of heterogeneous companies characterised by multidirectional flows of information, technology and materials. The two sectors coexist through a shifting mosaic of interlocking scientific, technological, organisational and strategic elements, held in place by the shared commercial goal of drug innovation. It remains highly unlikely that the incumbent industry will be dislodged from its dominant position, not least since large, broad drug pipelines

The new arrangements will most likely still be dominated by pharma rather than genomics companies

are needed to compete and these remain the exclusive province of the FIPCO. Moreover, as the drug pipelines of those genomics companies involved in drug development mature, they will, in all likelihood, be forced to look to the incumbent industry to progress candidates through to the market. The exact terms and conditions of any such arrangements remain to be negotiated and will, again in all likelihood, reflect the needs and preferences of pharma more than the ambitions of genomics companies.

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References and notes

1. For a recent critique of the 'hype' surrounding biotechnology, including genomics, see: Martin, P. and Nightingale, P. (2004), 'The myth of the biotechnology revolution', *Trends Biotechnol.*, Vol. 22(11), pp. 564–569. For a review of 'hype' and advances see: Glassman, R. H. and Sun, A. Y. (2004), 'Biotechnology: Identifying advances from the hype', *Nature Rev. Drug Discovery*, Vol. 3, pp. 177–183.
2. Rothman, H. and Kraft, A. (2005), Paper presented at 'The Evolution of the Life Sciences', Innogen, The University of Edinburgh, February.
3. Interview with senior executive from leading UK biotechnology company, AK/MH, 28th July, 2004.
4. Kraft, A., Martin, P. and Rothman, H. Manuscript in preparation.
5. The linear, reductionist 'gene-to-drug' model that underpinned much of the initial 'hype and hope' that surrounded genomics in the early 1990s has been superseded by a 'systems biology' approach with much revised timescales for development/delivery of genomics-based drugs. Glasner, P. (2002), 'Beyond the genome: Reconstituting the new genetics', *New Genetics Soc.*, Vol. 21, No. 3, pp. 267–277. For a recent review of genomics approaches to drug discovery see: Kramer, R. and Cohen, D. (2004), 'Functional genomics to New Drug Targets', *Nature Rev. Drug Discovery*, Vol. 3 (November), pp. 965–972.
6. Our analysis draws on and develops arguments in: Glasner, P. and Rothman, H. (2004), 'Splicing Life? The New Genetics and Society', Ashgate, Aldershot.
7. There is an extensive literature on alliances, see for example: Orsenigo, L. (1989), 'The Emergence of Biotechnology', Pinter, London; Senker, J. and Sharp, M. (1997), 'Co-operative alliances and organizational learning in biotechnology', *Technol. Anal. Strategic Manage.*, Vol. 9(1), pp. 35–51; Pisano, G. P. and Mang, P. Y. (1993), 'Collaborative product development and the market for know-how', *Res. Technol. Innovation Manage. Pol.*, Vol. 5, pp. 109–136.
8. Persidis, A. (1995), 'Enabling technologies and the business of science', *Bio/Technology*, Vol. 13, pp. 1172–1176.
9. On the productivity crisis see: Booth, B. and Zemmel, R. (2004), 'Prospects for productivity', *Nature Rev. Drug Discovery*, Vol. 3, pp. 451–456; 'Innovation and Stagnation', FDA Report. On spiralling R&D costs: Dickson, M. and Gagnon, J. P. (2004), 'Key factors in the rising cost of new drug discovery and development', *Nature Rev. Drug Discovery*, Vol. 3(5), pp. 417–429; Preziosi, P. (2004), 'Science, pharmacoeconomics and ethics in drug R&D: A sustainable future scenario?', *Nature Rev. Drug Discovery*, Vol. 3(6), pp. 521–526; Martin, P., Abraham J. *et al.* (forthcoming), 'Understanding the ''productivity crisis'' in the pharmaceutical industry', in Webster, A., Ed., 'Innovative Health Technologies', Palgrave Macmillan, London.
10. DeLamarter, J. (2003), 'Biotechnology partnerships – medicine for an ailing industry?', *Nature Biotechnol.*, Vol. 21, pp. 847–848.
11. Alliance data compiled by the authors from: Recombinant Capital ('Recap') Database.
12. In using this term we follow: Gambardella, A. (1995), 'Science and Innovation', Cambridge University Press, Cambridge.
13. Borman, S. (1998), *Chemical and Engineering News*, April, pp. 47–67; Whitehead, R. S. (1998), *Nature Biotechnol.*, January, pp. 2–3.
14. James, R. (2000), 'Differentiating genomics companies', *Nature Biotechnol.*, Vol. 18, pp. 153–155.
15. Glasner, P. and Rothman, H. (2004), 'Splicing Life? The New Genetics and Society', Ashgate, Aldershot, especially Chapter 7.
16. Identified through analysis of ten leading 'biotechnology industry' databases. We are grateful to Michael Morrison for assistance in

compiling the data from which the cohort was identified.

17. Some companies have created wholly owned subsidiaries for their 'platform' activities, exemplified by the formation in 2000 of '454 Life Sciences' by Curagen.
18. Those companies showing revenue in excess of R&D costs are: Millennium (FIPCO), Sequenom (Information Platform) and three Technology Platform companies, Affymetrix, Caliper and Ciphergen.
19. Arena Pharmaceuticals, SEC 10K Report, 2003, p. 28.
20. Allary, C. (2003), 'In search of a business model', *Scrip Magazine*, June.
21. Interview with Curagen executives, AK, 11.4.05. Fletcher, L. (2001), 'Curagen sets precedent in post genomics era', *Nature Biotechnol.*, Vol. 19, pp. 186–187.
22. Seeking regulatory approval and market launch require expertise that is different again and, in addition, requires vast amounts of money.
23. Alliance data analysis undertaken by the authors with IHT colleagues.
24. Ratner, M. (2005), 'Earlier stage biotechs attract partners', *Nature Biotechnol.*, Vol. 23, p. 509.
25. Nightingale, P. and Mahdi, S. (2005), 'The evolution of the pharmaceutical innovation process', in Dosi, G. and Mazzucato, M., Eds, 'Knowledge Accumulation and Industry Evolution: The Case of Pharma-Biotech', Cambridge University Press, Cambridge (forthcoming).
26. Lahteenmaki, R. and Baker, M. (2004), 'Public biotechnology 2003 – the numbers', *Nature Biotechnol.*, Vol. 22, pp. 665–670.
27. Comparative IP data compiled by the authors.
28. Dorey, E. (2001), 'Sequenom steps toward drug development', *Nature Biotechnol.*, Vol. 19, pp. 600–601.
29. Discussions with senior industry manager, AK, 19th September, 2005.