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# 1.13 The Role of Small- or Medium-Sized Enterprises in Drug Discovery

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## 1.13.1 Definitions of Small- or Medium-Sized Enterprises (SMEs)

In the US, the Asia-Pacific Economic Cooperation organization defined small- or medium-sized enterprises (SMEs) as "manufacturing companies with less than 500 employees, or nonmanufacturing companies with sales less than $5 M."[1] Similarly, the UK Government Small Business Service (an agency of the Department of Trade and Industry) in February 2005 defined "SME as a business with less than 250 staff."[2] In Japan the 2005 definition is sector-defined (Table 1),[3] but is broadly comparable to the above.

For the purpose of this chapter, an SME is defined as a company with fewer than 500 people in staff, but turnover is ignored. Readers should recognize that the fluid nature of the pharmaceutical industry (frequent start-ups, mergers, takeovers, and closures) indicates that companies described in this chapter may well not be around in their current forms even in 1–5 years' time. Conversely, some companies that were SMEs 10 or 20 years ago whose activities have impacted drug discovery greatly have now expanded beyond that definition. The impact of these (relatively few) companies which originated as SMEs is consequently great and is discussed below.

**Table 1** Japan's sector definition of what constitutes an SME in 2005

| *Industries* | *Capital size (million yen)* | *Number of employees* |
|---|---|---|
| Manufacturing and others | 300 or less | 300 or less |
| Wholesale | 100 or less | 100 or less |
| Retail | | 50 or less |
| Services | 50 or less | 100 or less |

http://www.chusho.meti.go.jp/sme_english/outline/02/01.html.

Traditional large, multinational pharmaceutical companies (big pharma) and small-sized regional or national pharma companies are not included in this chapter, except insofar as how their dealings with SMEs have impacted their own pipelines.

#### 1.13.1.1 Definitions of Drug Discovery

For the purpose of this chapter, drugs are considered to include not only small molecules, but also macromolecules, proteins, antisense agents, and antibodies – vaccines are also mentioned where pertinent to this chapter.

#### 1.13.1.2 Definitions of Drugs

The definition of what constitutes 'drug discovery' also needs delineating to put the chapter into context. For the purpose of this chapter, the author has taken activities up to phase IIa (proof of concept) clinical trial, when examining the roles SMEs have played over the past 10 years in drug discovery. One particular impact of SMEs on drug discovery (as far as the patient is concerned) is what proportion of the dugs that the patient takes actually originated within SMEs – consequently, a survey of the origin of such new chemical entities (NCEs) has been conducted.

### 1.13.2 Origins of Small- or Medium-Sized Enterprises Engaged in Drug Discovery

Each SME (which in this industry mostly tend to fall under the generic banner of the biotechnology or 'biotech' sector) originated with a group of scientists and entrepreneurs who have an idea, technology, intellectual property (IP), or vision that has been considered worthwhile converting to a business. Three types of origin can be discerned. The founders frequently originate from:

1. academic research institutes;
2. pharma companies that are divesting IP, research centers, and scientists; and
3. pharma companies looking to develop technologies outside the parent company.

#### 1.13.2.1 Small- or Medium-Sized Enterprises Originating from Universities and Academic Institutions

Public funding of medical research over the past 20 years has been concentrated in the clinical, genetic, genomic, molecular biology, and biochemistry fields rather than in straightforward medicinal chemistry/drug discovery. Such research to commercial ends tends to be regarded as beyond the proper use of public funds. Hence, discoveries and inventions that might lead to the discovery of a new drug made in the institutions conducting such academic research, have tended to be licensed to traditional pharma, possibly via a university technology transfer office. However, in many cases, particularly entrepreneurial scientists have elected to commercialize the IP themselves by founding a company, and a new SME (biotechnology sector company) is born.

Two examples are used to illustrate how universities and university/academic research clusters have spawned SMEs engaged in drug research.

*Biotechnology*, published in May 2001 by the Office of Economic Research of the California Trade and Commerce Agency,[4] described California as being home to 75 publicly funded research institutions that are now surrounded by 2500 biotechnology companies. These companies then employed some 212 700 scientists and co-workers, and had a turnover of about $212 billion. At that time, California was also in receipt of $1.7 billion in National Institute of Health grants.

Imperial College of Science, Technology and Medicine (IC) in London is one of Europe's largest centres of cross-disciplinary research; the medical school alone is a conglomerate of the former Chelsea and Westminster Hospitals, Charing Cross Hospital, the Hammersmith Hospital, North West London Hospitals, the Royal Brompton Hospital, and St Mary's Hospital.[5] Allied to existing chemistry, biochemistry, and molecular biology research departments, strong cross-disciplinary ties have led to recognition that IP generation may be managed by the creation of spinout companies from Imperial College. To this end, Imperial College Innovations was set up to facilitate spinouts as well as licencing IP to third parties. **Table 2** lists the Imperial College spinout companies (SMEs) as listed on the Imperial College Innovation website in 2005 that are engaged in drug research.[6]

**Table 2** Imperial College spinout companies (SMEs) engaged in drug discovery, as listed on the Imperial College innovation website

| *Imperial College spinout company* | *Year founded* | *Activity* | *Location* | *Fate by 2005* |
|---|---|---|---|---|
| Amedis Pharmaceuticals | 2001 | In silico prediction of pharmacokinetic, organosilicon drugs | Cambridge, UK | Acquired by Paradigm Therapeutics 2005 |
| Argenta Discovery | 2000 | Respiratory drug discovery, contract medicinal chemistry research | Harlow, UK | Independent |
| Atazoa | 2004 | Conducts research and development based upon technology emanating from Imperial College's Institute of Developmental and Reproductive Biology, and Cedars-Sinai Medical Center (California) | London, UK | Independent, but majority owned by Mitsubishi |
| Biogeny (Implyx) | 2004 | Preparing and purifying large proteins which will be capable of passing across the cell membrane to deliver drugs directly to individual cells | | |
| Cerestem | N/K | Stem cell company: develops mitogenic growth factors that can send stem cell differentiation down certain paths, e.g., neuro- or muscular lineages | | |
| D-Gen | 2000 | Develops screening tests and diagnostics for prion diseases in humans and animals | | |
| IC VEC | 2001 | Research and development of siRNA therapeutics using proprietary synthetic nanoparticle technology (CONZENTRx) developed for customized delivery of nucleic acids | | Majority owned by Mitsubishi |
| Lipoxen Technologies | 1997 | Drug and vaccine delivery technologies: molecule engineering, particle engineering, for large and small molecules | London | Independent |
| Lorantis Holdings | 2000 | Therapies to treat immune diseases and improve transplantation success | Cambridge | Independent |
| Metabometrix | 2002 | Characterizes the key biochemical changes caused by drug toxicity in animals and humans | London | Independent |
| Microscience | 1996 | Development of vaccines for infectious disease, in particular the identification and production of vaccines against group B streptococcus in pregnancy/newborns. The company is also working to determine genes critical to virulence (ability to cause disease) in bacteria | London | Private independent |
| NanoBioDesign | 2001 | High-throughput screening systems based on human and bacterial P450 enzymes | London | Independent |
| Polytherics | N/K | Develops novel polymers capable of enhancing drug delivery | London | Independent |
| Proteom | 1999 | Bioinformatics company designing in silico peptide ligands | Cambridge | |
| Protexeon | 2002 | Investigating use of xenon as anesthetic and to treat nerve damage | London | |
| Riotech | 2003 | Vaccines, biological antivirals, and small-molecule antivirals to hepatitis A, B, and C and other viral infections | | |

**Table 2** Continued

| *Imperial College spinout company* | *Year founded* | *Activity* | *Location* | *Fate by 2005* |
|---|---|---|---|---|
| Sterix | 1998 | Research and development of a new generation of steroid-based therapeutic products for use in oncology and metabolism or endocrine-related diseases | Bath | Acquired by Ipsen Beaufour 2004 |
| Synovis | 2004 | | | |
| Thiakis | 2004 | Novel medicines for the treatment of obesity and metabolic disease: exclusive licensee of four patent families relating to use of PYY3-36 and oxyntomodulin for the treatment of obesity and associated conditions | | |

http://www.imperialinnovations.co.uk/

### 1.13.2.2 Small- or Medium-Sized Enterprises with Origins in Big Pharma Rationalizations

The continued amalgamation of large pharmaceutical companies and subsequent rationalization of research groups have been a fertile source of new start-up companies from scientists determined to forge an independent path in research aimed at generating new drugs. The 2000 merger of Rhône-Poulenc and Hoechst-Marion-Roussel to create Aventis Pharmaceuticals led to the creation of Scynexis Inc. (Research Triangle Park, NC) and Argenta (Harlow, UK) from groups of scientists formerly employed at Aventis' rationalized sites at Research Triangle Park (NC) and Dagenham (UK), respectively. Similarly, the formation of the then Glaxo Wellcome in 1997 created BioFocus (initially located in Sittingbourne, UK), Arrow Therapeutics (London, UK), and Triangle Pharmaceuticals (NC). Closure of a midwest Amgen research site (Boulder, CO) gave birth to Array Biosystems. Major rationalizations of drug research groups by big pharma in Italy have led to the creation of Nikem and Newron Pharmaceuticals (both in Milan, Italy).

### 1.13.2.3 Small- or Medium-Sized Enterprises with Other Origins

In 2001, RJ Reynolds, the tobacco giant, spun out a pharmaceutical business called Targacept to continue work on the therapeutic indications of ligands binding to nicotinic acid receptors. Aventis Pharmaceuticals spun off its bone research group and assets at the Romainville site in Paris, France, which became known as Proskelia – this was merged into a similar company in Scotland, known as the Strachan Group – the merged entity now being known as the ProStrachan group. More recently, Sanofi-Aventis has spun off its antiinfectives group into the Paris-based company known as Novexel.[7] Novexel inherited an advanced portfolio of antiinfective programs and IP, and received €40 million in financing from life-science investors (Atlas Venture, Sofinnova, 3i, Abingworth, and Novo). Galapagos was a joint venture between Crucell of the Netherlands and Tibotec of Belgium and was founded in 1999 with funding and IP from both parent organizations.

## 1.13.3 Funding of Small- or Medium-Sized Enterprises

Fledgling biotech SMEs from whatever origin have a need for cash that is significant compared to SMEs in other industry sectors. Financing may come from private investors (business angels, venture capital (VC) companies) or from public investment. Typically, one, two, or three rounds of private funding may have occurred before a company has the IP assets, drug prospects, or revenues to make it an attractive proposition to public investors. Such public investment based upon a proper legal and financial prospectus is usually described as a flotation or initial public offering (IPO). Finally, investment income for drug discovery activities can also be supplemented or replaced if the SME has an income stream from services or products of its own.

### 1.13.3.1 Funding from Business Angels and Venture Capitalists

Business angels typically invest a few hundreds of thousands of dollars into a new business idea – within a short timeframe, a successful small company will then require a more substantive investment of several millions, up to tens of millions, of dollars, in exchange for equity in the company or as a loan or as a combination of both. Several rounds of VC investments (known as series A, series B, etc.) may well have occurred before the several years of research and development (R&D) necessary to translate ideas into assets have passed. Such rounds may be funded entirely by existing investors, or new investors may join – each round will have dilutive effects on existing shareholders and timings are usually critical to getting best terms and conditions for both existing and new investors. VC companies recognize the longevity of investments (3–7 years is typical of the time required to realize a substantial profit on investment). There are many VC companies that specialize in investing in life-science companies: 3i, Abingworth, Advent, Advent International, Merlin, and MVM are typical UK healthcare company financiers. In some cases, VC companies are associated with parent organization – MVM had its origins in the UK Medical Research Council's desire to exploit its own inspired IP.

The value of VC-funded SMEs to drug discovery was examined in a 2004 report commissioned by Pacific Bridge Life Sciences and the Weinberg Group.[8] Stolis and Goodman[8] examined the impact of VC investment on the treatment of chronic diseases and leading causes of death in the US, including cancer, heart disease, stroke, diabetes, asthma, and arthritis. The authors assert that venture-backed medical innovations are developed and made available to patients as much as three times faster than a 'bootstrapping' approach to product development. The report claims that more than 100 million (one in three) Americans have benefited from venture-backed medical innovations developed during the past 20 years.

### 1.13.3.2 Funding from Initial Public Offerings and Stock Market Listings

Refunding at VC exit usually takes one of two directions. The first is an IPO, where the public is invited to subscribe to the shares of the company and the venture capitalists are then able to liquidate a part, or all, of their shareholding. The timing of IPOs is very market-sensitive, not only to the individual company prospects but also to the public and analysts' perception of the industry sector as a whole. The so-called IPO windows can open and close in very short timeframes. Despite good news on a company's prospects (for example, Edinburgh (Scotland)-based Ardana Biosciences released a press release claiming that its prostate cancer treatment, Teverelix, was successful in phase II clinical trials[9]), sometimes IPOs fail to raise the money expected or needed. Ardana Bioscience achieved an IPO on Alternative Investment Market (AIM) in March 2005 but the share price achieved (£1.28) was apparently disappointing. It did, however, net Ardana some $38 million to $32 million after expenses. In certain cases, IPOs can be withdrawn at short order when a healthcare bad-news story impacts public confidence in share subscriptions, as occurred with the UK-based company Phytopharm (a company specializing in natural product research) in March 2005. Boston-based US SME/biotech CombinatoRx was due for an IPO in March 2005, and Valera Pharmaceuticals registered on Monday 14 March 2005 for an IPO of up to $74.75 million in common stock, according to a filing with the US Securities and Exchange Commission.[10] The second typical VC exit from an SME is described in Section 1.13.3.3, below.

A few SMEs raise their initial cash requirements by a listing on a public stock exchange – usually an exchange that is created for riskier ventures, and that can impose less regulation on the reporting of such listed companies. Examples of such exchanges are Ofex and the AIM (both UK), TecDAX (Germany), and NASDAQ (US). Examples are UK-based contract research organization BioFocus (UK), which raised its initial funding requirements through a placing on Ofex in 1997, and Cambridge (UK)-based structure-based drug discovery company Sareum, which listed on AIM in 2004.

### 1.13.3.3 Funding by Revenue Generation

A third source of revenue for SMEs engaging in drug discovery is to sell or license assets or technologies and services to other companies within the drug discovery sector. Typically offered are late-stage research or development products that big pharma considers essential to supplement in-house pipelines and for which SMEs struggle to resource the required cost of development. Typical deals can run into hundreds of millions of dollars (including upfront payments, milestone payments, and royalties). A listing of the impact that such in-licensing deals have had on the pipeline of the world's largest pharmaceutical company (as of January 2005), Pfizer, will be discussed in Section 1.13.9.1.

Alternatively, SMEs can seek to earn revenue by offering services to big pharma or other SME companies in technologies or areas of resource where such companies are deficient. For big pharma, such offerings can be for new technologies or in areas of expertise that, for whatever reason, the larger organization have elected to consider better

outsourced in whole or in part. The trade between SMEs themselves tends to be much greater, albeit SMEs have generally less cash to spend on deals and often seek partnerships described as 'shared-risk,' whereby each partner contributes resources to a project with the objective of sharing the rewards later. Typical SME technology and service companies in the drug discovery sector include those selling technologies to perform gene sequencing, target identification and validation, hit-finding, lead optimization compound profiling, good laboratory practice and good manufacturing practice preclinical and clinical studies, and pharmaceutical profiling, as well as chemical scale-up. Typical examples of such companies are discussed in Section 1.13.8.

The ultimate in revenue generation for a company is also the second alternative exit for VC investors. This is a trade sale of the company to another within the industry – such trade sales may be to big pharma or to other biotechnology companies. In each case, the incentive is a hunger for an asset, technology, workforce or, in some cases, cash, if the SME being acquired has a substantial reserve that the investors consider would be better placed elsewhere. As might be expected, the deep pockets of large pharma have financed some spectacular deals in the past 10 years – a survey of typical acquisitions by the main established pharmaceutical players is shown in **Table 3**. It is instructive to note that certain companies have been very active acquiring SMEs to bolster their internal drug pipelines or technology bases; however, other major pharma companies are conspicuous by their absence.

#### 1.13.3.4 Funding by Grants

Public bodies (governments, charities) will make grants available to companies setting up with new technologies, research projects, or in locations deemed useful to the public/national interest. Recent examples are the Wellcome Trust grant to Microscience (London, UK) for the development of a drinkable typhoid vaccine (2005), and in April 2004, the US National Institute of Health awarded the vaccine company Antigen a $192 000 grant to support development of its prostate cancer cell vaccine based on modulation of major histocompatibility complex class II expression.

### 1.13.4 Locations of Small- or Medium-Sized Enterprises

The rise of the biotechnology industry in the world has caused a profound shift in the geographical localization of the industry away from the traditional pharma centers, often located in large industrial cities, to clusters around major academic and publicly funded research foundations.

#### 1.13.4.1 North America

On the west coast of the US, two very large thriving clusters can be distinguished. The first of these clusters, which many regard as the birthplace of the biotechnology industry, is located around the San Francisco Bay area, California. This geographical concentration, termed 'Biotech Bay' by the US website Biospace, is clustered around the University of California (San Francisco, Davis, and Berkeley campuses). There are 262 companies and associated research institutions listed in this area as of March 2005.[11] Notable companies that began life as SMEs in this area are Genentec and Chiron, both of which are now major players and compete with big pharma in the worldwide pharmaceutical market. Other notable SMEs in this thriving region are Abgenix, Chemocentryx, CV Therapeutics, Discovery Partners International, Exelixis, Theravance (once known as Advanced Medicines), and Gilead.

The second US west-coast cluster is located in the south of California, around San Diego and Los Angeles and near the sites of the University of California (San Diego, Los Angeles, Santa Barbara, and Irvine campuses) together with the California Institute of Technology, the Salk Institute, and the Scripps Research Institute. Scientists from or who have trained at these institutions have launched or now work in a large number of local companies. This geographical concentration (266 companies and research institutions are listed) has been termed 'Biotech Beach' by the American website Biospace.[12] As one example, chemical research technologies associated with Professor KC Nicolaou at the Scripps Research Institute (radiofrequency tag-monitoring and barcode monitoring of vials used in combinatorial chemistry) were commercialized by the SME Irori (subsequently acquired by Discovery Partners International). The San Diego area of California has its own Biotech Discussion Group, facilitating intercompany exchanges of information.[13] Notable companies of the San Diego/Los Angeles area are: Amgen (now grown far greater than an SME), Agouron (now part of Pfizer), Idun (acquired by Pfizer in 2005), Cortex, IDEC (now part of the major Biotech company Biogen Idec), Invitrogen, Medigene, Mycogen, Sequenom, and Vical.

On the east coast of the US around Boston is a huge cluster of SME biotechnology companies, many of which owe their origins to scientists trained at Harvard University, Massachusetts Institute of Technology (MIT), Brandeis

**Table 3** SMEs involved in drug discovery acquired by big pharma 1995–2005

| *Acquirer* | *Target* | *Year* | *Deal size* | *Type of acquisition* |
|---|---|---|---|---|
| Abbott | – | – | – | – |
| AstraZeneca | KuDOS Pharmaceuticals | 2005 | $210 million | Cancer therapeutics company based in UK |
| Amgen | Tularik | 2004 | $1300 million | Tularik, founded in 1991, was a biopharmaceutical company engaged in the research and development of drugs that regulate gene expression and focuses on cancer, immunology, and metabolic disorders |
| Bayer | – | – | – | – |
| BMS | – | – | – | – |
| GSK | Affymax | 1995 | $450 million | Automated synthesis and screening technologies |
| Lilly | Applied Molecular Evolution | 2004 | $400 million | Protein and peptide technologies |
| | Sphinx Technologies | 1995 | | Automated synthesis and screening technologies |
| J&J | Transform Pharmaceuticals | 2005 | $230 million | Optimization of crystal form and formulation of drugs |
| | Egea Biosciences | 2004 | N/K | Biological design and molecular engineering company creating therapeutic proteins for the treatment of cancer, metabolic, and immunological diseases |
| | 3-D Pharmaceuticals | 2003 | $88 million | Automated synthesis and screening technologies and structural |
| | Scios | 2003 | $2400 million | Cardiovascular drug research company with two marketed products for the treatment of heart disease: Natrecor (nesiritide), for the treatment of acutely decompensated congestive heart failure, and Retavase |
| | Tibotec-Virco | 2002 | $320 million | Human immunodeficiency virus diagnostic services and products |
| | Discovery Laboratories | 2000 | | (Increased ownership) Development of surfactant replacement therapies based on engineered lung surfactant technology for the potential treatment of respiratory diseases |
| | Centocor | 1999 | $4900 million | Monoclonal antibodies |
| Merck | Aton Pharma | 2004 | | HDAC inhibitors |
| | Rosetta Inpharmatics | 2001 | | Analysis of gene data to predict how medical compounds will interact with different kinds of cells in the body, therefore potentially allowing scientists to select drug targets more accurately and speed up the development process |
| Novartis | Idenix Pharmaceuticals | 2003 | >$255 million | Antiviral drugs |
| | Grandis Biotech | 2000 | | Human growth hormone |
| Pfizer | Idun Pharmaceuticals | 2005 | Not disclosed | Idun's technology is focused on the control of caspase activity. Idun developed therapeutic applications focused on inhibiting caspase activity as potential treatments for liver disease and inflammation |

**Table 3** Continued

| *Acquirer* | *Target* | *Year* | *Deal size* | *Type of acquisition* |
|---|---|---|---|---|
| | Angiosyn | 2005 | $527 million | Biopharmaceutical company developing novel proprietary biologics for controlling angiogenesis |
| | Meridica | 2004 | $125 million | Drug delivery company, based in Cambridge, UK, specializing in inhaled, nasal, and parenteral drug administration routes |
| | Esperion Therapeutics | 2003 | $1300 million | Formed in July 1998. Esperion was a company specialized in developing high-density lipoprotein (HDL)-targeted therapies to treat cardiovascular disease, including atherosclerosis |
| Roche | – | – | – | Roche bought Genentech in 1990 |
| Sanofi Aventis | – | – | – | – |
| Schering-Plough | Neogenesis | 2005 | Not yet disclosed (21/2/2005) | NeoGenesis Drug Discovery was dedicated to the development of applied genomics and combinatorial chemistry |
| | Canji | 1996 | $54.5 million | Founded in 1990, Canji was a privately held gene therapy company before it was acquired |
| | DNAX | 1982 | | DNAX is a biotechnology research institute that was founded in 1980 |
| Takeda | Syrrx | 2005 | $270 million | Syyrx was founded in 1999 – high-throughput structural biology technology and drug discovery company |
| Wyeth | – | – | – | – |

University, and Boston University, together with research ideas spawned from scientists at institutions such as the Harvard Medical School, Brigham and Women's Hospital, the Dana-Farber Cancer Institute, and Massachusetts General. The Biospace website has dubbed this concentration of SME/biotech companies 'Genetown' and in 2005 listed some 206 companies in the area. Notable companies include Biogen (now merged with San Diego-based IDEC to form Biogen Idec), Vertex, Millennium, Sepracor (all of these biotechnology companies have grown beyond the scope of this chapter's definition of an SME), Affymetrix, Ariad, Arqule, Cubist, Curis, En Vivo Pharmaceuticals, Leukocyte (acquired by Millennium), Momenta, Oscient, and Repligen. In the US, the geographical concentration in the Boston area has become so important to the world drug discovery science base that the desire of the traditional large pharma companies to overcome geographical inertia and move their scientists to this biotech/university cluster has occurred. Both Merck and Novartis have built large research centers in Boston, MA since 2000.

Other US clusters are in New Jersey, Pennsylvania, and Michigan, and there is also a significant cluster in the Montreal/Quebec area of Canada.

### 1.13.4.2 Europe

Geographical clusters are also apparent in Europe. In the UK, the Eastern Region Biotechnology Industry (ERBI) association[14] represents SMEs in the Cambridge area, close to Cambridge University, the John Innes Research Centre, University of East Anglia, and the Human Genome Campus at Abington. Notable companies include Astex, Argenta Discovery, BioFocus Discovery, De Novo Pharmaceuticals, Celltech (which grew to a size greater than this chapter's SME definition before being acquired by the Belgian UCB Group in 2004), Arachnova, Biotica, Biowisdom, Cambridge Antibody, Cambridge Combinatorial (which became part of Millennium in 2001), Cellzome, Cytomix, Domantis, DanioLabs, De Novo Pharmaceuticals, Huntingdon Life Sciences, Kudos (acquired by AstraZeneca in December 2005), and Pharmagene. Some notable figures obtained from the ERBI website state that the region is home to almost 200 biotech companies together with some 250 specialist service providers with biotech expertise. These SMEs are

co-located around more than 30 research institutes and universities and four leading hospitals involved in research. The region is home to half of the UK's top 15 London Stock Exchange (LSE)-quoted biotech companies and venture capitalists have invested more than $1.8 billion of funds.[14]

In Europe, a remarkable cluster has grown up on either side of the Øresund, separating Sweden from Denmark. This SME/institution cluster, known as 'Medicon Valley,' has its own website.[16] Main academic centers in this area include the Royal Danish School of Pharmacy and the University of Copenhagen, both in Copenhagen (Denmark) and Lund University in Sweden. The Group of Povl Krogsgaard–Larsen at the Royal Danish School of Pharmacy has long conducted research into the treatment of neurodegenerative disorders, including research into muscarinic and nicotinic acid receptors. In 2002, the Boston Consulting Group published a 70-page report on Medicon Valley, which is available on the Medicon Valley website.[16] This report shows that this particular biotech cluster also owes much of its existence to a concentration of large and medium-sized pharma in the region: Pharmacia (much of which is now Biovitrum), AstraZeneca, Leo, Lundbeck and NovoNordisk, which have spawned a large number of SME companies. The Boston Consulting Group report[16] considers that the Medicon Valley diabetes research cluster is probably the strongest in the world, and there is also a strong emphasis on antiinflammatory and neuroscience drug discovery. Notable drug discovery and associated companies that are SMEs in Medicon Valley are 7-TM Pharma, Acadia Pharmaceuticals, BioImage, Zealand Pharmaceuticals, Maxygen, Pharmexa, Topotarget, and Active Biotech.

Other notable European clusters are located in the Oxford area of the UK, around Munich in Germany, Leiden in the Netherlands, and around Paris in France.

#### 1.13.4.3 Rest of the World

In the 1990s, Japan was one of the most important sources of new drugs, with origins in major companies like Yamanouchi, Fujisawa, and Takeda being paralleled by drug origins in much smaller research groups in Kirin Brewery, Nippon Flour Mills, Teijin, etc. A combination of past success and the reluctance of the industry to subject itself to merger and acquisition activities has probably been one reason why the emergence of biotech clusters as seen in Europe and in the US has not yet happened. The mergers of Fujisawa and Yamanouchi, announced in 2004, and the ambition of companies like Takeda may allow the emergence of similar concentrations of SMEs, but hitherto there are few such companies. One homegrown Japanese SME engaged in drug discovery, Sosei, is located in Tokyo – the founder of this company was Shinichi Tamura, the former chief executive officer of Genentech Japan.[17] It is interesting that one Japanese pharmaceutical company, Tanabe, has deliberately created a Biotech spinout, MediciNova, but this is based in San Diego.

Government assistance in the location of drug discovery SMEs should also not be ignored. Many governments recognize the assets that a strong biotechnology business can bring to their country, and tax advantages are often given to companies locating in certain territories. Few countries have been as ambitious as Singapore, which has created a large science park for this end.[18] The academic research centers that are at the core of the science park are: the Institute of Molecular and Cell Biology, the Natural Product Research (CNPR: privatized in 2003 to become MerLion Pharmaceuticals), the Genome Institute of Singapore (formed in 2000) and the Johns Hopkins Institute – an offshoot of the US-based institute of the same name. Of the major companies located in Singapore, GlaxoSmithKline and Novartis are present, whilst Chiron has established S*BIO, formed through a partnership with the Singapore Economic Development Board Investments (EDBI). S*BIO is a chemistry-driven, product-oriented company, with a focus on cancer, with the objective of identifying and developing novel, small-molecule anticancer drug candidates from its own leading-edge research, as well as through joint collaborations with external partners. Another notable company with a location in Singapore is Albany Molecular, the contract research organization headquartered in Albany (NY, US).

Clusters of high-tech SME companies engaged in drug discovery are also notable in the Bangalore region of India, and around Shanghai in China.

### 1.13.5 Fate of Small- or Medium-Sized Enterprises Engaged in Drug Discovery

#### 1.13.5.1 Small- or Medium-Sized Enterprises That Have Grown to be Major Players in Drug Discovery

Those companies that have grown to such a size as to challenge the major traditional pharma companies represent the 'most aspired to' ambition for companies that began as SME biotech companies. Of the many thousands of start-up companies, only a handful have reached this exalted position, but their success has been so phenomenal it has been one of the major causes why investors seek to fund SMEs that perform drug research.

**Table 4** SMEs that have become major players in the marketplace

| | *Amgen* | *Biogen Idec* | *Cephalon* | *Chiron* | *Genentech* | *Gilead* | *Ligand* | *Millennium* | *Sepracor* | *Vertex* |
|---|---|---|---|---|---|---|---|---|---|---|
| Year of founding | 1980 | 1978 | 1987 | 1981 | 1976 | 1987 | 1987 | 1993 | 1984 | 1989 |
| Drugs on market | 12 | 5 | 7 | 13 | 13 | 8 | 6 | 3 | 1 | 2 |
| Market capitalization ($ million) | 77 994 | 12 518* | 2954 | 6657 | 50 633 | 14 965 | 728 | 2882 | 6225 | 962 |
| Turnover ($ million) | 8356 | 679 | 714 | 1658 | 3300 | 867 | 141 | 434 | 344 | 69 |
| Profit (loss) ($ million) | 2280 | − 875 | 92 | 222 | 610 | − 72 | − 32.5 | 222 | − 135 | − 192 |

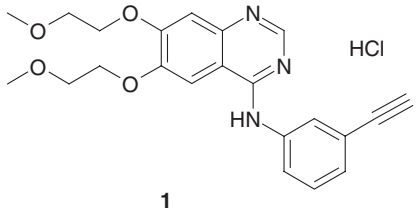
*Biogen Idec's market capitalization fell to this value in May 2005 (a drop of $10 000 million from the value in February 2005) after the disappointing news on its Tysabri product.[89]

Traditional big pharma prior to the 1980s was (with the exception of vaccine businesses) almost exclusively small-molecule-based. The rise of biologicals as pharmaceutical therapies based upon the molecular biology technologies of the 1980s and 1990s allowed several companies (Amgen, Genentech, Biogen Idec, and Chiron) that began life as SMEs to become world-class players in their own rights before or despite the best efforts of big pharma to compete with them or acquire them. Indeed, with the exception of Genentech (now majority-owned by Roche), the remainder have maintained their independence. It is, however, salient to realize that all these SMEs that have become big pharma players in their own rights were established to research and develop biological agents (antibodies, proteins) rather than (in the first instance) small molecules. Only subsequently, after success gained by getting biological products on the markets, have some turned to small-molecule research. The major success stories of SMEs turning into major competitors of traditional big pharma are shown in **Table 4**. Clearly, in the first tier (market capitalizations over $25 billion) are Amgen and Genentech (actually majority-owned by Roche but still separately quoted); in the second tier (market capitalizations greater than $5 billion) are Biogen Idec, Gilead, Chiron (at the end of 2005 Chiron had agreed to be acquired by Novartis), and Sepracor, and in tier 3 ($1–5 billion) are Millennium, Vertex, and Cephalon. It is instructive to note which products of these companies have reached the marketplace, and thus contributed to those companies achieving fully integrated pharmaceutical company (FIPCO) status.

*Genentec*. Genentec was founded in San Francisco in 1976 and was acquired by Roche in 1990 (with an initial investment of $1537.2 million in return for one-half of Genentech's then outstanding common stock). Genentech is a free-standing entity within Roche and now has an impressive range of (mostly) biological products.[19] These are

- Actimmune (IFN-γ1b), launched for the treatment of infections in patients with chronic granulomatous disease
- Alteplase (recombinant tissue plasminogen activator, marketed in the US in 1987 for the treatment of acute myocardial infarction, in 1990 for use in the treatment of acute pulmonary embolism, and in June 1996 for the treatment of acute ischemic stroke within 3 h of symptom onset)
- Bevacizumab (intravenously administered antivascular endothelial growth factor monoclonal antibody), an antiangiogenesis therapy for the treatment of colorectal cancer
- Dornase alfa, a DNase which has been developed and launched for the treatment of cystic fibrosis
- Efalizumab, a humanized anti-CD11a monoclonal antibody as a once-weekly subcutaneous formulation, for the treatment of moderate-to-severe plaque psoriasis
- Kogenate, a recombinant human factor VIII preparation used for treating hemophiliacs
- Omalizumab, an anti-IgE humanized monoclonal antibody for the treatment of asthma
- Recombinant somatotropin, first launched in 1987 for the treatment of growth hormone deficiency in children, children with chronic renal insufficiency, and children with short stature associated with Turner's syndrome
- Tenecteplase, an injectable, slower-clearing, fibrin-specific tissue plasminogen activator for the treatment of myocardial infarction, first launched in the US in June 2000 and in 2001 in the EU
- Trastuzumab, a humanized version of the anti-HER-2/neu monoclonal antibody, 4D5, and marketed for the treatment of metastatic breast cancer since 1998
- Roferon-A, a recombinant interferon-$\alpha_{2a}$ that has been developed and used for the treatment of various lymphomas, leukemias, and other neoplasms, and for the treatment of chronic hepatitis B and C virus (HBV and HCV) infections
- Ituximab, a mouse/human chimeric anti-CD20 monoclonal antibody, used for the treatment of B-cell nonHodgkin's lymphoma, including relapsed, refractory low-grade, or follicular lymphomas

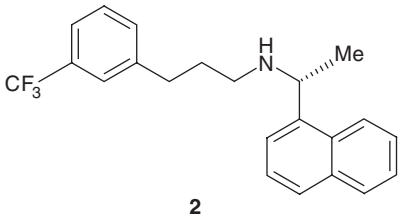
- Erlotinib (**1**), a small-molecule, orally active epidermal growth factor receptor tyrosine kinase inhibitor (discovered by but relinquished by Pfizer after the merger with Warner-Lambert), for the treatment of nonsmall-cell lung cancer.




**1**

*Amgen*. Amgen (formerly known as Applied Molecular Genetics; AMGen) was established in 1980 and is headquartered in Thousand Oaks, CA. Amgen was originally a biotechnology company focused on the development and commercialization of proteins, antibodies, and small molecules in the areas of oncology, inflammation, hematology and nephrology, neurology, metabolic diseases, and osteoporosis. Amgen has done its own share of acquisitions, including the purchase of Kinetix in 2000 for $170 million, Immunex in 2002 for $13 billion and Tularik in 2004 for $1.3 billion. Amger has an extensive portfolio of products.

- Anakinra is an interleukin-1 receptor antagonist, developed and launched extensively by Amgen for the treatment of rheumatoid arthritis. The drug was originally developed in collaboration with researchers at the University of Colorado
- Ancestim, a recombinant human stem cell factor, has been approved for the mobilization of stem cells in the treatment of cancer
- Darbopoetin alfa is a synthetic recombinant novel erythropoiesis-stimulating protein, for the treatment of anemia associated with renal disease
- Epoetin alfa is a recombinant human erythropoietin marketed in the US since 1989 as an orphan drug for the treatment of anemia resulting from kidney failure and was the first erythropoietin preparation to be approved for the treatment of anemia in premature infants
- Filgrastim is a granulocyte colony-stimulating factor product – the initial indication was reduction in the incidence of infection, as manifested by febrile neutropenia, in patients undergoing myelosuppressive chemotherapy
- Interferon alfacon-1 (consensus interferon) is indicated for use in the treatment of viral infections, particularly hepatitis
- Pegfilgrastim is a sustained-duration, pegylated form of recombinant granulocyte colony-stimulating factor used for the treatment of chemotherapy-induced neutropenia
- Etanercept is a soluble TNF receptor (TNFR) fusion protein, for the treatment of adult and juvenile RA and psoriatic arthritis
- Cinacalcet (**2**) is a calcimimetic for the treatment of primary and secondary hyperparathyroidism.




**2**

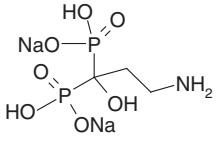
*Biogen Idec*. Biogen Idec was established in 1978 in Cambridge, MA and merged with IDEC (formed in 1985 in San Diego) in 2003, to form Biogen Idec. The number of marketed compounds was five in February 2005.[20] Marketed products from Biogen Idec are:

- Alefacept, a T-cell-inhibiting, CD2 antagonist, LFA3-IgG1 fusion protein, launched in 2003 for the treatment of psoriasis
- Avonex (interferon-$\beta_1$), used since 1996 as a treatment for relapsing-remitting multiple sclerosis

- Ibritumomab tiuxetan, an anti-CD20 murine monoclonal antibody conjugated to either yttrium-90 or indium-111 for the radioimmunotherapy of relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma
- Rituximab, a mouse/human chimeric anti-CD20 monoclonal antibody, used for the treatment of B-cell non-Hodgkin's lymphoma, including relapsed, refractory low-grade or follicular lymphomas.

*Chiron*. Chiron was founded in 1981. In 1984, the company cloned several HBV antigens and sequenced the human immunodeficiency virus (HIV) genome. In 1987, it sequenced the HCV genome. This IP has formed the basis of several Chiron products and also generates income through licensing. As of January 2004, Novartis owned 42% of Chiron's outstanding common stock, following an alliance established in January 1995. In February 2005, Chiron had 18 products on the market, of which the majority were vaccines. The nonvaccine products are:

- Aldesleukin, a recombinant interleukin-2 compound for the treatment of cancer
- Betaseron, a recombinant interferon $\beta_{1b}$ for the treatment of relapsing-remitting multiple sclerosis
- Tobi, an inhalant formulation of the antibiotic tobramycin, for the treatment of chronic pseudomonal lung infections in patients with cystic fibrosis
- Pamidronate disodium **(3)**, a calcium metabolism inhibitor discovered by Henkel (Düsseldorf, Germany) and licensed to both Novartis and Amgen for the treatment of moderate to severe Paget's disease and for hypercalcemia of malignancies such as multiple myeloma
- Dexrazoxane **(4)** (licensed from the British Technology Group), used against chemotherapy-induced cardiotoxicity in several major markets, including the US
- Pilocarpine hydrochloride (oral formulation) stimulates salivary and lacrimal secretion for the treatment of xerostomia and keratoconjunctivitis sicca arising from a number of conditions, including autoimmune diseases and radiotherapy to the head and neck.

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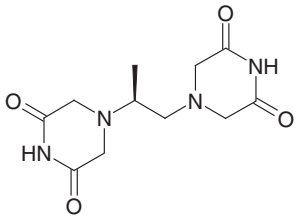
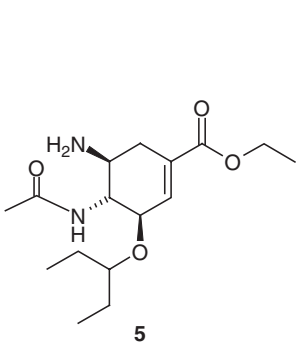



**4**

Chiron announced that it was to be acquired by Novartis for $5.1 billion in cash on October 31, 2005.

*Gilead*. In contrast to the biology-oriented SME successes, no SME that began life as a small-molecule drug discovery house has yet become a global competitor to traditional big pharma, although Gilead, Ligand, Sepracor, Vertex, and Millennium are probably the closest to achieving that ambition and have already grown well beyond the SME definitions given above. Gilead Sciences, headquartered in Foster City, CA, was founded in 1987 and has more than 1500 employees in 2005, making it too large to be fairly considered an SME. Gilead has several antiinfectious products on the market:

- Emtricitabine, a nucleoside analog licensed from Emory University that is structurally related to 3TC for the treatment of HIV infection
- Cidofovir, a specific nucleotide inhibitor of viral replication, which was launched in an injectable formulation in 1996
- Oseltamivir (Tamiflu: **5**), a neuraminidase inhibitor, for the treatment and prevention of influenza virus type A or B infections
- Tenofovir disoproxil fumarate **(6)**, an oral prodrug of the intravenously administered antiviral agent tenofovir used for the treatment and prophylaxis of HIV infection
- AmBisome, a liposomal formulation of amphotericin B, jointly developed by NeXstar and Lyphomed, marketed for systemic fungal infections and in the US for cancer and acquired immunodeficiency syndrome (AIDS) patients with blood-borne fungal infections
- Adefovir dipivoxil, an analog of the reverse transcriptase inhibitor adefovir for the treatment of HBV infection.



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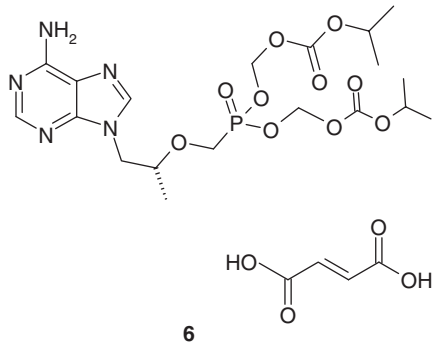

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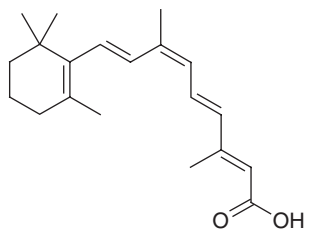
Gilead has made two major acquisitions of SMEs to bolster both its technology base and antiviral pipeline, NeXstar (1999) and Triangle Pharmaceuticals (Research Triangle Park (RTP), NC). In 2002 Gilead acquired Triangle Pharmaceuticals, formed by Dr David Barry, formerly of Burroughs Wellcome in 1995, at a cost of $464 million. Triangle had specialized in nucleoside analogs as antiviral agents, including IP licensed from the Universities of Emory and Georgia.

*Ligand Pharmaceuticals*. Ligand Pharmaceuticals (San Diego, CA) was founded in 1987 to develop gene transcription technologies, particularly an intracellular receptor (IR) technology and signal transducers and activators of transcription (STATs). The company has applied these technologies to discover and develop novel small-molecule drugs for the treatment of cancer and osteoporosis, as well as gynecologic, dermatologic, cardiovascular, and inflammatory diseases. Ligand is a company that has achieved the status of having launched products, and as of 2005, its portfolio included the following US Food and Drug Administration-approved drugs: morphine sulfate extended-release capsules, alitretinoin **(7)**, bexarotene, and denileukin diftitox.

*Vertex Pharmaceuticals*. Vertex Pharmaceuticals, founded in 1989 and initially focused on a structure-based approach to drug discovery, is headquartered in Cambridge, MA, and became a publicly owned biotechnology company in 1991. By July 2001, Vertex completed an agreement signed in April 2001 to acquire Aurora Bioscience (a screening technology company) in a stock-for-stock transaction, where the fully diluted equity value of the transaction was $592 million. As of February 2005, Vertex had only launched one product by itself: Fosamprenavir **(8)**, a prodrug of the existing HIV protease inhibitor amprenavir, for the treatment of HIV infection. In addition, Vertex's first original drug to be invented, amprenavir, is an oral, nonpeptidic HIV protease inhibitor and was licensed to and developed and launched extensively by Glaxo Wellcome (now GlaxoSmithKline), for the treatment of HIV infection and AIDS.



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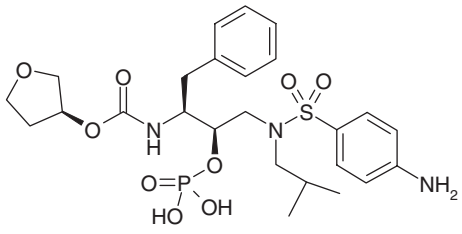

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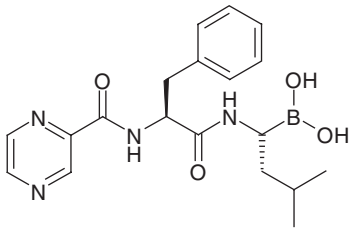
*Millennium Pharmaceuticals*. Millennium Pharmaceuticals was founded in 1993, and is a biopharmaceutical company focused on the discovery and development of small molecules, biotherapeutics (antibodies and proteins), and predictive medicine products. In February 2005, three products were reported to be marketed[21]:

- Alemtuzumab (Campath) is a lymphocyte-depleting humanized monoclonal antibody against CD52, for the treatment for chronic lymphocytic leukemia
- Eptifibatide, a synthetic peptide glycoprotein IIb/IIIa antagonist and platelet aggregation inhibitor derived from rattlesnake venom, is an intravenous treatment for acute coronary syndrome
- Bortezomib **(9)** is a ubiquitin proteosome inhibitor for the treatment of multiple myeloma.



9

### 1.13.5.2 Small- or Medium-Sized Enterprises That Have Been Acquired by Major Pharma

It is salutary to note that, in contrast to the biological drug houses listed above, big pharma has been quicker to recognize the value of small-molecule drug research houses and thus has prevented many from achieving the roles of FIPCOs due to them becoming acquisition targets of big pharma companies, including some of the new biotech majors listed above. In many cases SMEs have welcomed the takeover from major pharma companies as the only way to realize the value inherent in their IP portfolio. Illustrative acquisitions by the major pharma players are shown in Table 3.

### 1.13.5.3 Small- or Medium-Sized Enterprises That Have Been Acquired by Other Small- or Medium-Sized Enterprises

Many SMEs would have failed to realize any potential due to cash exigencies and have been encouraged to merge, or be acquired by, other SMEs, when the combination of the two companies appears synergistic and is the only way to realize further investment. Biotech hunger to acquire capabilities beyond its own, often specialized and narrow capabilities, equally encourages vertical mergers. Acquiring chemistry capability has been the logic behind the fusions of SMEs, including those of Lexicon Genetics with Coelacanth in the US in 2001, Etiologics with Argenta Discovery of the UK in 2004, and Paradigm with Amedis in the UK in 2005.

The acquiring of IP assets by a service company determined to become a therapeutics player can also engender acquisitions: Evotec-OAI purchased Evotec Neurosciences in 2005. Merging two therapeutics companies together to cut costs whilst maintaining synergies can also be an important cause of mergers: Ribotargets, British Biotechnology, and Vernalis performed a three-way merger in 2004, creating a single entity, now known only as Vernalis. Similarly, in the US, VI Technologies (Vitex) is the surviving company from the November 1999 merger of Pentose Pharmaceuticals and VI Technologies. Vitex merged again with Panacos Pharmaceuticals in early 2005 with a private placement of $20 million, allowing financial compliance with NASDAQ requirements. The deal would combine Vitex's antiinfective capabilities into therapeutic products, including Panacos' pipeline of antiviral drugs, and its antiviral drug discovery platforms.

### 1.13.5.4 Small- or Medium-Sized Enterprises That Have Failed

Finally, some companies – a merciful few – go out of business. Axxima AG's (Munich, Germany) filing for insolvency in December 2004 was followed by the acquisition of the company by GPC Biotech AG in 2005; however, the bankruptcy and total closure of Cambridge (UK)-based Axis Genetics in 1999 was a salutary experience for those in the industry.[22]

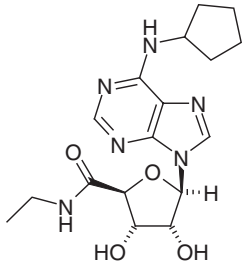
## 1.13.6 Small- or Medium-Sized Enterprises That Are Drug Discovery Houses

### 1.13.6.1 Multitherapeutic Disease Area Companies

Under this heading is grouped a multitude of companies, which are neither constrained by therapeutic area nor have as prime reason for existence research in a particular technological axis.

*Aderis Pharmaceuticals*. Aderis Pharmaceuticals (formerly Discovery Therapeutics) of Hopkinton, MA is a privately owned pharmaceutical company, founded in 1994, created upon the IP/research programs from Whitby Research, a division of Ethyl. Aderis focuses on the R&D of small-molecule therapeutics for use in the treatment of central nervous system (CNS), cardiovascular, and renal diseases. Rotigotine (licensed to Schwarz Pharma, Germany) has been

developed for early stage Parkinson's disease. Selodenoson **(10)** is a selective adenosine A1 agonist formulated for intravenous administration to control heart rate during acute attacks, and formulated for oral administration for the chronic management of atrial fibrillation. King Pharmaceuticals (Bristol, TN) is the partner on the binodenoson project (adenosine A2A receptor agonist for cardiac pharmacologic stress-imaging).



**10**

*Arakis*. Arakis (Saffron Walden, UK, founded January 2000) is a pharmaceutical company focusing on the treatment of inflammatory disease and oncology adjunctive therapy. The most advanced drugs in development are AD237 for chronic obstructive pulmonary disease (a muscarinic antagonist); AD 452, in development for rheumatoid arthritis, and apparently the single isomer of a racemic drug marketed for an unrelated indication; AD923, being developed for pain associated with cancer; and AD337, for emesis associated with cancer.[23] Arakis was acquired by the Japanese biotech Sosei in July 2005.

*Curagen*. Curagen (a public company located in New Haven, CT) was formed as a genomic company (single nucleotide polymorphism technology) that has more recently moved to a therapeutic axis. It is now a multitherapeutic axis company that has recently changed strategic direction to become a preclinical and clinical development company – a move to advance its pipeline of genomics-based therapeutics. Curagen is focusing on CG-53135 (human FGF-20 (fibroblast growth factor)) for the treatment of oral mucositis. Curagen is working with Abgenix on CR-002, a fully human monoclonal antibody that specifically recognizes and blocks the active form of PDGF-D (platelet-derived growth factor), for the potential treatment of kidney inflammation. CR-011 is a potential treatment of metastatic melanoma. Curagen and Bayer have a long-standing joint interest in new diabetic treatments. Curagen has also in-licensed the Topotarget HDAC inhibitor (itself acquired from the former UK SME Prolifix) PXD-101, for the potential treatment of cancer, and is also investigating it for the potential treatment of inflammation.

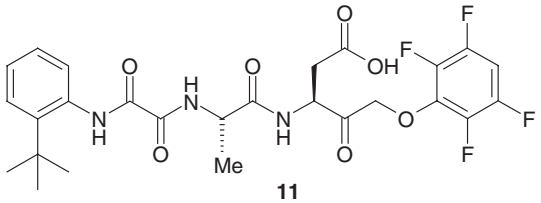
*Curis*. Curis, a public company headquartered in Cambridge (MA), was established in July 2000 through the merger of three biotechnology SME companies: Creative BioMolecules, Ontogeny, and Reprogenesis. The company specializes in the development of proteins and small molecules to modulate the regulatory pathways which control repair and regeneration of cells. This technology has been used to produce potential therapeutics for kidney disease, neurological disorders, cancer, hair growth regulation, and cardiovascular disease. Curis has specialized in therapeutic treatments that might ensue through interference with the so-called hedgehog pathways. Products include both biologicals – BMP-7 is a signaling protein that was discovered by scientists from Curis, and treatment with BMP-7 ameliorates two major complications of chronic kidney disease – and small-molecule hedgehog agonists and antagonists.

*Exelixis*. Exelixis (San Francisco, CA) is another genomics-based (model systems for pharmaceuticals include the fruitfly, nematode worm, zebrafish, and mouse) drug discovery company focusing mainly on developing therapies for cancer and other proliferative diseases. Scientists at Exelixis have done a large amount of work on receptor tyrosine kinases, and other enzymes important in angiogenesis and vascularization, e.g., the ADAM-10 metalloprotease. The three nuclear receptors – liver X receptor (LXR), farnesoid X receptor (FXR) and mineralocorticoid receptor (MR) – are the targets for small molecules for modulation. Such modulation is implicated in various metabolic and cardiovascular disorders. Oncology programs are focused on the inhibition of the RAF, Akt/S6k, and IGF1R kinases that are implicated in cancer and other therapeutic areas. In October 2004, Exelixis acquired another SME, X-Ceptor, once a private corporation that was formed by Ligand Pharmaceuticals in July 1999 to research and identify therapeutic products that target orphan nuclear receptors using technology under exclusive license from Ligand. X-Ceptor focused on the R&D of drugs for the treatment of cancer, cardiovascular disease, endocrine disorders, metabolic disease and inflammation. Exelixis and GlaxoSmithKline have an agreement on an R&D collaboration under which GlaxoSmithKline pays milestone payments to Exelixis upon filing of three investigational new drugs or successful completion of one phase I trial by the end of 2005 for products from the Exelixis stable.

*Fulcrum Pharmaceuticals*. IP from the University of Pennsylvania (Philadelphia, PA) and the Johns Hopkins University (Baltimore, MD) created Fulcrum Pharmaceuticals (New York) founded in 2002, a biotechnology company focused on

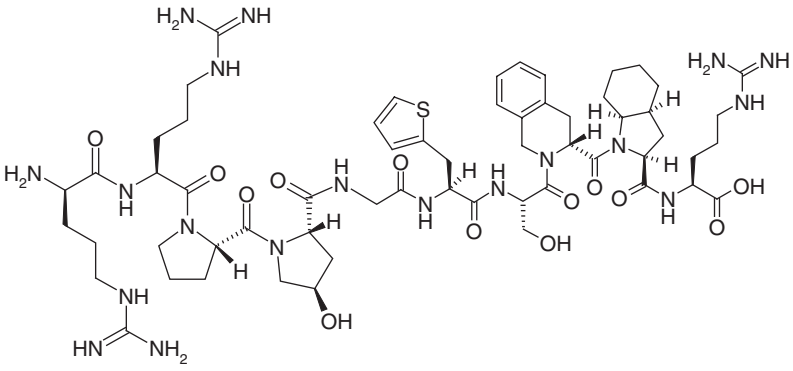
the development of small molecules for the treatment of inflammatory disease, osteoporosis, infectious disease. and oncology. Lead programs include small-molecule inhibitors of the tumor necrosis factor receptors and small-molecule inhibitors of the receptor activator of NFκB (RANK)/RANK ligand (RANKL) system.

*Idun Pharmaceuticals*. Idun Pharmaceuticals (San Diego, CA), founded in 1993, was a private company researching the caspase enzymes, a group of cellular proteases involved in the pathway of apoptosis and inflammation. IDN-6556 **(11)** is a first-in-class pancaspase inhibitor which is in phase II clinical trials of patients having had liver transplantation and in patients infected with hepatitis C virus. In 2005 the company was purchased by Pfizer, probably following encouraging results of its lead product in clinical trials for liver fibrosis.[24]



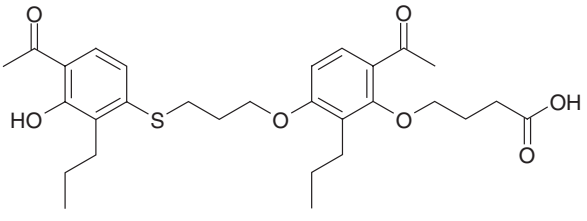

**11**

*Jerini*. The private company Jerini (Berlin, Germany) was spun off from the Medical Faculty at the Humboldt University, Berlin, in 1994. It uses a platform technology (SPOT) of high-density protein, peptide, and small-molecule arrays to map novel targets, leading to the identification and efficient optimization of lead compounds for drug discovery. Jerini has worked with Alcon, Baxter Healthcare, and Merck KGaA on eyecare and oncology projects. Jerini is developing the selective bradykinin $\beta_2$-antagonist icatibant **(12)** (under license from Sanofi-Aventis and previously known as Hoe 140) as a potential treatment for decompensated liver cirrhosis with resistant ascites, angioedema, and edema in severe burn patients.




**12**

*MediciNova*. MediciNova was founded in September 2000 by Tanabe Seiyaku of Japan (which has a controlling stake) and is located not in Japan but in San Diego, CA. Products and projects include MN-001, which is a novel, orally bioavailable compound for the treatment of bronchial asthma. MN-001 **(13)** has actions including leukotriene (LT) receptor antagonism and inhibition of phosphodiesterase IV. The ANG-600 series of benzimidazole carbamate vascular-targeting agents are potential angiogenesis inhibitors for the treatment of cancer.




**13**

*Myriad*. Myriad Genetics and Myriad Pharmaceuticals are two parts of the Salt Lake City (UT)-located SME. The two Myriad companies are publicly held and focus on gene discovery and analysis, the development of prophylactics and therapeutics (through its subsidiary, Myriad Pharmaceuticals), predictive mutations of the *BRCA1* breast cancer gene, and the discovery of the *HPC2* prostate cancer gene on chromosome 17p. The *HCP2* gene was to form the basis of Polaris, Myriad's predictive test for assessing a man's risk of developing prostate cancer. Drug discovery efforts target cancer, rheumatoid arthritis, acute thrombosis, Alzheimer's disease, HIV/AIDS, and other viral diseases.

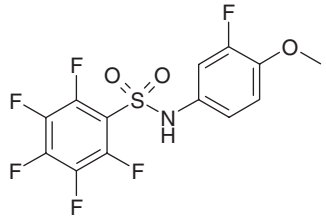
*Oxagen*. Oxagen (Abingdon, UK) was formed in April 1997 as a spinout genomics company from the Wellcome Trust Centre for Human Genetics, but then mutated into a biopharmaceutical company with a full drug pipeline for the treatment of metabolic diseases, such as type 2 diabetes, osteoporosis and endometriosis, and inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma. Oxagen is investigating antagonists of the chemoattractant G protein-coupled receptor (GPCR) expressed on Th2 cells (CRTH-2) for the potential treatment of asthma and allergy. A large second fundraising was completed in the second quarter of 2005.

*ReOx*. A 2004 spinout company, from Oxford University (UK), is ReOx, a drug discovery company whose technology is based on the body's biological response to a lack of oxygen (hypoxia) and in particular the mechanism by which the activity of the master regulator, hypoxia-inducible factor, is activated. The company will build on the research of the academics involved to develop therapies for a range of diseases in which it could be beneficial to regulate the body's response to oxygen.[25]

*Rigel*. Rigel (San Francisco, CA) has pioneered the inhibition of syk kinase as potential treatment of respiratory diseases. In 2004 Rigel entered into collaboration with Pfizer to pursue the clinical development of such molecules. Other compounds from the Rigel syk kinase portfolio are being developed for the possible treatment of rheumatoid arthritis. Rigel is also developing R-803, a small-molecule, non-nucleoside HCV RNA polymerase inhibitor, for the potential treatment of HCV infection. Merck is in collaboration with Rigel on inhibition of ubiquitin ligases as potential therapies in oncology, and is also developing inhibitors of aurora kinase as potential cancer drugs.

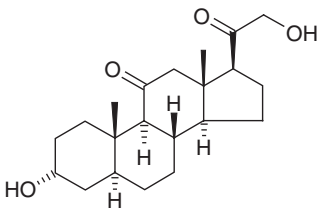
*Sosei*. Sosei was founded in 1990 and is based in Tokyo, Japan. It is a biopharmaceutical company that has projects for contraception, cancer, incontinence, asthma, and other allergies. The company's main strategy is to use its drug-reprofiling program to optimize or find new indications for discontinued drug candidates, mainly from Japanese companies. Sosei is unusual – it is one of the few Japanese SME biotech companies, and it has a policy of in-licensing compounds that are already marketed or at the late stages of development, from US/EU companies and of in-licensing compounds from Japanese companies via its drug-reprofiling platform.[26] Sosei acquired the UK biotech Arakis in July 2005.

*Tularik*. Tularik (San Francisco, CA) was founded in 1991, and was a biopharmaceutical company engaged in the R&D of drugs that regulate gene expression and focused on cancer, immunology, and metabolic disorders. Amgen acquired Tularik in 2004. From the Tularik stable, Amgen now has batabulin (**14**) in development. Batubulin is a tubulin polymerization inhibitor, for the potential treatment of various cancers.




**14**

*Vernalis*. Vernalis is the name of a company created from the fusion of British SME biotechnology companies Vernalis (already incorporating Vanguard Medica), Ribotargets, and British Biotechnology (founded as British Biotech in 1986). Vernalis is a biotechnology company headquartered in Winnersh, UK. Its R&D focus is on migraine, thrombotic diseases, pain, and Parkinson's disease, with additional early stage research in oncology, obesity, inflammation, and depression. One of Vernalis' predecessor companies, RiboTargets, licensed alfadolone **(15)** for development from Monash University, Australia. Alfadolone **(15)** is a steroid GABA A agonist for the potential treatment of pain, especially that associated with cancer. Vernalis has done deals with Novartis on an hsp90 oncology target project. Under another agreement, Biogen IDEC received exclusive worldwide rights to Vernalis' adenosine A2A receptor antagonist program. Under this agreement, Biogen IDEC received exclusive worldwide rights to develop and commercialize Vernalis' program including the compound VER 6323 **(16)**.

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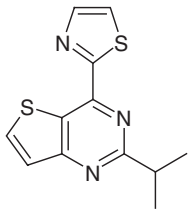


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### 1.13.6.2 Antiinfectious Diseases Companies

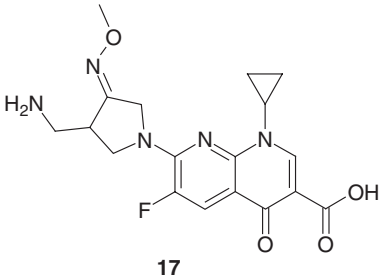
It is a truism to say that, by 2005, traditional big pharma has largely abandoned the previously lucrative antibacterial field to the biotechnology sector – despite the rise in cases of patients with hospital-acquired infections of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The public perception of danger is not yet a commercial driver sufficient to warrant reinvestment of large pharma research groups and, in this field, discovery of new treatments will largely be due to the efforts of SMEs in the next few years. Antifungal and antiviral drug discovery, however, remain the preserve of both traditional large pharma and of biotech.

*Rib-X*. Rib-X (New Haven, CT) is a spinout of the University of Yale (founders Dr Thomas Steitz and Dr Peter Moore) that focuses on its licensed proprietary knowledge of the structure of the human ribosome to discover new antibacterial agents of the macrolide family. Structural information has been obtained for a number of antibiotics complexed with the 50S subunit and reveals that 50S-targeting antibiotics bind in a tunnel in the central part of the ribosomal subunit. This binding thus blocks access to the pocket where peptide bond formation in growing proteins takes place.

*Athelas*. Athelas (Geneva, Switzerland) is a private company founded in 2002 by Professor Pierre Cosson and Dr Jean-Pierre Paccaud (University of Geneva). The company focuses on the development of bactericidal antivirulence drugs, the identification of bacterial genes involved in the virulence mechanisms, and their use as new drug targets with a proprietary cell-based screening technology called DiVi.[27]

*Novexel*. Novexel (Paris, France) is an SME spinoff from Aventis after its merger with Sanofi-Synthelabo. Novexel inherited a portfolio of antiinfective drugs in phase I clinical trial, including NXL-103, an oral antibiotic against bacterial respiratory infections, an oral streptogramin consisting of a 70/30 combination of RPR-202868 (type 1 streptogramin), and RPR-132552 (type 2 streptogramin) for the potential treatment of community-acquired pneumonia and respiratory tract infections, and also NXL-201, which is being developed for the treatment of severe fungal infections.

*Oscient Therapeutics*. Oscient Therapeutics (Cambridge, MA) incorporated what was Genome Therapeutics, an antiinfectives company, in 2004. This company originally focused on the discovery of new antibacterial drugs and had a long-standing (9–year) research agreement with Schering-Plough to discover new antibacterial targets using its proprietary genetics technology base, including a database licensed in by several companies, PathoGenome. Oscient has changed business focus as from 2004, becoming a more commercial organization. It has one launched product – gemifloxacin **(17)** (licensed from LG Life Sciences in 2002).



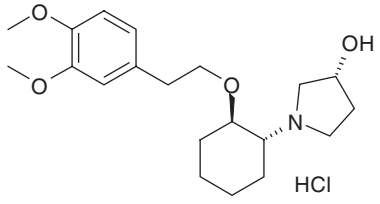

17

*Arrow Therapeutics*. Arrow Therapeutics (London, UK), founded in 1998, was created after the acquisition of Wellcome by Glaxo and the closure of the former Wellcome research facilities in south London. Arrow is a privately owned antiinfective drug discovery company, focused on targets for antiviral and antibacterial therapies utilizing a genome-based approach. In the antiviral sector, a lead compound against respiratory syncytial virus infection completed phase I trials in June 2004. Arrow also has a hepatitis C program, which entered preclinical studies in March 2004, with clinical trials planned for the first half of 2005.[28]

### 1.13.6.3 Cardiovascular Disease Companies

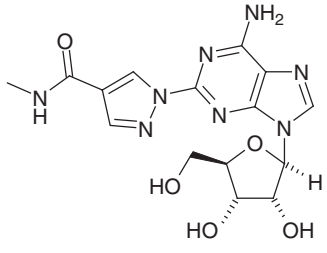
Cardiovascular disease is an area of focus for both major pharma and biotech companies – most SMEs have arisen from academic origins.

*Cardiome*. Cardiome (formerly Nortran Pharmaceuticals of Vancouver, Canada) is a drug discovery and development company focused on the treatment and prevention of cardiac diseases. Cardiome focuses its development within two areas of cardiac disease: arrhythmia and congestive heart failure. In clinical trial is RSD 1235 **(18)** for arrhythmia and also oxypurinol for congestive heart failure. Ion channel research is a specialty of this company.




**18**

*CV Therapeutics*. CV Therapeutics (Palo Alto, CA), which was founded in 1990, performs R&D in cardiovascular disease. Regadenoson **(19)** is a selective A2A-adenosine receptor agonist for potential use as a pharmacologic stress agent in myocardial perfusion imaging studies, developed by CV Therapeutics and the Japanese company Fujisawa. Tecadenoson **(20)** is a selective A1-adenosine receptor agonist for the potential reduction of rapid heart rate during atrial arrhythmias. Adentri is a selective A1-adenosine receptor antagonist for the potential treatment of heart failure, and has been licensed to Biogen Idec. CV Therapeutics, under license from Roche, is also developing ranolazine, a metabolic modulator and a partial fatty acid oxidation inhibitor, for the potential treatment of angina and acute coronary syndromes.

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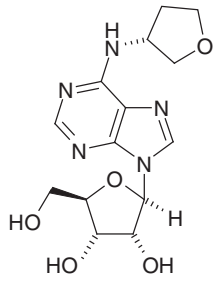
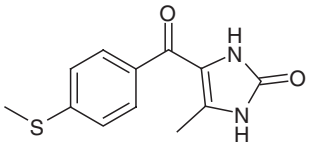



**20**

*Artesian Therapeutics*. Artesian Therapeutics (Gaithersburg, MD) is a privately held biopharmaceutical company focused on novel disease-modifying and disease-reversing therapeutics for the treatment of cardiovascular disease. Artesian is another company developing 'dual-pharmacophore' molecules (which contain the individual pharmacophoric moieties needed to inhibit two targets linked together by a flexible chemical tether into a single molecule).

*Myogen*. Myogen, founded in 1996 and based in Westminster (CO), is a biopharmaceutical company engaged in the discovery, development, and commercialization of small-molecule therapeutics for the treatment of cardiovascular disorders, based on research undertaken at the University of Colorado Health Sciences Center. Myogen, under license from Aventis (now Sanofi-Aventis), is developing an oral formulation of the vasodilating phosphodiesterase III inhibitor enoximone **(21)** for the potential treatment of advanced heart failure. Under license (from Abbott) is an oral endothelin A antagonist darusentan **(22)** for the potential treatment of uncontrolled hypertension. Under license from an Abbott research group (formerly BASF Pharma) is ambrisentan **(23)**, an endothelin ET-A antagonist, for the potential treatment of cardiovascular diseases. In terms of target discovery, scientists at Myogen have discovered that nonfailing human ventricular myocardium contains a larger amount of the fast-contracting alpha-myosin heavy chain (alpha-MyHC) isoform mRNA. In contrast, in myocardial failure, alpha-MyHC mRNA is markedly downregulated, and the slow-contracting isoform beta-MyHC is upregulated. Thus, it might be expected that agents that can cause reversal of the MyHC gene switch would provide therapeutic benefit.



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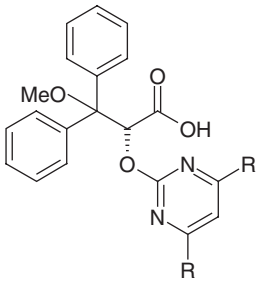


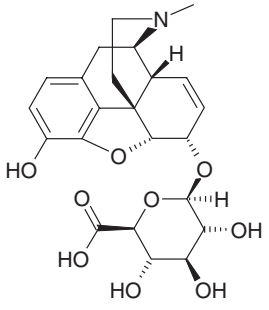
22 R = MeO
23 R = Me

*Zealand Pharma*. Zealand Pharma (Glostrup, Denmark) was founded in 1998 and is a private biopharmaceutical company that focuses its R&D efforts on developing peptides by investigating gap junction modulation and peptide modification chemistry using its structure-inducing probe technology. The company's therapeutic focuses are type 2 diabetes, acute heart failure, and arrhythmia.

### 1.13.6.4 Central Nervous System Disease and Antiaging Companies

The unmet need for new therapies to treat CNS disorders is one that is especially attractive to scientists, clinicians, and investor backers. Consequently, a large number of companies have been created to examine many new approaches for a huge variety of CNS indications. Some particularly informative examples of the impact these SMEs are having on CNS drug discovery are listed below.

The treatment of pain has barely changed from the two centuries' use of morphine and its long-known derivative diamorphine, with all the well-known addiction and respiratory depression side effects these drugs can cause. Companies like CeNeS (Cambridge, UK) have pioneered the use of morphine-7-glucuronide **(24)**, whilst Exton (PA)-based Adolor (the name is derived from the Spanish meaning 'no pain') launched itself on the back of an IP estate licensed in from Eli Lilly and has researched a range of approaches in the field. In 2003, Adolor struck a deal with GlaxoSmithKline to codevelop and comarket Adolor's μ-opiate receptor antagonist product alvimopan **(25)** to treat the gastrointestinal effects associated with prolonged use of opiate analgesics.



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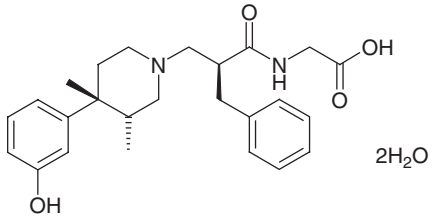

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Another Pennsylvania-based company, Theraquest Biosciences, was established in 2000 and researches into nonsteroidal antiinflammatory drugs for the treatment of pain.

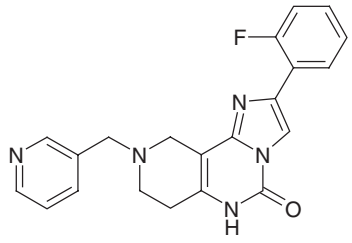
*Ionix Pharmaceuticals*. Cambridge (UK)-based Ionix Pharmaceuticals conducted research into nonopiate treatments of pain associated with using proprietary drug targets that are involved in the perception and signaling of pain in the peripheral nervous system. Such treatments might be useful for pain associated with chronic debilitating diseases such as osteoarthritis, rheumatoid arthritis, multiple sclerosis, and diabetic neuropathy. Ionix was a typical SME having to outsource much of its research to partners – it collaborated with Evotec and with Tripos on the design and synthesis of drug-like chemical compounds for evaluation as potential inhibitors of its own targets, and with Xenome on the design, synthesis, and screening of toxins as potential inhibitors of proprietary Ionix drug targets. The IX-2000 series are small-molecule blockers of the calcium ion channel that are able to enter the spinal cord. In preclinical pharmacokinetic investigations in a neuropathic pain model, administration of IX-2100 resulted in an almost identical concentration in

the spinal cord and plasma and > 40% reversal of neuropathic hyperalgesia was observed for almost 6 h. Ionix was acquired by Vernalis of the UK in July 2005.

*Chronogen*. Chronogen (Montreal, Canada) was founded in 1998 to develop therapeutics to counter the effects of aging. Chronogen has focused on the identification and characterization of longevity genes, which were cloned from *Caenorhabditis elegans* mutants that exhibited a long lifespan phenotype. Those genes that were the most relevant to human diseases were selected as the basis of the company's drug discovery programs. In 2002, Chronogen secured an exclusive worldwide license to the proteins CLK-1, CLK-2, and ISP-1, in addition to a series of targets, from McGill University (Montreal, Canada). Targets under investigation include isp-1, which regulates levels of reactive oxygen species, and clk-1, which regulates ubiquinone synthesis.

*Targacept*. Targacept (RTP, NC) is a 2000 spinout from the tobacco company RJ Reynolds and has products under research for postoperative pain (TC-2696) and Alzheimer's disease. Targacept is researching novel approaches to treat pain, including $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors that are known to have pain-relieving effects in animals.

*Neurogen*. Neurogen, incorporated in 1987, is a neuropharmaceutical company focused on the R&D of small-molecule therapeutics for the treatment of neurological, inflammatory, pain, and metabolic disorders. Neurogen is developing NGD-2000-1, the lead in a series of oral C5a antagonists, for the potential treatment of inflammatory conditions, including rheumatoid arthritis and asthma. As well as treatment of inflammatory conditions, Neurogen is developing NG-2-73, a selective GABA modulator, for the potential treatment of insomnia. In December 2004, the company initiated a phase I oral dose escalation trial with the drug. Neurogen and Pfizer are also developing the GABA-A agonist, NGD-96-3 (**26**) for the potential treatment of insomnia.

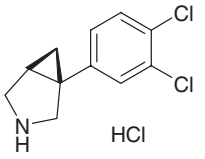



**26**

*En Vivo Pharmaceuticals*. The treatment of Alzheimer's disease is a severe unmet medical need and novel approaches are being examined by a variety of companies. En Vivo Pharmaceuticals (Cambridge, MA) founded in 2001, is a biopharmaceutical company dedicated to discovering and developing drugs for CNS disorders, with its initial focus on Alzheimer's, Parkinson's, and Huntington's diseases and spinocerebellar ataxias. Using technology licensed from the Baylor College of Medicine (Houston, TX), the company inserts known human brain disease genes into *Drosophila* (fruitfly) and examines the effects of candidate drugs on the whole species. In 2004, En Vivo pharmaceuticals struck a deal with Methylgene (Quebec, Canada) to examine the use of the latter's portfolio of histone deacetylase inhibitors (which hitherto have been almost exclusively an oncology therapy) in its Alzheimer's disease models.

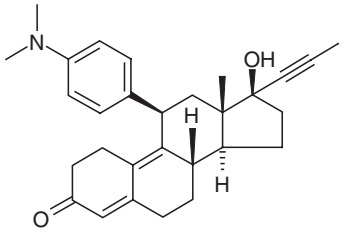
*Evotec Neurosciences*. Evotec Neurosciences (Hamburg, Germany) was founded in May 1999 by Evotec BioSystems and Professor Nitsch. Evotec Neurosciences received a €25 million Series A funding in 2004 from Evotec OAI and five venture capitalists (TVM Techno Venture Management (Munich, Germany), 3i (London, UK), MVM (London, UK), Ventech (Paris, France), and Star Ventures (Munich, Germany)). Research focus was on Alzheimer's disease and other neurological disorders. Licensed in from Roche is a series of NR1/NR2B subtype-selective *N*-methyl-D-aspartate antagonists for the potential treatment of neurodegenerative diseases, including stroke.[29] Evotec Neurosciences was reacquired in its entirity from its VC investors by Evotec OAI in March 2005.

*DOV Pharmaceutical*. New drugs to treat depression and Parkinson's disease are a speciality of DOV Pharmaceutical, a biopharmaceutical company formed in 1996. The products of this company have attracted the attention of Merck, which is developing under license DOV-21947 (possible structure shown as (**27**)), a triple (serotonin, norepinephrine, and dopamine) reuptake inhibitor, for the potential treatment of depression. Merck licensed exclusive worldwide rights to DOV-21947 for all therapeutic indications and exclusive worldwide rights to DOV-216303 for the treatment of depression, anxiety, and addiction. The size of the deal struck with Merck is impressive: DOV would receive a $35 million upfront licensing payment, $300 million for achieving certain milestones, and up to $120 million upon achievement of certain sales thresholds. Merck would assume responsibility for the full development, manufacturing, and commercialization of DOV-21947. DOV is investigating DOV-51892, the lead in a series of GABA-A modulators, for the potential treatment of panic disorder. A further CNS product from DOV Pharmaceutical is ocinaplon (DOV-273547) for the potential treatment of generalized anxiety disorder.




**27**

*Corcept*. Corcept (San Francisco, CA) is an SME studying the use of mifepristone (RU-486) **(28)** which (as of March 2005) is in phase III clinical trials for the treatment of the psychotic features of psychotic major depression, a disorder that affects approximately 3 million people in the US each year and for which there are no Food and Drug Administration-approved treatments. Corcept has sponsored further research in conjunction with Argenta Discovery (Harlow, UK) on this indication.

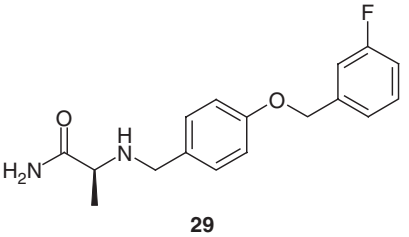



**28**

*Neurocrine Biosciences*. Neurocrine Biosciences (San Diego, CA) was founded in 1992 and focuses on drug discovery of small-molecule therapeutics to treat diseases of the central nervous, immune, and endocrine systems. Neurocrine is developing NBI-30702, a second-generation corticotrophin-releasing factor receptor antagonist, for the potential treatment of cerebrovascular ischemia leading to stroke. NBI-30702 is one of a series of compounds resulting from Neurocrine's work with excitatory amino acid transporter modulators.[30]

*Memory Pharmaceuticals*. Memory Pharmaceuticals (Montvale, NJ), founded in 1998, also researches and develops potential drugs to treat Alzheimer's disease, depression, schizophrenia, vascular dementia, mild cognitive impairment, and memory impairments associated with aging. The company (in alliance with big pharma partners, including Roche) is looking for compounds that will modulate the L-type calcium channel. Such compounds modulate neuronal calcium channels and regulate calcium ion flow into neurons, preventing the deleterious consequences of excessive levels of calcium entry. One of the benefits of this modulation is that neurons remain more responsive to incoming signals, counteracting the reduced activity that normally occurs during aging. In March 2005, at least one such compound (MEM-1003) had entered clinical trials. Research workers at Memory are also looking at an unusual use of phosphodiesterase type IV inhibitors for mild cognitive impairment.[31] One such compound, MEM 1414, has been reported as effective in hippocampus-dependent memory tasks over a very wide dose range. Memory also has a project examining the use of nicotinic $\alpha_7$ receptor agonists, including MEM 3454, for schizophrenia and Alzheimer's disease.[31]

*Newron Pharmaceuticals*. Newron Pharmaceuticals is a 1999 spinout formed from the closure of the former Pharmacia & Upjohn's research center in Milan (Italy). Newron is a private biopharmaceutical company funded privately – more than €25 million was injected in two rounds of financing led by Atlas Venture and Apax Partners in 2002. This funding has been supplemented by another €23 million in 2005. Newron focuses on the discovery and development of diagnostics and therapeutics of the nervous system, particularly epilepsy, neurodegenerative disorders, and pain. The company runs preclinical research up to the early phases of clinical development, then pursues partners for continued development. The lead compound, safinamide **(29)**, was licenced from Pharmacia & Upjohn and is a sodium-channel blocker, calcium-channel modulator, glutamate release inhibitor, and a dopamine metabolism modulator (monoamine oxidase B inhibition/dopamine uptake inhibitor), with potential for the treatment of epilepsy, Parkinson's disease, and restless-legs syndrome.




**29**

### 1.13.6.5 Genitourinary Tract Diseases and/or Reproductive Health Companies

*Ardana Bioscience*. Ardana (Edinburgh, Scotland) was formed in 2000 and has exclusive rights to commercialize research developed by the Medical Research Council Human Reproductive Sciences Unit (Edinburgh, Scotland). Ardana became a public company in 2005 as a result of a London IPO, raising $38 million. Products and projects include: a testosterone replacement therapy for male hypogonadism (confirmed by clinical features and biochemical tests), which was launched in June 2004; a compound for prostate cancer, benign prostatic hyperplasia, and infertility related to endometriosis and uterine fibroids; and a compound to prevent premature ovulation in ovulation induction.[32]

### 1.13.6.6 Metabolic Disease Companies

*Metabolex*. Metabolex (Hayward, CA), founded in 1991, is a private biopharmaceutical company focused on developing treatments for diabetes and related metabolic disorders. Metabolex works closely with Pfizer and Yamanouchi to develop treatments for type 2 diabetes, selecting targets from its proprietary database. With Pfizer, a deal was struck whereby Metabolex was to receive more than $50 million to develop its β-cell program designed to target insulin secretion defects. With Yamanouchi, a program began in March 2002 to develop drugs for type 2 diabetes, insulin resistance, impaired glucose tolerance, and obesity by evaluating 100 targets selected from Metabolex's database. Metabolex is developing MBX-2044, the lead in a series of peroxisome proliferator-activated receptor modulators and insulin sensitizers for the potential treatment of type 2 diabetes. In March 2005, the drug was shown to be well tolerated in a phase I trial.[33]

*Arexis*. Arexis AB (Molndal, Sweden) is a drug discovery and development company focusing on metabolic and inflammatory diseases, founded by Professors Holger Luthman, Rikard Holmdahl, Leif Andersson, and Dr Vidar Wendel-Hansen (who had common interests in genetics and genomics) in 1999. The company is biology-driven, with proprietary technology and a strong focus on product development, and uses forward genetics for a high-resolution molecular dissection of causative disease mechanisms. A typical project is to enhance the action of bile salt-stimulated lipase, a naturally occurring human enzyme (found in mature pancreas and in mother's milk) with a key function of degrading a large spectrum of lipids in food. For pharmaceutical use, recombinant human bile salt-stimulated lipase will be administered orally and manufactured in a cell culture system.[34]

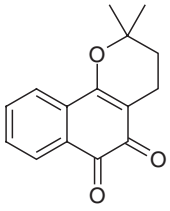
### 1.13.6.7 Musculoskeletal Disease Companies

*The Prostrakan Group*. Prostrakan (Galashiels, Scotland) is the merged entity created between the Strakan Group and the former Aventis spinout SME, Proskelia (Paris, France), created in 2004. Proskelia was the former bone research group of Hoechst Marion Roussel, located at the former Romainville site in Paris (France). Proskelia now forms the research arm of this women's health and musculoskeletal company. In 2005 the Prostrakan Group employed some 280 people, making the combined entity still an SME by definition. The company is essentially European in focus, with projects around two anabolic pathways: bone morphogenetic proteins and the high-bone-mass gene (*LRP5*).[35]

### 1.13.6.8 Oncology Companies

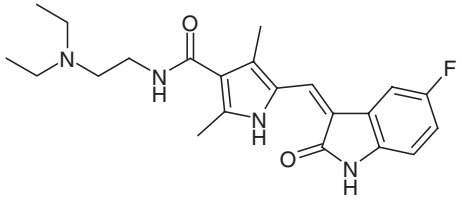
There are many SME companies specializing in drug discovery to treat cancer, reflecting a large area of unmet medical need, and the availability of funding for the research into treatments with major economic potential. Big pharma retains major interest in this therapeutic area, and consequently few spinouts originate from former big pharma research groups.

The perceived ease of clinical development has persuaded several former drug discovery service SME companies to change business model and wholly or partly engage in proprietary therapeutic research in this field, notably Arqule and Array Biosciences. Thus, Arqule (Woburn, MA) is developing ARQ-501 **(30)**, which is a topoisomerase I inhibitor isolated from the lapacho tree that causes cell cycle arrest at G1/S, for potential use in chemotherapy of breast, ovarian, colorectal, prostate, and other cancers. Array Biopharma (Boulder, CO) has investigated the potential of MEK inhibitors for the potential treatment of cancer.



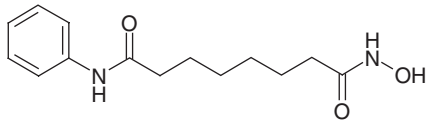

**30**

*Sugen*. One of the original SMEs engaged in discovering inhibitors of kinases as anticancer therapies was Sugen (San Francisco, CA), which was acquired by Pharmacia (now part of Pfizer) in 1999. The former research of Sugen has been responsible for a number of clinical drug candidates now in development by the parent organization. For example, SU-11248 **(31)** is an orally active inhibitor of vascular endothelial growth factor receptor kinase (VEGFR2), PDGFR-β, KIT, and Flt3 tyrosine kinase signaling pathways that is being developed as a potential anticancer agent.



**31**

*Aton Pharmaceuticals*. Aton Pharmaceuticals (Tarrytown, NY) developed cancer drugs based on research by Professor R Breslow of Columbia University Department of Chemistry and Sloan Kettering. In 2004 Merck acquired Aton for its portfolio of drugs, including its clinical candidate SAHA **(32)**, which inhibits histone deacetylase enzymes.



**32**

*Biotica Technology*. Biotica Technology (Saffron Walden, UK) is a spinout from the University of Cambridge (UK) based on intellectual property generated partly in Professor James Staunton's group. Biotica is focused on the production of novel biopharmaceuticals through targeted alteration of biosynthetic pathways leading to polyketides. An initial focus on polyketides as antiinfectious agents appears to have been displaced by potential use in oncology. Biotica has polyketide mammalian target of rapamycin (mTOR) inhibitors, 90 kDa heat shock protein inhibitors and novel angiogenesis inhibitors. Biotica's technology platform comprises methods for the genetic engineering of polyketide synthase and associated postpolyketide synthase genes.

*Cytokinetics*. Cytokinetics, established in 1998 and headquartered in San Francisco (CA), is a biopharmaceutical company focused on the R&D and commercialization of novel small-molecule drugs. In June 2001, Cytokinetics and GlaxoSmithKline entered into strategic collaboration for the R&D and commercialization of novel small-molecule therapeutics targeting mitotic kinesins for applications in the treatment of cancer and other diseases. Cytokinetics and GlaxoSmithKline are developing CK-0238273 (SB-71599), a mitotic kinesin spindle protein inhibitor, for the potential treatment of various cancers. Cytokinetics and GlaxoSmithKline are developing SB-743921, the lead from a series of mitotic kinesin spindle protein inhibitors, for the potential treatment of cancer.

*EiRx Therapeutics*. Another company with an interest in kinases as potential treatments for cancer is genomics-based EiRx Therapeutics (Cork, Ireland), a public (LSE-AIM) company founded in 1999 and researching apoptotic mechanisms of cell death. The company has identified over 200 apoptosis-associated gene targets using its proprietary genomics model system (ALIBI), and has silencing RNA technology.[36]

*GPC Biotech*. GPC Biotech (Munich, Germany), formed in 1997 and headquartered in Munich, Germany, is a publicly owned genomics and proteomics-based company focused on the discovery, development, and commercialization of anticancer drugs – antiinfectives research was abandoned in 2003. The company changed its name to GPC Biotech in March 2000, following its acquisition of US-based SME Mitotix. GPC Biotech acquired all the assets of the insolvent Axxima, a specialist kinase company, in March 2005.

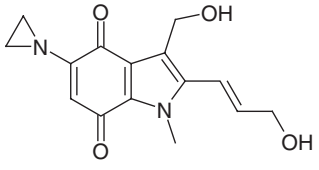
*KuDOS*. KuDOS (Cambridge, UK) is a private oncology company that has access to IP from Professor Stephen Jackson's laboratory at the University of Cambridge (UK). KuDOS and Cancer Research UK are developing lomeguatrib, an alkyltransferase inhibitor (discovered by the Paterson Institute for Cancer Research and Trinity College, Dublin). KuDOS also has interest in an in-licensed (originator De Montfort University) candidate drug, AQ4N, a hypoxia-selective cytotoxic prodrug, as a potential oncology treatment.[37] KuDOS was acquired by AstraZeneca at the end of 2005.

*MethylGene*. MethylGene, formed in 1996 (Quebec, Canada), is an SME engaged in the R&D and commercialization of enzyme inhibitors for the treatment of cancer (and also infectious diseases). The company was formed in 1996 as a

joint venture between Hybridon and three Canadian VC partners. MethylGene has IP in the fields of histone deacetylase inhibitors and DNA methyltransferase inhibitors. Methylgene and MGI Pharma are developing MG-98, a second-generation antisense oligonucleotide which inhibits expression of the DNA methyltransferase-1 gene, for the potential treatment of cancer.

*S*BIO*. S*BIO (*see* Section 1.13.3) is another cancer company, partly funded by Chiron, located in Singapore.[38]

*Spectrum Pharmaceuticals*. Spectrum Pharmaceuticals (formerly NeoTherapeutics) of Irvine (CA), a listed company is now a specialist oncology in-licensing company – the CNS research axis having been curtailed in 2002. Spectrum is developing the former EORTC (European Organisation for the Research and Treatment of Cancer) compound apaziquone **(33)** (first synthesized in 1987) for the potential treatment of bladder cancer and as a radiation sensitizer for solid tumors. Licensed from BMS is elsamitrucin **(34)**, a topoisomerase I and II inhibitor with anti-DNA gyrase activity and an actinomycete fermentation product, for the potential treatment of non-Hodgkin's lymphoma. Spectrum has also licensed in a series of endothelin B agonists from Chicago Labs, which in turn obtained them from the University of Illinois.

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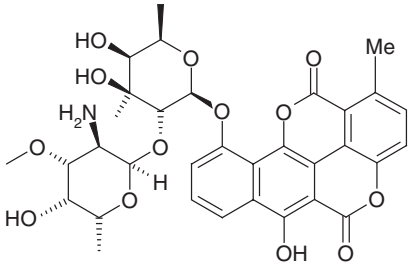


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*Sterix*. Sterix is formerly a spinout of Imperial College of Science, Technology and Medicine, located in Bath (UK). Sterix was focused on steroid-based therapeutics for hormone-dependent cancers, women's health, and other hormone-associated diseases. Sterix was acquired by the French medium-sized pharma company, Ipsen Beaufour, in 2004.

*Strida Pharma*. Strida Pharma, a spinoff from McGill University (Quebec, Canada) and founded in 2002, develops small-molecule therapeutics based on the anticancer target, methylenetetrahydrofolate reductase (MTHFR). Strida used antisense technologies to validate MTHFR as an oncology target.

*Topotarget*. Topotarget (Copenhagen, Denmark), founded in 2000, is a specialist oncology company focused on the discovery and development of small-molecule drugs for cancer. Its lead compound is a topoisomerase II inhibitor for a niche indication of extravasation. Topotarget acquired the Abingdon (UK) oncology SME Prolifix in 2003, along with PXD101, an oncology product with action against histone deacetylase.

### 1.13.6.9 Respiratory Disease and Inflammation Companies

New small-molecule drugs to treat rheumatoid arthritis, inflammatory bowel disease, and respiratory diseases are rare, even from the big pharma stables, some of which (but not all) have abandoned interests in these domains. Bayer's withdrawal from the respiratory therapeutics area, for example, initiated the formation of two spinoff companies by former Bayer scientists (Etiologics, UK: see below) and Aerovance (2004, Berkeley, CA). Aerovance began with two ex-Bayer products, a recombinant human interleukin-4 that is both an antagonist at interleukin-4 and interleukin-13 receptors for severe asthma, and a recombinant human protease inhibitor which inhibits a sodium ion channel, that may be a therapy for cystic fibrosis patients.[39]

*Theravance*. Theravance (formerly Advanced Medicines) of San Francisco, US, although not entirely specialized in the respiratory therapeutic area, has performed major research into long-acting β-agonists and multimer pharmacophore approaches to new respiratory drugs and struck a major deal to codevelop drugs in this domain with GlaxoSmithKline in 2004. Under this agreement, in March 2005, Theravance licensed its novel dual-acting $\beta_2$ antagonist/muscarinic agonist molecules to GlaxoSmithKline.[40]

*Argenta Discovery*. Argenta Discovery (Harlow, UK) is originally a spinout from IC (London, UK) and the former Rhône-Poulenc group at Dagenham. After its merger with Etiologics in 2004, Argenta declared itself an internal discoverer of new drugs for chronic obstructive pulmonary disease by virtue of Etiologics' prior acquisition of the preclinical research group of Bayer, UK, in 2003.[41]

*Avidex*. Avidex (Oxford, UK) is a private drug discovery company which was formed in 1999 as a spinout from Oxford University to exploit technology arising in the Institute of Molecular Medicine. The company focuses on developing

T-cell receptor-based therapeutics for the treatment of cancer and autoimmune diseases. Avidex has a license from Active Biotech for the exclusive development and marketing rights to CD80 antagonists for the potential treatment of autoimmune diseases, including rheumatoid arthritis.[42]

*Topigen*. Topigen (Quebec, Canada) was founded in 2000, and is a biotechnology company engaged in the R&D of antisense drugs for asthma, allergic rhinitis, and other respiratory diseases such as chronic obstructive pulmonary disease.[43]

*CoTherix*. CoTherix (formerly Exhale Therapeutics), based in San Francisco (CA), is a privately held biopharmaceutical company and was formed in February 2000 to commercialize research performed at Columbia University (New York). CoTherix has exclusive US development and marketing rights to iloprost, a synthetic prostacyclin analog for the treatment of primary pulmonary hypertension, first developed by Schering. Before the company changed its name, Exhale was focused on developing therapies to treat inflammatory lung disease.[44]

## 1.13.7 Small- or Medium-Sized Enterprises That Specialize in Drug Discovery in Specific Target Classes or Disciplines

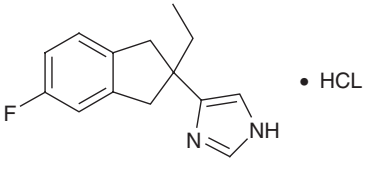
### 1.13.7.1 G Protein-Coupled Receptor Companies

*Arena Pharmaceuticals*. Arena Pharmaceuticals (San Diego, CA), founded in 1997, specializes in the discovery and development of therapeutics, particularly those that act at orphan GPCRs using its constitutively activated receptor technology (and melanophore technology. Arena is developing a series of orally active, small-molecule 5HT2c agonists for the potential treatment of obesity and diabetes, and a 5HT2a inverse agonist, for the potential treatment of insomnia. Arena has agonists of the GPCR 21AX for the potential treatment of inflammatory diseases, including asthma, pulmonary fibrosis, and inflammatory bowel disease. Arena Pharmaceuticals and Ortho-McNeil are investigating orally active agonists of the GPCR 19AJ for the potential treatment of type 2 diabetes.[45]

*7TM Pharma*. 7TM Pharma (Horshoom, Denmark) is investigating a series of antagonists of the CRTH2 receptor (chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells) for the potential treatment of allergy, asthma, and inflammation.[46] 7TM has also identified a ureidobenzamide compound as a melanin-concentrating hormone receptor type 1 antagonist. The company also has an interest in ghrelin receptor agonists as potential treatments for obesity.[47]

*Adenosine Therapeutics*. Adenosine Therapeutics (Charlottesville, WV) is a biotechnology company focused on the R&D of agonists and antagonists of adenosine receptor subtypes for medical imaging and for the potential treatment of inflammation, chronic obstructive pulmonary disease, diabetes, asthma, Parkinson's disease, pain, angiogenesis, and epilepsy.[48]

*Juvantia Pharma*. Juvantia Pharma (Turku, Finland) was founded in 1997. It is a company that discovers and develops small-molecule pharmaceuticals active in transmembrane signaling via GPCRs. Its programs include developing treatments for neurodegenerative diseases, mental disorders, and vascular wall disorders. Projects include an $\alpha_2$ adrenoceptor antagonist (fipamezole) **(35)**, for the potential treatment of Parkinson's disease, and a G protein-coupled $\alpha_{2b}$ adrenoceptor antagonist for the potential treatment of cardiovascular ailments.[49]

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### 1.13.7.2 Chemokine Receptor Companies

ChemoCentryx (San Francisco, CA) is a private company engaged in seeking therapeutics for infectious and inflammatory diseases based on the biology of chemokines and chemokine receptors. ChemoCentryx has products against the CCR9 receptor for inflammatory bowel disease, the CCR2 receptor for cardiovascular indications, and the CXCR4 and CXCR7 receptors for cancer. In addition, ChemoCentryx has partnered programs: a CCR1 antagonist for autoimmune disorders with Forest Laboratories and a small molecule targeting CXCR3 with Tularik (now Amgen).[50]

### 1.13.7.3 Ion Channel Companies

Xention (Cambridge, UK) is a 2002-founded company that acquired the CeNeS ion channel drug discovery business, Channelwork. This included the AutoPatch high-throughput target-screening technology, an automated patch-clamp system. Xention has patented novel thienopyrimidine derivatives, their salts, and their use as potassium channel inhibitors for the prevention and treatment of arrhythmia. The compounds are particularly useful as Kv1.5 channel inhibitors.[51]

### 1.13.7.4 Kinase Enzyme Companies

Kinases are a very popular target class for drug discovery, particularly in the oncology field, and also in inflammation. Consequently, many companies already discussed as oncology specialty companies could have equally been placed in this section.

*Sugen*. Sugen (San Francisco, CA) was a major independent SME player in kinases until acquired by Pharmacia (now part of Pfizer) in 1999.

*Activx*. Activx (San Diego, CA) is a company specializing in kinase and protease drug discovery. Activx Biosciences originally licensed technology from Scripps Research Institute that formed the basis of its proteomics platform. Activx is now a subsidiary of the Japanese company Kyorin.[52]

*Axxima*. Axxima (Munich, Germany) specialized in research into kinases, but was subsumed into GPC Biotech AG, a specialist anticancer company, in March 2005.[53]

*Cellular Genomics*. Cellular Genomics (Branford, CT) is a company specializing in the fields of functional genomics, target validation, and drug discovery. Among its assets, CGI has exclusive licenses to proprietary gene and protein analysis technologies from Yale and Princeton Universities. Cellular Genomics has generated lead series of kinase inhibitors that demonstrate concurrent inhibition of a critical set of angiogenesis and cancer-related kinases, including VEGFR, Tie2, and c-Kit.[54]

*PIramed*. PIramed (2003, Slough, UK) was formed as a spinout of several academic cancer research organizations such as the Ludwig Institute for Cancer Research, Cancer Research UK, and the Institute of Cancer Research UK. PIramed's drug discovery research is on signal transduction inhibitors, principally the superfamily of lipid kinases, exemplified by phosphatidylinositol 3-kinase.[55]

*Upstate Biotechnology*. Upstate Biotechnology (a subsidiary of Serologicals of Atlanta (GA) offers a broad-spectrum kinase-screening service to the industry – showing kinase selectivity in kinase projects is often required due to the presence of approximately 600 kinase enzymes in the superfamily.[56]

### 1.13.7.5 Zinc Finger-Binding Domain Companies

*Sangamo Biosciences*. Sangamo (Richmond, CA), specializes in finding drugs that act on zinc finger-binding domains, for example drugs that upregulate VEGF and VEGF receptors to treat coronary artery disease and peripheral arterial disease. Sangamo has also entered into a joint collaboration with Edwards to develop ZFP-Therapeutics for the downregulation of phospholamban, a gene target with a role in calcium flux in heart muscle and that is believed to be directly involved in congestive heart failure.

### 1.13.7.6 Antibody, Protein, siRNA Therapy, and Gene Therapy Companies

Given the success that SME companies specializing in new biological entities have had in becoming powerful companies in the pharmaceutical industry, it is instructive to see what new companies in this field are doing.

*Abgenix*. Abgenix (Fremont, CA) was incorporated in June 1996 as a wholly owned subsidiary of Cell Genesys, but subsequently became independent. Its valuation in February 2005 was $774 million, ranking it well below Biogen Idec, but better than many small-molecule companies. Abgenix uses its XenoMouse technology to enable the rapid generation of high-affinity, fully human antibody product candidate medicines. Abgenix has alliances with AstraZeneca (36 cancer targets), with Sosei (CRTH2), with Amgen (panitumumab – a human monoclonal antibody against the epidermal growth factor receptor for use as a monotherapy and in combination with other agents in the treatment of solid tumors), and with CuraGen (CR-002 – a fully human monoclonal antibody that specifically recognizes and blocks the active form of platelet-derived growth factor D, for the potential treatment of immunoglobulin A nephropathy).

*Alligator Bioscience*. Alligator Bioscience (Lund, Sweden) was founded in 2001, and develops new and optimizes existing therapeutic and diagnostic products. In the Alligator pipeline are potential treatments for rheumatoid arthritis; for acute myocardial infarction; and for acute inflammation. Alligator has a proprietary Fragment-INduced Diversity

(FIND) technology to conduct protein optimization. This technology involves fragmenting DNA encoding a particular protein of interest, recombining it and testing expressed proteins for improvement over the original.

*Domantis*. Domantis (Cambridge, MA, US, and Cambridge, UK), a private company founded in 2000 using IP from Sir Greg Winter and Dr Ian Tomlinson from the Medical Research Council Laboratory of Molecular Biology, is a drug discovery company developing antibody molecules. Human domain antibodies are therapeutic molecules that are small and highly stable, but, like human antibodies, can be designed to have specificity and high affinity for the biological target of interest. Domantis has more than a dozen proprietary domain antibody therapeutic programs, primarily in the fields of inflammation and oncology, including human domain antibodies that neutralize cytokines.[57]

*Medarex*. Medarex (Princeton, NJ), a public US company, was founded in 1987 and is a biopharmaceutical company focused on the discovery and development of fully human antibody-based therapeutics to treat life-threatening and debilitating diseases, including cancer, inflammation, autoimmune, and infectious diseases. Using its UltiMab human antibody development system, the company can create human antibodies using transgenic mice. Medarex has collaborations with BMS on the investigational fully human anti-CTLA-4 antibody, MDX-010, which is in clinical trial for metastatic melanoma, and with Amgen.[58]

*MorphoSys*. MorphoSys, based in Martinsried/Planreg, Germany, was founded in 1992 and is a biotechnology company focused on the development of antibody-based products for treating infectious diseases, cancer, and inflammation. The company's proprietary technology includes the Human Combinatorial Antibody Library. Projects declared on the Morphosys website include MOR 101 and MOR 102, which are fully human HuCAL Gold antibodies directed against the inflammation target intercellular adhesion molecule-1, also known as CD54. MOR 101, a Fab fragment, will be developed to treat skin burn (deep dermal burn), and MOR 102, an immunoglobulin G antibody, is intended for psoriasis.[59]

*XOMA*. XOMA (Berkeley, CA) is a biopharmaceutical company that develops and manufactures genetically engineered protein, peptide, and monoclonal antibody pharmaceuticals. Targets include cancer, immunological disorders, inflammatory disorders, and infectious diseases. Its primary drug development platform is bactericidal/permeability-increasing protein, a human host defence protein with multiple antiinfective properties. With its partners Genentech and Serono, XOMA has now marketed a new biological entity: efalizumab, a therapy for continuous control of chronic moderate-to-severe plaque psoriasis.

*Cambridge Antibody Technology*. Cambridge Antibody Technology (CAT; Cambridge, UK) began life as a subsidiary of Peptide Technology (now Peptech) in January 1990. CAT was spun-off as a freestanding entity in 1996, and in 1997 completed its IPO. CAT develops novel human monoclonal antibody-based therapeutic products based on its proprietary antibody phage display technology platform, as well as licensing its technology and capabilities to others to develop products. CAT's first product, adalimumab, was isolated and optimized in collaboration with Abbott and has been approved for marketing as a treatment for rheumatoid arthritis in 51 countries. CAT also has a broad collaboration with Genzyme for the development and commercialization of antibodies directed against transforming growth factor-ß, a family of proteins associated with fibrosis and scarring.[60] In May 2006, CAT was under offer to be acquired by AstraZeneca.

*Isis Pharmaceuticals*. Isis Pharmaceuticals (Carlsbad, CA) was founded in 1989 in order to explore the potential of antisense technology. The company's antisense drugs are designed to treat bone, cardiovascular, infectious, metabolic, and inflammatory diseases, as well as cancer. A research area where Isis has a strong focus is ribonuclease H. Isis research workers have published on a small interfering RNA motif consisting entirely of 2′-O-methyl and 2′-fluoro nucleotides, which display enhanced plasma stability and increased in vitro potency.[61]

*Oxford BioMedica*. Oxford BioMedica (Oxford, UK) was established in 1995 as a spinout of Oxford University and is a biopharmaceutical company involved in developing gene therapy treatments with a focus on oncology and neurotherapy. Oxford BioMedica has developed a lentivirus, lacking many accessory genes, which is claimed to cause fewer unwanted side effects when used as a gene therapy. Oxford BioMedica is investigating lentivirus vectors for potential use in gene therapy. The vectors have been used in the company's ProSavin, ChanEx, and ProCaStat candidate gene therapies for Parkinson's disease, cystic fibrosis, and prostate cancer, respectively.

### 1.13.7.7 Vaccine Companies

*Antigen Express*. Antigen Express (Worcester, MA) has been a subsidiary of Generex Biotechnology Corporation (Toronto, Canada) since 2003. The company's technology focuses on modulating immune responses mediated by T-helper cells. Antigen is developing vaccine formulations based on the expression and use of the invariant chain protein – a regulator of antigen presentation by major histocompatibilty class molecules – for the treatment of breast and prostate cancer, HIV infection, and severe acute respiratory syndrome (SARS). Development of a smallpox vaccine is being conducted in 2005 with Emory University (Atlanta, GA) and Imperial College (London).

*Microscience*. Microscience is an IC (London) spinout specializing in vaccine research (**Table 2**). In 2005, the Wellcome Trust charity awarded Microscience an award of $3.6 million, the largest it has ever made, for the development of its drinkable typhoid vaccine.

*Oxxon Therapeutics*. Oxxon Therapeutics (formerly Oxxon Pharmaccines), a biotechnology company developing immunotherapeutics for cancer and chronic infectious diseases, is headquartered in Oxford (UK) but also operates in Boston (MA). Its IP is based on its PrimeBoost technology.[62] Oxxon has established five development programs in hepatitis, melanoma, and HIV, two of which are in phase II clinical trials.[63]

## 1.13.8 Small- or Medium-Sized Enterprises That Focus on Providing Services on Part of the Drug Discovery Value Chain

### 1.13.8.1 Target Validation Companies

*DanioLabs*. DanioLabs was established in May 2002 and is located in Cambridge, UK. A major part of the DanioLabs platform involves the use of zebrafish as an experimental species to enable the identification of in vivo activity of experimental compounds.

*Deltagen*. Deltagen is a privately funded biotechnology company focused on using knockout mouse molecular genetics to unlock the in vivo function of novel genes in order to develop new therapeutic targets. Deltagen has agreements with Roche, Merck, Tularik (now Amgen), and Pfizer to provide this service.

*DeVgen*. DeVgen, founded in 1997 and headquartered in Ghent, Belgium, achieved an IPO in June 2005 and is a privately owned, genomics-based, biotechnology company, focused on the use of the model organism *C. elegans* in target validation in drug discovery.

*Galapagos*. Galapagos (Cambridge, UK) was established in 1999 and is a functional genomics company. Galapagos has two technologies based on the PER.c6 adenoviral vector system, and a high-throughput miniaturization and automation platform. Galapagos achieved an IPO in May 2005 and acquired BioFocus (Saffron Walden, UK) in October 2005 establishing itself as a broad-based target and drug discovery company.

*Jurilab*. Jurilab (Kuopio, Finland) is a privately owned company founded in 1999 from the Research Institute of Public Health at the University of Kuopio, Finland. Jurilab has developed a proprietary method of identifying and verifying DNA variations known as hierarchical phenotype-targeted sequencing, a means of finding new functionally important mutations in humans and other species. The technology has been used to identify novel variants, associated with prostate cancer and type 2 diabetes, which have the potential to be used in both predictive tests and as therapeutic targets.

*Lexicon Genetics*. Lexicon Genetics (The Woodlands, TX) was founded in 1995 with gene targeting and embryonic stem cell technologies IP from Baylor College of Medicine. Lexicon uses this proprietary gene knockout technology to identify suitable targets from the human genome and then investigates ligands for these proteins to develop treatments for metabolic disorders, cardiovascular diseases, immunological disorders, neurological disorders, and cancer. In July 2001, Lexicon completed a merger with the chemistry service company Coelacanth, which has since become the drug discovery arm of the original target discovery company.

*Paradigm Therapeutics*. Paradigm Therapeutics is a discovery company focused on novel drug targets identified from the human genome. Paradigm was started as a spinout company from the University of Cambridge and it has since established a platform based on mouse transgenic technology for defining the biological functions of previously uncharacterized human druggable proteins. Paradigm has a collaboration with Medivir to identify novel protease drug targets and to discover small-molecule protease inhibitor drugs. Paradigm acquired a chemistry arm in 2005 (Amedis Pharmaceuticals).[64]

*Pharmagene*. Pharmagene (Royston, Cambridge) was founded in April 1996 as the first UK company to focus entirely on the use of human tissue for drug discovery and focusing on expression and function of genes and gene products. It has offered its target validation service TargetEvaluator to provide information on the expression of genes in a range of diseased and nondiseased tissues to a large number of companies.[65]

### 1.13.8.2 Computer-Aided Drug Design Companies

Computer-aided drug design plays a major part in hit-finding activities (in silico screening by docking of ligands into protein cavities), optimization, and prediction of potencies and properties of molecules. Computer-aided prediction is now often sufficient to be a guide to the value of making a compound or not.

*4SC*. 4SC is a company based in Martinsried (near Munich, Germany), founded in 1997, which uses its technologies to predict and rank biological properties. Martinsried has provided such services for major companies like Sanofi-Aventis and for smaller companies like Estève (Spain).

*Accelrys*. Accelrys (San Diego, CA) has been a long-standing supplier of both software and service to the worldwide pharmaceutical drug discovery. It has undergone a series of name changes and acquisitions, and its products have formerly been marketed under the Molecular Simulations, Synopsis, Pharmacopeia, and Oxford Molecular names.[66]

*Cresset Biomolecular Discovery*. Cresset Biomolecular Discovery (Letchworth, UK) is a recently created SME with a field-based virtual screening technology, which has been used, for example, by partners such as the James Black Foundation (London) and BioFocus.[67]

*De Novo Pharmaceuticals*. De Novo Pharmaceuticals is a spinout of the pharmacology department at the University of Cambridge, UK (2000), and has proprietary computational software for structure-based drug design to create novel, patentable lead molecules as candidates for drug development.[68] The scientists at De Novo have recently advanced the understanding of hydrophobic groups in drug–protein docking interactions.[69]

*Inpharmatica*. Inpharmatica (London, UK) was spun out of University College London in 1998, with the aim of identifying novel drug targets by integrating computer-modeling techniques with genomics data. As well as providing such services to other drug discovery players, to signal the success of its techniques, workers at Inpharmatica have reported the identification of the molecular basis for the biological role of nicastrin, a potential new protein drug target for Alzheimer's disease. Using its proprietary database, the company found that a portion of the protein has significant similarity to some known proteases, suggesting that this region confers peptide-binding function to nicastrin.[70]

*Libraria*. Libraria (San Jose, CA), has proprietary software to capture and evaluate structure–activity and chemical synthesis relationships to automate the recognition of relevant patterns that permit the design of new patentable small molecules. The company's initial focus is on kinases.

*Tripos*. Tripos (St Louis, MO) is a longstanding (founded 1979) SME supplier of computer-aided drug design services and also works in chemistry drug discovery using its UK subsidiary Tripos Discovery Research. Most recently, Tripos has pioneered the idea of 'lead hopping' to get patentable series.

### 1.13.8.3 Hit-Finding Companies

A large number of companies offer services to the industry in hit-finding techniques. In 2005, those companies offering hit-finding technologies and products (including companies specializing in providing large libraries of novel compounds made by automated methods to big pharma) include DPI (from June 2006 BioFocus DPI), Evotec-OAI, Array Biopharma, Pharmacopeia (Princeton, NJ), and Albany Molecular (Albany, NY). However, commodification of this area is seeing a profound shift of service provider companies to the Far East, either from indigenous organizations (Dr Reddy's subsidiary, Aurigene (Bangalore, India), GVK Bio (Hyderabad, India), Wuxi Pharmatech (Shanghai, China)), or by the previously established companies electing to set up subsidiaries taking advantage of high-technology – and cheaper – workforces (Albany Molecular, Singapore). The apparent improvement of the ability of companies to enforce IP rights in India and China is partly responsible for the increased shift in outsourcing of drug discovery activities to these countries. One consequence of this shift has been the willingness for some US service providers to set up satellite operations in India or in Singapore (Pharmacopeia) to take advantage of reduced cost bases in competitive markets.

High-technology biological screening engines have long been sourced from expert engineering companies: Technology Partnership (Melbourn, UK) formed a consortium with Rhône-Poulenc and AstraZeneca to develop its laser-screening engine for cellular screening. This instrument is in competition with another SME-inspired device, the optical high-throughput screening engine developed by Axon Instruments (which was acquired on July 1, 2004 by Molecular Devices (Union City, CA)). Developing this theme, SMEs have continued to develop difficult screening technologies, particularly ion channel screening, where the required personnel with biophysics disciplines are rare in typical drug discovery companies; these include CeNeS (Cambridge, UK) and Axon Instruments (CA). The latter has developed two products for ion channel screening: (1) a parallel electrophysiology system in which ion channel activity in eight oocytes at a time can be recorded automatically; and (2) an instrument for the parallel recording of ion channels in mammalian cell lines using the patch-clamp technique.

SME companies performing high-throughput screening services include BioFocus Discovery and also Evotec Technologies (an affiliate of Evotec-OAI) (Germany). Evotec pioneered ultrahigh-throughput screening in the mid-1990s; development was supported by a consortium including GlaxoSmithKline and Novartis. Evotec has performed contract high-throughput screening on targets from Novartis.[71]

### 1.13.8.4 Hit and Lead Optimization Companies

Companies offering services in medicinal chemistry and biological screening include Cerep (France), Discovery Partners International (DPI) (San Diego, CA), Array Biosciences (Boulder, CO), Albany Molecular (Albany, NY), Pharmacopeia

(US), BioFocus DPI (Saffron Walden, UK), Argenta Discovery (Harlow, UK), Evotec-OAI (Hamburg, Germany and Oxford, UK) and Nikem (Milan, Italy). Big pharma partners include GlaxoSmithKline (Nikem, Argenta), J&J (BioFocus DPI), and Novartis (Argenta Discovery). In general, big pharma outsources such activities because of internal capacity constraints, rather than a perceived lack of technology – the critical factor is generally recognized that medicinal chemistry optimization is a stage where experience is very valuable. To this end, companies like Biofocus Discovery have concentrated on projects where substantial in-house expertise has been built up – projects involving kinase targets, ion channel targets, and 7-TM targets. In some cases, niche technology areas can be acquired by SMEs performing contract drug discovery. Big pharma has largely abandoned natural products as a source of hits and drugs in the late 1990s; nonetheless, natural products SMEs exist and in one case (Biofrontera), the company has recently been acquired by DPI (March 2005).[72] It may be that natural product research will be kept alive in the future by specialist SME companies rather than in big pharma research centers.

#### 1.13.8.5 Drug Candidate Validation Companies

Companies offering expert pharmacological validation that compete with established major players include Renasci (Nottingham, UK)[73] in metabolic, obesity, and CNS disease areas, Oncodesign (Dijon, France)[74] in oncology, and Argenta Discovery[41] in respiratory disease.

#### 1.13.8.6 Other Technology Service Providers

A huge number of other companies offer services to those interested in drug discovery (in fact there are few, if any, disciplines that cannot be purchased). Some important adjunct service providers are listed. These include protein x-ray crystallography to aid drug discovery from crystalline drugable targets. Some examples of structural biology companies are: (1) Astex Technologies, Cambridge, UK, a structural biology company formed in July 1999 that has recently moved into proprietary oncology drug discovery[75]; (2) Syrrx (1999, San Diego, CA) with internal IP in oncology targets including histone deacetylase – this company was purchased outright by Takeda of Japan in 2005; (3) Crystal Genomics (Korea)[76]; (4) Structural GenomiX (San Diego, CA)[77]; and (5) Plexxicon (Berkeley, CA). Plexxicon, like many service companies, has also moved into proprietary drug discovery. Plexxicon has a c-Kit inhibitor developed project in collaboration with Phenomix for the treatment of cancer and inflammation.[78]

Custom radiosynthesis to assist in compound validation can be offered by SMEs like Selcia (Ongar, UK), which became independent of its former parent, Scynexis in 2006.

### 1.13.9 Value of Small- or Medium-Sized Enterprises in Drug Discovery

#### 1.13.9.1 The Last 10 Years

An analysis of the effect that SMEs have had on drug discovery, of course, should be taken from the patient point of view. It is difficult to give an overall assessment of which recently launched drugs have had any form of input from an SME organization. It is, however, possible to perform an analysis of all drugs that have reached the market in the past 10 years for those whose IP originated in an SME. This can be performed by analyzing the chapters entitled "To market, to market" in the 10 years' editions of *Annual Reports in Medicinal Chemistry* from 1993 to 2002.[79–88]

The survey of the origins of new drugs over 10 years between 1993 and 2002 shows (**Table 5** and **Figure 1**) that the proportion of new drugs originating from the laboratories of big/traditional pharma has stayed steady at around 50–75% depending on individual company. The proportion of new drugs originating from the biotech sector – companies which are SMEs, or were SMEs when patents were filed – has grown substantially to 25–33%. Academic sources of drugs remain steady at 5–10%. The sector that has contracted is that of the small pharma organization, once a subsidiary of a larger conglomerate or pharmaceutical manufacturing or generics company. Many such Japanese companies were sources of new drugs in the early part of these 10 years. It should be noted that, over the years surveyed, the majority of the new drugs that were invented by SMEs were brought to the market by traditional pharma companies (after licenses were taken to third-party products or the originating SME companies were acquired).

Although the contribution of SMEs to drug discovery is clear, a similar analysis (not shown) over 1993–2002 reveals that few products invented by SMEs are actually marketed by them, particularly in the early years of a company, and when marketing has become viable, most such SMEs have become FIPCOs in their own right – Amgen, Genentech, Serono, etc. For most SMEs, the route to market of their precious candidate drugs still lies with the traditional pharma companies having licensed the product or acquired the company.

**Table 5** NCEs/ new biological entities (NBEs) 1993–2002 as reported by *Annual Reports in Medicinal Chemistry 1994–2003*, showing the origin of each individual drug

| *Year* | *Number originating in big/traditional pharma* | *Number originating in biotech-type SMEs* | *Number originating in academic laboratories* | *Number originating in other types of organization*[a] | *Total number of new drug launches* |
|---|---|---|---|---|---|
| 1993 | 25 | 4 | 2 | 12 | 43 |
| 1994 | 29 | 5 | 1 | 9 | 44 |
| 1995 | 25 | 3 | 0 | 7 | 35 |
| 1996 | 29 | 7 | 0 | 2 | 38 |
| 1997 | 30 | 4 | 2 | 3 | 39 |
| 1998 | 23 | 3 | 0 | 1 | 27 |
| 1999 | 16 | 15 | 1 | 3 | 35 |
| 2000 | 19 | 10 | 3 | 3 | 35 |
| 2001 | 13 | 9 | 3 | 0 | 25 |
| 2002 | 26 | 5 | 2 | 1 | 34 |

[a] Typically this covers generic laboratories, pharmaceutical manufacturing companies that have had R&D laboratories attached, pharmaceutical subsidiaries of larger, broader organizations like Nippon Flour Mills, and small FIPCO traditional pharma companies, many of which have since been acquired or merged.

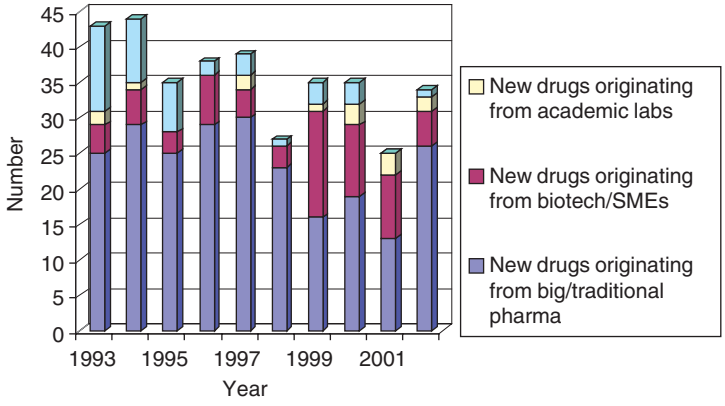


**Figure 1** Graph of NCEs/NBEs 1993–2002 as reported by *Annual Reports in Medicinal Chemistry* 1994–2003, showing the origin of each individual drug.

At the time of writing (2005), the largest pharmaceutical company in the world was Pfizer. An analysis of its 2005 R&D pipeline in terms of compound origin (Table 6) allows a crude estimate that some 10% of the products that Pfizer might make available to patients in the future might have been invented in SME/biotech companies.

### 1.13.9.2 Summary

When the first edition of *Comprehensive Medicinal Chemistry* was being written, the majority of drug discovery was performed in the established large and small pharma, with no company having over 4% market size. Companies put into clinical trials drugs that were either discovered by the in-house teams of chemists, or cross-licensed between the large companies – little cross-licensing occurred before the clinical development stage. The companies were usually traditionally located close to their industrial roots, often relatively far apart geographically.

The situation in 2005 is vastly different. The impact of mergers since 1990 has created mammoth companies (SmithKline and Beecham, Wellcome, and Glaxo, all now part of GlaxoSmithKline; Warner Lambert, Pharmacia, and

**Table 6** Product origins for 2005 Pfizer R&D projects by therapeutic area, analyzed from data reported by the Investigational Drug Database IDDB3

| *Therapeutic area* | *Originated with Pfizer and acquired traditional pharma subsidiaries* | *Originated with traditional pharma* | *Originated with universities/ academic groups* | *Originated with biotech* | *Total* |
|---|---|---|---|---|---|
| Oncology | 61 | 2 | 6 | 12 | 61 |
| Cardiovascular | 60 | 6 | 2 | 8 | 76 |
| Neurology | 50 | 8 | 0 | 5 | 63 |
| Mental health | 39 | 5 | 0 | 2 | 46 |
| Musculoskeletal | 35 | 4 | 1 | 0 | 40 |
| Nonviral antiinfectives | 31 | 4 | 0 | 4 | 39 |
| Metabolic disorders | 28 | 2 | 1 | 4 | 36 |
| Respiratory | 22 | 5 | 1 | 8 | 36 |
| Gastrointestinal | 22 | 5 | 1 | 4 | 32 |
| Endocrine | 18 | 7 | 1 | 4 | 30 |
| Pain/anesthesia | 24 | 6 | 0 | 1 | 31 |
| Genitourinary and renal | 24 | 1 | 0 | 4 | 29 |
| Blood disorders | 19 | 0 | 1 | 3 | 23 |
| Viral infections | 11 | 2 | 1 | 5 | 19 |
| Dermatologicals | 12 | 1 | 1 | 4 | 18 |
| Immune disorder | 13 | 2 | 0 | 2 | 17 |
| Sensory organs | 9 | 0 | 1 | 6 | 16 |
| Other | 3 | 0 | 0 | 2 | 5 |
| Total projects | 481 | 60 | 17 | 78 | 617 |
| Total drugs at this date (many drugs overlap therapeutic areas) | | | | | 387 |

http://www.iddb.com/

Pfizer all now being known as Pfizer). However, the combination of the major pharmaceutical companies has spawned a whole host of spinout companies, many in the field of drug discovery. In addition, many universities recognize the worth of the IP they generate and create spinout SME companies to maximize it. Drug discovery is such a multidisciplinary task that few SMEs ever become proficient in all disciplines, and the majority of SME companies have become intensely interdependent on each other. Such enforced sharing of objectives and ideals has formed the biotech communities of California, Massachusetts, and Medicon Valley, amongst others, and is being emulated in territories like Singapore. Each localized community has provided a forum for intellectual discussions that lead to innovation. This is now being recognized by big pharma which in some cases is moving its own R&D sites to such geographical clusters.

Of the many thousands of biotech/SMEs created in the past 30 years, only two have reached the exalted BIG PHARMA status, but another 10 or so are poised to join that exalted throng. It is salutary that, with the exception of a very few – Celltech (UK: now part of UCB) and Serono (Switzerland: an acquisition target in early 2006) – most are in the US.

In terms of drug discovery, in any one year, up to 10–33% (depending on company) of marketed products have their origins in biotech companies. This is because the vast development sums required to develop and market each potential medicine are usually too large for biotech to resource. As of 2005, big pharma appears to have maintained its traditional preponderance of invention of drugs. Nonetheless, it is likely that biotech will be a significant (if not

ultimately the major) source of new drugs to big pharma and ultimately the patient population. The concept that big pharma may entirely abandon its own research groups and source its compounds entirely from SME/biotech organizations, however, still looks unjustified in 2006, and on the basis of the analysis of Pfizer's pipeline, remains some way from happening.

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## Biography

**Chris G Newton** has been Senior Vice President at BioFocus DPI (a Galapagos company) located both in the Netherlands and in the UK since 2005. Prior to joining BioFocus DPI he was a board member, scientific founder and CSO at the UK service company Argenta Discovery from 2000 to 2005. Before moving to the biotech/service industry sector, Chris spent 21 years in Big Pharma, with the French group Aventis/Rhone-Poulenc Group of companies, holding senior management positions in Medicinal Chemistry, New Lead Generation, and Process Chemistry. He participated in many drug discovery and development programs, and between 1985 and 1987 was project leader for the anticancer agent temozolomide, now on the market with Schering Plough. He has also participated in the discovery of many

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