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# DRUG DISCOVERY PARTNERSHIPS



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and boutique  
western firms  
are forming  
research  
alliances that  
could challenge  
Big Pharma



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# The new drug discovery partnerships

**T**HE town of Goregaon, being a suburb of Mumbai, is one of the most crowded places on earth. A quick tour of the place reveals little that is modern. Yet, behind a mall, concealed inside a commercial complex, is one of the most sophisticated drug discovery research centres in India. Even allowing for the contrasts in Mumbai, the sheer beauty and technical sophistication of the Nicholas Piramal research and development (R&D) centre would strike any visitor. Scientists here work in splendid isolation, shielded from the squalor and congestion only a few metres away. But they are building strong intellectual bridges with labs outside India.

Last week, Nicholas Piramal signed an agreement with the UK drug discovery firm Morvus Technology. Nicholas Piramal will use the technology of Morvus to develop drugs in areas such as cancer, diabetes and arthritis. We could shrug it off as a routine development, but for two reasons. One, it is the third R&D collaboration agreement that Nicholas Piramal has signed with an overseas company in the last year and a half. Two, it is the sixth R&D collaboration between an Indian and a foreign company within the last three months. Several more are being negotiated and will be signed within a few months, say sources. Have the Indian pharma and biotech companies found a new strategy for drug discovery and development?

Do not confuse these collaborations with drug discovery services. A long history of services does not always translate into partnerships. The best example is India's IT industry, which, despite a services track record of two decades, does not have R&D partnerships with foreign companies. The pharma and biotech industries, however, are making the transition to partnerships quickly, spurred no doubt by the different environment there. The list of Indian companies partnering for drug R&D is lengthening and now include large ones like Zydus Cadila, Nicholas Piramal, Ranbaxy, Dr. Reddy's and Biocon. It also includes Orchid, Suven Life Sciences, Connexios and Syngene. The smaller and medium-sized companies seemed to be more enthusiastic about partnering initially, but

Indian and small western companies are together creating a drug discovery ecosystem that could challenge the might of Big Pharma.

By P. Hari

the mood is spreading to everybody now.

Dr. Reddy's licensed its molecule ragaglitazar as early as 1998. In the strict sense, it was a collaboration of sorts. But this story is about partnerships of a different kind, where the initial breakthrough or technology development happens in the West, or at least as a joint effort. The western partner is almost always a small company, usually a recent start-up. The Indian partner brings key inputs to the partnership, apart from an ability to do things cheaply. Finally, the Indian partner stands to get a healthy share of profits, if the drug makes it to the market one day. Small western companies are not keen to collaborate with big multinationals because the spoils may not be shared equitably.

Through careful selection of partners, Indian and small western companies are together creating a drug discovery ecosystem that can challenge the might of the Big Pharma one day. The small western companies add specialised knowledge, often in the area of biology, and the Indian companies bring in skills like chemistry, pharmacology and clinical



## PHARMA

science. So far, the small companies have been licensing their molecules or selling the firm outright to big companies, but partnerships give them an opportunity to stay in the game a bit longer. The big pharmaceutical companies themselves can come into a partnership at some stage — when the drug advances into late clinical trials — but the original partners would have added enough value for them to get large amounts of money.

For Indian companies, purely indigenous discovery is a high-risk project that has a low chance of success. Pure services is a low-risk game with high success rates and margins, but the small size of the market puts a ceiling on expansion. Partnering for drug discovery comes in the middle of these two extremes, a region Indian firms are now only too keen to occupy. The good news is this: western pharma and biotech companies, big or small, are keen to partner with Indian companies and that, too, very early in the discovery value chain.

**A**T the ripe young age of 46, Swaminathan Subramaniam can be considered a drug discovery industry veteran by Indian standards. He had moved back from the US in 1995 to work on the first anti-cancer molecule of Dr. Reddy's. A traditional career path would have seen this doctor-pharmacologist now heading big teams in pharma companies in the country. But he leads a three-member team in the India liaison office of Rheoscience, a Danish biotech start-up. Swami's situation suggests a paucity of high-profile jobs in drug discovery research. But it is also the sign of a new opportunity that is as rewarding as leading large teams.

The Rheoscience office is in a two-storey house in HSR

**PARTNER HUNTERS: Ramani Aiyer and Somesh Sharma of Nicholas Piramal**

SAVIT KUNDU

## Building intellectual bridges

INDIAN COMPANY	OVERSEAS COMPANY	AREA OF ALLIANCE
NICHOLAS PIRAMAL	(1) Biosyntech (2) Institute of Biological Sciences (3) Morvus Technology	Drug delivery systems Vaccine technology Cancer, diabetes, arthritis
ORCHID	Bexel Pharmaceuticals	Diabetes, inflammation and other chronic diseases
DR. REDDY'S	(1) Rheoscience (2) Argenta (3) Clin Tech	Developing anti-diabetes molecule Respiratory diseases Development of anti-cancer compound
CONNEXIOS	Rheoscience	Diabetes
SUVEN LIFE SCIENCES	Eli Lilly	Nervous system disorders
RANBAXY	Medicines for Malaria Ventures	Malaria
BIOCON	CIMAB	Anti-cancer drugs
SYNGENE	Innate Pharmaceuticals	Anti-infectives
ZYDUS CADILA	Onconova	Cancer



# cover story

Rheoscience's **Swami Subramaniam (L)** and **Suri Venkatachalam of Connexios**

**"We are using biology and computation to discover drugs"**

Layout, a residential locality in the outskirts of Bangalore. There is nothing that suggests research here, apart from a few computers. Rheoscience has no intentions of starting a large laboratory in India. Swami's mandate is to find research teams — several ones in fact — in India that can complement the expertise of Rheoscience in Denmark, and then make them work together to discover and develop new drug molecules. It was not a career path he had seen for himself 10 years ago, but then the drug discovery landscape has changed completely in a decade. Despite his low profile, Swami uses his scientific knowledge frequently in his job: "I now focus entirely on science and strategy, and do not worry about organisational politics or administration."

Rheoscience was set up by a few Danish scientists with expertise in obesity and diabetes. It has something nobody in India has: a good animal model for these diseases. Yet Rheoscience is no powerhouse. It lacks computational expertise or the ability to do cell-based assays, not to speak of synthetic chemistry and other key drug discovery skills. Rheoscience had taken up Dr. Reddy's balaglitazone for development last year and had given Aurigene a few projects to screen molecules, an experiment that has resulted in a recent hit. These are good relationships, but Swami recently worked out one at a completely different level with Connexios, a Bangalore start-up with complementary expertise.

Funded by N.S.Raghavan of Nadathur Holdings two years ago, Connexios has developed expertise in computation and molecular biology. It has also worked out, through analysis of research literature, some molecular networks that are active in diabetes and obesity. From this knowledge, it has developed assays — tests — to try out potential drug candidates in cell cultures. The collaboration strategy between the two companies worked itself out easily. Rheoscience has two sets of rats: those with induced obesity (a disease closely linked to diabetes), and those that are resistant to obesity. It also knows a bit about the genes that are active in these rats. Connexios takes this information and compares it with its data on metabolic networks, an exercise that is likely to throw up potential drug targets for obesity and diabetes. The drugs against these targets are tested first in the cell cultures of Connexios, and later on Rheoscience's obese rats, before moving on to clinical trials if they are found good. Says Suri Venkatachalam, director, Connexios: "This partnership gives us access to real biology."

A partnership at this depth and such an early stage in the drug discovery value chain is probably being formed for the first time in India. For the last six or seven years, western companies had used Indian firms primarily as service providers. Indian companies were given a specific job, for which they were paid a specific amount. All the intellectual property belonged to the customer. Once or twice, like in Dr. Reddy's



VENKAT MISHRA

## 1. EARLY DISCOVERY

**Bioinformatics,**  
**biochemistry,**  
genomic technologies,  
high throughput screening

## 2. PRECLINICAL

Toxicity/  
**ADME,**  
animal models,  
pharmacology  
medicinal chemistry  
regulatory

**Black & bold: Strong capabilities**  
Grey: Emerging capabilities



ragaglitazar, molecules were licensed out for development. Indian companies were not partners in this game because their expertise in drug discovery was limited. Now, things are changing rapidly and, as the Connexios example shows, western companies are willing to involve Indian firms at very early stages of drug discovery.

One could go back to see when this trend began, and most observers would cite the partnership of Zydus Cadila with the US company Onconova in 2001 as the first sign. But partnerships came in a trickle for the next two years: Biocon with the Cuban institute CIMAB, Orchid Pharmaceuticals with the US-based Bexel Biotechnology, and Ranbaxy with the Geneva-based Medicines for Malaria Venture (MMV). There were no more partnerships for two years. Then they came in a flurry.

Last year, Nicholas Piramal made a strategic investment in the Canadian firm Biosyntech, a company that makes gels for regenerative medicine. This year, Dr. Reddy's formed two partnerships with UK-based firms: with Argenta for developing Asthma drugs, and Clin Tech for commercialising its anti-cancer molecule. Last month, Syngene, the services subsidiary of Biocon, signed a deal with the Swedish firm Innate Pharmaceuticals to collaborate on drug development. Then came the Nicholas Piramal and Connexios deals.

As we wrote this, more partnerships were being discussed and a few would be announced soon. Nicholas Piramal is discussing another partnership. Two services companies, Advinus and Jubilant Biosys, are also set to sign collaboration agreements soon. All these partnerships involve one novel thing: adding to the work of someone else with no clear idea of

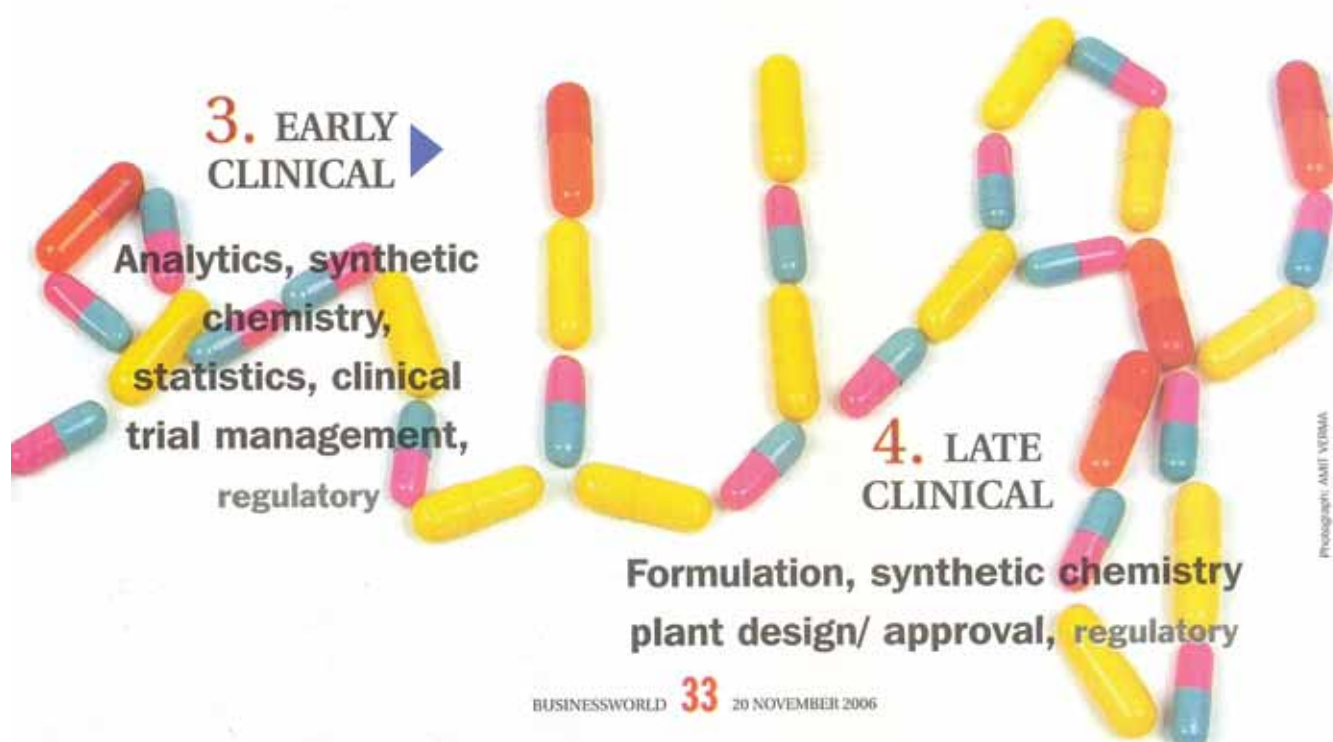
the returns. The money being spent is small in some cases and large in others, but for the Indian company the conceptual leap involved in a real collaboration has been big every time. It is now clear to many Indian companies that doing drug discovery research alone is probably not going to give good results, unless one is very lucky.

**W**HY should a drug discovery company collaborate with another of the same sort? To be more specific, why should a company in Europe or the US, with rich resources to draw from, collaborate with a company in a developing country with little resources in terms of money or experience? The answer lies in the way pharma and biotech industries have evolved in the last decade. Both industries have had to contend with increasing costs and decreasing returns for R&D. More importantly, a burst of scientific discoveries and technological innovation has pushed drug discovery R&D to a level of sophistication that is too broad and difficult for any company to take on single-handedly.

In the old days, only 10 years ago, drug researchers were still using a hit-or-miss approach to drug discovery. There was no real genomics at that time, no bioinformatics, and no systems biology. You could not quickly find out, as they now do using microarrays, the genes that are being switched on and off in a diseased cell. Many genes that are now implicated in diseases were not discovered in 1996. The science of proteomics was in its infancy. Scientists were beginning to talk about rational drug discovery, but the tools to practise this method were far from adequate.

## The India advantage

Where the strengths of Indian companies lie in drug discovery and development.





When science and technology made rapid advances, drug discovery methods changed completely. Meanwhile, Indian companies became known for their synthetic and analytic chemistry. India also became a great place for clinical development. Both these are important aspects of drug development, a stage that comes after the initial discovery. Doing chemistry and clinical development in India would help western companies stretch their resources and put more molecules into development. More importantly, it helps them hit the market faster. "There is enormous benefit in bringing a drug to the market three years earlier," says Rashmi Barbhaiya, CEO, Advinus. "This benefit is more important than saving costs."

This need to use the expertise of Indian companies does not easily translate into partnerships with them. Ideally, a western firm would like to use the Indian company as a services provider because it helps them preserve the intellectual property. Which was why Indian companies were providing services for the past six or seven years, but not treated as partners. A recent study by the British market research firm Cambridge Healthtech Associates showed that three-quarters of the top 50 pharma companies conduct drug development in India. This is more than from any other emerging country, and forms the basis of partnering for drug R&D. As the skills in India grew through services and in-house programmes, the smaller western companies began to see them as partners.

For instance, the UK-based company Argenta has a services arm and an in-house drug discovery unit. The in-house discovery programme focuses on respiratory diseases such as asthma and cystic fibrosis. Like Rheoscience, Argenta has something that no Indian company has: a special laboratory model for lung diseases, and a method for screening molecules for their efficacy against these diseases. It is an expertise that an Indian company would find it difficult to replicate because biology is a poorly developed field in India, if you exclude two or three top-notch government labs. On the other hand, Argenta is too small and focused for it to use its knowledge in a wider sense. So it worked out a partnership with Dr. Reddy's to discover drugs jointly.

The partnership works like this. Argenta will have access to some molecules in the library of Dr. Reddy's. Argenta will test these molecules using its models and screens. If they are found to be good for treating a respiratory disease, Dr. Reddy's will join in their further development. The two companies have agreed to jointly fund the molecules till the proof of concept stage, and then either takes it to the market on its own or licenses out to another company. Dr. Reddy's does have the specialised expertise in respiratory diseases, and without specialised expertise it is difficult to do drug discovery research in depth. Says CEO G.V. Prasad: "Indian companies are only beginning to move into the innovation economy. So it is difficult to find such specialised expertise here." This is also the reason why Nicholas Piramal, in spite of having a sophisticated R&D

**G.V. Prasad, CEO, Dr. Reddy's**

**"Indian firms are only beginning to move into the innovation economy. So it's hard to find such specialised expertise here"**

centre, went to Canada for strategic collaboration with Biosyntech and licensing deals with other companies.

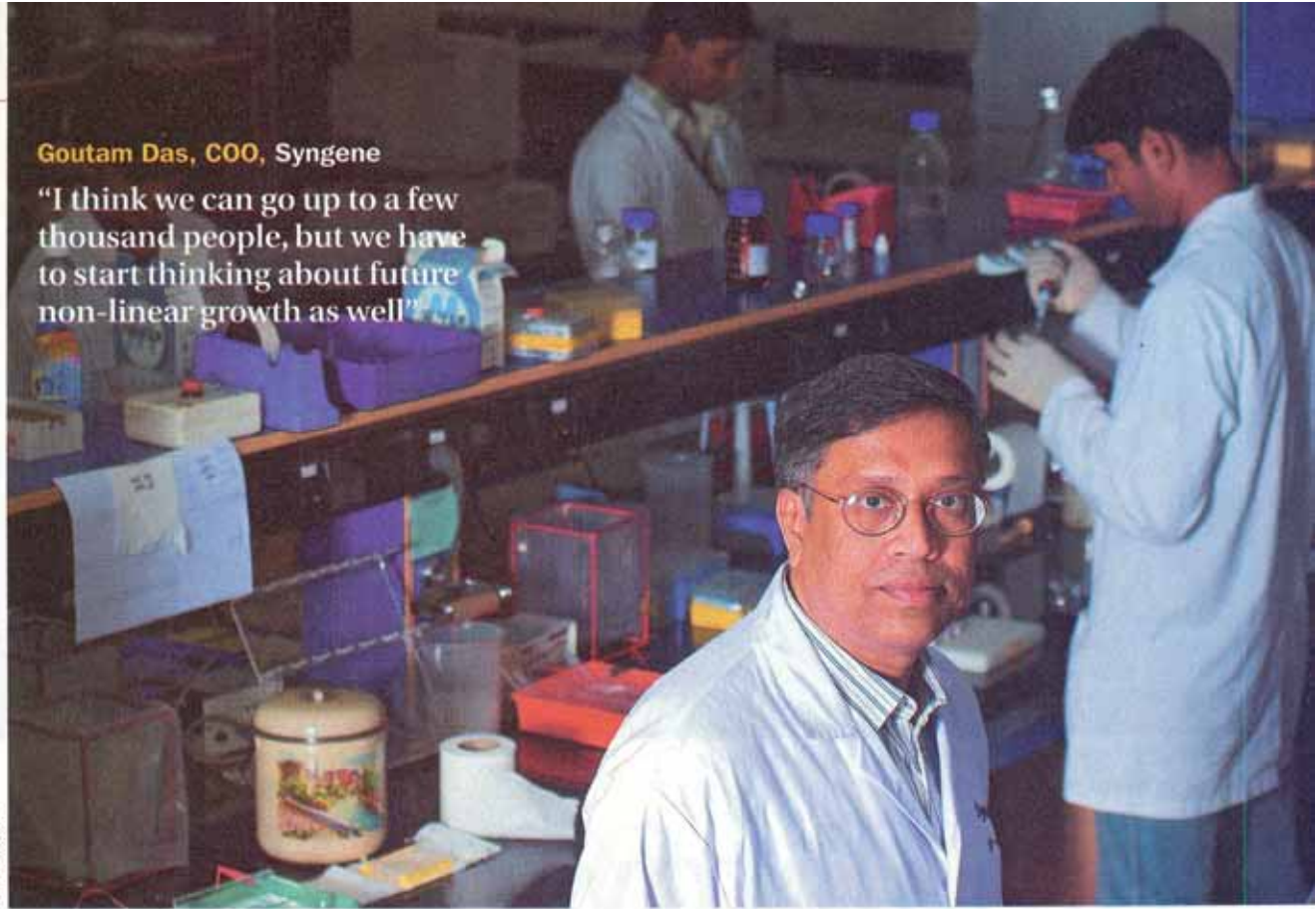
The Nicholas Piramal deal with the Institute of Biological Sciences in Ottawa fits beautifully with domestic programmes on vaccine development. The institute has a technology that boosts the immune systems while delivering the vaccine to the right place. Nicholas would use this technology to develop its own vaccines, and the Canadian institute would get royalties if a product gets to the market. Similarly, Biosyntech also has proprietary technologies in drug delivery and regenerative medicine. A \$6-million investment in that company gave Nicholas access to this technology as well as a knowledge partner for future R&D. Says Ramani Aiyer, senior vice-president (strategic planning, R&D), Nicholas Piramal: "Application of novel drug delivery technologies can add value to many existing drugs."

In sum, partnerships with small western companies are bringing specialised knowledge to Indian drug discovery companies. Even large multinationals sometimes want to collaborate with Indian companies. Take the Eli Lilly deal with Sugen. Companies like Eli Lilly have too many ideas at an early stage but lack the resources to try out all of them. So Eli Lilly gave a few concepts — in the area of nervous system disorders



DALEEP PIRAMAL





**Goutam Das, COO, Syngene**

"I think we can go up to a few thousand people, but we have to start thinking about future non-linear growth as well"

— to Suven and asked it to try them out. Eli Lilly's input comes only at the concept stage. Interestingly, the deal was signed as a partnership and not as a services contract.

THE last few years were great years for Indian drug discovery and development services companies. No company exemplifies this abundance more than Syngene, a subsidiary of Biocron. Syngene is now the largest drug R&D services company in India. It has 600 people and a large campus with state-of-the-art equipment. Yet Syngene has to deal with a fundamental problem: the curse of linear growth. It can grow with handsome margins — as high as 50 per cent in some cases — but only by hiring more and more people. And yet the limited market puts a ceiling on expansion, although no one knows where the limit lies. No one knows when the margins will come down either. Says Syngene's chief operating officer Goutam Das: "I think we can go up to a few thousand people, but we have to start thinking about future non-linear growth as well." To expand non-linearly, Syngene has to develop its own products and sell them. However, there is a conflict of interest with its customers here.

When a drug discovery company outsources from another, it makes sure that the services company is not a competitor. This means the services company cannot develop drugs on its own. Somewhat like the IT industry. To continue in business, a Wipro or an Infosys will have to always remain as services companies. However, the market for IT services is very big, while in life sciences it is relatively small. So life sciences companies such as Syngene are caught in a bind. On the one hand, it needs to develop drugs of its own if it is to become big, but on the other hand it cannot do in-house drug discovery if it has to

continue the services business. It seemed a hopeless task till Syngene found a way out through partnering.

One month ago, the company entered into a partnership with Innate Pharmaceuticals in Sweden. Innate is a small company by any standards; it has about 10 people. Yet it has high scientific expertise as it was formed out of three world-class institutions: Umeå University, the Karolinska Institute and Stockholm University. It works in antibacterials, an area that has a large market. And it uses a method that is not so common: stopping the bacteria from becoming virulent instead of killing it completely. This company will soon start developing potential antibacterials. But with a small team it cannot go ahead without a partner. It found one in Syngene.

Nothing stops Syngene from developing drugs that have already been patented; there is no conflict of interest with its customers because Syngene itself is not patenting products. Yet there is considerable value to add for Syngene since the distance from a patent to a drug is quite large. Syngene can get a share of profits one day, without really conflicting its current business interest. It can get royalties on products without being a product company.

Other services companies are also trying to partner, but in different ways. Jubilant Biosys, a Bangalore-based services company, has been on an expansion mode of late, building a large R&D campus in Bangalore with more than 500 people. While it works on services projects, it is also nurturing three in-house projects that could be developed into collaborations. Similarly, Bangalore-based Advinus is also looking at collaborations as a strategy to expand its orbit. The day may not be far off when most of the major services companies start collaborating for drug discovery. ■