PHARMACEUTICAL RESEARCH AND DEVELOPMENT IN INDIA

MICHELE ARDUENGO, PROMEGA CORPORATION

Here we speak with Dr. Pradip Bhatnagar, Senior V.P. of Drug Discovery at Ranbaxy Laboratories Ltd. in India. We discuss the frontier of drug discovery in India and the challenges and opportunities facing pharmaceutical research and development.

"India is one of the most exciting places in the world to work."

Dr. Pradip Bhatnagar has a contagious enthusiasm for his work at Ranbaxy Laboratories in India. He came to the United States in 1971 to pursue his M.S. and Ph.D. in medicinal chemistry at the University of Wisconsin-Madison, and after that his science took him across the Unites States in both industry and academia. In 2005, he returned to India to serve as the Senior Vice President of Drug Discovery at Ranbaxy Laboratories Ltd. During the three decades he was in the United States, the pharmaceutical industry in India was undergoing a sea change. Today, Dr. Bhatnagar is excited to be a part of that transformation.

Cell Notes talked to Dr. Bhatnagar about drug discovery in India, the challenges facing new drug development on the global stage, and his advice for scientists in training.

India's Pharmaceutical Industry: Intellectual Property and Infrastructure

In the 1950s and 60s, the pharmaceutical industry in India produced only low-level active pharmaceutical ingredients (APIs). By the 1980s, India had grown its generic pharmaceutical industry and was manufacturing more prominent APIs, and in the mid-1980s, the industry became globalized as Indian companies began to interact with the U.S. market and drug companies.

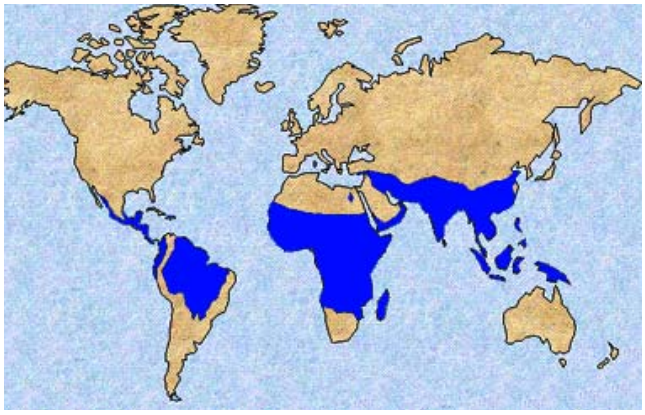
However, real change in the industry did not arrive until the mid-1990s, when India signed the World Trade Organization (WTO) TRIPS agreement (Trade-Related Aspects of Intellectual Property Rights). In signing that agreement, India agreed to recognize innovator patents and enforce intellectual property rights in accordance with WTO guidelines. As a result of signing this agreement, India began its own serious innovative research in medicinal chemistry.

In addition to conceptual changes about intellectual property, Indian science has also benefited from amazing advances in the available infrastructure for doing science. Dr. Bhatnagar says that some things are still chaotic, but the research labs at Ranbaxy are the envy of anything in the United States. "I cannot produce the excuse of not being able to do science because of lack of infrastructure."

New drug discovery and development is still in its infancy in India, and no Indian-based company has the financial muscle to compete with the well known international pharmaceutical giants, according to Dr. Bhatnagar. However, there is a significant cost advantage to drug development in India. Ranbaxy reinvests approximately 8% of its annual revenue in research and development. "When you factor in the low cost of doing research and development in India compared to western countries, the investment of 105 million in real dollars increases three- to sixfold and translates to 400 to 600 million."

"The excitement at Ranbaxy is incredible." Dr. Pradip Bhatnagar is Senior Vice President of Drug Discovery at Ranbaxy Laboratories, Ltd in India. He received his M.S. in organic chemistry from Meerut University in India before coming to the United States to study at the University of Wisconsin-Madison where he earned a Ph.D. in medicinal chemistry. After serving as Director of Alliance Management for Glaxo Smith Kline and earning his MBA from Temple University, he returned to his homeland of India and Ranbaxy. He notes the availability of modern laboratories and other infrastructure that enable leading edge research in India.

FEATURED INTERVIEW



World-wide distribution of malaria. Malaria is one of the neglected diseases for which Ranbaxy is developing new therapeutics. Image credit: U.S. Centers for Disease Control and Prevention.

"The excitement at Ranbaxy is incredible. The international team of scientists that I lead has a great desire to succeed; it's a very dedicated and powerful team."

Dr. Bhatnagar sees himself as a global citizen and science as an enterprise that is too big for any one country, and more and more, people around the world are thinking about how to do science right. Even so he is committed to seeing what he can do for his homeland. "It's very exciting to think of a new drug coming from an Indian lab."

New Drug Discovery Research at Ranbaxy Laboratories

At Ranbaxy, Dr. Bhatnagar oversees a team of 300 scientists who work on Ranbaxy's new drug discovery initiatives, which include therapeutics targeted toward alleviating neglected diseases of developing nations such as malaria, dengue fever and tuberculosis. Additionally, the population in India also struggles with diseases traditionally associated with developed countries including COPD, asthma and diabetes. The annual increase in diabetes in India is three times higher than the global average. Some have even described India as the diabetic capital of the world.

With these problems in mind, Ranbaxy has focused its new drug discovery efforts in four areas: anti-infectives, metabolic syndrome, inflammation, and cancer. Ranbaxy plans to initiate Phase II clinical trials on a malaria drug.

Dr. Bhatnagar brings his expertise as former Director of Medicinal Chemistry and Director of Alliance Management for Glaxo Smith Kline (GSK) to his work at Ranbaxy, and alliances are central to Ranbaxy's drug discovery efforts. Ranbaxy's strengths, currently, lie in the middle of the drug discovery continuum: hit-to-lead (optimization of hits from primary screens); lead-to-clinical (developing druggable compounds from those leads); and early phase proof of concept in humans (Phase I clinical trials). Consequently, Ranbaxy works with other companies that have strengths in the initial screening stages or the later clinical trials and marketing. They are also hoping to leverage the close relationship between Ranbaxy and Daiichi Sankyo Co. in Japan, the major stakeholder in Ranbaxy, for later clinical phases of drug discovery.

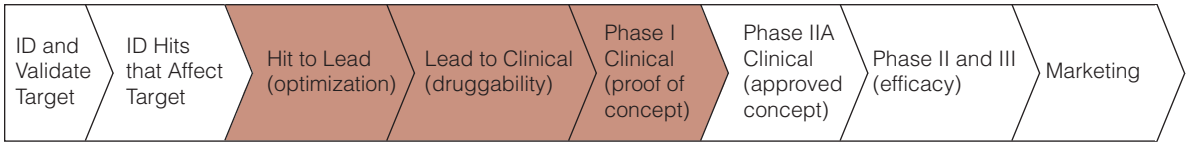
The Future of Drug Discovery: Economics, Stem Cells and Systems Thinking

"There is a commonly held belief that the pharmaceutical industry has matured to a point that it is no longer innovative and that its productivity can only decrease," says Dr. Bhatnagar. However, he views the situation a little differently. "What may be actually happening is that the pharmaceutical industry is failing at commercializing innovation."

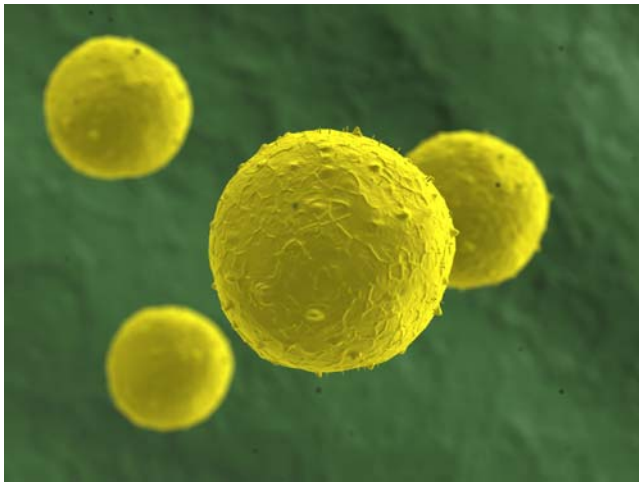
Dr. Bhatnagar says that, viewing drug discovery as a curve, the industry is at the plateau, and incremental advances in efficacy and safety at this stage are accompanied by exponential increases in cost. So, one thing that the drug industry needs to consider is the pharmacoeconomics of a new drug. Some regulatory agencies are even including pharmacoeconomics in their evaluations of new drugs. What is the advantage a new drug produces economically? Generic drugs are answering some of the economic viability questions.

Another area that Dr. Bhatnagar sees as unexplored opportunity for the pharmaceutical industry with regard to medicinal chemistry is stem cell biology. Small molecules that could control stem cell cycles and differentiation could be the next big thing for the pharmaceutical industry. Pharmaceuticals targeted against cancer have extended the life span of individuals with cancer, but cancer still remains uncured. Small molecules that target cancer stem cells may represent a potential cancer therapy innovation.

Traditionally medicinal chemistry has pursued a "minimalist" approach. The mantra of drug discovery has been to find the most selective compound possible to modulate a single target. However complex diseases that involve misregulation of many pathways, like cancer or diabetes, might benefit from an approach that prefers a "selectively broad spectrum"



Drug discovery and development continuum. Ranbaxy seeks to form alliances with companies that have expertise at the early and late stages of drug development.



Are small molecule modulators of stem cell cycles and differentiation an unexplored opportunity for drug development?

molecule—one molecule that can modulate several related pathways in a desirable manner. Pan-active compounds, such as some kinase inhibitors, would fall into this category.

Developing the New Drug Discovery Researcher: Advice to Young Scientists

It is clear that Dr. Bhatnagar sees plenty of room for innovation and new developments in the pharmaceutical industry. His vision and his energy for seeing that vision become reality are very much a part of who he is.

"My dad is a chemistry professor, so I grew up in the chemistry lab. Chemistry is just part of my life."

Dr. Bhatnagar also credits his graduate advisor and mentor, Dr. Dan Rich, for helping him learn to be inquisitive and to trust everybody but believe no one.

"I remember approaching him one time about ways to tackle a particular research problem. He suggested several approaches, and I went into the lab and tried them all. None of them worked. When I reported this to him, he asked me why I had not gone to the library and done some reading. Why didn't I test things before trying them? I learned then to analyze situations for myself."

When *Cell Notes* asked him what advice he has for the scientist in training, Dr. Bhatnagar said that he's a little concerned with the trend of getting the Ph.D. and the MBA simultaneously. He says, "If you want to be a scientist, focus on the science. Get the training, develop the expertise, at least for the first part of your career. Then you can branch out into other areas like business."

"Most of all, though," he says, "work ethic is important. Working hard always pays off."

NOVEL DUAL-REPORTER PRECLINICAL SCREEN FOR ANTIASTROCYTOMA AGENTS IDENTIFIES CYTOSTATIC AND CYTOTOXIC COMPOUNDS

HAWES, J.J. *ET AL*. 2008. *J. BIOMOL. SCR*. **13**, 795-805. (http://DX.DOI.ORG/10.1177/10877057108321085)

Astrocyte gliomas are the most common malignant form of brain cancer. No truly effective surgical or pharmacological treatment exists for these cancers, and the five-year survival rate is less than five percent. Consequently a robust in vitro model system for high-throughput screening will be a valuable tool to identify potential therapeutic compounds.

The authors of this paper created a mouse model for in vitro assays to screen for therapeutic compounds specifically active against astrocytic gliomas. A Green/Red luciferase (G/R-*luc*) dual-reporter system was created in KR158 cells (derived from grade III aggressive mouse anaplastic astrocytoma). The green click beetle luciferase gene (from pCBC68-Basic Vector) was placed under the control of the E2F1 promoter, and the red click beetle luciferase gene (from pCBR-Basic Vector) was placed under the control of the CMV promoter. The dual-reporter assay simultaneously evaluates E2F1 promoter activity and assesses cytotoxicity; the assay also distinguishes cytostatic from cytotoxic compounds. The initial high-throughput screen described in this paper identified several compounds selective against astrocytoma cells over primary astrocytes.

Ordering Information

Product	Size	Cat.#
Chroma-Glo™ Luciferase Assay System*	10ml	E4910
pCBR-Basic Vector	20µg	E1411
pCBG68-Basic Vector	20µg	E1451

*Additional Sizes Available.