funded by the Indo-French Centre for Promotion of Advanced Research.

Though young in age, NII is firmly poised to fulfil its mandate of carrying out basic research of a high calibre and developing new vaccines, immunodiagnostics and other biomedical products of utility to the country.

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Raj Raghupathy and Seyed E. Hasnain are in the National Institute of Immunology, Shahid Jeet Singh Marg, New Delhi 110 067.

Strongly goal-oriented biomedical research—Astra Research Centre India

J. Ramachandran

Using collaboration with a Swedish pharmaceutical giant to advantage, a biomedical research centre lays emphasis on time-targeted projects.

Astra Research Centre India (ARCI) in Bangalore, inaugurated by the prime minister of India on 7 January 1987, was established by AB Astra of Sweden, a research-intensive pharmaceutical company well known for its efficacious drugs for the treatment of infectious, neurological, gastrointestinal, cardiovascular and respiratory diseases. AB Astra's intent to organize a research centre in India was based on the scientific talent and competence available, particularly in molecular biology, biochemistry and biophysics. The Government of India approved the request of AB Astra and recommended that the research centre be formed as a society. The centre was registered as a non-profit society in 1985 under the Karnataka State Registration of Societies Act. A building of 4052 square metres was rented from IDL Chemicals Ltd, in the campus of the IDL Nitro-Nobel Basic Research Institute (INBRI) located near the Indian Institute of Science (IISc). The present governing board is chaired by Sune Bergström,

Embarking on challenging drug-discovery projects

discoverer of prostaglandins and winner (with Bengt Samuelsson and John Vane) of the Nobel prize for physiology or medicine in 1982, and includes S. Rosell (AB Astra), J. R. Tata (Medical Research Council, UK), C. F. Cooney (Massachusetts Institute of Technology, USA), J Holmgren (University of Gothenburg, Sweden), J. Ramachandran (director of ARCI), C. N. R. Rao (IISc), O. Siddiqi (Tata Institute of Fundamental Research, Bombay), G. Padmanaban (IISc), G. P. Talwar (National Institute of Immunology, New Delhi), and K. Banerjee (National Institute of Virology, Pune).

Objectives

The objective of the centre is the pursuit of scientific research leading to the discovery of new diagnostic procedures, novel therapeutic products, and targets for rational drug design for diseases afflicting large populations in both developing and developed countries. In this endeavour, the powerful tools of molecular biology, immunology, cell biology, molecular dynamics and molecular graphics are employed in highly focused, time-targeted projects. Close interactions with the research groups of AB Astra, IISc and universities in India and abroad are promoted through collaborative efforts, extramural support to projects of mutual interest, and sponsoring scientific meetings on relevant topics.

Research projects

In the initial stages of building up the organizational structure while recruiting scientific staff and procuring equipment, short-term projects were initiated with limited objectives. It was decided that, in the first two years, methods of preparation of various biochemicals used in recombinant-DNA research be developed. Many of these biochemicals, such as restriction enzymes, DNA ligases, kinases, polymerases and other DNA-modifying enzymes, were being imported from either the USA or Europe in dry-ice shipments. The non-availability of these reagents readily in India has hampered the growth of recombinant-DNA research and the successful accomplishment of tasks. ARCI therefore developed know-how for the preparation of several crucial reagents used in molecular-biology research. Another short-term objective was the design and development of diagnostic procedures using DNA probes and immunological methods for the diagnosis of some infectious diseases. The choice of the diseases was based on the inadequacy of the currently available method(s) and the clinical or epidemiological needs. Novel methods for detection of the malarial parasite *Plasmodium falciparum* in human blood samples, virulent *Shigella* and/or other enteroinvasive bacteria in stool samples, and *Cysticercus cellulosae* in cerebrospinal fluids of neurological patients (neurocysticercosis) have been developed at ARCI.

A 21-base-pair sequence repeated many times in tandem in the *Plasmodium falciparum* genome was identified as a DNA sequence specific for the parasite[1]. Using this repeat motif, a DNA probe labelled with biotin was synthesized and a novel procedure of hybridization and detection of the parasite was developed. The procedure uses a drop of blood from a finger prick, and detection of parasite DNA hybridized to the probe is achieved by the development of colour. The procedure does not include any special apparatus and requires no special training[2,3]. In the project on the molecular mechanisms of pathogenesis of *Shigella*, three membrane proteins were identified as virulence-associated factors[4]. Using antibodies against one of these proteins, a rapid, sensitive and specific diagnostic test was developed[5]. The test format, which gives the antibiotic-sensitivity profile simultaneously, takes about 8 hours to complete, while the conventional microbiological procedure takes about 72 hours. Neurocysticercosis is a neurological disease caused by the tapeworm *Taenia solium*. The disease manifests in a number of neurological syndromes, including epilepsy, intracranial tension, psychosis, encephalitis and chronic meningitis. There are no simple tests available for the specific diagnosis of neurocysticercosis. The diagnosis by the presence of dense spots in CT scans is often confused with tuberculous meningitis. Use of a mixture of antigens obtained from cysts isolated from pig muscle for the detection of antibodies in the cerebrospinal fluid (CSF) showed up cross-reactivity with antibodies to mycobacterial antigens, making the differential diagnosis difficult. ARCI's use of partially purified excreted or secreted antigens of the parasite in culture have led to a highly specific and sensitive ELISA test[6] for the detection

of cysticercal antibodies in CSF. A double-blind study confirmed the sensitivity of the procedure (>95%) and showed no interference by mycobacteria-specific antibodies in CSF. A second-generation test will include an antigen produced by recombinant-DNA technology. In a project on tuberculosis, an immunogenic protein was identified that could be used for serodiagnosis of tuberculosis[7]. The sensitivity and specificity are being assessed by double-blind studies. In all these studies the centre has received the cooperation of scientists at IISc, the National Institute of Mental Health and Neurosciences (NIMHANS) and St John's Medical College. In addition to these studies, basic research on the molecular aspects of pathogenesis of bacteria causing diarrhoea was also pursued. The gene coding for the heat-stable toxin elaborated by enterotoxigenic *E. coli* was cloned and hyperexpressed[8]. The localized adhesion of enteropathogenic *E. coli* to epithelial cells was shown to involve specific carbohydrate structures of glycolipids[9]. Search for a good target in the malarial parasite for rational drug design led to the cloning and expression of the hypoxanthine-guanine phosphoribosyl transferase-encoding cDNA from *P. falciparum*. At the initiative of the protein-structure group of the Department of Biochemistry, IISc, the complete amino-acid sequence of xylanase isolated from *Thermoascus aurantiacus* was determined[10]. A molecular-dynamics and computer-graphics unit was set up to provide theoretical support for all the projects at ARCI.

Decision making

With the setting up of a state-of-the-art laboratory and the assembling of competent scientific staff, the centre is now poised to embark on more challenging drug-discovery projects. In selecting long-range projects where large investments are made, expertise available at ARCI and the research units of AB Astra are optimally utilized. Several factors are considered in the decision-making process. These considerations are (a) the medical need, (b) the biological target suitable for drug design, (c) probable time required to identify a candidate drug, (d) competition from other drug companies, and (e) estimate of financial support required. These aspects are discussed in a forum consisting of scientists from a number of disciplines, university professors, medical experts, finance managers and marketing experts. At the present time, discussions are under way to design a novel class of antibacterial agents.

Research in modern biology is a multidisciplinary activity. It is absolutely essential to have a coordinated team to accomplish the set tasks in the predetermined time frame. Therefore team work is highly emphasized. Quite often it becomes necessary to reassign personnel and material resources depending on the progress made in a research project and the expertise it may require to resolve a problem. Therefore all projects are reviewed each week by the project team along with colleagues from other projects to solve problems and to assign priorities to experimental work. Personnel in projects where the goals are accomplished or where they are unproductive are reassigned to other projects where their expertise is required. All personnel are evaluated annually by predetermined peers and on tasks earlier agreed upon. The reward system includes increase in salary, perquisites and/or job title on the basis of performance.

A unique feature of ARCI is that scientists are able to devote all their time to the pursuit of science rather than dealing with bureaucracies of various types that generally affect the productivity of scientists adversely in many institutions. This has been accomplished at ARCI with the help of a small but dedicated administrative staff, which has worked hard to eliminate or minimize bureaucratic delays in purchase of equipment and supplies and maintenance of equipment, and in providing uninterrupted power supply, water and other essentials.

Technology transfer

The proprietary information on the processes for the preparation of molecular-biology research tools developed at ARCI during the first two years has been transferred to a company called Genei (Gene India). It is a unique company formed by two enterprising scientists, P. Babu, formerly of the Tata Institute of Fundamental Research, and K. Prasad, a non-resident-Indian scientist-entrepreneur. Technology Development and Information Corporation of India (TDICI) provided financial support to Genei. Bangalore Genei is already marketing many restriction enzymes, DNA-modifying enzymes and vectors, for which the know-how was given by ARCI [see advertisement, back cover]. Discussions are under way with a pharmaceutical company for the manufacture and sale of the diagnostic procedures developed at ARCI.

Strategic collaboration and funding

The idea of setting up the research centre was to build a collaborative venture with AB Astra on a long-term basis since the development of therapeutics is a long and arduous process that is highly competitive and capital-intensive. Investigations leading to the development of a drug require inputs from various disciplines. The association with AB Astra gives this centre a unique opportunity to collaborate with the research units of AB Astra as an equal partner, keeping the efforts of both collaborators complementary to each other. In this context, it must be noted that R&D companies in the developed world have realized that it is most cost-effective to participate in strategic collaboration, pooling resources and expertise[11]. This is more prevalent in the case of biotechnology-based products where developmental costs are very high[12-14]. The organizational structure of ARCI must be viewed as a strategic collaboration with AB Astra. The Swedish company has so far invested about rupees 120 million in the centre. Each year a budget proposal from the centre is reviewed by a research committee of AB Astra.

A strong commitment to scientific research through collaboration with academic scientists in goal-oriented research projects has been Astra's corporate policy. In pursuance of this policy, AB Astra has endowed a chair of 'Astra Professor' at IISc. ARCI supports, through extramural grants, projects of mutual interest with IISc, NIMHANS and St John's Medical College in Bangalore.

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J. Ramachandran is Director, Astra Research Centre India, P. O. Box 359, Malleswaram, Bangalore 560 003.

Department of Biotechnology

(From page 523)

long-term R&D projects. Sericulture is one of the important agro- and forest-based industries in India and provides gainful employment to over six million people, the majority of whom are in rural areas. The proposed programme visualizes improving the economy of this sector.

New areas

Some important new areas where programmes have been evolved include human genetics, leather biotechnology, biotechnological approaches with medicinal plants, *Drosophila* research, neurosciences, enhanced oil recovery through microbes and oil degradation and pollution control, microbial technology, and biochemical engineering. The six centres of plant molecular biology are working in genetic engineering and plant molecular biology of selected crops.

Bilateral cooperation

Since its inception, DBT has embarked upon bilateral cooperation programmes with several developed and developing countries. Bilateral programmes have been tied up or are being explored with the USA, the USSR, Germany, Switzerland, China, the Netherlands, Cuba, Poland, Sweden, Vietnam, France, the UK and Mongolia.

International centre

An agreement was signed between the Government of India and UNIDO (United Nations Industrial Development Organization) on 25 March 1988 for the establishment of the New Delhi component of the International Centre for Genetic Engineering and Biotechnology (ICGEB). (The other component is in Trieste, Italy.) The programme at ICGEB New Delhi includes biotechnology research and development in agriculture and human and animal health.

Future perspective

During the nineties and years after, the world will move rapidly into the age of modern biology and biotechnology, which will offer tools for rapid agricultural, industrial and socioeconomic progress. Biotechnology is a highly science-based, knowledge-intensive, interdisciplinary field in which spectacular advances are taking place all over the world. It cuts across the boundaries of physics, chemistry, biochemistry, biology, engineering, biomedical science, agricultural sciences and so on. The primary objective of biotechnology is the development of products, processes and technologies whose large-scale application would result in societal benefits.

A critical mass of scientists in the life sciences is required. While DBT will support basic research in highly selected areas of relevance, there will be a major effort in basic research that is oriented towards direct application. Greater interaction between R&D institutions, universities, industries and financial institutions will be ensured, and science–industry consortia set up in different locations in the country, preferably in universities or other academic institutions.

In addition to supporting priority research, a major thrust will be given to development of simple biotechnological tools and technology packages for the benefit of rural areas and for providing employment opportunities (biofertilizers, sericulture, biomass production on large scale, human and animal health care, aquaculture, etc.).

Every effort will be made to disseminate information on biotechnology through appropriate publicity and use of mass-communication media. A good base has been prepared by way of development of training programmes, infrastructure, and some product development and manufacture. Conditions are now ripe for a take-off in making the benefits of biotechnology available to the common man.

S. Ramachandran is Secretary, Department of Biotechnology, Ministry of Science and Technology, Block 2, CGO Complex, Lodi Road, New Delhi 110 003.