

## 11. INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY (ICGEB), NEW DELHI

ICGEB, New Delhi, is actively involved in research in the areas of Mammalian Biology as well as Plant Biology. The main focus of research under mammalian biology is malaria, virology, immunology and recombinant gene products.

### **Malaria**

The malaria research program focuses to understand the biology of malaria parasites and their interaction with the human host with a view to developing novel drugs and vaccines against malaria. Studies on the molecular interactions that mediate invasion of erythrocytes and hepatocytes by malaria parasites have yielded insights into these critical processes. Vaccines based on parasite proteins that mediate invasion are under development. A rhesus monkey model for testing these vaccines has been developed and has provided promising initial results. Due to the spread of resistance to chloroquine, there is an urgent need to develop alternative chemotherapeutic strategies. Proteins such as cysteine-proteases responsible for haemoglobin degradation, which are unique to parasites and play critical roles in their growth, are being used as targets for the development of novel antimalarial drugs. Another target is the heme polymerisation pathway. A rapid screening system to identify inhibitors of heme polymerisation has been developed. A *P. falciparum* diagnostic kit is being developed.

### **Hepatitis and AIDS**

Hepatitis B virus (HBV) is a highly infectious agent that is responsible for acute and chronic hepatitis in man, leading to liver cancer. The role of HBV X gene in disease pathogenesis is being studied. The modular nature of its encoded protein, HBxAg, has been studied for its transcription regulating properties. A transgenic mouse model of HBV-related liver cancers has been developed. This will be useful for studying the basic mechanisms of cellular transformation and for screening anti-cancer drugs. Patents for this mouse model have been filed in India and USA. Hepatitis E virus (HEV) is an agent responsible for sporadic and epidemic forms of viral hepatitis prevalent in India and other developing countries. There are currently no vaccines or drugs available against this form of viral hepatitis. The role of HEV proteins in disease pathogenesis is being studied. Some of these studies have led to insights into virus-host interactions that can be exploited for drug development. The HEV major capsid protein has been expressed in various eukaryotic systems. Virus-like particles (VLPs) engineered using a baculovirus system are a prime candidate for vaccine development. A modified gene has been engineered into plants for the development of an edible vaccine and vectors have been constructed for DNA vaccines. The HEV cysteine protease has been cloned and expressed in insect cells as a potential target for drug development. Human immunodeficiency virus (HIV) infection has reached epidemic proportions in India. The biological properties of subtype C HIV-1 prevalent in India are being studied. A vaccine for HIV-1 subtype C is being developed using fusion competent virus-like particles and DNA immunisations (under consideration for funding by DBT).

### **Immunology**

In the past year the efforts have been to understand processes governing modulation and regulation of antigen-specific B cell responses. It has been demonstrated that memory B cell differentiation, in germinal centres, is stringently dependent upon the prior presence of antigen-containing immune complexes on Follicular Dendritic cells. It was found that the memory B cell differentiation in germinal centres is driven in a specificity-autonomous fashion and that the extent of memory B cell differentiation is guided by the kinetics of antigen exchange between activated B cells, and the immune complexes - a process which also confers the high degree of antigen-fidelity to memory B cells. The kinetics of antigen-B cells interactions was found to influence by regulation the extent of costimulatory molecule expression on B cells. This, in turn, defines the ability of these B cells to recruit T cell help in a competitive milieu.

### **Recombinant Gene Products**

This group is part of ICGEB's commitment towards the application of biotechnology. This is being carried out by developing commercially viable technologies for the production of important protein drugs. Recombinant human interferon gamma has shown promise in the treatment of many diseases. Our product has cleared toxicity and safety studies and is being evaluated for the treatment of drug-resistant tuberculosis. Recombinant human interferon alpha 2b is used for the treatment of viral hepatitis and some forms of cancer. Our product is available for clinical trials. Recombinant hepatitis B vaccine has been developed and is in phase II clinical trials.

### **Plant Molecular Biology and Biotechnology**

The major emphasis is to understand the mechanisms of abiotic and biotic stress in plants and to develop technologies for gene transfer in important crop plants.

**Plant Molecular Biology:** The mechanisms by which plants adapt to various environmental conditions are being studied. Various components in signalling and genes responding to light and abiotic stress have been identified. Two such genes coding for calcium binding proteins when transferred conferred tolerance to abiotic stress in the recipient plants. Regulatory elements and genes of various proteins responsible for DNA replication and cell division cycle are being isolated with a view to controlling and manipulating cell division. These studies will also be utilised for understanding viral DNA replication in host cells to develop virus resistance in plants. The replication and division of chloroplasts, the primary cellular organelles on which all life depends as a source of food, fuel and oxygen is being studied.

**Plant Transformation:** This group focuses on the development of new strategies for the introduction and expression of heterologous genes in the nucleus and chloroplast. A series of chloroplast transformation vectors have been developed and tested for the expression of pharmaceutically and industrially important proteins. Currently, this group is focusing on the extension of plastid transformation to crop plants such as cotton, potato and rice. This would enable one to express various agronomically useful genes at high levels. In

addition, this group is involved in the production of transgenic rice and potato for insect resistance and stress tolerance.

### **Insect Resistance**

The research of this group focuses on understanding the mechanisms of resistance to insect pests and on developing eco-friendly pesticides. We have developed methods to combat emergence of resistance in insects towards insecticides of *Bacillus thuringiensis*. This is achieved by (a) overproducing the desired toxin by expression in chloroplast and (b) by combing structurally unrelated toxins which interact at different receptors at the mid gut of susceptible larvae.

### **Plant Resistance**

The mechanisms of resistance in rice against its major pest-gall midge has been studied. Two resistance genes have been tagged and mapped. More resistance genes are currently being mapped. PCR based markers have been developed and are being used by plant breeders in marker-assisted selection. Cosmid of a region on chromosome 4 that encompasses the gall midge resistance gene Gm2 has been completed. Susceptible plants have been transformed and regenerated using these cosmids in complementation experiments. Different biotypes of gall midge found in India have been fingerprinted. PCR-based markers have been developed to differentiate different biotypes of gall midge.

### **Training**

ICGEB has long term as well as short term training programmes. Under the former, postdoctoral fellows and Ph.D. students from developing countries receive advance training. A Ph.D. programme for Indian students is also being run in collaboration with Jawaharlal Nehru University, New Delhi. For short-term training, ICGEB, New Delhi, conducts practical training courses, meetings and symposia for scientists from India and other developing countries in areas of modern molecular biology and biotechnology. In 1999, 'First ICGEB Plant Signal Transduction Symposium' was held in which a large number of national and international scientists participated. Two training courses on 'Plant Transformation' and 'Recombinant Gene Products' were organised; 40 young scientists from India and abroad participated. ICGEB facilities are freely available and indeed used by a large number of students from other Indian institutes.

### **Collaborations**

ICGEB collaborates extensively with research groups at various institutions in India and abroad as well as several industrial partners in India. ICGEB is also involved in the national Jai Vigyan S&T mission on vaccines.