

Advancing frontiers of molecular genetics: Where does India stand*

How far has India progressed in molecular genetics research and teaching since the 15th International Congress of Genetics held in New Delhi in 1983 under the Presidency of M.S. Swaminathan? This question was considered at a symposium organized by the Genetics Congress Trust. The Trust was set up as a follow up to the Congress, with the main objective of promoting molecular genetics research in India. The Indian Society of Genetics and Plant Breeding, organizers of the Congress, believed that the presence of leading molecular geneticists from all over the world and the presentation of their latest work would sensitize the science policy makers and research institutions in India to make greater investments in molecular genetics research and teaching. India in the early 1980s was lagging behind in molecular biology at a time when rapid progress was being made in many other countries, especially in USA and European countries. The Congress was attended by 2500 scientists, including eight Nobel laureates from 51 countries. The Nobel laureates called on Indira Gandhi, the then Prime Minister of India, and briefed her about the economic and social implications of their work, specially the expected impact on medicine and agriculture.

The two-day symposium was attended by 40 scientists from major research centres in the country, active in molecular genetics research and teaching. They reviewed the global advances made in the past 20 years and described the work in progress in different research institutions in India. Nine different themes relating to molecular genetics were selected for the review. A base paper was prepared by a working group in each of the following selected areas: Gene expression and regulation, Molecular genetics of development and evolution, Structural and functional genomics, Transgenic crops: production, testing and commercialization, Molecular mapping and marker-assisted breeding, Isolation of useful genes and promoters,

Biodiversity characterization and utilization, Teaching and training in molecular genetics, and Creation of national facilities.

The participants noted that there has been continued progress in molecular genetics research worldwide in the past two decades since the organization of the 15th International Congress of Genetics at New Delhi. Thus, starting with the mid-1980s, there have been breakthroughs in the understanding of the molecular basis of development and differentiation. The discovery of transcription factors and of the ubiquitous DNA sequence – the homeobox which appears to have been conserved during several billion years of evolution, and of the homeotic mutants in *Drosophila*, led to an understanding of the spatial and temporal switching on and off of genes in the developing embryo. At about the same time, the phenomenon of signal transmission through messenger molecules such as the hormones showed how genes are activated to start transcription. Another group of discoveries during this period led to an understanding of the role of retroviruses in giving rise to oncogenes. The discovery of split genes, overlapping genes, pseudogenes, alternative splicing, epigenetic modification of DNA, DNA rearrangements and more recently, 'RNA only genes' (including anti-sense RNA, Si RNA, micro RNA, riboswitches), provided newer insights into gene structure and expression.

The genetic basis of antibody diversity reflected in the formation of billions of these proteins was understood in terms of shuffling and joining in various ways of segments of DNA and RNA in the course of the immune system development. The 1980s also saw the development of techniques for production of transgenic plants and animals, including the deployment of transgenic livestock as drug factories.

The early 1990s was marked by major developments in the new field of the molecular basis of evolution. Fossil records which had been the main tools of evolutionary biologists, were supplemented by evidence of a different kind – far more direct and precise, going to the very heart of the evolutionary process. Molecular biologists were now analysing nucleotide substitutions in mitochondrial DNA and

in the DNA of the Y-chromosome, to determine the chronological record of polymorphisms in different populations of the human species and in some of the other species from which humans diverged millions of years ago.

The century ended with the announcement of the first draft of the human genome nucleotide sequence. The findings surprised many scientists. The total number of genes was found to be about 39,000, far less than 100,000 widely assumed earlier. With the publication of these results on structural genomics, the emphasis is now shifting to functional genomics. A related aspect has been the large-scale identification and mapping of single nucleotide polymorphisms, which provide molecular markers for the identification of disease-causing genes. With these molecular markers distributed all over the genome and greater understanding of the molecular basis of human diseases, customized drug development has become a distinct possibility.

How has India fared during the post-Genetics Congress period? The participants observed that in the last 20 years, India has taken important steps in creating the basic infrastructure of molecular biology research in the country, with the Department of Biotechnology (DBT) playing a major role in this endeavour. In addition to setting up centres of plant molecular biology in a number of conventional/agricultural universities, a total of nine research institutes and corporations, including the National Institute of Immunology, Delhi; National Centre for Cell Science, Pune; Centre for DNA Fingerprinting and Diagnostics, Hyderabad; National Centre for Plant Genome Research, Delhi; National Brain Research Centre, Manesar; Institute for Bioresources and Sustainable Development, Imphal; Institute of Life Sciences, Bhubaneswar, Bharat Immunologicals and Biologicals Corporation Limited, Bulandshahr and Indian Vaccines Corporation Limited Gurgaon have been established. These institutions are equipped with world-class instrumentation and have been provided with highly competent human resources. In terms of financial allocation, DBT has been receiving a steady in-

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crease in its budget over the years. It was US\$ 28.57 million in the 7th Plan (1985–90), while in the 10th Plan an outlay of around US\$ 300 million has been made. DBT has been interfacing its activities through a number of organizations such as ICAR, ICMR, CSIR, MOEF, DOS, UGC/academic institutes, DAE and some NGOs. In addition to M Sc programmes in biotechnology in about 50 universities/institutions, a large number of research projects in various disciplines of agriculture, medicine, environmental sciences, food and sericulture biotechnology as well as in areas of basic research such as, stem cell research, bio-informatics and social development are being supported by DBT. Many of these organizations, more prominently ICAR, ICMR and DOS, have also established and strengthened biotechnology research in their own institutes. The collective efforts of all these organizations and institutions in the past 20 years have started yielding some success stories, primarily in the domain of knowledge generation. Some of the leads have been translated into products; most others, however, are still awaiting conversion into deliverables.

Participants in the symposium felt that with all this impressive beginning, the country must now move to the second phase of strengthening of molecular genetics and biotechnology research. The first phase has been marked by a selective approach leading to the creation and strengthening of a number of institutes and university departments. This has been a good strategy considering the limitation of resources, specially scientific manpower. The tools and techniques of molecular biology developed in the past 50 years, however, have become increasingly integrated with all the disciplines of biological sciences, be it systematics, physiology, pathology or any other. It may no longer be possible to carry out much meaningful research in most disciplines of biological sciences, unless investigators supplement their classical methods with those based on advances in molecular biology. The second phase must, therefore, be characterized by a more comprehensive approach for the transformation of biological research and teaching in the country with the strengthening of all the university departments and other research institutes, which have remained largely isolated from continuing advances in molecular biology. What is needed is an integration of the classi-

cal and molecular techniques in India, which has already taken place in most of the developed countries. This will call for a major commitment of resources, both for laboratory equipment and for human resource development. The University Grants Commission and the Department of Science and Technology, in addition to DBT, will have a major responsibility for the second phase of modernization of biological research and teaching in the country, taking on-board the continuing advances in DNA technology.

The second phase should also be marked by the organization of a number of national research programmes in selected areas with intra- and inter-institutional collaboration. The existing isolated efforts, valuable though they have been, should be supplemented by collaborative research, so that the limited resources of different institutions can be focused in areas where India may have a comparative advantage. A good example of such programmes is provided by the Chinese experience. Chinese scientists have collectively decided to create, through a multi-institutional collaboration, 300,000–400,000 knockout mutations in rice as part of their research in functional genomics. India could take a lead by mobilizing the expertise available in the country in the fields of tissue culture and plant breeding, and produce a large number of such mutations in *indica* rice through retro-transposon and chemical mutagenesis as well as ecotilling of existing germplasm for assigning functions to some of the DNA sequences, which are now freely available from rice genome sequence data provided by the International Rice Genome Sequencing Programme. India is a partner in this international effort and the country is also the home of *indica* rice. Once functions are assigned to nucleotide sequences, they can become a tradable commodity.

Another example of a collaborative and coordinated approach would be for the development of transgenic crop varieties, which have been one of the major rewards of modern biotechnology. India has one of the world's largest number of highly trained plant breeders, who have developed many improved seed varieties, which lie at the core of the Green Revolution technology. The development of transgenic varieties, however, requires much more than this kind of expertise. The basic infrastructure needed for the purpose is the creation of accredited

laboratories, which will offer facilities of testing for biosafety for human health and for ecological impact. Involvement of classical plant breeders and other specialists such as plant pathologists and entomologists along with molecular biologists is needed from the conceptualization of the project to the product-delivery stage. Most of the existing efforts in this field in the public sector research are centred around individual scientists, with the result that there is little to show in terms of transgenic varieties released to the farmers. Above all, production of transgenic varieties and their release and marketing will call for collaboration between the public and private sector institutions.

In this second phase, molecular biology research must also address new concerns arising out of globalization of trade and the emergence of IPR protection regimes to which India is committed as a member of the World Trade Organization. For this purpose, India should create a number of strategically located research-cum-service centres equipped with the latest tools for structural and functional genomics so that well-focused, coordinated programmes directed towards the isolation of new and novel genes and promoters can be initiated to avoid dependence on import of IPR-protected technologies. One component of this new infrastructure would be a repository service, where useful genes/sequences/promoters/constructs can be maintained and made available on request under proper Material Transfer Agreements. Unfortunately, much of the useful material developed currently gets lost because of the personal and professional movement of the scientist in the absence of a national facility of this kind.

In contrast to research, teaching of molecular genetics has received much less attention in the past twenty years. Many of the universities under the UGC system as also the state agricultural universities do not have well equipped laboratories for practical work in molecular genetics. The traditional Departments of Botany and Zoology in most of the universities have seen little integration of the evolving concepts and techniques of molecular biology in their course curricula. There appears to be little appreciation of the fact that molecular biology is a natural, logical and inevitable extension of classical biology, and the two must be fully integrated as has happened in the developed countries.

Keeping this in view, the participants observed that in the second phase teaching of basic principles and techniques of molecular biology must become a significant part of all courses in biological sciences. This will call for a major reorganization of laboratory facilities in the universities for teaching and training. A seed money of Rs 5,000,000 would be needed for setting up a fairly good practical laboratory, with a provision of an additional grant of Rs 500,000 per annum for consumables.

As part of this teaching and training infrastructure, five strategically located institutions responding to the training needs of university teachers and serving as centres of excellence for technology-

oriented upstream research should be set up. These institutions should be named as Indian Institutes of Molecular Biology and Biotechnology and should be established on the pattern of the Indian Institutes of Technology.

To summarize, the participants in the symposium reviewed advances in molecular biology research in the past 20 years following the organization of the 15th International Congress of Genetics in New Delhi in December 1983. Taking stock of the situation in India, they observed that the country has come a long way in the past 20 years in creating an impressive infrastructure for molecular biology research, with the setting up of a large number of new research institutes and

university departments. The country now stands ready to move into the second phase of this process, so that the contributions of Indian scientists in this rapidly developing discipline are widely recognized. Also, the country should derive greater benefits from the commercialization of modern biotechnology products in agriculture, medicine and in food processing industry.

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RESEARCH NEWS

Population genomic and bioinformatic studies reveal evolutionary history of *Drosophila ananassae*

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During the nineteenth century, Charles Darwin¹ proposed that new species originate by a force of evolution, which he termed as natural selection. After the rediscovery of Mendelian genetics during the early parts of the twentieth century, geneticists carried out experiments to understand if Darwin's theory of evolution could be explained in genetic terms (detecting genetic differentiation) involving single or closely-related species populations. Such studies, interestingly, could detect fair amount of genetic differentiation between species sub-populations almost across the whole biological taxa. The results explained the fact that population genetic studies could provide a priori information on the micro-evolutionary processes at the species level. Studies of evolutionary history (i.e. the origin, population structure and demography) of species populations have thus been a great challenge to the evolutionary geneticists.

With gradual development in the biotechnological fields, evolutionary biologists have employed different genetic markers (from chromosome to genome) in order to find out answers to the age-old ques-

tion – which exact evolutionary force(s) have shaped the extant genetic variations in the species populations: Darwinian natural selection or random genetic drift? With classical genetic markers, it initially appeared that most of the observed genetic variations could be explained by natural selection. However, Kimura², with his mathematical wand, came up with the idea that random genetic drift might be the sole cause of evolution at the molecular level, while accepting the fact that Darwinian selection could explain the observed variation at the phenotypic level. A breakthrough came while analysing the nucleotide variation at the *adh* gene in *Drosophila melanogaster*, suggesting the role of balancing selection (a form of natural selection)³. At almost the same time, Begun and Aquadro⁴ reported a positive correlation between the nucleotide heterozygosity and rate of recombination in *D. melanogaster* genome that was later confirmed in the biological taxa studied so far. These two studies have generated renewed interests among the evolutionary biologists to use genomics as a preferred tool to understand evolutionary

processes in natural populations. With the parallel development in the field of theoretical population genetics (e.g. coalescent theory⁵), large-scale DNA sequence analyses using different mathematical models have geared up. A possible utilization of combined genomic–bioinformatic approaches has generated new vigour amongst the evolutionary biologists not only to infer evolutionary history of species populations, but also to understand the relative role of different evolutionary forces shaping genetic variation leading to origin of new species.

In this respect, species of the fruit fly *Drosophila* are preferred model organisms for a variety of reasons. *D. ananassae* is especially interesting since it has a wide-spread distribution across the tropical and semi-temperate regions⁶ of the globe, being highly abundant in the South and South East Asian localities and strictly human commensal⁷. Amongst several other genetic peculiarities⁸, it displays high population substructure across the whole distribution range, thus making the evolutionary inference much more complicated than the species with less substructure (e.g. *D.*