

News and Views:

The spectacular announcement made in June 2000 by the international leaders of the Human Genome Project (HGP) confirming that 90% of the Human Genome project had been completed before schedule, followed by its publication in February 2001 in special issues of *Science* and *Nature* thrilled everybody, not only in the scientific community but also at all levels of society. Most importantly, this gigantic task has raised a lot of questions. While its scientific value is beyond any doubt, its ethical and social implications are often poorly known and in many cases misinterpreted, mostly due to insufficient information.

To give us some insight on the subject, **Mohammed El-Mezgueldi, PhD** and Lecturer at the Imperial College of Medicine at the National Heart and Lung Institute (London, United Kingdom), kindly agreed to share his opinion in respect to two relevant questions.

Q1: Could you explain to our readers what is the Human Genome Project?

Why is it considered a great achievement - as

some describe the step like traveling to the moon in

biology

A1: Living bodies are made up of organs. Organs are formed of tissues and tissues are made up of cells. Cells are small compartments filled with a concentrated aqueous solution of chemicals and bounded by a membrane. Inside the cell is stored the information that tells the cell what to do and how to do it.

The transfer of life from one generation to another (and therefore from one living body to another) has fascinated humanity since the time of Aristotle. The science of genetics started when it was realized that an organism does not pass on a copy of itself to the next generation but instead provides it with material containing the information needed to construct an offspring organism. Now we know that the information required for self replication resides in the genetic material (or genome) as molecules called deoxyribonucleic acid or DNA. DNA is made up of a linear chain of four chemicals repeated millions or billions of times throughout a genome. These four chemicals are called bases and abbreviated A (for Adenine), T (for Thymine), C (for Cytosine) and G

(for Guanine) and the human genome for example has 3 billions pairs of bases. The particular order of the four bases is extremely important and underlies the structure and the function of the different cells, tissues, organs and ultimately bodies. Information is useful only if means exist for its expression. In living creatures the information in a short sequence of DNA (or gene) is copied into a related molecule called ribonucleic acid or RNA. The information contained in the RNA is then translated to yield a protein. Proteins are the chemicals responsible for the physiological functions expressed by a living body and necessary for its maintenance, growth and development. Defects in proteins result in abnormal physiological functions and therefore in diseases.

The human genome project is an international project started in 1990 and aimed at determining the complete sequence of the three billion DNA bases and discovering all the approximate 100,000 genes found in the human genome. The human genome project is managed by the human genome organization (HUGO). HUGO was established in 1989 and has over 1000 members representing over 50 countries, some of them are developing countries such as Brazil, Mexico, India or Oman. The major players are the USA (with the involvement of the Department of Energy and the National Institute of Health) and the UK (involving the Wellcome Trust Charity and the publicly funded Medical Research Council), but other countries including Germany, France and Italy play an important role.

The goal of the Human Genome Project was to determine the complete sequence of the three billion DNA bases and to discover all the approximately 30,000 genes found in the human genome. All diseases have a genetic component, whether inherited or resulting from the body's response to environmental stress like viruses, toxins and radiations. The obvious aim is to use the human genome data to develop new ways to predict, diagnose, treat, cure or even prevent the thousands of diseases that afflict humankind. But the road from gene identification to effective and safe treatment is long, and the public is rather misled on the immediate use of the human genome data by the publicity surrounding the human genome project. The full sequencing of the human genome is just the first step and only lays the foundations to revolutionize

medicine. In the future however, traditional medicine that focus mostly on treating symptoms using drug therapy will be shadowed by the newly-born allow the development of new drugs for previously untreatable diseases. Drugs may be manufactured depending on individual needs and this will lower the risk of side effects. In organ transplantation surgery a large problem responsible for relatively low success is organ rejection. The use of genetic information of the donor and the recipient will undoubtedly improve the match and lower the risk of rejection. Ultimately for many diseases drug therapy may be replaced by gene therapy (simply by replacing the old faulty gene by a new healthy gene). Prediction and diagnosis will also be certainly improved by the use of genetic information. Many people have genetic predisposition to develop certain kidney or heart diseases or certain forms of cancer (although the disease may not be directly related to a defect in a specific gene) and predicting which people will be susceptible to develop a particular disease will help them make a lifestyle choice that lowers their risk of acquiring the illness. Genetic counseling is already in use to inform parents who carry a genetic disease about the risk for their babies. The spectrum of diseases dealt with and the quality of genetic counseling will improve drastically. At the extreme, editing the genetic material of the reproductive cells (germline gene therapy) may help parents carrying a genetic disease to conceive a healthy baby. The consequence of this is potentially huge not only for the individuals but for humans as a species. It can be envisaged to lower the prevalence of unhealthy modification of the human genome and to improve the long term survival of the human species.

The application of the Human Genome Project goes far beyond medicine to many other areas of science which include forensic science, agriculture, environment, energy production and DNA-based computing. Forensic science aims at identifying potential suspects or exonerating innocent people wrongly accused of crimes. Already DNA forensics is playing an important role in court rooms, but is limited by the precision of its result due to the use of short segments of DNA. The characterization of very large DNA segments or even the whole genome will overcome this limitation and increase the confidence in this technique. In agriculture the development of genetically modified crops resistant to disease, insect and drought has potentially huge benefits to the farming industry and to the consumer. Introducing beneficial genes for human health in the genome of

molecular medicine which seeks to cure the causes of diseases (genetic defects). Molecular medicine will

plants and animals used for food purposes can increase human resistance to some diseases or improve the nutritional value of food products.

In summary the human genome project is probably the biggest task achieved by humans. It will affect our daily life a great deal more than man landing on the moon. Healthcare, food, policy insurance and employment of individuals are all going to be affected by the knowledge of the human genome.

In conclusion there is no doubt that scientific discoveries are changing the shape of humanity. Early in the 20th century Marie Curie, Albert Einstein and Neil Bohr formulated ideas that made this century a century of physics, particularly nuclear and quantum physics and electronics. The benefits of these developments are unfortunately still in the hands of the very few wealthier countries. The discovery of the mechanism of genetic material transmission by James Watson and Francis Crick in 1953 laid the ground work for modern biology and prompted the 21st century to be a century of biology, particularly genetics, biotechnology and molecular medicine. The challenge to humanity is to make positive use of these discoveries and to share their benefits with the whole of humanity and not just the few wealthier countries.

Q2: Higher on the agenda of health authorities in developing countries are urgent issues such as provision of adequate clean water, food supply and combating diseases, how would the developing countries benefit from decoding the human genome?

A2: In my view the knowledge of the human genome is not going to have a great impact on developing countries, at least not in the foreseeable future. There are far more important problems to tackle in developing countries. Tuberculosis, malaria and AIDS are having devastating effects in Africa. Drought, famine and wars are preventing the poor countries from eradicating basic problems such as malnutrition and illiteracy.

More important to developing countries are the genomes of parasites, bacteria and viruses which kill their people. Indeed in the scientific magazine *Nature*, an Imperial College Research Team published an article (Catterucia et al. (2000), *Nature*, 405, 959-962) on genetically engineered insects resistant to malaria. This raises hope that problems facing the developing

countries could be solved using a genetic approach.

Finally, as I said earlier the 21st century is going to be a century of biology and any society seeking to have a sustainable development will have

to master the knowledge of genetics. My fear is that unless a great deal of effort and money is put in by developing countries the gap between rich countries and poor countries will widen even further.

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Scientific career:

I was born in Taza, Morocco on 1st June 1967. I did my high school studies in Taza. After my undergraduate studies in the University Mohammed V in Rabat, Morocco, I moved to France in 1989. I spent my first year in Professor C. Bonne's laboratory working on free radicals. This led to the award of the French degree DEA necessary for a registration in a PhD. This was my first contact with the scientific research and I really enjoyed it. Thereafter, I registered for a PhD in the CNRS-INSERM U249. During my PhD my work was devoted to the investigation of the structure and the mechanism of the regulation of smooth muscle contraction by thin filament regulatory proteins caldesmon and calponin. In particular, I have investigated the interface between caldesmon and

calponin and their targets proteins using a wide range of biochemical techniques. After completion of my PhD, my interest in the regulation of smooth muscle contraction was growing and I decided to deepen my research in this field. I therefore chose a leading group in this field, Professor S. Marston's group. During my postdoctoral research the Wellcome Trust supported me. I built up on my previous work on both calponin and caldesmon. In 1999 I have been promoted a Lecturer in Imperial College School of Medicine. Last year I obtained A Research Career Development Award from the Wellcome Trust to develop research on the mechanism of regulation of smooth muscle contraction and cell motility by actin binding proteins. As part of this award, I am visiting two laboratories in the USA to deepen my knowledge in enzyme kinetics, a technique necessary for me to successfully accomplish my project. My research group in London is comprised of myself and two PhD students. I have published a total of 16 papers and over 40 abstracts on caldesmon and calponin structure-function. 5 of the publications are in the prestigious Journal of Biological Chemistry, 5 are in Biochemistry.