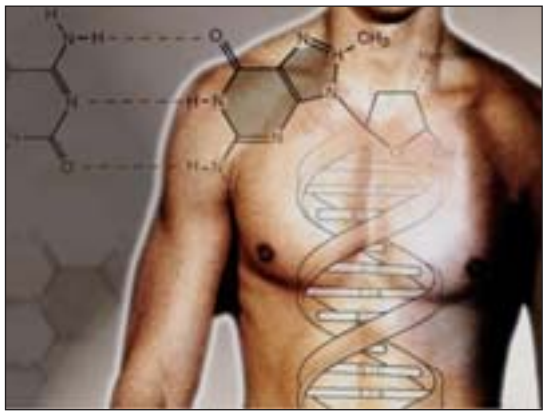
1,000 Genomes

Two a Day

An international research consortium, the "1,000 Genomes Project", is producing a detailed map of human genetic variation to support the discovery and understanding of genetic variants that influence human disease.



"The 1,000 Genomes Project will examine the human genome at a level of detail that no one has done before," said Richard Durbin, co-chair of the consortium. "Such a project would have been unthinkable only two years ago. Today, thanks to amazing strides in sequencing technology, bioinformatics and population genomics, it is now within our grasp. So we are moving forward to build a tool that will greatly expand and further accelerate efforts to find more of the genetic factors involved in human health and disease."

At the genetic level, human individuals differ by less than 1% of their 3 billion base pairs. Identifying and understanding these small variations may help to explain individual differences to disease susceptibility, drug response or reaction to environmental factors. The new project will scan the genetic make-up of at least a 1000 people from populations tracing back to Europe (e.g. Tuscan), Africa (Maasai and Luhya from Kenya), Japan, China (living in Denver), India (Gujarats in Houston) and Mexico.

The original Human Genome Project, completed in 2003, took 13 years to sequence a single individual's genome. The 1,000 Genomes Project will depend on large-scale implementation of new DNA sequencing techniques to keep the overall costs down to around US-$50 million (a tenth of what it would cost using older technology).

Recently developed catalogues of human genetic variation, such as the haplotype map, HapMap, have allowed identification of over 100 genomic regions containing genetic variants associated with risk of common human diseases such as diabetes, coronary artery disease, prostate and breast cancer and rheumatoid arthritis. However, these existing maps are not very detailed, necessitating further costly and time-consuming DNA sequencing to help pinpoint the disease-related genetic variants at the base pair level.

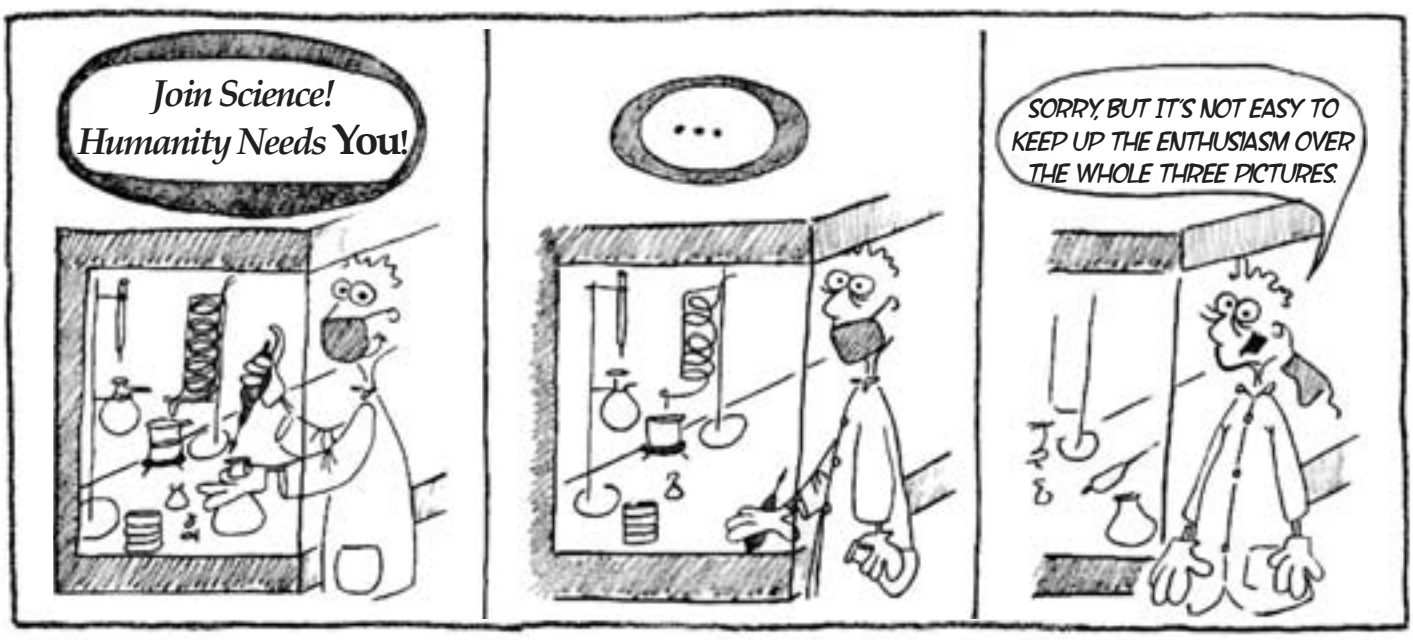
Three pilot projects will be used to evaluate the best approaches for using the new sequencing platforms in the final project. The first pilot, expected to be completed by the end of the year, will involve intensive sequencing of the genomes (obtained from blood samples) from two nuclear families (mother, father and child) with 20 passes of each genome, providing a comprehensive dataset for six people. In the second pilot, the genomes of 180 people will be sequenced at low coverage with an average of two passes of each genome. The third pilot will concentrate on the exons of around 1,000 genes in 1,000 people and is aimed at exploring how best to obtain an even more detailed catalogue in the 2% of the genome that codes for proteins.

In the final phase of the project, 1,000 genomes will be lightly sequenced (two times) across the entire genome, with extra sequencing in the gene regions. During its two-year production phase, sequence data will be produced at an average rate of 8.2 billion bases per day, the equivalent of more than two human genomes every 24 hours.

The sequencing work will be conducted by the Wellcome Trust Sanger Institute (Cambridge, UK), Beijing Genomics Institute (Shenzhen, China) and the US National Human Genome Research Institute's Large Sequencing Network. The data generated will be stored and distributed from the European Bioinformatics Institute (EBI) and the National Center for Biotechnology Information (NCBI). -JGA-

PAUL THE POSTDOC

BY RAFAEL FLORÉS



ERC Starting Grants

97% Failure Rate

The European Research Council (ERC), an EU funding body, launched in 2007 with a 7 year €7.5 billion budget, has announced the 201 confirmed winners and the 229 reserve winners (should more funds become available) of its first ever funding round for Starting Independent Investigators, incidentally providing all sorts of statistical analyses about the profile, nationality and location of the winners.

Starting Grants for up to €2 million over 5 years are designed to boost the careers of researchers, who may be working in any area of science or scholarship, at the time they are establishing themselves as independent research leaders, 2 to 9 years after completion of their PhDs. By the deadline in April 2007, some 9,167 applications were submitted by Principal Investigators (PIs), representing 88 nationalities, in conjunction with host institutions based in all parts of the EU and countries associated to the research framework programme. Over 800 scientists and scholars from throughout the world participated as peer reviewers for the ERC.

However, with a total allocation of only €290 million, there was an amazingly high failure rate of over 97% of applicants. After the first round, 554 investigators went on to submit full proposals, of which 431 passed the quality thresholds for excellence. Of these, 201 are confirmed winners but ERC hopes to finally fund around 100 more from the ranked reserve list. The 300 eventual winners will represent 32 nationalities of PIs and around 170 host institutions in 21 countries.

Overall, the average age of successful grantees is 35, of whom 26% are women, and the majority have more than 6 years post-thesis experience. However, life science research only accounts for a third of successful grants with just 20% of these from women.

Analysis of the institutional affiliations of the grant finalists has thrown up some surprises and has already led to some political friction. France's Centre National de la Recherche Scientifique (CNRS) provided the highest number of finalists (20); the University of Cambridge and Spain's Consejo Superior de Investigaciones Cientificas tie in second place with 12 finalists each. Fourth is Vrije Universiteit Amsterdam with 10, fifth Imperial College London with 9.

The winning countries by host institution were Britain (with 19% of winners), France (13%) and Germany (11%), with the Netherlands, Italy, Spain and Israel each contributing 8%, and Switzerland 5%. Meanwhile, Austria, Denmark, the Czech Republic and Portugal only had one each and Poland none. The winning nationalities of principal investigators were: German (13%), Italian (12%), French (11%), British (10%) and Israeli (8%).

Surprisingly, the ERC statistics suggest that Cyprus has the highest rate of suc- ▸▸

Synthetic Biology

Playing LEGO in Cells

Ever heard of bacteria smelling like mint while they are growing and like banana when they are done? This was the result of one of the projects presented at the International Genetically Engineered Machines (iGEM) competition 2006 at the MIT in Boston.

In 2004 the annual, worldwide graduate and undergraduate competition in synthetic biology took place for the first time. Last year 54 teams participated, 12 were from eight different European countries of which 4 were prizewinners.

The concept of iGEM resembles the RoboCup competition in electronics, where teams assemble robots to compete in a Jamboree for the best functional system created. Similar to this competition, the students are provided with a library of standardised "BioBrick" biological parts (the starter kit contains 1,400 DNA pieces encoding enzymes and other molecules). The participants can use them or add their own "Bricks", in order to design and build simple biological systems from interchangeable parts and operate them in living cells. It's a bit like playing LEGO, except that in the end you have, for example, banana-scented bacteria.

The aim of the iGEM competition is mainly an educational one. Synthetic biology is, by nature, a cross-faculty discipline. It encompasses very different basic methodologies, genetic engineering and mathematical modelling followed by computer simulations. In many curricula, however, genetic engineering is taught in Biology classes and mathematical modelling is taught in Mathematics, Physics or Engineering classes, while simulation of the model relies on expertise acquired in Physics or Computer Science classes. Thus, the methodological components Synthetic Biology are treated as separate planets that will never meet on the path of any given student. By inducing a collision of these two planets, iGEM wants to change this view, attempting to make both planets more attractive and ludic to the student.

The results achieved by the students are often remarkable and sometimes even almost ripe for application. Take, for example, the London team that last year created the "Infector Detector", a biological sensor that catches infections on hospital catheters at an early stage. Or the bacteria able to detect arsenic, presented by students from Edinburgh.

The final iGEM competition events usually take place during November at MIT in Boston. The project phase starts in April so, whoever wants to participate this year should quickly go to *www.igem.org* for more information. European iGEM activities are being organized by a new group, iGEM Europe. RNE-

▸▸ cess with well over 2 grants per million population (it only has 0.75 million inhabitants), followed by Switzerland with a little over 2 per million. However, the obvious winner, Israel, is absent from the analysis because apparently the ERC lacks population statistics for Israel which, with a population close to Switzerland's 7.5 million inhabitants, easily has 3 grants per million. Expressing the number of grants per 1,000 researchers, Cyprus again wins (over 3), with The Netherlands second at 0.7, but this time, in addition to missing Israeli figures, the ERC has also lost its data on the total number of UK researchers!

The ERC Scientific Council says it will evaluate the selection process and outcome, in order to fine-tune the grant scheme for the next Starting Independent Researcher Grant call, which will be published by the summer of 2008. -JGA-

Novartis Foundation

Doors Closed

Brainstorming and debate! Both are regarded as key ingredients of the recipe on how to prepare and maintain excellent science

For nearly 60 years the historic building of the Novartis Foundation (formerly Ciba Foundation) in London has been one of the most prominent places worldwide for biomedical scientists to do exactly that – brainstorming and debate. Ulf von Euler, for example, reported that his idea of how neurotransmitters are stored and released first emerged in 1960 during discussions at one of the typical three day-symposia held by the foundation.

However, after having run more than 400 symposia, as well as a publishing programme and other activities, the Novartis Foundation finally closed its doors at the end of last month. Novartis, the pharmaceutical giant, had succinctly decided that the foundation was no longer relevant to its interest and struck the meeting activities off its list.

The historical building at 41 Portland Place will be taken over by the Academy of Medical Sciences charity. It is unlikely, however, that it will be able to continue with the building's tradition of intimate symposia, including intense brainstorming and debate. -RNE-

Infections Made Possible

European researchers add two new mouse models for virus-caused human diseases to their list.

How does the sneeze of a mouse sound? Never heard one? Sebastian Johnston *et al.* probably have. Recently, a team led by him at the Imperial College London, collaborated with researchers in Italy, France and elsewhere in the UK, to succeed in breeding mice susceptible to infections from the rhinovirus, which causes about three quarters of common cold cases in humans (*Nature Genetics* 14(2):199-204).

For more than fifty years, the common view was that mice and other small animals were resistant to rhinoviruses. A couple of years ago, however, Johnston and Co. found that rhinoviruses are actually capable of reproducing themselves inside mouse cells. The problem for the virus was rather how to get into the cells.

Of the 100 known rhinovirus strains, 90% use human intercellular adhesion molecule-1 (ICAM-1) as their cellular receptor but do not bind mouse ICAM-1; the remaining 10% use a member of the low-density lipoprotein receptor family and can bind the mouse counterpart. Subsequently, Johnston's team genetically modified BALB/c mice in order to express a mouse-human ICAM-1 chimera and thus, successfully, created an entry door for the virus into their cells.

The infected mice subsequently reacted as expected: they developed symptoms of a common cold comparable to those in humans, particularly the augmentation of allergic airway inflammation. Moreover, when combined with an allergen such as ovalbumin, which can cause an allergic reaction in the lungs, the simultaneous infection with rhinovirus made the response worse and led to a mouse version of asthma shock.

Of course, hopes are now high that these mice will prove to be useful in the development of future therapies for colds and asthma exacerbations.

Similar hopes have recently been raised by another new mouse model. A French team, led by Marc Lecuit at the Institute Pasteur in Paris, has, for the first time, developed a mouse strain mimicking the symptoms of a severe chikungunya virus (CHIKV) infection (*PLoS Pathog* 4(2): e29).

CHIKV is transmitted to humans by mosquito bites and has only recently re-emerged, causing a massive outbreak in the Indian Ocean region and India. A flu-like syndrome typically characterises the infection, however, cases of severe infection involving the central nervous system have recently been described, notably in neonates.

The CHIKV mouse model carries a deletion of the IFN-α/βR gene leading to partial or complete disruption of the type-I interferon pathway. Neonates were susceptible to CHIKV and neonatal disease severity was age-dependent. Adult mice with a partial or complete defect developed a mild or severe infection, respectively.

In contrast to rhinovirus-infections, however, relatively little is known about the pathophysiology of CHIKV-infections. Therefore, the CHIKV-mouse model will be used primarily to shed light on the mechanisms of infection and dissemination. The potential development of treatments and vaccine candidates will only be the second step.

-RNE-

(More research results from European labs on p. 24-29)

Recently Awarded

▸ **Naama Barkai**, associate professor at the Weizmann Institute of Science in Rehovot, Israel, is the first-ever winner of the **FEBS/EMBO Women in Science Award**. With this new annual award, worth €10,000, the European Molecular Biology Organization (EMBO) and the Federation of European Biochemical Societies (FEBS) want to recognise the exceptional achievements of a female scientist in life sciences research over the previous five years. Naama Barkai was chosen as the inaugural winner because of her contributions to systems biology and the mathematical modelling of biological systems. Combining theory and experiments over the last years, she has successfully unravelled principles that govern the design and function of biological networks as different as chemotaxis, embryonic development and the organisation of the cellular transcription programmes.

▸ **Hans Robert Schöler** (Münster/Germany), **Irving Weissman** (Stanford/USA) and **Shinya Yamanaka** (Kyoto/Japan) will receive the **Robert Koch Prize** 2008, endowed with €100,000. In 2003, Schöler and his team were the first to differentiate cultured mouse embryonic stem cells to egg-like cells. Earlier, he had discovered the gene Oct4 in embryonic stem cells, which meanwhile has become known as the key gene for the pluripotency. One of the latest proofs was provided last year when Shinya Yamanaka, with the help of Oct4 and three additional genes, succeeded in taking back adult skin cells into a pluripotent state. Weissman, the third awardee, is an expert for adult stem cells. Among other achievements, he was the first to isolate blood-forming stem cells from mice and humans, as well as human stem cells capable of generating various types of brain cells.

The **Robert Koch Gold Medal** 2008 will be presented to **Philip Leder** (Harvard/USA). Leder was among the pioneers elucidating the genetic code, co-discovered the oncogene *c-myc*, and was scientific father of the famous "oncomouse", an *in vivo* model for cancer which became the world's first patented animal.

Research Letter from…

The Heel of Italy

By our Corresponding Author, Zampa di Cane.

Are our fashionable handmade shoes really so bad for ladies' health? One of our illustrious research signoras, Dr Maria Cerruto, from Verona University (nearer to the knee of Italy's boot), has rushed to the defence of the much-maligned height-boosting heel on women's shoes.

In her letter to the Editor in the journal *European Urology* entitled, "Women pay attention to shoe heels: Besides causing schizophrenia they might affect your pelvic floor muscle activity!!" (In press, available online 24 Jan 2008), Dr Cerruto begins:

"A few months ago, when I read the article in the *Daily Mail* (29/10/07) concerning the hypothesis that heeled footwear might cause schizophrenia, I jumped in my chair, horrified. Why? Because as many other women, I like heeled shoes and although they are sometimes uncomfortable, I continue to wear them in an effort to appear more slender and taller… As a paladin of all women who love heeled shoes, I tried to find something healthy in them, and at the end I reached my goal."

Although Dr Cerruto normally looks at penis-sparing treatment for squamous cell carcinoma and sperm retrieval from obstructed tubes, she speedily developed a series of tests to study the benefits for pelvic floor muscles when holding the heel higher. Wiring up the pelvic muscles of 66 women under 50, she measured the pelvic floor muscle activity at rest and during maximal contractions according to different heel heights and shoe sizes.

She claims that women holding their feet at a 15 degree angle to the ground, equivalent to a 5 cm heel, had more relaxed pelvic muscles with less electrical activity.

"Heels work the pelvic muscles and reduce the need to exercise them. Wearing heels during daily exercise may reduce the need for the pelvic floor exercises necessary to keep that part of a woman's anatomy toned and elastic." The pelvic floor exercises to which she refers involve clenching the muscles one would use to prevent oneself urinating. For 50 years, women have been advised to perform such exercises to strengthen their muscles before and after childbirth, to prevent incontinence.

Although some might quibble over her lack of statistically meaningful data analysis, Dr Cerruto's conclusion that high heels "might affect pelvic floor muscle activity, reducing myofascial pelvic pain, relaxing the pelvic floor and improving pelvic organ well-being!" has been seized upon by the world's media, resulting in headlines like, "Heels boost sex life", "Heal your sex life with heels", "Wear high heels! You'll have better sex", and "Baggy vaginas are out for 2008: stiletto-therapy agenda science."

Not surprisingly, Manolo Blahnik, the stiletto-obsessed fashion shoe designer, welcomed Dr Cerruto's three paragraph research letter as fabulous news for the "male species". "I know men who tell me that heels have saved their marriage!"

Some uncharitable sceptics have preferred to point to another phrase in Dr Cerruto's now-celebrated letter. "I remain astonished in the face of bizarre medical theories published in non-scientific journals in the absence of any scientific filter or key reading, because they might be misunderstood."

However, not to be outdone, an English continence physiotherapist, Dr Grace Dorey, claims that pelvic floor exercises "help men too". The exercises were found to help men with erectile dysfunction, as much as taking Viagra. "Pelvic floor exercises improve function in a physical way, in a more natural way." So far, this line of male pelvic research has not called for men to don higher heels in order to improve their sex life. At least, not yet…