'There is a balance between pro- and anti-inflammatory compounds [that is] genetically controlled,' Franceschi told delegates at last month's *Biochemical Society* meeting held at Imperial College in London (see http://www.biochemistry.org; http://www.ic.ac.uk). People with certain genes that trigger an imbalance between a pro- and an anti-inflammatory cytokine are more likely to suffer from chronic inflammation related to ageing, he said.

Although 25–30% of longevity is the result of a genetic background, says Efstathios Gonos, Director of Research Specialized in Ageing at the National Hellenic Research Foundation in Athens (http://www.eie.gr), 'It is extremely unlikely that there is a single gene causing longevity.'

The genetic make up of centenarians can thus provide a useful tool in the investigation of age-related diseases. Indeed, Franceschi brands centenarians 'extreme phenotypes' that comprise all the genetic elements that are necessary to avoid age-related diseases. Conversely, high IL-6 levels can be considered as a genetic marker for morbidity and mortality in the elderly.

Functionality of IL-6

This does not come as a surprise to researcher of age-related diseases Jonathan Powell, from Unilever Research in the UK (http://www.unilever.com). Pro-inflammatory cytokine IL-6 is not only linked to the immune system but is also a major metabolic regulator found in primitive organisms, such as tubeworms and starfish, which have no immune system. 'IL-6 has acquired some other functionality as we have evolved. But those old metabolic functions are still there in us,' said Powell.

'As more and more and more of these associations are found, we'll have a better idea of the predictive value of those genotypes,' he said. Genetic markers could then, one day, help to identify subjects at higher risk, and could aid in the development of a new preventative medicine. 'Inflammation does not describe all of ageing but it has a significant component, ' said Powell.

'Major age-related diseases all share an inflammatory pathogenesis,' said Franceschi. Different diseases, such as arthritis and Alzheimer's disease, share the same inflammatory mechanism, he adds. People treated with anti-inflammatory compounds for arthritis have a lower risk of getting Alzheimer's disease.

The finding of a genetic susceptibility to age-related disease also fits with an evolutionary perspective. Centenarians present low levels of pro-inflammatory cytokine IL-6, which protects them from age-related inflammatory diseases. According to Franceschi, showing a strong inflammatory response is an advantage before the age of 50 but it is detrimental in later life when the reproduction-driven force of evolution decreases. 'From an evolutionary perspective, the objective is not to live long but to be fit enough to reproduce', agreed Gonos.

In addition, Franceschi has identified a difference in cytokine levels between men and women. He believes that genetics has a greater role in protecting men from inflammatory disease than protecting women, because women have more protective hormones. 'Women are less prone to having high inflammatory status because it is detrimental for bearing children,' he said.

Improving drug response with pharmacogenomics

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Adverse drug reactions, which in the USA are estimated to account for 100,000 hospitalizations annually at a cost of US$15 billion, could be halved by the implementation of personalized medicine, says David Gurwitz of the Sackler Faculty of Medicine at Tel-Aviv University in Israel (http://www.tau.ac.il/medicine/). However, Gurwitz claims that this can only be achieved by updating medical school curricula [1].

Pharmacogenomics – the study of how genes affect drug action – promises a brave new medical world in which a quick genetic analysis reveals a patient's response to a drug, enabling treatment to be personalized and drug efficacy to be optimized. Although this vision could still be decades away, pharmacogenomics must be incorporated into medical teaching now, says Gurwitz.

A new curriculum

'The need to incorporate the teaching of pharmacogenomics into the medical curriculum is quite urgent,' said Gurwitz, who this academic year has

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launched such a course at Tel-Aviv University, which he hopes will stimulate other medical schools to follow. 'Pharmacogenomics must be incorporated within a few years... into the general MD curriculum,' he said.

The consequence of not doing so, he says, could be that any therapeutic benefits of the Human Genome Project will be severely delayed. The next generation of doctors will not have an adequate understanding of the interplay between genetics and drug metabolism, he warns.

But some experts point out that pharmacogenomics is only part of the problem. The lightning acceleration of genetics in the last decade has left the medical profession lagging behind on many fronts. 'Medical schools have been slow to take on board human genetics, as well as pharmacogenomics,' said Dan Nebert of the Cincinnati Children's Hospital Medical Center (http://www.cincinnatichildrens.org).

'The challenge in training physicians in pharmacogenomics is that there is probably inadequate attention to teaching clinical pharmacology in general, at least in US medical schools,' added Mark Ratain, Chairman of the Committee on Clinical Pharmacology and Pharmacogenetics at the University of Chicago (http://www.uchicago.edu).

Advanced pharmacogenomics

Physicians regularly practice rudimentary pharmacogenomics by asking patients for their family histories of drug sensitivity. More advanced DNA-based pharmacogenomics is already a feature of chemotherapy, where genetic analysis of cancer tissue helps oncologists choose a drug regime that will attack tumour cells most effectively.

Many genes have also been identified that have an effect on drug receptors and metabolism, says Katie Prickett, Commissioning Editor of *Pharmacogenomics*. 'CYP2D6 and apolipoprotein E status are just two of many other examples of genetic measures that could provide valuable information for drug prescribing,' she said. 'It's disappointing that genetic testing is not yet an accepted and routine part of the process in determining optimal and individualized pharmacotherapy.'

Personalized medicine is feasible, and is almost within reach, says Gurwitz, whose opinions are published in the March issue of *Trends in Pharmacological Sciences* [1]. The obstacle to further progress is the dearth of tools for rapid patient screening, he says.

'Hopefully, within 20 to 30 years, we shall be able to have genetic screening tools for choosing the most appropriate medicine for each patient, based on his or her genetics,' he said.

Reference

1 Gurwitz, D. *et al.* (2003) Education: teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine. *Trends Pharmacol. Sci.* 24, 122–125

News in brief

Infectious diseases

Genetic puzzle of influenza solved

Scientists have recently solved a long-standing puzzle about how the influenza A virus assembles its genetic contents into infectious particles [1], which enables the virus to spread from cell to cell. The influenza A virus is the most virulent and potentially dangerous 'flu virus, including the strains responsible for pandemics, which kill millions or people worldwide. Scientists believe it is only a matter of time before another pandemic occurs, and therefore, these new findings about the pathogenicity of influenza A virus are crucial.

The influenza A virus genome comprises eight viral RNA segments. Although the products of all eight of these segments must be present for viral replication, little is known about the mechanism responsible for their incorporation into virions.

New research, from Yoshihiro Kawaoka's group of the University of Wisconsin-Madison School of Veterinary Medicine (http://www.uwm.edu/), has uncovered a molecular signal encoded by a single RNA strand that is crucial in the infection process. The signal recruits the necessary set of eight viral RNA strands to make a complete influenza genome within the infectious particles for the influenza A strain.

According to Kawaoka, the data indicate that the individual RNA segments each make a unique contribution towards the recruitment and assembly of disparate RNA fragments into a complete influenza genome, and therefore support the selective model of virion generation, in which specific structures in the individual RNA segments are responsible for combining the eight genetic fragments into a virion.

This insight into the genetic mechanisms that lead to 'flu infection provide a better basic understanding of how influenza and other viruses work and also has significant promise for new and better vaccines and drugs to combat the infection by exposing the genetic trick that influenza A virus uses to form infectious particles.

1 Fujii, Y. *et al.* (2003) Selective incorporation of influenza virus RNA segments into virions. *Proc. Natl. Acad. Sci. U. S. A.* 10.1073/pnas.0437772100 (http://www.pnas.org)

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