group. Nevertheless, the selection bias used in this sort of study requires the use of randomized trials to demonstrate the efficacy of substitutive oestrogens in the primary prevention of AD.

An antihypertensive treatment prevents dementia according to evidence in the Systeur Dementia Project. The incidence of AD-type dementia rate was significantly lower in a group treated with nitrendipine, as first line antihypertensive drug, than in the placebo group, suggesting a neuroprotective effect by some types of calcium inhibitors.

If one considers the hypothesis of the primary pathogenic role of the β-amyloid peptide in AD, it might be useful to destroy this protein therapeutically, as stated by Einar M. Sigurdsson (New York University Medical Center, NY, USA). A 'β-sheet breaker' that dissociates already formed peptides was shown to prevent the destruction of rat neurons by antibody and to reduce microglia inflammation around the deposits of antibody. This may be a promising treatment to prevent or reduce the amyloid brain lesions of AD.

Overall, this Institut Pasteur EurΩconference presented several forms of treatment for AD and allowed a vivid debate concerning methodologies to improve AD trials.

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Pharmacogenetic-oriented drug development

Drug pharmacokinetics and target interactions vary among individuals, sometimes leading to limited efficacy or adverse reactions [Lichter, J.B. *et al.* (1997) *Curr. Opin. Biotechnol.* 8, 692–695]. These variable reactions are sometimes more common among members of certain ethnic groups than in others [Bertilsson, L. *et al.* (1997) *Acta Psychiatr. Scand.* (Suppl.) 391, 14–21]. A large segment of drug development today is carried out in the USA, Canada and Europe. Consequently, many drug trials recruit largely Caucasian subjects. This is particularly true during Phase I trials, which often enlist few healthy subjects at a single clinical center. The resulting under-representation of minority groups in the early-phase trials sometimes leads to efficacy and adverse reaction problems later, often arising in subjects from such minority groups.

Polymorphic sites and drug design

Variable levels of drug efficacy and side effects often reflect a polymorphic site in a gene coding for one of the drug's metabolizing enzymes, such as a sulphatase [Tomatsu, S. *et al.* (1998) *Hum. Mutat.* (Suppl.) 1, S42–S46] or a methyltransferase [Preuss, C.V. *et al.* (1998) *Mol. Pharmacol.* 53, 708–717]. Polymorphic sites in drug metabolizing enzymes could have powerful pharmacokinetic impact. The polymorphic sites need not be situated in a coding region of the gene; intronic polymorphic sites could result in large expression alterations, leading to robust effects on drug clearance. For example, the expression of tyrosine hydroxylase is strongly affected by an intronic tetranucleotide polymorphic microsatellite sequence [Meloni, R. *et al.* (1998) *Hum. Mol. Genet.* 7, 423–428]. In other instances, the variability may reflect a polymorphic site in the gene coding for the drug's target protein itself, such as a membrane receptor or ion channel, so that certain individuals would be less responsive to the drug, or in other instances, too sensitive to its consumption.

Such adverse effects, if not detected early during drug development, could become serious obstacles during later phases. The best way to combat the reduced efficacy and adverse reactions arising in some individuals, caused by the inherently large human genetic variation, is to recruit subjects from several ethnic groups for the clinical trials. However, this is often an unrealistic solution, given the already complex setup of drug trials. When the genes coding for the drug target and its metabolizing enzymes are known, a simpler and more modest solution is feasible: studying the polymorphism of the relevant genes in a large collection of DNA samples of individuals from a diverse ethnic background. In this way it may become possible to detect in advance polymorphic sites in the relevant genes, which may affect the drug's interaction with its target protein or with its metabolizing enzymes [Linder, M.W. *et al.* (1997) *Clin. Chem.* 43, 254–266].

Proteomics and pharmacogenetics

Proteomics – the study of protein expression under diverse situations and in

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various tissues – is on its way to becoming a major tool for drug target discovery in the 21st century [see recent reviews by Page, M.J. *et al.* (1999) *Drug Discovery Today* 4, 55–62, and Wang, J.H. and Hewick, R.H. (1999) *Drug Discovery Today* 4, 129–133]. Following the completion of the Human Genome Project, when our entire three-billion-nucleotide sequence would be deposited on the Internet, many new protein targets are expected to become available for the competitive drug market. Dealing with the enormous amount of drug-related genomic information will be the next step. Making the right choices between newly discovered targets could dictate the fate of many future drug development projects. This could include using proteomics to search for proteins whose expression by cultured human cells is strongly affected (increased or decreased by at least twofold) by prototype drugs. The strategy often includes running 2-D gels of human cell lines exposed to the drug in question. In this context also, it would be wiser to compare the effects of candidate drugs in human cell lines obtained from individuals from numerous ethnic groups in order to verify that the drug-sensitive protein expression profile obtained is consistent over a large sample of unrelated individuals.

Unique human variation-oriented DNA and cell line collection

Presently there are several large public collections of human cell lines and DNA samples that may be useful for pharmacogenetic-oriented drug development. Most are non-profit, government-affiliated cell line repositories devoted to individuals with known genetic disorders. The National Laboratory for the Genetics of Israeli Populations at Tel-Aviv University, Israel offers a unique potential among the available repositories. It functions as a national repository for human cell lines and DNA samples, collected from healthy individuals that represent the large ethnic variation in Israel. These include individuals from Jewish, Muslim and Druze ethnic background. The Jewish population of Israel presents a particularly large ethnic variability, because many communities, who were isolated for many generations, immigrated to Israel after it won its independence in 1948. These include Jewish communities from Algeria, Ethiopia, Georgia, India, Iran, Iraq, Libya, Morocco, Poland, Romania, Russia, Tunis, Turkey and Yemen, among others. The human cell line and DNA collection available from this laboratory is therefore a valuable source for investigators interested in human variation in the context of pharmacogenetic-oriented drug design. The laboratory has so far established nearly 1500 cell lines from healthy unrelated individuals and from representative families of the various ethnic groups living in Israel, and has already distributed several thousands DNA samples to researchers in the USA, Canada, Europe and Japan.

The individuals who donated the blood samples for preparing the DNA and cell-line collection have signed informed consent allowing the study of their complete genetic makeup. The samples are being kept with strict confidentiality – only sex and ethnic background are supplied along with the DNA or cell lines.

It is hoped that using ethnic diversity-oriented human cell-line and DNA collections will benefit both the scientific community and the pharmaceutical industry by concentrating on the least polymorphic and best candidate drug targets. For further details on sample availability, fees and restrictions see http://www.tau.ac.il/medicine/NLGIP/nlgip.htm or contact David Gurwitz.

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In short...

Corus (Concord, CA, USA) has filed a registration statement with the Securities and Exchange Commission for the public offering of two million shares of common stock. The company expects to use the net proceeds of the offering to fund R&D, including clinical trials, and for general and administrative expenses, capital expenditures and working capital. The registration statement has not yet become effective, and these securities may not be sold nor may offers to buy be accepted prior to the registration statement becoming effective.