

dangerous and likely to fail.' Even so, the panel agreed that any ban should be revisited in five years because of probable research advances in related fields. (*Science* 295, 601–602) *DM*

## Multipotent adult stem cells

Catherine Verfaillie *et al.*, have filed a patent for a stem cell found in the bone marrow of adults that can develop into every single tissue type in the body. It was thought until now that only embryonic stem cells were able to do this, but experiments detailed in the patent show that the cells, dubbed multipotent adult progenitor cells (MACPs) have the potential to do this. (Patent WO0111011, <http://www.european-patent-office.org/espacenet/info/index.htm>) *DM*

## Smallpox still here



Picture courtesy of CDC.

The World Health Organization's (WHO's) governing board has agreed to delay the destruction of the last known samples

of smallpox, which are currently kept at two high-security facilities in Russia and the USA. This decision reflects the consensus that these stocks might be needed to defend humanity against the possible use of smallpox as a bioweapon. In 1967, when WHO started its international eradication efforts, smallpox was estimated to have afflicted more than 15 million people annually, of whom some two million died, with millions more left disfigured and sometimes blind. The successful eradication of smallpox is one of WHO's greatest accomplishments, and in 1980 WHO certified that the disease had been eradicated. (*Science* 295, 598–599; or <http://www.who.int/home-page/>) *DM*

## EU playing catch-up with US biotechnology

Erkki Liikanen, the European Union (EU) commissioner for Enterprise and the Information Society, says that Europe is lagging behind the USA in the biotechnology industry, in terms of company size, market capitalization, number of employees and co-operation between centres of excellence. He has proposed a four-track approach to address this differential: harnessing potential; governing life sciences and biotechnology;

responding to global challenges and implementing strategy. A rolling programme of legislation and review of the life sciences and biotechnology industries in the EU is planned to support their development. This will be coupled with wider public debate to ensure that consumers are able to make informed choices about biotechnology products. [*Chemistry and Industry* 4 February (2002), p4] *MJD*

## Stem cells reveal Downs syndrome secrets

A recent report describes how studies on stem cells have identified genes and cellular processes that are disrupted during the development of Downs syndrome. Scientists from the University of Cambridge and University College, London, UK and the University of Wisconsin (Madison, WI, USA) studied stem cells derived from normal and Downs syndrome fetuses. They found that significantly less cells from the Downs syndrome tissue progressed to form neurons. Also, nerve fibres that were formed were shorter and irregular. The team also identified candidate genes responsible for these changes, offering the hope of gene or drug therapies for Downs syndrome in the future. (*Lancet*, 359, 275–276) *MJD*

## German stem cells

Germany's stem cell debate took a decisive turn recently, when its parliament voted to allow researchers to use a limited number of human embryonic stem cell lines. The vote got a cautious reception from researchers some of who are concerned about restrictions in the new law. Germany will now allow embryonic stem cell lines created before 30 January 2002 to be imported. Applications will be vetted by a new national ethics committee with only high-priority research projects, ranked by a new regulatory body, being allowed. The regulator will ensure that permission is obtained from the parents of the embryo from which the cell line was extracted, and that there is no alternative means of doing the research. (*Nature* 415, 566) *DM*

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## Letters

## The worm in us – *Caenorhabditis elegans* as a model of human disease

In the post-genomic era, the identification and validation of potential human disease-causing or disease-associated genes are of major importance. Model organisms have an essential role in this process and might help to make these genes and their products amenable to pharmacological intervention. Usually, the activity of a candidate gene in the animal model is first eliminated by knockout techniques or reduced by mutations and the phenotypic consequences of the functional loss are monitored to analyze the role of the gene and its encoded protein. This strategy had been successfully applied to individual genes in the mouse and also in the much simpler fruitfly, *Drosophila*. However, genetic manipulations in these organisms are time-consuming and, owing to limitations in space, manpower and financial funding cannot be scaled up proportionally to analyse many genes at a time.

The soil nematode *Caenorhabditis elegans* (see Fig. 1) offers several advantages to study the function of disease genes and their worm homologues. In 1998, it was the first multicellular organism of which the genome has been sequenced completely [1]. One surprising result of this approach was that ~65% of the human disease genes have a counterpart in the worm [2]. Screens to identify gene knockouts can be automated and large-scale setups have been devised with the recently developed RNA interference approaches that allow the temporal gene inactivation of hundreds, if not thousands, of genes in parallel experiments using microtiter-plate assays [3]. Phenotyping the mutant morphology and behaviour is greatly facilitated by a complete cell lineage map and the existence of a wiring diagram of all 302 neurons. Despite its obvious simplicity, organogenesis and even complex neuronally controlled behaviors (e.g. associative learning and the response to noxious stimuli) can be studied and dysfunctions can be

attributed to defects in individual cells [4,5]. In addition, the animals are amenable to molecular, genetic and biochemical analyses allowing the identification of protein interactions and suppressor mutants and, thus, to the dissection of entire regulatory pathways.

Several studies in recent years have established *C. elegans* as a superb model to evaluate the function of disease genes. They suggest that indeed the large degree of sequence similarity found in genes in *C. elegans* and human genomes results in a significant functional similarity of the encoded proteins. Most importantly, the major signaling pathways of *C. elegans* and vertebrates, including Ras, Notch, TGF $\beta$ , wnt/wingless and insulin signaling are remarkably conserved. The validity of using *C. elegans* to study genes and pathways related to human health and disease has probably been most elegantly demonstrated by dissecting the pathway controlling apoptosis. These studies have nicely demonstrated the potential and also the limitations of this invertebrate model. Interactions of the genes that were isolated in the *C. elegans* pathway allowed researchers to define the regulatory network of apoptosis. Probably most functional aspects of these interactions are conserved in vertebrate models and, probably, also in humans. However, the search for similar factors in mammals clearly suggests that the regulation of apoptosis is significantly more complicated, involving many more genes that have evolved from the factors found in the worm [6].

Recently, considerable effort has been made to study *C. elegans* genes whose mutations in the human counterparts result in the onset of complex neurological disorders, such as Alzheimer's, Huntington's and Parkinson's diseases. For example, mutations in the human presenilin PS1 are associated with an early onset familial Alzheimer's disease, whereas the mutants of the respective *C. elegans* gene *sel-12* only show neurological deficits in few neurons but a highly penetrant egg-laying defect [5,7]. Despite this obvious phenotypic discrepancy between invertebrate and mammalian dysfunction, a remarkable degree of functional conservation was demonstrated in several studies by rescuing the worm defects through transgenic expression of the respective human wild-type genes [5,7]. Such an

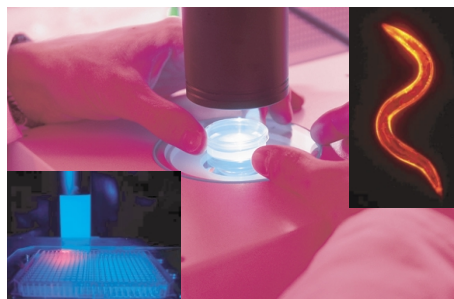


Fig. 1. Until recently, the consequences of mutations and drug exposure on *Caenorhabditis elegans* were typically examined by dissecting microscopy (center). Life staining with green fluorescent protein and DsRed (right inset) and animal growth in microtiter plates (left inset) now facilitate the automated analysis of large numbers of worms.

ultimate proof of functional conservation can probably be devised for many homologous genes found in both human and worm genome. Transgenic *C. elegans* strains can easily be obtained by microinjection of DNA hosting the gene of interest, a promoter expressed in all or selective tissues, and a marker to identify the transgenic progeny. If the human transgene can take over the function of the defective worm gene, the rescue of the mutant phenotype indicates identical roles of both factors.

Some surprising results have been obtained using *C. elegans* to study factors implicated in human diseases. Bessou and colleagues recently suggested *C. elegans* as an excellent model to study Duchenne muscular dystrophy [8]. Until recently, it was widely accepted in the field that the progressive deterioration of muscle function typical for this disease might be the consequence of a functional conservation between dystrophin and its close relative, utrophin. However, worms only have one dystrophin gene but nevertheless showed a progressive dystrophy in a genetically sensitized background [8]. The superb genetic tools of *C. elegans* can now be exploited to identify modifier genes that might define the cellular mechanisms these factors are involved in. Look out for more examples of functional conservation, perhaps even of entire pathways, in the near future!

In addition to the ease of genetic manipulations, this tiny nematode has one major advantage that might develop it into a superb tool for the biotech industry – *C. elegans* can easily be grown in microtiter plates in both 96- and 384-well formats. Because its receptor pharmacology is remarkably similar to

that of humans, drugs and side effects can be tested in large scale using *C. elegans* and its mutants as an *in vivo* model. Methods to automate the readout, for example to measure behavioural differences such as motility defects or the response to intoxication, are being developed at several places [9]. Drug development using 'humanized worms' (e.g., *C. elegans* knockout strains expressing the homologous human disease mutant) on a large scale is therefore feasible [10]. And, perhaps the first effective medication against Alzheimer's disease or Duchenne Muscular Dystrophy will, one day, be the result of a high-throughput pharmacological screening procedure using *C. elegans* as a whole-animal model.

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