

## In this issue

### DNA vaccine for rabies

Health and disease defy easy definition and understanding. Biology and medical practice have had close links for centuries and have mutually influenced each other. In the post-cartesian world, reductionism has influenced biological research more than anything else. The successes in drug development are but one example of the reductionist view of biology. Purification and production of hormones for therapy, the use of transgenic animals for physiological research, the explanation of even 'behaviour' in molecular terms are other examples to prove the stranglehold of reductionism in biology both teaching and research and as a consequence of medical practice. Spectacular developments and successes of molecular biology have only reinforced our faith in this approach.

Vaccination against infectious organisms as a prophylactic method has come a long way since Jenner's days. While protein antigens and synthetic peptide epitopes can replace the whole infectious organism in some cases, the use of surface antigens or epitopes derived from them has not been able to tackle one problem faced by researchers and medical practitioners, i.e. polymorphism in coat protein antigens observed in various isolates. This is deeply frustrating as this would envisage separate vaccines against each of the isolates. Work in early nineties (Ulmer *et al.* 1993) provided promise to overcome this problem. The problem was rightly diagnosed as inability to stimulate a cell-mediated immune response involving cytotoxic T-lymphocytes (CTL) as this would react with endogeneously expressed antigens while humoral immune response would be essentially against released surface antigens. The work also demonstrated that immunization with plasmid DNA containing the appropriate insert could result in expression of endogenous (infectious agent's) protein in the immunized host

and hence recruitment of CTL. On page 1012 Biswas *et al.* demonstrate protective immunity in mice by administering a rabies DNA vaccine. Not only is this a dramatic development confirming the advent of 'DNA vaccine era' but is also significant in another feature. They have been able to do so without the use of immunostimulatory sequences (ISS) present in ampicillin resistance conferring gene. The latter is part of the plasmid construct. Biswas *et al.* have used, instead, kanamycin resistance conferring gene in their plasmid construct. This obviously does not contain the ISS. Hence, their results assume tremendous significance as this unambiguously demonstrates the efficacy of a DNA vaccine for rabies. The more interesting fact is that the animals were challenged intracerebrally, which is an acute challenge. That even then, sufficient CTL and humoral antibodies have been built up to take care of the invasion is indicative of the strong immune response that this 'DNA vaccine' has been able to elicit. It is obvious that the plasmid containing the insert DNA has integrated with host cells and produced the viral antigen. It would be interesting to know to what cells of the host, the CTL response is directed against?

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### Very old DNA at its infancy

With the popularization of the polymerase chain reaction (PCR) technique, there are unprecedented attempts to amplify and study DNA samples from diverse sources and the reasons are manifold. In a normal PCR or *in vitro* replication cycle, the generation of the replicating molecules from the initial population is like bifurcating paths, each point of bifurcation represents separation of two strands of DNA at the step of denatura-

tion. Thus, ideally they are asexual, separated paths evolved independently from each other. For quite sometime now, it has been possible to study the relationship among different organisms through genetic studies at the DNA sequence level, or by analysing the ribosomal RNA, etc. However, with the possibility of PCR amplification of minute DNA samples, this method has become most attractive. In reality, however, two separated product of a PCR cycle do not evolve independently of each other. Recombination of genetic material does take place due to various reasons like formation of incomplete strands owing to fragmentation and premature termination.

Keeping such limitations in mind, one wonders the reach of PCR amplification technique when one goes through a series of publications started sometime around 1990, each describing the recovery of DNA from ancient human and animal remains. Singh *et al.* review (page 879) the current trend in ancient DNA studies.

Mitochondrial DNA is a preferred tool for ancient DNA studies since it accumulates mutations at a much higher rate and thus can be studied to uncover population history. Secondly, mitochondrial genome is maternally inherited and therefore there is no recombination between maternal and paternal genes.

One question that comes first in anyone's mind is how stable is the ancient DNA today! The question of stability is relative. DNA is a very stable species compared to RNA or some proteins. But in a million-year time scale, they undergo various damages limiting the possibility of amplification of even a small fragment. Controversy surrounds the analysis of DNA samples from biological species aged many-million years and the authors have pointed this out adequately.

Sometime back a report indicated that there was even an attempt to PCR amplify a portion of the 'shroud of Turin'! What is the sequence of DNA from ...?

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