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The Molecular Medicine Revolution

Even in this age of advanced electronic communications, face-to-face meetings still provide one of the best ways to develop cooperation, understanding and collaboration between groups that are otherwise unlikely to meet. It was for this reason that *Nature Medicine*, in collaboration with our Nature Japan colleagues, hosted a two-day, multidisciplinary meeting in Tokyo (November 9–10th).

Molecular medicine involves studying fundamental aspects of disease in model systems (purely artificial *in vitro* settings, animal models or humans) and then applying the lessons learned to patients. It is a long-term approach to tackling the fundamental basis of disease (as opposed to treating symptoms), with the experiments of today perhaps yielding clinical benefits in five or ten years. The conference was conceived to reflect these endeavors.

One way of accelerating the process of research and discovery that will eventually lead to effective treatments is to take advantage of the breadth of knowledge and experience available to the research community. All too often, conferences, journals, institutions and the other structures that support biomedical research focus on a narrow field. Although many would argue that such a focus is necessary to achieve progress in a highly competitive research environment, to focus too narrowly is to miss the opportunities beyond a particular specialty. With this mind, The Molecular Medicine Revolution brought together some of the world's preeminent scientists in a setting that encouraged interdisciplinary discussion.

Akira Kakizuka

Like so many countries, Japan is experiencing a gradual but accelerating demographic switch to an older population structure. With this switch comes the expectation of an increased incidence of those diseases commonly found in the elderly, such as heart disease, cancer and neurodegeneration. And no country is immune to the effects of HIV. Thus we settled on four topics to illustrate the challenges facing the biomedical research community (see below). In each of these fields, impressive advances have been made. Yet much more remains to be done before we can reasonably claim to be able to effectively treat or cure any of these diseases.

Dennis Selkoe

Although it is impossible to claim any immediate collaborative or health-related benefit from such a meeting (other than the obvious interest it can elicit in participants), one does not have to look far to see the parallels and common interests between otherwise distinct fields: whether it is the use of HIV-based vectors as central nervous system gene delivery tools; the similarities in inflammatory response between Alzheimer disease pathology and cardiovascular disease; the common evolutionary and selective pressures driving diseases as diverse as cancer, neurodegeneration and infectious diseases; or the problems of how best to selectively and effectively deliver therapeutics.

As *Nature Medicine* approaches its fourth anniversary (the journal was launched in January 1995), we will redouble our efforts to encourage the biomedical research community to take advantage of these common interests, and to foster better communications between the many disciplines that contribute to the rich landscape of biomedical research.

Neurodegeneration

Chairs: Katsuhiko Mikoshiba (RIKEN Brain Institute & University of Tokyo) and Fred Gage (The Salk Institute).

Although increasing life expectancy is a sure sign of progress in the fight against disease, getting older also means an increased risk of developing neurodegenerative disorders.

Many such diseases share the common feature of progressive loss of cognitive functions often accompanied by physical impairments. Alzheimer and Parkinson diseases have another pathological hallmark in common—the production and accumulation of β-sheet protein structures that are clearly associated with neuronal loss.

The amyloid precursor protein (APP) is a chief component of the amyloid plaques found in the brains of Alzheimer patients. Dennis Selkoe (Harvard) described work showing that PS1 is absolutely required for the processing of APP, a finding that will surely redirect the efforts of pharmaceutical companies seeking compounds to inhibit or delay the formation of these protein deposits.

Akira Kakizuka (Osaka Bioscience Institute) discussed the group of neurodegenerative disorders caused by the inappropriate expansion of stretches of CAG triplets. Although it has been known for a few years that CAG expansion (and the resulting long stretches of polyglutamines) are essential to the development of these triplet-repeat diseases, the mechanism by which the polyglutamine stretches alter the function of the appropriate proteins and give rise to neurodegeneration remains unknown. Kakizuka has established model systems in cell culture, *Drosophila* and mice to recapitulate the process observed in patients. He suggested that altered protein processing may be the mechanism to target for therapeutic intervention, with the identification of the downstream events that lead to cell death or apoptosis.

An alternative approach to tackling neurodegenerative disorders was discussed by Fred Gage (The Salk Institute) and Ole Isacson (McLean Hospital and Harvard Medical School), both of whom are devel-

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oping strategies to replace lost neurons.

Gage presented recently published data (*Nature Med.* **4**, 1313; 1998) demonstrating neurogenesis in the adult human brain. Besides overturning the earlier dogma that adult human brain is not capable of cell division, this work opens an avenue for therapeutic intervention that would take advantage of the replicative capacity of these neurons.

Fred Gage

Isacson described trials in which Parkinson disease patients were grafted with pig fetal neurons. In addition to a video presentation showing a few startling examples of patients with advanced disease demonstrating substantial recovery after grafting, this work showed that in animal models, axons from different species are capable of forming connections with the host brain.

Cardiovascular disease

Chairs: Toshio Ogihara (Osaka University Medical School) and Russell Ross (University of Washington School of Medicine).

Russell Ross reviewed the steps leading to atherosclerosis, clarifying the nature of the early protective inflammatory reaction against modified lipoproteins and altered endothelial function, and the subsequent development of a complicated lesion that in turn modifies this inflammatory response.

The plasma and cellular concentration of the angiotensin-1 converting enzyme (ACE), an essential enzyme in the renin–angiotensin system, is strongly influenced by a common polymorphism of the gene. Several studies have reported associations between this polymorphism and a variety of diseases, many of which involve the cardiovascular system. Florent Soubrier (INSERM U358) briefly reviewed this field before describing his efforts to define the mechanism responsible for the effects of the ACE polymorphism.

John Fabre (Institute of Liver Studies) considered the main challenges to successful organ transplantation, focusing on the role of the vasculature in organ allografts. Donor vascular endothelial cells are probably the most important source of damaging antigens in terms of immune rejection, and his studies have focused on the possibility of suppressing MHC class II expression in these cells using dominant negative mutants of the class II transactivator.

Despite some success in identifying genes involved in monogenic hypertensive syndromes, it has been more difficult to identify the many genetic factors involved in regulating blood pressure in normotensive subjects. Herbert Schuster (Max Delbruck Center for Molecular Medicine) reviewed the most appropriate methods for dissecting out the multifactorial components of blood pressure regulation.

Cancer

Chairs: Takashi Sugimura (National Cancer Center) and Walter Bodmer (Hertford College, Oxford).

Using colorectal cancer as an example of the now widely accepted multi-step model of tumorigenesis, Walter Bodmer reviewed the principal players involved in the development of cancer. In particular, Bodmer stressed the importance of selection in cancer development, arguing that increased genetic instability and mutation, often assumed to be a prerequisite for cancer development, is not required for cancer progression.

Yusuke Nakamura (University of Tokyo) presented his most recent efforts to identify p53 target proteins. Using yeast two-hybrid assays and differential display methods, he has found a series of candidate sequences, including an interesting new gene, with no known homology, that seems to behave as a brain-specific inhibitor of angiogenesis.

Andrew Feinberg (Johns Hopkins University) presented his most recent data (*Nature Medicine* **4**, 1276; 1998) on loss of imprinting in tumors. Surprisingly, these epigenetic changes were also observed in the normal tissue surrounding colorectal tumors.


Stephen O'Brien and Anthony Fauci

Despite considerable advances in our understanding of disease mechanisms and the possibility of introducing all manner of therapeutics to prevent, delay or treat disease, the effective and selective delivery of these therapeutics is a principal unmet need. Rakesh Jain (Massachusetts General Hospital and Harvard Medical School) discussed a series of problems encountered in the delivery of tumor therapeutics, concluding that better models of tumorigenesis are required to mimic the human situation before substantial progress in this field can be made.

HIV

Chairs: Mitsuaki Yoshida (Institute of Medical Science) and Anthony Fauci (National Institutes of Health).

Anthony Fauci reviewed the host factors that influence the pathogenesis of HIV disease, with particular emphasis on the relationship between cytokines and the latently infected pool of CD4 T cells. Although highly active anti-retroviral treatment (HAART) has proved effective at reducing circulating levels of virus to below 50 copies/ml (the limit of detection using common assays), there remains a serious concern that lower levels of circulating virus endure and may be activated after HAART is stopped. Fauci reported preliminary results showing that a small number of patients who had been treated with HAART combined with intermittent IL-2 failed to show any replication-competent virus despite examination of up to 300 million cells. Although it seems unlikely that we will ever be able to claim the complete eradication of the virus from a patient, these results are most promising and suggest that it may be possible to take patients off HAART at some stage.

Stephen O'Brien (National Cancer Institute) has examined a wide range of factors that contribute to the considerable variation in infection and disease progression, and reviewed the influence of three genes in particular: CCR5, CCR2 and SDF1. In contrast, Luc Montagnier (Institut Pasteur), co-discoverer of HIV, provided a broad-ranging review of the role that accessory proteins play in HIV pathogenesis, and briefly discussed prospects for incorporating these into vaccines.

David Ho (Aaron Diamond AIDS Research Center) reviewed the viral dynamics seen in patients treated with HAART that have given rise to estimates of the size of the latent reservoir of HIV-1. By examining viral sequence diversity in patients with very low levels of residual virus, Ho and colleagues have been able to show that, contrary to earlier assumptions, such patients harbor a low level of replicating virus. This clearly has implications for the eradication of HIV-1 and indicates that current anti-viral therapies cannot completely shut off viral replication and that the problem of a persistent reservoir of virus may have been overestimated.

• *Abstracts of all presentations given at the conference are available on the Nature Japan website at www.naturejpn.com*

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