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GILLIAN PATRICIA BATES

Summary of Scientific Activity

I first started to work on Huntington's disease (HD) in 1987 when I became a postdoctoral fellow in Hans Lehrachs' research group at the Imperial Cancer Research Fund in London. The HD gene had been mapped to the short arm of chromosome 4 three years previously by Jim Gusella. In order to isolate the gene itself, a collaborative group of scientists had been brought together by Dr. Nancy Wexler, President of the Hereditary Disease Foundation (HDF). This included six research groups in the USA and UK headed by Jim Gusella, Hans Lehrach, David Housman, John Wasmuth, Francis Collins and Peter Harper. Over the next six years we worked together to generate the necessary resources and develop the required technology to pinpoint the HD gene. This was an extraordinary training. Hans' laboratory was a leading light in developing technologies for both the positional cloning of genes and also the genome project. The HDF provided the opportunity to interact regularly in an informal setting with a group of extremely talented and gifted scientists. The collaborative group published the identification of the HD gene in 1993. It was found that the only difference between the DNA sequence of this gene in people that do not develop HD and those that become affected is the length of a repeated DNA sequence (CAGCAGCAG), very close to the beginning of the gene.

At the beginning of 1994, I became a Senior Lecturer at what is now the GKT School of Medicine, King's College and initiated my independent research programme. An understanding of the HD mutation made it possible for the first time to generate a mouse model of HD. This was extremely important, as an accurate mouse model would allow us to uncover the very early molecular events in the disease course and to test possible therapies. Initially, I focussed my work in this direction and we published the first mouse model of HD in 1996. One of these transgenic lines, known as R6/2 has an early age of onset and has proved to be particularly useful as it has been possible to carry out an extensive characterisation of these mice in a very short time. Dr. Stephen Davies carried out a neuropathological analysis of these mouse brains and made the first major insight that arose from their study. He found that the transgene protein (made from the HD mutation that we had inserted into the mouse DNA) formed aggregates in the nuclei of nerve cells (neuronal intranuclear inclusions) in the transgenic mouse brains. The significance of these structures was not immediately apparent, as protein deposits had never been described in

Huntington's disease. However, since their identification in the mice, polyglutamine aggregates have been widely reported in HD post mortem patient brains. Max Perutz in Cambridge, UK and Erich Wanker, working with Hans Lehrach at the Max Planck Institute for Molecular Genetics in Berlin showed that these fibres have a cross-β-sheet structure more commonly known as amyloid.

For the past three and a half years, the R6/2 mice have been distributed to the research community either by my own lab or by the Jackson Laboratory in the USA. There are already around forty publications describing research that has been conducted on these mice by many groups. Insights into the early molecular stages of HD are arising. Polyglutamine aggregates form very early in some brain regions, before the onset of symptoms. Work initiated with Jang Ho Cha and Anne Young and MGH, Boston, showed that selective genes, many known to be important for nerve cell function, are turned down early in the transgenic mouse brains. Finally, the mice have been used for testing pharmaceutical compounds and two drugs are already entering the early stages of clinical trials in the UK and USA. The mouse model has revolutionised our knowledge of this disease and in the space of only four years is already beginning to have an impact on the treatment of HD.

STEPHEN WHITWORTH DAVIES

Research Interests

My laboratory has a long standing interest in molecular mechanisms of transcriptional regulation in the striatum following neuronal injury

I am currently focussing on the mechanism of neurodegeneration in Huntington's disease and other diseases caused by trinucleotide repeat expansions. These studies are in collaboration with Dr. Gillian Bates (UMDS). Current research projects are: immunocytochemical characterisation of neuropathological changes in Huntington's disease, post-mortem brain and transgenic mouse models of HD (Barbara Cozens and Elizabeth Slavik-Smith), ultrastructural and biochemical characterisation of *in vitro* and *in vivo* fibrous aggregates of Huntington's disease (Aysha Raza), transcriptional regulation in transgenic mouse models of Huntington's disease, and ultrastructural and molecular characterisation of sub-domains within the neuronal nucleus (Dr. Michael Gilder), ultra-