CSF markers, is likely to get smaller. So the challenge for clinical trials then becomes how to identify the high-risk and prodromal participants for clinical trials from an ever more diluted pool. Although CSF markers have high utility in stratifying for prodromal states, they are problematic as screening tools. Blood biomarkers might have utility in clinical trials as screens to enrich for prodromal states before further classification with CSF markers or functional imaging.

It is too soon to argue for the utility of blood-based biomarkers, but increasing evidence suggests that the abundance of such markers might be altered very early in the disease process, might yield useful understanding about Alzheimer's disease pathogenesis and might find a place in clinical trials together with CSF markers and imaging, either sequentially or in combination. It may too soon to suggest the usefulness of these blood markers, but it is also too soon to ignore them.

Simon Lovestone[1]

[1]*King's College London, London, UK.*
e-mail: simon.lovestone@kcl.ac.uk

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Common mechanisms in neurodegeneration

To the Editor:

Why, with all the progress in the field of neurodegeneration, do we still lack disease-modifying drugs that tackle the primary defect of severe cell loss? Part of the issue is that many cells are already dead before the symptoms appear, and we are probably attempting to treat the patients too late to make a difference. We still do not know whether the neurodegenerative disorders follow a unifying mechanism for disease initiation and propagation[1]. Accordingly, it is too soon to decide whether all these disorders should be treated in a similar fashion.

Neurodegeneration often results from the accumulation of misfolded aggregated proteins in different areas of the aging brain, and this process yields cell death and inflammatory damage in those brain areas. However, in some disorders, such as Huntington's disease, protein aggregates could have the opposite function, carrying out a protective role[2]. A recent study has challenged some of our ideas about Alzheimer's disease, concluding that tau aggregates seem to be a consequence rather than a cause of neurodegeneration[3]. Thus, it is unclear whether blocking this aggregation therapeutically would be beneficial or harmful.

The existence of common mechanisms for the pathogenesis of various neurodegenerative diseases could facilitate the development of new drugs to prevent these disorders. A probable common link among some of these disorders is the appearance of oxidative damage that results in neurodegeneration[4]. However, there is not enough work being done in the pharmaceutical industry to look for compounds that prevent oxidative stress or mitochondrial dysfunction.

More research should be done to determine whether there are common mechanisms for the different neurodegenerative disorders. This will aid in our understanding of disease mechanisms and will move drug development forward.

Jesús Avila[1]

[1]*Centro de Biologia Molecular Severo Ochoa, Madrid, Spain.*
e-mail: javila@cbm.uam.es

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Modeling clinical features of neurodegeneration

To the Editor:

In basic Parkinson's disease research, one major obstacle is that animal models and *in vitro* studies do not recapitulate features or incorporate mechanisms associated with the onset of Parkinson's disease. Animal models rarely take into account essential clinical characteristics of Parkinson's disease such as the age of onset, the focal onset of clinical features, limited pathology (cell loss is initially restricted to substantia nigra dopaminergic neurons and the presupplementary motor area), the slow progression, and the appearance of clinical signs beyond the classic triad of tremor, bradykinesia and rigidity. Indeed, degeneration of the substantia nigra might occur naturally only in humans, which would imply that the selective vulnerability of these dopaminergic cells is a unique feature of our development and functional connectivity. If so, animal models using toxins or transgenically overexpressed proteins are invoking mechanisms that do not mimic pathologically relevant disease triggers in humans. The same could be said for *in vitro* studies, where, despite attempts to model alterations in specific cellular components (such as the proteasome, lysosome and mitochondria), the relevance of these processes to disease pathogenesis remains disputable. For instance, labeling of Lewy bodies or Lewy-like inclusions is a common feature of Parkinson's disease, but real Lewy bodies have not been seen in any animal or in cell culture. Thus, efforts should be focused on developing etiologically relevant models that closely mimic clinical features of Parkinson's disease. Further basic research would also benefit from the use of tissue and cell lines from affected individuals and human controls to identify relevant pathogenic mechanisms. Although research into specific defects in a fundamental signaling pathway may guide development of neuroprotective therapies for neurodegenerative diseases, to my mind, the feasibility of this approach is remote if the approach to modeling pathogenesis of disease does not take into account clinically relevant features.

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José A Obeso[1]

[1]*Department of Neurology, Clínica Universitaria and Medical School of Navarra, Neuroscience Centre, Center for Applied Medical Research, Universidad de Navarra, Pamplona, Spain.*
e-mail: jobeso@unav.es