

Interview with Jean de Barry, co-founder of Innovative Health Diagnostics (IHD), Strasbourg, France

“We Invested Our Own Money”

The Alsatian biotech company IHD develops tests for Alzheimer’s disease detection, that can be performed even before the first clinical symptoms appearance. If IHD succeeds in commercialising its tests during 2009, the French will be one of the first companies with blood diagnostic tests for Alzheimer’s disease. *Lab Times* reporter Jeremy Garwood had a meeting with IHD’s co-founder, Jean de Barry.

Lab Times: You have been working on protein kinase C (PKC) for 15 years. What was your original interest in this protein?

Jean de Barry: I wanted to look at the regulation of neurotransmission, in particular the neurotransmitter receptors and the regulation of their activity by phosphorylation.

You have discovered changes in the conformation of PKC which can be followed using fluorescent probes, notably the fluorescein-coupled bis-indoylmaleimide) Fim-1?

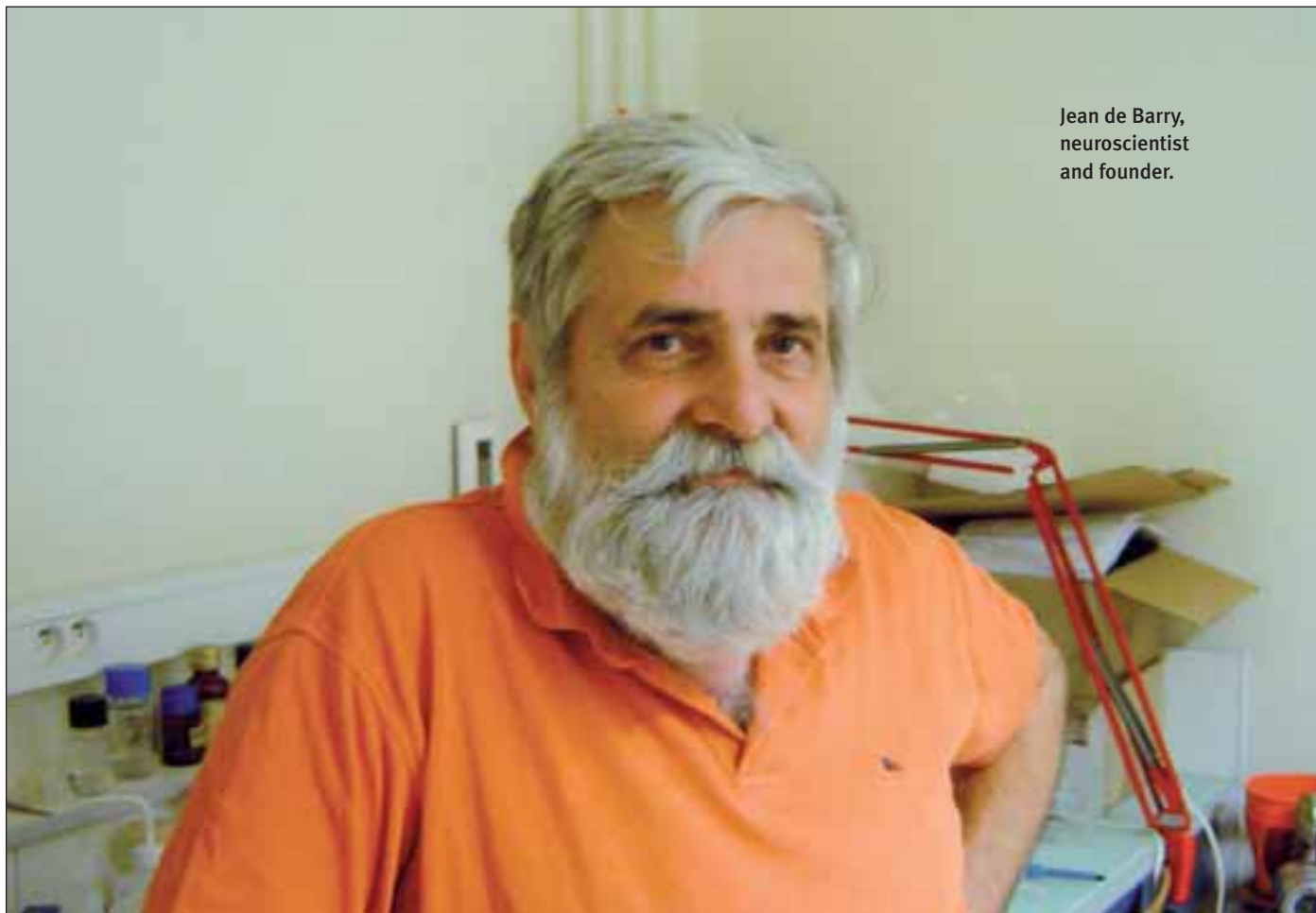
de Barry: This was first observed in 1994. We also worked with other probes, but Fim-1 gave the best results. It was when we were characterising the probe in sea urchins that we realised we could visualise conformational changes. We then worked on

this using more classical models such as PC12 cells and slices of nervous tissue. We also looked at the biochemistry and biophysics of the probe’s interaction with purified PKC.

“Our reasoning was that we might see a difference in the erythrocytes of Alzheimer’s disease patients, to those of healthy persons.”

Are the conditions you describe in your 2006 paper (“Alteration of protein kinase C conformation in red blood cells: A potential marker for Alzheimer’s disease but not for Parkinson’s disease” *Neurobiology of Aging* 27, 245–251) optimal?

de Barry: In effect, staurosporine is a PKC inhibitor, which binds to the same site as the Fim-1 probe, so we use it to confirm the specificity of the signal. On the other hand, TPA (12-o-Tetradecanoylphorbol-13-acetate) activates the PKC protein – it is this chemical that induces the conformational change in PKC.



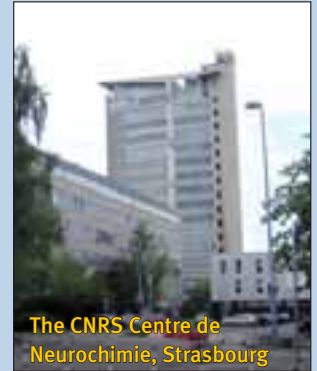
Jean de Barry, neuroscientist and founder.

About

Innovative Health Diagnostics (IHD) ...

... was founded in 2008 by the CNRS* researcher, Jean de Barry, to exploit a research discovery from his laboratory in the Institute of Cellular and Integrative Neuroscience (INCI) at the CNRS Centre de Neurochimie in Strasbourg. As an aside to long-term neuroscience research into the function of Protein Kinase C, a collaboration with Francois Sellal, a clinician specialising in Alzheimer's disease, revealed a striking difference in blood samples from Alzheimer's sufferers – the conformation of protein kinase C in their red blood cells is altered. Based on this observation, IHD is currently developing blood diagnostic tests for Alzheimer's disease (termed Diagalz). They claim that their test is 99% reliable compared to around 90% for existing clinical examinations that combine psychoneurological tests and brain scans. Furthermore, their blood test will be quick and easy to administer. IHD intends to commercialise the test in 2011 at a price that might eventually lead to routine screening for Alzheimer's Disease among people over 65. The blood test could result in an earlier, more reliable detection of sufferers, improving their personalised care. It could also enhance clinical research into the treatment and cure for Alzheimer's by facilitating the selection of known sufferers for such studies.

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The CNRS Centre de Neurochimie, Strasbourg

*CNRS (Centre national de la recherche scientifique) is the largest governmental research organisation in France.

And Fim-1 binds to a calcium-binding site on PKC?

de Barry: Mechanistically, the PKC protein has to be competent – first, there is a phosphorylation of PKC, then a binding of calcium, which induces a change of conformation; this is followed by binding to the membrane via phosphatidyl-serine and then a binding of diacylglycerol. That sequence of events leads to activation of PKC.

What made you look for a difference in patients suffering from Alzheimer's disease?

de Barry: That comes from another observation. In Alzheimer's patients, there is a change in their transport of chlorine ions. The chlorine transporter is regulated by another protein, called Band 3, and Band 3 is phosphorylated by PKC. Our reasoning was that PKC intervenes in this phenomenon and that perhaps we might see a difference in the erythrocytes of Alzheimer's patients. That's how we started and discovered this striking particularity in the PKC profile of Alzheimer's patients. However, we still don't know what the nature of this alteration is. For the moment, nothing is clear.

From an organisational viewpoint, you're still a research director with the CNRS but you also work for your company, IHD? How do you balance the two?

de Barry: There a clear separation between the students who work in the CNRS laboratory and the six paid persons who work for the company. The fundamental research questions are dealt with in the laboratory, while the development, applied research, and part of the clinical research, is performed by the company.

Do you find the CNRS's system for aiding the development of start-up companies derived from its research works well?

de Barry: I haven't had any problems but I know others who have had lots of problems to get this statute, so I think it varies a lot from one project to another.

Do you think your development of a diagnostic test might have benefitted from the famous controversy surrounding the development of the AIDS blood test in the 1980's?

de Barry: Well, Alzheimer's is also a disease with a major social impact – as with AIDS, there are also many emotional impli-

cations for society associated with Alzheimer's Disease. It's not just the impact on the elderly who have the disease. If you talk to young people, three times out of ten they know people in their family circle who have been affected. ►►

►► *How are you advancing with the development of your test?*

de Barry: We formally started the company in October, 2008. We are currently performing all the controls that will allow us to define the test's limits and to standardise it. We no longer use Fim-1 because it is a relatively unstable probe. We have since developed new probes. In six months time, we intend to pass on to the industrial development of the test – we're currently at the pre-industrial stage. These controls are of course also necessary

“Our test could, for example, help contract research organisations (CRO's) to recruit and organise their cohorts for clinical trials.”

in order to obtain the relevant authorisations – in Europe, the USA, etc. After a further 6 months' pre-industrial development, we envisage a year of industrial development. We hope to have a functional commercial test ready for the start

of 2011. However, we are also developing another test. This second method consists in determining the beta-amyloid peptide on the cell membranes of erythrocytes in blood samples from patients. It uses another fluorescent probe, developed in collaboration with chemists here in Cronenbourg (Strasbourg).

Is there also a clear distinction between Alzheimer's sufferers and controls?

de Barry: We can't answer that question yet because the clinical studies are still progressing but the results on the cell and animal models are absolutely convincing.



Corinne Mbebi-Liégois, a previous Aventis employee, is now head of research and development at IHD.

Photo: Jeremy Garwood

How do you envisage growing as a business? Are you already seeking partners?

de Barry: Our business plan involves initially offering a research service to biotechnology and pharmaceutical companies to test their drugs *in vitro* at the pre-clinical stage. In particular, the characterisation of disease modifiers, because we are looking at the metabolism of β -amyloid. If they have drugs they think might be disease modifiers, or that might influence the secretase activity, etc., then we could propose a collaboration. That's the first step. The second step is going to be to initiate a collaboration with the CROs – the contract research organisations – who coordinate the clinical assays. Our test could be used in helping them to recruit and organise their cohorts. We're also looking at initiating collaborations with speciality labs – medical analysis laboratories with special certificates from the FDA or equivalent European authorities that allow them to practice in-house tests with drugs that do not yet have full authorisation. In the US, they're called CLIA, in Europe, speciality labs. The third step involves finding industrial partners for the fabrication and the commercialisation of the test, taking account of differences in the organisation of health services in different countries, which could have a big influence on the marketing and presentation of the product.

You started in October 2008. How are you financing IHD?

de Barry: We won several prizes, we invested some of our own money, and we obtained loans. We are currently organising a 'levee de fonds' for a further €1.5 million. This will permit us to balance our budget within the business plan. After that, there are several ways to proceed. For example, getting quoted on the stock market. Another advantage we have is that the CNRS has agreed to accommodate us. In the first years, we will remain here to effectively develop our 'know-how' at the start.

Who else works with you at IHD?

de Barry: We have three founding associates. Xavier Regnaud is a scientist who specialised 15 years ago in the management of start-ups. Francois Sellaal is the hospital specialist responsible for treatment of Alzheimer's disease in the Alsace region. And then I, who originated the technology. In addition, we have recruited people with a lot of experience in neuroscience, especially Alzheimer's. Corinne Mbebi-Liégois is in charge of the development of the test. She has several years' post-doctoral experience looking at APP (amyloid precursor protein) in Alzheimer's disease. Our project manager has a PhD in neuroscience and followed a complementary formation in management. He can compile and present the demands for pre-clinical authorisations, fiscal questions, demands for financial aid from public sources, etc.

Well, I am very conscious of my limits. I would never have launched such a project if I had not found people who provided complementary input.

INTERVIEW: JEREMY GARWOOD



Photo: Secci/CNRS

IHDs' diagnostic kit uses fluorescent probes to detect Alzheimer's disease biomarkers from red blood cells.