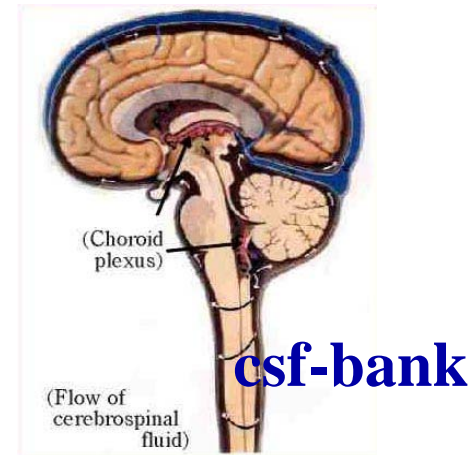


# Biobanking for diagnostic markers in neurological disorders

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Amsterdam, The Netherlands  
[www.brainbankconsultants.com](http://www.brainbankconsultants.com)



*ESF, Biobanking, 1-6 november 2008*

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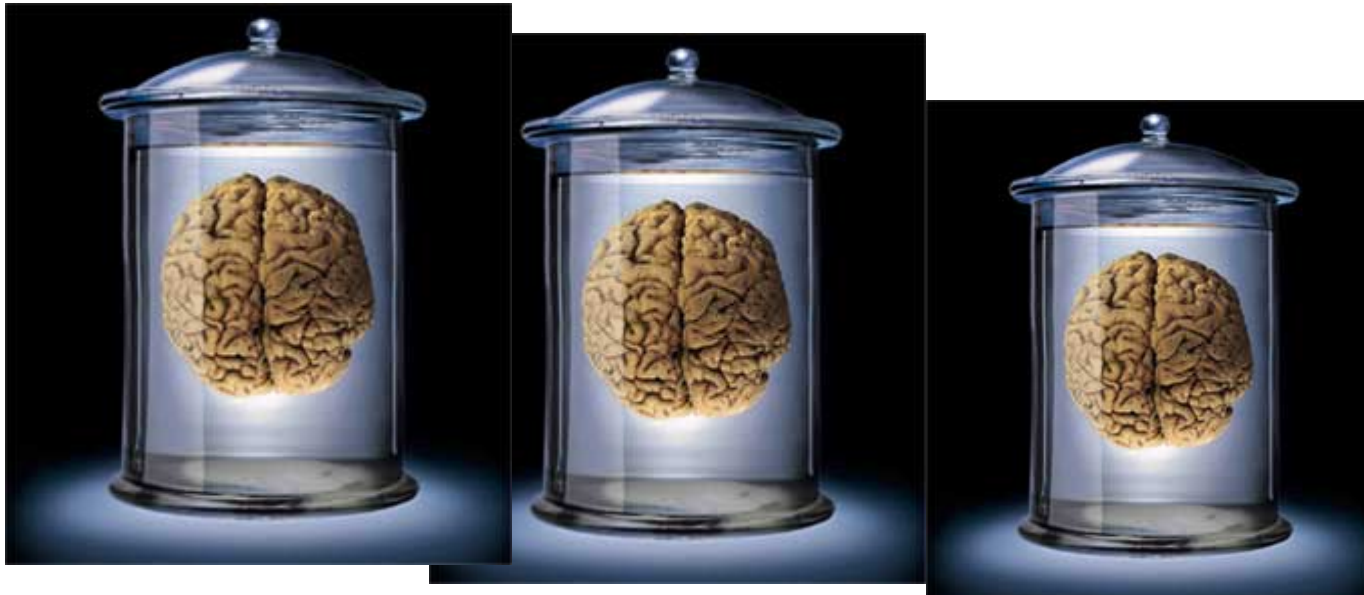


# Biomarkers; what's in a name???

- A **biomarker** is a substance used as an indicator of a biologic state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
- **No controversy**; we need an array of biomarkers both in the living patient and at post mortem autopsy.
- Biomarkers have an important role in early diagnostics, predictive value of disease progression and in target development.



- **BIOBANKS;** what's in a name???
- **BTB Banks : Brain/tissue/bio banks**
- **No: a collection of brains in big jars**



**Yes: collaborative effort of many disciplines:**Neurlogy, Pathology, Radiology, Genetics, Psychiatry and Ethics



Cell Tissue Banking (2008) 9:151–167  
DOI 10.1007/s10561-008-9101-4

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REVIEW PAPER

## **Standard Operating Procedures, ethical and legal regulations in BTB (Brain/Tissue/Bio) banking: what is still missing?**

**Rivka Ravid**

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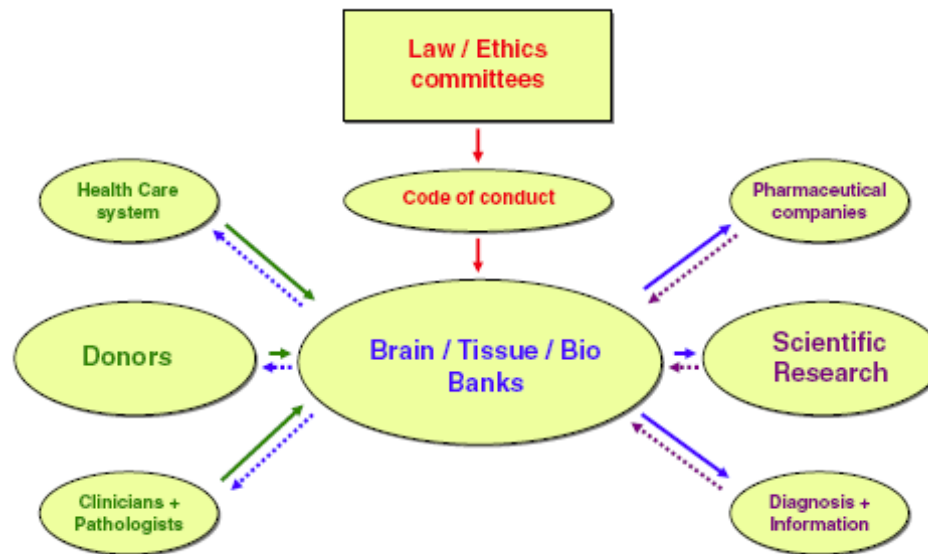


Fig. 1 *Flowchart of BTB-banks interfaces* This scheme illustrates BTB-banks as intermediaries to facilitate the availability of specimens for research. The middle line shows the three main parties who make this combination a success; the donors on the one hand, the BTB-banks and the scientific

research community on the other hand. The local health care system, policy makers, clinicians, pathologists are the supporting elements and it is obvious that the main core of the banks is adherence by local legislation, ethics review committee and a solid code of conduct



# 7 golden standards of BTB Banking

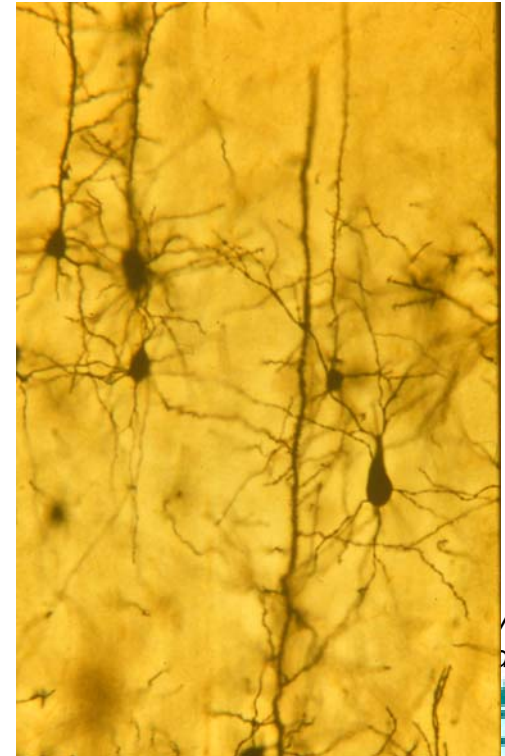
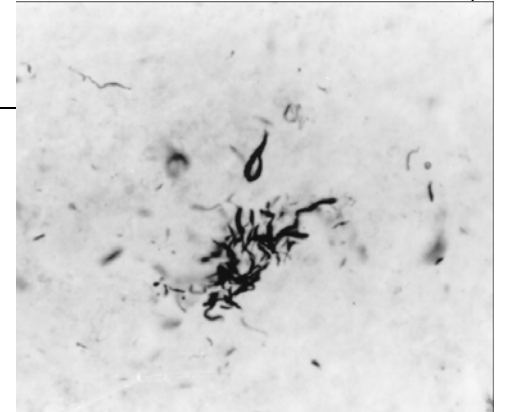
1. A well established local donor system in which consent is obtained for the use of tissues for scientific research and access to the medical records.
2. Rapid autopsies with a very short post-mortem delay and a fresh dissection; these are a prerequisite for an increasing range of technical procedures and new systems such as neuronal cultures.
3. Compatibility of protocols for tissue procurement, management, preparation and storage for diagnostics and scientific research.
4. A generally accepted consensus on the clinical and neuro-pathological diagnostic criteria.
5. Quality control of the disseminated samples (pH/agonal state).
6. Abiding internationally accepted guidelines for the ethical and legal aspects conform the local medico-legal system.
7. Monitoring proper safety procedures.





Alzheimers disease

What went wrong?

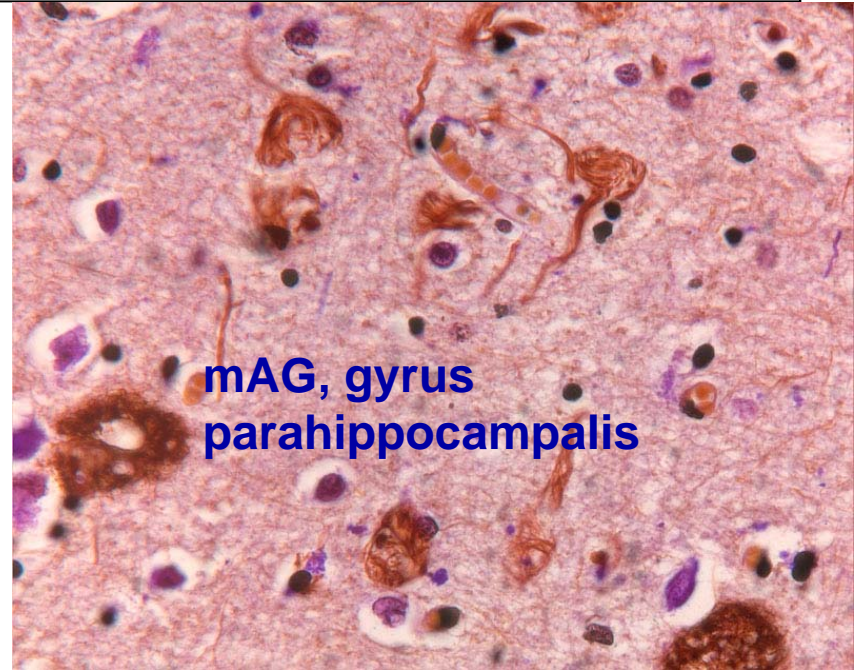


Age matched control

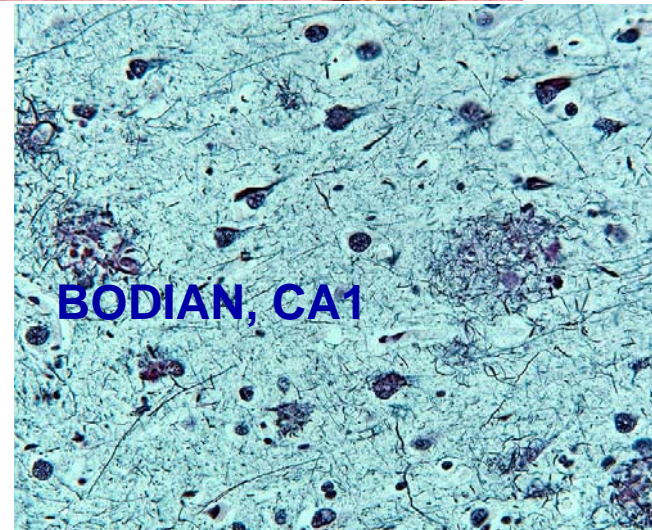




# Neuropathological diagnosis



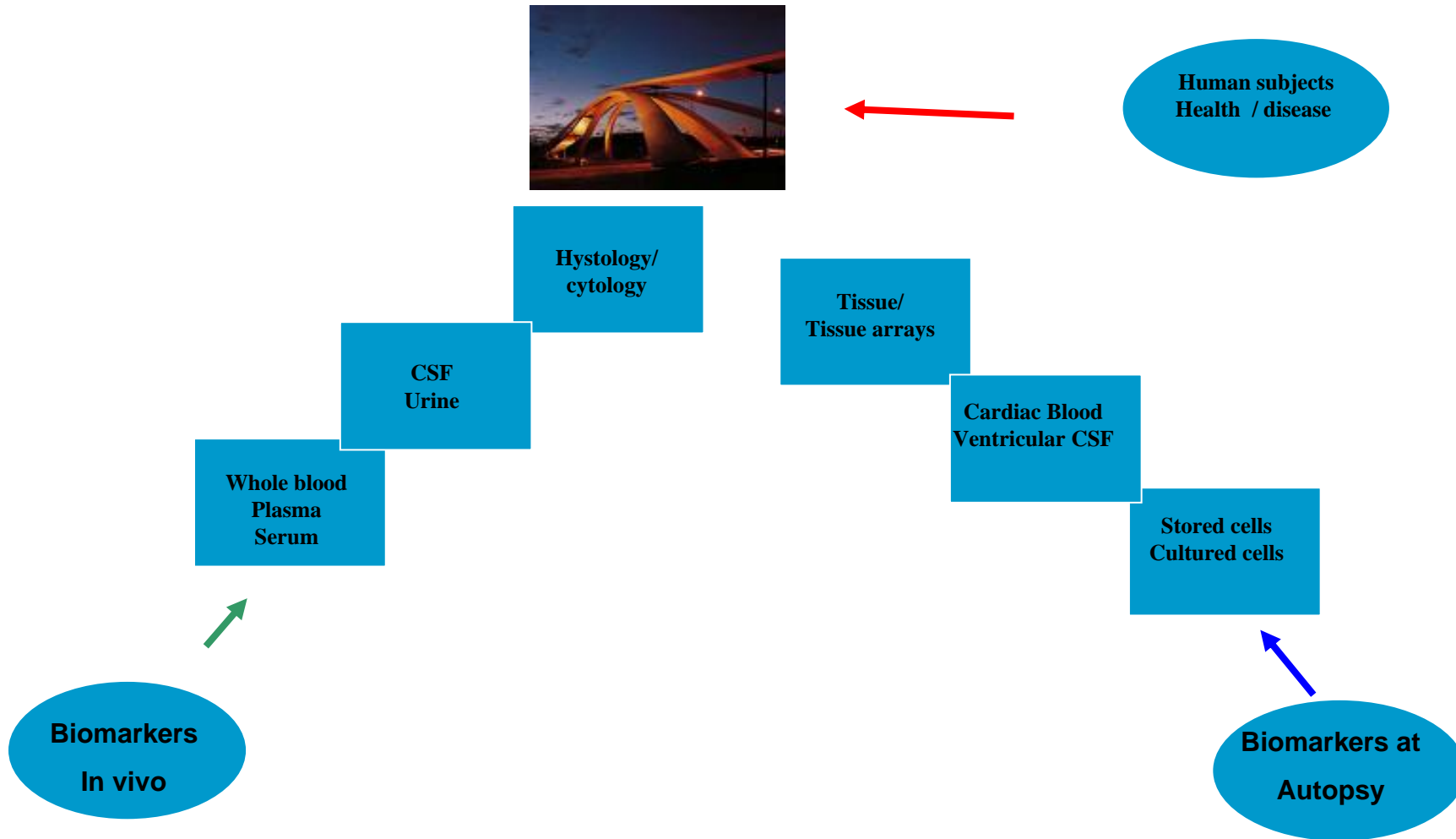
**mAG, gyrus  
parahippocampalis**



**BODIAN, CA1**

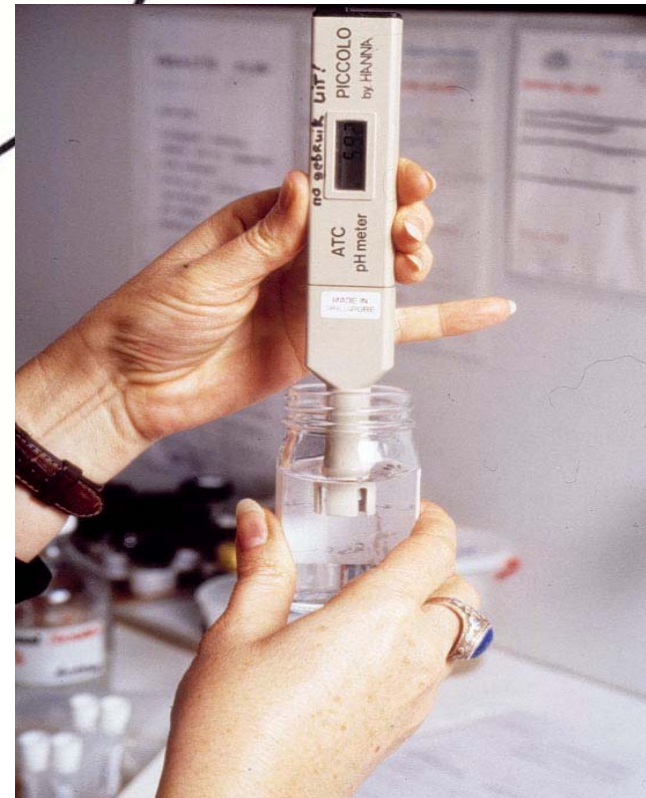
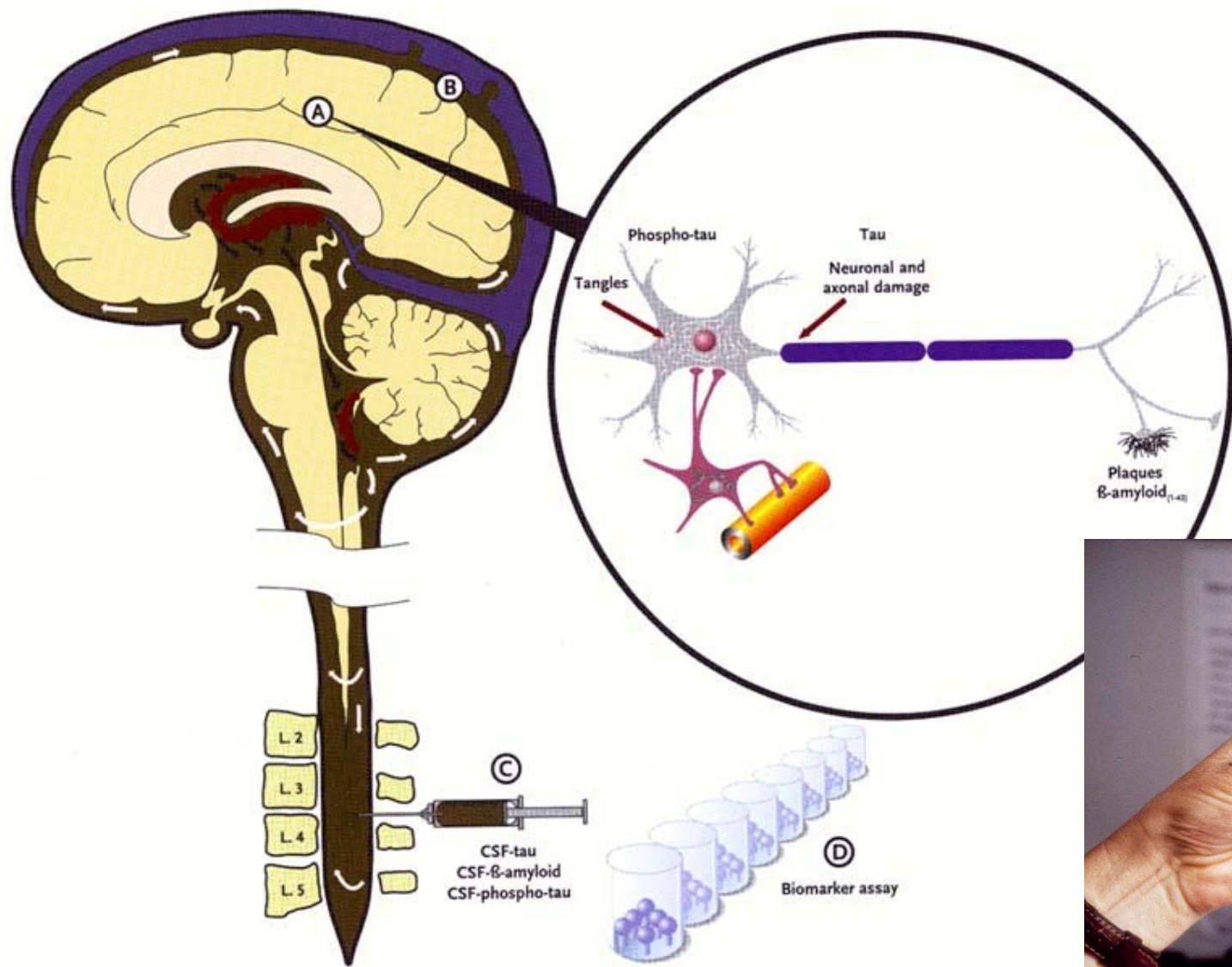


# BioBanks – The Da Vinci bridge to finding Biomarkers



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Cell Tissue Banking (2008) 9:217–227  
DOI 10.1007/s10561-008-9078-z

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## Electronic tracking of human brain samples for research

Christian E. Keller · Maria del Pilar Amaya ·  
Etty Paola Cortes · Katerina Mancevska ·  
Jean Paul G. Vonsattel

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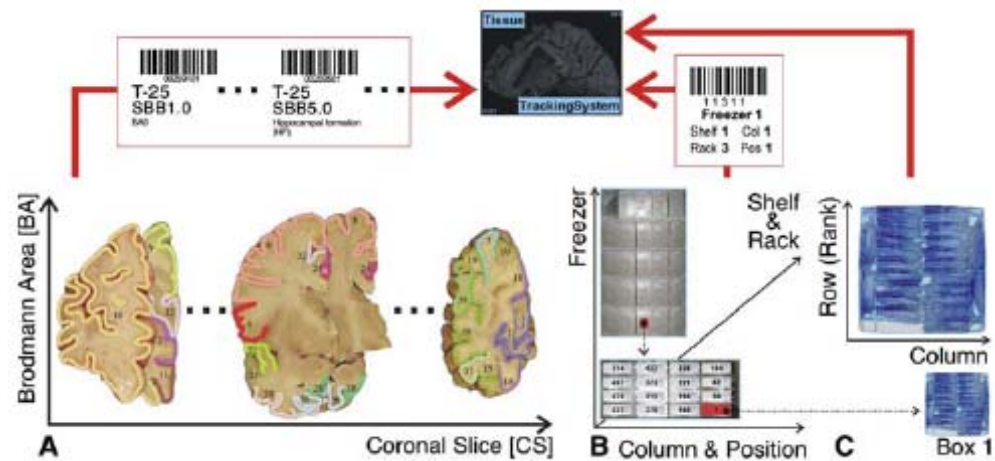


Fig. 3 Schematic of NYBB Tracking System storage information. The relational database (*NYBB Tracking System*) correlates a bar coded, unique sample identifier (panel a) with a unique set of bar coded coordinates in the 3D freezer space (panel b). Both the unique identifier and the freezer coordinates

are bar coded to minimize the incidence of data entry error. The box position (panel c) is assigned by the computer and depends on the availability of the open (not filled) boxes as well as the sampled region (optional)



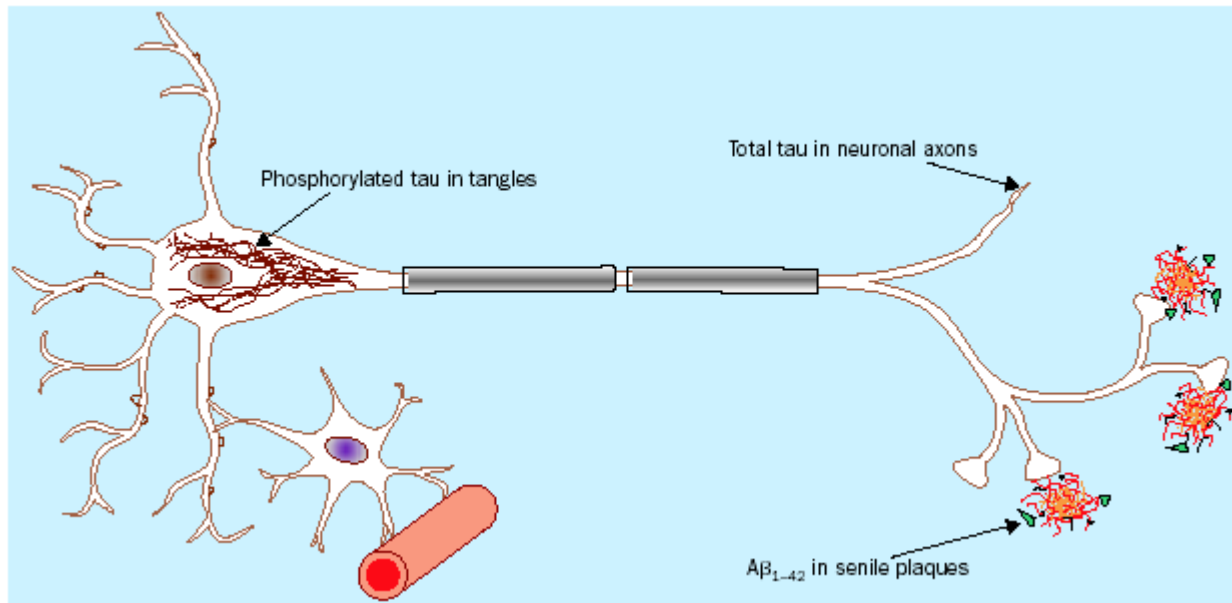
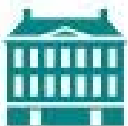


Figure 1. Schematic drawing of a neuron with an adjacent astrocyte and capillary. The central pathogenetic processes in AD and their corresponding biochemical markers are depicted. Total concentration of tau protein is a marker of neuronal and axonal degeneration, Aβ<sub>1-42</sub> concentration is a marker of plaque formation, and concentration of phosphorylated tau is a marker for hyperphosphorylation of tau and formation of tangles.







# CSF markers for incipient Alzheimer's disease-

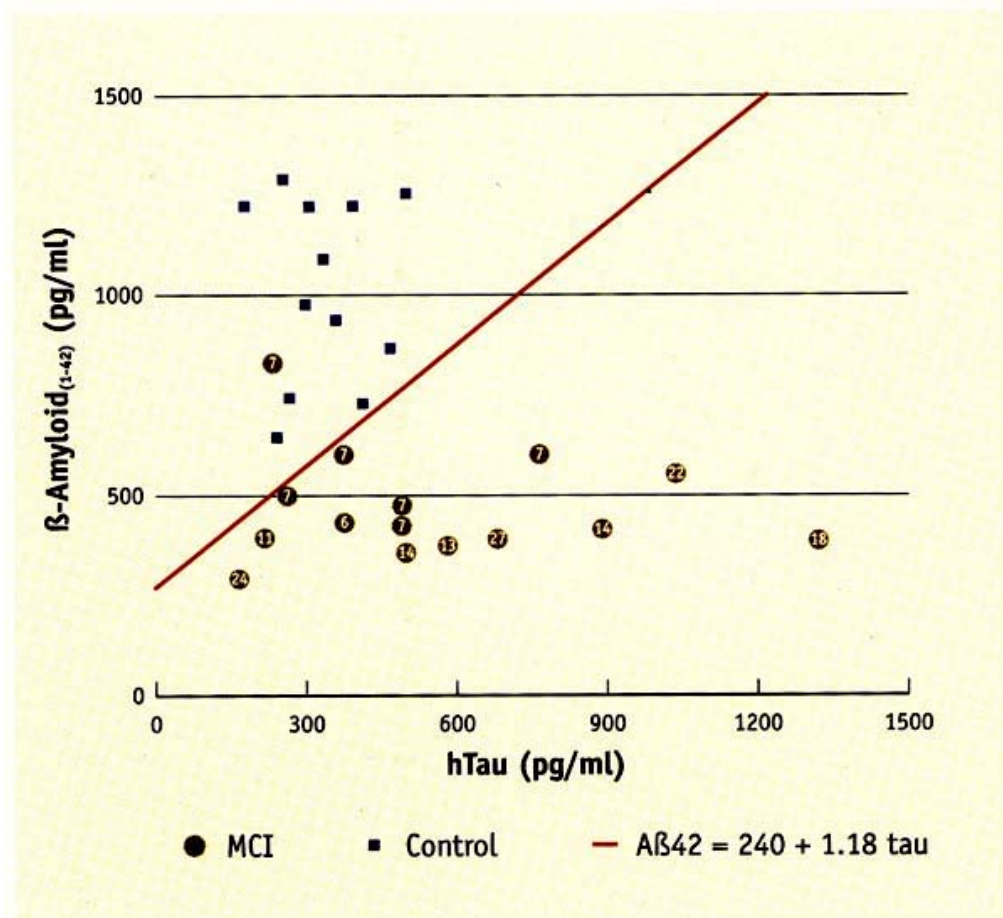
Kaj Blennow and Harald Hampel

Department of Clinical Neuroscience, Gothenburg University,  
Sweden and Department of Psychiatry, Ludwig-Maximilian  
University, Munich, Germany.

Lancet Neurol 2003; **2**: 605–13

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Amsterdam*





*Relationship between mild cognitive impairment (MCI) and development of Alzheimer's disease (see p. 40).*

*Data points below the red discrimination line (low CSF  $\beta$ -Amyloid and high CSF-hTau) have a high predictive value for the development of AD in MCI patients. Figures in gold circles indicate the number of months between test performance and clinical diagnosis of AD.*

*(Adapted from Andreasen et al. Neurosci Lett 1999;273:5-8)*



# Matching Factors in Bio/Tissue banking

## ■ Ante-mortem:

- **Age**
- **Gender**
- **Clinical diagnosis**
- **Agonal State**
- **Medication**
- **Circadian variation**
- **Seasonal variation**
- **Lateralization**
- **Family history/genetic load**

## ■ Post-mortem:

- **Post-mortem delay**
- **Organ weight**
- **CSF / Tissue pH**
- **Cause of death**
- **Clock time of death**
- **Date of death**
- **Death to refrigeration**
- **Freezing / fixation**
- **Storage time**



# THE DRUGS DON'T WORK



**D**r Allen Roses, worldwide Vice President of Genetics at GlaxoSmithKline and a pre-eminent figure in the field, stated last year that more than 90 percent of drugs only work in 30-50 percent of people. While this wasn't news to his colleagues, many were surprised by such an admission, a shocked public were concerned that the blind faith many placed in the medicines they take was perhaps misplaced, and the wake up call that the drugs don't necessarily work was a bitter pill to swallow.

Asked about the response he received to the statement in the media he acknowledges that by some, "My remarks were sensationalised. But others could not understand what the fuss was about. We need to improve drug therapy, people

know that; that is why the pharmaceutical industry exists."

## SHOULD THIS COME AS A SURPRISE?

According to Roses, the answer is a resounding no. "Not every drug will work for everybody. This should come as news to no one. Most people have had the experience of going to the doctor and getting a medicine and having to go back and try another one. I think everybody has it in their experience that multiple drugs have been used for their headache or multiple drugs have been used for their backache or whatever."

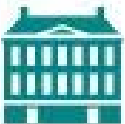
To highlight the extent of the situation, at a scientific meeting in London last year Roses cited figures on how well different classes of drugs work in real patients. For





# OPTIMIST

**A PERSON WHO HASN'T BEEN  
GIVEN ALL THE FACTS YET.**



Don't take your  
organs to heaven.

Heaven knows  
we need them  
here.





## Nederlandse Hersenbank

Codicil nr: [200501]

Meibergdreef 33  
1105 AZ Amsterdam

[C]

Name : A. Trevalyan  
D. o. B. : 14/02/1937  
Address : Battersea highway 2001  
Postal code : 2001 AT Town : Comden

I herewith give consent for a post-mortem brain autopsy and declare that my brain may be used for scientific research in the frame work of the Brain Bank project. I also give consent for acces to my medical file and use of the information for research purposes.

Signature:

Date:

### General Practitioner:

Name : Dr F. Bloggs  
Tel. Nr : 020 – 123654

### Next of kin:

Name : ms L. Trevalyan  
Tel. Nr. : 06 – 32145678

In case of demise, please contact AS SOON AS POSSIBLE:

monday to Friday, during office hours, the Brainbank : 020 – 566 5499

outside office hours, the VUMC emergency desk : 020 – 444 4330

*R. Ravid  
Amsterdam*



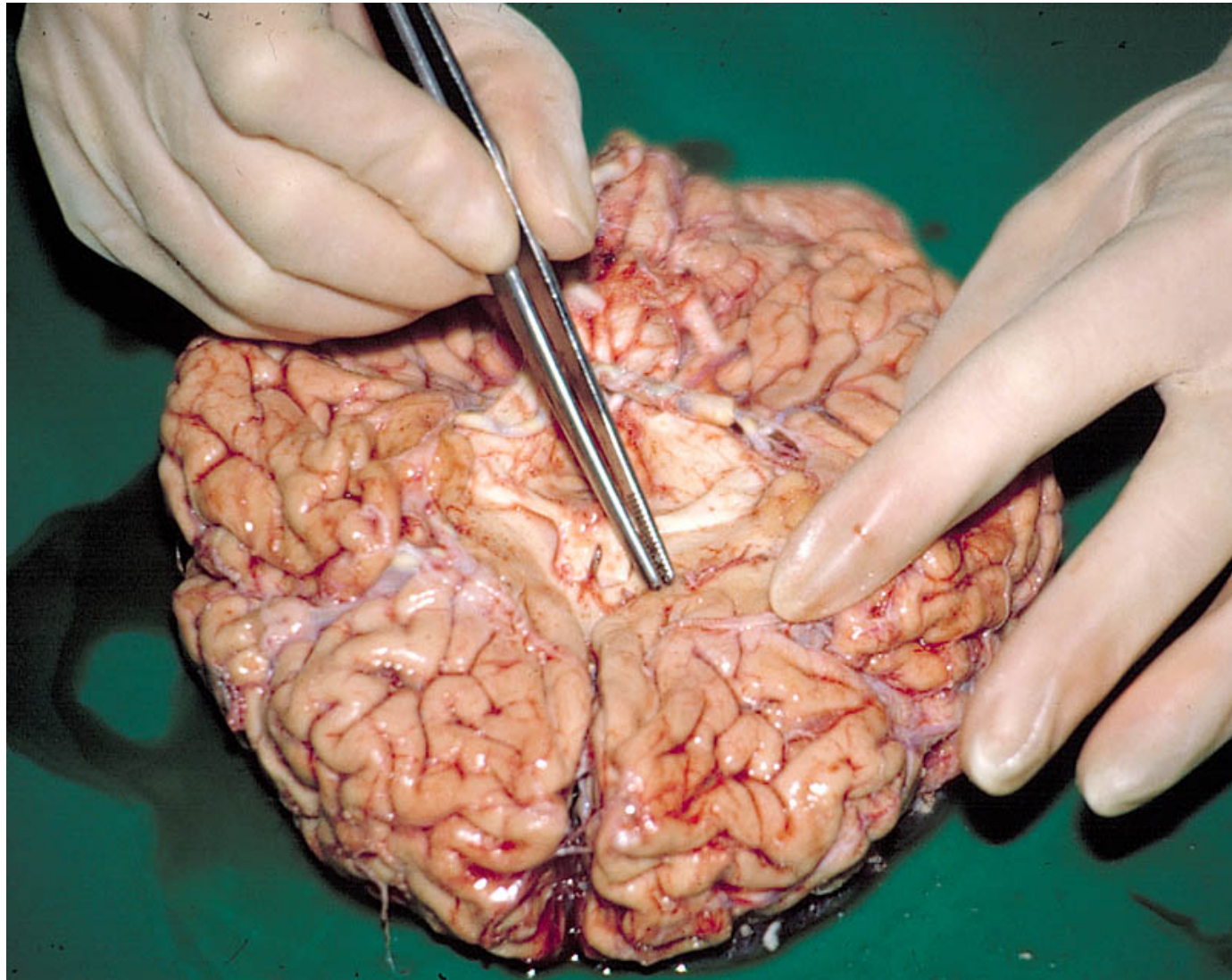




R. Ravid  
Amsterdam







*R. Ravid  
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NOTHING RIGHT  
IN MY LEFT BRAIN



NOTHING LEFT  
IN MY RIGHT BRAIN





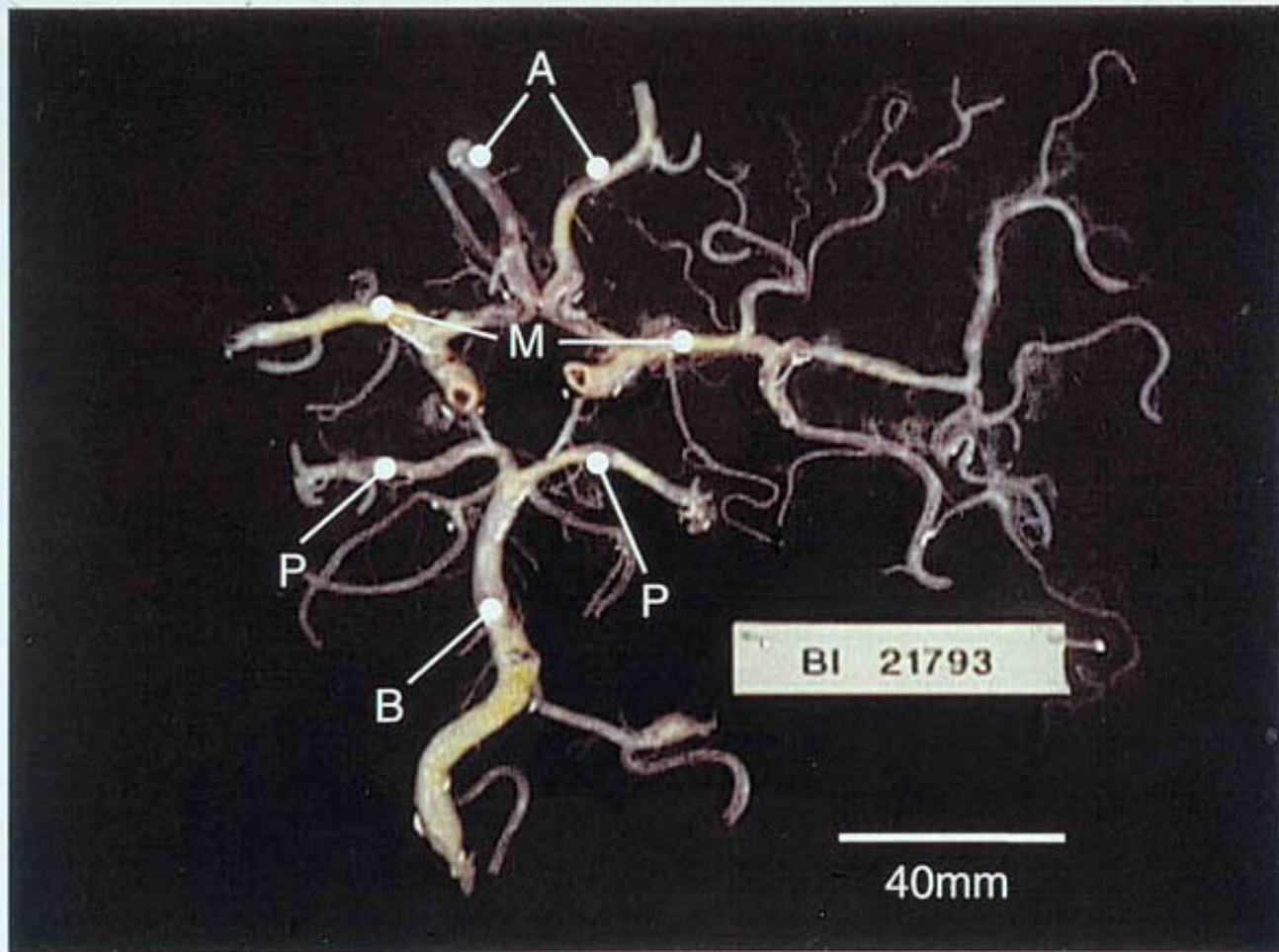
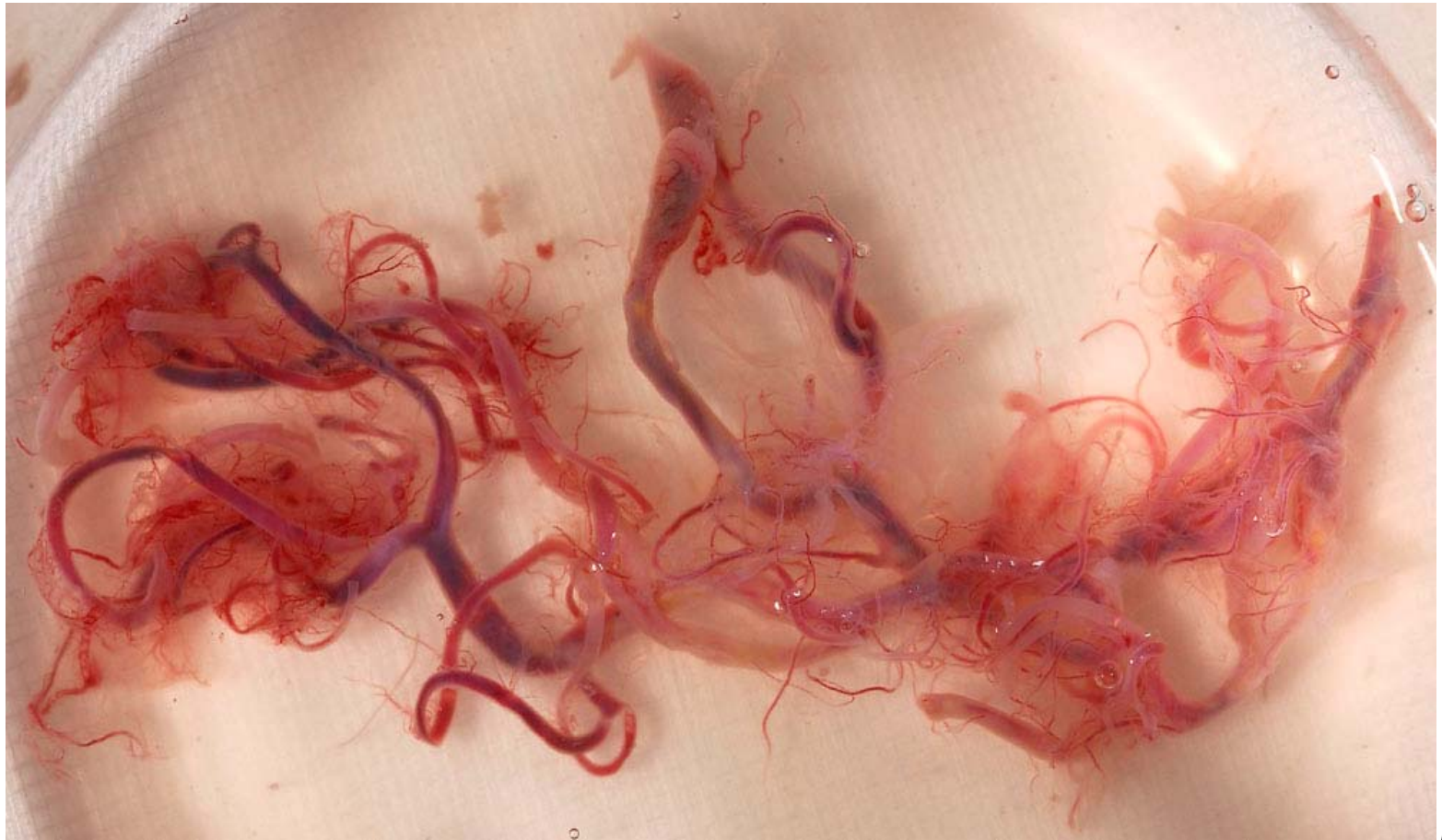


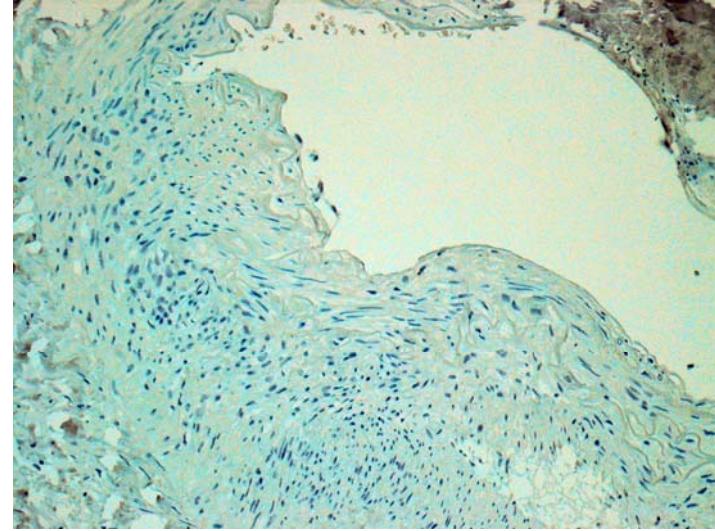
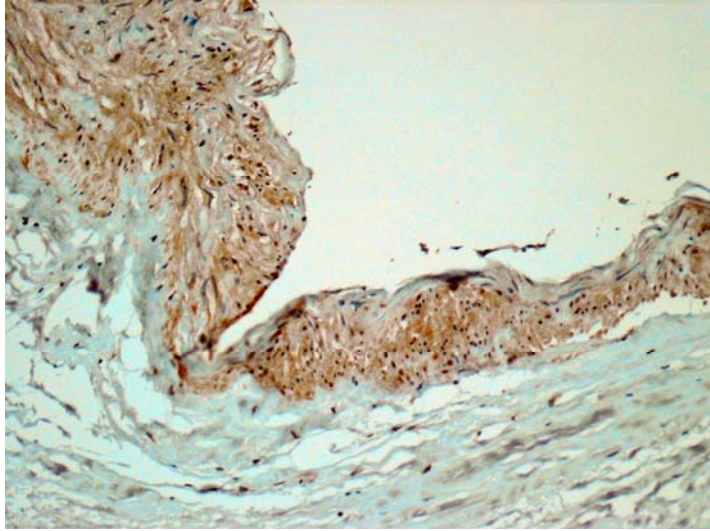
Figure 1. Photograph of human cerebral arterial blood vessels showing anterior (A), middle (M), posterior (P) and basal (B) cerebral arteries.



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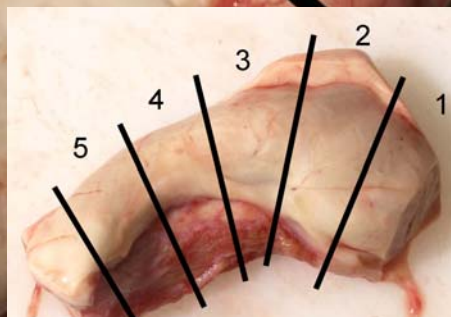
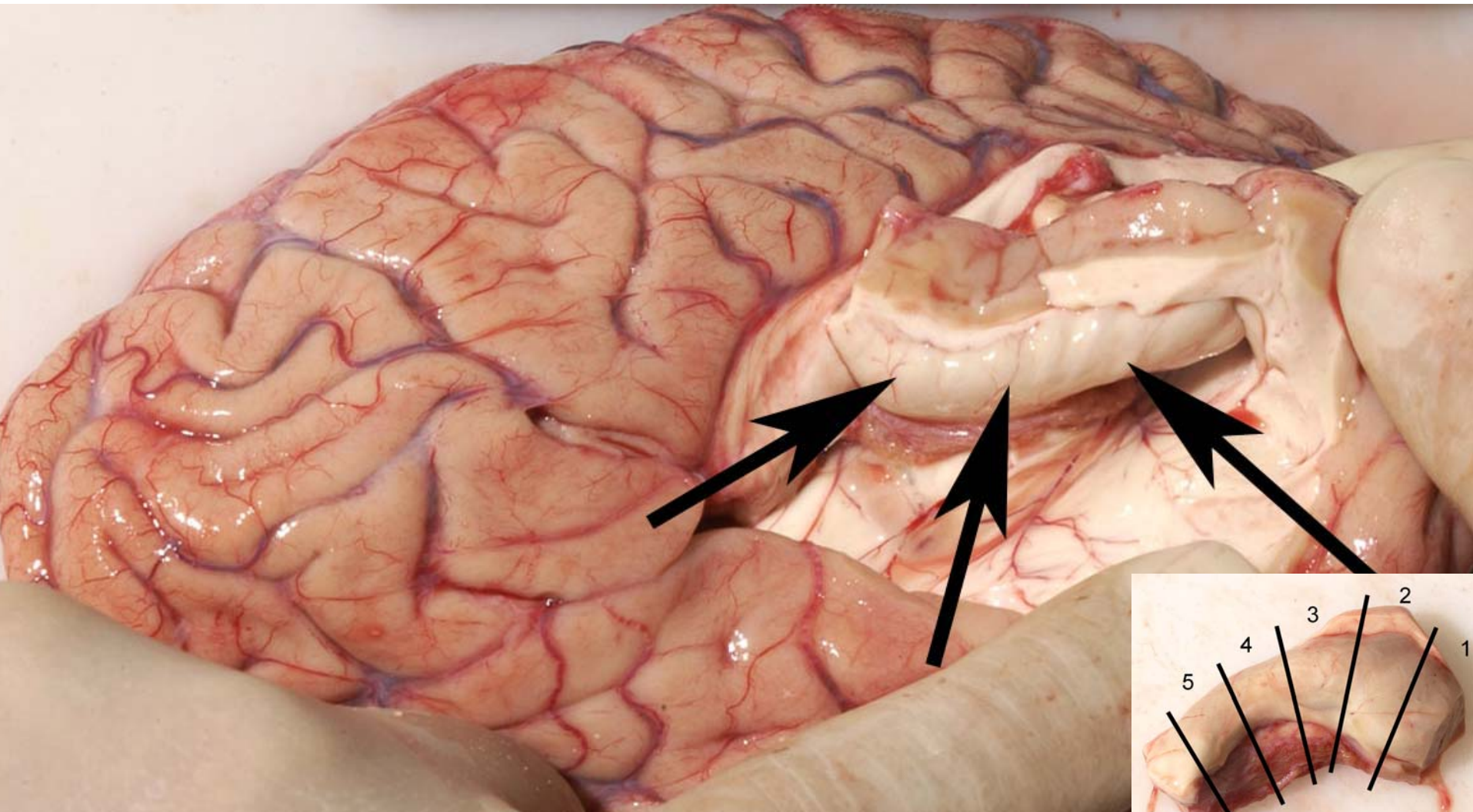
# EP<sub>4</sub> receptor immunoreactivity in the meningeal artery

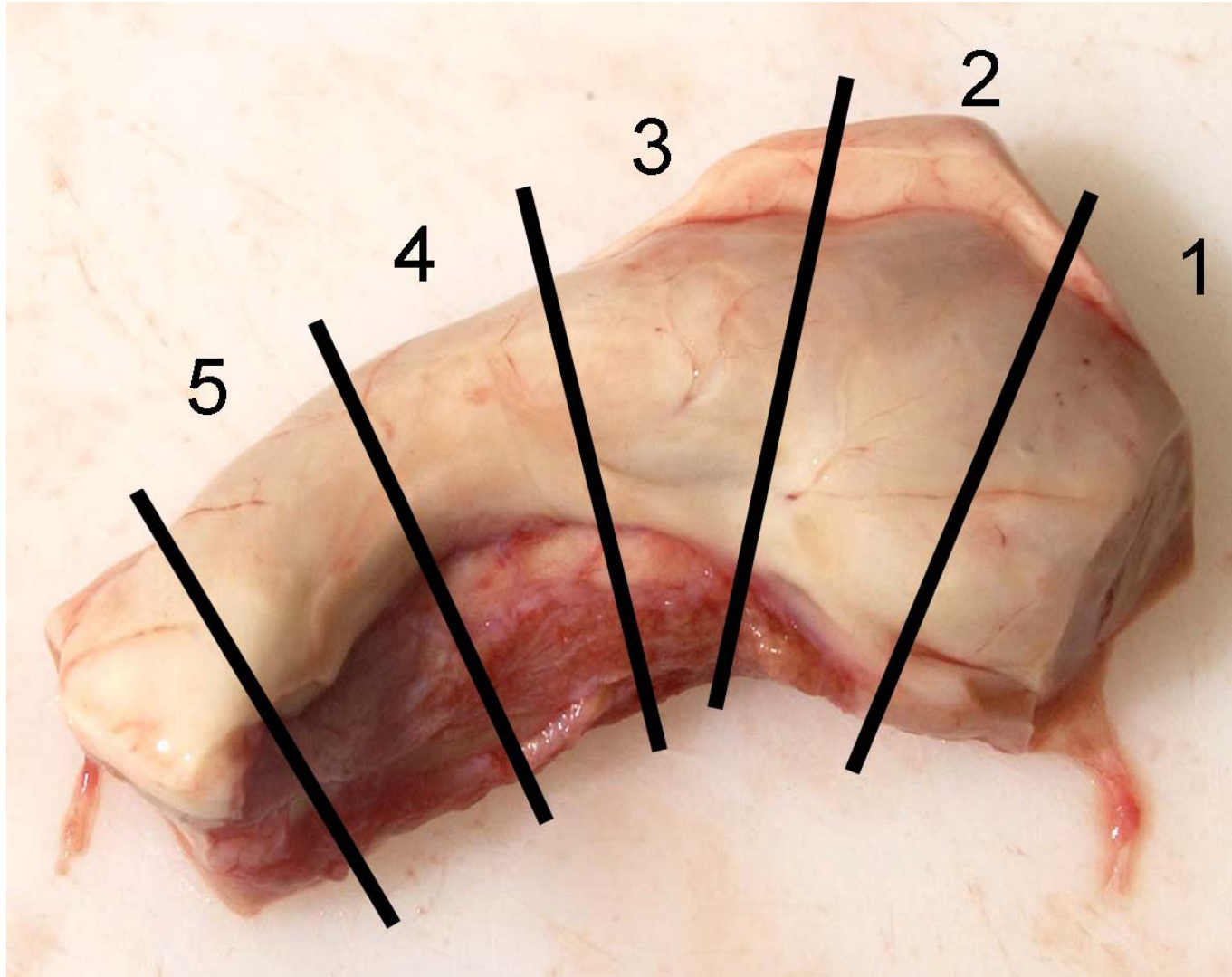


EP<sub>4</sub> immunoreactivity observed in the endothelium and smooth muscle of the meningeal artery











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Amsterdam





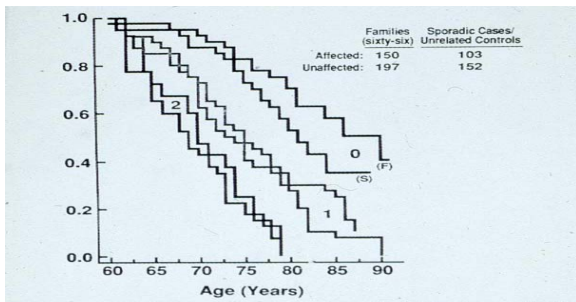
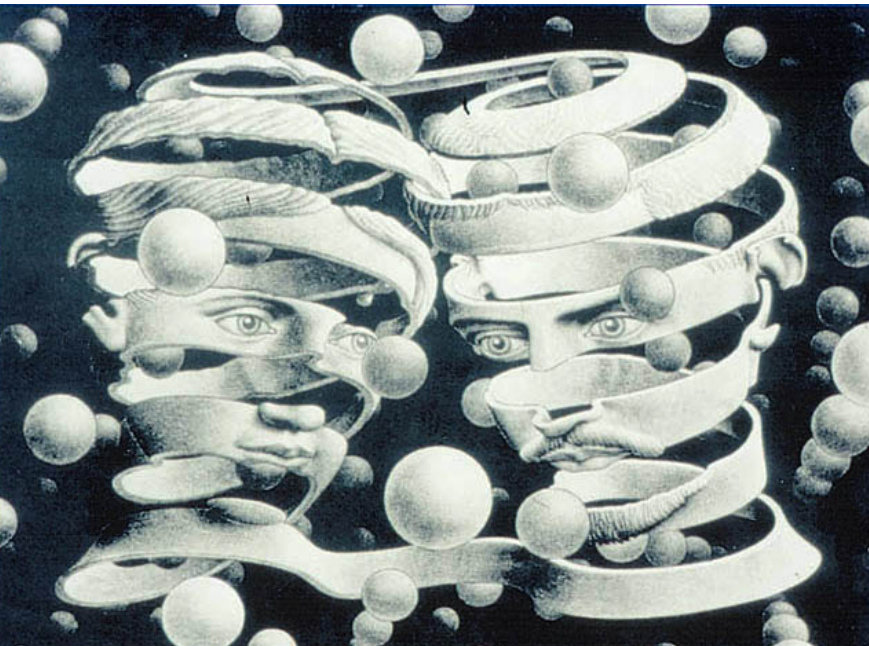


Fig. 1: Age of onset for subjects in late-onset familial and sporadic Alzheimer's disease with 0, 1, and 2 APOE4 alleles. Cumulative probability of remaining unaffected. Each curve is labeled by the number of inherited APOE4 alleles. Onset curves were estimated by Kaplan-Meier product limit distributions (SAS Institute Inc.). For example, at age 75, an estimated 20% of subjects without APOE4 were diagnosed with AD compared to approximately 60% of subjects with one APOE4 allele and more than 80% of subjects with two APOE4 alleles. Note that there is a dose-dependent of each APOE4 allele in both the familial and sporadic cases. Although the data for familial cases and sporadic cases are plotted separately, there are no significant differences. The late-onset familial cases used in this analysis are probably slightly skewed to an older age since families with a mean age of onset less than 60 years were not included.

Alle mensen zijn ongelijk

Prof.H. Galjard



# GAB2 Alleles Modify Alzheimer's Risk in APOE ε4 Carriers

Eric M. Reiman,<sup>1,2,3,17,18,\*</sup> Jennifer A. Webster,<sup>1,17,18</sup> Amanda J. Myers,<sup>4,5,18</sup> John Hardy,<sup>5,6</sup> Travis Dunckley,<sup>1,17</sup> Victoria L. Zismann,<sup>1,17</sup> Keta D. Joshipura,<sup>1,17</sup> John V. Pearson,<sup>1,17</sup> Diane Hu-Lince,<sup>1,17</sup> Matthew J. Huentelman,<sup>1,17</sup> David W. Craig,<sup>1,17</sup> Keith D. Coon,<sup>1,7,17</sup> Winnie S. Liang,<sup>1,17</sup> RiLee H. Herbert,<sup>1,17</sup> Thomas Beach,<sup>8,17</sup> Kristen C. Rohrer,<sup>5</sup> Alice S. Zhao,<sup>5</sup> Doris Leung,<sup>5</sup> Leslie Bryden,<sup>5</sup> Lauren Marlowe,<sup>5</sup> Mona Kaleem,<sup>5</sup> Diego Mastroeni,<sup>8</sup> Andrew Grover,<sup>8,17</sup> Christopher B. Heward,<sup>9</sup> Rivka Ravid,<sup>10</sup> Joseph Rogers,<sup>8,17</sup> Michael L. Hutton,<sup>11</sup> Stacey Melquist,<sup>11</sup> Ron C. Petersen,<sup>12</sup> Gene E. Alexander,<sup>13,17</sup> Richard J. Caselli,<sup>14,17</sup> Walter Kukull,<sup>16</sup> Andreas Papassotiropoulos,<sup>1,15</sup> and Dietrich A. Stephan<sup>1,2,17,\*</sup>

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<sup>18</sup> These authors contributed equally to this work.

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DOI 10.1016/j.neuron.2007.05.022

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Amsterdam





**Gene expression profiling of parkinsonian substantia nigra  
pars compacta; alterations in ubiquitin-proteasome, heat  
shock protein, iron and oxidative stress regulated proteins,  
cell adhesion/cellular matrix and vesicle trafficking genes**

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N. Amariglio<sup>3</sup>, G. Rechavi<sup>3</sup>, J. Li<sup>1</sup>, R. Ravid<sup>4</sup>, W. Roggendorf<sup>5</sup>,  
P. Riederer<sup>1,\*</sup>, and M. B. H. Youdim<sup>2,\*</sup>**

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Technion-Rappaport Family Faculty of Medicine, Haifa, and

<sup>3</sup> Functional Genomics Unit, Institute of Hematology, Sheba Medical Center,  
Tel-Aviv, Israel

<sup>4</sup> Netherlands Brain Bank, Amsterdam, The Netherlands

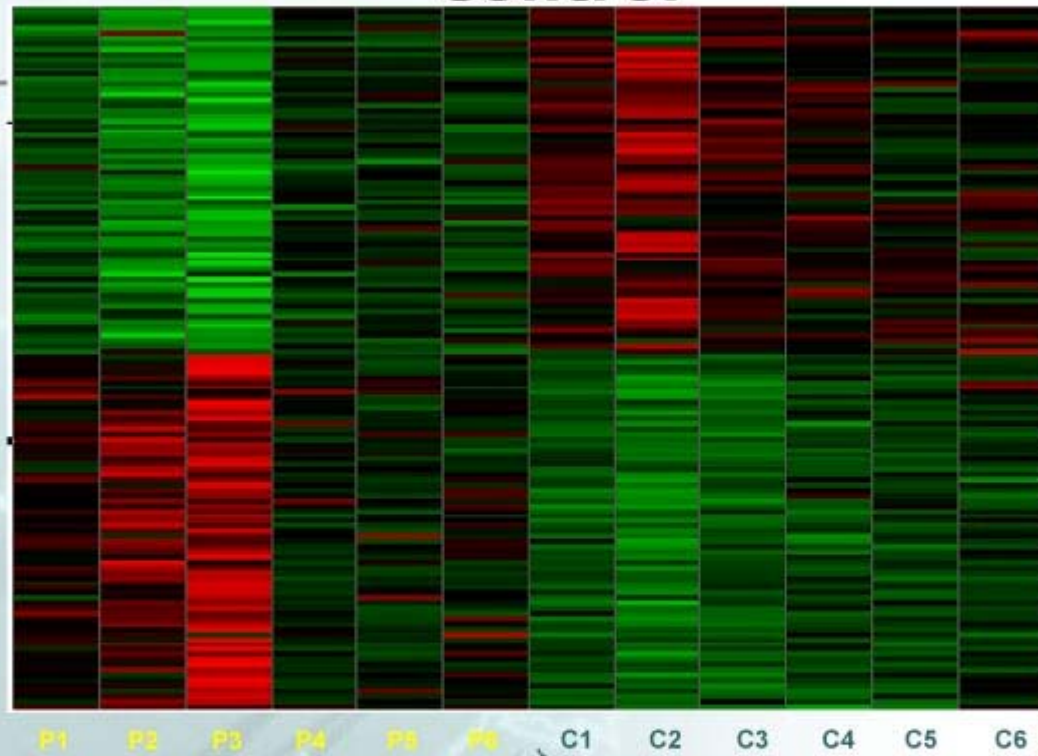
<sup>5</sup> Department of Neuropathology, Institute of Pathology,  
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Received July 14, 2004; accepted August 2, 2004  
Published online September 30, 2004; © Springer-Verlag 2004

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Amsterdam



# Heat Map of the 137 Genes Differentially Expressed in PD SNpc Compared to Matched Control



Affymetrix technology

PD

Controls

Green for values less than the mean

Red for values greater than the mean.

Grünblatt et al. *J. Neural Transm.* 2004

Only genes that met the criteria of being altered by a factor of 1.5 relative to control and passed the Wilcoxon test at the significant level of  $p < 0.05$  were included.

id  
lam

# Frontotemporal Dementia

## Correlation between genetic factors and neuropathology

*J. Van Swieten, Department of Neurology*

*P. Heutink, Clinical genetics, VUMC, Amsterdam*

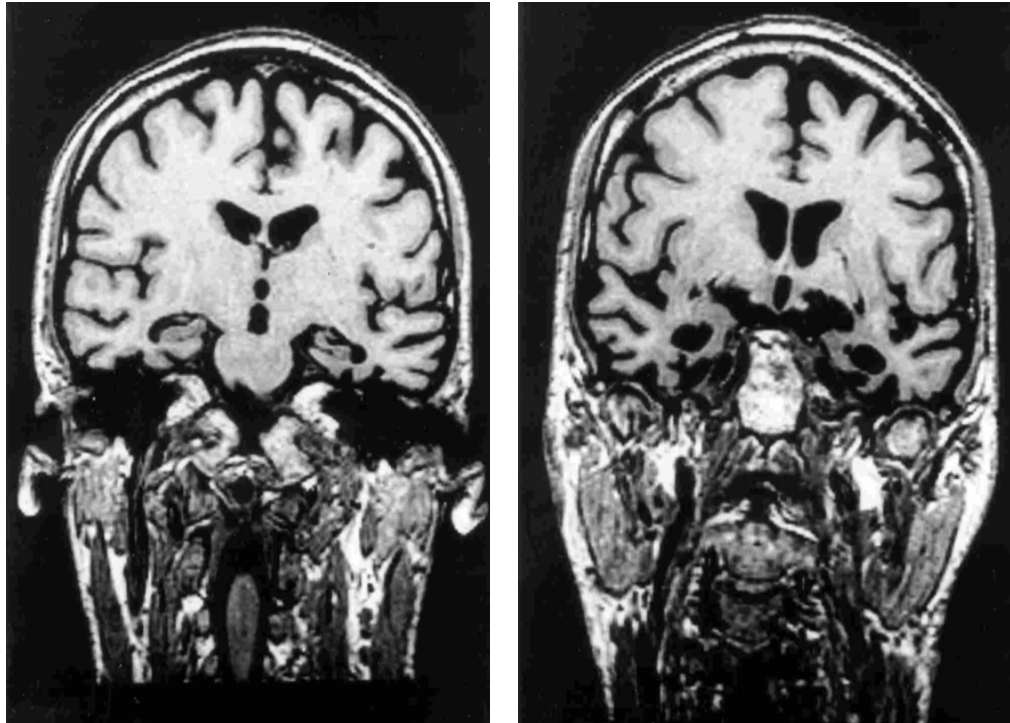
*R. Ravid, W. Kamphorst, Netherlands Brain Bank*

*R. Ravid  
Amsterdam*



# MRI of patient with mutation S320F

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Atrophy most prominent in temporal lobes (including hippocampus)

*Rosso et al, Annals of Neurology 2002*

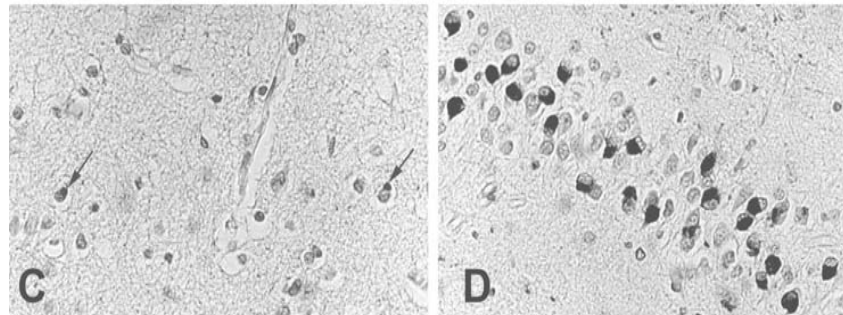
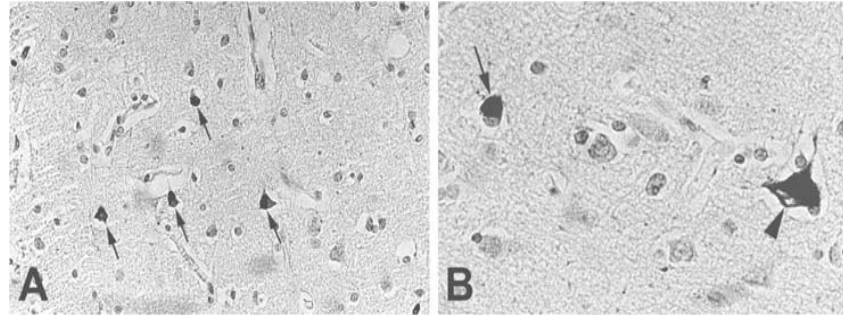
R. Ravid  
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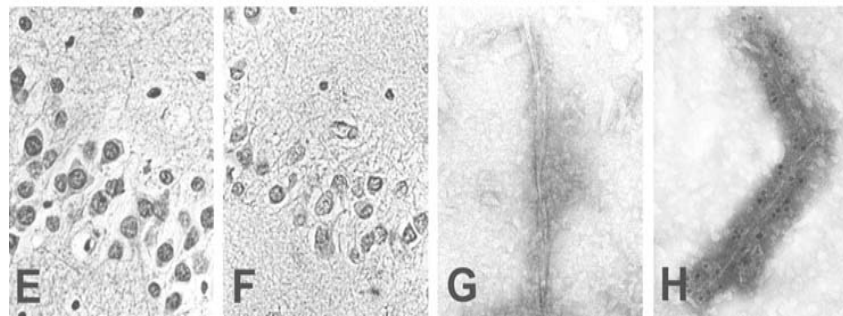


# Tau pathology in S320F mutation

*A-C Tau deposits in affected temporal cortex*



*D. Pick-like bodies in dentate gyrus of hippocampus*



*G-H. Tau positive filaments with electron microscopy*

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Amsterdam





# MRI guided pathology of Multiple Sclerosis

MS donors

Neurology – clinical diagnosis


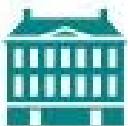
Radiology – MRI

Neuropathology  
Immunology


Tissue bank

samples for research

R. Ravid  
Amsterdam




NETHERLANDS BRAINBANK



STICHTING MS RESEARCH

Don't take your organs to heaven. Heaven knows we need them here.



MR versus Histopathology

Incidence versus T2 lesion

LCA

HLA-DR

ORO

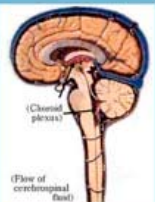
Incidence on T1

MTR: 0.32


T1-CR: 0.56

Axonal density: 95%

Boonin

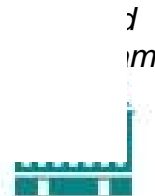
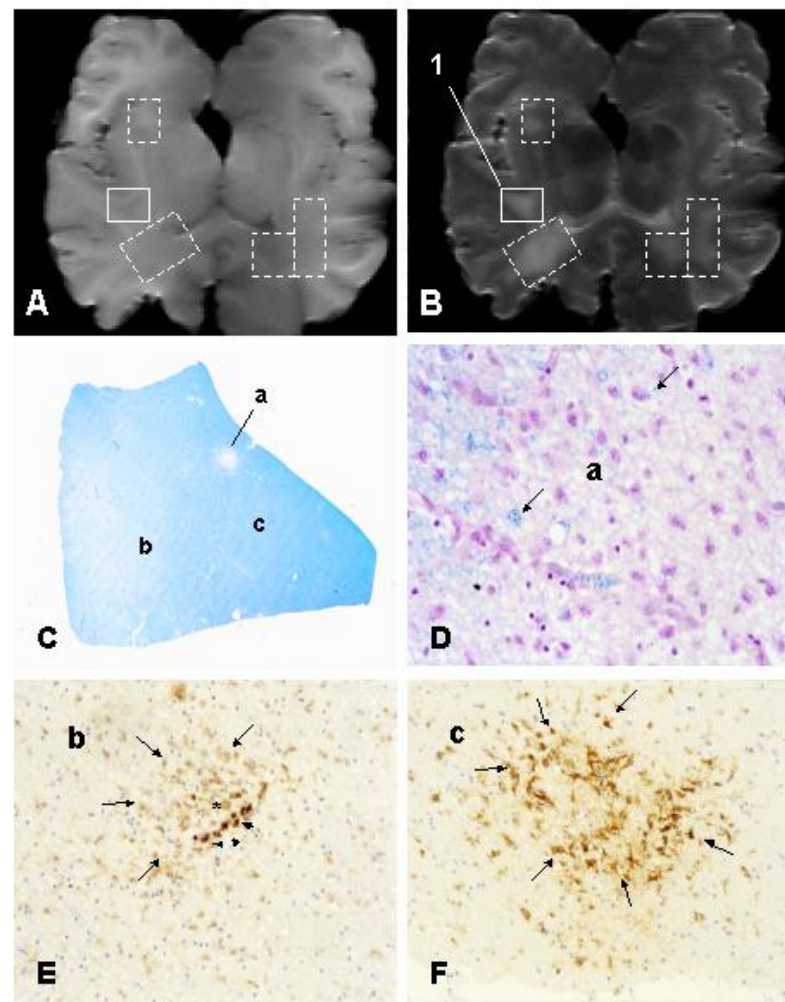


MS-liquorbank



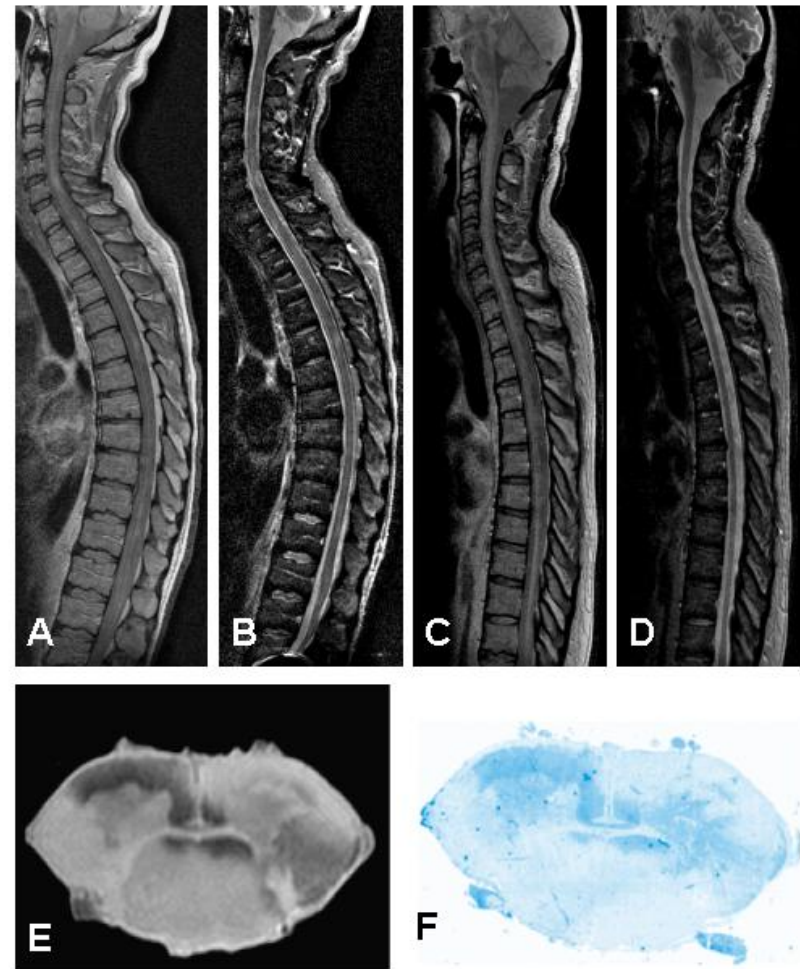
## Figure 1

Correlation of MRI with histopathology. Coronal slice of MS brain imaged post mortem by  $T_1$ - (A) and  $T_2$  (B) - weighted MR. Frames with dotted lines are areas that were excised, but are not depicted here. Frame 1 include a white matter area of hyperintensity on  $T_2$ -weighted MRI (B) that is slightly hypointense on the  $T_1$ -weighted image (A). These abnormalities were not macroscopically visible or palpable at autopsy. A white matter area tissue block obtained from the area of frame 1 is stained with LFB (C,D), and immunohistochemically stained with CD45 (LCA) antibody (E) and HLA-DR (LN3) antibody (F). The tissue specimen contained a small active demyelinating MS lesion (a, in panel C), with abundant phagocytic macrophages containing LFB-positive myelin breakdown products (a, arrows, in panel D), and two so-called (p)reactive lesions (b and c, in panels C,E,F). The (p)reactive lesion in panel E contains CD45-positive leukocytes within a small blood vessel (arrowheads) and surrounding CD45-positive activated microglia (asterisk, arrows). The preactive lesion in panel F contains numerous HLA-DR-positive activated microglia (arrows). Scale bars D = 1  $\mu$ m, E and F = 1  $\mu$ m (haematoxylin staining of nuclei).



## Figure 2

Sagittal *in situ* spinal cord MRI of MS patients with focal (A,B) and diffuse (C,D) abnormalities, and an axial high-resolution MRI of cervical spinal cord (E) of an MS patient, with the corresponding LFB-stained paraffin-embedded tissue section. Patients are imaged using proton density (A,C) and T<sub>2</sub>-weighted sequences (B,D,E). Focal areas of signal intensity are clearly delineated by both proton density MRI (A, arrows) and T<sub>2</sub>-weighted MRI (B, arrows), while areas of diffuse signal intensity increase are detectable by proton density MRI (C, arrow), but not visible in T<sub>2</sub>-weighted images (D). High-resolution axial MRI of the spinal cord (E) offer an accurate depiction of areas of total or partial myelin loss, as shown by the corresponding LFB-stained tissue section (F).



Research report

**Tissue pH as an indicator of mRNA preservation  
in human post-mortem brain**

Ann E. Kingsbury <sup>a</sup>, Oliver J.F. Foster <sup>b,\*</sup>, Angus P. Nisbet <sup>c</sup>, Nigel Cairns <sup>d</sup>, Louise Bray <sup>c</sup>,  
David J. Eve <sup>c</sup>, Andrew J. Lees <sup>c</sup>, C. David Marsden <sup>b</sup>

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# Sample pH

Importance of sample pH has been recognized since 1980s.  
Sample pH was associated with terminal condition of death.  
DNA microarray works revealed that sample pH affect  
global gene expression pattern systematically.  
(Li et al 2005, Tomita et al 2005)

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## Systematic changes in gene expression in postmortem human brains associated with tissue pH and terminal medical conditions

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Studies of gene expression abnormalities in psychiatric or neurological disorders often involve the use of postmortem brain tissue. Compared with single-cell organisms or clonal cell lines, the biological environment and medical history of human subjects cannot be controlled, and are often difficult to document fully. The chance of finding significant and replicable changes depends on the nature and magnitude of the observed variations among the studied subjects. During an analysis of gene expression changes in mood disorders, we observed a remarkable degree of natural variation among 120 samples, which represented three brain regions in 40 subjects. Most of such diversity can be accounted for by two distinct expression patterns, which in turn are strongly correlated with tissue pH. Individuals who suffered prolonged agonal states, such as with respiratory arrest, multi-organ failure or coma, tended to have lower pH in the brain; whereas those who experienced brief deaths, associated with accidents, cardiac events or asphyxia, generally had normal pH. The lower pH samples exhibited a systematic decrease in expression of genes involved in energy metabolism and proteolytic activities, and a consistent increase of genes encoding stress-response proteins and transcription factors. This functional specificity of changed genes suggests that the difference is not merely due to random RNA degradation in low pH samples; rather it reflects a broad and actively coordinated biological response in living cells. These findings shed light on critical molecular mechanisms that are engaged during different forms of terminal stress, and may suggest critical targets of protection or restoration.

### INTRODUCTION

Major depression and bipolar disorder are two of the most common and most debilitating psychiatric disorders, represent-

ing as the primary site of abnormality. Genetic studies, taken as a whole, have not generated replicable evidence for specific chromosomal regions that harbor the susceptibility genes (2) for either disorder, though the most robust association is most

## Effect of Agonal and Postmortem Factors on Gene Expression Profile: Quality Control in Microarray Analyses of Postmortem Human Brain

Hiroaki Tomita and Marquis P. Vaeter and David M. Walsh, Simon J. Evans, Prabhakara V. Choudary, Jun Li, Kevin M. Overman, Mary E. Atz, Richard M. Myers, Edward G. Jones, Stanley J. Watson, Huda Aki, and William E. Bunney, Jr.

There are major concerns that specific agonal conditions, including coma and hypoxia, might affect ribonucleic acid (RNA) integrity in postmortem brain tissues. We report that agonal factors significantly affect RNA integrity and have a major impact on gene expression profiles in microarrays. In contrast to agonal factors, gender, age, and postmortem factors have less effect on gene expression profiles. The Average Correlation Index (ACI) is proposed as a method for evaluating RNA integrity on the basis of consistency of microarray profiles. Reducing the variance due to agonal factors is critical in microarraying small but validated gene expression differences in microarray brain tissues for psychiatric patients and control subjects.

**Key Words:** Agonal; Unfolded protein response; Bipolar disorder; Bipolar disorder; Post-mortem; Post-mortem; Major depression; Disorder; Post-mortem; Post-mortem

Microarray studies using postmortem brain tissue have become particularly valuable in profiling gene expression patterns related to psychiatric disorders of unknown etiology (Baker et al 2001; Bunney et al 2003; Huhak et al 2001; Marder et al 2001; Van Dillen et al 2002). However, because postmortem brain tissue, the variability of ribonucleic acid (RNA) integrity has been a major concern. There have been two major factors that affect RNA integrity in gene expression studies using postmortem brain: (1) agonal factors, defined as specific agonal conditions at the time of death and agonal duration; and (2) postmortem factors, defined as the condition of the postmortem brain tissue after death, including the delay between death and the time the tissue is frozen (postmortem interval (PMI)) and the duration the brain tissue is stored in a freezer (storage interval (SI)). These factors and duration of storage significantly affect the integrity of RNA, whereas postmortem factors have relatively small effects on RNA integrity (Baker et al 2001; Bunney et al 2003; Collier et al 2001; Huhak et al 2001; Johnson et al 1996; Kanyehy et al 1995; Leonard et al 1995; Poret et al 1996; Ried et al 2001; Van Dillen et al 2002). However, because microarray technology has been shown to work on RNA extracted by agonal factors (Baker et al 1995; Huhak et al 1997; Johnson et al 1995, 1996), gene expression studies in the brain in the context of previous postmortem studies in this area, in which investigators have only analyzed restricted numbers of agonal

and postmortem factors and RNA integrity in microarray study of postmortem brain. The hypothesis raised in the present study was that agonal factors adversely affect integrity of mRNA and influence microarray expression profiles more than the postmortem factor or other biological factors, such as gender, age, or diagnosis of psychiatric disorder. The hypothesis was tested with 60 well characterized postmortem brains. We show that agonal factors and RNA integrity can be evaluated by correlation of expression profiles between microarrays. As a tool, the Average Correlation Index (ACI) is presented to evaluate the agonal factor and RNA integrity on the basis of the similarity of gene expression profiles for each microarray among a total set of microarray data.

### Evaluation of Agonal and Postmortem Factors

Specific agonal conditions, including coma, hypoxic anoxia, asphyxia, dehydration, hypoglycemia, multiple organ failure, head injury and ingestion of toxic substances at time of death have been evaluated with regard to influence on brain activity and RNA integrity in postmortem brain tissue (Baker et al 1995; Choudary et al 2001a, 2001b, 2001c, 2001d, 2001e, 2001f, 2001g, 2001h, 2001i, 2001j, 2001k, 2001l, 2001m, 2001n, 2001o, 2001p, 2001q, 2001r, 2001s, 2001t, 2001u, 2001v, 2001w, 2001x, 2001y, 2001z, 2002a, 2002b, 2002c, 2002d, 2002e, 2002f, 2002g, 2002h, 2002i, 2002j, 2002k, 2002l, 2002m, 2002n, 2002o, 2002p, 2002q, 2002r, 2002s, 2002t, 2002u, 2002v, 2002w, 2002x, 2002y, 2002z, 2003a, 2003b, 2003c, 2003d, 2003e, 2003f, 2003g, 2003h, 2003i, 2003j, 2003k, 2003l, 2003m, 2003n, 2003o, 2003p, 2003q, 2003r, 2003s, 2003t, 2003u, 2003v, 2003w, 2003x, 2003y, 2003z, 2004a, 2004b, 2004c, 2004d, 2004e, 2004f, 2004g, 2004h, 2004i, 2004j, 2004k, 2004l, 2004m, 2004n, 2004o, 2004p, 2004q, 2004r, 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2048s, 2048t, 2048u, 2048v, 2048w, 2048x, 2048y, 2048z, 2049a, 2049b, 2049c, 2049d, 2049e, 2049f, 2049g, 2049h, 2049i, 2049j, 2049k, 2049l, 2049m, 2049n, 2049o, 2049p, 2049q, 2049r, 2049s, 2049t, 2049u, 2049v, 2049w, 2049x, 2049y, 2049z, 2050a, 2050b, 2050c, 2050d, 2050e, 2050f, 2050g, 2050h, 2050i, 2050j, 2050k, 2050l, 2050m, 2050n, 2050o, 2050p, 2050q, 2050r, 2050s, 2050t, 2050u, 2050v, 2050w, 2050x, 2050y, 2050z, 2051a, 2051b, 2051c, 2051d, 2051e, 2051f, 2051g, 2051h, 2051i, 2051j, 2051k, 2051l, 2051m, 2051n, 2051o, 2051p, 2051q, 2051r, 2051s, 2051t, 2051u, 2051v, 2051w, 2051x, 2051y, 2051z, 2052a, 2052b, 2052c, 2052d, 2052e, 2052f, 2052g, 2052h, 2052i, 2052j, 2052k, 2052l, 2052m, 2052n, 2052o, 2052p, 2052q, 2052r, 2052s, 2052t, 2052u, 2052v, 2052w, 2052x, 2052y, 2052z, 2053a, 2053b, 2053c, 2053d, 2053e, 2053f, 2053g, 2053h, 2053i, 2053j, 2053k, 2053l, 2053m, 2053n, 2053o, 2053p, 2053q, 2053r, 2053s, 2053t, 2053u, 2053v, 2053w, 2053x, 2053y, 2053z, 2054a, 2054b, 2054c, 2054d, 2054e, 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# PMI does not affect microarray data quality

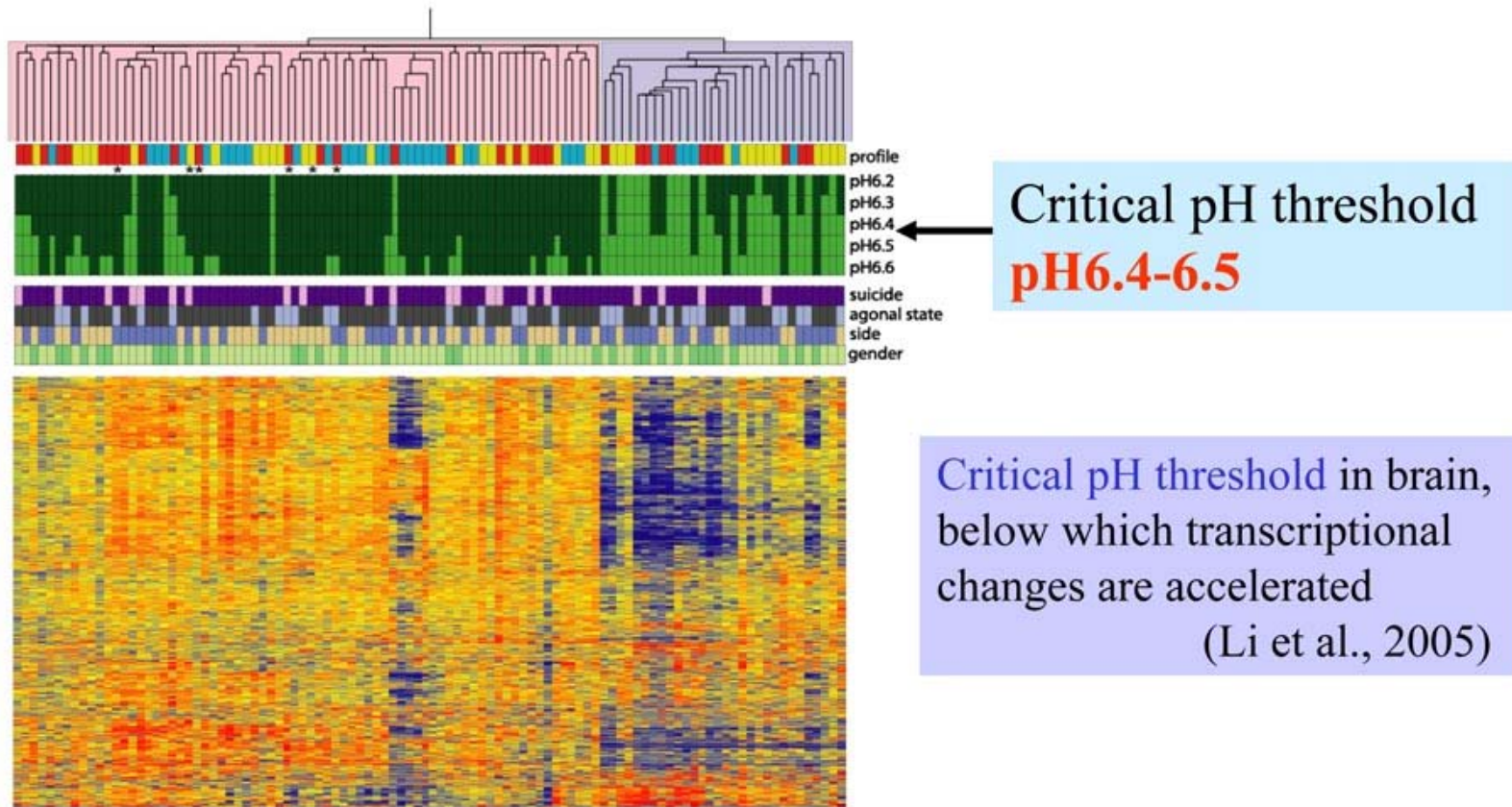
		18S/28S ratio	<i>ACTB</i> ratio	<i>GAPDH</i> ratio	Deg. slope	Median	% presence
18S/28S ratio	<i>R</i>	1.000	-0.149	-0.111	-0.093	-0.023	0.041
	<i>P</i>	.	0.134	0.268	0.351	0.822	0.682
Sample pH	<i>R</i>	0.041	<b>-0.455</b>	<b>-0.485</b>	<b>-0.515</b>	0.122	<b>0.185</b>
	<i>P</i>	0.685	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.224	<b>0.063</b>
PMI	<i>R</i>	0.091	-0.095	-0.151	-0.110	0.015	-0.056
	<i>P</i>	0.361	0.345	0.129	0.272	0.878	0.577

18S/28S ribosomal RNA ratio and PMI do not affect DNA microarray data quality

Sample pH directly affects microarray data quality



# Critical pH threshold in mitochondria-related genes



Two-way hierarchical clustering based on the expression levels of 676 mt-probe sets.

(Iwamoto et al., 2005)





## Factors interfering with tissue preservation

- Prolonged agonal state
- Metabolic disease
- Infectious diseases. Fever
- Seizures.
- Coma, intracranial pressure
- pH of the tissue/CSF
  
- Post-mortem delay between death and tissue processing
- Temperature of the corpse before processing
- Storage of the fixed samples. Fixation procedures and periodic changes of the fixative solution: paraformaldehyde, formalin. Paraffin blocks
- Storage of the frozen samples:  $-80^{\circ}\text{C}$ . Thawing







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# Suggested precautions for handling bio specimens

Human tissue and fluids may contain highly infectious agents and have potential risks of diseases that are highly communicable to other humans. All such tissues and fluids should be treated as being a risk for such transmission and handled carefully. Studies have shown several extremely hazardous agents (viruses, bacteria, prions) to be very stable.

The Creutzfeldt-Jakob (C-J) agent, for example, has been shown to be active in tissue which has been fixed for 30 years and could still be transmissible. The agent has also been shown to withstand conventional autoclaving. Although relatively rare, there is no quick screening method for such agents, and adequate caution must be exercised.

It is recommended that work with biospecimens, especially when fresh/non-fixed would be performed under a biohazard hood with all personnel taking special care. Any waste material should be treated as a biohazard and discarded according to local safety procedures for handling such material, which may include autoclaving, burial, or other methods.





Geoff Tompkinson/ SPL

# Inquiry finds brains were removed without consent

BMJ VOLUME 326 17 MAY 2003

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# Ethical / Legal Issues in Tissue banking

The use of human tissue in medical research is the focus of public and professional concerns and had recently been the subject of several reports on bio-ethics.

To create and develop the right infrastructure underlying brainbank activities, one should have medico-legal and ethical support according to local legislation including the following issues:

- **Tissue procurement**: all factors related to the donor programme and informed written consent of the donor.
- **Tissue management**: factors related to collection, handling and preservation of tissues.
- **Tissue dissemination**: factors related to scientific research and supplying samples of high scientific quality and properly matched for specific projects.
- **Confidentiality**: the anonymity of tissues and patient's records should be protected at all times. Samples supplied for research should be coded by the Tissue Bank and a tissue tracking system should be established to guaranteed the anonymity of the donor.
- **“Financial gain”**: from a legal and ethical point of view it is highly important to establish tissue banks as non-profit making sources for human tissues for scientific research. The tissue bank acts as custodian of tissue and the tissues must not be commercially handled.
- **Genetic testing**: the tremendous advances in genetic research in our decade raise serious ethical problems and complexities; there is sometimes conflicting interest in the need for knowledge and information on the one hand and the use and implications of this information for the people involved.

*R. Ravid  
Amsterdam*



COOKING...



... LIKE A BRIT  
AVAILABLE...

# THE PERFECT EUROPEAN

SHOULD



BE ...

DRIVING...



... LIKE  
THE FRENCH



... AS A BELGIAN



TALKATIVE... AS A FINN



HUMOROUS... AS A GERMAN  
PATIENT..."



... AS A PORTUGUESE  
CONTROLLED..."



FLEXIBLE...  
... AS A SWEDE



... AS A LUXEMBOURGER



... AS AN AUSTRIAN



... AS AN ITALIAN  
DISCREET...



SOBER...  
... AS THE IRISH



HUMBLE...  
... AS A SPANIARD



GENEROUS...  
... AS A DUTCHMAN



ORGANISED...  
... AS A GREEK



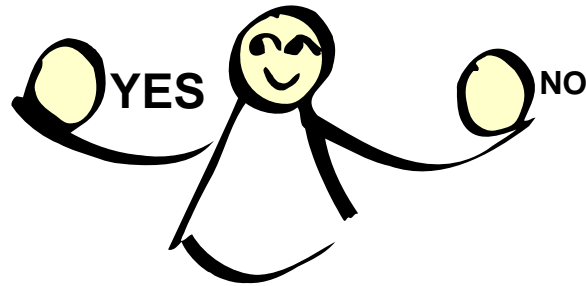
... AS A DANE



# BrainNet Europe II



## Network Decisions



- **In May 2000, the International Society for Biological and Environmental Repositories was officially chartered,**
- **to promote specimen banking and enhanced repository**
- **operations world-wide.**



*R. Ravid  
Amsterdam*





# MARBLE ARCH WORKING GROUP ON INTERNATIONAL BIOBANKING

- **Marble Arch Working Group**

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- **The Marble Arch Working Group on International Biobanking** was created in response to a growing need to harmonize approaches in regional and national Biobanks that address the critical issues in managing a modern human specimen Biobank. The participant funded Marble Arch group has proven to be an invaluable forum for the candid exchange of information, ideas and expertise.
- 
- Following the inaugural meeting in London in December 2005, the Marble Arch Working Group gained significant visibility in the respective member organisations and the scientific community at large. With the recognition the group has received to date, it is anticipated the Marble Arch Working Group will be a relevant scientific voice on Biobanking human specimens for research.
- 
- The 2nd meeting of the Marble Arch Working Group, hosted by the Centro Nacional de Investigaciones Oncológicas in Madrid, was attended by 19 expert participants and was honoured with the presence of two guest speakers, one from the World Health Organisation - International Agency for Research on Cancer and the other from the United States - National Cancer Institute.
- Ten countries were represented from 3 continents.
- The following topics were addressed at the meeting:
- Privacy Protection and the potential impact research;
- Cost Recovery and Researcher Requirements;
- US:NCI initiatives (focus on International harmonization efforts and caBIG).
- A number of key tasks were identified and working parties established to address these tasks. The group will continue its work and aims to meet again in the winter of 2006 and the spring of 2007.
- 
- The Marble Arch Working Group also aims to develop a public website to provide information about its activities. [Contact Us](#) | [T&C's](#) | [Site Map](#)

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## Biobanking for better healthcare

Peter H.J. Riegman<sup>a,\*</sup>, Manuel M. Morente<sup>b</sup>, Fay Betsou<sup>c</sup>, Pasquale de Blasio<sup>d</sup>, Peter Geary<sup>e</sup>, the Marble Arch International Working Group on Biobanking for Biomedical Research<sup>1</sup>

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<sup>d</sup>BioRep srl, Via Fantoli 16/15, 20138 Milano, Italy

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### ABSTRACT

Translational cancer research is highly dependent of large series of cases including high quality samples and their associated data. Comprehensive Cancer Centers should be involved in networks to enable large-scale multi-center research projects between the centers [Ringborg, U., de Valeriola, D., van Harten, W., Llombart-Bosch, A., Lombardo, C., Nilsson, K., Philip, T., Pierotti, M.A., Riegman, P., Saghatchian, M., Storme, G., Tursz, T., Verellen, D., 2008. Improvement of European translational cancer research. Collaboration between comprehensive cancer centers. *Tumori* 94, 143-146]. Combating cancer knows many frontiers. Research is needed for prevention as well as better care for those who have acquired the disease. This

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*Marble Arch open meeting*  
*Biorepositories in developing countries*  
October 9th 2008

*Fondazione IRCCS Istituto Nazionale dei Tumori Via Venezian 1, Milan - Italy*

**09:15 Welcome**

*Alberto Scanni* - General Manager, Fondazione IRCCS INT

*Marco Pierotti* – Scientific Director, Fondazione IRCCS INT and President of OECI

**09:30 Session 1: Working Group - Italy - Sudan**

*Chair: Marco Pierotti* Fondazione IRCCS INT and *Ida Biunno* - ITB-CNR

**09:30 The INMO Cancer Institute of Wad Medani - Sudan**

*Nasr Eldin Elwaly* - Director of INMO

**10:00 Promoting collaborations between Europe and Africa**

*Andrea Micheli* - Fondazione IRCCS INT

**10:30 Tumour Diagnostic Training and Support program**

*Massimo Barberis* - Riuniti Hospital of Bergamo

**10:45 International PhD program for Sudanese Students**

*Renato Mariani Costantini* - University of Chieti

**11:00 Proposal for the construction in Sudan of Anatomy Pathology and Tissue Bank Facility**

*Pasquale De Blasio* - CEO BioRep Milan

**11:15 Coffee Break**

**11:30 Session II: International and European Biorepositories initiatives**

*Chair: Manuel Morente* CNIO Spain and *Fay Betsu* Biobank de Picardies France

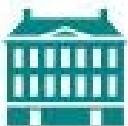
**11:30 Marble Arch Expert Group: The importance of Networking**

*Peter Geary* - Canadian Tumour Institute Network

**12:00 OECI- Tubafrost European Tissue Bank Network**

*Peter Riegman* - Erasmus University, Rotterdam

*R. Ravid*  
*Amsterdam*



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