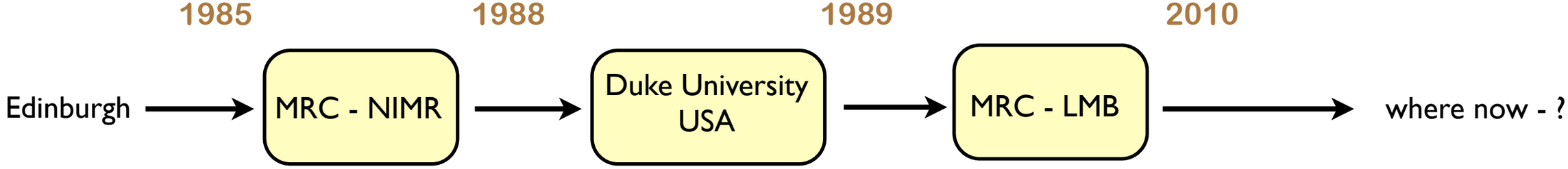
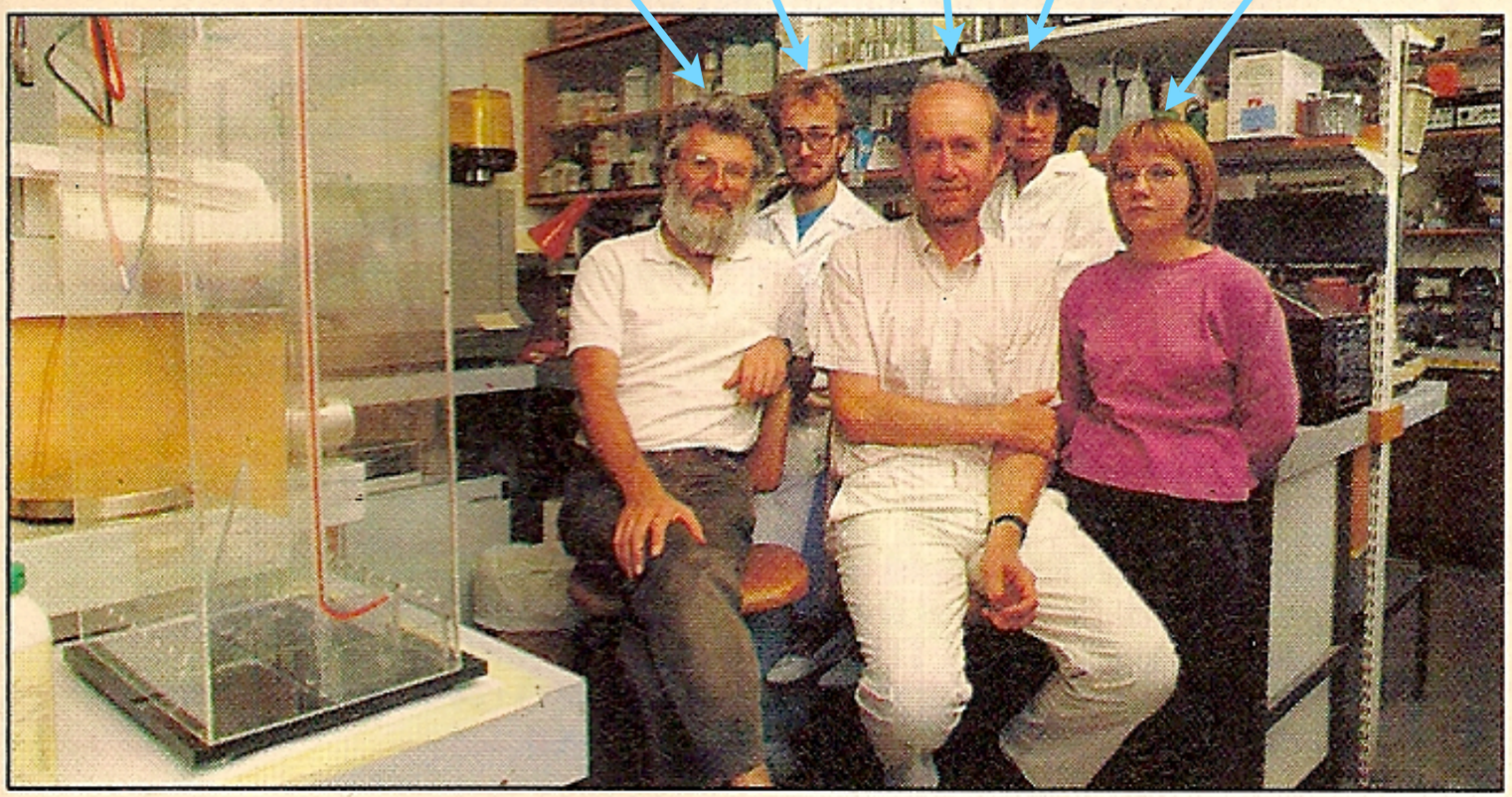
A potted, subjective history of my scientific life



DNA - sequencing - genes and evolution

John Sulston Trevor Hawkins Alan Coulson Ratna Shownkeen Molly Craxton



Pete Addis

Joint effort: the Cambridge team considers the worm, p 38

New Scientist 1990

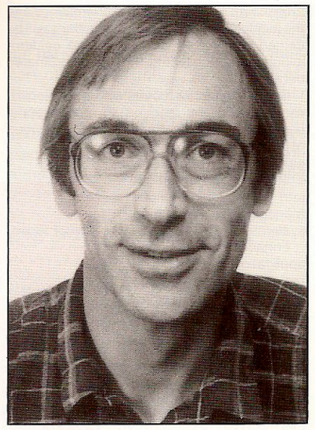
OBITUARIES

Dr Robert William Honess

Bob Honess, Head of Virology at the National Institute for Medical Research, died on September 28th 1990. He was 43. His short career which was exclusively devoted to the study of herpes viruses began in Peter Wildy's department in Birmingham with an analysis of the cross-neutralising determinant of herpes simplex viruses and of the thymidine kinase protein under the supervision of Douglas Watson. As a Jane Coffin Childs memorial fellow in Chicago he continued these studies with Bernard Roizman and described the temporal control of protein synthesis during herpes virus infection in a now classical series of publications. He returned to his native Yorkshire and to Douglas Watson's department in Leeds in 1975 to concentrate his research on the role of DNA replication in the control of gene expression and the molecular basis of the resistance of the herpes DNA polymerase to phosphono acetic acid and there began his considerations of the diversity of the structure of herpes virus genomes in relation to their distinct biological properties.

To the great benefit of this Institute he joined the Virology Division in 1977 with the object of extending his interests to the lymphotropic herpes virus, Herpes saimiri, and more recently to the newly discovered HHV-6. His commitment to understanding the genetic organisation and the evolutionary relationships of these viruses to others in the herpes group became the central features of his research during the last ten years. They led to a complete description of the molecular genetic maps of the viruses and extensive sequencing of their genomes and in the process to the identification and characterisation of their immediate early genes and to the discovery of herpes virus thymidylate synthase.

Bob was an intellectual leader in herpes virology, an area of research which is outstandingly successful in the United Kingdom, and was awarded the Fleming Lectureship of the Society for General Microbiology in 1984. From his undergraduate studies at Queen Elizabeth College where the quality of his first class Honours degree was recognised by the Helen R White prize, his strict respect for logic dominated his approach to research and his conception of the responsibilities of a scientist and the high standard which he set for himself as a consequence, made him a uniquely valuable and constructive critic, examiner and reviewer. He derived great pleasure in forcefully presenting his considered views for discussion and was generous to a fault with the time which he would devote to assist and advise his colleagues and students. His dedication to science with time overwhelmed his considerable talent as an artist but yielded an outstanding contribution to virology in a tragically curtailed and incompletely fulfilled career.



Dr R W Honess

For us who came to depend on his enormous knowledge, his generosity and his friendship he is irreplaceable.

Dr J J Skehel FRS is the Director of the National Institute for Medical Research in London. □

HOME
ABOUT OUR CENTER
TYPES OF CANCER
MAKE AN APPOINTMENT
CLINICAL TRIALS
MAKE A GIFT
OUR EXPERTS
SPECIALTY CENTERS AND CLINICS
FOR OUR PATIENTS AND FAMILIES
RESEARCH PROGRAMS
NEWS AND EVENTS
PUBLICATIONS
TRAINING PROGRAMS
CIGARETTE RESTITUTION FUND
JOHNS HOPKINS MEDICINE
JOHNS HOPKINS NURSING

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

Our Experts

John Nicholas, Ph.D.

Fax: (410) 955-0125

Interests:

Molecular biology of oncogenic herpesviruses, mechanisms of viral pathogenesis, signal transduction by viral cytokines and chemokine receptors.

Properties and Roles of Viral Cytokines in HHV-8 Related Malignancies

Titles

Associate Professor of Oncology

Joint Appointment in Molecular Microbiology and Immunology

Schools/Degrees

Ph.D., National Institute for Medical Research, London, U.K.

Training

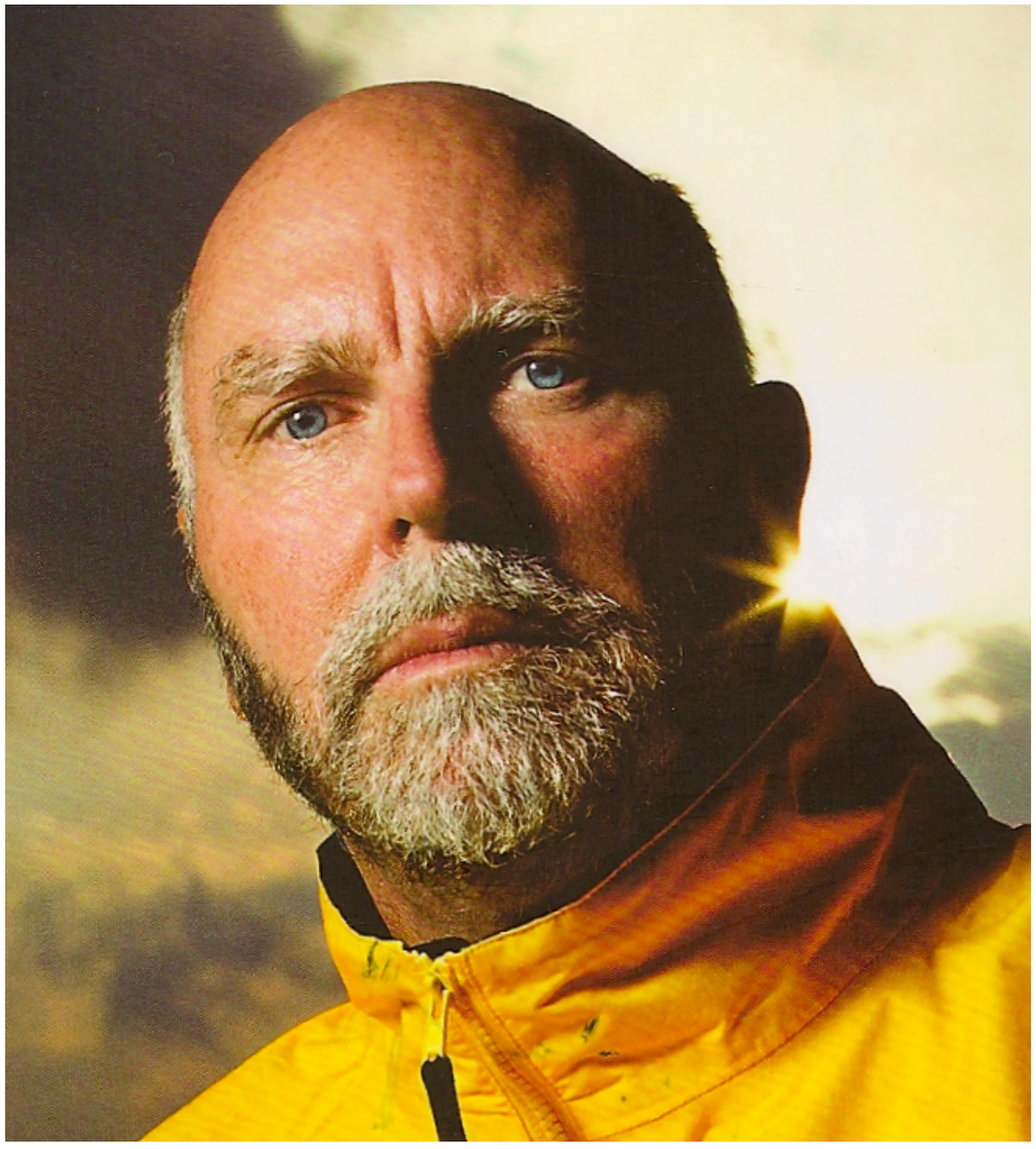
Fellow, Molecular Virology, Duke University, Durham, NC

Fellow, Molecular Virology, National Institute of Medical Research

Research Summary

Research in this laboratory is directed toward understanding the relevance of captured cellular gene homologues to replication and pathogenesis of human herpesvirus-8 (HHV-8), an oncogenic virus associated with endothelial tumor Kaposi's sarcoma (KS) and B cell malignancies primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD). Like other herpesviruses, HHV-8 is able to undergo lytic replication to produce new infectious particles and also to establish latent infections, which for some gamma (lymphotropic) herpesviruses can lead to neoplasia. HHV-8 specifies a homologue of interleukin-6 (vIL-6), three chemokine homologues (vCCL-1, vCCL-2, vCCL-3), and a chemokine receptor-related G protein-coupled receptor (vGPCR) that have been implicated as contributors to HHV-8-associated neoplasia because of their angiogenic, proliferative and anti-apoptotic activities. The virus encodes several other cellular homologues, including four viral interferon regulatory factors (vIRFs 1-4), which function to evade innate cellular defenses against virus infection by inhibiting host IRF functions and via other mechanisms.

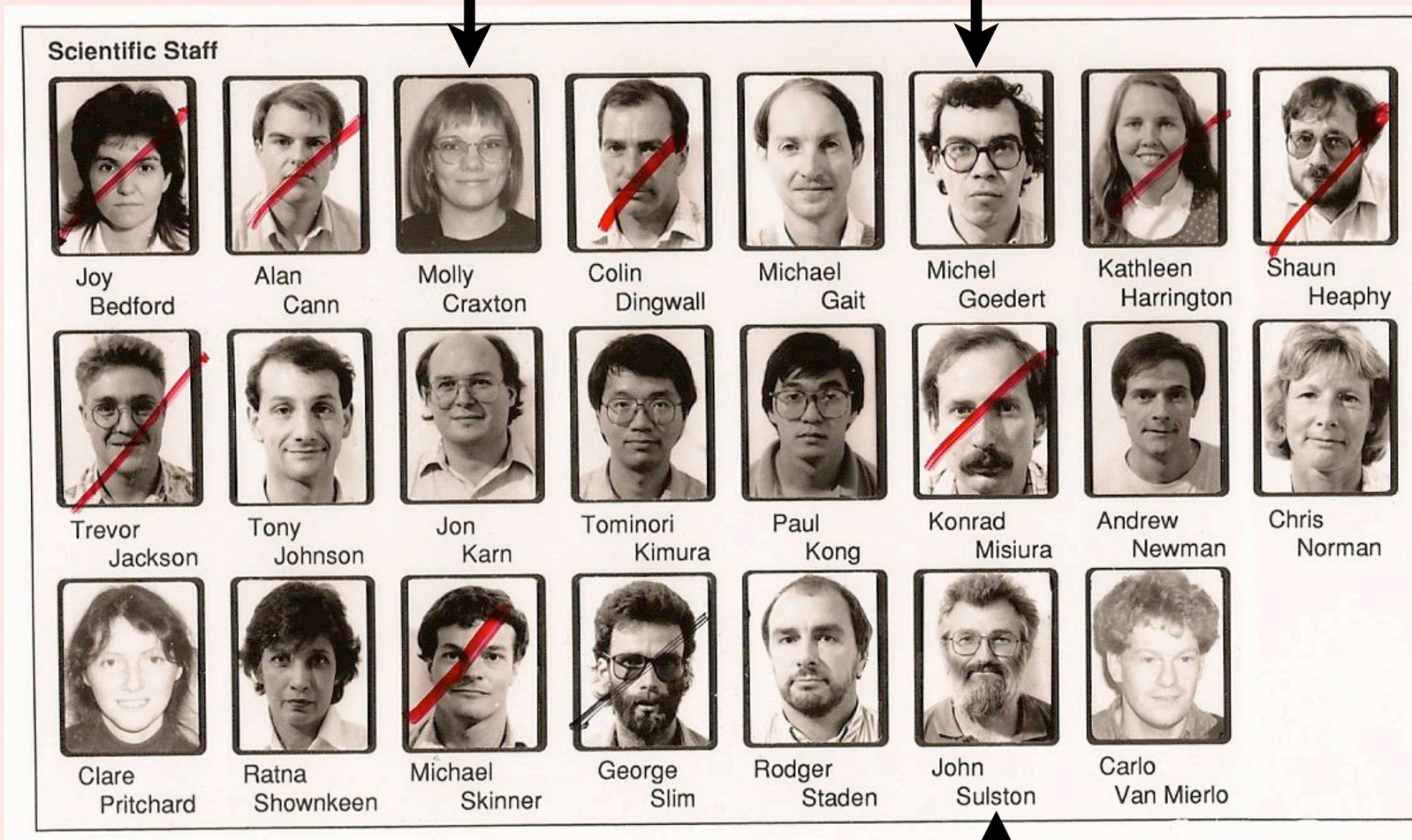
Research projects currently being undertaken in this laboratory are aimed at addressing: (1) the mechanisms by which vIL-6 is



Sydney Brenner

LMB Director
1986

Director's section
(Aaron Klug) 1990



Head of Genome Studies
1992

IDENTIFICATION AND CHARACTERISATION OF PROTEINS FROM DEVELOPING BRAIN.

M Goedert	Scientific Staff	20%
M Craxton	Scientific Staff (from 11.92)	100%

A typical mammalian genome contains of the order of 100,000 genes and the majority of the corresponding gene products is believed to be expressed in the central nervous system. To date, only a minority of these gene products has been identified and even fewer proteins are understood at a functional level. Thus, current thinking about the functioning of the central nervous system in molecular terms is based on the knowledge of only a small percentage of the molecules involved. This is especially true of the development of the nervous system, where the making of a structure as complex as the cerebral cortex is likely to require a large number of genes.

In order to gain a better understanding of the molecules involved in the development of the cerebral cortex we have recently started to tag-sequence cDNA clones from developing rat cerebral cortex. A cDNA library was made from cortical tissue of 19 day old rat fetuses. This stage was chosen, since morphological studies have shown that large numbers of connections between nerve cells are being established around this time.

synaptotagmin

English [edit]

Noun [edit]

Wikipedia has an article on:
Synaptotagmin

synaptotagmin (*plural* **synaptotagmins**)

1. (*biology*) Any of a family of membrane-trafficking proteins characterised by an N-terminal transmembrane region, a variable linker, and two C-terminal C2 domains (C2A and C2B).

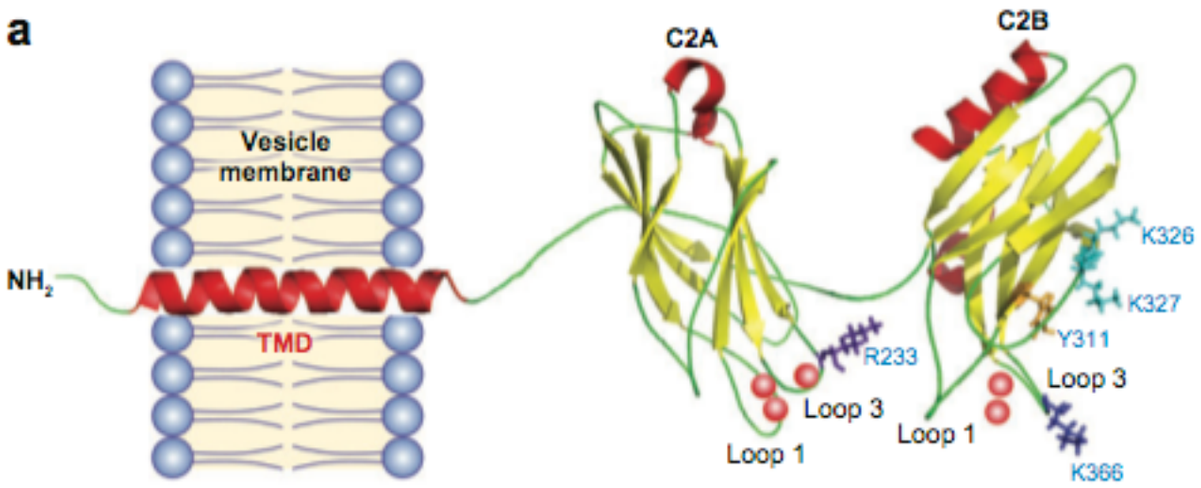
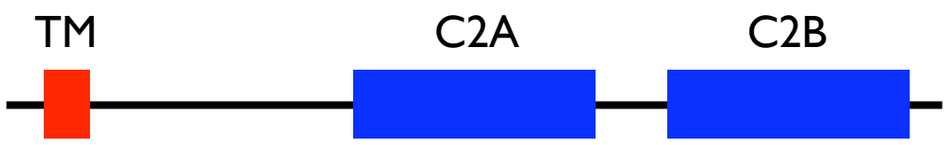


Figure from Chapman Ann.Rev.Biochem 2008



Identification of a Synaptic Vesicle-Specific Membrane Protein with a Wide Distribution in Neuronal and Neurosecretory Tissue

J.Cell Biol. 1981

WILLIAM D. MATTHEW, LARISA TSAVALER, and LOUIS F. REICHARDT
Departments of Physiology, and Biochemistry and Biophysics, School of Medicine, University of California, San Francisco, California 94143

Nature of the Antigens and Antibodies

To determine the specificity of the antibodies and properties of the antigens bound by them, we denatured synaptic plasma membranes (29) in boiling SDS and separated the denatured proteins by size on polyacrylamide gels (33). After electrophoresis was completed, the proteins were fixed in the gels and antibody molecules were allowed to bind the proteins in the gel (5). In Fig. 5 (lanes *b* and *d*), it is evident that each antibody binds a single protein in these gels, which has a molecular weight of ~65,000. A mixture of the antibodies also binds only one band, Fig. 5*f*, so the antigenic determinants must be on proteins of similar molecular weight. In fact, the results in Fig. 6 show that each monoclonal antibody is able to block subsequent binding by an isotope-labeled preparation of the other antibody. This result implies that the two antibodies bind antigenic determinants on the same 65,000-dalton protein. The two antibodies are not identical, however. Serum 48 clearly binds with greater affinity than serum 30 (Fig. 6). In addition, they are members of different IgG allotype groups (data not shown). The protein is a minor component, not evident in the corresponding Coomassie Blue–stained gel strip (Fig. 5*a*, *c*, and *e*).

Further studies were done on the antigen using a quantitative radioimmune assay. The results in Table IV show that the antigen is associated almost exclusively with the particulate fraction from a brain homogenate. Less than 1% of the antigen is found in the soluble fraction. The antigen is not released from the particulate fraction by high or low salt, but is solubilized with Triton X-100. The results in Table IV also show that the antigen can be almost completely destroyed by incubation with trypsin. Therefore, the antigen has the properties of an integral membrane protein. These results are compatible with the observed association of the antigenic determinants with the outer surface of synaptic vesicles.

Cell homogenate	1.0
Protein A–polyacrylamide bead	10.6

Immunoprecipitation of [^{3}H]NE from a PC12 homogenate containing [^{14}C]leucine-labeled proteins. PC12 cells were grown in the presence of [^{14}C]leucine for 5 d before a 60-min incubation in [^{3}H]NE. The ratio of [^{3}H]NE to [^{14}C]leucine was normalized to the value found in the homogenate which has been defined as 1.0.

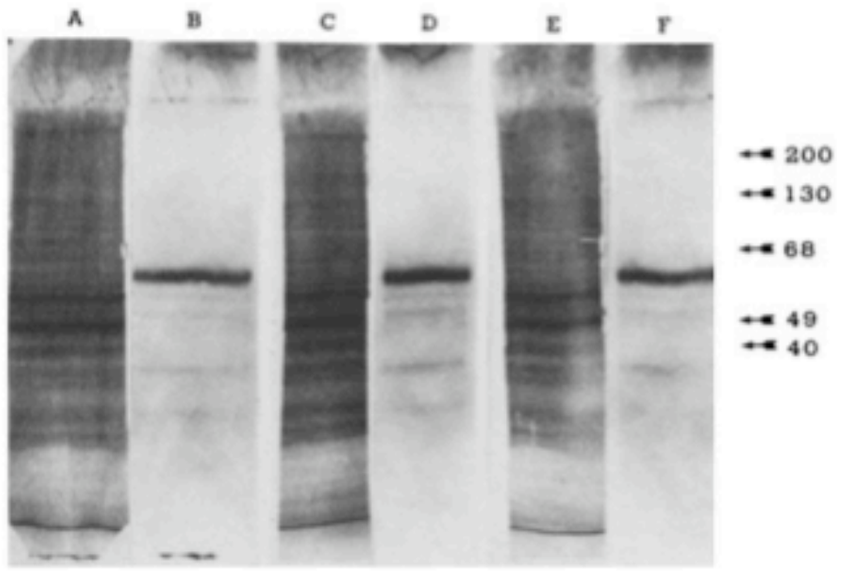


FIGURE 5 Identification of antigens. Synaptic plasma membranes were dissolved in SDS mercaptoethanol and fractionated in 10% polyacrylamide gels in a discontinuous buffer system (33). The antigens were identified by initial incubation with the monoclonal antibody, subsequent incubation with [^{125}I]-goat-anti-mouse-kappa chain affinity purified immunoglobulins (5). Lanes *A*, *C*, and *E* are Coomassie Blue–stained gel lanes; lane *B* is the autoradiograph of a gel treated with serum 30; lane *D* with serum 48; and lane *F* with both serum 30 and serum 48. The migration pattern of protein standards with molecular weights measured in thousands is shown on the right. Gels incubated with [^{125}I]-goat-anti-mouse-kappa antibody, but not either monoclonal antibody did not have detectable binding.

synaptotagmin

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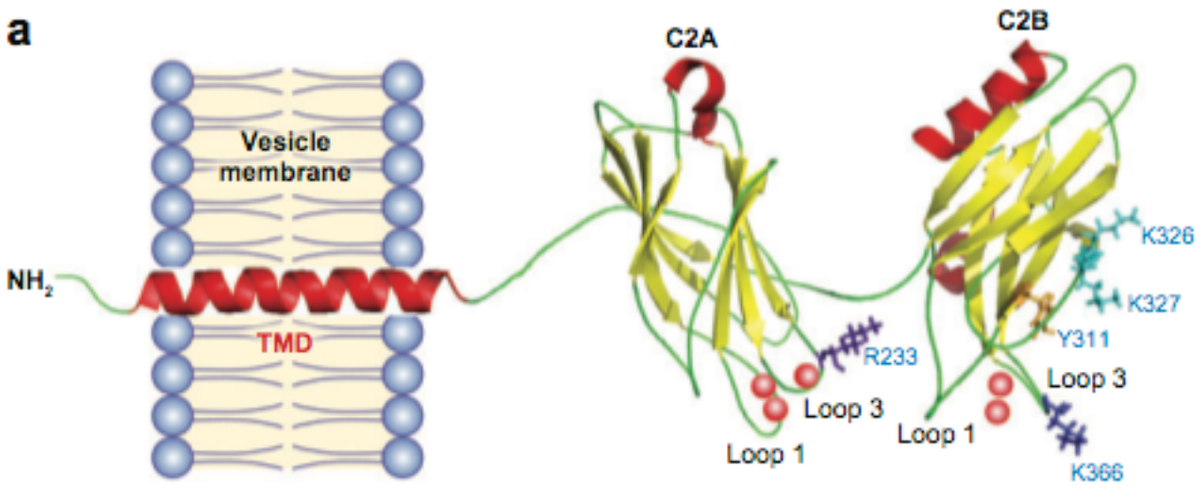
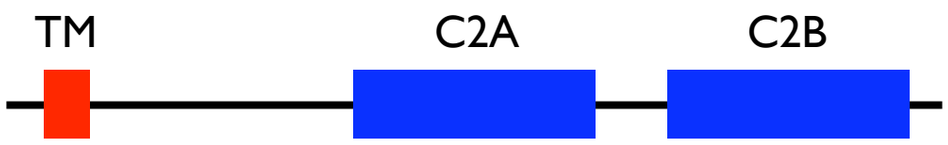


Figure from Chapman Ann.Rev.Biochem 2008



Syt gene expression in Rat

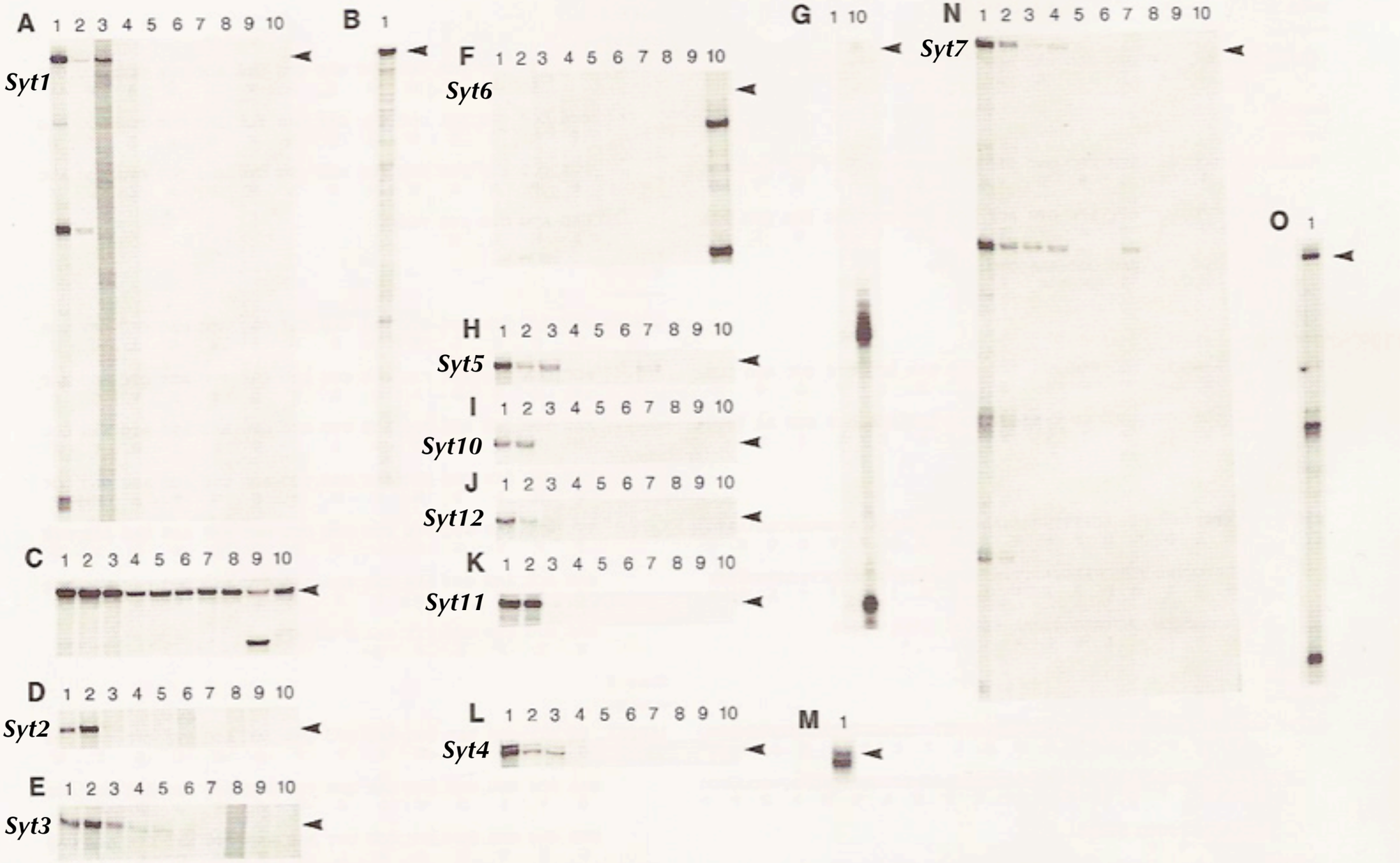


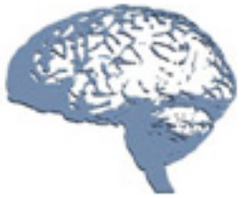
Fig. 3. RPA results. Probes A–O are detailed in Table 1. Arrowheads indicate full-length products, the sizes of which are: A 431 nt, B 430 nt, C 476 nt, D 402 nt, E 334 nt, F 357 nt, G 395 nt, H 455 nt, I 458 nt, J 330 nt, K 481 nt, L 579 nt, M 242 nt, N 520 nt, O 340 nt. Tissue mRNAs are: 1 adult brain, 2 adult spinal cord, 3 E17 embryo forebrain, 4 adult heart, 5 adult kidney, 6 adult liver, 7 adult lung, 8 adult spleen, 9 adult testis, 10 adult thymus.

Group Leaders

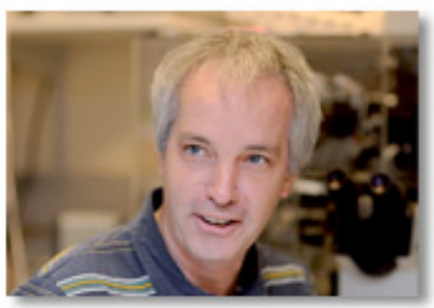
- Anne Bertolotti - Cellular aspects of protein misfolding in neurodegenerative diseases
- Bazbek Davletov - Molecular mechanisms of vesicle fusion
- Michel Goedert - Molecular mechanisms of neurodegeneration
- Ingo Greger - Glutamate-gated ion channels: Biogenisis and trafficking
- Michael Hastings - Molecular neurobiology of circadian timing
- Gregory Jefferis - Olfactory perception in the fruit fly
- Leon Lagnado - Synaptic transmission in the visual system of zebrafish
- Harvey McMahon - Sculpting cell membranes

Bazbek Davletov

Molecular mechanisms of vesicle fusion

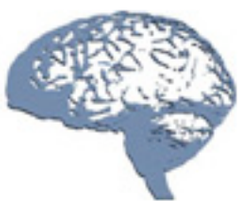


Neurobiology



Harvey McMahon

Sculpting cell membranes



Neurobiology

2004

Research article

Open Access

Synaptotagmin gene content of the sequenced genomes

Molly Craxton
Medical Research Council, Laboratory of Molecular Biology, Hills Road, Cambridge, CB2 2QH, UK

author email corresponding author email

BMC Genomics 2004, **5**:43 doi:10.1186/1471-2164-5-43

The electronic version of this article is the complete one and can be found online at:
http://www.biomedcentral.com/1471-2164/5/43

Received: 6 April 2004
Accepted: 6 July 2004
Published: 6 July 2004

2007

Research article

Open Access

Evolutionary genomics of plant genes encoding N-terminal-TM-C2 domain proteins and the similar FAM62 genes and synaptotagmin genes of metazoans

Molly Craxton
Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, UK

author email corresponding author email

BMC Genomics 2007, **8**:259 doi:10.1186/1471-2164-8-259

The electronic version of this article is the complete one and can be found online at:
http://www.biomedcentral.com/1471-2164/8/259

Received: 22 November 2006
Accepted: 31 July 2007
Published: 31 July 2007

2010

Research article

Open Access

A manual collection of *Syt*, *Esyt*, *Rph3a*, *Rph3al*, *Doc2*, and *Dblc2* genes from 46 metazoan genomes - an open access resource for neuroscience and evolutionary biology

Molly Craxton
Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge, CB2 0QH, UK

author email corresponding author email

BMC Genomics 2010, **11**:37 doi:10.1186/1471-2164-11-37

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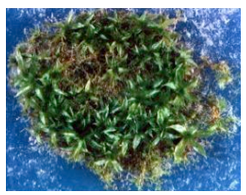
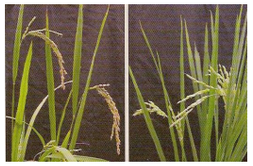
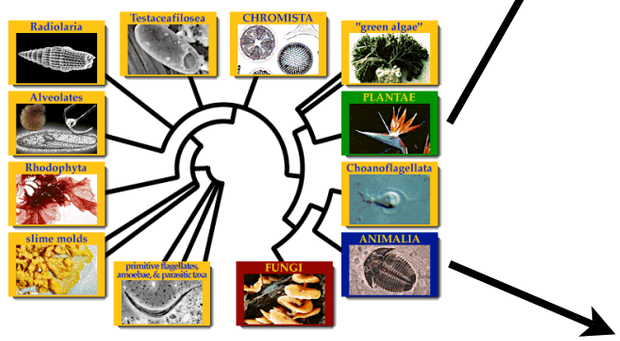
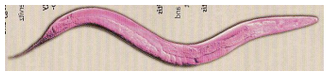
Published: 15 January 2010

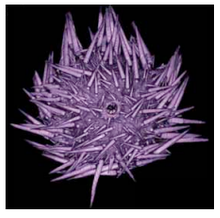


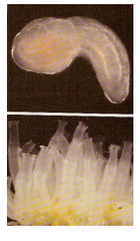


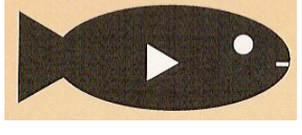

Radiolaria
Testaceafilosea
CHROMISTA
"green algae"
Alveolates
PLANTAE
Rhodophyta
Choanoflagellata
slime molds
ANIMALIA
primitive flagellates, amoebae, & parasitic taxa
FUNGI

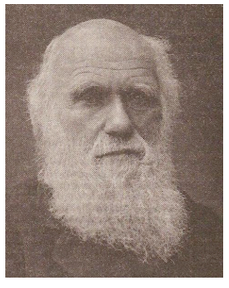

TM
C2A
C2B

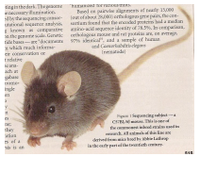












Marine Invertebrates

Trichoplax adhaerens
http://www.jgi.doe.gov

Gene Name

Syt1
Syt7
Syt21
Syt22
Syt23
Dblc2
Esyt2
Rph

No neurons

Nematostella vectensis
http://www.jgi.doe.gov

Gene Name

Syt1
Syt7
Syt21
Syt24
Syt25
Syt26
Syt27
Syt28
Syt29
Syt30
Syt31
Syt32
Syt33
Syt34
Syt35
Syt36
Syt37
Syt38
Syt39
Syt40
Syt41
Syt42
Syt43
Dblc2
Esyt2a
Esyt2b
Esyt2c
Rph

So many!

Capitella sp. I
http://www.jgi.doe.gov

Gene Name

Syt1
Syt4
Syt7
Syt9
Syt12
Syt15
Syt16
Syt17
Syt44
Sytalpha
Dblc2
Esyt2
Rph

Helobdella robusta
http://www.jgi.doe.gov

Gene Name

Syt1a
Syt1b - sequence starts within C2AB region
Syt1c
Syt1d
Syt1e
Syt4
Syt7a
Syt7b
Syt7c
Syt7d
Syt7e
Syt7f
Syt15a
Syt15b
Syt16
Syt45
Syt46
Esyt2a
Esyt2b
Rph

Lottia gigantea
http://www.jgi.doe.gov

Gene Name

Syt1
Syt4
Syt7
Syt9
Syt12
Syt15a
Syt15b
Syt16
Syt17
Syt18
Syt21
Syt47
Sytalpha
Dblc2
Esyt2
Rph

Ciona savignyi
http://www.broad.mit.edu

Gene Name

Syt1
Syt7
Syt15
Syt16
Sytalpha1
Sytalpha2
Dblc2
Esyt2
Rph

Ciona intestinalis
http://www.jgi.doe.gov

Gene Name

Syt1
Syt7
Syt15
Syt16
Sytalpha1
Sytalpha2
Dblc2
Esyt2
Rph

Stongylocentrotus purpuratus
http://www.hgsc.bcm.tmc.edu

Gene Name

Syt1
Syt4
Syt7
Syt9a
Syt9b
Syt12
Syt15
Syt16
Syt17
Syt18
Syt21
Syt48
Syt49
Syt50
Syt51
Sytalpha
Dblc2
Esyt2
Rph - gap in genome sequence

Branchiostoma floridae
http://www.jgi.doe.gov

Gene Name

Syt1a
Syt1b
Syt4
Syt7
Syt9
Syt12
Syt15a
Syt15b
Syt16
Syt17
Syt18
Syt52
Syt53
Syt54
Sytalpha
Dblc2
Esyt2a
Esyt2b
Rph

Rather few!

Ecdysozoa

Ixodes scapularis
http://www.jcvi.org
http://www.broad.mit.edu

Gene Name

Syt1
Syt4
Syt9
Syt13
Syt15a
Syt15b
Syt16
Syt55
Esyt2
Rph - gap in genome sequence

Daphnia pulex
http://www.jgi.doe.gov

Gene Name

Syt1
Syt4
Syt7
Syt13
Syt15
Syt16
Syt17
Syt56
Syt57
Esyt2
RphI

Acyrthosiphon pisum
http://www.hgsc.bcm.tmc.edu

Gene Name

Syt1
Syt4
Syt7
Esyt2

Tribolium castaneum
http://www.hgsc.bcm.tmc.edu

Gene Name

Syt1
Syt4
Syt7
Syt9
Syt12
Syt13
Syt15
Syt16
Esyt2a
Esyt2b
Esyt2c
Rph

Nasonia vitripennis
http://www.hgsc.bcm.tmc.edu

Gene Name

Syt1
Syt4
Syt7
Syt9
Syt12
Syt13
Syt16
Syt20
Sytalpha
Esyt2

Apis mellifera
http://www.hgsc.bcm.tmc.edu

Gene Name

Syt1
Syt4
Syt7
Syt9
Syt12
Syt13
Syt16
Syt20
Esyt2
Rph

Anopheles gambiae
http://www.jcvi.org
http:///genome.wustl.edu

Gene Name

Syt1
Syt4
Syt13
Syt16
Sytalpha
Esyt2

Drosophila melanogaster
http://flybase.org

Gene Name http://flybase.org

Syt1
Syt4
Syt7
Syt12
Syt13 (Sytbeta)
Syt16 (Syt14)
Sytalpha
Esyt2 (CG6643)
Rph

Drosophila simulans
http://flybase.org

Gene Name

Syt1
Syt4
Syt7
Syt12
Syt13 (Sytbeta)
Syt16 (Syt14)
Sytalpha
Esyt2 (GD6643)
Rph

1985 1988 1989 2010

Edinburgh → MRC - NIMR → Duke University USA → MRC - LMB → where now - ?

Michel Goedert

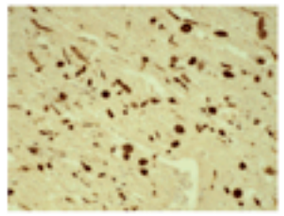
Molecular mechanisms of neurodegeneration

Neurobiology

Delobel, P., Lavenir, I., Ghetti, B., Holzer, M. & Goedert, M. (2006) Cell-cycle markers in a transgenic mouse model of human tauopathy: Increased levels of cyclin-dependent kinase inhibitors p21Cip1 and p27Kip1. *Am.J. Path.* **168**, 878-887.

Tofaris, G.K., Reitböck, P.G., Humby, T., Lambourne, S.L., O'Connell, M., Ghetti, B., Gossage, H., Emson, P.C., Wilkinson, L.S., Goedert, M. & Spillantini, M.G. (2006) Pathological changes in dopaminergic nerve cells of the substantia nigra and olfactory bulb in mice transgenic for truncated human α-synuclein (1-20): Implications for Lewy body disorders. *J. Neurosci.* **26**, 3942-3950.

Goedert, M. & Spillantini, M.G. (2006) Neurodegenerative α-synucleinopathies and tauopathies. In: Basic Neurochemistry, 7th Edition. (G.J. Siegel, R.W. Albers, S. Brady and D.L. Price, eds.), pp. 745-759. *Elsevier Academic Press* 2006.



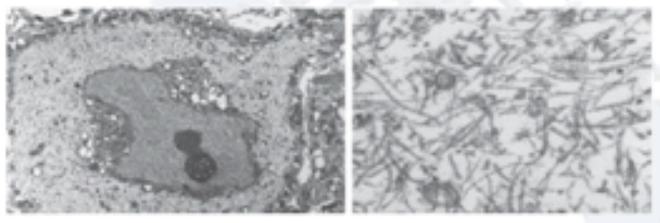
Alzheimer's disease and Parkinson's disease are characterized by the presence of abnormal filamentous assemblies within some nerve cells. Similar assemblies are found in several related disorders. The events leading to filament formation or the mere presence of filaments are believed to produce nerve cell degeneration.

Our work has shown that the intraneuronal filaments found in these diseases are made of either microtubule-associated protein tau or α-synuclein.

In Alzheimer's disease hyperphosphorylated tau protein forms the major component of paired helical and straight filaments. The discovery of mutations in the tau gene in inherited frontotemporal dementia has firmly established that dysfunction of tau protein can cause neurodegeneration and dementia.

The α-synuclein gene is mutated in rare cases of inherited Parkinson's disease and α-synuclein is the major component of the filamentous lesions that characterize Parkinson's disease and other Lewy body disorders, as well as multiple system atrophy. It is therefore central to the pathogenesis of these diseases.

Current work is aimed at developing experimental animal models of tauopathies and α-synucleinopathies and at identifying disease modifiers.



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Pete Addis

Joint effort: the Cambridge team considers the worm, p 38

DNA - sequencing - genes and evolution


Double
Concerto
for One
Violin