HumanAfrican trypanosomiasis (HAT)(Sleeping sickness) and Variclla-Zoster virus (VZV) research

Specific areas:

- **HAT-**mouse model
- Neuropathogenesis
- Blood-Brain barrier function
- Novel drugs for HAT
- **VZV**-Viral gene expression in latency
- Post-herpetic neuralgia and sodium ion currents

People:

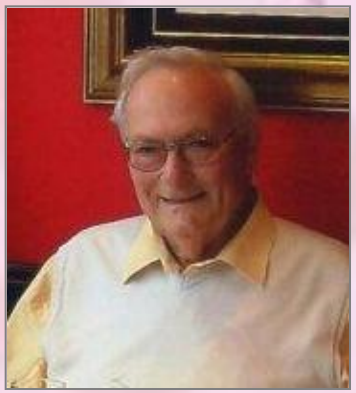
- Peter Kennedy (PI)
- Jean Rodgers
- Barbara Bradley
- Paul Montague
- Max Murray

Main funders:

- Wellcome Trust
- MRC

Human African trypanosomiasis - mouse model

Murine model
Trypanosoma brucei brucei GVR35



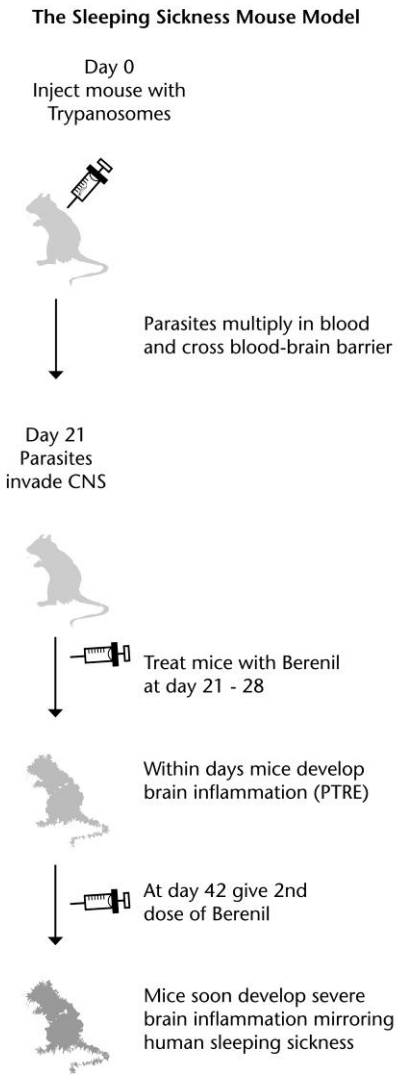
Frank Jennings

Model developed in late 1970's
Well established & characterised

Barbara Bradley

- Acute
- Early CNS
- Late CNS
- Post treatment reactive encephalopathy (PTRE)

Main Methods Used

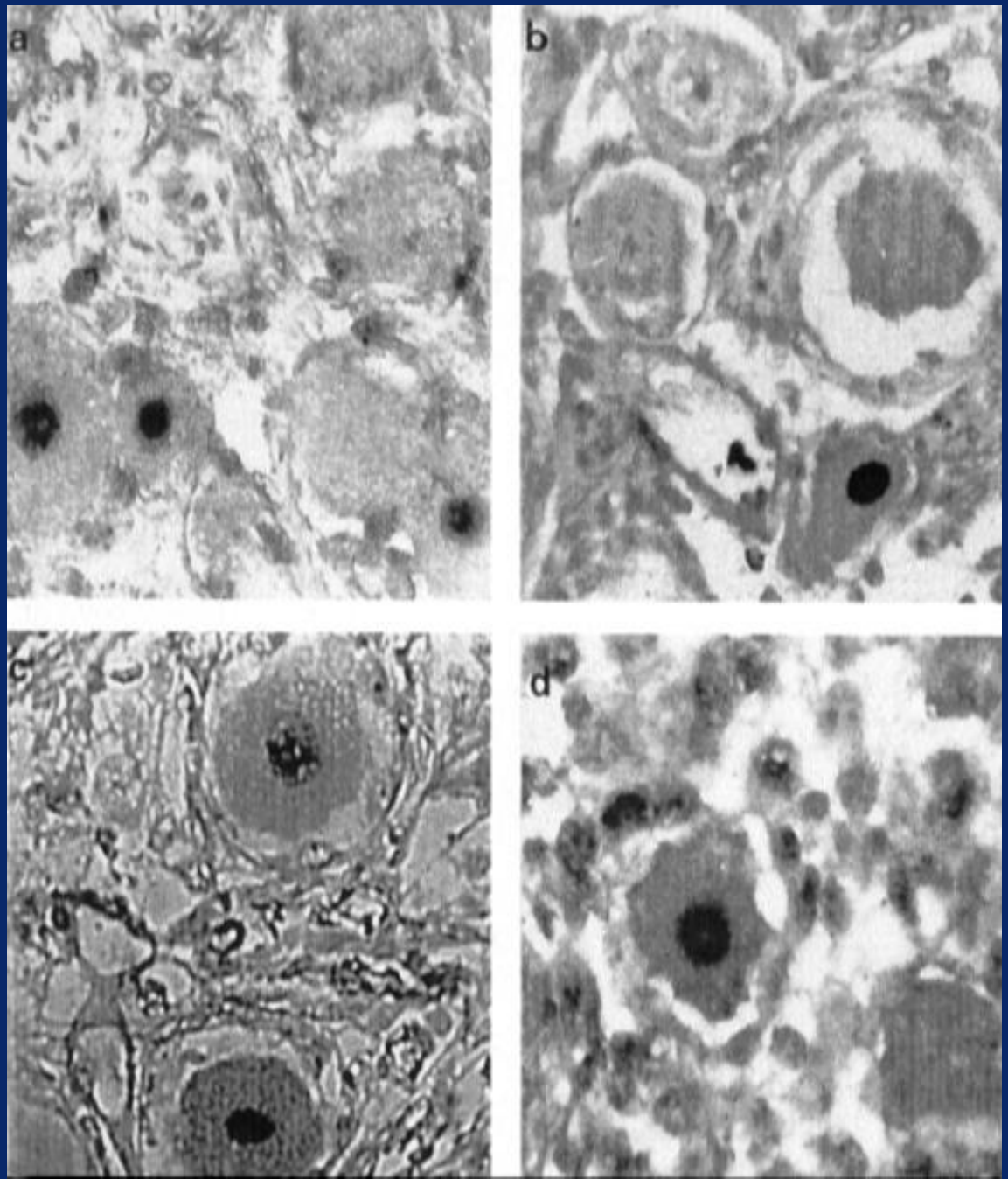


Research areas:

- Immunopathogenesis of neuroinflammation- role of cytokines, chemokines, neuropeptides-PCR, ICC, mouse KO, antagonists, tryp. load
- Identification of target molecules of potential relevance to treatment
- Blood-Brain Barrier function during experimental infection using small bore MRI.
- Microarray analysis of host genes upregulated 1-28 days post-infection
- African field studies.Phase 2 study of oral complexed melarsoprol in *T.b.rhodesiense (*Uganda*)*

PCR IN SITU HUMAN TG WITH VZV GENE PROBES

NORMAL TG GENE 18

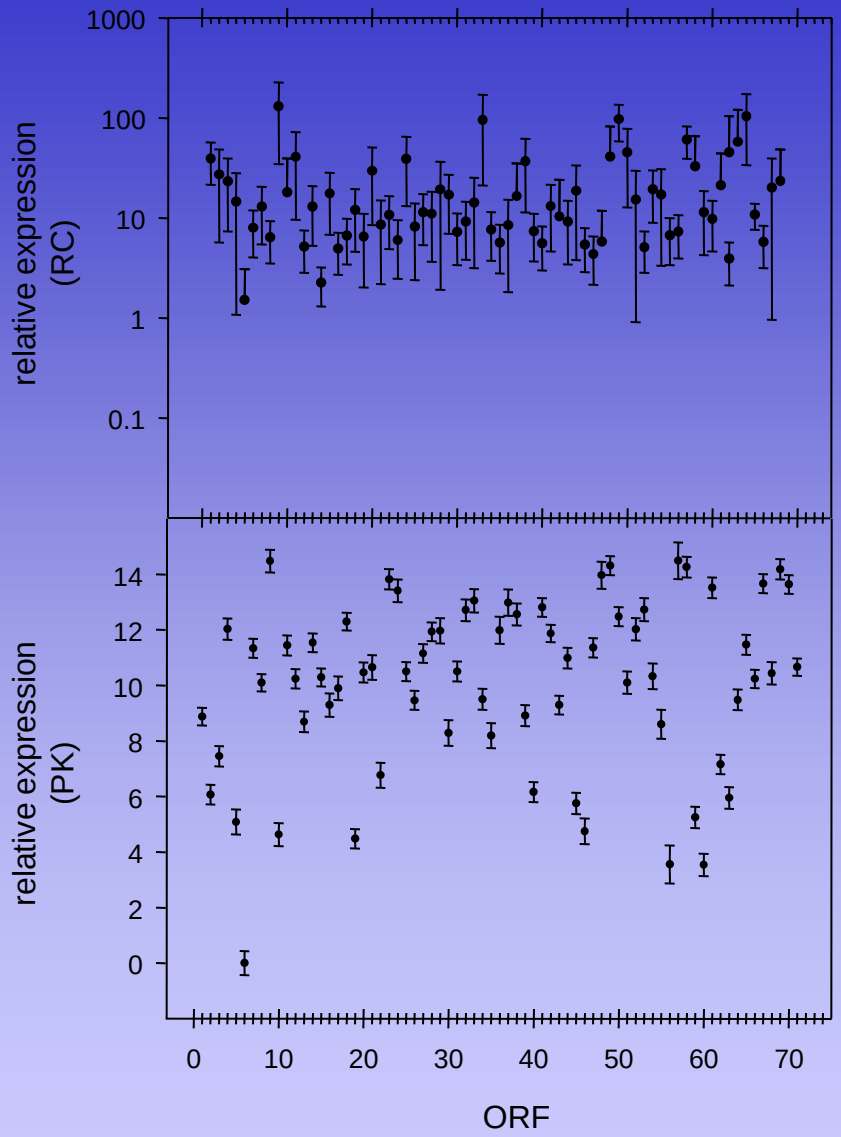


NORMAL TG GENE 29

DIFFERENT NORMAL GENE 29

NORMAL TG GENE 29 INDIRECT

Kennedy et al PNAS, 1998

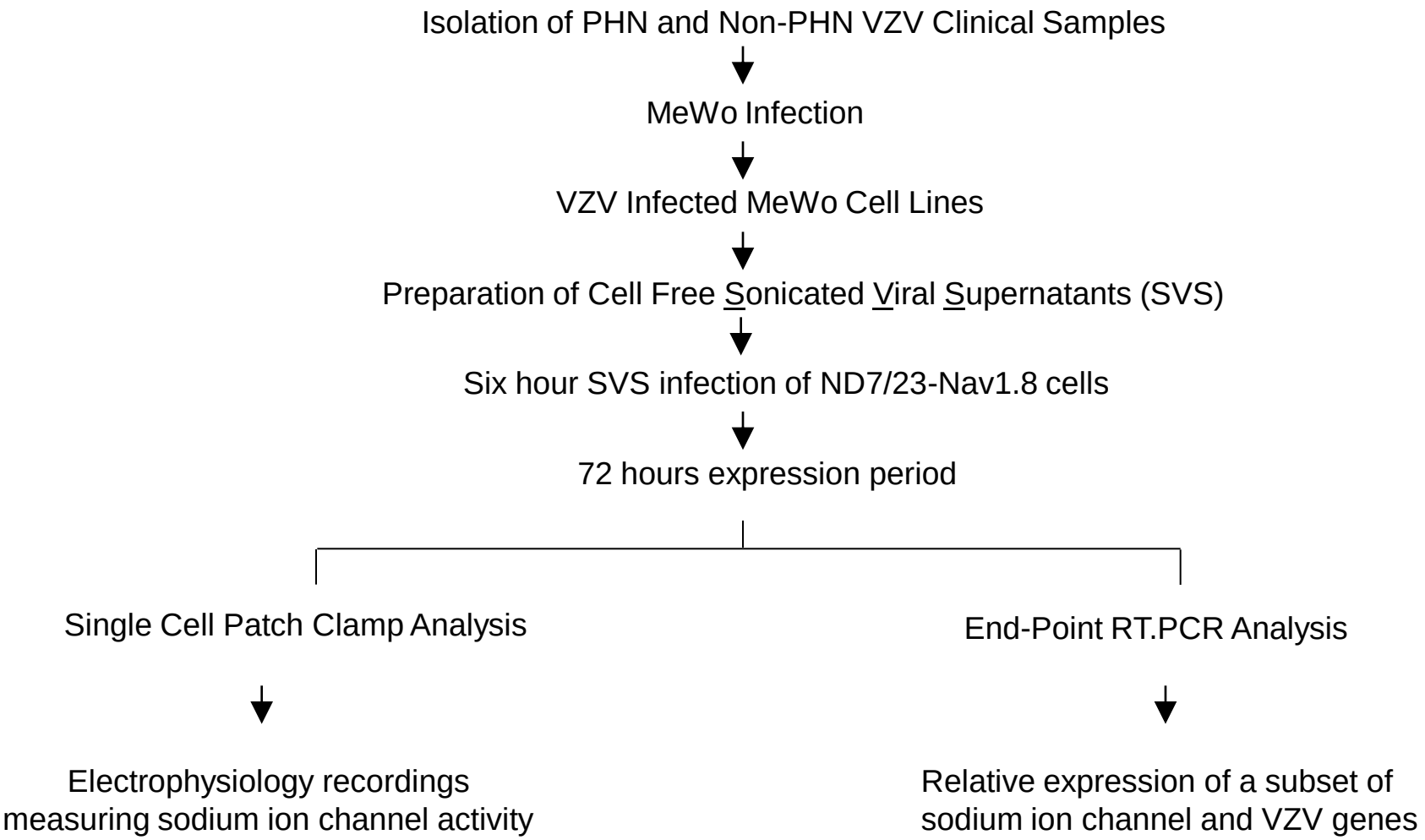


Top Ten

PK	RC
57	9
9	64
49	49
58	33
69	57
48	63
23	50
67	62
70	48
61	11

COMPARISON OF MOST HIGHLY EXPRESSED ORFs IN DENVER VS GLASGOW/EDINBURGH ARRAYS

Experimental flow chart to assay sodium ion channel activity in VZV infected rodent neuroblastoma cells



Key recent observations in Trypanosomiasis

Discovered the key role and mechanism of the neuropeptide Substance P (SP) in generating the inflammatory response in experimental trypanosomiasis.

Reported the first use of 7T cranial MRI to visualise Blood-Brain Barrier breakdown in experimental trypanosomiasis, the first application in an experimental parasitic infection.

Demonstrated the ability of exogenously administered IL-10 to both prevent neurroinflammaiton and decrease parasite load in experimental trypanosome infection

Recently showed that a new form of melarsoprol, called complexed melarsoprol, is effective orally and non-toxic in experimental CNS trypanosomiasis, and a phase II clinical trial of this compound in Uganda for CNS *rhodesiense* disease is currently being planned.

Key recent observations in Varicella-Zoster virus (VZV)

Carried out novel studies of VZV gene expression during human ganglionic latency and microarray analysis of viral gene expression during acute lytic VZV infection.

Discovered a novel *in vitro* neuronal sodium channel modulating effect of VZV associated with post-herpetic neuralgia.

Collaborations

Trypanosomiasis

- Glasgow Experimental MRI Centre
- FIOS company, Edinburgh
- Karolinska Institut, Stockholm
- University of Verona
- University of Aberdeen
- Universiry of Yaounde, Cameroon
- UNHRO, Uganda
- Makerere University, Uganda

Varicella-Zoster Virus

- Strathclyde University
- University College London
- University of Colorado
- University of Edinburgh

Current Requirements

Grant Funding!!

Continuation and expansion

Under evaluation: MRC (VZV), EDCTP (HAT)

In preparation: Wellcome Trust Collaborative Award