Human African trypanosomiasis (HAT) (Sleeping sickness) and Varicella-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

Model developed in late 1970's
Well established & characterised

Frank Jennings
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

DIFFERENT NORMAL GENE 29

NORMAL TG GENE 29 INDIRECT

Kennedy et al PNAS, 1998
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

Isolation of PHN and Non-PHN VZV Clinical Samples

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MeWo Infection

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VZV Infected MeWo Cell Lines

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Preparation of Cell Free Sonicated Viral Supernatants (SVS)

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Six hour SVS infection of ND7/23-Nav1.8 cells

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72 hours expression period

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Single Cell Patch Clamp Analysis

End-Point RT.PCR Analysis

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Electrophysiology recordings measuring sodium ion channel activity

Relative expression of a subset of sodium ion channel and VZV genes
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
- University 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