Virology in the Department of Microbiology at UAB

Virus/Host Interactions

Uninfected

HCMV infected

Genomics/Viral Evolution

Structural Virology
Identification of Host Factors Involved in Viral Amplification

1. Infect cells with virus
2. Crosslink proteins to viral RNA in vivo
3. Identify proteins
4. Determine their role in the viral life cycle

Sunnie Thompson
RPS25 is essential for translation initiation by the *Dicistroviridae* and hepatitis C viral IRESs

Landry et al. (2009) 23: 2764

**CrPV IGR IRES**

**HCV IRES**

Depletion of RPS25 inhibits HCV replication in cell culture.

RPS25 is not an essential protein.

RPS25 is a good target for antiviral or anticancer therapeutics.

**Future Directions:**

1. Can HCV develop escape mutants that no longer require RPS25.
2. Use yeast genetics to identify which Rps25p amino acids interact with the IRESs
3. Identify inhibitors to RPS25 to develop antivirals
Probe the natural history of human herpes simplex virus infections to determine virulence factors.

Engineer Herpes Simplex Virus to be used for therapeutic purposes:
- Therapy of Glioblastoma multiforme
- Express foreign genes
- Use as a vector for HIV antigens
- Develop a live attenuated herpes simplex vaccine
Identification of Novel Antivirals against Dengue and Other Mosquito-Borne Diseases

• Drug discovery and development
  – Antivirals
    • Dengue virus (Flaviviridae) and other Arboviruses
    • Bluetongue virus (Reoviridae)
  – Anti-malaria
    • Plasmodium falciparum

• Host-vector-pathogen interactions
  – Mechanism of action studies for novel antivirals
  – Antiviral efficacy evaluation in animal models
  – The role of apoptosis during Arbovirus infection
1) Assembly of Human Cytomegalovirus
2) Immunological Control of Virus Infection of CNS
3) Inflammation and Altered Neurodevelopment
4) Vaccine development for Human Cytomegalovirus
5) Role of Virus Induced Inflammation and Allograft Loss
Key Questions:
Why are certain infections **rapidly** controlled?
Why are certain infections **never** controlled?

Approaches:
Determining the cellular, molecular, and biochemical properties of “protective” and “exhausted” T cell responses
Successful versus Unsuccessful Infection Control

**Acute Infection**
- Virus rapidly cleared
- e.g. LCMV-Armstrong Infection of Normal Adult Mice

**Protracted Infection**
- Virus slowly cleared
- e.g. LCMV-clone 13 Infection of Normal Adult Mice

**Lifelong Infection**
- Virus never cleared
- e.g. LCMV Infection of Certain Immunocompromised Mice
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<th>Terje Dokland</th>
<th>Peter Prevelige</th>
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Biochemical, Biophysical and Structural Biology Tools are employed to study HIV-host interactions

HIV particle

3D structure of HIV-2 MA

Targeting of HIV-1 Gag mutant to MVB compartments

Adopted: Wikimedia Commons

Jamil Saad
State-of-the-art 700 MHz NMR Instrument

Protein-protein interactions studied by NMR methods

Nuclear Magnetic Resonance (NMR)

Jamil Saad
The N-terminus and an extended loop near the C-terminal domain make extensive cross-molecule interactions, required for encapsidation of the RNA.
Hemagglutinin (HA)
glycoprotein trimer

Influenza virus Attachment and Entry

Influenza virus entry

Ming Luo
Cryo-electron microscopy allows biological structures to be visualized in their native state, in the absence of staining, fixation and dehydration artifacts.
Cryo-electron microscopy of viruses

HIV VLPs

Staphylococcus aureus bacteriophage 80α

- 13 Å 3D reconstruction of 80α

Terje Dokland
Capsid is 60 nm diameter, 420 protein subunits
10 nm holes allow solvent access
Stable to high temperature
Can insert peptides that are displayed on outside
Can vary the number of peptide tags to tune the avidity
Can do in vivo phage display to target tumors
Can carry cargo inside:
  ✓ fluorophores and gadolinium for imaging
  ✓ semiconductors for energy
  ✓ proteins for therapy

http://www.microbio.uab.edu/faculty/prevelige/index.html
In vivo fluorescence imaging (FMT) of carotid arteries

**HFn injected mouse**

**RGD4C-HFn injected mouse**

Peter Prevelige
Collaborations

• Collaborator with Model System where there is a need for improved imaging

• Facility with animal model and willingness to participate

• Identification of targeting tags for initial development stage
Viral genomics and Evolution

• Role of individual genes in virus replication, host interaction, virulence, and pathogenesis

• Analysis of genome sequence, gene expression, immune interaction, and host pathway interaction information utilizing (and developing) bioinformatics tools and techniques

• Understanding the process and consequences of virus diversity and evolution
Origins of Poxvirus HT Genes

Elliot Lefkowitz
Immunogenetic determinants in AIDS

Richard Kraslow

Approach:

• Molecular genetics and epidemiology are applied to examine how human gene variations determine the occurrence and outcome of infectious and other diseases of immunity.

Findings:

• Demonstrated the strong influence of multiple combinations of polymorphic markers in the HLA region on the outcome of HIV-1 infection
Origin and Evolution of Lentiviruses

◆ First to describe the genetic variability of HIV-1

◆ Traced the Origins of HIV-1 to Cameroon

◆ Discovered that recombination between highly divergent viruses represents a major driving force of HIV and SIV diversification

◆ Discovered that SIVcpz is pathogenic (AIDS-like disease) in wild-living chimpanzees
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<th>Additional Faculty</th>
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<tr>
<td>Paul Goepfert, M.D.</td>
<td>Virology; vaccines</td>
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<tr>
<td>John Kappes, Ph.D.</td>
<td>HIV; molecular virology and pathogenesis</td>
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<tr>
<td>Casey Morrow, Ph.D.</td>
<td>Viral morphogenesis and replication gene therapy and vaccines</td>
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<tr>
<td>George Shaw, M.D.</td>
<td>Human retroviruses; molecular virology and pathogenesis</td>
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<tr>
<td>Wayne Sullender, M.D.</td>
<td>Respiratory syncytial virus; antigenic diversity</td>
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<tr>
<td>Mark Pritchard, Ph.D.</td>
<td>Herpes and Orthopox Antivirals</td>
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