

# Cell Biology and Molecular Genetics

GRADUATE PROGRAM

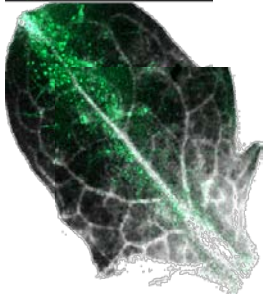
SPECIALIZATION IN

***VIROLOGY***

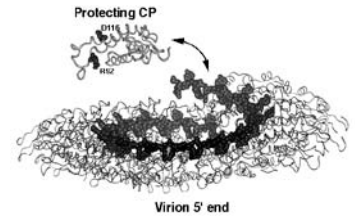
Supplemental  
**HANDBOOK**

2011 – 2012





# VIROLOGY



This handbook is designed as a supplement to the Cell Biology and Molecular Genetics (CBMG) Graduate handbook. The main difference between the traditional BISI MOCB concentration area and the Virology Specialization within MOCB are the First Year Student Committee, the NIH/NCI rotation, required coursework, monthly Virology meetings and the yearly retreat. With these exceptions noted, the requirements for graduate degrees can be found in the BISI web site (<http://chemlife.umd.edu/biologicalsciencesgraduateprogrambisi>), MOCB Concentration.

The Virology Program web site, <http://www.clfs.umd.edu/CBMG/Research/Virology/index.html>, is an excellent resource for current information on the program, including seminars, journal club papers, monthly meeting schedule and links to all major Virology sites.

## PREAMBLE

Viruses are extremely diverse and have evolved to infect nearly all life forms. Amid this diversity, viruses with similar genome organizations exhibit major conserved themes in their replication strategies. Once inside a cell, all viruses must uncoat, replicate and transcribe their genomes, and then repackage their genomes into viral progeny that are released from cells. RNA viruses in particular must coordinate the switch between plus and minus strand synthesis and between replication and transcription while protecting their genomes from cellular nucleases. Because of the conserved nature of a virus's intracellular life cycle, fundamental advances in our understanding of replication have come from viruses that infect both animal and non-animal hosts. The Virology Program at the University of Maryland brings together animal, plant and fungal virologists in an integrative program that broadens the research perspective and abilities of new virologists. The proximity of world-class virus and viroid research programs at the University of Maryland (College Park), the Virginia-Maryland Regional College of Veterinary Medicine (College Park), the National Institutes of Health (Bethesda), the National Cancer Institute (Fort Detrick), and the United States Department of Agriculture (Beltsville) makes this training opportunity possible.

This Virology Training Program is one of the most diverse and unique Virology Training Programs in the country and is the only program of its kind supported by an NIH Training Grant. You will be able to select laboratories that study a wide breath of virus and virus-like pathogens, from prions and viroids through poxviruses. Your dissertation committees will be composed of members from all units in the program, giving you additional expertise far beyond what is traditionally available in more limited programs. In addition, since all faculty participate in teaching their research subjects in the two semester course, Special Topics in Virology I and II, you will learn about the full range of experimental systems used to study viral replication, gene expression, pathogenesis and vaccine development, a unique facet of this training program.

Faculty were selected to participate in the Virology Training Program by virtue of their outstanding contributions to fundamental virology and their commitment to training students at the pre-doctoral level. Two of the faculty are members of the National Academy of Science (Moss and Wickner), one is a senior editor of *Journal of Virology* (Simon) and one is senior editor of the journal

*Virology* (Moss). Drs. Simon and Culver study replication and gene expression of plus sense, ssRNA viruses that infect plants, with Dr. Culver also specializing in using viruses as nanoparticles; Drs. Nuss, Dinman and Wickner study replication, gene expression and signal transduction in fungal dsRNA viruses; Drs. DeStefano and Green study replication and epidemiology of plus sense, ssRNA viruses of animals. Drs. Perez works on Influenza virus genomics and host-determinants; Drs. McBride and Moss study the life cycle of ds DNA viruses; Drs. Freed, Dinman, and DeStefano study different aspects of the HIV life cycle. Dr. Nuss studies RNA silencing as applies to viruses. Vaccine development based on knowledge that includes virus replication mechanisms is a major strength of the program, with Drs. Green, Moss, Zhu, Pierson and Perez active in this research area.

The need for well-trained and imaginative virologists in the public health community is clear. During the next 25 years, the world population will increase by 2.5 billion people (mostly in developing countries). Increasing global trade, changes in insect vector populations, global climate change and possible bioterrorism all demand that the U.S. view viral diseases from a world health perspective. In spite of significant advances in the development of vaccines and antiviral agents, the death toll from viral diseases continues to climb. Many vaccine strategies rely on the attenuation of viruses to produce “live” vaccines. Knowledge of viral replication is essential to understanding the molecular basis for attenuation because genetic lesions in attenuated viruses are often located in replicase proteins or in non-coding regions of the genome. A particularly promising area of vaccine research applies knowledge of viral replication to the design of improved second-generation vaccine candidates using reverse genetics systems. Additionally, a detailed knowledge of virus evolution and adaptation is critical for understanding vaccine efficacy over time.

The importance of viruses, however, extends well beyond their disease-causing potential. When properly harnessed, viruses can be powerful research tools for dissecting cellular processes. Viruses also offer great promise as expression and delivery systems for vaccines and therapeutic genes (“gene therapy”). This program is designed to prepare you to meet research challenges common to all viruses- which includes developing strategies to protect humans, animals, or plants from viral diseases as well as exploiting viruses as tools to improve the quality of life.

## COURSE WORK

All Virology Program Graduate Students must complete the required courses within the [Molecular and Cellular Biology concentration within BISI](#). These are:

- Cell Biology I: Structure/Function (2 credits, 7 weeks) - Fall Semester
- Nucleic Acids (2 credits, 7 weeks) - Fall Semester
- A choice of one (1) of the following:
  - Genetics I\*: Transcription/Translation (2 credits, 7 weeks) - Spring Semester
  - Genetics II: Genomics/Molecular Genetics (2 credits, 7 weeks) - Spring Semester
  - Protein Structure/Function: (2 credits, 7 weeks) - Spring Semester
- Bioethics (2 credits) - Fall or Spring
- Research Experiences (2 credits) - both Fall and Spring
- Teaching Science (1 credit) - Fall Semester (required for all teaching assistants)

Genetics I is highly recommended for Virology Program Students and is taught by a Virology Program Faculty Member. Protein Structure/Function is also highly recommended to take as an additional course

In addition, Virology Program Students are required to take:

- CBMG 688K Molecular Virology (2 cr)- Fall Semester
- MICB 688U Special Topics in Virology (2 cr)- Spring Semester (must be taken in two consecutive years)
- CBMG 688V Virology Journal Club (2 cr) or equivalent- Fall Semester (first year students sit in and students in years 2 on take for credit)

| <b>Typical Course Schedule For Pre-doctoral Students in Their First 3 Years in the Virology Training Program (sign up once in Fall and once in Spring for the classes in Red)</b> |  |  |  |  |
|---|--|--|--|--|
|   | <b>Fall</b>  |  | <b>Spring</b>  |  |
|   | <b>Module 1</b>  | <b>Module 2</b>  | <b>Module 1</b>  | <b>Module 2</b>  |
| <b>Year 1</b>   | <p>CBMG 688D Special topics: Cell Biology I (2 cr)</p> <p>BCHM661 Nucleic acids I (2 cr)</p> <p>CBMG 688A Research experience (3 cr)</p> <p>CBMG 688Z Teaching science (1 cr) (if you are a TA)</p> <p>Seminars</p> <p>Monthly Group Meeting</p> | <p>CBMG 688K Molecular Virology (2 cr)</p> <p>CBMG 688A Research experience</p> <p>Seminars</p> <p>Monthly Group Meeting</p> | <p>CBMG 688F Genetics I (2 cr)</p> <p>MICB 688U (2 cr) Special topics in Virology</p> <p>CBMG 688C Research experience (2 cr)</p> <p>Seminars</p> <p>Monthly Group Meeting</p>                     | <p>CBMG 688I Genetics II</p> <p>MICB 688U Special topics in Virology</p> <p>CBMG 688C Research experience</p> <p>CBMG 688B BioEthics (2 cr)</p> <p>Seminars</p> <p>Monthly Group Meeting</p> |
| <b>Year 2</b>   | <p>CBMG 688V Virology Journal Club (2 cr)</p> <p>CBMG898 Pre-Candidacy Research (1-8 cr)</p> <p>Seminars</p> <p>Monthly Group Meeting</p>  | <p>CBMG 688V Virology Journal Club</p> <p>CBMG898 Pre-Candidacy Research</p> <p>Seminars</p> <p>Monthly Group Meeting</p>    | <p>MICB 688V (2 cr) Special topics in Virology</p> <p>CBMG898 Pre-Candidacy Research (1-8 cr)</p> <p>Elective module (Protein structure/function)</p> <p>Seminars</p> <p>Monthly Group Meeting</p> | <p>MICB 688V (2 cr) Special topics in Virology</p> <p>CBMG898 Pre-Candidacy Research</p> <p>Seminars</p> <p>Monthly Group Meeting</p>  |

|                   |  |   |
|-------------------|--|---|
| <b>Year<br/>3</b> | <b>CBMG 688V Virology Journal Club (2 cr)</b><br><br><b>CBMG898 Pre-Candidacy Research (1-8 cr)</b><br><br>Seminars<br><br>Monthly Group Meeting         | <b>CBMG898 Pre-Candidacy Research (1-8 cr)</b><br><br>Seminars<br><br>Monthly Group Meeting         |
| <b>Year<br/>4</b> | <b>CBMG 688V Virology Journal Club (2 cr)</b><br><br><b>CBMG898 Doctoral Dissertation Research (1-8 cr)</b><br><br>Seminars<br><br>Monthly Group Meeting | <b>CBMG898 Doctoral Dissertation Research (1-8 cr)</b><br><br>Seminars<br><br>Monthly Group Meeting |

### Description of the Core Courses:

**BCHM 661 and 662 Nucleic Acids I and II.** (Nucleic Acids I is required. Nucleic Acids II is highly recommended) These courses concern the structure and function of nucleic acids and the mechanisms of nucleic acid transactions: a biochemical approach to molecular genetics and biological information processing. A background including undergraduate organic chemistry, general chemistry, and molecular biology/genetics is assumed. Both prokaryotic and eukaryotic systems are covered, emphasizing common logic and mechanisms, especially regarding bioenergetics and fidelity. These courses complement CBMG modules on Gene Expression (688F) and Genetics/Genomics (688I). Module I covers Chemistry and structure of DNA and RNA, from nucleotides to chromatin, chromosomes, and genomes, and methods for studying, synthesizing, sequencing and manipulating nucleic acids. Selected aspects of the biochemistry and regulation of DNA replication, repair, and recombination, and how these processes interact with each other. Module II covers Interactions between nucleic acids and ligands such as cations, drugs, and especially proteins. Sources of binding affinity and specificity. Selection-amplification methods. Description of protein-nucleic acid complex structures. DNA/RNA engineering. RNA Biology: Basic biochemistry of transcription and translation. Regulation of gene expression by RNA, RNA processing and decay, RNA catalysis, the origin of life, mobile genetic elements

**CBMG 688D Cell Biology I, Structure and Function** This course focuses on the basic concepts and recent advances in cell biology and experimental methodologies and current approaches in cell biology research. Lectures are combined with research literature discussion to teach students how to read research papers, how to define a scientific question, how to find experimental approaches to answer a question, how to interpret experimental data, and how to write a research proposal.

**CBMG688F Genetics I** This course discusses molecular mechanisms of gene expression. The class covers the broad topic of gene expression with emphasis on core concepts and current topics. The first three classes cover core concepts in molecular biology and biochemistry, and how these provide the foundations for the tools used by today's investigators. The next section covers prokaryotic transcription, with special emphasis on regulatory networks and DNA/protein interactions. This sets the stage for more advanced discussion of regulation of eukaryotic transcription. Regulation of gene expression at the post-transcriptional level is discussed next, including mRNA splicing, capping and

polyadenylation, rRNA and tRNA processing, mRNA editing, and RNAi. This is followed by an in depth discussion of protein translation including strong emphasis on structural biology, quality control and translational recoding. The final module explores signal transduction in the context of regulatory crosstalk and feedback among the transcriptional, post-transcriptional and translational machinery.

**CBMG 688I Genetics II** Course in advanced genetics emphasizing genetic analyses of model organisms. Primary species are yeast *Saccharomyces cerevisiae*, worm *Caenorhabditis elegans*, plant *Arabidopsis thaliana*, fruit fly *Drosophila melanogaster*, mouse (*Mus musculus*), and humans (*Homo sapiens*). For each model organism both forward genetics (methods for the identification and analysis of informative mutations revealing new genes or new gene functions) and reverse genetics (methods for testing the expression of modified genes) will be considered. Applicable genomics resources and bioinformatics tools are also covered, as is the application of information from model organisms to important species that lack the tools available in model organisms.

**CBMG 688K Molecular Virology (2 cr)** This course uses the text “Principles of Virology” by S.J. Flint et al. and concentrates on animal RNA/DNA viruses and host responses to viral infections. In addition to topics on replication and gene expression, students become familiar with the latest research on retroviruses, pathogenesis, virus evolution and establishment of the antiviral state. Modern methods of purifying viruses and viral components, determining virus structure and assessing virus titers are also covered. Near the end of the semester, small groups of students present a seminar and recent journal paper on topics that focus on the replication and gene expression of RNA viruses and retroviruses. At the completion of the course, students have an advanced understanding of molecular mechanisms of virus replication for several important families of animal viruses.

**CBMG 688U Special Topics in Virology I and II** This course is taken twice for credit by students in their second and third years and students are encouraged to sit in on the class during their remaining years. The course is team taught by all Virology Program faculty, with each faculty member presenting two weeks of lectures on his/her research area every other year. This course allows students to become familiar with virus replication and gene expression (and other topics in Virology) in a wide variety of systems including DNA and RNA viruses with human, animal, plant and fungal hosts and such unusual infectious agents as viroids and prions. Students become familiar with the research process by having prominent virologists describe not only recent results but the history of their project. In addition, students become familiar with how research is conducted in a number of systems and thus help breakdown barriers that exist between studies on replication and gene expression in plant, animal, and fungal systems. Since many faculty work on vaccine development, students learn how basic research is applied to real life problems in health and agriculture.

**CBMG 688V Virology Journal Club.** In the semester that the Special Topics in Virology course does not meet (i.e., Fall semester), students are required to participate in the Virology Journal Club, either at University of Maryland or at NIH (The NIH journal club is organized by advanced Virology Program students). Journal Clubs are also attended by post-doctoral researchers and faculty. Pre-doctoral students present papers on a variety of topics and systems in Virology with an emphasis on virus replication and translation. Students learn to become comfortable with the literature on a number of different systems and learn how to critically analyze experiments and results. In addition, students learn how to review papers by reviewing anonymous manuscripts submitted to the journal Virology, and comparing their reviews with those of professional science reviewers.

**CMBG 688B Bioethics** This course provides an introduction to ethics, the social foundations of science, responsibilities of student and advisor, treatment of data, collaborations, conflicts of interest, use of animals and humans in research and other topics that you will routinely encounter as a scientist

**Additional elective module and full semester courses:**

Students are required to take one additional module course and may elect to take additional module courses or full semester courses in consultation with their research director and their dissertation committee.

| <b>Partial list of additional Courses available for students in the Virology Training Program</b> |                 |                 |  |                     |                            |
|---|-----------------|-----------------|--|---------------------|----------------------------|
| <b>#</b>  | <b>SEM</b>      | <b>Course #</b> | <b>Title</b>   | <b>Professor</b>    | <b>Department</b>          |
| 2   | Fall/<br>Spring | BCHM 671        | Protein Chemistry and Enzyme Catalysis   | Laronde-Leblanc, N. | Chem Biochem               |
| 3   | Fall            | BCHM 898E       | Biological Mass Spectrometry   | C. Fenselau         | Chem Biochem               |
| 4   | Fall            | BCHM 889J       | Nucleic Acid Structures  | J. Kahn             | Chem Biochem               |
| 5   | Fall            | BCHM 889K       | Protein Folding  | V. Munoz            | Chem Biochem               |
| 6   | Fall            | CBMG 688J       | Special Topics in Cell Biology and Molecular Genetics: Immunology and Host Defense         | D. Mosser           | CBMG                       |
| 7   | Fall            | CBMG 688M       | Special Topics in Cell Biology and Molecular Genetics: Microbial Genetics                  | D. Stein            | CBMG                       |
| 8   | Fall            | CBMG 688P       | Special Topics in Cell Biology and Molecular Genetics: Plant Development and Physiology I  | Z. Liu              | CBMG                       |
| 9   | Fall            | CBMG 688W       | Special Topics in Cell Biology and Molecular Genetics: Principles of Microscopy            | S. Wolniak          | CBMG                       |
| 10  | Spring          | CBMG 688R       | Special Topics in Cell Biology and Molecular Genetics: Plant Development and Physiology II | H. Sze              | CBMG                       |
| 11  | Spring          | CBMG 688L       | Special Topics in Cell Biology and Molecular Genetics: Microbial Pathogenesis              | V. Briken           | CBMG                       |
| 12  | Spring          | CBMG 688H       | Special Topics in Cell Biology and Molecular Genetics: Bioinformatics                      | C. Delwiche         | CBMG                       |
| 13  | Spring          | CBMG 688T       | Special Topics in Cell Biology and Molecular Genetics: Developmental Biology;              | L. Pick             | CBMG                       |
| 14  | Spring          | BCHM 675        | Biophysical Chemistry  | D. Beckett          | Chemistry and Biochemistry |
| 15  | Spring          | BCHM 676        | Biological Mass Spectrometry   | C. Fenselau         | Chemistry and Biochemistry |

## Description of the module courses available for students

### **CBMG688J Special Topics in Cell Biology and Molecular Genetics: Genetics: Immunology and Host Defense**

This class uses the text "Cellular and Molecular Immunology" by Lichtman and Abbas. A comprehensive series of lectures on innate and adaptive immunology, including cellular and humoral immunity, is complemented by original research articles and a review of technical approaches to immunological problems. There are two examinations and each student presents a research article to the class on a selected topic. At the completion of the class students are expected to have a thorough understanding of immunological concepts, a broad-based understanding of immunological techniques, and an introduction to signal transduction events during immune cell activation.

### **CBMG688M Special Topics in Cell Biology and Molecular Genetics: Genetics: Microbial Genetics**

This course focuses on the review and discussion of research literature to examine experimental design, methodology, and interpretation of both historical and contemporary relevance to microbial genetics. The fundamental concepts of bacterial and bacteriophage genetics including mutagenesis, mechanisms of both vertical and horizontal genetic transfer, gene regulation, and genetic approaches to study complex cellular processes will be covered. Special emphasis is placed on the requirements for gene expression in bacteria.

**CBMG 688H Bioinformatics: Genome Analysis.** The course provides a graduate-level introduction to the concepts and principles that form the basis for bioinformatic techniques, particularly similarity search and pairwise alignment algorithms (e.g., BLAST, FASTA, Needleman-Wunch, Smith-Waterman), and techniques for homology assessment and functional inference. No prior experience with programming is required, but students should be comfortable working with computers.

### **CBMG688L Microbial Pathogenesis (2 cr)**

This course aims to introduce graduate students to important molecular and cellular mechanisms of host-pathogen interactions. The subject areas covered include: I) General structure-function aspects of microbial cell and the molecular secretory pathways; II) Adherence and entry of pathogens into non-phagocytic or phagocytic cells; III) Interaction of pathogens with host innate immunity; IV) Interaction of pathogens with host acquired immunity. In this course, the basic concepts of host-pathogen interactions will be structured based upon the studies of intracellular bacterial pathogens (e.g. *Mycobacterium*), but certain protozoan (e.g. *Leishmania*) and viral (*Adenovirus*) pathogens will be touched upon to expand the concepts of common themes/diverse mechanisms of host-pathogen interactions at the molecular and cellular level. Each of the four subject areas is composed of two classes of lectures (four hours) followed by one class (two hours) of papers (of the subject area) presentation/discussion by the students. Each student will have an opportunity to present one journal paper.



## LABORATORY ROTATIONS

**Fall and Spring, Year 1.** Laboratory rotations follow the rotations of the MOCB Concentration. Two rotations lasting 7 weeks each are required in the first semester. You will have the opportunity to participate in some aspect of research within the lab. It is also your opportunity to interact with principal investigators (PIs), postdoctoral researchers and graduate students, learn about the systems being studied, the techniques being used and the questions being addressed (see **Appendix B** for sample schedule and ideas on questions to ask the professor and students in each lab). You are expected to spend at least 10 hours a week in the rotation lab. Remember that several students may be vying for a single slot in a lab and the Professor will likely choose the student who is the most dedicated.

**Intersession - Year 1.** The multi-institutional nature of the Virology Training Program is a great strength and we want all Virology students to experience the breadth of the training opportunities available. The Intersession Rotation has been especially designed for you to rotate with investigators at the NIH or NCI. This choice will be made in consultation with the First Year Student Committee. This NIH/NCI rotation will be conducted during intersession (in January- can start right after classes end in December as well) since you will have no teaching or course work, allowing for ease in commuting to the NIH/NCI campuses. (See **Appendix C** for information you need to provide to Teresa Thompson ([teresa@umd.edu](mailto:teresa@umd.edu); 5-8990), the Virology Program Assistant, before you can begin the rotation at NIH/NCI. It is very important that you provide the information by the times indicated).

Spring - Year 1. Students have many flexible choices in Spring semester. You can choose one of the rotation labs from the Fall or you can choose to rotate in 1-2 labs in the Spring before choosing a permanent place.

**Summer - Year 1.** You can elect to remain in one of your rotation labs as your thesis lab (providing that the PI agrees), or conduct a summer rotation at NIH/NCI or in another Virology lab. You are required to choose a dissertation laboratory by Fall of your second year, at the latest. When you have made a decision, the information needs to be conveyed to Ms. Thompson

## MONTHLY GROUP MEETINGS

**Monthly group meets are usually held the third Monday of each month at 12:00 noon in 1130 Plant Sciences Building.** Informal interactions between faculty and students is an integral part of our training program. At each monthly group meetings, faculty and students in the program gather to hear the latest results from two faculty labs. Talks are given by faculty, postdocs, and senior predoctoral trainees and include guest talks from other Virology researchers at nearby institutions, including other investigators at NIH and Fredrick Cancer Research Center . These talks lead to many lively discussions and a much better appreciation and understanding of different systems by both faculty and students. Some of the labs break into groups after the meeting to discuss specific research topics in more detail.

## YEARLY RETREAT

With the large number of labs in the Virology Program, you may not have the opportunity to present

your research more than once at the monthly group meetings. For that reason, and to foster increased interactions by members of the Virology Training Program, the Virology Program holds an annual retreat in October in the Plant Sciences Building at the University of Maryland. In addition to guest speakers, there are talks from faculty, predoctoral and postdoctoral trainees in the program, and a poster session where all students not presenting talks present their research, starting in their third year. This will allow you the opportunity to become familiar with describing your research to a diverse virology audience in preparation for similar presentations at national and international virology meetings. This year (2011), the retreat is Saturday, October 22.

## **SEMINARS**

All Units with faculty involved in the Virology Training Program sponsor weekly seminar speakers. All first year students are required to attend the CBMG seminar series. After the first semester, you can continue to attend the CBMG seminars or attend the weekly seminars presented in the program units of your laboratory director.

## **ADVANCEMENT TO CANDIDACY**

The Ph. D. student has two important meetings with the student's research committee in the third year. Specific details regarding the preliminary committee meeting and the requirements for the qualifying exam can be found [here](#)

It is expected that the student should be able to complete the research necessary for writing the Ph. D. dissertation within two to three years following the candidacy examination. The student is required to meet with the Research Committee on a yearly annual basis. The research for the Ph. D. degree must establish the student's ability to perform independent and creative scholarly research that makes a substantial contribution to our knowledge about an important question in biology. The ability to do high-quality research must be demonstrated by the submission and the defense of a Ph. D. dissertation.

## **MONITORING AND GUIDANCE OF STUDENTS**

The Virology Training Program places great emphasis on the monitoring and guidance of trainees. When students first arrive, they have meetings with both Dr. Simon and the First Year Student Committee, which is currently composed of Dr. Kim Green and Dr. Jim Culver. The First Year Student Committee helps students choose laboratories for their three rotations (based on the interests of the students) and help them navigate the logistics of the fourth rotation at the NIH/NCI and USDA (e.g., transportation, security and parking). Students contact the committee members as needed during their first year to help with any classroom, TA, or research situations that arise. When students choose a dissertation laboratory, the guidance duties switch to the laboratory's Virology faculty member and the Program Director. In addition, students who have chosen laboratories at NIH/NCI/USDA have a Virology faculty member from CBMG as their associate research advisor (if possible, someone with whom the student did a rotation). The associate research advisor usually talks with their students monthly at the group meetings.

Trainee progress is monitored at the end of the first year with regards to coursework, teaching and research by the CBMG Program Director. Such monitoring is the first line of evaluation of each pre-doctoral trainee. In addition, since pre-doctoral traineeship awards are made on a yearly basis, the Selection Committee evaluates all trainees who request renewal of their support for a additional year to determine research progress as well as if they are fulfilling the requirements of the program, participating in seminars, monthly meetings and journal

clubs. Trainees, and their mentors, will be asked to provide input to the evaluation process and the trainees are given feedback as to the findings of the Selection Committee. The previous records of Virology Program Members indicate great success at placing students in quality post-doctoral positions and many of our previous students are now heading their own laboratories in Academia or Industry.

## PROGRAM FACULTY



**Please consult the Virology Program web site:**

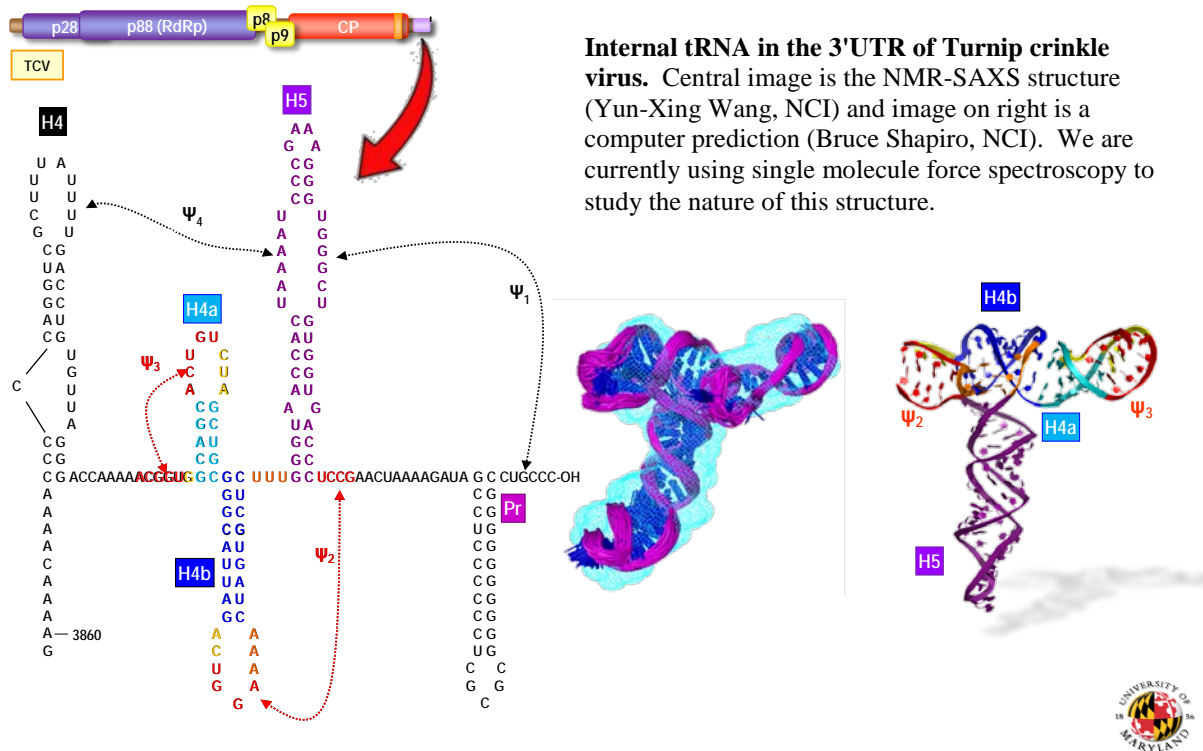
<http://www.life.umd.edu/CBMG/research/virology/facultylink.html>

**for links to individual faculty laboratories where you will find more information and lists of recent publications**

**Anne E. Simon - *Program Director*.** Professor, Department of Cell Biology and Molecular Genetics (CBMG), University of Maryland, College Park.

*Honors and Awards:* Editor – *Journal of Virology*; Guest editor- *Current Protocols in Microbiology*; Guest editor- *Current Opinion in Virology*; Plant Councilor for American Society of Virology.

*General Research Area:* Upon cell entry, the genome of a positive-strand RNA virus first serves as a template for the translation of proteins that are required to initiate genome amplification before serving as a transcription template for synthesis of complementary strands. Efficient translation initiation requires that viral 5' and 3' ends be brought into proximity, similar to requirements for translation of cellular mRNAs as specified by the closed-loop model. Dr. Simon's research program focuses on sequences and structures involved in replication and translation of four viruses that have no 5' cap or 3' polyA tail and thus must use alternative means for translation. These viruses have similar structures at their 3' ends but have evolved different 3' cap-independent translational enhancers (3' CITEs). Turnip crinkle virus (TCV; 4054 bases) contains an unusual 3' CITE containing a critical hairpin (H4), a long unstructured region, and partially overlaps a ~100-nt internal T-shaped structure (TSS) composed of three hairpins (H4a, H4b, H5) and two pseudoknots ( $\Psi_3$  and  $\Psi_2$ ). The internally located TSS binds to the P/E-site of 80S ribosomes through the 60S ribosomal subunit, and this binding is important for efficient translation. The TSS also functions as a stable scaffold for interaction with external sequences through the large internal symmetrical loop of H5. RNA-dependent RNA polymerase (RdRp) interaction with the 3' end of TCV causes a widespread conformational shift that structurally rearranges the TSS and surrounding region, including elements required for efficient ribosome binding, suggesting that the RdRp may feedback and inhibit its own translation by disrupting the structure of the 3' CITE. Recent results suggest that ribosomes may be mediating an interaction between the 5' and 3' ends of the virus. A second studied virus, Pea enation mosaic virus, also has a TSS in its 3' end and an internal element that also assumes a T-shaped structure and binds to ribosomes. Additionally, there are several RNA:RNA interactions that circularize the genome permitting translation factors bound to additional 3' CITE to be brought to the 5' end. A third virus, Saguaro cactus virus, contains a Y-shaped element that interacts with the 5' end and possibly the 3' end as well. The evolution of such varied ways of promoting translation in related viruses remains a mystery and will be the subject of investigations in the future.



**Jonathan D. Dinman** –Professor, Department of Cell Biology and Molecular Genetics (CBMG), University of Maryland, College Park.

*Honors and Awards:* Thomas Alva Edison Patent Award , University of Maryland College of Life Sciences Faculty Excellence Award for Research, Outstanding Invention of 2003, Life Sciences, Merck-Frosst Seminar (U. Montreal), Fogarty International Research Collaborative Award, The Foundation of UMDNJ Award, American Cancer Society Junior Faculty Research Award, NIH Staff Fellowship, NIH IRTA Fellow, Fredrick B. Bang Award, Sigma Xi Student Research Grant.

*General Research Area:* The Dinman lab has capitalized on the ability of viruses to reprogram cellular ribosomes to probe the mechanisms governing translational fidelity. In the past 11 years, Dr. Dinman has developed a highly varied toolbox, enabling the group to address a wide array of questions. Programmed Ribosomal Frameshifting (PRF), in particular provides a unique window into the molecular machinery that normally controls reading-frame maintenance. They have found that altering the efficiency of frameshifting changes the balance of viral structural to enzymatic proteins, which in turn interferes with virus particle assembly and viral propagation. Thus, PRF represents an important target for potential antiviral therapies. The development of a yeast-based frameshifting system has also provided Dr. Dinman with a unique set of tools to probe the mechanisms governing translational fidelity. They use genetic, biochemical and molecular methods to characterize the *trans*-acting factors, and the physical and biochemical parameters that ultimately determine the frequency with which ribosomes shift reading frame. These tools have enabled Dr. Dinman to lend his expertise in ribosome biochemistry in collaboration with Dr. Simon's study of the tRNA-like element of TCV. In combination with the high-resolution structural understanding of ribosomes, their approaches are leading to new insights into ribosome structure/function relationships and are using this information to identify targets for antiviral agents. Currently, Dr. Dinman's laboratory is focused on three projects: (1) Programmed -1 ribosomal frameshifting (-1 PRF) of the SARS-associated coronavirus; (2) using

translational recoding mechanisms to probe the relationships between structure and function of the ribosome; and (3) identification and characterization of -1 PRF signals in cellular mRNAs.

**Jeffrey DeStefano** –Professor, Department of Cell Biology and Molecular Genetics (CBMG), University of Maryland, College Park.

*Honors and Awards:* Phi Kappa Phi inductee.

*General Research Area:* Research in Dr. DeStefano's laboratory has focused on studying the role of HIV-reverse transcriptase (RT) and nucleocapsid protein (NC) in the processes of retroviral recombination and replication. They also analyze basic properties of these proteins including how they interact with specific nucleic acid sequences involved in replication and how the activities of the proteins as defined in the test tube, function in cellular replication. Other projects are aimed at isolating nucleic acid inhibitors (aptamers) that can bind very tightly to RT and other viral proteins to inhibit their function. Dr. DeStefano also studies poliovirus replication, specifically by examining the polymerase (3Dpol) and 3AB proteins. His group was the first to show that 3AB, like HIV NC, is a nucleic acid chaperone protein that aids in the folding of viral nucleic acids and may be involved in other steps in the viral life cycle including recombination. His lab has an active collaboration with Dr. Craig Cameron's lab at Penn. State University aimed at understanding the role of chaperone proteins in picornavirus replication. Recombination is one of the mechanisms that retroviruses like HIV use to generate genetic diversity. By producing genetic variants viruses are able to circumvent the host immune response and escape drug therapies. Currently Dr. DeStefano works on several aspects of recombination, including the basic mechanism(s) by which recombination occurs, NC's role in stimulating recombination, and the role of specific viral sequences in recombination. Their basic approach has been to use in vitro systems that mimic recombination and replication in the cell to understand the processes. Dr. DeStefano's group also collaborates with those of Drs. Eric Arts and Matteo Negroni on a project to study how intersubtype recombinants arise (Baird et al., 2006). These are HIV viruses that form by recombination between two different subgroups (A and D for example to produce an A/D recombinant). Intersubtype recombinants are becoming more prevalent, especially in Asia and Africa. This could complicate attempts to produce effective vaccines and drugs as therapies developed against the more common B and C type viruses may not be effective against other types or intersubtypes.

**Brenda Fredericksen**- Assistant Professor, Cell Biology and Molecular Genetics (CBMG), University of Maryland, College Park.

Flaviviruses have been associated with human disease for over a century. To date, 40 of the 73 identified species of the *Flavivirus* genus have been shown to be associated with significant human morbidity and mortality world-wide. Pathogenic flaviviruses include yellow fever virus, dengue virus, Japanese encephalitis virus, St. Louis virus, tick-borne encephalitis virus, and more recently, West Nile virus (WNV). In areas of the Middle East, Asia and Africa, where WNV has been endemic for many years, infections are typically asymptomatic or associated with a mild febrile illness in children. In sharp contrast to this, recent outbreaks in Europe, Israel and the United States have been associated with a marked increase in both the number of reported cases and the severity of disease among mammals and birds, suggesting that a more pathogenic strain has emerged. The molecular mechanisms for the increased pathogenesis of WNV are unknown but are likely to include novel virus-host interactions that allow WNV to overcome or evade the host innate and/or adaptive immune

response. Dr. Fredericksen's laboratory is interested in defining the molecular mechanism(s) by which flaviviruses evade and/or block the host innate antiviral response and to clarify how this regulation contributes to viral pathogenesis and disease. The ability of viruses to control and/or evade the host antiviral response is critical to the establishment of a productive infection. As eukaryotic anti-viral programs evolved to combat invading pathogens, viruses evolved processes to escape the anti-viral effects of these programs. The molecular mechanisms by which WNV overcomes the host cell anti-viral response are beginning to be elucidated. Using microarray analysis, they have recently demonstrated that the induction of ISGs in response to infection with WNV-NY is attenuated, which suggested that WNV-NY modulates the host antiviral response. One of the strategies WNV uses to circumvent the host response is to delay the activation the transcription factor interferon regulatory factor 3 (IRF-3), which is critical for the initiation of the antiviral response. The delayed activation of IRF-3 allows WNV-NY to replicate virtually unchallenged by the host cell at early times post-infection and is essential for maximal virus production. Dr. Fredericksen further demonstrated that unlike many other viruses, which impose a nonspecific block to the IRF-3 pathway, WNV-NY simply eludes detection by the host cell at early in infection. To better understand this process, they assessed the role of the pathogen recognition receptor (PRR), RIG-I, in sensing WNV-NY infection. RIG-I null mouse embryo fibroblasts (MEFs) retained the ability to respond to WNV-NY infection; however, the onset of the host response was delayed compared to WT MEFs. This suggests that RIG-I is involved in initially sensing WNV-NY infection while other PRRs sustain and/or amplify the host response later in infection. The delayed initiation of the host response correlated with an increase in WNV-NY replication in RIG-I null MEFs compared to WT MEFs. The lab's data suggest that activation of the host response by RIG-I early in infection is important for controlling replication of WNV-NY. Furthermore, pathogenic strains of WNV may have evolved to circumvent stimulation of the host response until after replication is well underway.

**Donald Nuss** - Professor, Department of Cell Biology and Molecular Genetics, University of Maryland College Park.

*Honors and Awards:* Group Honor Award for Excellence, U.S. Secretary of Agriculture; Distinguished Alumnus Award, Edinboro University of Pennsylvania and the University of New Hampshire. AAAS Fellow. Editorial Board, *Journal of Virology*

*General Research Area:* Dr. Nuss's laboratory has been studying a family of mycoviruses, the hypoviruses that attenuate virulence of the chestnut blight fungus, *Cryphonectria parasitica*. The hypovirus/*C. parasitica* system is one of the very few eucaryotic systems for which both a virus and its host can be genetically manipulated with ease. A very robust DNA transformation system is available for *C. parasitica* allowing disruption, silencing or over-expression of fungal genes. Dr. Nuss's laboratory has constructed infectious cDNA clones of two hypovirus RNA genomes, CHV1-EP713 and CHV1, Euro7, providing the only viral reverse genetics system for the entire Kingdom Fungi. This development has allowed the construction of "engineered" hypoviruses with enhanced biocontrol potential and the extension of virus host range to include several other pathogenic fungi. Hypovirus CHV1-EP713 causes very severe phenotypic changes in the infected fungal host while hypovirus CHV1-Euro7 causes mild symptoms. Although these two viruses cause quite different phenotypic changes, they are similar enough in nucleotide sequence to allow the construction of viable chimeras that can be used to map symptom determinants and fine-tune the interaction between *C. parasitica* and its plant host. Several lines of evidence indicate that hypovirus infection results in alterations of signal transduction pathways involved in normal fungal gene expression. Chimeric and mutant hypoviruses

are being used to map viral-encoded modifiers of cellular signaling pathways with the aid of fungal strains stably transformed with novel promoter/reporter gene constructs. These studies are being expanded with the aid of a *C. parasitica* EST database and microarray analyses to gain deeper insight into virus-host interactions and test the fundamental hypothesis that RNA silencing in fungi evolved as an antiviral defense mechanism. Combined basic and technical advances are providing new opportunities for broadening the potential application of hypoviruses for purposes of understanding and controlling fungal pathogenesis.

**James Culver** – Professor, Institute for Bioscience and Biotechnology Research and Department of Plant Sciences and Landscape Architecture, University of Maryland College Park.

*Honors and Awards:* Early CAREER Development Award, National Science Foundation;

*General Research Area:* Research in the Culver laboratory is multidisciplinary with efforts directed at understanding virus biology and its role in disease as well as studies aimed at engineering viruses and other biological components for application in nano-based systems and devices. They utilize a multitude of approaches in our studies and collaborate with scientists in fields ranging from structural biology to microfabrication. Specific areas of study include:

**Virus Host Interactions,** Viruses cause significant reductions in food, fiber and forage throughout the world. Yet despite their importance we still understand relatively little of the disease processes through which viruses function to reduce crop productivity. Our biological studies focus on understanding how viruses cause disease or induce resistance responses. To examine these interactions the Culver lab utilizes Tobacco mosaic virus (TMV) as an important pathogen model. Ongoing studies are directed at understanding the signaling pathways involved in disease development. These studies utilize genomic approaches, such as cDNA microarrays and RNA-seq to identify the host genes and pathways that are altered during the infection process. Culver's long-term goal is to modifying these pathways to produce plants that are incapable of supporting virus replication and/or disease development.

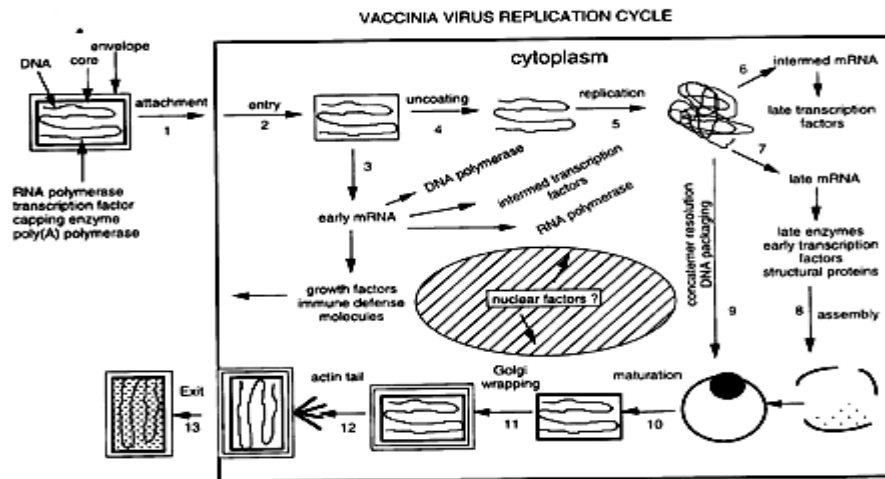
**Virus Based Nanotechnology:** Advances in nanotechnology offer significant improvements in a range of applications including, light weight materials with greater strength, increased energy efficiency from electronic devices, and better sensors for a range of environmental and manufacturing uses. However, these advances will require the development of systems for the design, modeling, and synthesis of nanoscale materials. Interestingly, many biological molecules function on this scale and possess unique properties that impart the ability to assume defined conformations and assemblies, as well as interact with specific chemical or biological substrates. Specific studies in the Culver laboratory utilize simple RNA plant viruses as templates for the self-assembly and patterning of novel nanomaterials. They are interested in developing methodologies to produce assembled arrays of functionalized viruses for use in sensors, energy harvesting and drug delivery. They combine both genetic and chemical approaches to address our bioengineering efforts with the long-term aim of integrating renewable biological components into the manufacture of nanoscale materials and devices.

**Bernard Moss** – Chief, Laboratory of Viral Diseases, National Institutes of Health.

*Elected Memberships:* National Academy of Sciences, *Fellow*, American Association for the Advancement of Science; American Academy of Microbiology; Alpha Omega Alpha; Sigma Xi; Phi Beta Kappa.

*Honors and Awards:* Bristol-Myers Squibb Award for Distinguished Achievement in Infectious Disease Research; Taylor International Prize in Medicine; Sackler Scholar, University of Tel Aviv; ICN International Prize in Virology; Invitrogen Eukaryotic Expression Award; Dickson Prize for Medical Research; Solomon A. Berson New York University Medical Alumni Achievement Award; PHS Distinguished Service Medal; Science Digest's 100 Most Innovative Scientists of 1985; PHS Meritorious Service Medal.

*General Research Area:* The goals of the Moss lab are to determine the mechanisms used by viruses to infect cells, express and replicate their genomes, assemble infectious particles, and evade the host immune response. Basic information obtained from these studies is used to design antiviral agents and live and subunit recombinant vaccines. In addition, viruses are engineered as expression vectors for biotechnology. Poxviruses have provided unique opportunities to combine molecular, genetic, microscopic, and immunologic approaches to achieve many of the above goals. Recent studies have also been directed to the characterization and testing of candidate vaccines for human and simian immunodeficiency viruses. Dr. Moss's principal research is directed to the biology of poxviruses including regulation and expression of viral genes, synthesis and processing of viral mRNA, replication of viral DNA, assembly of virions, virus-host interactions, and determinants of virus virulence. In addition, Dr. Moss's research group works on the development of vaccinia virus into an expression vector with application to immune response to virus infections, live recombinant vaccines and gene therapy.



**Reed Wickner** – Chief, Laboratory of Biochemistry and Genetics, NIDDK, NIH.

*Elected Honor Society Memberships:* National Academy of Sciences, American Academy of Microbiology, American Academy of Arts and Sciences.

*Honors and Awards:* U.S. Public Health Service Meritorious Service Medal, U.S. Public Health Service Outstanding Service Medal, American Society of Clinical Investigation, U.S. Public Health Service Commendation Medal.

*General Research Area:* Dr. Wickner's studies of infectious elements of *S. cerevisiae* have led to the

discovery of prions, dsRNA viruses, and naked ssRNA replicons, their similarities with similar elements in animal cells and some clues of the mechanisms by which they are propagated and interact with their host. They have discovered two prions of the yeast, *Saccharomyces cerevisiae*. Genetic evidence led them to propose that the non-Mendelian genetic elements, [URE3] and [PSI], are each prions (infectious proteins). A prion is an altered form of a normal protein that may have lost its normal function, but has acquired the ability to convert the normal form of that protein to the abnormal (prion) form. [URE3] is an altered form of the URE2 protein whose normal function is to turn off utilization of poor nitrogen sources if a good nitrogen source is present. [PSI] is the prion form of the SUP35 protein which is involved in translation termination. The Wickner lab also studies double-stranded RNA viruses of yeast. They have developed the classical genetics, molecular cloning and enzymology of the replication of the L-A virus, its satellites and their interactions with the host. They have established template-dependent in vitro replication and transcription systems for this virus, the first for a dsRNA virus, and have used them to elucidate the sites on the RNA necessary and the viral proteins that participate in these processes. They have defined the packaging site on the RNA, the packaging domain on the viral Pol protein and obtained evidence for the mechanism of the packaging process. The L-A virus has two open reading frames, the 5' gag, encoding the major coat protein, called Gag, and the 3' pol, encoding a multifunctional protein domain called Pol that includes the RNA-dependent RNA polymerase. Pol is expressed only as a Gag-Pol fusion protein formed by a -1 ribosomal frameshift event whose mechanism is identical to that used by retroviruses for the same purpose. We have described chromosomal genes whose mutation alters the efficiency of ribosomal frameshifting and thereby impairs virus propagation. The Wickner lab discovered a set of chromosomal genes, SKI1, SKI2, SKI3, SKI6, SKI7 and SKI8, which repress viral propagation and prevent the L-A virus and its satellite RNAs from harming the cell. Their data indicate that SKI2, SKI3, SKI6, SKI7 and SKI8 control viral propagation by inhibiting the translation of the viral messages because they lack 3'poly(A).

**Kim Y. Green** - Chief, Caliciviruses Section, Laboratory of Infectious Diseases, NIAID, National Institutes of Health.

*Honors and Awards:* Teaching Excellence Award, University of Maryland; NIA, NIAD Award for Recognition and Appreciation of Special Achievement; US DHHS, PHS, NIH

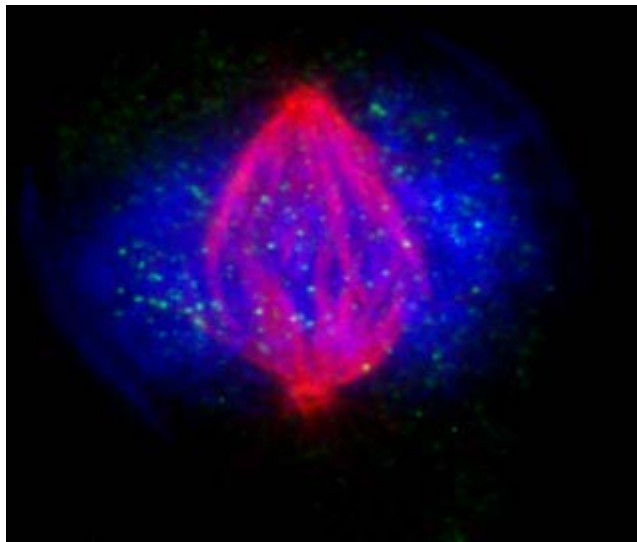
*General Research Area:* Dr. Green studies noroviruses in the *Caliciviridae*, which are major etiologic agents of epidemic gastroenteritis. Numerous attempts to grow these viruses in cell culture or to develop animal models for the study of infection and disease have failed. The overall goals of this research program are to establish the role of these viruses as agents of human diarrheal disease and to develop experimental systems for study of the molecular basis for viral replication and pathogenicity. Recent breakthroughs include the development of new diagnostic assays that use recombinant virus-like particles derived from expression of the major structural capsid protein from several different human calicivirus strains. Our recent epidemiologic studies have increased knowledge of the scope of these antigenically diverse viruses as agents of acute gastroenteritis in several settings, including nursing homes and U.S. military operations. An additional breakthrough was the first report of an infectious cDNA clone for a calicivirus genome. These studies employed the feline calicivirus (FCV), a member of the *Caliciviridae* that replicates efficiently in cultured cells. FCV has become an important model system in our laboratory for the establishment of experimental approaches for study of the noncultivable human caliciviruses. Studies in progress include mapping genetic determinants

in FCV and human caliciviruses involved in cell tropism and growth restriction, and study of the basic features of the viral replication cycle using infectious cDNA clones.

**Alison McBride-** Head, DNA Tumor Virus Section

*Honors:* Editorial Board, *Journal of Virology* and *Virology*

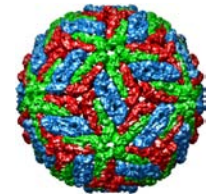
*General Research Area:* The papillomaviruses are small DNA viruses that induce persistent benign epithelial lesions. In some cases these lesions can progress to malignant carcinomas, the most notable of which is cervical cancer. The viral E1 and E2 genes regulate viral transcription, replication, and genome segregation. Dr. McBride's objective has been to understand the mechanisms by which they control the viral life cycle. My laboratory studies the ways in which the E2 proteins regulate viral gene expression and how the E1 and E2 proteins act in concert to replicate papillomavirus DNA. These studies have provided detailed information about how the proteins interact with the viral DNA and with each other and how their activities are regulated within infected cells. The E2 transactivator protein is required for viral transcriptional regulation, DNA replication, and stable episomal maintenance of viral genomes. They have shown that papillomavirus genomes are tethered to mitotic chromosomes by the E2 transactivator protein. This ensures that viral genomes remain in the nucleus and are segregated to daughter cells in approximately equal numbers. The figure below shows a mitotic cell with spindle (red), chromosomes (blue), and E2 protein (green).



Papillomaviruses induce proliferative epithelial lesions and can only undergo vegetative replication in terminally differentiated keratinocytes. This has hampered the study of the complete viral life cycle because of the difficulties in generating a differentiated stratified epithelium in tissue culture. Using a combination of organotypic raft cultures and xenografts on nude mice, Dr. McBride has developed a system in which they can generate fully differentiated epithelium in which papillomaviruses can replicate and produce infectious viral particles. This system is being used for a genetic analysis of the roles of the E1 and E2 viral gene products in the complete viral life cycle. In the majority of carcinomas, papillomavirus genomes are found integrated into cellular chromosomes such that the E1 and/or E2 genes are disrupted. This has led to the hypothesis that disruption of the E1 and E2

regulatory functions is a critical step in progression to a carcinoma. They are currently studying the role of the E1 and E2 regulatory functions in keratinocyte growth and differentiation. Because the E1 and E2 proteins have both positive and negative effects on the viral life cycle and on malignant progression, a detailed understanding of their regulatory mechanisms is crucial for the design of antiviral strategies.

**Ted Pierson**- Chief, Viral Pathogenesis Section, Laboratory of Viral Diseases, NIAID, NIH



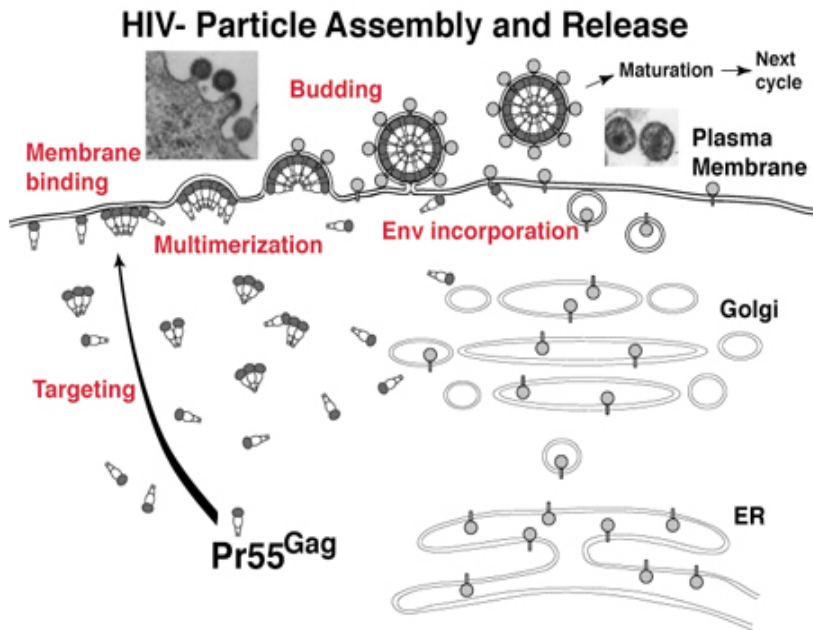
*Honors and Awards:* Editorial Board, *Journal of Virology*

*General Research Area:* Flaviviruses are a group of small RNA viruses responsible for considerable morbidity and mortality worldwide. Humoral immunity is a critical aspect of host protection against flaviviruses; eliciting protective antibodies is a primary focus of ongoing vaccine development efforts for several of these viruses, including dengue virus (DENV). Complicating these efforts is the potential for antibodies elicited by natural infection or vaccination to modulate pathogenesis and enhance disease. The biochemical and functional properties of a protective antibody response are not known. **The primary goal of the Pierson laboratory is to understand the mechanisms of humoral immunity against flaviviruses in biochemical and structural detail.** Using West Nile virus (WNV) and DENV as models, they are working to define the factors that govern the potency of neutralizing antibodies, their potential for antibody-dependent enhancement of infection (ADE), and their mechanism of action. Using quantitative functional methods developed by the Pierson laboratory, they have defined the stoichiometric requirements for neutralization and ADE of WNV. This estimate of the number of antibodies required to neutralize and enhance WNV infection has provided a useful foundation to explore the genetic and biochemical complexity of factors that modulate antibody function. More recently, the Pierson laboratory has been applying the principles identified using the reductionist approaches and monoclonal antibodies described above, toward the study of the humoral response to flavivirus infection and vaccination. Their goal is to deconstruct human polyclonal antibody responses in order to identify the functionally-significant components. To that end, the Pierson lab is actively developing functional approaches to map the composition and dynamics of the polyclonal response to flavivirus infection, with the goal of identifying epitopes recognized by antibodies that are important for neutralization and protection. Initial efforts are focused largely on DENV, allowing study of the complexity arising from the existence of four different serotypes of virus and the requirement to develop a vaccine to simultaneously protect individuals against each of them. They are confident that many of the concepts explored in both basic science and translational efforts will share common features with humoral immunity in other viral systems.

**Eric Freed** - Chief, Virus-Cell Interaction Section, National Cancer Institute

*Honors and Awards:* Editorial Board, *Journal of Virology*

*General Research Area:* The Freed lab is focused on elucidating a number of key aspects of HIV-1 replication, with a particular emphasis on virus assembly, release, and maturation. The lab is investigating 1) the viral and cellular determinants of HIV-1 Gag trafficking to the plasma membrane, 2) the role of lipid rafts and phosphoinositides in membrane association and virus assembly, 3) the mechanism by which the viral envelope glycoproteins are incorporated into virions, and 4) the cellular



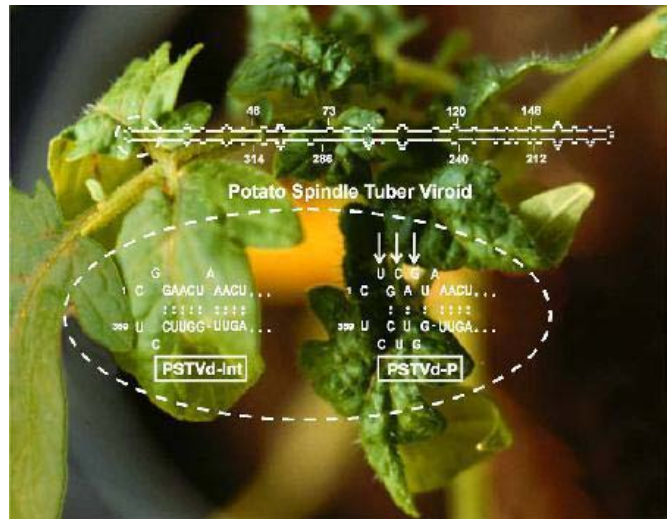
machinery involved in the release of retroviral particles from the plasma membrane. The lab has also been examining the role of membrane cholesterol in HIV-1 entry by studying the antiviral target and mechanism of action of the cholesterol-binding compound amphotericin B methyl ester (AME) and continues to play a key role in elucidating the molecular basis for the activity of the novel HIV-1 maturation inhibitor PA-457. A variety of molecular, biochemical, virological, and microscopy-based techniques are used in the lab to address these questions. The isolation and characterization of drug-resistant HIV-1 isolates has played a key role

in the AME and PA-457 studies.

**Robert Owens** – Research Chemist, USDA Agricultural Research Service; Adjunct Professor, Center for Biosystems Research, UMBI.

*Honors and Awards:* J. Merrill and Adeline Wallace Award, International Organization of Citrus Virologists (2000)

*General Research Area:* Dr. Owens’ lab studies viroids, which are small, unencapsidated, circular RNA molecules that lack mRNA activity and are the smallest, autonomously replicating pathogens yet described. Viroid replication and pathogenesis provide a model system in which the molecular mechanisms controlling plant-pathogen interaction and gene expression in uninfected cells are accessible to experimental manipulation. The Owens laboratory uses a combination of reverse genetics and cell biology to explore the relationship between the biological properties of viroids and their unusual secondary/tertiary structure. Areas of current interest include (i) identification of structural features controlling viroid host range, (ii) characterization of pathways used by viroids to enter and exit the nucleus, move from cell to cell, and transit the vascular system, and (iii) development of improved viroid-based citrus dwarfing agents.

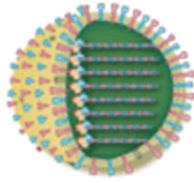


**Daniel Perez** - Associate Professor, Virginia-Maryland Regional College of Veterinary Medicine.

Dr. Perez heads the Avian influenza virus program at the University of Maryland.

*General Research*

*Area:* The Perez lab focuses on interspecies transmission and pathogenesis of influenza A viruses, which are members of the Orthomyxoviridae



**Avian Influenza Virus Program**



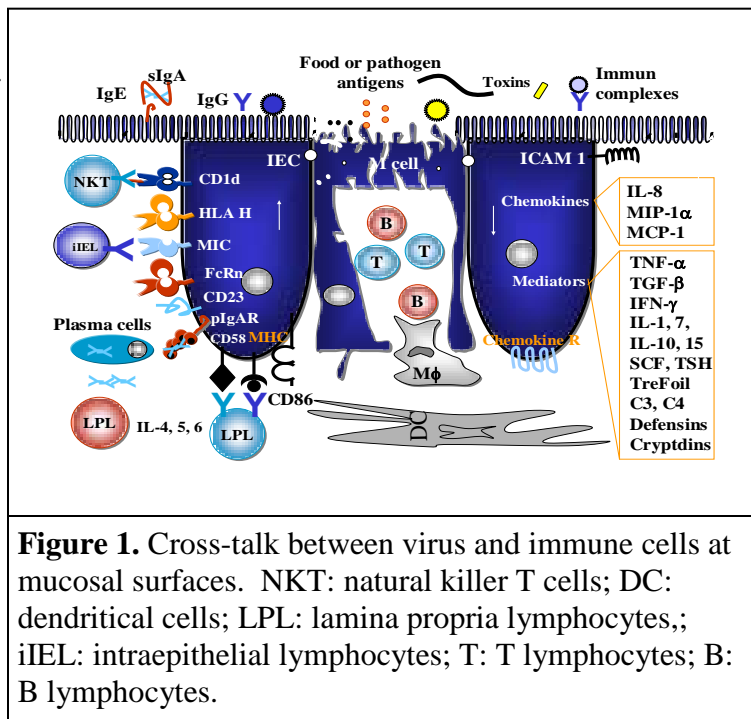
**VIRGINIA-MARYLAND**  
REGIONAL COLLEGE OF VETERINARY MEDICINE

family. Influenza A viruses have caused devastating pandemics and are responsible for recurrent epidemics in humans. The natural reservoir of influenza A viruses is considered to be wild aquatic birds. The current understanding is that viruses from the natural reservoir eventually cross to other animals, including humans, in which they cause major outbreaks or pandemics. The molecular basis that allows the interspecies transmission of influenza is poorly defined and the presence of potential intermediate host is considered a pre-requisite for such event. The Perez lab has focused on the role of quail as an important intermediate host in which influenza viruses from the natural reservoir acquires molecular features that allow crossing the species barrier a second time. Studies performed in Dr. Perez's lab have shown that quail was likely responsible in the emergence of influenza viruses that crossed recently to humans. Such viruses, known as H9N2, have acquire amino acid changes that provide the ability to infect human airway epithelial cells in a manner similar to the one observed for human influenza viruses. A second area of research in the Perez lab focuses on the development of live attenuated avian influenza viruses with potential use as vaccines. The Perez lab has been successful at generating an avian influenza backbone that is attenuated, provides appropriate immune responses, and protects birds and mammals against challenge with wild type viruses. Such strategy would have universal application in the development of vaccines for poultry, livestock and humans.

**Xiaoping Zhu**- Associate Professor, Virginia-Maryland Regional College of Veterinary Medicine, University of Maryland, College Park.

*General Research Area:* Defense mechanisms against viral infection in the mucosa. The mucosal surfaces lining respiratory, intestinal, and genital tract are not only the entry sites of infection for viruses but also places of initiating local defense against viral infection. At mucosal tissues, viruses are initially detected and destroyed non-specifically by innate immune mechanisms, but if the viruses escape the early defense mechanisms, they are detected and eliminated specifically by adaptive immune mechanisms. Innate immune responses include the production of virus-induced cytokines, such as interferon and natural killer (NK) cell activity, activation of signaling pathway by toll-like receptors or intracellular sensors, and defensins, etc. The major adaptive immune mechanisms include specific secretory IgA and IgG antibodies in viral elimination by forming immune complexes shortly after infection and T lymphocytes in the recovery from viral infection. To further understand the defensive mechanism at the mucosal surfaces, our laboratory is currently studying the interaction of mucosally transmitted viruses with those of mucosal epithelial cells and immune cells lining or within the mucosal surfaces (**Figure 1**). For example, we address questions whether viral infections of mucosal antigen presenting cells influence the mucosal immune response by thwarting the capacity of antigen presentation or how the mucosal inflammation is triggered and regulated during viral

infections. Study of host-virus interactions at mucosal surfaces will be crucial to understanding the process of mucosal immunity and immune evasion during viral infections, and provides an essential knowledge for the development of effective vaccine and immunotherapeutic strategies to mucosal infections.



**George Belov**- Assistant Professor, Virginia-Maryland Regional College of Veterinary Medicine, University of Maryland, College Park.

Dr. Belov's lab is studying mechanisms of virus-cell interaction during picornavirus infection. Positive strand RNA viruses infect almost all known eukaryotic organisms. Many of these viruses cause human, animal and plant diseases resulting in significant public health burden and economic losses. This group includes hepatitis C virus, Foot and Mouth Disease virus, poliovirus, Dengue virus and many other important pathogens. A large number of them still cannot be controlled with vaccines or available anti-viral drugs. The small genomes of these viruses encode only a limited number of proteins; yet they can modify cellular metabolism so profoundly that infected cells within a few hours redirect practically all of their resources for virus propagation. It is likely that due to the limited coding capacity of their genomes these viruses rely on a few evolutionary successful strategies to commandeer the control of cellular metabolism, and that different viruses share requirements for the same cellular factors and processes. Supporting this concept, for example, is the fundamental dependence of replication on cellular membranes shared by all known positive strand RNA viruses.

Dr. Belov's research is focused on the investigation of mechanisms these viruses use to hijack and subvert normal cellular pathways for the development of viral replication complexes. They employ modern molecular biology and virology techniques to study the contribution of cellular factors to the replication of positive strand RNA viruses including members of the Picornaviridae family such as poliovirus, Coxsackieviruses, Encephalomyocarditis virus and others. They are particularly interested in how these viruses disassemble elements of normal cellular membrane metabolism and then combine them into new configurations to remodel cellular membranes into viral replication organelles. Understanding these processes will provide new and effective measures against those pathogens which are markedly resistant to the conventional therapies. Investigation of viral strategies of manipulating host metabolism also elucidates intricate machinery of cellular regulatory networks which is applicable to broad areas of human health from inflammation to cancer.

# APPENDIX A

## Contact Information for Training Faculty

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|---------------------|--|--------------|--------------|---|
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| James Culver        | <a href="mailto:jculver@umd.edu">jculver@umd.edu</a>               | 301-405-2912 | 301-314-9075 | SVPAAP-IBBR<br>Plant Sciences Building<br>University of Maryland College Park<br>College Park, MD 20720   |
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| Alison McBride      | <a href="mailto:alison_mcbride@nih.gov">alison_mcbride@nih.gov</a> | 301-496-1370 | 301-451-5330 | NIH - Laboratory of Viral Diseases<br>Nat'l Institute of Allergy & Infec. Diseases<br>Bethesda MD 20892-0445  |
| Bernard Moss        | <a href="mailto:bmoss@nih.gov">bmoss@nih.gov</a>                   | 301-496-9869 | 301-480-1147 | NIH - Laboratory of Viral Diseases<br>Nat'l Institute of Allergy & Infec. Diseases<br>Building 4, Room 229, 4 Center Drive, MSC<br>0445<br>Bethesda MD 20892-0445 |
| Donald Nuss         | <a href="mailto:dnuss@umd.edu">dnuss@umd.edu</a>                   | 240-314-6218 | 240-314-6255 | SVPAAP-Institute for Bioscience &<br>Biotechnology Research<br>9600 Gudelsky Drive<br>Rockville, MD 20850   |
| Robert Owens        | <a href="mailto:owensr@ba.ars.usda.gov">owensr@ba.ars.usda.gov</a> | 301-504-6209 | 301-504-5449 | 10300 Baltimore Avenue<br>Room 118, Bldg. 004<br>Beltsville, Maryland 20705   |
| John Patton         | <a href="mailto:john.patton@nih.gov">john.patton@nih.gov</a>       | 301-594-1615 | 301-496-8312 | NIH-NIAID<br>Building 50 – Louis B Stokes Lab, 6314   |

|              |                          |              |              |  |
|--------------|--------------------------|--------------|--------------|--|
|              |                          |              |              | 50 South Drive<br>Bethesda, MD 20892   |
| Dan Perez    | dperez1@umd.edu          | 301 314-6811 | 301 314-6855 | VA-MD Regional College of Veterinary Medicine<br>8075 Greenmead Drive<br>University of Maryland<br>College Park, MD 20742-3711 |
| Ted Pierson  | theodore.pierson@nih.gov | 301-451-7977 | 301-451-7978 | NIH-NIAD<br>Building 33-C W Bill Young Center, 1E19A.2<br>33 North Dr.<br>Bethesda, Md 20892                                   |
| Reed Wickner | wickner@helix.nih.gov    | 301-496-3452 | 301-402-0240 | Bldg. 8, Room 225, NIH<br>8 Center Drive MSC 0830<br>Bethesda, MD 20892-0830   |
| Xiaoping Zhu | xzhu1@umd.edu            | 301-314-6814 | 301-314-6855 | College of Veterinary Medicine<br>8075 Greenmead Dr.<br>College Park, MD 20742-6814  |

## APPENDIX B

### Some Ideas for a Successful Rotation

1. Have detailed conversations with the PI about the research in the lab. Ask questions about:
  - a. Funding of research and graduate students.
  - b. Publications of the lab and average number of publications for PhD students.
  - c. Where the PhD students have gone to after leaving the lab and their current careers.
  - d. Average length of the degree program for past graduate students.
  - e. The research in the lab. What projects are available. Where they see this research going. How is this research perceived by the field?
  - f. Ask for papers to read (from the lab and any review articles on the research subject).
  - g. Ask to look at some dissertations from the lab. The introductions should be particularly useful to find out about the lab's research and whether the students are developing good research projects in the lab.
  
2. Have detailed conversations with all lab members. Ask questions about:
  - a. What are the interactions like in the lab. Are people helpful? Friendly?
  - b. Is the PI accessible? How often does the PI discuss the research with the students? Are there regular lab meetings?
  - c. Who do the students mainly learn from, the PI or the other members in the lab?
  - d. Is the PI very "hands on" or "hands off"? Do the students enjoy the atmosphere in the lab? Are they making good progress? And if not, is the PI doing enough to help.
  - e. Discuss the lab member's research. Does it sound interesting? Is the student excited by

- what they are doing?
- f. Does the PI help the students learn how to write? Give talk? Review papers? Are there opportunities to go to meetings?
  - g. You may want to get in touch with recently departed lab members and ask them about their experience.
3. Some of the techniques that you will hear about should be of interest. Ask the students if you can observe them doing particular techniques. Make notes of the unique techniques that different labs are doing for future reference.
  4. Remember, there are no “right” or “wrong” answers to these questions. Think about how you would fit into the lab given the answers. For example, would you prefer a lab where the PI talked to you everyday or left you alone?

End of December and Intersession will be rotations at NIH. These will be discussed at the new student meeting.

# APPENDIX C

There are several forms that must be completed and submitted before you can begin your rotation at NIH. Forms are to be submitted to:

**Ms. Teresa Thompson**  
**2104 Microbiology Building**  
**301-405-8990**  
**teresa@umd.edu**

These forms include (attached):

- Certificate of Medical Examination
- Special Volunteer and Guest Researcher Assignment
- NIH Special Volunteer Agreement
- Supporting Documentation for Non-NIH Visiting Program Participant. (This form is only required for non-U.S. citizens)
- Proof of Candidate's Health Insurance
- Candidate's Updated Curriculum Vitae/Bibliography

## Deadline for Submission of NIH Forms

- |  |
|--|
| <ul style="list-style-type: none"><li>❖ 3 WEEKS PRIOR TO REQUESTED EFFECTIVE DATE FOR U.S. CITIZENS AND PERMANENT RESIDENTS.</li><li>❖ 15 WEEKS PRIOR TO REQUESTED EFFECTIVE DATE FOR NONCITIZENS WHO ARE ABROAD.</li><li>❖ 19 WEEKS PRIOR TO REQUESTED EFFECTIVE DATE FOR NONCITIZENS WHO ARE IN THE U.S.</li></ul> |
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