SUMMARY STATEMENT
(Privileged Communication)

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Application Number: **1 R01 AI076331-01A1**

Principal Investigator

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Applicant Organization: PURDUE UNIVERSITY WEST LAFAYETTE

Review Group: **VIRA**
Virology - A Study Section

Meeting Date: **02/12/2008**
Council: **MAY 2008**
Requested Start: **07/01/2008**

RFA/PA: **PA07-070**
PCC: **M32B B**

Project Title: **Structure and Function of Flaviviruses**

SRG Action: **Priority Score: 114 Percentile: .3**
Human Subjects: 10-No human subjects involved
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested	Estimated Total Cost
1	491,718	743,917
2	496,256	750,782
3	494,979	748,850
4	489,163	740,051
5	494,514	748,147
TOTAL	2,466,630	3,731,748

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

REVISION NOTE

1R01AI076331-01A1 ROSSMANN, MICHAEL

REVISED

RESUME AND SUMMARY OF DISCUSSION: This exciting application proposes to continue structural studies on the conformational changes that occur during maturation of flavivurses from immature particles to mature particles and on the changes that occur during fusion with the cell membrane. Flaviviruses are important human pathogens, and theses studies will provide important information that could lead to new antiviral and vaccine strategies. The Principal Investigator and his collaborators are at the forefront of structural virology, and the sophisticated approaches being developed will be applicable to other systems as well. The combination of sophisticated structural methods, mutant viruses, neutralizing monoclonal antibodies, and particles bound to receptor molecules promises to yield important insights. Overall enthusiasm is extremely high for this project to investigate important structural transformations that occur during the flavivirus life cycle.

DESCRIPTION (provided by applicant): Flaviviruses are major human pathogens. They include West Nile, yellow fever and dengue viruses. These viruses result in significant morbidity and mortality each year in temperate and tropical regions of the Earth. West Nile virus has spread throughout the US in the last decade, having caused 4052 recorded infections and 146 deaths in 2006 alone. We intend to continue our structural studies of the viral life cycle in order to elucidate the processes by which the different viral components are assembled first into immature particles and then metamorphose into mature infectious virions. We also plan to continue our structural studies of the path by which these viruses infect their hosts, including the initial host cell recognition, fusion with the host cell plasma membrane initiating endocytosis and, finally, the release of the viral genome into the host cell's cytoplasm. A maturation process that occurs in the final moments before release of infectious virions from a cell is required by most viruses that infect mammals. The immature virions must protect themselves against premature interaction with the cell's own membranes before being released to infect other cells. Last, but not least, we intend to extend our studies of the interaction between antibodies and flaviviruses in order to establish the various mechanisms of neutralization as an aid to the development of vaccines that do not cause antibody-dependent enhancement of infection. Over the past few years we have learned to produce purified dengue (various strains) and West Nile virus in milligram quantities of sufficient quality for structural studies. West Nile virus is especially suitable because of its greater stability, but requires bio-safety level 3 facilities and precautions. These viruses will be used to produce cryo-electron microscopy three-dimensional reconstructions to study immature and mature flaviviruses complexed with various neutralizing antibodies and with cellular receptor molecules. Some of the antibodies inhibit virus maturation or fusion at specific intermediate steps in the viral life cycle. We plan to exploit our recent success in determining the crystal structure of the immature virus' heterodimer ectodomain consisting of the precursor membrane protein (prM) and envelope (E) glycoprotein. This structure has made it possible to build pseudo-atomic models of immature dengue virus and of a low pH intermediate prior to the release of the pr polypeptide and maturation into infectious particles. Mutational and structural studies will now permit determination of the amino acids that control the very large conformational changes that occur when the virus matures into infectious particles. These studies are essential for developing anti-viral and vaccine strategies to establish viable defenses against natural epidemics or bio-terrorist attacks based on using flaviviruses as a weapon. PUBLIC HEALTH RELEVANCE: Flaviviruses, which include West Nile, yellow fever and dengue viruses, are significant human pathogens that give rise to major concerns for human health the World over. Dengue virus alone causes 50 million or more cases of infection worldwide each year, resulting in 24,000 deaths. We propose in-depth studies of the structural changes that occur in the assembly pathway and infection process during the life cycle of flaviviruses, in particular West Nile and dengue viruses. Such information is essential for the development of antiviral drugs and vaccines and for determining the best response in the event of any possible epidemic.

CRITIQUE 1:

Significance: The family of flaviviruses includes hepatitis C virus plus a large number of viruses transmitted by insect vectors (mosquito or tick). Among the insect-borne group are important human pathogens including the viruses that cause dengue, yellow fever, Japanese B encephalitis, West Nile fever and tick-borne encephalitis. There are good vaccines for yellow fever and JBE, but a vaccine or therapeutic would be most welcome for others, particularly for dengue, which causes 50-100 million cases of dengue fever worldwide each year and hundreds of thousands of cases of dengue hemorrhagic fever. Recent tests of a killed dengue virus vaccine failed when it was observed that vaccinees were more rather than less sensitive to a subsequent infection. Enhanced sensitivity was traced to an effect of antibodies to promote uptake of virus into macrophages, presumably by opsonization.

The flavivirus virion is icosahedral in shape with a plus strand RNA genome and a membrane envelope. Infection begins when the virion is taken up into a sensitive cell by endocytosis. This is followed by fusion of the virus and endosome membranes to release the viral RNA into the cytoplasm where it is replicated and where progeny RNA strands are packaged into capsids. Capsids acquire a glycoprotein-containing envelope by budding into a cytoplasmic membrane compartment where the glycoproteins mature prior to virion release by fusion of vesicle and cytoplasmic membranes (see Fig. 3, pg. 96).

The virion membrane contains 180 copies each of two glycoproteins, M and E, that undergo dramatic conformational changes as the virus matures and as the mature virus becomes competent for fusion. In the immature form, 180 M-E heterodimers are arranged as 60 trimeric spikes that project outward from the particle surface. These flatten and re-arrange into 90 dimers to create the mature virion, and then revert back to trimeric spikes in the fusion-competent form. Dr. Rossmann and his colleagues are using structural methods to characterize the envelope morphological transformations with the idea that they would serve as attractive targets for inactivation of the virus by antibodies or by small molecule inhibitors.

Approach: The proposed project involves the use of cryo-electron microscopy and X-ray crystallography to study the structures of immature, mature and fusogenic forms of West Nile virus and dengue virus type 2. Cryo-EM and X-ray structures will be combined by docking a high resolution structure of the glycoprotein into lower-resolution cryo-EM structures to create a “pseudo-atomic” model. This method was developed and enhanced by Dr. Rossmann who has used it successfully to examine the structures of other viruses including bacteriophages T4 and phi29. In the current application the crystallographic structure of the prM-E heterodimer, recently determined in Dr. Rossmann’s laboratory (see Fig. 14, pg. 104) will be docked into cryo-EM structures of the immature and mature capsid in an effort to infer the molecular dynamics that link the two states (aim 1). Success in this project will depend critically on advances in using cryo-EM to enhance the resolution of existing structures of the immature virion and the immature virion at low pH (whose structure is the same as the mature virion). Description of the maturation pathway will be enhanced by the results of mutagenic studies designed to create and analyze amino acid changes designed to alter or abort the pathway (see aim 1c, pg. 107).

Aim 2 resembles aim 1 except that it focuses on the transition from the mature virion to the virion in the fusogenic state where the M-E protein is organized as protruding trimers. The study will involve mature virions treated at low pH to induce the fusogenic state and also studies of virions interacting with receptor molecules (aim 2c) and neutralizing monoclonal antibodies (aim 2d, pg. 116). As in the case of aim 1, the goal here will be to describe the pathway of molecular dynamics that links the mature and fusogenic or post-fusogenic forms of the virion.

The project seems to me to be very well conceived. Quite dramatic conformational changes accompany maturation of the flavivirus glycoprotein and equally significant changes are found as the mature virion becomes fusogenic. Both sets of events are required for flavivirus replication, and it is easy to imagine that inhibiting them with appropriate antibodies or small molecules will abort virus growth. The proposed

project is well suited to identifying steps in the two processes that would constitute targets for novel vaccines or therapeutics.

There are many other things to be enthusiastic about in the proposed project. Dr. Rossmann, for instance, is one of the premier structural virologists of our time. Success with plant viruses, rhinoviruses, bacteriophage and other projects have prepared him for the present analysis. He is now master of all the X-ray crystallography, cryo-EM, molecular fitting and computational methods required for success of the project. Dr. Rossmann has collaborated successfully with Dr. Kuhn, an expert in flavivirus structure and replication, to complete the extensive prior studies described here. Together Drs. Kuhn and Rossmann have risen to the top of the field of flavivirus structural virology.

The present application is an extension of a program project award in which quite remarkable progress was made in identifying and clarifying the steps of flavivirus glycoprotein maturation. For example, cryo-EM methods were used to compute reconstructions of dengue virus at 9.5A resolution (ref. 12), West Nile virus at 7A resolution (unpublished; see pg. 99), dengue virus immature virions at 16A resolution (ref. 3), and West Nile immature virions at 24A resolution (ref. 4). Other contributions relevant to the proposed project include: (a) use of cryo-EM to determine the structure of West Nile virus bound to a neutralizing monoclonal antibody (Fab E16; see Fig. 8, pg. 100); (b) use of X-ray crystallography to determine the structure of the dengue E protein domain III bound to the Fab of a neutralizing monoclonal (see pg. 100); and (c) use of X-ray crystallography to determine the structure of a prM-E fusion protein (unpublished; see pg. 104). The latter structure is central to the research proposed in aim 1 as it will be fit into the current reconstructions of mature and immature virions to determine how conformational changes in M-E create the global conformational changes that are the basis of virion maturation. Information gained from this approach will improve as the resolution of the virions (mature and immature) improves. Examination of glycoprotein mutants and the effects of bound antibodies have the potential to define intermediates in the transition from the immature to mature virion structure.

It is easy to see how rapid progress can be made in aim 1. Dr. Rossmann is an expert in the molecular fitting central to success of the proposed approach; his contributions will insure the most information possible is extracted from the available structures. I am also most enthusiastic about the potential for mutant analyses and antibody studies to reveal novel steps in the maturation process.

Aim 1g differs from the other projects proposed in aim 1 in that it is focused on the capsid. The flavivirus capsid is assumed to be icosahedral, but its morphology has not been defined in any of the cryo-EM structures computed to date. Either the capsid is disordered in the virion or it differs in individual flavivirus particles. In aim 1g it is proposed to use cryo-EM tomography to determine the structure of the core (pg. 111). Tomography represents a new initiative for Dr. Rossmann and his collaborators. The method is well suited to the flavivirus capsid problem if sufficient resolution can be obtained. Success with this project could move the field forward significantly.

Compared to aim 1, aim 2 is a greater challenge because, as Dr. Rossmann points out, the end of the process is a fused structure not expected to have icosahedral symmetry. Structural analysis therefore may involve different methods. There are, however, some assets that can be used including low pH treatment to induce transition to the fusogenic state, structural analysis of capsids containing bound receptor molecules (pg. 114) and capsids bound to neutralizing antibodies (pg. 116). I am particularly enthusiastic about structural analysis of virions bound at low pH to phospholipid vesicles. Analysis of such complexes has the potential to reveal the structure of intermediates in the fusion process. Mutant analysis here, as in aim 1, has the potential to be highly revealing about the identity of specific amino acids involved in re-arrangement to the fusogenic state.

I feel the application would be strengthened by an explicit effort to identify specific antibody or small molecule inhibitors of the maturation pathway and by a more thorough description of the research proposed in aim 2a. Dr. Chen’s limited experience with flaviviruses is also a weakness of the application.

Innovation: Dr. Rossmann and the structural virology group at Purdue are well known for all types of advances in the field. For the present application, it is most relevant that Dr. Rossmann has been a leader in describing and applying methods for fitting X-ray structures into lower resolution maps determined by cryo-EM. Novel methods described in the application have been devised for handling specimens of pathogenic viruses for cryo-EM and for X-ray crystallography.

Investigators: Dr. Michael Rossmann is a Professor in the Department of Biological Sciences at Purdue University where he has served since 1964. He is best known for his use of X-ray crystallography to study virus structure and he has risen to the top of the virus structure field. His work has been well recognized as indicated by the many honors he has received (see pg. 24). He is perhaps best known for his studies of picornaviruses, bacteriophages and flaviviruses, but he has made important contributions to the study of other viruses as well. He has trained many talented students and post-doctoral fellows. Faculty members who have served in the Purdue structural biology group include some of the top people in the field. For example, Drs. Jack Johnson, Tim Baker and Wladek Minor are among this group.

Dr. Richard Kuhn is Professor in the same Department where he has served since 1991. He is well known for his structural and other studies emphasizing alphaviruses and flaviviruses. He has collaborated extensively and productively with Dr. Rossmann since joining the faculty at Purdue.

Dr. Jue Chen is an Associate Professor in the Department of Biological Sciences where she has served since 2002. Prior to joining the Purdue faculty she was exceptionally well trained in X-ray crystallography having post-doctoral experience with Dr. Wiley at Harvard and Dr. Quiocho at Baylor. She has been highly productive at all stages of her academic career.

The Principal Investigators will benefit from interaction with collaborators offering expertise in cryo-EM (Dr. Jiang) and flavivirus-specific monoclonal antibodies (Drs. Aaskov, Diamond and Fremont).

Environment: The structural biology laboratory at Purdue is among the best such facilities anywhere. All the latest equipment is available for protein crystallization, X-ray diffraction, cryoelectron microscopy and the computational operations required to determine the structures and interpret them. Dr. Rossmann is the center of this group and it is his vision that has brought the group to its current preeminent state. The group will soon move into a new building with enhanced facilities for all aspects of the proposed project.

Overall Evaluation: The proposed project will involve use of cryo-EM and X-ray crystallography to define the morphogenetic steps that link the immature and mature flavivirus particles and also the steps from mature to fusion competent virions. Most work will be done with West Nile and dengue type 2 viruses. The overall pathway to be defined is rich in potential targets for novel immunization strategies and novel small molecule inhibitors that would be particularly welcome in the case of dengue virus infections. The project is well conceived at the macro level in that the two aims address sequential parts of the same pathway. It is also well integrated at the micro level where progress in one project has the potential to cross-feed others. I am particularly optimistic about proposed studies to fit X-ray structures into lower resolution cryo-EM maps and about studies of the effects of glycoprotein mutants and glycoprotein-specific monoclonal antibodies. There are many other things, however, to be enthusiastic about in this proposed project. I feel the application would be strengthened by explicit efforts to identify inhibitors of the maturation pathway.

Biohazards: Pathogenic strains of West Nile and dengue viruses will be used in the proposed research.

Budget: The proposed budget is appropriate.

CRITIQUE 2:

Significance: Flaviviruses are a group of enveloped viruses that enter the cells by viral glycoprotein mediated membrane fusion. The glycoprotein is present in a metastable conformation on the viral surface. To assemble a viral particle in a high energetic state, the virus employs a step-by-step process to produce an infectious particle from an immature or intermediate particle to a mature particle that is released from an infected cell. When the mature particle recognizes the host cell receptor, the association of the glycoprotein with the receptor and subsequent steps of internalization of the particle into an acidic vesicle trigger the release of the stored energy in the metastable glycoprotein in the form of a large conformational change. This conformational change inserts the fusion peptide into the host cell membrane and leads to fusion of the viral membrane with the host cell membrane as a vital step in virus entry. The studies in this application are aimed at mapping each critical step structurally and biochemically in order to have a more detailed understanding of this process. Assembly and entry are the most critical aspects in a virus replication cycle, in addition to the replication of the viral genome. The results from this application will undoubtedly have a profound impact on our understanding of flavivirus replication. The knowledge will help in the discovery of innovative strategies for the design of effective vaccines and antiviral drugs of flaviviruses, which include serious human pathogens.

Approach: This applciation is information intensive since it covers a broad range of topics. In the previous funding period, the team at Purdue University has developed a solid system that can be employed to tackle a number of challenging problems in structural studies of flaviviruses. Key achievements include structures of immature virus particles, high resolution structures of mature particles, crystal structures of glycoproteins, virtual atomic structures by combining EM and crystal structures, structures of particles in complex with a receptor domain or Fabs, and crystal structures of preM-E and fitting it in the immature particle. More recently, the structure of the immature particle at low pH was solved and the result showed how structural changes may be correlated to the maturation process. These results not only advanced the field in giant steps, but also laid the foundation for future studies as proposed in this application. Articles reporting these novel findings are in principle accepted for publication in a prestigious journal. There is no doubt that the results generated by experiments proposed in this application will stimulate advances of many studies in this field. If there is any perceived weakness, it may be the expected difficulty in growing crystals of full virus particles, mature or immature. The outcome of such an effort is uncertain despite the expertise of the Purdue team and the strong track record of past successes.

Innovation: The experiments proposed in this application combine multiple approaches to solve the complicated problems in studying the dynamic changes of flaviviruses during assembly and entry. Novel methods are developed by the Purdue team to study relevant particles at different replication stages structurally and biochemically. In addition, site-directed mutagenesis will be used to probe the functionally critical regions of glycoproteins as guided by various structures. New techniques will also be applied to determine the core structure.

Investigators: The Principal Investigator and other key personnel form a strong team that has no match in structural virology. The track record of this team as demonstrated by the impressive list of outstanding publications provides the strongest support for the success of the project.

Environment: The institutions of the Principal Investigator and his collaborators provide excellent environments and facilities for the experiments proposed in this application.

Overall Evaluation: Dr. Rossmann and other key personnel at Purdue University constitute a highly productive team that has generated a tremendous amount of new results in structural studies of flaviviruses. The application aims at expansion of the previous accomplishment to further investigate the mechanism and pathway of assembly and entry of flaviviruses. The Purdue team established a solid system for structural studies of particles that represent various steps in the virus replication cycle. The sources of materials and techniques developed during the past period are more than adequate for

continuing the studies proposed in this application. The results expected from these experiments will provide new insights on the pathway of assembly and entry of flaviviruses. Difficulties and new experimental directions are par for the course of such studies. The Purdue team has an indisputable track record of success for making major breakthroughs in structural studies of whole virus particles.

Budget: The proposed budget is adequate

CRITIQUE 3:

Overall Evaluation: This is an outstanding application that has as its overall goal the determination of flavivirus structures, beginning with the assembly of immature virions, through to the transformation to mature, infectious particle, to the changes that take place when the infectious virions infect cells. As well, structures will be determined for several monoclonal antibodies complexed to virions, and for DC-SIGN receptor molecules complexed with virus. Most of the studies will be done with West Nile and dengue viruses, pathogens of great medical significance, but the findings will certainly have application for all flaviviruses.

The application is ambitious and far-reaching, but given the track record of Dr. Rossmann and his colleagues it is well within reach. The accomplishments of this group within the past five years, during which time they had a Program Project Grant, are very impressive, and have provided elegant new insights into the details of how flaviviruses are assembled and the changes that occur upon exposure to a low pH, as occurs in endosomes. This is documented by the large number of publications.

The application is a first resubmission. In the Introduction, Dr. Rossman replies strongly and in a convincing fashion to the questions and criticisms raised in the reviews of the original application.

In this revision Dr. Rossmann outlines in detail the use of cryo electron microscopy and X-ray crystallography to markedly improve the resolution of structures that have already been described, and to describe new structures or new virus complexes. The structural studies will be combined with appropriate use of mutant viruses and with functional studies of viruses at various stages of development. Dr. Rossmann has assembled a most productive team. This reviewer is confident that their work and their results will continue to impact the flavivirus field enormously.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

REVISION NOTE: The roster has been corrected.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NOTICE: The NIH has modified its policy regarding the receipt of amended applications. Detailed information can be found by accessing the following URL address: http://grants.nih.gov/grants/policy/amendedapps.htm

NIH announced implementation of Modular Research Grants in the December 18, 1998 issue of the NIH Guide to Grants and Contracts. The main feature of this concept is that grant applications (R01, R03, R21, R15) will request direct costs in $25,000 modules, without

budget detail for individual categories. Further information can be obtained from the Modular Grants Web site at http://grants.nih.gov/grants/funding/modular/modular.htm

MEETING ROSTER

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.