OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Kirchdoerfer, Robert Nicholas

eRA COMMONS USER NAME (credential, e.g., agency login): KIRCHDOERFER

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| University of Wisconsin, Madison | B.S | 05/2006 | Genetics and Biochemistry |
| The Scripps Research Institute | Ph.D. | 05/2012 | Biophysics |
| The Scripps Research Institute | Post-Doctoral | 07/2019 | Biophysics |

**A. Personal Statement**

**Research in my laboratory focuses on combining biochemical and structural biology approaches to illuminate mechanisms of virus life cycles, extending from viral entry to viral RNA replication. In particular, we study coronavirus RNA synthesis through the recombinant expression of viral protein subunits and *in vitro* reconstitution of protein-protein and protein-RNA complexes as well as assessment of viral enzyme activity. My structural biology background encompasses both X-ray crystallography and single-particle cryo-electron microscopy and is strengthened by broad skills in biophysical and biochemical characterization of protein-protein and protein-RNA interactions. My virology experience extends from negative-strand RNA viruses such as influenza and Ebola viruses to positive-strand RNA viruses such as SARS-coronavirus promoting a great breadth in perspective for generating new hypotheses and drawing parallels among viruses. The current proposal to examine the RNA-bound SARS-CoV-2 polymerase complexes with the nsp14 exonuclease is excellently supported by my past research studies of viral polymerases and RNA-binding proteins. These studies will draw on my strong background in combining structural techniques such as single-particle cryo-electron microscopy with hypothesis driven biochemical characterizations to examine protein-protein interactions and viral enzyme function. This merger in scientific strengths will accelerate coronavirus research to rapidly illuminate mechanistic processes in SARS-CoV-2 RNA replication and inhibition by antiviral nucleotide analogues.**

**B. Positions and Honors**

**Positions and Employment**

**2006-2012 Graduate Student,**

**Dept. of Molecular Biology, The Scripps Research Institute, La Jolla, CA**

**2012-2016 Post-doctoral Fellow,**

**Dept. Immunology and Microbial Sciences, The Scripps Research Institute, La Jolla, CA**

**2016-2019 Post-doctoral Fellow,**

**Dept. Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA**

**2019- Assistant Professor**

 **Department of Biochemistry, University of Wisconsin-Madison, Madison WI**

**Professional Memberships**

**2012-2019 Member, American Society for Virology**

**C. Contributions to Science**

**Topic, Major need or question, major findings, impact of contributions,**

1. **After entering host cells, viral genomes must be replicated and transcribed to produce new virions. Viral RNA genomes are dependent on virus encoded machinery for this activity. The viral RNA synthesis machineries are composed of multi-protein complexes where protein subunits interact with each other, substrates and RNA for their full activity. My studies have used both X-ray crystallography and cryo-electron microscopy to examine viral protein-protein and protein-RNA interactions. This has included studies of the influenza ribonucleoprotein complex that distinguished transcriptional and replicational states. I also examined interactions among Ebola virus proteins contributing to viral nucleocapsid assembly and function. In addition, my recent single-particle cryo-electron microscopy studies have produced the first structure of a polymerase complex from coronaviruses and illuminated interactions of the viral polymerase with viral co-factors. These studies are shaping the way these virology fields are interpreting sequence and functional data and have shifted paradigms for mechanisms of viral protein function.**
	1. **Kirchdoerfer RN, Ward AB (2019). Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. Nat Comm. 10: 2342.**
	2. **Kirchdoerfer** **RN**, Saphire EO, Ward AB (2019). Cryo-EM structure of the Ebola virus nucleoprotein-RNA complex. Acta Crystallogr F Struct Biol Commun. 75:340-347.
	3. **Kirchdoerfer** **RN**, Abelson DM, Li S, Wood MR, Saphire EO (2015). Assembly of the Ebola Virus Nucleoprotein from a Chaperoned VP35 Complex. Cell Rep. 12:140-149.
	4. Moeller A, **Kirchdoerfer** **RN**, Potter CS, Carragher B, Wilson IA (2012). Organization of the influenza virus replication machinery. Science. 338:1631-4.
2. **To infect host cells, enveloped viruses must fuse their exterior membranes with those of the cell releasing their genomes into cells to initiate infection. For coronaviruses, the process of recognizing host receptors and carrying out the membrane fusion process is facilitated by the viral spike protein. Using cryo-electron microscopy, I determined the first structure of a human coronavirus spike. This structure demonstrated the interfolded arrangement of spike receptor-binding domains and how they cover and stabilize the spike fusion machinery. This first structure was instrumental in the design of novel mutations to stabilize the pre-fusion spike proteins of other betacoronaviruses and allowed us to determine structures of spikes of SARS- and MERS-coronavirus spikes. This also included an analysis of SARS-coronavirus spike bound to its host receptor, ACE2 which binds only a particular conformation of the spike receptor-binding domain. These studies have illuminated not only spike structures but are also producing blueprints for creation of pre-fusion spike proteins to be used as vaccine immunogens.**
	1. **Kirchdoerfer RN, Wang N, Pallesen J, Wrapp D, Turner HL, Cottrell CA, Corbett KS, Graham BS, McLellan JS, Ward AB. (2018). Stabilized coronavirus spikes are resistant to conformational changes induced by receptor recognition or proteolysis. Sci Rep. 8:15701.**
	2. Pallesen J, Wang N, Corbett KS, Wrapp D, **Kirchdoerfer RN**, Turner HL, Cottrell CA, Becker MM, Wang L, Shi W, Kong WP, Andres EL, Kettenbach AN, Denison MR, Chappell JD, Graham BS, Ward AB, McLellan JS. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci U S A. 2017 114:E7348-E7357
	3. **Kirchdoerfer RN**, Cottrell CA, Wang N, Pallesen J, Yassine HM, Turner HL, Corbett KS, Graham BS, McLellan JS, Ward AB. Pre-fusion structure of a human coronavirus spike protein. Nature. 531:118-21.

**Complete List of Published Work in MyBibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1jMrGuPZElIAI/bibliography/9393999/public/?sort=date&direction=descending>

**D. Additional Information: Research Support and/or Scholastic Performance**

**Current Research Support**

**R00 AI123498 Kirchdoerfer (PI) 7/14/2017-current**

**Structural studies of the coronavirus lifecycle.**

**The goal of this study was to characterize the molecular mechanisms leading to coronavirus RNA transcription and examine the impact of host-receptor binding on coronavirus spikes.**

**Role: PI**