BIOGRAPHICAL SKETCH

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NAME: **Jamsen, Joonas**

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

POSITION TITLE: **Assistant Professor of Biochemistry and Molecular Biology**

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	Completion Date	FIELD OF STUDY
University of Turku, Finland	Integrated B.Sc. & M.Sc.	02/2006	Biochemistry
University of Helsinki, Finland	Civil Service	12/2010	Structural Biology
City of Hope National Cancer Center, Duarte, CA	Training	05/2012	Cell & Molecular Biology
University of Turku, Finland	PhD	09/2012	Biochemistry
Institute of Molecular Oncology, Milan, Italy	Training	12/2013	Cell & Molecular Biology
Washington University in St. Louis, MO	Training	08/2014	Biochemistry
NIEHS, Research Triangle Park, NC	NIH Training	06/2022	Structural Biology

A. Personal Statement

Research environment and vision of my laboratory. I started my independent research laboratory at the University of Arkansas for Medical Sciences (UAMS) in the summer of 2022. My research is focused on understanding the molecular basis of DNA replication and repair, especially in the context of cancer-related forms of DNA damage. My laboratory employs cutting-edge structural and biophysical approaches to study DNA repair.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – present Assistant Professor, Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences (Little Rock, AR)
2019 – 2022 Research Fellow, Genome Integrity & Structural Biology Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health (Research Triangle Park, NC)
2014 – 2019 Visiting Fellow, Genome Integrity & Structural Biology Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health (Research Triangle Park, NC)
2014 Postdoctoral Fellow, Department of Biochemistry, Washington University School of Medicine (St. Louis, MO)
2013 Postdoctoral Fellow, Institute for Molecular Oncology (Milan, Italy)
2013 Postdoctoral Fellow, Cancer Research UK (Potters Bar, United Kingdom)

Awards and Honors

2021 NIH Future Research Leader
2018 K99/R00 Pathway-to-Independence Award
2014 NIH Visiting Fellow
2013 IFOM Fellowship

2011 Alfred Kordelin Foundation Pre-Doctoral Award
2010 Teaching Award, University of Turku, Finland
2006 National Graduate School in Informational and Structural Biology Fellowship
2006 Multiple travel awards from Finnish foundations

Other Experience and Professional Memberships

2022 – present Society for Biological Inorganic Chemistry (SBIC)
2019 – present American Crystallographic Association
2016 – 2017 Genome Integrity & Structural Biology Laboratory Trainees Action Committee Member
2016 – present Environmental Mutagenesis and Genomics Society (EMGS)
2009 – present Biophysical Society

C. Contributions to Science

1. Early career - Comparative molecular phylogenetics to dissect protein structure and function

My early (summer 2001) scientific contributions in molecular phylogenetic characterization and computational modelling of G-protein coupled receptors (GPCRs) in the laboratory of Dr. Mark Johnson at the Abo Akademi University in Turku (Finland) characterized structural attributes of ligand binding by adrenergic receptors. GPCRs are important drug targets (~50% of FDA approved drugs) as GPCR signaling is critical to physiology & disease. My role was to perform sequence searches and alignments to facilitate computational modelling with the aim of supporting characterization of how GPCR ligands interact with their receptor binding sites to inform drug discovery and development (publication a). While high school students and undergraduates were not allowed to be listed as contributors to publications in Finland at the time I performed this research, I employed this earlier experience while completing my final thesis work for an integrated B.Sc. & M.Sc. degree in Biochemistry to uncover the structure and function of membrane-bound proton-pumping inorganic pyrophosphatases (PPases) from bacteria and archaea. At that time, the structure of this fourth primary proton pump was unknown. My role was to identify a class of receptors that would be amenable to purification strategies that would enhance the fraction of active enzyme in unilamellar vesicles, develop kinetic assays to measure single turnover PPase activity in vesicles, and structural analysis. I successfully developed a technique for single turnover kinetic characterization of PPase activity using a chemical quenched flow approach, identified favorable purification conditions for activity assays, dissected the kinetic mechanism of Mg^{2+}-dependent PP_i hydrolytic activity, and successfully identified structural features of an archaeal homologue using fluorescence labeling. These experiences in protein engineering, expression, purification, and kinetic analysis allowed for a rapid transition to characterize allosteric nucleotide binding effects on the kinetic and biophysical properties of a novel type II soluble inorganic PPase subfamily that I discovered. Our initial focus centered on a Co^{2+}/Mn^{2+}-dependent PPase with a cystathionine-β-synthase (CBS)-like nucleotide- binding domain found in a thermophilic Co^{2+}-dependent bacterium using molecular evolutionary analysis.

a. **Jämsén J**, Tuominen H, Salminen A, Belogurov GA, Magretova NN, Baykov AA & Lahti R. (2007) A CBS domain-containing pyrophosphatase of *Moorella thermoacetica* is regulated by adenine nucleotides. *Biochem J* 408, 327-333. PMCID: PMC2267367.

2. Structure and mechanism of adenosine-nucleotide regulation of Type II CBS-domain containing soluble inorganic pyrophosphatase.

My graduate work focused on the discovery, biophysical and biochemical characterization of the catalytic and regulatory mechanisms of a novel subtype of nucleotide- regulated type II soluble inorganic pyrophosphatase (PPase) containing an allosteric auto-inhibitory cystathionine-β-synthase (CBS) domain. Single point mutations in CBS domains cause heritable human disorders in CBS domain-containing proteins (e.g., CLC-chloride channels, AMPK, IMPDH, and others). The results of my work provided new details into the mechanism(s) of CBS domain protein regulation and allowed for further understanding of how malfunctions in these evolutionarily wide-spread domains cause inherited human diseases. I characterized the metal, adenosine nucleotide and substrate dependence of activity transitions of the PPase from a thermophilic bacterium (publication a). Structural analysis of the isolated CBS domain in complex with an inhibitor and novel activator (diadeosine tetraphosphate, Ap4A) helped elucidate the structural basis for competitive inhibition and allosteric activation by adenosine nucleotides (publication b). Based on this structural analysis, I identified disease relevant point mutations in CBS-PPases and I then performed in-depth characterization of the kinetic

mechanism of nucleotide regulation of the mutant metalloenzymes (publication c). Lastly, I discovered that these enzymes are regulated by the tight-binding activators diadenosine polyphosphates using transient kinetic methods (publication d). My studies challenged the paradigm in the field that inorganic PPases only hydrolyze pyrophosphate (PPi) and showed that these type II inorganic PPases hydrolyze tripolyphosphate (P3) at efficiencies higher than PPi.

a. **Jämsén J**, Baykov AA & Lahti R. (2010) Substrate-induced conformational transition of the nucleotide-regulated CBS-PPase of Moorella thermoacetica. *Biochemistry* 49, 1005-13. PMCID *in process at journal*; PMID: 20038140.
b. Tuominen H, Salminen AS, Oksanen E, **Jämsén J**, Baykov AA, Goldman A & Lahti R. (2010) Crystal structures of the CBS and DRTGG domains of the regulatory region of Clostridiumperfringens pyrophosphatase complexed with the inhibitor, AMP, and activator, diadenosine tetraphosphate. *J Mol Biol.* 398, 400-13. PMCID *in process at journal*; PMID: 20303981.
c. **Jämsén J**, Tuominen H, Baykov AA & Lahti R. (2011) Mutational analysis of residues in the CBS domain of Moorella thermoacetica pyrophosphatase corresponding to disease-related residues of human proteins. *Biochem J.* 433, 497-504. PMCID *in process at journal*; PMID: 21067517.
d. **Jämsén J**, Baykov AA & Lahti R. (2012) Fast kinetics of nucleotide binding to Clostridium perfringens family II pyrophosphatase containing CBS and DRTGG domains. *Biochemistry (Moscow)* 77, 165-70. PMCID *in process at journal*; PMID: 22348476.

3. Post-translational modifications and regulation of DNA replication and repair.

During my graduate studies, I engaged in a year-long research project to provide a link between post-translational modifications and cell cycle regulation of FEN1 activity during the period 6/2010-5/2011. FEN1 endonuclease cleaves 5′ flaps generated in lagging strand DNA replication. Unregulated nuclease activity, however, is deleterious and programmed degradation of FEN1 is essential for genome integrity. My role was to uncover aspects of the phosphorylation and ubiquitination reactions that promote the degradation of FEN1 as a function of cell cycle progression. I also performed in vitro validation of the identity of the SUMO E3 ligase (publication a). I also collaborated on a project to characterize the role of TatDN1 nuclease in zebrafish chromosome segregation. My role was to perform in vitro biochemical assays to characterize the metal dependence of TatDN1 nuclease activity with circular catenated and various other types of substrates (publication b). My postdoctoral studies began with two breaks immediately after completing my PhD to follow up on my passion for DNA repair. During the period 1/2013-10/2013 at the Cancer Research UK (London, UK) and later at the IFOM (Milan, Italy) I characterized the role of BRCA2 and other homologous recombination factors in DNA replication and repair, in Xenopus egg extract and human cancer cell lines.

a. Guo Z, Liu N, Kanjanapangka J, Liu N, Liu S, Liu C, Wu Z, Wang Y, Loh T, Kowolik C, **Jamsen J**, Zhou M, Truong K, Chen Y, Zheng L & Shen B. (2012) Sequential post-translational modifications program FEN1 degradation during cell cycle progression. *Mol Cell* 47, 444-56. PMCID: PMC3518404.
b. Yang H, Liu C, **Jamsen J**, Wu Z, Wang Y, Chen J, Zheng L & Shen B. (2012) The DNase domain-containing protein TATDN1 plays an important role in chromosomal segregation and cell cycle progression during zebrafish eye development. *Cell Cycle* 11, 4626-32. PMCID: PMC3562307

4. DNA polymerase strategies of oxidized nucleotide insertion in double strand break repair.

At the National Institute of Environmental Health Sciences (NIEHS) in the laboratory of Dr. Samuel Wilson from 10/2014-06/2022 I deciphered mechanisms of DNA polymerases using a novel technique called time-lapse crystallography. I employed this technique in combination with oxidized DNA substrates or nucleotides to uncover how DNA polymerases mediate repair of oxidative stress induced DNA damage. The approach requires collection of many intermediate catalytic structural states or “snapshots” along the reaction pathway to piece together the events that occur when an enzyme catalyzes its reaction. My published work using this technique includes a study in the journal *Nature communications* (publication a) where I revealed in unprecedented detail how DSB repair polymerase μ inserts nucleotides into a DSB repair intermediate. A recent study also in the same journal uncovered how this polymerase readily creates oxidative damage employing a unique low fidelity discrimination mechanism that promotes mutagenesis in DSB repair (publication b). A follow-up study uncovered that oxidized ribonucleotide insertion by this polymerase can lead to persistent mutagenesis (publication c). These observations are significant as this damage can directly cause cancer and

other pathologies. A related follow-up study uncovered novel features of how a DNA polymerase discriminates against mismatched nucleotide insertion and revealed hidden polymerase fidelity determinants (publication d).

a. **Jamsen JA**, Beard WA, Pedersen LC, Shock DD, Moon AF, Krahn JM, Bebenek K, Kunkel TA & Wilson SH. (2017) Snapshots of a Double-Strand Break Repair Polymerase in Action. *Nat Commun*. 8, 253. PMCID: PMC5557891.
b. **Jamsen JA**, Sassa A, Shock DD, Beard WA & Wilson SH. (2021) Watching a Double Strand Break Repair Polymerase Insert a Pro-Mutagenic Oxidized Nucleotide. *Nat commun* 12, 2059. PMCID: PMC8024293.
c. **Jamsen JA***, Sassa A, Perera L, Shock DD, Beard WA & Wilson SH*. (2021) Structural Basis for Proficient Oxidized Ribonucleotide Insertion in Double Strand Break Repair. *Nat commun* 12, 5055. PMCID: PMC8379156.
d. **Jamsen JA***, Shock DD & Wilson SH*. (2022) Watching Right and Wrong Nucleotide Insertion Reveals Hidden DNA Polymerase Fidelity Checkpoints. *Nature commun* 13, 3193. PMCID: PMC9184648.

*Denotes corresponding authorship; [1]Co-first authorship

Complete List of Published Works in My Bibliography:

https://www.ncbi.nlm.nih.gov/pubmed/?term=jamsen+j