UNIVERSITY OF MANITOBA

CANADA FOUNDATION FOR INNOVATION 13-10
Innovation Fund

Notice of Intent

1. Completed NOIs must be submitted by the Associate Dean (Research)/Research Liaison Officer of the "Lead" Unit to the Office of Research Services to: Birtukan.Gebretsadik@umanitoba.ca by May 15, 2018.

Proposed name of project: **Centre for Structural Biology (CSB)**	**Estimated Total Project Costs:** **$6.2Mio**

Designated Project Leader/Faculty/Dept:Stetefeld, Science/ Chemistry **CV:** x

List Principal Users/Faculty/Dept:

1. Stetefeld, Joerg/ Science/Chemistry CV: x
2. Budisa, Ned/Science/Chemistry CV: x
3. Mark, Brian/ Science/ Microbiology CV: x
4. McKenna, Sean/ Science/ Chemistry CV: x
5. Prehna, Gerd/ Science/ Microbiology CV: x
6. CV: x

'Lead' Unit ADR/RLO:

Name: Faculty of Science; Dr. Ivan Oresnik

Briefly describe (max 2 pages, 12 pt. font size, 2 cm margins):

- The proposed research and how it is world-class, innovative and demonstrates clear benefits to Canada.
- The infrastructure and how it will enhance the University's existing research capacity.
- The excellence of the team, including expertise and existing collaborations necessary to conduct the proposed research.
- Plans to secure matching funds and the potential funding sources for the operation and maintenance of the infrastructure.

Proposed Research- Fundamental challenges in current structural biology research are the limited number of proteins for which high-resolution structural information exists. This creates formidable barriers to our understanding of disease processes and the development of novel and innovative strategies to advance medicine and biotechnology. With the **Center for Structural Biology (CSB),** we propose to establish a 3D structural biology technology center that will enable world-class atomic (X-ray crystallography) to near-atomic (cryo-3D **T**ransmission **E**lectron **M**icroscopy) resolution structural biology research that will provide unprecedented insights into the molecular mechanisms of disease, synthetic biology, virus-host interactions and structure-based drug design. Cryo-3D TEM has recently undergone a technical revolution, often coined the 'resolution revolution', which has enhanced the resolving power of electron microscopy so dramatically that large biomolecular systems once thought impossible to study in atomic detail can now be studied at near atomic resolution. By combining state-of-the-art cryo-3D TEM and X-ray crystallography technologies, we aim to establish the capacity to generate unprecedented visual insights into the molecular basis of life to address fundamental questions in modern medicine and biotechnology. The unrivaled resolving power of next generation cryo-3D TEM combined with modern protein X-ray crystallography will be made even more powerful with the support of previously CFI-funded projects.

Benefits to Canada- The CSB will enable 3D structural biology research aimed at addressing some of the most pressing scientific problems of our time, including the molecular basis of cancer, antibiotic drug resistance and new structure-based approaches to accelerate modern drug design and discovery. Further, in conjunction with the University of Alberta as collaborative institution, we aim to establish for the first time, a cutting edge cryo-3D TEM network for atomic-scale structural biology research in the Canadian prairie provinces. CSB will support discoveries in areas of research excellence in cancer, biomonitoring/remediation, virology, genetic diseases, nano-therapeutics and synthetic structural biology. The CSB is a critical strategic investment into the rapidly emerging field of integrated near-atomic structural imaging and advanced 3D ultrastructural biomedical research. The CSB will serve a broad research community at UM and foster synergies with industry to enable novel and innovative biomedical research, improving the lives of Canadians through groundbreaking biomedical discoveries.

Infrastructure- The proposed CSB will form a satellite site for the Regional Centre for Molecular Microscopy in the Canadian Prairies (RCMCP) being led out of the University of Alberta. The CSB will also build upon existing CFI funded infrastructure at the UM including in-house SAXS and analytical ultracentrifugation capacities. Importantly, the CSB will house specialized cryo-TEM equipment that synergizes with the CFI-funded Manitoba Institute for Material Sciences (MIM). Key imaging components of CSB are the cryo-3D TEM TALOS Arctica (FEG 200keV) and X-ray diffractometer XtalLAB that each have distinct and non-interchangeable applications needed to cover near-atomic to atomic resolution studies. The TALOS is a game changer in protein structure analysis at near-atomic resolution and will extend X-ray crystallography and other structural methods by allowing structural analysis of membrane proteins, highly post-translationally modified proteins and macromolecular or oligomeric structures that cannot be crystallized easily or are large and difficult to analyze by conventional crystallography. The TALOS has high-throughput capability and maximal flexibility through use of three high-end detectors for single-particle analysis by near-atomic resolution (<4Å). The XtalLAB will enable atomic-scale resolution protein crystallography research by applying newly developed chemical fingerprint techniques combined with silicon hybrid pixel detector systems, operating in a revolutionised single-photon-counting mode. Structural information obtained with in-house NMR and SAXS equipment will be synced with the new TALOS TEM and XtalLAB imaging systems. The RCMCP is following the "synchrotron model", where UA will acquire a high-end 300keV Titan Krios TEM and allow users from across 6 Prairie Universities to access the infrastructure. The local CBS at UM will not only prepare for negative stain and sample preparation, it will independently create

cutting-edge cryo-EM data in publication quality. The applicants provide essential protein synthesis and expression technology for cryoprotein preparation and crystallizations for structural imaging by EM and X-ray crystallography.

Enhance existing research capacity- New atomic structure-function information on mutated proteins, drug-receptor or microbial-host interactions fuels crucial discoveries in protein biology and the development of new drug candidates to improve therapeutic strategies. The requested infrastructure will provide modern integrated TEM and X-ray crystallography tools and build upon internationally recognized structural biology research at UM, enhancing the innovative capacity and success of protein structural studies and the in-depth biophysical characterization of proteins in action. Over the last decade, UM structural biologists have established modern facilities to produce high quality purified biomolecules from bacteria, insect cells, and human cells for study using the proposed center. The CSB facility is both appropriate and essential to facilitate the advancement in structure-function relationships of proteins relevant to human health and disease. The primary users form a strategic network of researchers from UM, research institutes, and NML in Winnipeg. Only the University of Toronto and McGill University have a comparable setup, but their facilities are heavily oversubscribed, making their use by outsiders inaccessible and problematic. CSB will bring modern high-resolution cryo-EM technologies to Manitoba, providing cutting edge, internationally competitive research capacity in structural biology to UM research groups.

Team and Collaborations- The team of researchers is uniquely qualified to carry out the proposed research. Drs Stetefeld (Tier-1 CRC in Structural Biology), Budisa (Tier-1 CRC in Synthetic Biology), Mark (former Research Manitoba Chair 2011-2016), McKenna and Prehna have numerous joint research collaborations successfully established and are funded by CIHR (Stetefeld, Mark, McKenna), NSERC, GlycoNet, Merck Animal Health, Cystic Fibrosis Canada and Cancer Society, Multiple Sclerosis Society and Heart and Stroke Foundation. The establishment of the CSB will provide the required infrastructure for Manitoban structural biologists, biochemists, and biomedical/ clinical researchers, enabling them to answer key questions and devise potential methods to address pressing health-related problems. Laboratories of all applicants have already established strong collaborations with the National Microbiology Laboratory, the Manitoba Center for Proteomics & Systems Biology, College of Medicine, and local and international biotechnology industries. Through these collaborations, our research teams can identify, produce and investigate proteins unavailable elsewhere in the world. The CSB will foster and benefit from the implementation of cutting-edge structural biology technology. The RCMCP is orchestrated by UA (Young and Glover), including US (Cygler), UL (Kothe), UC (Schreimer) and UM (Stetefeld).

Matching funds AND operation and maintenance- The CSB facility provides essential infrastructure for the PI, Co-PIs and their collaborators. Industry collaborations of the Stetefeld team include the newly established Center for Oil and Gas Research and Development (COGRAD) and rely on expertise in determining structural features and conformational changes upon binding of drugs. Instrumentation at CSB is a powerful incentive to advance these and foster new collaborations. CSB will be a consortium of key researchers and administrators at UM. In negotiations with suppliers an in-kind discount of 20% is guaranteed. In addition, a 5-year service/warranty contract is requested in the cost of the purchase of the TALOS and XtalLab instruments. A key feature of CSB is an online fee-based EM service for researchers with the vision that the CSB quality services with the proposed new technologies be made accessible to the broad research community across Canada. Interest in the use of CSB services and new research collaborations has been expressed by the leadership and researchers at UA and Grand Forks (ND, USA).