L-15 **Session B, Wednesday, 15.06., 9^{40} - 10^{20}**

Extended Abstract

Review of biological application facilities at the Canadian Light Source

P. Grochulski[1,2]* M. Fodje[1], S. Labiuk[1], T. W. Wysokinski[1], G. Belev[1], G. Korbas[1] and S. M. Rosendahl[1]

[1]*Canadian Light Source Inc., 44 Innovation Boulevard, Saskatoon, SK S7N 2V3, Canada*
[2]*College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK S7N 5E5, Canada*

Keywords: synchrotron radiation, macromolecular crystallography, medical imaging, infrared spectroscopy, X-ray absorption spectroscopy

*e-mail: pawel.grochulski@lightsource.ca

The Canadian Light Source Inc. (CLS) is a mid-size 3rd generation 2.9 GeV synchrotron located on the campus of the University of Saskatchewan in Saskatoon (www.lightsource.ca). Last year, the CLS celebrated its 10th anniversary of operation. Currently there are 15 beamlines operating at the facility, with an additional two being commissioned and five under construction. A current summary of Bio/Life Sciences department publication activity is shown in Figure 1.

The Bio/Life Science department at the CLS was created one year ago to facilitate support and research in the biological and health related fields. It is composed of the following facilities: Canadian Macromolecular Crystallography Facility (CMCF), Mid Infrared Spectromicroscopy (Mid-IR), Biomedical Imaging and Therapy (BMIT) and, recently built, Biological X-ray Absorption Spectroscopy (BioXAS) which is currently being commissioned.

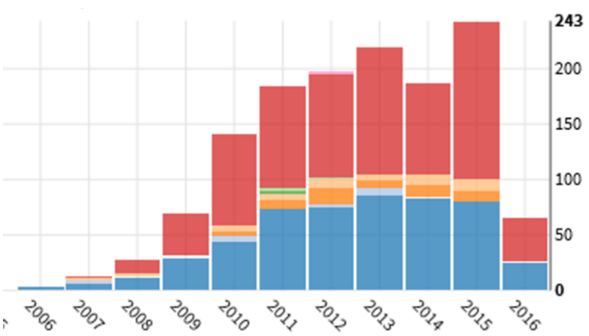

Figure 1. CLS Bio/Life Sciences department activity summary. Number of publications containing data from associated beamlines by year, including: peer-reviewed articles (blue), conference proceedings (light blue), doctoral theses (orange), masters theses (light orange), magazine articles (green), book/chapter sections (light green), PDB depositions (red) and patents (pink).

The sector is well equipped to study biological objects ranging from atomic resolution (CMCF and BioXAS) to cells and tissues (BioXAS and Mid-IR) through to larger samples such as organs, live animals and plants (BMIT). Since 2006, researches acquired data at the Bio/Life Sciences beamlines to produce a total of 516 peer-reviewed articles, 59 doctoral theses and 49 masters theses making use of data acquired at the associated beamlines.

The CMCF is composed of two beamlines (08ID-1 and 08B1-1) and it serves more than 65 Canadian and some international labs. The main techniques available at the CMCF are as follows; high resolution macromolecular X-ray crystallography, Multi/Single wavelength Anomalous Dispersion (MAD/SAD), small molecule crystallography and EXAFS on crystals. Since its inception 10 years ago, 390 peer reviewed papers were published with data collected at the CMCF and more than 720 structures deposited in the PDB. Drug development is an important area of Canadian research and we outline here an example of a successful path from a high-resolution crystal structure to a therapeutic antibody. About 2 in 5 Canadians will develop cancer in their lifetime, and about 1 in 4 Canadians will die of cancer. In 2015, it is estimated that 196,900 Canadians developed cancer, and 78,000 died of cancer. More than half of new cancer cases (51%) are lung cancers. Netrin-1 is a protein involved in neuronal navigation, immune cell migration and cell survival. Its interaction with receptor (UNC5) is responsible for cell proliferation, therefore finding a molecule that would interrupt this interaction would trigger tumor cell death. Using the high-resolution capabilities of the CMCF beamlines at the CLS, a Canadian-European collaboration was able to identify the part of Netrin-1`s structure that actually performs this function [1]. Using this information the researchers were able to design an antibody to target that area of Netrin-1, and showed it triggers death of cancer cells under laboratory conditions. The antibody, now named NP137, is currently in clinical trials.

BMIT is composed of two beamlines (05ID-2 and 05B1-1). The following techniques are available at BMIT; conventional absorption imaging, Diffraction Enhanced Imaging (DEI), K-edge Subtraction (KES), Multiple Image Radiography (MIR) and Phase Contrast Imaging both in planar and Computed Tomography (CT) mode [2]. The research conducted at BMIT over the last 5 years has been described in 68 publications and contributed to 23 theses. Ongoing core research programs include; bone and cartilage growth and deterioration, cardiovascular and lung imaging and disease, human and animal reproduction, cancer imaging and therapy, spinal cord injury and repair, developmental biology, as well as the introduction of new imaging methods. A recent example of work done at BMIT is related to arthritis. Arthritis is the leading cause of long-term disability in Canada, with osteoarthritis being the most common form of the disease. Unfortunately, most cases of osteoarthritis are identified only once the disease is well advanced and irreversible damage has occurred. To better understand the causes of osteoarthritis, investigators introduced a strontium tracer into joints developing osteoarthritis, and spatially mapped the temporal changes in bone, using K-edge subtraction synchrotron micro-CT [3]. 3D imaging indicated clear differences between healthy bone, which showed a uniform distribution of strontium, and subjects developing osteoarthritis, which showed pathological changes occurring in the bone microstructure. In particular, tracer was found beneath the cartilage and at bone margins, which eventually develop into bone spurs and limit normal joint movement. New X-ray optical instrumentation projects are being pursued at the BMIT beamlines to address the needs for various imaging programs, for example, an expander for dynamic real life imaging (Figure 2) [4] which allows the imaging of larger objects using a single frame.

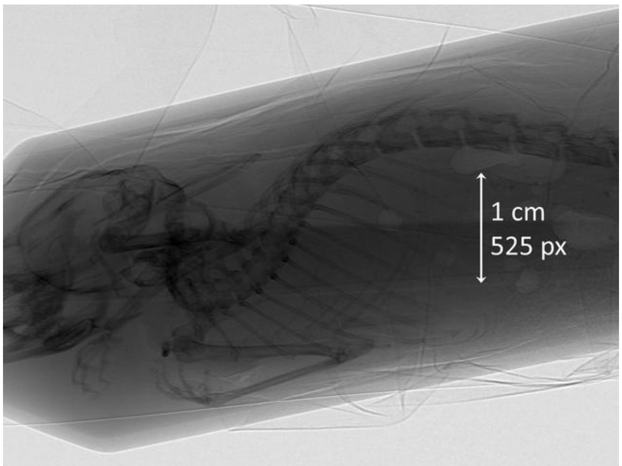

Figure 2. Full field phase image of euthanized mouse.

At the Mid-IR beamline, the following experiments are performed; full field spectromicroscopy at diffraction-limited spatial resolutions (single point mapping and large area mapping utilizing a Focal Plane Array detector), Photoacoustic Spectroscopy, Polarization Modulation IR Spectromicroscopy and Time-Resolved measurements. Since 2006, Mid-IR users have published 68 peer-reviewed articles, while 7 doctoral theses and 8 masters theses were defended using data from the beamline. Mid-IR can be used to obtain biochemical, structural and dynamical information about biological systems. Since normal and cancerous cells differ in their biochemical and/or structural natures, Fourier transform infrared spectroscopy (FTIR) can be utilized to differentiate them. Using this method one can detect chemical changes in the very early stages of cancer, before any morphological changes occur. At the CLS, FTIR was successfully applied to samples from breast and skin cells [5].

BioXAS is composed of 3 beamlines. Two of them are dedicated to X-ray absorption spectroscopy and are being commissioned, while one will be a multi-mode X-ray fluorescence imaging line. Techniques include X-ray Fluorescence (XRF), X-ray Absorption Spectroscopy (XAS) Imaging, multi-mode X-ray fluorescence imaging & micro-XAS. The beamlines are tailored for biological and health-related studies of metals in living systems using X-ray absorption spectroscopy (XAS) and XAS-imaging. These techniques allow determination of molecular form and location of metals in almost any type of material, including purified metal-containing proteins, intact biological tissues and living organisms [6].

Acknowledgments: This work was supported by The Canadian Light Source is supported by the Canada Foundation for Innovation, Natural Sciences and Engineering Research Council of Canada, the University of Saskatchewan, the Government of Saskatchewan, Western Economic Diversification Canada, the National Research Council Canada, and the Canadian Institutes of Health Research.

[1] M. Gradin *et al., Cancer Cell* **29**(2) (2016) 173.
[2] S. Wiebe *et al., Synchrotron Radiation News* **28**(5) (2015) 16.
[3] P. Arash, D. Cooper, M. Doschak, *Journal of Orthopedic Research* **33**(11) (2015) 1655.
[4] M. Martinson *et al., J. Synchr. Rad.* **22** (2015) 1.
[5] H. Ukkonen *et al., Vibr. Spectroscopy* **79** (2015) 24.
[6] M. Korbas *et al., ACS Chem. Biol.* **8** (2013) 22.