1. From the Editors

CICR at the AACR Annual Meeting 2016 (April 16-22, 2016)

In April, cancer research scientists from all over the world attended the AACR (American Association for Cancer Research) Annual Meeting in Philadelphia. The theme for the 2016 meeting was "Delivering Cures Through Cancer Science", reflecting the optimism that cancer science is beginning to deliver effective therapies. CICR hosted a variety of sessions and events at the Annual Meeting. Highlights included three educational sessions on the topic "From Chemistry to the Clinic: Pathways from Drug Discovery and Development", two sessions on "New Drugs on the Horizon", major symposia including "Targeted Covalent Inhibitors in Cancer", CRISPR in Drug Discovery", "Evolution of the Cancer Drug-Resistant State" and several "Meet-the-Expert Session". For full details on CICR-organized events at the AACR Annual Meeting, see here.

At the CICR Town Hall Meeting, the outgoing CICR Steering Committee Chairperson, David E. Uehling (Ontario Institute for Cancer Research, Toronto), gave an overview of CICR activities over the past year. Dr. Uehling also informed that the community had grown by 3% during the past year to now include nearly 2,800 members. 215 Chemistry and 1,032 Experimental Therapeutics abstracts of 6,000 proffered papers were presented, illustrating the increasing impact of CICR science at the AACR meeting. Incoming Chairperson (2016-2017) Dr. Steven K. Davidsen (AbbVie Inc.) thanked Dr. Uehling for his CICR leadership in 2015-2016, presenting him with a plaque to honor his service (*see photo*). He then thanked outgoing Committee Members, Drs. Stephen A. Munk (former CICR Past Chairperson, of Ash Stevens Inc.); Patrick T. Gunning (University of Toronto); Juan I. Luengo (GlaxoSmithKline, retired); Joachim Rudolph (Genentech, Inc.); Danzhou Yang (University of Arizona College of Pharmacy) for their contribution to the CICR leadership. He also welcomed new Chairperson-elect Dr. Melissa M. Vasbinder (Associate Director, Medicinal Chemistry, Ribon Therapeutics, Inc.) and new Steering Committee members, Drs. Christopher J. O'Donnell (Pfizer, Inc.), Angela N. Koehler (Koch Institute of the Massachusetts Institute of Technology), Alan G. Olivero (Genentech, Inc.) and John (Yuan) Wang (H3 Biomedicine, Inc.). He then thanked continuing Steering Committee members, Drs. Paul J. Hergenrother (University of Illinois); Sean M. Kerwin (Texas State University); Michael R. Michaelides (AbbVie Inc.); and Vinod F. Patel (Sanofi).

After presenting CICR working group statistical information, Dr. Davidsen also spoke about the Chemical Probes Initiative (see the CICR Chemical Probes webpage for some relevant information); Drug Discovery in Academia; and how to promote the next generation of chemists in drug discovery – especially in an era where biologics and immunotherapy are gaining momentum. The CICR editorial board welcomes such debate and would like to encourage the CICR members to use the newsletter as a voice for debating such issues.

To view photos from the CICR Town Hall, please see here.

Award for Outstanding Achievement in Chemistry for Cancer Research

Congratulations to James E. Bradner, MD, who is the tenth recipient of the AACR Award for Outstanding Achievement in Chemistry in Cancer Research. During his time at the Dana-Farber Cancer Institute, Bradner worked as a physician-scientist and research team leader in chemical biology. Bradner is recognized for his significant achievements in basic and translational research at the chemical biological interface. Notable discoveries include the development of small molecules to target BET Bromodomains, which are in the late preclinical stage or undergoing Phase I clinical evaluation. Bradner who was recently appointed to President of Novartis Institutes for BioMedical Research (NIBR) in Cambridge, Massachusetts, delivered his award lecture entitled "Chemical Biology of BET Bromodomains" at the AACR Annual Meeting in New Orleans, Louisiana, on April 16, 2016. The CICR award is sponsored by Ash Stevens Inc.

Cancer Metabolism

The remaining part of this spring newsletter is devoted to Cancer Metabolism, Only a few years ago, an issue in *Science* featured a Special Section on metabolism and the introductory article by Dr. L. Bryan Ray which was motivated by Dr Steven McKnight who admonished that “Metabolism is Not Boring” (http://www.ncbi.nlm.nih.gov/pubmed/21127242). Indeed, cancer metabolism was a theme that featured in many workshops and symposia at the AACR meeting in New Orleans and better understanding of its role in cancer resistance mechanisms or ways to exploit metabolism pathways will no doubt improve treatment outcomes. Recent areas of studying metabolism have been supported by cancer researchers in three main streams. First, metabolic enzymes and their functions have been traditionally been the source of interest by academia and industry given their potential for anti-cancer therapeutic developments. A milestone was Gertrude E. Elion’s Nobel Lecture entitled “The Purine Path to Chemotherapy” in 1988, which helped to support metabolic enzymes in purine metabolism for drug discovery exploitation. Over the past decade, the much debated Warburg effect has re-entered the cancer setting with force and unleashed many investigations on cancer-specific roles or modifications on the enzymes in the glycolysis and TCA cycles providing new targets for drug discovery. Second, high-resolution mass spectrometry-aid isotope tracing assays have revolutionized the way we view the metabolic network. The complicated network of metabolism is no longer considered a simple roadmap, but one that includes the added complexity of multidirectional regulation of metabolic fluxes fueling key cellular pathways. Third, a network interaction between metabolic and signaling pathways has attracted molecular biology-oriented cancer researchers into cancer cell metabolism research. This has helped to increase our understanding of the connection between oncogenic signaling and metabolic pathways. Collectively, cancer cell metabolism has emerged as a central theme for biochemistry, bioanalytical chemistry, metabolic engineering, molecular biology and system biology. Scientists with multidisciplinary skills to understand the complexity of cancer metabolism are in increasing demand and Dr Christian Metallo, an Assistant Professor at the University of California, San Diego is this issue’s profile of an Early Career Scientist carving a career in

development and application of tools for metabolomics analysis, thereby contributing to an improved understanding of cancer metabolism.

Editorial co-author: Dr Songon An

2. Selected Research Highlights

Novel personalized pathway-based metabolomics models reveal key metabolic pathways for breast cancer diagnosis. Despite ongoing discovery efforts, blood-based biomarkers for breast cancer remain elusive. Metabolomic studies have suggested a variety of biomarker candidates, however findings are often difficult to replicate. Huang et al. have recently reported a strategy that uses a higher-order functional representation of metabolomics data. This approach extracts pathway-based metabolomics feature that can be used as biomarkers. The computational method assigns personized pathway dysregulation scores for disease diagnosis and was applied to breast cancer. Their results suggest that their all-stage and early-stage diagnostic models were highly accurate in two sets of blood samples with high sensitivity and specificity. The pathway models were further validated by TCGA breast cancer data. Critical pathways metabolic pathways were further elucidated for early breast cancer diagnosis. This study suggests that such an approach may be applied to other omics data types for cancer diagnosis.

Mass Spectrometry-Based Metabolomics Identifies Longitudinal Urinary Metabolite Profiles Predictive of Radiation-Induced Cancer. Exposure to ionizing radiation, a known carcinogen, is a matter of public health importance. Given the long latency period for cancer caused by ionizing radiation, new strategies to monitor disease state over time and detect cancer early are desirable. Cook et al. hypothesized that metabolites in urine would be able to predict malignancy in mice exposed to radiation before the presence of a palpable lesion. In this study, mice were exposed to total body ionizing radiation and urine was collected. Mass spectrometry was used to measure metabolites in the urine. Over the course of a year, the longitudinal studies showed that urinary metabolomic signatures could identify mice with hematopoietic, solid, and benign neoplasms as early as three months following total body ionizing radiation. The different types of malignancies could also be distinguished post-radiation. Furthermore, urinary metabolic profiles for radiation-exposed mice six months post exposure were found to be similar to non-irradiated control mice, suggesting that ionizing radiation accelerates aging. These results suggest that urinary metabolomics profiles may have utility for early diagnosis and treatment of cancer caused by ionizing radiation.

EGFR Signaling Enhances Aerobic Glycolysis in Triple-Negative Breast Cancer Cells to Promote Tumor Growth and Immune Escape. Glycolysis is well known to be aberrant in cancer. Oncogene signaling alters cancer cell metabolism to dysregulate glycolysis in a manner conducive to tumor growth. Lim et al. suggest that the evasion of immunosurveillance by cancer cells and the role of metabolic regulators in T-cells suggest that metabolic reprogramming caused

by oncogenes may be linked to immune escape. In this study, the authors examined the relationship between Epidermal Growth Factor (EGF) signaling in triple negative breast cancer and glycolysis. It was shown that in triple negative breast cancer cells, EGF signaling initiated the first step in glycolysis and impeded the last step, resulting in metabolic intermediates. Lim et al. further demonstrated that one such intermediate, fructose 1, 6 biphosphate binds EGFR and enhanced its activity, resulting in lactate excretion and further inhibition of local T-cell activity. Furthermore, experiments demonstrated that a glycolysis inhibitor combined with an EGFR inhibitor suppressed proliferation and tumor growth in triple negative breast cancer. These results suggest a possible novel strategy for breast cancer treatment.

mTORC1-dependent metabolic reprograming underlies escape from glycolysis addiction in cancer cells. Pusapati *et al.* investigated metabolic differences between cancer cells that are either metabolically glucose-dependent or conditioned to be metabolically glucose-independent. Pusapati et al. found that glucose-independent cells were insensitive to treatment with 2-deoxyglucose, suggesting that these cells use alternative means to overcome this metabolic block. Metabolic flux analysis provided evidence that glucose-independent cells shunt early glycolytic metabolites into the pentose phosphate pathway in the presence of 2-deoxyglucose, but later the intermediates return to glycolysis for ATP and biomass production. This suggests a distinct metabolic pathway which glucose-independent cells use to overcome a block of glycolysis. The authors further identified the regulatory action of mTORC1 pathways on metabolic rewiring observed in glucose-independent cells. Importantly, suppression of glycolysis together with mTORC1 signaling pathways impaired oxidative phosphorylation and biomass productions in glucose-independent cells, resulting in blocking cancer cell growth. This work has demonstrated that cancer cells can rewire their metabolic network to overcome the blockage of glycolysis, providing a potential explanation of why glycolytic inhibitors have not been successful in clinical trials.

Reductive Carboxylation Supports Redox Homeostasis during Anchorage-Independent Growth. Jiang *et al.* have investigated a mechanism of metabolic adaptation during the transition from monolayer culture to anchorage-independent spheroid formation of cancer cells. The scientists behind the study revealed metabolic signatures of spheroids relative to monolayer culture of cancer cells. In spheroids, oxidation of glucose and glutamine was suppressed, whereas reductive formation of citrate from glutamine was enhanced. Cytosolic isocitrate dehydrogenase-1 (IDH1) appeared to regulate the reductive glutamine metabolism, reducing the formation of mitochondrial reactive oxygen species (ROS). Metabolic flux analysis further revealed that isocitrate/citrate formed by reductive carboxylation in the cytosol entered the mitochondria, producing NADPH by mitochondrial IDH2 in spheroids. In turn, the NADPH formed in mitochondria led to suppression of mitochondrial ROS and thus maximized growth of spheroids. Collectively, metabolic adaptation to anchorage independence includes a rewiring of citrate metabolism in which IDH1-dependent reductive carboxylation in the cytosol regulates the levels of ROS in mitochondria for growth in spheroids.

NRF2 regulates serine biosynthesis in non-small cell lung cancer. DeNicola *et al.* has investigated a regulatory mechanism of serine biosynthesis in a large panel of non-small cell lung cancer (NSCLC) cell lines. The authors performed metabolic isotope tracing assays on the panel of NSCLCs along with gene expression profiling. Although the metabolic activity of serine biosynthesis was confirmed to be heterogeneous in NSCLCs, their gene set enrichment analysis revealed that the expression of the transcription factor nuclear factor erythroid-2-related factor 2 (NRF2) was largely correlated with serine biosynthesis. In addition, the expression of the key enzymes in serine biosynthesis was under control of NRF2 in NSCLCs. It appears that NRF2 reprograms serine biosynthesis via Activating Transcription Factor 4 (ATF4) and phosphoglycerate dehydrogenase (PHGDH) to supply the substrates for glutathione and nucleotide production in NSCLCs. Collectively, as the authors mentioned, this approach integrating metabolic tracing and transcriptional profiling assays would be "a powerful tool for determining the mechanisms responsible for the differential regulation of metabolic pathways" in association with genetic alterations in cancers.

A PHGDH inhibitor reveals coordination of serine synthesis and one-carbon unit fate. Serine is a required amino acid in the synthesis of purines, as it serves as a source of one-carbon units carried by tetrahydrofolate in purine biosynthesis. Genetic studies have suggested that targeting synthesis of serine could be a useful approach in cancer therapy. One of the enzymes involved in serine synthesis is 3-phosphoglycerate dehydrogenase (PHGDH), which converts 3-phosphoglycerate to phosphohydroxypyruvate. Based on in vitro and in vivo results, the study indicated that the selective toxicity and tolerability of PHGDH inhibitors may be therapeutically useful.

Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. *MTAP,* which is the gene that encodes methylthioadenosine phosphorylase, is frequently deleted in many cancers because of its proximity to the commonly deleted tumor suppressor gene *CDKN2A*. This study has used short hairpin RNA screening (shRNA) to identify protein arginine methyl transferase 5 (PRMT5) as a protein that is depended upon for survival in MTAP-deleted cells. MTAP degrades methylthioadenosine, which is an inhibitor of PRMT5. Further inhibiting PRMT5 with small molecules, like the orally bioavailable EPZ015666, could be a potential therapeutic strategy to take advantage of this sensitivity to PRMT5 inhibition.

MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. Kyokov et al. discovered that loss of MTAP confers a selective dependence on PRMT5 and its binding partner WDR77. The study reported on increased intracellular concentrations of methylthioadenosine (MTA, the metabolite cleaved by MTAP) in cells harboring MTAP deletions and observations that MTA specifically inhibited PRMT5 enzymatic activity. Administration of either MTA or a small-molecule PRMT5 inhibitor showed a modest preferential impairment of cell viability for MTAP-null cancer cell lines

compared with isogenic MTAP-expressing counterparts, revealing PRMT5 as a potential therapeutic strategy.

4. Profile of a Young Scientist

Employment	
2011–present	Assistant Professor, University of California, San Diego, Department of Bioengineering
2008–2011	Postdoctoral Fellow, Massachusetts Institute of Technology
2003–2008	Graduate Fellow, University of Wisconsin, Madison
2000–2003	Staff Biochemical Engineer, Merck Research Laboratories
Education	
2008	PhD in Chemical Engineering, University of Wisconsin-Madison
2005	MS in Chemical Engineering, University of Wisconsin-Madison
2000	BS in Chemical Engineering, University of Pennsylvania

Dr. Christian Metallo is currently an Assistant Professor at the University of California, San Diego in the Department of Bioengineering. He obtained his BS in Chemical Engineering in 2000 from the University of Pennsylvania. Following his undergraduate studies, he worked as a Staff Biochemical Engineer at Merck Research Laboratories. From there he went on to obtain his MS and PhD at the University of Wisconsin-Madison in Chemical Engineering. His graduate work with Sean Palecek and Juan de Pablo

focused on directed differentiation of human pluripotent stem cells to epithelial lineages. Dr. Metallo was an American Cancer Society postdoctoral fellow at Massachusetts Institute of Technology in Chemical Engineering in the lab of Greg Stephanopoulos where he explored how hypoxia and oncogenes/tumor suppressors regulate oxidative and reductive tricarboxylic acid (TCA) metabolism.

Dr. Metallo's current research is focused on developing and applying tools for metabolomics analysis to better understand cancer biology. His group is focused on the role of oncogenes, tumor suppressors, and hypoxia in controlling metabolic processes. His lab uses their expertise in cancer metabolism and metabolic flux analysis - combining isotope tracers and mass spectrometry - to study cancer cell systems. They are interested in understanding how oncogenes and tumor suppressors reprogram carbohydrate, amino acid, and lipid metabolism to support tumor growth and survival. In recent work, Dr. Metallo's group has identified metabolic deficiencies of cancer cells expressing IDH1, which makes them sensitive to inhibitors of mitochondrial metabolism. They have also developed new tools to study redox metabolism within specific cellular compartments. He has published 39 manuscripts and won numerous awards, including a NSF CAREER Award, a Searle Scholar Award, a Hellman Faculty Fellowship, and the Rita Schaffer Young Investigator Award. His research is supported by federal, state, and industry sources that include the National Institutes of Health, the California Institute for Regenerative Medicine, and the National Science Foundation.

5. Spotlight on World News

Zymeworks Inc. and GlaxoSmithKline have established a new licensing agreement on Azymetric drug discovery platform technology. Zymeworks Inc. and GlaxoSmithKline (GSK) have established a new licensing agreement for the R&D and commercialization of novel bi-specific antibodies designed using Zymeworks' Azymetric drug discovery platform. The agreement means that GSK will have an option to develop and commercialize multiple bi-specific drugs across a variety of disease areas including cancer. The Azymetric antibody ZW25 and the Azymetric antibody-drug conjugate ZW33 is expected to enter into human clinical trials later this year. In part to enable this, GSK will make upfront and preclinical payments to Zymeworks of up to $36 million, with the potential for up to $152 million in development and clinical milestone payments and commercial sales milestone payments of up to $720 million. Zymeworks is also eligible to receive tiered royalties on potential sales. For more details

MedImmune and Regeneron have established a new licensing agreement on pyrrolobenzodiazepine (PBD)-based warhead and linker technology to produce antibody-drug conjugates MedImmune, the global biologics research and development arm of AstraZeneca, and Regeneron Pharmaceuticals Inc. have announced a new licensing agreement under which the latter will apply MedImmune's pyrrolobenzodiazepine (PBD)-based warhead and linker

technology to produce antibody-drug conjugates (ADCs) as potential cancer treatments. Although details were disclosed about this agreement, it is expected that Regeneron will gain exclusive rights to use MedImmune's proprietary PBD technology to develop ADCs against several cancer targets and pay MedImmune an upfront payment, development and commercial milestone payments, as well as single-digit royalties on net sales of such products.

Blueprint Medicines Corp. has set up a deal with Roche regarding kinase-targeting small-molecules with potential in immunotherapy. Blueprint Medicines Corp. has set up a deal with Roche for the discovery, development and commercialization of up to five small-molecule therapeutics targeting kinases that are believed to be important in cancer immunotherapy. The upfront cash payment is $45 million but could accumulate to $965 million in option fees and milestone payments, for a total of more than $1 billion if all goes according to its hopes and plans. As for what will net Blueprint the bulk of the cash, the $965 million in contingent option fees and milestone payments are related to specified research, preclinical, clinical, regulatory and sales-based milestones across all five potential programs. Blueprint and Roche hope to modulate the tumor immune response by targeting immunokinases with small molecules, enabling an improvement in response rates and broaden the utility of using cancer immunotherapies to treat various cancer types.

6. Career Forum

   https://cancercareers.org/Pages/default.aspx

   http://www.nature.com/naturejobs/science/jobs

   http://jobs.rsc.org/

   http://chemistryjobs.acs.org/

7. Conferences

   High Throughput Chemistry & Chemical Biology
   June 14-19, 2016. Colby-Sawyer College, New London, NH, USA

   National Medicinal Chemistry Symposium
   June 26-29, 2016, Chicago, IL

   Chemical Biology in Drug Discovery
   June 16-17, 2016. Weston Boston Waterfront, Boston, MA, USA

   National Medicinal Chemistry Symposium
   June 26-29, 2016. Chicago, IL, USA

   Fifth JCA-AACR Special Joint Conference on the Latest Advances in Hematological Cancer Research: From Basic Science to Therapeutics

July 13 - 15, 2016. Urayasu, Japan

EFMC-ISMC 2016: XXIV EFMC International Symposium on Medicinal Chemistry
August 28 - Sept 1, 2016. Manchester, UK

EMBO Chemical Biology conference
August 31-Sept 3, 2016. EMBL Heidelberg, Germany

EORTC-NCI-EMA-AACR International Conference on Innovation and Biomarkers in Cancer Drug Development
September 8 - 9, 2016. Brussels, Belgium

Second CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival
September 25 - 28, 2016. New York, New York

DNA Repair: Tumor Development and Therapeutic Response
November 2 - 5, 2016. Montreal, Quebec, Canada

EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium
November 29 - December 2, 2016. Munich, Germany

8. Other