

CICR Newsletter Template

1. From the Editors

Happy New Year! We hope all our members have had a good start in 2014. Here at CICR we welcome five new editorial board (EB) members: Songon An (University of Maryland), Sharon Pitteri (Stanford University), Jonel Saludes (Washington State University), Basar Bilgicer (University of Notre Dame), and Christopher Van (University of Massachusetts). They will join the EB in bringing you CICR news over the next 2 years, click [here](#) to learn more and access the CICR newsletter archive.

Cancer drug discovery is becoming more and more multidisciplinary and the upcoming annual AACR meeting in San Diego (5-9 April) highlights a plethora of different strategies that are being used in combating cancer. In many of the [plenary sessions](#), [major symposia](#) and forums, bioinformatics and the many "omics" fields are playing key roles in the unravelling of new targets and in the interaction of chemical probes and therapeutics in perturbing biological pathways. In this newsletter, we have decided to feature recent research highlights in bioinformatics, proteomics and metabolomics. The latter is one of the emerging "omics" fields that have the potential to depict both the steady-state physiological state of a cell or organism and their dynamic responses to genetic or small molecule modulations. Our profile of a young scientist making a career in this field is Dr. Chi Chen, who is currently an Assistant Professor of Nutritional Metabolomics at the University of Minnesota.

Be sure to view the CICR [webpage](#) to view a list of chemistry-related sessions to be held at the Annual Meeting, including the marquis [New Drugs on the Horizon](#) sessions, and we hope to see you at the [Town Hall](#).

2. Selected Research Highlights

[A Metabolomics Investigation of Non-genotoxic Carcinogenicity in the Rat](#)

Dr. Julian L. Griffin's group at University of Cambridge in collaboration with Syngenta used metabolomics and lipidomics approaches in combination with pathology and clinical chemistry to profile perturbations produced by ten compounds that represent a range of rat non-genotoxic hepatocarcinogens (NGCs). The authors find that changes in liver metabolite concentration differentiate the treated groups across different time points and good predictions could be made when differentiating NGCs from non-NGCs. Among the discriminatory metabolites, they identified free fatty acids, phospholipids, and triacylglycerols, as well as precursors of eicosanoids and the products of reactive oxygen species linked to processes of inflammation, proliferation, and oxidative stress. Their findings indicate that metabolic profiling might be able to identify changes due to the pharmacological mode of action of xenobiotics and contribute to early screening for non-genotoxic potential.

Proteogenomic Analysis of Human Chromosome 9-Encoded Genes identified 15 lung cancer-selective proteins

The Chromosome-centric Human Proteome Project (C-HPP) was recently initiated as an international collaborative effort. Dr. Je-Yoel Cho's group at Seoul National University and collaborators performed a bioinformatics and proteogenomic analysis to catalog Chr 9-encoded proteins from normal tissues, lung cancer cell lines, and lung cancer tissues. In their recent publication, they report the identification of approximately 28% of newly-detected missing proteins (46 of 162) on Chr 9. They also report that 15 proteins from Chr 9 such as prostaglandin reductase 1, perilipin-2, sialic acid synthase, and dipeptidyl peptidase 2 were detected only in lung cancer tissues. In addition, they conducted a proteogenomic analysis to discover Chr 9-residing single nucleotide polymorphisms (SNP) and mutations, and identified 21 SNPs and four mutations containing peptides on Chr 9 from normal human cells/tissues and lung cancer cell lines, respectively.

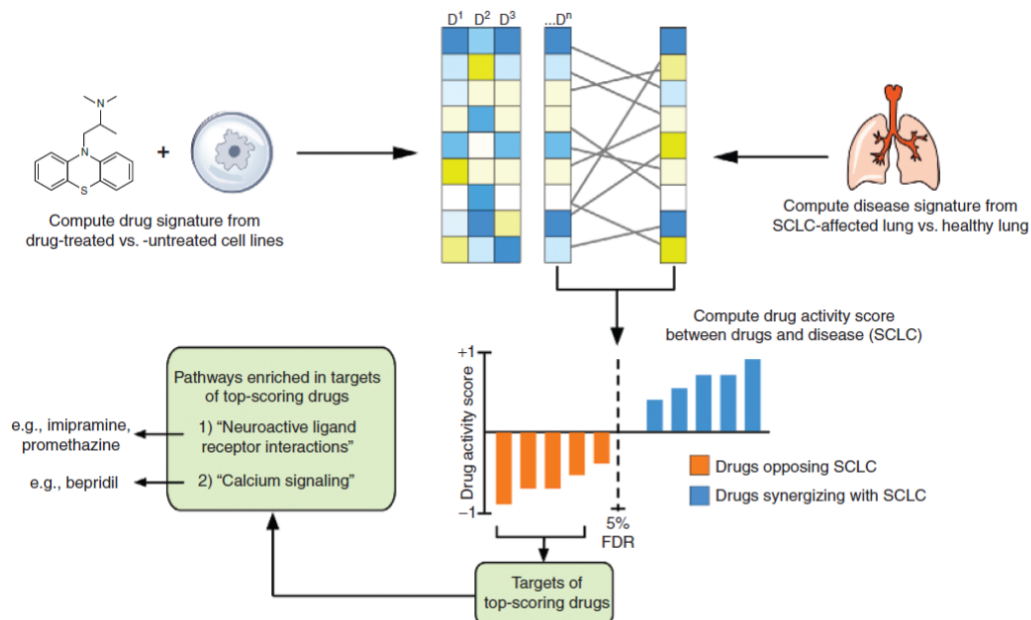
Casting doubt on the traditional approach of cancer biomarker discovery through proteomics

Recently, Dr. Tadashi Kondo at the National Cancer Center Research Institute of Japan published an editorial on Expert Review of Proteomics. Dr. Kondo commented that although the discovery of novel biomarkers at the dawn of proteomics was a promising development, only a few identified biomarkers seemed to be beneficial for cancer patients. The study of biomarkers is essentially a study of diseases and the biochemistry relating to peptide, protein, and post-translational modifications is only a tool. Therefore, a problem-oriented approach should be used in biomarker development. Clinician participation in the study of biomarkers would lead to realistic, practical, and interesting biomarker candidates, which justify the time and expense involved in validation studies.

Bioinformatics-based drug repositioning identified tricyclic antidepressants as inhibitors of small cell lung cancer and other neuroendocrine tumors

The repositioning of drugs already approved for human use mitigates the costs and risks associated with early stages of drug development, and offers shorter routes to approval for therapeutic indications. Recently, Drs. Sage's and Butte's groups at Stanford University reported their findings that tricyclic antidepressants have the potential to be developed as chemotherapeutic agents for small cell lung cancer (SCLC) and other neuroendocrine tumors. They used a bioinformatics approach that evaluated the therapeutic potential of FDA-approved drugs for a given disease by comparing gene expression profiles in response to these drugs in multiple cell types across multiple diseases. Neuroactive ligand-receptor interaction and calcium signaling pathways were significantly enriched among top-scoring SCLC-repositioning hits. They then selected an initial group of six drugs from these two modules for experimental validation, namely, imipramine, clomipramine, promethazine, tranylcypromine, pargyline, and bepridil. These drugs potently induced apoptosis in both chemo-naïve and chemo-resistant SCLC cells. Particularly, imipramine,

promethazine, and bepridil were efficacious against SCLC allograft and xenograft in mouse models, and endogenous tumors from a mouse model of human SCLC. Their study identified novel targeted strategies that could be rapidly evaluated in patients with neuroendocrine tumors.



Reprinted by permission from the American Association for Cancer Research: Jahchan, N.S., A Drug Repositioning Approach Identifies Tricyclic Antidepressants as Inhibitors of Small Cell Lung Cancer and Other Neuroendocrine Tumors, *Cancer Discov.* 2013 Dec;3(12):1364-77. doi: 10.1158/2159-8290.CD-13-0183.

TRAIL-coated leukocytes that kill cancer cells in the circulation. This study conducted by Mitchell et al. at Cornell University demonstrates a novel approach to target and induce apoptosis in colon and prostate cancer cells in blood circulation by using liposomes to present TRAIL and E-selectin adhesion receptor on the surface of leukocytes. The *in vitro* and *in vivo* results demonstrate the therapeutic potential of this approach as a way to neutralize circulating tumor cells in metastatic cancers.

Layer-by-Layer Nanoparticles for Systemic Codelivery of an Anticancer Drug and siRNA for Potential Triple-Negative Breast Cancer Treatment

Researchers at the Massachusetts Institute of Technology have developed a single nanoparticle platform to codeliver siRNA and a chemotherapeutic agent for breast cancer therapy. Layer-by-layer films were formed on nanoparticles by alternately depositing siRNA and poly-L-arginine to load up to 3500 siRNA molecules per bilayer. Studies *in vivo* demonstrated that an siRNA-loaded film atop doxorubicin-loaded liposomes effectively decreased tumor volume ~8-fold compared to control treatments, with no observed toxicity.

ERK1/2 Blockade Prevents Epithelial-Mesenchymal Transition in Lung Cancer Cells and Promotes Their Sensitivity to EGFR Inhibition

Recent work from the lab of Matthew J. Lazzara at the University of Pennsylvania demonstrates the ability of chronic MEK inhibition to prevent and reverse epithelial-mesenchymal transition (EMT) in non-small cell lung cancer (NSCLC) cells. Chronic exposure of NSCLC cells to MEK kinase inhibitors also reduced cellular migration speeds and promoted cellular response to EGFR kinase inhibitors, but those effects were only observed after MEK had been inhibited sufficiently long enough to observe changes in epithelial and mesenchymal marker expressions. Interestingly, chronic MEK inhibition also promoted response to EGFR inhibitors in NSCLC cells with acquired resistance to EGFR inhibitors. These results suggest that novel approaches for scheduling MEK and EGFR inhibitors in the clinic, such that an epithelial phenotype is promoted in tumor cells prior to administration of EGFR inhibitors, could help to improve tumor response and patient outcomes.

Crystal Structure of TET2-DNA Complex: Insight into TET-Mediated 5mC Oxidation

TET (ten-eleven translocation) enzymes are a recently discovered family of enzymes responsible for cytosine demethylation and regulation of gene expression, development, and inheritance of epigenetic marks. Loss of TET activity is a characteristic feature of human myeloid leukemias and melanomas. In a recent Cell paper, Hu et al. have generated the first crystal structure of a TET2-DNA complex. The amino acids involved in substrate binding, metal ion chelation, and catalysis are highly conserved and are mutated in patient-derived samples, providing a mechanistic basis for disease onset. Importantly, the structure identifies how TET2 mediates sequential oxidation of 5mC to demethylated cytosine. This study provides key structural information for rational drug design to modulate the activity of TET family enzymes.

Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity

A major source of DNA damage is ribonucleotide misincorporation during DNA replication. Incomplete repair of these errors results in adenylated DNA and single-strand breaks causing genomic instability, a hallmark of cancer. Aprataxin deadenylase (APTX) removes adenylation lesions and loss of APTX is implicated in the neurodegenerative disorder Ataxia oculomotor apraxia (AOA1). Tumbale, Williams, and Schellenberg et al. used a combination of *in vitro* and *in vivo* data to link APTX function with ribonucleotide excision repair to prevent cell cycle arrest and promote growth. Furthermore, by generating X-ray crystal structures of APTX bound to an RNA-DNA substrate, a transition-state analog, or a product, they identified the two-step reaction mechanism of the deadenylation catalytic reaction. These results suggest that heritable loss-of-function mutations in APTX lead to AOA1 through accumulation of DNA damage from RNA misincorporation.

Genome-wide localization of small molecules

Anders et al. developed a novel technique called Chem-seq to identify genome-wide interactions of therapeutic

small molecule ligands. Adapting the principle of chromatin immunoprecipitation and DNA sequencing (ChIP-seq), they attached a biotin moiety to a compound of interest and isolated bound chromatin fragments using streptavidin-coated beads. As proof of principle, genomic loci bound by a biotinylated JQ1 bromodomain inhibitor aligned almost perfectly with ChIP-seq data from the targeted BET bromodomain enzymes. Additionally, biotinylation had no effect on JQ1 growth inhibition of multiple myeloma cell lines. This technique was also applied to AT5719, a Cdk9 cyclin dependent kinase inhibitor, and psoralen, a DNA crosslinking agent. Chem-seq is a valuable tool that will facilitate discovery of *in vivo* mechanisms of action of potential drug candidates as well as their specificities throughout the human genome.

Reaction-based Fluorescent Sensor for Investigating Mobile Zn²⁺ in Mitochondria of Healthy Versus Cancerous Prostate Cells The loosely bound (mobile) form of Zn(II) accumulates in the mitochondrion and plays an important physiological role, especially in the prostate. The study conducted by Chyan et al. at the Massachusetts Institute of Technology describes the development of a mitochondria-localized fluorescent probe selective for mobile Zn(II). The fluorescein-derived probe, called DA-ZP1-TPP, is rendered non-fluorescent through acetylation of the phenolic oxygen atoms of the xanthene ring but is activated by Zn(II) coordination-promoted ester hydrolysis. Tumorigenic (RWPE-2) and metastatic (PC-3) prostate cells lose the ability to sequester Zn(II) compared to normal epithelial cells (RWPE-1), demonstrating the inability of malignant prostate cells to accumulate mobile Zn(II) in their mitochondria. This finding is consistent with the notion that tumors need an active mitochondrial aconitase to support the high-energy demands of rapidly dividing cells.

Improved Quenched Fluorescent Probe for Imaging of Cysteine Cathepsin Activity Researchers at the Stanford School of Medicine developed a novel class of cysteine cathepsin quenched fluorescent activity-based probes (qABP). The researchers enhanced the imaging properties of this new class of qABPs by introducing an additional electron-withdrawing amide functionality at the *para*-position of the 2,3,5,6-tetrafluorophenoxy methyl ketone (PMK) electrophile to increase reactivity and broader selectivity to cathepsin targets. Furthermore, the authors improved the qABPs biodistribution by introducing a sulfonated quencher to increase hydrophilicity and by shortening the length of the spacer to decrease lipophilicity. The study demonstrated that this new class qABPs has overall improvement in *in vivo* tumor imaging properties compared to those of existing qABPs.

Discovery of PTPRJ Agonist Peptides That Effectively Inhibit in Vitro Cancer Cell Proliferation and Tube Formation PTPRJ is a ubiquitous receptor-type protein tyrosine phosphatase involved in various cellular processes and oncogenic transformation. Ortuso et al. carried out SAR studies and generated a panel of peptides based on their previously reported PTPRJ agonist peptide, PTPRJ-pep19, by alanine scan analysis. The study demonstrated that a cyclic

structure is a requirement for biological activity and the substitution of 4Asn with Ala dramatically improved the antiproliferative activity and *in vitro* tube formation against MCF-7 and SKBr3 breast cancer cells, while it showed no effect on HMEC, indicating non-toxicity to normal cells. Solution phase NMR experiments and Monte Carlo calculations of the lead peptide, PTPRJ-pep19.4 showed a β -turn structure and a propensity for dimerization. This work contributes to significant advancements in the SAR knowledge of the PTPRJ agonist peptide class.

Integrative radiogenomic profiling of squamous cell lung cancer Radiation therapy is a commonly used method to kill cancer cells. The relationship between the radiation sensitivity of cancer cells and genomic characteristics is poorly understood. Abazeed et al. used a novel high throughput platform to measure radiation survival *in vitro*, and the results were correlated with genomic parameters from squamous cell lung cancer cell lines. Biological pathways that correlated with radiation sensitivity were identified. This study demonstrates a strategy for correlating radiation response and genomic alterations.

Covalent inhibitors against the traditionally “undruggable” K-Ras protein K-Ras has long been one of the major anti-cancer targets considered undruggable, until recently. Researchers report now two small molecules that irreversibly inhibit the K-Ras protein by targeting its specific G12C mutation. These small molecules block the oncogenic residue Cys12 on the K-Ras protein by covalently attaching to it. At the same time, two spatially different sites on the K-Ras protein are targeted. Collectively, these two studies appear to provide exciting starting points in the war against K-Ras cancers:

Therapeutic targeting of oncogenic K-Ras by a covalent catalytic site inhibitor (Study 1)

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions (Study 2)

4. Profile of a Young Scientist

	Employment	
	2008-present	Assistant Professor, Department of Food Science and Nutrition, University of Minnesota, Twin Cities
	2005-2008	Visiting Fellow, Laboratory of Metabolism, National

	Education	Cancer Institute, NIH
	2004	Ph.D. in Pharmaceutical Science, Rutgers, the State Univ. of New Jersey
	1998	M.S. in Pharmacognosy, West China Univ. of Medical Sciences
	1993	B.S. in Pharmacy, China Pharmaceutical University

Chi Chen is currently an Assistant Professor of Nutritional metabolomics at the Department of Food Science and Nutrition, University of Minnesota at Twin Cities. His Ph.D. dissertation research on transcriptional factor Nrf2 and chemopreventive phytochemicals was advised by Dr. Ah-Ng Tony Kong at Rutgers. Following his interest in metabolism, he conducted his postdoctoral research in metabolomics and chemical toxicology under the supervision of Dr. Frank Gonzalez at NCI, NIH. In 2008, he took his current position as a tenure-track faculty at the University of Minnesota with both research and teaching responsibilities.

Chi's main research interest is on the identification of novel metabolic changes induced by dietary, chemical, microbial, and pathophysiological challenges and the characterization of underlying biochemical mechanisms. His research combines mass spectrometry-based untargeted metabolomics and targeted metabolite analysis, stable isotope tracing, *in vitro* biochemical analysis, and animal models. He also collaborates with clinical faculty to study the metabolic events in human intervention treatment. Untargeted global metabolite profiling and targeted metabolite analysis in his lab cover both endogenous metabolites (lipids, amino acids, organic acids, aldehydes, ketones, and microbial metabolites) and exogenous metabolites (phytochemicals, pharmaceuticals, carcinogens, and their metabolites) in biofluids, wastes, tissue and cell extracts. Using metabolomics as a discovery tool, his research studies have generated new insights on ethanol metabolism, cocaine- and acetaminophen-induced hepatotoxicity, fecal microbiota transplantation, metabolic effects of consuming oxidized lipids, and biotransformation of carcinogen and therapeutic agents. Recently, he has started to investigate prostate carcinogenesis by integrating

proteomics, transcriptomics, and metabolomics. Prof Chi's research is in part funded by NIH, USDA, and industrial collaborators.

5. Spotlight on World News

[Juno Therapeutics received \\$120 million in early funding to develop cancer drugs](#) - the largest such early financing deal in biotech history. Juno Therapeutics has secured \$120 million in its first-round bid for venture capital to support the development of cancer drugs using an innovative immunotherapy platform. This is the largest such early financing deal in biotech history, which was granted without milestones. The company reprograms T cells from people with cancer to recognize molecules expressed on the surface of cancer cells. The goal is that when these cells are reintroduced into the patient, they will identify malignant cells and destroy them. Source: Drug Discovery @ Nature.com

[A snapshot of the UK academic drug discovery efforts in 2013](#) Pharmaceutical companies have moved away from conducting early-stage preclinical research in-house in recent years, and are instead partnering with academic institutions to pursue programmes around emerging targets. Simultaneously, various funding organizations have invested in building drug-discovery capabilities in academic institutions. A study of UK institutions focusing on drug discovery showed that in the UK there is a need for developing multidisciplinary centers with capabilities equivalent to those found in small biotechnology companies, achieving sustainable funding, and coordinating sharing of skills and capabilities among UK academic groups to address the multidisciplinary requirements and high cost of drug discovery. Source: Drug Discovery @ Nature.com

[Genentech's glyco-engineered antibody to succeed Rituxan](#) Obinutuzumab, a glyco-engineered antibody developed as a successor to the blockbuster rituximab, has received FDA approval for chronic lymphocytic leukemia. It is the first such antibody to reach Western markets, and the first candidate to gain approval under the FDA's breakthrough therapy pathway. Source: Drug Discovery @ Nature.com

[Roche allies with Molecular Partners against cancer](#) Roche and fellow Swiss company Molecular Partners AG were brought together in a research collaboration and licensing agreement to discover, develop, and commercialize several proprietary therapeutics incorporating Molecular Partners' DARPin biologics conjugated to toxic agents developed at Roche for the treatment of cancer. The conjugates aren't the antibody-drug conjugates (ADCs) that have made the news so often—instead of antibodies, the partners are engineering small proteins to carry out the work of delivering therapeutics where they are needed. Source: Drug Discovery News

6. Career Forum

[Scientist, Clinical Immunology \(Amgen\)](#)

[Institutional Head & Neck/Colon Rector Cancer Tumor Specialist \(Bristol-Myers Squibb\)](#)

[Postdoctoral Fellow, T-Cell Therapy \(Fred Hutchinson Cancer Center\)](#)

[Senior Scientist Immuno-Oncology; in Vivo Pharmacology \(Genentech\)](#)

[Institute Research Scientist Medicinal Chemistry \(MD Anderson Cancer Center\)](#)

More jobs in:

[Cancercareers.org](#)

[Nature](#)

[The Royal Society of Chemistry](#)

7. Conferences

[**AACR Annual Meeting 2014**](#)

April 5-9, 2014, San Diego, California

[**Chemistry and Biology of Peptides**](#)

February 23-28, 2014. Ventura, CA

[**RAS Oncogenes: From Biology to Therapy**](#)

February 24-27, 2014 • Lake Buena Vista, FL

[**Maintenance of Genome Stability**](#)

March 3-6, 2014 St. Kitts

[**DNA Damage, Mutation, and Cancer**](#)

March 16-21. Ventura, CA, USA

[**9th European Breast Cancer Conference \(EBCC-9\)**](#)

19-21 March 2014, Glasgow, UK

[**G Protein-Coupled Receptors: Structural Dynamics and Functional Implications**](#) March 30-April 4, 2014. Snowbird, UT

[**Epigenetic Programming and Inheritance**](#)

April 6-10, 2014. Boston, MA, USA

Drug Discovery Chemistry

April 23-24, 2014. San Diego, CA, USA

Chromatin: From nucleosomes to chromosomes

April 30-May 2, 2014. Cambridge, UK

Exosomes and Microvesicles

April 30-May 3, 2014. Rotterdam, The Netherlands

Crossing Boundaries: Linking Metabolism to Epigenetics

May 1-2, 2014. Cambridge, MA, USA

<http://www.gtcbio.com/conference/cancer-drug-research-development-overview> May 6-7, 2014. Berlin, Germany

Accelerating Anticancer Agent Development and Validation Workshop

May 7-9, 2014 • Bethesda, MD

Peptide Therapeutics

May 8-9, 2014. Boston, MA

Oligonucleotide and Peptide Therapeutics

May 12-15, 2014. Providence, RI

Chromatin Structure and Function

June 8-13, 2014. Waltham, MA, USA

AACR Precision Medicine Series

Drug Sensitivity and Resistance: Improving Cancer Therapy

June 18-21, 2014 • Orlando, FL

Genomic Instability

July 6-11, 2014. Hong Kong, China

Mechanisms and Models of Cancer

August 19-23, 2014. Cold Spring Harbor, NY, USA

Epigenetics and Chromatin

September 9-13, 2014. Cold Spring Harbor, NY, USA

Targeting PI3K-mTOR Networks in Cancer

September 14-17, 2014 • Philadelphia, PA

2014 World Molecular Imaging Congress

Sept 17-20, 2014. Seoul, Korea

Global Cancer Summit

September 16-18, 2014. Hyderabad, India

Advances in Melanoma: From Biology to Therapy

September 20–23, 2014 • Philadelphia, PA

EORTC-NCI-AACR International Symposium on Molecular Targets and Cancer Therapeutics

November 18-21, 2014 • Barcelona, Spain

Tumor Immunology

December 1-4, 2014 • Orlando, FL

World Cancer Congress

December 3-6, 2014. Melbourne, Australia