

1. From the Editors

CICR at the AACR Annual Meeting 2014 (5-9 April)

In early April over 18,000 people attended the AACR (American Association for Cancer Research) Annual Meeting in San Diego. This meeting is the premier cancer research event drawing together scientists engaged in basic and translational research, patient advocates, clinicians and other professionals. The theme for the 2014 meeting was, “Harnessing Breakthroughs – Targeting Cures”, reflecting a bold statement rooted in the increasing progress made in translating basic science into clinical advancement. This progress is of course vital for designing and developing better drugs to treat cancer patients. The CICR working group was instrumental in bringing new drug discovery initiatives to the forefront of the 2014 AACR meeting, which included high-profile speakers from both academia and industry. Topics included sessions on (i) Applications of Nanotechnology for Cancer Diagnosis, Treatment, and Prevention, (ii) New Drugs on the Horizon, (iii) Pathways for Drug Discovery and Development, (iv) New Approaches for Accessing Chemical Diversity and (v) Chemical Genetics and Biology. [See here for full overview of CICR-organized sessions.](#)

During CICR Town Hall Meeting departing Chairperson Michael J. Luzzio (Novartis) of the Senior CICR committee gave a detailed overview of the present status and future directions of how to shape the research interests of the chemical community while also providing an account of who makes up the current CICR community. Dr Luzzio also provided a warm welcome to new Chairperson Stephen A. Munk (Ash Stevens Inc.) and Chairperson-Elect Dr David E. Uehling (Ontario Institute for Cancer Research, Toronto) for 2015/16. The Town Hall meeting was well attended and included Dr. Mansukh C. Wani, co-discoverer of paclitaxel, pictured right with CICR newsletter editor Klaus Pors.



Award for Outstanding Achievement in Chemistry for Cancer Research



Congratulations to Professor Dale Boger from Scripps Institute, San Diego who is the eighth recipient of the AACR Award for Outstanding Achievement in Chemistry in Cancer Research for his pioneering work in the discovery of natural product chemistry, especially for his mechanistic explorations of the ultrapotent duocarmycins, now a subject for clinical development of antibody-directed conjugates. Prof. Boger gave a fascinating lecture entitled ***Uniquely Effective Synthetic Analogs of the Complex Antitumor Natural Products Vinblastine and the Duocarmycins*** at the AACR Annual Meeting 2014, which was well received at the award ceremony.

2. Selected Research Highlights

Enhancement of cancer therapy efficacy by trastuzumab-conjugated and pH-sensitive nanocapsules with the simultaneous encapsulation of hydrophilic and hydrophobic compounds

<http://www.ncbi.nlm.nih.gov/pubmed/23891983>

Recently, San-Yuan Chen's research group has developed a nanoparticle platform for a dual drug delivery approach in cancer therapy. Double emulsion nanocapsules (DENCs) were used to encapsulate hydrophilic doxorubicin and hydrophobic paclitaxel simultaneously and were designed to selectively release the sequestered drug in acidic environments, while remaining stable at neutral pH. Additionally, the nanoparticles were surface modified with Trastuzumab to target HER2 overexpressing breast cancer cells, demonstrating selectivity towards HER2-positive SK-BR-3 over MD-MB-231 cells. *In vivo*, the targeted, dual-drug loaded nanoparticles showed superior anti-tumor efficacy over non-targeted and free drug groups, making this combination treatment a powerful tool for cancer therapy.

Chiang et al., Nanomedicine:NBM, 2014, 10, 99-107.

Co-delivery of Cisplatin and Rapamycin for Enhanced Anticancer Therapy through Synergistic Effects and Microenvironment Modulation

<http://pubs.acs.org/doi/abs/10.1021/nn5010815>

Researchers at the University of North Carolina have developed a novel method

to coencapsulate cisplatin and rapamycin into poly(lactic-co-glycolic acid) (PLGA) micelles in order to exploit their synergistic effects and enhance their therapeutic efficacy. These nanoparticles (NPs) demonstrated a sustained drug release, improved cytotoxicity against melanoma cells in vitro, and significantly inhibited tumor growth in vivo. Furthermore, NPs significantly reduced the number of tumor-associated fibroblasts and collagen levels and normalized tumor blood vessels which significantly enhanced NP penetration into xenograft tumors.

Guo. et al., ACS Nano, 2014, 8 (5), 4996–5009.

Targeting MLL1 H3K4 Methyltransferase Activity in Mixed-Lineage Leukemia

<http://www.ncbi.nlm.nih.gov/pubmed/24389101>

MLL1 is a member of the mixed-lineage leukemia (MLL) family of histone methyltransferases and catalyzes Histone H3K4 methylation to facilitate transcription initiation. Chromosomal translocation of MLL1 can create oncogenic fusions that lead to AML or ALL, and duplication and amplification of MLL1 are also implicated in MLL. MLL1 activity is regulated through complex formation with genes WDR5, ASH2L, and RbBP5. Cao et al. have developed a noncompetitive small molecule inhibitor of MLL1 activity, MM-401, that binds to WDR5 and prevents complex formation. Importantly, MM-401 is specific for MLL1 and does not inhibit other MLL methyltransferases, due to the unique dependence of MLL1 on WDR5 for its activity. In vivo, MM-401 specifically reduced levels of H3K4 di- and tri-methylation and reduced expression of MLL1-regulated genes to levels similar to MLL1 knockout cells. Importantly, MM-401 caused growth inhibition, apoptosis, and differentiation in both mouse and human cell lines containing MLL1 translocations. The specificity and efficacy of this MLL1 inhibitor is extremely promising for treatment of this molecular subtype of leukemia and potentially other diseases.

Cao et al., Mol Cell. 2014, 53 (2), 247-261.

Automethylation activities within the mixed lineage leukemia-1 (MLL1) core complex reveal evidence supporting a "two-active site" model for multiple histone H3 lysine 4 methylation

<http://www.ncbi.nlm.nih.gov/pubmed/24235145>

MLL1 contains a SET domain that catalyzes monomethylation of H3K4. While it is known that WDR5, RbBP5, and ASH2L are needed for di- and tri-methylation activity, the mechanism of this monomethylation reaction has been debated. Patel et al. examine the reaction kinetics of MLL1 activity by itself or complexed with WDR5, RbBP5, and ASH2L and demonstrate that MLL1 operates through a "two-active site" model. Monomethylation is mediated by the MLL1 SET domain, followed by dissociation of the H3 tail and rebinding to a novel reaction surface comprised of MLL1 and the other complex members, which catalyzes di- and tri-methylation. Additionally, the authors identify a highly conserved automethylation reaction in MLL1, which may have roles in its regulation or localization.

Patel et al., *J Biol Chem.* 2014. 289 (2), 868-884.

Defining the Oligomerization State of γ -Synuclein in Solution and in Cells

<http://www.ncbi.nlm.nih.gov/pubmed/24367999>

γ -Synuclein, also called breast cancer-specific gene product 1, is highly expressed in human-infiltrating breast carcinoma and thought to be unfolded in its native state; the protein forms oligomers of varying sizes, but does not readily form fibrils. The exact biological function of γ -Synuclein is unknown, although it is co-expressed with phospholipase C β (PLC β 2) that hydrolyzes phosphatidylinositol 4,5-bisphosphate in invasive breast cancer, suggesting their complementary role in increased cell migration and proliferation. Golebiewska and co-workers from Stony Brook University investigated the oligomerization propensity of γ -synuclein in their attempt to define its role in cell signaling processes. They investigated γ -synuclein expressed in *E. coli* and found that, under denaturing electrophoresis conditions, the protein appears monomeric but forms trimers and tetramers in a concentration-dependent manner on a native gel, indicating weakly associating oligomers. These oligomers were disrupted upon treatment with PLC β 2 and phospholipid vesicles and, when injected into HEK293 cells, they remained monomeric even at 100 nM concentration. These observations led to a working model, whereby small oligomeric γ -synuclein may form although they are not the protein's native functional state. These oligomers may then dissociate to bind protein partners, which in turn may modulate signaling cascades, and thus protein function and integrity.

Golebiewska et al., *Biochemistry*, 2014, 53, 293-299.

Molecular assessment of surgical-resection margins of gastric cancer by mass-spectrometric imaging.

<http://www.pnas.org/content/early/2014/01/29/1400274111>

The complete resection of solid tumors is correlated with better prognosis in most malignancies. In gastrointestinal cancer surgeries, histopathologic evaluation of frozen tissue sections is typically performed to evaluate surgical margins. In this manuscript, the utility of desorption electrospray ionization mass spectrometric imaging (DESI-MSI) was evaluated for classifying cancerous and normal tissues, as a potential alternative to traditional pathology-based methods. Banked gastric cancer and normal gastric tissue samples were subjected DESI-MSI analysis to identify mass spectral features and build statistical methods to distinguish cancerous versus normal tissue. The method was further applied to tissue-margin samples prospectively obtained from gastric cancer patients. The results suggest that DESI-MSI has potential utility for intraoperative assessment of surgical margins during surgical resection of gastrointestinal tumors.

Eberlin LS et al. *Proc Natl Acad Sci*, 2014, 111(7):2436-2441.

An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage.

<http://www.nature.com/nm/journal/vaop/ncurrent/full/nm.3519.html>

Circulating tumor DNA (ctDNA) is DNA shed from the tumor into the bloodstream and has the potential to be used as a blood-based biomarker for a variety of cancers. This manuscript introduces cancer personalized profiling by deep sequencing (CAPP-Seq), a method of quantifying ctDNA in clinical blood samples. Unlike other methods, CAPP-Seq is highly sensitive and has potentially broad clinical applicability. CAPP-Seq was used to identify mutations in ctDNA from non-small-cell lung cancer (NSCLC) patients. ctDNA was detected in 50% of earlier stage disease patients and 100% of later stage disease patients. Levels of ctDNA were found to correlate with tumor burden and detected response to treatment at earlier stages than traditional radiographic imaging. These results suggest great promise on developing new methods for detecting and monitoring cancers.

Newman et al. Nat Med. 2014 Apr 6. [Epub ahead of print]

Targeting lactate dehydrogenase-a inhibits tumorigenesis and tumor progression in mouse models of lung cancer and impacts tumor-initiating cells

<http://www.ncbi.nlm.nih.gov/pubmed/24726384>

The enhancement of aerobic glycolysis, i.e., the Warburg effect (lactate production in the presence of adequate oxygen), has been reported in various types of cancers. Targeting cancer metabolism via anti-glycolytic therapies might offer a therapeutic opportunity as it represents a key converging step for multiple deregulated signaling pathways. The upregulation of lactate dehydrogenase-A (LDH-A), a key enzyme implicated in the Warburg effect in cancer cells that catalyzes the inter-conversion of pyruvate and lactate, is associated with aggressive cancer outcomes. In a paper recently published at Cell Metabolism, the authors revealed that genetic inactivation of LDH-A in mouse models of NSCLC driven by oncogenic K-RAS or EGFR, led to decreased tumorigenesis and disease regression in established tumors. Using stable isotope-resolved metabolomics (SIRM), they further investigated the metabolic effect of LDH-A attenuation in vivo and ex vivo in freshly prepared human NSCLC tissue slices. In agreement with their in vitro data, glycolytic production of ¹³C-lactate from ¹³C-6-glucose was attenuated in LDH-A suppressed mouse lung tumors and LDH-A inhibitor-treated human tumor slices, but the Krebs cycle activity was not activated either in vivo or ex vivo. More importantly, using a specific small molecule LDH-A inhibitor, they demonstrated that LDH-A was essential for cancer-initiating cell survival and proliferation.

Xie et al., Cell Metab. 2014, 19(5), 795-809.

Quantitative chemical proteomics identified novel targets of the anti-cancer multi-kinase inhibitor E-3810

<http://www.ncbi.nlm.nih.gov/pubmed/?term=24696502>

Chemical proteomics (chemoproteomics, which combines affinity chromatography and proteomic profiling) is an ideal approach for the systematic identification of drug targets, as well as off-targets, in their natural context. E-3810 is a novel multi-kinase inhibitor currently in clinical trials for its anti-angiogenic and anti-tumor activity. The cellular receptors for vascular endothelial growth factor (VEGFRs) and fibroblast growth factor (FGFRs) are the principal targets for E-3810. However, E-3810 can also inhibit the growth of tumor cells with low to undetectable levels of these proteins in vitro, suggesting that additional relevant targets exist. Dr. Bonaldi's group at University of Milan recently reported their findings on novel targets of E-3810 in Mol. Cell Proteomics. They first immobilized the drug to a resin and then exploited stable isotope labeling by amino acid in cell culture (SILAC) to design experiments that allowed the detection of novel interactors and the quantification of their dissociation constant for the immobilized drug. They identified six novel candidate kinase targets (DDR2, YES, LYN, CARDIAK, EPHA2 and CSBP) and validated the results using biochemical assays. These targets need to be followed up in future development of E-3810, the information will be essential to evaluate the strength and the limits of chemical proteomics as an important approach for drug target deconvolution.

Colzani et al., Mol Cell Proteomics. 2014 Apr 2. [Epub ahead of print]

Resource: Glycoproteomic and glycomic databases

<http://www.ncbi.nlm.nih.gov/pubmed/24725457>

Aberrant glycosylation of proteins has been associated with many illnesses such as cancer. Scientists at John Hopkins University reviewed 15 different publicly available databases and identified their key elements so that users can identify the most applicable platform for their analytical needs. These databases include biological information on the experimentally identified glycans and glycopeptides from various cells and organisms such as human, rat, mouse, fly and zebrafish. The review was published at Clinical Proteomics this month.

Baycin et al., Clin Proteomics. 2014, 11(1), 15.

4. Profile of a Young Scientist

	Employment	
	2011-present	Senior Lecturer in Biological Chemistry, Imperial College London (ICL), U.K.
	2005-2011	Lecturer in Biological Chemistry, ICL, U.K.
	2001-2005	Postdoctoral Research Associate, Imperial College London, U.K.
	Education	
	1997-2001	PhD in Structural Biology, Oxford University
	1993-1997	MChem, Oxford University

Dr. Hector Keun is a Senior Lecturer in biological chemistry in the Department of Surgery & Cancer, Imperial College London. He graduated in chemistry from New College, University of Oxford and under the supervision of Prof. Iain Campbell FRS, completed his doctoral thesis on structural studies of extracellular matrix proteins using NMR spectroscopy. In 2001 Dr Keun joined the Biological Chemistry section at Imperial College London, which under the leadership of Prof. Jeremy Nicholson was advancing the use of NMR to generate metabolic profiles of body fluids and tissues as part of the concept of 'metabonomics'. As a postdoctoral researcher, Dr. Keun developed approaches for spectral pattern recognition and toxicity classification in preclinical studies using metabonomics. In 2005, Dr. Keun took up a Lecturer position within the Imperial College, Faculty of Medicine and was promoted in 2011 to Senior Lecturer.

Dr. Keun's research interests are now directed towards the discovery of novel metabolic biomarkers and drug targets for the prevention and treatment of cancer. His research work has focused on the use of metabolic profiling techniques such as NMR spectroscopy and mass spectrometry to characterize metabolism in body fluids, tumours and cancer cells. He also uses bioinformatics approaches to integrate these data with gene expression profiles and other molecular data ('systems biology'). His work to date has resulted in publications

detailing the evolution of metabolic perturbations in gastrointestinal cancer and the links between metabolism and response to chemotherapy. His current work seeks to define and explain the metabolic phenotypes linked to carcinogen exposure, cancer risk, and tumorigenesis. Part of this research involves the characterization of biological samples collected as part of large prospective studies on cancer risk such as EPIC. Further work will seek to understand how cancer-associated metabolic changes are linked causally to epigenetic alterations, in particular to tumour suppressive or oncogenic microRNAs. Dr. Keun is also working with AstraZeneca/CRUK to develop pharmacodynamic and predictive biomarkers for novel agents targeting tumor metabolism, e.g. lactate transport, for patient stratification and personalized medicine.

Dr. Keun's group is funded from various sources including a number of European Union FP7 consortia, AstraZeneca, BBSRC, Cancer Research UK and notably a European Chemical Industry Council (CEFIC) Long Range Initiative award for Innovative Science (2009).

5. Spotlight on World News

Surgeons develop personalized 3-D printed kidney to simulate surgery prior to cancer operation

<http://www.sciencedaily.com/releases/2014/04/140414100801.htm>

A group of surgeons from Kobe University in Japan has combined the 3D imaging capabilities of Computer Tomography with 3D printing, to produce exact scale model of kidneys prior to surgery. This technique allows surgeons to simulate surgery prior to the real operation and the models can be personalized to each patient, giving doctors a 3-D model of each individual's tumor. The model assists surgeons in accurately determining the margins of the kidney tumors and visualizing blood vessels prior to surgery.

Source: European Association of Urology, Science daily

Cancer treatment: The immune revolution

<http://www.nature.com/news/cancer-treatment-the-killer-within-1.14955>

Therapeutic targeting of inhibitory receptors on T cells can boost immune responses to tumors and improve patient survival. The first immunotherapy drug was approved in 1992, but since then efforts in developing new immunotherapies failed to live up to their promise in the clinic. Now, clinical-trial successes in the past five years suggest that a new generation of approaches has potential against several forms of cancer that resist conventional treatments. Some analysts predict that in the next ten years, immunotherapies will be used for 60% of people with advanced cancer, and will comprise a US\$35-billion market.

Source: Nature News

Missing link between cholesterol and cancer

<http://www.ddn-news.com/index.php?newsarticle=8340>

Purdue researchers discovered a link between prostate cancer aggressiveness and the accumulation of a compound produced when cholesterol is metabolized in cells. Moreover, the findings suggest that a class of drugs previously developed to treat atherosclerosis might be repurposed for treatment of advanced prostate cancer.

Source: Cell Metabolism, Drug Discovery News

MD Anderson Cancer Center and GSK partner for cancer research

<http://www.ddn-news.com/news?newsarticle=8325>

The University of Texas MD Anderson Cancer Center has announced the establishment of a research alliance with GlaxoSmithKline (GSK) to further its pursuit of immunotherapies for fighting cancer. The collaboration is part of a plan to partner with pharmaceutical companies to advance the development of immunotherapies as part of MD Anderson's Moon Shots Program, a 10-year initiative to speed the development of therapies and other interventions that can significantly reduce cancer deaths.

Source: Drug Discovery News

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

Drug Discovery & Therapy, World Congress 2013

16 – 19 June, 2014, Boston, USA.

<http://www.ddtwc.com/>

Mechanisms and Models of Cancer

August 12-16, 2014. Cold Spring Harbor, NY, USA

<http://meetings.cshl.edu/meetings/2014/cancer14.shtml>

Gordon Research Conference on Drug Carriers in Medicine & Biology

August 17-22, 2014, Waterville Valley, NH. USA.

<http://www.grc.org/programs.aspx?year=2014&program=drugcarr>

Epigenetics and Chromatin

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

<http://meetings.cshl.edu/meetings/2014/epich14.shtml>

Global Cancer Summit

September 15-17, 2014, Hyderabad, India

<http://www.cancersummit.org/index.php#links>

European Cancer Conference 2014: 'Precision Medicine in Cancer Care.

26 – 30 September, 2014, Madrid, Spain

<http://www.esmo.org/events/european-cancer-congress.html>

AICR Annual Research Conference

October 29-31, 2014, Washington, D.C., USA

<http://www.aicr.org/cancer-research/conference/>

Keystone Symposium on Cell Death Signaling in Cancer and the Immune System

October 28-November 2, 2014, Sao Paulo, Brazil.

<https://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1321>

10th National Cancer Research Institute Cancer Conference

2–5 November 2014, Liverpool, UK

<http://conference.ncri.org.uk/>

World Cancer Congress

December 3-6, 2014, Melbourne, Australia.

<http://www.uicc.org/convening/world-cancer-congress/2014-world-cancer-congress-melbourne>

8. Other