1. From the Editors

Einstein once said that he had “little patience with scientists who take a board of wood, look for its thinnest part and drill a great number of holes where drilling is easy.” In an attempt to honor the spirit of Einstein’s philosophy in this summer issue, we have decided to drill holes in the thicker part of the board and report on the progress of exploiting protein-protein interactions (PPIs) for therapeutic intervention. We now know that PPIs play key roles in many biological pathways and signaling events that are vital in many cancer diseases. However, this research area is often considered as an attempt to “drug the undruggable” with many scientists in the research community being skeptical about the slim chances of success in developing clinically useful protein-protein inhibitors to treat cancer patients.

Perhaps the challenge ahead of us can be likened to the early encounters of climbing Mount Everest. Prior to New Zealander Sir Edmund Percival Hillary and the Nepalese Sherpa Tenzing Norgay reaching the summit of Mount Everest on 29 May 1953, it was thought of as impossible to conquer the mountain. Now, more than 70 years later, climbing Mount Everest is still demanding, but it is a challenge that can be mounted by anyone due to advances in training, technology and the perception that it can be achieved. Likewise, scientific evidence is laying the foundation for drugging several PPIs, and the path to clinical success is certainly more accessible than a few years ago.

Accordingly, approaches to modulate PPIs with small molecules have gained much attention over the past decade, yet there are still a number of challenges that need to be overcome before clinical candidates can be routinely developed. Interestingly, achieving further progress may also stem from employing macromolecules such as monoclonal antibodies to block PPIs between T-cell checkpoint receptors and their cognate ligands. Exciting prospects of using immuno-oncology in combination with PPI-targeted agents may soon be a possibility. In this issue, we highlight recent research articles and reviews focused on the chemistry-biology interface of unravelling and exploiting PPIs in cancer.

James Bradner, our profile scientist in this summer issue, is a young physician and researcher, who has been fascinated and motivated by the challenge of targeting PPIs associated with gene regulatory pathways. His laboratory recently developed JQ1, a bromodomain inhibitor which is widely used in several laboratory applications as a tool molecule and is distributed free of charge.

We would like to bring to the attention of the CICR community new Funding Opportunities from the NIH Common Fund Glycoscience Program. The scheme encourages investigators to develop accessible and affordable new tools and technologies for studying carbohydrates that will allow biomedical researchers to significantly advance our understanding of the roles of these complex molecules in health and disease. This program will enable investigators who might not otherwise conduct research in the glycosciences, to undertake the study of carbohydrate structure and function. More information can be found here: https://commonfund.nih.gov/Glycoscience

Finally, on behalf of the CICR Steering Committee, we invite you to join us at 12:30 p.m. on Friday, November 6th at the AACR-NCI-EORTC International
Conference on Molecular Targets and Cancer Therapeutics Meeting in Boston, Massachusetts for the CICR Town Hall and Reception. Don’t miss this opportunity to see and network with colleagues.

2. Selected Research Highlights

**Overcoming Chemical, Biological, and Computational Challenges in the Development of Inhibitors Targeting Protein-Protein Interactions.**

Laurie, et al. summarize the specific challenges of developing PPI inhibitors and detail the recent advances in chemistry, biology, and computation that facilitate overcoming them. They conclude by providing a perspective on the field and outlining four innovations they view as key enabling steps for successful development of small-molecule inhibitors targeting PPIs.

**Big Opportunities for Small Molecules in Immuno-Oncology.**

Adams, et al. highlight immuno-oncology pathways and mechanisms that can be best or solely targeted by small-molecule medicines.

**Inhibition of Ras Signaling by Blocking Ras-Effector Interactions with Cyclic Peptides.**

Upadhyaya et al. report on a family of cyclic peptide inhibitors that block the intracellular interactions between Ras and its downstream effectors. A combinatorial peptide library construction and evaluation and subsequent structure-activity relationship analysis led to the identification of a group of cyclic Ras inhibitors, namely cyclorasins. As an example, compound 9A5 was extensively investigated for its binding effect to Ras, its inhibitory action in the Ras-Raf interaction, and its influence on Ras-mediated downstream cascades including Raf/MEK/ERK and PI3K/PDK1/Akt pathways was also studied. Since the cell permeability and apoptotic effect to lung cancer cells of compound 9A5 is substantially improved from previous studies, it is anticipated that this class of cyclic peptides has the potential to serve as a promising pharmacophore for further development into therapeutic agents.

**Validation of the Hsp70–Bag3 Protein–Protein Interaction as a Potential Therapeutic Target in Cancer**

Li et al. validate the interaction between Hsp70, a chaperone protein important for protein homeostasis and cell survival, and Bag 3, which helps to guide the chaperone activity. Hsp70 inhibition had previously been considered a challenging task due to the active site being located in a deep groove of the nucleotide-binding domain. However, a novel small molecule inhibitor, JG-98, which allosterically binds Hsp70 is shown in this article to weaken the Hsp70-Bag3 interaction and induce cell death in vitro as well as reduced tumor growth in vivo in multiple models. Further, the authors determined that JG-98 has antiproliferative activity across cancer cell lines from multiple origins and also resulted in modulation of signaling proteins linked to the Hsp70-Bag3 complex. In summary, this proof-of-concept article provides sufficient evidence for Hsp70-Bag3 as a potential target in cancer and JG-98 as a useful chemical probe for studying this protein-protein interaction.
Discovery of a Dihydroisoquinolinone Derivative (NVP-CGM097) - a Highly Potent and Selective MDM2 Inhibitor Undergoing Phase 1 Clinical Trials in p53wt Tumors.

This article provides an overview of the discovery of a new p53-MDM2 inhibitor, NVP-CGM097, which is currently in phase 1 clinical development. Aspects covered in the article include scientific rationale, mechanism of action, binding mode, medicinal chemistry, pharmacokinetic and pharmacodynamic properties and in vivo pharmacology/toxicology of the compound in preclinical species.

A Modular Toolkit to Inhibit Proline-Rich Motif-Mediated Protein-Protein Interactions.

Small-molecule inhibitors of protein-protein interactions are urgently needed for functional analysis of large-scale genomics and proteomics data. Opitz et al. recently described a modular strategy to obtain an extendable toolkit of chemical fragments (ProMs) designed to replace pairs of conserved prolines in recognition motifs. As proof-of-principle, the authors developed a small, selective, peptidomimetic inhibitor of Drosophila enabled (Ena) /vasodilator-stimulated phosphoprotein (VASP) homology 1 (EVH1) domain interactions, which was used to probe highly invasive MDA-MB-231 breast-cancer cells. Interestingly, the peptidomimetic inhibitor revealed displacement of VASP from focal adhesions, as well as from the front of lamellipodia and strongly reduced cell invasion. The authors also demonstrated that such a strategy could be employed in the design of an ErbB4-derived ligand targeting the Yes-Associated Protein 1 (YAP1)-WW domain.

AMPK Activation via Modulation of De Novo Purine Biosynthesis with an Inhibitor of ATIC Homodimerization.

Asby et al. have elaborated a regulatory mechanism of the adenosine monophosphate-activated protein kinase (AMPK)-mediated cellular energetics in MCF-7 breast cancer cells by employing an inhibitor disrupting the homodimerization of a bifunctional enzyme in human de novo purine biosynthesis, namely ATIC. The ATIC enzyme uses 5-aminoimidazole-4-carboxamide ribonucleotide (known as ZMP) as a substrate to complete de novo purine biosynthesis, but freestanding ZMP has been known to allosterically activate AMPK. Nonetheless, the crosstalk between purine metabolism and AMPK activation through ZMP has not been investigated in detail. In this work, the authors used a peptide inhibitor, which was previously identified as a selective inhibitor of ATIC in vitro. The authors demonstrated that the increased level of endogenous ZMP, produced by the inhibition of ATIC homodimerization, activated AMPK in MCF-7 cells. Due to the therapeutic potential of selective AMPK activation in the treatment of metabolic disorders, including cancers and diabetes, the authors further showed the in vivo effect of the peptide inhibitors in an obese mouse model. Metformin and its derivatives, activating AMPK, or methotrexate and another antifolates, inhibiting the ATIC’s transformylase activity, display various on- and off-target effects. Hence, the presented peptide inhibitor, which disrupts the ATIC homodimerization, now shows a great potential to selectively regulate de novo purine biosynthetic enzymes, thus increasing AMPK activity.
Other research highlights not related to PPI


Post-menopausal hormone therapy including synthetic progestins has been shown to increase the risk of breast cancer. In estrogen receptor (ER) positive breast cancers, progesterone receptor (PR) is often used as a marker of ER function and of disease prognosis, however the function of PR signaling remains largely unknown. An article by Mohammed et al. demonstrates the novel finding that PR is associated with ER and modulates its behavior. The authors demonstrate that when using PR antagonist ligands, PR associates with ER and directs chromatin binding events in breast cancer cells to give a unique gene expression pattern that is associated with positive clinical outcome. Using cell lines, xenografts, and primary tumors, the authors further demonstrated that progesterone-inhibited growth had anti-proliferative effects when coupled with an ER antagonist. The finding that PR controls ER chromatin binding and transcriptional activity has important prognostic and therapeutic implications in breast cancer.


**Spatially resolved metabolic phenotyping of breast cancer by desorption electrospray ionization mass spectrometry.**

The molecular heterogeneity of breast cancer provides a substantial challenge for disease diagnosis and stratification and for targeted therapeutic intervention. In this manuscript, Guenther et al. used desorption electrospray ionization mass spectrometry imaging (DESI MSI) to evaluate the utility of the method for diagnosis and characterization of metabolic changes in breast cancer tissue and the tumor microenvironment. 126 tissue biopsies from 50 patients undergoing surgical resections were analyzed. Using the metabolic information provided by DESI, adipose, stromal, and glandular tissues were distinguished. Profiles of tumor and tumor-associated stromal tissue showed differences in fatty acid and phospholipid composition compared to normal tissue. Further evidence was presented to demonstrate the ability of DESI MSI to diagnose breast cancer (accuracy of 98.2%), and to correlate metabolomics profiles with tumor grade and hormone receptor status. These results suggest that DESI MSI may have utility in breast cancer diagnosis.

**M-Trap: Exosome-Based Capture of Tumor Cells as a New Technology in Peritoneal Metastasis**

This study describes a novel approach that aims to disrupt the process of metastasis by interfering with the communication between the tumor and the environment that governs metastasis. Proteomics and adhesion assays identified exosomes purified from the ascitic fluid of ovarian cancer patients as intermediaries of tumor cell attachment. A novel tumor cell capture device was fabricated by embedding exosomes onto a 3D scaffold (metastatic trap [M-Trap]). Efficacy of M-Trap to capture metastatic cells disseminating in the peritoneal cavity was evaluated using murine models of ovarian metastasis. M-Trap served as a preferential site for metastasis formation and completely remodeled the pattern of peritoneal metastasis in clinically relevant murine models of ovarian cancer. Most importantly, M-Trap demonstrated a statistically significant benefit in survival outcomes. Thus, M-Trap has the potential to transform a systemic, fatal disease into a focalized disease, where proven therapeutic approaches such as surgery can extend survival.
Reprogramming of the tyrosine kinase-regulated proteome in breast cancer by combined use of RNAi and SILAC quantitative proteomics.

Tyrosine kinases (TKs) protein abundance as well as alterations in the total and/or phosphorylated levels of proteins encompassed in TK signaling pathways can contribute to carcinogenesis. However, less than half of the TKs have been thoroughly studied and a global functional analysis of their proteomic portrait is lacking. In this paper, the authors conducted a combined approach of RNAi and stable isotope labeling with amino acids in cell culture (SILAC)-based quantitative proteomics to decode the TK-regulated proteome and associated signaling dynamics. They discovered a broad proteomic repertoire modulated by TKs upon silencing of the 65 TKs expressed in MCF-7 breast cancer cells. In that repertoire, they identified 10 new distinctive TK clusters according to similarity in TK-regulated proteome. They further provided functional analyses and determined critical pathways for each cluster based on their common downstream targets. The whole dataset supported the role of TKs in regulating major aspects of cellular activity, but also revealed redundancy in signaling, explaining why kinase inhibitors alone often fail to achieve their clinical aims. The TK-SILACepedia provided a comprehensive resource for studying the global function of TKs in cancer.

4. Profile of a Young Scientist

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<tr>
<th>Employment</th>
<th>Education</th>
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<tr>
<td>2014-present</td>
<td>Postgraduate Training, Brigham &amp; Women's Hospital</td>
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<tr>
<td>2008-2013</td>
<td>Fellowship in Medical Oncology and Hematology, DFCI and Brigham and Women's Hospital</td>
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<tr>
<td>2004-2008</td>
<td>Postdoctoral Research at Broad Institute of Harvard &amp; MIT (Adviser Prof Stuart Schreiber)</td>
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<tr>
<td>2005-present</td>
<td>Physician at DFCI in Hematological Malignancies</td>
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<tr>
<td>2002-2005</td>
<td>Assistant Professor of Medicine, Harvard Medical School</td>
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<tr>
<td></td>
<td>Associate Professor of Medicine, Harvard Medical School</td>
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Dr. James Bradner is a physician in the Division of Hematologic Malignancies at Dana-Farber Cancer Institute with appointments as an Associate Professor at Harvard Medical School and Associate Director of the Center for the Science of Therapeutics at the Broad Institute. He received his M.D. from the University of Chicago in 1999, followed by a residency in Internal Medicine at Brigham and Women’s Hospital and a fellowship in Medical Oncology and Hematology at Dana-Farber and Brigham and Women’s Hospital. He is the Scientific Founder of Syros Pharmaceuticals, Acetylon Pharmaceuticals, Shape Pharmaceuticals, and Tensha Therapeutics. His numerous honors and awards include a Damon Runyon-Rachleff Innovation award, the Smith Family Award for Excellence in Biomedical Research, and teaching awards from both Harvard Medical School and Brigham and Women’s Hospital.

Research in the Bradner lab utilizes chemistry, biology, and bioinformatics to establish new therapeutic strategies to treat cancer. In particular, they have identified a critical role for bromodomain (BRD) proteins in cancer cell growth and metastasis. Bromodomains bind acetylated lysine residues and these proteins are closely involved in regulating gene expression programs, DNA repair, and chromatin structure. In 2010, the Bradner lab developed the structure of the first bromodomain family inhibitor, JQ1, which is used as a probe molecule in laboratory applications. Furthermore, the Bradner lab has made this molecule publicly available to all labs to accelerate the pace of epigenetic research. Dr. Bradner is a strong proponent of open source drug discovery and has presented a TEDx talk about this subject. The Bradner lab also discovered a novel role for BRD proteins in regulating “superenhancers” that drive cancer gene expression programs and most recently, established a novel chemical strategy using “degromimids” to induce targeted degradation of BRD proteins. These discoveries have launched a number of biotech companies with the goal to deliver innovative therapeutics for serious medical needs.

5. Spotlight on World News

Idera Pharmaceuticals partners with UT – MD Anderson Cancer center to advance clinical development of anti-cancer therapeutics

Idera Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company developing toll-like receptor and RNA therapeutics for patients with cancer and rare diseases, has entered into a strategic clinical research alliance with The University of Texas MD Anderson Cancer Center to advance clinical development of intratumoral TLR9 agonist in combination with checkpoint inhibitors. IMO-2125 is a TLR9 agonist, which has been evaluated subcutaneously in over 80 human subjects, was well tolerated, and was shown to induce immune responses.

Source: Drug Discovery News
Baxter acquires Italian-based Oncaspar for $900M
Baxter International Inc. announced it has signed a definitive agreement to acquire the Oncaspar (pegaspargase) product portfolio from Italian company Sigma-Tau Finanziaria S.p.A. The acquisition reportedly “further accelerates the innovation capabilities and the commercial presence of Baxter BioScience in growing oncology markets for rare and orphan diseases.” The Illinois-based company says that the deal gains it the leading marketed biologic treatment Oncaspar, the investigational biologic calaspargase pegol and an established oncology infrastructure with clinical and sales resources.
Source: Drug Discovery News

Oregon Health & Science University Cancer Center raises $1 billion
Philip Knight, the billionaire co-founder of sportswear brand Nike, donated $500M to the Oregon Health & Science University Cancer Center (OHSU) on the condition that his donation is matched in pledges within two years in a fund-raising campaign. On 25 June 2015, OHSU announced that it had reached its target in 22 months. It is the largest amount a US institution has ever raised to win a challenge grant, according to the Indiana University Lilly School of Philanthropy in Indianapolis. Druker, a renowned physician and researcher who initiated the fundraising campaign for OHSU has laid the groundwork for the revolutionary leukaemia drug Gleevec (imatinib). The drug was approved by US regulators in 2001, and turned chronic myeloid leukaemia (CML) — once a death sentence for 70% of people diagnosed with it — into a long-term, manageable disease for 90% of patients. Druker aims to rapidly hire up to 30 principal investigators, and to provide researchers with a funding cushion intended to free them from the burden of constantly applying for grants. The institute will focus on detecting cancers early in their development, when treatments generally have a better chance of success. Druker also wants the institute to take advantage of emerging technologies to develop better tests that would reduce false diagnoses.
Source: Nature

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

Discovery on Target
September 21-25, 2015. Boston, MA, USA

Epigenetics Discovery Congress
September 24-25, 2015. London, UK
Chromatin and Epigenetics in Cancer  
September 24-27, 2015. Atlanta, GA, USA.

Genome Engineering: The CRISPR/Cas9 Revolution  

14th Human Proteome Organization World Congress  
September 27-30, 2015. Vancouver, Canada

2nd Annual Drug Discovery USA Congress  
October 29-30, 2015. Boston, MA, USA

AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics  
November 5-9, 2015. Boston, Massachusetts, USA  
*Plan to attend the CICR Town Hall on Friday, November 6 @ 12:30-2 p.m., Hynes Convention Center, Room 210!*

Epigenomics of Common Diseases  
November 6-9, 2015. Hinxton, UK

Basic Epigenetic Mechanisms in Cancer  

8. Other

Nothing for the August 2015 issue.