

## 1. From the Editors

Clinical drug formulation is a scientific field that does not often make the headlines, yet it remains very much an integral part of drug development. Pharmaceutical, biotechnology and academic sectors are involved in ensuring that new drug candidates possess optimal characteristics for clinical evaluation. The clinical drug formulation underpins a key part of manufacturing and connects the preclinical phase to clinical trial operations. Drug formulation strategies are not only relevant for 'new chemical entities' but also existing drugs. Indeed, this year marks the 50th anniversary since the discovery of cisplatin - one of the most successful drugs to treat endocrine-related cancers like ovarian and testicular carcinomas. Ample research is still being carried out on platinum-based agents including formulation strategies such as encapsulation with macrocycles to reduce/decelerate or prevent their degradation by proteins and peptides. Moreover, attachment of these agents to nanoparticles to target solid tumors through the enhanced permeability and retention effect is also actively pursued. No new medicine containing a platinum-based drug has reached the market, partly owing to problems with consistent drug loading, controlling the location and timing of drug release and the inherent toxicity of some of the drug delivery vehicles. Nanotechnology strategies are being increasingly pursued as a means for efficient drug delivery and formulation with advantages over traditional formulation schemes, i.e., improvement in solubility, pharmacokinetics and biodistribution of traditional pharmaceuticals. A recent 2015 review shed light on new advances in platinum-containing formulations, while another highlights nanotechnology carriers for the challenging clinical translation of nucleic acid-based therapeutics. Our chosen research highlights consist of a mix of conventional strategies and novel applications, including the use of silk-based drug carriers for pulmonary delivery of cisplatin for lung cancer.

We are also pleased to announce the new [CICR Community Resources webpage](#), which features information and references for Chemical Probes. The CICR Working Group is delighted to provide this service to all interested researchers.

Finally, please remember that the abstract submission deadline for the [AACR Annual Meeting 2015](#) is 1<sup>st</sup> of December, 2015 (11:59 p.m. U.S. ET) and the early registration deadline is 18<sup>th</sup> of December 2015. Please access the Annual Meeting website (listed here) for further information.

- 2.
3. Selected Research Highlights

### ***Drug Formulation Strategies***

## **Strategy for selecting nanotechnology carriers to overcome immunological and hematological toxicities challenging clinical translation of nucleic acid-based therapeutics.**

### **The state-of-play and future of platinum drugs**

#### **Formulation of Biologically-Inspired Silk-Based Drug Carriers for Pulmonary Delivery Targeted for Lung Cancer**

The benefits of using silk fibroin, a major protein in silk, are widely established in many biomedical applications including tissue regeneration, bioactive coating and in vitro tissue models. However, Kim et al have for the first time used silk as carriers for pulmonary drug delivery of cisplatin with increase in anticancer activity. The new formulation demonstrated high aerosolization performance through the measurement of in vitro lung deposition, which is at the level of commercially available dry powder inhalers. These novel inhalable silk-based drug carriers have the potential to be used as anti-cancer drug delivery systems targeted for the lungs.

#### **Oral delivery of a platinum anticancer drug using lipid assisted polymeric nanoparticles**

Liu and colleagues have prepared self-assembled cholesterol-asplatin-incorporated nanoparticles (SCANs) for oral delivery of a Pt(IV) prodrug and shown such SCANs to exhibit high gastrointestinal stability, sustained drug release and enhanced cell uptake. In addition, oral administration of SCANs efficaciously inhibited tumor growth with negligible toxicity.

#### **Abraxane, the Nanoparticle Formulation of Paclitaxel Can Induce Drug Resistance by Up-Regulation of P-gp.**

P-glycoprotein (P-gp) can actively pump paclitaxel (PTX) out of cells and induces drug resistance. Abraxane, a nanoparticle (NP) formulation of PTX, has multiple clinical advantages over the single molecule form. However, it is still unclear whether Abraxane overcomes the common small molecule drug resistance problem mediated by P-gp. However, a study to address this gap in knowledge was established. An Abraxane-resistant cell line was established from the lung adenocarcinoma cell line A549 and used to compare the transcriptome of A549/Abr resistant cell line to that of its parental cell line using RNA-Seq technology. Several pathways were found to be up or down regulated and P-glycoprotein was shown to be overexpressed indicating that this efflux pathway may contribute to Abraxane resistance in the clinic.

#### **Nanomicellar Formulation of Clotrimazole Improves Its Antitumor Action toward Human Breast Cancer Cells**

The antifungal agent clotrimazole (CTZ) has been shown to possess anticancer properties due to its properties to inhibit cell proliferation by inhibiting glycolysis and thereby interfering with the Warburg effect. Marcondes et al prepared a water-soluble nanomicellar formulation of CTZ (nCTZ) and found enhanced

inhibitory activity of glycolytic and other cytosolic and mitochondrial enzymes than free form of CTZ. Moreover, this increased activity was also observed for lactate production, intracellular ATP content, ROS production and antioxidant potential which warrants further investigations of nCTZ.

#### **Activity of MM-398, Nanoliposomal Irinotecan (nal-IRI), in Ewing's Family Tumor Xenografts Is Associated with High Exposure of Tumor to Drug and High SLFN11 Expression**

The object of this study was to determine the pharmacokinetics and the antitumor activity of MM-398, a nanoliposomal irinotecan (nal-IRI) in pediatric cancer models. Plasma and tumor concentrations of irinotecan and SN-38 (active metabolite) were approximately 10-fold higher for nal-IRI than for irinotecan. Two doses of nal-IRI (10 mg/kg/dose) achieved complete responses maintained for > 100 days in 24 of 27 EFT-xenografted mice. Event-free survival for mice with rhabdomyosarcoma (RMS) and neuroblastoma (NB) was significantly shorter than for Ewing's sarcoma family of tumors (EFT). Nonetheless, in these pediatric solid tumor xenografts, nal-IRI demonstrated higher systemic and tumor exposures to SN-38 and improved antitumor activity compared with the current clinical formulation of irinotecan. Clinical studies of nal-IRI in pediatric solid tumors (especially EFT) and correlative studies to determine if SLFN11, a putative DNA/RNA helicase, expression can serve as a biomarker to predict nal-IRI clinical activity are warranted

#### **Exploring Drug Delivery for the DOT1L Inhibitor Pinometostat (EPZ-5676): Subcutaneous Administration as an Alternative to Continuous IV Infusion, in the Pursuit of an Epigenetic Target**

Epizyme has advanced Pinometostat, a DOT1L inhibitor, into Phase I clinical trials. DOT1L is aberrantly recruited and activated in mixed lineage leukemia and DOT1L inhibition has been shown to selectively target leukemia cells. Pinometostat is currently delivered through a continuous IV infusion in order to maintain a therapeutic level in plasma. Waters et al. report on alternate sustained release technologies to improve patient convenience. A subcutaneous bolus administration of pinometostat formulated in 0.2% hydroxypropyl-B-cyclodextrin in saline resulted in complete bioavailability in mouse and dog models. In conjunction with additional extended release formulations, this will lead to a more convenient dosing regimen for patients.

#### ***Other Research Highlights***

#### **Targeting Drug Resistance in EGFR with Covalent Inhibitors: A Structure-Based Design Approach**

Mutations of the epithelial growth factor receptor (EGFR) have been associated with the growth, development, and progression of non-small cell lung cancer (NSCLC). Here, Engel et al. utilized a structure-based design approach to design novel pyrimidine- and quinazoline-based EGFR inhibitors that selectively and irreversibly bind to mutated EGFR. The authors used the cSrc kinase as a model

system for structural design and computational screening from which they selected several small molecules to synthesize for in vitro evaluation. Ultimately, two pyrimidine-based molecules demonstrated significant activity in NSCLC cells. Using their approach could further promote the development of potent inhibitors for variety of cancers.

### **Comprehensive assessment of cancer missense mutation clustering in protein structures**

The decreasing costs and increasing availability of genomic sequencing has resulted in numerous large scale tumor sequencing studies in recent years. These studies have used computational approaches to identify new cancer genes; however, the relationship between the genomic information and the resulting protein function remains ambiguous. Kamburov et al describe a new method to integrate the mutation information from these sequencing studies with protein structure information. Using this method, somatic mutation data from more than 4500 tumors in the PanCan database was integrated with 3D protein structure information in the Protein Data Bank. 3D clustering of mutations was observed on known oncoproteins (e.g. HRAS, EGFR, and PIK3CA). Tumor suppressor genes (e.g. FXW7, VHL, and STK11) also showed 3D clustering. Enrichment of missense mutations at interfaces with protein, nucleic acid, and small molecules were also identified. These results suggest that consideration of the location of gene mutations with respect to 3D protein structure may increase understanding of function of these cancer mutations.

### **Identification and Characterization of an Irreversible Inhibitor of CDK2**

Anscombe et al. describe NU6300, an ATP-competitive inhibitor of the cyclin-dependent kinase CDK2. CDK2 is a potential therapeutic target in malignant glioma and ovarian cancer in which CDK2's binding partner is overexpressed. NU6300 is a vinyl sulfone that binds covalently in the ATP-binding site, verified by crystallography, and inhibits Rb phosphorylation in cell-based assays. NU6300 is the first irreversible inhibitor of CDK2 that has been identified and the vinyl sulfone group presents an additional moiety to improve specificity and potency.

### **PDK1-Dependent Metabolic Reprograming Dictates Metastatic Potential in Breast Cancer.**

Dupuy *et al* investigated the metabolic profiles of metastatic breast cancers, which had spread to varying organs. Bioenergetics profiling and stable isotope tracer analysis revealed that metastasized breast cancers had a high propensity to utilize both glycolysis and oxidative phosphorylation. Distinct metabolic profiles were monitored in a metastasized organ-specific manner. Particularly, the authors reported that liver-metastatic breast cancer cells showed elevated glycolysis, but reduced glutamine metabolism and oxidative phosphorylation. However, bone- or lung-metastatic breast cancer cells exhibited opposite trends; that is, decreased glycolysis and increased oxidative phosphorylation. Further investigation demonstrated that hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) and its

downstream target, pyruvate dehydrogenase kinase 1 (PDK1), were identified as important molecular players for the observed metabolic alteration in liver-metastatic breast cancer cells. It appears that microenvironment of the metastatic sites of breast cancers defines metabolic fates of carbon flux in metastatic breast cancers

**AMPK and PFKFB3 mediate glycolysis and survival in response to mitophagy during mitotic arrest.**

Domenech et al. investigated the mechanism of mitotic cell death, which has potential to unlock a way to impair proliferation of tumor cells. To understand important biological responses during mitotic arrest, a combination of pharmacological and RNA interference approaches was used to investigate the roles of apoptotic and autophagy pathways. Specifically, the authors revealed the mitophagy-dependent loss of mitochondria during mitotic arrest accompanied by reduced ATP levels and the activation of AMP-activated protein kinase (AMPK). Glycolysis, which is activated through AMPK-dependent phosphorylation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB3), was determined as an essential pathway for cell survival in mitosis. Consequently, autophagy promotion or inhibition of AMPK or PFKFB3 resulted in increased cell death in mitosis. The authors propose here that the cellular network between the cell cycle and metabolic pathways would be a potential therapeutic target for better cancer treatment.

4. Profile of a Young Scientist

 <p>Matthew Lazzara</p>	<p><b>Employment</b> 2008-present</p>	<p>Assistant Professor, School of Engineering and Applied Science, University of Pennsylvania</p>
	<p>2008-2013</p>	<p>Member, Institute for Medicine and Engineering, University of Pennsylvania</p>
	<p>2004-2008</p>	<p>Postdoctoral Fellow, NCI National Research Service Award, Biological Engineering, MIT</p>

	<b>Education</b>	
	2003	Ph.D. Chemical Engineering (Minor in Pathology), MIT
	1997	B.S. Chemical Engineering, University of Florida

Dr. Matthew Lazzara is an Assistant Professor in the department of Chemical and Biomolecular Engineering at University of Pennsylvania. Upon graduating with highest honors in chemical engineering from University of Florida, he went on to pursue a Ph.D. degree with Dr. William Deen in the Department of Chemical Engineering at the Massachusetts Institute of Technology (MIT). During this time he pursued scientific research on fundamental aspects of molecular penetration and partitioning into physiological membranes in the kidney microvasculature. After obtaining his Ph.D., he remained at MIT in the lab of Professor Douglas Lauffenburger to study biochemical cell signaling networks in cancer. During that time, he received a National Research Service Award from the National Cancer Institute to support his work studying aberrant cell signaling by the ErbB receptors in lung cancer and published several reports on his findings in prestigious scientific journals. In 2008, he began his independent research career in the Department of Chemical and Biomolecular Engineering at University of Pennsylvania. Research in the Lazzara Lab employs a combination of computational modeling and biochemical and cell biology experiments to develop quantitative understanding of how networks of oncogenic cell signaling pathways dictate cancer cell phenotypes including response to targeted therapeutics. Dr Lazzara has received the S. Reid Warren, Jr. Teaching Award (2011) and recently been awarded a Research Scholar Grant by the American Cancer Society to develop data-driven models of the regulation of cell signaling in glioblastoma by Sprouty2, a purported tumor suppressor in several carcinomas that was recently surprisingly identified by the Lazzara lab as a driver of proliferation and therapeutic resistance in glioblastoma.

## 5. Spotlight on World News

### [Human Reovirus Formulation Receives FDA Orphan Drug Designation for Fallopian Tube Cancer](#)

Oncolytics Biotech has announced that the FDA has granted Orphan Drug designation for its proprietary formulation of the human reovirus (Reolysin) for the treatment of ovarian cancer. This sanction follows two Oncolytics Biotech-sponsored clinical studies assessing the reovirus in the treatment of ovarian



cancer. The first was a phase I/II clinical trial (OSU-07022) for patients with metastatic ovarian, peritoneal, and fallopian tube cancers using concurrent intravenous and intraperitoneal administration of the human reovirus that provided evidence of viral targeting and replication in peritoneal and ovarian cancer cells. The second is an ongoing randomized phase II trial (GOG186H) of weekly paclitaxel vs weekly paclitaxel with the reovirus in patients with persistent or recurrent ovarian, fallopian tube or primary peritoneal cancer. The second trial completed enrollment in September 2014. The results pave the way for a more targeted approach to the treatment of gynecologic cancers.

**BioDelivery Sciences Announces FDA Approval of New Formulation of ONSOLIS® (fentanyl buccal soluble film) CII**

BioDelivery Sciences International, Inc. (NASDAQ: BDSI) announced the approval by the FDA of a Supplemental New Drug Application (sNDA) for a new formulation of ONSOLIS® (fentanyl buccal soluble film) CII for the management of breakthrough pain in patients with cancer who are opioid tolerant. ONSOLIS remains an important differentiated fentanyl containing product for this indication given that it is the only product for buccal administration, providing patients with an alternative dosing option.

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

**EORTC-NCI-EMA-AACR International Conference on Innovation and Biomarkers in Cancer Drug Development**

December 3-4, 2015. Brussels, Belgium.

**Noncoding RNAs and Cancer**

December 4-7, 2015. Boston, Massachusetts, USA

**Metabolism, Transcription and Disease**

January 10-14, 2016. Snowbird Resort, Snowbird, Utah, USA

**Cancer Immunotherapy: Immunity and Immunosuppression Meet Targeted Therapies**

January 24-28, 2016. Vancouver, British Columbia, Canada

**New Approaches in Medicinal Chemistry**

27 January 2016, Stevenage, Herts, United Kingdom

**The Cancer Genome**

February 7-11, 2016. Fairmont Banff Springs, Banff, Alberta, Canada

**Advances and Progress in Drug Design**

February 15-16, 2016. London, United Kingdom

**New Frontiers in Understanding Tumor Metabolism**

February 21-25, 2016. Fairmont Banff Springs, Banff, Alberta, Canada

**Enhancer Malfunction in Cancer**

February 21-24, 2016. Santa Fe Community Convention Center, Santa Fe, New Mexico, USA

8. Other