1. From the Editors

Have you registered for the [Molecular Targets and Cancer Therapeutics meeting in Barcelona, Spain (Nov 18-21)](#)? If not, no time to waste! This meeting is hosted by the European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) and the American Association for Cancer Research (AACR). The 2014 Symposium will bring together more than 2,000 academics, scientists, and pharmaceutical industry representatives from across the globe to discuss innovations in drug development, target selection and the impact of new discoveries in molecular biology. During the last few years, numerous innovative agents have been discovered as a result of tremendous developments in the understanding of the molecular basis of cancer. Further clinical progress in cancer treatment will be accomplished mainly through the conduct of translational research projects, efficient new drug development, and the execution of large, prospective, randomised, multicenter cancer clinical trials. Plenary sessions include Antibody-based Novel Cytotoxics, Epigenetic Targets, Oncolytic Viruses, Targeting RAS, and workshops topics such as Cancer Metabolism and Management of Toxicity of Molecular Targeted Agents.

In this newsletter we have focused our attention on biomarker research. This is an exciting time for scientists engaged in this field–and everyone else who is benefitting from it! Although there is much optimism for discovering new biomarkers in order to create novel methods for improving diagnostic and prognostic monitoring of cancer patients, it is proving to be a difficult challenge. Research highlights in this newsletter include exploration of the role exosomes in regulating the immune system, in tumorigenesis, as well as in conditioning future metastatic sites for the attachment and growth of tumor tissue (see Figure 1). Interestingly, exosomes are now also emerging as indirect/direct targets for novel cancer treatments and cancer biomarkers. Dr Christian Frezza, our profile of a young scientist, is exploring the use of metabolomics to identify metabolic biomarkers of cancer, which can be used for diagnostic and patient stratification.

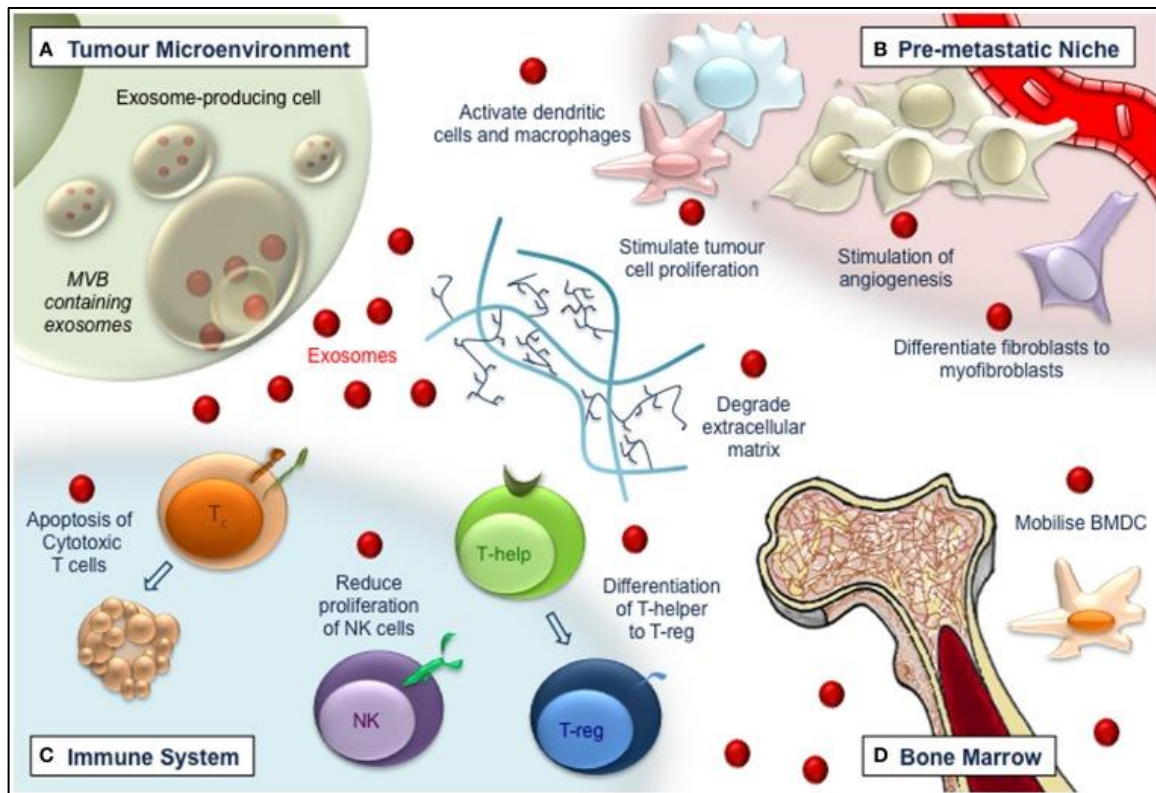We hope you enjoy the read and what remains of the summer.

FIGURE 1 Exosomes (red dots) have multiple roles in tumorigenesis.
Reprinted with permission. Tickner JA, Urquhart AJ, Stephenson S-A, Richard DJ and O'Byrne KJ (2014) Functions and therapeutic roles of exosomes in cancer. Front. Oncol. 4:127. doi:10.3389/fonc.2014.00127

2. Selected Research Highlights

Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. Exosomes are small vesicles present in most bodily fluids with molecular composition that mimics the cells of origin. There has been much interest in using exosomes for diagnostic purposes in cancer. However, isolation, labeling, detection, and molecular profiling of these vesicles have presented numerous technical challenges. Researchers at Harvard Medical School have developed a nano-plasmonic exosome (nPLEX) assay to overcome some of these challenges and provide a label-free high-throughput method for quantitative exosome analysis. The approach combines surface plasmon resonance and functionalized antibodies against surface proteins and proteins in exosome lysate. The improved sensitivity over other methods is demonstrated. The nPLEX is used to isolate exosomes in ascites samples from ovarian cancer patients and the expression of CD24 and EpCAM is correlated with ovarian cancer cells. The technology is also portable and has promise for future sensitive cancer diagnostic applications.

Recent exosome reviews:
Exosomes and microvesicles: Identification and targeting by particle size and lipid chemical probes.
Functions and therapeutic roles of exosomes in cancer

Tracing Compartmentalized NADPH Metabolism in the Cytosol and Mitochondria of Mammalian Cells. Lewis et al. reports on the development of a biochemical approach to resolve NADP(H)-dependent pathways present in both the cytosol and the mitochondria of eukaryotic cells. Unlike using carbon tracing for metabolites in cells, the authors utilized deuterium-labeled molecules in combination with isoform-specific mutants of isocitrate dehydrogenase (IDH) that are designed to specifically localize in either the cytosol or the mitochondria. The technique used by collaborators based in Cambridge (MA) and San Diego (CA) shows a novel way of combining biochemical knowledge of metabolic network with an up-an-coming isotopic tracing method to understand the compartmentalization of metabolic processes in the cell. As the authors indicated, this strategy has great potential to "improve our understanding of metabolism in normal and disease state."

Alkylphosphocholin Analogs for Broad-Spectrum Cancer Imaging and Therapy. Weichert et al. have demonstrated the uses of alkylphosphocholine derivatives in molecular imaging and radiotherapy of cancer. The group of scientists based at University of Wisconsin and Cellectar Biosciences, found that cancer cell uptake of 124I-radioisotope labeled 18-(p-iodophenyl)octadecyl phosphocholine (124I-CLR1404) is higher than in normal cells. Particularly, the authors were able to show that 124I-CLR1404 provides several important advantages over 18F-2-deoxyglucose in PET imaging, including the detection of human glioblastoma stem-like cells, the longer radioactive half-life (4 days vs 110 min), and the higher selectivity of tumor-to-normal cells. One step further, radiotherapeutic I131-labeled CLR1404 was also examined in both human tumor xenograft models and human cancer patients, revealing its significant effects on tumor growth suppression and survival benefit. The authors clearly demonstrated that their alkylphosphocholine derivatives would be not only as promising tumor-targeting vehicles as antibodies, viruses, peptides and nanoparticles, but also possibly better for cancer chemotherapy due to their ability to detect cancer stem or stem-like cells, which are usually undetectable by other methods.

Circulating proteolytic signatures of chemotherapy-induced cell death in humans discovered by N-terminal labeling
http://www.pnas.org/content/111/21/7594
Chemotherapy causes cell death, during which cellular proteases are released and activated. Researchers at UCSF speculate that proteolytic fragments released from apoptotic cells could serve as biomarkers of cell death in chemotherapy. Here, they use a strategy to enzymatically label the N-termini of free peptides in plasma from hematologic patients undergoing chemotherapy and mass spectrometry to detect the labeled peptides. Signatures of apoptosis were

identified in plasma from these patients following chemotherapy. In a hematologic cancer cell line treated with chemotherapeutic reagents, the peptides in the media were also labeled and detected. Overlap was observed between peptides in patient sera and in cell culture media and candidate markers of cellular apoptosis were identified. A subset of these peptides was verified in additional pre- and post- chemotherapy patient plasma samples. These results suggest that such an approach might be useful for monitoring cell death in patient samples. Wiita et al., Proc Natl Acad Sci, 2014, 111(21), 7594-7599.

Assessing the clinical utility of cancer genomic and proteomic data across tumor types. In order to systematically evaluate the benefits of integrating molecular data with traditional clinical variables in advancing the clinical management of cancer, Drs. Han Liang, Gad Getz, Adam A. Margolin, and their research teams retrospectively predicted patient survival using diverse molecular data (somatic copy-number alteration, DNA methylation and mRNA, microRNA and protein expression) from 953 samples of four cancer types from The Cancer Genome Atlas project (TCGA). They found that incorporating molecular data with clinical variables yielded statistically significantly improved predictions (FDR < 0.05) for three types of cancer (renal clear cell carcinoma, ovarian serous cystadenocarcinoma and lung squamous cell carcinoma). However, those quantitative gains were limited (2.2–23.9%). In clinically relevant genes, they identified 10281 somatic alterations across 12 cancer types in 2928 of 3277 patients (89.4%). Many of those alterations could not be revealed in single-tumor analyses. This study provides a starting point and resources, including an open-access model evaluation platform, for building reliable prognostic and therapeutic strategies that incorporate molecular data.

Specific glycosylation of membrane proteins in epithelial ovarian cancer cell lines: glycan structures reflect gene expression and DNA methylation status. Cell surface glycosylation plays an important role in a variety of cell processes including cell adhesion and cell signaling, which can be disrupted in cancer. The relationship between alterations in glycosylation and aberrant gene regulation is poorly understood in cancer. This study seeks to help understand this relationship in ovarian cancer by performing comparative glycomics of normal human ovarian surface epithelial cell lines and serous ovarian cancer cell lines. Glycans released from cell surface proteins were analyzed and characterized by LC-MS. Glycosylation differences were identified and the gene expression levels of the glycosyltransferases responsible for the synthesis of the glycans of interest were measured. Furthermore the cell lines were treated with a DNA methylation inhibitor demonstrating that the expression of the MGAT3 glycosyltransferase was associated with DNA hypomethylation, resulting in the expression of a unique type of glycans on the surface of serous ovarian cancer cells. This study provides new biological understanding that has implications for developing new cancer therapeutics and diagnostics.

In vivo modulation of hypoxia-inducible signaling by topographical helix mimetics. Arora and co-workers at New York University and the University of
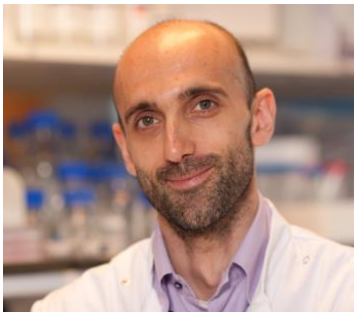
Southern California have used computational and experimental fragment-based screening to mimic the orientation and disposition of a key alpha-helical domain at the interface of hypoxia-inducible factor1 alpha (HIF1alpha) and its coactivator protein p300 to develop inhibitors of hypoxia inducible signaling. Inhibitors of hypoxia-inducible genes may serve as useful tools for understanding hypoxia signaling in tumors because of the latter's role in directing downstream signaling network that modulates cancer progression. The inhibitors were designed from oxopiperazine helix mimetic scaffolds that were assembled from naturally occurring amino acids with the nitrogen atoms of neighboring backbone amides constrained with ethylene bridges to afford a nonpeptidic chiral scaffold that possess protein-like properties. OHM 1, the most promising peptidomimetic, reduced the median tumor volume of murine tumor xenografts derived from the triple-negative breast cancer cell line MDA-MB-231 compared with the untreated group. This finding supports the notion that rational design of topographical mimics of protein secondary structures is a viable approach for developing PPI inhibitors.

Targeting Transcriptional Regulation in Cancer With a Covalent CDK7 Inhibitor. Cyclin-dependent kinases (CDKs) regulate cell-cycle dependent transcriptional programs and can often drive oncogenic transformation. However, inhibitors targeting this family of enzymes are often non-specific due to the similarity of the kinase domain active site. Using a kinase selectivity assay, Kwiatkowski et al. have identified a novel covalent inhibitor of CDK7, THZ1. They demonstrate through mass spectrometry that THZ1 binds allosterically via an acrylamide moiety to a cysteine residue outside of the kinase domain, and that this interaction can be abrogated by mutation of the cysteine residue to a serine. Cellular assays testing the efficacy of THZ1 show that it has an irreversible effect on CDK activity by inhibiting phosphorylation of RNAP polymerase II. THZ1 also caused growth inhibition when tested against a broad panel of cancel cell lines as well as in a mouse xenograft model. This suggests a new model for designing more specific next generation inhibitors for CDKs as well as other enzyme families.

A Nanoparticle Carrying the p53 Gene Targets Tumors Including Cancer Stem Cells, Sensitizes Glioblastoma to Chemotherapy and Improves Survival. Glioblastoma multiforme is the most deadly brain tumor in adults largely due to cancer stem cells (CSCs) with developed resistance to the first-line chemotherapeutic, temozolomide. Upregulation of O6-methylguanine-DNA methyltransferase (MGMT) is linked to this resistance, but has been shown to be modulated by p53, a well characterized tumor suppressor gene. Kim et al demonstrate the utility of a cationic liposome delivery platform that is administered systemically, capable of crossing the blood-brain barrier, and delivers p53 to tumor cells. scL-p53 down-regulated MGMT in vivo, increased the sensitivity of CSCs and bulk tumor cells to temozolomide, and resulted in enhanced apoptosis and mouse survival, showing the potential of gene delivery to improve efficacy in brain cancer therapy.

Opinion: Cancer chemoprevention is not a failure. In response to Dr. JD Potter's recently published review "The failure of cancer chemoprevention (Carcinogenesis 2014; 35: 974-82)", Drs Adhami, Bailey and Mukhtar published their Letter to the editor "Cancer chemoprevention is not a failure" in the same journal. They disagreed with Dr. JD Potter's rather pessimistic contention that chemoprevention of cancer was an almost universal failure and argued that if modeled in the right way chemoprevention could offer an effective alternate strategy for the management of cancer at least for high-risk individuals. After describing several successful stories on cancer chemoprevention, they point out several issues, which currently confound successful chemoprevention of cancer. Prominent among these issues are the absence of robust surrogate markers of efficacy which would help assessment of success or failure of early clinical trials; lack of interest of the pharmaceutical industry; lack of prevention awareness of members of the health care team; the public's fatalistic attitude and of course unfounded skepticism towards the prevention approach among some basic scientists. They believe that persistence and careful assessment of proof of principles, measured improvements to further enhance the benefit/risk ratio and a greater diversity of effort towards cancer chemoprevention are likely to lead to success.

4. Profile of a Young Scientist

	Employment	
	2012-present	Group Leader, Medical Research Council (MRC) Cancer Unit, University of Cambridge, UK
	2010-2012	Postdoctoral fellow, Cancer Research UK Beatson Institute, Glasgow
	2008-2010	Postdoctoral EMBO Long Term fellow, Cancer Research UK Beatson Institute, Glasgow
	Education	
	2008	Ph.D. in Neurobiology, University of Padova, Italy
	2002	MSc in Medicinal Chemistry, University of Padova, Italy

Christian Frezza is currently a group leader at the MRC Cancer Unit at the University of Cambridge, Cambridge, UK. His PhD work focused on studying mitochondrial dynamics and apoptosis in the laboratory of Dr. Luca Scorrano at the University of Padova, Italy. In 2008 he moved to the Beatson Institute of Cancer Research in Glasgow (UK), as recipient of an EMBO Long Term Fellowship, where he investigated the role of mitochondrial defects in tumorigenesis under the guidance of Prof. Eyal Gottlieb. In 2012 he started his independent career at the MRC Cancer Unit at University of Cambridge, UK.

His laboratory uses a combination of metabolomics, systems biology, and cell biology to unravel the metabolic intricacies of cancer cells. In particular, his group is investigating how the loss of the Krebs cycle enzyme Fumarate Hydratase (FH) predisposes to kidney cancer. Using this multidisciplinary approach he has contributed to reveal several metabolic pathways that are essential for growth and proliferation of FH-deficient cancer cells, including the heme biosynthesis and degradation pathway, the urea cycle, and glutathione biosynthesis, and also elucidated the metabolic rewiring that occurs under hypoxia. In the future, he is aiming to follow this approach to better comprehend the role of metabolic reprogramming during cancer transformation and to exploit this knowledge to find novel pharmacological targets for cancer therapy. Furthermore, Dr. Frezza is exploring the use of metabolomics to identify metabolic biomarkers of cancer, which can be used for diagnostic and patient stratification. Dr. Frezza's has recently won the Cambridge Cancer Centre Pump Priming Award and secured funding from the Association for International Cancer Research to carry out some of this research.

5. Spotlight on World News

Nektar Therapeutics makes progress against high-grade glioma. Nektar Therapeutics announced that the Phase 2 study of the company's NKTR-102 (etirinotecan pegol) in patients with Avastin-refractory (resistant) high-grade glioma has produced positive results. NKTR-102 is a topoisomerase I inhibitor, designed to concentrate in the tumor tissue and increase its antitumor activity in the brain and is based on Nektar Therapeutics PEGylation and advanced polymer conjugation technology platforms. NKTR-102 is also currently being evaluated in a Phase 3 clinical study in patients with advanced breast cancer. Source: Drug Discovery News

Roche acquires Seragon Pharmaceuticals for $725M. Genentech, a member of the Roche Group, has entered announced the acquisition of Seragon Pharmaceuticals Inc., a privately held biotechnology company based in San Diego. With this acquisition, Genentech obtains rights to Seragon's entire portfolio of investigational next-generation oral selective estrogen receptor degraders (SERDs), for the potential treatment of hormone receptor-positive

breast cancer in the hope of producing new drugs against hormone receptor-positive breast cancer. This type of breast cancer depends on estrogen and the estrogen receptor to grow and spread and accounts for up to 60% of all breast cancers. Seragon's lead product candidate, ARN-810, is a next-generation SERD that is currently in Phase 1 clinical trials for patients who have hormone receptor-positive breast cancer and have failed current hormonal agents.
Source: Drug Discovery News

Johnson & Johnson Innovation and Janssen Biotech enter a collaboration agreement with Dana-Farber Cancer Insititute. Cambridge, Mass.—Johnson & Johnson Innovation, Boston, and Janssen Biotech, Inc. have announced the launch of a three-year immuno-oncology lung cancer collaboration with the Dana-Farber Cancer Institute. Under the collaboration, Janssen scientists will collaborate with the researchers at Dana-Farber's Belfer Institute for Applied Cancer Science to investigate the clinical setting for select immuno-oncology agents in Janssen's pipeline for lung cancer. No financial details were disclosed. The teams will leverage the Belfer Institute's proprietary lung cancer research platform and models to evaluate immunotherapy agents in conditions that can mimic the physical environment of human lung cancer tumors. In addition, the teams will also seek to identify the most effective ways of combining immunotherapy drugs, to identify biomarkers and to explore the biological mechanisms responsible for drug resistance. Under this partnership, the researchers will also investigate molecular weaknesses found in lung cancer cells that could provide new immunotherapy targets.
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

   Epigenetics and Chromatin
   September 9 -13, 2014, Cold Spring Harbor, NY, USA

   Targeting the PI3K-mTOR Network in Cancer

September 14 - 17, 2014, Philadelphia, PA

Global Cancer Summit
September 15 -17, 2014, Hyderabad, India

Hematologic Malignancies: Translating Discoveries to Novel Therapies
September 20 - 23, 2014, Philadelphia, PA

Advances in Melanoma: From Biology to Therapy
September 20 - 23, 2014, Philadelphia, PA

European Cancer Conference 2014: Precision Medicine in Cancer Care.
September 26 – 30, 2014, Madrid, Spain

13th Annual AACR International Conference on Frontiers in Cancer Prevention Research
September 28 - October 1, 2014 | New Orleans, LA

Cancer Immunotherapy: Out of the Gate
October 6-8, 2014, New York, NY, USA

New Horizons in Cancer Research: Harnessing Breakthroughs – Targeting Cures
October 9 - 12, 2014, Pudong, Shanghai

Translational Cancer Research for Basic Scientists Workshop
October 26 - 31, 2014, Boston, MA

AICR Annual Research Conference
October 29-31, 2014, Washington, D.C., USA

Keystone Symposium on Cell Death Signaling in Cancer and the Immune System
October 28-November 2, 2014, Sao Paulo, Brazil.

10th National Cancer Research Institute Cancer Conference
November 2–5, 2014, Liverpool, UK

The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved
November 9 - 12, 2014, San Antonio, TX

The 10th Annual Personalized Medicine Conference
November 12 - 13, 2014, Boston, MA

Personal Genomes: Discovery, Treatment, and Outcomes

November 12-15, Cold Spring Harbor, NY, USA

EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics
November 18 - 21, 2014, Barcelona, Spain

Tumor Immunology and Immunotherapy: A New Chapter
December 2014, 1-4, Orlando, FL, USA.

World Cancer Congress
December 3-6, 2014, Melbourne, Australia.

San Antonio Breast Cancer Symposium
December 9 - 13, 2014, San Antonio, Texas

MYC: From Biology to Therapy
January 7-10, 2015, La Jolla, CA, USA.

Keystone Symposium on Epigenetics and Cancer
January 25-30, 2015, Keystone, Colorado, USA.

Gordon Research Conference on Stem Cells & Cancer
February 15-20, 2015, Ventura, CA, USA.