1. From the Editors

Each quarter the Editorial Board selects an area to highlight from the broad range of topics that fall under the umbrella of Chemistry in Cancer Research. Our topic this quarter is "Structure Based Design and Molecular Modeling in Cancer Drug Discovery." Editorial Board member and Editor-elect Dr. Zoe Cournia has taken the lead in assembling an overview of the topic.

Structure Based Design and Molecular Modeling in Cancer Drug Discovery

Although high throughput screening remains the method of choice for drug discovery in the pharmaceutical industry, the various drawbacks of this method, namely the high cost, the time-demanding character of the process as well as the uncertainty of the mechanism of action of the active ingredient have led to the increasing employment of rational drug design. Rational drug design using computational techniques is becoming an essential tool in assisting fast and cost-efficient lead discovery and optimization because it aims to understand the molecular basis of a disease and utilizes the knowledge of the three-dimensional structure of the biological target in the process (structure-based drug design) or the activity of known binders to the target of interest (ligand-based drug design). In recent years, significant advances in structure-based drug design and molecular modeling have contributed to the discovery of several drugs now in the market such as sorafenib, (VEGFR inhibitor, renal cell carcinoma, Bayer & Onyx, 2005), sunitinib (kinase inhibitor, gastrointestinal cancer, Pfizer, 2006), lapatinib (kinase and HER2 inhibitor, breast cancer, GSK, 2007), crizotinib (ALK inhibitor, NSCLC, GSK, 2011). As in the current pharmaceutical landscape rarely any drug reaches the market without going through a phase of molecular modeling, we have dedicated this issue to examining this topic.

Modeling techniques are applied to several phases of pharmaceutical discovery. Given a known protein binding pocket, where a potential drug can bind, the first task is to map key interactions between ligands and their binding sites, and at the same time to evaluate energetics of the resulting complexes. In this process it is advised to use diverse methods of virtual screening, utilizing both ligand- and structure-based approaches and implementation of consensus protocols, which allow the identification of a small number of diverse compounds for wet lab experiments. The recent patent cliff that has affected blockbuster drugs, led the pharma industry to also explore alternative strategies such as discovering allosteric binding sites to tackle binding site promiscuity and cancer drug resistance arising from active site mutations, disrupting protein-protein interactions, and targeting previously-thought undruggable targets, e.g. KRas or Myc. The most famous commercial example of exploiting protein allostery using computational methods is perhaps the acquisition of Nimbus Therapeutics from Gilead in 2016 for $1.2B. Nimbus is a molecular modeling drug design company specializing in allosteric inhibitors targeting KRas and Acetyl-CoA Carboxylase in metabolic disease as well as cancer. Molecular modeling techniques also play an

increasing role in predicting ADMET properties of candidate compounds, and systematic analysis of experimental and computational data to derive meaningful structure-activity relationships leading to the creation of drug candidates. Finally, candidate drug or lead optimization computational methods are gaining increasing popularity due to advent of GPU coding and advances in the underlying scientific methods (more accurate force fields and sampling algorithms). Janssen, Bayer, and Pfizer already published in 2016 several prospective applications of relative binding affinity free energy calculations, which are now becoming accessible to the lead optimization of the drug discovery process.

We are already beginning to see an upturn in prospective applications showing that *in silico* approaches can indeed accelerate the pace of drug discovery efforts, and expect this trend to continue in the immediate future, using novel methodologies as we move forward such as machine learning, neural networks, and deep learning.

One of the developers of new technologies for molecular modeling is Dr. Rommie Amaro, an Associate Professor of Chemistry and Biochemistry in University of California, San Diego and the Director of the National Biomedical Computation Resource. Her work is highlighted in this issue's Profile of an Early-career Researcher.

In this issue's Career Forum, we are pleased to offer some thoughts from Christopher I. Bayly Ph.D., Senior Scientist with OpenEye Scientific Software on how his interests led him to a career in computational chemistry.

Updates from the 2017 AACR Annual Meeting and other items

The 2017 AACR Annual Meeting featured over 6,400 abstracts and over 21,900 participants from more than 80 countries. The CICR Working Group sponsored a number of sessions, which are detailed in the News from the CICR Steering Committee section of the newsletter. The CICR Town Hall Meeting on Sunday evening was well attended, with 100 members attending the presentation by CICR leadership and the reception following. Outgoing CICR Chair Dr. Steve Davidsen provided an update on the 2016 activities and accomplishments outlined in the February 2017 Newsletter, followed by a brief update from the Newsletter Editors and an outline by incoming CICR Chair Dr. Melissa Vasbinder of planned CICR activities for the coming year. For those unable to attend, a summary of these plans are in the News from the CICR Steering Committee section below. Pictures of the event can be viewed here. Thanks to everyone who offered suggestions and encouragement to the Newsletter editors during the reception.

The Editors welcome Dr. Jordan L. Meier to the newsletter team as our newest member of the CICR Editorial Board. Dr. Meier has graciously volunteered to fill

an open slot on the board for the remainder of 2017, and we look forward to his participation.

Finally, as part of the ongoing effort to provide content of interest to the CICR membership, we are undertaking an initiative with the editors of the AACR journal *Molecular Cancer Therapeutics* to heighten awareness of the journal among CICR members. For our first installment, we highlight this article summary provided by the editors of MCT. Keep your eyes open for future content.

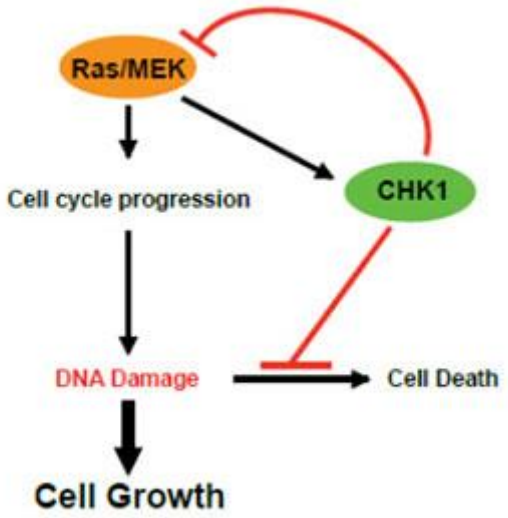
From *Molecular Cancer Therapeutics*:

Ras–MEK Signaling Mediates a Critical Chk1-Dependent DNA Damage Response in Cancer Cells

Ho-June Lee, Yi Cao, Victoria Pham, Elizabeth Blackwood, Catherine Wilson, Marie Evangelista, Christiaan Klijn, David Stokoe and Jeff Settleman

About the Article

Using high-throughput profiling of cancer cell lines with candidate anti-cancer agents, Lee and colleagues identified determinants of the response to inhibitors of the Chk1 kinase, a mediator of the DNA damage response. While sensitivity to Chk1 inhibition was previously linked to p53 mutation status, these new findings revealed an unexpected requirement for Chk1 in cells experiencing genotoxic stress after Ras-MEK pathway activation. Chk1 inhibition combined with DNA-targeted chemotherapeutics led to enhanced cell killing in some osteosarcoma, ovarian, and breast cancer cells. These findings provide insight on how to improve the efficacy of Chk1 inhibition in a subpopulation of patients.



DOI: 10.1158/1535-7163.MCT-16-0504 Published April 2017

Learn more about *Molecular Cancer Therapeutics*, the AACR journal that specializes in the discovery and development of cancer therapeutics.

2. Selected Research Highlights

Perspectives Article
"The evolution of drug design at Merck Research Laboratories"
Frank K. Brown, Edward C. Sherer, Scott A. Johnson, M. Katharine Holloway and Bradley S. Sherborne
J. Comput. Aided Mol. Des., **2017,** *31,* 255-266.
doi: 10.1007/s10822-016-9993-1
This perspectives article describes the evolution and expansion of Merck's drug design function over the period from 2010-2016. The authors point out the potential benefits achievable by applying a "design first" approach beyond the past efforts to inform small molecule optimization to encompass all phases of the discovery process from lead identification to first in human. The importance of improving human, organizational and technical factors is emphasized. Although the implementation and organizational details differ, the "design first" approach has become prevalent in most major pharma organizations. This perspective offers a useful overview for those interested in an introduction to the application of calculations, modelling and data analysis to contemporary drug discovery.

"Predictions of Ligand Selectivity from Absolute Binding Free Energy Calculations"
Matteo Aldeghi, Alexander Heifetz, Michael J. Bodkin, Stefan Knapp and Philip C. Biggin
J. Am. Chem. Soc., **2017,** *139,* 946-957.
DOI: 10.1021/jacs.6b11467
Achieving binding selectivity within a protein family is a long-standing challenge in Drug Discovery. Likewise, attempts to understand, predict and design for selectivity has long been an area of intense effort for the modelling and design community. This recent paper describes an effort to apply contemporary Molecular Dynamics approaches to Free Energy calculations to the binding of small molecule bromodomain inhibitors to multiple bromodomains, with comparisons of the calculated values to experimental data. Encouraging agreement of the calculated and experimental results was obtained for a set of three inhibitors for binding to 7 of the 8 bromodomains of the BET-family of proteins. A more challenging effort to calculate affinity of the broad-spectrum inhibitor bromosporine to 22 more structurally diverse bromodomains showed a reduced concordance with experimental data, although reparameterization of the values used for the sulfonamide moiety present in bromosporine improved the agreement somewhat. The authors feel that these results are encouraging, and that the approach should be examined for additional families of protein targets.

"Predicting "Hot" and "Warm" Spots for Fragment Binding"
Prakash Chandra Rathi, R. Frederick Ludlow, Richard J. Hall, Christopher W. Murray, Paul N. Mortenson and Marcel L. Verdonk
Journal of Medicinal Chemistry, **2017,** ASAP.
DOI: 10.1021/acs.jmedchem.7b00366

This article from scientists at Astex Pharmaceuticals examines methods for computational studies of fragment binding. The authors provide a validation set of 52 fragments identified in multiple co-crystal structures in the pdb which can be used to validate and compare computational approaches. The authors also describe an algorithm called PLImap to predict fragment binding, and use the validation set to compare it to other techniques. The fragment validation set is downloadable through the supporting information, and PLImap is publicly available from https://bitbucket.org/AstexUK/pli. This effort to integrate computational techniques into the typically experimental data driven fragment-based approach potentially extends the scope of this powerful methodology.

"Structural basis of PROTAC cooperative recognition for selective protein degradation"
Morgan S. Gadd, Andrea Testa, Xavier Lucas, Kwok-Ho Chan, Wenzhang Chen, Douglas J. Lamont, Michael Zengerle and Alessio Ciulli
Nature Chemical Biology, **2017,** *13,* 514–521.
doi:10.1038/nchembio.2329
Proteolysis Targeting Chimeras (PROTACs) are bifunctional molecules that degrade a protein target of interest by simultaneously recruiting an ubiquitin ligase, and they are the subjects of considerable current research efforts. Gadd *et al.* recently described the first x-ray crystal structure of the ternary complex of a PROTAC, ubiquitin ligase, and protein target. The authors report the structure of PROTAC MZ1, which links the E3 ligase VHL and protein target Brd4. Through several biophysical and biochemical techniques, the authors demonstrate that the MZ1 ternary complex displays positive cooperativity in binding, providing a basis for the observed preferential degradation of Brd4 over relater BET-family proteins. The authors used the structure of BD1 to create a new, highly selective Brd4 degrader, AT1.

"Spatial-temporal delivery of OX40 agonist and PD-1 inhibitor using nanoparticles improves therapeutic efficacy of cancer immunotherapy"
Yu Mi, Christof C. Smith, Feifei Yang, Jonathan Serody, Benjamin Vincent, Andrew Z. Wang
AACR Annual Meeting Abstract 978

Preliminary data reported at the 2017 annual meeting of the AACR by Wang and co-workers from the University of North Carolina Lineberger Comprehensive Cancer Center (Abstract 978) suggests that the efficacy of immunotherapy drugs can be further enhanced via the use of nanoparticles. This preclinical work utilized a nanoparticle to co-deliver a checkpoint inhibitor and an investigational OX40 agonist into T-cells. This co-delivery had the effect of increasing T-cell stimulation and resulted in corresponding increases in preclinical survival rates.

"Chemically Induced Degradation of Sirtuin 2 (Sirt2) by a Proteolysis Targeting Chimera (PROTAC) Based on Sirtuin Rearranging Ligands (SirReals)"

Matthias Schiedel, Daniel Herp, Sören Hammelmann, Sören Swyter, Attila Lehotzky, Dina Robaa, Judit Oláh, Judit Ovádi, Wolfgang Sippl, and Manfred Jung
Journal of Medicinal Chemistry, **2017,** ASAP.

Initiating the degradation of intracellular proteins with chimeric small molecules that combine a high affinity ligand to a protein of interest along with a small molecule that is capable of recruiting an E3 ligase has become a new area of extremely high interest in medicinal chemistry. In a recent paper in the *Journal of Medicinal Chemistry*, Jung and co-workers describe this PROTAC (Proteolysis Targeting Chimera) approach to the Sirt2 protein. This work utilizes a thalidomide derivative that is known to recruit the Cereblon E3 ligase and a recently identified Sirt2 inhibitor from the authors' lab. Their chimeric compound induces the degradation of Sirt2 in HeLa cancer cell lines and is believed to be the first reported example of targeting an epigenetic eraser protein with this degradation strategy. One of the challenges with this approach is the design and synthesis of the linker that establishes the chimeric bifunctional combination of the two small molecules. Notably, the authors employ in this work a "click" chemistry strategy to assemble the chimeric linker, thus creating a thalidomide conjugate that can conceivably be utilized for a number of other ligands for other target proteins of interest.

"Phosphoproteomics of Primary Cells Reveals Druggable Kinase Signatures in Ovarian Cancer"
Chiara Francavilla, Michela Lupia, Kalliopi Tsafou, Alessandra Villa, Katarzyna Kowalczyk, Rosa Rakownikow Jersie-Christensen, Giovanni Bertalot, Stefano Confalonieri, Søren Brunak, Lars J. Jensen, Ugo Cavallaro and Jesper V. Olsen
Cell Rep. **2017**,*18* (13):3242-3256.
doi: 10.1016/j.celrep.2017.03.015.

Protein phosphorylation is an important post-translational modification that plays a variety of critical roles in cellular function. In this manuscript, Francavilla et al. reported the application of single-shot mass spectrometry-based phosphoproteomics to primary cells created from tiny tissue biopsy samples from epithelial ovarian cancer. The proteome and phosphoproteome was studied in *ex vivo* cultured cells and expression levels of proteins and phosphorylation sites were compared from patient-matched epithelial ovarian cancer versus healthy cells (ovarian surface epithelium and fallopian tube epithelium). Complementary information was obtained from protein and phosphosite expression levels in developing a tissue specific signature. Particular proteins of interest were further confirmed by western blot and immunohistochemistry on tissue microarrays. Kinase signatures were also developed for epithelial ovarian cancer. CDK7 targets were shown to be especially important in controlling epithelial ovarian cancer cell proliferation in primary and ovarian cancer cell lines. Inhibition of CDK7 was also demonstrated to repress proliferation of epithelial ovarian cancer cells. This study provides a substantial contribution of information to the NCI

Clinical Proteomic Tumor Analysis Consortium (CPTAC) database, and suggests the utility of phosphoproteomics for identifying novel druggable pathways in cancer.

"Proteogenomic integration reveals therapeutic targets in breast cancer xenografts"
Kuan-lin Huang, Shunqiang Li, Philipp Mertins, Song Cao, Harsha P. Gunawardena, Kelly V. Ruggles, D.R. Mani, Karl R. Clauser, Maki Tanioka, Jerry Usary, Shyam M. Kavuri, Ling Xie, Christopher Yoon, Jana W. Qiao, John Wrobel, Matthew A. Wyczalkowski, Petra Erdmann-Gilmore, Jacqueline E. Snider, Jeremy Hoog, Purba Singh, Beifang Niu, Zhanfang Guo, Sam Qiancheng Sun, Souzan Sanati, Emily Kawaler, Xuya Wang, Adam Scott, Kai Ye, Michael D. McLellan, Michael C. Wendl, Anna Malovannaya, Jason M. Held, Michael A. Gillette, David Fenyo¨, Christopher R. Kinsinger, Mehdi Mesri, Henry Rodriguez, Sherri R. Davies, Charles M. Perou, Cynthia Ma, R. Reid Townsend, Xian Chen, Steven A. Carr, Matthew J. Ellis and Li Ding
Nat Commun. **2017** Mar 28;8:14864. doi: 10.1038/ncomms14864.

Next-generation genomic sequencing has the promise to identify opportunities in cancer to drug aberrancies in the genome for personalized medicine. However, the concept of the druggable genome largely assumes that the genome is reflected in the downstream proteome which is the primary drug target. It is reasonable to assume that the direct study of the proteome provides opportunities to validate genomic aberrations, as well as to identify new opportunities for targeted therapies. Huang et al. recently conducted such a proteogenomic study of 24 breast cancer patient-derived xenograft mouse models. Integrated analysis of protein and gene-expression data revealed gene expression signatures were well correlated with non-stromal protein expression. The integrated analysis also confirmed predicted genomic targets in a variety of receptor tyrosine kinases. Proteomic and phosphoproteomic findings also revealed novel signatures that were not reflected in the genomic profiling, suggesting novel druggable opportunities. Further drug treatment experiments supported identified response predictions. This study demonstrates the complementary information that can be obtained by both genomic and proteomic studies, and the utility of proteomic analysis in cancer.

"Phosphoproteins in extracellular vesicles as candidate markers for breast cancer"
I-Hsuan Chen, Liang Xue, Chuan-Chih Hsu, Juan Sebastian Paez Paez, Li Pan, Hillary Andaluz, Michael K. Wendt, Anton B. Iliuk, Jian-Kang Zhu and W. Andy Tao
Proc Natl Acad Sci U S A. **2017** Mar 21;114(12):3175-3180.
doi: 10.1073/pnas.1618088114. Epub 2017 Mar 7.

A blood-based test for cancer early detection remains the Holy Grail for diagnostics. Protein phosphorylation is well known to play a critical role in

regulating cellular function and is postulated to be important in early cancer. Despite the known importance of phosphorylation, relatively few studies have exploited the biological modification for diagnostic purposes. In this recent paper, Chen et al. describe a strategy to study phosphoproteins in extracellular vesicles isolated from human plasma. In recent years, extracellular vesicles have gained much attention as a means of transporting molecular information from cancer cells in blood circulation. Approximately 10,000 unique phosphopeptides were identified in extracellular vesicles isolated from cancer patient plasma samples. A subset of 144 phosphoproteins had increased levels in breast cancer patients compared to healthy controls. Some candidate biomarkers were further validated by parallel reaction monitoring. This study suggests that phosphoproteins in extracellular vesicles may have promise in cancer diagnostics.

"The allosteric inhibitor ABL001 enables dual targeting of BCR–ABL1"
Andrew A. Wylie, Joseph Schoepfer, Wolfgang Jahnke, Sandra W. Cowan-Jacob, Alice Loo, Pascal Furet, Andreas L. Marzinzik, Xavier Pelle, Jerry Donovan, Wenjing Zhu, Silvia Buonamici, A. Quamrul Hassan, Franco Lombardo, Varsha Iyer, Michael Palmer, Giuliano Berellini, Stephanie Dodd, Sanjeev Thohan, Hans Bitter, Susan Branford, David M. Ross, Timothy P. Hughes, Lilli Petruzzelli, K. Gary Vanasse, Markus Warmuth, Francesco Hofmann, Nicholas J, Keen and William R. Sellers
Nature, **2017**, 543(7647), 733-737.
DOI: 10.1038/nature21702.

A new allosteric small-molecule inhibitor of BCR-ABL1 is described, asciminib (ABL001). Unlike other inhibitors which are ATP competitive and bind to the catalytic site, ABL001 binds to the myristoyl pocket of BCL-ABL1 inducing the formation of an inactive kinase conformation. Although ABL001 has a similar cellular potency to second generation catalytic inhibitors, it contains a different spectrum of activity against various BCR-ABL1 resistance mutations. ABL001 is active against all known catalytic site mutations (including Thr315Ile) while catalytic site inhibitors are active against myristyl-site mutations. Such a pattern of non-overlapping resistance profiles was thought to provide a perfect test for the hypothesis that such a drug pair might prevent the emergence of resistant disease. Crystallography indicates that ABL001 and nilotinib can co-bind to a single BCR-ABL1 molecule. Furthermore, *in vitro* cellular studies show the additive effects of ABL001 in combination with nilotinib, imatinib or dasatinib. In a CML xenograft study, the combination of ABL001 and nilotinib led to complete disease control and eradicated the tumor. Unlike single agent dosing of either agent, no resistance emerged during or after the cessation of treatment. These results offer the possibility of treatment-free remission for CML patients and clinical trials with ABL001 in combination with nilotinib, imatinib and dasatinib are ongoing.

"Phosphatidylinositol 3-kinase δ blockade increases genomic instability in B cells"

Mara Compagno, Qi Wang, Chiara Pighi, Taek-Chin Cheong, Fei-Long Meng, Teresa Poggio, Leng-Siew Yeap, Elif Karaca, Rafael B. Blasco, Fernanda Langellotto, Chiara Ambrogio, Claudia Voena, Adrian Wiestner, Siddha N. Kasar, Jennifer R. Brown, Jing Sun, Catherine J. Wu, Monica Gostissa, Frederick W. Alt and Roberto Chiarle
Nature, **2017**, 542(7642), 489-493.
DOI: 10.1038/nature21406.

The authors found three FDA approved targeted therapies, used in the treatment of B-cell driven tumors, unexpectedly increased DNA damage in both normal and tumor cells. In particular, PI3Kδ inhibitors idelalisib (Zydelig), duvelisib and ibrutinib (Imbruvica) increase genomic instability in B-cells by affecting the expression of activation-induced cytidine deaminase (AID), a B-cell specific enzyme. While idelalisib and duvelisib directly inhibit PI3Kδ, ibrutinib inhibits BTK, which is thought to support PI3Kδ activity through a large multiprotein complex. AID is normally only expressed in immune response activated B-cells and the enzyme action is targeted at immunoglobulin genes to initiate class switch recombination and somatic hypermutation. Both idelalisib and duvelisib increase AID expression in activated B-cells leading to a higher number of on-target mutations. However, *in vitro* treatment also resulted in a higher frequency of off-target mutations, a situation which may lead to the development of certain human B-cell tumors. The authors performed *in vivo* experiments which showed that all three drugs increased the development of AID-dependent B-cell tumors, in a mouse model. Studies of blood obtained from CLL patients before and after treatment with idelalisib showed increased mutational levels by AID. All three drugs were recently approved and are given to patients indefinitely raising the need for follow-up of patients to see whether the mouse results are also observed in the clinic. These results show the potential for a targeted therapy to cause the same mutagenic DNA damage that occurs with some classic chemotherapeutic strategies.

3. Profile of an Early-career Researcher:

Rommie E. Amaro, Ph.D.

Rommie E. Amaro is a Professor and Shuler Scholar in the Department of Chemistry and Biochemistry at the University of California, San Diego. She received her B.S. in Chemical Engineering (1999) from the University of Illinois at Urbana-Champaign and subsequently worked for two years for Kraft Foods, Inc. as an Associate Research Engineer. She left Kraft to pursue her Ph.D. (in Chemistry, 2005) at the University of Illinois at Urbana-Champaign, under Prof. Zaida Luthey-Schulten. Rommie was a NIH postdoctoral fellow with Prof. J. Andrew McCammon at the University of California, San Diego from 2005-2009, and she started her independent research program in 2009 at the University of California, Irvine in the Department of Pharmaceutical Sciences. In 2012 Rommie

moved her lab to the Department of Chemistry and Biochemistry at the University of California, San Diego.

Rommie's scientific interests lie at the intersection of computer-aided drug discovery and biophysical simulation methods. She has a long-standing interest in incorporating structural and dynamical information derived from all-atom molecular dynamics simulations in drug discovery programs, and has worked in a variety of disease areas, including infectious diseases and cancer. Her lab's work on p53 revealed a novel druggable pocket that clarified the mechanism of action for a compound in clinical trials; this work served as the basis for the formation of a start-up company related to the development of p53 reactivation drugs, Actavalon, Inc. Rommie is a co-founder, on the scientific advisory board, and an equity shareholder in Actavalon, Inc.

Her scientific vision revolves around the continued development of molecular dynamics simulations in drug discovery programs, particularly in expanding the range and complexity of molecular constituents represented in such simulations, and novel multiscale methods for elucidating their time dependent dynamics. She is the Director of the NIH P41 National Biomedical Computation Resource and a co-Director of the NIH U01 Drug Design Data Resource.

Rommie is the recipient of an NIH New Innovator Award, the Presidential Early Career Award for Scientists and Engineers, the ACS COMP OpenEye Outstanding Junior Faculty Award, the ACS Kavli Foundation Emerging Leader in Chemistry National Lecturer, and the 2016 Corwin Hansch Award.

4. Spotlight on World News

The American Chemical Society establishes a new framework for reporting possible assay interference compounds.

In an editorial shared across several journals sponsored by the American Chemical Society (ACS), a joint panel of the journals' Editors-in-Chief clarified and publicized the stance of the organization on the reporting of compounds that may interfere in assays for a variety of reasons. It has become well known in the chemical literature that screening hits and other compounds can display misleading activity in a wide range of biochemical assays. These interference mechanisms can include unexpected redox activity, spectroscopic interference, and colloidal aggregation, among other reasons. In this communication, the editors outline several of these mechanisms and common methods by which such interference can be detected. Further, they state a revised policy in which any author reporting results in one of the ACS journals will be *required* to detail an analysis of active compounds from any source against lists of known inhibitors and to provide multiple pieces of experimental evidence that establish that the reported data for potentially interfering compounds is in line with expectations and not a result of artifactual activity. Read the related blogpost.

Warp Drive Bio and GSK team up to tackle difficult targets

Warp Drive Bio and GlaxoSmithKline (GSK) recently announced a new collaboration that will combine elements of both companies' technology to discover drugs against "undruggable" targets of high potential value in cancer and other diseases. The intent is to use the GSK Encoded Library Technology (ELT) to create a library containing up to 200 million compounds based on Warp Drive's Small Molecule-Assisted Receptor Targeting (SMART™) technology. This enormous new collection may have promise for discovering leads for conventionally intractable drug targets, as the SMART™ compounds rely on binding to an intracellular receptor that can then bind to a protein without a traditional small molecule binding site. In effect, this would commandeer an intracellular protein to create, in situ, a tailored biologic agent that would be capable of affecting the target protein. Initial targets are expected to center on the Ras protein, as well as SHP2 and Cbl-b.

FDA Approves Ribociclib (Kisqali) for the Treatment of HR+/HER2 Non-amplified Metastatic Breast Cancer.

The cyclin D1/CDK4 & CDK6 Inhibitor ribociclib (Novartis) was approved on March 13, 2017 for HR+/HER2- advanced or metastatic breast cancer, in combination with an aromatase inhibitor. Approval was based on the outcome of the MONALEESA-2 international clinical trial. This is the second approval of a CDK4/6 inhibitor, the first being palbociclib (Pfizer, 2016). A number of other clinical trials are currently ongoing including as a first-line therapy for HR+/HER2- premenopausal advanced breast cancer. See related blogpost.

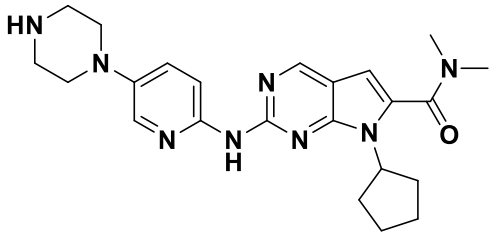


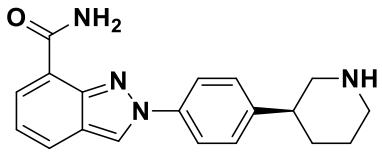
image source: Anypodetos, own work, CC0

FDA Approves Avelumab (Bavencio) for the Treatment of Metastatic Merkel Cell Carcinoma.

On March 23, 2017, the PD-L1 targeting human monoclonal antibody avelumab (EMD Serono) was approved for metastatic Merkel cell carcinoma (MCC). This is the first FDA-approved treatment for metastatic MCC, a rare and aggressive skin cancer. The compound is also being evaluated in a various investigational clinical trials including for other indications including non-small cell lung cancer (NSCLC), bladder, breast and renal cell carcinoma (RCC). Avelumab joins the other FDA-approved PD/PD-L1 approved antibodies in this competitive space including pembrolizumab (Merck, 2014), nivolumab (Bristol-Myers Squibb, 2014) and atezolizumab (Roche Genentech, 2016). See related blogpost.

FDA Approves Niraparib (Zejula) for the Treatment of Recurrent Ovarian, Fallopiant Tube, or Primary Peritoneal Cancer.

The poly(ADP-ribose)polymerase (PARP) inhibitor niraparib (Tesaro) was approved on March 27, 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The compound joins two other PARP inhibitors already approved, olaparib (AstraZeneca, 2014) and rucaparib (Clovis Oncology, 2016) with a number of others in advanced clinical development. Other clinical trials are ongoing including for first-line ovarian cancer and for Her2-/BRCA+ breast cancer. See related blogpost.



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5. News from the CICR Steering Committee, contributed by Dr. Melissa Vasbinder, Chairperson

   On behalf of our CICR Working Group, we are pleased to report another successful Annual Meeting recently held in Washington, DC. Excellent representation of chemistry was spread throughout the meeting program, including the three-part Chemistry to the Clinic series, two New Drugs on the Horizon sessions, two fora, one major symposium, five meet-the-expert sessions, seven minisymposia and fifty-one poster sessions. We were also pleased to congratulate Dr. Craig Crews, Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology, Yale University, who received the Eleventh Annual AACR Award for Outstanding Achievement in Chemistry in Cancer Research, an award generously funded by Ash Stevens. Meeting attendees gathered to hear more about the work in the Crews laboratory as presented by Dr. Crews in his award lecture - PROTACSs: targeted protein degradation as a therapeutic strategy.

   During the Annual Meeting, our CICR Working Group sponsored a Town Hall and networking reception which was a well-attended event that gathered scientists interested in hearing more about our CICR events and provided an opportunity for informal networking. During our Town Hall reception, we recognized the outstanding leadership provided by Past Chairperson Dr. Steve Davidsen (V.P. Oncology Discovery, AbbVie) and welcomed to the team Chairperson-Elect Dr. Julian Blagg (Deputy Directory & Head of Chemistry of the Cancer Research UK Cancer Therapeutics Unit at the Institute of Cancer Research, London, UK). On behalf of myself, Steve, and Julian, we are excited to work with the CICR community to continue to promote increasing awareness of chemistry and its positive impact throughout the cancer research community.

Our CICR Steering Committee for the 2017-2018 term also met face-to-face for the first time during the Annual Meeting to plan topics for the upcoming Annual Meeting in 2018 and agree on goals we aim to address for the 2017-2018 term.

We welcomed to the CICR Steering Committee the following four members who represent an increasingly wide spectrum of the CICR community.

Stephen V. Frye, PhD
Professor, Chemical Biology and Medicinal Chemistry
University of North Carolina at Chapel Hill

Philip Jones, PhD
Executive Director and Head of Drug Discovery
Institute for Applied Cancer Science
UT MD Anderson Cancer Center

Ian P. Street, PhD
CSO, Cancer Therapeutics CRC
Walter & Eliza Hall Institute of Medical Research

Zhao-Kui (ZK) Wan, PhD
Head of Chemistry
Janssen Pharmaceutical Companies, Johnson & Johnson

The following members will continue serving on the CICR Steering Committee or commence new terms.

Vinod F. Patel, PhD
Chief Scientific Officer
APC Therapeutics

Angela N. Koehler, PhD
Assistant Professor
Koch Institute of the
Massachusetts Institute of Technology (MIT)

Alan G. Olivero, PhD
Senior Director, Discovery Chemistry
Genentech, Inc.

John (Yuan) Wang, PhD (2016-2018)
Distinguished Scientist
Head of Target Modulation
Andover Innovative Medicine
Eisai, Inc.

We thank the following members for their past service: David Uehling, Paul Hergenrother, Sean Kerwin, Michael Michaelides, and Christopher O'Donnell.

For the 2017-2018 term, our CICR working group will continue making progress around expanding our outreach by increasing geographic diversity within CICR, and ensuring that CICR members have opportunities to connect with chemists outside of the annual AACR meetings. We are pleased that within our CICR Steering Committee we have representation from the US, Europe, Asia, and Australasia and we plan to capitalize on our ties within each of these regions to help drive our outreach efforts. We are working on plans to increase the chemistry presence at the AACR-NCI-EORTC International Symposium on Molecular Targets & Cancer Therapeutics meeting as well as the New Horizons in Cancer Research Conference. We are also working on proposals for a CICR special conference that would provide an additional venue for chemists to meet and share science and will be looking for input and volunteers from the CICR community as we move forward.

As part of our outreach efforts, we also aim to provide support to early-career researchers through sponsoring CICR scholar-in-training awards. The award would provide the funds necessary for the next generation of chemistry researchers to attend the AACR Annual Meeting. We are particularly interested in fostering attendance from scientists in related research areas, as well as researchers from outside of the USA who would not normally attend the AACR Annual Meeting. We are happy to help to direct any inquiries around sponsorship opportunities to the appropriate individuals within AACR. We will also be continuing to progress initiatives that were started under the leadership of Drs. Uehling and Davidsen focused on the optimal use of chemical probes and sharing academia/industry collaboration best practices.

We encourage any CICR members interested in contributing to any of the plans outlined above to reach out to either myself, Steve, or Julian below and we can provide you with more information and opportunities to get involved. We also encourage all CICR members to urge your colleagues to join the CICR Working Group in order to increase our leverage and influence within AACR. We appreciate all ideas and input to driving our chemistry vision within AACR and look forward to hearing from you.

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6. Career Forum

In keeping with this issue's focus on Structure Based Design and Molecular Modeling in Cancer Drug Discovery, we are pleased to offer some thoughts from Christopher I. Bayly, Ph.D., Senior Scientist with OpenEye Scientific Software on how his interests led him to a career in this field.

I started off my education with a B.Sc. in Biochemistry because I couldn't decide between biology and chemistry. From there I followed my interest into organic chemistry, initially doing synthetic organic chemistry. I gradually realized that I was much more interested in the behavior of organic small molecules than in making them, so I switched into theoretical organic chemistry for my Ph.D. There was a price to be paid: my biochemistry undergrad had not suitably prepared me so it cost me over a year to catch up. It turned out to be completely worth it because I have since then worked in a scientific domain I have really enjoyed; I think this tradeoff is an important consideration when thinking about changing domains. The "academic training" part of my career finished up with a postdoc with Peter Kollman at UCSF, tying together my biochemistry, organic chemistry, and theoretical chemistry by working on protein-ligand simulations… a marvelous experience.

From my postdoc I joined a large pharma's drug discovery research site, starting up the computational chemistry and informatics group at that site. That was where I got another education: working with a team of scientists from different domains, spanning the range from *in vivo* pharmacology through biology to medicinal chemistry. Suddenly I had to put my comp chem domain into context with all those other areas, discern how my science could complement the overall team effort, and communicate my results to colleagues who knew little of my science and jargon. It was challenging and addictive, spawning many enduring friendships. When that research site closed (a painful experience) I chose to follow a new direction with a scientific software company, allowing me to pursue again my love for developing new methods, still directed towards small-molecule drug development. Now my interdisciplinary team is composed of software and systems engineers and computational chemists, instead of biologists and medicinal chemists, but still there is the focus on the science and the challenge to develop a useful product with the resources at hand. Looking back I believe I could not have known the "right" direction for my career at the outset; I had to

figure it out as I went along. I am glad I took some risks to change domains a couple of times, even though there was a time and training cost each time, because otherwise I would have been unhappy in my career. As it is, I am thankful that I am still enjoying my science, that I have been able to make some useful contributions, and that I have gotten to know and work with many wonderful people along the way.
Christopher I. Bayly, Ph.D.
Senior Scientist, OpenEye Scientific Software

Resources to assist you in your job search are provided below:

https://cancercareers.org/Pages/default.aspx

http://www.nature.com/naturejobs/science/jobs

http://jobs.rsc.org/

http://chemistryjobs.acs.org/

7. Conferences

NovAliX Biophysics in Drug Discovery
June 6-9, Strasborg, France

Bioorganic Gordon Research Conference
June 11-16, 2017, Andover, NH

American Peptide Society Meeting
June 17-22, 2017. Whistler, BC, Canada

Gordon Research Conference in Heterocyclic Compounds 2017
June 18-23, 2017. Newport, RI

ACS MEDI-EFMC: Medicinal Chemistry Frontiers 2017
June 25-28, 2017, Philadelphia, Pennsylvania

Gordon Research Conference in Computer Aided Drug Design 2017
July 16-21, 2017. West Dover, VT

Gordon Research Conference in Organic Reactions & Processes 2017
July 23-28, 2017. Easton, MA

Royal Australian Chemical Institute Centenary Congress
July 23-28, Melbourne, Australia

Gordon Research Conference in Natural Products & Bioactive Compounds 2017
July 30 – August 4, 2017. Andover, NH

Gordon Research Conference in Medicinal Chemistry 2017
August 6-11, 2017, New London, NH

Gordon Research Conference in Hormone-Dependent Cancers
August 6-11, 2017, Newry, ME

254th ACS National Meeting & Exposition
August 20-24, 2017, Washington, DC

EFMC-ASMC'17 European Federation for Medicinal Chemistry International Symposium on Advances in Synthetic and Medicinal Chemistry
August 27-31, 2017, Vienna, Austria

AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics
October 26-30, 2017, Philadelphia, Pennsylvania

AACR Annual Meeting 2018
April 14-18, 2018. Chicago, IL.