1. From the Editors

From the Editors, with Dr. Alex Waterson, Editorial Board Member

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 *targeting oncogenic RAS*. CICR editorial board member Alex Waterson has taken the lead in assembling an overview of the topic.

RAS: A challenging target for therapeutic intervention

RAS is a small GTPase that acts as a central control node for a vast multitude of cellular processes and has been called the “beating heart of signal transduction”. This moniker results from its mechanism of action and regulation processes, which together involve a coordinated switching of conformational states, cycling between inactive and active states that interact with a differing array of downstream partners in response to various upstream signals and subsequent binding to two different nucleotides. Perhaps unsurprisingly, then, dysregulation of RAS and its various signaling partners has a number of potentially unfavorable cellular consequences, not the least of which is tumorigenesis and maintenance of a transformed phenotype.

Indeed, *RAS* was among the very first oncogenes discovered, and still ranks as among the most important. Famously, the three members of the RAS family (encoded by *HRAS*, *KRAS*, and *NRAS*) together comprise the most common oncogenes in human cancer. Mutations in the family result in over-active downstream signaling, typified by an inability of the protein to revert to an inactive state. These activating mutations are found in ~30% of all human cancers, with the incidence of *RAS* mutations approaching 90% in some tumor types. Further, the presence of such mutations is generally associated with extremely poor patient outcomes and resistance to most therapies, targeted and otherwise.

It is somewhat surprising, then, that no true RAS-targeted drugs are currently approved. The reason behind this is partly tied to an extreme difficulty in designing or identifying molecules that can effectively interfere with RAS function. RAS is the classic “undruggable” target, with signaling interactions driven by a wide diversity of protein-protein interactions and no easily accessible pockets able to bind to small molecules with high affinity. Indeed, the only pocket on RAS known to bind a small molecule with high affinity is already occupied the nucleotides GDP or GTP, both of which bind to the protein with picomolar affinities and are present in cells at extremely high concentrations.

However, because of the critical nature of RAS signaling in cancer, drug discovery efforts have continued for decades. One of the earliest attempts to inhibit RAS was based on inhibition of farnesyl transferases, with a goal of affecting RAS function by inhibiting the post-translational modification of the

protein. However, this approach has not achieved widespread clinical success. Numerous efforts to discover and apply inhibitors of multiple kinase-based cellular signaling components downstream of RAS have likewise failed to produce meaningful clinical impact in RAS-driven cancers. However, studies to better understand the utility of combinatorial inhibition of multiple pathways downstream of RAS simultaneously continue unabated, as highlighted by one of our feature articles, from *Molecular Cancer Therapeutics*, in this newsletter.

Recent years have also seen a dramatic “renaissance” in discovery efforts aimed at direct inhibition of RAS. For example, the National Cancer Institute has organized a RAS Initiative to bring together experts from numerous disciplines (including chemists, structural biologists, biochemists, cellular biologists, etc.) and from multiple backgrounds (industry, academia, and government-funded institutions), all working toward both a better understanding of RAS and uncovering novel approaches toward its inhibition. It is clear from this initiative, which is the subject of a yearly update symposium at the AACR annual meetings, as well as from decades of prior work, that exceptional means will be necessary to achieve meaningful inhibition of RAS function. In keeping with that thought, the use of non-traditional discovery efforts, including fragment-based screening and covalent inhibitors, have produced some of the more exciting recent advancements.

In our early career profile, we highlight Dr. Jonathan Ostrem, who, as a MD/PhD student in the Shokat lab at UCSF, played a key role in the discovery of covalent modifiers of RAS that take advantage of a new pocket on the protein and a nucleophilic thiol that arises from an oncogenic *RAS* mutation. Two of our highlight papers in this issue demonstrate the continued impact of this discovery, showing improved covalent inhibitors and potential ways to extend the utility of this covalent modification strategy. With these leads, when considered alongside new leads from fragment-based initiatives at Genentech, Vanderbilt, and other institutions, the medicinal chemistry community seems poised to make significant inroads into the discovery of RAS inhibitors with clinical utility.

Changes to the Newsletter Editorial Board for 2018

This is the final newsletter issue for 2017, and I would like to take the opportunity to thank outgoing Editorial Board Members Dr. Gunnar Boysen and Dr. Sharon Pitteri, as well as Past Editor Dr. Klaus Pors, for their service. Dr. Zoe Cournia will take up the reins as Editor with the next issue. The CICR Steering Committee has selected the Editor-Elect for 2018 and several new members for the Newsletter Editorial Board. Current Editorial Board member Dr. Alex G. Waterson, Research Associate Professor of Pharmacology and Chemistry at Vanderbilt University will be Editor-Elect in 2018 and become Editor in 2019. Replacing Alex for the remainder of his 2017-2020 term will be Dr. Daniel A. Heller, Assistant Member in Molecular Pharmacy and Chemistry at Memorial Sloan Kettering Cancer Center. The Steering Committee has selected three

members for 2018-2021 terms: Dr. Martin Swarbrick, Senior Group Leader, Discovery Chemistry at the Institute of Cancer Research UK, Dr. Zhao-Kui Wan, Head of Chemistry at Janssen Pharmaceutical Companies in Shanghai, and current board member Dr. Jordan L. Meier, Investigator in the Chemical Biology Laboratory at the National Cancer Institute. Thanks to all of them for their willingness to step up and serve.

Share your science at the upcoming AACR 2018 Annual Meeting

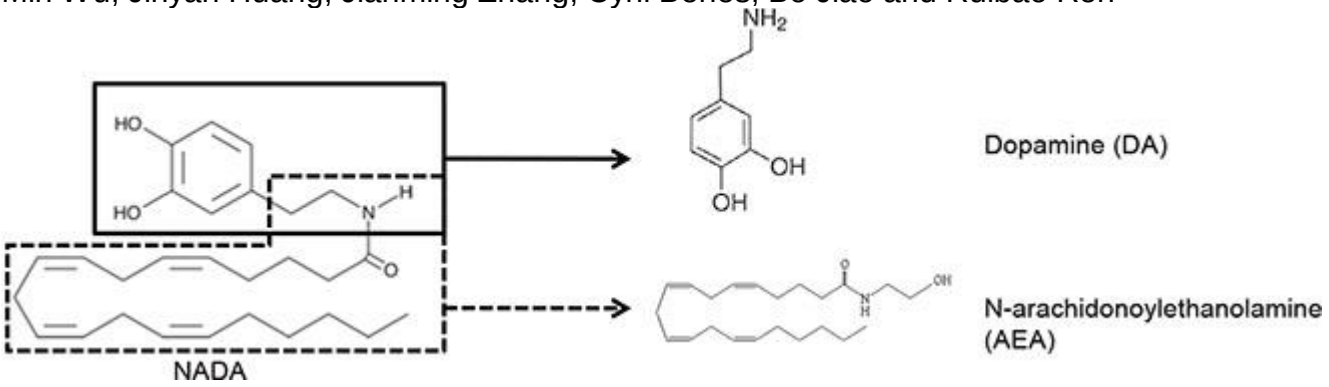
The AACR 2018 Annual Meeting will be held on April 14-18 2018 in Chicago, Illinois. The deadline for Abstract submission is December 1, and Early Registration closes December 15. Many CICR members have commented that the number of presentations featuring chemistry and preclinical drug discovery at AACR Annual Meetings seems to be in decline. The CICR leadership makes every effort to create opportunities for these types of talks in the program, and all of us can help by submitting abstracts and sharing our science. The Program Committee chooses symposium and mini-symposium topics for the Annual Meeting based, in part, on the number of abstracts submitted in various areas, so please consider submitting an abstract for next year's annual meeting. For information on some CICR activities planned for the Annual Meeting, check out the News from the CICR Steering Committee section of the newsletter.

From *Molecular Cancer Therapeutics*:

In this issue, we highlight these *Molecular Cancer Therapeutics* (*MCT*) articles focusing on RAS and tumors associated with KRAS activity.

N-Arachidonoyl Dopamine Inhibits NRAS Neoplastic Transformation by Suppressing Its Plasma Membrane Translocation

Min Wu, Jinyan Huang, Jianming Zhang, Cyril Benes, Bo Jiao and Ruibao Ren

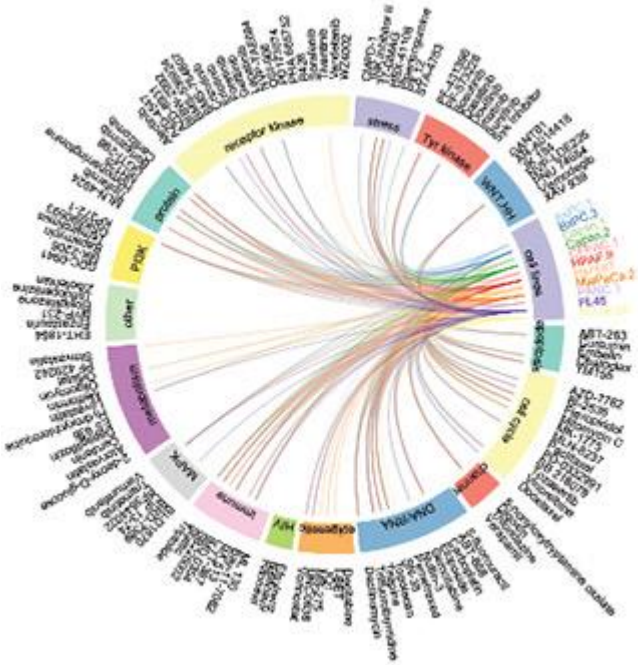


RAS oncogenic mutations are common in human cancers, but RAS proteins have been difficult to target. RAS proteins rely upon lipid modifications, and RAS regulates lipid metabolisms in cancer cells. A new class of inhibitors for RAS transformation was discovered after screening a bioactive lipid library using a RAS-specific cell viability assay. Compounds in the class are represented by endocannabinoid N-arachidonoyl dopamine (NADA), which inhibits NRAS and

KRAS4A plasma membrane translocation by targeting a novel molecular process.

Combinatorial Screening of Pancreatic Adenocarcinoma Reveals Sensitivity to Drug Combinations Including Bromodomain Inhibitor Plus Neddylation Inhibitor

Casey G. Langdon, James T. Platt, Robert E. Means, Pinar Iyidogan, Ramanaiah Mamillapalli, Michael Klein, Matthew A. Held, Jong Woo Lee, Ja Seok Koo, Christos Hatzis, Howard S. Hochster and David F. Stern



Pancreatic adenocarcinoma (PDAC), with a high prevalence of KRAS activation, is associated with dismal survival rates and is the fourth-leading cause of cancer death in the United States. Very few therapeutic options exist for PDAC patients. Langdon and colleagues describe a combinatorial drug screen to identify therapeutic regimens that can inhibit the growth of PDAC cells. One of several effective combinations, consisting of the bromodomain inhibitor JQ1 and neddylation inhibitor MLN-4924, super-additively inhibited the growth of PDAC cells and xenografts. Dysregulation of reactive oxygen species-induced DNA damage responses contributed to the impact of this combination. These, and other high-ranking combinations including US FDA-approved agents, offer some promise for control of PDAC.

Learn more about *Molecular Cancer Therapeutics*, including the new article categories, and explore the latest issue.

2. Selected Research Highlights

Review Article

"Latest Advances Towards Ras inhibition: A Medicinal Chemistry Perspective"
Brice Sautier, Carl F. Nising and Lars Wortmann
Angew. Chem., **2017**, *55*, 15982-15988.

This review provides an overview of the current state of the art for the direct targeting of the RAS protein. In particular, recent advances with covalent inhibitors targeting the $KRAS^{G12C}$ mutant and small molecule and peptide inhibitors of RAS-effector interactions are described. The authors compare and evaluate all described compounds from a medicinal chemistry perspective, with a useful assessment of compound liabilities.

Perspectives Article

"Drugging the 'undruggable' cancer targets"
Chi V. Dang, E. Premkumar Reddy, Kevan M. Shokat and Laura Soucek
Nature Rev. Cancer **2017**, *17*, 501-508.

This perspectives article uses a question and answer format to present the authors' opinions on advances and challenges in pursuing 'undruggable' targets, including RAS. The article points out that 'difficult to drug' or 'yet to be drugged' may be a more appropriate way to think about these targets. Each of the authors offers their thoughts on these four questions: 1) What would you say are the key so-called undruggable targets in cancer (and why)? 2) What are the potential benefits of targeting these molecules or pathways? 3) Where are we now in terms of making these targets druggable? 4) What are the future challenges for this field of research?

Primary Research Articles

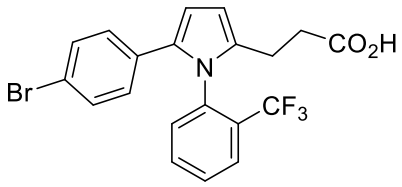
"Potent and Selective Covalent Quinazoline Inhibitors of KRAS G12C"
Mei Zeng, Jia Lu, Lianbo Li, Frederic Feru, Chunshan Quan, Thomas W. Gero, Scott B. Ficarro, Yuan Xiong, Chiara Ambrogio, Raymond M. Paranal, Marco Catalano, Jay Shao, Kwok-Kin Wong, Jarrod A. Marto, Eric S. Fischer, Pasi A. Jänne, David A. Scott, Kenneth D. Westover and Nathanael S. Gray
Cell Chemical Biology, **2017**, *24*, 1005-1016.

In a recent paper in *Cell Chemical Biology*, a collaborative effort between scientists at the Dana Farber Institute and UT Southwestern discloses covalent

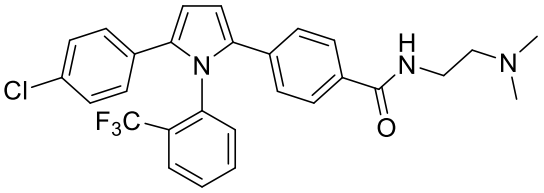
inhibitors of RAS with greatly improved potency and selectivity. Beginning with a molecule previously reported in the patent literature, the authors prepared several derivatives with new substitutions that improved the covalent labeling of RAS, despite having no changes in the acrylamide warhead. Using X-ray co-crystallography, it was found that the new substituents induce different conformations of the protein and also engage in new interactions with a specific residue at the periphery of the binding site. These improved molecules are capable of disrupting RAS-driven phospho-ERK signaling at submicromolar concentrations, thus ranking amongst the most potent inhibitors of RAS yet reported.

"Modulating Protein-Protein Interactions of the Mitotic Polo-like Kinases to Target Mutant KRAS"
Ana J. Narvaez, Suzan Ber, Alex Crooks, Amy Emery, Bryn Hardwick, Estrella Guarino Almeida, David J. Huggins, David Perera, Meredith Roberts-Thomson, Roberta Azzarelli, Fiona E. Hood, Ian A. Prior, David W. Walker, Richard Boyce, Robert G. Boyle, Samuel P. Barker, Christopher J. Torrance, Grahame J. McKenzie, and Ashok R. Venkitaraman
Cell Chemical Biology **2017**, *24*, 1017–1028.

Based on an HTS diversity screening campaign, the authors, primarily at the University of Cambridge, identified a compound, named Poloppin, that inhibits the binding of a labeled peptide to the to the Polo-box domain of the kinase Plk1. The work is reported in *Cell Chemical Biology*. As may be expected from a compound that interferes with Plk1 function, the compound was shown to disrupt normal mitotic processes, resulting in mitotic arrest. However, the method of action appears to be different than that displayed by ATP-competitive inhibitors. Further, Poloppin was found to kill cancer cells bearing *KRAS* mutations in several settings. An optimized analog, Poloppin II, displayed inhibition of tumor growth in a murine xenograft study after oral dosing. This mechanism of action may less susceptible to the development of resistance versus ATP-competitive inhibitors, and thus may represent a more attractive therapeutic strategy.



Poloppin



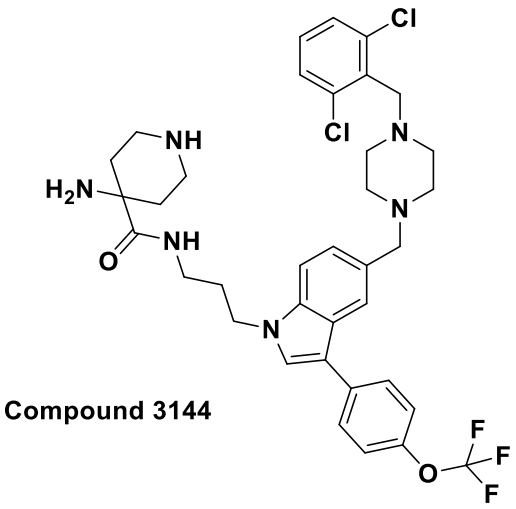
Poloppin II

"Expanding the Scope of Electrophiles Capable of Targeting K-Ras Oncogenes"
Lynn M. McGregor, Meredith L. Jenkins, Caitlin Kerwin, John E. Burke, and Kevan M. Shokat
Biochemistry **2017**, *56*, 3178−3183.

The Shokat group at the University of California, San Francisco was the first team to report selective reaction of a small molecule with RAS^{G12C}, reinvigorating efforts toward a bona fide drug targeting this important oncogene. The same group has now greatly expanded the arsenal of electrophiles shown to be capable of labeling $KRAS^{G12C}$, as published in *Biochemistry*. However, RAS has many oncogenic variations that do not possess a mutation that a drug researcher can take advantage of in this way, highlighted by $KRAS^{G12D}$. Remarkably, some of the electrophiles surveyed were shown to react with the aspartate of this mutated protein, albeit fairly weakly. Indeed, some of the new electrophiles, when attached to a ligand known to be effective in the context of a G12C labeling compound, even show selectivity for reaction with carboxylates over free thiols. The data presented in their new manuscript has wide ranging implications for covalently modulating proteins. In particular, the observed changes in the rate of reaction and the binding mode of the inhibitor that were caused by relatively minor changes in the electrophile further highlight the need to carefully fine tune any electrophilic molecule for optimal interactions with its protein partner.

"Multivalent Small-Molecule Pan-RAS Inhibitors"
Matthew E. Welsch, Anna Kaplan, Jennifer M. Chambers, Michael E. Stokes, Pieter H. Bos, Arie Zask, Yan Zhang, Marta Sanchez-Martin, Michael A. Badgley, Christine S. Huang, Timothy H. Tran, Hemanth Akkiraju, Lewis M. Brown, Renu Nandakumar, Serge Cremers, Wan Seok Yang, Liang Tong, Kenneth P. Olive, Adolfo Ferrando and Brent R. Stockwell
Cell, **2017**, *168*, 878-889.

The article describes the discovery of small-molecule pan-RAS ligands, designed to interact with adjacent sites on the surface of oncogenic KRAS. Structural analysis of the oncogenic $KRAS^{G12D}$ mutant and its effector proteins found three adjacent sites that could be targeted to block their interactions. Through the virtual screening of designed chemical fragments into each of these sites on $KRAS^{G12D}$, small-molecules were designed spanning two or three of the sites. The most promising molecules were synthesized and the most promising candidate identified was as compound 3144. Using thermophoresis, NMR and isothermal calorimetry (ITC), compound 3144 was found to bind to $KRAS^{G12D}$ proteins with a K_D of about 10-20 μM. The compound also bound to other members of the RAS family such as HRAS and NRAS, identifying it as a multivalent pan-RAS inhibitor. The compound was found to inhibit the proliferation of cell lines with a RAS dependence, while also having some stability in metabolic assays and exhibiting activity in xenograft mouse cancer models. However, observed toxicity and the low biochemical potency of the compound raise the issue of off-target activity for this compound. In spite of this, the results indicate a useful approach towards the direct inhibition of RAS proteins in human cancers, complementary to other approaches such as covalent molecules targeting KRAS Ras^{G12C}.



Compound 3144

"Inhibition of RAS function through targeting an allosteric regulatory site"
Russell Spencer-Smith, Akiko Koide, Yong Zhou, Raphael R Eguchi, Fern Sha, Priyanka Gajwani, Dianicha Santana, Ankit Gupta, Miranda Jacobs, Erika Herrero-Garcia, Jacqueline Cobbert, Hugo Lavoie, Matthew Smith, Thanashan Rajakulendran, Evan Dowdell, Mustafa Nazir Okur, Irina Dementieva, Frank Sicheri, Marc Therrien, John F Hancock, Mitsuhiko Ikura, Shohei Koide and John P O'Bryan.
Nature Chemical Biology, **2017,** *13,* 62-68.

Spencer-Smith *et al*., have developed a synthetic monobody (NS1) that binds to both GDP- and GTP-bound HRAS and KRAS with nanomolar affinities. Using X-ray crystallography, the authors determined that NS1 disrupts RAS dimerization by binding to the α4-α5 interface, which represents a novel surface for RAS binding and a novel mechanism of action for inhibiting RAS function.

"Panobinostat sensitizes KRAS-mutant non-small-cell lung cancer to gefitinib by targeting TAZ"
Wen-Ying Lee, Pin-Cyuan Chen, Wen-Shin Wu, Han-Chung Wu, Chun-Hsin Lan, Yen-Hua Huang, Chia-Hsiung Cheng, Ku-Chung Chen and Cheng-Wei Lin
Int. J. Cancer, **2017**,*141*, 1921-1931.

Mutation of *KRAS* in non-small-cell lung cancer (NSCLC) is associated a poor response to epidermal growth factor receptor (EGFR) inhibitors and chemotherapy. Lee *et al.* report that panobinostat, a clinically available histone deacetylase inhibitor, overcame resistance to gefitinib in *KRAS*-mutant/*EGFR*-wild-type NSCLC. Combined panobinostat and gefitinib synergistically reduced tumor growth *in vitro* and *in vivo*. Mechanistically, they identified that panobinostat, but not gefitinib, inhibited TAZ transcription, and the combination of panobinostat and gefitinib synergistically downregulated TAZ and TAZ downstream targets, including EGFR and EGFR ligand. Inhibition of TAZ by panobinostat sensitized *KRAS*-mutant/*EGFR*-wild-type NSCLC to gefitinib. Their

findings identify that targeting TAZ-mediated compensatory mechanism is a novel therapeutic approach to overcome gefitinib resistance in *KRAS*-mutant/E*GFR*-wild-type NSCLC.

"Discovery of a selective catalytic p300/CBP inhibitor that targets lineage-specific tumours."
Loren M. Lasko, Clarissa G. Jakob, Rohinton P. Edalji, Wei Qiu, Debra Montgomery, Enrico L. Digiammarino, T. Matt Hansen, Roberto M. Risi, Robin Frey, Vlasios Manaves, Bailin Shaw, Mikkel Algire, Paul Hessler, Lloyd T. Lam, Tamar Uziel, Emily Faivre, Debra Ferguson, Fritz G. Buchanan, Ruth L. Martin, Maricel Torrent, Gary G. Chiang, Kannan Karukurichi, J. William Langston, Brian T. Weinert, Chunaram Choudhary, Peter de Vries, John H. Van Drie, David McElligott, Ed Kesicki, Ronen Marmorstein, Chaohong Sun, Philip A. Cole, Saul H. Rosenberg, Michael R. Michaelides, Albert Lai, Kenneth D. Bromberg
Nature, **2017,** *550,* 128–132.

Lysine acetylation is a reversible posttranslational modification that plays a critical role in regulating oncogenic gene expression. Efforts to target the readers and erasers of acetylation (bromodomains and lysine deacetylases, respectively) have been successful and have led to the development of a large number of clinical and pre-clinical agents. In contrast, the lysine acetyltransferase (KAT) enzymes that write acetylation lack high quality chemical probes, and have largely remained an "undruggable" target in the field of epigenetic drug discovery. In this study, Lasko *et al.* disrupt this paradigm by reporting the first reversible inhibitors of the p300/CBP KAT catalytic domain. Using virtual screening and synthetic optimization they identify a small molecule (A-485) that inhibits p300 with nanomolar affinity. Crystallographic studies define key interactions between A-485 and p300, including a key hydrogen bonding interaction with p300's L1 loop that provides a structural basis for the compound's selectivity. Detailed biological studies find A-485 exhibits antitumor activity in castration-resistant prostate cancer models. This appears to be due its ability to antagonize androgen receptor-mediated gene expression, which requires p300's acetyltransferase activity, even in prostate cancer models that have become resistant to anti-androgens. In addition to providing first-in-class molecules for probing the role of p300/CBP in cancer, this study unambiguously demonstrate the tractability of KATs to small molecule inhibition, and thus may prove pivotal in revitalizing interest in this class of epigenetic drug targets.

"Global Protease Activity Profiling Provides Differential Diagnosis of Pancreatic Cysts"
Sam L. Ivry, Jeremy M. Sharib, Dana A. Dominguez, Nilotpal Roy, Stacy E. Hatcher, Michele T. Yip-Schneider, C. Max Schmidt, Randall E. Brand, Walter G. Park, Matthias Hebrok, Grace E. Kim, Anthony J. O'Donoghue, Kimberly S. Kirkwood and Charles S. Craik
Clinical Cancer Research **2017**, *23*, 4865-4874.

With increased use of high resolution abdominal imaging, incidental findings of pancreatic cysts are becoming increasingly common. There is currently no clinical diagnostic to distinguish benign cysts from those with malignant potential. Ivry *et al.* recently described a study that investigated protease activity as a means for distinguishing benign nonmucinous cysts from premalignant mucinous cysts. First, they used a global approach to perform protease profiling and measure protease activities in a set of cyst fluid samples. Proteases of interest were further validated in a larger set of cyst fluid samples using a targeted assay requiring only 5 µL of cyst fluid. Two proteases, gastricsin and cathepsin E, were found to be highly elevated in mucinous cyst fluid. Immunohistochemistry was performed to investigate the relationship of each protease with dysplasia grade. Both proteases showed encouraging specificity and sensitivity for differentiating mucinous from non-mucinous cysts, and gastricsin outperformed CEA, the clinical marker. These results suggest that gastricin and cathepsin E may have diagnostic potential and clinical utility for distinguishing high risk lesions that require treatment from benign lesions that can be spared unnecessary surgery.

"Chemical Proteomics Identifies Druggable Vulnerabilities in a Genetically Defined Cancer"

Liron Bar-Peled, Esther K. Kemper, Radu M. Suciu, Ekaterina V. Vinogradova, Keriann M. Backus, Benjamin D. Horning, Thomas A. Paul, Taka-Aki Ichu, Robert U. Svensson, Jose Olucha, Max W. Chang, Bernard P. Kok, Zhou Zhu, Nathan T. Ihle, Melissa M. Dix, Ping Jiang, Matthew M. Hayward, Enrique Saez, Reuben J. Shaw, and Benjamin F. Cravatt

Cell **2017**, *in press*.

In this recent paper Bar-Peled *et al.* utilized a chemical proteomics approach to map druggable proteins in genetically defined non-small cell lung cancer (NSCLC) cells. Mutations in *KEAP1* often activate the transcription factor NRF2, a regulator of cellular antioxidant stress in NSCLC. Directly inhibiting NRF2 is challenging, however its activation is thought to cause a series of downstream changes in biological pathways which may be more easily targeted. The chemical proteomics experiments identified novel potentially druggable proteins that are expressed in *KEAP1*-mutant NSCLC cell lines. NR0B1 emerged as a leading possible target. NR0B1, an orphan receptor, was shown to engage in a key protein complex that regulates transcription in *KEAP1*-mutant NSCLC cells. In addition, the authors identified small molecules that targeted NR0B1, and demonstrated that these molecules disrupted NR0B1 complexes and impaired a critical growth pathway in the cells. These findings suggest that NR0B1 is a novel druggable target in NRF2-dependent lung cancers.

"Endogenous androgen receptor proteomic profiling reveals genomic subcomplex involved in prostate tumorigenesis"

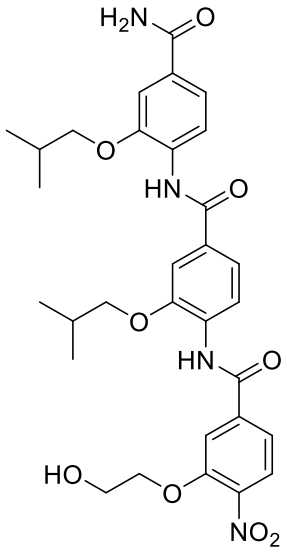
S. Stelloo, E. Nevedomskaya, Y. Kim, L. Hoekman, O. B. Bleijerveld, T. Mirza, L. F. A. Wessels, W. M. van Weerden, A. F. M. Altelaar, A. M. Bergman and W. Zwart

Oncogene **2017**, in press

Androgen receptor (AR) has long been known to play a key role in prostate cancer. Stelloo *et al.* recently sought to identify novel proteins involved in the AR transcriptional complex in LNCaP prostate cancer cells. With synthetic androgen, 66 established and new AR interacting proteins were identified. A subset of these proteins required for proliferation of LNCaP cells were further studied using chromatin immunoprecipitation assays and sequencing. These experiments identified novel genomic subcomplexes of AR interacting proteins including novel subgroups associated with selective gain of function for AR behavior in tumorigenesis. The combination of the proteomic and genomics approaches helped uncover novel AR transcriptional complexes which were able to distinguish normal AR behavior from malignant AR behavior. These results suggest that AR-interacting proteins may play key roles in AR function in manner specific to genomic location.

"Estrogen receptor coregulator binding modulators (ERXs) effectively target estrogen receptor positive human breast cancers"
Ganesh V Raj, Gangadhara Reddy Sareddy, Shihong Ma, Tae-Kyung Lee, Suryavathi Viswanadhapalli, Rui Li, Xihui Liu, Shino Murakami, Chien-Cheng Chen, Wan-Ru Lee, Monica Mann, Samaya Rajeshwari Krishnan, Bikash Manandhar, Vijay K Gonugunta, Douglas Strand, Rajeshwar Rao Tekmal, Jung-Mo Ahn, and Ratna K Vadlamudi.
eLife, **2017,** *6,* e26857.

The estrogen receptor is an important marker in breast cancer, as 70% of breast cancer patients have estrogen receptor-positive breast cancer. Raj *et al*., have developed a small molecule, ERX-11, that binds to the estrogen receptor, but not at the typical ligand-binding site; rather, it binds at the coregulator binding region of estrogen receptor and blocks the interaction with coregulator proteins. The molecule is orally bioavailable and shows good activity in a tumor xenograft model and in decreasing the growth of patient-derived explants.



ERX-11

Profile of an Early-career Researcher:

Profile of an Early-Career Researcher: Dr. Jonathan Ostrem

“Mutant RAS protein”. It is a chilling phrase – one that strikes fear into doctors and patients alike, as they understand that, with very few effective treatment options available, the battle may be even tougher than they thought. The same phrase produces a similar reaction in the drug discovery scientist who understands just how difficult it has been to discover and develop new drugs that reign in the rampant excessive Ras-based cellular signaling that underlies nearly 30% of all human cancers.

This issue's Early Career Profile highlights Dr. Jonathan Ostrem, whose thesis work at the University of California, San Francisco comprises one of the more dramatic recent advancements toward the goal of discovering a targeted RAS therapy. This work has earned Dr. Ostrem several accolades, including being named to the Forbes 30 under 30 in Science and Healthcare in 2014. After obtaining a Bachelor of Science in 2007 from the University of California, San Diego, where he was presented with the Joseph E. Mayer Award for outstanding research in chemistry (among several other awards and decorations), Dr. Ostrem completed his Ph.D. in late 2013 at UCSF and subsequently his Doctor of Medicine in 2016. He is currently a Clinical Fellow in residence at Brigham and Women's Hospital in Boston, Massachusetts.

Dr. Ostrem's graduate work, performed in the lab of Professor Kevan Shokat, introduced to the world a new direction toward the discovery of true, targeted RAS inhibitors. In the novel approach discovered by Ostrem and colleagues, an electrophilic small molecule is presented to the cysteine inherent to a common *RAS* mutant, G12C.

The small molecules inhibitors, which can contain disulfide, vinyl sulfonamide, or acrylamide electrophiles, were originally discovered using the tethering screening platform first utilized by Professor Jim Wells. The new inhibitors that the team discovered were found, by X-ray co-crystallography, to bind to a pocket on the RAS protein underneath the Switch II region. Utilizing an iterative structure-guided design process, the team improved on the initial hits to obtain compounds that more effectively react with the mutant protein.

The Switch I and II regions of RAS are conformationally labile and form the basis for the protein-protein interactions that drive both the regulation of RAS and its downstream effector signaling. Importantly, binding to this new pocket disrupts both switches and causes RAS to preferentially bind GDP, resulting in an inactive protein incapable of initiating downstream oncogenic signals. Indeed, the new compounds were shown to impair RAS signaling and induce apoptosis in RAS^{G12C}-containing cancer cell lines.

While this work has clearly opened new doors to the inhibition of RAS, significant concern over the use of an electrophilic molecule will remain in the minds of most chemical biologists, chemists, and drug discovery scientists. However, Ostrem and colleagues demonstrated that these inhibitors do not react with several other proteins and do not affect cell lines lacking the key G12C mutation. It is this confirmation of selectivity, perhaps, that has given confidence to other researchers in the field that these may be a true breakthrough toward the elusive goal of Ras inhibition.

Follow-up efforts from the Shokat lab and from a small pharmaceutical company that has spun off from the work have demonstrated that electrophilic molecules

that utilize this pocket and novel mechanism of action sample intracellular RAS in its GDP-bound state and thus sequester it in the inactive form. Further, electrophiles targeting the nucleophilic cysteine in mutant *RAS* can be made to be exquisitely selective, and have demonstrated *in vivo* activity. Further, recently reported efforts following up on Ostrem's original work are aimed at the extension of this approach to additional oncogenic *RAS* mutants.

The work of Dr. Ostrem described above has had a profound effect on the Ras community, and has formed part of the so-called "Ras renaissance". It has served to reinvigorate pharma and academic efforts toward the discovery of true, targeted RAS inhibitors.

Going forward, Dr. Ostrem will start fellowship training in oncology in 2018 and intends to continue a career in the field of chemical biology, with a focus toward small molecule development for cancer therapy as well as the development of chemical tools to study cancer signaling. He also expresses an interest in the application of chemical biology to immunotherapy - particularly in the design of even more sophisticated cell-based therapies. This researcher has already made waves in the community and we look forward to additional, exciting developments in the future.

3. Spotlight on World News

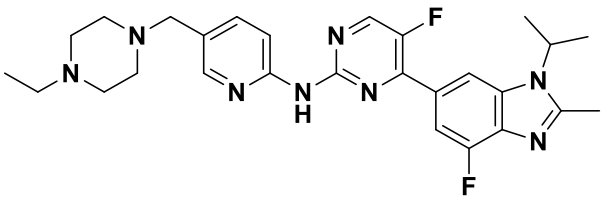
Eli Lilly becomes the latest large Oncology drug developer to undergo significant downsizing

In a continuation of a disappointing trend that now spans more than a decade, Eli Lilly & Co. announced recently that they plan to shed as much as 8.5% of their total workforce. This amounts to as much as 3,500 positions, with around 2000 of these in the United States. Some of these reductions will apparently come from the shuttering of research facilities in New Jersey and Shanghai, but the company also plans to encourage a number of early retirements. While the business reasons behind the cuts, which have the potential to save as much as $500 million per year, may stem from looming patent expirations, Lilly believes that the reductions will allow improved focus on newer drugs. Source: https://www.bloomberg.com/news/articles/2017-09-07/lilly-to-cut-3-500-jobs-close-sites-as-drugmaker-streamlines

FDA Approval of Abemaciclib (Verzenio)

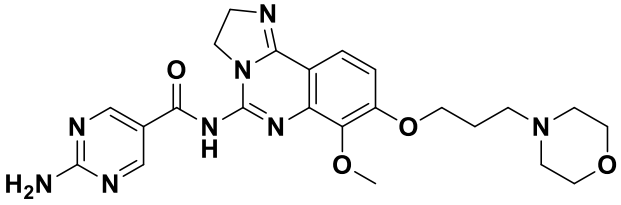
The selective CDK4/6 inhibitor abemaciclib (Eli Lilly) was approved on September 28, 2017 for adults with HR+/HER2- advanced or metastatic breast cancer that has advanced after endocrine therapy. This is the third approval of a CDK4/6 inhibitor, following palbociclib (Pfizer, 2015) and ribociclib (Novartis, 2017). The approval is based on the MONARCH 1 & 2 clinical studies, which showed efficacy in combination with fulvestrant (endocrine therapy), or on its own

depending on the treatment the patient had already received. See related blogpost.



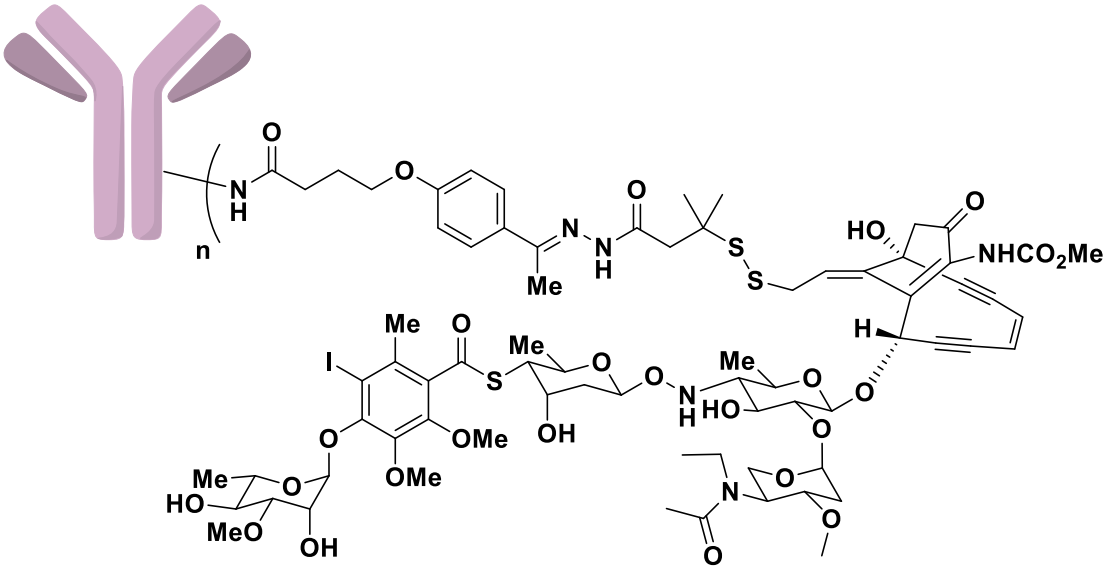
FDA Approval of Copanlisib (Aliqopa)

The class I phosphoinositide 3-kinase (PI3K) inhibitor copanlisib (Bayer) was approved on September 14, 2017 for the treatment of adults with relapsed follicular lymphoma that has returned after two or more treatments. Follicular lymphoma is a slow-growing type of non-Hodgkin lymphoma, a cancer of the lymph system and a hematologic malignancy. Copanlisib is known to target the alpha and delta isoforms of PI3K with sub-nanomolar IC50 values, although it also inhibits beta and gamma isoforms and mTOR with somewhat weaker activity. See related blogpost.



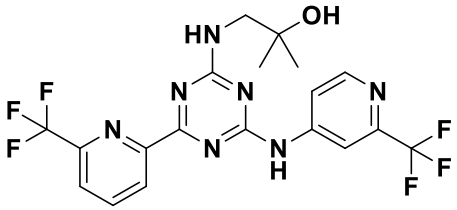
FDA Approval of Inotuzumab Ozogamicin (Besponsa)

The CD22 targeting antibody drug conjugate (ADC) inotuzumab ozogamicin (Pfizer) was approved on August 17, 2017 for adults with relapsed or refractory acute lymphoblastic leukemia (ALL). The drug consists of a humanized anti-CD22 antibody covalently linked via an acetylphenoxybutanoic acid linker to an acyl hydrazide derivative of calicheamicin cytotoxic agent. The cytotoxic agent and linker are the same as in Mylotarg (gemtuzumab ozogamicin), a CD33 targeting ADC which was approved to treat acute myeloid leukemia (AML) from 2000-2010, then withdrawn and re-approved by the FDA on September 1, 2017. See related blogpost.



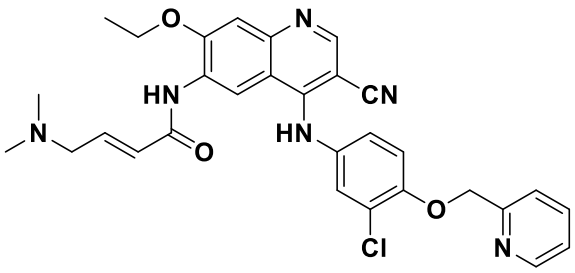
FDA Approval of Enasidenib (Idhifa)

The isocitrate dehydrogenase 2 (IDH2) inhibitor enasidenib (Agios/Celgene) was approved on August 1, 2017 to treat relapsed or refractory acute myeloid leukemia (AML). IDH2 enzymes catalyze the conversion of isocitrate to α-ketoglutarate (αKG) in the mitochondria. Mutations in *IDH2* occur in about 12% of patients with AML. Mutated forms of *IDH2* reduce αKG to produce the oncometabolite 2-hydroxyglutarate (2-HG), which inhibits αKG dependent enzymes leading to DNA and histone hypermethylation. The approval occurred with a companion diagnostic to check specific mutations in the *IDH2* gene in patients with AML. See related blogpost.



FDA Approval of Neratinib (Nerlynx)

The kinase inhibitor neratinib maleate (Puma Biotechnology) was approved on July 17, 2017 for the extended adjuvant treatment of early stage Her+ breast cancer. Neratinib is a covalent kinase inhibitor with activity against Her2 and EGFR kinases. Approval was based on the ExteNET clinical trial, which showed that extending adjuvant treatment with neratinib reduced the risk of recurrence relative after one year of trastuzumab. See related blogpost.



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

On behalf of the CICR Steering Committee, I am pleased to tell you about recent membership outreach efforts at CICR Town Halls held in the USA and in Asia! The CICR Town Hall held on November 9 during the *New Horizons in Cancer Research 2017* Conference in Shanghai, China, was the first AACR working group-organized social event held outside of North America. Since there is major interest in drug development in Asia, this was a great venue to highlight the important role of chemistry – and the CICR specifically – in AACR's programming. Featured presentations were given by CICR Steering Committee member, John (Yuan) Wang, on "Natural Product-inspired Drug Discovery at Eisai"; and by Dr. Charles Z. Ding, the Vice President of Medicinal Chemistry at WuXi AppTec in Shanghai on "Pre-clinical Discovery and Profile of WB1-340, a PARP Inhibitor." Attendees enjoyed a bountiful luncheon, as guests of your CICR Working Group, as well as a stimulating program. We look forward to future international possibilities for CICR to increase this demographic in our membership and for further interaction between chemists overseas.

Additionally, a lunch-hour reception was held as part of the CICR Town Hall on October 27 during the *AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics: Discovery, Biology, and Clinical Applications* in Philadelphia, Pennsylvania. As the host, I was happy to network with CICR members and other chemists during this social event, which also provided the opportunity to invite non-CICR members to join this vital scientific working group.

Remember, CICR members, to plan to attend the following chemistry sessions during the AACR Annual Meeting 2018 in Chicago, Illinois, April 14-18, 2018. Come hear your colleagues present their recent research and then network afterwards!

Saturday, April 14, 2018
From Chemistry to the Clinic (3-part session)
Chemical Probes for Identifying and Validating Drug Targets
Lead Optimization in Cancer Drug Discovery
Approaches to Drug Design for Neuro-Oncology

Sunday April 15, 2018
New Drugs on the Horizon (2-part session)
Topics to be announced

CICR Town Hall

To take place immediately after the New Drugs on the Horizon session on Sunday, April 15.
McCormick Place Convention Center
Join our CICR group for an informative discussion on current issues in chemistry in cancer research. Refreshments will be served.

Also, remember that all AACR Annual Meeting 2018 abstracts are due on Friday, December 1st. The CICR Steering Committee and I look forward to seeing you all in Chicago next April!

5. Career Forum

Career building tip: Did you know that LinkedIn has a large number of groups on topics related to Cancer Research, Drug Discovery and Chemistry? You can follow them just like you can follow Schools or Companies. Joining (or creating) groups focused on areas of interest can help you stay on top of new developments in your field as well as providing opportunities to expand your circle of professional contacts. You can search for groups by name or key word in the search box at the top of your LinkedIn home page by typing in key words, running the search and clicking on the Groups tab. In some cases you will need to apply for membership.

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/

6. Conferences

Atlantic Basin Conference on Chemistry
January 23-26, 2018, Cancun, Mexico

Keystone Symposium on Tumor Metabolism
January 21-25 2018, Snowbird, Utah

First Alpine Winter Conference on Medicinal and Synthetic Chemistry
January 28-February 1, 2018, St. Anton am Alberg, Austria

Keystone Symposium on Cancer Epigenetics: New Mechanisms, New Therapies
February 10-14, Breckenridge, Colorado

255th ACS National Meeting & Exposition
March 18-22, 2018. New Orleans, Louisiana

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

ACS 36th National Medicinal Chemistry Symposium
April 29-May 2, 2018, Nashville, Tennessee

Keystone Symposium on Precision Medicine in Cancer
May 6-10 2018, Stockholm, Sweden

Gordon Research Conference on Medicinal Chemistry
August 5-10, 2018, New London, New Hampshire

FLDB (Fragment Based Lead Discovery) 2018
October 7-10, 2018, San Diego, California

30th EORTC-NCI-AACR Symposium
November 13-16, 2018, Dublin, Ireland