From the Editors

This quarter, following the AACR Annual Meeting 2018, we have chosen to focus on "Contributions of Rational Drug Design towards Precision Medicine." CICR Editor, Dr. Zoe Cournia, and CICR Editor-elect, Dr. Alex Waterson, along with CICR Editorial Board members, Drs. Iain Watson; Terry Moore; and Martin Swarbrick, have assembled an overview of the topic.

In this newsletter, you will also find Selected Research Highlights on precision medicine and recent FDA approvals and the related Profile of the Early-career Researcher, Dr. Steve Staben, of Genentech, along with Global News, Upcoming Conferences, Funding Opportunities, and, of course, an update from Prof. Julian Blagg, CICR Working Group Chairperson, on CICR news and activities.

Contributions of rational drug design towards precision medicine

Rational drug design began to rise to prominence in the 1980s, superseding a model for drug discovery based more on synthetic organic chemistry and high throughput screening, fueled by significant and continual increases in computing power and advances in structural biology. The antiviral **zanamivir** is widely acknowledged as one of the first marketed drugs to have been identified by rational design: in what now seems a very familiar approach, X-ray crystallographic data facilitated an understanding of the structure of neuraminidase leading to the discovery and development of this transition-state analogue inhibitor. Additional drugs designed rationally in the 1990s include **Saquinavir**, discovered based on peptide derivatives that were transition-state mimetics of a sequence found in several retroviral substrates, and ritonavir, utilizing rational design on the structure of the C2-symmetric homodimer structure of HIV-1 PR, which has a single active site. Although the 1990s witnessed a resurgence in a more chemistry-driven, empirical approach, through the rise of high throughput screening and combinatorial chemistry, rational drug design can only continue to grow, as our understanding of the structure and function of biological targets increases.

Early computational studies enabled the use of techniques such as pharmacophore modeling, which uses a set of structural features in a molecule that are recognized at the receptor site and are responsible for that molecule's biological activity in the absence of presence of structural data as well as Quantitative Structure-Activity Relationships (QSAR). **Zolmitriptan** owes its discovery mainly to the generation of a pharmacophore model of known active molecules and QSAR enabled the discovery of norfloxacin. The advent of the post-genomic era was accompanied by significant advances in X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy, which generated a wealth of three-dimensional structures of pharmacological targets in recent years and spurred also advances in computer-aided drug design. Three examples of anti-cancer drugs, which were developed based on a combination of visual inspection, detailed structural description of protein-ligand interactions and computational tools are **crizotinib**, which targets the anaplastic lymphoma kinase (ALK); **nilotinib**, which was rationally designed based upon the crystal structure of imatinib/Bcr-Abl tyrosine kinase complexes; and **sunitinib**, a multi-targeted receptor tyrosine kinase (RTK) inhibitor. **Brigatinib**, targeting the anaplastic lymphoma kinase (ALK) for the treatment of ALK+ non-small-cell lung cancers, which have progressed on or are intolerant to crizotinib, was also rationally designed. The development of the earliest PARP inhibitors in the 1990s provided valuable information about the pharmacophore requirements for achieving suitable inhibition profiles towards these enzymes. This is demonstrated by the development of the drugs **olaparib**, **rucaparib** and **niraparib**, which relied on the structure of nicotinamide, a weak PARP inhibitor. **Rucaparib**, a novel tricyclic PARP-1 inhibitor, was approved in 2016 for the treatment of patients with

deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies, and this year olaparib was also FDA-approved for treating HER2-negative breast cancer with an inherited BRCA1/2 mutation.

We are continuing to see a surge of rationally designed drugs against cancer targets and over the last few years the FDA has been approving drugs for patients with specific genetic characteristics that are identified by diagnostic tests. Last year, 10 out of the 13 FDA-approved drugs were based on the principle of precision medicine, which is the tailoring of medical treatment to the individual genetic characteristics of each patient. As reviewed in the CICR February 2018 Newsletter, **Enasidenib**, an isocitrate dehydrogenase 2 (IDH2) inhibitor was approved to treat relapsed or refractory acute myeloid leukemia (AML); **Neratinib**, a covalent kinase inhibitor with activity against HER2 and EGFR kinases, for the extended adjuvant treatment of early stage Her+ breast cancer; **Inotuzumab ozogamicin**, a CD22 targeting antibody drug conjugate (ADC) for adults with relapsed or refractory acute lymphoblastic leukemia (ALL); **Abemaciclib**, a selective CDK4/6 inhibitor to treat HR+/HER2- advanced or metastatic breast cancer; **Acalabrutinib**, a Bruton's tyrosine kinase (BTK) inhibitor for the treatment of adults with mantle cell lymphoma (MCL); **Copanlisib**, a class I phosphoinositide 3-kinase (PI3K) inhibitor for the treatment of adults with relapsed follicular lymphoma that has returned after two or more treatment; **Ribociclib**, another CDK4/6 inhibitor for the treatment of HR-positive/HER2-negative advanced or metastatic breast cancer; **Midostaurin** targets several related molecules called tyrosine kinase receptors, including FLT3 and KIT, for the treatment of patients acute myeloid leukemia (AML) harboring a mutation in the FLT3 gene.

An additional example of the power of rational drug design for precision medicine is illustrated by Prof. John Katzenellenbogen, recipient of the 2018 AACR Award for Outstanding Achievement in Chemistry in Cancer Research. During his award address at the AACR Annual Meeting 2018, and in a recent perspective in *Nature Reviews Cancer*, Prof. Katzenellenbogen described somatic mutations to the estrogen receptor ligand-binding domain that cause the receptor to become constitutively active—that is, active in the absence of ligand. These mutations are thought to be present in up to 40% of estrogen receptor-positive metastatic breast cancers. Prof. Katzenellenbogen and his collaborator Dr. Geoffrey Greene have used Molecular Dynamics simulations and X-ray crystallography to understand the molecular mechanisms by which this constitutive activity arises. In their perspective, the authors discuss how understanding receptor conformation that is regulated by a ligand may inform design of new drugs that are active against mutant and wild-type estrogen receptors. This Perspective is covered in greater detail in this issue's Selected Research Highlights.

Many other sessions at the AACR Annual Meeting 2018 were dedicated to precision medicine efforts. The *New Drugs on the Horizon* two-part session highlighted efforts on inhibitors of CDK9, RAF kinase, BET bromodomains, DLL3, MPS1, DHODH, and eIF4A, as well as drugs based on the biomarkers MT1-MMP and B7-H4. Moreover, "Targeting Target RET-altered Cancers" (see related blogpost) was presented with data from the approximately 170 clinical trials presented at the meeting. AACR President 2017-2018, Dr. Michael A. Caligiuri, summarized the exciting, practice-changing data from immunotherapy clinical trials for non-small cell lung cancer, including KEYNOTE-189 and Checkmate -227, as well as data from clinical trials of targeted therapeutics, including the ARROW trial of BLU-667 for RET-altered cancers; data from the PALOMA-3 trial of palbociclib for HER2-negative breast cancer with the CCNE1 biomarker protein; and data from several early-phase clinical trials.

Webcasts of the sessions are available to registrants here.

A method, which is gaining interest in rational drug discovery efforts, is “fragment-based drug discovery (FBDD)”. Since the original reports of fragment-based methods for drug discovery in the late 1990s, the field has undergone a significant broadening and maturing. FBDD has now become a well-accepted alternative to more traditional screening techniques. While the original application of the method tended toward the discovery of leads for challenging protein targets, eventually culminating in the approval of ventoclax (believed to be the first FBDD-derived protein-protein interaction inhibitor approved in patients), FBDD is now commonly applied to many target classes. Indeed, the approved BRAF kinase inhibitor vemurafenib achieved FDA approval over 5 years ago and is believed to be the first approved FBDD-based molecule to do so.

With this expansion of methods and targets, FBDD now plays a key role in the discovery of new molecules for a host of targets. Of particular relevance to this issue’s theme, FBDD is at its most powerful when coupled with detailed structural information to delineate binding to the protein target. This coupling enables rational design, typically resulting in rapid optimization progress for molecules binding to new proteins that are validated as novel targets or as clinical resistance factors. Indeed, recent clinical progress from several FBDD sourced compounds - including the only known clinical ketohexokinase (KHK) from Pfizer, an MNK1/2 inhibitor from eFFECTOR, and a clinical ERK2 inhibitor from Genentech - has been reported, highlighting the power of the approach.

The ongoing “-omics” revolution promises to continue to produce new target ideas that will lead to patient benefit in specific genetic settings. The accessibility of fragment libraries (numbering in the few thousands), the applicability of FBDD to a broad range of target classes, and the speed with which an FBDD program can achieve useful levels of affinity and activity likewise promises to help our community validate these ideas with probe compounds and produce new clinical options for treatment.

In this issue of the Newsletter, we have provided a historical perspective as well as some recent examples of the use of rational drug design in cancer research. We present articles that exemplify the use of both fragment-based design and structural approaches to inhibitor development and clearly show the power of these methods in the discovery and development process. Potent and selective inhibitors of Mcl-1, USP-7, SPRK1/2, ATM kinase, and MNK1/2 are identified, engaging and effecting cancer related pathways. We are also pleased to highlight the work of Dr. Steve Staben, an Associate Director and Senior Scientist in the Discovery group at Genentech. Dr. Staben has been at the forefront of medicinal chemistry research in oncology, working on inhibitors of NIK, PAKs and PKD1. At the AACR Annual Meeting 2017, he presented his work on the discovery of GDC-0077, a highly isoform selective inhibitor of PI3Kα at the Sunday New Drugs on the Horizon Session. Dr. Staben’s work is highlighted in this issue’s Profile of an Early-Career Researcher.

CICR Newsletter Archives

For past issues of the CICR Newsletter, please visit the CICR Newsletter Archives.

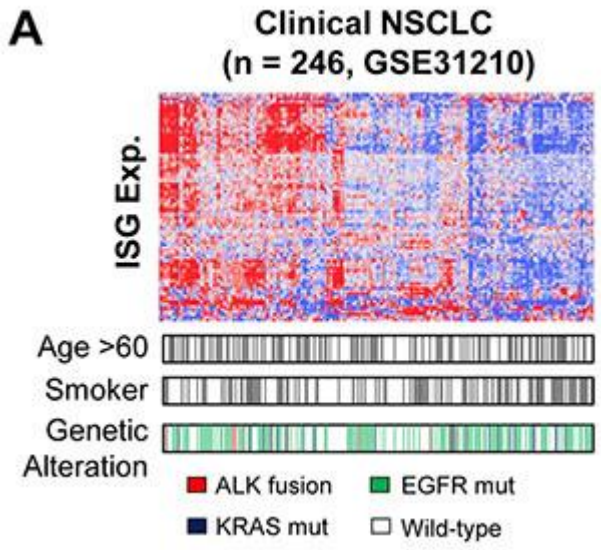
Search Underway for Editor-in-Chief of Molecular Cancer Therapeutics

The CICR Editorial Board and the CICR Steering Committee extends sincere appreciation to present Editor-in-Chief of *Molecular Cancer Therapeutics* (*MCT*), Dr. Napoleone Ferrara, for his leadership of this important AACR chemistry-related journal. His dedication and guidance has ensured the success of the journal during his tenure.

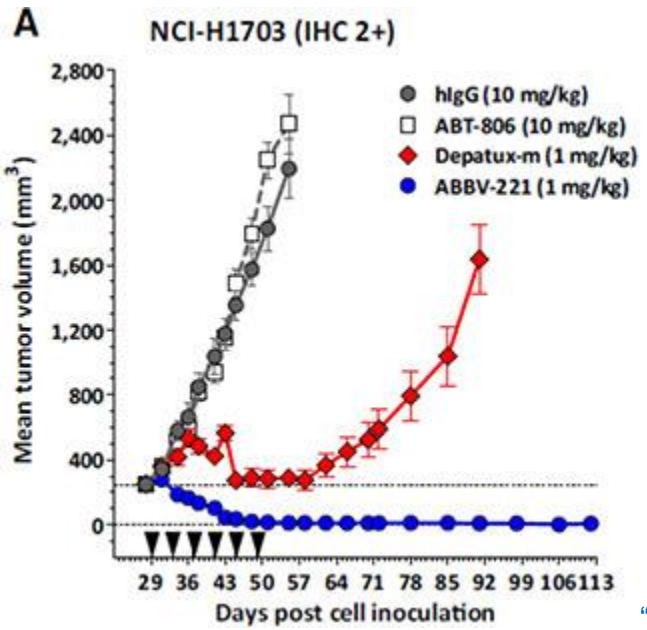
The search is underway for Dr. Ferrara’s successor. For more information, please visit the MCT website.

Molecular Cancer Therapeutics

You may be interested in these two articles from Molecular Cancer Therapeutics (MCT):



"JAK2 Inhibitor SAR302503 Abrogates PD-L1 Expression and Targets Therapy-Resistant Non–small Cell Lung Cancers" by Sean P. Pitroda, et al.



"Characterization of ABBV-221, a Tumor-Selective EGFR-Targeting Antibody Drug Conjugate" by Andrew C. Phillips, et al.

News from the CICR Steering Committee

Contributed by Prof. Julian Blagg, Chairperson

On behalf of our CICR Working Group, we are pleased to report a very successful AACR Annual Meeting 2018 recently held in Chicago. Chemistry was highly represented throughout the meeting, including a well-attended three-part *Chemistry to the Clinic* series, that was organized by the CICR Steering Committee. This series comprised sessions entitled "Chemical Probes for Identifying and Validating Drug Targets" (chair, Dr. Angela Koehler), "Lead Optimization in Drug Discovery" (chairs, Drs. Phil Jones and John Wang) and "Approaches to Drug Design for Neuro-Oncology" (chair, Dr. Tim Heffron); a further Educational Session entitled “The Use and Abuse of Chemical Probes” was chaired by Prof. Paul Workman. Two heavily attended and CICR-sponsored *New Drugs on the Horizon* sessions highlighted first disclosures of 10 new cancer therapeutic agents in clinical trials, both small molecule and biologics, and a topical Major Symposium on controlled proteostasis was chaired by Prof. Craig Crews, recipient of the 2017 AACR Award for Outstanding Achievement in Chemistry in Cancer Research. The 2018 recipient of this prestigious Award, generously sponsored by Piramal Pharma Solutions, is Prof. John A. Katzenellenbogen, University of Illinois at Urbana-Champaign, who gave his well-received Award Lecture during the Annual Meeting on nuclear hormone receptors, PET imaging and advances in understanding therapy resistance in breast and prostate cancer.

Our CICR Working Group sponsored a well-attended Town Hall followed by a networking reception. Thank you to all those who supported these events. At the Town Hall, Dr. Melissa Vasbinder shared recent progress towards the CICR mission. In her role as Editor of the CICR Newsletter, Dr. Zoe Cournia shared key aims and future topics for inclusion in the Newsletter; and as the CICR incoming Chairperson, I outlined key CICR goals for 2018/19, including further growth of CICR membership; increased chemistry influence on the 2019 Annual Meeting program; increased CICR presence at other AACR meetings; and securing funding for a potential CICR Scholar-in-Training Award. During our Town Hall, we recognized the outstanding leadership of Past Chairperson, Dr. Melissa M. Vasbinder (Director, Ribon Therapeutics), and welcomed Dr. Andrew J. Phillips (President and CEO, C4 Therapeutics) as CICR Chairperson-elect.

Photo below: Presentation of CICR Chair Award Plaque to Dr. Melissa M. Vasbinder

More photos of the CICR Town Hall can be viewed here. The CICR Working Group leadership team are excited and motivated to work with and to represent the CICR community and to continue to promote increasing awareness of chemistry and its positive impact throughout the cancer research community.

Our CICR Steering Committee for 2018-2019 also met face-to-face during the Annual Meeting to select nominations for chemistry-sponsored

sessions at the AACR Annual Meeting 2019 in Atlanta, Georgia, and to set priority goals for 2018-2019. We also welcomed four new members to the CICR Steering Committee.

• Jim Bischoff, Global Head Targeted Therapy – Oncology, Roche Applied Science, Basel

• Michael Brands, Vice President, Medicinal Chemistry, Bayer Pharma AG, Berlin

• Sara J. Buhrlage, Assistant Professor of Biological Chemistry and Molecular Pharmacology, Dana-Farber Cancer Institute, Boston.

• Julian Adams, Executive Chairman, Vedantra, Inc. Boston.

The following members will continue serving on the CICR Steering Committee.

• 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

• Vinod F. Patel, PhD. Chief Scientific Officer. APC Therapeutics

We thank the following members of the 2017-2018 Steering Committee for their dedication and past service to the CICR Working Group: Steven K. Davidsen (Past Chair); Zhao-Kui (ZK) Wan, Angela N. Koehler, Alan G. Olivero and John (Yuan) Wang.

Throughout 2018/19, our CICR working group will continue to expand the geographical outreach of CICR and increase opportunities for CICR members to connect outside of the annual AACR meetings. We will continue our presence at the AACR-NCI-EORTC International Symposium on Molecular Targets & Cancer Therapeutics, which will be held in Dublin, Ireland in November 2018, and we look forward to seeing CICR members at the CICR Town Hall meeting there.

As indicated above, and as part of our outreach efforts, we also aim to provide support to early-career researchers through sponsoring CICR scholar-in-training awards. Such Awards will provide funding 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 assist with any inquiries regarding sponsorship opportunities.

The importance of appropriate and well-informed use of chemical probes continues to be an important aspect of CICR influence and we will continue to educate, inform and communicate best practice across the cancer research community.

We encourage CICR members interested in contributing to CICR plans to reach out to myself, Melissa, or Andrew; we will be very happy to provide you with more information and opportunities to get involved. Thank you to those who have contacted us in person in Chicago and by email since the meeting; we very much appreciate your support. We also encourage all CICR members to urge your colleagues to join the CICR Working Group - the more members we have, the more leverage we have in support of chemistry-related sessions at the AACR Annual Meeting and beyond.

We also look forward to hearing from you; see our email addresses below as well as the general CICR Working Group mailbox:

Prof. Julian Blagg, Chairperson, CICR Deputy Director and Head of Chemistry of the Cancer Research UK Cancer Therapeutics Unit at the Institute of Cancer Research.
julian.blagg@icr.ac.uk

Dr. Melissa Vasbinder, Past-Chairperson CICR, Director, Ribon Therapeutics.
mvasbinder@ribontx.com

CICR Working Group mailbox: cicr@aacr.org

Thank you for your CICR membership!

Selected Research Highlights

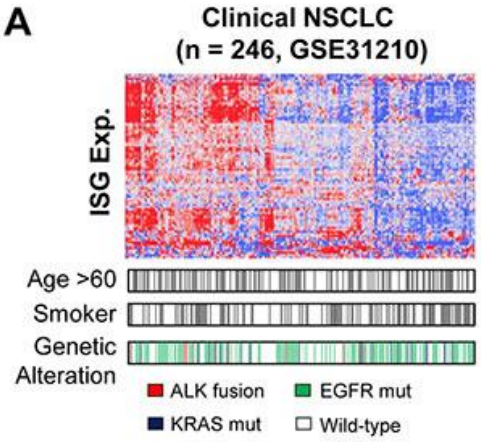
Review Article

Structural underpinnings of oestrogen receptor mutations in endocrine therapy resistance

Katzenellenbogen JA, et al. Nature Reviews Cancer 2018;[Epub ahead of print]
In this article, a recent sea change in breast cancer therapy and drug discovery has been brought about by the realization that up to 40% of metastatic estrogen receptor-positive breast cancers express one of a few mutations in the estrogen receptor ligand-binding domain. These mutations render the estrogen receptor constitutively active and relatively resistant to conventional selective estrogen receptor modulators and selective estrogen receptor downregulators. In a recent perspective in Nature Reviews Cancer, Katzenellenbogen et al discuss the molecular basis of this constitutive activity, and they compare and contrast estrogen receptor mutations with mutations in the androgen receptor that confer resistance in prostate cancer. The authors contend that a more thorough understanding of the relationship between receptor function and ligand-regulated conformation in mutant and wild-type receptors may lead to new breast cancer therapies.

Research Articles

JAK2 Inhibitor SAR302503 Abrogates PD-L1 Expression and Targets Therapy-Resistant Non–small Cell Lung Cancers
Pitroda S, et al. Mol Cancer Ther 2018;17:732 – 9. AuthorChoice.

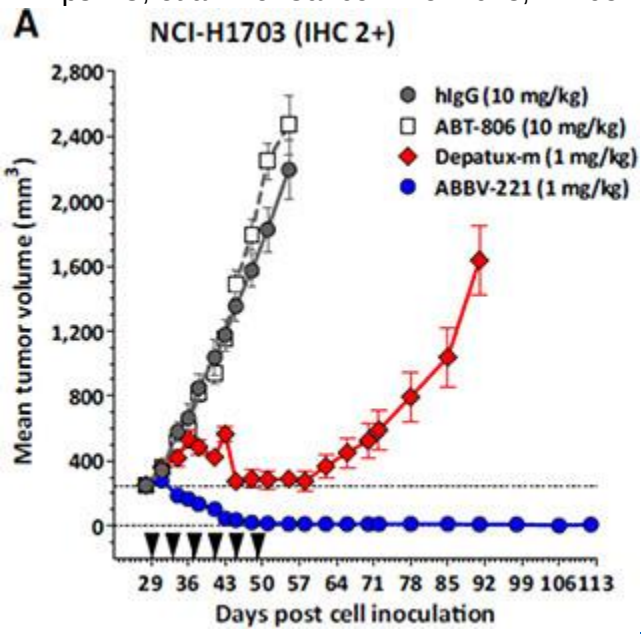


This article informs that lung cancer is the leading cause of cancer-related deaths, and ~85% of all lung cancers are non–small cell lung cancer (NSCLC). Modern treatment strategies for NSCLC target driver oncogenes and immune

checkpoints. However, less than 15% of patients survive beyond 5 years. In this article, Pitroda et. al. test a selective JAK2 inhibitor, SAR, on NSCLC cell lines and tumors, and show that SAR is cytotoxic to NSCLC cells, which exhibit resistance to genotoxic therapies such as ionizing radiation, cisplatin, and etoposide. Their findings suggest that SAR can be used both as a novel monotherapy in NSCLCs resistant to genotoxic therapies, and in tandem with immune checkpoint inhibition.

Characterization of ABBV-221, a Tumor-Selective EGFR-Targeting Antibody Drug Conjugate

Phillips AC, et al. Mol Cancer Ther 2018;17:795 – 805.



In their research, the authors describe preclinical characterization of ABBV-221, an EGFR-targeting antibody drug conjugate comprised of an affinity-matured anti-EGFR antibody
ABT-806, conjugated to monomethyl auristatin E (MMAE). ABBV-221 binds to a similar EGFR epitope as depatux-m and retains tumor selectivity with increased binding to EGFR-positive tumor cells and greater in vitro potency. ABBV-221 displays increased tumor uptake and antitumor activity against wild-type EGFR-positive xenografts with a greatly reduced incidence of corneal side effects relative to depatux-m. ABBV-221,utilizing an EGFR-targeting antibody with increased affinity, has broader utility against tumors with more modest EGFR overexpression, while mitigating the risk of corneal side effects. Based on these results, ABBV-221 has advanced to a phase I clinical trial in patients with advanced solid tumors associated with elevated levels of EGFR.

The identification of potent, selective and orally available inhibitors of Ataxia Telangiectasia Mutated (ATM) kinase: the discovery of AZD0156

Pike KG et al. J Med Chem 2018;61:3823-41.
Following on from an earlier AstraZeneca publication of compounds suitable for use as in vivo probes, this manuscript describes in detail the discovery of AZD0156, which is currently undergoing clinical evaluation with irinotecan and olaparib. Of note is the focus on achieving properties ultimately consistent with a low predicted human dose (<50 mg), via increasing volume of distribution to maximize predicted half-life. A fascinating insight into lead optimization strategy and approach at AstraZeneca.

Structure-based design of pyridone-aminal eFT508

Reich SH et al, J Med Chem 2018;61:3516-40.
eFFECTOR Therapeutics were well represented at the AACR Annual Meeting 2018, with a presentation, including structural disclosure, on their eIF4A1 inhibitor eFT226, and two posters on their MNK1/2 inhibitor eFT508. In this article, published shortly before the Meeting, the structure-based design of eFT508 is described in detail. Six initial fragment-like compounds are presented, co-crystallized with a mutated form of MNK2. The focus on ligand efficiency – a mainstay of fragment-based drug design – is apparent from the very beginning. Of particular note are the 'strategic' potency losses – where properties are improved such that efficiency indices are unaffected – which are discussed in an overall summary of the journey from hit to candidate. A valuable concept for any optimization campaign, whatever the origin of the hit matter.

Towards small molecule inhibitors of the Wnt pathway

Zhang M et al. J Med Chem 2018;61:2989–3007.
The Wnt pathway is a well-known oncogenic signaling paradigm that plays a key role in tumorogenesis, particularly in colon cancer. However, due to the nature of the pathway, which is driven primarily by protein-protein interactions downstream of the activating mutations in ß–catenin, APC, and Axin, the discovery of bona fide Wnt inhibitors has been difficult. The Ji group, having recently moved from the University of Utah to the Moffitt Cancer Center in Florida, has nonetheless attempted to tackle this issue. In their latest findings, published recently in the Journal of Medicinal Chemistry, they disclose sub-micromolar inhibitors of the ß–catenin::Bcl-9 interaction. As many of the binding sites for proteins that attach to ß–catenin are shared with one another, it is remarkable that these compounds show nearly 2000-fold selectivity for other associated interactions.

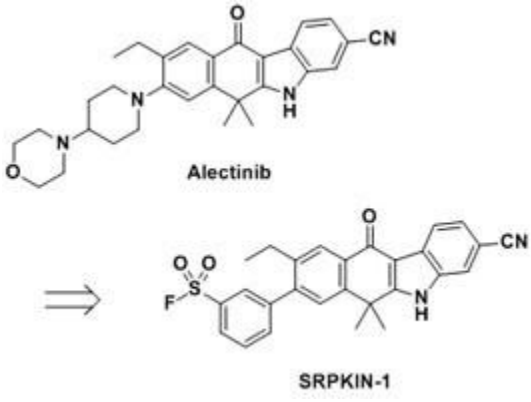
In related news, Professor Ji described, at the AACR Annual Meeting 2018, inhibitors of the ß–catenin::TCF4 interaction. The presentation was highlighted by a tantalizing slide showing the electron density of one of the inhibitors bound to ß–catenin. This would represent the first co-crystal structure reported, and would constitute a major advancement in the field!

A highly selective c-MET inhibitor

Ai J et al.; Mol Cancer Ther 17: 751-62.
The protein kinase c-MET has been a target of interest for drug discovery for more than a decade. However, available inhibitors suffer from limitations in potency, selectivity, and/or tolerability, and no c-MET inhibitors have yet been approved. In a recent issue of Molecular Cancer Therapeutics, a collaborative group (Ai, Geng, Ding, and colleagues) based in Shanghai have reported the discovery of SCC244, also known as Glumetinib, a subnanomolar inhibitor of c-MET with >2000-fold selectivity over other kinases. The compound displays excellent in vitro and in vivo activity, including a wide safety margin in preclinical studies. This promising compound is currently in Phase I clinical trials and may represent a new option for the patients with MET-addicted cancers.

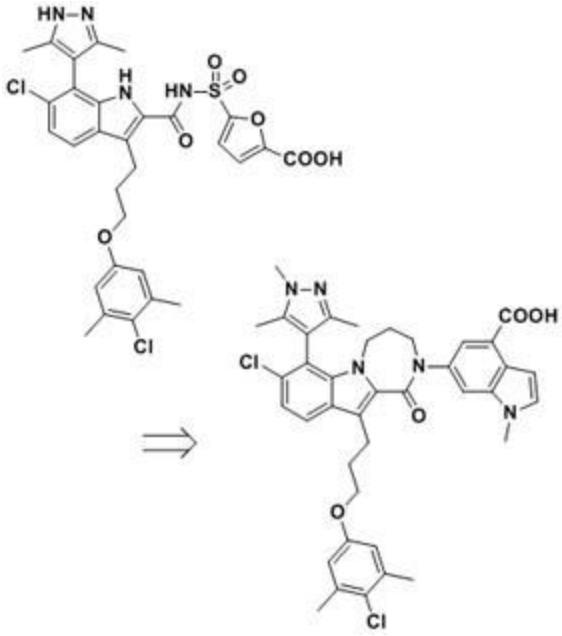
SRPKIN-1: A Covalent SRPK1/2 Inhibitor that Potently Converts VEGF from Pro-angiogenic to Anti-angiogenic Isoform

Hatcher JM, Wu G, Zeng C, et al. Cell Chem Biol 2018; 25:460-70.e6.



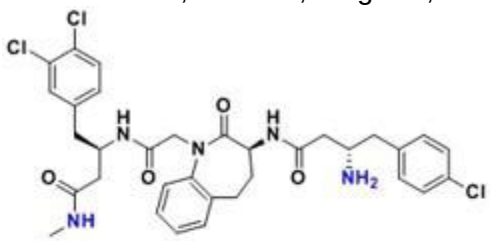
The article describes the development of the first irreversible SRPK inhibitor, SRPKIN-1. SRPK is a family of kinases, which regulate pre-mRNA splicing. Misregulation of SRPK1 expression induces aberrant splicing events which are linked to cell proliferation, migration and angiogenesis in a number of cancer types. By screening known kinase inhibitor libraries, the FDA approved ALK-inhibitor Alectinib was discovered to target SRPK-1 (IC50 = 11 nM by an in vitro kinase assay). By using co-crystal structures, the binding mode of alectinib and its analogues were determined and additional clashing interactions between the morpholinopiperidine and Tyr-227 and Leu-231 observed. Further evidence for this negative interaction was provided by the improved affinity of a compounds containing a smaller pyrazole ring. In order to improve the selectivity profile of the inhibitor, a covalent strategy was sought. Targeting Tyr-227 with the known tyrosine targeting sulfonyl fluoride substituent. This compound, SRPKIN-1 (IC50 36 nM) was shown to covalently bind to the protein via mass spec analysis and results in a more selective inhibitor in a kinome wide screen.

Optimization of Potent and Selective Tricyclic Indole Diazepinone Myeloid Cell Leukemia-1 Inhibitors Using Structure-Based Design
Shaw S, Bian Z, Zhao B, et al. J Med Chem 2018;61:2410–21.

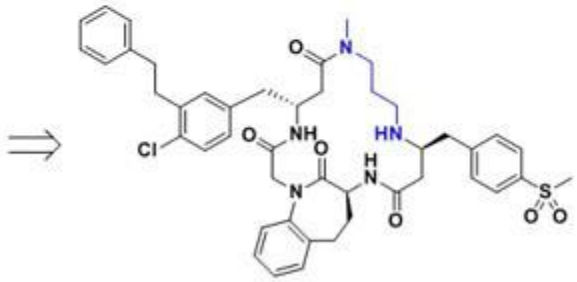


This article describes the development of a series of tricyclic indole diazepinone Mcl-1 inhibitors, optimized using rational structure-based design. Development started from the research group's previously disclosed extended 2-indole acylsulfonamide leads. Although these leads were very potent and selective, they failed to achieve acceptable potency in cellular assays, due to their poor cellular permeability. In order to improve permeability, coplanar amide and indole nitrogens were linked to form a tricyclic indole-diazepinone, resulting in enhanced potency and cellular permeability. By using co-crystal structural information, new electrostatic contacts were targeted and engaged at the R263 hydrophobic shelf region using aryl acid head groups. Mcl-1 upregulation is associated poor survival, and resistance to chemotherapy. Mcl-1 is an anti-apoptotic member of the Bcl-2 family of proteins that is an attractive target to many groups and organizations. A number of Mcl-1 inhibitors are currently in development of undergoing clinical trials including a number disclosed at the 2017 AACR Annual Meeting (CICR New Drugs on the Horizon 1, AMG 176, AZD5991).

Structure Based Design of Non-Natural Peptidic Macrocyclic Mcl-1 Inhibitors
Johannes JW, Bates S, Beigie C, et al. ACS Med Chem Lett 2017;8:239–44.



Mcl-1 FRET IC_{50} = 2 μM



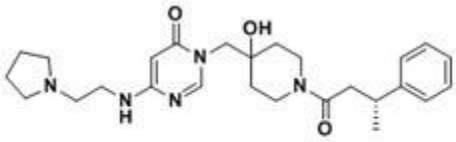
Mcl-1 FRET IC_{50} = <3 nM

The article describes the development of a Mcl-1

inhibitor, beginning with a 1.5 μM hit from a DNA-encoded library. Evidence of the compound's mode of binding by X-ray crystallography demonstrated a β-turn conformation with the two ends of the molecule in close proximity. Linking of the two ends to form a macrocycle resulted in a 10-fold improvement in potency, while the addition of other key hydrophobic interactions and the engagement of Arg-256 on the Mcl-1 protein led to additional potency improvements. The optimized compound binds with affinity less than 3 nM against Mcl-1, with selectivity against Bcl-2 and Bcl-xL, and induces cleavage of caspase-3 in MV4−11 cells.

Identification and Structure-Guided Development of Pyrimidinone Based USP7 Inhibitors

O'Dowd CR, Helm MD, Rountree JSS, et al. ACS Med Chem Lett 2018;9:238–43.

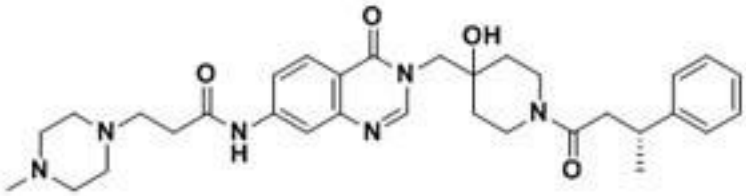


USP7 IC_{50} 0.1 μM

Ubiquitin specific protease 7 (USP7) is a deubiquitinase enzyme (DUB) known to modulate Mdm2 levels and therefore, also p53 levels. The article describes the development of potent and selective inhibitors of USP7, using both rational and structure-guided design, enabled by high-resolution co-crystallography. Initial hits were developed using fragment screening and scaffold-hopping approaches to provide weak micromolar binders. Truncation of the core, followed by the addition of linked basic residues allowed engagement of Asp-295, resulting in nanomolar binders. Efforts to profile the ADME and pharmacokinetic profiles of the compounds are described and efforts to improve these parameters are ongoing.

Structure-Guided Development of a Potent and Selective Non-covalent Active-Site Inhibitor of USP7

Lamberto I, Liu X, Seo HS, et al. Cell Chem Biol 2017;24:1490–1500.

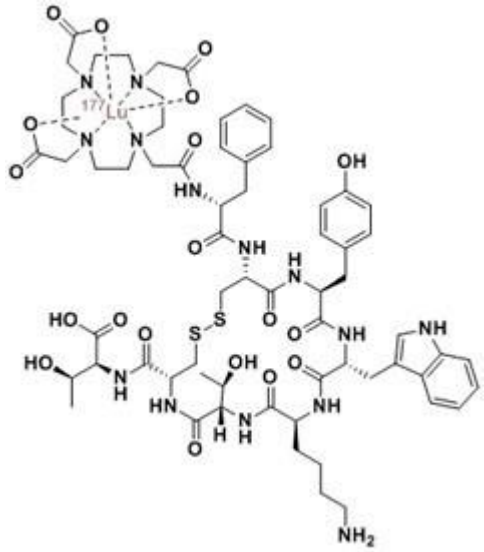


XL188 USP7 IC_{50} 0.09 μM

Sara Buhrlage reported on this work as part of her presentation at a Saturday morning "Chemical Probes" Educational Session at the AACR Annual Meeting 2018 in Chicago. The article describes a rational structure guided approach to the development of probe compound XL188, a potent and selective inhibitor of USP7, from a micromolar hit. Unlike other known USP7 inhibitors, XL188 is a non-covalent active site inhibitor and does not target the catalytic cysteine.

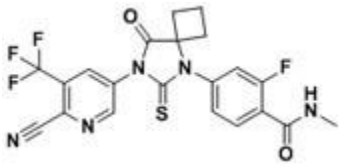
Recent FDA Approvals

FDA Approval of Lutetium Lu 177 dotatate (Lutathera)



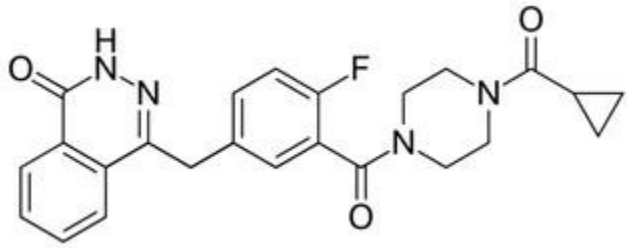
The radiopharmaceutical 177Lutetium (177Lu) dotatate (Advanced Accelerator Applications/Novartis) was approved on January 26, 2018 to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GET-NETs). The compound is comprised of dotatate complexed to the therapeutic radionucleotide 177Lu, a medium energy beta-emitter. Dotatate (DOTA-octreotate) comprises two parts. The first, somatostation antagonist octreotate, is a cyclic octapeptide structurally related to other somatostatin analogues such as Sandostatin (octreotide) and Somatuline (lanreotide). The second, a covalently attached complexing agent DOTA (tetrazetan), a tetracarboxylic acid containing compound with a central 12-membered macrocyclic tetra-aza ring. A related 68Gallium (68Ga) dotatate compound is used as an imaging agent to measure tumor somatostatin receptor density via combined positron emission tomography/computed tomography (PET/CT) imaging. See related blogpost.

FDA Approval of Apalutamide (Erleada)



The non-steroidal antiandrogen (NSAA) apalutamide (Janssen) was approved on February 14, 2018 to treat non-metastatic, castration-resistant prostate cancer using a novel clinical trial endpoint. The approval of this second generation NSAA follows enzalutamide (Astellas, 2012), a structurally similar analogue. This is the first approval to use the metric of metastasis-free survival (MFS) as an endpoint, defined as the time of first evidence of distant metastasis, or death due to any cause. See related blogpost.

FDA Approval of olaparib (Lynparza) for treating certain patients with metastatic, HER2-negative breast cancer



Before this approval, there were no molecularly targeted therapeutics approved for treating HER2-negative breast cancer with an inherited BRCA1/2 mutation. For those patients whose disease was also hormone receptor–positive, endocrine therapy was an option. However, chemotherapy was the only treatment option for those whose disease lacked the hormone receptor and was said to be triple-negative. See related blogpost.

Profile of an Early-career Researcher: Dr. Steven T. Staben

Associate Director and Senior Scientist
Genentech, Inc.
South San Francisco, California

Our theme for this issue involves the contributions of rational drug design to precision medicine. This month's profiled Early-Career Investigator has spent a good portion of his first years in the pharmaceutical industry doing exactly this type of work.

Steve Staben, PhD is currently an Associate Director and Senior Scientist in the Discovery Chemistry group at Genentech, in South San Francisco, California, USA. He joined Genentech in 2007 after completing his PhD with Prof. Dean Toste at the University of California, Berkeley. Part of Prof. Toste's first class of graduate students, Staben discovered and developed new organic- and transition-metal-catalyzed methodologies and contributed to the total synthesis of three natural products. While at UC Berkeley, he received several awards including the Gerald K. Branch Fellowship in 2004; the Klaus and Mary Saegebarth Fellowship in 2006; and the Roche Excellence in Chemistry Award in 2005. Prior to his graduate studies, he obtained his Bachelor's degree in chemistry in 2002 from Western **Washington** University, where he pursued undergraduate research with Professor James Vyvyan and was recognized as a University Outstanding Graduate.

Historically known for success in large molecule therapeutics, Genentech has more recently established expertise, commitment, and significant success in small molecule research. Today, small molecules represent roughly half of Genentech's research pipeline and Steve leads a large chemistry team and interdisciplinary project teams in this space. As a medicinal chemist, Steve leverages an organic chemist's knowledge of physical properties, reactivity, molecular conformation, and interaction energies to design inhibitors of a variety of therapeutic targets.

Steve has spent a majority of his time at Genentech devoted to kinase inhibitor discovery for oncology and other indications – publishing work detailing the discovery of inhibitors of NF-κB inducing kinase (NIK), group-II p21-activated kinases (PAKs), protein kinase D1 (PKD1), and

phosphoinositide-3-kinase (PI3K) inhibitors with variant isoform selectivity profiles. Within this work, he has demonstrated use of property- and structure-based design concepts to control inhibitor potency and selectivity as well as ADME properties. Most notably, Steve is a key contributor to a series of PI3K inhibitors including clinical molecules GDC-0032 (taselisib) and GDC-0077. Steve led the interdisciplinary project team that discovered GDC-0077 – a highly PI3Kα-isoform selective inhibitor that promotes the selective loss of mutant-p110α over wild-type-p110α.

He has coauthored 25+ peer-reviewed publications and has over 20 published patent applications. He has been an invited speaker to give first disclosures of some of this work, including the 2017 AACR *New Drugs on the Horizon* Session, the 2016 and 2018 Gordon Medchem Conference, and the Spring 2018 ACS Medi Young Investigator Symposium. Steve maintains basic research interests in chemical biology, unique therapeutic modalities, and novel strategies for inhibitor design and continues to publish new methodologies in these areas. We look forward to additional discoveries emerging from the lab of this outstanding young drug hunter!

Global News

Vanderbilt University signs agreement with Boehringer Ingelheim for the development of MCL1 inhibitors

An existing collaboration between Boehringer Ingelheim and the Fesik lab at Vanderbilt has been extended to a third drug discovery target. Vanderbilt have previously reported on the discovery of potent myeloid cell leukemia 1 (MCL1) inhibitors, a project that had its genesis in an NMR-based fragment screen and subsequent structure-based optimization. This new agreement builds on the initial discoveries, with a partnership that will press these compounds toward clinical development. Overexpression of MCL1, which occurs in many cancer cell lines, can enable tumors to escape the normal mechanisms of programmed cell death, and continue unabated growth. Inhibitors of the protein should thus force cancer cells into apoptosis. See also the research highlight in this issue: "Optimization of Potent and Selective Tricyclic Indole Diazepinone Myeloid Cell Leukemia-1 Inhibitors Using Structure-Based Design"
Shaw S, Bian Z, Zhao B, et al. J Med Chem 2018;61:2410–21.
Source: Fiercebiotech

Deerfield invests heavily in partnerships with academic research institutions

Deerfield Management is an investment team that has recently launched a concerted effort to initiate agreements with multiple universities and not-for-profit institutions to support and accelerate the development of novel therapeutics, leveraging emerging science from each institution. Deerfield has previously announced agreements with the Broad Institute and Johns Hopkins University. In the latest of these announcements, Deerfield Management and Vanderbilt University have formed a new company, Ancora Innovation, LLC, that will aim to capitalize on innovative therapeutic ideas for cancer and several other indications via a $65 million commitment.
Sources: Broad Institute; Johns Hopkins University; and Vanderbilt University

Regulatory environment continues to improve in China

Taking an advantage of recent government regulatory overhaul, Merck got a speedy green light for Gardasil 9 approval in just 9 days! Read more on this China landmark nod for Gardasil 9, a HPV vaccine from Merck, with lightning speed.
Source: Fiercepharma

China's largest CRO to build biologics plant in Ireland

China's largest CRO Wuxi AppTec announced that its subsidiary WuXi Biologics to build biologics plant in Ireland that will employ 400.
Source: Fiercepharma

Takeda acquires Shire in the biggest pharma M&A in years

Shire was finally seduced by Takeda, and agreed to terms with a $64B deal, the biggest pharma M&A in years. For Details see:
Source: Fiercepharma

Artificial intelligence (AI) continues to pick up steam in Asia

The South Korean government plans to invest $33.4 million to build a homegrown medical AI system to analyze patients' medical data to offer personalized diagnostics and treatment plans.
Source: Biospectrum Asia

Funding Opportunities

The AACR offers the following opportunities:

AACR-AstraZeneca Stimulating Therapeutic Advancements through Research Training (START) Grants
Deadline: 6/1/2018

AACR-Bayer Innovation and Discovery Grants
Deadline: 6/29/2018

2019 Cancer Research Early Career Award
Deadline: 1/7/2019

Pancreatic Cancer Collective New Therapies Challenge
Deadline: 7/2/2018

AACR-AstraZeneca Clinical Immuno-oncology Research Training Fellowships
Deadline: 7/6/2018

SU2C T-Cell Lymphoma Dream Team Translational Research Grant
Deadline: 7/2/2018

Conferences and Events

Fifth NovAliX Conference on Biophysics in Drug Discovery
June 13-15, 2018, Boston, Massachusetts

Gordon Research Conference in Heterocyclic Compounds 2018
June 17-22, 2018, Newport, Rhode Island

Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application
June 22-26, 2018, Boston, Massachusetts

54th International Conference on Medicinal Chemistry (RICT 2018)
July 4-6, 2018, Strasbourg, France

Sixth JCA-AACR Special Joint Conference on the Latest Advances in Lung Cancer Research: From Basic Science to Therapeutics
July 10-12, 2018, Kyoto, Japan

Gordon Research Conference in Organic Reactions & Processes 2018
July 15-20, 2018, Easton, Massachusetts

Controlled Release Society Annual Meeting and Exposition
July 22-July 24, 2018, New York, New York

Gordon Research Conference in Computational Chemistry 2018
July 22-27, 2018, Mount Snow, Vermont

Gordon Research Conference in Natural Products & Bioactive Compounds 2018
July 29-Aug. 3, 2018, Andover, New Hampshire

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

Multidisciplinary and Multimodal Approaches to Drug Delivery: Translation from Principles to Patients
Aug. 12-17, 2018, West Dover, Vermont

256th ACS National Meeting & Exposition

Aug. 19-23, 2018. Boston, Massachusetts

XXV EFMC International Symposium on Medicinal Chemistry (EFMC-ISMC 2018)
Sept. 2-6, 2018, Ljubljana, Slovenia

12th Biennial Ovarian Cancer Research Symposium
Sept. 13-15, 2018, Seattle, Washington

Fragment-Based Lead Discovery (FBLD)
Oct. 7-10, 2018, San Diego, California

EACR-AACR-ISCR Conference: The Cutting Edge of Contemporary Cancer Research
October 9-11, 2018, Jerusalem, Israel

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

AACR Annual Meeting 2019
March 30-April 3, 2019, Atlanta, Georgia

EFMC-ACSMEDI: Medicinal Chemistry Frontiers 2019
June 10-13, 2019, Krakow, Poland

Gordon Research Conference in Computer-Aided Drug Design 2019
July 14-19, 2019. West Dover, Vermont