



From the Editors

With Dr. Xiaojing (Gina) Wang, Editorial Board Member



Principal Scientist and Project Team Lead

Genentech, Inc.

South San Francisco, California

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. This quarter, we are focusing on *emerging druggable targets*. CICR editorial board member Gina Wang has taken the lead in assembling an overview of the topic.

Emerging Druggable Targets in Cancer Research

Research into emerging targets in drug discovery highlight frontier research and can set the path for future transformative therapies; therefore, they are of unparalleled prominence in the field. There are, of course, various kinds of targets for which a number of diversified modalities exist, including traditional therapies such as antibodies, peptides, natural products, and small molecules, which now extend to antibody-drug-conjugates, oligonucleotide, chimeric molecules, etc.

Here, we present a focused view of emerging druggable targets and concepts in cancer research; in other words, we highlight targets that may be modulated by small molecules (preferably orally bioavailable) as novel cancer therapies. Some of these targets may exist or have been identified for years, but have remained “undruggable” until very recently. Such breakthroughs are especially noteworthy, as novel targets under investigation become increasingly challenging. Indeed, many of these involve

protein-protein interactions (PPI) and/or otherwise lack a binding pocket for traditional small molecules to perturb the target functions.

RAS gain-of function mutations exist in 20-30% of all human cancers. Despite this critical importance, the protein has been considered undruggable for ~30 years, owing to the absence of known allosteric regulatory sites and extremely tight binding to the endogenous ligands, GTP and GDP. Therefore, RAS has been considered a “Holy Grail” in cancer drug discovery. In 2013, seminal work by Kevan Shokat, et al. using covalent inhibitors to target KRAS^{G12C} mutant allosterically, sparked major efforts in the industry. At this year’s AACR annual meeting (2019), there were several abstracts on KRAS^{G12C} inhibitors, including three oral presentations on AMG 510 by Amgen and a poster on MRTX1257 from Mirati. Both molecules demonstrated *in vivo* efficacy following oral dosing in mice. Two months later, in an oral presentation at this year’s ASCO annual meeting, AMG 510 was shown to exhibit preliminary monotherapy efficacy with five partial responses out of ten NSCLC patients in Phase 1 clinical testing. These data highlight the beginning of an extremely exciting new era for an “undruggable” target that has long been an important goal for new cancer therapeutic discovery.

The core of a highly conserved signaling Hippo pathway involves the interaction between transcriptional co-activators YAP/TAZ and transcription factor TEAD. Dysregulation of the pathway is associated with a number of human cancers. Various research efforts targeting effectors of this pathway have been carried out; recently reviewed by A Dey, et al. ([Trends In Cancer, 2019](#)). At this year’s AACR annual meeting, novel small molecule inhibitors of the YAP/TAZ-TEAD PPI were disclosed by Vivace and Kyowa Kirin. Tumor growth inhibition in mice was observed using orally bioavailable leads according to both presentations. In addition, Vivace presented the latest update at a focused AACR meeting on “The Hippo Pathway: Signaling, Cancer, and Beyond”. Please see [Hippo Pathway Meeting](#) for more details.

Cbl-b is a E3 ligase in the ubiquitin proteasome system that is responsible for tagging various phosphorylated substrates with ubiquitin and thus triggering their proteasomal degradation. In particular, Cbl-b serves as a negative regulator of T cells by causing the degradation of key effectors and internalization of the T-cell receptor, which consequently shuts down T cell activity. In 2007, JM Penninger, et al. [published compelling data](#) that a Cbl-b deficient mouse rejected tumor growth spontaneously, suggesting that inhibition of Cbl-b may be a novel approach for cancer immunology. Twelve years later, at this year’s AACR, J Gosling, from Nurix, presented the first orally bioavailable small molecule inhibitors targeting Cbl-b. In primary human T cells, small molecule inhibitors of Cbl-b activated T cells, evidenced by increased cytokine levels. In addition, tumor growth inhibition in CT26 syngeneic model was shown with an orally administered small molecule inhibitor. As we embark on the journey to discover orally bioavailable immuno-oncology therapeutics, such results are extremely encouraging, especially against hard-to-drug target such as Cbl-b.

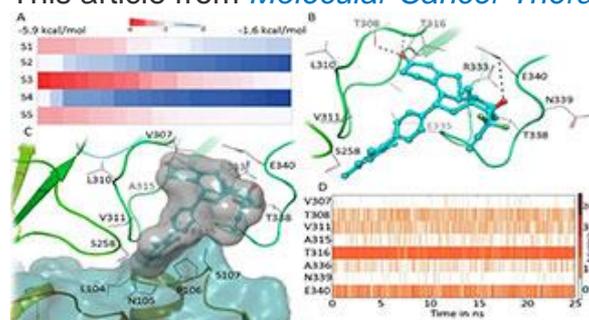
One of the most important advances in the history of cancer immunotherapy is arguably the blocking of immune regulatory checkpoints, such as the pathway involving the programmed cell death 1 (PD-1) receptor and its associated ligand (PD-L1). Breakthrough therapies blocking this pathway include five FDA approved antibodies. More details can be found in a recent [review](#) by A Ribas and JD Wolchok in *Science*. At this year’s AACR annual meeting, small molecule PD-L1 inhibitors were showcased by L-C Wang and P Liu from Incyte. In their presentations, orally bioavailable small molecule PD-L1 inhibitors were shown to induce PD-L1 internalization and inhibit tumor growth in *in vivo* models. The first-in-human phase 1 study has been initiated. Even though no chemical structure was revealed at the oral

presentations, it is remarkable to see another example of small molecule intercepting a PPI. How the small molecule inhibitors would compare with antibodies remains to be seen. Another effector in the PD-1/PD-L1 pathway is a nonreceptor protein tyrosine phosphatase (SHP2). There are at least three SHP2 small molecule inhibitors currently in the clinical trials, namely JAB-3068 from Jacobio Pharmaceuticals, RMC-4630 from REVOLUTION Medicines/Sanofi, and TNO155 from Novartis. Like others highlighted here, phosphatases are not considered to be a highly druggable target class, therefore advances in identifying orally bioavailable small molecule inhibitors are worth noting.

Finally, we turn our attention to another validated, but heretofore undruggable pathway: Wnt. Mutations in the Wnt pathway result in excessive amounts of β -catenin, which can inappropriately activate the developmental transcriptional program initiated by this pathway, resulting in oncogenesis. Such mutations are known to be among the first in the development of colon cancer. Indeed, as much as 90-95% of all colon cancers present with such mutations. However, as the pathway relies heavily on PPIs, the discovery of small molecule modulators has been notoriously difficult. Recent advancements in the field, typically using alternative modalities for inhibition, may be beginning to lift the veil. For example, the Ji group has [recently reported](#) advancements in the discovery of peptidomimetic compounds that interrupt a key PPI in the pathway. Others have turned to biological means of inhibiting the pathway, for example, the use of a sophisticated nanoparticle-based delivery of β -catenin [RNAi](#). Further, new ways of affecting the pathway with small molecules continue to be found. This includes the recently reported [molecular glue](#) approach, in which researchers have discovered a unique way to stabilize the interaction of β -catenin and the E3-ligase SCF ^{β -TrCP}, which can lower the amount of β -catenin in cells. While still early days in this pathway, the advancements presented here, alongside the work in other pathways, represents a great deal of future promise for the discovery of compounds that can inhibit the Wnt pathway in colon cancer.

In this editorial, we have tried to provide recent examples of some of the breakthroughs in research and discovery that are transforming “undruggable” targets to “druggable” targets. We intentionally selected highly attended presentations at major conferences to highlight the most innovative and the newest. We are also pleased to highlight the excellent work of Dr. Thomas Maimone, an Associate Professor of Department of Chemistry at the University of California-Berkeley. Dr. Maimone’s research centers around synthetic organic chemistry focusing on natural products and further dissecting their mechanism of action for the anti-cancer activity. Some of the more hard-to-drug targets have been identified using natural products as probes, such as nimbolide as a tool to better understand the E3 ligase RNF114. His work is highlighted in this issue’s Profile of an Early-Career Researcher.

This article from *Molecular Cancer Therapeutics* may be of interest:



EC359-A first-in-class small molecule inhibitor for targeting oncogenic LIFR signaling in triple negative breast cancer

DOI: 10.1158/1535-7163.MCT-18-1258

Leukemia inhibitory factor (LIF) is the most pleiotropic member of the IL-6 family of cytokines, and its signaling through LIF receptor (LIFR) activates signaling pathways including JAK, STAT, MAPK, AKT, and mTOR. Therefore, inhibiting LIFR may provide a strong benefit to overall survival in multiple solid tumors. To accomplish this, Viswanadhapalli and colleagues optimized compounds using the crystal structure of LIF/LIFR, balancing the binding of LIFR against off-target binding to the glucocorticoid receptor. The resulting compound, EC359, inhibited LIFR downstream signaling and reduced the stemness of triple negative breast cancer (TNBC) cells. EC359 showed potent anti-tumor activity in vivo in mouse xenografts and ex vivo in patient-derived explants. Taken together, EC359 is a potent LIFR inhibitor prepared for translation into clinical TNBC patients.



News from the CICR Steering Committee



Contributed by CICR Chair, Andrew J. Phillips, PhD
President and Chief Executive Officer
C4 Therapeutics
Watertown, Massachusetts

Join the conversation on the new CICR LinkedIn Network!

We are pleased to announce the launching of the [CICR LinkedIn Network](#) to enhance communication among CICR members and the greater cancer research community interested in cancer chemistry research! Become part of this exciting forum to interact and connect, while sharing recent research updates of interest. Click the link above to access the network; join; and contribute. Be sure to share with your colleagues!

Reference URL: <https://www.linkedin.com/groups/8813575/>

Plan to Attend the CICR Town Hall Meeting and Reception at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics

Oct. 26-30, 2019 in Boston, Massachusetts

I look forward to this this exciting conference and to welcoming all attendees to the CICR Town Hall on Sunday, Oct. 27, 2:30-3:30 p.m., for an update on CICR initiatives. Come and enjoy some cordial networking with colleagues, known and yet-to-be-known, at the reception after a brief program. Refreshments will be served. Learn more about the event and register. Late Breaking Abstract Submission Deadline: Thursday, Sept. 12, 2019, 11:59 p.m. ET; Advance Registration Deadline: Friday, Sept. 13, 2019.

CICR Scholar-in-Training Awards (SITAs) to be presented at the AACR Annual Meeting 2020

Early-career investigators, be sure to keep checking the AACR Annual Meeting 2020 website to learn how you can submit an abstract to be considered for one of these inaugural travel awards to the AACR Annual Meeting 2020 in San Diego, California. Generous support of these awards is provided by WuXi AppTec.

Contact us at cicr@aacr.org.



Selected Research and Review Highlights

[EC359-A first-in-class small molecule inhibitor for targeting oncogenic LIFR signaling in triple negative breast cancer](#)

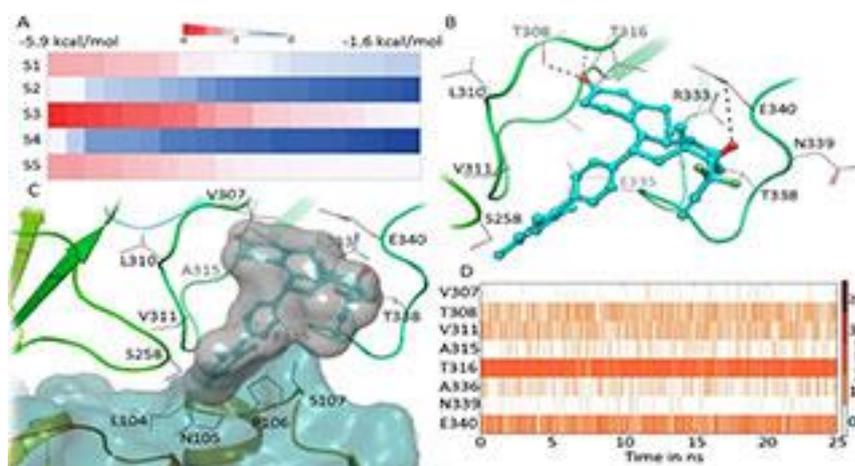
Viswanadhapalli, S, et al

Mol Canc Ther 2019

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Leukemia inhibitory factor (LIF) is the most pleiotropic member of the IL-6 family of cytokines. Its signaling, through the LIF receptor (LIFR), activates several signaling pathways, including JAK,

STAT, MAPK, AKT, and mTOR. Therefore, inhibiting LIFR may provide a strong benefit to overall survival in multiple solid tumors. To accomplish such inhibition, Viswanadhapalli and colleagues optimized compounds using the crystal structure of LIF/LIFR, balancing the binding of LIFR against off-target binding to the glucocorticoid receptor. The resulting compound, EC359, inhibited LIFR downstream signaling and reduced the stemness of triple negative breast cancer (TNBC) cells. EC359 showed potent anti-tumor activity in vivo in mouse xenografts and ex vivo in patient-derived explants. Taken together, EC359 is a potent LIFR inhibitor that may be poised for translation into clinical TNBC patients.

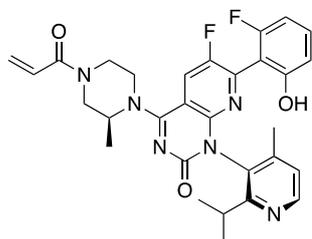


KRAS Section

The KRAS-related work reported below was preceded by the [seminal report](#) from Shokat and Ostrem describing irreversible inhibitors bound to the mutant cysteine of KRAS^{G12C} selectively over the wild-type protein and revealing a new allosteric pocket. Through the binding of the small molecule, KRAS^{G12C} is locked in the inactive GDP bound stage, impairing binding to RAF, decreasing viability, and increasing apoptosis of lung cancer cell lines.

“Discovery of AMG 510, a First-In-Human Covalent Inhibitor of KRAS^{G12C} “

At the 2019 AACR Annual Meeting, Amgen highlighted their successes in the discovery of the first clinical KRAS inhibitor. A series of oral and poster presentations showcased the work – highlights of these follow.

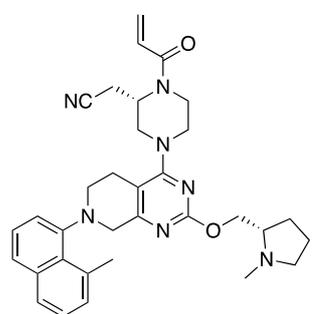


AMG 510

In the Next-Generation Small Molecules: From Hits to Leads to Candidates section at the 2019 AACR Annual Meeting, BA Lanman described Amgen’s effort in hybridizing two scaffolds utilizing structure-based drug design. Extensive optimization of leads culminated in the nomination of AMG 510 for clinical development (Lanman, B. A.; et al. *AACR Annual Meeting 2019*, Atlanta, Abstract #4455, Oral Presentation). It is especially noteworthy that atropisomers of an early compound differed in potency by 10-fold. But, through stabilizing the atropisomer and subsequently installing a pyridyl nitrogen to improve crystalline solubility, AMG 510 was identified as a highly potent, selective, and well tolerated molecule. The cell viability IC₅₀ in MIA PaCa-2 cells is 5 nM, while in A549 cells 38.5 nM. *In vivo* clearance in mouse, rat, and dog ranges from low to high and oral bioavailability across all three species are moderate (30-34 %). In mouse xenograft models, tumor regression and inhibition of ERK phosphorylation were observed following once daily oral administration at 30 and 100 mg/kg doses.

In the Novel Therapeutics session, AY Saiki shared more biology insights into the action of AMG 510 (Saiki, A. Y.; et al. *AACR Annual Meeting 2019*, Atlanta, Abstract #4484, Oral Presentation). It was shown that AMG 510 is highly selective for KRAS^{G12C} across the cellular cysteine proteome. Rapid and selective engagement of KRAS^{G12C} leads to the inhibition of downstream signaling and impairment of viability. The combination of AMG 510 with targeted agents such as MEK/PI3K or chemotherapeutic agents such as carboplatin demonstrated enhanced tumor cell killing *in vitro* and *in vivo*.

Further, in the New Drugs on the Horizon session, JR Lipford presented additional *in vivo* mouse models (Lipford, J. R. *AACR Annual Meeting 2019*, Atlanta, Oral Presentation). Most interestingly, AMG 510 increases CD8+ T cells and MHC presentation, enhances sensitivity to PD-1 checkpoint inhibition, and drives durable cures in a CT-26^{KRAS p.G12C} syngeneic model. Cured mice show resistance to parental CT-26 and CT-26^{KRAS p.G12C} challenge, indicating an adaptive immune response.



MRTX1257

“Insights Towards Therapeutic Susceptibility of KRAS Mutant Cancers from MRTX1257, a Novel KRAS G12C Mutant-Selective Small Molecule Inhibitor”

Mirarti and Array presented *in vitro* and *in vivo* data on a research tool molecule, MRTX1257 (Hallin, J.; et al G. *AACR Annual Meeting 2019*, Atlanta, Abstract #LB-271, Poster Presentation). In a cellular biomarker assay measuring pERK, the compound has an IC₅₀ of 0.9 nM. It also shows relatively high plasma protein binding (99%) in mouse and moderate oral bioavailability (31.1%). MRTX1257, administered orally, induces 30% or greater tumor regression in 18 of 23 cell lines and patient-derived xenograft models. Combining MRTX1257 with other targeted therapies, including a SHP2 inhibitor, a CDK4/6 inhibitor, and an mTor inhibitor, results in increased anti-tumor responses. MRTX849, structure not shown, is currently under evaluation in clinical trials.

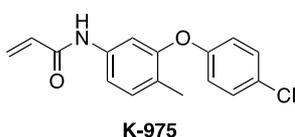
“Another Gap in the Undruggable Armor: New, Reversible KRAS Inhibitors”

<https://doi.org/10.1073/pnas.1904529116>

In a recent publication in *Proceedings of the National Academy of Sciences (USA)*, D Kessler and colleagues, representing a collaborative team from Boehringer Ingelheim and Vanderbilt University, report the use of fragment screening technology and structure-based design to discover compounds that bind directly to KRAS at a site between the conformationally labile Switch I and II regions. This site is present in both the inactive (GDP-bound) and active (GTP-bound) forms of all RAS family members; thus, these reversibly binding proteins utilize a mechanism of action quite different from the G12C-specific compounds. The probe molecule identified in this work, BI-2852 (which will be made available to the scientific community), binds to RAS with affinity under 1 μ M and can interrupt multiple RAS effector PPIs. Further, the compound shows dose-responsive effects on downstream RAS-mediated signaling and can inhibit the proliferation of tumor cells in a 3D setting at low micromolar concentrations. Considered alongside prior work reported from a team at Oxford ([Rabbitts, et al PNAS 2019](#) and [Rabbitts, et al Nature Communications 2018](#)), it is clear that ongoing dramatic advancements in the discovery of reversible inhibitors of RAS are further changing the image of RAS into a formerly undruggable target.

Hippo pathway section

For further information on the next two highlights, readers are encouraged to consult an excellent recent [review on the Hippo pathway](#) by A Dey, et al. from Genentech. It discusses the latest research advances in understanding the pathway, the relationship between genetic aberrations and the development of cancers, and also the ongoing efforts to target the pathway. Outstanding questions and future outlooks are summarized in conclusion.



“Targeting the Hippo-YAP Pathway with Novel Small Molecule Inhibitors of the YAP-TEAD Transcription Activity”

At the minisymposium on Novel Therapeutic Agents and Screening Approaches, TT Tang from Vivace shared detailed biology studies of inhibitors of YAP-TEAD protein-protein interaction and briefly discussed about the properties of their compound (Tang, T. T.; et al. *AACR Annual Meeting 2019*, Atlanta, Abstract #2693, Oral Presentation). A YAP reporter assay was used to screen a 160K compound library and several hits were identified and expanded. Vivace compounds block the YAP-TEAD protein-protein interaction in cells by western blot, yet do not prevent YAP or TEAD nuclear translocation in a immunofluorescence assay. In addition, Vivace compounds inhibit TEAD palmitoylation in cells by western blot and are selective against RAS or Wnt palmitoylation. Incubation with TEAD palmitoylation inhibitors induce a thermal shift of the recombinant TEAD, indicating strong direct binding. Complete growth inhibition of NF2 mutant xenografts was observed at 3 mg/kg by once daily oral dosing. Vivace inhibitors have IC₅₀ values in the YAP reporter assay below 10 nM and anti-proliferation IC₅₀ values in the NF2 mutant cells below 30 nM. Their oral bioavailability is higher than 50% in rats and dogs.

“Discovery of a First-in-Class TEAD Inhibitor which Directly Inhibits YAP/TAZ-TEAD Protein-Protein Interaction and Shows a Potent Anti-tumor Effect in Malignant Pleural Mesothelioma”

Kyowa Kirin disclosed the structure of an irreversible YAP/TAZ-TEAD inhibitor, K-975 (Kaneda, A.; et. al. *AACR Annual Meeting 2019*, Atlanta, Abstract #3086, Poster

Presentation). The co-crystal structure of K-957 and TEAD1 was obtained, showing that the compound binds to a highly conserved cysteine residue in the YAP binding domain of TEAD. Selectivity against other cysteine containing targets was not mentioned. K-975 inhibited cell growth at a GI₅₀ of 30-180 nM using three different cell lines. K-975 suppresses tumor growth and exhibit survival benefit at 300 mg/kg by daily oral doses in human malignant pleural mesothelioma xenograft models. After 2 weeks of treatment with K-725, a K-975 derivative, proteinuria with increased hyaline cast and accumulation of hyaline droplet in tubule was observed in rat and monkey kidneys. No other abnormal findings were found.

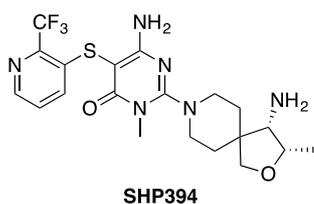
SHP2 Section

Phosphatases can be considered the protein counterparts to the more well-known kinases. These proteins act together in numerous signaling pathways to respectively remove and install phosphates onto various protein residues. In contrast to kinases, for which numerous drugs are now approved, the discovery of molecules to modulate the action of phosphatases has been more difficult. The next two highlights disclose a significant advancement in the field.

“Optimization of Fused Bicyclic Allosteric SHP2 Inhibitors”

<https://pubs.acs.org/doi/10.1021/acs.jmedchem.8b01725>

SHP2 is a nonreceptor protein tyrosine phosphatase. Activation of SHP2, including activating mutations of the protein, are associated with multiple cancer types, including both hematological and solid tumors. Given the role of SHP2 in the PD-1/PD-L1 pathway, inhibition of SHP2 is expected to counter immunosuppression and restore T-cell activation. Therefore, small molecule SHP2 inhibitors are highly sought after as a potential cancer immunotherapy. However, the selective inhibition of phosphatases is considered a very difficult task. In the first of two consecutive papers, MJ LaMarche, et al. described scaffold morphing and subsequent optimization of novel SHP2 inhibitors using both structure- and property-based drug discovery. Significant progress was made in optimizing the potency and hERG selectivity of the inhibitors. A robust PK-PD correlation in a mouse tumor xenograft model was demonstrated. However, combining SHP2 potency, selectivity against the hERG channel, and decent pharmacokinetic properties into one molecule was not achieved.



“6-Amino-3-methylpyrimidinones as Potent, Selective, and Orally Efficacious SHP2 Inhibitors”

<https://pubs.acs.org/doi/10.1021/acs.jmedchem.8b01726>

In the second of the two consecutive papers, MJ LaMarche, et al. describe their continued efforts in the optimization of allosteric SHP2 phosphatase inhibitors. By core hopping and mix-matching the best substituents, potent, selective, and orally efficacious SHP2 inhibitors were identified. The lead molecule, SHP394, demonstrated dose dependent reduction in tumor volume in a Detroit-562 mouse model, and achieved tumor stasis at 40 mg/kg twice daily oral doses for 21 days.

PD-L1 Section

Targeting the immune system to generate new therapies for cancer treatment is one of the hottest areas of current research. This work has been led by the discovery of antibody-based inhibitors of several immune checkpoint proteins. Many of these are approved for use in patients and have had a significant impact on outcomes. However, corresponding small molecule inhibitors are much rarer, and none have yet been approved. This section presents some new discoveries aimed at changing this situation.

“Discovery and *in vivo* Activity of Potent and Selective Oral PD-L1 Antagonists”

In a presentation at the recent AACR Annual meeting (Wang, L.-C.; et al. *AACR Annual Meeting 2019*, Atlanta, Abstract #4480, Oral Presentation), an orally bioavailable small molecule PD-L1 inhibitor, INCB090244, was profiled. INCB090244 displays an IC₅₀ of 1.9 nM against human PD-L1, with no effect against the mouse protein. INCB090244 is orally bioavailable (cyno %F = 100) and it is highly selective against panels of kinases, ion channels, and transports. INCB090244 potently activates CD8⁺ T cells in culture. *In vivo*, INCB090244 exhibits single agent activity and increases infiltrating T cells in two humanized mouse models. INCB086550, a structurally distinct, yet functionally similar, analog of INCB090244, is currently being studied in a Phase 1 human clinical trial. Unfortunately, the chemical structure of neither compound was disclosed.

“Novel Small-Molecule Antagonists of the PD-1/PD-L1 Axis that Mediate Cell Surface PD-L1 Dimerization and Internalization”

At the same meeting, P Liu described a project with the objective to discover small-molecule inhibitors of PD-1/PD-L1 interaction with drug-like properties and activity equivalent to therapeutic antibodies (Liu, P.; et al. *AACR Annual Meeting 2019*, Atlanta, Abstract #4483, Oral Presentation). Mutagenesis experiments showed partially overlapping residues that are critical for binding of PD-L1 to either PD-1 or the inhibitor. In-depth mechanistic studies were carried out to understand an observed lack of correlation between biochemical potency and functional cellular activity. It was found that the inhibitors that showed functional activity in cells induced dimerization of PD-L1. In addition, compounds that induced dimerization of PD-L1 were able to reduce PD-L1 at the cell surface through PD-L1 internalization.

Other Research Highlights

“A new way to target the Wnt pathway”

<https://doi.org/10.1038/s41467-019-09358-9>

The degradation of proteins as a possible new approach to the discovery of therapeutics has been a hot topic of late. Recent work by a collaborative group led by Nurix Therapeutics and the U of California, Berkeley, has revealed a new application of this strategy that is distinct from the more common PROTACs paradigm. This new work has identified small molecule compounds that enhance the interaction between β -catenin, the central molecule of the oncogenic Wnt pathway, and the E3 ligase SCF ^{β -TrCP}. This ligase is well known to induce ubiquitination and subsequent degradation of β -catenin. The “molecular glue” represented by these new compounds have optimized interactions with two proteins in a naturally occurring protein-protein interaction and can potentiate the degradation of β -catenin in cells.

“A Hypoxia-Inducible Factor 2 α (HIF-2 α) Inhibitor for the Treatment of Clear Cell Renal Cell Carcinoma”

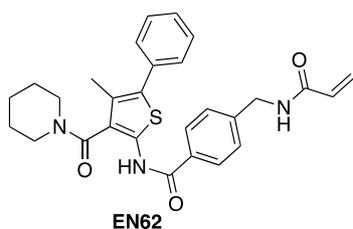
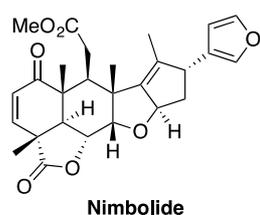
<https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b00719>

In this *Drug Annotation*, the Peleton Therapeutics team describe how the improved back-up molecule PT2977 was discovered, after the first inhibitor (PT2385) was found to have variable and dose-limiting pharmacokinetics despite demonstrating proof of concept clinical activity. Ultimately, a very simple structural modification resulted in a significant improvement in pharmacokinetic properties, and clinical data for PT2977 indeed demonstrated improved exposure and reduced variability. Within the report is described a fascinating and systematic study of the influence of fluorine substitution and stereochemistry on glucuronidation, and the resulting effects on human pharmacokinetics.

“Genetic and Pharmacological Evaluation of the Ubiquitin Ligase Cbl-b as a Small Molecule, Tumor Immunotherapy Target”

At a minisymposium on Preclinical Drug Development: Dedicated to the Memory of John Mendelsohn, J Gosling from Nurix disclosed their small molecule inhibitors of Cbl-b (Gosling, J.; et al. *AACR Annual Meeting 2019*, Atlanta, Abstract #2696, Oral Presentation). Interest in this target may be based on an earlier report of [compelling *in vivo* data](#) which supports that notion that inhibition of Cbl-b stimulates immunity against cancer, and may thus be a therapeutic approach.

The most potent inhibitor listed in the current work has an IC₅₀ of 5 nM in the biochemical assay. Biochemical potencies track well with IL-2 induction and proliferation of primary human T cells. Cbl-b inhibitors increase IFN- γ levels, restoring the response in exhausted T cells. At 10 μ M concentration, Cbl-b inhibitors achieve similar level of IFN- γ induction as the PD-1 inhibitor Nivolumab. *In vivo*, Cbl-b inhibitor NRX-2, dosed twice daily orally, increases T cell activation markers CD25 and CD69, indicating enhanced T cell activation. Statistically significant tumor growth inhibition was demonstrated using NRX-2 at 45, 90, and 180 mg/kg doses in a CT26 syngeneic mouse model. NRX-2 was well tolerated over 28 days in the efficacy study. The chemical structures of the Cbl-b inhibitors were not shared.



“Harnessing the Anti-cancer Natural Product Nimbolide for Targeted Protein Degradation”

<https://doi.org/10.1038/s41589-019-0304-8>

This recent publication highlights the excellent work of the profiled early career researcher, Thomas Maimone. Nimbolide is a complex natural product with 9 chiral centers, 5 fused rings, and a reactive cyclic enone. Nimbolide has been shown to inhibit tumorigenesis and metastasis without causing any toxicity or unwanted side effects across a wide range of cancers. Utilizing activity-based protein profiling chemoproteomic platforms, nimbolide was found to react with a cysteine group of E3 ubiquitin ligase RNF114 at its substrate recognition site. Nimbolide impairs breast cancer cell proliferation, in part by disrupting RNF114- substrate recognition, leading to inhibition of ubiquitination and degradation of tumor suppressors such as p21, resulting in their rapid stabilization. A screen for synthetically more tractable covalent ligands against RNF114 identified EN62 as an early hit targeting the same cysteine moiety of RNF114. In addition, Nimbolide was used as a binder to RNF114 and was linked with a BRD4 inhibitor JQ1 to demonstrate that targeted protein degradation is achievable. The combination of tool molecules such as Nimbolide and chemoproteomic platforms is a powerful way in identifying potential new pockets and consequently transforming undruggable targets into druggable targets.

Profile of an Early-Career Researcher

Thomas Maimone, Ph.D.



Associate Professor
Department of Chemistry
University of California-Berkeley
826 Latimer Hall
Berkeley, CA 94720
[Research Group Site](#)

Thomas Maimone is an Associate Professor in the chemistry department at the University of California-Berkeley. His research centers around synthetic organic chemistry, with a particular focus on natural products chemistry. To date, the Maimone group has completed the chemical syntheses of over twenty complex natural products, with a major goal of improving synthetic efficiency through both strategic design and reaction discovery. Most notable is his work on the total synthesis of complex terpenes, including the cytotoxic ophiobolin sesterterpenes and the neuroactive *Illicium* sesquiterpenes. His group has also reported several methods for C–C bond formation and has utilized these methods in complex molecule synthesis.

In collaboration with the Nomura lab at UC-Berkeley, the Maimone group is also invested in mapping the protein targets of covalently acting natural products and turning such molecules into useful chemical tools. One recent investigation, involving the natural product nimbolide, identified the RING E3 ligase RNF114 as a target of this anti-cancer molecule. By binding at a presumed substrate recognition domain of RNF114, nimbolide could then be made into a PROTAC for use in targeted protein degradation. This work is featured in the research highlights this fall. Much of Prof. Maimone's translational work centers around The Novartis-Berkeley Center for Proteomics and Chemistry Technologies, of which he is a member.

Prof. Maimone obtained his B.S. degree in chemistry in 2004 from The University of California-Berkeley, wherein he was introduced to synthesis research by Prof. Dirk Trauner. From 2005-2009, he was a member of Phil Baran's research group at The Scripps Research Institute, wherein he completed total syntheses of the alkaloids hapalindole U and ambiguine H and was also part of the team that completed the synthesis of the diterpene vinigrol, a longstanding challenge in the field. In 2009, he began a NIH post-doctoral fellowship at MIT under the guidance of Prof. Stephen Buchwald. At MIT, Prof. Maimone studied Pd-catalyzed methods to make carbon-oxygen and carbon-fluorine bonds. His work also uncovered that many Buchwald biaryl phosphines are modified *in-situ*, generating new, bulkier supporting ligands. In 2012, he returned to UC-Berkeley as an assistant professor and was granted tenure in 2018.

The work reported by the Maimone research group has not gone unnoticed. He has been recognized with a number of academic and pharmaceutical awards, including a 2019 Arthur C. Cope Scholar Award, 2017 National Fresenius Award, 2016 Cottrell Scholar Award, 2016 NSF Career Award, and a 2015 Alfred P. Sloan Fellowship. He is the recipient of synthetic organic young investigator awards sponsored by Bristol Myers Squibb, Novartis, Eli Lilly, and Amgen. We are very pleased to highlight the excellent work of Professor Thomas Maimone and his research group.



Spotlight on World News

Please Note: Discussion of any FDA approvals for this issue are limited to new chemical entities approved to treat cancer since the previous CICR Newsletter issue (May 2019)

KRAS's Undruggability Cracks?

At the recent annual meeting of the American Society of Clinical Oncology (ASCO), Amgen reported results from their ongoing trials of the G12C KRAS inhibitor AMG 510 (see also the Research Highlights). A majority of the 45 enrolled patients with either non-small cell lung cancer or colorectal cancer achieved stable disease or a partial response upon treatment. Other companies, such as Mirati Therapeutics (MRTX849) and Wellspring Biosciences/Johnson & Johnson (ARS-3248), also have similar molecules at advanced stages. Although this clinical success is exciting, the G12C mutation is only found in a small subset of cancers. Other KRAS mutants will be harder to target via this overall strategy. In a different approach, Moderna and Merck have developed an mRNA cancer vaccine, mRNA-5671, that encodes for four commonly found KRAS mutations. The long-held myth of undruggability for this important oncogene may finally be cracking.

Sources : [Nature Reviews Drug Discovery](#), [Amgen Press Release](#).

Mirati teams up with Novartis

Mirati Therapeutics will collaborate with Novartis on a clinical trial to evaluate the combination of MRTX849, a KRAS G12C inhibitor, and the latter's TNO155, a SHP2 inhibitor, in patients with solid tumors that harbor KRAS G12C mutations.

Source: [SeekingAlpha](#)

Gilead teams up with Nurix

Nurix Therapeutics is a biotech company that is focused on the use of E3 ligases to enhance the targeted degradation of proteins. In recent deal, Gilead Sciences has partnered with Nurix to create new cancer therapies and medicines for other challenging diseases. The deal is worth \$45 million upfront, and could reach up to \$2.3 billion if all milestones are met. This deal continues the trend of increasing pharma action in the protein degradation space.

Sources: [FierceBioTech](#)

Bristol-Meyers reorganizes its R&D

Bristol-Meyers Squibb is one of the largest drug makers in the world, and has recently been involved in a major merger [deal with Celgene](#). Recently, they have announced plans to restructure operations at the new, combined company. The new-look R&D portion of the organization will be split into early discovery and late-stage divisions, with the early-stage group led by Rupert Vessey, of Celgene, and the late-stage team led by Samit Hirawat, who moves over from Novartis. Similar adjustments have been made with senior leaders across the new organization. Only time will tell how this will trickle down into the rest of the company. Source: [PharmaPhorum](#)

GSK joins forces with the University of California

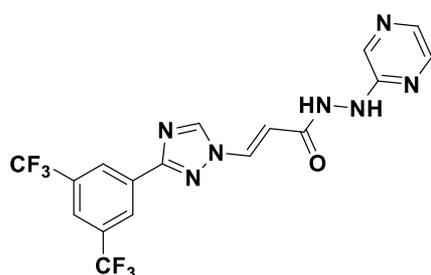
To advance genomic research and improve drug discovery, GlaxoSmithKline becomes the latest pharma company to announce a strategic collaboration with leaders in the field of functional genomics to harness the power of CRISPR technology in drug discovery research. The new 'Laboratory for Genomics Research' unites CRISPR pioneers with industry expertise to help unravel mysteries of the human genome.

Source: [GSK](#)

AbbVie acquires Allergan

In a deal worth \$63 billion in cash and stock, AbbVie will acquire Allergan. The move looks to be driven by an effort to supplement AbbVie's portfolio with Allergan's franchises in eye care, CNS, and medical aesthetics, possibly in a bid to generate additional revenue streams as the loss of protection on Humira looms.

Source: [PRNewswire](#)



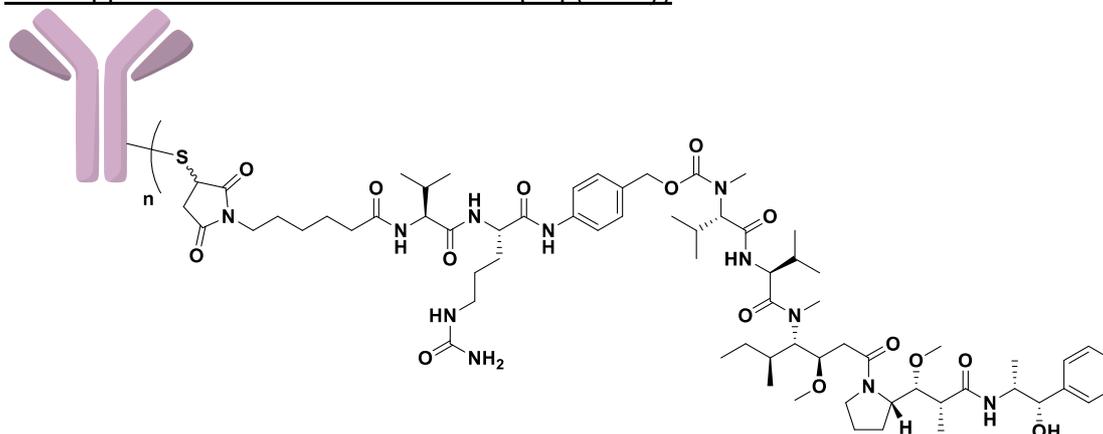
FDA Approval of Selinexor (Xpovio)

On July 3, 2019 Karyopharm received FDA approval for the nuclear export inhibitor selinexor (Xpovio) to treat adult patients with relapsed or refractory multiple myeloma. Selinexor is an antagonist of the nuclear export protein exportin-1 (CRM1/XPO1), whose inhibition leads to the accumulation of tumor suppressor proteins in the cell nucleus. XPO1 is

overexpressed in multiple myeloma and is correlated with poorer overall survival. See related [blogpost](#).

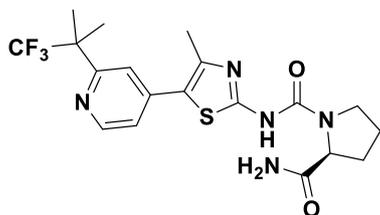
Source: [FDA](#)

FDA Approval of Polatuzumab Vedotin-piiq (Polivy)



The CD79b targeting antibody drug conjugate (ADC) polatuzumab vedotin-piiq (Polivy, Genentech/Roche) was approved on June 10, 2019 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). DLBCL is the most common type of non-Hodgkin lymphoma, diagnosed in more than 18,000 people in the US each year. The drug is based on a humanized anti-CD79b antibody that targets the B-cell antigen receptor complex-associated protein beta chain (CD79b). This antibody is conjugated covalently via a protease-cleavable linker (valine-citrulline; maleimidocaproylvaline-citrulline-p-aminobenzoyloxycarbonyl or MC-VC-PABC) to the dolastatin analog monomethyl auristatin E (MMAR), a highly cytotoxic agent. This constitutes the fifth FDA approval of an ADC after Mylotarg (2017, gemtuzumab ozogamicin, Wyeth/Pfizer), Adcetris (2011, brentuximab vedotin, Seattle Genetics/Millennium), Kadcyla (2013, trastuzumab emtansine, Genentech/Roche),

and Besponsa (2017, inotuzumab ozogamicin, Wyeth/Pfizer). ADCs are an active area of research in oncology and there are more than 50 ADCs in clinical development. Research in this area is still growing and expanding and was highlighted in an earlier AARC CICR Newsletter, which focused on the topic. See related [blogpost](#). Source: [FDA](#)

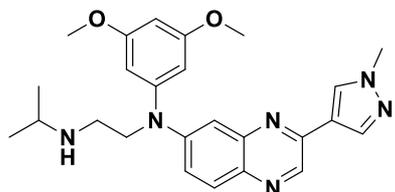


FDA Approval of Alpelisib (Piqray)

Novartis received approval for their phosphatidylinositol 3-kinase alpha (PI3Kalpha) inhibitor Alpelisib (Piqray) on May 24, 2019 for the treatment of breast cancer. The FDA also approved a companion diagnostic test to detect the PIK3CA mutation. The approval marks the first PI3K inhibitor

to demonstrate a clinically meaningful benefit in treating patients with this type of breast cancer. See related [blogpost](#).

Source: [FDA](#)



FDA Approval of Erdafitinib (Balversa)

On April 12, 2019 Janssen Pharmaceuticals received approval for the pan-FGFR inhibitor erdafitinib (Balversa) when used for the treatment of adult patients with locally advanced or metastatic bladder cancer with an FGFR3 or FGFR2 alteration. Fibroblast Growth Factor Receptor (FGFR) is a

receptor tyrosine kinase consisting of four family members. Alterations in one of the FGFR genes are present in up to 30 percent of urothelial carcinomas. Erdafitinib is currently in clinical development for the treatment of non-small cell lung cancer, gastric cancer, esophageal cancer and cholangiocarcinoma. See related [blogpost](#).

Source: [FDA](#)



Upcoming Conferences

[258th ACS National Meeting and Exposition](#)

Aug. 25-29, 2019, San Diego, California

[BrazMedChem2019](#)

Sept. 1-4, 2019, Pirenopolis, Goias, Brazil

[EFMC-ASMC '19: EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry](#)

Sept. 1-5, 2019, Athens, Greece

[20th SCI/RSC Medicinal Chemistry Symposium](#)

Sept. 8-11, 2019, Churchill College, Cambridge, UK

[17th CHI Discovery on Target](#)

Sept. 17-19, 2019, Boston, Massachusetts

[Fifth CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival](#)

Sept. 25-28, 2019, Paris, France

[Cancer Research UK-AACR Joint Conference: Engineering and Physical Sciences in Oncology](#)

Oct. 15-17, 2019, London, United Kingdom

[AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics](#)

Oct. 26-30, 2019, Boston, Massachusetts

[Canadian Cancer Research Conference](#)

Nov. 3-5, 2019, Ottawa, Ontario, Canada

[Third FBDD Down Under](#)

Nov. 12-15, 2019, Melbourne, Australia

[15th CHI Fragment-Based Drug Discovery](#)

April 13-17, 2020, San Diego, California

[AACR Annual Meeting 2020](#)

April 24-29, 2020, San Diego, California



Funding Opportunities

[Stand Up To Cancer Gastric Cancer Interception Research Team](#)

Grant Amount: \$3 million
Grant Term: Three Years
Application Deadline: Aug. 30, 2019

[AACR-AstraZeneca Clinical Immuno-oncology Research Training Fellowships](#)

Grant Amount: \$100,000
Grant Term: One Year
Application Deadline: Sept. 27, 2019