

**CICR Spring 2020 Newsletter**



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## From the Editors, with Dr Iain Watson, Editor

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 (CICR). This quarter, we are focusing on new drugs on the horizon. CICR Editor Dr. Iain D. G. Watson has taken the lead in assembling an overview of the topic.



**Iain D.G. Watson, PhD, Editor**

Senior Scientist, Drug Discovery, Ontario Institute for Cancer Research (OICR)

Toronto, Ontario Canada

The unprecedented events of the past few months have impacted all aspects of society. With scientists all over the world social distancing and staying home to reduce the spread of COVID-19, international conferences have been cancelled, and this includes the April AACR Annual Meeting in San Diego. However, in its place, the AACR Board of Directors hosted the AACR Virtual Annual Meeting I on April 27-28, 2020. This virtual conference was attended by more than 61,000 registrants from 140 countries and included a total of 102 oral presentations and 126 posters. The AACR Virtual Meeting II is planned for June 22-24, 2020, and like the first virtual conference, registration fees will be waived.

At the AACR Annual Meetings, the New Drugs on the Horizon sessions provide first disclosure of the chemical structures of novel agents against emerging cancer targets. These sessions occurred virtually this year as part of the Virtual Annual Meeting I on April 27-28, 2020. For chemists working in cancer research, these sessions are a highlight of the Annual Meeting. The novel agents presented are typically in the early stages of clinical evaluation and provide insight into the biology of cancer targets. This year's presentations were selected from more than 30 proposals from industry and academia. For the first time, the AACR hosted three New Drugs on the Horizon sessions, a feature that I hope will continue. While these sessions usually host hundreds of attendees packed into conference and overflow rooms, over ten thousand participants were able to log into the second session (making it a top 5 session). These talks are currently available for [on-demand viewing](#) through the virtual meeting platform until the launch of the AACR Virtual Annual Meeting II on June 22-24.

In this issue of the Newsletter, we have focused on the eight research talks presented at this year's New Drugs on the Horizon sessions. Our first research highlight is the disclosure of a novel Menin-MLL1 antagonist from Jerry McGeehan of Syndax Pharmaceuticals. Our second highlight is the talk from Bayer's Ilona Gutcher, who described the first Aryl Hydrocarbon Receptor (AhR) inhibitor to enter phase I clinical development. Our Newsletter also features the disclosure of a glutaminase inhibitor being developed for KEAP1/NFE2L2 mutant NSCLC, from Jeffrey Kovacs at MD Anderson. Xiaojing Wang from Genentech presented on a non-phenolic oral estrogen receptor antagonist and degrader. Other presentations summarized include a first-in-class PARP7 inhibitor from Ribon Therapeutics, a SHP2 inhibitor from Novartis, a novel 2+1 T cell recruiting bispecific antibody targeting STEAP1 and CD3 from Amgen, and a new covalent EGFR inhibitor from ARIAD Pharmaceuticals. In addition to these

excellent talks we describe 5 presentations from the Advances in Cancer Drug Design Session disclosing inhibitors of EED, CD73, PARP14, SHP2 and an oral SERD.

In the past year, the CICR Editorial Board has initiated a social media presence with the creation of the CICR LinkedIn group. We thought the New Drugs on the Horizon sessions were the perfect opportunity to instantly communicate with our members. As such, the research highlights and associated newly disclosed structures were first published on the LinkedIn platform, only hours after these structures were disclosed. I invite all our readers to [join our new group](#) and engage with your fellow scientists on this platform.

Continuing this theme of first disclosures, we also highlight two recent articles from *Molecular Cancer Therapeutics* (MCT) that are the inaugural reports in their new [First Disclosures](#) article type. This article type reports on the structure and activity of a new drug for the first time in published literature. The articles highlight 7A5, a human CD137 receptor binding monoclonal antibody, and tucatinib, a new HER2-selective tyrosine kinase inhibitor. We hope this format will make MCT the central hub for the first disclosure of cancer drug candidates!

We are also pleased to highlight the work of Dr Brian Lanman, a Principal Scientist in the Medicinal Chemistry Department at Amgen. Brian leads cross-functional teams in the discovery and pre-clinical development of new therapies and has been heavily involved in the oncology therapeutic area. Recently, Brian led Amgen's chemistry efforts investigating covalent inhibitors of KRAS(G12C), leading to AMG-510, the first investigational KRAS(G12C) inhibitor to enter human clinical trials. This molecule was debuted at last year's AACR Annual Meeting in Atlanta GA in an exciting New Drugs on the Horizon [talk](#). The complete webcast of the AACR Annual Meeting 2019 is currently freely available [online](#). This and other aspects of Brian's career path are highlighted in this issue's Profile of an Early-Career Researcher.

### **Join the new AACR-CICR LinkedIn Network Group**

We look forward to your participation in our conversations that are designed to enhance your CICR initiative. Join the [LinkedIn Group](#)!

### **View the CICR Newsletter Archives & the CICR Early-career Researcher Profiles**

For past issues of the CICR Newsletter, visit its [Archives](#). We are also pleased to provide past issues' Profiles of Early-career Researchers in its own [Archives](#).



## News from the CICR Steering Committee



**Contributed by CICR Chair, Philip Jones, PhD**

VP of Therapeutics Discovery; Head of Drug Discovery  
Institute for Applied Cancer Sciences  
MD Anderson Cancer Center  
Houston, Texas

### JOIN US AT THE AACR ANNUAL MEETING 2020-VIRTUAL SESSIONS in JUNE!

CICR members, I am pleased to serve as your Chairperson for the 2020-2021 term. As the present Chair, and, on behalf of all the [CICR Steering Committee members](#), allow me to say that we all look forward to your participation in the June 22-24, 2020 virtual sessions! They are expected to be as stimulating and informative as those virtual sessions held in April. For further details, visit [AACR Annual Meeting 2020](#).

We regret that, due to the COVID-19 crisis, we were unable to see many of you at the on-site AACR Annual Meeting 2020 in San Diego that needed to be cancelled for everyone's well-being. The CICR Steering Committee and I certainly look forward to a future opportunity to network with you in an exciting exchange of ideas that was planned for the on-site CICR Town Hall, please reach out on the e-mail address below if you have any ideas. We were also expecting a high attendance at the always-popular *New Drugs on the Horizon* sessions, that inaugurated its third part in 2020 and comprises exciting presentations on first disclosures of new anticancer agents in or soon to be in clinical trials. These sessions have always proven to be an excellent opportunity to learn about the next wave of innovative cancer drugs progressing in the clinic, and indeed that proved to be the case with this year's virtual format. There were more than ten excellent presentation covering a broad range of modalities and targets, and vibrant Q+A. We are already anticipating the on-site 2021 sessions at the AACR Annual Meeting next April in Washington, DC.

Additionally, the CICR Steering Committee has organized a stimulating three-part *Chemistry to the Clinic* educational session that will be held during the June 2020 virtual sessions program. These three sessions are programmed to provide informative content to benefit cancer chemistry research, and the topics and cochairs are listed as follows:

- Lead Optimization Case Studies in Cancer Drug Discovery, chaired by Michael Brands and Joachim Rudolph

- Irreversible Inhibitors as Potential Anticancer Agents, chaired by Sara J. Buhrlage and Richard A. Ward
- Next-Generation Medicines on Clinically Useful Targets, chaired by Xiaojing (Gina) Wang and Stephen E. Fawell

We encourage you and your colleagues to participate in the *Chemistry to the Clinic* sessions during the June virtual program, since a positive turnout will support the efforts of the CICR Working Group to organize such exciting sessions in the future and emphasize the crucial role that chemistry plays in cancer research.

### **JOIN THE AACR-CICR LINKEDIN NETWORK GROUP!**

If you haven't done so already, make sure to join this exciting [LinkedIn Group](#) that focuses on "all things CICR!" We hope that this becomes a venue for broadcasting information/discoveries relevant to the CICR community. We look forward to your active participation to ensure stimulating conversations as well as research and programming updates.

### **CONTACT US**

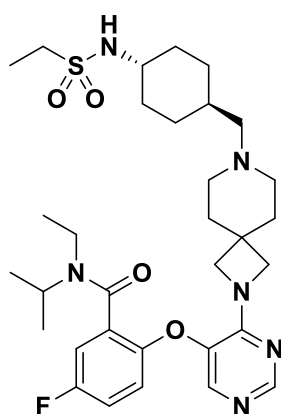
Thank you for your continued support! For questions or comments, please email [cicr@aacr.org](mailto:cicr@aacr.org). We are happy to hear from you!



## Selected Research Highlights

The following research highlights are taken from Chemistry in Cancer Research (CICR) related content from the recent AACR Virtual Annual Meeting I which occurred on April 27-28, 2020. These highlights are from the three New Drugs on the Horizon Sessions and the Advances in Cancer Drug Design Session. Individual session videos are posted for on-demand viewing and will remain available on the platform through the end of the AACR Virtual Annual Meeting II (June 22-24).

**A first-in-class Menin-MLL1 antagonist for the treatment of MLL-r and NPM1 mutant leukemias.** McGeehan, J., AACR Annual Meeting 2020, [New Drugs on the Horizon Session 1](#), Abstract: DDT01-01, Oral Presentation.



**SNDX-5613**

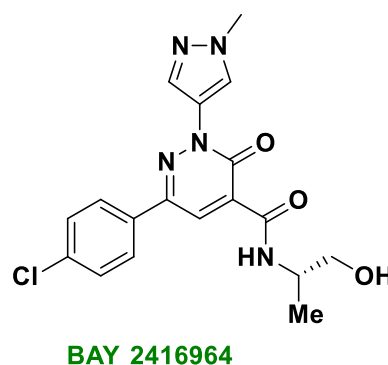
Syndax Pharmaceutical's Jerry McGeehan presented on the menin-MLL1 protein-protein interaction, an important epigenetic contact in leukemia. The targeting of the MEN:MLL1 interaction in MLL-r and NPM1 mutant AML blocks cell proliferation. *De novo* structure-based drug design led to the ultimate development of SNDX-5613, an inhibitor that occupies the MLL1 binding pocket on menin. SNDX-5613 is a potent ( $K_i = 0.149$  nM), selective and bioavailable ( $F = 29\%$  in rat) drug candidate. The compound removes menin from chromatin and showed single-agent activity in multiple preclinical xenograft models, including MOLM-13 xenografts. SNDX-5613 is currently in ongoing phase 1 trials and initial patient responses were described.

**BAY 2416964: The first Aryl Hydrocarbon Receptor (AhR) inhibitor to enter phase I clinical development as a novel cancer immunotherapy.** Gutcher, I. *et al.*, AACR Annual Meeting 2020, [New Drugs on the Horizon Session 1](#), Abstract: DDT01-02, Oral Presentation.

The AhR has a role in regulating immunosuppression in the tumor microenvironment. The enzyme is part of the IDO/TDO-kynurenine-AhR axis and its inhibition is expected to enhance anti-tumor immune responses and decrease tumor growth. Ilona Gutcher described Bayer's approach towards the development of an AhR inhibitor, starting from a screen using a cellular reporter gene assay. Leads generated from this approach progressed to BAY-218 which was presented at last year's AACR meeting. Further

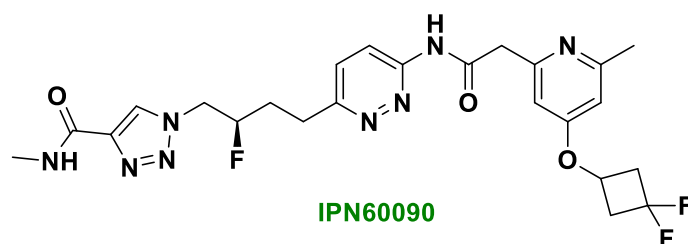


development lead to BAY 2416964, a potent (hAhR  $IC_{50}$  = 22 nM), selective and orally bioavailable (F = 83% in mouse) AhR inhibitor. Tumor growth inhibition is observed with the compound in syngeneic CT26 and B16F10-OVA models. BAY 2416964 exhibits pro-inflammatory effects in human immune cell populations and combined with a PDL-1 inhibitor further enhances T-cell activation. The compound has a favorable safety profile and is currently being investigated in a phase I clinical trial.



**IPN60090: A potent and selective inhibitor of glutaminase being developed for KEAP1/NFE2L2 mutant NSCLC and ASNS-low HGSOC patients.** Kovacs, J. J., AACR Annual Meeting 2020, [New Drugs on the Horizon Session 1](#), Abstract: DDT01-03, Oral Presentation.

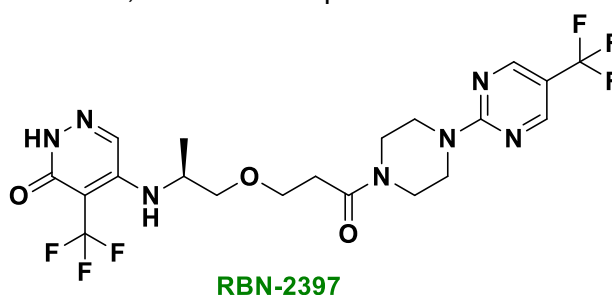
Glutaminase (GLS1) is a target for tumor metabolism. Jeffrey Kovacs described MD Anderson's discovery of IPN60090 as a potent (GLS1  $IC_{50}$  = 26 nM), selective and bioavailable (F = 89% in mouse) inhibitor of GLS1 with anti-proliferative effects. The compound's differential profile across the cancer cell lines lead the team to recognize the dysregulation of the KEAP1/NRF2 pathway as a predictor of responsive NSCLC lines. In ovarian lines, low levels of the glutamate producing enzyme ASNS were predictive of response. Furthermore, IPN60090 inhibits tumor growth in PDX models



expressing low levels of ASNS and synergizes with a dual TORC1/2 inhibitor in KEAP1 mutant NSCLC models. The compound is currently in a phase I clinical trial in patients with advanced solid tumors.

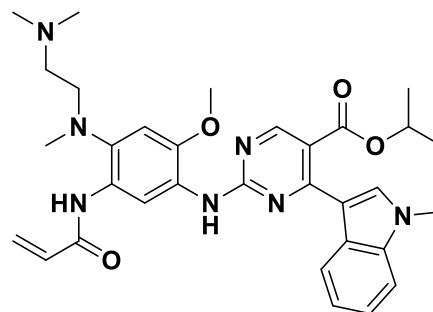
**RBN-2397: A first-in-class PARP7 inhibitor targeting a newly discovered cancer vulnerability in stress-signaling pathways.** Vasbinder, M.M. *et al.*, AACR Annual Meeting 2020, [New Drugs on the Horizon Session 2](#), Abstract: DDT02-01, Oral Presentation.

Ribon Therapeutics has a platform that focuses on finding selective inhibitors for mono-PARPs, a family of NAD<sup>+</sup> dependent ADP-ribose transfer enzymes. One of these, PARP7 is switched on by cancer stresses, such as the toxins in cigarette smoke, and is highly expressed in lung tumors. Melissa Vasbinder described the team's development of a clinical PARP7 inhibitor, starting from a 9  $\mu$ M hit from a PARP family cross-screen. Optimization lead to RBN-2397, a NAD<sup>+</sup> competitive inhibitor with a PARP7 potency less than 3 nM and greater than 20-fold selectivity across the PARP family. The compound is orally bioavailable and demonstrated robust single agent activity in human NSCLC NCI-H1373 xenografts and in a CT26 syngeneic model. The compound is currently in clinical development.



**TAK-788: An EGFR inhibitor, currently in Phase II clinical trials, targeting lung cancers with Exon20 insertion mutations.** Gonzalvez, F., AACR Annual Meeting 2020, [New Drugs on the Horizon Session 2](#), Abstract: DDT02-03, Oral Presentation.

Exon 20 insertions of EGFR are a family of resistant mutants that have been detected in the clinic. There are currently no approved drugs that are effective against this mutant. Francois Gonzalvez from ARIAD Pharmaceuticals described an approach to developing a clinical candidate against this EGFR subtype. The team focused on compounds that maximized the EGFR mutant potency over that of wild type. Starting from known EGFR inhibitor osimertinib, an isopropyl ester was added to the pyrimidine core to give TAK-788, which had enhanced exon 20 affinity. The compound is currently involved in a phase 1/2 clinical trial.



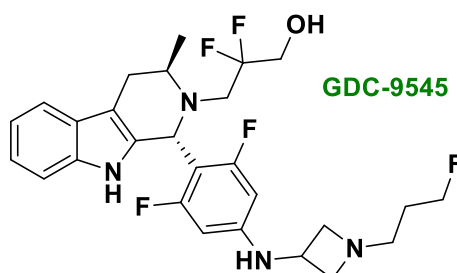
**TAK-788**

**AMG 509: A novel, humanized, half-Life extended, bispecific STEAP1 × CD3 T cell recruiting XmAb® 2+1 antibody.** Nolan-Stevaux, O., AACR Annual Meeting 2020, [New Drugs on the Horizon Session 2](#), Abstract: DDT02-04, Oral Presentation.

STEAP1 is a tumor associated antigen that is overexpressed in metastatic castration-resistant prostate cancer (mCRPC) and Ewing sarcoma (EWS). Olivier Nolan-Stevaux presented Amgen's program for the development of AMG 509, a novel 2+1 T cell recruiting bispecific antibody targeting STEAP1 and CD3. AMG 509 mediated T cell redirected lysis is specific for STEAP1 expressing target cells and varies with cell surface expression. Treatment with the antibody caused regression of 22RV1 STEAP1 prostate xenograft tumors and ES-7 EWS xenograft. AMG 509 is currently in a phase 1 study in adult patients with mCRPC.

**GDC-9545: Discovery of an oral estrogen receptor antagonist, degrader, and immobilizer for the treatment of ER+ breast cancer patients.** Wang, X., AACR Annual Meeting 2020, [New Drugs on the Horizon Session 2](#), Abstract: DDT02-05, Oral Presentation.

Xiaojing Wang from Genentech presented on a new selective estrogen receptor degrader (SERD). There are currently no approved orally bioavailable SERD molecules and the team had to start from a new core with more optimal lipophilicity. The new core lacked the phenolic OH present in estradiol that was believed to be indispensable for activity. Further optimization led to GDC-9545, a potent degrader with an excellent oral PK profile that enables once daily dosing. The candidate is currently in clinical phase 1 studies.

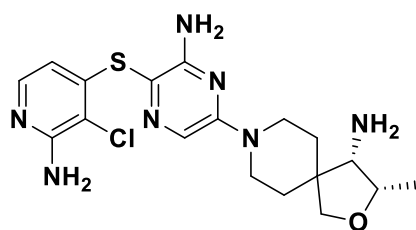


**GDC-9545**



**The discovery of TNO155: A first in class SHP2 inhibitor.** LaMarche, M.J., AACR Annual Meeting 2020, [New Drugs on the Horizon Session 3](#), Abstract: DDT03-02, Oral Presentation.

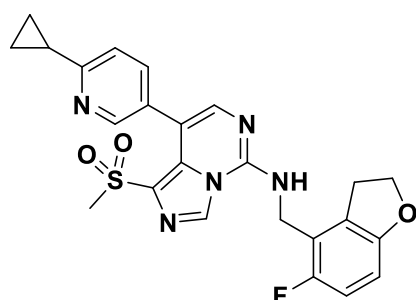
SHP2 is an enzyme of the protein tyrosine phosphatase (PTP) family that regulates various cellular processes down the critical MAPK pathway. Matthew LaMarche from Novartis described the discovery of SHP inhibitors that interact at an allosteric tunnel between the phosphatase and SH2 domains. Avoiding active site binders with an



**TNO155**

active site PTP domain counter-screen was critical to the group's strategy. Initial aminopyrimidines hits had phototoxic properties, although they were optimized from 12 to 0.070  $\mu\text{M}$  in a ligand efficient manner. Further optimization of the series removed this liability along with hERG and permeability problems, resulting in TNO155, a potent, orally bioavailable SHP2 inhibitor.

**Discovery of a highly potent, efficacious and orally active small-molecule inhibitor of embryonic ectoderm development (EED).** Wang, C. *et al.*, AACR Annual Meeting 2020, Advances in Cancer Drug Design Session, Abstract: 1036, Oral Presentation.

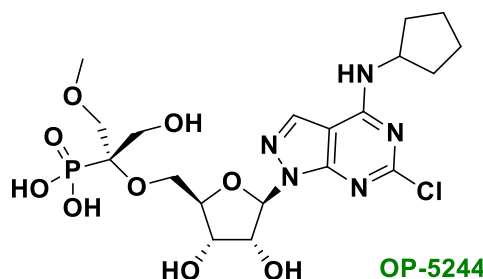


**EEDi 5285**

Shaomeng Wang's group at the University of Michigan and Ascentage Pharma presented their efforts towards an inhibitor of embryonic ectoderm development (EED). EED is an epigenetic target that interacts with EZH2 and histone deacetylase proteins as a key component of PRC2. Changwei Wang described the discovery of EEDi 5285, an orally bioavailable small-molecule inhibitor of EED. This compound showed activity in a Karpas 422 xenograft model along with a related analog.

**Orally available small molecule CD73 inhibitor reverses immunosuppression through blocking of adenosine production.** Du, X. *et al.*, AACR Annual Meeting 2020, Advances in Cancer Drug Design Session, Abstract: 1037, Oral Presentation.

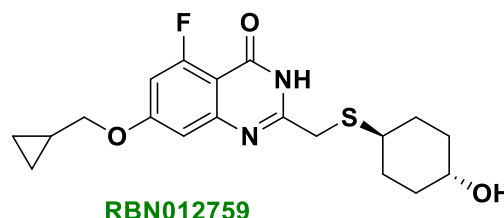
CD73 is a cell surface enzyme which converts AMP to adenosine. As such, CD73 may mediate immunosuppression and chemoresistance through adenosine receptor signaling. Xiaohui Du from ORIC Pharmaceuticals detailed the development of OP-5244, a monophosphonate CD73 inhibitor. The development began from a known ligand and focusing on linker substitution using rational design principles and X-ray crystallographic structural information. This resulted in OP-522, a novel orally bioavailable mono-phosphonic acid CD73 inhibitor ( $\text{IC}_{50} = 0.25 \text{ nM}$ ) with measurable cellular functional effects, such as the suppression ADO production in tumor cells. The company also has a development candidate, ORIC-533 for which further data will be presented soon.



**OP-5244**

**A potent and selective PARP14 inhibitor decreases pro-tumor macrophage function and elicits inflammatory responses in tumor explants.** Schenkel, L. *et al.*, AACR Annual Meeting 2020, Advances in Cancer Drug Design Session, Abstract: 1038, Oral Presentation.

PARP14 is a member of the monoPARP family and has some IO functions as a regulator of macrophage differentiation. Laurie Schenkel described Ribon Therapeutics approaches towards the identification and optimization of a potent and selective PARP14 inhibitor. Starting from a 1  $\mu$ M hit and with X-Ray structural information, the Ribon team used rational design to develop RBN012759, a less than 3 nM inhibitor with more than 300-fold selectivity against other PARP family members.

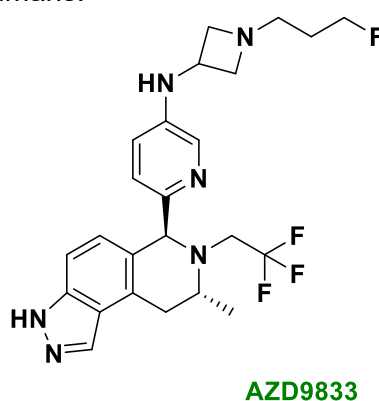


**Fragment-based drug discovery to identify small molecule allosteric inhibitors of SHP2.** Day, P.J. *et al.*, AACR Annual Meeting 2020, Advances in Cancer Drug Design Session, Abstract: 1039, Oral Presentation.

Christopher Johnson presented work on SHP2, an enzyme of the protein tyrosine phosphatase family that regulates various cellular processes down the RAS-RAF-MEK-ERK pathway. The work, part of an Astex and Taiho Pharmaceuticals collaboration, described a fragment screen for the discovery of allosteric SHP inhibitors that interact at a 'tunnel site' between the phosphatase and SH2 domains. Using NMR, ITC and SPR biophysical assays, early leads were developed by fragment growing to give a 1000-fold improvement in affinity. This optimization has resulted in a single digit nanomolar orally bioavailable candidate preclinical candidate, although no structures of the series were disclosed. The compound is selective against a panel of 20 phosphatases, including SHP1.

**Preclinical pharmacokinetic and metabolic characterization of the next generation oral SERD AZD9833.** Gangl, E.T. *et al.*, AACR Annual Meeting 2020, Advances in Cancer Drug Design Session, Abstract: 1042, Oral Presentation.

The final talk of the session was a presentation from AstraZeneca on a next generation selective estrogen receptor degrader (SERD). There are currently no approved orally available SERD molecules and Eric Gangl described the PK characteristics of AZD9833, a potent degrader which has an excellent oral PK profile and the team's desired half-life profile in humans.



## Molecular Cancer Therapeutics Highlights

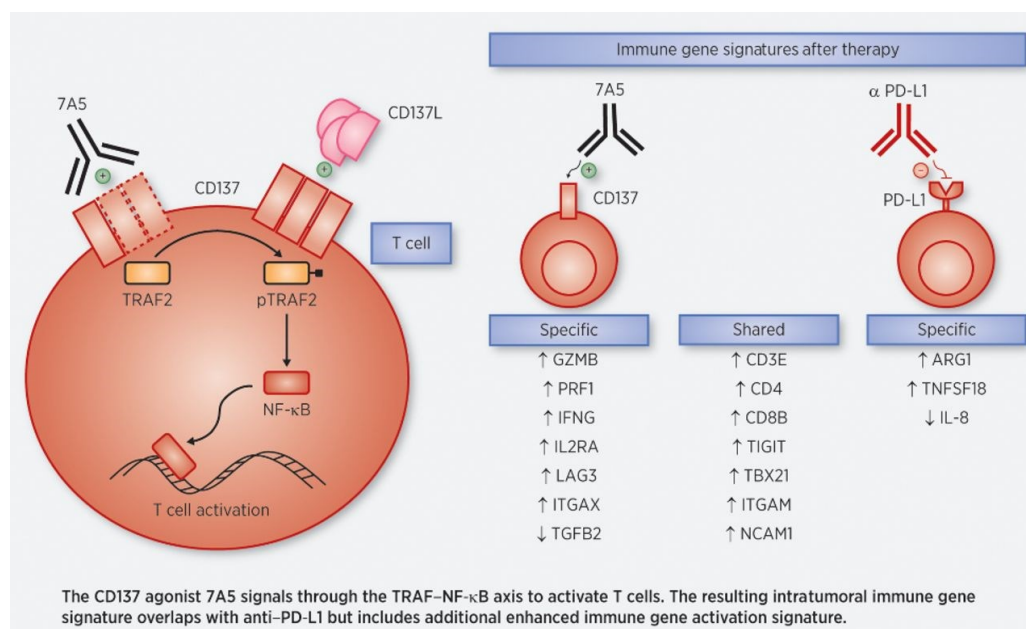
We highlight a recent article from *Molecular Cancer Therapeutics* in every Newsletter. This quarter's highlight is related to the issue's topic on new drugs in the horizon. The article is also included in the Research Highlights section.

*Molecular Cancer Therapeutics* announces the new **First Disclosures** article type, presenting drugs for the time in published literature. MCT has been a source for first disclosures since its inception in 2001, when we published Rusnak, *et al.*'s [manuscript on lapatinib](#). We are now expediting these reports of drug structure and activity as First Disclosure articles, which receive rapid review, feature graphical abstracts, and are heavily promoted across the scientific community, making MCT the central hub for the first disclosure of cancer drug candidates.

The two articles below are our inaugural First Disclosure articles.

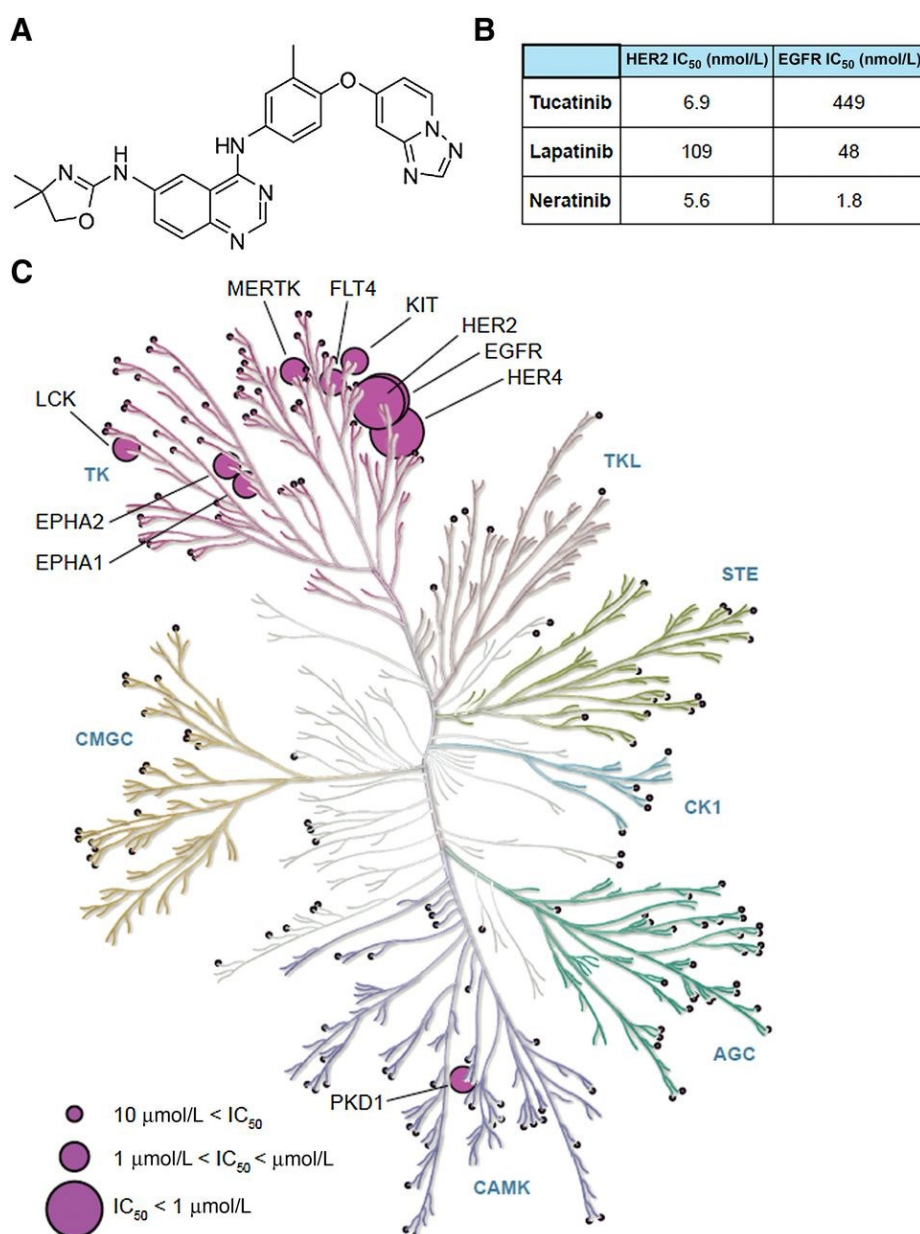
### Characterization of 7A5: A Human CD137 (4-1BB) Receptor Binding Monoclonal Antibody with Differential Agonist Properties That Promotes Antitumor Immunity Kotanides, H. *et al.* *Mol. Cancer Ther.*, 2020;19:988-98.

CD137 agonism is hypothesized to reinvigorate potent anti-tumor immunity due to its role in T-cell expansion and effector function. Previous CD137 agonists were limited by liver toxicity and modest activity. In this article, Kotanides and colleagues disclose 7A5, a novel antibody agonist for CD137. Treatment with 7A5 demonstrated a T-cell activated intratumoral immune gene expression signature and generated anti-tumor activity that was further enhanced by anti-PD-L1 therapy.



**Preclinical Activity of HER2-Selective Tyrosine Kinase Inhibitor Tucatinib as a Single Agent or in Combination with Trastuzumab or Docetaxel in Solid Tumor Models** Kulukian, A. et al. *Mol. Cancer Ther.*, 2020;19:976-87.

Current small molecule inhibitors for HER2 (augmented in breast, bladder, colorectal, non-small cell lung, esophageal, and gastric cancers) have nearly equipotent inhibition of EGFR and HER2 which contribute to the severity of adverse events. In this article, Kulukian and colleagues disclose tucatinib, a selective HER2 inhibitor 1,000 times more potent for HER2 than EGFR in cellular signaling assays.



## Profile of an Early-Career Researcher



**Dr Brian Lanman**

Principal Scientist, Medicinal Chemistry, Amgen

Thousand Oaks, California, USA

This issue's Early Career Profile highlights Dr. Brian Lanman, a Principal Scientist in the Medicinal Chemistry department at Amgen in Thousand Oaks, California, USA. Brian leads cross-functional teams in the discovery and pre-clinical development of new therapies, principally in the oncology therapeutic area. A synthetic organic chemist by training, Brian also directly supervises a team of medicinal chemists in the design of new lead molecules, relying extensively on structure-based design, computational modeling, and state-of-the-art high-throughput experimental platforms. Most recently, Brian led Amgen's chemistry efforts investigating covalent inhibitors of KRAS(G12C), coordinating efforts across an international team in the identification of AMG 510 (p1NN sotorasib), the first investigational KRAS(G12C) inhibitor to enter human clinical trials. Brian received his A.B. in Chemistry from Harvard University (1998), where he performed undergraduate research on the total synthesis of Taxol® in the lab of Yoshito Kishi, and had his first exposure to pharmaceutical research as a summer intern at Schering-Plough Pharmaceuticals. Brian subsequently completed his doctoral studies at Harvard as an NSF research fellow under the guidance of Andrew Myers, receiving A.M. (2000) and Ph.D. (2004) degrees for his work on the solid-supported synthesis and biological characterization of tetrahydroisoquinoline antitumor antibiotics. In 2004, Brian joined Larry Overman's group at UC Irvine as an NIH postdoctoral fellow, where he developed new synthetic methods to access the architecturally complex bis-guanidine marine natural product palau'amine and contributed to its structural revision.

Brian joined Amgen's medicinal chemistry department in 2006. His early research focused on the optimization of sphingosine-1-phosphate receptor-1 (S1P1) agonists for the treatment of multiple sclerosis, leading to the identification of the investigational agent AMG 369. Brian subsequently began work in the oncology therapeutic area, contributing to research on PI3K $\alpha$  and PIM kinase inhibitors. This work, which leveraged unique kinase structural features to impart kinome selectivity and led to the identification of the investigational PI3K $\alpha$  inhibitor AMG 511, initiated a long-standing research focus on structure-based drug design.

After a brief foray into cardiovascular research—exploring lipid conjugation as a strategy for the half-life extension of APJ agonist peptides—Brian returned to oncology research to lead medicinal chemistry teams focused on the disruption of protein-protein interactions. During this time, Brian contributed to the discovery of AMG 397, Amgen's investigational oral Mcl-1 inhibitor, and led chemistry efforts in the development of covalent  $\beta$ -catenin/TCF4 inhibitors for the potential treatment of colorectal cancer.

Brian became involved with KRAS inhibitor efforts in 2013. Following an initial exploration of published non-covalent binders in the design of Cys12-reactive covalent inhibitors and the identification of several promising starting points from in-house screening efforts, research efforts accelerated in 2015, when new hits from focused covalent inhibitor libraries were found to occupy a previously unknown cryptic pocket on the KRAS protein. Binding to this “H95-pocket” significantly enhanced inhibitor potency, and kick-started an intense period of research, during which Brian led efforts to optimize early leads and, subsequently, to leverage knowledge of this new pocket to develop novel inhibitor scaffolds with improved pharmacokinetic properties. By 2017, optimization efforts had overcome multiple pre-clinical development hurdles (e.g., atropisomer configurational stability, metabolic liabilities, moderate permeability, and poor aqueous solubility) to culminate in the identification of the clinical development candidate AMG 510. Ph1 studies of AMG 510 were initiated in August 2018, and initial clinical results in KRAS(G12C)-mutant NSCLC and CRC were first reported in June 2019. Ph1 combinations studies (with select MAPK-pathway inhibitors as well as anti-PD-1 immunotherapy) have recently been initiated and are currently enrolling. A Ph2 trial investigating AMG 510 as a monotherapy in NSCLC is also currently underway.

The aforementioned research has led to Brian’s co-authorship of more than 25 peer-reviewed publications, to his role as a co-inventor on over 25 patent applications and issued patents, and to multiple national and international invited lectures. In his current role at Amgen, Brian continues to lead international cross-functional teams with the aim of integrating world-class capabilities in genomic target identification, DNA-encoded library screening technology, and cutting-edge structural biology in the discovery and development of new small-molecule therapies to treat grievous disease.





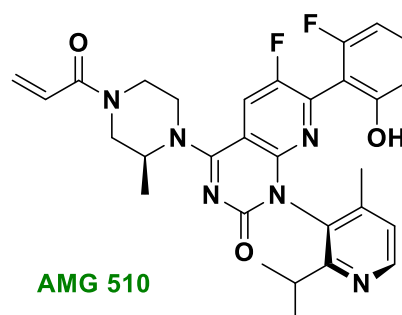
## Global News

**Note: Discussion of FDA approvals for this issue are limited to new chemical entities approved to treat cancer since the previous issue.**

### Merck is consolidating HQ in Rahway

During the release of its first quarter results, the pharma stalwart Merck & Co. announced plans to consolidate its New Jersey sites into one headquarters campus in Rahway by 2023. Sources: [FiercePharma](#), [Merck Press Release](#).

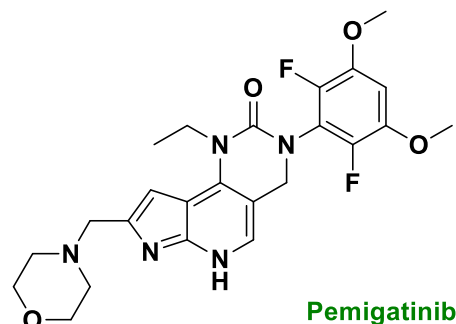
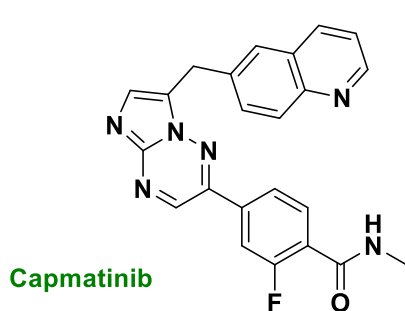
**What is the true impact of Covid-19 on Cancer research:** No one knows how the current viral pandemic will truly affect benchtop or clinical cancer research, but we all hope that the impact is minimal. Amgen, for one, has stated that progression of their headliner AMG-510 KRAS inhibitor, at least, is not expected to suffer significantly. Great news for the patients!



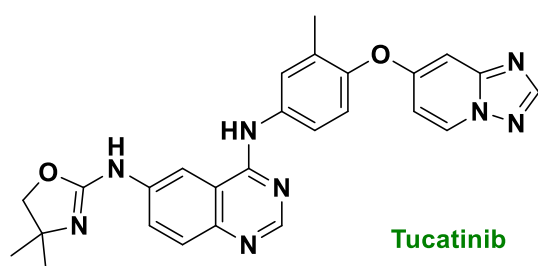
**FDA approval of sacituzumab govitecan-hziy (Trodelyv):** The FDA approved the antibody drug conjugate (ADC) sacituzumab govitecan on April 22, 2020, to treat adult patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease. This ADC consists of a Trop-2 directed antibody conjugated to a topoisomerase inhibitor (SN-38, the active metabolite of irinotecan). ADCs are a therapeutic modality that has exploded in recent years with many new approvals and advances and the topic has recently been highlighted in the [May 2019 CICR Newsletter](#). Source: [FDA](#).

**FDA approval of capmatinib (Tabrecta):** On May 6, 2020, the FDA granted approval of the tyrosine kinase inhibitor capmatinib (Novartis) to treat patients with non-small cell lung cancer (NSCLC) that has spread to other parts of the body. This is the first FDA-approved therapy to treat NSCLC with specific mutations, the mesenchymal-epithelial transition or MET exon 14 skipping mutation. Capmatinib is a c-Met inhibitor. Source: [FDA](#).

**FDA approval of pemigatinib (Pemazyre):** On April 17, 2020, the FDA granted approval to pemigatinib for the treatment of patients with cholangiocarcinoma, a rare form of cancer that forms in bile ducts. Pemigatinib is a small-molecule fibroblast growth factor receptor (FGFR) inhibitor. Source: [FDA](#).

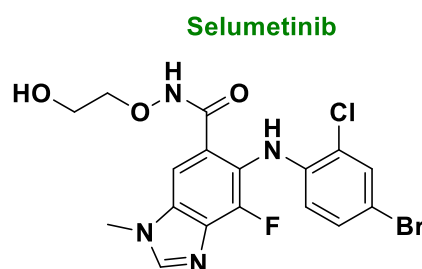


**FDA approval of tucatinib (Tukysa):** The FDA approved tucatinib (Seattle Genetics) on April 17, 2020 to treat advanced unresectable or metastatic HER2-positive breast cancer. Tucatinib is a selective orally active ErbB-2 inhibitor with selectivity for HER2



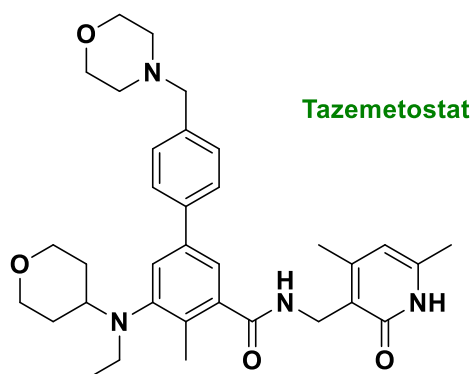
over the related receptor tyrosine kinase EGFR and greater than 1,000-fold enhancement in potency for HER2 in cell signaling assays. The [first disclosure](#) of this molecule was announced in the new [First Disclosures](#) article type in MCT, just slightly ahead of the approval. Sources: [FDA](#).

**FDA approval of selumetinib (Koselugo):** On April 10, 2020, the FDA granted approval to selumetinib (AstraZeneca) for pediatric patients with type 1 neurofibromatosis type 1 (NF1). Selumetinib is a non-ATP competitive MEK1/2 inhibitor ( $IC_{50} = 14$  nM) with no inhibition against more than 40 other serine/threonine kinases. Source: [FDA](#).



**FDA approval of isatuximab (Sarclisa):** The FDA approved isatuximab (Sanofi-Aventis) on March 2, 2020 for the treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone. The drug is cytolytic monoclonal antibody that targets CD38, a cell surface marker that is overexpressed on multiple myeloma cells. Sources: [FDA](#), [AACR Alert](#), [AACR Cancer Research Catalyst blog](#).

**FDA approval of tazemetostat (Tazverik):** On January 23, 2020, the FDA granted accelerated approval to tazemetostat (Epizyme Inc) for the treatment of adults and pediatric patients with metastatic or locally advanced epithelial sarcoma. Epithelioid sarcoma is a rare sub-type of soft tissue sarcoma that often occurs in young adults. Although the disease accounts for less than one percent of all soft tissue sarcomas, this constitutes the first treatment option for patients with this disease. Tazverik blocks the activity of EZH2, a histone methyltransferase writer and WDR-domain protein. This marks the first approval of a drug for this target although several other EZH2 inhibitors are currently in



the clinic. Other epigenetic targets such as DNMT1, a DNA methyltransferase writer, and HDACs, a class of histone deacetylase erasers, already have several inhibitors approved. Tazemetostat is also being examined in trials for follicular lymphoma, mesothelioma and prostate cancer. Sources: [FDA](#), [AACR Alert](#), [AACR Cancer Research Catalyst blog](#).



## Upcoming Conferences and Events

To aid those who are contemplating attending a conference we compile a list of upcoming meetings that might interest a scientist in the field of chemistry in cancer research. However, due to the COVID-19 emergency, conference schedules have been thrown into disarray. Border closures and travel restrictions have made it difficult to predict the possibility that previously planned meetings will proceed. We have updated the status of the following advertised conferences, but please check the individual websites before booking travel. For an extensive calendar of AACR related meetings please check the searchable [AACR Meetings and Workshops Calendar](#) on the AACR website.

### [AACR Virtual Annual Meeting I](#)

April 27-28, 2020 – [available for free on-demand viewing](#)

### **Cancelled** – [102nd Canadian Chemistry Conference and Exhibition](#)

May 24-28, 2020; Winnipeg, Manitoba, Canada

### [AACR Virtual Annual Meeting II](#)

June 22-24 – *Free Registration!*

### **Cancelled** – [Gordon Research Conference in Heterocyclic Compounds 2020](#)

June 21-26, 2020; Newport, Rhode Island

### **Cancelled** – [Gordon Research Conference in Organic Reactions & Processes 2020](#)

July 19-24, 2020; Smithfield, Rhode Island

### **Cancelled** – [Gordon Research Conference in Natural Products & Bioactive Compounds 2020](#)

August 2-7, 2020; Andover, New Hampshire

### **Cancelled** – [Gordon Research Conference in Medicinal Chemistry 2020](#)

August 9-14, 2020; New London, New Hampshire

### [15th CHI Fragment-Based Drug Discovery – New Dates!](#)

August 25-26, 2020; San Diego, California

### [260th ACS National Meeting & Exposition](#)

August 16-20, 2020; San Francisco, California

### **Cancelled** – [Fragment-Based Lead Discovery 2020](#)

Sept. 20-23, 2020; Cambridge, United Kingdom

32nd EORTC-NCI-AACR Symposium  
October 28-30, 2020, Barcelona, Spain

PacifiChem 2020 Symposium  
December 15-20, 2020, Honolulu, Hawaii, USA

American Chemical Society Spring 2021 National Meeting & Expo  
March 21-25, 2021, San Antonio, Texas, USA

Kinase 2020: 9th RSC/SCI Symposium on Kinase Inhibitor Design – *New Dates!*  
July 5-6, 2021, London, UK

8th NovAliX Conference – *New Dates!*  
March 10-12, 2021; Boston, Massachusetts

RICT 2020, 56th International Conference on Medicinal Chemistry – *New Dates!*  
July 7-9, 2021; Bordeaux, France

ACS MEDI 37th National Medicinal Chemistry Symposium – *New Dates!*  
July 27-30, 2021; New York, New York



## Funding Opportunities

Please check the searchable [AACR Funding Opportunities](#) page for a current listing of available AACR grant opportunities.

### [AACR-MPM Oncology Charitable Foundation Transformative Cancer Research Grants](#)

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**Grant Amount:** \$400,000 USD **Letter of Intent Deadline:** 06/17/2020 **Application Deadline:** 10/05/2020 **Decision Date:** Nov. 2020

**Start of Grant Term:** 12/01/2020 **Grant Duration:** 2 Years

### [AACR-Bayer Stimulating Therapeutic Advances through Research Training \(START\) Grants](#)

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**Grant Amount:** \$225,000 USD **Application Deadline:** 06/30/2020 **Decision Date:** 09/2020

**Start of Grant Term:** 10/01/2020 **Grant Duration:** 3 Years



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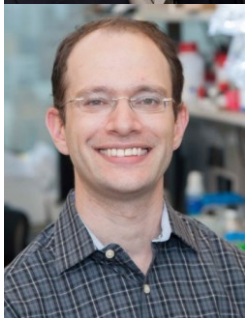
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