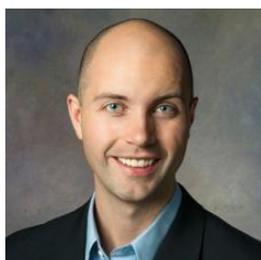




From the Editors



With Editorial Board Member, Jordan Meier, PhD

Investigator, Chemical Biology Laboratory
National Cancer Institute
Frederick, MD

This quarter we have chosen to highlight the topic “metabolic and epigenetic signaling pathways in cancer: towards epigenetics therapies”. Editorial Board member Dr. Jordan Meier has assembled an overview of the topic.

Metabolic Regulation of Epigenetics: Towards Epigenetic Therapies

One of the most surprising features of modern cancer genome sequencing studies has been the discovery of driver mutations in genes encoding primary metabolic enzymes including isocitrate dehydrogenase 1 and 2 (*IDH1/2*), succinate dehydrogenase (*SDHA* and *SDHB*), and fumarate hydratase (*FH*). Traditionally regarded as “housekeeping genes,” recent studies have revealed that the dysregulated activity of these metabolic enzymes can actually cause broad rewiring of cellular biology, similar to the signaling programs mediated by transcription factors and oncogenes. Mechanistic studies indicate this is due to the remarkable ability of metabolic dysregulation to directly impact epigenetic signaling pathways. For example, early studies of *IDH1* and *IDH2* mutations observed that cancers harboring these genomic lesions often possessed aberrant cytosine methylation profiles. While the link between metabolism and DNA methylation was at first puzzling, two landmark studies helped clarify this connection. First, it was found that in acute myeloid leukemia (AML), mutations in *IDH1* and *IDH2* were almost mutually exclusive with those in “*Ten-eleven translocation 2*” (*TET2*), an epigenetic dioxygenase involved in DNA demethylation. Such mutually-exclusive genetic relationships can imply that two mutations are functionally equivalent, suggesting that mutation of *IDH1* and *IDH2* may inhibit DNA demethylation. Next, a landmark study discovered the oncogenic mutations in the

metabolic enzymes IDH1 and IDH2 were actually neomorphic in nature, re-directing these enzymes away from the production of 2-ketoglutarate, a TET2 cofactor, and towards the production of 2-hydroxyglutarate (2-HG), an endogenous TET2 inhibitor. The ability of 2-HG to directly alter epigenetic signaling through non-metabolic roles has led to it, as well as related molecules, being termed “oncometabolites.” Importantly, while the discovery of gain-of-function mutations of IDH enzymes stemmed from studies of glioblastoma and acute myeloid leukemia, similar mutations have been since been observed in a wide variety of blood cancers and solid tumors. These studies illustrate the powerful and often unexpected mechanisms by which metabolism can alter epigenetic signaling in cancer.

As might be expected, the discovery that gain-of-function mutations in IDH play a driver role in many different types of cancer has spurred significant efforts towards therapeutic intervention. The unique active-site of the cancer-associated IDH mutants establishes not only a neomorphic enzyme activity, but also an opportunity for selective small molecule targeting. In 2013, Agios Therapeutics reported two small molecules that selectively inhibited two commonly occurring malignant IDH mutants (IDH1 R132H, found in AML, and IDH2 R140Q, found in glioma). These inhibitors were found to reduce 2-HG levels and reverse the putative transforming effects of IDH1 mutants in vitro as well as in vivo. Later, GSK reported a chemically distinct piperazine-based scaffold that showed similar effects. Importantly, this second class of molecules was also shown to reverse aberrant DNA methylation associated with IDH1 mutation. This is important, as it indicates not only that IDH mutants may be selectively targeted, but also that the epigenetic changes, which they stimulate, can be reversed for therapeutic benefit. Clinical trials of IDH inhibitors are underway in patients with relapsed AML (NCT01915498) as well as other hematologic malignancies harboring IDH mutations (NCT02074839).

The specific example of IDH mutations in cancer highlights both the clinical relevance of the intersection of epigenetics and metabolism, as well as a broader paradigm indicating that multiple classes of enzymes, which regulate chromatin and DNA, may be regulated by the metabolic state of the cell. For example, fumarate and succinate are two additional “oncometabolites” which accumulate to high levels in hereditary kidney cancers and paragangliomas, and have been found to competitively inhibit TET as well as mechanistically related lysine demethylase enzymes. These examples indicate dicarboxylate metabolites as crucial mediators of chromatin demethylation. Gut microbiota break down complex carbohydrates to butyrate, a known inhibitor of histone deacetylases. Depending on the genetic background of the mouse, high levels of butyrate can epigenetically stimulate gene expression in a manner that either promotes or represses the initiation of tumors in the colon, providing a potential epigenetic input into the effects of dietary components, such as fiber, on tumor formation. Finally, histone acetyltransferase are highly dependent on production of their metabolic cofactor, acetyl-CoA, itself derived from either glucose or the micronutrient acetate. These emerging examples suggest that environmental exposures, as well as how a cell’s metabolism is inherently wired to process nutrients, may exert substantial influences on chromatin structure and gene expression.

In addition to fundamental biology, the identification of links between metabolism and epigenetics may have repercussions for therapy. For example, one implication of this emerging science is that specific metabolic contexts may influence susceptibility to emerging classes of epigenetic-targeted inhibitors. Indeed, studies performed to identify effective therapies for IDH mutant cancers recalcitrant to direct small molecule targeting have found these cancers are unusually susceptible to inhibition of BET bromodomains. These agents inhibit acetylation-dependent signaling cascades, and are currently the subject of several clinical trials. In addition, several of the enzyme

classes known to be competitively inhibited by metabolites such as histone demethylases (inhibited by 2-HG) and histone deacetylases (inhibited by butyrate) are active targets for therapeutic development. By analogy with fragment-based drug discovery, understanding the selectivity and molecular interactions of these endogenous “fragments of life,” with different members of these enzyme classes may highlight novel opportunities for inhibition and drug development.

In this issue of the Newsletter, we have provided a perspective of metabolic regulations of epigenetics. We also present articles that exemplify the potential of epigenetic therapies as anti-cancer treatments. We are also pleased to highlight the work of Dr. Kabirul Islam, an Assistant Professor in the Department of Chemistry at the University of Pittsburgh. Prof. Islam is at the forefront of employing organic synthesis, bioorganic chemistry, protein engineering and structural biology to edit epigenetic processes for cell fate reprogramming, as well as correcting aberrant gene expression in human diseases like obesity and cancer. Prof. Islam’s work is highlighted in this issue’s Profile of an Early-Career Researcher



News from the CICR Steering Committee



Contributed by CICR Chairperson, Prof. Julian Blagg

EORTC Meeting Dublin Ireland, November 2018

The CICR Steering Committee cordially invites you to join us at the [EORTC Molecular Targets and Cancer Therapeutics Conference in Dublin, Ireland](#) (November 13th to 16th 2018) during which myself and Dr. Andrew Phillips (CICR Chair-Elect) will host a Town Hall and Networking Session, watch for more details as the conference approaches. We will present on our CICR activities, including our work to promote the optimal use of chemical tools in bioscience research to sponsor CICR Scholar-in-Training Awards for the 2019 Annual Meeting, and our work, in collaboration with the CICR Newsletter Editorial Board, to increase the membership and networking potential of CICR and to promote the importance of chemistry in cancer research through the scientific program committees of AACR meetings. Please come along to share your views in an informal setting. The Town Hall also provides an excellent opportunity to network with colleagues and we look forward to seeing you for light refreshments.

2019 AACR Award for Outstanding Achievement in Chemistry in Cancer Research

We would like to remind you of the opportunity to nominate contenders for the prestigious 2019 AACR Award for Outstanding Achievement in Chemistry in Cancer Research. This award honors a chemist whose research has led to important contributions to the fields of basic cancer research, translational cancer research, cancer diagnosis, the prevention of cancer, or the treatment of patients with cancer. Such research may include, but is not limited to, drug discovery and design, structural biology, proteomics, metabolomics and mass spectrometry, chemical aspects of carcinogenesis, imaging agents and radiotherapeutics, and chemical biology. The winner will be invited to give a Plenary Lecture at the 2019 Annual Meeting in Atlanta. Nominations are now open and the deadline for nominations is Sept. 19. <https://www.aacr.org/Research/Awards/Pages/Awards-Detail.aspx?ItemId=4>

CICR Chairperson Elect

We would like to remind CICR members to participate in the election of the CICR Chairperson Elect for 2019/20 to succeed Dr Andrew Phillips (C4 Therapeutics and Current Chairperson-Elect). The election will take place in October 2018 and all CICR members will be notified by email of the opportunity to vote.



Selected Research Highlights

TAS-114, a First-in-Class Dual dUTPase/DPD Inhibitor, Demonstrates Potential to Improve Therapeutic Efficacy of Fluoropyrimidine-based Chemotherapy

W Yano, et al. Mol Cancer Ther 2018

<https://doi.org/10.1158/1535-7163.MCT-17-0911>

Both deoxyuridine 5'-triphosphate nucleotidohydrolase (dUTPase) and dihydropyrimidine dehydrogenase (DPD) are critical to the intercellular metabolism of 5-Fluorouracil (5-FU). In this study, Yano and colleagues specifically designed TAS-114, a novel small molecule inhibitor that can enhance the antitumor activity of fluoropyrimidine-based therapy through complete inhibition of dUTPase and moderate and reversible inhibitory activity on DPD. Dual dUTPase/DPD inhibitor like TAS-114 has great potential to improve the therapeutic efficacy of fluoropyrimidine-based chemotherapy in cancer.

Anti-leukemic efficacy of BET inhibitor in a preclinical mouse model of MLL-AF4+ infant ALL

M Bardini, et al. Mol Cancer Ther 2018

<https://doi.org/10.1158/1535-7163.MCT-17-1123>

Therapies targeting epigenetic regulators have recently shown promise in the rare but very aggressive MLL-rearranged acute lymphoblastic leukemia (ALL). Here, Bardini and colleagues demonstrated the *in vitro* and *in vivo* evidence that the BET inhibitor I-BET151 is effective in reducing the growth of MLL-AF4+ leukemic cells, sensitizes glucocorticoids-resistant MLL-rearranged cells to Prednisolone, and works synergistically with HDAC inhibitors on the treatment of MLL-AF4+ infant ALL.

Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations

Intlekofer et al., Nature, 2018, 559, 125–129

<https://doi.org/10.1038/s41586-018-0251-7>

IDH2 is a main contributor to the pathogenesis of acute myeloid leukemia (AML) through the accumulation of high levels of 2-hydroxyglutarate (2-HG), an oncometabolite that interferes with α -ketoglutarate-dependent enzymes such as histone lysine demethylases. This article describes an investigation into the cause of a novel resistance mechanism observed during clinical trials of the mutant isocitrate dehydrogenase 2 (IDH2) inhibitor enasidenib. Patients with relapsed acute myeloid leukemia (AML) were treated with enasidenib after confirmation of the IDH2^{R140Q} somatic mutation, the mutation for which this drug is indicated. After initial success, two patients presented with resistance and elevated 2-HG levels following less than 1 year of treatment. Through sequencing analysis of these patient samples, each patient had developed a novel *in trans* mutation, a mutation that resides on the allele that is

wild-type for the original neomorphic mutation. These researchers hypothesized that the mutations were involved in the binding of enasidenib to IDH2. Through structural mapping studies, both mutations were found to reside in the IDH2 dimer interface, which directly interacts with enasidenib, and both mutations were shown to abrogate binding. These mutations were then studied *in vitro* and *in vivo*, providing evidence that resistance against enasidenib was, in fact, due to these novel *in trans* mutations, and that these mutations were directly responsible for the increase in 2-HG accumulation and further disease progression observed clinically. These new insights into *in trans* mutational resistance mechanisms have the potential to be more broadly applied to other important cancer targets, such as EGFR.

Biomimetic Artificial Epigenetic Code for Targeted Acetylation of Histones.

Taniguchi et al., J Am Chem Soc, 140, 7108-7115.

<https://pubs.acs.org/doi/abs/10.1021/jacs.8b01518>

Histone acetylation is a posttranslational modification that plays a crucial role in gene expression and cancer, promoting changes in chromatin structure as well as the recruitment of bromodomain-containing transcriptional activators. Inhibitors of histone-bromodomain interactions have been explored in clinical settings for their ability to disrupt oncogenic gene expression and thwart tumor development and progression. In this study, Taniguchi et al. conjugate a previously reported 3,5-dimethylisoxazole bromodomain inhibitor to a sequence-specific DNA-binding pyrrole-imidazole polyamide to create a bifunctional molecule capable of sequence selective directed acetylation. *In vitro* studies were used to show that the bifunctional molecule is capable of recruiting a bromodomain-containing histone acetyltransferase (p300/CBP) to reconstituted nucleosomes, promoting their acetylation. Transfection of these molecules into cells was found to drive modest changes in expression of genes containing the polyamide-binding sequence, suggesting this mechanism may also be operable in cells. These results suggest a novel strategy for chemically targeting histone acetylation to alter gene expression, as well as opportunities to improve upon the selectivity and potency of these molecules.

Time-Resolved Analysis Reveals Rapid Dynamics and Broad Scope of the CBP/p300 Acetylome,

Weinert et al., Cell, 2018, 174, 231-244.

<https://doi.org/10.1016/j.cell.2018.04.033>

The lysine acetyltransferases p300 and CBP constitute a family of multifunctional transcriptional activators whose aberrant activity has been implicated in cancer and many other diseases. One challenge in the study of p300/CBP is differentiating biology driven by their catalytic protein acetyltransferase activity as opposed to other domains of the protein, many of which mediate powerful protein-protein interactions. In this study, Weinert et al. employed quantitative proteomics together with a suite of chemical inhibitors and traditional genetic knockout methods to define the first ever system-wide map of the p300/CBP acetylome. Key insights include the discovery that p300/CBP-regulated protein acetylation is relatively dynamic (half-lives <30 min), the identification of novel histone acetylation sites that are highly regulated by p300/CBP, and the inference that acetylation primarily alters protein abundance via changes gene expression rather than competing with alternative posttranslational modifications such as ubiquitylation. In addition, these studies define a subset of rapidly regulated acetylation sites that may be critical for changes in the expression of specific genes. Overall, this work provides an initial view into how the acetylation landscape is reshaped by small molecule inhibitors of p300/CBP, and highlight opportunities for employing these molecules as inhibitors of oncogenic signaling networks.

Small Molecule Targeted Recruitment of a Nuclease to RNA

Matthew G. Costales, et al. J Am Chem Soc 2018; 140, 6741-6744

<https://doi.org/10.1021/jacs.8b01233>

Costales et al. describe the development of RIBOTACs (ribonuclease targeting chimeras). Conceptually similar to Proteolysis Targeting Chimeras that degrade protein targets, RIBOTACs are bivalent small molecules that degrade transcripts by recruiting a ribonuclease to a specific RNA sequence. In this paper, the authors recruited RNase L to the microRNA miR-96, a downregulator of the tumor suppressor protein FOXO1. Degrading miR-96 triggered apoptosis in breast cancer cells (MDA-MB-231). RT-qPCR analysis suggested that the likely target was miR-96, in good agreement with the proposed mechanism of action.

Where do Recent Small Molecule Clinical Development Candidates Come From?

Brown and Boström, J Med Chem 2018; Article ASAP

<https://pubs.acs.org/doi/10.1021/acs.jmedchem.8b00675>

In this review 66 clinical candidates which have been described in the *Journal of Medicinal Chemistry* are analyzed to understand if certain lead generation strategies are more successful than others in terms of the identification of drug candidates. Although the use of published data means that the sample size is relatively small, the principle finding – that starting points derived from previously known compounds are the most fruitful – is in line with historical observations. Also included is analysis of physicochemical property changes during the hit-to-clinical candidate journey, and it is noted that more than 50% of clinical candidates are structurally very different (more complex) from their start points.

Discovery of reversible DNA methyltransferase and lysine methyltransferase G9a inhibitors with antitumoral in vivo efficacy

Obdulia et al, J Med Chem 2018, Article ASAP

<https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b01926>

Using knowledge- and structure-based approaches, the authors designed and synthesized reversible chemical probes that simultaneously inhibit the activity of two epigenetic targets, histone 3 lysine 9 methyltransferase (G9a) and DNA methyltransferases (DNMT), at nanomolar ranges. Enzymatic competition assays confirmed the design strategy, which was centered on substrate competitive inhibitors. Next, an initial exploration around one of their hits was pursued to identify an adequate tool compound for *in vivo* testing. *In vitro* treatment of different hematological neoplasia cell lines led to the identification of molecules with clear antiproliferative efficacies (GI₅₀ values in the nanomolar range). On the basis of epigenetic functional cellular responses (levels of lysine 9 methylation and 5-methylcytosine), an acceptable therapeutic window (around 1 log unit) and a suitable pharmacokinetic profile, this compound was selected for *in vivo* proof-of-concept (Nat. Commun. 2017, 8, 15424). Herein, the compound achieved a significant *in vivo* efficacy: 70% overall tumor growth inhibition of a human acute myeloid leukemia (AML) xenograft in a mouse model.

Improved Aldehyde Dehydrogenase 1A1 inhibitors

Yang et al, J Med Chem 2018, 61, 4883-4903

<https://pubs.acs.org/doi/10.1021/acs.jmedchem.8b00270>

The aldehyde dehydrogenases (ALDHs) have important functions in the control of various toxicological and physiological processes. Overexpression of ALDH1A1 is associated with malignancy and poor patient prognosis. Indeed, preliminary results using biological means of silencing ALDH1A1, as well as non-specific inhibitors, have

provided support for the validation of this enzyme's function as a target for cancer drug discovery. In the highlighted work, a collaborative group from the National Center for Advancing Translational Sciences (NCATS), the University of Oxford (UK), and Yale University (New Haven, Connecticut) report in a recent *Journal of Medicinal Chemistry* issue improved ALDH1A1 inhibitors that feature nanomolar inhibition of the enzyme, robust cellular target engagement, and superior inhibition of cellular ALDH function. The specificity of these compounds over other ALDHs and a promising ADME profile (both *in vitro* and *in vivo*) point toward the use of these compounds to better define the scope and utility of ALDH1A1 inhibitors for cancer therapy.

Agios details the discovery of Ivosidenib, a first-in-class mutant IDH1 inhibitor

Popovici-Muller et al, ACS Med Chem Lett 2018, 9, 300-305

<https://pubs.acs.org/doi/10.1021/acsmedchemlett.7b00421>

Gain of function mutations in isocitrate dehydrogenase 1 (IDH1) result in increased production of D-2-hydroxyglutarate (2-HG), a so-called oncometabolite that may be responsible for certain alterations in epigenetic and differentiation processes in some cancers. In a recent issue of *ACS Medicinal Chemistry Letters*, Agios describes the optimization process that led from the previously reported inhibitor AGI-5198 to a clinical molecule. Key to the optimization effort was improvement in the metabolic stability profile by blocking sites of metabolism in the former lead molecule. The team next had to balance the physical properties, walking a fine line between PXR activation with lipophilic compounds and poor cellular permeability with more polar analogs. They ultimately arrived at AG-120, a compound that demonstrated good cellular potency, suitable pharmacokinetics in multiple species, and reduced tumor burden in xenograft models. Recently, AG-120, now known as ivosidenib, entered into clinical trials as a first-in-class IDH1 inhibitor and is reported as the first inhibitor of mutant IDH1 to achieve a proof of concept in the clinic. See Spotlight on World News to learn about the FDA approval.

Profile of an Early-Career Researcher

Kabirul Islam, PhD



**Assistant Professor
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA**

Our theme for this month's issue involves exploring the emerging intersections between epigenetics and metabolism, and this month's Early Career Investigator's research encompasses both of these areas. Kabirul Islam, Ph.D. is currently an Assistant Professor at the University of Pittsburgh, Pittsburgh, Pennsylvania, USA. Kabirul started his independent career at Pitt in 2013 after completing his postdoctoral studies with Minkui Luo at Memorial Sloan Kettering. One of the Luo lab's first trainees, Kabirul developed "bump-hole" strategies for studying protein methyltransferase enzymes involved in epigenetic regulation of gene expression. Specifically, Islam showed that synthetic S-adenosylmethionine (SAM) analogues could be used by engineered ("bumped") methyltransferases to discover novel enzyme substrates using click chemistry followed by LC-MS/MS proteomics. Prior to the Luo lab, Kabirul did a short fellowship in Tarun Kapoor's group at Rockefeller University developing inhibitors of the cytoskeletal motor myosin V. Kabirul earned his PhD in chemistry at the Indian Institute of Science in 2008 under the tutelage of Goverdhan Mehta, where he worked on the total synthesis of natural products.

In his independent career at the University of Pittsburgh, Kabirul's group has extended his interest in novel applications of enzyme engineering and "bump-hole" strategies towards two distinct areas. First, they have developed functionalized analogues of 2-ketoglutarate that are biologically inert towards most lysine demethylases, but can specifically activate enzymes engineered to accommodate their increased steric bulk in the active site. In the future, this chemical control may be used in combination with cell permeable analogues to rapidly activate lysine demethylases in cells and permit the identification of direct enzyme substrates. Alternatively, these molecules can be readily converted to substrate analogues, which could allow engineered 2-ketoglutarate-dependent dioxygenases, but not other natural dioxygenases, to be turned off with exquisite temporal control. Notably, several lysine demethylases have been proposed to be targets of "oncometabolites" such as 2-HG. The development of bump-hole methods may highlight novel targets of these enzymes for whom disrupted demethylation plays a critical role in IDH-mediated tumorigenesis. In a second and related project, the Islam group has pioneered the use of photoactivatable amino acids to identify novel proteins that interact with epigenetic reader proteins. These approaches use unnatural amino acid mutagenesis to insert photocrosslinkers such as azidophenylalanines into active-sites that interact with specific epigenetic protein modifications, allowing the capture of normally transient interaction partners. This "interaction-based protein profiling" approach has the potential to identify novel protein-protein interactions of epigenetic reader proteins known to play important roles in cancer, such as BRD4, and thus may provide new insights into their mechanism as well as therapeutic targeting. Kabirul has coauthored 29 peer-reviewed publications and has been invited to present his work in prestigious settings including Pacificchem, the 2016 FASEB Kabirul Acetylation Meeting, and the 2018 Bioorganic

Gordon Research Conference. We look forward to additional discoveries at the metabolism epigenetics interface from Kabirul!



Global News

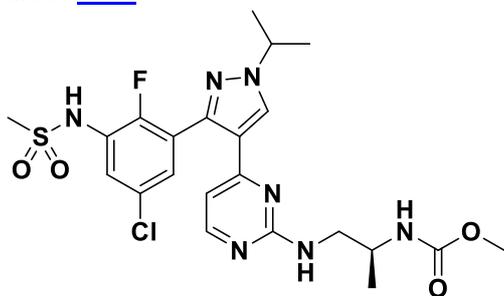
eLife is seeking new Editor-in-Chief

eLife, the non-profit organisation launched and supported by research funders to improve science publishing, is looking for an Editor-in-Chief. Reporting to the Board of Directors, the Editor-in-Chief is the public champion and leader of eLife, responsible for eLife's goals as an open-access publisher of excellent science, a developer of new tools and technology, and a voice for change. The job description can be found [here](#). Source: [eLife](#)

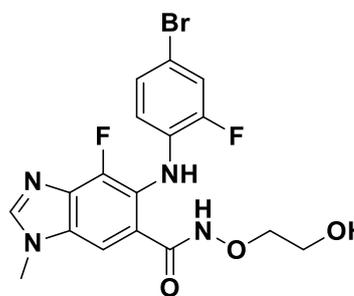
FDA Approval of Encorafenib (Braftovi) and Binimetinib (Mektovi)

The combination of encorafenib and binimetinib (Array BioPharma) was approved on June 27, 2018 for patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. Following approval of BRAF inhibitors vemurafenib (Plexxikon, 2011) and dabrafenib (GSK, 2013), combination therapy with BRAF and MEK inhibitors replaced monotherapy as the first line treatment. Encorafenib is a BRAF inhibitor while binimetinib is a MEK inhibitor. The approvals are the result of the COLUMBUS trial involving 577 patients. At the same time, the FDA approved the THxID BRAF kit as a companion diagnostic for the combination therapeutics. [See the related blogpost here](#).

Source: [FDA](#)



Encorafenib (Braftovi)



Binimetinib (Mektovi)

FDA Approves Ivosidenib (Tibsovo) to Treat Relapsed or Refractory Acute Myeloid Leukemia Harboring Certain IDH1 Mutations

The FDA approved ivosidenib (Tibsovo) on July 20, 2018 for treating adults with acute myeloid leukemia (AML) that has not responded to or has relapsed after other treatments, and that harbors a specific mutation in the IDH1 gene as determined by an FDA-approved test; see main theme of this newsletter for more detail. The approval was based on results from a phase 1 clinical trial showing that more than 30 percent of patients treated with ivosidenib had complete remission lasting for a median of 8.2 months. [See related blogpost here](#).

Source: [FDA](#)

FDA Approves Iobenguane I-131 for the Treatment of Rare Neuroendocrine Tumors

On July 30, 2018, the FDA approved Iobenguane I-131 (AZEDRA) for the treatment of adult and pediatric patients (12 years and older) with Iobenguane scan-positive (also known as MIBG), unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. The approval was granted priority review, orphan product, fast track status, and breakthrough therapy designation after 22% of patients in the phase 2 trial saw their tumors shrink. Iobenguane binds to the norepinephrine transporters present on the majority of pheochromocytomas and paragangliomas and is used to locate the neuroendocrine tumors, whereas the I-131 conjugated version delivers localized radiation to destroy the tumor(s).

Source: [FDA](#)

Scientists Create a Complete Atlas of Lung Tumor Cells

Researchers used single-cell RNAseq technology to study almost 100,000 individual cells, focusing on both cancerous cells and non-cancerous cells in tumors such as blood vessels, immune cells and fibrous cells to create the very first 'atlas' of cell phenotypes found in lung tumors. Their results reveal that tumors are much more complex than previously appreciated, distinguishing 52 different types of cells. This information can be used to identify new research lines for treatment. The study was published in Nature Medicine.

Source: [Drug Discovery Today](#)

Increased Mergers and Acquisitions in Pharma in 2018

Last year represented a relative lull in mergers and acquisitions (M&A) among pharmaceutical companies. However, according to one report by FiercePharma, 2018 is off to a hot start, with ~\$100 billion spent through the midway point of the year. This increased activity is highlighted by two acquisitions by Celgene, a \$12.6 billion acquisition of a Biogen spin-off by Sanofi, and an announced takeover of Shire by Takeda worth \$62 billion. According to the report, even more activity is likely in the later part of the year, with the increased activity possibly stemming from a change in the U.S. tax code.

Source: [Fierce Pharma](#)

First of its kind vaccine to treat lung cancer tested by Cancer Research UK

A first of its kind treatment vaccine has moved into a phase I clinical trial for patients with non-small cell lung cancer (NSCLC), under a collaboration agreement between Cancer Research UK and Asterias Biotherapeutics Inc. Cancer Research UK will manage the initial clinical development of AST-VAC2, a promising immunotherapy candidate derived from a standardized human embryonic stem cell line, which was brought to the charity through its Clinical Development Partnerships (CDP) scheme. If shown to be safe and effective, it's hoped that AST-VAC2 could be used as an additional treatment for patients who no longer have advanced disease but whose lung cancer is at high risk of coming back, or in combination with other treatments for patients with advanced disease.

Source: [Drug Discovery Today](#)

Industry-Academia Partnerships Rundown

In \$65M deal, Deerfield Management partners with Northwestern University to create Lakeside Discovery, LLC. Source: [Northwestern](#). Abbvie teams up with California Institute for Biomedical Research (CalIBR), a division of the Scripps Research Institute, in CAR-T deal. Source: [C&E News](#). Ipsen and University of Texas MD Anderson Cancer Center partner for cancer drug development partnership. Source: [MD Anderson Center](#). Eisai joins with six research organizations in nucleic acid drug discovery and delivery deal. Source: [Pharmabiz](#).



Upcoming Conferences and Events

[American Chemical Society Fall Meeting 2018](#)

August 19-23, Boston, USA

[22nd EuroQSAR: Translational and Health Informatics](#)

September 16-20, 2018, Thessaloniki, Greece

[Second AACR International Conference on Translational Cancer Medicine Cancer Discoveries for Clinical Application](#)

September 27 - 29, 2018, São Paulo, Brazil

[Immuno-Oncology 2018](#)

September 26-27, 2018, London, UK

[The European Drug Safety Summit 2018](#)

October 17-18, 2018, London, UK

[EORTC Molecular Targets and Cancer Therapeutics Conference](#)

November 13-16, 2018, Dublin, Ireland

[Innovation and Biomarkers in Cancer Drug Development: A Joint Meeting Presented By EORTC, NCI, EMA, and AACR](#)

November 29 - 30, 2018, Brussels, Belgium

[Targeting PI3K/mTOR Signaling](#)

November 30 - December 3, 2018, Boston, Massachusetts

[4th International Conference on Drug Discovery, Development and Lead Optimization](#)

December 3-5 2018, San Francisco, USA

[Targeting RAS-Driven Cancers](#)

December 9 - 12, 2018, San Diego, California

[Melanoma: From Biology to Target](#)

January 15 - 18, 2019, Houston, Texas

[AACR Annual Meeting 2019](#)

March 29 - April 3, 2019, Atlanta, Georgia

[EFMC-ACSMEDI: Medicinal Chemistry Frontiers 2019](#)

June 10-13 2019, Krakow, Poland