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Editorial

Virtual Special Issue: Epigenetics 2022

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Without question, epigenetics is one of the fastest growing, and most impactful, fields in chemical biology, neuroscience, medicinal chemistry, and drug discovery today. Recognizing the importance of this area, in 2020 we invited submissions for a virtual special issue on this topic hosted by *ACS Chemical Biology*, *ACS Chemical Neuroscience*, *ACS Infectious Diseases*, *ACS Medicinal Chemistry Letters*, *ACS Pharmacology & Translational Science*, and the *Journal of Medicinal Chemistry*. We are now delighted to present the Epigenetics 2022 virtual special issue. Below, content from each of the journals involved in this collection of papers is highlighted.

■ ACS CHEMICAL BIOLOGY

Chemical modifications on DNA and histone proteins add tremendous complexity on top of the genetic code. New tools and probes are needed in order to dissect this additional layer of gene expression regulation in eukaryotes. The molecular-level understanding of regulatory mechanisms underlying different epigenetics modifications require new methods and molecular probes. Chemical biologists are playing increasingly important roles in this fast-developing field of biology. We have included reviews that introduce chemical biology approaches to inhibit histone methyltransferase[1] and chromatin interacting proteins,[2] visualize ensembles of the nucleosome,[3] summarize recent progresses on histone modification reader proteins,[4] and propose new concepts on dynamic regulation through reversible histone modifications.[5]

We also include several research articles that develop chemical probes to study chromatin,[6,7] study an emerging glycation on histones,[8] and investigate how the local chemical environment may perturb the histone acetylation reaction.[9] With chemical changes on DNA and histones constituting the molecular basis for epigenetic regulation, chemical biologists will continue to play vital roles in this broad area of biology that affects almost every life process in high eukaryotes.

We are grateful for the invaluable efforts and insight of our *ACS Chemical Biology* Guest Editor, Jordan L. Meier, and his contributions to compiling this collection.

■ ACS CHEMICAL NEUROSCIENCE

The complexity of the human brain is governed, to a large degree, by its transcriptional program: neurons have tremendous diversity of protein expression for synaptic signaling; microglia "activate" and change phenotype, and even physical morphology, in response to their environment; oligodendrocytes reprogram to facilitate myelination repair. These dynamic processes and the diversity of functions created are controlled at the level of epigenetics. Chemical neuroscience through cell biology, chemical probe development, and animal behavior can help deconstruct the epigenetic mechanisms that ultimately define brain function.

In this joint virtual special issue, you will see contributions spanning the neuroepigentic landscape from some of the top authors in the field. Of particular note are several exceptional Perspective and Review papers covering epigenetic mechanisms of memory,[10] activity-dependent brain plasticity,[11] neurodegeneration,[12] and chronic pain.[13] Beyond this, you will find new research that points to the therapeutic potential of epigenetic regulation in a number of disease contexts. Epigenetic modulation of the brain will be a key driver of therapeutic strategies in the future of human health. *ACS Chemical Neuroscience* is proud to highlight this area of research and welcomes future contributions from the field.

■ ACS INFECTIOUS DISEASES

The World Health Organization has declared antimicrobial resistance one of the top 10 global public health threats that humanity is facing. As an urgent global hazard, new strategies and ways of thinking are necessary to control it. Otherwise, modern medicine's progress in treating infections risks being set back decades. The menace is even more dramatic for endemic infectious diseases, where the options available are very limited. The application of genetic tools to manipulate the genome of pathogens, such as CRISPR/Cas9, and advances in the understanding on how hosts react to infections are opening a new chapter in antimicrobial therapy. In this context, the manipulation of epigenetic processes to control an infection is emerging as a novel promising therapeutic opportunity.

ACS Infectious Diseases is contributing to this joint virtual special issue focused on epigenetics with 11 publications in the form of nine innovative research articles, one Perspective, and one Viewpoint. Not surprisingly, histone deacetylase (HDAC) is the target class with a major presence (four research articles), as HDAC has already shown its therapeutic potential

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to treat infectious diseases.[14−17] Also notable is the increase of interest in bromodomains in protozoa; their potential as novel targets against protozoans-mediated diseases is discussed in a Viewpoint[18] and two articles.[19,20] Finally, the characterization of acetyl-CoA synthetase as an interesting target for the development of antiplasmodial drugs,[21] the profiling of epigenetic modulators against hemoprotozoan parasites,[22] and two publications focused on the role of the host[23,24] complete the contributions from *ACS Infectious Diseases* to this virtual special issue. We thank Drs. Kelly Chibale and Nathaniel Jones, who served as Guest Editors for *ACS Infectious Diseases*.

■ ACS MEDICINAL CHEMISTRY LETTERS

As the role of epigenetic targets in disease is unraveled, medicinal chemists and drug discovery scientists have rapidly developed an impressive catalog of small molecules that modulate various aspects of chromatin and RNA modification. This emergence is evidenced by the increasing numbers of papers on epigenetic modulators that have appeared in *ACS Medicinal Chemistry Letters* in the past 5 years vs the first 5 years of the journal's history. As part of this joint virtual special issue, we continue this trend. Farrow and co-workers report on EZM0141, a potent selective inhibitor of SETD2 which is in Phase I clinical trials for cancer.[25] The development of brain penetrant EZH2 (enhancer of zeste homologue 2) inhibitors for cancers is reported by Liang, Phillips, and co-workers.[26] Also focusing on brain cancers, and in particular neuroblastoma, Dev et al. describe a formulation strategy that delivers a pool of acetate together with a chemotherapeutic agent with the goal of rebalancing the aberrant methylation/acetylation state of cancer cells.[27] Niwa et al. define the structural requirements of the phenylcyclopropylamine scaffold for covalent inhibition of lysine-specific demethylase 1 (LSD1/KDM1A), another cancer target.[28] The removal of hERG and microsomal stability liabilities from this *trans*-phenylcyclopropylamine scaffold is described by Koyama, Umehara, and co-workers.[29] Bushweller et al. describe the development of assays for 11 CXXC domains (readers of DNA methylation) and use of the assay to screen a library of covalent fragments.[30] Finally, in a cautionary tale, Moreno-Yruela and Olsen highlight the need for careful analysis of kinetic data when characterizing HDAC inhibitors. The importance of epigenetic targets to drug discovery is also reflected in the patent literature.[31] We capture that in 11 Patent Highlights devoted to novel chemical matter that modulates various epigenetic targets such as protein arginine *N*-methyltransferases (PRMT5), bromodomains, and HDACs, which have potential utility in various disease states such as HIV, Alzheimer's disease, cancer, fibrosis, inflammation, and cardiovascular disease.[32−42] It is clear that epigenetic regulation will continue to be an important area for medicinal chemistry and drug discovery scientists. *ACS Medicinal Chemistry Letters* benefited from the expertise and efforts of Guest Editor Robert Copeland (Accent Therapeutics, Inc.), and we thank him for his contributions.

■ ACS PHARMACOLOGY & TRANSLATIONAL SCIENCE

Several epigenetic drugs have already been approved by the authorities and are used for the treatment of various types of cancer. Moreover, a significant number of drugs for the different epigenetic target classes is currently evaluated in clinical trials. A major focus is still cancer, as exemplified by several papers published in this joint virtual special issue, e.g., focusing on the development of murine leukemia virus integrase-derived peptides that interact with the bromodomain 4 (Brd4) and suppress acute myeloid leukemia,[43] or describing the characterization of small-molecule inhibitors of lysine-specific histone demethylase 1 (LSD1) in oncology.[44] However, epigenetic drugs are increasingly studied in other contexts and developed for treating a range of disorders. Examples published in this collection include the effects of arginine methylation inhibitors on blood platelets,[45] a role for histone kinase inhibitors in neurodegenerative diseases,[46] and the validation of histone deacetylase 8 (HDAC8) inhibitors for the treatment of acute kidney injury.[47] A noteworthy paper focuses on methods for determining cellular target engagement of inhibitors of selected deacetylases.[48]

■ JOURNAL OF MEDICINAL CHEMISTRY

The editors of the *Journal of Medicinal Chemistry* are thrilled to be a part of this joint virtual special issue, highlighting the most recent advances in the field of epigenetics, new ligands, new discovery/assay/DMPK (drug metabolism and pharmacokinetics) paradigms, and key lessons learned in this important field of drug discovery. There are approximately 40 *Journal of Medicinal Chemistry* papers in this virtual special issue, reflecting the intense medicinal chemistry in epigenetics. What is notable about this collection of papers is the diversity of targets and approaches that are described. It is exciting to see a range of contemporary medicinal chemistry techniques applied to epigenetics targets, including covalent inhibitors,[49] fragment-based approaches to ligand development,[50] machine learning,[51] and DNA-encoded libraries.[52]

The acetyl-lysine-reading bromodomains continue to be an important target in epigenetics. The maturity of the bromodomain and extraterminal domain (BET) proteins as targets is reflected by the reports of pan-BET ligands developed for clinical studies.[53] In addition, there are reports of ligands that are selective for either the first[54] or second[55] bromodomains of these proteins and their use as tools to selectively probe the function of these bromodomains. The use of a PET radiotracer for imaging has been applied to studying the distribution of BET proteins in mice brains.[56] There are also reports of ligand development for non-BET bromodomains including ATAD2,[57] BPTF,[58] and CREBBP.[59] While there has been significant progress in the development of ligands for bromodomains, ligands for methyl-lysine readers have been more challenging, so it is encouraging to see papers focusing on the development of peptidomimetic ligands for the plant homeodomain (PHD) of plant homeodomain finger protein 1 (PHF)[60] and for the CBX5 chromodomain.[61]

The lysine/histone deacetylases (K/HDAC) are an established epigenetic therapeutic target. In this collection there are reports of HDAC inhibitors being investigated for the treatment of T-cell prolymphocytic leukemia[62] and the repurposing of human HDAC6 inhibitors to treat multi-drug-resistant malaria-causing parasites.[63] There is also a Perspective discussing the potential for using selective HDAC6 inhibitors as a treatment for aspects of cystic fibrosis-associated lung disease.[64] The development of dual inhibitors of the BET bromodomains and the HDAC enzymes as drug leads to treat leukemia is also described.[65]

Methyltransferase enzymes are also an area of significant activity in epigenetic medicinal chemistry. This is exemplified

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by a Drug Annotation reporting the discovery of development candidate MRTX1719.[66] MRTX1719 is a potent binder to the PRMT5·MTA complex that selectively inhibits PRMT5 activity in *MTAP*-deleted cells over *MTAP*-wild-type cells. This compound is being investigated as a way of inhibiting this new synthetically lethal drug target for the treatment of *MTAP*-deleted cancers. There is also a report of an orally bioavailable inhibitor of the WDR5-mixed lineage leukemia (MLL) protein−protein interaction, which prevents MLL histone methylransferase activity.[67] There are additional papers reporting inhibitors of PRMT5,[68] PRMT4,[69] and nicotinamide *N*-methyltransferase.[70] Compounds that bind to the EED subunit of PRC2 and that act as allosteric inhibitors of PRC2 methyltransferase[71] activity are disclosed. These compounds are orally bioavailable EED ligands with good solubilities. Lysine-specific demethylase (LSD1) inhibitors[72] are also reported, demonstrating that there is also interest in these enzymes.

Taken together, this collection of papers shows the wide range of activities that are underway in the field of epigenetic drug discovery. The reports of orally bioavailable compounds and clinical candidates indicate that epigenetic targets represent a major component of the global medicinal chemistry effort. We are very grateful to our *Journal of Medicinal Chemistry* Guest Editors, Paola Arimondo, Jian Jin, Cheryl Arrowsmith, and Cheng Luo, who have been invaluable in helping to curate this excellent collection of papers. We hope that you enjoy reading them.

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Notes

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