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Editorial

Presenting a Special Issue on "Medicinal Chemistry: From Targets to Therapies"

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This year, *ACS Medicinal Chemistry Letters* celebrates its 10th anniversary. To recognize this occasion, we are publishing a Special Issue entitled "Medicinal Chemistry: From Targets to Therapies".[1] Much has happened since our original call in July 2019 for contributions to this anniversary issue. Indeed, the coronavirus SARS-CoV has overtaken the world amidst a global pandemic. Consequently, antiviral research and vaccine development and production have been catapulted into the spotlight. In the face of the problem of viral and bacterial resistance, there is a pressing need for enhanced, sustained research on anti-infective agents. At the same time, pharmaceutical treatments in many other fields are still urgently needed. Medicinal Chemistry is called upon to answer gaps and inequalities in addressing public health needs, more than ever on a moment's notice.

We are honored to be able to present expert articles covering a wide diversity of topics from some of the most prominent and creative research groups. These papers address numerous therapeutic areas, such as autoimmune and inflammatory diseases, anxiety disorders, bacterial and viral infections, cachexia and anorexia, cancer, gout, ischemia, pain, metabolic disorders, chronic obstructive pulmonary disorder (COPD), asthma, rheumatoid arthritis, psoriasis, lysosomal storage disorders, and neurodegenerative diseases.

Thirty-three Letters, two Viewpoints, three Innovations and three Patent Highlights have been contributed by prominent players in their respective fields. Letters cover subjects such as cyclooxygenase 1 detection (by Malerba et al.),[2] FAK-targeting PROTACs (Gao et al.),[3] a chimeric inhibitor of macrophage migration inhibitory factor (Cirillo et al.),[4] Bruton's tyrosine kinase (BTK) inhibitors (Zhang et al.),[5] oximes for acetylcholine esterase reactivation (Gambino et al.),[6] Zika virus inhibitors (Coluccia et al.),[7] phosphodiesterase 4B (PDE4B) inhibitors (Vadukoot et al.),[8] sirtuin 1−3 inhibition (Rajabi et al.),[9] analogs of the Gram-negative antibiotic zafirlukast (Howard et al.),[10] screens for hepatitis B (HBV) antiviral discovery (Hartman et al.),[11] A_3 adenosine receptor (A_3AR) agonists (Tosh et al.),[12] fibroblast growth factor receptor 4 (FGFR4) inhibitors (Liu et al.),[13] inactivators of γ-aminobutyric acid aminotransferase (GABA-AT) (Shen et al.),[14] bitopic agonists of dopamine D_3R (Battiti et al.),[15] harmaline analogs as COX-2 inhibitors (Uddin et al.),[16] imaging approaches in osteoarthritis (Uddin et al.),[17] HIV-1 protease inhibitors (Ghosh et al.),[18] brain-permeable tafamidis analogs (Sinha et al.),[19] melanocortin receptor antagonists (Ericson et al.),[20] choline antimetabolites (Bollenbach et al.),[21] bromodomain and extra-terminal (BET) inhibitors (Altenburg et al.),[22] raltegravir photoaffinity labels (Pala et al.),[23] selective orexin-1 antagonists (Préville et al.),[24] folate receptor targeting agents (Jin et al.),[25] intracellular peptide delivery (Ng et al.),[26] gibberellin-based inhibitors of NF-kB (Annand et al.),[27] agonists of a cannabinoid-activated GPCR (Schoeder et al.),[28] ceramide galactosyltransferase enzyme inhibitors (Thurairatnam et al.),[29] thermoresponsive perfluorocarbon hydrogels (Herneisey et al.),[30] a sigma-2 receptor agonist that could be effective in COVID-19 (Colabufo et al.),[31] a uric acid uptake inhibitor (Uda et al.),[32] and cationic photosensitizers (Mazumdar et al.).[33] A Featured Letter describes the discovery of A-1331852, a first-in-class orally active BCL-XL inhibitor that can serve both as a tool compound as well as a lead structure for apoptosis-inducing anticancer drugs (Wang et al.).[34]

Viewpoints provide perspectives on isosteric replacements of anilines (Sodano et al.)[35] and deuterium-switches (DeWitt et al.).[36] Innovations demonstrate the utility of phenotypic drug discovery strategies (Childers et al.),[37] allosteric modulators (Han et al.),[38] and brain-penetrant EGFR tyrosine kinase inhibitors (Tsang et al.).[39] The Patent Highlights discuss the development of dual specificity tyrosine phosphorylation regulated kinase-1 A (DYRK1A) inhibitors (Kargbo),[40] a SMARCA2/4 PROTAC (Kargbo),[41] and C-RAF and EGFR combination therapy (Kargbo).[42]

Our 10-year anniversary issue includes contributions from authors in Australia, China, Denmark, Germany, Italy, Japan, Poland, Singapore, Taiwan, and the USA, reflecting the truly international nature of contemporary Science. As an ensemble, these articles showcase the diversity and state-of-the-art of medicinal chemistry in 2020, as well as implications for future therapeutic developments.

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Notes

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REFERENCES

(1) Maryanoff, B. E.; Wipf, P. Medicinal Chemistry: From Targets to Therapies. *ACS Med. Chem. Lett.* **2019**, *10* (7), 1014.

(2) Malerba, P.; Crews, B. C.; Ghebreselasie, K.; Daniel, C. K.; Jashim, E.; Aleem, A. M.; Salam, R. A.; Marnett, L. J.; Uddin, M. J. Targeted Detection of Cyclooxygenase-1 in Ovarian Cancer. *ACS Med. Chem. Lett.* **2019**, DOI: 10.1021/acsmedchemlett.9b00280.

(3) Gao, H.; Wu, Y.; Sun, Y.; Yang, Y.; Zhou, G.; Rao, Y. Design, Synthesis, and Evaluation of Highly Potent FAK-Targeting Protacs. *ACS Med. Chem. Lett.* **2019**, DOI: 10.1021/acsmedchemlett.9b00372.

(4) Cirillo, P. F.; Asojo, O. A.; Khire, U.; Lee, Y.; Mootien, S.; Hegan, P.; Sutherland, A. G.; Peterson-Roth, E.; Ledizet, M.; Koski, R. A.; Anthony, K. G. Inhibition of Macrophage Migration Inhibitory Factor by a Chimera of Two Allosteric Binders. *ACS Med. Chem. Lett.* **2019**, DOI: 10.1021/acsmedchemlett.9b00351.

(5) Zhang, X.; Sheng, X.; Shen, J.; Zhang, S.; Sun, W.; Shen, C.; Li, Y.; Wang, J.; Lv, H.; Cui, M.; Zhu, Y.; Huang, L.; Hao, D.; Qi, Z.; Sun, G.; Mao, W.; Pan, Y.; Shen, L.; Li, X.; Hu, G.; Gong, Z.; Han, S.; Li, J.; Chen, S.; Tu, R.; Wang, X.; Wu, C. Discovery and Evaluation of Pyrazolo[3,4-*d*]Pyridazinone as a Potent and Orally Active Irreversible BTK Inhibitor. *ACS Med. Chem. Lett.* **2019**, DOI: 10.1021/acsmedchemlett.9b00395.

(6) Gambino, A.; Burnett, J. C.; Koide, K. Methyl Scanning and Revised Binding Mode of 2-Pralidoxime, an Antidote for Nerve Agent Poisoning. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00586.

(7) Coluccia, A.; Puxeddu, M.; Nalli, M.; Wei, C.-K.; Wu, Y.-H.; Mastrangelo, E.; Elamin, T.; Tarantino, D.; Bugert, J. J.; Schreiner, B.; Nolte, J.; Schwarze, F.; La Regina, G.; Lee, J.-C.; Silvestri, R. Discovery of Zika Virus Ns2b/Ns3 Inhibitors That Prevent Mice from Life-Threatening Infection and Brain Damage. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00405.

(8) Vadukoot, A. K.; Sharma, S.; Aretz, C. D.; Kumar, S.; Gautam, N.; Alnouti, Y.; Aldrich, A. L.; Heim, C. E.; Kielian, T.; Hopkins, C. R. Synthesis and SAR Studies of 1H-Pyrrolo[2,3-*b*]Pyridine-2-Carboxamides as Phosphodiesterase 4B (PDE4B) Inhibitors. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00369.

(9) Rajabi, N.; Nielsen, A. L.; Olsen, C. A. Dethioacylation by Sirtuins 1−3: Considerations for Drug Design Using Mechanism-Based Sirtuin Inhibition. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00580.

(10) Howard, K. C.; Gonzalez, O. A.; Garneau-Tsodikova, S. Second Generation of Zafirlukast Derivatives with Improved Activity against the Oral Pathogen Porphyromonas Gingivalis. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00614.

(11) Hartman, G. D.; Kuduk, S. D.; Espiritu, C.; Lam, A. M. P450s under Restriction (Pure) Screen Using HepaRG and Primary Human Hepatocytes for Discovery of Novel HBV Antivirals. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00630.

(12) Tosh, D. K.; Salmaso, V.; Rao, H.; Campbell, R.; Bitant, A.; Gao, Z.-G.; Auchampach, J. A.; Jacobson, K. A. Direct Comparison of (N)-Methanocarba and Ribose-Containing 2-Arylalkynyladenosine Derivatives as A_3 Receptor Agonists. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00637.

(13) Liu, H.; Niu, D.; Tham Sjin, R. T.; Dubrovskiy, A.; Zhu, Z.; McDonald, J. J.; Fahnoe, K.; Wang, Z.; Munson, M.; Scholte, A.; Barrague, M.; Fitzgerald, M.; Liu, J.; Kothe, M.; Sun, F.; Murtie, J.; Ge, J.; Rocnik, J.; Harvey, D.; Ospina, B.; Perron, K.; Zheng, G.; Shehu, E.; D'Agostino, L. A. Discovery of Selective, Covalent FGFR4 Inhibitors with Antitumor Activity in Models of Hepatocellular Carcinoma. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00601.

(14) Shen, S.; Doubleday, P. F.; Weerawarna, P. M.; Zhu, W.; Kelleher, N. L.; Silverman, R. B. Mechanism-Based Design of 3-Amino-4-Halocyclopentenecarboxylic Acids as Inactivators of GABA Aminotransferase. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00672.

(15) Battiti, F. O.; Newman, A. H.; Bonifazi, A. Exception That Proves the Rule: Investigation of Privileged Stereochemistry in Designing Dopamine D_3R Bitopic Agonists. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00660.

(16) Uddin, M. J.; Xu, S.; Crews, B. C.; Aleem, A. M.; Ghebreselasie, K.; Banerjee, S.; Marnett, L. J. Harmaline Analogs as Substrate-Selective Cyclooxygenase-2 Inhibitors. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00555.

(17) Uddin, M. J.; Vemulapalli, A.; Niitsu, H.; Crews, B. C.; Oltman, C. G.; Kingsley, P. J.; Kavanaugh, T. E.; Bedingfield, S. K.; McIntyre, J. O.; Milad, M.; Aleem, A. M.; Coffey, R. J.; Duvall, C. L.; Marnett, L. J. Molecular Imaging of Inflammation in Osteoarthritis Using a Water-Soluble Fluorocoxib. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00512.

(18) Ghosh, A. K.; Grillo, A.; Raghavaiah, J.; Kovela, S.; Johnson, M. E.; Kneller, D. W.; Wang, Y.-F.; Hattori, S.-i.; Higashi-Kuwata, N.; Weber, I. T.; Mitsuya, H. Design, Synthesis, and X-Ray Studies of Potent HIV-1 Protease Inhibitors with P2-Carboxamide Functionalities. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00670.

(19) Sinha, A.; Chang, J. C.; Xu, P.; Gindinova, K.; Cho, Y.; Sun, W.; Wu, X.; Li, Y. M.; Greengard, P.; Kelly, J. W.; Sinha, S. C. Brain Permeable Tafamidis Amide Analogs for Stabilizing TTR and Reducing APP Cleavage. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00688.

(20) Ericson, M. D.; Freeman, K. T.; Haskell-Luevano, C. Peptoid NPhe4 in AGRP-Based C[Pro1-Arg2-Phe3-Phe4-Xxx5-Ala6-Phe7-DPro8] Scaffolds Maintain Mouse MC4R Antagonist Potency. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00641.

(21) Bollenbach, M.; Ortega, M.; Orman, M.; Drennan, C. L.; Balskus, E. P. Discovery of a Cyclic Choline Analog That Inhibits Anaerobic Choline Metabolism by Human Gut Bacteria. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00005.

(22) Altenburg, B.; Frings, M.; Schöbel, J.-H.; Goßen, J.; Pannen, K.; Vanderliek, K.; Rossetti, G.; Koschmieder, S.; Chatain, N.; Bolm, C. Chiral Analogues of PFI-1 as BET Inhibitors and Their Functional Role in Myeloid Malignancies. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00625.

(23) Pala, N.; Esposito, F.; Tramontano, E.; Singh, P. K.; Sanna, V.; Carcelli, M.; Haigh, L. D.; Satta, S.; Sechi, M. Development of a Raltegravir-Based Photoaffinity-Labeled Probe for Human Immunodeficiency Virus-1 Integrase Capture. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00009.

(24) Préville, C.; Bonaventure, P.; Koudriakova, T.; Lord, B.; Nepomuceno, D.; Rizzolio, M.; Mani, N.; Coe, K. J.; Ndifor, A.; Dugovic, C.; Dvorak, C. A.; Coate, H.; Pippel, D. J.; Fitzgerald, A.; Allison, B.; Lovenberg, T. W.; Carruthers, N. I.; Shireman, B. T. Substituted Azabicyclo[2.2.1]Heptanes as Selective Orexin-1 Antagonists: Discovery of JNJ-54717793. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00085.

(25) Jin, X.; Zhang, J.; Jin, X.; Liu, L.; Tian, X. Folate Receptor Targeting and Cathepsin B-Sensitive Drug Delivery System for Selective Cancer Cell Death and Imaging. *ACS Med. Chem. Lett.* **2020**, *11* (8), 1514−1520.

(26) Ng, S.; Juang, Y.-C.; Chandramohan, A.; Kaan, H. Y. K.; Sadruddin, A.; Yuen, T. Y.; Ferrer-Gago, F. J.; Lee, X. E. C.; Liew, X.; Johannes, C. W.; Brown, C. J.; Kannan, S.; Aronica, P. G.; Berglund, N. A.; Verma, C. S.; Liu, L.; Stoeck, A.; Sawyer, T. K.; Partridge, A. W.; Lane, D. P. De-Risking Drug Discovery of Intracellular Targeting Peptides: Screening Strategies to Eliminate False-Positive Hits. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00022.

(27) Annand, J. R.; Henderson, A. R.; Cole, K. S.; Maurais, A. J.; Becerra, J.; Liu, Y.; Weerapana, E.; Koehler, A. N.; Mapp, A. K.; Schindler, C. S. Gibberellin JRA-003: A Selective Inhibitor of Nuclear

https://dx.doi.org/10.1021/acsmedchemlett.0c00508
ACS Med. Chem. Lett. 2020, 11, 1780−1782

Translocation of IKKα. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00613.
(28) Schoeder, C. T.; Mahardhika, A. B.; Drabczyłska, A.; Kieć-Kononowicz, K.; Müller, C. E. Discovery of Tricyclic Xanthines as Agonists of the Cannabinoid-Activated Orphan G-Protein-Coupled Receptor GPR18. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00208.
(29) Thurairatnam, S.; Lim, S.; Barker, R. H.; Choi-Sledeski, Y. M.; Hirth, B. H.; Jiang, J.; Macor, J. E.; Makino, E.; Maniar, S.; Musick, K.; Pribish, J. R.; Munson, M. Brain Penetrable Inhibitors of Ceramide Galactosyltransferase for the Treatment of Lysosomal Storage Disorders. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00120.
(30) Herneisey, M.; Salcedo, P. F.; Domenech, T.; Bagia, C.; George, S. S.; Tunney, R.; Velankar, S.; Hitchens, T. K.; Janjic, J. M. Design of Thermoresponsive Polyamine Cross-Linked Perfluoropolyether Hydrogels for Imaging and Delivery Applications. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00198.
(31) Colabufo, N. A.; Leopoldo, M.; Ferorelli, S.; Abate, C.; Contino, M.; Perrone, M. G.; Niso, M.; Perrone, R.; Berardi, F. Why PB28 Could Be a Covid 2019 Game Changer? *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00271.
(32) Uda, J.; Kobashi, S.; Miyata, S.; Ashizawa, N.; Matsumoto, K.; Iwanaga, T. Discovery of Dotinurad (FYU-981), a New Phenol Derivative with Highly Potent Uric Acid Lowering Activity. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00176.
(33) Mazumdar, Z. H.; Sharma, D.; Mukherjee, A.; Basu, S.; Shukla, P. K.; Jha, T.; Sengupta, D. Meso-Thiophenium Porphyrins and Their Zn(II) Complexes: A New Category of Cationic Photosensitizers. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00266.
(34) Wang, L.; Doherty, G. A.; Judd, A. S.; Tao, Z.-F.; Hansen, T. M.; Frey, R. R.; Song, X.; Bruncko, M.; Kunzer, A. R.; Wang, X.; Wendt, M. D.; Flygare, J. A.; Catron, N. D.; Judge, R. A.; Park, C. H.; Shekhar, S.; Phillips, D. C.; Nimmer, P.; Smith, M. L.; Tahir, S. K.; Xiao, Y.; Xue, J.; Zhang, H.; Le, P. N.; Mitten, M. J.; Boghaert, E. R.; Gao, W.; Kovar, P.; Choo, E. F.; Diaz, D.; Fairbrother, W. J.; Elmore, S. W.; Sampath, D.; Leverson, J. D.; Souers, A. J. Discovery of A-1331852, a First-in-Class, Potent, and Orally-Bioavailable BCL-XL Inhibitor. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00568.
(35) Sodano, T. M.; Combee, L. A.; Stephenson, C. R. J. Recent Advances and Outlook for the Isosteric Replacement of Anilines. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00687.
(36) DeWitt, S.; Czarnik, A. W.; Jacques, V. Deuterium-Enabled Chiral Switching (DECS) Yields Chirally Pure Drugs from Chemically Interconverting Racemates. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00052.
(37) Childers, W. E.; Elokely, K. M.; Abou-Gharbia, M. The Resurrection of Phenotypic Drug Discovery. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00006.
(38) Han, B.; Salituro, F. G.; Blanco, M.-J. Impact of Allosteric Modulation in Drug Discovery: Innovation in Emerging Chemical Modalities. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00655.
(39) Tsang, J. E.; Urner, L. M.; Kim, G.; Chow, K.; Baufeld, L.; Faull, K.; Cloughesy, T. F.; Clark, P. M.; Jung, M. E.; Nathanson, D. A. Development of a Potent Brain-Penetrant EGFR Tyrosine Kinase Inhibitor against Malignant Brain Tumors. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.9b00599.
(40) Kargbo, R. B. Selective DYRK1A Inhibitor for the Treatment of Neurodegenerative Diseases: Alzheimer, Parkinson, Huntington, and Down Syndrome. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00346.
(41) Kargbo, R. B. Smarca2/4 Protac for Targeted Protein Degradation and Cancer Therapy. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00347.
(42) Kargbo, R. B. Complete Regression of Carcinoma Via Combined C-RAF and EGFR Targeted Therapy. *ACS Med. Chem. Lett.* **2020**, DOI: 10.1021/acsmedchemlett.0c00159.

https://dx.doi.org/10.1021/acsmedchemlett.0c00508
ACS Med. Chem. Lett. 2020, 11, 1780−1782