

References

- (1) Cooper, G. M.; Hausman, R. E. The Development and Causes of Cancer. *Cell A Mol. Approach* **2007**.
- (2) Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R. L.; Soerjomataram, I.; Jemal, A. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA. Cancer J. Clin.* **2024**, *74*, 229–263.
- (3) Grant, T. J.; Hua, K.; Singh, A. Molecular Pathogenesis of Pancreatic Cancer. In *Progress in Molecular Biology and Translational Science* **2016**, *144*, 241–275.
- (4) Siegel, R. L.; Miller, K. D.; Fuchs, H. E.; Jemal, A. Cancer Statistics, 2022. *CA. Cancer J. Clin.* **2022**, *72*, 7-33.
- (5) Manji, G. A.; Olive, K. P.; Saenger, Y. M.; Oberstein, P. Current and Emerging Therapies in Metastatic Pancreatic Cancer. *Clin. Cancer Res.* **2017**, *23*, 1670-1678.
- (6) Sarantis, P.; Koustas, E.; Papadimitropoulou, A.; Papavassiliou, A. G.; Karamouzis, M. V. Pancreatic Ductal Adenocarcinoma: Treatment Hurdles, Tumor Microenvironment and Immunotherapy. *World Journal of Gastrointestinal Oncology.* **2020**, *12*, 173–181.
- (7) Aguirre, A. J.; Bardeesy, N.; Sinha, M.; Lopez, L.; Tuveson, D. A.; Horner, J.; Redston, M. S.; DePinho, R. A. Activated Kras and Ink4a/Arf Deficiency Cooperate to Produce Metastatic Pancreatic Ductal Adenocarcinoma. *Genes Dev.* **2003**, *17*, 3112-26.
- (8) Biswal, B. N.; Das, S. N.; Das, B. K.; Rath, R. Alteration of Cellular Metabolism in Cancer Cells and Its Therapeutic Prospects. *J. Oral Maxillofac. Pathol.* **2017**, *21*, 244-51.
- (9) Baggetto, L. G. Deviant Energetic Metabolism of Glycolytic Cancer Cells. *Biochimie* **1992**, *74*, 959-74.

- (10) Chang, Y. L.; Gao, H. W.; Chiang, C. P.; Wang, W. M.; Huang, S. M.; Ku, C. F.; Liu, G. Y.; Hung, H. C. Human Mitochondrial NAD(P)⁺-Dependent Malic Enzyme Participates in Cutaneous Melanoma Progression and Invasion. *J. Invest. Dermatol.* **2015**, *135*, 807-815.
- (11) Lu, Y. X.; Ju, H. Q.; Liu, Z. X.; Chen, D. L.; Wang, Y.; Zhao, Q.; Wu, Q. N.; Zeng, Z. lei; Qiu, H. B.; Hu, P. S.; Wang, Z. Q.; Zhang, D. S.; Wang, F.; Xu, R. H. ME1 Regulates NADPH Homeostasis to Promote Gastric Cancer Growth and Metastasis. *Cancer Res.* **2018**, *78*, 1972-1985.
- (12) Liao, R.; Ren, G.; Liu, H.; Chen, X.; Cao, Q.; Wu, X.; Li, J.; Dong, C. ME1 Promotes Basal-like Breast Cancer Progression and Associates with Poor Prognosis. *Sci. Rep.* **2018**, *8*, 16743.
- (13) Nakashima, C.; Yamamoto, K.; Fujiwara-Tani, R.; Luo, Y.; Matsushima, S.; Fujii, K.; Ohmori, H.; Sasahira, T.; Sasaki, T.; Kitadai, Y.; Kirita, T.; Kuniyasu, H. Expression of Cytosolic Malic Enzyme (ME1) Is Associated with Disease Progression in Human Oral Squamous Cell Carcinoma. *Cancer Sci.* **2018**, *109*, 2036–2045.
- (14) Ren, J. G.; Seth, P.; Clish, C. B.; Lorkiewicz, P. K.; Higashi, R. M.; Lane, A. N.; Fan, T. W. M.; Sukhatme, V. P. Knockdown of Malic Enzyme 2 Suppresses Lung Tumor Growth, Induces Differentiation and Impacts PI3K/AKT Signaling. *Sci. Rep.* **2014**, *4*, 5414.
- (15) Yang, M.; Chen, X.; Zhang, J.; Xiong, E.; Wang, Q.; Fang, W.; Li, L.; Fei, F.; Gong, A. ME2 Promotes Proneural–Mesenchymal Transition and Lipogenesis in Glioblastoma. *Front. Oncol.*, published online July 23 **2021**; DOI: 10.3389/fonc.2021.715593.
- (16) Zhou, J. J.; Xiao, Y.; Li, H.; Wu, C. C.; Chen, D. R.; Chen, L.; Deng, W. W.; Zhang, W. F.; Sun, Z. J. Overexpression of Malic Enzyme 2 Indicates Pathological and Clinical Significance in Oral Squamous Cell Carcinoma. *Int. J. Med. Sci.* **2020**, *17*, 799-806.

- (17) Zhang, Q.; Li, J.; Tan, X. P.; Zhao, Q. Effects of ME3 on the Proliferation, Invasion and Metastasis of Pancreaticancer Cells through Epithelial-Mesenchymal Transition. *Neoplasma* **2019**, *66*, 896-907.
- (18) Dey, P.; Baddour, J.; Muller, F.; Wu, C. C.; Wang, H.; Liao, W. T.; Lan, Z.; Chen, A.; Gutschner, T.; Kang, Y.; Fleming, J.; Satani, N.; Zhao, D.; Achreja, A.; Yang, L.; Lee, J.; Chang, E.; Genovese, G.; Viale, A.; Ying, H.; Draetta, G.; Maitra, A.; Wang, Y. A.; Nagrath, D.; Depinho, R. A. Genomic Deletion of Malic Enzyme 2 Confers Collateral Lethality in Pancreatic Cancer. *Nature* **2017**, *542*, 119-123.
- (19) Sheth, G.; Shah, S. R.; Sengupta, P.; Jarag, T.; Chimanwala, S.; Sairam, K. V. V. M.; Jain, V.; Talwar, R.; Dhanave, A.; Raviya, M.; Menon, S.; Trivedi, S.; Chitturi, T. R. In the Quest for Potent and Selective Malic Enzyme 3 Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma. *ACS Med. Chem. Lett.* **2023**, *14*, 41-50.
- (20) Zhang, Y. J.; Wang, Z.; Sprous, D.; Nabioullin, R. In Silico Design and Synthesis of Piperazine-1-Pyrrolidine-2,5-Dione Scaffold-Based Novel Malic Enzyme Inhibitors. *Bioorganic Med. Chem. Lett.* **2006**, *16*, 525-8.
- (21) Hsieh, J. Y.; Li, S. Y.; Tsai, W. C.; Liu, J. H.; Lin, C. L.; Liu, G. Y.; Hung, H. C. A Small-Molecule Inhibitor Suppresses the Tumor-Associated Mitochondrial NAD(P)⁺-Dependent Malic Enzyme (ME2) and Induces Cellular Senescence. *Oncotarget* **2015**, *6*, 20084–20098.
- (22) Wen, Y.; Xu, L.; Chen, F. L.; Gao, J.; Li, J. Y.; Hu, L. H.; Li, J. Discovery of a Novel Inhibitor of NAD(P)⁺-Dependent Malic Enzyme (ME2) by High-Throughput Screening. *Acta Pharmacol. Sin.* **2014**, *35*, 674-84.
- (23) Ranzani, A. T.; Nowicki, C.; Wilkinson, S. R.; Cordeiro, A. T. Identification of Specific Inhibitors of Trypanosoma Cruzi Malic Enzyme Isoforms by Target-Based HTS. *SLAS Discov.* **2017**, *22*, 1150–1161.
- (24) Jafari, R.; Almqvist, H.; Axelsson, H.; Ignatushchenko, M.; Lundbäck, T.; Nordlund, P.; Molina, D. M. The Cellular Thermal Shift Assay for

- Evaluating Drug Target Interactions in Cells. *Nat. Protoc.* **2014**, *9*, 2100-22.
- (25) Langebäck, A.; Bacanu, S.; Laursen, H.; Mout, L.; Seki, T.; Erkenschulze, S.; Ramos, A. D.; Berggren, A.; Cao, Y.; Hartman, J.; van Weerden, W.; Bergh, J.; Nordlund, P.; Löf, S. CETSA-Based Target Engagement of Taxanes as Biomarkers for Efficacy and Resistance. *Sci. Rep.* **2019**, *9*, 19384.
- (26) Deer, E. L.; González-Hernández, J.; Coursen, J. D.; Shea, J. E.; Ngatia, J.; Scaife, C. L.; Firpo, M. A.; Mulvihill, S. J. Phenotype and Genotype of Pancreatic Cancer Cell Lines. *Pancreas.* **2010**, *39*, 425-35.
- (27) Grbovic-Huezo, O.; Pitter, K. L.; Lecomte, N.; Saglimbeni, J.; Askan, G.; Holm, M.; Melchor, J. P.; Chandwani, R.; Joshi, S.; Haglund, C.; Iacobuzio-Donahue, C. A.; Chiosis, G.; Tammela, T.; Leach, S. D. Unbiased in Vivo Preclinical Evaluation of Anticancer Drugs Identifies Effective Therapy for the Treatment of Pancreatic Adenocarcinoma. *Proc. Natl. Acad. Sci. U.S.A.* **2020**, *17*, 30670-30678.
- (28) Chou, T. C. Drug Combination Studies and Their Synergy Quantification Using the Chou-Talalay Method. *Cancer Research.* **2010**, *70*, 440-6.
- (29) Shuai, W.; Wang, G.; Zhang, Y.; Bu, F.; Zhang, S.; Miller, D. D.; Li, W.; Ouyang, L.; Wang, Y. Recent Progress on Tubulin Inhibitors with Dual Targeting Capabilities for Cancer Therapy. *Journal of Medicinal Chemistry.* **2021**, *64*, 7963-7990.
- (30) Gerlach, M.; Claus, E.; Baasner, S.; Müller, G.; Polymeropoulos, E.; Schmidt, P.; Günther, E.; Engel, J. Design and Synthesis of a Focused Library of Novel Aryl- and Heteroaryl-Ketopiperazides. *Arch. Pharm. (Weinheim).* **2004**, *337*, 695-703.
- (31) Waltemate, J.; Ivanov, I.; Ghasemi, J. B.; Aghaee, E.; Daniliuc, C. G.; Müller, K.; Prinz, H. 10-(4-Phenylpiperazine-1-Carbonyl)Acridin-9(10H)-Ones and Related Compounds: Synthesis, Antiproliferative Activity and

- Inhibition of Tubulin Polymerization. *Bioorganic Med. Chem. Lett.* **2021**, 32, 127687.
- (32) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. Development and Testing of the OPLS All-Atom Force Field on Conformational Energetics and Properties of Organic Liquids. *J. Am. Chem. Soc.* **1996**, 118, 11225–11236.
- (33) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J. Med. Chem.* **2004**, 47, 1739-49.
- (34) Rodriguez, J. M. G.; Hux, N. P.; Philips, S. J.; Towns, M. H. Michaelis-Menten Graphs, Lineweaver-Burk Plots, and Reaction Schemes: Investigating Introductory Biochemistry Students' Conceptions of Representations in Enzyme Kinetics. *J. Chem. Educ.* **2019**, 96, 1833–1845.