【无机化学论坛】**Molecular prodrug engineering towards precision drug delivery system**

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Molecular prodrug engineering towards precision drug delivery system

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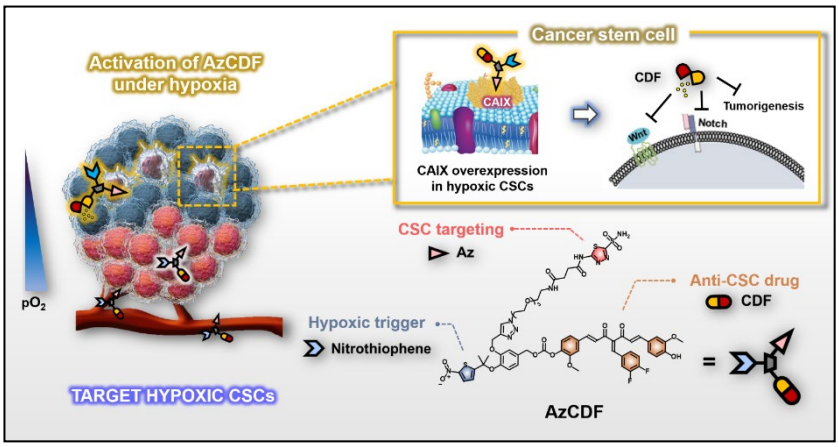
Breast cancer consists of heterogenic subpopulations, which determine the prognosis and response to chemotherapy. Among these subpopulations, a very limited number of cancer cells are particularly problematic. These cells, known as breast cancer stem cells (BCSCs), are thought responsible for metastasis and recurrence. They are thus major contributor to the unfavorable outcomes seen for many breast cancer patients. BCSCs are more prevalent in the hypoxic niche. This is an oxygen-deprived environment that is considered crucial to their proliferation, stemness, and self-renewal, but also one that makes BCSCs highly refractory to traditional chemotherapeutic regimens. We report a small molecule construct, **AzCDF**, that allows the therapeutic targeting of BCSCs and which is effective in normally refractory hypoxic tumor environments. A related system, **AzNap**, has been developed that permits CSC imaging. Several design elements are incorporated into **AzCDF**, including the CAIX inhibitor, acetazolamide (Az)



to promote localization in MDA-MB-231 CSCs, a dimethylnitrothiophene subunit as a hypoxia trigger, and a 3,4-difluorobenzylidene curcumin (CDF) as a readily released therapeutic payload. This allows **AzCDF** to serve as a hypoxia-liable molecular platform that targets BCSCs selectively that decreases CSC migration, retards tumor growth, and lowers tumorigenesis rates as evidenced by a combination of in vitro and in vivo studies. To the best of our knowledge this is the first time a CSC-targeting small molecule has been shown to prevent tumorigenesis in an animal model.[1-4]

1) J. H. Kim, P. Verwilst, J. Lee, M. Won, J. L. Sessler, J. Han, J. S. Kim, *J. Am. Chem. Soc.* **143**, 14115-14124 (2021).
2) M. Won, S. Koo, H. Li, J. Y. Lee, A. Sharma, J. S. Kim, *Angew. Chem. Int. Ed.* **60,** 3196-3204 (2021).
3) P. Jangili, N. Kong, J. H. Kim, J. Zhou, H. Liu, X. Zhang, W. Tao, J. S. Kim, *Angew. Chem. Int. Ed.* **61,** e202117075 (2022).
4) S. Koo, M.-G. Lee, A. Sharma, M. Li, X. Zhang, K. Pu, S.-G Chi, J. S. Kim, *Angew. Chem. Int. Ed.* **61,** e202110832 (2022).

Speaker's Profile – Prof. Jong Seung Kim (院士)

Jong Seung Kim, FRSC, received his Ph. D. from the Department of Chemistry and Biochemistry at Texas Tech University in 1993. He has worked at University of Houston as a post-doc in 1994. Currently he is a full professor in Department of Chemistry at Korea University in Seoul. He has published about 530 papers in prestigious journals with h-index 106. His research interests are application of organic chemistry in drug delivery and theranostics. He is a member of the Korea Academy of Science and Technology. He has been selected as a Highly Cited Researcher since 2014.