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Drug Des 2018, Volume 7
DOI: 10.4172/2169-0138-C1-023

Boosting the anti-cancer potential of COOH-bearing PAK1-blockers by increasing their cell-permeability via click chemistry

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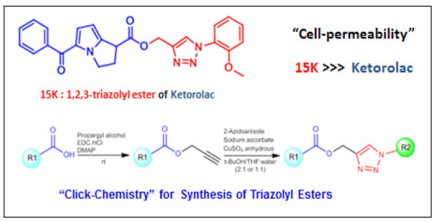

PAK1 is the major oncogenic/ageing Ser/Thr kinase that is activated by p21 (RAC/CDC42) and several other signal transducers such as PIX, three distinct Tyr-kinases (ETK, FYN and JAK2) and CK2 (casein kinase-2) in cells. PAK1 is essential for robust growth of almost all solid tumors which require PAK1-dependent angiogenesis. Besides, this kinase is required for many other diseases/disorders such as neurofibromatosis, Alzheimer's disease, Parkinson's disease, depression, epilepsy, autism, schizophrenia, a variety of infectious and inflammatory diseases, diabetes (type-2), obesity and even hyperpigmentation. Thus, the potential market value of PAK1-blockers is enormous. However, so far only a few PAK1-blockers are available on the market, such as FK228, Gleevec and the old antibiotic called Minocycline, but with a very limited FDA approval for cancer therapy. Thus, for a last decade, we have taken a great effort for identifying PAK1-blockers among natural or old (generic) products as well as the robust potentiation of their anti-cancer/anti-PAK1 activity mainly by increasing their cell-permeability. Here in this lecture, we will introduce a few successful examples including 1,2,3-triazolyl esters of natural or generic COOH-bearing PAK1-blockers such as ursolic acid, artepillin C, caffeic acid, ketorolac and mycophenolic acid, in which esterisation by a simple reaction called Click Chemistry boosts their anti-cancer potential by 100-5000 times, depending on target cancer cell lines and the final chemical products. Some of them have been proven to suppress the embryonic angiogenesis in ovo (fertilized chicken eggs) IC50 around 1 nmol/egg and extend significantly the healthy lifespan of C. elegans by 30% at 50 nM, strongly suggesting that they could cure most of solid tumors without any severe side effect.

Recent Publications

1. Takahashi H, Nguyen B C, Uto Y, Shahinozzaman M, Tawata S and Maruta H (2017) 1,2,3-Triazolyl esterization of PAK1-blocking propolis ingredients, artepillin C (ARC) and caffeic acid (CA), for boosting their anti-cancer/anti-PAK1 activities along with cell-permeability. Drug Discov. *Ther.;* 11: 104-109.
2. Nguyen B C, Takahashi H, Uto Y, Shahinozzaman M D, Tawata S and H Maruta H (2016) 1,2,3-Triazolyl ester of Ketorolac: A click chemistry-based highly potent PAK1-blocking cancer-killer. Eur. J. *Med. Chem.;* 126: 270-276.

Biography

Hiroshi Maruta has his expertise in both molecular oncology and the major oncogenic/ageing kinase PAK1 which is essential for a wide variety of diseases/disorders such as cancer, Alzheimer's disease, diabetes (type-2), hypertension and a variety of infectious and inflammatory diseases. His team found that PAK1-deficient mutant of C. elegans lives 60% longer than the wild-type, clearing indicating that PAK1 shortens the healthy lifespan. Currently, his click chemistry team recently developed a series of potent (highly cell-permeable) 1,2,3-triazolyl esters of COOH-bearing PAK1-blockers which are potentially useful for both cancer therapy and longevity-promotion.

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