Drug Des 2015, 4:2
http://dx.doi.org/10.4172/2169-0138.S1.008

Targeting the Notch signaling pathways of hepatocarcinoma and glioblastoma multiform using ultra small iron oxide nanoparticles conjugated gamma secretase inhibitor

Anamaria Orza
Emory University School of Medicine, USA

Recent developments in cancer biology have identified the existence of a sub-population of cells—cancer stem cells—that are immune to most traditional therapies (e.g., chemotherapy and radiotherapy) and have the ability to repair their damaged DNA. Here, we show the resistance of hepatocarcinoma stem cells and glioblastoma multiform stem cells to both radiation and therapy. Also, we show the efficiency of the conjugated iron oxide nanoparticles for the in vivo disruption of Notch signaling by the gamma secretase inhibitor DAPT [N-(N-((3,5-Difluorophenacetyl))-L-alanyl)-S-phenylglycerin t-butyl ester. By introducing these targeted conjugated nanoparticles, detection, targeting, and destruction of the Hepatocarcinoma and glioblastoma stem cells was achieved. An efficient alternative treatment for the incurable disease of cancer could be provided.

anamaria.orza@emory.edu

Expanding the scope of fragment screening libraries: Thinking in 3D

Angelo Pugliese
Cancer Research UK Beatson Institute, UK

Fragment-based drug discovery (FBDD) methods are a proven strategy for hit identification, providing diverse, high quality start points for numerous drug discovery programmes. Many fragment hits have been optimised and transitioned to the clinical setting with one, namely Vemurafenib gaining FDA approval to treat late stage V600E mutant B-Raf driven malignant melanoma. Critical for successful fragment screening is a high quality compound library. Whilst fragment screening techniques have evolved over the years, increasing in sensitivity and throughput, fragment library molecules have received less attention. Many fragment libraries are chemically diverse and have been selected based on a good balance of properties, however, they all tend to have limited 3-dimensional diversity, typically being composed of flat sp2-rich aromatic and heteroaromatic compounds. This move towards "flatter" molecules not only reduces the sampling of chemical space available for fragments but also fails to capitalise on the additional attributes of sp3 character. Recently, two groups have independently published data showing the improvements in profile and project progression by, for example, increasing the proportion of sp3 centres contained in molecules or reducing lipohilicity. In addition, there are multiple examples in the literature reporting the positive impact of increasing sp3ness or 3-dimensionality through inducing conformational twist. This talk will discuss fragment library composition along with suggestions and practical examples of how future, more structurally diverse fragments which occupy different regions of chemical space to the vast majority of current fragment libraries can be designed and selected.

A.pugliese@beatson.gla.ac.uk

Notes: