Formulated pyrazolo[3,4-*d*]pyrimidines active on GBM cell lines

Chiara Greco,[a] Robert Cavanagh,[b] Vincenzo Taresco,[b] Helena Petromilo,[a] Francesca Musumeci,[a] Ruman Rahman,[b] Cameron Alexander,[b] Silvia Schenone,[a]

a Department of Pharmacy, University of Genoa, Viale Benedetto XV 3, 16132 Genoa, Italy
b School of Pharmacy, University of Nottingham, University Park, NG7 2RD, Nottingham, UK
greco.phd@difar.unige.it

Glioblastoma multiforme (GBM) is the most aggressive type of brain cancer and shows a high rate of recurrence, and a poor prognosis. A series of patient derived GBM cell lines have been isolated from both the central tumor core and from the invasive margin of the tumor. These latter are associated with disease reoccurrence, due to the difficulty in removing these cells during surgical procedures. [1] Therefore, targeting these invasive cells (in addition to tumor core cells) represents an important step in the fighting of GBM.

Some members from our large library of pyrazolo[3,4-*d*]pyrimidines inhibit both the tyrosine kinases Src, Fyn and the serine-threonine kinase SGK1 in the nanomolar range. Moreover, these compounds show antiproliferative effects on several cancer cell lines *in vitro* and *in vivo*. [2]

The aim of the project was to test three of our lead compounds (a Fyn inhibitor, a Src inhibitor and SGK1 inhibitor) on the GBM cell lines isolated from both the central tumor core and from the invasive margin of the tumor.

Since our derivatives generally suffer from poor water solubility which negatively affects the bioavailability and *in vivo* efficacy, we have generated solid dispersions where the inhibitors are molecularly dispersed in an inert hydrophilic polymeric carrier, in order to overcome the problem and generate formulations for oral administration.

Data demonstrate that kinase inhibitors are attractive candidates for the treatment of GBM. Moreover, we report a formulation strategy that can be successfully applied to increase the water solubility and does maintain the potency of the inhibitors, and thus provides a viable approach for development of oral formulations.

[1] Smith SJ, *et al., Int J Mol Sci.* **2017**; *18*(11):2342.
[2] Tintori C, *et al., J Med Chem*. **2015**; 58(1):347-61.