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Control/Tracking Number: 19-A-763-CRS
Activity: Abstract
Current Date/Time: 7/29/2019 7:19:44 AM

Formulation Of Pyrazolo[3,4-*d*]pyrimidines Kinase Inhibitors For The Treatment Of Glioblastoma Multiforme

Presenter Biography:
Chiara Greco is completing her PhD with Professor Silvia Schenone at University of Genoa in Italy focusing on the synthesis of potential kinase inhibitors. She joined the group of Prof. Cameron in Nottingham for seven months as a visitor PhD student. In this period she had the opportunity to work in a possible formulation of a set of pyrazolo[3,4-*d*]pyrimidines derivatives previously synthesized in Genoa.

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Abstract:
Introduction: We have previously demonstrated that pyrazolo[3,4-*d*]pyrimidines derivatives from the extensive library of compounds we have synthesized display inhibitory action on the tyrosine kinases Src, Fyn and serine-threonine kinase SGK1 in the nanomolar range. Moreover, these compounds show antiproliferative effects on several cancer cell lines *in vitro* [1]. Glioblastoma multiforme (GBM) is the most aggressive subset of brain cancer, showing high probability of recurrence and poor patient survival. Thus, our project was to test three of our lead compounds on a series of patient derived GBM cell lines isolated from both the central tumor core and cells from the invasive margin of the tumor; the latter of which are associated with disease reoccurrence due to the difficult nature in removing these cells during surgical procedures [2]. Therefore, performing *in vitro* testing on these invasive cells (in addition to tumor core cells) represents an important step in the discovery and development of drugs for the treatment of GBM. Unfortunately, one main lack of those pyrazolo[3,4-*d*]pyrimidines derivatives is their limited solubility in water, which affects bioavailability and *in vivo* efficacy. Accordingly, we have generated solid dispersions whereby the inhibitors are molecularly dispersed in an inert hydrophilic polymeric carrier [3], in order to overcome these limitations and generate formulations more viable for oral administration.
Methods: A miniaturized screening process, based on an inkjet printing technology, able to identify the best formulation to enhance the apparent water solubility was performed on the three selected kinase inhibitors. On the basis of the ΔA% average results, we selected the best polymers able to solubilize the pyrazolo[3,4-*d*]pyrimidines in water. The drugs formulated with the selected polymers were then tested against GBM cell lines and the potency compared to the drugs solubilized either in water or 0.5% DMSO.

Results: It was found that Src and SGK1 inhibitors demonstrated the most potency against GBM cells. Furthermore, *in vitro* testing illustrates that printing 5 µg/mL of drug into polymer dispersions at a level of 90% is a viable method for formulation, as potency was comparable to that of drug prepared in DMSO solutions.
Conclusion/Implications: Data demonstrate that our kinase inhibitors are attractive candidates for the treatment of GBM. Moreover, we report on a formulation strategy that can be successfully applied to increase the water solubility of the inhibitors in a manner that does not compromise on potency, and thus provide a viable approach for development of oral formulations.
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Topic (Complete): 11. Micro-/Nano-Particle Delivery ; 20. Focus Group Scientific Session: Oral Drug Delivery (OrDD)
Abstract Additional (Complete):
References: : [1] Radi M, Brullo C, Crespan E, Tintori C, Musumeci F, Biava M, Schenone S, Dreassi E, Zamperini C, Maga G, Pagano D, Angelucci A, Bologna M, Botta M. Bioorg Med Chem Lett. 2011. 5928–5933. [2] Smith SJ, Diksin M, Chhaya S, Sairam S, Estevez-Cebrero MA, Rahman R. Int J Mol Sci. 2017. 2342. [3] Sanna M, Sicilia G, Alazzo A, Singh N, Musumeci F, Schenone S, Spriggs KA, Burley JC, Garnett MC, Taresco V, Alexander C. ASC Med Chem Lett. 2018. 193-197.
Learning Objective 1: : Explain the strategies for formulate potential kinase inhibitors for the treatment of GBM
Learning Objective 2: : Identify the bests polymers able to solubilize in water pyrazolo[3,4-d]pyrimidines derivatives
Learning Objective 3: : Differentiate between GBM cell lines isolated from the central tumor core and cells from the invasive margin of the tumor
Area of Interest 1: Oral Drug Delivery

Presentation Preference (Complete): Poster
Employment (Complete):
Are you professionally employed by academia or industry?: Not Applicable
Are you currently looking or planning to look for a new job/position?: Yes

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