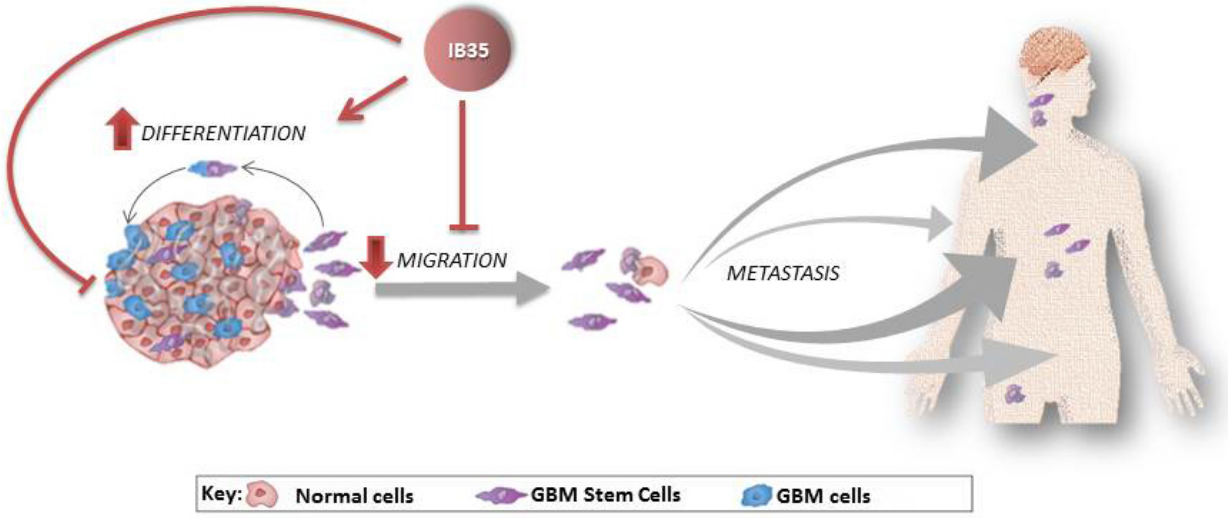
Glioblastoma (GBM): another tool to make a hit

Cancer is a multifactorial disease caused by the accumulation of "mistakes" in the production of proteins involved in the control of important cellular processes. These processes, such as cell division, cell growth and programmed cell death (i.e. apoptosis), are regulated by dense networks between proteins, called signalling pathways.

Recent findings revealed that the irregular activation of different cell signaling pathways play a critical role in tumor progression. For instance, the aberrant activation of such pathways mediates cancer survival and growth and stimulates the production of new blood vessels (angiogenesis) necessary to feed the malignant cells. Moreover, it has been recently noticed that these pathways play a key role in the acquisition of resistance to chemo- and radiation- treatments.



To date, the most investigated strategy for cancer therapies focuses on finding treatments able to target the molecular pathways that sustain tumors (*targeted therapy*). The development of targeted therapies requires identification of new pharmacological targets, and that's why, sometimes, these compounds are also referred to as " *rationally designed molecules*".

Furthermore, the birth of a new era based on *personalized medicine* should ensure that the right drug is given to the right patient at the right time.

Among the intricated networks in the cell, PI3K/PDK1/Akt pathway seems to have a significant role in cancer development, progression and diffusion; not surprisingly the deregulation of this signalling pathway is very common in tumors. In particular, within this network, the PDK1 enzyme showed to influence growth, proliferation, survival and migration in cancer cells. Consistently, over the past years, it showed a great interest to identify new selective molecules able to block PDK1 activity.

In particular, our currently research project is devoted to develop pioneering agents and novel strategies for treatment of glioblastoma (GBM), one of the most aggressive, resistant and deadly tumor type. We recently synthetized a series of molecules designed to block the activity of PDK1. Within the new molecules, compound 8, namely IB35, showed to block PDK1 in its “inactive” state, thus avoiding its activation. More importantly, the in vitro evaluation of the biological effects, showed that IB35 has a significant antiproliferative activity, killing GBM cells with a good potency. Additionally, IB35 proved to be active also on GBM-derived stem cells (GSCs). The subpopulations of GSCs drive cancer growth, invasiveness, *migration* and formation of secondary *metastases* and to make matters worse, are very resistant and unresponsive to treatment with chemotherapeutics. The new molecule IB35 showed to accelerate the *differentiation* of GSCs in tumor cells (thus becoming more sensitive to the chemotherapy) and to slow down the migration (antimetastatic activity). Our preliminary results disclose IB35 as a prototype of a new generation of PDK1 inhibitors which could represents the starting point for the development of novel treatment against aggressive and chemoresistant/rare tumors, such as GBM.

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Publication

Locking PDK1 in DFG-out conformation through 2-oxo-indole containing molecules: Another tools to fight glioblastoma.
Sestito S, Daniele S, Nesi G, Zappelli E, Di Maio D, Marinelli L, Digiacomo M, Lapucci A, Martini C, Novellino E, Rapposelli S
Eur J Med Chem. 2016 Aug 8