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Seeking novel anticancer strategies around the druggable clock

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Disruption of the circadian clock has been associated with a variety of human pathologies, including metabolic dysfunctions and cancer. Nevertheless, whether pharmacological targeting of circadian regulators is a viable approach to cancer therapy remained to be determined. We recently reported that the circadian regulator REV-ERBβ is overexpressed in many tumor cells and it plays an unexpected role in sustaining cancer cell survival when the autophagy flux is compromised. Our studies also identified the first compound with a dual inhibitory activity toward autophagy and REV-ERBβ, which showed a more potent anticancer activity than the clinically relevant autophagy inhibitor, chloroquine (CQ), against different human tumor tissue cells. Further structure-activity relationship (SAR) analysis on the hit compound identified a class of molecules with a higher inhibitory potency toward REV-ERBβ, resulting in higher cancer-specific cytotoxicity. Notably, in a number of CQ-resistant cancer cell lines, our dual REV-ERB/autophagy inhibitors inhibited growth at low micro-molar concentration, suggesting their use as novel anticancer agents for the treatment of chloroquine-resistant tumors. In addition, we obtained preliminary data indicating a REV-ERBβ-mediated regulation of cancer metabolism, which it has recently become one of the most exciting and promising areas for the development of antitumor drugs. As a consequence, REV-ERBβ inhibition may be suitable for combinatorial therapy with a number of metabolic-related anticancer agents.

In addition to provide a scaffold for the development of novel anticancer agents, these dual inhibitors can be used as valuable pharmacological tool for elucidate novel crosstalk between circadian rhythm, cancer metabolism and autophagy.

Biography:

Dr. Benedetto Grimaldi obtained in 2001 the degree in Biological Science with a *summa cum laude* from the University of Rome “La Sapienza”.

After obtained a PhD in Genetics and Molecular Biology at University of Rome, specializing in the study of epigenetics and signal transduction, Dr. Grimaldi transitioned into a postdoctoral fellowship under the mentorship of Prof. Sassone-Corsi (University of California, Irvine, USA), a leader in the field of circadian clock, metabolism and epigenetics. Since 2015, Dr. Grimaldi works as a Senior Researcher at the IstitutoItaliano di Tecnologia (Italy), focusing on the study of the links between clock factors and human pathologies, and on the identification and evaluation of novel molecules with “clock modulator” activity for therapeutic applications.