UNIVERSITÀ DEGLI STUDI
MAGNA GRÆCIA DI CATANZARO

DOTTORATO DI RICERCHE
IN SCIENZE DELLA VITA

UNIVERSITÀ DEGLI STUDI *MAGNA GRÆCIA* DI CATANZARO
- DIPARTIMENTO DI SCIENZE DELLA SALUTE -
- DOTTORATO DI RICERCHE IN SCIENZE DELLA VITA -
- SCUOLA DI SPECIALIZZAZIONE IN FARMACIA OSPEDALIERA -

SEMINARIO CORSO CV_S_053

TARGETING MYELOID DIFFERENTIATION IN ACUTE MYELOGENOUS LEUKEMIA (AML) USING POTENT AND INNOVATIVE HUMAN DIHYDROOROTATE DEHYDROGENASE (HDHODH) INHIBITORS

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Acute myelogenous leukemia (AML) is a clinically devastating disease with dismal prognosis and survival rate. Efforts to identify new therapeutic targets to overcome myeloid differentiation blockade were largely unsuccessful until the breakthrough study in 2016 (Sykes *et al*., 2016, Cell 167, 171–186) who demonstrated that *brequinar*, the most potent *dihydroorotate dehydrogenase* (*h*DHODH) inhibitor known, was able to enable myeloid differentiation *in vivo* on mouse AML models. In this lecture will presented the state-of-the-art designing paradigms (including synthesis, SAR, crystallographic and molecular modelling studies, biological assays (*cell viability, proliferation, cytotoxicity, immunosuppression and myeloid differentiation),* and physicochemical characterization) that we have recently followed during the discovery a new generation of *h*DHODH inhibitors based on the hydroxypyrazole-pyridine scaffold. The most representative compound the series, although being comparable to *brequinar* in terms of *h*DHODH inhibitory activity, is able to restore the myeloid differentiation in leukemia cell lines U937 at a 1-log lower concentration compared to its lead *brequinar*, causing a massive death of cells. To our knowledge, this compound is one of the most potent *h*DHODH inhibitor so far discovered and, because its safety profile, a valuable candidate for *in vivo* experiments.

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