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_038

DEVELOPMENT OF ASPARAGINE SYNTHETASE INHIBITORS

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Cancer cells require the adequate provision of energy and nutrients to support cell growth, consistent with the idea that alteration of key metabolic processes often enhance tumorigenesis. As a result, "nutrient deprivation" has become a promising strategy for anti-cancer therapies. Several very recent studies have shown that L-asparagine is a key metabolic nutrient for solid tumors including sarcoma, breast cancer, hepatocellular carcinoma and castration-resistant prostate cancers. Validating ASNS as a cancer target requires, however, access to potent cell-permeable, highly selective, small molecule ASNS inhibitors. This lecture will discuss the use of a high-resolution X-ray crystal structure of human ASNS in computational studies aimed at delineating the mode of interaction between a sulfoximine-based inhibitor and the enzyme. In addition, the results of an activity-based assay will be presented that establish that this inhibitor is highly selective in its interactions with the cellular proteome. The final part of the lecture will outline additional computational studies aimed at evaluating whether the ASNS inhibitor will interact with the enzyme NAD+ synthetase, which is also a drug target.

References

[1] Ikeuchi, H. et al Bioorg. Med. Chem. **2012**, *20*, 5915-5927.
[2] Hettmer, S. et al eLife **2015**, 10.7554/eLife.09436.
[3] Rosenblum, J.S. FEBS Lett. **2013**, *587*, 1870-1877.

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