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
DESIGN AND SYNTHESIS OF DRUGS:
FROM TRADITIONAL TO NOVEL DRUG TARGETS.

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Our research group has used in recent years an appropriate iterative combination of molecular modeling, organic synthesis and biological evaluation, which has provided us with a large number of interesting prototypes and drug candidates. As in most medicinal chemistry research groups, these projects begin with the selection of the appropriate therapeutic target. In recent years, we have worked with different targets involved in cancer, such as enzymes: metalloproteases, CK2, CDK2, HDAC; nuclear receptors: estrogen receptor, nucleic acids; and peptides with angiogenic activity such as adrenomedullin or PAMP.

However, traditional drug design strategies based on a single target has serious difficulties in developing new therapies for diseases such as cancer. The use of cocktails of various anticancer agents interfering with different mechanisms has been the standard treatment to prevent the problems of resistance. An alternative approach is to design multi-target modulators, directed to different disease mechanisms. That is the approach we have most recently chosen, where we seek to design, synthesize and evaluate new dual agents based on the inhibition of three enzymes involved in the development and progression of tumor processes: HDAC1, CK2 and MMP2. Due to the existing synergy with several antitumor agents, HDACs are enzymes prone to be combined with other targets in the design of dual inhibitors. On the other hand, our research group has demonstrated that CK2 is a regulator of the activity of MMP2, and therefore the use of dual modulators of these two enzymes constitutes an innovative strategy. Design of multitarget modulators is carried out making use of a variety of computational techniques depending on the drug target.

Most recently we have chosen novel drug targets such as Protein tyrosine phosphatases (PTP) which are well-characterized phosphatases responsible for dephosphorylation processes. Nowadays PTPs have become interesting druggable targets due to their relationship with several diseases such as diabetes, obesity, cancer and neurological disorders. Selective modulation of phosphatases is a challenging objective due to the high sequence and structural homology among all PTPs. Our research group has recently reported a series of new selective inhibitors of thisprotein as candidates for CNS disorders. Our next challenge is to achieve allosteric inhibition as a strategy to avoid multiple PTPs activity modulation. Different computational techniques will be used to reach this goal.

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