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TEFARCO Innova

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Presso l'Aula C del Dipartimento di Farmacia

il Prof. Claudiu Supuran

Dipartimento Neurofarba
Università degli Studi di Firenze

terrà un seminario dal titolo:

Carbonic anhydrases as drug targets

Il coordinatore
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Carbonic anhydrases as drug targets

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Carbonic anhydrases (CAs, EC 4.2.1.1), a group of ubiquitously expressed metalloenzymes, are involved in numerous physiological and pathological processes, including gluconeogenesis, lipogenesis, ureagenesis, tumorigenicity and the growth and virulence of various pathogens [1,2]. In addition to the established role of CA inhibitors (CAIs) as diuretics and antiglaucoma drugs, it has recently emerged that CAIs could have potential as novel anti-obesity, anticancer and anti-infective drugs. This presentation will discuss the biological rationale for the novel uses of inhibitors or activators of CA activity in multiple diseases, and highlights progress in the development of specific modulators of the relevant CA isoforms, some of which are now being evaluated in clinical trials. For example, CA IX, a membrane-bound, hypoxia-inducible enzyme is highly expressed in many types of solid tumors, showing restricted expression in normal tissues [1,2]. CA IX plays an important functional role in processes critical for tumor cell growth and metastasis, including pH regulation, survival, adhesion and migration [1,2]. The tumor-specific expression of CA IX and its association with cancer progression and poor treatment outcome has led to interest in targeting it for cancer therapy. The development of pharmacologic inhibitors that selectively target tumor-associated, extracellular CAs without "off-target" inhibition of cytosolic isoforms is critical for their use as cancer therapeutics [1,2]. We have recently described novel ureido-substituted benzenesulfonamides and glycosyl coumarins that selectively and potently inhibit CA IX activity *in vitro*, and reduce breast tumor growth and metastasis *in vivo* [3-5]. Such studies provide the "proof of principle" data for the therapeutic inhibition of CA IX activity for breast tumor growth and metastasis formation, and one compound is currenbtly in Phase I clinical studies.

Many pathogens encode CAs belonging to the α-, β-, γ- or η-CA families. The α-CAs from *Neisseria spp*. and *Helicobacter pylori* as well as the β-class enzymes from *Escherichia coli, H. pylori, Mycobacterium tuberculosis*, *Brucella spp., Streptococcus pneumoniae*, *Salmonella enterica* and *Haemophilus influenzae* have been cloned and characterized in detail, with various classes of inhibitors (anions, sulfonamides and sulfamates) being reported. Bacterial CAs represent promising targets for obtaining antibacterials devoid of the resistance problems of the clinically used such agents but further studies are needed to validate these and other less investigated enzymes as novel drug targets [6,7]. Recently, in collaboration with the Griffith Univ. Team we discovered the η-CA family, present in *Plasmodium falciparum* and related species [8]. The salient features leading to this discovery and the characterization of this new family of CAs will be highlighted.

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