SOCIÉTÉ CHIMIQUE DE GENÈVE

Novel strategies for identifying targets of cysteine-reactive inhibitors by mass spectrometry

Prof. Alexander ADIBEKIAN

Department of organic chemistry, UNIGE
NCCR Chemical Biology

Cysteines are the most nucleophilic amino acid residues in proteins. The nucleophilicity of each single cysteine in the proteome is fine tuned to perform a specific biochemical task. So-called hyperreactive cysteines are often involved in nucleophilic and reductive catalysis and are found on diverse families of enzymes of biomedical importance such as proteases, kinases and oxidoreductases.[1] Hyperreactive cysteines can be chemoselectively targeted with moderately reactive electrophilic inhibitors such as chloroacetamides and α,β-unsaturated amides. However, the fact that such drugs may also react with proteins other than the desired target, has caused anxiety concerning the long-term health risk of using covalent drugs. Accordingly, many high-throughput drug discovery endeavors have historically tended to avoid irreversible inhibitors. Nonetheless, covalent binders often display certain advantageous properties in comparison to their reversible counterparts, namely easily achievable high potency and a strongly prolonged duration of action.[2]

I will present novel mass spectrometry-driven strategies that can be used to globally profile the selectivities of cysteine-reactive drugs *in vitro* and *in situ*. The knowledge acquired from these experiments can be utilized for designing more selective covalent inhibitors that may ultimately find biomedical application.

1. Weerapana, E., et al., Nature (2010) 468, 790-U79.
2. Singh, J., et al., Nature Rev. Drug Discovery (2011) 10, 307-317.

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sochimge@unige.ch
www.unige.ch/sochimge/

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