

CEA / Saclay - 91191 Gif-sur-Yvette Cedex  
**Service d'Ingénierie Moléculaire des Protéines**

**SEMINAIRE**

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Vendredi 17 février 2012 - 11h00

SIMOPRO - Salle de réunion - Bât. 152

**Development of specific inhibitors of proteasome  
active sites and their use to define distinct roles of  
these sites as drug targets in cancer**

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Proteasomes degrade the majority of proteins in mammalian cells, are involved in the regulation of multiple physiological functions, and are established targets of anti-cancer drugs. The proteasome has three types of active sites: chymotrypsin-like, trypsin-like and caspase-like sites. All inhibitors used clinically were developed to block the chymotrypsin-like sites but they also co-inhibit other two sites. Whether inhibition of caspase- and/or trypsin-like sites is important for cytotoxicity was not clear. In order to answer this question we developed specific inhibitors of all three sites and demonstrated that inhibitors of caspase-like and trypsin-like sites sensitize malignant cells to inhibitors of chymotrypsin-like sites. Thus, trypsin-like and caspase-like sites have to be considered co-targets (with chymotrypsin-like sites) for anti-neoplastic agents; inhibition of two types of sites is needed to achieve maximal cytotoxicity of proteasome inhibitors.

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