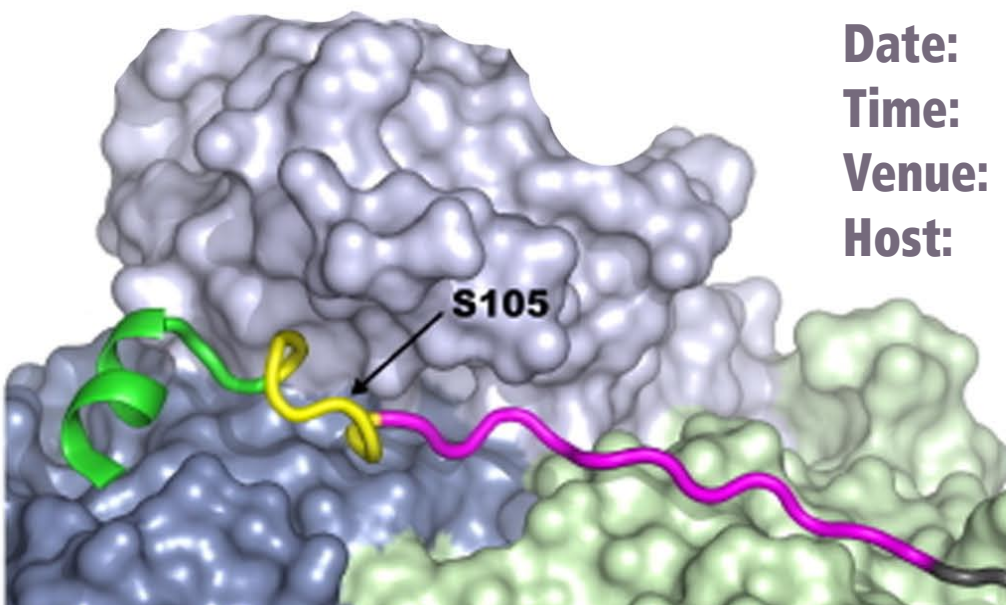


Calpains: the calcium-dependent cysteine proteases of the cell

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Structural analysis of calpain is revealing how these complex, calcium-dependent, intracellular proteases function. The calcium-free structure of the heterodimeric calpain 2 has provided an explanation for why the enzyme is inactive without its cofactor. The catalytic triad is not aligned for catalysis in the absence of calcium. The realization that the papain-like protease core of calpain has two novel calcium binding sites that act cooperatively to align the catalytic triad for catalysis allowed us to use the core for substrate and inhibitor analysis/profiling without the complications of autoproteolysis. Several covalent inhibitors have been crystallized bound to calpain cores. Their structures are providing a wealth of information for structure-based design of specific inhibitors that can potentially be used to treat calpain-related diseases such as post-ischemic injury, cataract, and Alzheimer disease. Recently, we have solved the structure of calpain 2 bound to its specific intracellular protein inhibitor, calpastatin, which binds to and inhibits calpain only when calcium is present. This structure revealed the calcium-bound form of the enzyme, the mechanism of inhibition by calpastatin, and how this inhibitor – an intrinsically disordered protein – avoids being cleaved by calpain. Supported by the Canadian Institutes for Health Research.



Date: Fri, 20 Feb 2009

Time: 4pm

Venue: LT 20

Host: Dr Liou Yih Cherng