## MS.79.5

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### Crystal structure of the NS3 protease-helicase from Dengue virus

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Several flaviviruses are important human pathogens including dengue virus, a disease against which neither a vaccine nor specific antiviral therapies currently exist. During infection, the flavivirus RNA genome is translated into a polyprotein, which is cleaved into several components. The non-structural protein 3 (NS3) carries out enzymatic reactions essential for viral replication, including proteolysis of the polyprotein through its serine-protease N-terminal domain, with a segment of 40 residues from the NS2B protein acting as a cofactor. The ATPase/helicase domain is located at the C-terminus of NS3. Atomic structures are available for these domains separately but a molecular view of the full length flavivirus NS3 polypeptide is still lacking. We report two distinct crystallographic structures of a complete NS3 molecule fused to 18 residues of the NS2B cofactor: structure I, the protease domain sits beneath the ATP binding site, giving the molecule an elongated shape; structure II, the protease domain self-rotates 161 degree. The relative orientation between the protease and helicase domains is drastically different compared to the scNS3-NS4A molecule from hepatitis C virus (HCV), which was caught in the act of cis cleavage at the NS3-NS4A junction. The domain arrangements found in the crystal structures fit well into an envelope determined ab-initio using small angle X-ray scattering experiments in solution, suggesting a cluster of molecular conformations. The affinity for both ATP and ADP is approximately 10 fold higher for full length NS3 compared to the helicase domain, mdeasured using fluorescence correlation spectroscopy. It indicates that the protease domain plays an important regulatory role for NS3 NTPase and helicase activity.

Keywords: NS2B-NS3 protease, NS3 helicase, NS3 bifunctional enzyme crystal structure

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### Understanding and controlling polymorphism

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In order to control polymorphism we must understand it－so understanding becomes the first priority. What do we want to understand and what do we want to control? Understanding requires addressing and answering questions regarding similarities and differences of structure, energetics, crystallization kinetics and thermodynamics. For instance, if we want to control polymorphism we have to be able to answer with reasonable confidence the question of why some simple molecules exhibit a propensity for polymorphic behavior, while other simple molecules, crystallized perhaps countless times, show apparently no proclivity to crystallize in more than one crystal structure. Control of polymorphism allows us to obtain consistently and robustly the polymorph with the most desirable properties, to avoid obtaining polymorphs with less desirable properties, and to prevent the appearance of new and less desirable polymorphs. While recent years have witnessed considerable and impressive advances in our understanding and control of polymorphism, especially for individual molecular systems, there are still major challenges to be met for many other individual systems and, more significantly, for the overall fundamental understanding and control of polymorphism. This talk will review some of the recent advances and current challenges.

Keywords: crystal form, crystal growth, structure-property relationships

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### Dehydration process of lisinopril, investigated by *ab initio* powder crystal structure analysis

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Lisinopril, which is a widely used ACE inhibitor, has three crystalline phases, dihydrate, monohydrate and anhydrate. The dehydration process of Lisinopril hydrates has been studied by thermal analysis and IR spectroscopy, however, the crystal structures have been unknown because of the difficulty in preparing single crystals.
In order to elucidate the dehydration mechanism, crystal structures of Lisinopril dihydrate and anhydrate were successfully revealed using *ab initio* powder crystal structure analysis from synchrotron X-ray powder diffraction data. Both structures are almost isostructural in