# Form still comes before function: Why design still matters to crystal engineering.

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That composition and structure profoundly impact the functional behavior of crystalline solids has provided impetus for exponential growth in the field of *crystal engineering*[1] over the past 20 years. This presentation will address how crystal engineering has evolved from a focus upon design to the control of properties. The historical development of crystal engineering will be summarized before recently delineated but evolutionary strategies for the generation of two classes of multi-component materials will be addressed:

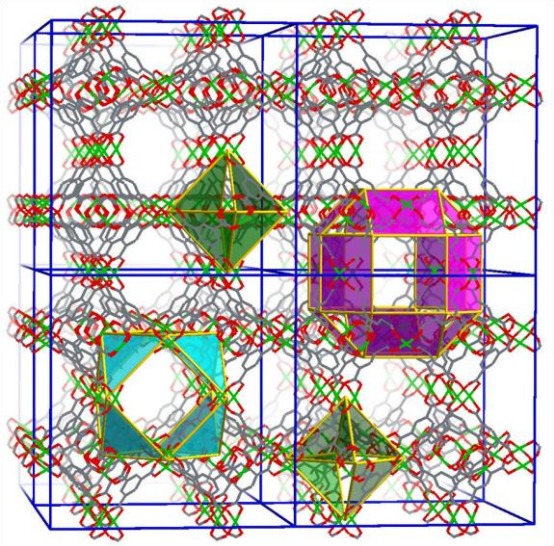
- ***Pharmaceutical cocrystals***[2] have emerged as a fixture at the preformulation stage of drug development because their modular and designable nature facilitates discovery of a wide range of new crystal forms of active pharmaceutical ingredients, APIs, with changed physicochemical properties. However, this does not mean that cocrystal discovery is yet routine and three issues will be addressed in this context:

  **The "supramolecular synthon rule".** Supramolecular synthons are key to rationalizing the crystal structures of molecular solids and are especially valuable in cocrystal design. The concept of supramolecular heterosynthons will be explained as it applies to cocrystals and new examples will be highlighted.

  **How to choose a cocrystal former library.** Whereas carboxylic acids are most typically used as cocrystal formers this does not mean that they are always likely to be effective for an API. New ideas about cocrystal former libraries will be presented including the use of nutraceuticals, zwitterions and inorganic salts.

  **The "solubility effect" of cocrystals.** The dissolution profiles of several classes of cocrystals that remain stable for >24hours in water have been measured in our laboratory. Our results will be placed in the broader context by comparing our in-house data with published solubility data on cocrystals and pharmaceutical cocrystals. We shall address whether or not the solubility of the cocrystal correlates with cocrystal former solubility, cocrystal melting point or the supramolecular synthons that sustain the cocrystal.
- ***Metal-Organic Materials*** (MOMs) that are built from metal or metal cluster "nodes" and organic "linkers" have captured the imagination of materials scientists because they are amenable to crystal engineering and they offer unprecedented levels of porosity. MOMs that contain two or more cages,[3] for which HKUST-1[4] is the prototype (see Figure), will be highlighted. We have studied such MOM platforms in the context of separations and catalysis. In the case of separations, the functionality of the walls of the MOMs profoundly influences uptake of gases or exchange of small organic molecules. In the case of oxidation catalysis, MOMs that contain encapsulated porphyrins exhibit enhanced stability and size selectivity when compared to the reaction conducted with the same catalyst in solution. Such MOMs have the potential to be used in the context of fine chemicals synthesis and for the controlled release of drugs.

**Figure.** HKUST-1 exhibits 3 distinct cages



To summarize, this lecture will emphasize how crystal engineering has reached the "end of the beginning", i.e. practical considerations now guide the design of pharmaceutical cocrystals and MOMs, rather than *vice-versa*. However, this does not diminish the importance of design.

**References:**

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4. Chui, S. S. Y.; Lo, S. M. F.; Charmant, J. P. H.; Orpen, A. G.; Williams, I. D. *Science* **1999,** *283*, 1148-1150.