A protein crystallization strategy for structure-based drug design

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STOP (Same-Target-Other-Pathogens) is our structure-based drug-discovery effort that targets proteins in the non-mevalonate pathway of multiple pathogens (1). These include *Mycobacterium tuberculosis* (tuberculosis); *Plasmodium falciparum* and *P. vivax* (malaria); and the ESKAPE bacteria (a group implicated in hospital-acquired infections).

At STOP we use a minimalist approach to screen for crystallization conditions. How well does this approach work? I will present our experiences with it and also discuss choosing a screen, protein formulation, and seeding with homologues (2), Fig. 1.

Our experiences at STOP may be relevant to other small academic and medium-throughput laboratories. The lecture will also be of interest to researchers interested in crystallization strategy in general.

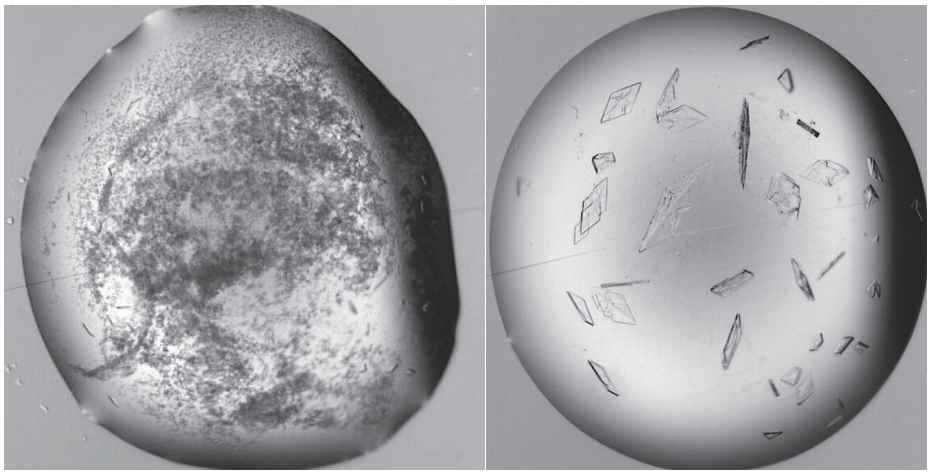

Fig. 1. Cross-seeding of *Plasmodium falciparum* IspC. Crystals were difficult to obtain until the drops were cross-seeded with crystals from a homologue, the *P. vivax* IspC. The homologues have 70% sequence identity. The micrographs show the droplets with *P. falciparum* IspC protein at 1 hour (left) and 12 hours (right) after seeding with *P. vivax* IspC crystals. The crystals on the right are 0.15 mm in their longest direction and diffract to 1.6Å.

References

1. Sooriyaarachchi, S., et al. (2016) ChemMedChem 11, 1-14.
2. D'Arcy, A., Bergfors, T., Cowan-Jacob, S.W. and Marsh, M. (2014) Acta Cryst F70, 1117-1126.