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Targeting FPPS by fragment-based lead discovery

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Trypanosoma cruzi (*T. cruzi*) is the causative agent of Chagas disease, which is considered a neglected disease. Medication for this disease is based on empirically discovered drugs with low efficacy, difficulties in administration and severe side effects. The development of a safe and efficient drug is therefore urgently needed.

Farnesyl pyrophosphate synthase (FPPS) is a key enzyme in isoprenoid biosynthesis. The parasite is dependent on isoprenoids, such as ergosterol, as they cannot be acquired by other mechanisms. Bisphosphonates (BPs) are active site directed FPPS inhibitors. They are used in the clinic as drugs for bone diseases due to their ideal pharmacokinetics in targeting bone tissue. They can also combat *T. cruzi* flagellates but are not ideal to treat Chagas disease. Several non BP inhibitors that bind to an allosteric pocket were found for human FPPS by fragment-based screening (FBS). More recently it was shown that the product of FPPS, farnesyl pyrophosphate (FPP) can bind to this pocket and locks the enzyme in an open and inactive state.

Encouraged by these findings, we started our investigations by FBS against *T. cruzi* FPPS. Screening and validation of 1806 fragments by NMR spectroscopy revealed 118 diverse fragment hits. Counter screening against human FPPS and *T. brucei* FPPS, the causative agent of African sleeping sickness, showed selectivity of the fragments at this early stage of screening. To enable follow up by X-ray crystallography, a crystallization system was set up that yielded apo-crystals of *T. cruzi* FPPS with a diffraction limit of around 1.6 A. 72 fragments were employed to soaking experiments that resulted in two structures. One ligand was active site directed and the other binding to the homodimer interface. The major break trough was achieved by FBS by X-ray crystallography at the XChem facility in Harwell, UK, and the HTXlab in Grenoble, France. In total 1113 data sets were collected and analyzed using the statistical analysis tool Pan-Dataset Density Analysis (PanDDA). More than 50 hits with non-bisphosphonate scaffolds were obtained. Binding sites were distributed over the entire protein, including the active site, the allosteric site, the homodimer interface, sites on the surface and a new site in close proximity to the active site.
In summary, we found active site binders of a novel scaffold and discovered the first allosteric site binders for *T. cruzi* FPPS. Both will deliver starting points for medicinal chemistry. Thus, the herein reported findings will give new impulses in drug discovery for Chagas disease.

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