Inhibition of CPSF3: A new approach to control infections by apicomplexan parasites

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Apicomplexans are unicellular protozoan parasites that infect humans or animals and can cause severe diseases. Among these diseases, malaria, toxoplasmosis and cryptosporidiosis represent a major threat to global human health. The current therapies are unsatisfactory either because: 1) have limited efficacy, particularly in those at higher risk (children and immunocompromised patients); 2) there are frequent toxic effects; or 3) the rapid emergence of resistance, notably in *Plasmodium* species, jeopardizes the use of effective drugs. Altogether, it highlights the urgent need for new drugs, ideally directed to novel targets of these parasites.

We recently reported a benzoxaborole, AN3661, which has potent activity against *Toxoplasma* and *Plasmodium* and that, by an unknown mechanism, appears to block a novel target. Parasites resistant to AN3661 had mutations in the gene CPSF3, a putative endonuclease that in some eukaryotes (including mammals) cleaves the 3-end of newly synthesized transcripts (pre-mRNAs). Point mutations in CPSF3 recapitulated the resistance phenotype when introduced into wild-type parasites by CRISPR–Cas9. Importantly, when orally administered in mice, AN3661 protected the animals from acute toxoplasmosis and malaria with similar efficacy to clinically relevant drugs and without signs of toxicity. Here we will present high-resolution crystal structures revealing the novel inhibition mechanism of CPSF3 by AN3661 in apicomplexan parasites. Comparison of these structures to the structure of the mammalian homologous protein (CPSF73) shows significant differences that might explain the selectivity of the inhibitor for these parasites. This study exemplifies the crucial role of the HTX crystallography lab, accessed via the iNEXT program, for understanding a novel inhibition mechanism and provides the atomic basis to design potent and selective antiparasitic drugs.

References

Palencia et al. Targeting CPSF3 Toxoplasma gondii CPSF3 As a New Approach to Control Toxoplasmosis. ***EMBO Mol Medicine*** 2017.