Targeting cleaving and Polyadenylation Specificity Factor Complex (CPSF) of apicomplexan parasites as a new therapeutic approach

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Apicomplexa 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 or 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 *in vitro* activity against *Toxoplasma* and *Plasmodium* growth and that, by an unknown mechanism, appears to block a novel target [1,2]. Parasites selected to be resistant to AN3661 had three distinct mutations in the gene CPSF3, which belongs to a family of endonucleases that cleave the 3-end of newly synthesized transcripts (pre-mRNAs) in some eukaryotes, including mammals. Point mutations in CPSF3 recapitulated the resistance phenotype when introduced into wild-type parasites using 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 on-going structural studies to understand the inhibition mechanism of CPSF3 in parasites and the basis of the selectivity respect to the human homologous protein (CPSF73).

References

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