Fungal infection, such as systemic candidiasis is becoming an increasingly serious medical problem. Recent work has established the phosphatase suppressor of TCR signaling (Sts proteins) as key negative regulators of the host anti-fungal response. We have successfully solved the active site structure of two members of human Sts protein: Sts-1 and Sts-2 via X-ray crystallography. Couple of promising inhibitors which are targeting Sts-1HP were identified from High throughput screening. These results have established human Sts-1 as a viable drug target and will serve as a starting point for structure-guided design of highly effective inhibitors targeting Sts1 in the future.