

Using Genome Database and In Silico Chemical Library Screening Data To Discover New Antimalarial Drugs

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Millions die from malaria each year. Resistance to available antimalarial drugs continues to spread, and an effective malaria vaccine remains years away. Thus, there is a dire need to rapidly discover new antimalarial drugs or drug combinations. Unfortunately, structure based drug design and virtual (*in silico*) screening and optimization of antimalarial drugs is in its relative infancy. Yet, major advances in these techniques have been made in other fields, including cancer pharmacology and anti - cancer therapeutics. The recent availability of the *P. falciparum* genome and the current plethora of genome exploration tools now makes, in theory, many of these techniques accessible to the malaria community. In this paper, we demonstrate one interesting and very rapid translation of well established, yet novel, drug design methodology from the cancer therapeutics arena to antimalarial drug design.

Specifically, AKT ser / thr kinases perform particularly vital functions at key cellular signal transduction branch points that overlap cellular metabolism, growth and differentiation. In the case of malarial parasites, cellular metabolism, growth and differentiation are unusual, rapid, and tightly coordinated by poorly understood signal transduction pathways. Identifying key branch point malarial kinases is essential. Based on homologies to human AKT enzymes, we have recently identified and modeled two *P. falciparum* AKT kinases (PfAKT) that, interestingly, appear to be apicoplast targeted. We have screened libraries of compounds *in silico* by first using CHARM to model PfAKT structure, followed by docking and scoring using the FlexX and Cscore modules of Sybyl (Tripos Inc., St. Louis MO), respectively. Novel compounds thus designed to inhibit AKT were then screened vs. chloroquine resistant (CQR) and sensitive (CQS) malaria via a novel high throughput assay. Via this approach, we have very rapidly identified several enticing lead compounds for further development. Computational chemistry methods are now being applied to further optimize these *in silico*. Synthetic chemistry schemes for their production have already been perfected in the context of earlier anti cancer drug discovery work. That is, using the substantial body of rapidly accumulating digital genome data, an extensive array of well developed synthetic chemistry pioneered in cancer therapeutics laboratories, and emerging computational chemistry *in silico* drug design methods, it is now possible to rapidly identify and optimize new antimalarial drug leads. In this example, we define one new class of drugs directed against a new crucial antimalarial drug target, PfAKT2.

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