Significance

The control of infectious disease has largely been viewed as a "solved problem" from the context of many major pharmaceutical companies. Indeed, the inability of for-profit antimicrobial research programs to deliver blockbuster drugs has led to the excision of these programs from many major pharmaceutical pipelines particularly in light of the recent contraction of many such organizations.[5] While such strategies are sound from an economic standpoint, this down prioritization has little to do with the reality that infectious diseases such as tuberculosis and HIV contribute approximately equally to the worldwide DALY (disability-adjusted life years) impact as chronic diseases such as neoplastic, cardiovascular, and neurological disorders (603,993 vs. 731,652 years respectively).[8] It is also important to point out that the major burden of infectious disease is borne out by children and individuals of lower socioeconomic status while chronic disorders tend to be problems of the "modernized" world and usually afflict individuals in their mid- to later years; it is for this reason that absolute mortality is often a poor indication of the true impact of infectious disease worldwide. For these reasons, the current arsenal of drugs utilized for the treatment of many infectious diseases, particularly those that afflict the third world, are outdated; in many cases these drugs exhibit off-target toxicity profiles that provide an extremely narrow therapeutic index.

Malaria is a protozoan-based disease that mainly transmitted by the *Anopheles* mosquito. There are four major human malaria parasite species from the *Plasmodium* genus; these are *falciparum*, *ovale*, *malariae*, and *vivax*. Malaria causes one of the greatest overall mortality levels of the known infectious diseases; according to the WHO, malaria accounted for nearly one million deaths in 2008, and the majority of

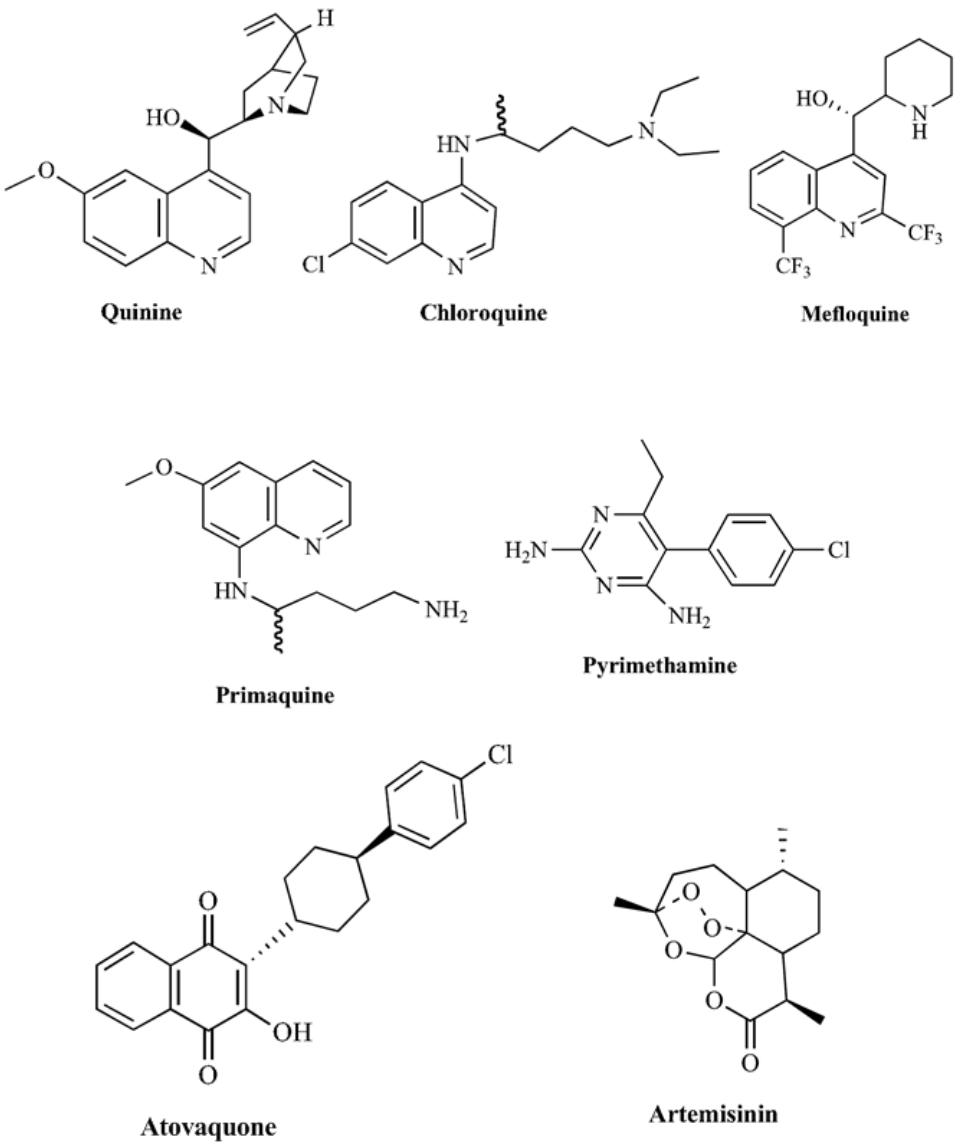


Figure 1. Drugs Utilized for the Treatment of Malaria

these were among African children.[9] Unlike related protozoan pathogens such as *T. brucei* and *T. cruzi*, the traditional therapies used for treatment of malaria are relatively safe and highly efficacious. The critical factor that has led to an insufficient malaria treatment arsenal in recent years is the rapid evolution of drug resistance within species endemic to South Eastern Asia and Africa.[9, 10] For this reason, some of the most

successful antimalarials (e.g. chloroquine Figure 1) have been rendered nearly useless in regions where they are needed most. Fortunately, the timely release of artemisin-based drugs and combination therapies (e.g. atovaquone + proguanil) have provided a modicum of respite during which time new treatments can be evaluated clinically.[10, 11]

In addition to the issues of drug resistance, two of the major *Plasmodium* species (*P. vivax* and *ovale*) are not entirely eliminated by routine treatment with most antimalarials. Often, symptomatic malaria caused by parasitemia will be successfully treated with chemotherapy only to result in relapse several months later. Malaria relapse in these instances results from the ability of these species to exist in a dormant "hypnozoite" form within hepatic tissues. Currently, pamaquine and primaquine are the only treatments known to successfully eliminate the hypnozoite form of the parasite, and it is necessary to co-administer with quinine or chloroquine to be maximally effective in this role.[12] The mechanism for this ability to act as a tissue schizonticide is not well understood. It is important to consider that many patients who are afflicted with *P. vivax* or *ovale* may not receive dormant liver-stage treatments if the parasite is incorrectly identified, and such identification usually requires technically trained personnel to carry out a definitive blood film analysis. Therefore, it is clearly of considerable interest to develop novel antimalarials that are effective against drug-resistant and/or liver forms of the parasite. Any strategy that enhances the utility of the *known* antimalarials is also highly valuable, especially since these drugs are already well characterized from a clinical standpoint and can be more rapidly deployed.

Both quinine and artemisinin highlight the importance of natural products in the realm of antimicrobials. Indeed, many of the most effective treatments for infectious disease have been derived from natural products by the pharmaceutical industry. Unfortunately, many of the same issues described above for synthetic drugs plague natural products that serve as first-line therapies for third world infectious diseases. Two examples are the use of avermectin-based drugs for onchoceriasis and amphotericin B formulations for treatment of visceral leishmaniasis (Figure 2).[13, 14]

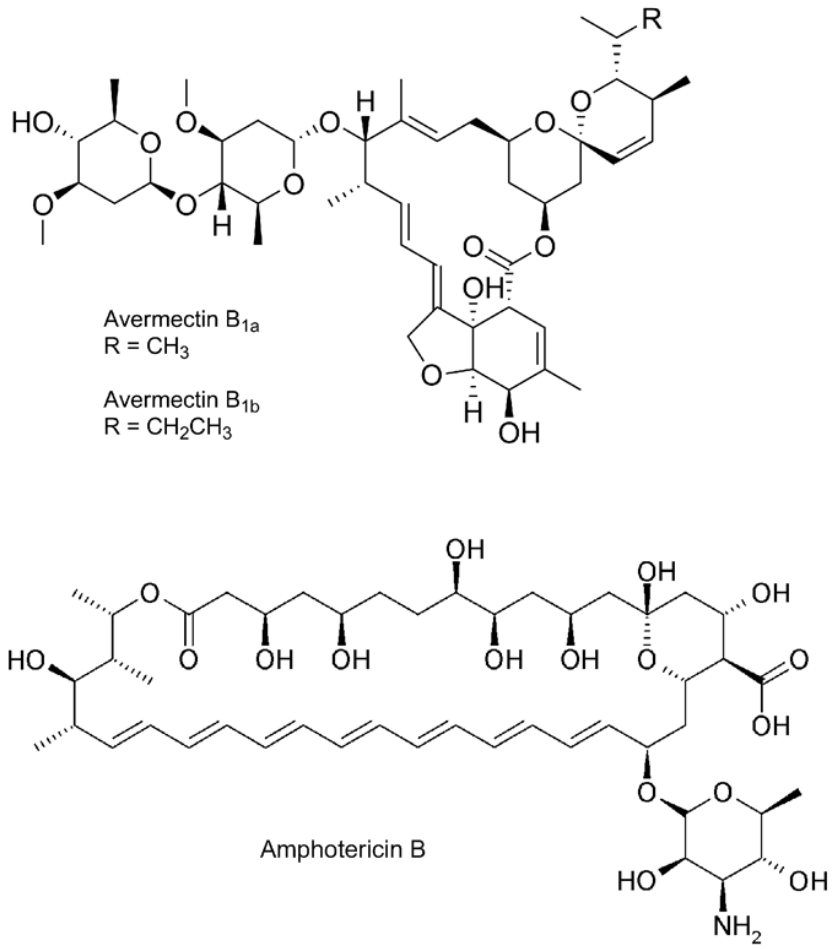


Figure 2. First-line Natural Product Therapeutics

Onchoceriasis, or river-blindness, is caused by transmission of the nematode *Onchocerca volvulus* by the *Simulium* black fly. In total, 18 million people are infected with *Onchocerca* microfilariae, the young form of the organism that is largely responsible for the clinical symptoms of the disease. Approximately 270,000 individuals are blind due to this affliction and hundreds of thousands more have severely restricted vision.[15] Ivermectin (an avermectin-based therapy) has been critical for the treatment of this disorder, as it is safe, orally dosed, and is extremely effective at eliminating the pathogenic microfilariae. As with some of the most successful malaria treatments, however, recent reports have emerged indicating an emergence of ivermectin resistant *Onchocerca* strains in African sub-regions.[16, 17] The success of ivermectin as a treatment for onchoceriasis has left armamentarium for secondary treatments non-existent, and it is therefore prudent to investigate alternatives that may retain activity against emerging strains.

Amphotericin has played a comparable role to ivermectin in the context of treatments for leishmaniasis, a protozoan pathogen that is transmitted by the bite of *phlebotomine* sandflies.[18] Unlike ivermectin, however, amphotericin is far from an ideal therapeutic in that it causes a number of side effects and its physicochemical properties make IV administration essential. Top alternatives to amphotericin (and often a substitution when cost is prohibitive) are pentavalent antimonials (e.g. pentostam), hence the inherent toxicity of amphotericin is often considered manageable. Significant improvements have been made recently in the formulation of amphotericin as a liposomal suspension (AmBisome) that dramatically increases drug efficacy while minimizing issues such as kidney toxicity. Although these improvements are

substantial, it is clear that amphotericin is still far from an ideal drug. Modifications that would improve the properties of this agent, particularly its off-target toxicity profile and its negligible oral bioavailability, would be truly beneficial to treatment of disease in areas where minimal public health infrastructure exists to facilitate proper drug administration.

Specific Aims

The following specific aims are proposed to establish a research paradigm that will be able to discover anti-infective agents with new modalities for several of the targets specified above (*vide supra*) and to develop these compounds into small molecules with appropriate physicochemical properties for *in vivo* studies in animal models of disease:

1. Design of additional chemotherapies for hepatic-stage malarial parasites and hypnozoites; additionally, screen for synergistic effect with chloroquine against Plasmodium sp. (e.g. PfCRT and other parasite transporter substrates/inhibitors).

2. Development of a context-specific battery of transition metal and biocatalytic transformations enabling modification of natural products that represent first-line infectious disease treatments (specifically, Avermectin and Amphotericin B).

Research Strategy

Specific Aim 1 – Design of Transporter Substrates to Treat Liver-Stage Malaria or to Sensitize CR Strains

As described above, two areas that limit modern malaria treatments are (1.) the inability for most to treat liver-stage schizonts and hypnozoites and (2.) the rapid evolution of drug resistance. Interestingly, it seems that a single strategy could potentially be utilized to develop compounds that will address both issues.

The reasons that antimalarial aminoquinolines such as primaquine are the only compounds effective for the treatment of liver stage malaria are poorly understood. It is known, as mentioned previously, that the efficacy of these drugs falls off dramatically for the elimination of hypnozoites if they are given without other quinoline antimalarials (e.g. chloroquine). It is also well known that the *in vivo* efficacy of the quinoline antimalarials is largely driven by their localization to the digestive vacuole of the parasite within erythrocytes.[10, 12] It therefore follows that the local drug concentration within the host cell cytoplasm would play a major role in activity against the parasite. As erythrocytes lack any significant mechanism for drug transport, the local concentrations of the quinoline antimalarials is driven exclusively by passive permeability, which is quite high for these particular compounds.

On the other hand, hepatocytes are heavily adorned with a variety of transporters (e.g. P-gp, BSEP, MRP, OATP) in order to facilitate drug metabolism and excretion (Figure 3).[19] One hypothesis for the lack of activity of many quinoline antimalarials is that they could be rapidly removed from the hepatocyte *via* transporter efflux while aminoquinolines possess a recognition element that establishes a reasonable

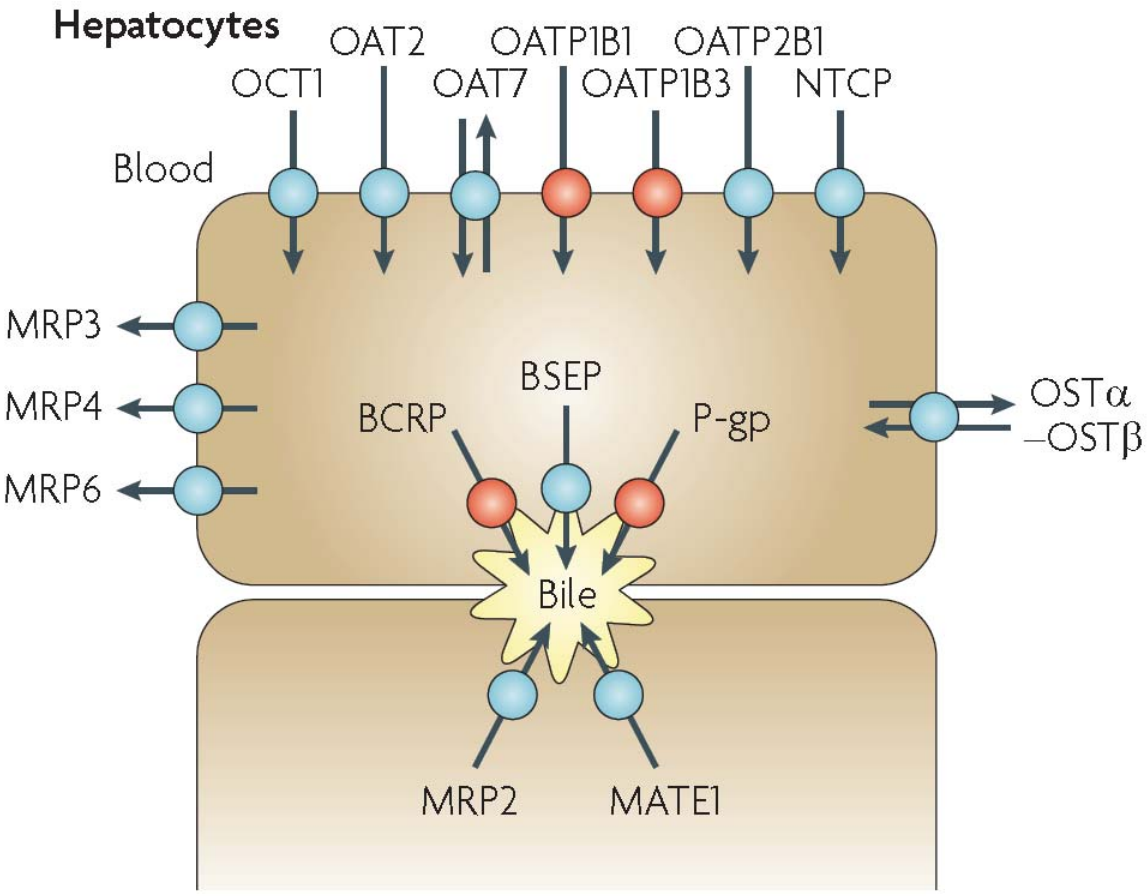


Figure 3. Key Hepatocyte Transporters[6]

concentration within hepatocytes. This hypothesis could also explain the need to co-administer additional quinoline antimalarials since they could serve as surrogates for the aminoquinolines, thus effectively saturating efflux pumps and enhancing the activity of these chemotherapies. The key point here is that drugs such as chloroquine do not lack requisite schizonticidal activity; they simply do not have the proper physicochemical properties to enable their localization to targets within hepatocytes. At the same time, primaquine appears to have structural elements that make it moderately effective as a liver schizonticide. Based on the inherent activity of primaquine, however, this drug and other representatives of its class are far from ideal and these properties could certainly

be enhanced.

In regards to the CR strains of malaria, it has recently been determined that the expression of constitutive ATP-dependent quinoline efflux pumps is responsible for rendering these organisms resistant to *cinchona* alkaloid-derived chemotherapeutics.[10, 12, 20, 21] One particularly well studied example is the PfCRT transporter expressed in resistant strains of *P. falciparum* (Figure 4).[7] These pumps are able to counter the localization of quinoline antimalarials to the *P. falciparum* digestive vacuole. One strategy for counteracting such transporters, as alluded to above in the discussion of hepatic efflux, is the co-administration of more effective efflux substrates. Even if these compounds possess limited inherent efficacy as antimalarials,

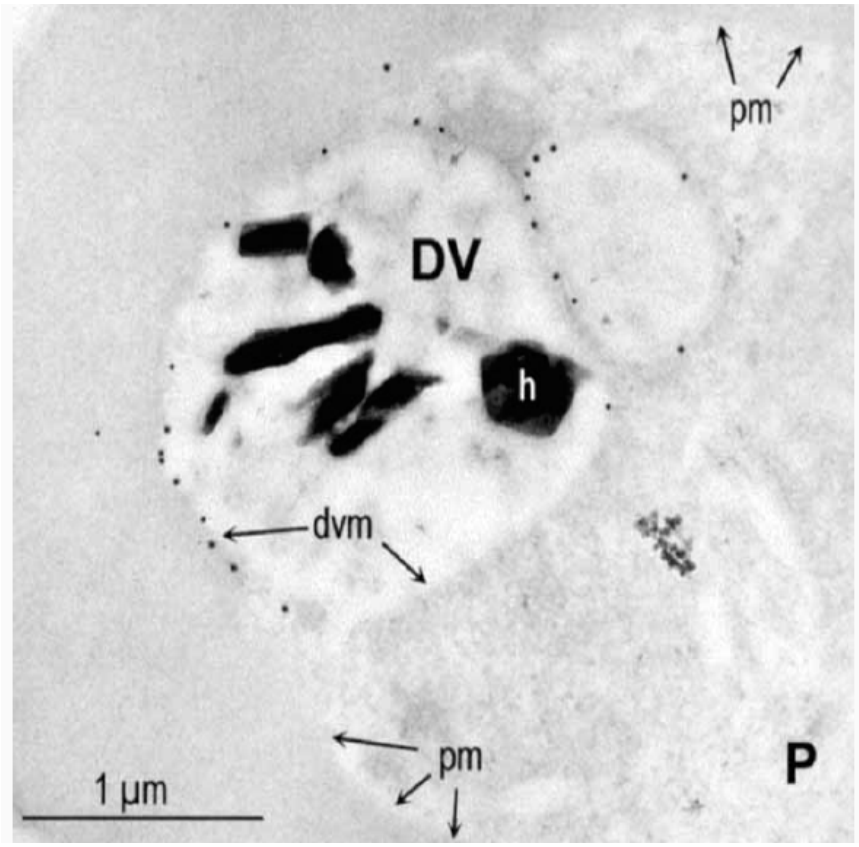


Figure 4. Localization of PfCRT Transporters to Surface of the P. Falciparum Digestive Vacuole[7]

they can be effective in sensitizing the target organism to the true cytotoxic agent if they are more effective substrates for the transporter. There have been attempts to develop compounds that chemosensitize the malaria parasite against the quinolines; some of these compounds also exhibit inherent antimalarial activity, thus rendering them possible candidates for synergistic co-administration.[22] Unfortunately, many of these early studies disclose compound classes that appear unlikely to be drugs given their unappealing structural motifs and physicochemical properties.[23]

It seems reasonable that developing quinoline-derived compounds that are highly effective transporter substrates may be a unified strategy to both derive more active therapies for liver stage malaria and to sensitize chloroquine resistant parasites.[10, 12, 20, 21] One highly general strategy for increasing hepatic transport across multiple chemotypes is the integration of carboxylate motifs. A list of targeted carboxylate-containing quinoline derivatives and their calculated parameters is presented below (Figure 5). These compounds are unknown in the literature and the calculated properties appear outstanding in all instances. The initial goal would be to prepare these compounds and directly measure activity against various *Plasmodium* sp. *in vitro*. Following this work, these compounds would be tested for the chemosensitization of resistant malaria mutants (e.g. PfCRT-expressing *P. falciparum*) to chloroquine; this work would likely be carried out in collaboration with more technically experienced groups with access to such malaria strains. In addition to these studies, simple studies to measure relative concentrations within cultured hepatocytes can be carried out to demonstrate enhanced uptake or efflux. Follow-up studies would need to be designed with collaborators to assess the activity of these compounds as mono- or combo-

therapies for the treatment of liver stage malaria.

Although the carboxylate motif serves as a general substrate for transported-mediated cellular uptake, this process is by no means specific to hepatocytes. Indeed, related organic anion transporters (OATPs) are expressed in organs such as the kidney and gut.[19] A secondary strategy for targeting anti-schizonticides specifically to hepatic tissues must rely on uptake mechanisms that are exclusively conserved within the liver. An interesting strategy has recently been described utilizing the

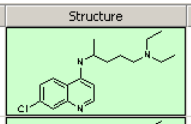
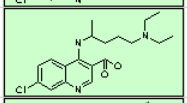
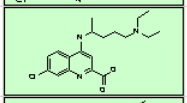
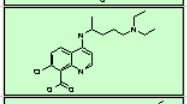
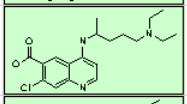
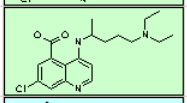
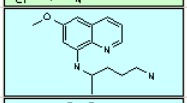
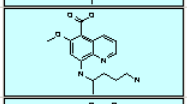
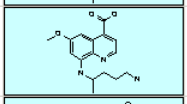
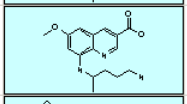
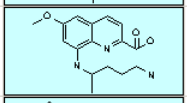
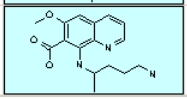
Id	Structure	MW	RO5	CLOGP	cELOGD	PSA	NOCNT	HBDONORCNT	HBACCPTCNT	ROTBNDCNT
Chloroquine		**319.8721**	**1**	**5.06**	**1.89**	**28.16**	**3**	**1**	**2**	**8**
Chloroquine-AC1		363.8816	0	3.567	1.59	65.46	5	2	4	9
Chloroquine-AC2		363.8816	0	3.137	1.51	65.46	5	2	4	9
Chloroquine-AC3		363.8816	0	2.224	1.14	65.46	5	2	4	9
Chloroquine-AC4		363.8816	0	2.224	1.05	65.46	5	2	4	9
Chloroquine-AC5		363.8816	0	2.824	1.38	65.46	5	2	4	9
Primaquine		259.3467	0	2.598	0.106	60.17	4	3	3	6
Primaquine-AC1		303.3562	0	-0.024	-0.465	97.47	6	4	5	7
Primaquine-AC2		303.3562	0	0.451	-0.374	97.47	6	4	5	7
Primaquine-AC3		303.3562	0	0.451	-0.498	97.47	6	4	5	7
Primaquine-AC4		303.3562	0	0.651	-0.333	97.47	6	4	5	7
Primaquine-AC5		303.3563	0	0.606	0.254	97.47	6	4	5	7

Figure 5. Targeted Carboxylic Acid Functionalized Quinoline Antimicrobials for Modulation of Hepatic and CR Malaria Uptake

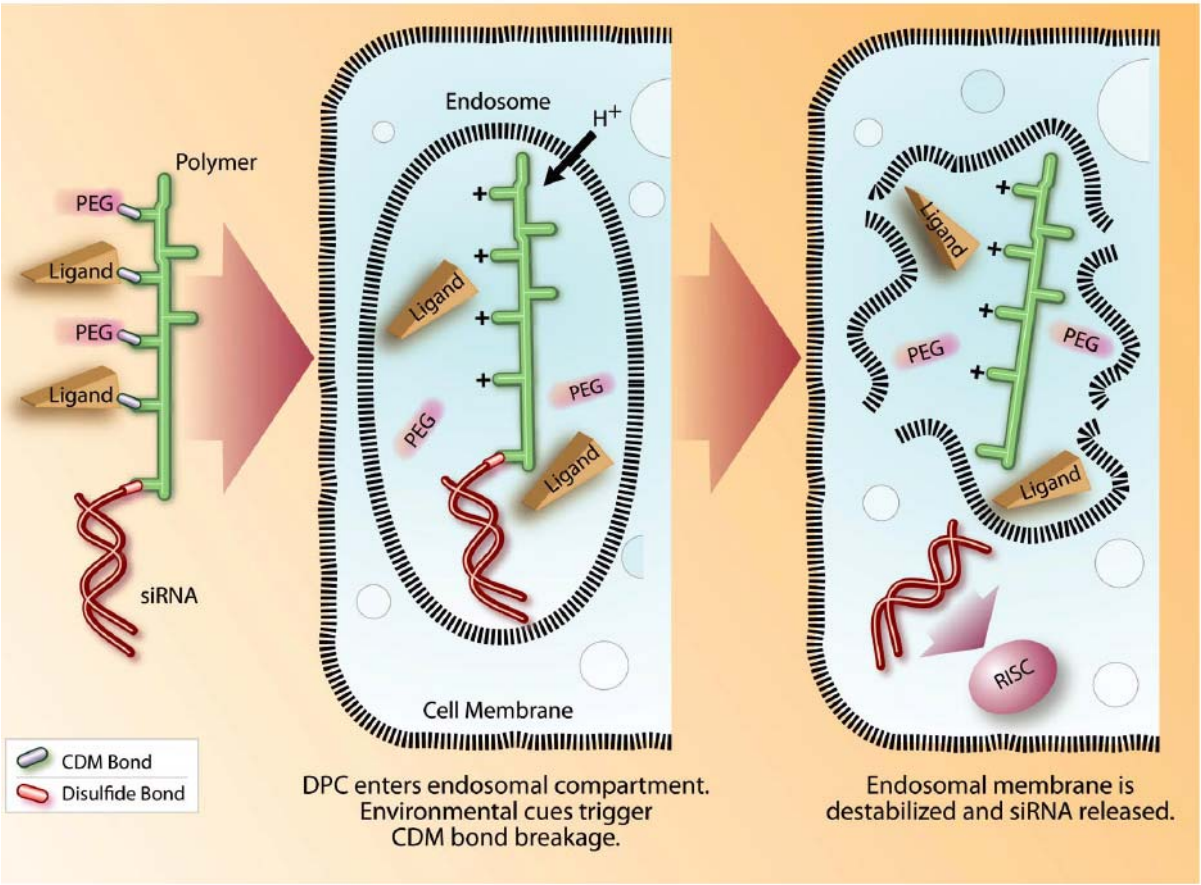


Figure 6. Targeting of siRNA to Hepatocytes Using Asialoglycoprotein Receptor (ASGPR)[3]

asialoglycoprotein receptor (ASGPR) to target various molecules of interest to hepatocytes.[3] ASGPR recognizes carbohydrate motifs (lectins) displayed on numerous glycoproteins and serves to absorb these substrates through receptor-mediated endocytosis of these entities. This process has been directed mainly towards absorption of biomolecules as exhibited below, but could be reasonably adapted to small molecule targets by recently outlined strategies (Figure 6).[3, 24] Conjugation of the small molecule drug Primaquine through a non-essential functional group handle to the carbohydrate targeting motif would theoretically provide a highly potent functional ligand that is specifically directed via ASGPR to hepatic tissues (Figure 7).[24]

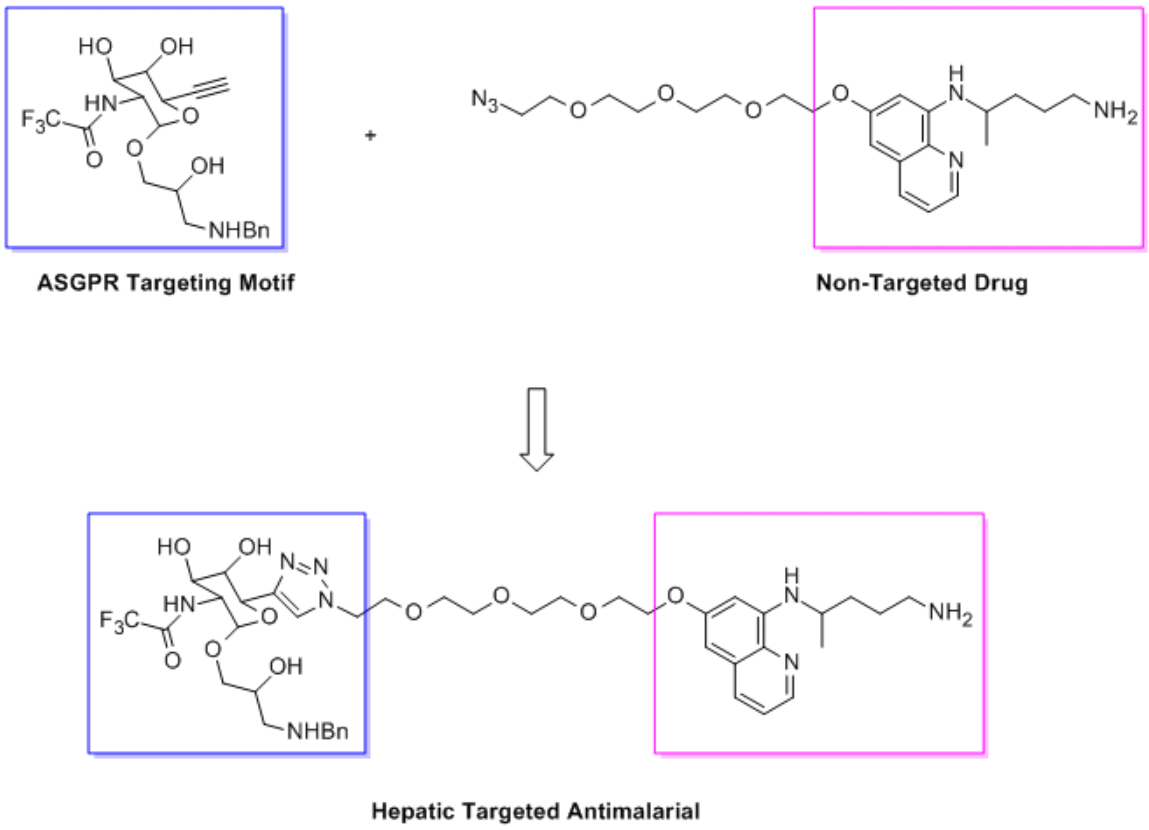


Figure 7. Small Molecule Targeting of Primaquine to Hepatocytes through ASGPR

Specific Aim 2 – Development of Context-Specific Functional Manipulations for First Line Natural Product Antimicrobial Therapeutics

For the reasons described above, continued work on derivation of bioactive natural products remains a highly active field within academic research. The majority of the efforts in this area focus on the structural elucidation and total synthesis of a target that presents a synthetic challenge. In many cases these compounds also possess interesting bioactivity and the preparation of even milligram quantities of the target molecule is highly valuable. In limited cases, derivatives are also prepared based on certain synthetic intermediates and enabling methodology, but access to these

derivitives is usually constrained by the established synthetic route. Pharmaceutical research on bioactive natural products traditionally employs an orthogonal approach. In these cases, the natural product is used as a starting material and accessible functionality is modified using robust, selective methods (e.g. amide coupling, reductive amination). Although this is a useful method of modifying a bioactive compound to improve issues such as potency and pharmacokinetics, the available structural modifications are even more limited than in the case of total synthesis. The various commercial analogs of the artemisinin-based therapeutics are an instructive example in this instance.

Part of the challenge faced here are the time constraints in an industrial setting; there is little interest in exploring novel chemistry that is *contextual* to the natural product scaffold in question when libraries of compounds can be prepared from single-site perturbation. One could make the case that developing chemical methodology that is specific to a particular natural product class is counter-productive compared to approaches that have broad substrate generality.[25] Although this seems reasonable, a counter argument can be made; the development of contextual chemical methodology could be highly valuable when it leads to completely novel analogs of *critically important natural product classes*. The recent development of many novel chemical methods that are highly tolerant of sensitive functionality and often exhibit tunable selectivities makes this exercise particularly appealing in the current synthetic environment.[1, 2, 26-29] Two specific examples of these methods are highlighted above (Figure 8). In addition to chemocatalysis, contemporary biocatalytic methods present an alternative for investigating these context-specific transformations.[30]

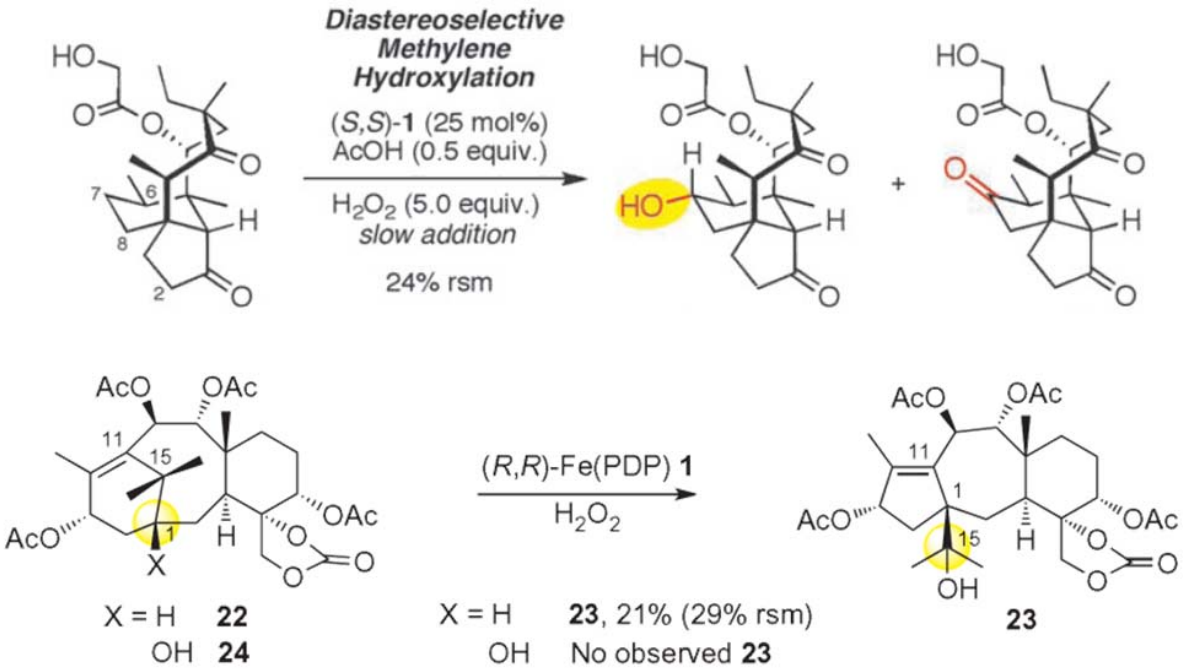


Figure 8. Context-Specific Natural Product Transformations[1, 2]

Avermectin and amphotericin B are proposed as targets for these studies for the reasons specified previously in addition to the fact that their chemical structures provide a variety of “targets” for catalytic functionalization and because both compounds are commercially available at a nominal cost (ivermectin~15$/g, amphotericin B~80$/g). Two strategies are proposed; the first is screening a battery of known catalytic systems under a variety of conditions to discover site-specific methods for accessing novel analogs (Figure 9). The second strategy would rely on less specific methods of functionalization in addition to exogenous reactants (e.g. olefin metathesis with various alkenes).[31] Different mixtures would be obtained under divergent reaction conditions (e.g. temperatures, concentrations, stoichiometeries, reaction times), but each independent reaction would be repeatable if performed appropriately. The mixtures could then be screened for activity, and although these activity numbers would not be

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(bdsteven@gmail.com)

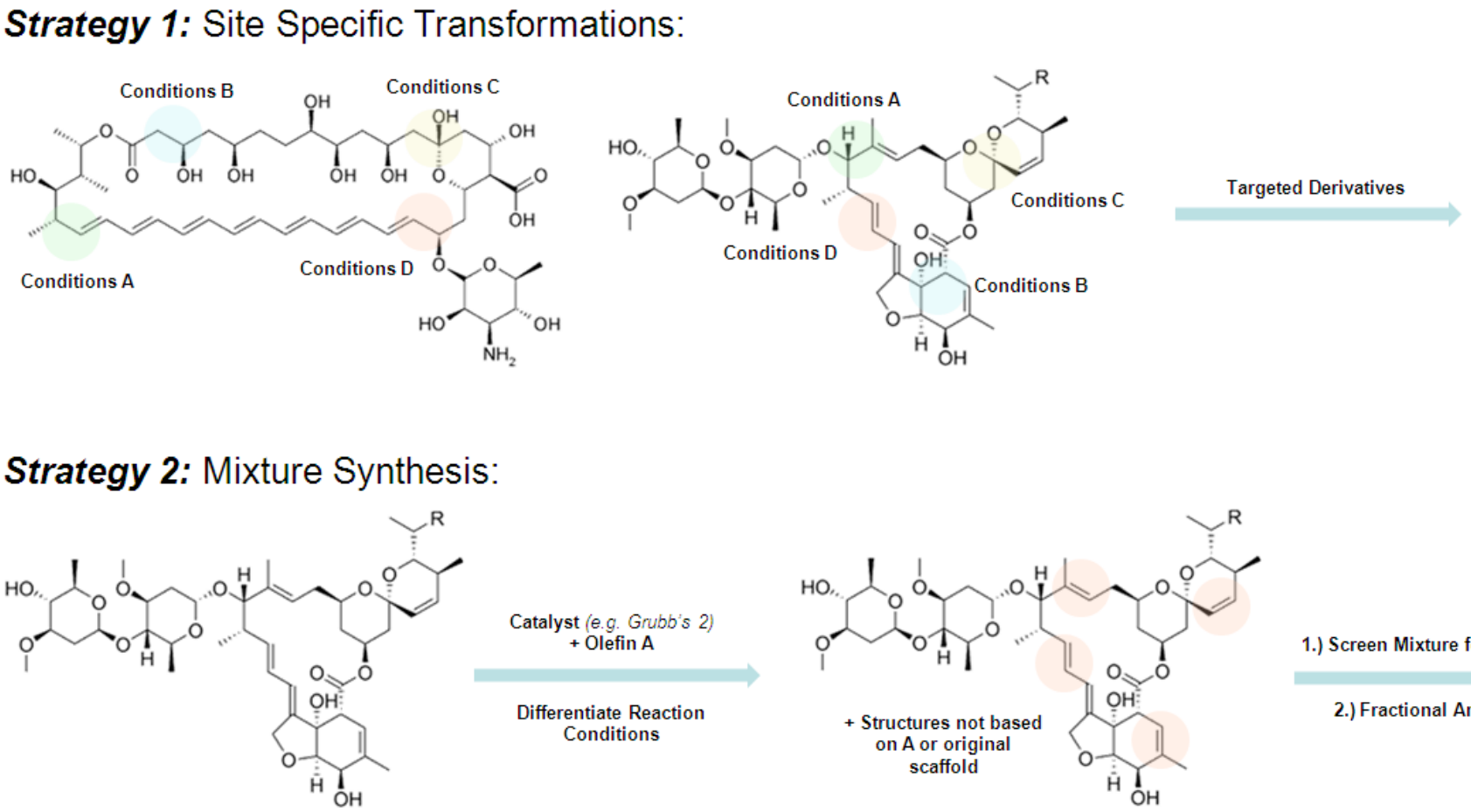

Figure 9. Two Strategies for Evaluation of Context-Specific Natural Product Modification

quantitatively relevant (i.e. the concentration of the active agent would not be known), useful data would still be obtained.

Evaluation against ivermectin-resistant nematodes would present a particularly interesting test case. Alternative *in vitro* methods for mixture screening could also be leveraged for compound classes that have well defined targets (e.g. affinity mass spectrometery).[32, 33] Following identification of a hit, the reaction could be scaled, the active compound isolated, and its structure determined by methods similar to those carried out in natural product isolation groups. This approach is clearly not limited to the compounds above, and could be readily applied to fully synthetic therapeutics as well.

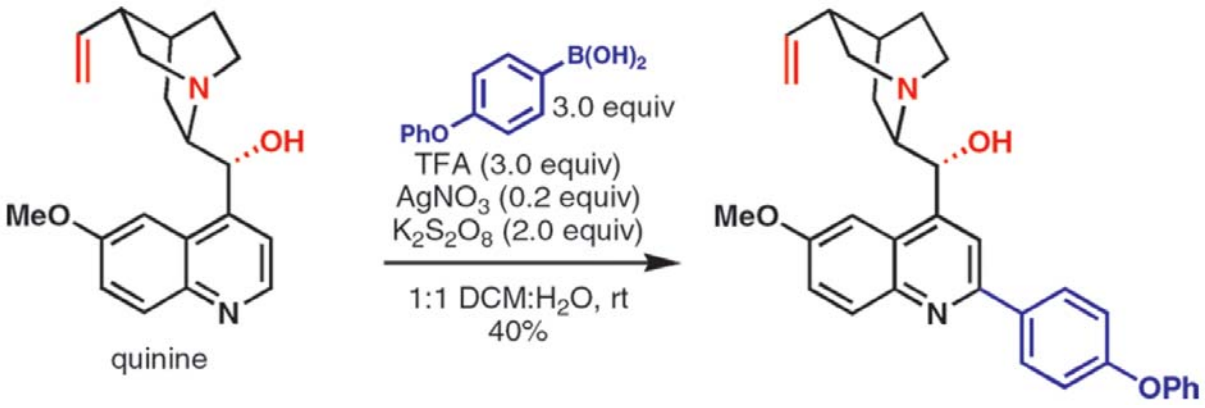

Figure 10. Direct Modification of Quinine Highlighting Strategic Approach Applied to Antimalarials[4]

For example, the same approaches can be outlined for the cinchona alkaloids in order to derive specific, targeted analogs of antimalarials or complex mixtures of potentially novel compounds (Figure 10). A related strategy has recently been described enabling access to specific analogs of quinine in a single transformation through C-H activation.[4] De novo synthesis of this compound would typically prove difficult and would require considerable investment in time and resource, however,

methodology directed at modifying the cinchona alkaloid entity directly led to rapid derivation into this analog of interest.[4] This approach could be applied to direct modification of other antimalarials such as Primaquine.

Summary

The projects described above represent a multi-faceted strategy directed at the overall goal of developing novel antimicrobial agents for areas of unmet medical need. The specific goals outlined under aims 1 and 2 present opportunities for delivering on this long term goal, particularly in the context of the malaria parasite. The two strategic approaches also have considerable flexibility and likely can be combined in a synergistic fashion to discover chemotherapeutics with novel mechanisms of action and then to optimize their efficacy through targeting to specific tissues (e.g. hepatocytes for malaria). The capability to tune exposures for these agents also offers the considerable benefit of limiting exposures in peripheral or non-relevant tissues that could narrow the effective therapeutic index.

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