Combinations of candidates: a TPP for malaria treatment

The following is an excerpt from “Designing the next generation of medicines for malaria control and eradication”. For references, please refer to the full paper.

The challenge of combining these candidates to design an ideal medicine against malaria (Table 5) is formidable. There are still many unknown factors, not the least of which is that only a limited number of new classes of molecules have reached clinical evaluation. It is clear that a single molecule can have more than one attribute: a molecule can for example meet the criteria of more than one candidate profile (Figures 4 and 5), but it is essential that combinations of molecules will be needed, not least to combat resistance.

Table 5 TPP-1 for the treatment of uncomplicated malaria in children and adults

<table>
<thead>
<tr>
<th>Parameter to be demonstrated for the combination in clinical evaluation</th>
<th>Minimum essential</th>
<th>Ideal SERCaP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of onset of action</td>
<td>At least one component acts rapidly; patient fever decreased at 24 h</td>
<td>Both components act immediately; patient fever decreased within 24 h</td>
</tr>
<tr>
<td>Proportional Reduction in Parasite Load</td>
<td>&gt;12 log unit reduction in asexual blood stage load</td>
<td>100%</td>
</tr>
<tr>
<td>Clinical efficacy (day 7) including patients from areas known to be drug-resistant to current first-line medications</td>
<td>100%</td>
<td></td>
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<tr>
<td>Clinical efficacy (ACPR at day 28 or later, per protocol)</td>
<td>&gt;95% PCR-corrected</td>
<td>&gt; 95% non PCR-corrected</td>
</tr>
<tr>
<td>Transmission blocking</td>
<td>No: preclinical models still need to be validated as predictors of clinical outcome</td>
<td>Yes</td>
</tr>
<tr>
<td>Relapse prevention: prevents the relapse of <em>P vivax</em>, and by inference <em>P ovale.</em></td>
<td>No: preclinical models still need to be validated as predictors of clinical outcome</td>
<td>Yes</td>
</tr>
<tr>
<td>Confirmation in clinical studies capable of distinguishing prevention from delay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioavailability/ Food Effect</td>
<td>&gt;30% for each molecule, &lt;3-fold</td>
<td>&gt;50% for each molecule, none</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>No unmanageable risk in terms of solid state or pharmacokinetic interactions</td>
<td>No risks in terms of solid state or pharmacokinetic interactions</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Oral, two-three doses</td>
<td>Oral, once</td>
</tr>
<tr>
<td>Safety</td>
<td>Few drug related SAEs in phase III</td>
<td>No drug related SAEs; minimal drug-related AEs</td>
</tr>
</tbody>
</table>
Use in patients with G6PD deficiency
Pregnancy
Formulations
Cost of treatment course
Shelf life of formulated product (ICH guidelines for Zones III/IV; combination only)
Susceptibility to loss of efficacy due to acquired resistance

Testing not obligatory due to low risk
Not contra-indicated in second and third trimester
Co-formulated tablets or equivalent, with taste masking for pediatrics
≤ $1.00 for adults; $0.25 for infants under two years
≥ 2 years
Low (better than atovaquone or pyrimethamine monotherapy); no cross resistance

No enhanced risk
Not contra-indicated
Co-formulated tablets for adults. Dispersible or equivalent with taste masking for pediatrics
≥ 5 yr
Very low (similar to artemisinin or chloroquine); no cross resistance. Resistance markers identified.

Figure 4 Breakdown of the ideal medicine into different target candidate profiles. * Minimum Parasiticidal Concentration. ** Delivering a molecule that will remain in human blood for as long as mature gametocytes circulate is extremely challenging in the absence of a rapid gametocytocide; therefore, vector-stage parasite killing is seen as a desirable rather than critical activity.

Figure 5 Diagram of the *Plasmodium* lifecycle and parasite load (z-axis, logarithmic) with stages targeted by the various TCPs.

Safety is clearly a paramount concern for any new medicine. The challenge with developing new medicines against malaria is that the current medicines are relatively safe, and serious adverse events rare (less than 1:10,000). This means that any new medicine will be expected to measure up to such a standard, and that in turn requires extensive safety monitoring after launch of a new product. Confirmation that such safety has been achieved will only come with extensive pharmacovigilance, across a wide range of patient ethnicities. In countries planning malaria elimination there has been much discussion of strategies for mass drug administration, or mass screening and treatment. It is important to underline that for mass drug administration the safety profile has to be even more stringent, given the different risk-benefit balance of administering medicines to subjects who may not have the disease. Here, as with vaccines, even 1 in 10,000 adverse events will be problematic. Aiming for a SERCaP places considerable challenges in addition. Giving all the active ingredients as a single dose increases the maximum exposure of each individual molecule, and may reduce the overall clinical safety margin. The benefits of a single dose therapy from a compliance and delivery perspective have to be carefully weighed against the potential risks.

The question of duration of treatment cannot be considered in isolation from the emergence of artemisinin-tolerant strains of the parasite. In countries or districts where artemisinin combination therapies are clinically effective, then clearly the SERCaP brings considerable advantages in terms of directly observed therapy, and potential cost savings, since packaging and distribution will be much simpler (Figure 3). In these countries or districts a new three
day course of treatment will offer much less of an advantage. The cost of goods may be lower, but this is set against the extensive clinical safety database for ACT. The rationale for developing a new therapy for this particular segment is much more challenging. However, in the countries and districts where artemisinin combination therapies are no longer effective, because of artemisinin ineffectiveness rather than resistance to the partner, then the scenario is different. Here, a three-day course of treatment with similar safety and efficacy as the current ACT would be acceptable. A single dose cure would still be an advantage, but the risk-benefit calculation would be different. The challenge for drug development is three-fold. Without a molecular biomarker for ‘artemisinin resistance’, it is difficult to assess currently how many people fall into this high-risk group. Second, in any case, there are no models showing how the population which cannot be effectively treated with ACT will develop over the next decade. Third, currently there are not sufficient numbers of patients with reduced parasite clearance rates to enable clinical studies of new therapies, and in any case the public health priority is to eliminate the parasite in these regions.

After considerations of safety and efficacy, the principal concern for a SERCaP will be to avoid the development of resistance. If the SERCaP is to help in driving malaria eradication it would be best if it did not have to be regularly ‘upgraded’, as happens with many vaccines against common bacterial or viral pathogens, and some drugs too. To avoid resistance, the key is to make sure that no one molecule is exposed to a large number of parasites on its own. The way this is achieved with an artemisinin combination therapy is that the artemisinin analogue reduces the parasite numbers by at least 4 log units over a three-day course, though this still leaves a maximum of $10^8$ parasites for the partner to face alone. The closest current gold standard combination against which to judge a SERCaP would therefore be an ACT plus primaquine (to prevent transmission). This is a combination of TCP-1, -2 and -3b. However, an ACT plus primaquine fails to meet the TPP because single dose primaquine does not prevent relapse. Other combinations are of course possible. The problem of leaving a partner to face the parasite alone is mitigated by having TCP1s with higher rates of parasite clearance than the artemisinins (clearly a major challenge) or extended durations of exposure (to ensure a greater overall reduction in parasite burden). The ultimate mitigation, however, is a strategy of matched pharmacokinetics and potency (for example a combination of two TCP-1 molecules plus a TCP-3, all with similar pharmacokinetic-potency characteristics). Clinical data suggests that logarithmic additivity in parasite killing activity should not be assumed with anti-malarial combination treatments: for example, the parasite reduction over time with artesunate-mefloquine is no faster than artesunate [58]. These observations are also reflected in in vitro measurements of the parasite reduction rate with combinations (L. Sanz, unpublished data). Thus, for compounds with matched pharmacokinetics where no logarithmic additivity is seen, both molecules are likely to need to achieve a PCR-corrected ACPR of greater than 95% as single agents. This additional stringency may make it difficult to identify suitable candidates. Should additivity be observed, as a result of complementary stage specific action then the individual ACPR will be less. In addition, a combination of two short-acting molecules will provide poor post-treatment prophylaxis and hence not deliver a formal SERCaP; operationally this could be a major disadvantage in high-transmission areas. Another interesting question is whether the gametocyte-killing activity needs to be in the TCP-3 molecule; a TCP-1 molecule with additional anti-gametocyte properties would allow a TCP-1/3b, TCP-2, TCP-3a combination, for example. Although several of the new fast-killing TCP-1 candidates have highly potent activity against stage V gametocytes, it is not clear yet whether this is sufficient to block transmission in a clinically meaningful way. Artemether is an excellent killer of gametocytes in culture, but artemether-lumefantrine does
not successfully block transmission on its own, presumably due to the poor pharmacokinetics of the artemisinins [51,59].
MMV’s Target Candidate Profiles (TCPs) define a stringent set of biological attributes to select and prioritize NCEs.

<table>
<thead>
<tr>
<th>Critical Attributes</th>
<th>Desirable Attributes</th>
<th>Current Gold Standard</th>
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</table>
| **Fast Parasite Clearance** | • Minimum 99.9% parasite clearance over 48 hours  
• >6 log total parasite reduction | Artemisinin |
| **Long Duration** | • Time > MPC* critical  
• >80% ACPR Day 28 monotherapy  
• Delivers >95% ACPR Day 28 when combined with TCP1 | 4-aminoquinolines |
| **Transmission Blocking/Relapse Prevention** | • Gametocytocidal activity  
• Hypnozoitocidal activity  
• Vector-stage activity** | Primaquine |
| **Chemoprotection** | • Liver schizontocide  
• Slow onset asexual blood stage  
• Supports 1x/ month use (min.: 1x/ week)  
• High safety  
• Vector-stage activity to deplete mosquito reservoir  
• Gametocytocidal activity  
• Orthogonal MoA to minimize resistance development to drugs used for treatment | Atovaquone/ Proguanil/ Mefloquine |

*Minimum Parasitcidal Concentration

Delivering a molecule that will remain in human blood for as long as mature gametocytes circulate is extremely challenging in the absence of a rapid gametocytocide; therefore, vector-stage parasite killing is seen as a desirable rather than critical activity.
Figure 4

Asexual stage (human blood cell)

A Liver-stage schizonts
B Blood-stage schizonts
C Gametocytes
D Micro- and macro-gametocytes
E Ookinetes
F Oocysts
G Sporozoites

TCP-3/4

Transmission to man

TCP-1/2/3

Transmission to man

TCP-3

Sexual stage (mosquito gut)
<table>
<thead>
<tr>
<th>Areas where current treatments are ineffective</th>
<th><strong>One day</strong> therapeutic efficacy safely achievable</th>
<th><strong>Three day</strong> therapeutic efficacy safely achievable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High compliance</td>
<td>• Back up therapy when all existing ACT fail</td>
<td></td>
</tr>
<tr>
<td>• Directly observed therapy</td>
<td>• No need for compliance advantage</td>
<td></td>
</tr>
<tr>
<td>• Need to show activity in defined artemisinin</td>
<td>• Need to show activity in defined artemisinin-resistant strains</td>
<td></td>
</tr>
<tr>
<td>resistant strains</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Areas where current treatments are still effective</th>
<th>• Limited interest to replace ACTs where they are still active</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High compliance</td>
<td>• Potential advantages could be significant decrease in cost of goods and in stability in Zone IV conditions</td>
</tr>
<tr>
<td>• Potential low cost of goods</td>
<td></td>
</tr>
<tr>
<td>• Challenge to position with respect to well established therapies</td>
<td></td>
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</tbody>
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