roundtable discussion with recent MSc and PhD graduates successful in careers beyond academia. We find it useful to conduct some of this training at the annual off-site 2-day bootcamp, where trainee and faculty members participate in all activities.

How Does the HPI Program Operate?

Initially, student scholarships from the NSERC-CREATE grant provided some leverage to encourage faculty and trainee engagement. Whilst this was a valuable catalyst to kick-start the program, it was not a sustainable model for continued success. The HPI Program remains vibrant beyond the original grant-term due to the enthusiasm and engagement of trainees and faculty. The trainees recognize the opportunities provided by the Program and operate in volunteer mode to keep the group active on numerous fronts. The faculty recognizes the benefits to their students, their research programs, and the enhanced profile of parasitology at their institutions.

The driving force behind HPI Program activities is the trainee operations committee on which membership rotates annually to ensure leadership opportunities and committee work experience for the maximum number of trainees, with administrative support provided by the program manager (Figure 1A).

Community Engagement as a Professional Development Tool

Another emphasis of the HPI Program is community engagement and education; this has been a stellar success, reaching over 20 000 members of the community, of all ages, over the past 7 years. Effective communication is paramount in any career, and scientists often have a less than flattering reputation in their ability to relay science to a lay audience. Sessions with experts in science communication made it clear that it is an emotional connection with an individual/audience and not bombardment with facts that resonates with the public. The trainees developed a series of interactive modules (games, specimens, displays) they use to convey the sophistication of parasite life cycles, anthelmintic resistance, and the impact of parasites on the individual and ecological health to schoolchildren and the public. One signature event organized and delivered by HPI trainees was at the TELUS Spark Science Centre in Calgary that was attended by ~1250 members of the public even though it was at 7–10 p.m. in mid-January! The response to these outreach events has been overwhelming. The trainees grew in confidence, and many became adept at stimulating a curiosity about how parasites affect the world around them. Event organizers and teachers are keen to have continued participation of the HPI Program trainees (faculty mentors attend events for moral support as the trainees deliver the material in an accessible way). Watching the public enthuse (or recoil) in wonder and amazement that swimmers itch is because of a juvenile schistosome, or that the masterful regulation of host immunity by helminths could be exploited to treat autoinflammatory disease, underscores to the trainees the value of their research.

Concluding Remarks

Globalization, environmental, societal, and climate change, and emerging – and in some cases widespread – drug resistance are making parasitic diseases in humans and animals increasingly relevant and problematic. Advanced research in these areas requires motivated, highly qualified personnel that can convert the benefit of their training into successful careers of their choice. The HPI Program was not designed to solve the problem of parasitic infections; rather, we sought to build community, enhance the graduate experience, and provide students with transferable skills training to follow any chosen career path. Parasitology can be invigorated by the recruitment of high-caliber trainees who will enhance the visibility of the discipline and keep parasitology at the leading edge of innovative research – for this to happen, the trainee's needs, beyond their parasitological expertise, must be held as the primary objective.

Acknowledgments

Financial support for the HPI Program from NSERC CREATE and the Office of the Vice-President Research, the Cumming School of Medicine, the Faculty of Science and the Faculty of Veterinary Medicine at the University of Calgary is gratefully acknowledged.

Resources

[i]www.ucalgary.ca/hpi/
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https://doi.org/10.1016/j.pt.2019.05.001

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Spotlight

Bed Nets, Insecticides, and Antimalarials: Where to Next?

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Insecticide-impregnated bed nets have saved millions from fatal malaria, but their effectiveness is

waning due to mosquito insecticide resistance. A new strategy (Paton *et al.*, *Nature*, 2019) to deliver parasiticidal compounds into mosquitoes to kill transmission-stage parasites could enhance the effectiveness of bed nets and get around the perennial problems of resistance.

Bed nets impregnated with insecticides have drastically reduced malaria infections and deaths. By reducing the number of infectious bites incurred, and/or killing infected mosquitoes responsible for transmission, bed nets have saved nearly 7 million people between 2000 and 2015, which is about 1200 per day [1]. But the decline in malaria cases has stalled in recent years [2], and mosquito resistance to insecticides in the bed nets is largely to blame [3]. To break through this plateau of malaria reduction, and continue the drive to eradication, new strategies for blocking transmission are needed.

Selection for resistance is an almost inevitable consequence of trying to combat a biological agent with chemicals. Any individual that survives our chemical assault has a greater chance to contribute to the next generation and pass on the trait(s) that allowed it to survive. Therefore, the rise of resistance is not so much a matter of 'if', but 'when'? Late-acting insecticides – which would reduce selection for resistance yet still block parasite transmission by preferentially killing old mosquitoes – are on the horizon [4], but insecticide toxicity and environmental considerations oblige us to pursue additional transmission-blocking strategies.

One widely publicized transmission-blocking strategy is to deploy a gene drive to push traits rendering mosquitoes immune to malaria parasites into the entire population of malaria-transmitting mosquitoes [5]. Gene drives hold great promise but still face significant biological, technical, and regulatory hurdles before they can be deployed [5]. Another strategy is to deliver a chemical or antibody into the mosquito that blocks parasite development within the invertebrate host. Mosquitoes take up relatively large volumes of blood when feeding, so it is feasible to deliver a chemical or antibody to the insect from the plasma of the individual being bitten. Several different drugs and vaccine strategies have shown promise as transmission-blocking treatments, but they all face ethical and compliance hurdles. To be effective, the transmission-blocking drug or vaccine would have to be mass administered, but it would not provide a direct benefit to the individuals receiving the treatment. Rather, the benefit is to their community, which would enjoy reduced transmission of malaria. Is it ethically sound to treat people solely for the good of others, and how do we convince them to take 'medicine' that they do not directly benefit from – particularly if there are real or perceived side effects? For these reasons, transmission-blocking activity is mainly viewed as a desirable side-benefit of new drugs targeted primarily against asexual blood-stage parasites [6]. But what if we had a potent compound that killed mosquito stages of the malaria parasite and had no action on the asexual human blood stages? Is there a way to ethically and safely deliver such an antimalarial? A new publication from the Catteruccia laboratory [7] offers a tantalizing solution.

Paton *et al.* tested delivery of antimalarials directly to mosquitoes via coated surfaces [7]. Mosquitoes were allowed to rest on bed-net-like surfaces treated with the antimalarial compound atovaquone whilst feeding on *Plasmodium falciparum*-infected blood [7]. Even brief exposure to small amounts of atovaquone decimated the malaria parasites in the insect gut [7]. Atovaquone is apparently taken up through the legs of the mosquitoes and conveyed to the insect midgut, where it rapidly aborts parasite development [7]. Other surface-deployed drugs also performed well in preventing *P. falciparum* infection of mosquitoes, suggesting that this strategy might be widely applicable and could well abrogate transmission in the field [7]. Parasiticidals can thus be delivered directly to mosquitoes via nets, baits, or even wall coatings [7]. Surface delivery promises to be a devastating new weapon in the fight against malaria, especially considering that surface-delivered parasiticidals sidestep many of the problems that beset development of drugs for human use.

Of course, this new approach of targeting the parasite rather than the insect still faces the problem of resistance. But targeting mosquito stages, where parasite numbers are small relative to the abundance at blood stage, at least reduces the pool for selection. Atovaquone, the compound used on the bed nets [7], is a component of Malarone™, a successful antimalarial that abrogates mitochondrial electron transport [8]. The potency of atovaquone on mosquito-stage parasites makes sense because these stages rely heavily on mitochondrial electron transport to grow [9]. But atovaquone is very prone to parasite resistance [10]. Point mutations in the target gene, mitochondrial *cytB*, render parasites insensitive to atovaquone [10], and application as a surface-delivered antimalarial would likely select for further atovaquone resistance. Indeed, we believe this selection, which would act on mosquito-stage parasites, could have dire consequences. *cytB* mutations conferring atovaquone resistance in blood-stage parasites are not readily transmitted because they confer a serious fitness deficit in the mosquito stages of the parasite [11], which rely on robust mitochondrial electron transport [9,12]. Using atovaquone in bed nets would presumably drive selection for resistance mutations that maintain high levels of electron transport chain activity, which would allow the resistant parasites to survive in the mosquito

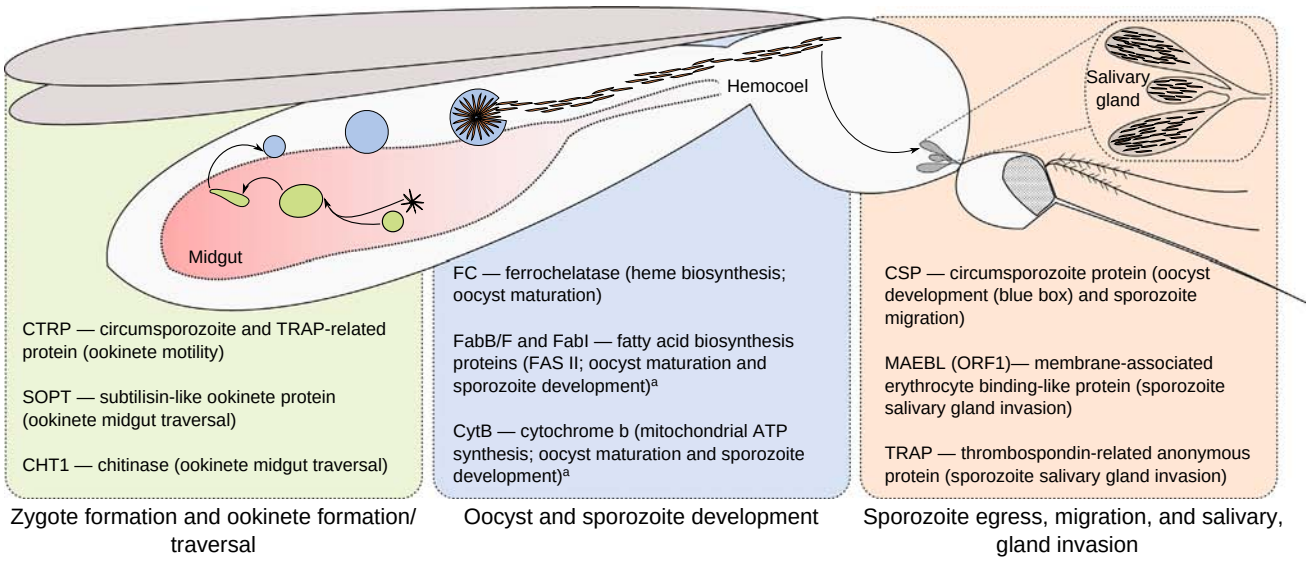

Figure 1. Essential Genes and Pathways in *Plasmodium falciparum* Mosquito Stages as Ideal Targets for Surface-Delivered Antimalarials. [a]Pathways/targets for which inhibitors are known. Surface delivery of parasiticidals to mosquitoes [7] could resurrect targets previously deemed obsolete or too difficult to pursue for drugs. The diagram depicts gene products/pathways essential for mosquito stages in *P. falciparum* but dispensable in asexual blood stages, and hence poor drug targets. Targeting parasite pathways essential for early (green box), mid (blue box), or late (orange box) stages of *P. falciparum* development in the mosquito by surface delivery of compound combinations would minimize resistance just as it does with combination therapies. Moreover, targeting pathways dispensable in asexual blood stages reduces the risk of selecting for 'super' parasites, as any potential transmissible escapees should still be susceptible to drugs that treat disease. Many more targets are known to be essential in mosquito stages of the rodent malaria parasite *Plasmodium berghei* but are yet to be validated in *P. falciparum* mosquito stages. Yet more targets for surface-delivered parasiticidals will likely emerge when genes identified as nonessential during asexual blood stages in *P. falciparum* are characterized across the life cycle.

host and likely undergo transmission – a very undesirable outcome.

Paton *et al.* acknowledge that atovaquone is not a suitable compound to douse bed nets with, and they encourage a search for safe, stable, low-cost compounds with which to hinder mosquito-stage parasites [7]. Indeed, surface delivery allows us to think outside-the-box when considering targets (Figure 1). For instance, apicoplast fatty-acid biosynthesis, which is nonessential in asexual blood stages, and hence not a drug target [13], is essential for *P. falciparum* insect-stage development [14]. Perhaps the panoply of compounds inhibiting apicoplast fatty-acid biosynthesis [13] could be surface-delivered on bed nets. Similarly, the tricarboxylic acid cycle, mitochondrial ATP synthesis, and heme biosynthesis – all of which are insect-stage-essential but not currently the focus of drug development – could come into play as targets for surface-delivered antimalarials (Figure 1).

Eradication of malaria depends on multiple approaches to reduce parasites [6]. Bed nets have done a lot already. Enhancing them with suitable parasiticidal compounds should make them even more useful.

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https://doi.org/10.1016/j.pt.2019.06.009

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