AWARD NUMBER: W81XWH-15-2-0033

TITLE: Identifying New Chemical Entities that Treat and Prevent Relapsing vivax and Drug-Resistant falciparum Malaria in US Military Personnel

PRINCIPAL INVESTIGATOR: David A. FIDOCK

CONTRACTING ORGANIZATION: Columbia University
NEW YORK, NY 10032

REPORT DATE: OCTOBER 2019

TYPE OF REPORT: Annual report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland, 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2019	Annual	30SEP2018 - 29SEP2019

4. TITLE AND SUBTITLE

Identifying New Chemical Entities that Treat and Prevent Relapsing vivax and Drug-Resistant falciparum Malaria in US Military Personnel

5a. CONTRACT NUMBER
W81XWH-15-2-0033

5b. GRANT NUMBER
PR140137

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. David A. Fidock, Dr. Robert Campbell

E-Mail: df2260@columbia.edu; robert.f.campbell96.civ@mail.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

For Dr. Fidock: Trustees of Columbia University in the City of New York
630 W 168th St., FL 4, New York NY 10032-3725

For Dr. Campbell: Walter Reed Army Institute of Research Room 3A36A
503 Robert Grant Avenue, Silver Spring, MD 20910-7500

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland, 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our project aims to identify antimalarial compounds that are active against blood and liver stage of *Plasmodium* parasites and that have selectivity and pharmacological profiles that allow them to proceed as candidates for preclinical development aimed at developing new drugs to safely prevent or treat malaria in US Military personnel. We have made substantial progress with this project. We have now completed high-throughput screens against cultured *Plasmodium falciparum* asexual blood stages of 460,000 compounds from the National Center for Advancing Translational Sciences (NCATS) chemical library. From this we performed multiple validation assays with 4,300 compounds and tested 994 for activity against P*. berghei* liver stage parasites. 151 compounds were found to have submicromolar activity against blood and liver stage parasites and these were assayed against mammalian cells and also tested for pharmacological properties. From this extensive work, we now have six chemotypes that we have prioritized for medicinal chemistry and large compound analog studies are underway. We also have several back-up chemical series. We have extensive structure-activity relationship data for several compound series, and have identified improved compounds. We have also identified several drug targets including BC1 and DHODH. compounds that have improved potency and developing structure-activity relationships including one series that has desirable pharmacological properties of solubility, potency, stability and membrane permeability. Our intent in the coming year is to identify compounds that will serve as leads for further preclinical work.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	12	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents (numbers will be revised)

1. Introduction:

The goal of this project is to identify novel chemical compounds that are active against the blood and liver stage forms of malaria parasites and that are useful for both prophylaxis and treatment of *Plasmodium vivax* and *Plasmodium falciparum* infections. Malaria has been identified as one of the most significant threats to deployed troops worldwide. This disease is endemic to Southwest Asia including Afghanistan, Southeast Asia, Africa, the Middle East, the Pacific, and both Central and South America. The project combines expertise from Columbia University as the Initiating Institution, the Walter Reed Army Institute of Research (WRAIR) as the Partnering Institution, and the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) as a subsite affiliated with the WRAIR award. These teams combine chemistry, pharmacology and molecular and cellular parasitology to pursue a "hits to lead" program, whose primary objective is to generate and characterize compounds that could be developed into new medicines to treat and prevent malaria in US Military personnel.

2. Keywords:

Malaria, *Plasmodium falciparum*, asexual blood stages, liver stages, high-throughput screen, drug assays, cell culture, prophylaxis, *P. cynomolgi*.

3. Accomplishments:

3.1. Major Goals:

Our accepted statement of work (SOW) listed the following specific aims and tasks as part of our Year 4 work:

Specific Aim 1: Perform a high throughput screen (HTS)-based identification of antimalarial compounds. Our Major Tasks 1.1 and 1.2 from Years 1-3 were to confirm initial 2,045 hits from the first screen of 250,000 compounds and to implement a HTS with an additional ~100,000 compounds and confirm hits. This was completed on schedule. By the end of year 3, we completed all of these screens, going beyond our original proposal by screening a total of 460,000 compounds and combining all hits from our two initial screens into a further set of validation assays that resulted in 2,496 hit compounds. Our Milestone for this Aim was to move our second set of confirmed hits into downstream screens, which we met in year 2 by testing our hits for activity against mammalian HepG2 cells in order to examine parasite selectivity. We also curated an additional 1,757 compounds from a previous screening at NCATS of the Molecular Libraries Small Molecule Repository collection. By the end of year 3, all hits compounds were validated by concentration dose-response assays and profiled for *in vitro* cytotoxicity against HepG2 cells, resulting in a set of 994 compounds for further downstream selection.

Specific Aim 2: Screen for inhibitors of rodent liver stage parasites *in vitro*. Our Major Task 2.1 was to identify compounds that selectively inhibit *P. berghei* liver stage parasites *in vitro* at submicromolar concentrations. Our first Subtask was to perform *in vitro* liver stage screens. Our second Subtask was to screen out non-selective compounds that inhibit HepG2 cells. Our timeline for this Aim was the first 15 months. We completed this work on time, screening ~1000 blood stage-active compounds against *P. berghei* liver stages cultured *in vitro* by Year 3. Our completed Milestone for this Aim defined a list of compounds with parasite-specific sub-micromolar *in vitro* liver stage activity. In total, we identified 151 compounds with >50% liver-stage inhibition when tested at 1μM. 81 hits were validated in dose response assays and identified 46 candidates with ≤1 μM IC_{50} activity. These screens were all fully completed and the data was analyzed by the end of Year 3 (**Figure 1**).

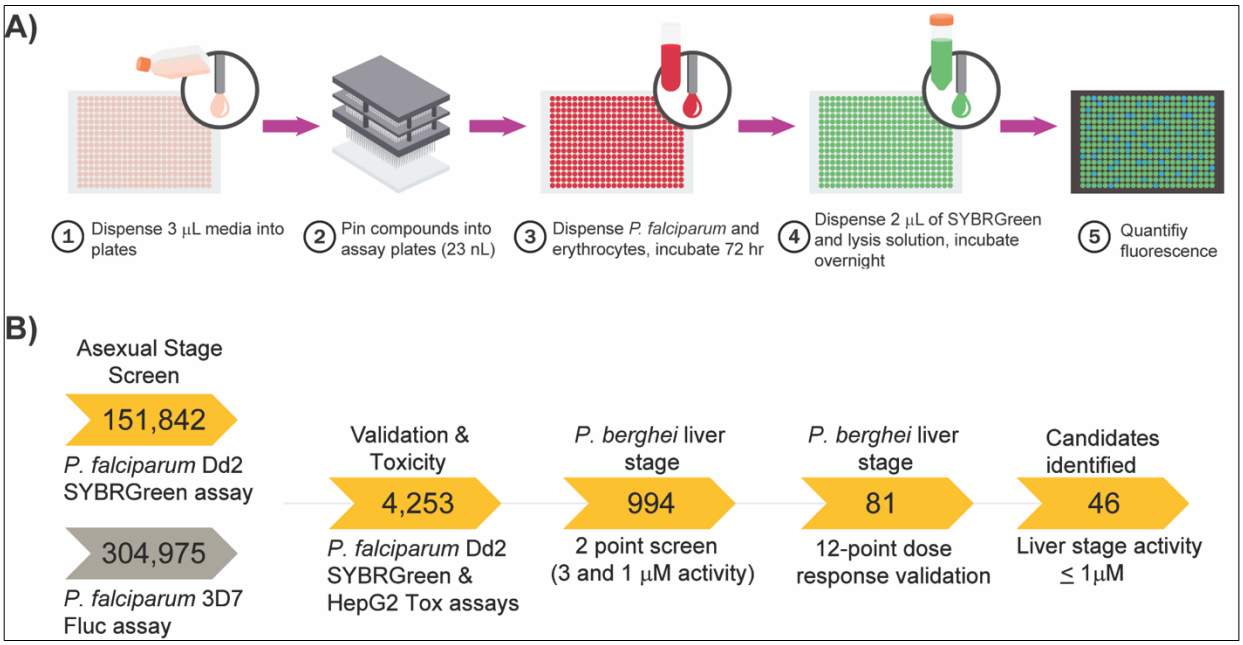

Figure 1. Schematic of screening cascade for 460,000 compounds screened against *P. falciparum* asexual blood stages, reducing to 46 compounds that were also potent against *P. berghei liver* stages and were parasite-selective without toxicity to HepG2 cells.

As part of our statement of work (SOW), we acquired IACUC and ACURO approval in Year 1. An ACURO document was submitted 10/29/2015 and approved on 12/28/2015, signed by Colonel Bryan Ketzenberger, Director of the Animal Care and Use Review Officer at the US Army.

Specific Aim 3: Test hits for *in vivo* prophylaxis and blood stage cure in rodents. Our Major Task 3.1 was to triage hits, assess toxicity and metabolism. Our first Subtask was to triage out known metabolic liabilities and toxicophores. Our second Subtask for the remaining pharmacophores was to assess toxicity and metabolism. Our Milestone for this work was to finalize a list of hits with acceptable pharmacophores. We successfully completed this work, and identified a set of six novel chemical series with dual blood and liver stage activity that merit further chemical investigation. Our Major Task 3.2 was to test hits for *in vivo* activity against *P. berghei* blood stages in mice. Our initial set of four *in vivo* candidates, which we confirmed to be non-toxic at the dosage, showed no *in vivo* activity in mice infected with *P. berghei* blood stages. We then decided that more emphasis needed to be placed on the medicinal chemistry and pharmacological profiling prior to selecting compounds for *in vivo* testing in mice.

Our Major Task 3.3 was to test hits for *in vivo* activity against *P. berghe*i liver stages in mice. Our Milestone for this Task was to define hits with evidence of *in vivo* curative and prophylactic activity, which we had estimated could be achieved by month 21. In the third year, we revised our work plan to devote more resources to pursuing medicinal chemistry to optimize our prioritized series. This involved synthesizing or commercially purchasing analogs, investigating the structure-activity relationships by examining *in vitro* potency against cultured *P. falciparum* asexual blood stage parasites, and measuring metabolic stability, solubility and membrane permeability. As described below, we have made strong progress in this area.

Specific Aim 4: Test down-selected hits for *in vitro* activity against *P. cynomolgi* proliferating and hypnozoite liver stages. Our Major Task 4.1 was to develop a *P. cynomolgi* assay at WRAIR for compound screens. Our Major Task 4.2 was to employ this assay for routine screening of our blood and liver stage hit compounds, as well as for our synthesized analogs of promising hit scaffolds. In Year 3 we made considerable progress and achieved this Aim by the end of Year 4 as described below.

Specific Aim 5: Optimize hits, evaluate derivatives *in vivo* and *in vitro*. Our Major Task 5.1 was to perform medicinal chemistry-based derivation of analogs and then perform pharmacological studies to assess toxicity and metabolic stability. Major Task 5.2 was to test analogs *in vitro* for activity against drug-resistant *P. falciparum* blood stages. These tasks were estimated to require continuous work through the end of our four-year project, where we were able to design and synthesize appropriate compounds from multiple series for SAR analysis. Our Major Tasks 5.3 and 5.4 were to test analogs *in vivo* for activity against *P. berghei* and *in vitro* against *P. cynomolgi* proliferating and hypnozoite liver stages respectively. Strong progress on these tasks has been made and we have identified sets of compounds, both from the initial primary screen and from the synthesized derivatives of the hits, which have been profiled in the *P. cynomolgi* assay. Furthermore, we identified two candidates with good solubility and rat microsomal stability that have been tested *in vivo* to assess their pharmacokinetic (PK) suitability for downstream *in vivo* efficacy screening.

3.2. Accomplishments made under these goals:

3.2.1. Major activities:

In Year 4, a major focus was on the optimization and selection of compounds to advance into *in vivo* efficacy studies. This involved the synthesis of analogues from selected series in order to improve potency, metabolic stability, permeability and solubility. We also prioritized compounds that potentially have novel modes of action and/or resistance or show unique mutations in known targets in resistance selection experiments. The data on our first two series, the thiadiazines and pyrimidine azepines, which showed mutations in cytochrome B in resistance selection experiments, has been consolidated and a manuscript describing the results and structure activity relationships has been prepared for submission within the next 1-2 months.

We have also made significant progress on the medicinal chemistry optimization of the triazoloquinazoline (TAQ) series. The hit compound from this series showed unique mutations in DHODH in resistance selection experiments. The medicinal chemistry team at NCATS has synthesized ~300 TAQ derivatives and have successfully optimized the potency of series down to ~15-115 nM, within the range comparable to DSM265, the frontrunner DHODH inhibiting antimalarial in clinical trials. A large SAR profile for this series with various structural position changes has been characterized with IC_{50}s ranging from 15 nM to >14 uM. Furthermore, solubility has been improved by the addition of a fluoro-substituent on the core or by changing the core phenyl to furan or thiophene in combination with a tetrahydroquinoline substituent to maintain potency. Metabolic stability and PAMPA permeability have also been measured for almost all our synthesized compounds, showing groups for which these properties are optimal and allowing for the design of analogues with optimized potency, solubility, permeability and metabolic stability.

In Year 4 we were able to achieve the desired properties to test two TAQ derivatives in *in vivo* mouse PK studies. These showed good exposure in blood and in the liver and were classified as suitable for an *in vivo* efficacy study.

One compound was tested in the IVIS liver stage efficacy experiment and the Modified Thompson Test blood stage experiment using the *P. berghei* ANKA strain, expressing a luciferase reporter and whole blood stage infection detected by luciferase positive IVIS imaging.

Compounds synthesized in Year 3 and 4 were also tested against the DHODH mutant parasite lines selected for in resistance selection experiments with the original hit TAQ compound. Cross resistance with these mutants was observed for the analogs, with increased sensitization to the C276Y mutant lines that are resistant to DSM265. This suggested that DHODH is the primary drug target for this series. For further validation, we have acquired recombinant PfDHODH protein, which will be employed in enzymatic DHODH assays for confirmation of mode of action for the TAQ and other series. Furthermore, a collaboration with the Seattle Structural Genomics Center for Infectious Disease is underway to solve the crystal structure of our TAQ inhibitors bound to DHODH and assess the binding site interactions.

Three TAQ compounds were tested for *P. berghei* liver stage potency and all three showed potent activity <0.22 μM and low HepG2 activity (>20 μM). These compounds, together with two from the thiadiazine series were submitted for an *in vitro* liver stage *P. cynomolgi* assay. Primary rhesus hepatocytes are used, which maintain metabolic activity for 40 days. The latter makes use of sporozoites from *P. cynomolgi* (B-strain) mosquitoes from AFRIMS, which are dissected to yield 80,000-200,000 sporozoites per mosquito. The test compound (with an 8-fold dilution) and sporozoites are added at the same time on day 0 for prophylactic mode, and treated with compound for three days. In radical cure mode, the drug is dosed after 5 days, and again dosed for 3 days. For each assay, media is changed daily with compound to excluded any drug metabolic activity from impacting the results. Imaging takes place on day 8 with an anti-GAPDH antibody. With the atovaquone control, no schizonts and only hypnozoites are seen by day 8. When primaquine (5 μM) is added as the positive control, no parasites are seen by day 8. This assay is carried out routinely at WRAIR. Six compounds showed 1.7-4.9 μM activity against *P. cynomolgi* schizonts in prophylactic mode, however no compounds were active at <10 μM in radical cure mode.

We also performed *in vivo* assays in mice to examine activity against asexual blood stages as well as liver stages. Results are presented below.

Blood Stage Thompson Test-WR930196-2

TT-98	Start date:	4-Nov-19		End date:	2-Dec-19								
Core Temperature (^{0}C)		Dose	11/4/19	11/5/19	11/6/19	11/7/19	11/8/19	11/11/19	11/12/19	11/13/19	11/14/19	11/15/19	11/18/19
Mouse #	LOT #	(mg/kg)	D3	D4	D5	D6	D7	D10	D11	D12	D13	D14	D17
1	VCX001-1	0	39.1	36.7	26.8	EUTH							
2	VCX001-1	0	38.5	38.5	38.5	32.5	EUTH						
3	VCX001-1	0	38.9	38.4	38.4	34.1	EUTH						
4	VCX001-1	0	39.1	38.3	38.6	35.8	33.2	EUTH					
5	VCX001-1	0	38.9	38.3	38.4	37.3	29.0	EUTH					
6	WR930196-2	80	38.8	38.7	37.3	37.7	37.9		38.5	37.4	38.0	39.2	EUTH
7	WR930196-2	80	38.8	39.1	37.7	28.7	EUTH						
8	WR930196-2	80	39.1	38.2	36.4	37.0	36.9		35.8	33.8	EUTH		
9	WR930196-2	80	38.8	38.3	37.9	38.2	37.2		37.1	37.4	34.5	EUTH	
10	WR930196-2	80	38.3	37.3	37.5	36.8	37.0		31.3	EUTH			
11	WR930196-2	40	38.4	38.4	37.3	37.5	37.0		FDIC				
12	WR930196-2	40	38.7	38.9	37.1	37.4	38.0		36.1	33.1	EUTH		
13	WR930196-2	40	38.1	38.5	37.4	38.0	37.4		36.7	35.9	33.4	EUTH	
14	WR930196-2	40	38.2	38.1	37.3	38.1	37.6		36.6	31.9	EUTH		
15	WR930196-2	40	38.9	38.3	37.8	37.8	36.9		35.0	EUTH			
16	TAF(WR238605-53)	30	39.2	38.1	37.6	37.5	38.2		38.9	38.8	38.6	38.1	
17	TAF(WR238605-53)	30	38.9	38.0	35.2	37.9	38.0		38.5	38.5	38.4	38.5	
18	TAF(WR238605-53)	30	39.3	37.8	37.4	37.1	37.6		38.5	38.6	38.5	37.5	
19	TAF(WR238605-53)	30	39.1	37.6	37.1	37.0	38.4		38.6	38.5	38.1	37.8	
20	TAF(WR238605-53)	30	38.7	38.1	37.6	37.6	38.1		38.3	38.5	38.5	37.7	

Mice 1-5 were infected but not treated, and were euthanized on days 6-10. Mice treated once daily for three days with the compound WR930196-2 (NCGC00600302-03) at 40 mg/kg or 80 mg/kg saw delayed progression of disease, but were not cured and required euthanasia. WR238605 is tafenoquine, which proved curative until the last day of observing the mice (day 17).

Liver Stage IVIS-WR930196-2

W-160. WR918137, WR918204, & WR930196 in B6 Albino female with iv 10K *P. berghei* luciferase SPZ

Test drug from Rob, Christina **Investigators:** Lisa, Jing, Qiang, Norma, Ping, Hsiuling, Tesfaye, Courtney, Diana, Qigui — Inoculation (D0): 10/29 — Dose 10/28-30/2019

					Regimen			Liver-stage		Blood Stage											
PR140137		Dose	BW	PO	10/28	10/29	10/30	10/30	10/31	11/1	11/4	11/6	11/8	11/13	11/15	11/20	11/22	11/27	11/29	Notice
5 µl = 1 qm BV	ID	mg/kg	g	µl	- D1	D0	D1	24h (D1)	48h (D2)	72h (D3)	D6	D8	D10	D15	D17	D22	D24	D29	D31	
					PO	PO	PO	IVIS	IVIS	IVIS	Flow Cytometry-Parasitemia (%)									
WR930196-2	W160-17	40	19.4	100	√	√	√	255400	627800	3741000	0.3	1.1	2.0	37	euth					
	W160-21	40	20.1	100	√	√	√	1593000	9496000		0.6	1.7	5.1	23	euth					
	W160-22	40	21.4	110	√	√	√	0	0	0	0	0	0	failed in infection.						
	W160-29	40	22.8	115	√	√	√	760400	1550000	5969000	0.1	1.3	1.2	30	euth					
	W160-39	40	18.2	90	√	√	√	1891000	4872000	15440000	0.9	1.4	3.1	22	euth					
								-46.4	-93.9	-98.4										
WR930196-2	W160-4	80	18.7	95	√	√	√	124400	313900	1558000	0.2	0.8	3.2	41	euth					
	W160-14	80	20.3	100	√	√	√	393700	703000	1616000	0.2	0.9	7.0	38	euth					
	W160-26	80	18.8	95	√	√	√	244500	1287000	4844000	0.4	2	3.6	18	euth					
	W160-34	80	18.4	90	√	√	√	366600	0	1333000	0.3	0.2	1.3	43	euth					
	W160-36	80	21.5	110	√	√	√	707100	1002000	2982000	0.3	1.2	13	euth						
								-78.1	-98.8	-99.2										
WR181023-7 BE50003 PC	W160-3	5	18.2	90	√	√	√	0	0	0	0	0	0	0	0	0	0	0	0	euth
	W160-15	5	20.3	100	√	√	√	0	0	0	0	0	0	0	0	0	0	0	0	euth
	W160-18	5	20.2	100	√	√	√	0	0	0	0	0	0	0	0	0	0	0	0	euth
	W160-25	5	18.3	90	√	√	√	0	0	0	0	0	0	0	0	0	0	0	0	euth
	W160-37	5	18.2	90	√	√	√	0	0	0	0	0	0	0	0	0	0	0	0	euth
								-100	-100	-100										
VC	W160-1	0	18.3	90	√	√	√	1510000	46700000	237100000	4.6	7.2	euth							
	W160-2	0	18.5	90	√	√	√	576000	23020000	97630000	3	5.6	8.7	40	euth					
	W160-7	0	16.3	80	√	√	√	2723000	113200000	678600000	6.2	euth								
	W160-13	0	16.6	85	√	√	√	1605000	2729000	8906000	4.3	5.7	euth							
	W160-19	0	17.7	90	√	√	√	1978000	86000000	577900000	4.4	6.7	19	41	euth					
								1678400	54329800	320027200										

Mice treated with WR930196 saw a slight delay in progression of blood stage infection following drug treatment, however protection was not achieved. WR181023 is an analog of primaquine that provides prophylactic protection in these conditions.

3.2.2. Specific objectives: Our major objective for Year 4 was to pursue an in-depth hit to lead campaign with our prioritized list of chemotypes, with the goal of identifying compounds that are potent *in vitro* against *P. falciparum* asexual blood stages and *P. berghei* liver stages. Our experiments have investigated structure-activity relationships in two main series, the thiadiazines and TAQs, allowing us to improve pharmacological properties via chemical optimization. Our goal was to produce and characterize compounds for *in vivo* testing in blood stage *P. berghei* models and most of our efforts were centered on trying to generate lead compounds from the TAQ series. Another aim was to test promising candidates in the newly available *P. cynomolgi* liver stage assay. Several batches of compounds from both our primary hits and synthesized thiadiazine or TAQ derivatives were successfully tested in this assay.

3.2.3. Significant results and key outcomes: These are described above.

3.2.4. Other achievements: Nothing to report.

3.3. Training and professional development opportunities: Nothing to report.

3.4. Dissemination of results to communities of interest: We presented this project to the JPC-2 MIDRP In-Progress Review (IPR) on 4 April 2017, at Fort Detrick, MD. Review officers included Colonel Michael P. Kozar, Ph.D, MT(ASCP), Director, Military Infectious Diseases Research Program Chair, Joint Program Committee-2 Military Infectious Diseases Assistant Corp Chief for Medical Allied Sciences, US Army Medical Service Corp, and CAPT David J. Bacon, Ph.D., MSC, US Navy Liaison Officer. I gave the presentation, with my partnering PI LTC(P) Waters in attendance as well as key personnel from WRAIR (Drs. Mark Hickman and Rick Sciotti) and NCATS (Dr. Bryan Mott) in attendance.

3.5. Plans during next reporting period to accomplish goals: We have requested an extension until 31 March 2020 to conclude our lead optimization program aimed at obtaining compounds that display antimalarial potency in mice and that demonstrate potent activity against *Plasmodium* liver and blood stages. We also need to conclude our two manuscripts in progress.

4. Impact:
4.1. Impact on development of principal discipline of the project: Nothing to report.

4.2. Impact on other disciplines: Nothing to report.

4.3. Impact on technology transfer: Nothing to report.

4.4. Impact on society beyond science and technology: Nothing to report.

5. Changes/Problems:
5.1. Changes in approach and reasons for change: Nothing to report.

5.2. Actual or anticipated problems or delays and actions or plans to resolve them: Nothing to report. We are on track with our statement of work, timeline and milestones.

5.3. Changes that had a significant impact on expenditures: (needs updating once numbers come back from Geneva) No major changes.

5.4. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to report.

6. Products:

6.1. Publications, conference papers and presentations: One manuscript describing the HTS and screening results is nearly ready for submission, and another describing the medical and synthetic chemistry behind our two lead series is being prepared. .

6.2. Websites: Nothing to report.

6.3. Technologies or techniques: This project has enabled NCATS to optimize their quantitative HTS studies with cultured *P. falciparum* asexual blood stage parasites that allows them to derive IC_{50} values for hundreds of thousands of compounds in a period of several months. These data provide this project with an outstanding set of novel compounds to drive our malaria drug discovery program.

6.4. Inventions, patent applications and/or licenses: Nothing to report.

6.5. Other products: Our project shares and regularly updates a Master file that lists compound structures and names, blood and liver stage activity, IC_{50} values for parasites and HepG2 cells, and pharmacological properties (metabolic stability, permeability and solubility). We also have compound potency data for four *P. falciparum* strains: D2, W2, C235 and C2B, which include mechanisms of resistance to chloroquine, atovaquone, pyrimethamine and mefloquine. We have produced DNA plasmids that have generated recombinant *P. cynomolgi* parasites for assessment of compound activity against proliferating or hypnozoite liver stage parasites.

7. Participants & Other collaborating organizations:
7.1. Individuals that have worked on the project:

Name	David Fidock (CUMC). ORCID 0000-0001-
Project role	Initiating PI
Nearest person month worked	2
Contribution to project	Led project, organized monthly teleconference calls and distributed
Funding support	CDMRP, NIH, Bill & Melinda Gates

Name	Kathryn Wicht
Project role	Postdoctoral Scientist
Nearest person month worked	3
Contribution to project	*In vitro* parasite studies with compounds and assisted with compound analysis
Funding support	CDMRP, NIH

Name	Judith Straimer
Project role	Postdoctoral Scientist
Nearest person month worked	1
Contribution to project	Molecular biology on *P. cynomolgi* plasmids
Funding support	CDMRP, NIH

Name	Dr. Robert Campbell
Project role	Senior Medicinal Chemist
Nearest person month worked	12
Contribution to project	Performed pharmacologic and efficacy studies with active compounds
Funding support	WRAIR

Name	Juan Marugan (NCATS)
Project role	Project manager at NCATS subsite
Nearest person month worked	1
Contribution to project	Managed project resources including personnel and lab operations
Funding support	NIH/NCATS

Name	Daniel Jansen
Project role	Staff chemist
Nearest person month worked	12
Contribution to project	Performed compound synthesis, managed compound procurement and
Funding support	NIH/NCATS

Name	Richard T. Eastman
Project role	Postdoctoral Scientist
Nearest person month worked	2
Contribution to project	Tested compound efficacy against
Funding support	NIH/NCATS

Name	Katie Pohida
Project role	Post Baccalaureate fellow
Nearest person month worked	6
Contribution to project	Performed compound synthesis
Funding support	NIH/NCATS

Name	Santha K. Tiruppadiripuliyur (CUMC)
Project role	Postdoctoral Scientist
Nearest person month worked	9
Contribution to project	Worked on *in vitro* parasite studies with compounds
Funding support	CDMRP, NIH

Name	Manu Vanaerschot
Project role	Postdoctoral Scientist
Nearest person month worked	6
Contribution to project	*In vitro* parasite studies with compounds
Funding support	CDMRP, NIH

Name	LTC Norman Waters (WRAIR)
Project role	Partnering PI
Nearest person month worked	1
Contribution to project	Managed WRAIR contribution to pharmacology and compound testing
Funding support	CDMRP and WOC

Name	Dr. Richard Sciotti (WRAIR)
Project role	Medicinal Chemist
Nearest person month worked	2
Contribution to project	Medicinal chemistry of promising hits
Funding support	CDMRP and WOC

Name	Wenwei Huang (NCATS). ORCID: 0000-
Project role	Partnering PI and Chemistry Lead at
Nearest person month worked	1
Contribution to project	Manged project resources and performed data analysis
Funding support	NIH/NCATS

Name	George Djorbal
Project role	Staff Biologist
Nearest person month worked	2
Contribution to project	Conducted high-throughput screens
Funding support	NIH/NCATS

Name	Alexey Zakharov
Project role	Informatics
Nearest person month worked	1
Contribution to project	Analyzed screen data
Funding support	NIH/NCATS

7.2. Change in active other support of the PD/PI or senior/key personnel since the last reporting period:

There are no changes in other support for either Drs. Fidock or Campbell since the time of the last annual report.

7.3. Other organizations involved as partners: Nothing to report.

8: Special reporting requirements:

8.1. Collaborative Awards: The Initiating PI Dr. David Fidock and the Partnering PI Dr. Robert Campbell are providing independent annual reports for this project (W81XWH-15-2-003 and W81XWH-15-2-0034 respectively). Each report has its own separate cover page, SF298 and quad chart.

8.2. Quad Chart: Please see next page. The quad chart for Dr. Campbell is provided in his separate report.

9: Appendices: None.