Non-invasive mobile phone diagnosis of malaria supported by an in vivo technique using aptamers conjugated with acridine orange

By

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Submitted to
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DECLARATION

I ARYANYIJUKA NOEL (14/U/127) declares that the content detailed in the research project report prepared under is part of the requirements necessary for the partial fulfilment of my Bachelor's degree in Biomedical Engineering at Makerere University Kampala (MAK). I affirm that the work in this report is original and has not been submitted anywhere.

Signature: .......................................................... Date: .................................................. 18-05-2018
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Signature: .......................................................... Date: .................................................. 28-11-2018
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ABSTRACT

Malaria is one of the parasitic diseases posing a large health burden in Uganda and other developing countries in Africa. Key efforts in handing the disease involve early and accurate diagnosis of the disease. Sadly, presumptuous treatment prevails especially in rural health units due to unavailability of light microscopy, a gold standard diagnostic technique recommended by World Health Organization. Several other researchers continue to uncover new diagnostic techniques and some of these are faced with several limitations as well. Nearly all the diagnostic techniques depend on invasive collection of blood so this research looks at development of a non-invasive technique that is painless and less technical compared to microscopic techniques hence leading to improved diagnosis of malaria.

Therefore, the aim of this research is to enable non-invasive malaria diagnosis by using a mobile phone. The research study will evaluate the ability to analyse fluorescence light emitted by Aptamers conjugated with acridine orange following that these Aptamers will be used to label malaria infected red blood cells in vivo. The approach to demonstrate the ability to use Aptamers that would bind to a specific malaria biomarker to permit malaria diagnosis will be carried out at the microbiology laboratory at Makerere University. Blood samples will be collected from patients at Mulago Regional Referral Hospital and these blood samples will be examined. Laboratory tests will be conducted in microbiology laboratory to test our hypothesis that: in vivo labelling of malaria biomarkers with fluorescent aptamers enables non-invasive diagnosis of malaria. The results obtained at the end of every method for the particular aims will be analysed.
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INTRODUCTION

Malaria is a life threatening disease that is caused by a parasite commonly known as Plasmodium [1]; the plasmodium parasite is transmitted from person to person through the bite of an infected Anopheles mosquito [2]. Malaria has historically been a serious health problem in Uganda with 90-95% of the population at risk [3]; and, major threat is posed to pregnant women and children under the ages of five [1]. The 2014-2015 Malaria Indicator Survey reported that the prevalence of malaria among children of ages 5 years and below was 19% when light microscopy was utilised, this prevalence was lower compared to the 30% prevalence obtained when Rapid diagnostic tests (RDTs) were used for this same assessment. The difference is majorly because RDTs detect the antigen to malaria parasites which may be present in blood even after the patient has been successfully treated. Additionally, a study conducted by Uganda Bureau of Statistics and ICF International in 2015 showed that malaria is responsible for 30 to 50% outpatient visits, 15 to 20 % admissions and 9 to 14% inpatient deaths[4].

Some of the malaria control strategies in Uganda include: early diagnosis and treatment, vector control and personal protection through use of insecticide-treated nets. Despite the numerous strategies undertaken by the Government of Uganda to manage the disease, it still causes a significant threat to people in Uganda especially due to the limitations faced in malaria diagnosis. Accurate malaria diagnosis is critical to avert any malaria fatalities and also prevent administration of antimalarial drugs that maybe unnecessary [5]. While several diagnostic modalities exist for example: light Microscopy and Rapid diagnostic Tests [5], they are each faced with several limitations so the health facilities in rural settings tend to over diagnose malaria patients [6]. This is because diagnosis in rural areas is based on the clinical presentation of fever and vomiting [7] which are traditionally considered as being equivalent to malaria [6].

The gold standard diagnostic modality recommended by World Health Organization which is microscopic examination of blood smears requires multiple conditions which are difficult to maintain in resource limited settings in Uganda [6]. This technique is challenged by lack of trained microscopists so over the last 15 years, numerous researchers have made effort to produce automated microscopy platforms. A complete automated microscopy system consists of: sample preparation, digital microscopy with automated scanning and a computer algorithm to analyse the captured images [5]. Reviews of this automated microscopy system indicate that different stain protocols are used which yields dissimilar images. The stain protocols may involve use of Giemsa stain or fluorescent stain. Furthermore, fluorescent staining shows better contrast therefore yielding better accuracy compared to Giemsa staining which is time consuming and inaccurate accuracy since the results depend on the skill of the microscopist [5, 8]. These two staining protocols will require the health personnel to invasively draw blood that will be used in the examination. This research takes the opportunity to combat the dangers and discomfort associated with drawing blood for examination thereby making staining of the malaria infected red blood cells in vivo such that diagnosis of malaria is non-invasive.

Rapid diagnostic tests (RDTs) were integrated into clinical guidelines to aid in malaria parasite diagnosis especially in malaria endemic countries. Rapid diagnostic tests utilise an immunochromatographic format to detect plasmodium antigens that is histidine rich protein 2 (HRP2) and lactate dehydrogenase (LDH). HRP2 is a water soluble protein produced by asexual stages and young gametocytes of plasmodium falciparum while LDH is an enzyme in the glycolytic pathway produced by all blood stage parasites. The performance of RDTs often results into false positives especially when using RDTs to detect HRP2. Also, the sensitivity of RDTs to a low parasite density below 100 parasites/μL of blood is problematic. In considering an antigen target to stain in vivo, we will look at attaining specificity for the lactate dehydrogenase which is a well-researched biomarker for malaria.
SPECIFIC AIMS

Globally, more than 400,000 malaria deaths occur and Africa carries 80% of this global malaria burden [3, 9, 10]. Therefore effective ways to diagnose malaria early and accurately are essential so that appropriate treatment is administered to relieve this malaria burden [11]. Research has shown that a class of nucleic acid molecules known as aptamers can be conjugated with fluorophores and that these aptamers bind with high specificity to selectively detect P.falciparum lactate dehydrogenase[12] in vitro. The possibility of in vivo detection of P. falciparum lactate dehydrogenase using aptamers conjugated with acridine orange which is a commonly used fluorescent dye [13, 14] has not been explored. Additionally, Acridine orange has affinity for the nucleic acid in the parasite nucleus so it attaches to the nuclei such that when excited by UV light at 490nm, the nucleus fluoresces strongly [15, 16]. And utilizing light to non-invasively excite the acridine orange conjugated to the aptamers, the fluorescent light emitted will be capture by a mobile phone [17, 18] hence this provides a painless and less technical diagnostic approach compared to microscopy. This technique also looks at improving point of care thereby improving detection rates and reduction in malaria fatalities.

The overall goal of this research is to enable non-invasive diagnosis of malaria thereby allowing visualization of the plasmodium parasites non-invasively using a mobile based device to address the challenges faced in remote areas such as poor laboratory infrastructure[8, 10] [19]. In line with this, we will develop a mobile phone based device that uses light to excite fluorophore labelled Aptamers attached to a malaria biomarker target and in this research, the fluorophore used is acridine orange. The following aims characterize the steps that will be involved in testing the hypothesis that: in vivo labelling of malaria biomarkers using aptamers conjugated with fluorophores enables non-invasive diagnosis of malaria.

Aim 1: To establish the adherence of Acridine orange coupled to aptamers in staining malaria infected cells

We will obtain plasmodium falciparum infected blood samples and load these with aptamers coupled with Acridine Orange at different concentrations [20, 21]. Fluorescent microscopy will be used to study the labelling of the aptamers with acridine orange and flow cytometry will be used to assess the binding affinity of the labelled aptamers in staining the malaria infected cells [22]. This will be done in vitro to determine the specificity and stoichiometry of this combination of aptamers and fluorophore (Acridine Orange) in staining malaria parasites [23].

Aim 2: To examine the excitation pattern of light and the malaria infected red blood cells stained with Acridine orange coupled to Aptamers

A light source will be used to produce monochrome light at different wavelengths to excite the aptamers labelled with acridine orange in the blood samples. This study will use fluorescent spectroscopy to study the absorption and emission patterns of the fluorescent labelled aptamers. Then Monte Carlo modelling will be used to model skin to understand the effect of other chromophores in skin on the absorption and emission of the Aptamers [24]. This is to understand quantitatively how much radiation will be required to penetrate skin to excite the fluorescent labelled aptamers as well as obtain an efficient emission.

Aim 3: To establish an approach to capture fluorescence non-invasively using a mobile phone.

Using an optical fibre probe, the emitted light will be collected and then creation of an algorithm to analyse the fluorescent light will be done. This extends to the design of the mobile based device capable of emitting light to excite Acridine Orange coupled to aptamers. The emissions given off will be captured non-invasively to progress malaria diagnosis which does not require blood and may be a step towards achieving home based diagnosis of malaria.
RESEARCH PLAN

Significance

The malaria cases following malaria infection have a comparable pattern and the 2017 world malaria report showed that in 2016, total of 216 million cases of malaria were documented which was an increase of 5 million cases over the previous year. The rate of deaths in this report was 445000 deaths and this number was the same as that reported in 2015[25]. Plasmodium falciparum is the most widespread malaria parasite in sub-Saharan Africa [26] and it continues to cause death especially in areas where parasite diagnostic testing is unavailable [25]. Diagnosis to detect malaria is complicated by several factors in poor resource areas [27] which often results in to malaria misdiagnosis [26]; malaria misdiagnosis is majorly because the clinicians base on symptoms such as fever [28] and this results in to overtreatment. This overtreatment exposes patients to unnecessary antimicrobial therapy that contributes to drug resistance [28]. The world Health Organization recommends detection of plasmodium parasites in patients as a step towards management of the disease [28].

Several approaches are utilised to diagnose malaria such as use of microscopy and rapid diagnostic tests (RDTs). However each of these diagnostic methods have limitations that contribute to persistence of malaria since early and accurate diagnosis is held up [29]. Microscopic diagnosis, though simple requires reagents and instrumentation such as microscopic slides, needles to extract blood, staining reagents for the case of fluorescence microscopy not forgetting skilled microscopists [28, 30]. With the absence of these supplies in rural settings [31], the World Health Organization introduced rapid diagnostic tests to overcome the absence of microscopic diagnosis. Rapid diagnostic tests are limited in their sensitivity as they are limited in detecting low density parasites [32]; additionally RDTs may not determine the magnitude of parasites in blood unlike microscopic diagnosis [28]. Whereas microscopy and RDTs rely on blood for detection of the disease, developments have been done to detect malaria infection non-invasively using urine and saliva. However, it is uncertain whether use of urine and saliva from malaria infected individuals is a representative of the parasite load in blood [29]. In addition, the use of urine and saliva shows moderate level of sensitivity compared to microscopy [29]. Alternative methods with higher performance are expensive often requiring specialized laboratories which do not exist in low and middle income countries [33].

This research looks at achieving a needleless diagnostic approach for malaria to reduce the risk of infection as well as the need for blood in malaria diagnosis. The risk of infection is present when needles are used to penetrate the skin which creates a pathway for pathogenic microorganisms into the body. Additionally, there is pain and discomfort associated with this invasive method and also a degree of allergic reactions to chemicals or materials used such as latex that may get in contact with the patient. Through our non-invasive technique, the need for high level of skill to accurately diagnose malaria will not be necessary. The non-invasive diagnosis will use a mobile phone to detect malaria parasites that are marked with a fluorophore in vivo. The implementation of mobile phone based diagnosis gives a simpler approach that is easy to use. Also, in our methods we look at integrating aptamers labelled with acridine orange to increase specificity in staining the malaria parasites. This is because research has shown that acridine Orange usage in fluorescent microscopy is nonspecific and stains nucleic acids from all cell types[16]. Hence our research results will broadly prove the hypothesis that Aptamers conjugated with fluorophores when attached to malaria parasites in vivo are capable of enabling non-invasive diagnosis of malaria. Clinically, this greatly improves the outcomes in the healthcare sector as malaria diagnosis is facilitated so that appropriate treatment is administered early.
Innovation

The development of Aptamers coupled with acridine orange, a known fluorescent dye used in malaria diagnosis to detect plasmodium falciparum lactate dehydrogenase will offer a noninvasive diagnostic modality that seeks to combat the dangers related with invasive diagnosis of malaria. Aptamers will be purchased from Archemix’s Stanton manufactures and these Aptamers will be chemically synthesized using the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process to generate specific Aptamers that bind to plasmodium falciparum lactate dehydrogenase [2]. Additionally, this possibility of staining plasmodium falciparum lactate dehydrogenase, a well-researched malaria biomarker with fluorescent marked aptamers will make the prospect of noninvasively detecting this malaria biomarker possible. For non-invasive imaging, the fluorescent dye labelled aptamers will be delivered using a capsule that can circulate in the body. Once in the body, controlled release of the aptamers will be done so that they bind to plasmodium falciparum lactate dehydrogenase in blood.

As far as non-invasively detecting this malaria biomarker targeted by the Aptamers, understanding the interaction pattern between light and the aptamers is key. The Aptamers coupled with acridine orange are able to fluorescence when excited by light so the light emitted back will be captured non-invasively and then analysed to enable diagnosis. This concept looks at utilizing a mobile phone that has an infrared filter on the camera side such that near infrared fluorescent light with wavelength of 650-950nm is produced to penetrate tissue. This light has good tissue penetration so it will excite the fluorescent marked aptamers and a sensor will be used to capture the emitted fluorescent light. The incorporation of mobile phones in this concept is to make diagnosis accessible to rural health facilities since mobile phones are slowly rising to take part in our healthcare system in Africa. In the long run, this technology will be used in home diagnosis as well as rural health facilities to address the lack of laboratory resources which often leads to misdiagnosis.

Approach

Study Setting
This research will be conducted at Mulago Regional Referral Hospital, which is located in Kampala City and doubles as a teaching hospital for Makerere University College of health sciences. The participants will be obtained from the hospital. After obtaining the samples, the department of medical microbiology at Makerere University will be utilised to do the experimental study. The medical microbiology department has various laboratories and these will be used: clinical Microbiology, Molecular Biology and Molecular Diagnostics. Clinical microbiology will be used to process and store blood samples. Molecular biology and molecular diagnostics laboratories will be used to synthesize the aptamers further and study the biological activity between the aptamers and plasmodium falciparum lactate dehydrogenase on a molecular level.

Study population
The population for this study will consist of two categories of individuals. These two categories will include: those who are infected with malaria and a control group consisting of those who are not infected with malaria. Socio demographic and laboratory data of these individuals will be collected from the hospital. Blood samples will be collected from a total of 40 participants. An inclusion criteria will be used to select participants who are between the ages of 20 and 40 years of age since this group may not require consent from their parents. An exclusion criteria will be used to exclude any participant that has an underlying disease that may compromise the diagnosis. Also if the patient has been on anti-malarial treatment within 24 hours prior to admission to the hospital, they will be excluded. The gold standard that is microscopy will be
used to detect the presence of malaria parasites in the blood samples. We look at having 20 samples that do not have malaria parasites and 20 samples that are infected with malaria parasites. Ethical approval for collecting the blood samples will be obtained from the Institutional Review Board of Makerere University and written informed consent will be obtained from all participants.

**Methods**

**Aim 1: To establish the adherence of Acridine orange coupled to aptamers in staining malaria infected cells**

This study is divided in two phases where phase one includes in vitro experimental study of the specificity of aptamers labelled with acridine orange in staining cells that are only infected with the malaria parasites. Aptamers are short synthetic single stranded DNA or RNA oligonucleotides which are specific and also have a high affinity binding to a target [34]. The binding process of Aptamers to their target is similar to antibody-antigen recognition and after interaction with the target, the aptamers fold into specific three dimensional structures [34].

**Sub aim 1: Aptamers binding to plasmodium falciparum lactase dehydrogenase**

Aptamers can be chemically synthesized and modified to bind with their specific target, here we will synthesize aptamers specific for the malaria biomarker plasmodium falciparum lactase dehydrogenase. So these DNA aptamers are designated by Systematic Evolution of Ligands by Exponential Enrichment (SELEX), a process of developing these oligonucleotide aptamers. The aptamer library has a complex of $1 \times 10^{15}$ different oligonucleotides and these will be exposed to plasmodium falciparum lactate dehydrogenase (pfLDH) and these will be incubated at 37 °C. The binding of pfLDH to aptamers will be observed dynamically using high speed Atomic Force microscopy. The aptamers that bind to this target biomarker will be separated using flow cytometry that is portioning of the unbound aptamer from the targetbound aptamer. The bound aptamers are enriched through PCR amplification to have a large pool. The generation of a larger pool provides enough aptamers so that the exposure to the pfLDH is repeated 10 times [35]. Three laboratories are documented to have worked on this technology: Larry Gold and Craig Tuerk at University of Colorado Boulder, Jack Szostak and Andy Ellington at Massachusetts General Hospital, and Gerald Joyce at The Scripps Institute in La Jolla, CA. Also a company known as Archemix’s Stanton manufactures custom aptamers at $50 or less per gram on manufacturing scale so we will obtain aptamers from this company.
Sub Aim 2: Aptamers labelling with Acridine Orange

Aptamers are flexible allowing their usage with fluorophores so in this case we look at Acridine orange and this acridine orange will be purchased from Tocris Bioscience. Since Aptamers are a class of nucleic acids, we look at using a coupling procedure based on a working Acridine orange acid staining procedure. Acridine Orange will be added to the aptamer specifically generated to mark pfLDH and this mixture will be incubated overnight at 4 °C [36]. Then an examination will be done using fluorescent microscopy to confirm the labelling of the Aptamers with acridine orange. The labelled aptamer sample will be stored at -20 °C until use [36].

Sub Aim 3: Transfer of aptamers labelled with Acridine Orange to malaria infected cells

The whole blood samples that will be collected will be grouped in two categories: blood with malaria parasites and the blood without the malaria parasites that will be used as controls. The aptamer pool (700ng) isolated to specifically detect pfLDH will be diluted with PBS buffer containing Calcium and Magnesium. Magnesium and calcium ions chelate the aptamer to form rigid structures for better binding to the target. The diluted aptamer will be heated to 95 °C for five minutes in an incubator to denature the Aptamers. After, cooling will be done to 4 °C for ten minutes to renature the Aptamers. This denaturation and renaturation procedure allows the aptamer sequence to form a unique secondary structure before binding to the target [37]. 500 μL of blood infected with the malaria parasite, 500 μL of the diluted aptamer and PBS buffer with Ca²⁺/ Mg²⁺ will be incubated at 37 °C for one hour [36, 37].

After incubation, 500 μL of PBS buffer at 37 °C will be used to suspend the RBC and Aptamers to wash away Aptamers that did not bind to Red blood cells. The mixture will be centrifuged for
5 minutes after which the unbound Aptamers will be discarded [37]. 20 samples of this will be done and in each of these samples, the concentration of the aptamer pool coupled with acridine orange will be varied. Another 20 samples of the blood not infected by malaria parasites will be used as the control and the same procedure will be followed. This concludes our overall aim in identifying the adherence of the acridine orange labelled Aptamers in staining malaria infected cells. The binding affinity of the aptamers will be assessed with flow cytometry and the same will be done with the controls so that the two categories of results are compared.

**Aim 2: To examine the excitation pattern of light and the malaria infected red blood cells stained with Acridine orange coupled to Aptamers**

The sample mixture solution containing blood stained with acridine orange coupled to Aptamers will be illuminated by excitation infrared fluorescent light. This light is of varying wavelengths and observations of the absorption and emission spectra will be measured by a fluorescent spectrometer at room temperature. The sample concentration will also be varied in order to evaluate any effect that this may have on the absorption and emission.

![Figure 2: Figure showing the experimental set up to be used in the study of the excitation patterns](image)

Under this aim, we also intend to understand the transfer of the emitted light within skin. Skin consists of different layers that the light must pass through since the overall device to be developed is non-invasive. Monte Carlo modelled skin will be used to understand the influence of skin structures and chromophores on light emitted or absorbed by acridine orange coupled with Aptamers when integrated in the skin model. Ultimately, the quantitative understanding of this will help to know the amount of transfer radiation needed to excite acridine orange coupled with Aptamers within skin. After understanding this, the next phase of this research will involve studies using animal models.

**Aim 3: To establish an approach to capture fluorescence non-invasively using a mobile phone**

In the in vitro study, an optical fibre probe will be used in acquiring the fluorescence. The fluorescence emitted at different concentrations of the aptamer pool will be measured using a sensor. The results will then be analysed to conduct complete diagnosis. This research will overall inform the design of the mobile phone based device that excites the fluorescent labelled aptamers; also this device will contain a sensor to capture the emitted light as it
attenuates and this light will be converted into signals that express diagnostic information. An algorithm will be needed to analyse the fluorescent light such that results of the parasite quantity in blood are obtained.

Table 1: Table showing the timelines for each of the activities to be executed within two years

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RESEARCH TEAM

PI Doctor Moses Kamya, is the professor and head of the department of Medicine at Makerere University College of Health Sciences. He has conducted malaria and HIV research at Makerere University for over 20 years and has more than 130 publications in this field. He also acts as a consultant on the Uganda Ministry of health Malaria Control Program and serves on several other programs.

Dr Robert Ssekitoleko, MEng. Doctor Ssekitoleko is a lecturer at Makerere University College of Health Sciences where he is in charge of the Biomedical Engineering course. He is also a biomedical Engineer with Uganda Maternal and New-born Hub. He continues to supervise and mentor various project teams at Makerere University in Biomedical Engineering mainly to develop medical equipment for low resource countries lie Uganda.
Mr. Calvin Abonga, Bsc. He is currently a lecturer at Makerere University where he offers mentorship in researches related to malaria. He also has particular experience in this area as he worked on a project focused on vector control as an intervention to reduce malaria transmission.

Noel Aryanyijuka, She is currently an undergraduate student at Makerere University pursuing a bachelor’s degree in Biomedical engineering. She has worked on developing affordable medical technologies especially for low and middle income countries. She is passionate about improving the healthcare system in Uganda thereby applying her engineering skills to solve community problems that are healthcare related.

RESOURCES AND ENVIRONMENT

This study will be conducted in two environments: the microbiology laboratory at Makerere University and Mulago Regional Referral Hospital. The microbiology laboratory has supported several research by undergraduates and other professionals in the area of malaria research. The laboratory also has state of art equipment that would be utilised in storing blood samples as well as carrying out the various laboratory experiments for this research. Then Mulago Regional Referral hospital is conveniently close to Makerere University where the microbiology laboratory is located and this is where the blood samples will be obtained from. The hospital also couples as a teaching hospital to support research especially student based research. Approval will be obtained from the Institutional Review Board of Makerere University. This approval is to ensure that the rights of individuals are not violated. Also, this approval will ensure that this research does not cause harm to the society and environment where the research will be carried out.
REFERENCES


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