

REPORT

SECTION 2

MALARIA INITIATIVE FOR AFRICA

“Gathering of Data on the Funding Mechanisms for Malaria Research and the Status of Malaria Research in South Africa”



Plasmodium falciparum model (measuring approximately 32"x20"x 7")
Created by Bill Burns
P. falciparum is responsible for the most severe form of malaria, including cerebral malaria. This model details an infected red blood cell whereby the vertical projection of the diseased part is exaggerated tenfold. Four species of protozoan parasites cause malaria in humans: Plasmodium falciparum, P. vivax, P. malariae, and P. ovale.

Date: October 2005

Dr Lorraine Thiel

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1 ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
ADME	Adsorption, distribution, metabolism and excretion
AMANET	African Malaria Network Trust
<i>An.</i>	<i>Anopheles</i>
ARC	Agricultural Research Council
MARA/AMRA	Mapping Malaria Risk in Africa
BioPAD	Biotechnology Partnerships and Development
BRICS	Biotechnology Regional Innovation Centers
BRTI	Biomedical Research and Training Institute
CBT	Cape Biotech Trust
CCM	Country Coordinating Mechanism
CSIR	Council for Scientific and Industrial Research
CRO	Contract Research Organisations
CSIR	Council for Scientific and Industrial Research
DANIDA	Danish International Development Agency
DGIS	Directorate-General for International Co-operation
DHFR	Dihydrofolate reductase
DNDi	Drugs for Neglected Diseases Initiative
DST	Department of Science and Technology
DTI	Department of Trade and Industry
ECoBio	East Coast Biotechnology Regional Innovation Centre
GLP	Good laboratory Practice
GMP	Good Manufacturing Practice
IOWH	Institute for One World Health
IKS	Indigenous Knowledge Systems
IND	Investigational New Drug Application
IPT	Intermittent Presumptive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide treated nets
LSDI	Lubombo Spatial Development Initiative
MIM	Multilateral Initiative for Malaria
MiTech	Missions in Technology
MMV	Medicines for Malaria Venture
MRC	Medical Research Council
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NICD	National Institute of Communicable Diseases
NIH	National Institute of Health
NRF	National Research Foundation
<i>P</i>	<i>Plasmodium</i>
PPP	Public Private Partnership
REDIBA	Research development initiative for black academics
RBM	Roll Back Malaria
R&D	Research and Development

RISA	Research and Innovation Support Agency
RPG	Research Project Grants
RU	Rhodes University
PPD	Product Process Development Scheme
RMCC	Regional Malaria Control Council
SANBI	South African National Biodiversity Institute
SATMERG	South African Traditional Medicines Group
SETI	Science, Engineering and Technology Institution
SME	Small and Medium Enterprises
SP	Sulphadoxine-pyrimethamine
SPII	Support Programme for Industrial Innovation
SU	Stellenbosch University
TAP	Technology Advancement Programme
THRIP	Technology and Human Resources for Industry Programme
UCT	University of Cape Town
UNICEF	United Nations Children's Fund
UP	University of Pretoria
USAID	US Agency for International Development
Wits	University of Witwatersrand
WHO	World Health Organisation
WHO/TDR	WHO Special Programme for Research and Training in Tropical Diseases

2 EXECUTIVE SUMMARY

Malaria is clearly a disease of poverty, and is commonly referred to as a “neglected disease”. These diseases also referred to as tropical or endemic diseases, affect millions of patients, but their lack of ability to pay for market-financed products results in insufficient market incentive to drive the development of innovative products by “Big Pharma”. The net effect is that only 10% of global R&D resources are directed at diseases, including malaria, that account for 90% of the global disease burden.

Reducing the burden posed by these neglected diseases will require increasing R&D for new drugs, vaccines and diagnostics. However, most pharmaceutical companies disengaged from research into tropical diseases in the 1970s, leaving a gap in the development of new and affordable tools to manage these diseases. The number of effective drugs to treat malaria is small; the few existing drugs are plagued by increasing resistance, particularly in the tropical regions, at a rate that outpaces the development of new antimalarial drugs. The most effective drugs used are combinations, which in the short term replace the ineffective drugs used today, and delay the development of resistance against any one of the individual drugs. These are however significantly more expensive than traditional antimalarials.

The public sector has long taken an interest in stimulating the discovery and development of new drugs, vaccines and diagnostics. A consolidated public-private and philanthropic approach, commonly known as public-private partnerships (PPP) has now replaced private sector investment in this market. The public-philanthropic sector provides funds to complement the R&D and other resources in the private sector. This new partnership approach, which operates through a virtual R&D methodology, brings many advantages coupled with many unique management and organizational challenges. The focus of these PPPs on neglected diseases, together with the availability of the malaria genome, is now believed to allow the full benefit of modern drug discovery research technologies to be applied to the development of improved drugs, vaccines and diagnostics for malaria.

The United Nations Development Programme, World Bank, and WHO special programme for research and training in Tropical diseases (WHO/TDR) was the first such organisation created in 1975, establishing a partnership between public sector organizations and private companies. This process has rapidly accelerated since the 1990s with the creation of the Medicines for Malaria Venture (MMV) and other such organizations. The MMV was the first organisation to put the theory of PPP drug discovery into practice and has initiated several virtual drug discovery projects. Other organizations managing public-private partnership malaria R&D include the Multilateral Initiative for Malaria (MIM), Drugs for Neglected Diseases (DNDi), Institute for One World Health (iOWH). These PPPs have structured themselves along the lines of industry practice with the goal of delivering to patients in developing countries new products and that meet unmet medical needs and that are appropriate and affordable. Central to this process is the concept of a product development team. The model is evolving as it is adapted to more projects, with numerous lessons being learned in the process, such as that a strong team spirit and commitment are vital when teams are operating at long distances.

Simultaneously, funds committed to malaria research have increased through national governments and philanthropic organizations such as the Gates Foundation. Overall, funds committed to malaria research have increased from an estimated \$ 85 million in 1995, to a level well over \$ 100 million. The National Institute of Allergy and Infectious Diseases (NIAID) increased its commitment by more than 150% between 1995 and 1999 and the Wellcome Trust doubled its expenditure. The Copenhagen Consensus

Initiative concluded that deploying effective malaria drugs had one of the highest cost-benefit ratios when opportunities for global investment across a number of segments were compared. The level of funding is however still believed to be low relative to the disease burden. A greater proportion of donor funding is allocated to the prevention, treatment, care and support of malaria in endemic countries. The global community has hence been urged to increase its funding for antimalarial R&D.

The Global Fund to Fight AIDS, Tuberculosis and Malaria is an international, independent public-private partnership which finances programmes for the prevention, treatment, care and support of AIDS, TB and malaria but does not implement programmes directly. Only a small proportion of the fund is for research. The Bill and Melinda Gates Foundation is a grant-making organisation with a mission to promote greater equity in global health. One of the Foundation's spearheads is the Global Health Programme focusing on poverty-related diseases including malaria. The largest proportion of the grants is on research to create and/or improve health tools such as vaccines, drugs, and diagnostics.

The National Institute of Health (NIH), an agency of the US Department of Health and Human Services, awards funds to research programmes concerning health issues such as malaria. NIAID, a component of the NIH, conducts and supports basic and applied research to better understand, treat and ultimately prevent infections. The US Agency for International Development (USAID), an American government agency, has a priority in the area of infectious diseases in the sustainable reduction of deaths due to malaria and the incidence of other infectious diseases of major public health importance. In addition to providing expanded support for prevention and control programmes, USAID supports the development of vaccines and new drug therapies for malaria. The support in development of new drugs is mainly in providing funding for clinical trials for new malaria treatment therapies.

The World Bank, a founding member of the Roll Back Malaria campaign, has been actively involved in efforts to reduce the burden of malaria globally. The Bank has declared malaria a corporate priority, but most involvement is in the area of control. In Africa there are currently more than 25 World Bank projects that currently provide support for malaria control activities. The Wellcome Trust is the world's largest independent medical research-funding charity that aims to improve human and animal health. The Wellcome Trust funds a broad spectrum of research on malaria including: genome sequencing, the biology of the parasite and mosquito, new vaccines and drugs, clinical research to improve treatment and to understand the pathology of the disease, disease transmission and epidemiology, health services research, and health policy research. The Trust also provides International Senior Research Fellowships for researchers from a number of countries, including South Africa.

The European Union (EU) funds research in member states and some other countries, and at the EU's own Joint Research Centre with the objective of building EU-wide platforms of excellence. Funding goes to projects that will benefit from a transnational approach, generally at least 2 of the participants must come from the EU member states, candidate countries or Switzerland. Projects must be integrated, involving a critical mass of scientific and industrial partners, and targeting significant products, processes or service applications. Grants can also go to EU participation in specific science and technology co-operation programmes set up jointly by certain governments or national research organisations.

There are also a number of funding agencies in the field of international development and co-operation, mostly linked to national governments. Agencies in this category include DGIS (The Netherlands), The UK Department for International Development (DFID), DANIDA (Denmark), and JICA (Japan). DFID for

example aims to fund research in four major themes, one of which is killer diseases. Within this area, DFID promotes public-private partnerships and multi-donor collaborations. DFID funds specific malaria knowledge programmes to develop the new generation of affordable drugs, rapid diagnostic kits and vaccine research.

In South Africa, most government funding for health research is through the Medical Research Council (MRC), a statutory council charged with conducting health research. It therefore plays an influential role in shaping health biotechnology as it identifies niche areas for development, focuses research efforts, and provides funding. The main objective is to produce science that results in improved health. It also carries out capacity development. Funding in malaria research in the MRC is through the Malaria Lead Programme.

The National Research Foundation (NRF) is the government's national agency responsible for the support of human resource capacity for research, technology and innovation in all fields of natural and social sciences, engineering, humanities and technology. The NRF therefore plays a critical role in the objectives of the National Research and Development strategy through educating and training scientists. Funding is largely directed towards academic research, developing high-level human resources, and supporting South Africa's national research facilities. In addition, other programmes managed by the NRF as a service provider, include the Innovation Fund, funded by the Department of Science and Technology (DST) and the Technology and Human Resources for Industry Programme (THRIP), funded by the Department of Trade and Industry (DTI). The Innovation Fund's core mandate is raising the level of competitiveness of the South African economic sector by promoting the commercialization of end stage research into tangible products and services. THRIP provides resources and mechanisms in support of collaborative research in the areas of science, engineering and technology. THRIP's priorities are funding mechanisms for students and staff, as well as women, black students and staff.

The Support Programme for Industrial Innovation (SPII), managed by the IDC on behalf of the Department of Trade and Industry, is designed to promote and assist technology development in South African industry through the provision of financial assistance for projects that develop innovative products and/or services. SPII is focused on the phase beginning at the conclusion of basic research and ends at the point where a prototype has been produced. The Department of Science and Technology has furthermore supported the creation of three biotechnology regional innovation centers to act as nuclei for the development of biotechnology platforms from which a range of new products and services can be developed. All three Innovation centers all of have human health as a portfolio: BioPAD (Gauteng), Cape Biotech Trust (Western Cape) and LIFElab (East Coast region).

Excluding the MRC malaria lead programme budget, CSIR parliamentary grant and funding through LIFElab, the annual funding of malaria research in South Africa is in the region of R 5 million. Most of this is directed at training of students, platform development and capacity building through the NRF and MRC. Whilst there are a number of programmes such as SPII, the BRICs and the Innovation fund directed at funding post "proof-of-concept", only two projects are being funded by this mechanism. This supports the conclusion by the 2003 Emerging Biotechnology Roadmap that there remains a substantial gap between innovation and commercialization.

It has been widely stated that the completed genomes of *Plasmodium falciparum* and the vector *Anopheles gambiae* open up new approaches to the development of drugs, vaccines, insecticides and insect repellents, as well as intervention into malaria transmission. In addition, advances in genetics

and biochemical engineering offer new and improved means understanding the dynamics and potential weak links in the complex interactive cycle of the malaria parasite and its vectors, and hence of characterizing potential targets. Bioinformatics tools can help predict the structure and function of gene products. The speed with which many compounds can be tested against protein targets has hence increased dramatically. Genetic tools will also allow the sampling of parasite, mosquito, and human genomes in malaria affected areas to support the malaria control activities. The Initiative has thus identified an opportunity and stated its key objective in the integration of researchers focusing on molecular aspects of malaria drug and insecticide discovery, molecular epidemiology and diagnostics, and capacity building in order to improve malaria prevention and control. Three programmes have been envisaged: the development of new and modified drugs and insecticides; the development and implementation of assays for epidemiological and diagnostic interventions; and capacity building programmes as a cross-cutting programme

Information relating to the malaria research currently being undertaken in South Africa in the various categories of interest to the Initiative was gathered. Vaccine development has therefore not been included. Four categories were included: epidemiology and diagnostic research, basic science, clinical studies, and training and capacity building. The summaries provided in the main body of the report clearly indicate that the majority of research groups in South Africa are involved in basic scientific research with most work directed at furthering the understanding of malaria cell biology, the cell biology of antimalarials, and the application of this research in the identification and validation of potential drug targets. Research projects involving medicinal chemistry, rational drug design and synthetic organic chemistry have also been identified. Very little research into the development of insecticides has been identified, with the only projects in this context being studies to detect novel compounds from indigenous plants that can be used as a mosquitocides, and the isolation of active ingredients from these plants.

Two groups, the MRC and NICD, are involved in epidemiological research. Research areas covered include the molecular identification and characterisation of mosquito vectors, molecular mechanisms of mosquito resistance to insecticides, biochemical basis of insecticide resistance and molecular mechanisms of drug resistance. One of the proposed MIA programmes is the application of molecular techniques to population studies and tracking of resistance through the application of molecular marker techniques to population studies and epidemiology. The focus will be on the movement of vectors and parasites, linked to trends in insecticide and drug resistance. This is already a core part of the research conducted by these two groups and hence the requisite skills already exist.

Two groups with interests in diagnostics have been identified, University of KwaZulu Natal (UKZN) and National Bioproducts Institute (NBI). NBI has developed a pair of monoclonal antibodies specific for HRPII that are suitable for use in a rapid diagnostic test. These antibodies are specific for *Plasmodium falciparum* and recognise different epitopes on this molecule. UKZN has developed an array of antibodies against anti-malarial drugs, which can be used to track malaria drugs in a range of cells, tissues and body fluids. Through an international collaboration in a MVI project, the team is developing reagents for a second generation of an ELISA diagnostic kit, the first generation being used as an experimental tool in malaria vaccine trials. Coupled with the complementary skills available in other MIA research groups, the development and implementation of assays for diagnostic interventions should be feasible.

The process of drug discovery and development involves a number of discrete stages, as does the process into insecticide discovery. However, due to the fact that there is currently very little research in

South Africa on the development of insecticides, this summary will focus on the drug development process. Mapping the activities of the current research programmes in South Africa against the range of skills and expertise required for the drug development process, indicates that whilst MIA has access to the full spectrum of scientific components required to discover and develop drugs and move from early discovery research through to preclinical and clinical development, some of these components are better developed than others. Most research projects are in the early stages of the process.

The following competencies relevant to the projects proposed by MIA are available in varying degrees that are: parasite biology and biochemistry, functional genomics, structural and computational biology, bioinformatics, medicinal chemistry, combinatorial chemistry, organic synthesis, analytical chemistry, high throughput biomolecular interaction analysis, high throughput *in vitro* screens, high throughput cellular/phenotype screens, national product chemistry linked to South Africa's biodiversity, animal models of malaria, ADMEtox testing of drug leads, development of formulations and delivery mechanisms, process development for large-scale development, and management of clinical trials.

The "genes to drugs" model needs more than the first step of basic exploratory biology on target identification. To convert validated targets into full drug discovery programmes, the use of upstream technologies such as genomics to identify targets, high-throughput screening, molecular modeling and screening and other techniques identified as being available in South Africa need to be optimally integrated with technologies such as medicinal chemistry, pharmacology and rational drug design in order to develop an early R&D pipeline. In addition, capacity in the downstream interface such as in the preclinical development phase needs to be enhanced and partnerships in the clinical development, dossier preparation and registration will have to be formed in order to strengthen this aspect of the development chain.

The integration and management of this entire process is critical for success in moving from discovery lead identification into drug candidates and finally through to a registered drug. Some elements of this integration have begun to be developed for example in the various collaborations between the University of Cape Town's Departments of Chemistry, Pharmacology and Institute of Infectious Disease and Molecular Medicine as well as the University of Stellenbosch and through the development of the national research and development platform for novel drug development from indigenous plants.

The efficacy and specificity of anti-malarial drugs rely on their ability to interfere with aspects of the metabolism of *Plasmodium* that differs significantly from the host. Parasite survival in the host erythrocytes requires several metabolic adaptations that render it susceptible to chemotherapy. Many potential drug targets have been identified based on an understanding of the cell biology of the malaria parasite. Whilst it has not possible within the scope of this report to outline all of these potential scientific opportunities, some are presented below in the main body of the report for indicative purposes only. Much of the research being conducted in South Africa falls within the context of many of these promising areas already identified.

The involvement of several academic and industrial partners in a virtual development model such as that proposed by MIA is relatively new, and involves a unique set of challenges. The model is however being followed successfully in the development of drugs and other tools to treat malaria by the PPPs internationally such as the MMV. Most of these organizations also recognize that the impact and long-term sustainability of drug R&D for poverty related diseases depends on the use of research capacity in developing countries. However, whilst a few of these countries have expertise in some of the scientific

components required, few have the capacity to perform all of the tasks necessary. As outlined above, South African has a core of excellent researchers and facilities in the malaria research field, a strong base in biomedical research, high-quality medical schools and a good infrastructure. Coupled with increasing financing for malaria research and involvement of various PPPs as outlined above, the prospect of the development of new, affordable drugs, diagnostics and insecticides in South Africa therefore appears to be a feasible opportunity.

A recent article in Nature Biotechnology stated that South Africa is poised to take the lead in developing health care biotechnology in the sub-Saharan African region. It recommended a good starting point as being the identification of a problem disease prevalent in the community and a technology that could be used to address this problem, and then to develop an infrastructure to support R&D in this area. Thus through its focus on malaria and the use of molecular technologies, MIA has identified a unique opportunity to position itself in sub-Saharan Africa and internationally through the integration and capacity building programmes as proposed in the initiative. Through applying the lessons learned by the PPPs in the establishment of a virtual development process, ensuring the optimization and focusing of its manpower, infrastructure and financial resources, coupled with careful management of the integration process, MIA should be well positioned to achieve success in its goals.

3 FUNDING INITIATIVES - INTERNATIONAL

3.1 INTRODUCTION:

Malaria is clearly a disease of poverty, and is commonly referred to as a “neglected disease”. These diseases also referred to as tropical or endemic diseases, affect millions of patients, but their lack of ability to pay for market-financed products results in insufficient market incentive to drive the development of innovative products by “Big Pharma”. The net effect is that only 10% of global R&D resources are directed at diseases, including malaria, that account for 90% of the global disease burden. Around the world, \$73 billion¹ annually is devoted to health research, and a mere \$ 100² million on malaria research.

Most pharmaceutical companies disengaged from research into tropical diseases in the 1970s, leaving a gap in the development of new and affordable drugs. As has been discussed in previous sections, the number of effective drugs to treat malaria is small. Almost all of the current drugs used today were developed over 30 years ago. The few existing drugs are plagued by increasing resistance, particularly in the tropical regions, at a rate that outpaces the development of new antimalarial drugs. The most effective drugs used are combinations, which in the short term replace the ineffective drugs used today, and delay the development of resistance against any one of the individual drugs. These are however significantly more expensive than traditional antimalarials.

Reducing the burden posed by malaria is thus generally agreed to require increased R&D for new drugs, vaccines and diagnostics. The pharmaceutical industry has advanced substantially in terms of its drug discovery and development process due to advances in molecular and structural biology, medicinal chemistry and the power of genomics and molecular genetics. Malaria research has therefore missed out on many of these opportunities. In order to overcome these shortcomings, new mechanisms have been established, involving a partnership between public and private sectors, together with a philanthropic approach to stimulate R&D for diseases such as malaria. This has resulted in what is now commonly referred to as public-private-partnership organizations (PPP). The public-philanthropic sector provides funds to complement the R&D and other resources in the private sector. The focus of these PPPs on neglected diseases, together with the availability of the malaria genome, is now believed to allow the full benefit of modern drug discovery research technologies to be applied to the development of improved drugs, vaccines and diagnostics for malaria.³

There are therefore two aspects to obtaining funds to perform R&D in malaria, either the provider of funds or the organizations that manage the research carried out within the PPP framework.

Overall, funds committed to malaria research have increased from an estimated \$ 85 million in 1995, to a level well over \$ 100 million. NIAID increased its commitment by more than 150% between 1995 and 1999. The Wellcome Trust doubled its expenditure. The level of funding is still believed to be low relative to the disease burden.⁴ The Copenhagen Consensus Initiative concluded that deploying effective malaria drugs had one of the highest cost-benefit ratios when opportunities for global investment across a number of segments were compared. The study calculated that US\$ 824 million annually for a package of interventions would be required to halve the malaria burden in sub-Saharan Africa by 2015. The direct economic benefit of this package would be US\$ 14 billion per year, an attractive cost benefit ratio of 17.⁵ The cost of R&D in context is therefore small on this global investment scale. This gap has been recognized by certain donors such as the Gates Foundation. The global community has hence been urged to increase its funding for antimalarial R&D.⁶

3.2 ORGANISATIONS MANAGING MALARIA R&D

Typically these organizations play a co-coordinating role in setting a disease-specific agenda, raising funds and managing the R&D projects. The strategy followed by the PPPs relies on market-based business models to simulate the development of drugs, whilst providing public resources to compensate for market failure. The aim is to bridge the existing R&D gaps in essential drugs for neglected diseases by initiating and co-coordinating R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners. This “virtual drug development” model minimises overhead costs whilst harnessing the existing but fragmented R&D capacity.

Most of these organizations issue a “call for proposals” from which to select projects. Selection of projects is through expert scientific advisory committee coming from both industry and academia, and covering the full range of expertise required to assess projects.

The public-private partnerships of relevance to malaria R&D are summarised below.

3.2.1 WHO/TDR⁷

The United Nations Development Programme, World Bank, WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) was created in 1975 following a World Health Assembly resolution. The TDR is housed within the WHO, which is also the executing agency. Its goals are to develop new tools and methodologies for control of ten target diseases and to strengthen research capacities in disease endemic countries. Projects are identified through calls for proposals and through networking of TDR scientists with others outside of the TDR network. The decision making process relies on technical and administrative advisory and governing bodies.

The organisation is funded mainly through international, government, and philanthropic contributions. TDR is co-sponsored by UNICEF, UNDP, the World Bank, and WHO. Other contributing partners are 23 governments/member states and 9 other foundations/agencies. The TDR budget for the 2004/2005 period is \$100 million. Of this budget, \$ 68 million is for operations, i.e. research in the form of research grants, contracts etc. Malaria accounts for the largest share of the operations budget i.e. 46.9% of this total or \$ 31.9 million.

TDR’s scope of activities includes the development of new and improved tools (drugs, vaccines, diagnostics, epidemiological and environmental tools) and new and improved intervention methods (for using existing tools). TDR’s research and training activities are organised into four functional areas. These are: (1) Strategic Discovery Research (2) Product Development and Evaluation, (3) Implementation Research and Methods, and (4) Research Capability Strengthening. In terms of the overall budget, 35.8% is spent on new and improved tools, 10.8% on new and improved methods, 20.1% on partnerships and capacity building, 9.6% on new and improved policies and strategies, and 7.5% on new basic knowledge. Technical information and management account for the balance.⁸

For more details of these workplans see the WHO/TDR web-site.

3.2.2 Multilateral Initiative on Malaria⁹

The Multilateral Initiative on Malaria (MIM) is an alliance of organisations and individuals concerned about the global burden posed by malaria. MIM recognised that the further development of human resources and institutional capacity in Africa is a fundamental requirement for establishing effective malaria control programmes. It aims to maximise the impact of scientific research against malaria in Africa, through the promotion of capacity building, and facilitation of global collaboration and co-ordination. MIM was launched in 1997, following the first Pan-African Malaria Conference where scientists from all over the world identified research priorities for malaria R&D.

A multilateral funding mechanism (MIM/TDR) was established at the TDR where MIM partners could directly contribute money for Research Capacity Strengthening in Africa in the form of peer-reviewed grants. MIM was subsequently broadened to include representative of industry and development agencies. Contributing partners include NIAID, The World Bank, WHO/AFRO, WHO/RBM, WHO/TDR, and Governments of Norway and Japan.

MIM/TDR Task Force supports research to strengthen African research groups. Membership of the Task Force comprises African scientists who are engaged in basic and/or applied science, investigators in developed countries, and corporate stakeholders. Grant applications must submit and be co-ordinated by an African national scientist working in a research group in Africa. Strategic priorities include but are not limited to: functional genomics, pathogenesis, drugs, epidemiology, vectors and socio-economic and behavioural research. MIM also holds training workshops for grantees, collaborators, and students from malaria endemic countries.

MIM/TDR has issued a call for Letters of Intent to be received by September 2005. The focus is on research useful in understanding malaria and reducing the disease burden as well as creating opportunities for developing African scientific and public health leadership in research management. The letters of intent should propose cross cutting or multidisciplinary “use inspired” research in the areas listed. A training and capacity building component must be included. The broad areas are: (1) chemotherapy and mechanism of antimalarial drug resistance, (2) health systems to improve malaria control in Africa, (3) Vector Control, (4) Research and Development of novel malaria control tools from natural products, (5) Research to facilitate malaria control interventions including introduction and evaluation of new strategies and policies. (6) Pathogenesis and immunology of malaria.

3.2.3 Medicines for Malaria Venture:¹⁰

Medicines for Malaria (MMV) was one of the first public-private partnerships to put the theory of PPP driven-virtual drug discovery into practice. It is a not-for-profit organisation established in 1999 in Geneva by WHO, the World Bank and several pharmaceutical companies. Its goal is to discover, develop and deliver one new antimalarial drug every five years through public-private partnerships. First registrations are envisaged for the end of 2006. A key aim is that the drug developed must have a low intrinsic cost of manufacture. It is funded mostly through international, government, and philanthropic foundation contributions. Since its foundation, MMV has been granted multi-year pledges from the Gates Foundation, the UK Department for International Development, the Swiss Agency for Development and Cooperation, USAID, Exxon Mobil, BHP Billiton, and the World Bank.

MMV manages a portfolio of drug development and discovery projects that are conducted by academic and pharmaceutical partners. Projects are solicited through a call for proposals and are sought out by MMV staff, as they become aware of possibilities. MMV's last call for proposals was in November 2004.

Out of 81 letters of interest, 5 projects were selected to be added to the portfolio. As of November 2004, MMV had 21 projects in its portfolio at different phases. All R&D work is outsourced and the degree of management by MMV is variable according to project needs. Projects are managed by product development teams with additional assistance from contract research organisations (CROs).

MMV had an income of \$ 28.7 million in 2004 and scientific project-related expenditure of \$ 25.4 million. Current forecasts for future expenditure are \$ 40 – 45 million in 2005, increasing to \$ 60 – 70 million annually as the developing portfolio necessitates and project move through clinical trials, registration, product launch and marketing. MMV has made a commitment to involve developing country scientists and institutions.

The MMV has achieved success following a three-year lead optimisation project based on an antimalarial peroxide. The team consisted of chemists in Nebraska, pharmacokineticists in Australia, and parasitologists in Switzerland, all linked to Hoffman la-Roche for guidance and toxicology expertise. A candidate antimalarial has been submitted for preclinical development. The compound has been licensed to Ranbaxy, which will co-develop the product with MMV.

3.2.4 Institute for One World Health¹¹

The Institute for One World Health (iOWH) is a relatively new initiative, formed in July 2000 funded by an unaffiliated individual scientist using personal resources. The institute has been established as a non-profit US pharmaceutical corporation located in San Francisco. Its mission is to develop and manufacture effective drugs and vaccines for people with infectious diseases in the developing world. The model followed by iOWH is to identify promising drug development opportunities, and take responsibility for driving those leads through the development process.

In 2004, iOWH was awarded a \$ 42.6 million grant from the Gates Foundation to work in partnership with the University of California, Berkeley, and Amyris Biotechnologies to perfect a fermentation process for the industrial production of artemisinin. The intent is to reduce the cost of treatment from the current \$ 2.40 to less than \$ 1.00.

Partnerships with pharmaceutical and biotechnology industries, non-profit hospitals, universities, government agencies and global health organisations are encouraged in order to obtain the resources necessary. The institute promotes the use of resources in developing world countries through increased funding for academic laboratories, and through working with such countries in clinical trials, drug manufacturing and distribution of the registered product.

Proposals from potential collaborative partnerships are invited. These are evaluated according to a number of criteria. Definitive guidelines are not provided, but criteria include the clinical need and availability of treatment, international standards of research, affordability, efficacy, etc.

3.2.5 Drugs for Neglected Diseases Initiative:¹²

The Drugs for Neglected Diseases Initiative (DNDi) was established in 2003 by 5 organisations from around the world, including 3 public sector institutions and 1 humanitarian organization, Médecines sans Frontières (MSF) and 1 international research organization, the UNDP/World Bank/WHO Special Programme for Research Training in Tropical Diseases (TDR). TDR acts as a permanent observer to the initiative. Most initial funding has come from MSF, agreeing to contribute up to \$ 7.5 million annually

for the initial 5 years. The EU agreed to provide up to € 1.5 million to fund artemisinin projects during the first two years. Other funders comprise public donors, international organisations, and private funders. The project budget for 2005 is \$ 19.4 million and over a 12 year period, the global budget is estimated at a minimum of \$ 258 million for an outcome of 6 – 8 registered drugs, and a pipeline of 8 projects.

The DNDi aims to develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Its business model is that of decentralised operations with a clear project specific focus. It does not conduct research and development itself, but capitalises on existing, fragmented R&D capacity, especially in the developing world and complements this with additional expertise if necessary. DNDi identifies medical needs and R&D projects proactively through expert consultations, literature searches, scientific meetings etc. It also calls for letter of interest requesting proposals focussing on specific diseases or research topics. The initiative fosters collaboration amongst developing countries and between developing and developed countries.

3.3 MALARIA FUNDING PUBLIC/PHILANTHROPIC ORGANISATIONS:

The list of organisations described here is not intended to be exhaustive, but includes most of the major groups funding malaria research and control in Africa in some manner. They represent the organisations most cited by researchers in South Africa as being potential sources of funds.

3.3.1 Global Fund to Fight AIDS, Tuberculosis and Malaria¹³

The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) is an international, independent public-private partnership which finances programmes for the prevention, treatment, care and support of AIDS, TB and malaria. The fund was created in 2002, after a decision by G8 countries in 2001 to help address the need to increase global funding to fight these diseases. The fund attracts, manages and disburses funds, but does not implement programmes directly as it is a financial instrument, and not an implementing entity. The Global Fund funds prevention, treatment and research. In the case of malaria, grants expand access to ITNs and provide health officials with tools and training. Proposals are evaluated through an independent review process. The funds are mostly disbursed through governmental organisations.

The Global Fund provides grants to locally-developed programs to prevent and treat AIDS, TB and malaria. Countries and organizations may apply for funding by submitting proposals in ongoing funding rounds. The proposals should support the scale up of effective existing programs and innovative projects that meet the Global Fund's criteria. Proposals submitted should also clearly demonstrate how the resources sought from the Global Fund will achieve additional results in partnership with existing programs. Calls for proposals are issued by the Global Fund Secretariat. The deadline for the Fifth Call of proposals was June 10th 2005, 26% of all proposals received were for malaria programmes worth \$ 870 million. 44% of all proposals received were from Africa.

Proposals for funding must generally be made through a Country Coordinating Mechanism (CCM). CCMs include representatives from both the public and private sectors, including governments, multilateral or bilateral agencies, non-governmental organizations, academic institutions, private businesses and people living with the diseases. These country-level partnerships develop and submit grant proposals to the Global Fund based on priority needs at the national level through consultation with a broad range of public and private stakeholders. As part of the proposal, the CCM nominates one

or a few Principal Recipients. In many cases, development partners assist in the preparation of proposal.

The Global Fund works together with other multilateral and bilateral organisations involved in health and development issues. Many of these organisations provide technical assistance during the development of proposals or implementation of programmes. The Global Fund started disbursements of funds in 2003. By the end of its first four funding cycles i.e. end 2004, the Global Fund had committed US\$ 3.1 billion in 127 countries. 31% of this has been allocated to proposals for the control of malaria. 56% of this amount is earmarked for distribution to Africa, of which 17% is for Southern Africa. The 5th round of financing has recently closed.

3.3.2 The Bill and Melinda Gates Foundation:¹⁴

The Bill and Melinda Gates Foundation's (Gates Foundation) mission is on promoting greater equity in global health, education, and public libraries. This foundation is a grant-making organisation. The Foundation has an endowment of \$ 28.8 billion. One of the spearheads of the Gates Foundation is the Global Health Programme that focuses especially on poverty-related diseases including malaria. There are two priority areas: research to create and improve health technologies, tools and strategies to accelerate access to these health interventions to those that need them. The largest proportion of the grants is on research to create and/or improve health tools such as vaccines, drugs, and diagnostics. This includes basic research, product development, clinical trials, and operations research.

Grants have included: \$150 million to the Malaria Vaccine Initiative for the development of promising malaria vaccines and \$ 65 million to MMV to support the discovery and development of affordable and effective antimalarial drugs. An amount of \$ 100 million was pledged to the Global Fund to support efforts at the country level to control the spread of HIV/AIDS, TB and malaria. The Foundation also funded the Gates Malaria Partnership (GMP), a collaboration between a number of academic institutions, philanthropic organisations, and public health organisations, which will wind down from the end of 2005.

A further \$450 million has been committed to the Grand Challenges in Global Health programme to accelerate research on crucial scientific and technological problems in developing world diseases. This programme is implemented in partnership with the National Institute of Health (NIH), the Wellcome Trust and the Canadian Institutes of Health Research (CIHR). 43 Grants have been awarded to scientists in 33 countries. Projects include the control of insect vectors *via* genetic or chemical strategies, limiting drug resistance, and curing infection *via* either therapies or immunological methods.

3.3.3 The National Institutes of Health:¹⁵

The National Institute of Health (NIH) is an agency of the US Department of Health and Human Services. In order to realise its mission defined as the "science in pursuit of fundamental knowledge about the nature and behaviour of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability", the NIH awards funds to research programmes concerning health issues such as malaria.

The NIH supports a number of award types including research project grants, training, career development and fellowship awards. Most research project grants (RPG) are through the R01, which are single research project grants. These grants provide support to an institution on behalf of a principal

investigator. Proposals are initiated through request for applications (RFA), request for proposals or programme announcements. These are published weekly in the NIH Guide for Grants and Contracts.

The National Institute of Allergy and Infectious Diseases (NIAID)¹⁶, a component of the NIH, conducts and supports basic and applied research to better understand, treat and ultimately prevent infections. NAID research has led to many new therapies, vaccines, diagnostic tests and other technologies. NIAID contributes to the Global Fund, as well as to research into new antimalarial combination drugs, and other targeted initiatives. The NIAID also has a malaria vaccine plan designed to accelerate research leading to the development of malaria vaccines. NIAID funding opportunities are published on their "Initiatives and Concepts" web-site divided into NIAID primary sponsorships, NIH-wide, and NIAID as co-sponsor.

3.3.4 US Agency for International Development:¹⁷

The US Agency for International Development (USAID) is an American government agency that supports long-term and equitable economic growth and advances US foreign policy objectives by supporting, for example, global health. One of USAID's Infectious Disease Initiative priority areas is the sustainable reduction of deaths due to malaria and the incidence of other infectious diseases of major public health importance among key populations in selected countries. USAID is working in close collaboration with the Roll Back Malaria partnership and others to reduce malaria impact on developing countries. On June 30, 2005 President George Bush pledged to increase funding of malaria prevention and treatment in sub-Saharan Africa by more than \$ 1.2 billion over 5 years.

In addition to providing expanded support for prevention and control programmes, USAID supports three critical research efforts: (1) the Agency's Malaria Vaccine Development Programme (MVDP); (2) the development of new drug therapies for malaria, and (3) operations research on behavioural, community, drug use and treatment regimen compliance issues. The support in development of new drugs is mainly in providing extra funding for clinical trials for new malaria treatment therapies.

3.3.5 World Bank:¹⁸

The World Bank was a founding member of the Roll Back Malaria campaign, and has thus been actively involved in efforts to reduce the burden of malaria globally. The Bank has declared malaria a corporate priority, but most involvement is in the area of control. Since 2000, total Bank commitment in all regions is about \$100 – 150 million. In Africa there are currently more than 25 World Bank projects that currently provide support for malaria control activities.

3.3.6 The Wellcome Trust:¹⁹

The Wellcome Trust is the world's largest independent medical research-funding charity that aims to improve human and animal health. The Trust awards grants to other bodies, and it also manages its own projects. Resources expended over 2002 – 2004 total £ 2.06 billion, of which 66% was in grants. Funding is offered in four general areas: biomedical science, technology transfer, medical humanities and public engagement. The biomedical science programme: immunology and infectious disease category includes all aspects of immunology and infectious disease in humans and animals. Malaria research therefore falls within this programme.

The Wellcome Trust funds a broad spectrum of research on malaria, including: genome sequencing, the biology of the parasite and mosquito, new vaccines and drugs, clinical research to improve treatment

and to understand the pathology of the disease, disease transmission and epidemiology, health services research, and health policy research. The research is funded both overseas – in particular in countries experiencing the full impact of malaria disease – and in the UK. The funding programmes support researchers at all stages of their careers – from junior fellows to principal researchers – and provides a career progression. The major overseas centres in Africa and South East Asia act as training centres for scientists from developing countries, and the Wellcome Trust Centres for Research in Clinical Tropical Medicine provide UK bases for training.

Research project support includes project grants, equipment grants, and programme grants. Categories within project grants include: hypothesis-driven research, development of technologies or drugs, vaccines or biological resources; and modest applications for pilot studies. Three year project grants in the range of £ 150,000 - £ 300,000 are awarded. Programme grants provide support for longer periods, up to 5 years, for internationally competitive research. Grants have not exceeded £ 1.2 million. In both projects and programme grants, collaboration between scientists in the UK or Ireland with scientists in developing countries is encouraged.

The Trust also provides International Senior Research Fellowships for researchers from a number of countries including South Africa. Duration of the fellowship is for 5 years. South African recipients of this Grant include Dr Heinrich Hoppe (UCT) and Professor Greg Blatch (Rhodes). Other fellowships in tropical medicine include Research Training Fellowships for Newly Qualified Scientists and Research Career Development Fellowships for mid career scientists.

3.3.7 The European Union:²⁰

The European Union (EU) funds research in member states and some other countries, and at the EU's own Joint Research Centre. The main tool is the 6th Framework Programme. Key EU objectives are to increase research spending by over 50% in real terms by 2010 to 3% of GDP. The objective is to build EU-wide platforms of excellence. The European Commission has a budget of some € 20 billion for 2002 – 2006 for building an European Research Area under its 6th Framework Programme known as FP6. About 75% of this budget is devoted to 7 priorities, which include: life sciences, genomics and biotechnology for health. In this area the budget is € 2,255 million.

Funding goes to projects that will benefit from a transnational approach. Many EU countries have co-operation agreements allowing them to benefit from this funding, but generally at least 2 of the participants must come from the EU member states, candidate countries or Switzerland. Funds go to cross-border networking among centres of excellence in universities, research bodies, and business enterprises. Projects must be integrated, involving a critical mass of scientific and industrial partners, and targeting significant products, processes or service applications. Grants can also go to EU participation in specific science and technology co-operation programmes set up jointly by certain governments or national research organisations.

Submission of proposals is in response to calls for proposals. Proposals are evaluated and selected for funding by the EU with the help of independent external experts. In terms of project management, consortia have great autonomy, one of the participants acting as co-ordinator.

3.3.8 Funding agencies in the field of international development and co-operation

These agencies are mostly linked to national governments. Agencies in this category include DGIS (The Netherlands), The UK Department for International Development (DFID)²¹, DANIDA (Denmark), and JICA (Japan). The manner in which grants regarding poverty related diseases such as malaria by these agencies may be different.

DFID for example aims to fund research in four major themes, one of which is killer diseases. Within this area, DFID promotes public-private partnerships and multi-donor collaborations. DFID has donated £48 million to the RBM (1999 – 2004), and is a key donor to the Global Fund to fight AIDS, TB and Malaria with pledges of £140 over the period 2005 – 2008. DFID has contributed £ 5 million to MMV and £ 2.86 million to the London School of Hygiene and Tropical Medicine malaria programme. All DFID's goals are directed at achieving the targets set in the Millennium Development Goals by 2015. DFID in addition funds specific malaria knowledge programmes to develop the new generation of affordable drugs, and rapid diagnostic kits. It also maintains an interest in vaccine research.

4 FUNDING INITIATIVES – SOUTH AFRICA

4.1 National Research Foundation²²

The National Research Foundation (NRF) is the government's national agency responsible for the support of human resource capacity for research, technology and innovation in all fields of natural and social sciences, engineering, humanities and technology including indigenous knowledge in South Africa. The NRF framework supports research within all sciences, including health sciences in as much as this is not catered for by the Medical Research Council. The NRF therefore plays a critical role in the objectives of the National Research and Development strategy through educating and training scientists.

Its key objective is therefore to support and promote research through funding, developing human resources and providing the necessary research infrastructure. Funding is largely directed towards academic research, developing high-level human resources, and supporting South Africa's national research facilities. The NRF's key driver is to produce large numbers of high-quality PhD graduates, which will motivate and underpin the work of all operational units of the NRF.

Within the context of the provision of funds for malaria research, the NRF's activities are through the Research and Innovation Support Agency (RISA) as the service provider. RISA as an agency covers the full range of activities in the innovation chain from fundamental research through to application and commercialization. RISA programmes and functions are largely supported by a parliamentary core grant. In addition, other programmes are managed by the NRF as a service provider. These include:

- Innovation Fund, managed for the Innovation Fund Board of Trustees and funded by the Department of Science and Technology (DST)
- Technology and Human Resources for Industry Programme (THRIP), funded by the Department of Trade and Industry (DTI).

4.1.1 Parliamentary Core Grant

RISA has identified a portfolio of 9 focus areas. Both basic and applied research may be carried out within these focus areas. Furthermore, the focus areas allow disciplinary, multi-disciplinary, inter-disciplinary and trans-disciplinary research to be carried out. Researchers may submit more than one proposal into the focus area of choice.

Focus areas include:

- Challenge of Globalisation: Perspective of Global South
- Conservation and Management of Ecosystems and Biodiversity
- Distinct South African opportunities
- Economic Growth and Competitiveness
- Education and the Challenges for Change
- Indigenous Knowledge Systems (IKS): The NRF receives a ring-fenced grant for IKS from the DST.
- Information and Communication Technology (ICT)
- Sustainable Livelihoods: The Eradication of Poverty
- Unlocking the Future: Advancing and Strengthening Strategic Knowledge

The focus areas are non-discipline specific, inviting research from across the knowledge spectrum to address these concerns. Researchers in natural sciences, engineering, social sciences, law and humanities employed at an NRF recognised institution either on a full or part-time basis may apply.

Rated researchers employed may receive funding for up to 5 years, and unrated researchers up to 2 years.

The focus areas cover on a competitive basis the entire range of South African research capacity development requirements. The interventions of relevance to malaria researchers include:

- Free-standing student support such as bursaries;
- The focus area programmes that provides grants to researchers and grant holder linked students;
- Thuthuka offering opportunities for researchers-in-training, women in research and the growth of black research staff (REDIBA);
- Science liaison grants to enable the internationalization of science; and
- Equipment and mobility grants.

A list of the NRF supported projects is attached as Appendix 1. This is the total amount for the grant duration of either 2 or 5 years. It has not been possible to separate out those projects which were of a shorter duration and have hence been completed. Current total committed NRF grants in malaria projects are worth R 7.35 million, representing an average annual expenditure of R 2.1 million. This total commitment should only be used as an approximation of the level of expenditure by the NRF in this area.

More details regarding the aims and objectives of the focus areas and instructions to applicants are provided in the NRF web-site.

4.1.2 Innovation Fund

The Innovation Fund was established by the Department of Science and Technology with the core mandate of raising the level of competitiveness of the South African economic sector by promoting the commercialization of end stage research into tangible products and services for the South African and international markets. The Fund invests in technologically innovative research and development. The NRF is the contracted agent managing the Fund.

A series of initiatives have been introduced that seek to enhance innovation in South Africa. These are:

Missions in Technology (MiTech):

To support the accelerated development of long-term, high-risk, market-driven, enabling technologies in all economic sectors in partnership with industry. It provides up to R 15 million in matching funds over a 5-year period to develop new technology platforms. Applications in all technology areas are considered, but priority is given to projects aligned with the National R&D strategy and Advanced Manufacturing Strategy.

Technology Advancement Programmes (TAP):

To build on the existing research and knowledge base, where a real or potential product has been identified. The proposed R&D budget will enable progress up to proof of concept or prototype stage. Funding is for 3 years to consortia, with a maximum grant of R 5 million per annum. Applications in any area are accepted, although biotechnology applications require prior screening by the Biotechnology Regional Innovation Centres (BRICS)

Seed and start-up financing:

This fund is aimed at supporting projects previously funded by the Innovation Fund that have demonstrated proof-of-concept and are seeking funding for commercialisation activities.

Malaria projects that have received Innovation Fund support in the past include:

- The MRC consortium project into the development of a GIS based decision support system for the Lubombo Spatial Development Initiative; and
- The MRC consortium project into the development of new antimalarial medicines from the medicinal plants of Southern Africa.

The only currently active Innovation Fund supported project is the “National Research and Development Platform for Novel Drug Development from Indigenous Plants”. The project falls under the MiTech programme and has a budget of R 15 million over 3 years. The project however covers the development of drugs for a number of diseases including malaria. It is estimated that the malaria portion is worth R 4 million, which over 3 years is an estimated R 1.33 million annually.

4.1.3 THRIP

THRIP is a joint venture between industry, research and education institutions, and government. It supports the development of technology and appropriately skilled people for industry to improve South Africa’s global competitiveness. THRIP provides resources and mechanisms in support of collaborative research in the areas of science, engineering and technology. THRIP’s priorities are funding mechanisms for students and staff, as well as women- and black students and staff. THRIP is not funding any malaria research projects at present.

4.2 Medical Research Council²³

The Medical Research Council (MRC) is a statutory research body in South Africa established in 1969 by an Act of Parliament. The MRC is a science, engineering and technology institution (SETI), largely funded by the government. Its work is in line with the national science and technology imperatives and the health priorities defined by the Department of Health, its main objective is hence to produce science resulting in improved health. The MRC conducts or supports research on its own or with experienced partners such as universities and scientific institutions.

Health research supported by the MRC is categorized into 6 national programmes corresponding to high-priority areas identified by the government. Each national programme has identified further focus areas resulting in Lead Programmes, one of which is the Malaria Lead Programme, which falls within the Infection and Immunity national programme. The directives of the Malaria Lead programme are: malaria information systems, control intervention, insecticide resistance, drug efficacy studies and resistance development. There are a total of 47 research units, groups, centers or lead programmes within the national programmes.

The MRC issues requests for proposals, which are independently advertised. Grants for “Self-initiated Research” are awarded for research covering a wide range of health-related subjects. The maximum grant is for 3 years, with a maximum grant of R 130,000 per project per annum. Letters of intent may be submitted at any time for inclusion into an assessment cycle. Cycle dates close on 14th January and 1st July. Applicants must have at least a Masters Degree or equivalent with 2 years of research. Principal investigators must be employed or hold a contract with a South African institution for the duration of the project. Research projects are hence undertaken by universities, technikons, and other institutions where academic personnel and a physical infrastructure already exist. Other grants, such as the Research Development Grant, are available for scientists that do not yet fulfill these requirements.

A list of the self-initiated projects currently receiving funding is attached as Appendix 2. The amounts of the grants are however confidential. Working on the basis that the maximum project amount has been awarded the total grant commitment per annum is in the region of R 1.3 million.

4.3 Support Programme for Industrial Innovation²⁴

The Support Programme for Industrial Innovation (SPII) is designed to promote and assist technology development in South African industry through the provision of financial assistance for projects that develop innovative products and/or services. SPII is focused on the phase beginning as the conclusion of basic research i.e. post proof of concept, and ends at the point where a prototype has been produced. Projects funded are therefore at the pre-competitive stage of development. The programme is managed by the IDC on behalf of the Department of Trade and Industry.

Three different schemes exist depending on the size of the company in terms of turnover and assets, as well as the size of grant required. The schemes are:

1. The Product Process Development Scheme (PPD): targeted at small and micro enterprises. The grant is between 65 and 85% of qualifying costs up to a maximum of R 0.5 million depending on the level of black shareholding. Company turnover must be less than R 13 million.
2. The Matching Scheme: targeted at SMEs with a turnover of less than R 51 million. The grant is up to 50% of qualifying costs up to a maximum of R 1.5 million.
3. The Partnership Scheme: provided in the form of a conditionally repayable grant of up to 50% of qualifying costs. The maximum grant is R 1.5 million.

At the moment, there are no malaria related projects in the SPII programme.

4.4 Biotechnology Regional Innovation Centres:

The Department of Science and Technology has created 3 Biotechnology Regional Innovation Centers (BRICS) as part of the overall National Biotechnology Strategy to ensure the stimulation of South African biotechnology. The 3 BRICs are regionally focused and all have human health as a portfolio.

The BRICS are:

1. BioPAD: Biotechnology Partnerships and Development, active in the Gauteng region
A human health portfolio has recently been added to the BioPAD focus areas.
2. CBT: Cape Biotech Trust in the Western Cape region
Focus areas of relevance to malaria research are: diagnostics, vaccines and drug delivery
3. ECoBio: East Coast Biotechnology Regional Innovation Centre (operating under the trade name LIFElab) in the East Coast region.
Focus areas are infectious diseases including malaria or projects, which develop the biotechnology platforms of the area.

The BRICS funding strategy is to fund on-going and new research and development projects and provide a supporting infrastructure for commercialization. Investment in technology development is generally directed at projects that are post “proof-of-concept” where a real or potential product has been identified and technology already exists. At present, the only malaria related project funded by the BRICS is the development of a rapid malaria diagnostic test by National Bioproducts Institute in collaboration with LIFElab.

4.5 Other funding sources

A number of funding sources other than those listed already have been used by research groups. A few institutions use funds, such as contract research funds generated by other activities to fund malaria research. Examples include the University of Stellenbosch and the University of Cape Town Pharmacology department. Other sources of funds that have been used include the Volkswagen Foundation. Mozal and the Business Trust were the first funders of the LSDI programme.

Funds from international pharmaceutical companies such as GlaxoSmithKline (UK) and Merck Pharma (US) have been awarded to specific researchers such as Professor Chibale, in most cases these are however related to projects broader than malaria. A number of researchers have accessed international funding from the sources already listed above, including the EU grants.

Within the CSIR, in addition to funding generated by research contracts with government departments, the private sector and research funding agencies locally and abroad, funding is received from an annual parliamentary grant *via* the Department of Trade and Industry. These funds are used primarily for investment in developing new areas of research, and undertaking early stage research still viewed as being too risky to investment by the private sector.

4.6 Conclusion:

South Africa has a variety of funding sources applicable to malaria research. They are active in the funding of R&D, research capacity building and technology transfer. Excluding the MRC malaria lead programme budget, CSIR parliamentary grant and funding through the BRICs, the annual funding of malaria research in South Africa is in the region of R 5 million. Much of this is directed at training of students, platform development and capacity building. Whilst there are a number of programmes such as SPII, the BRICs and the Innovation fund directed at funding post “proof-of-concept”, few projects are being funded by this mechanism. This supports the conclusion by the 2003 Emerging Biotechnology Roadmap that there remains a substantial gap between innovation and commercialization.

5 RESEARCH ENVIRONMENT: South Africa

MIA has stated its key objective in the integration of researchers focusing on molecular aspects of malaria drug and insecticide discovery, molecular epidemiology and diagnostics, and capacity building in order to improve malaria prevention and control. Three programmes are envisaged:

- The development of new and modified drugs and insecticides
- The development and implementation of assays for epidemiological and diagnostic interventions
- Capacity building programmes as a cross-cutting programme

This section serves to provide a brief overview of the malaria research currently being undertaken in South Africa in the various categories of interest to MIA. Vaccine development has therefore not been included.

5.1 EPIDEMIOLOGY and DIAGNOSTIC RESEARCH:

5.1.1 University of KwaZulu Natal

5.1.1.1 School of Molecular and Cellular Biosciences: Professor Dean Goldring

Area of Research: Tracking anti-malaria drugs, development of dipstick assays.

The team has developed an array of antibodies against anti-malarial drugs, which can be used to track malaria drugs in a range of cells, tissues and body fluids.

Through an international collaboration in a MVI project in Denmark and Ghana, the team is developing reagents for a second generation of an ELISA diagnostic kit. The first generation of the ELISA is being used as an experimental tool in malaria vaccine trials.

5.1.2 Medical Research Council of South Africa:

5.1.2.1 Malaria Research Programme: Director Dr Brian Sharp

Area of Research: Biology and control of malaria vectors and parasites
Molecular basis of drug resistance
Biochemical basis of insecticide resistance
Spatial and molecular epidemiology and health systems research.
Research capacity building for malaria

The Malaria Research Programme became a lead programme within the MRC Infection and Immunity National Programme in 1999 in order to stimulate malaria research, build capacity and transfer skills. Malaria control is a dynamic process requiring continual research input, and therefore the MRC research focus has the sustainability of control in the future as a key goal. Research is therefore aligned with informing effective policy and control. Focus areas include vector and parasite research, the epidemiology of the disease, drug and insecticide resistance, bio-prospecting and Geographical Information Systems (GIS) technology. Research is carried out in both laboratory and field, with the emphasis on applied research.

The summary below is not intended to be a comprehensive list of all the MRC malaria projects, but describes a select few of relevance to the outcome of the proposed MIA programme.

Malaria Information Systems:

The MRC was instrumental in the development and implementation of a vector based GIS based decision support system (DSS) for the Lubombo Spatial Development Initiative (LSDI). This is used for both management of the disease and research. Amongst other objectives the DSS supports the extension of malaria control into southern Mozambique and assess the impact of the intervention tools on disease prevalence and tourism. The MRC furthermore has investigated the underlying biotic and abiotic factors that drive malaria transmission in South Africa and has developed statistical malaria epidemic prediction models in order to better control the disease. This model is used as a health management tool within the LSDI.

The MRC was the main investigating centre for the "Mapping Malaria Risk in Africa" collaboration project, know as MARA/AMRA. This ongoing project, allowed the establishment of an atlas of malaria risk in Africa, i.e. a continental database of the spatial epidemiology of malaria including vector distribution, drug resistance, and insecticide resistance. This project used a geographic information system (GIS) and integrated different malaria, geographical and environmental data sets. The use of good spatial maps is vital part of any malaria control programme as malaria needs to be controlled regionally.

Lubombo Spatial Development Initiative:

In July 1999 the heads of state of South Africa, Swaziland and Mozambique signed the General Protocol which put in place a platform for regional cooperation and delivery, the Lubombo Spatial Development Initiative. In October 1999 the Lubombo Malaria Protocol and tri-national malaria programme was launched. The Regional Malaria Control Commission (RMCC) is the co-ordinating and decision – making body of the LSDI programme. The MRC Malaria Research Programme chairs the RMCC as well as undertaking the direct management of the programme on behalf of the RMCC and providing secretarial, financial management, fund-raising, and research support. Large scale malaria control covering >100 000 square kilometres in the 3 countries is being monitored and evaluated as part of this collaboration.

Insecticide resistance monitoring and management/ Gene flow

The MRC together with the National Institute of Communicable Diseases has developed and improved molecular and biochemical techniques aimed at determining the resistance levels in natural populations of the malaria vector to insecticides. In order to carry out research on the genetics of insecticide resistance and gene flow, research capacity in this area was developed through training at the University of Liverpool. The Malaria Programme also continually monitors the insecticide resistance situation in southern Africa.

To control the development of insecticide resistance; malaria control programmes are investigating the use of various insecticides in rotational spraying. This technique is being investigated to preserve the long-term effectiveness of current insecticides.

Molecular techniques such as polymorphic microsatellite and mitochondrial DNA markers have been used to describe the dynamics and population genetics of the seasonally fluctuating vector (*An. arabiensis*) population. This study compared the relative importance of resident mosquitoes with immigrants in founding the wet season population expansions and their role in malaria epidemics.

Antimalarial drug resistance/Gene Flow:

Antimalarial drug resistance poses a major threat to the control of malaria in Africa. Interventions such as drug policy or drug dosage changes rely on appropriate drug efficacy information being available to decision makers. This is the goal of including drug susceptibility/resistance data from Africa as an additional data collection component to the MARA project. The aim is to record antimalarial drug susceptibility and resistance data in a systematic manner.

Research into the emergence and spread of drug resistance is constantly conducted. The molecular genetic basis of drug resistance at parasite population level is investigated. Previous research has indicated that gene flow rather than new mutations has been the most common originator of sulfadoxine-pyrimethamine resistance in Africa. The determinants of resistance in KZN were found to share a common evolutionary origin with those found in Kilimanjaro, Tanzania, even though the two sites are 4000 km apart. Additional research collaboration has produced evidence that malaria parasites bearing high level pyrimethamine resistance originally arrived in Africa from SE Asia.

The MRC collaborates extensively with international research groups such as the London School of Hygiene and Tropical Medicine, the Swiss Tropical Research Institute, and the Liverpool School of Tropical Medicine. The MRC also has established links with scientists throughout Africa via the MARA network, the LSDI and other collaborative projects. Collaborators include scientists from Cameroon, Kenya, Madagascar, Mozambique, Mali, Tanzania, Malawi, Angola, Zimbabwe, Equatorial Guinea and Zambia.

5.1.3 National Bioproducts Institute

5.1.3.1 Dr Martin Bubb

Area of Research: Development and Optimised production of a rapid malaria diagnostic kit

The project forms part of a large project, together with Molecular Diagnostic Services and LIFElab, to develop a platform for the production of rapid and routine diagnostic tests of relevance to the Southern African region.

Microscopic examination of thick and thin films remains the gold standard for malaria diagnosis. In many rural settings, facilities capable of performing these evaluations are not available, and diagnosis is based on clinical symptoms. Rapid diagnostic tests based on the detection of malarial antigens e.g. Histidine rich protein II (HRP II), lactate dehydrogenase (LDH), and aldolase using immuno-chromatographic technology are being evaluated as an alternative.

It is essential that low parasitaemia levels can be detected in immune patients in endemic countries. NBI has developed a pair of monoclonal antibodies specific for HRP II that are suitable for use in a rapid diagnostic test. These antibodies are specific for *Plasmodium falciparum* and recognise different epitopes on this molecule. The antibodies are already being sold to overseas companies for incorporation into malaria rapid diagnostic kits. NBI is developing and optimising its own manufacturing process of a malaria diagnostic kit that is user friendly, easy to interpret, rapid and sensitive so as to capture this value addition in South Africa.

Dr Bubb is a WHO temporary advisor on Malaria Rapid Diagnostic Kits.

5.1.4 National Institute of Communicable diseases:

5.1.4.1 Vector Control Reference Unit: Professor Maureen Coetzee

Areas of Research: Molecular identification and characterisation of mosquito vectors.
Molecular mechanisms of mosquito resistance to insecticides.
Field studies for resistance management.

Research within the Vector Control Unit is aimed at determining the extent and distribution of insecticide resistance in mosquito populations. As part of a MIM/TDR funded project, the NICD and the MRC developed and implemented a molecular and biochemical capability for insecticide resistance monitoring and management in South Africa. The group was instrumental in the discovery of pyrethroid resistance in *An. funestus* in 1999 and hence the establishment of a policy for the choice of insecticide in South Africa.

The unit has over 20 mosquito colonies, most of which are not available elsewhere in the world. A rapid rDNA PCR-based diagnostic tool with the capability of differentiating between five species of the *An. funestus* group of vectors has been developed. The mechanisms that confer resistance to insecticides in these mosquitoes are under investigation leading to an increase in understanding of metabolically mediated resistance in *An. funestus*. In addition, resistance mechanisms in members of the *An. gambiae* complex from various parts of Africa are also being studied at the molecular and biochemical levels.

An understanding of malaria epidemiology is critical in the development of control strategies. This is doubly so when considering the use of genetically modified mosquitoes to prevent malaria transmission. Knowledge of population structure in the vector species and possible gene flow between populations, will impact not only on the spread of transgenic mosquitoes, but also the spread of insecticide resistance genes. Collaborative studies are ongoing with institutions in the USA and the UK to investigate these issues. Future research projects include studying the interactions between the vector and parasites and using microarrays to evaluate gene expression between resistant and susceptible mosquitoes.

Technologies used include DNA sequencing, PCR, real-time PCR, cloning, northern blots, microarrays, cytogenetics, *in-situ* hybridisation, ELISAs, mosquito rearing, and insecticide resistance testing.

5.2 CLINICAL and PRE-CLINICAL RESEARCH:

5.2.1 University of Cape Town

5.2.1.1 Department Of Pharmacology: Professor Peter Smith

Area of Research: Mechanism of chloroquine resistance reversal
Isolation and characterisation of novel antimalarials from medicinal plants
Pharmacokinetics of antimalarial drugs

The department has extensive expertise in drug assay development and pharmacokinetics of drugs in particular those used in tuberculosis and malaria. The research group has a well established culturing facility with 10 different malaria parasite strains available. Activity testing against a panel of drug-sensitive and drug-resistant *P. falciparum* is performed *in vitro*. An *in vivo* mouse model of malaria (*P. berghei*) has been established and *in vivo* assays for activity and toxicity testing with two parasites different in terms of their resistance to chloroquine is routinely performed. Pharmacokinetics and

pharmacodynamics of malaria drugs to determine the absorption in blood are supported by LC Mass Spectrometers. The department also collaborates extensively with other research groups in these activities in the drug discovery and development process using the infrastructure that has now been established.

The department conducts research into the mechanism of drug resistance in *P. falciparum* from a cell biology perspective. Additional research projects are through the South African Traditional Medicines Group (SATMERG) where plant extracts from traditional medicines are screened for anti-malaria activity. SATMERG is funded by the MRC. More than 500 plants have been investigated to date, with more than 25 showing significant activity against a number of strains of *P. falciparum* in crude extracts. Active crude extracts are fractionated to purify the active agents to homogeneity. Activities in this regard also form part of the Innovation Fund platform project.

The department has a well established Medicines Information Centre, an independent drug information service provided by trained pharmacists. The department has a number of people involved in drug regulatory affairs.

5.2.2 University of Pretoria

5.2.2.1 Department of Internal Medicine: Professor Anton Stoltz

Area of Research: Post-graduate training in infectious diseases.
Access to malaria patients for clinical trials

The Department of Internal Medicine: Infectious Diseases has the capacity to conduct all levels of clinical trials from early toxicity studies to human studies. Currently no malaria studies are being performed. The Department would however be in a position to provide access to patients and to other services offered should any research programme within MIA required it.

5.2.3 South East Africa Combination Anti-Malarial Therapy Evaluation

University of Cape Town Pharmacology Department: Dr Karen Barnes

Medical Research Council: Dr Brian Sharp

Mpumalanga Department of Health: Dr Dave Durrheim

Area of Research: An evaluation of the effect of anti-malaria therapy on the emergence of resistance.²⁵
Operational and policy research

South East Africa Combination Anti-Malarial Therapy (SEACAT) study is a joint initiative between South Africa, Mozambique, and Swaziland to investigate the effect of antimalarial therapy on the emergence of resistance. This study is being conducted on behalf of the Regional Malaria Control Commission as part of the LSDI programme. Financial support for the project has been received from the UNDP/World Bank/WHO TDR. The major source of funding at present is the Global Fund.

The MRC is collaborating with the University of Cape Town and the Mpumalanga Department of Health. There are also a number of international collaborators in the project, including the London School of Hygiene and Tropical Medicine, and US Centre of Disease Control and Prevention.

The study was initiated in order to provide data to advise drug policy making by the national Malaria Advisory Group. The project continually evaluates the implementation of combination antimalarial therapy at provincial and national levels in Mozambique, Swaziland and South Africa in terms of public health impact, safety, efficacy, etc. *In vivo* resistance, molecular markers of resistance, gametocyte carriage, drug utilisation and cost effectiveness are evaluated at each site biannually over a 6-year period. A goal of the evaluation is to ensure that the impact of large-scale treatment with the ACT antimalarials is optimised. The project is linked to concurrently funded projects including the evaluation of *in vitro* resistance and gene flow. This will allow evaluation of the impact of antimalarial therapy on the intensity and distribution of malaria in the region.

Other clinical studies in the use of ACT antimalarials in severe and uncomplicated malaria, pregnant women and children are also performed in Southern Africa. Most studies are performed in Southern Africa due to the difference in immunity between endemic and non-endemic areas such as South Africa. South Africa only has a limited role to play in these studies.

5.3 BASIC SCIENCE:

5.3.1 University of Cape Town

5.3.1.1 Department of Chemistry: Professor Kelly Chibale

Area of Research: Medicinal Chemistry and Synthetic Organic Chemistry

The Medicinal Chemistry programme focuses on the design and synthesis of novel anti-infectives, including antimalarial and antituberculosis agents. Potential antimalarial leads are based on a number of different biochemical pathways. One project is based on studying the purine salvage enzymes (hypoxanthine-guanine-phosphoribosyl-transferase) as the malaria parasite lacks the ability to produce purines itself. This project is in collaboration with Professor David McIntosh of the UCT Department of Pathology. Further potential drug target are the enzymes involved in the degradation of haemoglobin, for example cysteine proteases. Inhibitors of cysteine proteases would prevent host haemoglobin proteolysis in the food vacuole, hence denying the parasite its source of amino acids required for replication. Dr Heinrich Hoppe (UCT) and Professor Philip Rosenthal (University of California San Francisco, USA) are collaborators on this project. The group is also involved in anti-malarial drug combinations particularly with respect to chemical hybridization of two or more antimalarial drugs targeting more than one biochemical pathway so as to reverse drug resistance and retain the use of existing drugs such as chloroquine.

The group collaborates with the University of Cape Town Department of Pharmacology. Professor Peter Smith performs the *in vivo* studies in appropriate mouse models as well as determination of the pharmacokinetic profiles of potential lead compounds. This is a vital link in the chain of drug discovery and development in South Africa.

The Group is also involved in the Innovation Fund Novel Drug Platform from Indigenous Plants, as the leader of the programme dealing with the design and synthesis of chemical libraries of natural product-derivatives.

5.3.1.2 Department of Chemistry: Professor Tim Egan

Area of Research: Cell biological effects of antimalarials: mechanism of action of quinoline antimalarial drugs

The group is active in the investigation of the mechanism of action of quinoline antimalarial drugs in the haem detoxification process of the parasite. It has been proven that virtually all of the haem produced by the *P. falciparum* parasite is incorporated into malaria pigment, haemozoin, in the parasite food vacuole. Further research into aspects of this research is being carried out in order to further understand the pathway of haemozoin formation. This involves studying the mechanism and kinetics of formation of synthetic haemozoin, β -haematin, using both molecular modelling and chemical studies. Cellular studies are also underway. The structure-activity relationships of various synthetic quinoline analogues have been determined. Their inhibition of β -haematin and *in vitro* antimalarial inhibition are studied in order to gain insights into the mechanisms of action.

New research projects involve using structure-activity relationships to determine the relationship between quinoline structures and cross-resistance to chloroquine. This work will contribute to a clearer understanding of the mechanism of action of chloroquine and lead potentially to the development of new quinoline drugs that by-pass the resistance mechanism. A colorimetric high-throughput screening assay to measure the strength of inhibition of β -haematin formation has been developed. This best allows the screening of potential haemozoin inhibitors. The test is used in the Group's research programme and a pilot study is underway in the screening of natural product isolates obtained in the Innovation Fund study.

Techniques used include spectroscopy, diffraction and electron microscopy, molecular mechanics, molecular dynamics and simulated annealing calculations, organic synthesis (in collaboration with Professor Roger Hunter) and 2D QSAR methods. The Group collaborates extensively with the UCT Pharmacology Department, Electron Microscopy Unit, as well as with the University of Witwatersrand Departments of Physics (Dr Giovanni Hearne) and Chemistry (Professor Helder Marques).

5.3.1.3 Institute of Infectious Disease and Molecular Medicine: Malaria Cell Biology Group: Dr Heinrich Hoppe

Area of Research: Malaria cell biology focussed on endocytosis of malaria parasites
Cell biology of antimalarials and antimicrobials

The Institute's research activities are associated with understanding the fundamental molecular mechanism of action of endocytosis in malaria parasites. Apart from a morphological description of this pathway at the electron microscopy level, this process is poorly understood. The outcome of the research is to establish current and novel cell biology and genetic manipulation techniques and laboratory capability to be applied in the study of malaria.

The project focuses on the characterisation of 7 malaria homologues of proteins known to mediate endocytosis in other cells i.e. Clathrin, Dynamin, Adaptins, Coronin and Actin. Advanced technologies for manipulating the parasite at a molecular, cellular, and genetic level are used. These tools have been widely used in the characterisation of other organisms, but not as yet in malaria. The proteins are being characterised *via* two routes: sub-cellular localisation and functional characterisation. Tools include recombinant protein expression of genes in *E. coli*, mouse antiserum production, localization by

immunofluorescence, electron microscopy, and gene suppression by RNAi, heterologous malaria gene expression in *Dictyostelium* and transient transfection of parasites with dominant negative mutants.

The Institute is also involved in a number of other projects in the University of Cape Town Department of Chemistry: Professor Tim Egan and Professor Kelly Chibale as well as the University of Stellenbosch Department of Biochemistry: Dr Marina Rautenbach. The potential antimalarial drugs under development in these departments are provided to the group for testing in parasite culture systems to determine parasite viability and sensitivity to the antimalarial drug. The modes of action of potential drugs are investigated for example in the determination of the efficacy and cell biological effects of protease inhibitors through the application of endocytosis assays. The group is also furthermore characterizing several commonly used membrane-active antimicrobials as potential therapy in severe malaria cases.

Dr Hoppe holds a Wellcome Trust International Senior Research Fellowship. Collaborating partners and co-workers are the University of Cape Town Departments of Pharmacology and Chemistry, Stellenbosch University, the University of Pretoria Department of Biochemistry, Bernhardt Nocht Institute for Tropical Medicine (Germany) and Yale University.

5.3.1.4 Department of Chemical Pathology: Professor Dave McIntosh

Area of Research: Targeting of purine-based antimalarials

The department of Chemical Pathology's involvement in malaria research is in the area of antimalarial Drug Development. One project is based on studying the purine salvage enzymes as the malaria parasite upon which the parasite is dependant. Collaboration is with the Department of Chemistry: Professor Kelly Chibale. Funding has been applied for in order to obtain crystal structures of the enzyme compounds of interest.

5.3.2 Council for Scientific and Industrial Research

5.3.2.1 Biotechnology, Speciality and Fine Chemicals: Dr Dusty Gardiner/ Dr Colin Kenyon/Dr Chris Parkinson

Area of Research: Functional genomics and Proteomics
Structural biology and computational biology applicable to malaria parasite enzymes
Molecular recognition, structural and synthetic organic chemistry.

The CSIR has and continues to invest in the development of capacity in genomic and proteomic technologies. These technologies are being applied to the identification and elucidation of novel drug targets for diseases of importance to Africa. The CSIR is now applying this expertise in partnership with collaborators who are active in malaria research. Collaborative projects are being implemented in partnership with the MRC and the University of Pretoria. The CSIR's initial role in these partnerships is in the application of the above "systems biology" tools towards identifying the mechanism of action of potential drug leads and identifying new drug targets.

One research project involves cloning of the *E. coli* codon-adapted gene for glutamine synthetase, followed by expression of the functional enzyme. This would be novel in the malaria context. Another

research project involves cloning and expressing the glutathione S transferase enzyme from the *P. falciparum* parasite. In contrast to other organisms, the malaria parasite *P. falciparum* possesses only one glutathione S transferase enzyme, and it has been shown to be involved in some aspect of the haem detoxification process. It may therefore represent a promising target for antimalarial drug development. Tools used include protein molecular modelling, molecular biology and enzymology to characterize and define enzyme reaction mechanisms, as well as site directed mutagenesis. As the projects progress, the CSIR's involvement will be expanded to include rational design of new drug leads.

Research is conducted into the synthesis of the endoperoxide antimalarials i.e. the artemisinins. Two research proposals are in the process of being drafted. Activated artemisinins are known to form adducts with a variety of biological molecules including haem. It has now been shown that artemisinin derivatives act by inhibition of the PfATP6 protein outside the food vacuole after activation by iron.²⁶ Research chemists are now attempting to identify semisynthetic and fully synthetic endoperoxides that will retain the activity of artemisinin derivatives, but overcome some of their deficiencies, such as the short half-life and residual fears of neurotoxicity.²⁷ The potential for rational drug design of new artemisinin derivatives using established principles coupled with the understanding of the mechanism of action therefore exists.

The CSIR has skills in process and product development and scale-up, process and product commercialization and intellectual property development, packaging and commercialization which will be brought to the various projects as they progress through the development process.

5.3.2.2 Bioprospecting: Dr Marthinus Horak

Area of Research: Bioprospecting and new chemical entity discovery

This group's focus is on the value addition to medicinal plants and associated Indigenous Knowledge, plant collection, screening, analysis, bioassay guided fractionation, isolation and structure elucidation of active molecules and development of minimally processed forms of traditional medicines. Expertise is in the area of drug lead discovery through the isolation and structural elucidation of novel active ingredients in medicinal plants. An example is the invention and patenting of a mosquito repellent through the identification of chemotypes of a plant with superior repellent properties, followed by isolation and identification of the chemical constituents. In rural dwellings the plant is used to repel mosquitoes. Tests have shown that it is nearly 100% effective compared to 40% in existing products on the market. The group has successfully implemented agro-processing technology on five community-owned cultivation sites (approximately 20 ha each), including distillation technology to give the mosquito repellent essential oil. A community-owned mosquito repellent candle factory based on the indigenous oil was launched during August 2005.

This group is part of the consortium involved with the Innovation Fund: Novel Drug Platform from Indigenous Plants. The group's participation in the project includes the extraction of the active ingredient from the plant, isolation of the active compound, structure elucidation coupled with the supporting analytical techniques. In the long-term the group will be responsible for the controlled horticulture of any indigenous plants that are shown to contain therapeutically active substances, and the subsequent production of the extracts and purified compounds for clinical trials according to Good Manufacturing Practice (GMP).

5.3.3 University of KwaZulu Natal

5.3.3.1 School of Molecular and Cellular Biosciences: Professor Dean Goldring

Area of Research: Cell cycle regulation: molecular mechanisms controlling cell division and differentiation in malaria parasites.

The research team has a multifaceted approach to understanding the complex interactions between the malaria parasite and the host. Some research conducted in the group is part of a larger international project with Christian Doerig, INSERM - Wellcome Centre for Molecular Parasitology, and funded by the SA MRC, SA NRF and an EU INCO-DEV grant. This involves the identification, isolation and characterisation of 80 different malaria protein kinases involved in cell signalling and regulation of the cell cycle. The international project is focused on obtaining an understanding of the function of these proteins in the life cycle of the parasite, and at elucidating the structure of the regulatory networks in which they function. Structural insight of kinase-inhibitor complexes could potentially be used as a basis for the synthesis of derivatives with selectivity/activity towards the target kinase to pursue as possible anti-malarial drugs. Kinase identification is aided with the use of affinity purified chicken anti-peptide antibodies.

Other interests include research into the impact of antimalarial drugs on the immune system (immunomodulation) and the study of immunotherapy against cytoadherence. Electron probe X-Ray microanalysis is used to evaluate ion homeostasis under the influence of disease and anti-malarial drugs.

The team has identified a malaria protein that has promising vaccine potential. The expression, location and structure of the protein and identifying of immunogenic epitopes is being studied. Other experience in malaria research is in rosetting, cytoadherence (sequestration), monocytes in malaria, T-cell mediated immunity and mouse malaria models.

5.3.4 Medical Research Council

5.3.4.1 Innovation Fund: Project Leader Professor Peter Folb/Dr N Bhagwandin

Area of Research: National research and development platform for novel drug development from indigenous medicinal plants²⁸

The aim of the technology platform is to develop new medicines and tonics based on indigenous plants and local knowledge for the treatment of a number of important and neglected diseases in the African context. The focus is those diseases such as malaria, tuberculosis and diabetes, for which there are validated test systems, both *in vitro* and *in vivo*. Many of the plants that will be investigated are endemic to southern Africa, providing opportunities for discovery that are not available elsewhere. However, only indigenous plants, which can be utilised without creating any ecological problem, will be investigated.

The project is the result of extensive collaboration of a multidisciplinary team of 17 research units and 135 scientists across the country. The institutions involved include: the SA Medical Research Council (MRC), Agricultural Research Council (ARC), CSIR, South African National Biodiversity Institute (SANBI), University of Cape Town, University of Pretoria, University of KZN, University of Limpopo and the University of Johannesburg. The lead consortium member is the MRC.

The project has set up cross-linkages between the various disciplines, institutions, departments and government bringing together the potential to integrate the strengths of microbiology, chemistry, pharmacology and botany. Part of the innovation in the project is thus in the establishment of a platform through collaboration, hence creating new research and development models.

It is anticipated that successful implementation of the 3 year project will allow the discovery of 2 – 3 novel drugs and tonics to the point of “proof of principle”, suitable and ready for early clinical studies, After establishment of proof of principle, subsequent pharmaceutical and manufacturing development will be conducted in collaboration with pharmaceutical chemists, and the pharmaceutical industry in South Africa. The project is directed at achieving benefits for the public health sector, by virtue of the focus on neglected diseases. The programme is currently in its second year.

The project aims to follow a policy of corrective action, with training and capacity building critical to increase the number of high-level scientists in South Africa. A further outcome is the establishment of new agro-processing businesses for the supply of plant material required for new drugs. The goal of the project is to place South Africa as an international player in the development of plant-derived medicines.

5.3.4.2 Malaria Research Programme: Director Dr Brian Sharp

Area of Research: Evaluation of insecticides and repellents

The MRC has been designated as one of the main institutes to conduct efficacy trials for products to be registered with the Registrar of insecticides. New insecticides and different formulations of existing insecticides have been evaluated for commercial organisations, in order to obtain the necessary registration of their products.

As part of the Novel Drug Development Platform, the MRC is currently involved in studies to detect novel compounds that can be used as a mosquitocides. Indigenous plants that have been used by traditional healers or traditionally for the control of mosquitoes have been systematically evaluated through bioassay guided fractionation to get to pure compounds that are bioactive. This study has yielded some positive leads.

5.3.5 University of North West:

5.3.5.1 Department of Pharmacy Drug Research and Development :Professor Lotter

Area of Research: Formulation of antimalarial drugs

The antimicrobial biocide triclosan has been shown to potently inhibit the growth of *Plasmodium falciparum in vitro* and, in a mouse model, *Plasmodium berghei in vivo*. Triclosan is however not very soluble. The Department of Pharmacy has developed novel drug delivery systems, and oil formulation and soft gel capsules, which have shown high blood levels when tested. This research is however now complete, and would require more extensive bioavailability testing and testing in humans for further development.

5.3.6 University of Pretoria

5.3.6.1 Department of Immunology: Professor Ron Anderson

Area of Research: Drug Discovery

This group's involvement in malaria research is in the development of potential antimalarial drugs. A drug, which is already registered for another indication, has been identified as having potential antimalarial activity. This product is currently the subject of a potential patent application together with the Medical Research Council. Further details can therefore not be provided to ensure intellectual property protection rights. The product is being developed in collaboration with Dr ME Makgatho (University of Limpopo) and Professor Peter Smith (University of Cape Town).

Technologies used include screening of potential antimalarials, parasite viability tests, and *in vivo* animal model testing.

5.3.6.2 Department of Biochemistry: Professor Braam Louw

Area of Research: Metabolic enzymes of the malaria parasite as potential drug targets.
Functional genomics
Bioinformatics and structural genomics

The scientific goal of the research programme at the University of Pretoria is to characterise and validate novel malaria parasite targets to assist for the development of therapeutic intervention strategies. The focus is mainly on three enzymes of the polyamine and two of the folate metabolic pathways of *Plasmodium falciparum*. The polyamine metabolism is of particular interest as the parasite is dependent on polycations for normal division and differentiation but the enzymes of the pathway still need to be validated as drug targets. Only two enzymes of the folate pathway are validated as drug targets and the focus is on recently described enzymes of this pathway as potential targets. Studies on enzymes from both these pathways include improvements in the recombinant expression of the native genes or synthetic constructs followed by selected mutations for the characterisation of novel, parasite-specific features involved in the activity of these enzymes and protein-protein interactions.

The group is also active in determining the mechanism of action of potential antimalarial plant compounds and inhibitors by gene expression profiling using SSH and DNA microarrays of the malaria parasite under selective drug pressure. In this regard, the department is a member in the Innovation Fund consortium focussed on establishing a Novel Drug Discovery Platform from Indigenous Plants. Additional activities include DNA microarray and proteomic experiments of parasite populations treated with three well-defined inhibitors of the polyamine pathway in collaboration with the CSIR, Bernard-Nocht Institute for Tropical Medicine (Germany) and the University of Manchester (UK) to elucidate parasite drug responses and gene function and to identify novel gene targets.

The Bioinformatics and Computational Biology facility Unit undertakes structural modelling of enzymes from the parasite's metabolic pathways and is involved in the establishment of *in silico* methods for the design of drug-like molecules. A web interface named MADIBA (Micro Array Data Interface for Biological Annotation) is nearing completion to assist in the interpretation of data derived from gene profiling experiments and the elucidation of the mode of action of drugs or inhibitors. Other bioinformatics skills include: gene and protein sequence analysis and motif identification; algorithm design; microarray data

analysis; microsatellite and SNP analysis; combinatorial libraries and drug design; databases; pipelining and web interfaces.

5.3.7 Rhodes University

5.3.7.1 Department of Biochemistry, Microbiology and Biotechnology: Professor Greg Blatch

Area of research: Malaria Chaperones in biology, medicine and protein biochemistry

The research group is involved in the study of the role of heat shock proteins in disease and infection. The project therefore includes, but is not limited to, malaria. Heat shock proteins, also known as stress proteins or molecular chaperones, are a family of proteins that have been shown to be adapted to facilitate the correct folding of other proteins under physiological and stress conditions. The research project involves the investigation of the molecular basis of the cell stress response and the application of this knowledge in protein biotechnology leading to a fundamental understanding of how cells ensure the correct folding and functioning of proteins under physiological, stress and disease conditions. There are three programmes within this project:

Chaperone/co-chaperone interaction and the molecular basis of the cellular stress system.

The mechanism by which co-chaperones interact with and regulate molecular chaperones is being investigated in order to understand how these interactions provide cytoprotection. An understanding of the molecular basis of the specific interactions between partner chaperones and co-chaperones in pathogen systems will facilitate the identification of pathogen-specific chaperone targets for drug development.

The role of heat shock proteins in disease and infection

The project studies the similarities and differences between how parasites and their hosts deal with stress leading to an understanding of how parasites protect themselves.

Improved heterologous protein over-expression by co-expression of protein folding factors.

Molecular chaperones can be utilized in industrial biotechnology applications to improve the yield of recombinant protein production. The early steps of isoprenoid biosynthesis have been identified as valid targets for the therapy of malaria. Inhibitors of the 1-deoxy-D-xylulose 5-phosphate (DOXP) reductoisomerase (e.g. fosmidomycin) have been shown to have antimalarial activity *in vitro* and in animal mouse models.²⁹ The enzyme is difficult to produce *via* recombinant techniques; hence the use of a molecular chaperone could assist to improve the yield.

Professor Blatch holds a Wellcome Trust International Senior Research Fellowship. Expertise is in the isolation of genes and heterologous protein overproduction, affinity purification and *in vitro* and *in vivo* characterization of molecular chaperones of parasitic origin. Techniques include a range of molecular and cellular techniques including *in vitro* assays (protein binding assays, biological activity assays, protein folding/refolding assays), and *in vivo* assays (localisation and co-localisation studies using immunofluorescence staining and reporter tagging, genetic complementation assays)

5.3.8 University of Stellenbosch

5.3.8.1 Department of Biochemistry: Dr Marina Rautenbach

Area of Research: Haemolytic Peptides directed against the Malarial Blood Stage of *P. falciparum*

Dr Rautenbach is involved in the design, synthesis, purification, testing and determination of the mechanism of action of antimicrobial peptides and compounds. The BIOPEP Peptide facility, run under strict GLP rules, has the capability of producing peptides for industrial and diagnostic use.

The focus in the malaria area is on membrane active peptides and compounds. In collaboration with Dr H Hoppe (University of Cape Town Department of Pharmacology), a number of peptides and polyene antibiotics with known antimicrobial and haemolytic activity were investigated. The haemolytic activity of the polyketides, amphotericin and nystatin and several cyclic antifungal peptides were found to be effective against the trophozoite blood stage of the malaria parasite, *P. falciparum*. The selective lysis of the membranes of red blood cells infected with parasites was found to be up to 1,000 times that of non-infected erythrocytes.

These compounds would not be candidates for prophylaxis or in the treatment of uncomplicated malaria, but are believed to be promising candidates for treatment of severe malaria, as *in vitro* tests have shown killing of chloroquine resistant *P. falciparum* trophozoites within one hour. Additional work through collaboration with Professor Pieter Swart (University of Stellenbosch) is being conducted in order to find ways of lowering the cost of manufacture. One patent has been taken out on the polyketide results and a second patent on the cost-effective production and purification of candidate compounds and peptides is currently under investigation in this research programme.

5.3.9 University of Witwatersrand

5.3.9.1 Department of Molecular Medicine and Haematology/NHLS: Professor Theresa Coetzer

Area of research: Interaction of parasite proteins with the red blood cell membrane
Characterisation of proteins and metabolic pathways
Gene Regulation

Projects in the group are in the basic research phase, but the long term goal is geared towards the identification of potential drug targets. Specific research projects include the study of the mechanism whereby the parasite interacts with the red blood cell membrane proteins. The development of the parasite within human erythrocytes induces significant changes to the structure and function of the host membrane. The identification of interactions between proteins expressed by the parasite and proteins in the host red blood cell membrane (e.g. protein 4.1 and spectrin) is hence being studied. The characterisation of novel protein interactions will enhance the understanding of *P. falciparum* biology. Another project is the study of gametocytogenesis of the parasite for example by studying the gene regulation processes.

The group is also active in the characterisation of various proteins and metabolic pathways. One potential target has been identified through the discovery of a gene coding for the glycerol kinase enzyme in the parasite. This gene has been cloned and the recombinant protein will be expressed and assayed for functional activity. In addition, a putative gene encoding malaria telomerase has been

identified and this may provide another potential drug target. This research is also relevant to understand evolution of the genome.

Expertise within the group includes basic molecular biology techniques, creation of *P. falciparum* phage display libraries; purification of red blood cell membrane proteins; gametocyte culture; bioinformatics analysis; and the cloning, expression and purification of parasite proteins.

The department collaborates internationally with INSERM in Paris and SANBI at the University of the Western Cape.

5.3.9.2 Department of Clinical Pharmacology: Professor Ivan Havlik

Area of research: Malaria Cell Biology
Screening of potential antimalarial drugs
Clinical Trials of potential antimalarial drugs

The department researches various aspects of the *Plasmodium* protozoa, including drug testing, biochemical and molecular studies and conducts clinical trials.

Hundreds of novel compounds have been screened *in vitro* against sensitive and drug resistant parasites. This has been achieved by establishing numerous local and international collaborations who have synthesized various derivatives of hydroxyquinolines (University of the North West: Potchefstroom), thiosemicarbazones (Delhi), chalcones (Delhi), structurally diverse nucleoside phosphonic acids (Prague) and cyclin dependent kinase inhibitors (Paris). The potential antimalarial activity of traditionally used plants has also been investigated along with collaborators from the Universities of Wits, KZN and North West: Potchefstroom. Research into various aspects of iron metabolism in the malaria parasite is being conducted; including how iron is acquired and utilized by the parasite and how drugs interfere with its uptake; the formation of malaria pigment and whether various standard and novel drugs interfere with its formation as the hydroxyquinoline drugs are proposed to do.

The group conducts basic research on the functional characterization of *Plasmodium* kinases involved in cell cycle regulation and signal transduction. The current focus area is the *Plasmodium* homologues of cyclin G associated kinase, NIMA related kinases and phosphatidylinositol-3 kinase. This work is carried out in collaboration with Christian Doerig of the French INSERM Unit 609, located at the Wellcome Center for Molecular Parasitology, University of Glasgow, Scotland. The ultimate aim of this collaboration is the identification of compounds that will block differentiation of parasites into male and female gametocytes. In this context a large library of potential cyclin dependent kinase inhibitors have been screened for their effect on parasite survival.

The department has collaborated in preclinical studies of curdlan sulphate (CRDS), which showed *in vitro* inhibition of *P. falciparum* and a down-modulation of the immune response. Clinical studies in a small number of patients using CRDS as an adjunct medication to conventional artesunate therapy concluded that CRDS might benefit patients with severe/cerebral malaria presenting with no additional complications such as organ damage. Further funds will be required to manufacture new batch of CRDS and finance the clinical study to complete the investigation. Additional expertise is in the study of the formation of rosettes, the adherence of infected erythrocytes to uninfected erythrocytes, during the trophozoite stage of parasite development.

5.4 TRAINING AND CAPACITY BUILDING

5.4.1 University of Pretoria

5.4.1.1 Foundation for Professional Development: Professor Anton Stoltz

Area of Research: Post-graduate training in infectious diseases.

Professor Stoltz is a member of the Foundation for Professional Development. This organisation provides training courses for the medical profession, including general practitioners as well as specialists, in the management of infectious diseases such as malaria and HIV. Currently, and HIV training course in 10 countries in Africa is being carried out. A malaria course is under development. The course could in the future be taken into Africa.

5.4.2 University of Witwatersrand

5.4.2.1 Centre for Post-Graduate Studies: Professor Steve Chandiwana

Area of research: Research capacity building for malaria

Professor Chandiwana is Assistant Dean of Research and Postgraduate Studies in the Faculty of Health Sciences. The centre provides research and educational opportunities to scientists and professionals involved in health research, including malaria research, in three different areas.

Training in protocol/proposal design.

This course is teaches research methodology so as to ensure that scientists and researchers achieve their objectives.

Proposal/Grant Writing

This course covers issues such as how to mobilise funding sources, and how to write proposals. Researchers are taught techniques, which allow them to be more competitive in applying for global, research funds.

Research Analysis

This course is aimed at ensuring that scientists maximise the results of their research and can convert the analysis into reports or publications.

Refresher courses to middle level scientists working at research laboratories in Africa cover research methods based on epidemiology principles to ensure effective interventions, malaria immunology and preparation for vaccine trials. Young researchers and postgraduate students especially from previously disadvantaged groups such as black and female academics undertaking research projects are also mentored and supervised.

Dr Chandiwana has connections to many international malaria organisations including AMANET, the John Hopkins Malaria Institute Advisory Committee, the Biomedical Research and Training Institute (BRTI).

5.5 SUMMARY:

The above summaries clearly indicate that the majority research groups in South Africa are involved in basic scientific research. Most work is directed at furthering the understanding of malaria cell biology, the cell biology of antimalarials, and the application of this research in the identification and validation of potential drug targets. Some research projects involving medicinal chemistry, rational drug design and synthetic organic chemistry have however been identified. Limited research into the development of insecticides has been identified, with the only mention of insecticides being in the context of improving existing products by reformulation and in isolating active ingredients from natural repellents.

Two groups, the MRC and NICD, are involved in epidemiological research. Research areas covered include the molecular identification and characterisation of mosquito vectors, molecular mechanisms of mosquito resistance to insecticides, biochemical basis of insecticide resistance and molecular mechanisms of drug resistance. One of the proposed MIA programmes is the application of molecular techniques to population studies and tracking of resistance through the application of molecular marker techniques to population studies and epidemiology. The focus will be on the movement of vectors and parasites, linked to trends in insecticide and drug resistance. This is already a core part of the research conducted by these two groups and hence the requisite skills already exist.

Two groups with interests in diagnostics have been identified, University of KwaZulu Natal (UKZN) and National Bioproducts Institute (NBI). NBI has developed a pair of monoclonal antibodies specific for HRP2 that are suitable for use in a rapid diagnostic test. These antibodies are specific for *Plasmodium falciparum* and recognise different epitopes on this molecule. UKZN has developed an array of antibodies against anti-malarial drugs, which can be used to track malaria drugs in a range of cells, tissues and body fluids. Through an international collaboration in a MVI project, the team is developing reagents for a second generation of an ELISA diagnostic kit, the first generation being used as an experimental tool in malaria vaccine trials. Coupled with the complementary skills available in other MIA research groups, the development and implementation of molecular assays for diagnostic interventions should be feasible.

The process of drug discovery and drug development involves a number of discrete stages (Appendix 3), as does the process into insecticide discovery. However, due to the fact that there is currently very little research in South Africa on the development of insecticides, the analysis below will focus on the drug development process. The “genes to drugs” model needs more than the first step of basic exploratory biology on target identification. Validated targets must be developed. After lead identification, lead optimization and drug candidate selection is required. The downstream development process that needs to be managed once a candidate enters preclinical development includes process chemistry to determine the cost of manufacture, scalability, stability etc., as well as preclinical animal safety studies under Good Laboratory Practice (GLP) conditions, to assess the targets generated, provide good description of pharmacological properties to assess drug-like potential.

An overview of the drug discovery and development process together with a flow sheet of the insecticide development process is attached as Appendix 4 and the activities of the current research programmes are mapped against this chart. This chart indicates that whilst MIA has access to the full spectrum of scientific components required to discover and develop drugs and move from early discovery research through to preclinical and clinical development, some of these components are better developed than others. Most research projects are in the early stages of the process.

The following competencies relevant to the projects proposed by MIA are available in varying degrees are:

1. Parasite biology and biochemistry
2. Functional genomics
3. Structural and computational biology
4. Bioinformatics
5. Medicinal chemistry
6. Combinatorial chemistry, organic synthesis
7. Analytical chemistry
8. High throughput biomolecular interaction analysis
9. High throughput *in vitro* screens
10. High throughput cellular/phenotype screens
11. National product chemistry linked to South Africa's biodiversity
12. Animal models of malaria
13. ADMETox testing of drug leads
14. Development of formulations and delivery mechanisms
15. Process development for large- scale development
16. Management of Clinical trials

To move past the development of a technology platform and to convert the validated targets into full drug discovery programmes, a combination of genomics and biology-based expertise, practical experience of medicinal chemistry, pharmacology and clinical trials to generate compounds of therapeutic interest is critical. The use of upstream technologies such as genomics to identify targets, high-throughput screening, molecular modeling and screening and other techniques identified as being available in South Africa need to be optimally integrated with technologies such as medicinal chemistry, pharmacology and rational drug design in order to develop an early R&D pipeline. In addition, capacity in the downstream interface such as in the preclinical development phase needs to be enhanced and partnerships in the clinical development, dossier preparation and registration will have to be formed in order to strengthen this aspect of the development chain.

The integration and management of this entire process is critical for success in moving from discovery lead identification into drug candidates and finally through to a registered drug. Some elements of this integration have begun to be developed for example in the various collaborations between the University of Cape Town's Departments of Chemistry, Pharmacology and Institute of Infectious Disease and Molecular Medicine as well as the University of Stellenbosch and through the development of the national research and development platform for novel drug development from indigenous plants.

The efficacy and specificity of anti-malarial drugs rely on their ability to interfere with aspects of the metabolism of *Plasmodium* that differs significantly from the host. Parasite survival in the host erythrocytes requires several metabolic adaptations that render it susceptible to chemotherapy. The mechanism of action of existing drugs takes advantage of these innovations. In addition, potential drug targets have already been identified based on an understanding of the cell biology of the malaria parasite. Whilst it is not possible within the scope of this report to outline all of the potential scientific opportunities, some are presented below for indicative purposes only. The attached Appendix 5 shows the site of drug action and new drug targets currently being researched internationally.³⁰

Haemoglobin degradation and interaction with haem remain a focus area for drug discovery. Chloroquine which acts by interference with the malaria pigment haemozoin, allows the intraparasitic build-up of toxic free haem. This has defined the inhibition of haemozoin formation as an attractive drug target. The dihydrofolate reductase (DHFR) inhibitors, pyrimethamine and proguanil, are important antimalarials partly due to their relative selectivity for the parasite enzyme. The genetic resistance mechanism to the antifolate drugs is well understood, with pyrimethamine resistance being due to the accumulation of mutations in DHFR. The identification of improved inhibitors of DHFR that overcome resistance to pyrimethamine is therefore a research opportunity being studied by medicinal chemists.

The identification of semisynthetic and fully synthetic endoperoxides that will retain the activity of the artemisinin derivatives but overcome some of their deficiencies has already been mentioned as an area of activity. Unexploited targets in the food vacuole include the proteases associated with haemoglobin degradation. Cell signaling pathways, through protein kinases such as cysteine protease thus represents another opportunity. Fosmidomycin, an inhibitor of 1-deoxy-D-xylulose-5-phosphate synthase, originally identified in an industrial antibacterial drug discovery programme, is a potential antimalarial compound acting in the non-mevolonate pathway.

Much of the research described as being conducted in South Africa falls within the context of many of these promising areas already identified.

6 CONCLUSION:

It has been widely stated that the completed genomes of *P. falciparum* and the vector *An. gambiae* open up new approaches to the development of drugs, vaccines, insecticides and insect repellents, as well as intervention into malaria transmission. Advances in genetics and biochemical engineering offer new and improved means of characterizing potential targets.³¹ Bioinformatics tools can help predict the structure and function of gene products. The speed with which many compounds can be tested against protein targets has hence increased dramatically. Genetic tools will also allow the sampling of parasite, mosquito, and human genomes in malaria affected areas to support the malaria control activities.

MIA has stated its key objective in the integration of researchers focusing on molecular aspects of malaria drug and insecticide discovery, molecular epidemiology and diagnostics, and capacity building in order to improve malaria prevention and control. Three programmes are envisaged:

- The development of new and modified drugs and insecticides
- The development and implementation of assays for epidemiological and diagnostic interventions
- Capacity building programmes as a cross-cutting programme.

As summarized above, South Africa has access to the full spectrum of scientific components required to discover and develop drugs and move from early discovery research through to preclinical and clinical development, although some of these components are better developed than others. Nevertheless, South African has a core of excellent researchers and facilities in the malaria research field, a strong base in biomedical research, high-quality medical schools and a good infrastructure. Coupled with the increasing financing of malaria research and involvement of the pharmaceutical industry through the various public private partnerships as outlined above, the prospect of the development of new, affordable drugs, diagnostics and insecticides appears to be a feasible opportunity.

The involvement of several academic and industrial partners in a virtual drug discovery model such as that proposed by MIA is relatively new, and involves a unique set of challenges. The early stages of the process in particular will require a continuous, interactive exchange of ideas between scientists from a broad range of disciplines. The model is however being followed successfully in the development of drugs to treat poverty related diseases such as malaria by PPPs such as the MMV. Most of these organizations furthermore recognize that the impact and long-term sustainability of drug R&D for poverty related diseases depends on the use of research capacity in developing countries. However, whilst some of these countries have expertise in some of the scientific components required, few have the capacity to perform all of the tasks necessary.

A recent article in Nature Biotechnology stated that South Africa is poised to take the lead in developing health care biotechnology in the sub-Saharan African region. It recommended a good starting point as being the identification of a problem disease prevalent in the community and a technology that could be used to address this problem, and then to develop an infrastructure to support R&D in this area. Thus through its identified focus on malaria and the use of molecular technologies, MIA has identified a unique opportunity to position itself in sub-Saharan Africa and internationally through the integration and capacity building programmes as proposed in the initiative. Through applying the lessons learned by the PPPs³² internationally in the establishment of a virtual development process, ensuring the optimization and focusing of its manpower, infrastructure and financial resources, coupled with careful management of the integration process, MIA should be well positioned to achieve success in its goals.

7 INTERVIEWEES

Grateful thanks are extended to the following scientists, experts, and representatives of funding organisations and other interested parties who gave so freely of their time to support this work via interviews, discussions and a variety of other communications.

7.1 RESEARCHERS:

University of Cape Town

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University of Pretoria

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Professor Anton Stoltz

Rhodes University

Professor Greg Blatch

University of Stellenbosch

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University of Witwatersrand:

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Professor Steven Chandiwana

Professor Ivan Havlik

7.2 FUNDING ORGANISATIONS

Biotechnology Regional Innovation Centre:

BioPAD: Dr Agatha Masemola

CBT: Dr Joe Molete

LIFElab: Professor Indres Moodley

Godisa Incubator: Chemin

Mr Joe Kruger

IDC/SPII

Mr Areef Suleman

Innovation Fund:

Mr Vuyisele Phehane

Medical Research Council:

Professor Lynda Chalkley

Mr Clive Glass

National Research Foundation:

Mr Rob Drennan

THRIP:

Dr Mmbonbeni Muofhe

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**Appendix 1
NRF Projects 2005**

Initial	Surname	Organisation	Grant	Short title
L	VISSER	UP	R 211,610	VISSER L CGRS
L	VISSER	UP	R 298,000	VISSER L CGRS
L	VISSER	UP	R 20,000	VISSER L CGRS
TJ	EGAN	UCT	R 31,200	CHEMISTRY OF ANTIMALARIALS
L	VISSER	UP	R 95,825	OLIGOMERS AGAINST MALARIA & TB
HM L	MARQUES VISSER	UW UP	R 556,000 R 0	BIOINORGANIC CHEMISTRY & APPLICATION OLIGOMERS AGAINST MALARIA AND TB
AI	LOUW	UP	R 363,000	MALARIA PARASITE PROTEINS
I PI	HAVLIK FOLB	UW UCT	R 126,154 R 105,000	FRANCO / RSA AGREEMENT UK / RSA AGREEMENT
S	DAYA	RU	R 3,500	PROF R KALARIA
JPD BL	GOLDRING SHARP	UNPM MRC	R 122,000 R 145,000	DYE-ANTIBODY, ANTI-MALARIAL DRUGS UK/RSA AGREEMENT
KJ	NEL	UP	R 7,600	EXPRESSION OF CHIMERIC CONSTRUCTS
TL AI	COETZER LOUW	SAIM UP	R 68,000 R 120,000	MALARIA AND RED CELL MEMBRANES UK/RSA AGREEMENT
JPD K	GOLDRING CHIBALE	UNPM UCT	R 116,000 R 394,751	Development of dye based diagnostics NEW ANTIMALARIAL AGENTS
AP	LOTTER	PUCH	R 662,000	Cost effective Pharmaceuticals
AI	LOUW	UP	R 111,922	Malaria parasite protein properties
FR TL	VAN HEERDEN COETZER	RAU UW	R 66,000 R 87,000	African medicinal plant chemistry Malaria and red blood cell membranes
I BL AI	HAVLIK SHARP LOUW	UW MRC UP	R 0 R 98,921 R 0	FRANCO / RSA AGREEMENT UK/RSA AGREEMENT UK/RSA AGREEMENT

**Appendix 1
NRF Projects 2005**

Initial	Surname	Organisation	Grant	Short title
M	COETZEE	SAIM	R 59,000	Anopheles funestus in South Africa
JPD TL	GOLDRING COETZER	UNPM SAIM	R 24,000 R 130,000	Immunomodulation in malaria Malaria and red blood cell membranes
JAO	OJEWOLE	UDW	R 170,000	SWEDEN/SA AGREEMENT
TL K	COETZER CHIBALE	SAIM UCT	R 204,000 R 426,000	Malaria and red blood cell membranes NEW ANTIMALARIAL AGENTS
AI	LOUW	UP	R 509,500	Malaria parasite protein properties
DB HM	MCINTOSH MARQUES	UCT UW	R 542,000 R 427,250	Ion pumps and ABC transporters Bioinorganic Chemistry & Application
WJ	LUUS-POWELL	UNO	R 7,500	CONFERENCE
K	CHIBALE	UCT	R 120,000	INDO/RSA AGREEMENT
G	MAARTENS	UCT	R 139,000	SWED/RSA RESEARCH PARTNERSHIP
LL K	KOEKEMOER CHIBALE	SAIM UCT	R 35,000 R 235,000	Metabolic resistance in a major mala New Antimalarial Agents
LJ	MAMPURU	UNO	R 265,000	Novel Isoprenoids in Human Disease T
AI	LOUW	UP	R 80,250	Effects of drugs on malaria parasite
Y	JOUBERT	UP	R 33,000	Structural annotation of P.falciparu
MP	SEKHOACHA	UCT	R 55,000	Isolation of antimalarial compounds
K	DE VILLIERS	UCT	R 40,000	Not yet available
Y	JOUBERT	UP	R 5,000	Structural annotation of P.falciparum
			R 7,315,983	

Appendix 1
NRF Projects 2005

Long title

IDENTIFIKASIE, KARAKTERISERING EN IMMUNOLOGIESE AANWENDING VAN ANTIGENE VAN ENDO-(MALARIA) EN EKTOPARASITIESE (BOSLUISE) SOWEL AS BAKTERIESE OORSPRONG

DIE IDENTIFIKASIE, KARAKTERISERING VAN GENE OF PROTEINE EN ANTIGENE VAN PARASITIESE (MALARIA, BOSLUISE) SOWEL AS BAKTERIESE OORSPRONG.

DIE IDENTIFIKASIE, KARAKTERISERING EN IMMUNOLOGIESE AANWENDING VAN PROTEIENE EN ANTIGENE VAN ENDO- EN EKTOPARASITIESE (MALARIA, BOSLUISE) SOWEL AS BAKTERIESE OORSPRONG

CHEMICAL STRATEGIES FOR THE DEVELOPMENT OF ANTIMALARIALS: (A) THE MECHANISM OF ACTION OF QUINOLINE ANTIMALARIAL DRUGS AND (B) TRANSFERRIN AND IRON UPTAKE BY THE MALARIA PARASITE

THE DESIGN AND EVALUATION OF MODEL SYNTHETIC PEPTIDES AND OLIGONUCLEOTIDES AS ANTIMALARIAL AND ANTI-TUBERCULOSIS AGENTS

CHEMISTRY OF PORPHYRINS, CORRINS AND TRANSFERRINS, AND APPLICATIONS IN THE MODELLING OF BIOLOGICAL MOLECULES AND THE DESIGN OF ANTIMALARIALS

MOLECULAR AND FUNCTIONAL CHARACTERISATION OF PROTEINS REQUIRED BY THE MALARIA PARASITE, PLASMODIUM FALCIPARUM, FOR ITS METABOLISM AND DEVELOPMENT IN THE HUMAN ERYTHROCYTE.

PLASMODIUM FALCIPARUM PROTEIN KINASES: POTENTIAL TARGETS FOR NEW CEMOTHERAPEUTIC AGENTS AGAINST MALARIA

ANTIMALARIAL ACTIVITY OF TWO SOUTH AFRICAN TRADITIONAL PLANTREMEDIES TO GIVE A PLENARY LECTURE AT THE SYMPOSIUM OF THE SOUTHERN AFRICAN NEUROSCIENCE SOCIETY HOSTED BY PROF S DAYA.

DYE-ANTIBODY BASED ANTIGEN DETECTION TO DEVELOP COLOUR BASED DIAGNOSTIC REAGENTS. NEW DRUGS FOR MALARIA - SCREENING EXTRACTS OF PLANTS USED BY TRADITIONAL HEALERS AND TESTING QU

INSECTICIDE RESISTANCE MONITORING AND MANAGEMENT IN MALARIA VECTORS
EXPRESSION OF CHIMERIC CONSTRUCTS OF GLUCOSE TRANSPORTERS OF THE RAT AND MALARIA PARASITE IN ORDER TO LOCATE FUNCTIONAL AREAS OF MALAOTEIN
MOLECULAR STUDIES ON THE ROLE OF RED CELL MEMBRANE PROTEINS IN MALARIA INFECTION AND PATHOGENESIS

A POTENTIAL NEW ANTIFOLATE DRUG TARGET IN HUMAN MALARIA PARASITES

Attaching dyes to chicken antibodies for the detection step in the diagnosis of human(malaria), animal and plant diseases. Raising anti-malarial drug antibodies to detect drugs in patient plasma.

Malaria Parasite Proteases as Targets for the Rational Design of New Antimalarial Agents

Physico chemical properties of drugs and drug delivery technologies for designing more effective and cheaper medicines for South Africa with special emphasis on drugs for the treatment of epidemiological diseases such as TB and malaria.

Functional characterisation of malaria parasite proteins for identification of therapeutic targets to arrest its metabolism and development in the human erythrocyte.

Ethnopharmacology, phytochemistry and biological activity (antimicrobial, antimalarial and antiviral) of South African medicinal plants and the chemical synthesis of active compounds.

Molecular studies on the role of red cell membrane proteins in malaria infection and pathogenesis

PLASMODIUM FALCIPARUM PROTEIN KINASES: POTENTIAL TARGETS FOR NEW CEMOTHERAPEUTIC AGENTS AGAINST MALARIA

INSECTICIDE RESISTANCE MONITORING AND MANAGEMENT IN MALARIA VECTORS

A POTENTIAL NEW ANTIFOLATE DRUG TARGET IN HUMAN MALARIA PARASITES

Appendix 1
NRF Projects 2005

Long title
Biology of and insecticide resistance in the South African populations of the malaria vector mosquito <i>Anopheles funestus</i>
Immunomodulation in malaria: elemental composition of monocytes during antimalarial drug treatment and malaria infections
Molecular studies on the role of red cell membrane proteins in malaria infection and pathogenesis
PHARMACO-CHEMICAL EVALUATION OF PLANTS USED AS ANTIMALARIAL REMEDIES IN ZULU FOLK MEDICINE
Molecular studies on the role of red cell membrane and <i>Plasmodium falciparum</i> proteins in infection, pathogenesis and transmission of malaria
Malarial Parasite Cysteine Proteases as Targets for the Rational Design of New Antimalarial Agents
Functional characterisation of malaria parasite proteins for identification of therapeutic targets to arrest its metabolism and development in the human erythrocyte.
Mechanism and drug targeting of ion pumps, ABC transporters, and a purine salvage enzyme from normal cells, cancer cells, pathogenic bacteria, and the malaria parasite.
Bioinorganic Chemistry of Biologically Important Complexes and Application to the Study of Malaria
MRS W.J.LUUS-POWELL TO PARTICIPATE IN : THE JOINT MALARIA & BSP SPRING MEETING : MANCHESTER : 6 - 9 APRIL 2003
BIOCATALYTIC AND COMBINATORIAL APPROACHES TO NOVEL NATURAL PRODUCT BASED ANTITUBERCULOSIS AND ANTIMALARIAL AGENTS
NON LINEAR MODELLING OF THE POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIRETROVIRAL, ANTITUBERCULOUS AND ANTIMALARIAL DRUGS
The involvement of two classes of monooxygenases in a metabolic pyrethroid resistant population of a major malaria vector <i>An. funestus</i> (Diptera: Culicidae)
New antimalarial agents targeting cysteine protease enzymes in <i>Plasmodium falciparum</i>
Novel Isoprenoids in Human Disease Therapy: Characterisation and evaluation of the anti-neoplastic, antiviral and antimalarial properties of isoprenoids and related phytochemicals isolated from indigenous medicinal plants from Limpopo and Mpumalanga
Genome-wide expression profiling of the human malaria parasite, <i>Plasmodium falciparum</i> , under pharmacological challenge
Structural annotations of all putative protein products identified in the malaria genome, and preparing a database containing these annotations.
Identification and purification of antimalarial compounds from medicinal plants. Characterisation of the active compounds in vitro and in vivo. Characterisation of its pharmacokinetic parameters using mice models.
The exact details of the project are presently under consideration. However, i would like the outcomes of the project to be usefull beyond the research laboratories. In the bioinorganic field, this may take the form of developing novel antimalarials.
Structural annotations of all putative protein products identified in the malaria genome, and preparing a database containing these annotations.

REPORT

SECTION 2

MALARIA INITIATIVE FOR AFRICA

“Gathering of Data on the Funding Mechanisms for Malaria Research and the Status of Malaria Research in South Africa”



Plasmodium falciparum model (measuring approximately 32"x20"x 7")
Created by Bill Burns
P. falciparum is responsible for the most severe form of malaria, including cerebral malaria. This model details an infected red blood cell whereby the vertical projection of the diseased part is exaggerated tenfold. Four species of protozoan parasites cause malaria in humans: Plasmodium falciparum, P. vivax, P. malariae, and P. ovale.

Date: October 2005

Dr Lorraine Thiel

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1 ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
ADME	Adsorption, distribution, metabolism and excretion
AMANET	African Malaria Network Trust
<i>An.</i>	<i>Anopheles</i>
ARC	Agricultural Research Council
MARA/AMRA	Mapping Malaria Risk in Africa
BioPAD	Biotechnology Partnerships and Development
BRICS	Biotechnology Regional Innovation Centers
BRTI	Biomedical Research and Training Institute
CBT	Cape Biotech Trust
CCM	Country Coordinating Mechanism
CSIR	Council for Scientific and Industrial Research
CRO	Contract Research Organisations
CSIR	Council for Scientific and Industrial Research
DANIDA	Danish International Development Agency
DGIS	Directorate-General for International Co-operation
DHFR	Dihydrofolate reductase
DNDi	Drugs for Neglected Diseases Initiative
DST	Department of Science and Technology
DTI	Department of Trade and Industry
ECoBio	East Coast Biotechnology Regional Innovation Centre
GLP	Good laboratory Practice
GMP	Good Manufacturing Practice
IOWH	Institute for One World Health
IKS	Indigenous Knowledge Systems
IND	Investigational New Drug Application
IPT	Intermittent Presumptive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide treated nets
LSDI	Lubombo Spatial Development Initiative
MIM	Multilateral Initiative for Malaria
MiTech	Missions in Technology
MMV	Medicines for Malaria Venture
MRC	Medical Research Council
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NICD	National Institute of Communicable Diseases
NIH	National Institute of Health
NRF	National Research Foundation
<i>P</i>	<i>Plasmodium</i>
PPP	Public Private Partnership
REDIBA	Research development initiative for black academics
RBM	Roll Back Malaria
R&D	Research and Development

RISA	Research and Innovation Support Agency
RPG	Research Project Grants
RU	Rhodes University
PPD	Product Process Development Scheme
RMCC	Regional Malaria Control Council
SANBI	South African National Biodiversity Institute
SATMERG	South African Traditional Medicines Group
SETI	Science, Engineering and Technology Institution
SME	Small and Medium Enterprises
SP	Sulphadoxine-pyrimethamine
SPII	Support Programme for Industrial Innovation
SU	Stellenbosch University
TAP	Technology Advancement Programme
THRIP	Technology and Human Resources for Industry Programme
UCT	University of Cape Town
UNICEF	United Nations Children's Fund
UP	University of Pretoria
USAID	US Agency for International Development
Wits	University of Witwatersrand
WHO	World Health Organisation
WHO/TDR	WHO Special Programme for Research and Training in Tropical Diseases

2 EXECUTIVE SUMMARY

Malaria is clearly a disease of poverty, and is commonly referred to as a “neglected disease”. These diseases also referred to as tropical or endemic diseases, affect millions of patients, but their lack of ability to pay for market-financed products results in insufficient market incentive to drive the development of innovative products by “Big Pharma”. The net effect is that only 10% of global R&D resources are directed at diseases, including malaria, that account for 90% of the global disease burden.

Reducing the burden posed by these neglected diseases will require increasing R&D for new drugs, vaccines and diagnostics. However, most pharmaceutical companies disengaged from research into tropical diseases in the 1970s, leaving a gap in the development of new and affordable tools to manage these diseases. The number of effective drugs to treat malaria is small; the few existing drugs are plagued by increasing resistance, particularly in the tropical regions, at a rate that outpaces the development of new antimalarial drugs. The most effective drugs used are combinations, which in the short term replace the ineffective drugs used today, and delay the development of resistance against any one of the individual drugs. These are however significantly more expensive than traditional antimalarials.

The public sector has long taken an interest in stimulating the discovery and development of new drugs, vaccines and diagnostics. A consolidated public-private and philanthropic approach, commonly known as public-private partnerships (PPP) has now replaced private sector investment in this market. The public-philanthropic sector provides funds to complement the R&D and other resources in the private sector. This new partnership approach, which operates through a virtual R&D methodology, brings many advantages coupled with many unique management and organizational challenges. The focus of these PPPs on neglected diseases, together with the availability of the malaria genome, is now believed to allow the full benefit of modern drug discovery research technologies to be applied to the development of improved drugs, vaccines and diagnostics for malaria.

The United Nations Development Programme, World Bank, and WHO special programme for research and training in Tropical diseases (WHO/TDR) was the first such organisation created in 1975, establishing a partnership between public sector organizations and private companies. This process has rapidly accelerated since the 1990s with the creation of the Medicines for Malaria Venture (MMV) and other such organizations. The MMV was the first organisation to put the theory of PPP drug discovery into practice and has initiated several virtual drug discovery projects. Other organizations managing public-private partnership malaria R&D include the Multilateral Initiative for Malaria (MIM), Drugs for Neglected Diseases (DNDi), Institute for One World Health (iOWH). These PPPs have structured themselves along the lines of industry practice with the goal of delivering to patients in developing countries new products and that meet unmet medical needs and that are appropriate and affordable. Central to this process is the concept of a product development team. The model is evolving as it is adapted to more projects, with numerous lessons being learned in the process, such as that a strong team spirit and commitment are vital when teams are operating at long distances.

Simultaneously, funds committed to malaria research have increased through national governments and philanthropic organizations such as the Gates Foundation. Overall, funds committed to malaria research have increased from an estimated \$ 85 million in 1995, to a level well over \$ 100 million. The National Institute of Allergy and Infectious Diseases (NIAID) increased its commitment by more than 150% between 1995 and 1999 and the Wellcome Trust doubled its expenditure. The Copenhagen Consensus

Initiative concluded that deploying effective malaria drugs had one of the highest cost-benefit ratios when opportunities for global investment across a number of segments were compared. The level of funding is however still believed to be low relative to the disease burden. A greater proportion of donor funding is allocated to the prevention, treatment, care and support of malaria in endemic countries. The global community has hence been urged to increase its funding for antimalarial R&D.

The Global Fund to Fight AIDS, Tuberculosis and Malaria is an international, independent public-private partnership which finances programmes for the prevention, treatment, care and support of AIDS, TB and malaria but does not implement programmes directly. Only a small proportion of the fund is for research. The Bill and Melinda Gates Foundation is a grant-making organisation with a mission to promote greater equity in global health. One of the Foundation's spearheads is the Global Health Programme focusing on poverty-related diseases including malaria. The largest proportion of the grants is on research to create and/or improve health tools such as vaccines, drugs, and diagnostics.

The National Institute of Health (NIH), an agency of the US Department of Health and Human Services, awards funds to research programmes concerning health issues such as malaria. NIAID, a component of the NIH, conducts and supports basic and applied research to better understand, treat and ultimately prevent infections. The US Agency for International Development (USAID), an American government agency, has a priority in the area of infectious diseases in the sustainable reduction of deaths due to malaria and the incidence of other infectious diseases of major public health importance. In addition to providing expanded support for prevention and control programmes, USAID supports the development of vaccines and new drug therapies for malaria. The support in development of new drugs is mainly in providing funding for clinical trials for new malaria treatment therapies.

The World Bank, a founding member of the Roll Back Malaria campaign, has been actively involved in efforts to reduce the burden of malaria globally. The Bank has declared malaria a corporate priority, but most involvement is in the area of control. In Africa there are currently more than 25 World Bank projects that currently provide support for malaria control activities. The Wellcome Trust is the world's largest independent medical research-funding charity that aims to improve human and animal health. The Wellcome Trust funds a broad spectrum of research on malaria including: genome sequencing, the biology of the parasite and mosquito, new vaccines and drugs, clinical research to improve treatment and to understand the pathology of the disease, disease transmission and epidemiology, health services research, and health policy research. The Trust also provides International Senior Research Fellowships for researchers from a number of countries, including South Africa.

The European Union (EU) funds research in member states and some other countries, and at the EU's own Joint Research Centre with the objective of building EU-wide platforms of excellence. Funding goes to projects that will benefit from a transnational approach, generally at least 2 of the participants must come from the EU member states, candidate countries or Switzerland. Projects must be integrated, involving a critical mass of scientific and industrial partners, and targeting significant products, processes or service applications. Grants can also go to EU participation in specific science and technology co-operation programmes set up jointly by certain governments or national research organisations.

There are also a number of funding agencies in the field of international development and co-operation, mostly linked to national governments. Agencies in this category include DGIS (The Netherlands), The UK Department for International Development (DFID), DANIDA (Denmark), and JICA (Japan). DFID for

example aims to fund research in four major themes, one of which is killer diseases. Within this area, DFID promotes public-private partnerships and multi-donor collaborations. DFID funds specific malaria knowledge programmes to develop the new generation of affordable drugs, rapid diagnostic kits and vaccine research.

In South Africa, most government funding for health research is through the Medical Research Council (MRC), a statutory council charged with conducting health research. It therefore plays an influential role in shaping health biotechnology as it identifies niche areas for development, focuses research efforts, and provides funding. The main objective is to produce science that results in improved health. It also carries out capacity development. Funding in malaria research in the MRC is through the Malaria Lead Programme.

The National Research Foundation (NRF) is the government's national agency responsible for the support of human resource capacity for research, technology and innovation in all fields of natural and social sciences, engineering, humanities and technology. The NRF therefore plays a critical role in the objectives of the National Research and Development strategy through educating and training scientists. Funding is largely directed towards academic research, developing high-level human resources, and supporting South Africa's national research facilities. In addition, other programmes managed by the NRF as a service provider, include the Innovation Fund, funded by the Department of Science and Technology (DST) and the Technology and Human Resources for Industry Programme (THRIP), funded by the Department of Trade and Industry (DTI). The Innovation Fund's core mandate is raising the level of competitiveness of the South African economic sector by promoting the commercialization of end stage research into tangible products and services. THRIP provides resources and mechanisms in support of collaborative research in the areas of science, engineering and technology. THRIP's priorities are funding mechanisms for students and staff, as well as women, black students and staff.

The Support Programme for Industrial Innovation (SPII), managed by the IDC on behalf of the Department of Trade and Industry, is designed to promote and assist technology development in South African industry through the provision of financial assistance for projects that develop innovative products and/or services. SPII is focused on the phase beginning at the conclusion of basic research and ends at the point where a prototype has been produced. The Department of Science and Technology has furthermore supported the creation of three biotechnology regional innovation centers to act as nuclei for the development of biotechnology platforms from which a range of new products and services can be developed. All three Innovation centers all of have human health as a portfolio: BioPAD (Gauteng), Cape Biotech Trust (Western Cape) and LIFElab (East Coast region).

Excluding the MRC malaria lead programme budget, CSIR parliamentary grant and funding through LIFElab, the annual funding of malaria research in South Africa is in the region of R 5 million. Most of this is directed at training of students, platform development and capacity building through the NRF and MRC. Whilst there are a number of programmes such as SPII, the BRICs and the Innovation fund directed at funding post "proof-of-concept", only two projects are being funded by this mechanism. This supports the conclusion by the 2003 Emerging Biotechnology Roadmap that there remains a substantial gap between innovation and commercialization.

It has been widely stated that the completed genomes of *Plasmodium falciparum* and the vector *Anopheles gambiae* open up new approaches to the development of drugs, vaccines, insecticides and insect repellents, as well as intervention into malaria transmission. In addition, advances in genetics

and biochemical engineering offer new and improved means understanding the dynamics and potential weak links in the complex interactive cycle of the malaria parasite and its vectors, and hence of characterizing potential targets. Bioinformatics tools can help predict the structure and function of gene products. The speed with which many compounds can be tested against protein targets has hence increased dramatically. Genetic tools will also allow the sampling of parasite, mosquito, and human genomes in malaria affected areas to support the malaria control activities. The Initiative has thus identified an opportunity and stated its key objective in the integration of researchers focusing on molecular aspects of malaria drug and insecticide discovery, molecular epidemiology and diagnostics, and capacity building in order to improve malaria prevention and control. Three programmes have been envisaged: the development of new and modified drugs and insecticides; the development and implementation of assays for epidemiological and diagnostic interventions; and capacity building programmes as a cross-cutting programme

Information relating to the malaria research currently being undertaken in South Africa in the various categories of interest to the Initiative was gathered. Vaccine development has therefore not been included. Four categories were included: epidemiology and diagnostic research, basic science, clinical studies, and training and capacity building. The summaries provided in the main body of the report clearly indicate that the majority of research groups in South Africa are involved in basic scientific research with most work directed at furthering the understanding of malaria cell biology, the cell biology of antimalarials, and the application of this research in the identification and validation of potential drug targets. Research projects involving medicinal chemistry, rational drug design and synthetic organic chemistry have also been identified. Very little research into the development of insecticides has been identified, with the only projects in this context being studies to detect novel compounds from indigenous plants that can be used as a mosquitocides, and the isolation of active ingredients from these plants.

Two groups, the MRC and NICD, are involved in epidemiological research. Research areas covered include the molecular identification and characterisation of mosquito vectors, molecular mechanisms of mosquito resistance to insecticides, biochemical basis of insecticide resistance and molecular mechanisms of drug resistance. One of the proposed MIA programmes is the application of molecular techniques to population studies and tracking of resistance through the application of molecular marker techniques to population studies and epidemiology. The focus will be on the movement of vectors and parasites, linked to trends in insecticide and drug resistance. This is already a core part of the research conducted by these two groups and hence the requisite skills already exist.

Two groups with interests in diagnostics have been identified, University of KwaZulu Natal (UKZN) and National Bioproducts Institute (NBI). NBI has developed a pair of monoclonal antibodies specific for HRPII that are suitable for use in a rapid diagnostic test. These antibodies are specific for *Plasmodium falciparum* and recognise different epitopes on this molecule. UKZN has developed an array of antibodies against anti-malarial drugs, which can be used to track malaria drugs in a range of cells, tissues and body fluids. Through an international collaboration in a MVI project, the team is developing reagents for a second generation of an ELISA diagnostic kit, the first generation being used as an experimental tool in malaria vaccine trials. Coupled with the complementary skills available in other MIA research groups, the development and implementation of assays for diagnostic interventions should be feasible.

The process of drug discovery and development involves a number of discrete stages, as does the process into insecticide discovery. However, due to the fact that there is currently very little research in

South Africa on the development of insecticides, this summary will focus on the drug development process. Mapping the activities of the current research programmes in South Africa against the range of skills and expertise required for the drug development process, indicates that whilst MIA has access to the full spectrum of scientific components required to discover and develop drugs and move from early discovery research through to preclinical and clinical development, some of these components are better developed than others. Most research projects are in the early stages of the process.

The following competencies relevant to the projects proposed by MIA are available in varying degrees that are: parasite biology and biochemistry, functional genomics, structural and computational biology, bioinformatics, medicinal chemistry, combinatorial chemistry, organic synthesis, analytical chemistry, high throughput biomolecular interaction analysis, high throughput *in vitro* screens, high throughput cellular/phenotype screens, national product chemistry linked to South Africa's biodiversity, animal models of malaria, ADMEtox testing of drug leads, development of formulations and delivery mechanisms, process development for large-scale development, and management of clinical trials.

The "genes to drugs" model needs more than the first step of basic exploratory biology on target identification. To convert validated targets into full drug discovery programmes, the use of upstream technologies such as genomics to identify targets, high-throughput screening, molecular modeling and screening and other techniques identified as being available in South Africa need to be optimally integrated with technologies such as medicinal chemistry, pharmacology and rational drug design in order to develop an early R&D pipeline. In addition, capacity in the downstream interface such as in the preclinical development phase needs to be enhanced and partnerships in the clinical development, dossier preparation and registration will have to be formed in order to strengthen this aspect of the development chain.

The integration and management of this entire process is critical for success in moving from discovery lead identification into drug candidates and finally through to a registered drug. Some elements of this integration have begun to be developed for example in the various collaborations between the University of Cape Town's Departments of Chemistry, Pharmacology and Institute of Infectious Disease and Molecular Medicine as well as the University of Stellenbosch and through the development of the national research and development platform for novel drug development from indigenous plants.

The efficacy and specificity of anti-malarial drugs rely on their ability to interfere with aspects of the metabolism of *Plasmodium* that differs significantly from the host. Parasite survival in the host erythrocytes requires several metabolic adaptations that render it susceptible to chemotherapy. Many potential drug targets have been identified based on an understanding of the cell biology of the malaria parasite. Whilst it has not possible within the scope of this report to outline all of these potential scientific opportunities, some are presented below in the main body of the report for indicative purposes only. Much of the research being conducted in South Africa falls within the context of many of these promising areas already identified.

The involvement of several academic and industrial partners in a virtual development model such as that proposed by MIA is relatively new, and involves a unique set of challenges. The model is however being followed successfully in the development of drugs and other tools to treat malaria by the PPPs internationally such as the MMV. Most of these organizations also recognize that the impact and long-term sustainability of drug R&D for poverty related diseases depends on the use of research capacity in developing countries. However, whilst a few of these countries have expertise in some of the scientific

components required, few have the capacity to perform all of the tasks necessary. As outlined above, South African has a core of excellent researchers and facilities in the malaria research field, a strong base in biomedical research, high-quality medical schools and a good infrastructure. Coupled with increasing financing for malaria research and involvement of various PPPs as outlined above, the prospect of the development of new, affordable drugs, diagnostics and insecticides in South Africa therefore appears to be a feasible opportunity.

A recent article in Nature Biotechnology stated that South Africa is poised to take the lead in developing health care biotechnology in the sub-Saharan African region. It recommended a good starting point as being the identification of a problem disease prevalent in the community and a technology that could be used to address this problem, and then to develop an infrastructure to support R&D in this area. Thus through its focus on malaria and the use of molecular technologies, MIA has identified a unique opportunity to position itself in sub-Saharan Africa and internationally through the integration and capacity building programmes as proposed in the initiative. Through applying the lessons learned by the PPPs in the establishment of a virtual development process, ensuring the optimization and focusing of its manpower, infrastructure and financial resources, coupled with careful management of the integration process, MIA should be well positioned to achieve success in its goals.

3 FUNDING INITIATIVES - INTERNATIONAL

3.1 INTRODUCTION:

Malaria is clearly a disease of poverty, and is commonly referred to as a “neglected disease”. These diseases also referred to as tropical or endemic diseases, affect millions of patients, but their lack of ability to pay for market-financed products results in insufficient market incentive to drive the development of innovative products by “Big Pharma”. The net effect is that only 10% of global R&D resources are directed at diseases, including malaria, that account for 90% of the global disease burden. Around the world, \$73 billion¹ annually is devoted to health research, and a mere \$ 100² million on malaria research.

Most pharmaceutical companies disengaged from research into tropical diseases in the 1970s, leaving a gap in the development of new and affordable drugs. As has been discussed in previous sections, the number of effective drugs to treat malaria is small. Almost all of the current drugs used today were developed over 30 years ago. The few existing drugs are plagued by increasing resistance, particularly in the tropical regions, at a rate that outpaces the development of new antimalarial drugs. The most effective drugs used are combinations, which in the short term replace the ineffective drugs used today, and delay the development of resistance against any one of the individual drugs. These are however significantly more expensive than traditional antimalarials.

Reducing the burden posed by malaria is thus generally agreed to require increased R&D for new drugs, vaccines and diagnostics. The pharmaceutical industry has advanced substantially in terms of its drug discovery and development process due to advances in molecular and structural biology, medicinal chemistry and the power of genomics and molecular genetics. Malaria research has therefore missed out on many of these opportunities. In order to overcome these shortcomings, new mechanisms have been established, involving a partnership between public and private sectors, together with a philanthropic approach to stimulate R&D for diseases such as malaria. This has resulted in what is now commonly referred to as public-private-partnership organizations (PPP). The public-philanthropic sector provides funds to complement the R&D and other resources in the private sector. The focus of these PPPs on neglected diseases, together with the availability of the malaria genome, is now believed to allow the full benefit of modern drug discovery research technologies to be applied to the development of improved drugs, vaccines and diagnostics for malaria.³

There are therefore two aspects to obtaining funds to perform R&D in malaria, either the provider of funds or the organizations that manage the research carried out within the PPP framework.

Overall, funds committed to malaria research have increased from an estimated \$ 85 million in 1995, to a level well over \$ 100 million. NIAID increased its commitment by more than 150% between 1995 and 1999. The Wellcome Trust doubled its expenditure. The level of funding is still believed to be low relative to the disease burden.⁴ The Copenhagen Consensus Initiative concluded that deploying effective malaria drugs had one of the highest cost-benefit ratios when opportunities for global investment across a number of segments were compared. The study calculated that US\$ 824 million annually for a package of interventions would be required to halve the malaria burden in sub-Saharan Africa by 2015. The direct economic benefit of this package would be US\$ 14 billion per year, an attractive cost benefit ratio of 17.⁵ The cost of R&D in context is therefore small on this global investment scale. This gap has been recognized by certain donors such as the Gates Foundation. The global community has hence been urged to increase its funding for antimalarial R&D.⁶

3.2 ORGANISATIONS MANAGING MALARIA R&D

Typically these organizations play a co-coordinating role in setting a disease-specific agenda, raising funds and managing the R&D projects. The strategy followed by the PPPs relies on market-based business models to simulate the development of drugs, whilst providing public resources to compensate for market failure. The aim is to bridge the existing R&D gaps in essential drugs for neglected diseases by initiating and co-coordinating R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners. This “virtual drug development” model minimises overhead costs whilst harnessing the existing but fragmented R&D capacity.

Most of these organizations issue a “call for proposals” from which to select projects. Selection of projects is through expert scientific advisory committee coming from both industry and academia, and covering the full range of expertise required to assess projects.

The public-private partnerships of relevance to malaria R&D are summarised below.

3.2.1 WHO/TDR⁷

The United Nations Development Programme, World Bank, WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) was created in 1975 following a World Health Assembly resolution. The TDR is housed within the WHO, which is also the executing agency. Its goals are to develop new tools and methodologies for control of ten target diseases and to strengthen research capacities in disease endemic countries. Projects are identified through calls for proposals and through networking of TDR scientists with others outside of the TDR network. The decision making process relies on technical and administrative advisory and governing bodies.

The organisation is funded mainly through international, government, and philanthropic contributions. TDR is co-sponsored by UNICEF, UNDP, the World Bank, and WHO. Other contributing partners are 23 governments/member states and 9 other foundations/agencies. The TDR budget for the 2004/2005 period is \$100 million. Of this budget, \$ 68 million is for operations, i.e. research in the form of research grants, contracts etc. Malaria accounts for the largest share of the operations budget i.e. 46.9% of this total or \$ 31.9 million.

TDR’s scope of activities includes the development of new and improved tools (drugs, vaccines, diagnostics, epidemiological and environmental tools) and new and improved intervention methods (for using existing tools). TDR’s research and training activities are organised into four functional areas. These are: (1) Strategic Discovery Research (2) Product Development and Evaluation, (3) Implementation Research and Methods, and (4) Research Capability Strengthening. In terms of the overall budget, 35.8% is spent on new and improved tools, 10.8% on new and improved methods, 20.1% on partnerships and capacity building, 9.6% on new and improved policies and strategies, and 7.5% on new basic knowledge. Technical information and management account for the balance.⁸

For more details of these workplans see the WHO/TDR web-site.

3.2.2 Multilateral Initiative on Malaria⁹

The Multilateral Initiative on Malaria (MIM) is an alliance of organisations and individuals concerned about the global burden posed by malaria. MIM recognised that the further development of human resources and institutional capacity in Africa is a fundamental requirement for establishing effective malaria control programmes. It aims to maximise the impact of scientific research against malaria in Africa, through the promotion of capacity building, and facilitation of global collaboration and co-ordination. MIM was launched in 1997, following the first Pan-African Malaria Conference where scientists from all over the world identified research priorities for malaria R&D.

A multilateral funding mechanism (MIM/TDR) was established at the TDR where MIM partners could directly contribute money for Research Capacity Strengthening in Africa in the form of peer-reviewed grants. MIM was subsequently broadened to include representative of industry and development agencies. Contributing partners include NIAID, The World Bank, WHO/AFRO, WHO/RBM, WHO/TDR, and Governments of Norway and Japan.

MIM/TDR Task Force supports research to strengthen African research groups. Membership of the Task Force comprises African scientists who are engaged in basic and/or applied science, investigators in developed countries, and corporate stakeholders. Grant applications must submit and be co-ordinated by an African national scientist working in a research group in Africa. Strategic priorities include but are not limited to: functional genomics, pathogenesis, drugs, epidemiology, vectors and socio-economic and behavioural research. MIM also holds training workshops for grantees, collaborators, and students from malaria endemic countries.

MIM/TDR has issued a call for Letters of Intent to be received by September 2005. The focus is on research useful in understanding malaria and reducing the disease burden as well as creating opportunities for developing African scientific and public health leadership in research management. The letters of intent should propose cross cutting or multidisciplinary “use inspired” research in the areas listed. A training and capacity building component must be included. The broad areas are: (1) chemotherapy and mechanism of antimalarial drug resistance, (2) health systems to improve malaria control in Africa, (3) Vector Control, (4) Research and Development of novel malaria control tools from natural products, (5) Research to facilitate malaria control interventions including introduction and evaluation of new strategies and policies. (6) Pathogenesis and immunology of malaria.

3.2.3 Medicines for Malaria Venture:¹⁰

Medicines for Malaria (MMV) was one of the first public-private partnerships to put the theory of PPP driven-virtual drug discovery into practice. It is a not-for-profit organisation established in 1999 in Geneva by WHO, the World Bank and several pharmaceutical companies. Its goal is to discover, develop and deliver one new antimalarial drug every five years through public-private partnerships. First registrations are envisaged for the end of 2006. A key aim is that the drug developed must have a low intrinsic cost of manufacture. It is funded mostly through international, government, and philanthropic foundation contributions. Since its foundation, MMV has been granted multi-year pledges from the Gates Foundation, the UK Department for International Development, the Swiss Agency for Development and Cooperation, USAID, Exxon Mobil, BHP Billiton, and the World Bank.

MMV manages a portfolio of drug development and discovery projects that are conducted by academic and pharmaceutical partners. Projects are solicited through a call for proposals and are sought out by MMV staff, as they become aware of possibilities. MMV's last call for proposals was in November 2004.

Out of 81 letters of interest, 5 projects were selected to be added to the portfolio. As of November 2004, MMV had 21 projects in its portfolio at different phases. All R&D work is outsourced and the degree of management by MMV is variable according to project needs. Projects are managed by product development teams with additional assistance from contract research organisations (CROs).

MMV had an income of \$ 28.7 million in 2004 and scientific project-related expenditure of \$ 25.4 million. Current forecasts for future expenditure are \$ 40 – 45 million in 2005, increasing to \$ 60 – 70 million annually as the developing portfolio necessitates and project move through clinical trials, registration, product launch and marketing. MMV has made a commitment to involve developing country scientists and institutions.

The MMV has achieved success following a three-year lead optimisation project based on an antimalarial peroxide. The team consisted of chemists in Nebraska, pharmacokineticists in Australia, and parasitologists in Switzerland, all linked to Hoffman la-Roche for guidance and toxicology expertise. A candidate antimalarial has been submitted for preclinical development. The compound has been licensed to Ranbaxy, which will co-develop the product with MMV.

3.2.4 Institute for One World Health¹¹

The Institute for One World Health (iOWH) is a relatively new initiative, formed in July 2000 funded by an unaffiliated individual scientist using personal resources. The institute has been established as a non-profit US pharmaceutical corporation located in San Francisco. Its mission is to develop and manufacture effective drugs and vaccines for people with infectious diseases in the developing world. The model followed by iOWH is to identify promising drug development opportunities, and take responsibility for driving those leads through the development process.

In 2004, iOWH was awarded a \$ 42.6 million grant from the Gates Foundation to work in partnership with the University of California, Berkeley, and Amyris Biotechnologies to perfect a fermentation process for the industrial production of artemisinin. The intent is to reduce the cost of treatment from the current \$ 2.40 to less than \$ 1.00.

Partnerships with pharmaceutical and biotechnology industries, non-profit hospitals, universities, government agencies and global health organisations are encouraged in order to obtain the resources necessary. The institute promotes the use of resources in developing world countries through increased funding for academic laboratories, and through working with such countries in clinical trials, drug manufacturing and distribution of the registered product.

Proposals from potential collaborative partnerships are invited. These are evaluated according to a number of criteria. Definitive guidelines are not provided, but criteria include the clinical need and availability of treatment, international standards of research, affordability, efficacy, etc.

3.2.5 Drugs for Neglected Diseases Initiative:¹²

The Drugs for Neglected Diseases Initiative (DNDi) was established in 2003 by 5 organisations from around the world, including 3 public sector institutions and 1 humanitarian organization, Médecines sans Frontières (MSF) and 1 international research organization, the UNDP/World Bank/WHO Special Programme for Research Training in Tropical Diseases (TDR). TDR acts as a permanent observer to the initiative. Most initial funding has come from MSF, agreeing to contribute up to \$ 7.5 million annually

for the initial 5 years. The EU agreed to provide up to € 1.5 million to fund artemisinin projects during the first two years. Other funders comprise public donors, international organisations, and private funders. The project budget for 2005 is \$ 19.4 million and over a 12 year period, the global budget is estimated at a minimum of \$ 258 million for an outcome of 6 – 8 registered drugs, and a pipeline of 8 projects.

The DNDi aims to develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Its business model is that of decentralised operations with a clear project specific focus. It does not conduct research and development itself, but capitalises on existing, fragmented R&D capacity, especially in the developing world and complements this with additional expertise if necessary. DNDi identifies medical needs and R&D projects proactively through expert consultations, literature searches, scientific meetings etc. It also calls for letter of interest requesting proposals focussing on specific diseases or research topics. The initiative fosters collaboration amongst developing countries and between developing and developed countries.

3.3 MALARIA FUNDING PUBLIC/PHILANTHROPIC ORGANISATIONS:

The list of organisations described here is not intended to be exhaustive, but includes most of the major groups funding malaria research and control in Africa in some manner. They represent the organisations most cited by researchers in South Africa as being potential sources of funds.

3.3.1 Global Fund to Fight AIDS, Tuberculosis and Malaria¹³

The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) is an international, independent public-private partnership which finances programmes for the prevention, treatment, care and support of AIDS, TB and malaria. The fund was created in 2002, after a decision by G8 countries in 2001 to help address the need to increase global funding to fight these diseases. The fund attracts, manages and disburses funds, but does not implement programmes directly as it is a financial instrument, and not an implementing entity. The Global Fund funds prevention, treatment and research. In the case of malaria, grants expand access to ITNs and provide health officials with tools and training. Proposals are evaluated through an independent review process. The funds are mostly disbursed through governmental organisations.

The Global Fund provides grants to locally-developed programs to prevent and treat AIDS, TB and malaria. Countries and organizations may apply for funding by submitting proposals in ongoing funding rounds. The proposals should support the scale up of effective existing programs and innovative projects that meet the Global Fund's criteria. Proposals submitted should also clearly demonstrate how the resources sought from the Global Fund will achieve additional results in partnership with existing programs. Calls for proposals are issued by the Global Fund Secretariat. The deadline for the Fifth Call of proposals was June 10th 2005, 26% of all proposals received were for malaria programmes worth \$ 870 million. 44% of all proposals received were from Africa.

Proposals for funding must generally be made through a Country Coordinating Mechanism (CCM). CCMs include representatives from both the public and private sectors, including governments, multilateral or bilateral agencies, non-governmental organizations, academic institutions, private businesses and people living with the diseases. These country-level partnerships develop and submit grant proposals to the Global Fund based on priority needs at the national level through consultation with a broad range of public and private stakeholders. As part of the proposal, the CCM nominates one

or a few Principal Recipients. In many cases, development partners assist in the preparation of proposal.

The Global Fund works together with other multilateral and bilateral organisations involved in health and development issues. Many of these organisations provide technical assistance during the development of proposals or implementation of programmes. The Global Fund started disbursements of funds in 2003. By the end of its first four funding cycles i.e. end 2004, the Global Fund had committed US\$ 3.1 billion in 127 countries. 31% of this has been allocated to proposals for the control of malaria. 56% of this amount is earmarked for distribution to Africa, of which 17% is for Southern Africa. The 5th round of financing has recently closed.

3.3.2 The Bill and Melinda Gates Foundation:¹⁴

The Bill and Melinda Gates Foundation's (Gates Foundation) mission is on promoting greater equity in global health, education, and public libraries. This foundation is a grant-making organisation. The Foundation has an endowment of \$ 28.8 billion. One of the spearheads of the Gates Foundation is the Global Health Programme that focuses especially on poverty-related diseases including malaria. There are two priority areas: research to create and improve health technologies, tools and strategies to accelerate access to these health interventions to those that need them. The largest proportion of the grants is on research to create and/or improve health tools such as vaccines, drugs, and diagnostics. This includes basic research, product development, clinical trials, and operations research.

Grants have included: \$150 million to the Malaria Vaccine Initiative for the development of promising malaria vaccines and \$ 65 million to MMV to support the discovery and development of affordable and effective antimalarial drugs. An amount of \$ 100 million was pledged to the Global Fund to support efforts at the country level to control the spread of HIV/AIDS, TB and malaria. The Foundation also funded the Gates Malaria Partnership (GMP), a collaboration between a number of academic institutions, philanthropic organisations, and public health organisations, which will wind down from the end of 2005.

A further \$450 million has been committed to the Grand Challenges in Global Health programme to accelerate research on crucial scientific and technological problems in developing world diseases. This programme is implemented in partnership with the National Institute of Health (NIH), the Wellcome Trust and the Canadian Institutes of Health Research (CIHR). 43 Grants have been awarded to scientists in 33 countries. Projects include the control of insect vectors *via* genetic or chemical strategies, limiting drug resistance, and curing infection *via* either therapies or immunological methods.

3.3.3 The National Institutes of Health:¹⁵

The National Institute of Health (NIH) is an agency of the US Department of Health and Human Services. In order to realise its mission defined as the "science in pursuit of fundamental knowledge about the nature and behaviour of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability", the NIH awards funds to research programmes concerning health issues such as malaria.

The NIH supports a number of award types including research project grants, training, career development and fellowship awards. Most research project grants (RPG) are through the R01, which are single research project grants. These grants provide support to an institution on behalf of a principal

investigator. Proposals are initiated through request for applications (RFA), request for proposals or programme announcements. These are published weekly in the NIH Guide for Grants and Contracts.

The National Institute of Allergy and Infectious Diseases (NIAID)¹⁶, a component of the NIH, conducts and supports basic and applied research to better understand, treat and ultimately prevent infections. NAID research has led to many new therapies, vaccines, diagnostic tests and other technologies. NIAID contributes to the Global Fund, as well as to research into new antimalarial combination drugs, and other targeted initiatives. The NIAID also has a malaria vaccine plan designed to accelerate research leading to the development of malaria vaccines. NIAID funding opportunities are published on their "Initiatives and Concepts" web-site divided into NIAID primary sponsorships, NIH-wide, and NIAID as co-sponsor.

3.3.4 US Agency for International Development:¹⁷

The US Agency for International Development (USAID) is an American government agency that supports long-term and equitable economic growth and advances US foreign policy objectives by supporting, for example, global health. One of USAID's Infectious Disease Initiative priority areas is the sustainable reduction of deaths due to malaria and the incidence of other infectious diseases of major public health importance among key populations in selected countries. USAID is working in close collaboration with the Roll Back Malaria partnership and others to reduce malaria impact on developing countries. On June 30, 2005 President George Bush pledged to increase funding of malaria prevention and treatment in sub-Saharan Africa by more than \$ 1.2 billion over 5 years.

In addition to providing expanded support for prevention and control programmes, USAID supports three critical research efforts: (1) the Agency's Malaria Vaccine Development Programme (MVDP); (2) the development of new drug therapies for malaria, and (3) operations research on behavioural, community, drug use and treatment regimen compliance issues. The support in development of new drugs is mainly in providing extra funding for clinical trials for new malaria treatment therapies.

3.3.5 World Bank:¹⁸

The World Bank was a founding member of the Roll Back Malaria campaign, and has thus been actively involved in efforts to reduce the burden of malaria globally. The Bank has declared malaria a corporate priority, but most involvement is in the area of control. Since 2000, total Bank commitment in all regions is about \$100 – 150 million. In Africa there are currently more than 25 World Bank projects that currently provide support for malaria control activities.

3.3.6 The Wellcome Trust:¹⁹

The Wellcome Trust is the world's largest independent medical research-funding charity that aims to improve human and animal health. The Trust awards grants to other bodies, and it also manages its own projects. Resources expended over 2002 – 2004 total £ 2.06 billion, of which 66% was in grants. Funding is offered in four general areas: biomedical science, technology transfer, medical humanities and public engagement. The biomedical science programme: immunology and infectious disease category includes all aspects of immunology and infectious disease in humans and animals. Malaria research therefore falls within this programme.

The Wellcome Trust funds a broad spectrum of research on malaria, including: genome sequencing, the biology of the parasite and mosquito, new vaccines and drugs, clinical research to improve treatment

and to understand the pathology of the disease, disease transmission and epidemiology, health services research, and health policy research. The research is funded both overseas – in particular in countries experiencing the full impact of malaria disease – and in the UK. The funding programmes support researchers at all stages of their careers – from junior fellows to principal researchers – and provides a career progression. The major overseas centres in Africa and South East Asia act as training centres for scientists from developing countries, and the Wellcome Trust Centres for Research in Clinical Tropical Medicine provide UK bases for training.

Research project support includes project grants, equipment grants, and programme grants. Categories within project grants include: hypothesis-driven research, development of technologies or drugs, vaccines or biological resources; and modest applications for pilot studies. Three year project grants in the range of £ 150,000 - £ 300,000 are awarded. Programme grants provide support for longer periods, up to 5 years, for internationally competitive research. Grants have not exceeded £ 1.2 million. In both projects and programme grants, collaboration between scientists in the UK or Ireland with scientists in developing countries is encouraged.

The Trust also provides International Senior Research Fellowships for researchers from a number of countries including South Africa. Duration of the fellowship is for 5 years. South African recipients of this Grant include Dr Heinrich Hoppe (UCT) and Professor Greg Blatch (Rhodes). Other fellowships in tropical medicine include Research Training Fellowships for Newly Qualified Scientists and Research Career Development Fellowships for mid career scientists.

3.3.7 The European Union:²⁰

The European Union (EU) funds research in member states and some other countries, and at the EU's own Joint Research Centre. The main tool is the 6th Framework Programme. Key EU objectives are to increase research spending by over 50% in real terms by 2010 to 3% of GDP. The objective is to build EU-wide platforms of excellence. The European Commission has a budget of some € 20 billion for 2002 – 2006 for building an European Research Area under its 6th Framework Programme known as FP6. About 75% of this budget is devoted to 7 priorities, which include: life sciences, genomics and biotechnology for health. In this area the budget is € 2,255 million.

Funding goes to projects that will benefit from a transnational approach. Many EU countries have co-operation agreements allowing them to benefit from this funding, but generally at least 2 of the participants must come from the EU member states, candidate countries or Switzerland. Funds go to cross-border networking among centres of excellence in universities, research bodies, and business enterprises. Projects must be integrated, involving a critical mass of scientific and industrial partners, and targeting significant products, processes or service applications. Grants can also go to EU participation in specific science and technology co-operation programmes set up jointly by certain governments or national research organisations.

Submission of proposals is in response to calls for proposals. Proposals are evaluated and selected for funding by the EU with the help of independent external experts. In terms of project management, consortia have great autonomy, one of the participants acting as co-ordinator.

3.3.8 Funding agencies in the field of international development and co-operation

These agencies are mostly linked to national governments. Agencies in this category include DGIS (The Netherlands), The UK Department for International Development (DFID)²¹, DANIDA (Denmark), and JICA (Japan). The manner in which grants regarding poverty related diseases such as malaria by these agencies may be different.

DFID for example aims to fund research in four major themes, one of which is killer diseases. Within this area, DFID promotes public-private partnerships and multi-donor collaborations. DFID has donated £48 million to the RBM (1999 – 2004), and is a key donor to the Global Fund to fight AIDS, TB and Malaria with pledges of £140 over the period 2005 – 2008. DFID has contributed £ 5 million to MMV and £ 2.86 million to the London School of Hygiene and Tropical Medicine malaria programme. All DFID's goals are directed at achieving the targets set in the Millennium Development Goals by 2015. DFID in addition funds specific malaria knowledge programmes to develop the new generation of affordable drugs, and rapid diagnostic kits. It also maintains an interest in vaccine research.

4 FUNDING INITIATIVES – SOUTH AFRICA

4.1 National Research Foundation²²

The National Research Foundation (NRF) is the government's national agency responsible for the support of human resource capacity for research, technology and innovation in all fields of natural and social sciences, engineering, humanities and technology including indigenous knowledge in South Africa. The NRF framework supports research within all sciences, including health sciences in as much as this is not catered for by the Medical Research Council. The NRF therefore plays a critical role in the objectives of the National Research and Development strategy through educating and training scientists.

Its key objective is therefore to support and promote research through funding, developing human resources and providing the necessary research infrastructure. Funding is largely directed towards academic research, developing high-level human resources, and supporting South Africa's national research facilities. The NRF's key driver is to produce large numbers of high-quality PhD graduates, which will motivate and underpin the work of all operational units of the NRF.

Within the context of the provision of funds for malaria research, the NRF's activities are through the Research and Innovation Support Agency (RISA) as the service provider. RISA as an agency covers the full range of activities in the innovation chain from fundamental research through to application and commercialization. RISA programmes and functions are largely supported by a parliamentary core grant. In addition, other programmes are managed by the NRF as a service provider. These include:

- Innovation Fund, managed for the Innovation Fund Board of Trustees and funded by the Department of Science and Technology (DST)
- Technology and Human Resources for Industry Programme (THRIP), funded by the Department of Trade and Industry (DTI).

4.1.1 Parliamentary Core Grant

RISA has identified a portfolio of 9 focus areas. Both basic and applied research may be carried out within these focus areas. Furthermore, the focus areas allow disciplinary, multi-disciplinary, inter-disciplinary and trans-disciplinary research to be carried out. Researchers may submit more than one proposal into the focus area of choice.

Focus areas include:

- Challenge of Globalisation: Perspective of Global South
- Conservation and Management of Ecosystems and Biodiversity
- Distinct South African opportunities
- Economic Growth and Competitiveness
- Education and the Challenges for Change
- Indigenous Knowledge Systems (IKS): The NRF receives a ring-fenced grant for IKS from the DST.
- Information and Communication Technology (ICT)
- Sustainable Livelihoods: The Eradication of Poverty
- Unlocking the Future: Advancing and Strengthening Strategic Knowledge

The focus areas are non-discipline specific, inviting research from across the knowledge spectrum to address these concerns. Researchers in natural sciences, engineering, social sciences, law and humanities employed at an NRF recognised institution either on a full or part-time basis may apply.

Rated researchers employed may receive funding for up to 5 years, and unrated researchers up to 2 years.

The focus areas cover on a competitive basis the entire range of South African research capacity development requirements. The interventions of relevance to malaria researchers include:

- Free-standing student support such as bursaries;
- The focus area programmes that provides grants to researchers and grant holder linked students;
- Thuthuka offering opportunities for researchers-in-training, women in research and the growth of black research staff (REDIBA);
- Science liaison grants to enable the internationalization of science; and
- Equipment and mobility grants.

A list of the NRF supported projects is attached as Appendix 1. This is the total amount for the grant duration of either 2 or 5 years. It has not been possible to separate out those projects which were of a shorter duration and have hence been completed. Current total committed NRF grants in malaria projects are worth R 7.35 million, representing an average annual expenditure of R 2.1 million. This total commitment should only be used as an approximation of the level of expenditure by the NRF in this area.

More details regarding the aims and objectives of the focus areas and instructions to applicants are provided in the NRF web-site.

4.1.2 Innovation Fund

The Innovation Fund was established by the Department of Science and Technology with the core mandate of raising the level of competitiveness of the South African economic sector by promoting the commercialization of end stage research into tangible products and services for the South African and international markets. The Fund invests in technologically innovative research and development. The NRF is the contracted agent managing the Fund.

A series of initiatives have been introduced that seek to enhance innovation in South Africa. These are:

Missions in Technology (MiTech):

To support the accelerated development of long-term, high-risk, market-driven, enabling technologies in all economic sectors in partnership with industry. It provides up to R 15 million in matching funds over a 5-year period to develop new technology platforms. Applications in all technology areas are considered, but priority is given to projects aligned with the National R&D strategy and Advanced Manufacturing Strategy.

Technology Advancement Programmes (TAP):

To build on the existing research and knowledge base, where a real or potential product has been identified. The proposed R&D budget will enable progress up to proof of concept or prototype stage. Funding is for 3 years to consortia, with a maximum grant of R 5 million per annum. Applications in any area are accepted, although biotechnology applications require prior screening by the Biotechnology Regional Innovation Centres (BRICS)

Seed and start-up financing:

This fund is aimed at supporting projects previously funded by the Innovation Fund that have demonstrated proof-of-concept and are seeking funding for commercialisation activities.

Malaria projects that have received Innovation Fund support in the past include:

- The MRC consortium project into the development of a GIS based decision support system for the Lubombo Spatial Development Initiative; and
- The MRC consortium project into the development of new antimalarial medicines from the medicinal plants of Southern Africa.

The only currently active Innovation Fund supported project is the “National Research and Development Platform for Novel Drug Development from Indigenous Plants”. The project falls under the MiTech programme and has a budget of R 15 million over 3 years. The project however covers the development of drugs for a number of diseases including malaria. It is estimated that the malaria portion is worth R 4 million, which over 3 years is an estimated R 1.33 million annually.

4.1.3 THRIP

THRIP is a joint venture between industry, research and education institutions, and government. It supports the development of technology and appropriately skilled people for industry to improve South Africa’s global competitiveness. THRIP provides resources and mechanisms in support of collaborative research in the areas of science, engineering and technology. THRIP’s priorities are funding mechanisms for students and staff, as well as women- and black students and staff. THRIP is not funding any malaria research projects at present.

4.2 Medical Research Council²³

The Medical Research Council (MRC) is a statutory research body in South Africa established in 1969 by an Act of Parliament. The MRC is a science, engineering and technology institution (SETI), largely funded by the government. Its work is in line with the national science and technology imperatives and the health priorities defined by the Department of Health, its main objective is hence to produce science resulting in improved health. The MRC conducts or supports research on its own or with experienced partners such as universities and scientific institutions.

Health research supported by the MRC is categorized into 6 national programmes corresponding to high-priority areas identified by the government. Each national programme has identified further focus areas resulting in Lead Programmes, one of which is the Malaria Lead Programme, which falls within the Infection and Immunity national programme. The directives of the Malaria Lead programme are: malaria information systems, control intervention, insecticide resistance, drug efficacy studies and resistance development. There are a total of 47 research units, groups, centers or lead programmes within the national programmes.

The MRC issues requests for proposals, which are independently advertised. Grants for “Self-initiated Research” are awarded for research covering a wide range of health-related subjects. The maximum grant is for 3 years, with a maximum grant of R 130,000 per project per annum. Letters of intent may be submitted at any time for inclusion into an assessment cycle. Cycle dates close on 14th January and 1st July. Applicants must have at least a Masters Degree or equivalent with 2 years of research. Principal investigators must be employed or hold a contract with a South African institution for the duration of the project. Research projects are hence undertaken by universities, technikons, and other institutions where academic personnel and a physical infrastructure already exist. Other grants, such as the Research Development Grant, are available for scientists that do not yet fulfill these requirements.

A list of the self-initiated projects currently receiving funding is attached as Appendix 2. The amounts of the grants are however confidential. Working on the basis that the maximum project amount has been awarded the total grant commitment per annum is in the region of R 1.3 million.

4.3 Support Programme for Industrial Innovation²⁴

The Support Programme for Industrial Innovation (SPII) is designed to promote and assist technology development in South African industry through the provision of financial assistance for projects that develop innovative products and/or services. SPII is focused on the phase beginning as the conclusion of basic research i.e. post proof of concept, and ends at the point where a prototype has been produced. Projects funded are therefore at the pre-competitive stage of development. The programme is managed by the IDC on behalf of the Department of Trade and Industry.

Three different schemes exist depending on the size of the company in terms of turnover and assets, as well as the size of grant required. The schemes are:

1. The Product Process Development Scheme (PPD): targeted at small and micro enterprises. The grant is between 65 and 85% of qualifying costs up to a maximum of R 0.5 million depending on the level of black shareholding. Company turnover must be less than R 13 million.
2. The Matching Scheme: targeted at SMEs with a turnover of less than R 51 million. The grant is up to 50% of qualifying costs up to a maximum of R 1.5 million.
3. The Partnership Scheme: provided in the form of a conditionally repayable grant of up to 50% of qualifying costs. The maximum grant is R 1.5 million.

At the moment, there are no malaria related projects in the SPII programme.

4.4 Biotechnology Regional Innovation Centres:

The Department of Science and Technology has created 3 Biotechnology Regional Innovation Centers (BRICS) as part of the overall National Biotechnology Strategy to ensure the stimulation of South African biotechnology. The 3 BRICs are regionally focused and all have human health as a portfolio.

The BRICS are:

1. BioPAD: Biotechnology Partnerships and Development, active in the Gauteng region
A human health portfolio has recently been added to the BioPAD focus areas.
2. CBT: Cape Biotech Trust in the Western Cape region
Focus areas of relevance to malaria research are: diagnostics, vaccines and drug delivery
3. ECoBio: East Coast Biotechnology Regional Innovation Centre (operating under the trade name LIFElab) in the East Coast region.
Focus areas are infectious diseases including malaria or projects, which develop the biotechnology platforms of the area.

The BRICS funding strategy is to fund on-going and new research and development projects and provide a supporting infrastructure for commercialization. Investment in technology development is generally directed at projects that are post “proof-of-concept” where a real or potential product has been identified and technology already exists. At present, the only malaria related project funded by the BRICS is the development of a rapid malaria diagnostic test by National Bioproducts Institute in collaboration with LIFElab.

4.5 Other funding sources

A number of funding sources other than those listed already have been used by research groups. A few institutions use funds, such as contract research funds generated by other activities to fund malaria research. Examples include the University of Stellenbosch and the University of Cape Town Pharmacology department. Other sources of funds that have been used include the Volkswagen Foundation. Mozal and the Business Trust were the first funders of the LSDI programme.

Funds from international pharmaceutical companies such as GlaxoSmithKline (UK) and Merck Pharma (US) have been awarded to specific researchers such as Professor Chibale, in most cases these are however related to projects broader than malaria. A number of researchers have accessed international funding from the sources already listed above, including the EU grants.

Within the CSIR, in addition to funding generated by research contracts with government departments, the private sector and research funding agencies locally and abroad, funding is received from an annual parliamentary grant *via* the Department of Trade and Industry. These funds are used primarily for investment in developing new areas of research, and undertaking early stage research still viewed as being too risky to investment by the private sector.

4.6 Conclusion:

South Africa has a variety of funding sources applicable to malaria research. They are active in the funding of R&D, research capacity building and technology transfer. Excluding the MRC malaria lead programme budget, CSIR parliamentary grant and funding through the BRICs, the annual funding of malaria research in South Africa is in the region of R 5 million. Much of this is directed at training of students, platform development and capacity building. Whilst there are a number of programmes such as SPII, the BRICs and the Innovation fund directed at funding post “proof-of-concept”, few projects are being funded by this mechanism. This supports the conclusion by the 2003 Emerging Biotechnology Roadmap that there remains a substantial gap between innovation and commercialization.

5 RESEARCH ENVIRONMENT: South Africa

MIA has stated its key objective in the integration of researchers focusing on molecular aspects of malaria drug and insecticide discovery, molecular epidemiology and diagnostics, and capacity building in order to improve malaria prevention and control. Three programmes are envisaged:

- The development of new and modified drugs and insecticides
- The development and implementation of assays for epidemiological and diagnostic interventions
- Capacity building programmes as a cross-cutting programme

This section serves to provide a brief overview of the malaria research currently being undertaken in South Africa in the various categories of interest to MIA. Vaccine development has therefore not been included.

5.1 EPIDEMIOLOGY and DIAGNOSTIC RESEARCH:

5.1.1 University of KwaZulu Natal

5.1.1.1 School of Molecular and Cellular Biosciences: Professor Dean Goldring

Area of Research: Tracking anti-malaria drugs, development of dipstick assays.

The team has developed an array of antibodies against anti-malarial drugs, which can be used to track malaria drugs in a range of cells, tissues and body fluids.

Through an international collaboration in a MVI project in Denmark and Ghana, the team is developing reagents for a second generation of an ELISA diagnostic kit. The first generation of the ELISA is being used as an experimental tool in malaria vaccine trials.

5.1.2 Medical Research Council of South Africa:

5.1.2.1 Malaria Research Programme: Director Dr Brian Sharp

Area of Research: Biology and control of malaria vectors and parasites
Molecular basis of drug resistance
Biochemical basis of insecticide resistance
Spatial and molecular epidemiology and health systems research.
Research capacity building for malaria

The Malaria Research Programme became a lead programme within the MRC Infection and Immunity National Programme in 1999 in order to stimulate malaria research, build capacity and transfer skills. Malaria control is a dynamic process requiring continual research input, and therefore the MRC research focus has the sustainability of control in the future as a key goal. Research is therefore aligned with informing effective policy and control. Focus areas include vector and parasite research, the epidemiology of the disease, drug and insecticide resistance, bio-prospecting and Geographical Information Systems (GIS) technology. Research is carried out in both laboratory and field, with the emphasis on applied research.

The summary below is not intended to be a comprehensive list of all the MRC malaria projects, but describes a select few of relevance to the outcome of the proposed MIA programme.

Malaria Information Systems:

The MRC was instrumental in the development and implementation of a vector based GIS based decision support system (DSS) for the Lubombo Spatial Development Initiative (LSDI). This is used for both management of the disease and research. Amongst other objectives the DSS supports the extension of malaria control into southern Mozambique and assess the impact of the intervention tools on disease prevalence and tourism. The MRC furthermore has investigated the underlying biotic and abiotic factors that drive malaria transmission in South Africa and has developed statistical malaria epidemic prediction models in order to better control the disease. This model is used as a health management tool within the LSDI.

The MRC was the main investigating centre for the “Mapping Malaria Risk in Africa” collaboration project, know as MARA/AMRA. This ongoing project, allowed the establishment of an atlas of malaria risk in Africa, i.e. a continental database of the spatial epidemiology of malaria including vector distribution, drug resistance, and insecticide resistance. This project used a geographic information system (GIS) and integrated different malaria, geographical and environmental data sets. The use of good spatial maps is vital part of any malaria control programme as malaria needs to be controlled regionally.

Lubombo Spatial Development Initiative:

In July 1999 the heads of state of South Africa, Swaziland and Mozambique signed the General Protocol which put in place a platform for regional cooperation and delivery, the Lubombo Spatial Development Initiative. In October 1999 the Lubombo Malaria Protocol and tri-national malaria programme was launched. The Regional Malaria Control Commission (RMCC) is the co-ordinating and decision – making body of the LSDI programme. The MRC Malaria Research Programme chairs the RMCC as well as undertaking the direct management of the programme on behalf of the RMCC and providing secretarial, financial management, fund-raising, and research support. Large scale malaria control covering >100 000 square kilometres in the 3 countries is being monitored and evaluated as part of this collaboration.

Insecticide resistance monitoring and management/ Gene flow

The MRC together with the National Institute of Communicable Diseases has developed and improved molecular and biochemical techniques aimed at determining the resistance levels in natural populations of the malaria vector to insecticides. In order to carry out research on the genetics of insecticide resistance and gene flow, research capacity in this area was developed through training at the University of Liverpool. The Malaria Programme also continually monitors the insecticide resistance situation in southern Africa.

To control the development of insecticide resistance; malaria control programmes are investigating the use of various insecticides in rotational spraying. This technique is being investigated to preserve the long-term effectiveness of current insecticides.

Molecular techniques such as polymorphic microsatellite and mitochondrial DNA markers have been used to describe the dynamics and population genetics of the seasonally fluctuating vector (*An. arabiensis*) population. This study compared the relative importance of resident mosquitoes with immigrants in founding the wet season population expansions and their role in malaria epidemics.

Antimalarial drug resistance/Gene Flow:

Antimalarial drug resistance poses a major threat to the control of malaria in Africa. Interventions such as drug policy or drug dosage changes rely on appropriate drug efficacy information being available to decision makers. This is the goal of including drug susceptibility/resistance data from Africa as an additional data collection component to the MARA project. The aim is to record antimalarial drug susceptibility and resistance data in a systematic manner.

Research into the emergence and spread of drug resistance is constantly conducted. The molecular genetic basis of drug resistance at parasite population level is investigated. Previous research has indicated that gene flow rather than new mutations has been the most common originator of sulfadoxine-pyrimethamine resistance in Africa. The determinants of resistance in KZN were found to share a common evolutionary origin with those found in Kilimanjaro, Tanzania, even though the two sites are 4000 km apart. Additional research collaboration has produced evidence that malaria parasites bearing high level pyrimethamine resistance originally arrived in Africa from SE Asia.

The MRC collaborates extensively with international research groups such as the London School of Hygiene and Tropical Medicine, the Swiss Tropical Research Institute, and the Liverpool School of Tropical Medicine. The MRC also has established links with scientists throughout Africa via the MARA network, the LSDI and other collaborative projects. Collaborators include scientists from Cameroon, Kenya, Madagascar, Mozambique, Mali, Tanzania, Malawi, Angola, Zimbabwe, Equatorial Guinea and Zambia.

5.1.3 National Bioproducts Institute

5.1.3.1 Dr Martin Bubb

Area of Research: Development and Optimised production of a rapid malaria diagnostic kit

The project forms part of a large project, together with Molecular Diagnostic Services and LIFElab, to develop a platform for the production of rapid and routine diagnostic tests of relevance to the Southern African region.

Microscopic examination of thick and thin films remains the gold standard for malaria diagnosis. In many rural settings, facilities capable of performing these evaluations are not available, and diagnosis is based on clinical symptoms. Rapid diagnostic tests based on the detection of malarial antigens e.g. Histidine rich protein II (HRP II), lactate dehydrogenase (LDH), and aldolase using immuno-chromatographic technology are being evaluated as an alternative.

It is essential that low parasitaemia levels can be detected in immune patients in endemic countries. NBI has developed a pair of monoclonal antibodies specific for HRP II that are suitable for use in a rapid diagnostic test. These antibodies are specific for *Plasmodium falciparum* and recognise different epitopes on this molecule. The antibodies are already being sold to overseas companies for incorporation into malaria rapid diagnostic kits. NBI is developing and optimising its own manufacturing process of a malaria diagnostic kit that is user friendly, easy to interpret, rapid and sensitive so as to capture this value addition in South Africa.

Dr Bubb is a WHO temporary advisor on Malaria Rapid Diagnostic Kits.

5.1.4 National Institute of Communicable diseases:

5.1.4.1 Vector Control Reference Unit: Professor Maureen Coetzee

Areas of Research: Molecular identification and characterisation of mosquito vectors.
Molecular mechanisms of mosquito resistance to insecticides.
Field studies for resistance management.

Research within the Vector Control Unit is aimed at determining the extent and distribution of insecticide resistance in mosquito populations. As part of a MIM/TDR funded project, the NICD and the MRC developed and implemented a molecular and biochemical capability for insecticide resistance monitoring and management in South Africa. The group was instrumental in the discovery of pyrethroid resistance in *An. funestus* in 1999 and hence the establishment of a policy for the choice of insecticide in South Africa.

The unit has over 20 mosquito colonies, most of which are not available elsewhere in the world. A rapid rDNA PCR-based diagnostic tool with the capability of differentiating between five species of the *An. funestus* group of vectors has been developed. The mechanisms that confer resistance to insecticides in these mosquitoes are under investigation leading to an increase in understanding of metabolically mediated resistance in *An. funestus*. In addition, resistance mechanisms in members of the *An. gambiae* complex from various parts of Africa are also being studied at the molecular and biochemical levels.

An understanding of malaria epidemiology is critical in the development of control strategies. This is doubly so when considering the use of genetically modified mosquitoes to prevent malaria transmission. Knowledge of population structure in the vector species and possible gene flow between populations, will impact not only on the spread of transgenic mosquitoes, but also the spread of insecticide resistance genes. Collaborative studies are ongoing with institutions in the USA and the UK to investigate these issues. Future research projects include studying the interactions between the vector and parasites and using microarrays to evaluate gene expression between resistant and susceptible mosquitoes.

Technologies used include DNA sequencing, PCR, real-time PCR, cloning, northern blots, microarrays, cytogenetics, *in-situ* hybridisation, ELISAs, mosquito rearing, and insecticide resistance testing.

5.2 CLINICAL and PRE-CLINICAL RESEARCH:

5.2.1 University of Cape Town

5.2.1.1 Department Of Pharmacology: Professor Peter Smith

Area of Research: Mechanism of chloroquine resistance reversal
Isolation and characterisation of novel antimalarials from medicinal plants
Pharmacokinetics of antimalarial drugs

The department has extensive expertise in drug assay development and pharmacokinetics of drugs in particular those used in tuberculosis and malaria. The research group has a well established culturing facility with 10 different malaria parasite strains available. Activity testing against a panel of drug-sensitive and drug-resistant *P. falciparum* is performed *in vitro*. An *in vivo* mouse model of malaria (*P. berghei*) has been established and *in vivo* assays for activity and toxicity testing with two parasites different in terms of their resistance to chloroquine is routinely performed. Pharmacokinetics and

pharmacodynamics of malaria drugs to determine the absorption in blood are supported by LC Mass Spectrometers. The department also collaborates extensively with other research groups in these activities in the drug discovery and development process using the infrastructure that has now been established.

The department conducts research into the mechanism of drug resistance in *P. falciparum* from a cell biology perspective. Additional research projects are through the South African Traditional Medicines Group (SATMERG) where plant extracts from traditional medicines are screened for anti-malaria activity. SATMERG is funded by the MRC. More than 500 plants have been investigated to date, with more than 25 showing significant activity against a number of strains of *P. falciparum* in crude extracts. Active crude extracts are fractionated to purify the active agents to homogeneity. Activities in this regard also form part of the Innovation Fund platform project.

The department has a well established Medicines Information Centre, an independent drug information service provided by trained pharmacists. The department has a number of people involved in drug regulatory affairs.

5.2.2 University of Pretoria

5.2.2.1 Department of Internal Medicine: Professor Anton Stoltz

Area of Research: Post-graduate training in infectious diseases.
Access to malaria patients for clinical trials

The Department of Internal Medicine: Infectious Diseases has the capacity to conduct all levels of clinical trials from early toxicity studies to human studies. Currently no malaria studies are being performed. The Department would however be in a position to provide access to patients and to other services offered should any research programme within MIA required it.

5.2.3 South East Africa Combination Anti-Malarial Therapy Evaluation

University of Cape Town Pharmacology Department: Dr Karen Barnes

Medical Research Council: Dr Brian Sharp

Mpumalanga Department of Health: Dr Dave Durrheim

Area of Research: An evaluation of the effect of anti-malaria therapy on the emergence of resistance.²⁵
Operational and policy research

South East Africa Combination Anti-Malarial Therapy (SEACAT) study is a joint initiative between South Africa, Mozambique, and Swaziland to investigate the effect of antimalarial therapy on the emergence of resistance. This study is being conducted on behalf of the Regional Malaria Control Commission as part of the LSDI programme. Financial support for the project has been received from the UNDP/World Bank/WHO TDR. The major source of funding at present is the Global Fund.

The MRC is collaborating with the University of Cape Town and the Mpumalanga Department of Health. There are also a number of international collaborators in the project, including the London School of Hygiene and Tropical Medicine, and US Centre of Disease Control and Prevention.

The study was initiated in order to provide data to advise drug policy making by the national Malaria Advisory Group. The project continually evaluates the implementation of combination antimalarial therapy at provincial and national levels in Mozambique, Swaziland and South Africa in terms of public health impact, safety, efficacy, etc. *In vivo* resistance, molecular markers of resistance, gametocyte carriage, drug utilisation and cost effectiveness are evaluated at each site biannually over a 6-year period. A goal of the evaluation is to ensure that the impact of large-scale treatment with the ACT antimalarials is optimised. The project is linked to concurrently funded projects including the evaluation of *in vitro* resistance and gene flow. This will allow evaluation of the impact of antimalarial therapy on the intensity and distribution of malaria in the region.

Other clinical studies in the use of ACT antimalarials in severe and uncomplicated malaria, pregnant women and children are also performed in Southern Africa. Most studies are performed in Southern Africa due to the difference in immunity between endemic and non-endemic areas such as South Africa. South Africa only has a limited role to play in these studies.

5.3 BASIC SCIENCE:

5.3.1 University of Cape Town

5.3.1.1 Department of Chemistry: Professor Kelly Chibale

Area of Research: Medicinal Chemistry and Synthetic Organic Chemistry

The Medicinal Chemistry programme focuses on the design and synthesis of novel anti-infectives, including antimalarial and antituberculosis agents. Potential antimalarial leads are based on a number of different biochemical pathways. One project is based on studying the purine salvage enzymes (hypoxanthine-guanine-phosphoribosyl-transferase) as the malaria parasite lacks the ability to produce purines itself. This project is in collaboration with Professor David McIntosh of the UCT Department of Pathology. Further potential drug target are the enzymes involved in the degradation of haemoglobin, for example cysteine proteases. Inhibitors of cysteine proteases would prevent host haemoglobin proteolysis in the food vacuole, hence denying the parasite its source of amino acids required for replication. Dr Heinrich Hoppe (UCT) and Professor Philip Rosenthal (University of California San Francisco, USA) are collaborators on this project. The group is also involved in anti-malarial drug combinations particularly with respect to chemical hybridization of two or more antimalarial drugs targeting more than one biochemical pathway so as to reverse drug resistance and retain the use of existing drugs such as chloroquine.

The group collaborates with the University of Cape Town Department of Pharmacology. Professor Peter Smith performs the *in vivo* studies in appropriate mouse models as well as determination of the pharmacokinetic profiles of potential lead compounds. This is a vital link in the chain of drug discovery and development in South Africa.

The Group is also involved in the Innovation Fund Novel Drug Platform from Indigenous Plants, as the leader of the programme dealing with the design and synthesis of chemical libraries of natural product-derivatives.

5.3.1.2 Department of Chemistry: Professor Tim Egan

Area of Research: Cell biological effects of antimalarials: mechanism of action of quinoline antimalarial drugs

The group is active in the investigation of the mechanism of action of quinoline antimalarial drugs in the haem detoxification process of the parasite. It has been proven that virtually all of the haem produced by the *P. falciparum* parasite is incorporated into malaria pigment, haemozoin, in the parasite food vacuole. Further research into aspects of this research is being carried out in order to further understand the pathway of haemozoin formation. This involves studying the mechanism and kinetics of formation of synthetic haemozoin, β -haematin, using both molecular modelling and chemical studies. Cellular studies are also underway. The structure-activity relationships of various synthetic quinoline analogues have been determined. Their inhibition of β -haematin and *in vitro* antimalarial inhibition are studied in order to gain insights into the mechanisms of action.

New research projects involve using structure-activity relationships to determine the relationship between quinoline structures and cross-resistance to chloroquine. This work will contribute to a clearer understanding of the mechanism of action of chloroquine and lead potentially to the development of new quinoline drugs that by-pass the resistance mechanism. A colorimetric high-throughput screening assay to measure the strength of inhibition of β -haematin formation has been developed. This best allows the screening of potential haemozoin inhibitors. The test is used in the Group's research programme and a pilot study is underway in the screening of natural product isolates obtained in the Innovation Fund study.

Techniques used include spectroscopy, diffraction and electron microscopy, molecular mechanics, molecular dynamics and simulated annealing calculations, organic synthesis (in collaboration with Professor Roger Hunter) and 2D QSAR methods. The Group collaborates extensively with the UCT Pharmacology Department, Electron Microscopy Unit, as well as with the University of Witwatersrand Departments of Physics (Dr Giovanni Hearne) and Chemistry (Professor Helder Marques).

5.3.1.3 Institute of Infectious Disease and Molecular Medicine: Malaria Cell Biology Group: Dr Heinrich Hoppe

Area of Research: Malaria cell biology focussed on endocytosis of malaria parasites
Cell biology of antimalarials and antimicrobials

The Institute's research activities are associated with understanding the fundamental molecular mechanism of action of endocytosis in malaria parasites. Apart from a morphological description of this pathway at the electron microscopy level, this process is poorly understood. The outcome of the research is to establish current and novel cell biology and genetic manipulation techniques and laboratory capability to be applied in the study of malaria.

The project focuses on the characterisation of 7 malaria homologues of proteins known to mediate endocytosis in other cells i.e. Clathrin, Dynamin, Adaptins, Coronin and Actin. Advanced technologies for manipulating the parasite at a molecular, cellular, and genetic level are used. These tools have been widely used in the characterisation of other organisms, but not as yet in malaria. The proteins are being characterised *via* two routes: sub-cellular localisation and functional characterisation. Tools include recombinant protein expression of genes in *E. coli*, mouse antiserum production, localization by

immunofluorescence, electron microscopy, and gene suppression by RNAi, heterologous malaria gene expression in *Dictyostelium* and transient transfection of parasites with dominant negative mutants.

The Institute is also involved in a number of other projects in the University of Cape Town Department of Chemistry: Professor Tim Egan and Professor Kelly Chibale as well as the University of Stellenbosch Department of Biochemistry: Dr Marina Rautenbach. The potential antimalarial drugs under development in these departments are provided to the group for testing in parasite culture systems to determine parasite viability and sensitivity to the antimalarial drug. The modes of action of potential drugs are investigated for example in the determination of the efficacy and cell biological effects of protease inhibitors through the application of endocytosis assays. The group is also furthermore characterizing several commonly used membrane-active antimicrobials as potential therapy in severe malaria cases.

Dr Hoppe holds a Wellcome Trust International Senior Research Fellowship. Collaborating partners and co-workers are the University of Cape Town Departments of Pharmacology and Chemistry, Stellenbosch University, the University of Pretoria Department of Biochemistry, Bernhardt Nocht Institute for Tropical Medicine (Germany) and Yale University.

5.3.1.4 Department of Chemical Pathology: Professor Dave McIntosh

Area of Research: Targeting of purine-based antimalarials

The department of Chemical Pathology's involvement in malaria research is in the area of antimalarial Drug Development. One project is based on studying the purine salvage enzymes as the malaria parasite upon which the parasite is dependant. Collaboration is with the Department of Chemistry: Professor Kelly Chibale. Funding has been applied for in order to obtain crystal structures of the enzyme compounds of interest.

5.3.2 Council for Scientific and Industrial Research

5.3.2.1 Biotechnology, Speciality and Fine Chemicals: Dr Dusty Gardiner/ Dr Colin Kenyon/Dr Chris Parkinson

Area of Research: Functional genomics and Proteomics
Structural biology and computational biology applicable to malaria parasite enzymes
Molecular recognition, structural and synthetic organic chemistry.

The CSIR has and continues to invest in the development of capacity in genomic and proteomic technologies. These technologies are being applied to the identification and elucidation of novel drug targets for diseases of importance to Africa. The CSIR is now applying this expertise in partnership with collaborators who are active in malaria research. Collaborative projects are being implemented in partnership with the MRC and the University of Pretoria. The CSIR's initial role in these partnerships is in the application of the above "systems biology" tools towards identifying the mechanism of action of potential drug leads and identifying new drug targets.

One research project involves cloning of the *E. coli* codon-adapted gene for glutamine synthetase, followed by expression of the functional enzyme. This would be novel in the malaria context. Another

research project involves cloning and expressing the glutathione S transferase enzyme from the *P. falciparum* parasite. In contrast to other organisms, the malaria parasite *P. falciparum* possesses only one glutathione S transferase enzyme, and it has been shown to be involved in some aspect of the haem detoxification process. It may therefore represent a promising target for antimalarial drug development. Tools used include protein molecular modelling, molecular biology and enzymology to characterize and define enzyme reaction mechanisms, as well as site directed mutagenesis. As the projects progress, the CSIR's involvement will be expanded to include rational design of new drug leads.

Research is conducted into the synthesis of the endoperoxide antimalarials i.e. the artemisinins. Two research proposals are in the process of being drafted. Activated artemisinins are known to form adducts with a variety of biological molecules including haem. It has now been shown that artemisinin derivatives act by inhibition of the PfATP6 protein outside the food vacuole after activation by iron.²⁶ Research chemists are now attempting to identify semisynthetic and fully synthetic endoperoxides that will retain the activity of artemisinin derivatives, but overcome some of their deficiencies, such as the short half-life and residual fears of neurotoxicity.²⁷ The potential for rational drug design of new artemisinin derivatives using established principles coupled with the understanding of the mechanism of action therefore exists.

The CSIR has skills in process and product development and scale-up, process and product commercialization and intellectual property development, packaging and commercialization which will be brought to the various projects as they progress through the development process.

5.3.2.2 Bioprospecting: Dr Marthinus Horak

Area of Research: Bioprospecting and new chemical entity discovery

This group's focus is on the value addition to medicinal plants and associated Indigenous Knowledge, plant collection, screening, analysis, bioassay guided fractionation, isolation and structure elucidation of active molecules and development of minimally processed forms of traditional medicines. Expertise is in the area of drug lead discovery through the isolation and structural elucidation of novel active ingredients in medicinal plants. An example is the invention and patenting of a mosquito repellent through the identification of chemotypes of a plant with superior repellent properties, followed by isolation and identification of the chemical constituents. In rural dwellings the plant is used to repel mosquitoes. Tests have shown that it is nearly 100% effective compared to 40% in existing products on the market. The group has successfully implemented agro-processing technology on five community-owned cultivation sites (approximately 20 ha each), including distillation technology to give the mosquito repellent essential oil. A community-owned mosquito repellent candle factory based on the indigenous oil was launched during August 2005.

This group is part of the consortium involved with the Innovation Fund: Novel Drug Platform from Indigenous Plants. The group's participation in the project includes the extraction of the active ingredient from the plant, isolation of the active compound, structure elucidation coupled with the supporting analytical techniques. In the long-term the group will be responsible for the controlled horticulture of any indigenous plants that are shown to contain therapeutically active substances, and the subsequent production of the extracts and purified compounds for clinical trials according to Good Manufacturing Practice (GMP).

5.3.3 University of KwaZulu Natal

5.3.3.1 School of Molecular and Cellular Biosciences: Professor Dean Goldring

Area of Research: Cell cycle regulation: molecular mechanisms controlling cell division and differentiation in malaria parasites.

The research team has a multifaceted approach to understanding the complex interactions between the malaria parasite and the host. Some research conducted in the group is part of a larger international project with Christian Doerig, INSERM - Wellcome Centre for Molecular Parasitology, and funded by the SA MRC, SA NRF and an EU INCO-DEV grant. This involves the identification, isolation and characterisation of 80 different malaria protein kinases involved in cell signalling and regulation of the cell cycle. The international project is focused on obtaining an understanding of the function of these proteins in the life cycle of the parasite, and at elucidating the structure of the regulatory networks in which they function. Structural insight of kinase-inhibitor complexes could potentially be used as a basis for the synthesis of derivatives with selectivity/activity towards the target kinase to pursue as possible anti-malarial drugs. Kinase identification is aided with the use of affinity purified chicken anti-peptide antibodies.

Other interests include research into the impact of antimalarial drugs on the immune system (immunomodulation) and the study of immunotherapy against cytoadherence. Electron probe X-Ray microanalysis is used to evaluate ion homeostasis under the influence of disease and anti-malarial drugs.

The team has identified a malaria protein that has promising vaccine potential. The expression, location and structure of the protein and identifying of immunogenic epitopes is being studied. Other experience in malaria research is in rosetting, cytoadherence (sequestration), monocytes in malaria, T-cell mediated immunity and mouse malaria models.

5.3.4 Medical Research Council

5.3.4.1 Innovation Fund: Project Leader Professor Peter Folb/Dr N Bhagwandin

Area of Research: National research and development platform for novel drug development from indigenous medicinal plants²⁸

The aim of the technology platform is to develop new medicines and tonics based on indigenous plants and local knowledge for the treatment of a number of important and neglected diseases in the African context. The focus is those diseases such as malaria, tuberculosis and diabetes, for which there are validated test systems, both *in vitro* and *in vivo*. Many of the plants that will be investigated are endemic to southern Africa, providing opportunities for discovery that are not available elsewhere. However, only indigenous plants, which can be utilised without creating any ecological problem, will be investigated.

The project is the result of extensive collaboration of a multidisciplinary team of 17 research units and 135 scientists across the country. The institutions involved include: the SA Medical Research Council (MRC), Agricultural Research Council (ARC), CSIR, South African National Biodiversity Institute (SANBI), University of Cape Town, University of Pretoria, University of KZN, University of Limpopo and the University of Johannesburg. The lead consortium member is the MRC.

The project has set up cross-linkages between the various disciplines, institutions, departments and government bringing together the potential to integrate the strengths of microbiology, chemistry, pharmacology and botany. Part of the innovation in the project is thus in the establishment of a platform through collaboration, hence creating new research and development models.

It is anticipated that successful implementation of the 3 year project will allow the discovery of 2 – 3 novel drugs and tonics to the point of “proof of principle”, suitable and ready for early clinical studies, After establishment of proof of principle, subsequent pharmaceutical and manufacturing development will be conducted in collaboration with pharmaceutical chemists, and the pharmaceutical industry in South Africa. The project is directed at achieving benefits for the public health sector, by virtue of the focus on neglected diseases. The programme is currently in its second year.

The project aims to follow a policy of corrective action, with training and capacity building critical to increase the number of high-level scientists in South Africa. A further outcome is the establishment of new agro-processing businesses for the supply of plant material required for new drugs. The goal of the project is to place South Africa as an international player in the development of plant-derived medicines.

5.3.4.2 Malaria Research Programme: Director Dr Brian Sharp

Area of Research: Evaluation of insecticides and repellents

The MRC has been designated as one of the main institutes to conduct efficacy trials for products to be registered with the Registrar of insecticides. New insecticides and different formulations of existing insecticides have been evaluated for commercial organisations, in order to obtain the necessary registration of their products.

As part of the Novel Drug Development Platform, the MRC is currently involved in studies to detect novel compounds that can be used as a mosquitocides. Indigenous plants that have been used by traditional healers or traditionally for the control of mosquitoes have been systematically evaluated through bioassay guided fractionation to get to pure compounds that are bioactive. This study has yielded some positive leads.

5.3.5 University of North West:

5.3.5.1 Department of Pharmacy Drug Research and Development :Professor Lotter

Area of Research: Formulation of antimalarial drugs

The antimicrobial biocide triclosan has been shown to potently inhibit the growth of *Plasmodium falciparum in vitro* and, in a mouse model, *Plasmodium berghei in vivo*. Triclosan is however not very soluble. The Department of Pharmacy has developed novel drug delivery systems, and oil formulation and soft gel capsules, which have shown high blood levels when tested. This research is however now complete, and would require more extensive bioavailability testing and testing in humans for further development.

5.3.6 University of Pretoria

5.3.6.1 Department of Immunology: Professor Ron Anderson

Area of Research: Drug Discovery

This group's involvement in malaria research is in the development of potential antimalarial drugs. A drug, which is already registered for another indication, has been identified as having potential antimalarial activity. This product is currently the subject of a potential patent application together with the Medical Research Council. Further details can therefore not be provided to ensure intellectual property protection rights. The product is being developed in collaboration with Dr ME Makgatho (University of Limpopo) and Professor Peter Smith (University of Cape Town).

Technologies used include screening of potential antimalarials, parasite viability tests, and *in vivo* animal model testing.

5.3.6.2 Department of Biochemistry: Professor Braam Louw

Area of Research: Metabolic enzymes of the malaria parasite as potential drug targets.
Functional genomics
Bioinformatics and structural genomics

The scientific goal of the research programme at the University of Pretoria is to characterise and validate novel malaria parasite targets to assist for the development of therapeutic intervention strategies. The focus is mainly on three enzymes of the polyamine and two of the folate metabolic pathways of *Plasmodium falciparum*. The polyamine metabolism is of particular interest as the parasite is dependent on polycations for normal division and differentiation but the enzymes of the pathway still need to be validated as drug targets. Only two enzymes of the folate pathway are validated as drug targets and the focus is on recently described enzymes of this pathway as potential targets. Studies on enzymes from both these pathways include improvements in the recombinant expression of the native genes or synthetic constructs followed by selected mutations for the characterisation of novel, parasite-specific features involved in the activity of these enzymes and protein-protein interactions.

The group is also active in determining the mechanism of action of potential antimalarial plant compounds and inhibitors by gene expression profiling using SSH and DNA microarrays of the malaria parasite under selective drug pressure. In this regard, the department is a member in the Innovation Fund consortium focussed on establishing a Novel Drug Discovery Platform from Indigenous Plants. Additional activities include DNA microarray and proteomic experiments of parasite populations treated with three well-defined inhibitors of the polyamine pathway in collaboration with the CSIR, Bernard-Nocht Institute for Tropical Medicine (Germany) and the University of Manchester (UK) to elucidate parasite drug responses and gene function and to identify novel gene targets.

The Bioinformatics and Computational Biology facility Unit undertakes structural modelling of enzymes from the parasite's metabolic pathways and is involved in the establishment of *in silico* methods for the design of drug-like molecules. A web interface named MADIBA (Micro Array Data Interface for Biological Annotation) is nearing completion to assist in the interpretation of data derived from gene profiling experiments and the elucidation of the mode of action of drugs or inhibitors. Other bioinformatics skills include: gene and protein sequence analysis and motif identification; algorithm design; microarray data

analysis; microsatellite and SNP analysis; combinatorial libraries and drug design; databases; pipelining and web interfaces.

5.3.7 Rhodes University

5.3.7.1 Department of Biochemistry, Microbiology and Biotechnology: Professor Greg Blatch

Area of research: Malaria Chaperones in biology, medicine and protein biochemistry

The research group is involved in the study of the role of heat shock proteins in disease and infection. The project therefore includes, but is not limited to, malaria. Heat shock proteins, also known as stress proteins or molecular chaperones, are a family of proteins that have been shown to be adapted to facilitate the correct folding of other proteins under physiological and stress conditions. The research project involves the investigation of the molecular basis of the cell stress response and the application of this knowledge in protein biotechnology leading to a fundamental understanding of how cells ensure the correct folding and functioning of proteins under physiological, stress and disease conditions. There are three programmes within this project:

Chaperone/co-chaperone interaction and the molecular basis of the cellular stress system.

The mechanism by which co-chaperones interact with and regulate molecular chaperones is being investigated in order to understand how these interactions provide cytoprotection. An understanding of the molecular basis of the specific interactions between partner chaperones and co-chaperones in pathogen systems will facilitate the identification of pathogen-specific chaperone targets for drug development.

The role of heat shock proteins in disease and infection

The project studies the similarities and differences between how parasites and their hosts deal with stress leading to an understanding of how parasites protect themselves.

Improved heterologous protein over-expression by co-expression of protein folding factors.

Molecular chaperones can be utilized in industrial biotechnology applications to improve the yield of recombinant protein production. The early steps of isoprenoid biosynthesis have been identified as valid targets for the therapy of malaria. Inhibitors of the 1-deoxy-D-xylulose 5-phosphate (DOXP) reductoisomerase (e.g. fosmidomycin) have been shown to have antimalarial activity *in vitro* and in animal mouse models.²⁹ The enzyme is difficult to produce *via* recombinant techniques; hence the use of a molecular chaperone could assist to improve the yield.

Professor Blatch holds a Wellcome Trust International Senior Research Fellowship. Expertise is in the isolation of genes and heterologous protein overproduction, affinity purification and *in vitro* and *in vivo* characterization of molecular chaperones of parasitic origin. Techniques include a range of molecular and cellular techniques including *in vitro* assays (protein binding assays, biological activity assays, protein folding/refolding assays), and *in vivo* assays (localisation and co-localisation studies using immunofluorescence staining and reporter tagging, genetic complementation assays)

5.3.8 University of Stellenbosch

5.3.8.1 Department of Biochemistry: Dr Marina Rautenbach

Area of Research: Haemolytic Peptides directed against the Malarial Blood Stage of *P. falciparum*

Dr Rautenbach is involved in the design, synthesis, purification, testing and determination of the mechanism of action of antimicrobial peptides and compounds. The BIOPEP Peptide facility, run under strict GLP rules, has the capability of producing peptides for industrial and diagnostic use.

The focus in the malaria area is on membrane active peptides and compounds. In collaboration with Dr H Hoppe (University of Cape Town Department of Pharmacology), a number of peptides and polyene antibiotics with known antimicrobial and haemolytic activity were investigated. The haemolytic activity of the polyketides, amphotericin and nystatin and several cyclic antifungal peptides were found to be effective against the trophozoite blood stage of the malaria parasite, *P. falciparum*. The selective lysis of the membranes of red blood cells infected with parasites was found to be up to 1,000 times that of non-infected erythrocytes.

These compounds would not be candidates for prophylaxis or in the treatment of uncomplicated malaria, but are believed to be promising candidates for treatment of severe malaria, as *in vitro* tests have shown killing of chloroquine resistant *P. falciparum* trophozoites within one hour. Additional work through collaboration with Professor Pieter Swart (University of Stellenbosch) is being conducted in order to find ways of lowering the cost of manufacture. One patent has been taken out on the polyketide results and a second patent on the cost-effective production and purification of candidate compounds and peptides is currently under investigation in this research programme.

5.3.9 University of Witwatersrand

5.3.9.1 Department of Molecular Medicine and Haematology/NHLS: Professor Theresa Coetzer

Area of research: Interaction of parasite proteins with the red blood cell membrane
Characterisation of proteins and metabolic pathways
Gene Regulation

Projects in the group are in the basic research phase, but the long term goal is geared towards the identification of potential drug targets. Specific research projects include the study of the mechanism whereby the parasite interacts with the red blood cell membrane proteins. The development of the parasite within human erythrocytes induces significant changes to the structure and function of the host membrane. The identification of interactions between proteins expressed by the parasite and proteins in the host red blood cell membrane (e.g. protein 4.1 and spectrin) is hence being studied. The characterisation of novel protein interactions will enhance the understanding of *P. falciparum* biology. Another project is the study of gametocytogenesis of the parasite for example by studying the gene regulation processes.

The group is also active in the characterisation of various proteins and metabolic pathways. One potential target has been identified through the discovery of a gene coding for the glycerol kinase enzyme in the parasite. This gene has been cloned and the recombinant protein will be expressed and assayed for functional activity. In addition, a putative gene encoding malaria telomerase has been

identified and this may provide another potential drug target. This research is also relevant to understand evolution of the genome.

Expertise within the group includes basic molecular biology techniques, creation of *P. falciparum* phage display libraries; purification of red blood cell membrane proteins; gametocyte culture; bioinformatics analysis; and the cloning, expression and purification of parasite proteins.

The department collaborates internationally with INSERM in Paris and SANBI at the University of the Western Cape.

5.3.9.2 Department of Clinical Pharmacology: Professor Ivan Havlik

Area of research: Malaria Cell Biology
Screening of potential antimalarial drugs
Clinical Trials of potential antimalarial drugs

The department researches various aspects of the *Plasmodium* protozoa, including drug testing, biochemical and molecular studies and conducts clinical trials.

Hundreds of novel compounds have been screened *in vitro* against sensitive and drug resistant parasites. This has been achieved by establishing numerous local and international collaborations who have synthesized various derivatives of hydroxyquinolines (University of the North West: Potchefstroom), thiosemicarbazones (Delhi), chalcones (Delhi), structurally diverse nucleoside phosphonic acids (Prague) and cyclin dependent kinase inhibitors (Paris). The potential antimalarial activity of traditionally used plants has also been investigated along with collaborators from the Universities of Wits, KZN and North West: Potchefstroom. Research into various aspects of iron metabolism in the malaria parasite is being conducted; including how iron is acquired and utilized by the parasite and how drugs interfere with its uptake; the formation of malaria pigment and whether various standard and novel drugs interfere with its formation as the hydroxyquinoline drugs are proposed to do.

The group conducts basic research on the functional characterization of *Plasmodium* kinases involved in cell cycle regulation and signal transduction. The current focus area is the *Plasmodium* homologues of cyclin G associated kinase, NIMA related kinases and phosphatidylinositol-3 kinase. This work is carried out in collaboration with Christian Doerig of the French INSERM Unit 609, located at the Wellcome Center for Molecular Parasitology, University of Glasgow, Scotland. The ultimate aim of this collaboration is the identification of compounds that will block differentiation of parasites into male and female gametocytes. In this context a large library of potential cyclin dependent kinase inhibitors have been screened for their effect on parasite survival.

The department has collaborated in preclinical studies of curdlan sulphate (CRDS), which showed *in vitro* inhibition of *P. falciparum* and a down-modulation of the immune response. Clinical studies in a small number of patients using CRDS as an adjunct medication to conventional artesunate therapy concluded that CRDS might benefit patients with severe/cerebral malaria presenting with no additional complications such as organ damage. Further funds will be required to manufacture new batch of CRDS and finance the clinical study to complete the investigation. Additional expertise is in the study of the formation of rosettes, the adherence of infected erythrocytes to uninfected erythrocytes, during the trophozoite stage of parasite development.

5.4 TRAINING AND CAPACITY BUILDING

5.4.1 University of Pretoria

5.4.1.1 Foundation for Professional Development: Professor Anton Stoltz

Area of Research: Post-graduate training in infectious diseases.

Professor Stoltz is a member of the Foundation for Professional Development. This organisation provides training courses for the medical profession, including general practitioners as well as specialists, in the management of infectious diseases such as malaria and HIV. Currently, and HIV training course in 10 countries in Africa is being carried out. A malaria course is under development. The course could in the future be taken into Africa.

5.4.2 University of Witwatersrand

5.4.2.1 Centre for Post-Graduate Studies: Professor Steve Chandiwana

Area of research: Research capacity building for malaria

Professor Chandiwana is Assistant Dean of Research and Postgraduate Studies in the Faculty of Health Sciences. The centre provides research and educational opportunities to scientists and professionals involved in health research, including malaria research, in three different areas.

Training in protocol/proposal design.

This course is teaches research methodology so as to ensure that scientists and researchers achieve their objectives.

Proposal/Grant Writing

This course covers issues such as how to mobilise funding sources, and how to write proposals. Researchers are taught techniques, which allow them to be more competitive in applying for global, research funds.

Research Analysis

This course is aimed at ensuring that scientists maximise the results of their research and can convert the analysis into reports or publications.

Refresher courses to middle level scientists working at research laboratories in Africa cover research methods based on epidemiology principles to ensure effective interventions, malaria immunology and preparation for vaccine trials. Young researchers and postgraduate students especially from previously disadvantaged groups such as black and female academics undertaking research projects are also mentored and supervised.

Dr Chandiwana has connections to many international malaria organisations including AMANET, the John Hopkins Malaria Institute Advisory Committee, the Biomedical Research and Training Institute (BRTI).

5.5 SUMMARY:

The above summaries clearly indicate that the majority research groups in South Africa are involved in basic scientific research. Most work is directed at furthering the understanding of malaria cell biology, the cell biology of antimalarials, and the application of this research in the identification and validation of potential drug targets. Some research projects involving medicinal chemistry, rational drug design and synthetic organic chemistry have however been identified. Limited research into the development of insecticides has been identified, with the only mention of insecticides being in the context of improving existing products by reformulation and in isolating active ingredients from natural repellents.

Two groups, the MRC and NICD, are involved in epidemiological research. Research areas covered include the molecular identification and characterisation of mosquito vectors, molecular mechanisms of mosquito resistance to insecticides, biochemical basis of insecticide resistance and molecular mechanisms of drug resistance. One of the proposed MIA programmes is the application of molecular techniques to population studies and tracking of resistance through the application of molecular marker techniques to population studies and epidemiology. The focus will be on the movement of vectors and parasites, linked to trends in insecticide and drug resistance. This is already a core part of the research conducted by these two groups and hence the requisite skills already exist.

Two groups with interests in diagnostics have been identified, University of KwaZulu Natal (UKZN) and National Bioproducts Institute (NBI). NBI has developed a pair of monoclonal antibodies specific for HRP2 that are suitable for use in a rapid diagnostic test. These antibodies are specific for *Plasmodium falciparum* and recognise different epitopes on this molecule. UKZN has developed an array of antibodies against anti-malarial drugs, which can be used to track malaria drugs in a range of cells, tissues and body fluids. Through an international collaboration in a MVI project, the team is developing reagents for a second generation of an ELISA diagnostic kit, the first generation being used as an experimental tool in malaria vaccine trials. Coupled with the complementary skills available in other MIA research groups, the development and implementation of molecular assays for diagnostic interventions should be feasible.

The process of drug discovery and drug development involves a number of discrete stages (Appendix 3), as does the process into insecticide discovery. However, due to the fact that there is currently very little research in South Africa on the development of insecticides, the analysis below will focus on the drug development process. The “genes to drugs” model needs more than the first step of basic exploratory biology on target identification. Validated targets must be developed. After lead identification, lead optimization and drug candidate selection is required. The downstream development process that needs to be managed once a candidate enters preclinical development includes process chemistry to determine the cost of manufacture, scalability, stability etc., as well as preclinical animal safety studies under Good laboratory Practice (GLP) conditions, to assess the targets generated, provide good description of pharmacological properties to assess drug-like potential.

An overview of the drug discovery and development process together with a flow sheet of the insecticide development process is attached as Appendix 4 and the activities of the current research programmes are mapped against this chart. This chart indicates that whilst MIA has access to the full spectrum of scientific components required to discover and develop drugs and move from early discovery research through to preclinical and clinical development, some of these components are better developed than others. Most research projects are in the early stages of the process.

The following competencies relevant to the projects proposed by MIA are available in varying degrees are:

1. Parasite biology and biochemistry
2. Functional genomics
3. Structural and computational biology
4. Bioinformatics
5. Medicinal chemistry
6. Combinatorial chemistry, organic synthesis
7. Analytical chemistry
8. High throughput biomolecular interaction analysis
9. High throughput *in vitro* screens
10. High throughput cellular/phenotype screens
11. National product chemistry linked to South Africa's biodiversity
12. Animal models of malaria
13. ADMETox testing of drug leads
14. Development of formulations and delivery mechanisms
15. Process development for large- scale development
16. Management of Clinical trials

To move past the development of a technology platform and to convert the validated targets into full drug discovery programmes, a combination of genomics and biology-based expertise, practical experience of medicinal chemistry, pharmacology and clinical trials to generate compounds of therapeutic interest is critical. The use of upstream technologies such as genomics to identify targets, high-throughput screening, molecular modeling and screening and other techniques identified as being available in South Africa need to be optimally integrated with technologies such as medicinal chemistry, pharmacology and rational drug design in order to develop an early R&D pipeline. In addition, capacity in the downstream interface such as in the preclinical development phase needs to be enhanced and partnerships in the clinical development, dossier preparation and registration will have to be formed in order to strengthen this aspect of the development chain.

The integration and management of this entire process is critical for success in moving from discovery lead identification into drug candidates and finally through to a registered drug. Some elements of this integration have begun to be developed for example in the various collaborations between the University of Cape Town's Departments of Chemistry, Pharmacology and Institute of Infectious Disease and Molecular Medicine as well as the University of Stellenbosch and through the development of the national research and development platform for novel drug development from indigenous plants.

The efficacy and specificity of anti-malarial drugs rely on their ability to interfere with aspects of the metabolism of *Plasmodium* that differs significantly from the host. Parasite survival in the host erythrocytes requires several metabolic adaptations that render it susceptible to chemotherapy. The mechanism of action of existing drugs takes advantage of these innovations. In addition, potential drug targets have already been identified based on an understanding of the cell biology of the malaria parasite. Whilst it is not possible within the scope of this report to outline all of the potential scientific opportunities, some are presented below for indicative purposes only. The attached Appendix 5 shows the site of drug action and new drug targets currently being researched internationally.³⁰

Haemoglobin degradation and interaction with haem remain a focus area for drug discovery. Chloroquine which acts by interference with the malaria pigment haemozoin, allows the intraparasitic build-up of toxic free haem. This has defined the inhibition of haemozoin formation as an attractive drug target. The dihydrofolate reductase (DHFR) inhibitors, pyrimethamine and proguanil, are important antimalarials partly due to their relative selectivity for the parasite enzyme. The genetic resistance mechanism to the antifolate drugs is well understood, with pyrimethamine resistance being due to the accumulation of mutations in DHFR. The identification of improved inhibitors of DHFR that overcome resistance to pyrimethamine is therefore a research opportunity being studied by medicinal chemists.

The identification of semisynthetic and fully synthetic endoperoxides that will retain the activity of the artemisinin derivatives but overcome some of their deficiencies has already been mentioned as an area of activity. Unexploited targets in the food vacuole include the proteases associated with haemoglobin degradation. Cell signaling pathways, through protein kinases such as cysteine protease thus represents another opportunity. Fosmidomycin, an inhibitor of 1-deoxy-D-xylulose-5-phosphate synthase, originally identified in an industrial antibacterial drug discovery programme, is a potential antimalarial compound acting in the non-mevolonate pathway.

Much of the research described as being conducted in South Africa falls within the context of many of these promising areas already identified.

6 CONCLUSION:

It has been widely stated that the completed genomes of *P. falciparum* and the vector *An. gambiae* open up new approaches to the development of drugs, vaccines, insecticides and insect repellents, as well as intervention into malaria transmission. Advances in genetics and biochemical engineering offer new and improved means of characterizing potential targets.³¹ Bioinformatics tools can help predict the structure and function of gene products. The speed with which many compounds can be tested against protein targets has hence increased dramatically. Genetic tools will also allow the sampling of parasite, mosquito, and human genomes in malaria affected areas to support the malaria control activities.

MIA has stated its key objective in the integration of researchers focusing on molecular aspects of malaria drug and insecticide discovery, molecular epidemiology and diagnostics, and capacity building in order to improve malaria prevention and control. Three programmes are envisaged:

- The development of new and modified drugs and insecticides
- The development and implementation of assays for epidemiological and diagnostic interventions
- Capacity building programmes as a cross-cutting programme.

As summarized above, South Africa has access to the full spectrum of scientific components required to discover and develop drugs and move from early discovery research through to preclinical and clinical development, although some of these components are better developed than others. Nevertheless, South African has a core of excellent researchers and facilities in the malaria research field, a strong base in biomedical research, high-quality medical schools and a good infrastructure. Coupled with the increasing financing of malaria research and involvement of the pharmaceutical industry through the various public private partnerships as outlined above, the prospect of the development of new, affordable drugs, diagnostics and insecticides appears to be a feasible opportunity.

The involvement of several academic and industrial partners in a virtual drug discovery model such as that proposed by MIA is relatively new, and involves a unique set of challenges. The early stages of the process in particular will require a continuous, interactive exchange of ideas between scientists from a broad range of disciplines. The model is however being followed successfully in the development of drugs to treat poverty related diseases such as malaria by PPPs such as the MMV. Most of these organizations furthermore recognize that the impact and long-term sustainability of drug R&D for poverty related diseases depends on the use of research capacity in developing countries. However, whilst some of these countries have expertise in some of the scientific components required, few have the capacity to perform all of the tasks necessary.

A recent article in Nature Biotechnology stated that South Africa is poised to take the lead in developing health care biotechnology in the sub-Saharan African region. It recommended a good starting point as being the identification of a problem disease prevalent in the community and a technology that could be used to address this problem, and then to develop an infrastructure to support R&D in this area. Thus through its identified focus on malaria and the use of molecular technologies, MIA has identified a unique opportunity to position itself in sub-Saharan Africa and internationally through the integration and capacity building programmes as proposed in the initiative. Through applying the lessons learned by the PPPs³² internationally in the establishment of a virtual development process, ensuring the optimization and focusing of its manpower, infrastructure and financial resources, coupled with careful management of the integration process, MIA should be well positioned to achieve success in its goals.

7 INTERVIEWEES

Grateful thanks are extended to the following scientists, experts, and representatives of funding organisations and other interested parties who gave so freely of their time to support this work via interviews, discussions and a variety of other communications.

7.1 RESEARCHERS:

University of Cape Town

Professor Kelly Chibale
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Dr Marthinus Horak
Professor Jane Morris
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Professor Dean Goldring

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Dr Martin Bubb

National Health Laboratory Services/National Institute of Communicable Diseases

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Dr AP Lotter

University of Pretoria

Professor Ron Anderson
Professor Braam Louw
Professor Anton Stoltz

Rhodes University

Professor Greg Blatch

University of Stellenbosch

Dr Marina Rautenbach

University of Witwatersrand:

Professor Theresa Coetzer (NHLS)

Professor Steven Chandiwana

Professor Ivan Havlik

7.2 FUNDING ORGANISATIONS

Biotechnology Regional Innovation Centre:

BioPAD: Dr Agatha Masemola

CBT: Dr Joe Molete

LIFElab: Professor Indres Moodley

Godisa Incubator: Chemin

Mr Joe Kruger

IDC/SPII

Mr Areef Suleman

Innovation Fund:

Mr Vuyisele Phehane

Medical Research Council:

Professor Lynda Chalkley

Mr Clive Glass

National Research Foundation:

Mr Rob Drennan

THRIP:

Dr Mmbonbeni Muofhe

8 REFERENCES

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- 6 Medicines for Malaria Venture Annual Report September 2004
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- 9 <http://www.mim.su.se/english/>
- 10 <http://www.mmv.org>
- 11 <http://www.oneworldhealth.org/>
- 12 <http://www.dndi.org>
- 13 <http://www.theglobalfund.org/>
- 14 <http://www.gatesfoundation.org/GlobalHealth/>
- 15 <http://nih.gov>
- 16 <http://niaid.nih.gov/>
- 17 http://www.usaid.gov/our_work/global_health/id/malaria/techarea/tools.html
- 18 <http://web.worldbank.org>
- 19 <http://www.wellcome.ac.uk>
- 20 http://europa.eu.int/pol/rd/overview_en.htm
- 21 <http://www.dfid.gov.uk/news/files/devawareness/malaria-faq.asp>
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- 23 <http://www.mrc.ac.za>
- 24 <http://www.spii.co.za>
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- 30 Ridley, R: Nature, 415, 2002, 686 - 693
- 31 Reducing the Malaria's Burden: Global Health Council Technical Report 2003
- 32 Motari M. et al: Nature Biotechnology, 22 Supplement December 2004

**Appendix 1
NRF Projects 2005**

Initial	Surname	Organisation	Grant	Short title	Long title
L	VISSER	UP	R 211,610	VISSER L CGRS	IDENTIFIKASIE, KARAKTERISERING EN IMMUNOLOGIESE AANWENDING VAN ANTIGENE VAN ENDO-(MALARIA) EN EKTOPARASITIESE (BOSLUISE) SOWEL AS BAKTERIESE OORSPRONG
L	VISSER	UP	R 298,000	VISSER L CGRS	DIE IDENTIFIKASIE, KARAKTERISERING VAN GENE OF PROTEINE EN ANTIGENE VAN PARASITIESE (MALARIA, BOSLUISE) SOWEL AS BAKTERIESE OORSPRONG.
L	VISSER	UP	R 20,000	VISSER L CGRS	DIE IDENTIFIKASIE, KARAKTERISERING EN IMMUNOLOGIESE AANWENDING VAN PROTEIENE EN ANTIGENE VAN ENDO- EN EKTOPARASITIESE (MALARIA, BOSLUISE) SOWEL AS BAKTERIESE OORSPRONG
TJ	EGAN	UCT	R 31,200	CHEMISTRY OF ANTIMALARIALS	CHEMICAL STRATEGIES FOR THE DEVELOPMENT OF ANTIMALARIALS: (A) THE MECHANISM OF ACTION OF QUINOLINE ANTIMALARIAL DRUGS AND (B) TRANSFERRIN ANN IRON UPTAKE BY THE MALARIA PARASITE
L	VISSER	UP	R 95,825	OLIGOMERS AGAINST MALARIA & TB	THE DESIGN AND EVALUATION OF MODEL SYNTHETIC PEPTIDES AND OLIGONUCLEOTIDES AS ANTIMALARIAL AND ANTI-TUBERCULOSIS AGENTS
HM L	MARQUES VISSER	UW UP	R 556,000	BIOINORGANIC CHEMISTRY & APPLICATION R 0 OLIGOMERS AGAINST MALARIA AND TB	CHEMISTRY OF PORPHYRINS, CORRINS AND TRANSFERRINS, AND APPLICATIONS IN THE MODELLING OF BIOLOGICAL MOLECULES AND THE DESIGN OF ANTIMALARIALS
AI	LOUW	UP	R 363,000	MALARIA PARASITE PROTEINS	MOLECULAR AND FUNCTIONAL CHARACTERISATION OF PROTEINS REQUIRED BY THE MALARIA PARASITE, PLASMODIUM FALCIPARUM, FOR ITS METABOLISM AND DEVELOPMENT IN THE HUMAN ERYTHROCYTE.
I PI	HAVLIK FOLB	UW UCT	R 126,154 R 105,000	FRANCO / RSA AGREEMENT UK / RSA AGREEMENT	PLASMODIUM FALCIPARUM PROTEIN KINASES: POTENTIAL TARGETS FOR NEW CEMOTHERAPEUTIC AGENTS AGAINST MALARIA
S	DAYA	RU	R 3,500	PROF R KALARIA	ANTIMALARIAL ACTIVITY OF TWO SOUTH AFRICAN TRADITIONAL PLANTREMEDIES TO GIVE A PLENARY LECTURE AT THE SYMPOSIUM OF THE SOUTHERN AFRICAN NEUROSCIENCE SOCIETY HOSTED BY PROF S DAYA.
JPD BL	GOLDRING SHARP	UNPM MRC	R 122,000 R 145,000	DYE-ANTIBODY, ANTI-MALARIAL DRUGS UK/RSA AGREEMENT	DYE-ANTIBODY BASED ANTIGEN DETECTION TO DEVELOP COLOUR BASED DIAGNOSTIC REAGENTS. NEW DRUGS FOR MALARIA - SCREENING EXTRACTS OF PLANTS USED BY TRADITIONAL HEALERS AND TESTING QU
KJ	NEL	UP	R 7,600	EXPRESSION OF CHIMERIC CONSTRUCTS	INSECTICIDE RESISTANCE MONITORING AND MANAGEMENT IN MALARIA VECTORS
TL AI	COETZER LOUW	SAIM UP	R 68,000 R 120,000	MALARIA AND RED CELL MEMBRANES UK/RSA AGREEMENT	EXPRESSION OF CHIMERIC CONSTRUCTS OF GLUCOSE TRANSPORTERS OF THE RAT AND MALARIA PARASITE IN ORDER TO LOCATE FUNCTIONAL AREAS OF MALAOTEIN
JPD K	GOLDRING CHIBALE	UNPM UCT	R 116,000 R 394,751	Development of dye based diagnostics NEW ANTIMALARIAL AGENTS	MOLECULAR STUDIES ON THE ROLE OF RED CELL MEMBRANE PROTEINS IN MALARIA INFECTION AND PATHOGENESIS
AP	LOTTER	PUCH	R 662,000	Cost effective Pharmaceuticals	A POTENTIAL NEW ANTIFOLATE DRUG TARGET IN HUMAN MALARIA PARASITES
AI	LOUW	UP	R 111,922	Malaria parasite protein properties	Attaching dyes to chicken antibodies for the detection step in the diagnosis of human(malaria), animal and plant diseases. Raising anti-malarial drug antibodies to detect drugs in patient plasma.
FR TL	VAN HEERDEN COETZER	RAU UW	R 66,000 R 87,000	African medicinal plant chemistry Malaria and red blood cell membranes	Malaria Parasite Proteases as Targets for the Rational Design of New Antimalarial Agents
I BL AI	HAVLIK SHARP LOUW	UW MRC UP	R 0 R 98,921 R 0	FRANCO / RSA AGREEMENT UK/RSA AGREEMENT UK/RSA AGREEMENT	Physico chemical properties of drugs and drug delivery technologies for designing more effective and cheaper medicines for South Africa with special emphasis on drugs for the treatment of epidemiological diseases such as TB and malaria.
M	COETZEE	SAIM	R 59,000	Anopheles funestus in South Africa	Functional characterisation of malaria parasite proteins for identification of therapeutic targets to arrest its metabolism and development in the human erythrocyte.

**Appendix 1
NRF Projects 2005**

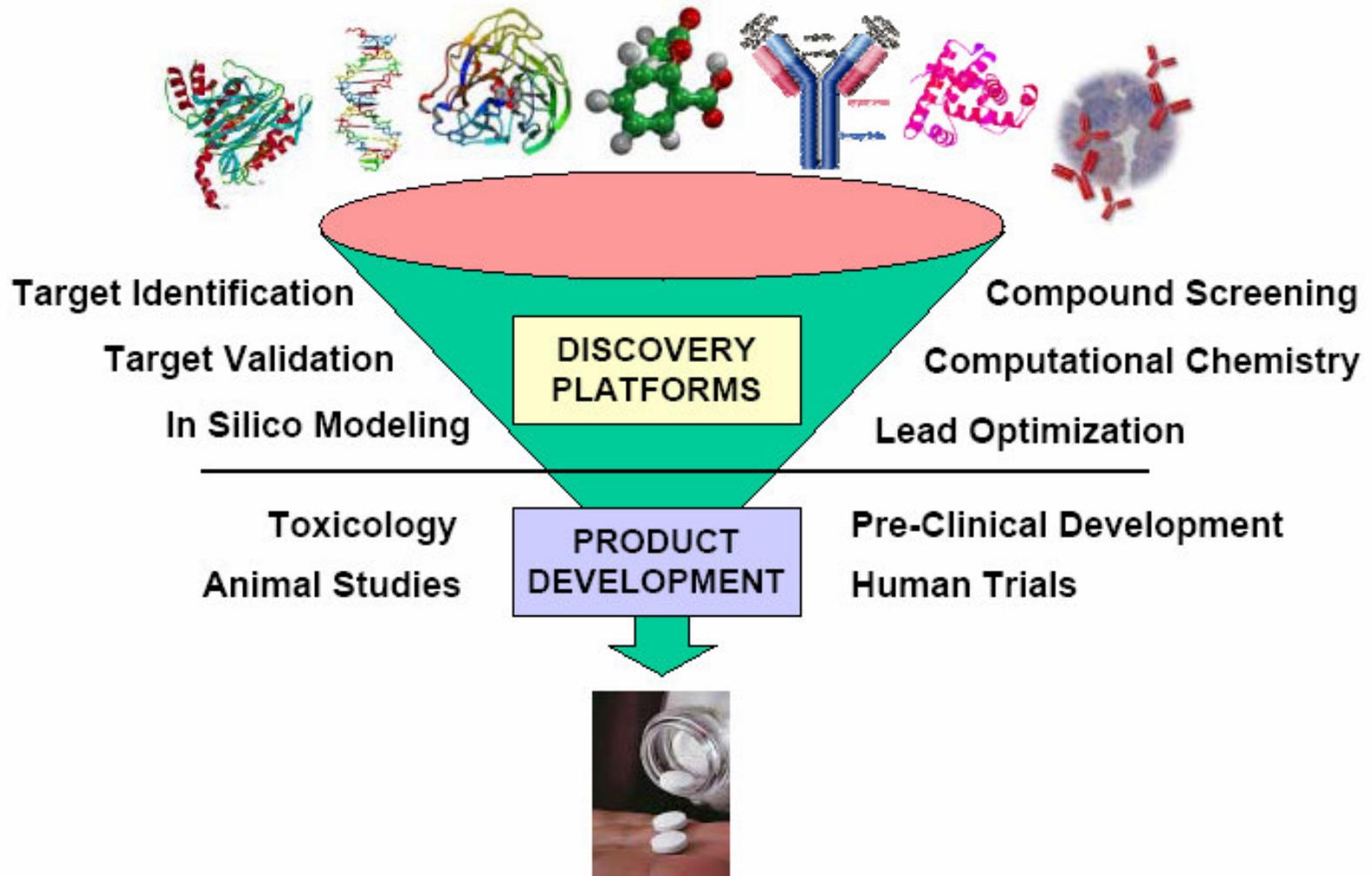
Initial	Surname	Organisation	Grant	Short title	Long title
JPD TL	GOLDRING COETZER	UNPM SAIM	R 24,000 R 130,000	Immunomodulation in malaria Malaria and red blood cell membranes	Immunomodulation in malaria: elemental composition of monocytes during antimalarial drug treatment and malaria infections Molecular studies on the role of red cell membrane proteins in malaria infection and pathogenesis
JAO	OJEWOLE	UDW	R 170,000	SWEDEN/SA AGREEMENT	PHARMACO-CHEMICAL EVALUATION OF PLANTS USED AS ANTIMALARIAL REMEDIES IN ZULU FOLK MEDICINE
TL K	COETZER CHIBALE	SAIM UCT	R 204,000 R 426,000	Malaria and red blood cell membranes NEW ANTIMALARIAL AGENTS	Molecular studies on the role of red cell membrane and Plasmodium falciparum proteins in infection, pathogenesis and transmission of malaria Malarial Parasite Cysteine Proteases as Targets for the Rational Design of New Antimalarial Agents
AI	LOUW	UP	R 509,500	Malaria parasite protein properties	Functional characterisation of malaria parasite proteins for identification of therapeutic targets to arrest its metabolism and development in the human erythrocyte.
DB HM	MCINTOSH MARQUES	UCT UW	R 542,000 R 427,250	Ion pumps and ABC transporters Bioinorganic Chemistry & Application	Mechanism and drug targeting of ion pumps, ABC transporters, and a purine salvage enzyme from normal cells, cancer cells, pathogenic bacteria, and the malaria parasite. Bioinorganic Chemistry of Biologically Important Complexes and Application to the Study of Malaria
WJ	LUUS-POWELL	UNO	R 7,500	CONFERENCE	MRS W.J.LUUS-POWELL TO PARTICIPATE IN : THE JOINT MALARIA & BSP SPRING MEETING : MANCHESTER : 6 - 9 APRIL 2003
K	CHIBALE	UCT	R 120,000	INDO/RSA AGREEMENT	BIOCATALYTIC AND COMBINATORIAL APPROACHES TO NOVEL NATURAL PRODUCT BASED ANTITUBERCULOSIS AND ANTIMALARIAL AGENTS
G	MAARTENS	UCT	R 139,000	SWED/RSA RESEARCH PARTNERSHIP	NON LINEAR MODELLING OF THE POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIRETROVIRAL, ANTITUBERCULOUS AND ANTIMALARIAL DRUGS
LL K	KOEKEMOER CHIBALE	SAIM UCT	R 35,000 R 235,000	Metabolic resistance in a major mala New Antimalarial Agents	The involvement of two classes of monooxygenases in a metabolic pyrethroid resistant population of a major malaria vector An. funestus (Diptera: Culicidae) New antimalarial agents targeting cysteine protease enzymes in Plasmodium falciparum
LJ	MAMPURU	UNO	R 265,000	Novel Isoprenoids in Human Disease T	Novel Isoprenoids in Human Disease Therapy: Characterisation and evaluation of the anti-neoplastic, antiviral and antimalarial properties of isoprenoids and related phytochemicals isolated from indigenous medicinal plants from Limpopo and Mpumalanga
AI	LOUW	UP	R 80,250	Effects of drugs on malaria parasite	Genome-wide expression profiling of the human malaria parasite, Plasmodium falciparum, under pharmacological challenge
Y	JOUBERT	UP	R 33,000	Structural annotation of P.falciparu	Structural annotations of all putative protein products identified in the malaria genome, and preparing a database containing these annotations.
MP	SEKHOACHA	UCT	R 55,000	Isolation of antimalarial compounds	Identification and purification of antimalarial compounds from medicinal plants. Characterisation of the active compounds in vitro and in vivo. Characterisation of its pharmacokinetic parameters using mice models.
K	DE VILLIERS	UCT	R 40,000	Not yet available	The exact details of the project are presently under consideration. However, i would like the outcomes of the project to be usefull beyond the research laboratories. In the bioinorganic field, this may take the form of developing novel antimalarials.
Y	JOUBERT	UP	R 5,000	Structural annotation of P.falciparum	Structural annotations of all putative protein products identified in the malaria genome, and preparing a database containing these annotations.
			R 7,315,983		

APPENDIX 2
MEDICAL RESEARCH COUNCIL
SELF-INITIATED PROJECTS

Lead Investigator	Institution	Title of Research
Blatch Prof G.	Rhodes University	The search for a new anti-malaria drug by targeting DOXPreductoisomerase
Bornman Prof M.	Univ. of Pretoria	DDT exposure in mothers and newborns in a high-risk malaria area in Limpopo, South Africa
Brooke Dr B.	National Health Laboratory Services	Stability of insecticide resistance in the Southern African malaria vector <i>Anopheles funestus</i>
Coetzer Prof T.	National Health Laboratory Services	Interaction of the malaria parasite with human erythrocyte membrane proteins
Coetzer Prof T.	National Health Laboratory Services	Malaria and red cell membrane proteins
Egan Prof T.	Univ. of Cape Town	Haemozoin formation as a drug target
Goldring Dr J.	Univ. of Kwazulu-Natal	Identification and characterisation of the <i>Plasmodium falciparum</i> malarial protein kinases that have a critical role in malarial cellular regulation and progression of the malaria cell cycle
Koekemoer Dr L.	National Health Laboratory Services	Investigating resistance mechanisms in insecticide resistant <i>An. arabiensis</i> , one of the major malaria vectors in South Africa
Louw. Prof A.	University of Pretoria	Microsatellite typing of <i>Plasmodium falciparum</i> merozoite surface protein 2 (MSP2) in field isolates.

Appendix 3

Drug Discovery and Development Process

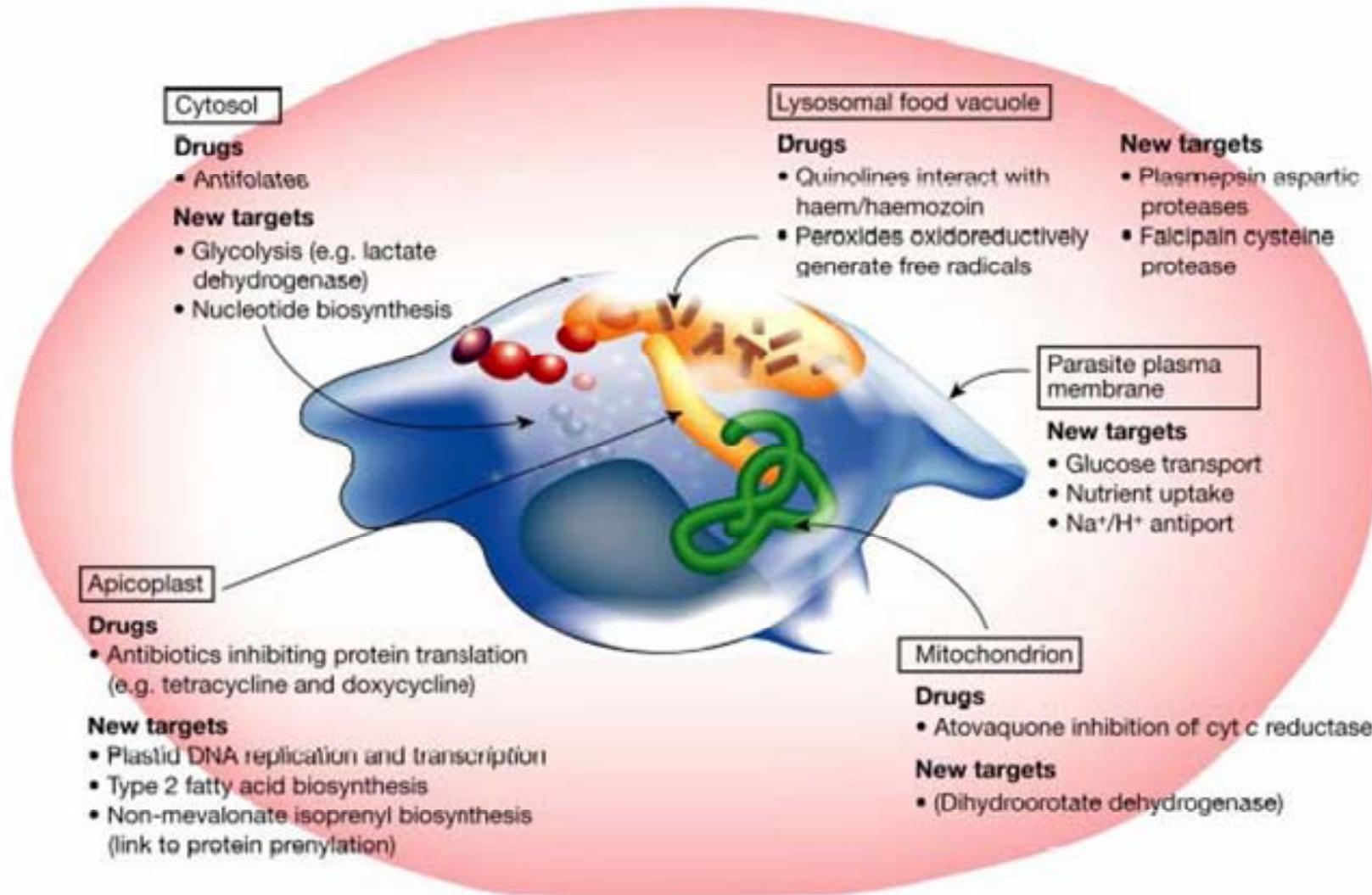


Appendix 4 Drug and Insecticide Discovery Model

	BASIC SCIENCE	DISCOVERY		DEVELOPMENT		REGULATORY
PROCESS FOR DRUG DISCOVERY	Exploratory, Early Discovery	Lead Identification	Lead Optimisation	Preclinical Transition	Phase I, II, III Clinical Trials	Registration
DESCRIPTION OF ACTIVITIES	Target identification and Validation (Basic biology, biochemistry, functional genomics) Develop Screening Assays	High-throughput screening Identify hits Medicinal chemistry to improve hits Confirm robustness of lead	Medicinal chemistry Improve potency <i>in vivo</i> mouse model testing Exploratory toxicology Exploratory pharmacokinetics	Complete toxicology (Safety studies in animal) Process Chemistry Scale-up, formulation, batch manufacture IND	I: First human studies I: Safety, tolerability, pharmacokinetics II: Clinical Proof of Principle II: Dose range finding, early side effect profile III: Large safety and efficacy studies	Submission of dossier to regulatory authority Manufacturing Post-launch trials First Sales
SOUTH AFRICAN PARTICIPANTS	MRC UCT: Pharmacology UCT: Chemistry UP: Biochemistry SU: Biochemistry RU: Dept of Biochem, Microbiology and Biotechnology CSIR Wits: Molecular Biology Wits: Chemistry Wits: Pharmacology	UCT: Pharmacology UCT: Chemistry UP: Biochemistry UP: Department of Immunology SU: Biochemistry RU: Dept of Biochem, Microbiology and Biotechnology CSIR Wits: Molecular Biology Wits: Chemistry Wits: Pharmacology	UCT: Pharmacology UCT: Chemistry	UCT: Pharmacology CSIR	MRC/ UCT: Pharmacology SEACAT UP: Internal Medicine Wits: Pharmacology	UCT: Pharmacology
	BASIC SCIENCE	DISCOVERY		DEVELOPMENT		REGULATORY
PROCESS FOR DEVELOPMENT OF INSECTICIDE	Basic Biology Screening Research	Laboratory, Greenhouse Trials Synthesis	Pilot Trials Toxicology: Mammals Environment: Metabolism Synthesis optimisation	Field trials for development and registration Toxicology Testing:mammals and environment Environment: metabolism, residues Process Chemistry Scale-up, formulation, batch manufacture	Pilot Plant Production	Official evaluation of registration Registration Manufacturing First Sales

Appendix 5

Enhanced Scientific Opportunities



Ridley R. Nature 2002