REQUEST FOR APPLICATIONS (RFA): SAMRC-RFA-GSK/NVS 01-2021

PROJECT AFRICA GRADIENT

Genomic Research Approach for Diversity and Optimising Therapeutics

TABLE OF CONTENTS

1. Introduction

Genetic diversity is greater in African populations relative to populations in other continents which has the potential to affect the way African patients respond to treatment[1]. Genetic diversity may affect pharmacokinetics (PK) (e.g. genetic polymorphisms in drug metabolising enzymes or drug transporters), pharmacodynamics (PD) and safety of medicines, leading to differences in patients' responses to treatment.

As an example, the published literature from different populations in Africa is most extensive on the potential effects of genetic polymorphisms in drug metabolizing enzymes of the CYP450 family. It is important to note that whilst the difference in frequency distribution of well-described CYP variants is generally low within European or Asian populations, the difference between some African populations is up to seven fold higher[2]. These findings suggest that Africa cannot be treated as a single entity in drug development and therapeutics. This is especially relevant in African populations with large variations in frequency distribution of CYP variants: metabolic activity may vary significantly from the originally tested populations, potentially leading to clinically relevant differences in drug exposure. These differences need to be considered when defining the dose rationale in the target patient population to ensure comparable efficacy and safety across populations.

Project Africa GRADIENT (Genomic Research Approach for Diversity and Optimising Therapeutics) was initiated in 2018 as a collaboration between GSK and Novartis[3]. The primary aim was to establish a consortium to collaborate with expert academic centers and organisations in Africa to support high quality research on African genetic diversity of relevance to drug therapeutics. The primary focus will be to evaluate genetic diversity as the contributing factor to variability in exposure, efficacy and/or safety to drugs used to treat tuberculosis (TB) and malaria in Africa[3]. All datasets collated or generated through the program are intended to be released in public databases with the ultimate goal of catalyzing a positive change in approaches to understanding treatment efficacy and toxicity for regionally appropriate standards of care for patients across the continent.

GSK and Novartis have partnered with the South African Medical Research Council (SAMRC) through its Grants, Innovation and Product Development (GIPD) unit, to facilitate the administration of Project Africa GRADIENT.

Project Africa GRADIENT aims to provide funding for up to 5 years, in two independent stages with the possibility of extensions.

2. Research question

An individual's genetic makeup is one of the important factors affecting the response to drugs. Treatment tailored to an individual's genetic makeup may be the ultimate goal with genotyping as a key component to achieve "precision-therapy". However, prospective genotyping can be challenging in many settings and may be unrealistic in resource constrained regions. In such settings, ethnicity may be regarded as a proxy of a patient's probable genotype risk, based on overall population frequency distribution data for the relevant genetic polymorphisms. Currently, such population information is missing or inconsistent for large populations in Africa. The understanding of genetic variations associated with specific populations, that can influence the safety and efficacy profile of therapeutic interventions, can therefore rationalize drug dosing and improve therapeutics. The primary focus of Project Africa GRADIENT will be on collecting, identifying and evaluating genetic diversity as the contributing factor to variability in exposure, efficacy and/or safety to drugs commonly used to treat TB and malaria in Africa.

3. Funding opportunity description

This research call is for Stage 1 of Project Africa GRADIENT. Stage 1 has two types of funding opportunities viz. Initiative A and B as outlined below.

The launch of Stage 2 will be dependent on the data generated during Stage 1.

3.1 Initiative A: Fellowships for individual researchers

Initiative A's focus will be on mining of the available data in public databases, biorepositories, published articles, case reports and other relevant literature and resources. The primary interest will be in identifying and evaluating genetic diversity as the contributing factor to variability in exposure and/or safety and efficacy to drugs commonly used to treat TB and malaria in Africa. The data will then be complemented by further integration with in silico technologies, including modelling and simulation. The expertise or at least previous experience in modelling and simulation, physiologically-based pharmacokinetic (PBPK) modelling and handling of clinical data, including 'big data' will be advantageous. Depending on their proposal, applicants may be given access for the use of advanced methodologies available at large pharmaceutical companies (i.e. in GSK or Novartis) that may not currently be available to local researchers. The priority will be given to proposals which aim to deliver the data to support the building of 'genetic maps' of Africa relevant to differences in TB and/or malaria drug responses. This may mostly include PK and safety data as the reliable and clinically relevant data on genetic diversity in genes encoding PD activity in African populations are comparatively less mature. Such data may be integrated into PBPK models enabling comparison and extrapolation of data across populations. Other sources of diversity such as: diet, climate, medical practice, concomitant medications and other relevant factors will be addressed at a later date. However, if the data on other sources of diversity in drug response are available, a proposal can be drafted to collect the data in parallel to allow for subsequent analyses.

Individual fellowships will be funded for up to 2 years.

We are seeking proposals that will address one or more of the following:

- Collate available data regarding drug response to TB and/or malaria treatments in African populations using existing databases, biorepositories or any other data in the public domain.
- Build a comprehensive resource for all variants that have been reported to have a clinically relevant pharmacogenomic effect in humans in response to TB and/or malaria treatment.
- Analyse and consider how current understanding of specific ADME (absorption, distribution, metabolism, and excretion) gene variants and other important genetic determinants in African populations can influence drug response to TB and/or malaria treatment.
- Help to support development of actionable prescribing decisions for TB and/or malaria drugs.
- Help to build genetic maps of Africa relevant for a specific response to drugs.
- Help to build PBPK or nonlinear mixed effects models relevant for a specific response to drugs, based on specific variants frequency dstirbution across different regions in Africa.

3.2 Initiative B: Investigator-sponsored research

Initiative B's focus will be on hypothesis driven research projects generating new data to understand regional variation in African genetic diversity and potential consequences on drug responses to TB and/or malaria treatment. Priority will be given to projects generating data from different African regions to facilitate the creation of 'maps of allele frequency' for ADME or other genetic variants that can influence exposure and potentially the response to drugs used for treatment of TB and/or malaria, and projects aimed at collecting or generating data from currently under-represented regions and improving the scientific robustness of inconsistent data.

It is anticipated that novel Africa specific genetic variants may be identified through this research. If so, further research to identify their functional properties would be of interest.

Proposals should reflect the highest possible scientific standards and include clear descriptions of their potential for therapeutic impact.

Investigator-sponsored research will be funded for up to 2 years.

We are seeking proposals that will addresss one or more of the following:

- Generate data regarding drug responses to TB and/or malaria treatment in African populations.
- Provide the basis for the data integration, analysis and modelling of the effect of specific ADME gene variants and other important genetic determinants in African populations that can influence drug responses to TB and/or malaria treatment.
- Extend foundational studies in pharmacogenomics to incorporate whole and partial genome sequence activities and other deep resequencing efforts to understand treatment failure of specific drugs for TB and/or malaria treatment.

- Seek to contribute to the building of an African genetic database.
- Help to build genetic maps of Africa relevant for a specific response to drugs (that is proposed by the candidate).
- Help to build PBPK or nonlinear mixed effects models relevant for a specific response to drugs, based on specific variant frequency distribution across different regions in Africa.

4. Eligibility criteria

This is an open call for proposals from researchers based at African (Northern, Western, Eastern, Central, and Southern Africa) universities or institutions, science councils (including the SAMRC) and other public research organizations, including:

- African registered not-for-profit research organizations whose primary purpose is to conduct research and/or product development – such entities should preferably have at least one local university or science council collaborator and may be subject to due diligence prior to the award of funds.
- African private/for-profit small-medium enterprises are eligible to apply as co-applicants/co-principal investigators if their expertise are required to execute the project.
- Research institutions should complete the SAMRC sub-award due diligence form and submit it with the letter of intent application.

The following entities are not eligible to apply for funding through this RFA but may be included as sub-contractors if they provide a necessary service or capability that is required by the project partners or organizations:

- Non-African private/for-profit companies and institutions;
- Non-African not-for-profit companies, research institutions, universities, civil society groups and non-governmental organizations.

In addition to the above, applicants/principal investigators must be African citizens or permanent residence holders. Applicants must have a PhD or equivalent qualification as a minimum requirement. While there is no limit to the number of applications submitted per institution, principal investigators may only submit one application each as the principal investigator but may be listed as co-investigator in other applications.

5. Application process

- **Applicant to complete an online form indicating their intention to submit using the following link: https://forms.gle/XgyYma468P26m7jd6**
- **Online form to be submitted by 01 March 2021. This will aid the review process.**
- **Letter of intent application to be submitted via email to gradient@mrc.ac.za by 29 March 2021 at 23h59 SAST.**
- **Clearly specify Initiative A or Initiative B in the subject line.**
- **No late applications will be considered.**
- **All applications must be submitted in English using the SAMRC letter of intent (LOI) application form. All correspondence preceding any award as well as all subsequent correspondence and verbal communication will be in English.**
- **All budgets to be submitted in South African Rands (ZAR). Including all applicable taxes.**
- **Funding to all institutions will be disbursed in ZAR.**

It is critical that applicants follow the instructions in this RFA.
Applications will not be considered for review if they:

- Are received after the deadline for submission;
- Are not aligned to the specific topics included in this RFA;
- Are from non-eligible institutions or organisations;
- Are incomplete, i.e. all sections of the LOI templates are not completed and all requested supporting documents are not attached;
- Do not comply with the **SAMRC sub-award due diligence**.

Required documentation to be submitted:

- **Online intention to submit deadline: 01 March 2021.**
- **LOI application: 29 March 2021 at 23h59 SAST**
  - **SAMRC sub-award due diligence document**
  - **CVs of PI and Co-PI(s)**

Applicants can only submit one application as a lead PI for only one of two initiatives but may be Co-PIs on other subsequent applications.

5.1 Initiative A: Fellowships

Maximum funding of ZAR 3,348,000 (South African Rands) over 2 years (maximum funding of ZAR 1,674,000 per annum). Including all applicable taxes.

The funding parties aim to fund four (4) fellowships. Initially, two (2) fellowships are planned to be funded in 2022. Based on the scientific merit of the applications and short-term (6-9 months) performance of Project Africa GRADIENT, and at discretion of the funders, two (2) additional fellowships may be funded from the successfully reviewed applications.

The project timeline should aim to commence in Quarter 1 of 2022 calendar year.

Successful applicants will need to pass a due diligence check by the funders. This process may include:
- Data management and data integrity policies implemented;
- ABAC (anti-bribery and corruption) risks;
- Human biological samples management (if applicable);
- Background check and history of performance of the institution;
- Check whether the institution is legitimate, whether any conflicts of interests exist, whether the institution has the experience, qualifications, capacity or resources to meet the requirements of the research collaboration agreement.

Fellows will be co-supervised by one of the funding partners. In addition to funding, GSK and Novartis are offering to provide scientific support throughout the duration of the grant term. The level of interaction will be determined through the application process and will be tailored to the individual needs of the project. GSK and Novartis scientists will collaborate throughout the duration of the grant and this will include discussing aspects of the project and sharing ideas based on their experience in the area of research.

A research collaboration agreement will be concluded with successful applicants and the funders. A funding agreement will be concluded between the host institution and SAMRC upon signing of the research collaboration agreement.

5.2 Initiative B: Investigator-sponsored research

Maximum funding of ZAR 5,022,000 (South African Rands) over 2 years project (maximum funding of ZAR 2,511,000 per annum). Including all applicable taxes.

The funding parties aim to provide initial funding for up to five (5) investigator-sponsored research projects in 2022. The project timeline should aim to commence in Quarter 1 of 2022 calendar year.

Successful applicants will need to pass a due diligence check by the funders. This process may include:
- Data management and data integrity policies implemented;
- ABAC (anti-bribery and corruption) risks;
- Human biological samples management (if applicable);
- Background check and history of performance of the institution;
- Check whether the institution is legitimate, whether any conflicts of interests exist, whether the institution has the experience, qualifications, capacity or resources to meet the requirements of the research collaboration agreement.

The funding parties will provide scientific support, consultation and collaboration where appropriate throughout the duration of the grant term. The level of interaction will be determined through the application process and will be tailored to the individual needs of the project. GSK and Novartis scientists will collaborate throughout the duration of the grant and are enthusiastic about discussing aspects of the project and sharing ideas based on their experience in the area of research.

A research collaboration agreement will be concluded with successful applicants and the funders. A funding agreement will be concluded between the host institution and SAMRC upon signing of the research collaboration agreement.

6. Budget allowable and non-allowable costs

6.1 Allowable cost

Allowable costs for this funding mechanisms are as follows (all direct line items must be auditable):

- Personnel: Soft-funded posts for individuals working on the project (e.g. post-docs, students, technicians, project managers) will be funded, provided an accurate estimation of time allocation is provided and they are not already funded from other means.
- Consultants: These may include both local and/or foreign consultants who provide a service or capability that is not available among the project partners but is essential for the completion of project deliverables.
- Equipment: Partial or full support for the cost of equipment may, be requested, provided that it is directly required for the project. A budget limitation may apply.
- Supplies, consumables and other direct laboratory or research costs.
- Sub-contracts: These may be to any local or international organization that provides a service or capability that is not available among the project partners but is essential for the completion of project deliverables.
- Travel and accommodation that is directly related to the execution of the project.
- Institutional overhead: An indirect costs rate of 5% to a maximum of R250k per year is allowed.

6.2 Non-Allowable

Non-allowable costs include the following:

- Salaries of permanent or fixed term staff, e.g. tenured staff, professors etc., that are fully covered by the host institutions.
- Purchase or construction of a building.
- Rental costs for space that is owned by the institutions participating in the project.
- Recruitment or retrenchment costs for staff.
- Purchase of office furniture.

7. Timeline

The timelines for the application process are shown in Table 1.

Table 1. Application timelines

RFA launch	18 January 2021
Online intention to submit deadline:	01 March 2021
LOI due date:	29 March 2021
Peer review of LOI applications	April- May 2021
Outcomes of LOI communications	June 2021
Invitation for full proposals	June 2021
Full proposal deadline	July 2021
Peer review of full proposals	August – September 2021
Awardees notified of outcome	November 2021

8. RFA and Supporting documents

- **Project Africa GRADIENT: RFA on SAMRC website**
- **Online intention to submit application form**
- **Letter of intent application form**
- **SAMRC sub-award due diligence form**

9. Review and evaluation of proposals

There will be a four-step evaluation and approval process:

1. LOI stage
   a. Applicants to submit a LOI for either Initiative A or B.

2. Internal screening by the funders for alignment
   a. Compliance to all the specified administrative and procedural provisions required in the RFA.
   b. Incomplete or unresponsive to the provisions and priority areas described in the RFA.
   c. Applications received after the submissions deadline.
   d. Responsive LOIs will proceed to review phase.

3. Review of LOIs and ranking of proposals
   a. LOIs will be peer reviewed by global experts.
   b. LOIs will be ranked (refer to peer review criteria below) and only the highest ranking LOIs will be invited to submit a full proposal.
   c. All proposals that do not receive an invitation for full proposal will be deemed unsuccessful at this stage.

4. Invitation to submit full proposals
   a. As appropriate, GSK and Novartis may facilitate interactions with GSK and Novartis scientists and the applicant to assess whether they are able to make in-kind scientific contributions to potentially enhance the project's chances of success.
   b. Once the full applications are submitted, the applications will undergo independent peer review and full proposals will be tabled at a panel meeting.

5. Award selection
   a. The award of grants emanating from this call will be determined by the joint steering committee for the program and the executive management committee of the SAMRC, considering the recommendation of the peer review panel meeting.
   b. Based on the scientific merit of the applications and/or budget limitations, the funders may award fewer grants than expected and may elect not to allocate all of the available funds to awards from this RFA.
   c. Full proposals may be subject to revisions based on reviewers' comments.
   d. Award letters will be sent to successful applicants, and all applicants will be notified of the outcome of their applications.
   e. A process of due-diligence may be conducted by the funders, both on the institution and the applicant.
   f. Successful applicants and institutions will be required to enter into a research collaboration agreement (and be subject to satisfactory due diligence checks) with GSK and/or Novartis.
   g. Successful applicants and institutions are required to enter into a funding agreement between their host institution and the SAMRC (subject to satisfactory SAMRC sub-award due diligence).

9.1 Peer review criteria

Each responsive and complete application received by the due date will be reviewed by local and international reviewers who are experts in the RFA priority areas. Reviewers will consider each of the review criteria below in determining scientific and technical merit and provide an overall score for the proposal. The review will be the same for both the LOI and full proposal stage.

Significance
Will the project help to generate data on genetic variations for specific populations that can influence treatment response?

Investigator(s) and research team
- Is the team a single institution or PI or large, multi-institutional and multi-disciplinary?
- If the project is collaborative in nature, do the investigators have complementary and integrated expertise?
- Are the PIs, collaborators, and other researchers well suited and qualified to undertake the project?
- Does the project team have international scientific standing in the field, including publications and citations?

Impact
Does the proposed project challenge and seek to shift current research or clinical practice paradigms?

Environment
Will the scientific environment in which the research will be conducted contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the proposed project? Will the project benefit from unique features of the scientific environment, patient populations, existing research programs, collaborative arrangements or other resources?

Methodology and approach
- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Are the milestones and deliverables clearly thought through and articulated?
- Are potential problems, alternative strategies, and benchmarks for success presented?
- Has sufficient preliminary or pilot work been done to inform the design and feasibility of the study?
- Is the proposed approach relevant to the socio-political, cultural, legislative and economic contexts of the study settings?
- Are the plans feasible, with realistic timelines?
- Is there credible supporting data on which the study is based (applicants must supply this).
- Are all of the necessary components for product development in place and/or available to the investigators?

10. Important additional information

- The SAMRC and the funders may seek to verify any information provided by applicants through independent research or by third parties approved by the SAMRC.
- The SAMRC and the funders assume no responsibility for costs incurred in responding to this RFA or any further invitations or communications.
- The SAMRC and the funders reserve the right to amend or withdraw the RFA at any time.
- Successful awards may be subject to addressing reviewer comments and/or negotiation of project plans, number of investigatiors and budgets.
- Grants will be paid to the institution where the principal investigator is employed, as set out in a funding agreement to be concluded between the parties.
- No grant funds will be provided for the research until proof of the necessary ethics and regulatory approvals for the project have been provided to the SAMRC. Should the investigators fail to obtain the necessary approvals within a reasonable time period, the SAMRC and the funders reserve the right to withdraw the award.
- The SAMRC and the funders may use text, video or other visual representation submitted by successful applicants on the respective website or on materials for publicity and/or public awareness.

11. Contact Details

Please direct any requests for information, questions and queries on this RFA by email to **gradient@mrc.ac.za**:

Morris Manuel
Study Coordinator
South African Medical Research Council
Grants, Innovation and Product Development

and

Candice Roux
Project Manager
South African Medical Research Council
Grants, Innovation and Product Development

12. References

1. Tishkoff S, et al. 2009. The genetic strucure and history of Africans and African Americans. Science 324, 1035-1044.
2. Rajman I, et al. 2017. African genetic diversity: implications for cytochrome 450 mediated drug metabolism and drug development. EBioMedicine 17, 67-74.
3. Rajman I and Della Pasqua O. 2019. Introducing project Africa GRADIENT. Drug Development Today 24, 2229-2230.