ELSEVIER

editorial

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Introducing Project Africa GRADIENT

In 2017, we highlighted the greater genetic diversity in CYP450s in Africa compared with other continental populations and called for more research into its relevance for drug development and therapeutics. CYP450, a family of enzymes with a significant genetic variability, is involved in the metabolism of many drugs. The different genetic variants can have wide-ranging metabolic activity, with phenotypes varying from poor to ultra-rapid metabolizers, which result in markedly different pharmacokinetics, potentially altering response to drugs that are substrates of a given CYP450 variant [1].

While the difference in frequency distribution (FD) of well-described CYP variants is generally low within European or Asian populations, the difference between some African populations is up to sevenfold. Our results showed that Africa cannot be treated as a single entity in drug development and therapeutics. This is especially relevant in African populations with a large difference in the frequency distribution of CYP variants: a high percentage of that population might have significantly different drug levels compared with originally tested populations. The efavirenz catastrophe in Zimbabwe illustrates the issue, where a significantly higher frequency distribution of CYP2B6*6 is observed in the local population. CYP2B6*6 is a variant with reduced enzymatic activity, potentially resulting in toxic efavirenz concentrations. The high number of serious adverse events, including deaths, led to subsequent discontinuation of efavirenz combinations as first-line HIV treatment in Zimbabwe [2]. Although efavirenz is an effective and generally well-tolerated antiviral drug, efficacy and safety data in populations with a significantly different frequency distribution for CYPs involved in its metabolism were missing at the time, despite some evidence on the increased frequency distribution of CYP2B6*6 in Zimbabwe [3]. A recent publication in indigenous South African populations demonstrated that CYP variants influencing efavirenz pharmacokinetics differ markedly within and between South African populations and other global populations. The authors suggested that the CYP genotype needs to be considered when defining efavirenz dosing recommendations for different populations [4]. Such differences imply that extrapolation of pharmacokinetics from other African or global populations might not always be accurate.

In our paper [1], we proposed establishing a consortium of pharmaceutical companies to collaborate with expert academic centers and regulatory authorities in Africa to support high-quality research on African genetic diversity. Following this appeal, a collaboration between Novartis and GlaxoSmithKline (GSK) was initiated in 2018, evolving into Project Africa GRADIENT (Genomic Research Approach for Diversity and Optimising Therapeutics) with a Legal Framework signed in March 2019.

The aim of Project Africa GRADIENT is to support research into genetic diversity in different African regions and its potential effect on therapeutics. The project will be administered by a local

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organization, which will communicate the application process by late 2019. Our Joint Steering Committee will oversee the review of submitted projects with priority being given to research aimed at collecting data from currently under-represented regions and improving the scientific robustness of inconsistent data.

The research projects will include mining of existing databases and/or biorepositories and new independent projects. The primary focus will be to evaluate genetic diversity as the contributing factor to variability in exposure and/or response to drugs used to treat malaria and tuberculosis in Africa. These data will be complemented by further integration with *in silico* technologies, including modeling and simulation [5]. Project Africa GRADIENT is set up to provide funding for up to 5 years, with a possibility of subsequent extensions.

Several potential outcomes of Project Africa GRADIENT might be of relevance for African patients. Genotyping could be helpful before treatment with drugs where drug exposure or drug effects are expected to be significantly different in some populations. Given that genotyping in clinical practice might not be a realistic expectation in resource-constrained regions, ethnicity could be regarded as a proxy of a patient's probable genotype, based on overall population FD data [6]. Currently, such population information is missing or inconsistent for large populations in Africa.

Project Africa GRADIENT will support the collection of data from different African regions to facilitate the creation of maps of allele frequency for CYPs of relevance for therapeutics in Africa. It is also anticipated that novel Africa specific genetic variants could be identified through this research. This collaboration will provide opportunities for the use of advanced methodologies that are often not locally available to researchers. Finally, the intent is also to provide broad training on drug development that can be shared and applied by other research groups in Africa.

Author contributions

I.R. drafted the manuscript, carried out an initial literature search and prepared the manuscript. O.D.P. performed a critical review and additional literature search and prepared the manuscript.

Declaration of interest

I.R. is an employee of Novartis Institutes for Biomedical Research, Novartis NKK, Japan. O.D.P. is an employee of GlaxoSmithKline (GSK), UK.

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References

1 Rajman, I. *et al.* (2017) African genetic diversity: Implications for cytochrome P450 mediated drug metabolism and drug development. *Ebiomedicine* 17, 67–74
2 Nordling, L. (2017) Putting genomes to work in Africa. *Nature* 544, 20–22
3 Nyakutira, C. *et al.* (2008) High prevalence of the CYP2B6 516G-T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur. J. Clin. Pharm* 64, 357–365
4 O'Conell, K.S. *et al.* (2018) Pharmacogenetics of antiretroviral drug response and pharmacokinetic variations in indigenous South African populations. *OMICS J. Int. Biol.* 22, 589–597
5 Muliaditan, M. *et al.* (2017) The implications of model-informed drug discovery and development for tuberculosis. *Drug Discov. Today* 22, 481–486
6 Shah, R.R. and Gaedigk, A. (2018) Precision medicine: does ethnicity information compliment genotype based prescribing decisions? *Ther. Adv. Drug Saf.* 9, 45–62

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