African giant rats for tuberculosis detection: a novel diagnostic technology

To alleviate this diagnostic problem in sub-Saharan Africa, Anti-Persoonsmijnen Ontmijnende Product Ontwikkeling (APOPO) came up with a novel technology: training and utilizing African giant pouched rats (Cricetomys gambianus) for TB diagnosis. This paper reports the successes achieved so far with this novel technology, the ongoing research activities, the way forward and the challenges to be overcome to finally make the technology fully operational. To this effect, a case study conducted on samples collected from selected urban health centres in Tanzania that resulted in a significant increase in TB case detection, as well as demonstrating detection of difficult sputum smear negative specimens, is presented.

APOPO is an award-winning social enterprise that researches, develops and deploys detection rat technology for humanitarian purposes. It utilizes a local resource, the African rats, for its detection technology. Using these rats as detectors is advantageous due to their efficiency in this role, and their acute sense of smell. Other benefits include their low cost for husbandry and maintenance, ease of transport and their wide availability. It has also been shown that once trained, they can reliably carry out repetitive tasks. Moreover, it is an appropriate tool since it does not depend on high tech equipment or highly skilled labour, increasing its accessibility in the countries of operation. Initially, APOPO proved the concept of its innovative technology for the detection of landmines and this result is currently operational in some countries seriously affected by landmines. As an extension of its knowledge and as a separate wing of its research activities, APOPO envisaged a completely new idea of using its technology for the benefit of the larger poor: rats detecting TB! This idea is based on the fact that the mycobacteria emit specific volatile organic compounds, that are likely to be detected by the rats through olfactory perception and the proof of this concept was recently published.

To explain the training and evaluation procedure briefly, beginning at the age of four weeks rats learn to associate the pop sound of a metal clicker, made by the trainer, with a reward of food (peanuts or banana pulp). They learn to...
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confirmed the agreement between results of the positive smear microscopy from the DOTS centres and APOPO’s microscopy as well as rats’ detection.

APOPO’s research outputs so far asserted that sniffer rats can analyse sputum samples faster and reliably with high sensitivity and specificity10. Furthermore, it demonstrated that rats can analyse an average of 70 sputum specimens in 20 minutes whereas an average of 20 specimens can be analysed by a microscopist in a day of eight working hours. Hence, using rats for detection reduces workload significantly in the TB diagnosis centres and improves the quality of results, which diminishes with increasing workload. The use of rats can also reduce transmission/spread of TB bacilli from infected patients who are undetected or misdiagnosed due to various reasons including workloads in laboratories and HIV status11. For example, the new 577 patients who were detected by rats but missed/undetected in the DOTS centres would have been able to transmit TB to between 5770 and 8655 people per year if they had remained undetected (one untreated person can transmit TB to between 10 and 15 people per year12,13). This shows the potential use of sniffer rats as a first-line screening tool in active case finding and referring suspected patients to DOTS centres for confirmation and early treatment. Similarly, culture laboratories could benefit from dealing with screened suspect positive samples only, which may improve work in these laboratories as well as the drug susceptibility testing facilities (DST). These may contribute to achieving the Global Plan to Stop TB and the target to save 14 million lives and achieve the proper treatment of 50 million people.

Current research activities are geared towards further improvement of the sensitivity and specificity of rats’ detection; refining sample collection, transport and pre-treatment procedures so as to avoid any cue the process might leave for the sniffer rats; automation of the evaluation cage so that any human error (bias from animal trainers) could be minimized; and installing a quality assurance and internal accreditation scheme for individuals or groups of trained rats. We are also planning to launch a clinical trial in Cape Town, South Africa where TB as well as TB-HIV co-infection is rampant but the expertise and the technology to run the confirmatory tests are present. Due to the relative technological advances in South Africa, the accreditation

Figure 1: Cassettes containing sputum samples for TB detection (a), a sniffer rat is being rewarded after positive indication of a tuberculosis sample in the evaluation line cage (b).

Figure 2: Tuberculosis case detection in the four selected DOTS centres in Dar es Salaam (microscopy) and APOPO trained African giant pouched rats (Cricetomys gambianus) (n = 15 041 patients).
procedure is in place and we anticipate swift accreditation once we successfully finish the clinical trial. Once we gain experience there, we may transfer this knowledge to Tanzania where the accreditation procedure is non-existent, assist our Tanzanian colleagues to establish one, and seek accreditation to implement the technology. The last steps will pave the way for seeking international accreditation to be officially part of the tool to curb the TB burden worldwide.

Access to funding remains the main challenge for APOPO’s innovative technology to be embraced in the global fight against TB. So far a number of organizations and foundations (such as The World Bank Development Marketplace, UBS Optimus Foundation and the US National Institutes of Health) have provided funding for this project. But as explained in the preceding paragraph we have a long way to go and numerous research activities to conduct to reach our ultimate goal. APOPO looks forward to continued partnering with interested parties as we work towards containing the spread of TB.

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**Bart Weetjens** is a product development engineer with a focus on appropriate technologies for developing countries. In 1998, Bart initiated the use of HeroRATS: trained giant African pouched rats as an alternative and sustainable landmine detector, in response to the global landmine challenge. Since 2000 APOPO has addressed humanitarian detection challenges in Africa: the detection of landmines and screening for TB. HeroRATS have received much international recognition. Bart is an ASHOKA Fellow and a SCHWAB Fellow, and a permanent member to the Global Agenda Councils. In 2009, he won the SKOLL Awards for social entrepreneurship. Bart is a Zen Buddhist monk and lives with his wife and two daughters in Tanzania.

**Georgies Mgode** is pursuing his PhD study at the Max Planck Institute for Infection Biology, Berlin, Germany. He has a Bachelors degree in zoology/botany from the Open University of Tanzania, and a Masters degree in zoology from the University of Pretoria, South Africa. At Sokoine University of Agriculture, Tanzania, Georgies has been involved in research on rodent-transmitted diseases of public health and veterinary importance (such as plague and leptospirosis), as well as rodent taxonomical studies. He is currently investigating the target compounds from TB organisms detected by the trained African giant pouched rats.

**B Witkind (Wit) Davis** is a volunteer for APOPO as part of her Masters of Public Health coursework in epidemiology and biostatistics at the Tufts University School of Medicine in Boston, USA. Prior to APOPO, Wit worked for the International Fund for Animal Welfare responding to international disasters and overseeing scientific documentation and policy development. Wit holds an MSc from the Tufts University School of Veterinary Medicine and a BSc from Bates College. She maintains a long-standing commitment to identifying ways where animals and people can improve each other’s health and welfare.

**Christophe Cox** is a Belgian national who has an MSc in product development and an MSc in development cooperation. He obtained three years’ grassroots experience working in Kenya as a volunteer in a rural community development project between 1994 and 1997. He then joined APOPO at the start of the project. Having been involved in all aspects of the development of APOPO, Christophe gained knowledge in animal behaviour, chemistry and olfaction, as well in financial and administrative management. He was appointed CEO of APOPO in 2008.

**Negussie Beyene**, PhD, is APOPO’s analytical chemist seconded by GICHD to manage APOPO’s analytical explosives chemistry lab at SUA, in support of the REST research programme. He was an assistant professor at Addis Ababa University, Ethiopia before resuming his current post. Negussie has conducted research in laboratories in Austria, South Africa and Spain. His prior experience as a clinical chemist and head of the Regional Public Health laboratory in Ethiopia, lectureship of clinical chemistry and research experience in the development of sensors and biosensors for compounds of biomedical importance has lead to a keen interest in biomedical sciences and to his active contribution in APOPO’s TB project.

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**Key messages**

- Using African giant pouched rats for TB detection significantly increases case detection including detection of sputum smear negatives mostly missed by microscopy.
- Utilizing sniffer rats reduces the time required to screen for TB (less than 6 minutes are needed to analyse an average of 20 specimens which may require 8 hours for examination by microscopy) in turn reducing the workload in DOTS centres, which is directly related to the quality of diagnostic results.
- There are a number of steps to pass through to reach to the ultimate goal of using APOPO’s new technology for the global fight against TB and the main challenge for the accomplishment of this task is funding.

References