

## PanACEA: a new approach to tuberculosis research

The completion of enrolment into the REMox TB study in January this year was an important milestone for the Pan-African Consortium for the Evaluation of Anti-Tuberculosis Antibiotics (PanACEA)—a network consisting of European research organisations, 11 sub-Saharan clinical trial sites, and three pharmaceutical companies. The trial aims to investigate the role of moxifloxacin in reducing treatment durations for tuberculosis, but the PanACEA network has wider ambitions: it hopes to establish collaboration rather than competition as a driving force to enable quality clinical and regulatory trials in resource-poor settings.

The roots of the project can be found in 2003. That was when the European Commission and 14 participating European countries established the European and Developing Country Clinical Trials Partnership (EDCTP). The EDCTP aims to “accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, tuberculosis and malaria, with a focus on phase II and III clinical trials in sub-Saharan Africa”.

May 31, 2007 saw the EDCTP host a stakeholder meeting in Dublin, Ireland. There, tuberculosis experts

mooted the idea of a consortium of groups applying jointly for a drug development grant, rather than competitively. A few months later, five applicants representing European and African institutions met for a brokering meeting in The Hague, Netherlands; from these groups PanACEA emerged. Funding—€27 million worth—comes from the EDCTP and individual grantees then find additional funding from other sources, national governments, perhaps, or the Bill & Melinda Gates Foundation. The objective is to investigate drugs that can contribute to the shortening of the duration of tuberculosis treatment.

Stephen Gillespie (University of St Andrews, UK) leads the REMox TB study—one of three PanACEA projects—in collaboration with, among others, the TB Alliance. ReMox TB is an international phase 3 clinical trial. 1900 patients have been enrolled in some 30 sites around the world in an effort to see whether treatment regimens for drug-sensitive tuberculosis can be cut from 6 months to 4 months by use of a new drug (moxifloxacin) in combination with existing treatments. Most patients are from Africa, and PanACEA hosts several of the trial sites.

“If we’re going to solve the tuberculosis problem, the paradigm of competitive research groups doesn’t really work”, Gillespie told *TLID*, “PanACEA is a different paradigm for solving a big problem.” It offers a model of a cooperative European operation interacting with counterparts in Africa. “We’ve brought the European groups together to set up common platforms for clinical trials methodologies in a way that allows other groups to join us”, Gillespie added.

“People are more and more aware that we can’t leave the cure of poverty-related and neglect diseases to the pharmaceutical industry”, explains Martin Boeree (Radboud University, Nijmegen, Netherlands). “There is a

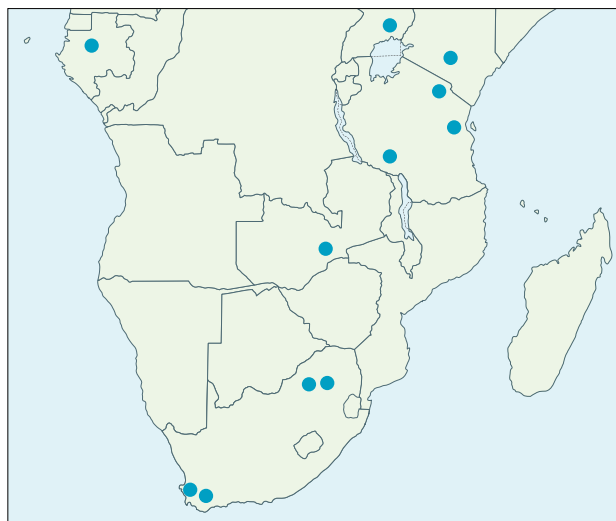
global responsibility to address these problems.” Boeree is coordinating HIGHRIFF, a series of clinical trials that will examine the efficacy of higher doses of rifampicin in reducing the length of tuberculosis treatment.

The final project is led by Michael Hoelscher at the University of Munich (Germany): the phase 2 clinical development of the new anti-tuberculosis drug candidate SQ109, which was developed by pharmaceutical company Sequella.

Needless to say, capacity building is a crucial component of the entire enterprise. The initial abilities of the African sites varied. “Some were already able to do academic studies, so we took those sites from doing academic studies to doing regulatory studies”, affirmed Gillespie. Others had never undertaken clinical tuberculosis trials, and PanACEA helped to facilitate the equipment and expertise to allow such work. The overarching goal is to help African institutions to do research according to the principles of good clinical practice. Mel Spigelman of the TB Alliance (New York, USA) believes this is well overdue. “One of the major limiting factors for our ability to do the sort of work that we’re ready to do is the lack of clinical trial capacity”, he said. “It’s probably second only to the lack of funding in terms of really keeping us from making rapid progress.”

It is not just Africa (although this is PanACEA’s focus). “Sites in India, China, Thailand, and Latin America require just as much work”, Spigelman noted. In fact, he reckons that a couple of African sites are among the most advanced. “The whole world has been neglected from the perspective of tuberculosis trials”, he stressed.

Improving matters in Africa will take a good deal of investment both in teaching and infrastructure, but there are already signs of success. More than half of the 11 sites—which are dotted across six sub-Saharan countries (Gabon, Kenya, Uganda,



11 sites in six countries make up the PanACEA network of study centres in Africa

Zambia, and several in both Tanzania and South Africa)—are up to good clinical practice standard, according to Boeree. PanACEA is also funding MSc and PhD candidates at several of these institutions. “We want to establish sustainable research capacity for the future so that these sites can trial new compounds as well”, concludes Boeree.

Take the Kilimanjaro Clinical Research Institute (KCRI) in Tanzania. The Kilimanjaro Christian Medical Centre had aspirations of establishing such an institute since its own foundation in the early 1970s. Funding from the Dutch Government and, subsequently, the EDCTP brought the project to fruition in 2009. The institute plays host to the PanACEA secretariat.

By October, 2010, KCRI was ready to host a clinical trial—part of the HIGHRIF project. Gibson Kibiki is the trial coordinator. “We have a team to carry out clinical trials in tuberculosis at the research institute and field sites, and it is almost complete”, he told *TLID*. “We have field workers, clinicians, pharmacists, nurses, and statisticians.” He started assembling the tuberculosis team almost 8 years ago, but the Dutch investment quickened the pace. Kibiki expects to have finished enrolling patients in March—already 100 of the 120 places have been filled. “This will be the first fully good clinical practice compliant trial”, he said, “and we can do more trials without problems—the team know what is needed.” There is still some way to go—the institute could do with more experts in related fields such as genetics, for example. But the past few years have seen some stark improvements.

“When we started most of the staff, including me, were trained abroad”, Kibiki revealed. “Now we are supervising students.” There are four research-oriented MSc programmes—from which the laboratory technicians tend to have graduated—while the medical college graduates 12 Phd students. Of course, there were teething problems. The initial case

record form proved inadequate, for one thing. Starting from scratch brings its own issues—it is an arduous business fitting out a lab, setting up viable internet connections, and addressing all the associated administrative work. “We’re working hard on getting good research administrators and finance officers”, Kibiki said. “But it takes time—we are doing research at the same time as building infrastructure.” He points out that Europeans are not always sensitive to the uniquely tricky problems faced by Africa in establishing this kind of infrastructure.

Still, there is plenty of cause for optimism. Kibiki’s trial has retained all but eight patients, all of whom had good reason for leaving the trial. Indeed, across the entire PanACEA clinical trial enterprise, the 18 month retention rate is more than 90%. REMox TB is a regulatory study, so its sponsors are establishing relationships with regulators in Africa and elsewhere (China, India, Malaysia, and Thailand are also hosting the trial). “All of our studies have been approved not only by the local ethics committee of the university but also by the local pharmaceutical regulators—the Medicines Control Council in South Africa, the Tanzania Food and Drug Agency, and so on”, explained Gillespie. He reckons PanACEA is effectively acting as a small pharmaceutical company.

All of this is occurring to a backdrop of diminishing funding for neglected diseases. The latest Global Funding of Innovation for Neglected Disease report highlighted a US\$125 million fall in public funding from the world’s richer nations into research and development of new products for neglected diseases in 2010. Admittedly, tuberculosis fared better than other diseases—2010 actually saw its funding increase—but it is a worrying trend nonetheless.

The first phase of the EDCTP will end in 2014. “We are very hopeful that there will be an EDCTP II, and we are very hopeful there will be a



Stellenbosch University, South Africa, is a leading centre for tuberculosis trials

PanACEA II”, Boeree said. The former, he hopes, will be budgeted with €1 billion to expedite the next stage of clinical trials in poverty-related diseases. For a prospective PanACEA II, Boeree reckons €50 million would allow for an investigation of trials based on the multiarm, multisite (MAMS) design. “It is an innovative design which makes us able to trial several combinations of drugs in a shorter period with fewer patients and in a more cost-effective manner”, he said. “We’re going to try this MAMS design with the compounds we have now. In the future we are aiming to get a PanACEA II with all the new compounds and combinations tried according to this principle.”

Gillespie also stresses the importance of the MAMS study, not just in and of itself, but as a means of keeping the infrastructure alive after the REMox TB trial has closed. PanACEA is driven by the ambition to create a self-sustaining operation, created by the consortium but subsequently taken over by other groups. “As the research portfolio expands, the infrastructure must—we’ll have to upgrade the equipment and make sure that we retain experts”, says Kibiki. It is, as always, a question of funding. “If the global funding is available”, Spigelman notes, “there is more than enough work to keep these centres running.”

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For more on funding for neglected diseases see <http://www.policycures.org/downloads/g-finder%20summary%202011.pdf>