DST-NRF CENTRE OF EXCELLENCE

ANNUAL PROGRESS REPORT

Reporting Period

1 January 2016 – 31 December 2016

Name of Director	Professor Gerhard Walzl
Names of Co-directors	Professor Valerie Mizrahi Professor Bavesh Kana
Name of CoE	DST / NRF Centre of Excellence for Biomedical TB Research
Abbreviated CoE Name	CBTBR
Host Institutions	Stellenbosch University University of Cape Town University of Witwatersrand
Date completed	May 2017

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EXECUTIVE SUMMARY

1. Financial Information (Funding of the CoE)

Table 1: Cumulative NRF funding for 2016

Total NRF Funding for 2016	R11 297 823,00
CoE Specific Funding from Hosts in 2016	
UCT	R164 778,00
Wits	R244 233,00
SU	R585 000,00
Funding from other sources to the CoE in 2016	R81 083 806,62
Total funding	**R93 368 756,62**

Table 2: Breakdown of Funding – UCT – 2016

Total funding for 2016 for UCT node:	**R17 866 179,00**	
CoE funding from NRF:	R1 578 942,00	
Other funding from NRF:	R751 736,00	[1]
Funding from UCT (excluding salaries):	157 894,00	[2]
Funding from other sources: [3]	R15 377 607,00	made up as follows:
MRC Unit (MMRU; Mizrahi)	R1 648 566,00	(1 Apr 2016 – 31 Mar 2017)
EU FP7 (MM4TB) (Mizrahi)	R659 218,00	(1 Feb 2016 – 31 July 2016)
FNIH (HIT-TB) (Mizrahi)	R2 535 309,00	(1 Sep 2015 – 31 Aug 2016)
Broad Institute (Mizrahi)	R1 082 410,00	(1 Mar 2016 – 28 Feb 2017)
HHMI SIRS grant (Mizrahi)	R1 378 380,00	(1 Oct 2015 – 30 Sept 2016)
MRC SHIP grant (Warner)	R1 499 340,00	(1 Jan 2016 – 31 Dec 2016)
MRC Flagship 1 (Warner/Mizrahi)	R534 739,00	(1 Jan 2016 – 31 Dec 2016)
US NIH U01 (Warner)	R2 003 348,00	(1 Jan 2016 – 31 Dec 2016) [4]
US NIH R21 (Warner)	R2 058 584,00	(1 Jan 2016 – 31 Dec 2016) [5]
Bill & Melinda Gates Foundation (Warner)	R1 977 713,00	(1 Jan 2016 – 31 Dec 2016)

1 SA/Germany Research Cooperation grant (V. Mizrahi – R 91,200); Incentive Funding for Rated Researchers (V. Mizrahi, R100,000; D. Warner – R 40,000) Competitive Programme for Rates Researchers (D. Warner – R 228,960); SA/Zambia Research Cooperation grant (D. Warner, R71,576); Community Engagement Award (D. Warner), R 220,000).
[2] One doctoral fellowships from UCT's Carnegie Corporation Developing Next Generation Academics program
[3] Where applicable, grant awards from external funders include indirect costs (IDC), and ZAR values are calculated based on landed e-rates
[4] UO1 grant awarded under the NIH-SAMRC South Africa-US program for Collaborative Biomedical Research
[5] R21 grant awarded under the NIH-SAMRC South Africa-US program for Collaborative Biomedical Research

Table 3: Breakdown of Funding – Wits – 2016

Total funding for 2016 - Wits node:	**R13 426 005,00**	
CoE funding from NRF:	R2 442 333,00	
Other funding from NRF:	R764 748,00	Made up of:
Incentive Funding (Kana)	R80 000,00	1
NRF CPRR Grant (Kana)	R290 000,00	2

[1] NRF Incentive Funding to BD Kana – Year 1
[2] Competitive Program for Rated Researchers to BD Kana Year 1

Swiss-SA (NRF/SNSF)	R394 748,00	[3]
Funding from Wits and NHLS:	R2 123 703,00	Made up of:
10% Wits Institutional Commitment	R244 233,00	
Research Incentive Funding	R60 998,00	[4]
Salaries	R1 618 586,00	[5]
TIA – WITS Seed Fund	R199 886,00	[6]
Funding from other sources:	R8 095 221,00	Made up as follows:
HHMI IECS grant	R1 733 416,00	[7]
BMGF Accelerator	R5 753 805,00	[8]
MRC Career Development Award	R600 000,00	[9]
FRC Individual Research Grant	R8 000,00	[10]

Table 4: Breakdown of Funding – SUN – 2016

Total Funding for 2016 SUN node	**R62 076 572,62**	
CoE Funding from NRF 2016	R7 276 548,00	
Funding from Institute - SUN	R1 731 452,00	Made up of:
CoE Specific Funding from Host Institute	R585 000,00	
Stellenbosch University - Animal TB	R130 500,00	
SUN – Faculty Temporary Research Assistance - CLIME	R29 952,00	
SUN – Faculty Early Career Research Funding - CLIME	R130 500,00	
SUN – NRF Incentive funding contribution - CLIME	R40 000,00	
SUN - Host Genetics	R130 500,00	
SUN FMHS Early Career Research Funding - Iron sulphur cluster	R100 000,00	
SUN - Harry Crossley and Postdoc Funding	R510 000,00	
Claude Leon- IRG	R50 000,00	
SUN- Early Career Research Funding- IRG	R25 000,00	
International Funding	R32 398 354,00	Made up of:
NIH LATE-PCR - CGDR	R1 950 000,00	
NIH Deep Sequencing - CGDR	R60 000,00	
NIH Fluoroquinolone - CGDR	R200 000,00	
Hain Lifescience - CGDR	R565 000,00	
FWO - CGDR	R1 000 000,00	
NIH TRUST - CGDR	R1 000 000,00	
CFAR - CGDR	R520 000,00	
NIH OpitQ - CGDR	R300 000,00	
AAZV Wild Animal Health Fund - Animal TB	R69 836,00	
WDA small grants - Animal TB	R54 825,00	
EDCTP - CLIME	R1 410 510,00	
Quidel Corporation - CLIME	R864 303,00	

[3] SA-Swiss Grant to BD Kana Y3
[4] Research Incentive funding for publications and student graduations
[5] Salary funds provided by Wits for BD Kana and NHLS for BG Gordhan
[6] Seed funds awarded to BD Kana Y1
[7] Howard Hughes Medical Institute International Early Career Scientist grant awarded to BD Kana Y5
[8] Bill and Melinda Gates Foundation Accelerator Grant awarded to BD Kana Y3
[9] MRC Career Development Award given to CE Ealand Y2
[10] Faculty of Health Sciences (Wits) Individual Committee Grant awarded to A Papadopoulos

Norwegian Institute of Public Health - CLIME	R15 790,00	
NIH ResisTB (6 months) - Host Genetics	R1 788 500,00	
EDCTP (ScreenTB project) - Immunology	R7 847 854,00	
NEXGEN (NIH) - Immunology	R1 625 000,00	
Horizon 2020 (FP7) Tandem - IRG	R2 100 000,00	
ICIDR (NIH) - IRG	R1 495 000,00	
TBVAC - IRG	R969 931,00	
CORTIS (BMGF) - IRG	R883 805,00	
ALERT (NIH) - IRG	R4 500 000,00	
VPM/SII - IRG	R2 200 000,00	
IDRI- IRG	R978 000,00	
National Funding	R10 810 391,62	Made up of:
MRC TB HART - CGDR	R250 000,00	
MRC NEXT - CGDR	R400 000,00	
Harry Crossley Project funding - Host Pathogen Mycobactomics	R129 768,00	
SAVF - Animal TB	R100 000,00	
MRC Flagship MalTB Redox Project - TB Drugs	R203 245,62	
MRC BAR-TB - CLIME	R1 257 378,00	
NHLS - Host Genetics	R250 000,00	
MRC - IRG	R1 500 000,00	
SAMRC - Baseline	R3 920 000,00	
MRC SHIP - SATBBI- Bioinformatics/IRG	R2 800 000,00	
Other NRF Funding	R9 859 827,00	Made up of:
NRF - KIC - Host Pathogen Mycobactomics	R25 000,00	
NRF - SARChI - Host Pathogen Mycobactomics	R1 758 313,00	
NRF - CSUR - Host Pathogen Mycobactomics	R265 000,00	
NRF - IRG - South Africa / Tunisia Research Cooperation Programme - Host Pathogen Mycobactomics	R203 000,00	
NRF Incentive Funding - PvH	R100 000,00	
NRF SARChI - Animal TB	R1 741 514,00	
NRF Incentive funding - CLIME	R40 000,00	
NRF Competitive Programme - CLIME	R650 000,00	
NRF Incentive funding for RR - Host Genetics	R120 000,00	
NRF CPRR X chrom - Host Genetics	R293 000,00	
NRF CSUR autophagy - Host Genetics	R204 000,00	
NRF Research career award - Iron sulphur cluster	R100 000,00	
NRF Research career award - CGDR	R300 000,00	
NRF Incentive funding - CGDR	R80 000,00	
NRF Competitive funding - CGDR	R430 000,00	
NRF - Career Award - CGDR (Dr E Streicher)	R150 000,00	
NRF SARChI- TB Biomarker	R2 500 000,00	
TIA	R400 000,00	
NRF- CSRR- IRG	R500 000,00	

CGDR - Comparative Genomics and Drug Resistance
CLIME - Clinical Mycobacteriology and Epidemiology
IRG - Immunology Research Group

2. Summary of progress against KPAs

(i) Research

The research productivity of the CBTBR remained high in 2016 as evidenced by the fact that 90 articles in peer-reviewed journals were published, and 108 conference presentations were made, including 11 plenary/ keynote lectures, and numerous invited talks. Of the research articles published, 74 were in journals with an impact factor (IF) >2 and 27 were in journals with impact factors >5. Forty nine (54%) of the papers published in 2016 had a CBTBR member as either first or last author, demonstrating a leading role in these outputs. Included in the outputs from 2016 were major papers from all three nodes that represented the culmination of many years of work. The production of research of the depth and quality embodied in these papers was attributable, to a large extent, to the sustained baseline support provided by the CoE. Importantly, 49/90 (54%) of the peer-reviewed publications in which the CBTBR was involved were first- and/or last-authored by a member(s) of the CBTBR, confirming that a significant proportion of our research outputs were CoE-led.

Progress against targets SLA 5 targets: The outputs under this KPA exceeded the SLA target (≥20 publications of which ≥5 are in journals with an IF ≥2).

(ii) Education and Training

A total of 13 PhD students, 19 MSc students and 17 Honours students from the CBTBR graduated or completed their training in 2016. All these postgraduate students completed degrees within their maximum allowable time agreed upon in the SLA. A number of new postdoctoral, PhD and MSc students were enrolled in the nodes of the CBTBR, and several students were afforded the opportunity to work in international labs. The student breakdown according gender (59% female) and percentage of postdoctoral fellows (54% of total student complement) exceeded the SLA targets of ≥50% and ≥10%, respectively. The proportion of black students (54%) exceeded the SLA target of ≥50%.

Progress against SLA 4 targets: The total of 127 postgraduate students associated with the CBTBR in 2016 greatly exceeded the SLA target of ≥35.

(iii) Knowledge Brokerage

All three nodes are actively involved in the sharing of knowledge amongst researchers within the CBTBR through work-in-progress and Journal Club meetings, held weekly at the three sites, which provide an opportunity to share ideas and new findings within and beyond our own institutions. Team members, staff and students have also continued to participate very actively in local and international conferences, often as invited speakers, where we have shared our work with the international community. Regular meetings have been held with the relevant health authorities, including the provincial Departments of Health of the Western and Eastern Cape, to share our findings and discuss their implications. Members of the CBTBR have also served as advisors to international organisations and have been involved in numerous public awareness activities, both locally and internationally.

(iv) Networking

Numerous recent funding opportunities have led to new networking initiatives that have enhanced the local and international footprint of the CBTBR. This activity is extensive, as outlined in Section 4 of the report. Our collaborative links range from institutional, regional, local, through Africa to many

international consortia and networked partners. The CBTBR regards this activity as central and vital to our activities and encourages it as far as possible.

(v) Service rendering

Whilst not our major activity, the CBTBR continues with this activity and intends to do so in future. The CBTBR continues to assist with countrywide roll out of the GeneXpert and now provides verification standards to over 20 countries, this innovation has allowed thousands of TB patients to access molecular diagnostics. These verification standards now also fall under the GLI label, for all GLI, CDC and WHO sites. We continue to provide technical/ scientific services to the Eastern and Western Cape Provincial Health Department, the gold mines, Tygerberg Hospital and various TB clinics. We continue with our provision of advice and assistance to individuals, research groups and institutions, locally (including NHLS) and abroad, committee membership and scientific review work at the institutional, regional, national and international levels. We continue to test antimycobacterials at all three sites, with the national drug screening platform supported by the SAMRC's SHIP division based in the UCT node having become increasingly involved in providing a screening service for investigators from other countries. Members of the CBTBR again played key advisory and participatory roles in the national and regional responses to the extensively drug-resistant (XDR) TB crisis. Assistance to SANParks, NZG, and others, such as the Namibian Wildlife Service regarding TB in wild animals continues to be given. SU continues to provide a genotyping service to the NHLS in Green Point to identify laboratory contamination and to identify the reasons for discordance between the Xpert and culture. SU is also assisting the NHLS to determine the reason for discordance between phenotypic isoniazid resistance and the absence of its detection on the MTBDRplus line probe assay.

3. Gender Impact

From the "Science by Women" perspective, it is important to note that 59% of all postgraduate students (including postdoctoral fellows) in the CBTBR in 2016 were female. This gender distribution has not changed significantly from the inception of the CBTBR and reflects the situation nationally for women scientists at this level within the health sciences. Importantly, however, there has been increased representation by women at higher levels as evidenced by the fact that two of the three NRF SARChI's recently granted to SU and closely associated with the CBTBR are women, as are two recently appointed NRF Research Career Awardees. Women scientists the CBTBR have continued to contribute to promoting women in science through various vehicles including membership of SAWISE and the mentorship of junior researchers. For example, Prof. Hoal was appointed to the Project Team for Women's Career Progression at SU and Prof Mizrahi serves as mentor and/or sponsor of a number of women scientists at UCT (outside the CoE).

PROGRESS REPORT

1. SCIENTIFIC RESEARCH

Overview and Highlights of Progress since the last report:

SU Node

The SU Node of the CoE is housed within the Division of Molecular Biology and Human Genetics at Stellenbosch University (SU), which also hosts the SAMRC Centre for Tuberculosis Research. The

research conducted within the SU node spans basic to translation and clinical research, largely focused on Tuberculosis (TB) and quality training of students. Various research teams form this node, each with its own research niche.

Theme 1: Immunology Research Group (IRG)

The main focus of the Immunology Research Group, led by Prof. Walzl (also NRF SARChI Chair for TB biomarkers), is the identification of immune biomarkers for use in trials for novel diagnostics, new treatment regimens and vaccines. The node works with several international consortia and with several US, European and African partners on large cohorts of participants, searching for biomarkers of TB infection and disease. They also focus on immune-endocrine interactions and particularly the role of Type 2 Diabetes Mellitus (DM) in TB susceptibility. Some of the key studies that started in the current reporting period include (i) Evaluation of host biomarker-based point of care tests for targeted screening for active TB, funded by the EDCTP (ii) The Correlate of Risk Targeted Intervention Study (CORTIS), which is funded by the BMGF and iii) the effect of type II DM on protective immune responses at the site of disease. In this work, they are performing bronchoscopy and broncho alveolar lavage to investigate cellular responses against TB in TB household contacts with and without DM.

Investigations into diagnostic host markers are ongoing. In this regard, pleural fluid IFN-γ levels were found to be highly sensitive with good specificity for TB pleuritis. This work has led to the production of a lateral flow test that can measure IFN-γ with a hand-held device, for which the node is now seeking funding for direct comparison with gold standard, yet very cumbersome set of diagnostic methods, which consist of a combination of pleural fluid chemistry (absolute protein, lactate dehydrogenase and adenosine deaminase content in fluid and ratios with serum levels), cell composition (lymphocyte over granulocyte predominance), microbiology (which is mostly negative for *M. tb*), the absence of malignant cells on cytological examination and histopathological examination of pleural biopsy samples. Another area of interest is TB meningitis, a condition with a very high mortality and morbidity, often affecting children, which is also very difficult to diagnose, where a three-marker cytokine signature was identified in cerebro spinal fluid that performed better than any other diagnostic modality on its own to diagnose TB meningitis in children. The SU node obtained funding from TIA to develop a simple diagnostic test based on this signature. Their pulmonary TB diagnostic program evaluated multiple mycobacterial proteins as stimulants for the production of multiple host inflammatory markers but test performance did not warrant the long lag time to obtaining a result. However, serum cytokine signatures were found with promising diagnostic potential and they are currently working on point of care, lateral flow-based tests to measure such signatures as part of screening tests for active TB. The SU node is now in year-two of an EDCTP-funded, multi-site clinical trial to develop a point of care device that will work on finger prick blood to serve a screening test for active TB. Dr. Chegou and Prof. Walzl serve as primary investigators on these studies.

Biomarkers for TB treatment response could facilitate clinical trials of new drugs and shortened treatment regimens and might also have application for routine clinical use. The SU node has recruited and followed up cohorts of TB patients from diagnosis to end of treatment and for the following one to two years to identify treatment outcomes and to discover host biomarkers that predict outcomes. They have used PET/CT imaging, microbiological, transcriptomic, metabolomics and serum protein assays in collaborative studies to discover biosignatures. They have found that baseline and early treatment markers can be used to stratify patients into risk groups for poor outcomes. We have obtained approximately US$ 20 million in a co-funded project led by Prof. Walzl

(European and Developing Countries Clinical Trial Partnership (EDCTP) arm of the study) and Prof. Barry (Bill and Melinda Gates Foundation (BMGF)-funded arm of the study) to evaluate the ability of these biomarker to identify patients who can safely stop TB treatment after 4 months instead of 6 months, even on current drug regimens. The preparatory work for this trial, with a starting date in May 2017, was conducted during the reporting period. Part of the preparatory work is funded by the NIAID through their International Collaborative Infectious Diseases Research program (ICIDR), in a study on which Prof John Belisle from Colorado State University and Prof. Walzl are co-principal investigators. The BMGF-funded work that laid the foundation for the biomarker-driven treatment shortening study, called the Biomarkers for TB Diagnosis and Cure, led by the Catalysis Foundation for Health from the USA, used PET/CT as imaging modality before, during and after TB treatment in HIV uninfected adult patients. The work led to a seminal publication in *Nature Medicine*, with Dr. Malherbe as first author and Prof. Walzl as senior author, and showed a surprising heterogeneity of imaging responses at the end of clinically curative treatment. Only 14% of patients had cleared their inflammatory changes in the lungs, over 50% had improved, yet ongoing, inflammation and about one third had new or intensified lesions, suggesting active new or unresolving lesions in spite of microbiological cure as assessed by sputum culture. The study also found mycobacterial mRNA in a large percentage of patients at the end of treatment, possibly indicating persistent mycobacteria or a hitherto unrecognized stability of mycobacterial mRNA long after bacterial killing in tissues. This work was done in close collaboration with Prof. Alland from Rutgers University in New Jersey, Prof. Schoolnik from Stanford University and Prof. Barry from NIAID.

Biomarkers for natural or vaccine-induced protective immunity against the progression to active TB could play an important role in the evaluation of new TB vaccines and might guide preventative measures after exposure to *M. tb*. The immunology group has participated in the recruitment and two-year follow-up of a large adult household contact cohort (>1.400 in Cape Town, which form part of the >4.000 contacts recruited across Africa by the BMGF-funded GC6-74 consortium). The study also served as validation cohort for a trial performed by the South African TB Vaccine Initiative (SATVI) at UCT in which a predictive signature for the development of incident TB was identified. The signature was successfully validated in the GC6 cohort and this work formed the basis of a Lancet publication in 2016. The immunology group is currently part of the ongoing clinical trial (CORTIS, funded by the BMGF) that is being led by SATVI in which the ability of the predictive signature to allow targeted preventative treatment is being assessed. In the follow-up study to GC6-74, called GC6-2013 and led by Prof. Walzl in his capacity as honorary researcher at UCT, biomarkers for incident TB were investigated through complimentary ‘omics’ technologies, including next generation RNA sequencing, metabolomics and proteomics. Several manuscripts that deal with this work have been under preparations during 2016 and will be submitted in 2017. This work is done in close collaboration with Dr. Zak and his team from the Centre for Infectious Diseases Research in Seattle, Prof. Kaufmann from the Max Planck Institute for Infection Biology in Berlin, Germany and with Dr. Scriba from SATVI at UCT.

The Immunology group is part of a NIH RePORT study led by UCT that includes Dr. Mathebula at Sefako Makgatho Health Sciences University. We also collaborate with Prof. Christoffels (UWC) via Prof. Tabb and a bioinformatics initiative that is funded by the MRC (the SATBBI project).

Theme 2: Comparative Genomics and Drug Resistance (CGDR)

Molecular characterization and drug susceptibility of isolates from MDR-TB patients in the Eastern Cape and North West Provinces of South Africa

In this study, the acquisition of second line drug resistance among MDR-TB patients was determined to assess the impact of a standardized TB treatment in the two provinces of South Africa. High rates of poor outcomes and acquisition of drug resistance to second line drugs during treatment were observed. Spoligotyping showed that almost half patients in a sub-cohort of MDR-TB patients were reinfected with a second strain. This led to the conclusion that use of inadequate standardized MDR-TB treatment increased the risk of amplification of resistance, which was compounded by hospitalization that also facilitated nosocomial spread in this setting.

Nucleoid gene regulation in mycobacteria

The study "nucleoid gene regulation in mycobacteria" aimed to develop a method which facilitated the identification of nucleic acid associated proteins using mass spectrometry. Nucleoprotein – Mass Spectrometry (NP-MS) targeted nucleoprotein complexes using an anti-RNA polymerase antibody secured onto a solid matrix prior to elution of nucleic acid proteins through on matrix tryptic digestion. Proteins were identified using tandem mass spectrometry at the Central Analytic Facility (CAF) at Stellenbosch University. Unfortunately, due to unforeseen ethical and supply problems with the antibody producing company, Santa Cruz, the protocol had to be reoptimized using an antibody obtained from a different supplier. This project could however not be completed in 2016 due to technical faults with the Orbitrap Fusion Tribird mass spectrometer at CAF. Final experiments for this project was completed in April 2016 and showed that NP-MS was successful in identifying nucleoproteins which are specific to stress conditions experienced by the mycobacteria.

Evolution of XDR-TB and associated proteome changes

This is the first proteomics study of XDR TB using sensitive mass spectrometry technology. It showed that XDR strains differ physiologically from susceptible strains. Particularly, XDR strains may exhibit increased tolerance to other antibiotics. The study also showed potential for synergy between iron metabolism inhibitors and fluoroquinolones. Other findings include the feasibility of treatment of fluoroquinolone resistant tuberculosis with a late-generation fluoroquinolone, moxifloxacin; an increased propensity of the Beijing lineage to acquire high-level fluoroquinolone resistance mutations; and no impact of nucleoside analogue antiretrovirals on acquired TB drug resistance. This work contributes to knowledge of optimal drug targets and treatment regimens.

Whole genome sequencing of members of the *Mycobacterium tuberculosis* complex

To date, we have whole genome sequenced ~2000 isolates of members of the *M. tb* complex (MTBC). Of these genome sequences, approximately 50 are from MTBC members infecting mainly animal hosts. The remaining sequences are from clinical isolates of *M. tb* (~1900) and *in vitro* generated mutants (~50) of *M. tb* clinical isolates and laboratory strains. The majority of the whole genome sequence data were generated on Illumina HiSeq or Illumina MiSeq instruments. The sequence data have been analysed with an in-house established next-generation sequence analysis pipeline to identify genomic variants (single nucleotide polymorphisms, insertions and deletions) with respect to a reference genome (*M. tb* H37Rv). Whole genome sequence data for approximately 70 MTBC isolates have been made publicly available via the European Nucleotide Archive after being included in peer reviewed publications. All whole genome sequence data have been contributed to the Relational Sequencing TB Data Platform (ReSeqTB) that catalogues genotypic, phenotypic and related metadata from *M. tb* strains to enable the development of clinically useful, WHO-endorsed *in vitro* diagnostic assays for rapid drug susceptibility testing of *M. tb*.

Physiological impact of the evolution of the *rpoB* mutation

Bacilli within an infected lung cavitary lesion spontaneously evolve mutations that confer resistance and are subsequently selected following antibiotic treatment. During this evolutionary process both drug susceptible and drug resistant bacilli may be present. This mixed state of susceptive and resistant bacilli captured at a distinct point in time may change during the course of infection and drug selection. The complexity of the population structure in each sputum sample may thus define the outcome of molecular and phenotypic drug resistance testing which in turn may determine how the patient will be treated. It has been hypothesized that the *rpoB* mutation will influence the transcriptome of the rifampicin mono-resistant isolate compared to the progenitor rifampicin susceptible isolate. They used a number of methods to prove this hypothesis. A sputum sample from an individual patient containing a heterogeneous population of both a rifampicin mono-resistant Beijing Ser531Leu clone and its susceptible progenitor was selected. DNA was extracted, sequenced and analysed using an in-house bioinformatics pipeline. RNA was extracted, sequenced and analysed using Chipster. They found that whole genome sequencing identified two different variants unique to the rifampicin mono-resistant isolate (excluding *rpoB* mutation) and two unique variants belonging to the susceptible isolate. The majority of the differentially expressed genes were transcription regulators as well as small subset of sigma factors/anti-sigma factors. In conclusion, the small number of variants between the two isolates suggests that the resistant isolate evolved from the susceptible progenitor. The comparative transcriptomic analysis demonstrated that microevolutionary events within the *rpoB* gene had a considerable influence on transcription. Consequently, the expression of bacilli's stress response sigma factors and regulatory genes were down-regulated. This in turn led to a down-regulation of expression of a large number of genes, suggesting that the rifampicin resistant mutant has an altered physiology.

Point source introduction of *Mycobacterium bovis (M. bovis)* at the wildlife-livestock interface can lead to clonal expansion of the disease in a single ecosystem

M. bovis infects multiple wildlife species and domesticated cattle across South Africa, and has a devastating effect on livestock trade and movement of wildlife for conservation purposes. *M. bovis* infection was first reported in the Kruger National Park (KNP) in South Africa during the 1990s, and has since spread to infect numerous animal host species throughout the park and across South Africa. Whole genome sequencing data of 17 *M. bovis* isolates were analysed to investigate the genomic diversity among *M. bovis* isolates causing disease in different animal host species from various locations in South Africa. *M. bovis* strains analysed in this study are geographic rather than host species-specific. The clonal expansion of *M. bovis* in the KNP highlights the effect of an introduction of a transmissible infectious disease leading to a rising epidemic in wildlife, and emphasizes the importance of disease control and movement restriction of species that serve as disease reservoirs. In conclusion, the point source introduction of a single *M. bovis* strain type in the KNP ecosystem lead to an *M. bovis* outbreak in this area that affects various host species and poses an infection risk in adjacent rural communities where HIV incidence is high.

Undetected isoniazid mono resistant TB in the GeneXpert era: a risk for MDR-TB?

The current South African TB diagnostic algorithm stipulates that all cases of probable TB be investigated by GeneXpert testing, which detects TB and rifampicin resistance. In TB cases where no rifampicin resistance is found, the patient is treated with the standard first-line regimen, without further investigation of other first-line drug resistances. This implies that cases with isoniazid mono-resistant TB will be treated with a suboptimal regimen, containing less than the recommended four effective drugs during initiation phase, and only one drug during continuation phase. Additionally, it is well-described that isoniazid resistance is commonly the precursor to rifampicin resistance, which

in combination constitutes multidrug-resistant TB (MDR-TB). This study aims to investigate the prevalence and relative outcomes of isoniazid mono resistant TB in a rural area of the Eastern Cape Province. Sample collection has commenced in April 2016, and baseline collection will be continued until the end of June 2017, with follow-up sample collection continuing for an additional 6 months. Culture-based isoniazid susceptibility and patient data capturing are done on a continuous basis, while an Honours student has been recruited to do genotyping experiments. The latter will commence in early June 2017. Preliminary culture-based susceptibility data suggest that the prevalence of isoniazid mono resistance is in line with findings from a recent survey (approximately 6% of all TB cases).

Pyrazinamide resistance

Michael Whitfield completed his doctoral degree in 2016, which was titled: “Pyrazinamide Resistance in *M. tb*”. His study investigated the rates of resistance prevalence of pyrazinamide globally and locally as well as across different resistant profiles. Pyrazinamide resistance is strongly associated with resistance to other anti-tuberculosis drugs. Targeted DNA sequencing of the *pncA* gene is an excellent surrogate for phenotypic drug susceptibility testing (DST). A novel technique was investigated for the development and evaluation of a novel virtual sequencing method for rapid DST. This study adds significant knowledge to the current understanding of drug resistance in *M. tb*. A DNA sequencing pipeline to be able to sequence the whole *pncA* gene of *M. tb* straight from prepared sputum samples was developed. This pipeline is being used in clinical trials where Pyrazinamide is used with new TB drugs. In the previous studies, a number of isolates that we were not able to PCR amplify and sequence the *pncA* gene, although they were positive for TB and other tests were identified. Investigation into this observation led to the discovery of large deletions that included the *pncA* gene. They have identified a number of large deletions of the *pncA* gene. These deletions make it impossible to PCR amplify the region and thus predict drug resistance. This is of particular importance, since the deletion will mean that the *M. tb* strain will be resistant, but amplification failure will be interpreted as a negative isolate. It was demonstrated that the deletion of the *pncA* gene leads to impaired growth in vitro compared to strains with an intact *pncA* gene with and without mutations. However, we demonstrated that these strains are still able to transmit in the community. Currently a manuscript is in advanced stages before submission to raise awareness of this cause of drug resistance and reason for false negative results in molecular drug resistant diagnostics. This work was presented by Dr. Streicher at the 37th Annual Congress of the European Society of Mycobacteriology, July 3 - July 6, 2016 Catania, Sicily (Italy)

The potential of using rifabutin to treat rifampicin resistant tuberculosis

Michael also investigated the potential of rifabutin in the treatment of rifampicin resistance tuberculosis, this holds significant value considering the extensive role out of GeneXpert to identify rifampicin resistance.

Within-patient evolution of MDR-TB to XDR-TB

It has previously been shown that XDR-TB can evolve within a patient during treatment, but the underlying mechanisms driving the evolution of XDR-TB are still not fully understood. To investigate the genomic changes and the chronology leading to the development of XDR-TB during treatment, 37 patients was identified from the Western Cape Province demonstrating evolution from MDR to XDR-TB. They whole genome sequenced 200 serial isolates of *M. tb* of these patients at CDC. Preliminary data analysis of a sub-set of these isolates showed the emergence of kanamycin resistance, which had not been found in the Western Cape Province previously. This suggests that these kanamycin-resistance conferring mutations have emerged recently. Moreover, several

different underlying sub-populations of *M. tb* were detected for almost all patients investigated. While for some patients sub-populations appear to have resulted from a reinfection with a very similar strain, clonal microevolution appears to be the cause of the observed variation in other patients. Taken together, these preliminary analyses show complex evolutionary dynamics during a TB infection and suggest that standardized, routine diagnostic procedures may fail to determine the full drug resistance profile of a patient, therefore leading to partially empiric treatment regimens with decreased effectiveness.

The first evaluation of the diagnostic performance of the Fluorotype MTBDR assay for the detection of *M. tb* and resistance to rifampicin and isoniazid

There has been a paradigm shift in the way that drug susceptibility testing is done routinely. Since 2008 two assays have been approved by the WHO. In South Africa the Gene Xpert MTB/RIF assay has been universally implemented as the primary screening tool, however these results need to be confirmed by a secondary assay, namely the Genotype MTBDRplus. This confirmatory test requires extensive laboratory infrastructure to prevent laboratory cross contamination, has multiple steps and only provides limited information on nucleotide variants conferring resistance. To evaluate the diagnostic performance of the Fluorotype MTBDR assay using smear positive and smear negative sputum specimens as well as cultured isolates, sputum specimens and correlating cultivated samples were retrospectively collected from the NHLS, Green Point, South Africa. A total number of 555 samples were collected for the study and tested with the FT MTBDR assay, using FluoroLyse kit as DNA extraction method and the FluoroCycler 96 for amplification and detection. This included 244 smear positive/culture positive sputum specimens, 99 smear negative/culture positive sputum specimens, 105 smear negative/culture negative sputum specimens, and 107 cultured isolates. The MGIT culture and GenoType (GT) MTBDRplus VER 2.0 results from the cultured isolates were used as method of comparison (gold standard). Discrepancies were resolved by sequencing and the Genotype MTBDRplus VER2.0 assay from sputum specimens. The sensitivity for the detection of *M. tb* using the Fluorotype MTBDR assay in smear positive sputum specimens, smear negative sputum specimens and cultured isolates was 97.9%, 91.8% and 100% respectively. The sensitivity and specificity for the detection of rifampicin and isoniazid resistance in smear positive sputum specimens was 99.2% and 100%, and 100% and 99.1% respectively. The sensitivity and specificity for the detection of rifampicin and isoniazid resistance in smear negative sputum specimens was 100% and 97.3%, and 100% and 97.8% respectively. The sensitivity and specificity for the detection of rifampicin and isoniazid resistance in cultured isolates was 100%. When compared to sequencing and the Genotype MTBDRplus VER2.0 results, the Fluorotype MTBDR assay showed a 97.9%, 97.0% and 97.2% accuracy for the correct identification of *rpoB, katG* and *inhA* promoter mutations respectively. The sensitivity and the specificity of the Fluorotype MTBDR assay for the detection of *M. tb* and rifampicin and isoniazid resistance was highly concordant to that of the Genotype MTBDRplus VER2.0 assay without the subjectivity of visually interpreting the hybridization patterns. The advantage of the FT MTBDR assay is that it is performed in a single tube without release of amplicons thereby eliminating the risk of laboratory cross contamination and reducing the laboratory infrastructure required to perform molecular based drug susceptibility testing. Besides the discrimination of RMP and/or INH resistance, the software also allows for the reliable identification of most significant associated mutations found in *rpoB*, *katG* and the promoter region of *inhA*.

INH resistance discrepancies

In collaboration with NHLS-Port Elizabeth, approximately 400 isolates with routine phenotypic and genotypic Isoniazid susceptibility testing discrepancies were collected. In order to identify the reason for the discrepancies, we have done the MICs of all isolates. Subsequently, they performed Sanger

sequencing of the classical INH resistance causing gene regions and spoligotyping of all the original cultures and all the cultures from the MIC determination in order to identify possible underlying hetero-resistance or mixed infections. For 53 of the isolates, no mutation was found in the classical INH resistance causing gene regions, but it was confirmed that they were indeed resistant at the critical concentration. They performed Whole Genome Sequencing, through an ongoing collaboration with the CDC, Atlanta, GA (Dr. Posey) on these isolates. One of the interesting observations from the WGS analysis was large deletions in the genome of *M. tb* that cause resistance to INH.

Theme 3: Clinical Mycobacteriology and Epidemiology (CLIME)

The CLIME group, led by Prof. Theron focuses on three key areas of research into tuberculosis. These include: 1) the diagnosis of TB and drug resistance, 2) the study of patient infectiousness and TB transmission, and 3) the pan-microbiome of TB patients. Members of the CLIME group have diverse backgrounds, and include fundamental scientists and clinical trials field staff. The group maintains close links with both the City of Cape Town and Provincial Departments of Health, with whom they closely conduct studies, as well as Tygerberg Academic Hospital. Some of the major projects that were initiated in the reporting period are as follows: (i) Evaluation of the yield and utility of the 'Determine' TB lipoarabinomannan lateral flow assay (Alere) for the detection of TB in HIV-positive inpatients in hospitals in South Africa: a two-stage descriptive study called 'LAM REFLEX'), (ii) Feasibility, accuracy, and effect of point-of-care Xpert MTB/RIF Ultra and Xpert HIV-1 viral load testing in HIV-positive patients initiating ART: a randomized controlled trial (ULTRA), (iii) The longitudinal microbiome of MDR-TB patients on treatment and association with outcome (TB-BIOME) and (iv) Investigating the infectiousness of TB patients and factors associated with the airborne survival of *M. tb* (TB-AIR). These studies are co-funded by the NRF, SAMRC and EDCTP.

CLIME has contributed to the translation of key research into globally important policy within the last year. This was chiefly via a systematic review and meta-analysis of the only commercially-available molecular test for resistance to the second-line drugs (which frequently form part of our "last resort" treatment regimen in patients with drug-resistant TB) called MTBDR*sl* (Hain Lifesciences). Prof. Theron, together with other members of the SU node, Prof Warren and international collaborators, co-authored this document, which Prof. Theron presented at a World Health Organization policy meeting in Switzerland. Prof. Theron subsequently provided expert and technical input into the policy decision making process, and the panel subsequently recommended that the WHO endorse this test. Several countries, including South Africa, are now initiating plans to follow this recommendation. Once implemented, it can potentially reduce the substantial (several months) diagnostic delay currently associated with culture-based methods of drug susceptibility testing, which in turn delays the initiation of appropriate treatment and increases transmission. The report written by Prof. Theron and colleagues formed the basis for the WHO policy document on this test.

During the above systematic review process, Prof. Theron and colleagues identified several research gaps, including the lack of data on the performance of the latest version of MTBDR*sl* (v2) and, in collaboration with scientists at the National Health and Laboratory Service (including his MSc student Ms. Pillay), initiated a pragmatic research project to address these gaps. Not only is this study answering important scientific questions, but it is also reporting the test results to health providers, thereby directly benefiting patients. Similarly, Prof. Theron has initiated a study of the LAM lateral flow assay (the only true point-of-care test for TB) at Tygerberg Academic Hospital, which is co-supported by the SU node. Although this test is endorsed by the WHO, it is yet to be adopted widely in South Africa. This study aims to provide evidence for its adoption in our local setting. Finally, as a recent member of the CoE, Prof. Theron has initiated several other research

projects which will likely have findings that will translate into changes in policy and clinical practice. One example includes the evaluation of next generation molecular diagnostics (such as Xpert Ultra) on extrapulmonary fluids. Previous work that Prof. Theron has co-authored on the prior generation of this test has been cited in several international and national policy documents.

Prof. Theron has several other ongoing early stage research projects that will likely have a translational impact. These are on topics such as the microbiome, which aims to establish it as a possible therapeutic target for improve TB treatment outcomes. This has attracted funding from the NRF Competitive Programme for Rated Researchers. Lastly, Prof. Theron is in the process of establishing an aerobiology research platform within the SU node, which will serve as a basis for several future projects.

Theme 4: Host Pathogen Mycobactomics

The overall research goal of the Host Pathogen Mycobactomics group, led by Prof. Sampson (NRF SARChI Chair), is to gain a better understanding of how the pathogen *M. tb* interacts with its host to cause disease. This research group developed a novel reporter system that allows the fractionation of *M. tb,* which has entered into a non-replicating but viable phase (drug tolerant state), rendering it resistant to conventional anti-tuberculous drugs. The team is currently screening novel compounds against bacteria in this growth phase by using a novel reported system and has identified a number of possible hits.
Specific research areas include advancing our understanding of: (i) TB host-pathogen interactions, with a particular focus on persistent mycobacteria, (ii) TB drug resistance (physiology of resistant isolates, assessing potential new anti-TB compounds, and epidemiology of drug resistant TB in Zambia) and (iii) PE/PPE proteins of *M. tb*.

Selected ongoing research:
Persisters. In 2016, the group embarked on a new study, funded by the NRF, to explore the isolation and characterization of *M. tb* persisters. Their aim is to understand the biology of non-replicating “persister” populations of *M. tb*, which are the underlying cause of latent *M. tb* infections and the reason for the lengthy period of antibiotic treatment. These “persister” bacteria are thought to be antibiotic-tolerant cells that exist as a small, viable, but non-replicating (VBNR) population that survives antibiotic treatment, despite the absence of genetic resistance. Little is known about persistent bacteria, since they are very difficult to isolate. However, the group has recently successfully developed a fluorescence-based system, Fluorescence Dilution (FD) that allows them to monitor single mycobacterial cell replication dynamics across whole populations and provides a means for isolating differentially replicating mycobacteria. The application of FD to characterise intracellular *M. tb* identified a distinct subpopulation of non-growing mycobacteria in murine macrophages. Furthermore, they demonstrated that macrophage uptake resulted in enrichment of VBNR “persisters” (as revealed by D-cycloserine treatment). This work was done in close collaboration with Prof. Holden and Dr. Helaine at Imperial College London and was published in SGM Microbiology in June 2016. The importance of this work and the TB epidemic was disseminated to a wider audience by publishing a paper in an online news website, “The Conversation”, which was followed up by invitations for television and radio interviews.

To investigate sub-populations of *M. tb* that could contribute to persistence, the group established a new collaboration with Prof. Wolfaardt, Director of Water Institute at Stellenbosch with the aim to exploit a combination of the fluorescence-based system and flow cytometry to investigate VBNR

“persister” bacteria within *M. tb* biofilms. As a result of this collaboration they are co-supervising an honours student, Ms. du Plessis in Microbiology, Stellenbosch University.

Proteomics. The Host-Pathogen Mycobactomics group collaborate closely with Prof. Blackburn and Dr. Soares from the Applied & Chemical Proteomic Group at the University of Cape Town as well as Dr. Vlok from the Proteomics Laboratory of the Central Analytical Facility of Stellenbosch University. These collaborations focus heavily on advanced quantitative mass spectrometry-based proteomic approaches to characterize the proteomes of clinical *M. tb* isolates and the interaction of *M. tb* with its host.

TB Drugs. The group have an active collaboration with several researchers at UWC to perform targeted screening of potential anti-TB compounds (host and bacterial-directed), and to conduct *in silico* modelling of *M. tb* targets in complex with selected compounds. SU researchers involved include: Prof. Sampson, Dr. Heunis, Dr. Mouton, Dr. Grobbelaar, Dr. de Vos, Dr. Streicher, Ms. Hanri Visser.) Characterization of selected compounds was carried out in consultation with Prof. Warner’s group (UCT).

Theme 5: TB Host Genetics

The TB Host Genetics Research Team, headed by Prof. Hoal, investigates the host genetic determinants of TB susceptibility using a number of different approaches. While the group has had successes in identifying genes involved in TB susceptibility in the general South African population, it is certain that additional susceptibility genes still remain to be identified. However, identifying these genes in a complex disease such as TB is challenging. This research team started a started a key study in the reporting period, namely exploring the human genetics of TB resistance in HIV-infected persons. This study is funded by the NIAID Two MSc students (Nicholas Bowker and Alma Polson) and one PhD student (Nikola Schlechter) graduated and manuscripts from these degrees are being prepared. The group also published 7 articles during 2016:

1: Prof. Hoal has a long-standing interest in the genetic control of human anti mycobacterial immunity. Interferon γ (IFN-γ) release assays (IGRAs) provide an in vitro measurement of anti-mycobacterial immunity that is widely used as a test for *M. tb* infection. IGRA outcomes are highly heritable in various populations, but the nature of the involved genetic factors remains unknown. The group conducted a genome-wide linkage analysis of IGRA phenotypes in families from a tuberculosis household contact study in France and a replication study in families from South Africa to confirm the loci identified. A major locus on chromosome 8q controlling IFN-γ production in response to stimulation with live bacillus Calmette-Guerin (BCG; LOD score, 3.81; $P = 1.40 \times 10^{-5}$) was identified. A second locus wdetected, on chromosome 3q, that controlled IFN-γ levels in response to stimulation with 6-kDa early secretory antigen target, when accounting for the IFN-γ production shared with that induced by BCG (LOD score, 3.72; $P = 1.8 \times 10^{-5}$). Both loci were replicated in South African families, where tuberculosis is hyper endemic. These loci differ from those previously identified as controlling the response to the tuberculin skin test (TST1 and TST2) and the production of TNF-α (TNF1).The identification of 2 new linkage signals in populations of various ethnic origins living in different *M. tb* exposure settings provides new clues about the genetic control of human anti-mycobacterial immunity.

2. The mechanisms involved in interactions between *M.tb* and host innate immune cells determine outcome. Antigen presenting cells, including macrophages and dendritic cells, express many pattern recognition receptors to identify pathogen-associated molecular patterns, thereby initiating an immune response. A major mycobacterial virulence factor, trehalose-6',6-dimycolate, is recognised

by the macrophage-inducible C-type lectin, Mincle, which leads to the activation of the Syk-Card9 signalling pathway in macrophages. Mincle is encoded by *CLEC4E* and Nicholas Bowker, a MSc student supervised by Dr. Möller, Dr. Kinnear and Prof. Hoal, investigated polymorphisms in this gene to assess its role in tuberculosis susceptibility. Four tagging single nucleotide polymorphisms (SNPs) (rs10841845, rs10841847, rs10841856 and rs4620776) were genotyped using TaqMan® SNP assays in 416 tuberculosis cases and 405 healthy controls. Logistic regression models were used for analysis. No association was detected with any of the SNPs analysed. This research highlights tuberculosis disease complexity where recognition proteins which specifically bind mycobacterial glycolipids cannot be conclusively associated with the disease in genetic studies.

3. The group previously demonstrated that Khoisan ancestry is associated with TB susceptibility. As part of this research theme a PhD student from the SU group, Ms. Uren (supervised by Dr. Möller and Prof. Hoal), investigated fine-scale population structure in Southern Africa. Recent genetic studies have established that the Khoisan populations of southern Africa are distinct from all other African populations and have remained largely isolated during human prehistory until about 2,000 years ago. Dozens of different Khoisan groups exist, belonging to three different language families, but very little is known about their population history. They examined new genome-wide polymorphism data and whole mitochondrial genomes for more than one hundred South Africans from the ≠Khomani San and Nama populations of the Northern Cape, analyzed in conjunction with 19 additional southern African populations. The analyses revealed fine-scale population structure in and around the Kalahari Desert. Surprisingly, this structure did not always correspond to linguistic or subsistence categories as previously suggested, but rather reflected the role of geographic barriers and the ecology of the greater Kalahari Basin. Regardless of subsistence strategy, the indigenous Khoe-speaking Nama pastoralists and the N|u-speaking ≠Khomani (formerly hunter-gatherers) shared ancestry with other Khoe-speaking forager populations that form a rim around the Kalahari Desert. Various computational programs showed that there is shared ancestry between the ≠Khomani San and Nama, but not to the extent expected. This allowed for combination of samples from these populations in the analyses of TB susceptibility in the South African Coloured population. Additionally, they reconstructed earlier migration patterns and estimated that the southern Kalahari populations were among the last to experience gene flow from Bantu-speakers, approximately 14 generations ago. It was concluded that local adoption of pastoralism, at least by the Nama, appears to have been primarily a cultural process with limited genetic impact from eastern Africa.

4. The group is also involved with wild-life genetics, specifically in identifying the genetic factors influencing bovine tuberculosis susceptibility. For this study Dr. Glanzmann, a postdoctoral fellow hosted by Dr. Möller, Prof. Hoal, Dr. Kinnear and Prof. van Helden, sequenced the genome of the African buffalo (*Syncerus caffer*), one of the most abundant and ecologically significant species of megafauna in the savannah ecosystem. It has become a species of interest in recent years because of its role as a wildlife maintenance host for a variety of infectious and zoonotic diseases such as corridor disease, foot-and-mouth disease and bovine tuberculosis. To date, no complete genome sequence for *S. caffer* had been available for study and the genomes of other species such as the domestic cow (*Bos taurus*) had been used as a proxy for any genetics analysis conducted on this species. Here, the high coverage genome sequence of the African buffalo (*S. caffer*) is presented. A total of 19,765 genes were predicted and 19,296 genes could be successfully annotated to S. caffer while 469 genes remained unannotated. Moreover, in order to extend a detailed annotation of *S. caffer*, gene clusters were constructed using twelve additional mammalian genomes. The *S. caffer* genome contains 10,988 gene clusters, of which 62 are shared exclusively between *B. taurus* and *S. caffer*. This study provides a unique genomic perspective for the *S. caffer*, allowing for the

identification of novel variants that may play a role in the natural history and physiological adaptations, including tuberculosis susceptibility.

5. Providing an evidence base for wildlife population management is difficult, due to limited opportunities for experimentation and study replication at the population level. Dr. le Roex, a post-doctoral fellow previously hosted by Prof. Hoal and Prof. van Helden, utilized an opportunity to assess the outcome of a test and cull programme aimed at limiting the spread of *Mycobacterium bovis* in African buffalo. Buffalo act as reservoirs of *M. bovis*, the causative agent of bovine TB (BTB), which can have major economic, ecological and public health impacts through the risk of infection to other wildlife species, livestock and surrounding communities. BTB prevalence data were collected in conjunction with disease control operations in Hluhluwe-iMfolozi Park, South Africa, from 1999 to 2006. A total of 4733 buffalo (250-950 per year) were tested for BTB using the single comparative intradermal tuberculin (SCIT) test, with BTB-positive animals culled, and negative animals released. BTB prevalence was spatially and temporally variable, ranging from 2.3% to 54.7%. Geographic area was a strong predictor of BTB transmission in HiP, owing to relatively stable herds and home ranges. Herds experiencing more intensive and frequent captures showed reduced per capita disease transmission risk and less increase in herd prevalence over time. Disease hot spots did not expand spatially over time, and BTB prevalence in all but the hot spot areas was maintained between 10% and 15% throughout the study period. The data suggest that HiP's test and cull programme was effective at reducing BTB transmission in buffalo, with capture effort and interval found to be the crucial components of the programme. The programme was thus successful with respect to the original goals; however, there are additional factors that should be considered in future cost/benefit analyses and decision-making. These findings may be utilized and expanded in future collaborative work between wildlife managers, veterinarians and scientists, to optimize wildlife disease control programmes and mitigate conflict at the interface of conservation, agricultural and urban areas.

6. One of the key projects involves the study of a group of Mendelian Primary Immunodeficiencies (PIDs) in which increased TB susceptibility is one the primary features. Genes found to be mutated in these PIDs can be investigated as TB susceptibility candidate genes in the general population. This study is headed by Drs. Kinnear and Möller and is currently being funded through a National Research Foundation Research grant (Dr. Möller) and an NHLS Developmental grant (Prof. Esser). The group has also established a working group of clinicians and molecular biologists to provide clinical and molecular diagnosis to PID patients in South Africa. This working group, called the Primary Immunodeficiency Diseases Genetics Network (PIDDGEN), is actively recruiting PID patients from across South Africa. The approach involves whole exome sequencing (WES) to study these patients and this technique has provided a means for researchers to gain access to a highly enriched subset of the human genome in which to search for variants that are likely to be pathogenic and possibly provide important insights into disease mechanisms. In developing countries, bioinformatics capacity and expertise is severely limited and wet bench scientists are required to take on the challenging task of understanding and implementing the barrage of bioinformatics tools that are available to them. They designed a novel method for the filtration of WES data called TAPER™ (Tool for Automated selection and Prioritization for Efficient Retrieval of sequence variants). TAPER™ implements a set of logical steps by which to prioritize candidate variants that could be associated with disease and this is aimed for implementation in biomedical laboratories with limited bioinformatics capacity. TAPER™ is free, can be setup on a Windows operating system (from Windows 7 and above) and does not require any programming knowledge. In summary, a freely available tool that simplifies variant prioritization from WES data in order to facilitate discovery of disease-causing genes has been developed.

7. The final paper described the implications of direct-to-consumer whole-exome sequencing in South Africa. It examined a number of vitally important ethical, legal and scientific concerns that have to be addressed to ensure proper and ethical implementation of direct-to-consumer whole-exome sequencing in South Africa. It concluded that individuals taking part in this endeavour must be fully informed of the positive and negative sequelae.

Theme 6: Bioinformatics

The Bioinformatics research team is co-lead by Prof. Tromp, Prof.Tabb and Prof. van der Spuy. Modern molecular experiments using massively parallel techniques produce tremendous volumes of data. The sheer volume can obscure valuable information. The bioinformatics team maximizes the information yield from these experiments. Prof. Tabb specializes in the development of data analysis pipelines starting from instrument outputs, with a particular emphasis on biological mass spectrometry. Prof. Tromp focuses on experiment design, statistical evaluation, and machine learning approaches, with special applications in high-throughput sequencing. Together, they lead the South African Tuberculosis Bioinformatics Initiative (SATBBI).

One of the team's primary engagement has come through interactions with the Proteomics Laboratory of the Central Analytical Facilities of Stellenbosch University. The team will shortly submit a manuscript on the proteogenomics (joining proteomics and genomics methods) for the recognition of strain-specific TB peptides; this manuscript will demonstrate that TB strain discernment is possible from peptide data. Prof. Tabb has also joined in existing efforts within the division, bringing statistical rigor to a manuscript linking TB strain distribution to geographic locations, currently in preparation by Prof. Warren. In the course of 2017, Prof. Tabb and others will seek methods to automate the recognition of high-resolution melt profile differences associated with key genes in mediating TB drug resistance. This automation is critical to making melt profiles applicable in large-scale population studies for TB drug resistance. Prof. Tabb interfaces with the Square Kilometer Array radio telescope project and will collaborate with that team in the creation of a Big Data summer school program.

Prof. Tabb has invested time in the development of bioinformatics at the University of the Western Cape, typically spending one day of each week at UWC. His interactions with the Biotechnology Honors students and with the ARC and UWC Proteomics Research and Services Unit have led to his appointment as a Professor Extraordinary by UWC. His interaction with the Square Kilometer Array project has led to participation in the careers day for the Data Science program at Sol Plaatje University in Kimberley. They hope to see more computer sciences students taking an interest in biomedical research as a result.

Theme 7: Mycobacterial physiology

This research team is led by Dr. Williams and a major focus of their work is studying the iron-sulphur (Fe – S) cluster biosynthetic pathway in mycobacteria. The primary Fe – S cluster assembly system in *M. tb* is encoded by a single gene cluster, namely *Rv1460-Rv1461-Rv1462-Rv1463-csd-Rv1465-Rv1466*, which is predicted to be essential in *M. tb* In a study conducted by a PhD. student in the team, Danicke Willemse, the regulation of this pathway was investigated in a mutant of *M. tb* producing a truncated Rv1460 protein. Rv1460 was shown to function as a repressor of the operon, and upregulation of the system increased the susceptibility of *M. tb* to oxidative stress. In addition, recombinant Rv1460 was shown to bind to sites upstream of *Rv1460* and *Rv1461* using electrophoretic mobility shift assays, demonstrating that regulation occurs due to direct binding of this transcription factor. The purified recombinant Rv1460 protein was used to generate an anti-

Rv1460 antibody, which represents a valuable tool for future studies. Complementation studies in *M. tb* identified three cysteine residues in the Rv1460 protein that are critical for its function. These residues are proposed to play a role in co-ordinating a Fe – S cluster within this protein. A manuscript detailing these findings is currently in preparation. In a follow-up study a PhD student, Lucinda Baatjies, is investigating the immunogenicity and diagnostic potential of Rv1460, in collaboration with Dr. André Loxton (Immunology research group).

One approach to understanding the functioning of the Fe – S cluster biogenesis system is to define the protein-protein interactions between its components. A PhD student in the team, Jessie Arries, has generated the expression constructs and *M. bovis* BCG strains for investigating these interactions by immune-precipitation and mass-spectrometry (IP-MS). The conditions for the IP-MS experiments are currently being optimised. A second approach is to study protein-protein interactions *in vivo*, using recombinant purified proteins. The constructs to produce and purify selected components of the system (SufB, SufC, SufD & Csd) in *E. coli* have been generated and tested. These constructs linked the mycobacterial proteins to fusion tags (6xHis, GFP and maltose binding protein), in an attempt to improve their solubility in the heterologous expression host. Unfortunately, none of the recombinant fusion proteins were sufficiently soluble for subsequent purification. A T7-based mycobacterial expression system is currently being explored.

One of the major questions in Fe – S cluster assembly in prokaryotes is the source of iron used to produce the co-factor. An MSc. student in the team, Nandi Niemand is exploring this question in mycobacteria by investigating two proteins, namely Rv2204c and its homologue MSMEG_4272. In collaboration with Prof. Trevor Sewel and Dr. Brandon Weber at UCT these proteins have been successfully produced and purified. The iron-binding properties of the proteins is currently being investigated using isothermal titration calorimetry. A previous study in the group revealed that MSMEG_4272 is essential in *M. smegmatis*. A protein depletion system was therefore employed to generate a strain of *M. smegmatis* in which MSEG_4272 protein levels could be modulated. Although MSMEG_4272 levels could be depleted slightly, this was not sufficient to study the role of the protein in *M. smegmatis*. The system has now been redesigned for more stringent control.

Theme 8: Host directed therapeutics and novel TB drug target identification

Drug Discovery – The TB Drugs research team is led by Dr. Baker and Prof. Wiid. The team has three main research focus areas:

(i) To test possible lead compounds against *M.tb* in vitro and ex vivo, in collaboration with local and international institutes. This work is led by Dr. Ngwane who was awarded an MRC career development award in 2016. It was demonstrated for the first time that some artemisins are active against *M.tb*, a project in collaboration with North-West University on the MRC Flagship MalTB Redox project. In this project, Artemisinins effective against malaria disease are evaluated for their efficacy against *M.tb* as it was observed before that antimalarial drugs also exert some activity against *M.tb* bacilli. IConsistent with this, it was demonstrated that certain artemisinin derivatived do show significant effectiveness against strains of *M.tb* and its effect combination with existing antituberculosis drugs are being evaluated. Elesclomol, a registered anti-cancer drug that works on the basis of copper chelation and exerts its effect through free radical killing of cancer cells, is also part of the MalTB Redox project and is presently evaluated against *M.tb* on its own and for synergism with existing antituberculosis drugs. They have shown the antimycobacterial activity of novel compounds such as furanone derivatives. These results have been published in the journal, IUBMB Life.

(ii) To identify unique metabolic pathways in *M.tb* through proteomic and metabolomic analyses and generating specific *M.tb* mutants to evaluate potential targets for drug intervention. This work is led by Dr. Sao Emani. Enzymes of the mycothiol and ergothioneine biosynthetic pathways are targets of choice not only because they are unique to mycobacteria but also because it protects mycobacteria against reactive oxygen species. They have knocked out a gene coding for EgtD (an enzyme involved in ergothioneine biosynthesis) from the wild type *M.smegmatis* and the mycothiol deficient mutant (Δ*mshA*) strains. In stress assays, the ergothioneine deficient single mutant (Δ*egtD)* and mycothiol deficient single mutant (Δ*mshA)* were slightly sensitive to oxidative stress conditions generated by cumene hydroperoxide relativel to the wild type, while the double mutant (Δ*mshA/egtD)* was significantly affected. This suggests a synergistic anti-oxidative role of ergothioneine and mycothiol in mycobacteria. As opposed to mycothiol, it was demonstrated that ergothioneine is secreted. In 2016, the *M.tb* mutants have been generated and investigated and a manuscript is being drafted in this regard.

(iii) To identify factors involved in the survival of mycobacteria in mouse and human macrophages employing transcriptomics and proteomics, and then investigating these targets in animal infection models with the long-term aim of developing novel host-directed therapeutics for Tuberculosis. This work is being led by Dr. Leisching. In the past, researchers have carried out numerous investigations on macrophages infected with mycobacterial strains that have been cultured in the presence of detergents such as Tween-80. In 2016, the SU node was one of the first research groups to employ mycobacteria uniquely cultured and filtered in the absence of detergent. A genome-wide RNA-Seq gene expression analysis on mouse bone marrow-derived macrophages infected with mycobacteria cultured in a detergent-free media was conducted. This revealed a robust response when detergent-free mycobacteria were used as compared to mycobacteria cultured in the presence of Tween-80. This work was published in the journal, *PlosOne*. It was further showed that the macrophage response to hypo- and hyper-virulent clinical mycobacterial strains differed dramatically. I identified host candidate genes potentially related to hypervirulence. This work was published in the journal, *Virulence*.

Theme 9: Animal TB

The Animal TB research program, led by Prof. Miller (NRF SARChI Chair) and Dr. Parsons takes a multi-pronged approach to improving knowledge of the epidemiology, pathogenesis and immunology of bovine tuberculosis (BTB) and other members of the *M. tb* complex that infect animals. This includes investigating the role of host genetics and immunology in susceptibility to BTB; the genetic diversity of mycobacterial pathogens and their impact on wildlife and livestock; and the development of diagnostic assays for numerous host species. The work incorporates a continuum of basic to applied research both in the laboratory and field.

TB in animals is a direct zoonotic threat, as well as impacting the socioeconomic status of a community through loss of income due to decreased production by animals and restrictions associated with animal disease. Wildlife TB presents a source of infection for spillover to both humans and other animals. In addition, the wildlife industry and ecotourism provides a significant contribution to the South African economy. There is a lack of diagnostic tests for detection of TB in wildlife. Therefore, the SU team has been investigating blood-based assays to distinguish infected from uninfected animals. Their work has led to implementation of tests using new biomarkers such as IP-10 measured in QFT tube supernatants for a test-and-cull program for buffalo TB in KwaZulu Natal. The investigation and optimization of the QFT assay for buffaloes has resulted in a collaboration with Qiagen, who are currently developing a bovine assay for commercial production.

The group has also been developing tools that have facilitated disease detection to establish preliminary estimates of disease prevalence in different species and locations. They have detected TB in white and black rhinoceros, and an elephant in Kruger National Park. The information was shared with the Department of Agriculture, Forest, and Fisheries (DAFF) and has resulted in issuance of a quarantine notice. TB tests adapted for rhinoceros in the Animal TB laboratory will now be used to survey populations and screen animals before movement if DAFF approves the proposed management plan. These studies were funded by the NRF SARChI Animal TB fund. Ongoing research objectives for the animal TB team include the following; (i) to investigate immunological responses to mycobacterial infection in wildlife species; (ii) to develop molecular and immunological tools for rapid detection of TB in animals; (iii) to apply novel techniques to understand the epidemiology of TB in animals in South Africa; and (iv) to provide information for translation of research findings to development of evidence-based policies on animal TB.

UCT Node

The research program of the UCT node involves an integrated suite of projects that are aimed at investigating aspects of the physiology and metabolism of *M. tb* of relevance to TB drug discovery, TB drug efficacy, mycobacterial persistence, and TB transmission. The research program falls under three broad themes: TB drug discovery; mycobacterial metabolism and physiology; and TB transmission. Four projects are built on areas of fundamental mycobacterial metabolism and physiology research. Two others are based on the application of strong inhereant capacity in mycobacterial genetics and physiology in the area of drug discovery; and in the seventh project, as partners in UCT's Flagship 1 project funded by the SAMRC, the UCT node is responsible for the microbiology component of this interdisciplinary research project, which has been significantly expanded to include a genomics component funded by a grant from the BMGF.

Theme 1: Mycobacterial metabolism and physiology

An SOS-inducible DNA repair system – the "mycobacterial mutasome" comprising DnaE2, ImuA', and ImuB – has been linked to transient hypermutation and the development of drug resistance in *M.tb*. In a study conducted by PhD students Michael Reiche and Zela Martin, and led by Digby Warner, fluorescent strains of *M. smegmatis* were developed to investigate expression and subcellular localization of ImuA' and ImuB in mycobacteria exposed to genotoxic stress. ImuB was observed to co-localize with the *dnaN*-encoded β clamp in discrete foci during mutagenic DNA repair; in contrast, ImuA' did not exhibit specific intrabacillary localization. A mutant strain deficient in the ImuB β clamp-binding site ($ImuB^{AAAAG}$) failed to co-localize with β, reinforcing the inferred essentiality of the ImuB-β protein-protein interaction for mutasome recruitment and induced mutagenesis. Moreover, exposure of *Mycobacterium smegmatis* to the novel β clamp-targeting antimycobacterial agent, griselimycin, prevented β localization during normal cellular replication, consistent with the demonstrated cidality of this compound. Notably, griselimycin also disrupted ImuB recruitment despite triggering full SOS induction, an observation which reveals the capacity of this agent to inhibit DNA replication as well as prevent DNA damage-induced mutagenesis by disrupting mutasome function. This result differentiates griselimycin from other inhibitors of DNA metabolic function which carry the often unavoidable liability of accelerating drug-resistance by inducing mutagenic DNA repair. As such, it suggests the potential application of griselimycin in novel therapeutic regimens designed to protect existing tuberculosis drugs. This study was conducted in close collaboration with researchers at the HHMI Advanced Imaging Centre (Janelia Campus), the EPFL (Lausanne), NICHD (USA), and the Helmholtz Institute for Pharmaceutical

Sciences (HIPS, Saarland, Germany). A manuscript describing this work is in preparation. Moreover, Michael Reiche was invited to present a short talk on this work at the ASM Conference on Tuberculosis, to be held in New York in April 2017. In a related new study supported by Digby Warner's UO1 grant from the NIH, MSc student Ryan Dinkele is investigating the phenomenon of filamentation as a potential link between phenotypic drug tolerance and genetic drug resistance in mycobacteria. These two projects are embedded within, and critically reliant on, the advanced microscopy platform that Digby Warner played a key role in establishing at UCT.

In a related study on the role of the mycobacterial mutasome in genetic adaptation of mycobacteria under conditions of stress, PhD student Sophia van Coller investigated the role of DnaE2 in the ability of a vitamin B_{12}-sensitive Δ*metH* knockout strain lacking the B_{12}-dependent methionine synthase, MetH, to withstand the growth-inhibitory effects of exposure to exogenous vitamin B_{12}. In prior work, B_{12}-resistant mutants had been shown to arise at a very high frequency (~10^{-3}) when plated on B_{12}-containing media, which was higher than could be explained by spontaneous mutagenesis alone. Hypothesizing that stress-induced induction of *dnaE2* might contribute to the elevated frequency of resistance observed in this assay, *dnaE2* was functionally inactivated in the Δ*metH* background by targeted mutagenesis of essential catalytic residues in the DNA polymerase active site, and the resulting double mutant strain plated on B_{12}-containing medium to select for suppressors. However, neither the frequency nor the mutational spectrum of B_{12}-resistance-conferring mutations were affected by loss of *dnaE2* function arguing against a role for the mycobacterial mutasome in induced mutagenesis under non-lethal stress in *M. tuberculosis a*nd suggesting the existence of an alternative system for stress-induced genetic adaptation in this organism.

The UCT node has had a long-standing interest in vitamin B_{12} metabolism. Ongoing work in this area has been focused on applying a chemical genetic approach to compare and contrast the capacity of mycobacterial species to biosynthesis, transport and assimilate various forms of the B_{12} cofactor. In a study led by postdoctoral fellows Gabriel Mashabela and Atica Moosa, a sensitive and highly specific LC/MS/MS method to detect and quantify vitamin B12 was developed and applied in the analysis of cytoplasmic and cell wall-associated fractions of mycobacterial cell extracts. This assay was validated using a set of wildtype and mutant strains of *M. tb* and *M. smegmatis* carrying mutations in genes that disrupt B_{12} biosynthesis at different steps of the biosynthetic pathway. A manuscript describing this work, which has biochemically confirmed key differences in B_{12} biosynthetic capacity between *M.tb* and other mycobacterial species inferred from genetic analyses, is in preparation. In related studies, PhD student Terry Kipkorir is using a genetic approach to investigate vitamin B_{12}-dependent riboswitch regulation of methionine biosynthesis and cobalt acquisition in *M.tb,* and MSc student Rendani Mbau is elucidating the genetic requirements for B_{12} biosynthesis and assimilation in *M. smegmatis* with the aim of constructing the corresponding pathway in the pathogenic *M.tb*. The latter project is one of three new studies in the UCT node that are applying transposon sequencing as a functional genomics tool.

Theme 2: TB drug discovery

Over the past year, four major studies in the area of TB drug discovery were completed and published. Each paper represents the culmination of between three and five years' work in the UCT node, conducted under the auspices of two international TB drug discovery consortia – *More Medicines for TB* (MM4TB), *Identification of High-Quality Hits for TB* (HIT-TB) – with complementary support through a grant from the SHIP division of the SAMRC.

The first paper reports the identification and validation of a new TB drug target, GuaB2. Working as part of the MM4TB consortium led by Stewart Cole (EPFL, Lausanne) and funded by the Seventh Framework Programme of the European Commission, UCT node postdoctoral fellow,

Vinayak Singh and a team of collaborators from institutions across Europe and the UK used a combination of chemical biology, genetics, enzymology, structural biology and time-lapse microscopy to identify the inosine 5-monophosphate dehydrogenase enzyme, GuaB2, as the target of a small molecule inhibitor of growth of *M. tb* that had been identified by phenotypic screening of compound library. GuaB2 was validated as a vulnerable new TB drug target by demonstrating that conditional depletion of this protein leads to very rapid loss of culturability followed by death of *M. tuberculosis* in *in vitro* culture and in infected macrophages. GuaB2 depletion was also shown to completely block the ability of *M. tb* to establish an infection in mice. This work was published in *ACS Infectious Diseases*. In a parallel study conducted under the auspices of the HIT-TB consortium, GuaB2 was independently identified as the target of a different chemical series. Important data reported in this paper, which was published in the same journal a month after the Singh et al. paper, suggested the possibility for subversion of GuaB2 essentiality in humans through purine salvage as a consequence of the high levels of guanine detected in diseases lung tissue from chronic TB patients. This finding has raised questions regarding the vulnerability of GuaB2 as a new TB drug target, as discussed in a Commentary article by Prof. L. Hedstrom published recently in *ACS Infectious Diseases*. Together, these studies have raised the bar for validation of TB drug targets in central metabolism and have underscored the critical importance of understanding the range of metabolites that *M. tb* can potentially access from the host – and the levels thereof – during the course of infection and progression to disease.

The second paper, led by Junior Research Fellow Joanna Evans, and Valerie Mizrahi, reported the identification and validation of CoaBC, a key enzyme in the coenzyme A (CoA) biosynthesis pathway as a new TB drug target. *M.tb* relies on its own ability to produce CoA, a cofactor that plays a key role in myriad biochemical processes. CoA is produced via a nine-step pathway catalyzed by eight different enzymes. This study, conducted under the auspices of the *HIT-TB* consortium of the TB Drug Accelerator program funded the BMGF, was aimed at identifying the optimal step for therapeutic intervention in the CoA pathway. CoaBC was found to be a uniquely bactericidal drug target in *M.tb*, with depletion of this enzyme resulting in death of *M.tb in vitro*. Transcriptional silencing of *coaBC* blocked the ability of *M.tb* to establish an infection in mice and also resulted in clearance of *M.tb* from the lungs and spleens of infected mice during both the acute and chronic stages of infection. These results provided convincing genetic validation of CoaBC as a new TB drug target. This work, which was carried out in collaboration with researchers at the NIAID and Weill Cornell Medical College was also published in *ACS Infectious Diseases*. In ongoing work, the UCT is providing the microbiology support for a target-led drug discovery effort against CoaBC involving collaborators at the University of Cambridge, University of Dundee and Weill Cornell Medical College.

In the third study, UCT postdoctoral fellow Vinayak Singh and Valerie Mizrahi collaborated with researchers in the MM4TB consortium to elucidate the mechanism of action of an aminopyrimidine sulfonamide (APYS1) – a small molecule discovered by phenotypic screening for growth inhibitors of *M. tb*. The APYS1 compound was shown to have potent bactericidal activity against *M. tb* and to act through an entirely novel mechanism that indirectly involves Wag31, a scaffolding protein that plays a central role in cell growth and division. This study involved a multi-institutional, mutlidisciplinary collaboration with research partners based at the École Polytechnique Fédérale de Lausanne (Switzerland), Vichem Chemie Research Ltd. (Hungary) and other institutions within the MM4TB consortium. This paper, which was published in *Molecular Microbiology*, was highlighted in a “Microreview” by Dr. H. Boshoff in the same issue of the journal.

In the fourth study, led by Digby Warner and published in *Antimicrobial Agents and Chemotherapy*, PhD student Krupa Naran and postdoctoral fellow Atica Moosa reported the development of bioluminescent reporters that allow the mechanism of action of compounds with

anti-TB activity to be rapidly assessed. This work was supported by a grant from the SHIP division of SAMRC as part of its commitment to fostering innovative TB drug discovery research in South Africa. These reporter strains were validated using TB drugs with known mechanisms of action and their utility for the early triage of compounds based on provisional mechanisms of action confirmed. The reporters have been fully integrated into the hit triage cascade developed by the HIT-TB consortium and applied for hit prioritization to all members of the TBDA. This cascade is designed to triage compounds identified through high-throughput screening to identify compounds with growth inhibitory activity against *M.tb*.

In addition to these original research articles, Vinayak Singh and Valerie Mizrahi also published a review article in *Drug Discovery Today* in which they provided an overview of TB drug target identification and validation of new TB drug targets, highlighting findings from the MM4TB project. This article was published in a special issue of the journal focused on TB. Other research under this theme focused on: (1) exploring the potential of synergistic drug combinations as a strategy for early-stage identification of novel TB drug partners, with particular emphasis on repurposed drugs that have limited anti-tubercular drug efficacy when employed on their own (Charles Omollo, PhD student; collaboration with Prof. Kelly Chibale, Department of Chemistry, UCT); (2) investigating drug permeation in the cellular lesion microenvironment in a macrophage infection model in order to identify disease-relevant physicochemical and pharmacological properties that drive permeation of compounds into *M.tb*-infected cells, with a view to utilizing these data to determine predictors of cellular drug distribution (Amanda Mabhula, PhD student; collaboration with Dr. Lubbe Wiesner, Division of Clinical Pharmacology, UCT); (3) investigating intrabacillary and intramacrophage pharmacokinetics and drug metabolism with the aim of determining optimal drug-like properties (Lloyd Tanner, MSc student; collaboration with Dr. Lubbe Wiesner); (4) elucidating mechanisms to accelerate the rate of antibiotic-mediated kill of *M. tb* – this is a new project funded by a grant from the Broad Institute of Harvard and MIT (Mandy Mason, postdoctoral fellow); and (5) biological profiling and mechanism-of-action elucidation of new compounds with anti-TB activity (Vinayak Singh, Joanna Evans and Atica Moosa, postdoctoral fellows). In this project, excellent progress has been made on elucidation of the mechanisms of action of natural products of myxobacterial origin as part of a collaboration with Prof. Rolf Muller, Helmholtz Institute for Pharmaceutical Sciences, supported by a SA/Germany Research Cooperation grant, and on compounds provided by Profs. Simon Teague (King's College London), and Richard Haynes (Rhodes University). A number of these projects will be completed and submitted for publication in 2017.

Theme 3: TB transmission

Over the past year, research on a project aimed at investigating the microbiological, immunological and environmental determinants of TB transmission, led by Prof. Wood and funded by a Flagship 1 grant from the SAMRC, focused on the development and evaluation of methods for the detection, quantification and genomic as well as physiological characterization of bacilli released by TB patients. The UCT node, led by Digby Warner, is responsible for the mycobacteriology component of this interdisciplinary project that is based in the IDM at UCT. This project is jointly funded by the BMGF under the TB Aerobiology program. The first paper from this project was published in *PLoS One a*nd several others are in preparation.

Wits Node

The research portfolio of the Wits node can be divided into four broad thematic areas that span from fundamental research to the delivery of TB diagnostics. The first theme involves the identification and validation of novel drug and vaccine targets for TB, with a particular focus on the bacterial peptidoglycan as a tractable area for the discovery of new drug targets. Enzymes that remodel the peptidoglycan are essential for bacterial cell division and the Wits node has uncovered a novel class of amidases and low molecular weight penicillin binding proteins that are essential for bacterial survival. In the search for new drug targets, the Wits node has also directed effort in studying enzymes involved in DNA repair. The second focus area encompasses the characterization of differentially culturable tubercle bacteria (DCTB) in patients with active TB disease. Treatment of TB is protracted, requiring six months of combination chemotherapy to obtain non-relapsing cure. It has been hypothesized that this long duration of chemotherapy is necessitated by the presence of organisms that are tolerant to drug treatment. The Wits node has further investigated this phenomenon through the quantification and characterization of DCTB in HIV-1 infected and uninfected TB patients with pulmonary disease prior to the initiation of TB treatment. Furthermore, they have established two longitudinal cohorts that are aimed that monitoring the response of these organisms to treatment and further follow up of patients to record any incidence of recurrent TB disease. The third focus area entails the construction, confirmation and bulk production of diagnostic verification reagents for molecular TB diagnostics. For the past 5 years, the Wits node has been providing support for the rollout of TB molecular diagnostics in over 30 countries. For this, a set of verification reagents that can be used to declare newly installed diagnostic devices as “fit for purpose” and for continuous external quality assurance programs have been developed by the Wits node. These reagents can be provided at low cost and do not require a cold chain, thus making them suitable for low resource settings. The fourth focus area is targeted at the development of novel screening modalities for new TB drugs. Screening for new TB drugs often involves testing the ability of compounds to inhibit growth of tubercle bacteria in axenic culture. Often, these culture conditions poorly mimic the environment encountered by bacteria in the human lung, thereby limiting the identification of compounds that would be active in the host. To address this, the Wits node of the CBTBR has developed counter screening models that generate drug tolerant bacteria to use in screening endeavors. Research highlights in these four thematic areas are detailed below.

Theme1: New Drug targets for TB

In 2016, research on mycobacterial amidases yielded new insight into the biological functioning of these proteins. It was previously demonstrated that deletion of MSMEG_6281 (Ami1) in *M. smegmatis* resulted in the formation of cellular chains, illustrative of cells that were unable to complete division. These findings were further advanced with the demonstration that viability in the Δ*ami1* mutant was maintained through atypical lateral branching, the products of which proceeded to form viable daughter cells. These ectopic cell poles and lateral buds resulted from mislocalization of DivIVA, a major determinant in facilitating polar elongation in mycobacterial cells. Failure of Δ*ami1* mutant cells to separate also led to dysregulation of FtsZ ring bundling. Loss of Ami1 resulted in defects in septal peptidoglycan turnover with release of excess cell wall material from the septum or newly born cell poles. A significant accumulation of 3-3 crosslinked muropeptides was noted in the Δ*ami1* mutant together with increased cell wall permeability and enhanced susceptibility to cell wall targeting antibiotics. These data have recently been accepted for publication in *Scientific Reports*. In contrast to the dramatic division defects that were noted with the *M. smegmatis* mutant, morphological analysis of the corresponding *M. tb* mutant revealed no substantive defects, However, time-lapse microscopy showed the formation of polar buds, which either produced viable daughter cells or failed to grow, suggesting mis-localization of the division apparatus to the cell

pole. This mutant also displayed reduced survival under acid stress conditions. To further study the effects of Ami1 deletion in *M. tb*, the survival of the mutant in J774 macrophages was assessed and it was noted that loss of Ami1 led to survival defects in activated but not unactivated macrophages. These and related effects are being studied further.

Bacterial M23 metallopeptidases form part of a highly diverse group of enzymes characterized by their endopeptidase activity in hydrolyzing peptide bonds found in peptidoglycan and elastin. Bioinformatics tools were used to identify LytM domain-containing homologues (M23 peptidases) in *M. smegmatis*, (designated MepB1-MepB4). These were deleted using standard allelic exchange mutagenesis and recombination techniques and the resulting mutants were assessed for cell wall related defects. It was demonstrated that mycobacterial LytM endopeptidases are dispensable for growth but have important roles in bacterial growth as demonstrated defective cell division in a Δ*mepB1* Δ*mepB2* deletion mutant. Spatial localization of new cell wall biosynthesis revealed the inability to degrade the septal bridge joining two daughter cells, pointing to a critical role for these enzymes in cell separation. MepB1 and MepB2 were also identified as novel components of the mycobacterial divisome through in vivo protein interaction studies. Collectively, these observations provide the first insight into a new group of potential drug targets for TB disease and notably enhance the overall understanding of peptidoglycan turnover in a group of clinically relevant pathogens.

During infection, *M. tb* encounters hostile conditions which result in the generation of host-derived reactive oxygen (ROS) and nitrogen species (RNS) as part of the immune response to control the infection. Exposure to these reactive radicals can lead to oxidative damage of DNA, which ultimately introduces mutations through defective repair. *M. tb* is well equipped with a number of DNA repair pathways such as the base excision repair pathway, which plays a role in maintaining genome stability and survival of the pathogen. A number of DNA glycosylases are involved in the BER pathway, including formamidopyrimidine (Fpg), Endonuclease VIII (Nei) and Endonuclease III (Nth), which are the initial enzymes responsible for recognition and excision of damaged DNA bases. It was previously demonstrated by the Wits node that combinatorial deletion of Nth and two Nei homologues in *M. smegmatis* resulted in reduced survival under oxidative stress conditions with a corresponding increase in mutation rates, suggestive of interplay between these enzymes. To understand the molecular basis of this interplay, the individual effects of the Nei homologues (NeiI and NeiII), together with Nth on survival and mutagenesis under oxidative stress conditions were further investigated. Deletion of *nth* combined with the *neiII* homologue led to reduced survival under oxidative stress conditions and an increase in spontaneous mutagenesis to rifampicin when compared to the deletion of *nth* combined with the *neiI* homologue. To further unravel the mechanistic basis of these observations, DNA replication was monitored in real-time. This analysis revealed that the deletion of Nth, individually or in combination, resulted in stalling of the replication fork during DNA replication. Collectively, the data indicates that the *neiII* homologue has a greater role, together with the Nth DNA glycosylase, in maintaining mycobacterial genome integrity compared to the *neiI* homologue. These effects are being studied further.

In a new development, the Wits node participated in a collaborative study with researchers at Tsinghua University, focused on translational fidelity in mycobacteria. Modulation of translational fidelity is expected to result in metabolic plasticity that could lead to drug tolerance and the ultimate emerge of drug resistant variants. During protein biosynthesis, translation fidelity is maintained by ensuring the correct charging of tRNAs with the codon-specific cognate amino acids. For the case of glutamine and/or asparagine, this process entails a two-step mechanism that requires the glutamine amidotransferase, GatCAB. This study demonstrates that modulation of GatCAB activity results in mistranslation in *M. tb*, thus leading to drug tolerance with first line TB antibiotics. A forward genetic screen was designed based on two complementary gain-of-function reporters that

directly measured mistranslation to identify high mistranslator mutants. Initially, a reporter strain carrying a point mutation in the gene conferring kanamycin resistance was used to identify high mistranslator mutants of mycobacteria. The phenotypically resistant mutants were subsequently screened using a dual-luciferase assay to identify mistranslator strains specific for asparagine to aspartate. Following whole genome sequencing, SNPs were identified in the *gatA* gene that correlated with these observations. Moreover, clinical isolates of *M. tb* containing *gatA* SNPs were specifically associated with high mistranslation rates and rifampicin-specific phenotypic resistance. These mutations cause partial loss of the GatCAB holoenzyme, resulting in an increase in mistranslation rates. Using single-cell transcription dynamics it was demonstrated that reduced *gatCAB* expression results in elevated mistranslation rates. Collectively, these observations highlight a novel adaptation strategy that the tubercle bacillus uses to establish drug tolerant populations, which are required for the evolution of genetically stable drug resistance. These data were published in 2016 in *Nature Microbiology*, a new Nature Publishing Group journal.

Theme 2: Identification and characterization of differentially culturable tubercle bacteria (DCTB)

It has been demonstrated that sputum from TB patients harbours drug tolerant DCTB that are unable to grow on solid media but can be recovered in liquid media supplemented with resuscitation promoting factors, a group of bacterial growth stimulatory enzymes secreted by *M. tb*. The phenomenon was investigated further by the Wits node in a cross-sectional observational cohort of patients. This study involved assessment of sputum from TB patients for DCTB and the impact of exogenous culture filtrate (CF) supplementation ex vivo. It was demonstrated that in addition to culture filtrate dependent-DCTB, sputum from TB patients harbour a comparably significant proportion of resuscitation promoting factor-independent DCTB. Enhanced recovery of DCTB through supplementation of sputum cultures with culture filtrate improved bacterial detection in sputum smear negative TB patients that are generally difficult to identify using standard diagnostics. Sputum from TB-HIV-1 infected individuals, with CD4 counts >200 cells/mm^3, displayed higher levels of culture filtrate-responsive organisms than sputum from TB-HIV-1 infected individuals with CD4 counts <200 cells/mm^3. This study represents the most comprehensive analysis of DCTB to date and reports the presence of phenotypically distinct bacterial subpopulations in TB diseased individuals. These findings have important implications for diagnosis of TB particularly in individuals with paucibacillary disease. Moreover, the quantitation of DCTB now provides a novel biomarker to assess treatment response and risk of disease recurrence. The data also provide preliminary microbiological evidence to validate the long-standing hypothesis that the host immune response to TB infection drives bacteria into phenotypically distinct, drug tolerant states. These results were published in the *American Journal of Respiratory Critical Care Medicine* (Impact Factor: 13.118) in 2016 and considering the importance of the finding, it was selected for an editorial piece (PMID: 27976945). The research was also selected for the Faculty of Health Sciences Research Prize, awarded to the most outstanding research in the Faculty of Health Sciences at Wits University.

Theme 3: Molecular diagnostics for TB

Due to the threat of bacterial drug resistance, more sensitive, reliable and rapid molecular diagnostic methods are now available for TB diagnosis. The GeneXpert MTB/RIF system is used for simultaneous identification of infection and rifampicin resistant *M. tb*. This system for TB detection was adopted by the South African National Department of Health and is also being used in over 40 countries worldwide. Previously, the Wits node of the CBTBR streamlined the production of verification controls for GeneXpert MTB/RIF, which allowed for the rollout of this diagnostic to all provinces in South Africa and has changed the way TB is diagnosed globally. The method involved

the creation of bacteria that mimic those that cause TB disease (this approach is known as bio-mimicry). As an expansion of this approach, the CBTBR has now undertaken a new project that uses the same methodology to create verification standards to detect resistance to other TB drugs in response to the projected rollout of new molecular TB diagnostics that detect composite forms of drug resistance. Many of these reagents were successfully created in 2016 and are now being field tested for stability and robustness.

In another new project, through collaboration with Dr. Bertozzi at Stanford University, the Wits node of the CBTBR is testing novel fluorogenic trehalose derivatives for the rapid and easy detection of TB infection. The probe to be used is a solvatochromic dye that only fluoresces when taken up by live mycobacterial cells and as such offers the possibility of a low signal to noise ratio. If successful, this approach will allow for the development of a smear-based tuberculosis diagnostic that can be easily scalable in resource limited, endemic settings**.**

Theme 4: Counter-screening models for TB drug development

As part of an MRC-SHIP funded project, the Wits node of the CBTBR developed counter-screening models for TB drug development. The aim of these endeavours was to provide drug development consortia with the ability to screen potentially interesting compounds under conditions that more closely mimic the human host. In 2016, the Wits node continued to provide these platforms in collaborative studies. In this regard, the Wits node undertook to test several phosphino palladium and platinum containing compounds for anti-mycobacterial activity. These analyses were carried out in partnership with Prof. Meyer from the University of Pretoria and the results were published in *Biometals* in 2016.

Joint Research and Training activities

Wits – SU

The WITS node is collaborating with the SU node on DCTB and these bacterial populations are being investigated against the background of the recent PET/CT findings of continued lung inflammation in patients at the end of clinically curative TB treatment. A post-doctoral fellow from SU, Dr. Beltran, received training at the WITS node for this culture technique and is applying this technique in clinical situations like at the end of TB treatment on induced sputum or broncho alveolar lavage fluid to evaluate the presence of live but conventionally not culturable *M.tb*. She is also applying this technique in clinical forms of TB where it is known that *M.tb* is difficult to culture, including spinal TB, ocular TB, TB meningitis and TB pericarditis.

UCT – SU

The joint SU-UCT bacterial flow cytometry forum continued to meet every 4 months to discuss ongoing work and related research in the field. This is co-organised by Dr. Mouton (SU), Prof. Sampson (SU), Mr. Reiche (UCT) and Prof. Warner (UCT). Prof. Mizrahi and Dr. Mukherjee (UCT) collaborated with Prof. Tabb (SU) on the data analysis of a proteomics study. The Host-Pathogen Mycobactomics group also collaborates closely with Prof. Blackburn and Dr. Soares from the Applied & Chemical Proteomic Group at the University of Cape Town as well as Dr. Mare Vlok from the Proteomics Laboratory of the Central Analytical Facility of Stellenbosch University. These collaborations focus heavily on advanced quantitative mass spectrometry-based proteomic approaches to characterize the proteomes of clinical *M. tb* isolates and the interaction of *M. tb* with its host. Numerous other collaborative studies involving TB researchers from UCT and SU are currently in progress. These are across various disciplines and are not funded by the CoE and are therefore not reported here. In an initiative led by Prof. Ruth McNerney from the Lung Infection and

Immunity Unit at UCT, and supported the establishment of the Western Cape Acid Fast Club as a forum for bringing researchers from across the region together to share ideas and build new research networks. Two meetings of the WCAFC were held in 2016, the first at UCT and the second at SU.

2. EDUCATION AND TRAINING

Breakdown of postgraduate students and postdoctoral fellows in the CBTBR in 2016

Student Category	Number / Percentage	Target based on SLA4 (for Extension Phase 2014-2018)
Total number of students	127	≥ 35
% Postdoctoral fellows	28%	≥10%
% PhD students	30%	N/A
% MSc students	28%	N/A
% BSc (Hons) students	13%	N/A
% Women students*	59%	≥ 50%
% Black students*	54%	≥ 50%

***Includes postdoctoral fellows**

Degrees conferred and postdoctoral fellowships completed

The CBTBR graduated 13 PhD, 19 MSc and 17 BSc (Hons) students in 2016.

Recruitment of new postgraduate students

A number of new students have joined the team during the course of 2016. At the SU node, for 2016 including the new students, 22 Postdoctoral fellows, 34 PhD students, 38 MSc students and 17 BSc (Hons) students were registered. At the UCT node a total of 4 Postdoctoral fellows, 1 MSc student and 3 BSc (Hons) students we registered. The Wits node registered 3 Postdoctoral fellows, 3 MSc students and 2 BSc (Hons) students for 2016.

Honours and awards to staff and students

- Prof. Kana was appointed to Board of Reviewing Editors of *eLife* - an open access journal established in 2012 by the Howard Hughes Medical Institute, Max Planck Society, and Wellcome Trust.
- Prof. Kana was appointed as a Research Associate at the Centre for AIDS Prevention Research in South Africa (CAPRISA).
- Prof. Kana was awarded a First-time Inventor's Award by Wits Enterprise for developing globally marketable diagnostic reagents for TB.
- Prof. Kana was awarded the First-time Innovator's Award for licensing his products to a Wits spinoff company, SmartSpot Quality Check.
- Prof. Kana and Dr. Gordhan were recognized for the outstanding research contribution and achievement at the Health Sciences Research Awards Breakfast on the 19th August 2016.
- Prof Mizrahi was elected as a Fellow of the African Academy of Sciences.
- Prof. Mizrahi appointed to the Editorial Advisory Boards of *Cell Chemical Biology*, *ACS Infectious Diseases, ACS Central Science* and *Genome Medicine*.
- Mr. Senzani won first prize for an oral presentation by a student in the Infectious Diseases Track at the Health Sciences Research Day and Postgraduate Expo 2016.

- Ms. Narrandes won first prize for an oral presentation by a student in the Molecular and Comparative Biosciences Track at the Health Sciences Research Day and Postgraduate Expo 2016.
- Dr. Singh won the UCT Faculty of Health Sciences *2015 Best Publication Award in the Basic Laboratory Sciences* for his paper published in *Chemistry & Biology.*
- Mr. Ralefeta won third prize for an oral presentation from the Faculty of Health Sciences at the Wits Annual Cross-Faculty Symposium.
- Dr. Chengalroyen was awarded a travel grant from the MRC Soweto Matlosana Collaborative Centre for HIV/AIDS & TB (SoMCHAT).
- Ms. Papadopoulos won the second prize for best oral presentation at the Molecular Biosciences Research Thrust, University of the Witwatersrand. 8 December 2016.
- Mrs. McIvor won second prize for the best poster presentation at the Molecular Biosciences Research Thrust, University of the Witwatersrand. 8 December 2016.
- Ms. Narrandes won third prize for the best poster presentation at the Molecular Biosciences Research Thrust, University of the Witwatersrand. 8 December 2016.
- Whitfield MG received HD Brede Award for Tuberculosis Research (Best Biomedical Research Publication) from Stellenbosch University 2016.
- Haylett W received ATPAF1 and SEPT9 are novel protein substrates of Parkin, 2nd Prize for poster presentation from Conference Organization Committee of the 11th Annual Meeting of the Genetic Epidemiology of Parkinson's Disease Consortium and the 3rd International Parkinson's Disease Symposium 2016.
- Pule C received WhiteSci Scientific Travel Award from Whitehead Scientific 2016.
- Pule C received International Scientific Travel Award from Stellenbosch University, RDSD 2016.
- Pule C received South African Women in Science Award: TATA Doctoral Scholarships category from TATA AFRICA and DST 2016.
- Bardien S received Stellenbosch University Vice-Rector Award for outstanding research outputs for 2014/2015 from Stellenbosch University 2016.
- Prof. Sampson completed the Postgraduate Diploma in Leadership Development at University of Stellenbosch Business School in 2016.
- Gina Leisching received a Bill and Melinda Gates Foundation Global Health Travel Award in 2016.
- Gina Leisching received a Travel Grant - Faculty of Medicine and Health Sciences in 2016.
- Caroline Pule received a Harry Crossley Foundation Research Project Funding Award, RDSD, Stellenbosch University (SU) December 2016.
- Andile Ngwane received an MRC Career Development Award.
- MSc student Rendani Mbau was awarded prestigious Master's scholarships from both the SAMRC and the NRF. Rendani is working under the supervision of Digby Warner on the use of forward genetic screens to investigate mechanisms of vitamin B_{12} transport and assimilation in *M. tuberculosis*.
- MSc student Ryan Dinkele was awarded a prestigious David and Elaine Potter Fellowship and Oppenheimer Memorial Trust scholarship. Ryan is also working under the supervision of Digby Warner.
- PhD student Bianca Masuku was awarded a SAHUDA-NIHSS Doctoral scholarship.
- MSc student Bevika Sewgoolam was awarded an NRF Masters Innovation Scholarship

- PhD student Amanda Mabhula was appointed as a member of the Golden Key Honour Society

Training courses implemented by staff and students

- Prof. Warner served as Co-Convenor of the BMedSc (Hons) programme, Faculty of Health Sciences, UCT.
- Prof. Warner served as Convenor, *Laboratory Research Methods* module of the BMedSc (Hons) programme, Faculty of Health Sciences, UCT. Prof. Warner and Dr. Joanna Evans lectured students taking this course.
- Prof. Warner served as Convenor of the *Bacterial Pathogenesis* module of the Infectious Diseases and Immunology Honours Programme in the Faculty of Health Sciences, UCT. Prof. Warner and Dr. Evans lectured in this course.
- Prof. Warner served as Convenor of the *Bacteriology* module of the Intercalated MBChB programme in the Faculty of Health Sciences, UCT. Prof. Warner also lectured in this course.
- Prof. Warner presented the *Tuberculosis* module in the *Defence and Disease* programme in the Department of Molecular and Cell Biology, Faculty of Science, UCT.
- Dr. Gordhan taught molecular diagnostics and basic bacteriology in the second-year Bioengineering Degree at Wits University.
- Prof. Kana gave delivered lectures on Recombinant DNA and Proteins and Gene Manipulation to the Registrars in 2016 (ANAP7000).
- Prof. Kana delivered a two-week lecture series on mycobacteria to the Honours Students in the Molecular Medicine and Haematology Department.
- Both Prof. Kana and Dr. Gordhan taught in the Bachelor of Health Sciences – 3rd Year Molecular Basis of Disease course.
- Prof. Tabb taught / presented R/Bioconductor Proteomics Workshop In-person multi-institutional training workshop in 2016.
- Prof. Kuivaniemi taught / presented a NIH Grants Writing Workshop RGMO, FMHS, SU Bellville in 2016.
- Prof. Miller taught / presented 2016 Wildlife Medicine Clinical Techniques Training Course Southeast Asian Zoo Veterinary Association Sandakan in 2016.
- Prof. Miller taught / presented Taipei Zoo Megavertebrate Training Worskhop Southeast Asian Zoo Veterinary Association Taipei in 2016.
- Prof. Tabb taught / presented Annual Conference of American Society for Mass Spectrometry Prof. Tabb and two American scientists San Antonio, TX in 2016.
- Prof. Tabb Tromp taught / presented Honours for Div. Molecular Biology and Human Genetics Division of Molecular Biology and Human Genetics Cape Town in 2016.
- NL Kriel taught BSc (Hons) molecular biology and human genetics class 2016 Protein Practical Course, Cape Town in 2016.
- Lennart Martens, Kathryn Lilley and David Tabb taught / presented Advanced topics in Proteome Informatics Cape Town in 2016.
- Dr. Jackson taught / presented Laboratory basics Stellenbosch University Cape Town in 2016.
- Prof. Tabb taught / presented R/Bioconductor Proteomics Workshop In-person multi-institutional training workshop in 2016.
- Prof. Sampson co-ordinated and taught the Mycobacteriology module for the BSc Hons Course.

- Prof. Warren taught the Practical training course on DNA fingerprinting: BSc Honours Practical Course 2016 Cape Town, (six days).
- Dr. Streicher and Mrs van Aarde taught a 3 Month training in DNA fingerprinting, Spoligotyping, DNA extraction and MIRU Typing – Abraham Tesfaye (Ethiopia). August to Oct 2016.
- Dr. Dippenaar trained Melissa Dalcina Chengalroyen, WGS analysis, University of Witwatersrand 25 - 29 July 2016.
- SU-IRG Presented and demonstrated the FACSCanto II at the Open day at the BD-CAF Flow Cytometry Centre, 09 March 2016.
- SU-IRG offered 2-day training to two students from Industry (Synexa), 1-2 June 2016.
- SU-IRG offered 4-day training to two students from UKZN, 2-5 August 2016.
- SU-IRG organized a 2-day GCP course (presented by CREDE) for all community recruiters, 24-25 August 2016.
- Ms. Du Plessis visited the Wigneshweraraj lab at Imperial College, London for 3 months in 2016

Training courses attended by staff and students

- Prof. Digby Warner and Michael Reiche (PhD student) from the UCT node, visited the Howard Hughes Medical Institute, Janelia Research Campus (USA) from 6-17 June under the auspices of the HHMI Visiting Scientist Program having been selected through a highly competitive process. They were hosted by Dr Teng-Leong Chew and Dr Jesse Aaron at the Advanced Imaging Centre and spent the time at Janelia learning about superresolution 3D PALM imaging and applying this state-of-the-art advanced imaging to mycobacteria.
- Michael Reiche attended the 1st International Global Bioimaging training courses for Core Facility Staff on “Challenges in Image Data Management and Analysis” as well as “Management and Operation of Imaging Core Facilities” from 13-18 November 2016 at the European Molecular Biology Laboratories, Heidelberg (Germany).
- Mr. Sibusiso Senzani visited EPFL in Lausanne, Switzerland for one month in 2016.
- Dr. Julian Peters visited Vanderbilt University, USA for ca. 6 weeks in 2016.
- Dr. Dippenaar attended the Molecular and Genetic Epidemiology course, hosted by McGill Summer Institute in Infectious Diseases and Global Health, 20 – 24 June 2016.
- Dr. De Vos attended the Advanced TB Diagnostics course, hosted by McGill Summer Institute in Infectious Diseases and Global Health, 20 – 24 June 2016.
- Ealand, C. MRC 10th Early Career Scientific Convention, SAMRC Head Office, Conference Centre, Parow, Cape Town, 19 – 20th October 2016.
- Papadopoulos, A.O. MRC Research and Capacity Development Presentation Skills Workshop, Indaba Hotel and Spa, Fourways, Johannesburg, 8 March 2016.
- Papadopoulos, A.O. MRC Research and Capacity Development Systematic Review Workshop, 4 August 2016.
- McIvor, A. MRC Research and Capacity Development Presentation Skills Workshop, Indaba Hotel and Spa, Fourways, Johannesburg, 8 March 2016.
- McIvor, A. Workshop: MRC Systematic Review Workshop, 4 August 2016.
- Senzani, S. Workshop: MRC Research and Capacity Development Presentation Skills Workshop, Indaba Hotel and Spa, Fourways, Johannesburg, 8 March 2016.
- Narrandes, N. Workshop: MRC Research and Capacity Development Presentation Skills Workshop, Indaba Hotel and Spa, Fourways, Johannesburg, 8 March 2016.

- Narrandes, N. Workshop: MRC Research and Capacity Development/Cochrane Institute Systematic Reviews Workshop, 4 August 2016.
- Ealand, C. Faculty of Health Sciences Emergent Researchers Writing Retreat, University of the Witwatersrand, The Philip V Tobias Health Sciences Building, 5, 12 and 19th May 2016.
- Maphatsoe, M. Faculty of Health Sciences MSc and PhD writing retreat, University of the Witwatersrand, The Philip V Tobias Health Sciences Building, 7- 10 November 2016.
- Chengalroyen, M. Retreat: Faculty of Health Sciences Postdoctoral writing retreat, University of the Witwatersrand, The Philip V Tobias Health Sciences Building, 16-18 August 2016.
- Chengalroyen, M. Retreat: Faculty of Science writing retreat, University of the Witwatersrand, APES museum, 22-25 November 2016.
- Narrandes, N. Retreat: Faculty of Health Sciences MSc and PhD writing retreat, University of the Witwatersrand, The Philip V Tobias Health Sciences Building, 1-2 August, 4-5 August 2016.
- Narrandes, N. Retreat: Faculty of Health Sciences MSc and PhD writing retreat, University of the Witwatersrand, The Philip V Tobias Health Sciences Building, 1-4 November 2016.
- Roos EO attended Molecular and Genetic Epidemiology 2016.
- Kleynhans L attended NIH/ICSSC Study Design and Statistics Training 2016.
- Kleynhans L attended Good Clinical Practice and Informed Consent Training (GCP)2 016.
- N du Plessis attended Project Management 2016.
- Whitfield MG attended GCP Basic Course 2016.
- Sylvester TT attended Writing a Literature Review 2016.
- Jackson J, attended GCLP 2016.
- Palmer Z attended Good Clinical Laboratory Practice 2016.
- M. Williams and J Arries attended Proteomics Data Analysis in R Workshop 2016.
- J Arries attended Proteomics Data Analysis in R Workshop 2016.
- Palmer Z attended Good Clinical Practice 2016.
- Palmer Z attended Biobanking 2016.
- Palmer Z attended Introduction to Research Ethics 2016.
- Haylett W attended Bioinformatics analysis and annotation of variants in NGS data 2016.
- Haylett W attended Proteomic data analysis in R 2016.
- Borrageiro G attended Whole transcriptome data analysis 2016.
- Warren RM attended Senior Management Training 2016.
- Tshivhula H, Ronacher K, Kleynhans L, Prins N, and Shabangu A attended Good Clinical Practice and Informed Consent Training 2016.
- Naidoo CC attended Approaches to Microbiome Data Analysis Course 2016.
- Venter R attended Short course on R 2016.
- Naidoo CC attended Good Clinical Laboratory Practice Training 2016.
- Reeve B attended Good Clinical Laboratory Practice 2016.
- Tshivhula H, Klazen J and Sechaba M attended Article Writing 2016.
- Reeve B attended Nucleic Acid Preparation, QC and Library building for Next Generation Sequencing 2016.
- Kitchin N attended Project Management for the Research Team 2016.
- Kitchin N attended Biobanking workshop 2016.
- Venter R attended Fire Marshall Training 2016.
- Reeve B attended First Aid level 1 2016.

- Kitchin N attended Nucleic Acid Preparation, QC and Library building for Next Generation Sequencing 2016.
- Kitchin N attended SHE Representative Basics 2016.
- Kitchin N attended Good Clinical Practice 2016.
- Tshivhula H, Prins N, May T, Selamolela M and Zvinairo K attended Good Clinical Practice: Beginner's Course 2016.
- Kitchin N attended Good Clinical Laboratory Practice 2016.
- Derendinger B attended GCLP 2016.
- Bardien S, Haylett W, Neethling A, Borrageiro G, Oluwole OG. Sebate B and Stemmet M attended Introduction to Scientific Writing Skills 2016.
- Derendinger B attended Short course on R 2016.
- Mujuru TN attended Nucleic Acid Preparation, QC and Library building for Next Generation Sequencing 2016.
- Mujuru TN attended Research protocol writing workshop 2016.
- Mujuru TN attended MS Word for large documents 2016.
- Pule C attended Statistical methods using R 2016.
- Pule C attended Young Women Leadership Workshop 2016.
- Pule C attended Systematic Review Workshop 2016.
- Bibi Sebate attended Introduction to Scientific Writing Skills 2016.
- Bibi Sebate attended Workshop in Scientific Writing for Thesis and Dissertations 2016.
- Bibi Sebate attended Harry Crossley Protocol Writing Workshop 2016.
- Bardien S and Stemmet M attended Biorepository Workshop 2016.
- Bardien S attended Project management workshop 2016.
- Stemmet M attended Workshop in scientific writing skills for research proposals 2016.
- Stemmet M attended Writing a successful NIH research grant 2016.
- Oluwole OG attended Scientific Writing Skills: The research proposal and ethics application 2016.
- Oluwole OG attended QC of samples and library preparations of DNA samples for NGS 2016.
- Oluwole OG attended International Brain Research Organization School in Neuropsychiatric Genomics 2016.
- Warren RM attended RESeqTB meeting 2016.
- Eileen Hoal, Marlo Möller, Craig Kinnear, Sihaam Boolay, Brigitte Glanzmann and Janice Theys attended Good Clinical Practise and Informed Consent Training Sponsored by the Division of Microbiology and Infectious Disease, NIAID, NIH (Cape Town, September 2016).
- Victoria Cole attended the Confocal Microscopy Course presented by the Central Analytical Facility, Stellenbosch University (Spetember 2016).
- Zama Mahlobo attended Workshop in Scientific Writing Skills for Theses and Dissertations 2016.
- Zama Mahlobo attended R/Bioconductor Proteomics Workshop In-person multi-institutional training workshop by Tabby DL 2016.

Online Courses

- Kleynhans L attended NIH Protecting Human Research Participants offered by NIH Web-based training course 2016.
- Tshivhula H attended NIH Web-based training course 'Protecting Human Research Participants'. offered by https://phrp.nihtraining.com/users/login.php 2016.

Exchange Visits

- Visser H visited Siouxsie Wiles at University of Auckland in New Zealand in 2016.
- Neethling A visited Prof Francois van der Westhuizen, Ms Hayley van Dyk, Mitochondrial lab at North West University in South Africa in 2016.
- Oluwole OG visited SIREN and Neurogenetics Lab at Obafemi Awolowo University in Nigeria in 2016.
- Eileen Hoal, Marlo Moller and Craig Kinnear (TB Host Genetics) were visited by: Dr. Brenna Henn, Assistant Professor, Dept. of Ecology and Evolution, Stony Brook University, New York, USA 5-30 June 2016.
- TB Host Genetics hosted Erwin Schurr, James McGill Professor, Medicine and Human Genetics, McGill University, Montréal, Canada, 1-14 December 2016.
- Haiko Schurz visited the Departement of Ecology and Evolution, Stony Brook University, New York (November 2016).
- Carine Soa Emani 2016 - Novartis-CRG Africa Mobility Grant for 6-months, Barcelona Spain

Conferences / Symposia Organised

- Prof. Mizrahi served as a co-organiser of TB2016, a conference arranged under the auspices of the International AIDS Society (IAS) and held in Durban of 16-17 July, immediately before the AIDS 2016 conference. This conference brought together more than 900 participants representing the areas of basic, clinical, translational and operational and implementation research, with advocates and those involved TB control programmes. This was the first satellite conference of the IAS AIDS conference dedicated to TB, and based on the very positive response, this will become a standard fixture in future IAS conferences. Importantly, TB2016 also served as the fourth South African TB Conference. (http://www.tb2016.org/Conference/About-TB2016).
- Prof. Mizrahi served on the International Organising Committee of the Institut Pasteur International Network Symposium on Biomarkers, which was held at the Institut Pasteur in Paris in December 2016.
- Prof. Kana served on the committee for the Faculty of Health Sciences Research Day and Postgraduate Expo 2016.
- Prof. Walzl hosted the start-up meeting for the EDCTP-funded Screen TB project in April 2016, attended by EU and African delegates.
- Prof. Walzl and SATVI hosted a GC6 project annual meeting in Cape Town, attended by US, EU and African delegates.

3. KNOWLEDGE BROKERAGE

The operational environment

All three nodes are actively involved in the sharing of knowledge amongst researchers within the CBTBR through lab meetings held at least weekly. Journal Club meetings, held weekly at the three sites, also provide an opportunity to share broader-based scientific issues and ideas within the field of biological sciences within and beyond CoE hosting institutions. Team members, staff and students also attend numerous local and international conferences, often as invited speakers, where

they shared their work with the international community. Regular meetings with the relevant health authorities, such as the Western and Eastern Cape Departments of Health, to share findings and

Knowledge translation to stakeholder groups

CBTBR members were involved in numerous public awareness activities countrywide in 2016:

Science communication, outreach activities, public awareness, public engagement, and publicity

- Prof. Mizrahi was interviewed by the Treatment Action Group (TAG, New York) on the state of global TB R&D investment, TAG Report 2016, and was quoted in this report.
- Dr. Joanna Evans assisted with facilitating the Biology Workshops conducted by the Eh! Woza public engagement programme, with the aim of educating learners aged 15 – 17 from Khayelitsha, Cape Town, about the intricacies of biomedical TB research, specifically TB drug discovery.
- Prof. Warner participated in a series of workshops in 2016 that were aimed at equipping Postdoctoral Fellows at UCT with the skills necessary to supervise postgraduate students.
- Prof. Warner and several members of the UCT node contributed to a series of interactive workshops organized by CBTBR alumnus, Dr. Anastasia Koch, and aimed at exposing learners from Ikamva Youth to current research programmes at UCT around HIV and TB through lectures, tutorials, and practicals.
- Members of the Wits node participated in the University open and exhibition days. They created and manned an exhibit to profile the work done at the CBTBR.
- In March 2016, Prof. Kana served as a judge for the 2015 (to be awarded in 2016) edition of the Discovery Health Journalism Awards. He reviewed health related journalism in different categories, including television, radio, print media and trade publications. He provided feedback to journalists regarding reporting style and made recommendations to improve health reporting in these sectors. Prof. Kana was also invited to attend the awards function on the 25th May 2016, where presentations were made to the journalists with winning entries.
- On World TB Day 2016, members of the Wits node participated in the Unmask Stigma Campaign aimed at reducing the stigma associated with TB-HIV. Students won a prize for their photographs posted on social media.
- Dr. Mouton and Prof. Sampson published a piece in an online news website, “The Conversation”, which was followed up by invitations for television and radio interviews (eNews (Dr. Mouton), Cape Talk Radio (Dr. Mouton), UNISA radio (Dr. Mouton and Prof. Sampson).
- SU-IRG Participated “Living the Legend” event, organized by Food for life Cape Town. The group collected funds and cooked food in Philippi to serve approximately 200 people, 23 July 2016.

4. NETWORKING

Networks and linkages

The three nodes of the CBTBR are involved in wide collaborative networks that involve TB researchers and research institutions in a large number of countries. Maintaining existing collaborative networks and developing new linkages is of critical importance to the CBTBR. For this reason, members continued to devote significant time and effort to networking.

International Collaborators

CoE Primary Contact	CoE Node	Collaborating Partner	Institution	Research Area	Country in which collaborating institution is based
Prof. Sampson	SU	Dr. Mardassi	Institut Pasteur de Tunis	Characterisation of LAM evolutionary history (2007-present).; Determining the role of PPE_MPTR proteins in TB pathogenesis: functional and computational analysis	Tunisia
Prof. Sampson	SU	Dr. Bitter	Vrije Universiteit	The trafficking of the *M. tuberculosis* PE and PPE proteins (2006 – present). ESX secretion in Beijing genotype strains	Netherlands
Prof. Warren	SU	Dr. Supply,	Institut Pasteur Lille	Evaluation of hypervariable VNTR regions for the discrimination of Beijing genotype strains	France
Prof. Warren	SU	Dr. Horseburgh	Boston University	Deep sequencing for fluoroquinolone resistance	USA
Prof. Warren, Dr. Streicher	SU	Prof. Gagneux	Swiss TPH, Basel	Collaboration on genome sequencing of clinical strains of *M. tuberculosis*	Switzerland
Prof. Warren, Dr. Streicher, Dr. de Vos	SU	Prof. Wangh and Prof. Kreiswirth	Brandis University, HPRI,	Evaluation of LATE PCR for the detection of resistance to first and second-line anti-TB drugs.	USA
Prof. Warren	SU	Prof. Kreiswirth	HPRI	Whole Genome Sequencing of NTMs	USA
Prof. van Helden	SU	Dr. Barry III, Dr. H Boshoff	Tuberculosis Research Section, Laboratory of Host Defenses, National Institute of Allergy & Infectious Diseases, NIH, MD	Ongoing collaboration on the HIT-TB project	
Prof. Walzl	SU			TB treatment response project	USA
Prof. Ronacher, Dr. Kleynhans	SU	Prof. Restrepo	University of Texas	ALERT: Altered endocrine axis during type 2	USA

				diabetes and risk for tuberculosis	
Prof. Ronacher, Dr. Kleynhans	SU	Prof. Schlesinger	Ohio State University	ALERT: Altered endocrine axis during type 2 diabetes and risk for tuberculosis	USA
Prof. Walzl, Dr. du Plessis, Dr. Loxton, Dr. Beltran and Dr. Fang	SU	Prof. Belisle	Colorado State University	Biosignatures/ICIDR:	USA
Prof. Walzl, Dr. Loxton	SU	Prof. Kaufmann	Max Planck IIB	TBVac	Germany
Prof. Walzl	SU	Prof. Dockrell	LSHTM	TBVac	United Kingdom
Prof. Ronacher, Prof. Walzl	SU	Prof. Dockrell	LSHTM	TANDEM – Concurrent Tuberculosis and Diabetes	United Kingdom
Prof. Walzl, Dr. Loxton and Dr. Chengou	SU	Prof. Ottenhoff	Leiden University	Ongoing collaboration of biomarkers for TB diagnostics	Netherlands
Prof. Warren	SU	Prof. Sterling	Vanderbilt University Tuberculosis Center	Fluoroquinolone resistance	USA
Prof. Warren, Dr. Streicher	SU	Prof. Murray	Florida University Harvard / Broad institute	Various project including the evolution of XDR-TB strains; other mechanisms of drug resistance (in addition to genomic mutations); mechanisms of resistance to 2nd line drugs; strain fitness; certain strain families may have both increased fitness and increased potential for acquiring drug resistance.	USA
Prof. Warren, Dr. Streicher	SU	Dr. Jacobson	Harvard University	1) GIS of drug resistant TB in the Western Cape	USA
Prof. Warren, Dr. Streicher	SU	Dr. Jacobson	Harvard University	2) Health systems reserach	USA
Dr. Smith, Prof. Warren	SU	Prof. McNerey	LSTHM	Whole genome sequencing of drug resistant M. tuberculosis strains	United Kingdom
Prof. Sampson, Prof. Warren	SU	Prof. Anab Pain	KAUST	Whole Genome Sequencing of Mycobacterial Species	Saudi Arabia

Prof. Hoal van Helden	SU	Prof. Erwin Schurr	McGill University	Genetic epidemiology.	Canada
Prof. Hoal van Helden	SU	Prof. Abel & Prof. Alcais	INSERM / Université	Analysis of genetic epidemiology.	France
Prof. Hoal van Helden	SU	Prof. Casanova	Rockefeller University	Human genetics of TB resistance in HIV-infected persons	USA
Prof. Hoal van Helden	SU	Prof. Fitzgerald	Weill Cornell	Human genetics of TB resistance in HIV-infected persons	USA
Prof. Hoal van Helden	SU	Prof. Geissmann	MSKCC (Sloan Kettering)	Human genetics of TB resistance in HIV-infected persons	USA
Prof. Hoal van Helden	SU	Prof. Glickman	MSKCC (Sloan Kettering)	Human genetics of TB resistance in HIV-infected persons	USA
Prof. Hoal van Helden	SU	Prof. Barreiro	University of Montreal	Human genetics of TB resistance in HIV-infected persons	Canada
Prof. Hoal van Helden	SU	Dr. Price	Harvard School of Public Health	Computational assistance with analysis of admixture mapping.	USA
Prof. Hoal van Helden	SU	Dr. Henn	Stony Brook University	Population Ancestry genetic determinations.	USA
Prof. Hoal van Helden	SU	Dr. Capelli	Oxford University	Population Ancestry genetic determinations.	United Kingdom
Prof. Hoal van Helden	SU	Prof. Schreiber, Dr. Nebel, Dr. Franke	Christian-Albrechts University	Investigation of candidate genes in TB.	Germany
Prof. Hoal van Helden	SU	Dr. Gignoux	Stanford University	Population Ancestry genetic determinations.	USA
Prof. Warren, Dr. Streicher, Prof. Theron	SU	Dr. Metcalfe	University of South Florida	Deep sequencing to identify heteroresistance	USA
Prof. Warren, Dr. Streicher, Prof. Theron	SU	Prof. Engelthaler	Translational Genomics Research Instituite (Tgen)	Deep sequencing to identify heteroresistance	TSA
Prof. Warren, Prof. Tromp	SU	Prof. van Rie,	UNC - Gillings School of Global Public Health	Evaluation of the Xpert MTB/RIF test.	USA
Prof. Sampson	SU	Prof. Wigneshweraraj	Imperial College London	The identification of novel inhibitors of RNA polymerase in *Mycobacterium tuberculosis*	United Kingdom
Prof. Sampson	SU	Dr. Massey	University of Bath	GWAS of M. tuberculosis strains	United Kingdom
Prof. Warren, Dr. Streicher	SU	Prof. Rastogi	Pasteur Institute	Spoligotyping TB in Africa	France
Dr. Baker, Prof. Wiid	SU	Dr. Carolis	Centre for Genomic Regulation	Screening for Ergothioneine specific anti-TB drugs	Spain

Dr. Kinnear, Dr. Möller	SU	Prof. Crow	University of Manchester	Identification of gene mutations that cause Primary Immunodeficiency Disorders.	United Kingdom
Dr. Kinnear, Dr. Möller	SU	Prof. Lung	University of Hong Kong	Identification of gene mutations that cause Primary Immunodeficiency Disorders.	China
Dr. Möller, Prof. Hoal van Helden	SU	Prof. van Furth	VU University Medical Center	Tuberculosis Meningitis	Netherlands
Dr. Möller, Prof. Hoal van Helden	SU	Dr. van der Kuip	VU University Medical Center	Tuberculosis Meningitis	Netherlands
Prof. Walzl, Dr. du Plessis, Dr. Loxton	SU	Dr. Reed	IDRI - Infectious Diseases Research Institute	ID-93 Vaccine	USA
Prof. Walzl, Dr. Loxton, Dr. Gutschmidt	SU	Dr. Grode	VPM - Vakzine Projekt Management	VPM1002 phase II vaccine trial	Germany
Dr. du Plessis, Prof. Walzl	SU	Dr. Dorhoi	MPIIB - Max Planck Institute for Infection Biology	Host-directed Therapy and MDSCS	Germany
Dr. du Plessis, Prof. Walzl, Dr. Kleynhans	SU	Dr. Lewinsohn	Ohio State University	MAIT cells	USA
Prof. Walzl, Dr. Loxton	SU	Dr. Macete	CISM - Centro de Investigação em Saúde de Manhiça	TESA	Mozambique
Dr. Loxton	SU	Dr. Chiodi	Karolinska Institute	Bcell phenotypes in TB and HIV	Sweden
Prof. Theron	SU	Prof. Segal	New York University	TB Microbiome	USA
Prof. Theron	SU	Dr. van denDriesche	Radboud University	TB Aerobiology	Netherlands
Prof. Theron	SU	Dr. McFall	Northwestern University	TB Diagnostics	USA
Prof. Theron	SU	Dr. Steingart	Cochrane Collaboration	Systematic reviews and meta-analyses	USA
Prof. Theron	SU	Prof. Nardell	Harvard University	TB infection control and transmission	USA
Prof. Mizrahi & Prof. Warner	UCT	Dr. Barry III and Dr. Boshoff	NIAID, NIH	TB drug discovery (HIT-TB consortium)	USA
Prof. Mizrahi	UCT	Prof. Cole	École Polytechnique Fédérale de Lausanne	TB drug discovery (MM4TB Consortium)	Switzerland
Prof. Mizrahi	UCT	Prof. Rizzi	University of Piemonte Orientale	TB drug discovery (MM4TB consortium)	Italy

Prof. Mizrahi	UCT	Prof. Mikusova	Comenius University Bratislava	TB drug discovery (MM4TB consortium)	Slovak Republic
Prof. Mizrahi	UCT	Prof. Blundell & Dr. Ascher	University of Cambridge	TB drug discovery (HIT-TB and MM4TB Consortia)	UK
Prof. Mizrahi	UCT	Dr. Pato & Gyorgy Keri	Vichem Chimie, Budapest	TB drug discovery (MM4TB consortium)	Hungary
Prof. Mizrahi	UCT	Drs. Lagrange and Mondesert	Sanofi-Aventis R&D	TB drug discovery (MM4TB consortium)	France
Prof. Mizrahi & Prof. Warner	UCT	Prof. McKinney & Dr. Dhar	École Polytechnique Fédérale de Lausanne	TB drug discovery (MM4TB Consortium); mutational mechanisms in mycobacteria	Switzerland
Prof. Mizrahi & Prof. Warner	UCT	Prof. Müller	Helmholtz Institute for Pharmaceutical Sciences	TB drug discovery focused on natural products	Germany
Prof. Mizrahi	UCT	Profs. Hung, Rubin & others	Broad Institute of MIT & Harvard, Harvard Medical School & Harvard School of Public Health	Factors mitigating TB drug efficacy (TB Gift consortium)	USA
Prof. Warner & Prof. Mizrahi	UCT	Dr. Woodgate	NICHD, NIH	The association between persistence and resistance in Mtb	USA
Prof. Warner	UCT	Prof. Russell	Cornell University	Drug permeation in Mtb	USA
Prof. Mizrahi, Dr. Evans & Prof. Warner	UCT	Prof. Rhee	Weill Cornell Medical College	Application of metabolomics in TB drug discovery	USA
Prof. Mizrahi & Dr. Warner	UCT	Profs. Schnappinger & Ehrt	Weill Cornell Medical College	In vivo phenotyping of Mtb mutants	USA
Prof. Warner & Prof. Mizrahi	UCT	Drs. Olsen & Young	Merck Research Laboratories	TB drug discovery (TB Drug Accelerator)	USA
Prof. Mizrahi & Prof. Warner	UCT	Prof. Wyatt, Dr. Green & Dr. Ray	University of Dundee	TB Drug discovery (HIT-TB consortium and TBDA)	UK
Prof. Warner & Prof. Mizrahi	UCT	Dr. Huwe	Bayer AG	TB drug discovery (TBDA)	Germany
Prof. Warner	UCT	Dr. Andrews	Stanford University	TB transmission	USA
Prof. Warner	UCT	Prof. Venclovas	Institute of Biotechnology, Vilnius	Homology modelling of DNA polymerases	Lithuania
Prof. Warner	UCT	Prof. Lamers	University of Cambridge	Enzymology of NA polymerases of mycobacterial origin	UK
Prof. Warner	UCT	Dr. Rock	Harvard School of Public Health	Replication fidelity in mycobacteria	USA
Prof. Mizrahi	UCT	Prof. Gordon	University of Oxford	Macrophage models of TB infection	UK

Prof. Warner	UCT	Dr. Mathema	Columbia University	Mtb genomics	USA
Prof. Mizrahi & Dr. Evans	UCT	Prof. Dowd	George Washington University	Targeting the CoA pathway for TB drug discovery	USA
Prof. Kana	Wits	Neeraj Dhar	École polytechnique fédérale de Lausanne	Single cell analysis of peptidoglycan remodelling and resuscitation in mycobacteria: Implications for TB disease.	Switzerland
Prof. Kana	Wits	Carolyn Bertozzi	Stanford University	Analysis of fluorogenic trehalose derivatives as diagnostic reagents for tuberculosis	USA
Prof. Kana	Wits	Sung Joon Kim	Baylor University	Compositional Analysis of peptidoglycan in mycobacteria	USA
Dr. Peters	Wits	Bryan Sheppard	Vanderbilt University	Characterization of differentially culturable tubercle bacteria in tuberculosis disease	USA

National Collaborators

CoE Primary Contact	CoE Node	Collaborating Partner	Institution	Research Area
Prof. van Helden	SU	Prof. Chibale and other members of H3D	H3D Drug Discovery & Development Centre, UCT	Ongoing collaboration on SATRII, HI-TB and H3-D TB drug discovery projects
Prof. Warren	SU	Prof. Wilkinson	CIDRI, IDM	Collaboration on sequence analysis of clinical strains of *M. tuberculosis*
Prof. van Hoal	SU	Prof. Wilkinson	CIDRI, IDM	Human genetics of TB resistance in HIV-infected persons
Prof. Warren, Dr. Streicher	SU	Dr. Cox	UCT	Evolution of drug resistance in HIV positive and negative individuals
Dr. Smith, Prof. Warren, Dr. Streicher	SU	Prof. Dheda	UCT	Molecular epidemiology of XDR-TB
Dr. Smith	SU			Whole genome sequencing of XDR-TB
Prof. Walzl	SU			Collaboration in diagnostic/biomarker project
Prof. Warren, Dr. Werely	SU	Prof. Christoffels	SANBI, UWC	Bioinformatic analysis of whole genome sequence data.Wet-lab testing of computationally identified inhibitors
Prof. Warren	SU	Dr. Ismail	NHLS	Drug resistant TB in South Africa
Prof. Warren	SU	Dr. Theron	Eben donges hospital, Worcester	New project on DOTS program on farms.
Prof. Warren	SU	Prof. Scott, Prof. Stevens	University of the Witwatersrand	Ongoing collaboration on the rollout of the GeneXpert diagnostic test and establishment of an external quality assurance system.

Prof. Warren	SU	Prof. Blackburn	IDM, UCT	Collaboration on lipidomic and proteomic analyses of *M. tuberculosis* strains
Prof. Warren, Prof. Sampson	SU	Prof. Mulder	CBIO, IDM, UCT	Collaboration on bioinformatic analysis of mycobacterial genomes and transcriptomes
Prof. Warren	SU	Dr. Chihota	Aurum Health	*M. tuberculosis* strain population structure in Africa.
Dr. Baker, Prof. Wiid	SU	Prof. Loots	North West University, Potchefstroom	Mouse Macrophage metabolome.
Prof. Warren	SU	Prof. Wright	NHLS Port Elizabeth	The diagnostic utility of FNAB
Dr. Baker, Prof. Wiid	SU	Dr. Haynes	North West University, Potchefstroom	Study novel artemisinins for antimycobacterial activity
Dr. Baker, Prof. Wiid	SU	Dr. Kruger	Chemistry, UKZN, Durban	Screen antituberculosis lead compounds
Prof. Warren, Dr. Streicher, Dr. De Vos	SU	Mrs. Dolby	NHLS , Green point	Collaborator provides routine samples.
	SU	Dr. Hesseling	SU	New collaboration to investigate genotype-immunological phenotype correlations in children.
Prof. Warren, Prof. Walzl	SU			Collaboration of developing a stool TB diagnostic
Prof. Ronacher, Dr. Kleynhans	SU	Prof. Jacobs	UCT	New collaboration to assess the impact of steroid hormones on protective immunity to *M. tb* in a mouse animal model.
Prof. Warren	SU	Dr. Walters	Department of Pediatrics and Child Health, Stellenbosch University	Improved detection of *M. Tb* by Xpert MTB/RIF in gastric aspirates and stool samples collected from children with suspected pulmonary TB.
Dr. Kinnear, Dr. Möller	SU	Dr. Esser	NHLS Immunology Unit, Tygerberg Hospital	Identification of gene mutations that cause Primary Immunodeficiency Disorders.
Dr. Möller	SU	Prof. Moosa	Dept. Medicine, SU	Investigating chromosome 22 genetic polymorphisms as risk factors for HIVAN in South African adults: a pilot case-control study
Dr. Möller	SU	Prof. van Toorn	Dept of Medicine, SU	Investigating susceptibility to tuberculous meningitis
Dr. Möller	SU	Dr. Solomons		
Prof. Walzl, Dr. Loxton, Dr.Chegou	SU	Kogie Naido	CAPRISA	Systems immunology project
Prof. Walzl, Dr. Loxton, Dr.Chegou	SU	Gavin Churchyard	Aurum Institute	Systems immunology project
Prof. Walzl, Dr.Loxton	SU	Prof. Hatherill	SA Tuberculosis Vaccine Initiative (SATVI), UCT	CORTIS: The Correlate of Risk Targeted Intervention Study
	SU	Prof. Scriba		
Prof. Walzl	SU	Prof. Scriba	SATVI, IDM, UCT	Ongoing collaboration on TB transmission
Prof. Walzl, Dr. Malherbe, Dr. Loxton	SU	Prof. Cotton	FamCru	CORTIS
Prof. Miller, Dr. Parsons	SU	Prof. Michel	Dept of Tropical Diseases,	Ongoing collaboration on TB diagnostics in buffalo and elephants

			University of Pretoria	
Prof. Miller, Dr. Parsons	SU	Dr. Cooper	Ezemvelo KwaZulu Natal Wildlife, KZN	Ongoing collaboration on TB test development in buffalo
Prof. Miller, Dr. Parsons	SU	Dr. Buss	South African National Parks - Kruger NP	Investigation of TB in rhinoceros, elephants, warthogs, lions, antelope
Prof. Miller, Dr. Parsons	SU	Dr. deKlerk-Loris	Office of the State Veterinarian, Kruger NP	Investigation of TB in rhinoceros, elephants, warthogs, lions, antelope
Prof. Miller, Dr. Parsons	SU	Dr. van Schalkwyk	Office of the State Veterinarian, Kruger NP	Investion of TB in rhinoceros, elephants, warthogs, lions, antelope
Prof. Miller, Dr. Parsons	SU	Dr. Foggin	Victoria Falls Wildlife Trust, Zimbabwe	Ongoing collaboration on TB in elephants and banded mongoose
Prof. Miller, Dr. Parsons	SU	Dr. Olea-Popelka	Colorado State University, Faculty of Vet. Med., USA	Long-term collaboration on TB projects in wildlife and zoonotic TB
Prof. Miller, Dr. Parsons	SU	Dr. Patterson	Royal Veterinary College, UK	Investigation of TB detection in meerkats
Prof. Miller, Dr. Parsons	SU	Dr. Ro, Dr. Bakere Austerman	National Veterinary Services Laboratory, USA	Collaborating on determining WGS on animal TB isolates
Prof. Miller, Dr. Parsons	SU	Dr. Lane	National Zoological Gardens of Pretoria	Collaboration on pathological changes associated with TB infection in wildlife species
Prof. Miller, Dr. Parsons	SU	Dr. Lyashchenko	Chembio Diagnostic SystDr Lizma Streicher, Inc, USA	Investigation of rapid serological tests for wildlife TB
Prof. Sampson	SU	Prof. Malan	School of Pharmacy, UWC	Investigating the Potential Anti-mycobacterial Effect of Novel Polycyclic Compounds on *Mycobacterium tuberculosis*
Prof. Sampson	SU	Dr. Dube	School of Pharmacy, UWC	Assessing the anti-mycobacterial and immuno-modulatory effect of nanoparticles
Prof. Sampson	SU	Prof. Wolfaardt	Stellenbosch University Water Institute	Mycobacterial persisters and biofilms
Dr. Baker, Prof. Wiid	SU	Prof. Chibale	Chemistry, UCT	Ongoing collaboration on TB drug discovery projects
Dr. Baker, Prof. Wiid	SU	Prof. Afolayan	Faculty Science and Agriculture, Fort Hare University	Identify anti-TB compounds from traditional herbal extracts
Dr. Baker, Prof. Wiid	SU	Prof. Kruger	Dept. of Chemistry, UKZN	Development of anti-TB compounds
Dr. Kinnear, Dr. Möller	SU	Dr. Loos	SU. Department of Physiological Scences	Study investigating the mechanisms of autophagy induction by different MTB strains
Prof. Warren, Dr. Streicher	SU	Tim Rodwell, FIND	FIND	Whole Genome Sequencing and phenotypic DST
Prof. Warren	SU	Helen Jenkins	BU	Spacial Medicine

Prof. Warren, Prof. Theron	SU	Prof. Perold	SU	Biosensors
Prof. Warren	SU	Marco Schito	CPTR	Whole Genome Sequencing
Prof. Warren, Dr. Streicher	SU	Cindy Heyens	NHLS - PE	Isoniazid discrepant DST
Prof. Warren, Dr. Streicher	SU	Yuri van der Heijden	Vanderbilt University Tuberculosis Center, Nashville, USA	Evolution of FQ resistance
Prof. Warren	SU	Prof. Clarke	LSTHM	Pacbio WGS
Dr. Kinnear, Dr. Möller	SU	Dr. van Vuuren	SU Division of Physiological Sciences	Investigting the regulation of phospotases in cardiomyocytes during hypoxia
Dr. Kinnear	SU	Dr. Peter	UCT Department of Medicine	Using whole exome sequencing to identify novel PID-causing genes as a measn to identiy novel TB susceptibility genes.
Dr. Möller	SU	Dr. Zaharie	Anatomical Pathology, Tygerberg Hospital	Tuberculosis Meningitis
Prof. van Hoal, Dr. Möller	SU	Dr. Chimusa	CBIO, IDM, UCT	Host genetic susceptibility to TB
Dr. du Plessis, Prof.Walzl	SU	Dr. Horsnell	UCT	Helminth-TB humoral responses
Prof. Warner & Prof. Mizrahi	UCT	Prof. Wood	UCT	TB transmission
Prof. Warner & Prof. Mizrahi	UCT	Profs. Scriba, Mulder & Blackburn	UCT	TB transmission
Prof. Warner	UCT	Prof. Chibale	UCT	TB drug discovery (co-supervision of students)
Prof. Warner	UCT	Dr. Wiesner	UCT	TB drug permeation (co-supervision of students)
Prof. Warner	UCT	Prof. Steyn	AHRI, UKZN	Energy metabolism in Mtb
Prof. Warner & Prof. Mizrahi	UCT	Prof. Wilkinson	UCT	Genome evolution in Mtb
Prof. Warner	UCT	Dr. Middlekoop	UCT	TB transmission
Prof. Warner	UCT	Prof. Egan	UCT	Small molecule permeation in mycobacteria
Prof. Mizrahi & Dr. Evans	UCT	Prof. Strauss	Stellenbosch University	Targeting the CoA pathway for TB drug discovery
Prof. Warner	UCT	Dr. Mhlanga	CSIR-UCT Biomedical Translational Research Initiative	Advanced imaging applied to mycobacteria
Dr. Gordhan	Wits	Debra Meyer	University of Pretoria and University of Johannesburg	Identification of small compounds with bioactivity again *Mycobacterium tuberculosis*
Dr. Chengalroyen	Wits	Stoyan Stoychev	Council for Scientific and Industrial Research	Peptidoglycan recycling in mycobacteria
Dr. Chengalroyen	Wits	Dr. Streicher	University of Stellenbosch	Genotyping of *M. tuberculosis* isolates
Prof. Kana	Wits	Xavier Padanilam	Sizwe Hospital	Genotypic and phenotypic heteroresistance of extensively drug resistant isolates

Dr. Chengalroyen	Wits	Nazir Ismail	National Institute for Communicable Diseases	Genotyping of *M. tuberculosis* isolates
Prof. Kana	Wits	Nesri Padayatchi/Kogie Naidoo	Centre for AIDS Prevention Research in South Africa	Various clinical projects (eg. Praxis)

5. SERVICE RENDERING

The following technical service, advice and assistance to local Government, regional services, institutions, research groups and individuals was provided in 2016:

Thesis examination

- Prof. Warner served as external examiner of a PhD submitted to the University of the Witwatersrand.
- Prof. Kana served as an external examiner for a PhD dissertations submitted to the University of Zimbabwe, Stellenbosch University and the University of KwaZulu Natal.
- Prof. Kana served as an external examiner for two MSc dissertations submitted to the University of KwaZulu Natal. Dr. Gordhan served as an external examiner an MSc dissertation submitted to the University of KwaZulu Natal.
- Prof. Kana served as an internal examiner for a PhD dissertation submitted to the University of the Witwatersrand.
- Prof. Walzl served as internal examiner for a PhD thesis from the Division of Virology.
- Dr. Loxton served as an external examiner for an MSc thesis from UKZN.
- Dr. Loxton served as an internal examiner for a PhD thesis from SU.
- Dr. Baker served as an internal examiner for a PhD thesis from the Department of Biomedical Sciences.
- Dr. Möller served as an internal examiner for a MSc thesis from the Division of Molecular Biology and Human Genetics.
- Dr. Kinnear served as an internal examiner for a MSc and PhD dissertations from the Division of Molecular Biology and Human Genetics.
- Dr. Kinnear served as an external examiner for a MSc thesis from the University of Kwazulu-Natal.
- Dr. Mouton served as an internal examiner of a MSc thesis of Mr. Bowker entitled, “Deciphering genetic susceptibility to tuberculosis meningitis” (supervised by Dr. Möller and Dr. Kinnear, SU).

Journal editing and reviews

- Prof. Mizrahi served on the Editorial Advisory Boards of *Tuberculosis* and *Cellular Microbiology*, and on the Editorial Boards of *Current Opinion in Microbiology*; *Pathogens & Disease; Emerging Microbes and Infection* and *Cell Chemical Biology* and was appointed to the Editorial Advisory Boards of *ACS Central Science*, *ACS Infectious Diseases* and *Genome Medicine*. Prof. Warner served on the Editorial Board of *PLoS One*, and as guest editor for *mBio*.
- Members of the UCT node reviewed manuscripts submitted to *Science*; *PLoS Pathogens*; *PNAS*; *Clinical Infectious Diseases*; *Cell Chemical Biology*; *ACS Infectious Diseases*; *Antimicrobial Agents and Chemotherapy*; *American Journal for Respiratory and Critical Care Medicine; Faculty of 1000; mBio; Infection Genetics and Evolution; Trends in Pharmacological Sciences; Tuberculosis; Acta Dermato-Venereologica*.
- Prof. Kana or Dr. Gordhan reviewed manuscripts for *eLife*, *mBIO*, *BMC Public Health*, *Current Pharmaceutical Design*, *FEMS Microbiology Letters*, *PLoS One*, *Scientific Reports*, *Mutation Research* and *Journal of Infectious Diseases*.

- Ms. Caroline Pule, Peer Reviewer of Abstracts submitted for the 47th Union World Conference on Lung Health, held in Liverpool in Liverpool, UK
- Prof. Miller M Associate editor for *Journal of Zoo and Wildlife Medicine* 2016.
- Prof. Miller M Reviewer for *Emerging Infectious Diseases, American Journal of Veterinary Research, Journal of Wildlife Diseases, Journal of Zoo* and *Wildlife Medicine* 2016.
- Mujuru TN Assistant at the Annual Academic Day 2016.
- Prof. Bardien Session chair at the 11th Annual Meeting of the Genetic Epidemiology of Parkinson's disease (GEoPD) Consortium 5-8 October 2016 2016.
- Prof. Kuivaniemi, Academic Editor for *PLoS ONE* 2016.
- Prof. Walzl is an associate editor of *Microbes and Infection.*
- Prof. Walzl reviewed for *Microbes and Infection, the New England Journal of Medicine, the Lancet, Lancet Infectious Diseases, the Journal of Infection.*

Expert panel or committee membership

- Prof. Mizrahi served on the Discovery Expert Group of the Bill & Melinda Gates Foundation.
- Prof. Mizrahi served on the 2017 Keystone Symposia Study Group and was appointed to the 2018 Keystone Symposia Study Group.
- Prof. Mizrahi served on the Scientific Advisory Committee of SDDC, a structure-guided drug discovery consortium, funded by the Bill & Melinda Gates Foundation, and led by the Structural Genomics Consortium at the University of Toronto.
- Prof. Mizrahi served on the Scientific Advisory Board of K-RITH, University of KwaZulu Natal.
- Prof. Mizrahi served on the Scientific Advisory Board of Innovative Medicines for Tuberculosis (iM4TB), EPFL, Switzerland.
- Prof. Mizrahi served on the National TB Think Tank.
- Prof. Mizrahi served on the Strategic Review Panel of the NHLS Grants Office.
- Prof. Warner and Prof. Mizrahi were appointed to UCT's Institutional Biosafety Committee, with Prof. Warner serving on the Executive of this committee.
- Prof. Mizrahi served on the Visiting Scholars Fund and Visiting Lecturers Fund Committee, UCT.
- Prof. Mizrahi chaired the Executive Committee of the IDM, UCT.
- Prof Mizrahi chaired the Membership Committee of the IDM, UCT.
- Prof. Warner chaired the Health & Safety Committee of the IDM, UCT.
- Prof. Warner chaired the Faculty of Health Sciences Biosafety Committee, UCT.
- Prof. Warner served as the MMRU Hazardous Chemical Coordinator, IDM, UCT.
- Prof. Warner served on the Education Task Team and Equipment Task Team of the IDM, UCT.
- Dr. Evans served on the Health & Safety Committee of the IDM, UCT.
- Dr. Mashabela served on the Operations and Administration Committee of the IDM, UCT.
- Prof. Kana served on the Scientific Advisory Committee of the Cape Town HVTN Immunology Laboratory.
- Prof. Kana served on the Board of the Sydney Brenner Institute for Molecular Biosciences.
- Prof. Kana served on the Board of the Microscopy and Microanalysis Unit at Wits University.
- Prof. Kana served as a member of the Global Alliance for TB Drug Development Working Group on New TB Drugs.
- Prof. Kana and Dr. Gordhan served on the Faculty Research Council (FRC), Faculty of Health Sciences, Wits University.

- Dr. Gordhan served as chair of the Research Entity Review Task Group, Faculty of Health Sciences, Wits UniversityProf. Kana served on the FRC Budget Task Group, Faculty of Health Sciences Wits University.
- Prof. Kana served on the Advisory Board for the Faculty of Health Sciences, Wits University.
- Prof. Kana served on the Executive Committee of the School of Pathology, Faculty of Health Sciences, Wits University.
- Prof. Kana served on the Research Entity Forum, Faculty of Health Sciences, Wits University.
- Prof. Kana served on the Faculty of Health Sciences Research Equipment Review Committee, Wits University.
- Prof. Kana served on the URC major and minor Equipment Review Committees, Wits University.
- Prof. Kana served on the Faculty of Health Sciences Imaging Committee, Wits University.
- Prof. Tromp participated as Scientific Advisory Board, H3ABioNet for the H3ABioNet is a pan-African bioinformatics network in support of the the H3Africa program. H3ABioNet annual general meeting held at River Club in Observatory, November 1 and 2, 2016.
- Prof. Tab participated as Chair of HUPO-PSI Quality Control Working Group for the Human Proteomics Organization Proteomics Standards Initiative in 2016.
- Dr. Jackson etc. participated as Safety Task Team for Field Staff for the Stellenbosch University in 2016.
- Dr. Werely participated as Human Research Ethhics Committee for the Stellenbosch University Faculty of Medicine & Health Sciences in 2016.
- Dr. Chegou participated as Junior Executive member for the South African Society for Immunology (SAIS) in 2016.
- Dr. Chegou participated as Member: Health Research Ethics Committee for the Stellenbosch University in 2016.
- Profs. Miller van Helden PD, Hoal E, Dr. Parsons, outside committee members participated as South African Wildlife TB STudy Group for the Stellenbosch University, University of Pretoria, SANParks, EKZN Wildlife, DAFF in 2016.
- Prof. Miller participated as U.S. Animal Health Association TB Scientific Advisory Subcommittee for the U.S. Animal Health Association in 2016.
- Prof. Miller participated as U.S. Animal Health Association Committe on TB for the U.S. Animal Health Association in 2016.
- Ms. Pule participated as Ambassador of the South African National Tuberculosis Association (SANTA) for the The South African National Tuberculosis Association (SANTA) in 2016.
- Ms. Pule participated as Chief Executive Officer of the Caroline Pule Science and Literacy Foundation (CPSLF) for the The Caroline Pule Science and Literacy Foundation (CPSLF) in 2016.
- Prof. Bardien participated as Member of Health Sciences Specialist Committee for Rating Researchers for the National Research Foundation Rating; 2013 - 2016 in 2016.
- Prof. Sampson is a member of the Faculty Research sub-com C and SU Biosafety and Environmental Ethics committee.
- Ms. Pule served on the Selection committee for 2016 Angus Honours Scholarship co-ordinated by SAWISE
- Prof. Walzl served as voting member of the TB Scientific Committee of the IMPAACT network
- Prof. Walzl is a peer review committee member of the FDA, NIAID and BMGF-funded Consortium for TB Biomarkers (CTB^2)

- Prof. Mizrahi, Prof. Kana and Prof. Walzl contribute to the SAMRC initiated TB Think Tank, which serves in an advisory capacity to the Department of Health
- Prof. Walzl serves on the Faculty of Medicine and Health Sciences Research Committee
- Prof. Walzl serves on the SU research committee, where he represents his faculty
- Prof. Walzl chairs the Division of Molecular Biology and Human Genetics Management Committee at his faculty
- Prof. Walzl chairs the Department of Biomedical Sciences Steering Committee at his faculty
- Prof. Walzl serves on the External Advisory Board of the TB Sequel project, a BMBF (German Ministry for Education and Science) funded initiative for "Research Networks on Health Innovations in sub-Saharan Africa", led by Dr Gavin Churchyard and Dr Michael Hoelscher.
- Prof. Mizrahi served as Co-Chair of TB2016, International AIDS Society Conference, Durban July 2016. This conference also served as the fourth South African TB Conference.

Selection of research funding reviews

- Prof. Mizrahi served as a reviewer of research and fellowship applications for the HHMI; the Fondation pour la Recherche Medicale (France), Institut Pasteur and the NRF (IEPD program), and as reviewer for promotions at the Crick Institute and Tsingua University (Beijing).
- Prof. Warner served as reviewer for international funding organizations including the Wellcome Trust (UK), and the Africa Research Excellence Fund (AREF) College of Experts (AREF). He was also a reviewer for major South African funding organizations (NRF, MRC) and the various programmes they administer, including competitive funding for un/rated researchers, and MRC self-initiated research grants, and NRF student funding applications. In addition, he served as an internal reviewer for numerous research proposals considered by the IDM Research Committee, the Human Research Ethics Committee, and the Faculty Biosafety Committee. Prof. Warner also served as reviewer of applications for the International Union against Tuberculosis and Lung Disease Conference, 2016.
- Members of the CBTBR Wits node reviewed for the NHLS Research Trust, Biotechnology and Biological Sciences Research Council (BBSRC, UK), South African Medical Research Council (various programs), Soweto Matlosana Collaborating Centre for HIV and TB (SoMCHAT), the NHLS Research Trust, and the National Research Foundation (Rating and Evaluation Program).
- Members of the Wits node of the CBTBR served on the following panels, selection committees:
    - Interview panel for the Diversifying of the Academy post of Lecturer, School of Pathology, Wits
    - MSc protocol assessment - assessed 5 MSc. protocols, Faculty of Health Sciences, Wits.
    - Application for general release of genetically modified organisms – poultry vaccine for Department of Agriculture, Forestry and Fisheries (DoAFF).
    - Poster session judge for the Faculty of Health sciences at the 7th cross-faculty postgraduate symposium, Wits (Judged 17 posters).
    - The BTC selection committee. Assessed 12 bursary applications.
- Prof. Walzl reviewed applications for the BMGF, the Wellcome Trust and the NRF
- Prof. Walzl acted as reviewer for a senior appointment at the University of Pennsylvania.
- Members of the SU node of the CBTBR served on the following panels, selection committees:

- Interview panels for promotion to Associate or Full Professor posts at SU
- MSc protocol assessments, Faculty of Medicine and Health Sciences, SU.
- PhD protocol assessments, Faculty of Medicine and Health Sciences, SU.

Beneficiation of other researchers by CBTBR

The SUN node also provides infrastructure and intellectual support to groups, even some who are not TB researchers and are therefore defined to be completely outside the CBTBR. For example, the lab housing the CBTBR genetics group also hosts a small group of lab researchers, mostly students working on the Genetics of Psychiatric Disorders, part of the NRF SARCHi research of Prof. Seedat. It also houses a small SUN group (Prof. Bardien) working on the genetics of Parkinsons disease in South Africans, and from time to time hosts a research student working on diseases of the prostate from the division of Urology. All of the PIs involved have or have had NRF support. They are also fully integrated with three SU based TB SARChI's and their researchers and students. A UCT based SARhI (Prof. Dheda) and his team also utilise CBTBR facilities. Other researchers within SU, such as numerous persons from Paediatrics, Medical Microbiology and Immunology also use CBTBR facilities. The SU BL3 lab has approximately 70 registered users, of whom about 50 are part of the SU CBTBR node.

The UCT node is an integral component of the Institute of Infectious Disease and Molecular Medicine (IDM) and a major contributor to the institute's shared research capacity and infrastructure, which is of direct benefit to all member groups involved in TB research. This includes a shared BSL3 laboratory, in which the UCT node has invested considerable resource. This laboratory serves the needs of 41 registered and 38 trainee users from across the IDM, only 12 of whom are supported directly by the CBTBR. The UCT node also provides extensive technical support and assistance in all aspects of mycobacteriology to staff, students and postdocs from the groups of three SARChI chairs, the Clinical Infectious Disease Research Initiative (CIDRI, recently incorporated into the Wellcome Centre for Clinical Infectious Disease Research in Africa), the Desmnod Tutu HIV Centre and the SA TB Vaccine Initiative (SATVI). The only outputs reported herein from the UCT node are those funded directly by the NRF grant to the CoE and resulting from the research and training programmes led by the two Team Members in this node, Prof. Mizrahi and Prof. Warner, and the member of the Scientific Staff, Dr. J Evans. However, Prof. Mizrahi and Prof. Warner have been major contributors to two new initiatives in the IDM and UCT Faculty of Health Sciences. First, Prof. Mizrahi is a PI and BSL3 Platform Lead of CIDRI-Africa, the first Wellcome Trust Centre established at a university outside the UK. Second, Prof. Warner has jointly led the establishment of an advanced Confocal and Superresolution Microscopy Facility in the UCT Faculty of Health Sciences, with funding from the Wellcome Trust, the NRF (NEP) and the Wolfson Foundation.

Other services rendered

The SU immunology group performs QFT tests for Tygerberg Academic Hospital, including special clinical diagnostic challenges and for visiting students and staff from low-TB endemic countries.

6. GENDER IMPACT OF RESEARCH

From the "Science by Women" perspective, it is important to note that 59% of all postgraduate students (including postdoctoral fellows) in the CBTBR in 2016 were female. This gender distribution has not changed significantly from the inception of the CBTBR and reflects the situation nationally for women scientists at this level within the health sciences. Importantly, there has been increased

representation by women at higher levels as evidenced by the fact that two of the three NRF awards granted to SU and closely associated with the CBTBR are women, as are two recently appointed NRF Research Career Awardees. Women scientists the CBTBR have continued to contribute to promoting women in science through various vehicles including membership of SAWISE and the mentorship of junior researchers. For example, Prof. Hoal was appointed to the Project Team for Women's Career Progression at SU and Prof. Mizrahi serves as mentor and/or sponsor of a number of women scientists at UCT (not linked to the CBTBR).

HUMAN RESOURCES

1. Core Team Members

Title	Surname	Nationality	Institution	Gender	Race	% Time spent in CBTBR
Prof.	Walzl	South Africa	SU	M	W	100
Prof.	Mizrahi	Italy	UCT	F	W	30[a]
Prof.	Kana	South Africa	Wits	M	B	100
A/Prof.	Warner	South Africa	UCT	M	W	100
Dr.	Gordhan	South Africa	Wits	F	B	100
Prof.	Warren	South Africa	SU	M	W	50[b]
Prof.	Martinson	South Africa	Wits	M	W	25[c]
Prof.	Hoal van Helden	South Africa	SU	F	W	100
A/Prof.	Theron	South Africa	SU	M	W	100
Prof.	Miller	South Africa	SU	F	W	100
Prof.	Sampson	South Africa	SU	F	W	100
Prof.	Wiid	South Africa	SU	M	W	100
Prof.	Van Helden	South Africa	SU	M	W	100

a. Director of IDM, UCT
b. Director of SAMRC Centre for Tuberculosis Research
c. Director of the Perinatal HIV Research Unit (PHRU)

2. Scientific Staff

Title	Surname	Nationality	Institution	Gender	Race	% Time spent in CBTBR
Dr.	Baker	South Africa	SU	M	B	100
Dr.	Loxton	South Africa	SU	M	B	100
Dr.	Chegou	Cameroonian	SU	M	B	100
Dr.	Kleynhans	South Africa	SU	F	W	100
Dr.	Du Plessis	South Africa	SU	F	W	100
Dr.	Williams	South Africa	SU	F	B	100
Dr.	Streicher	South Africa	SU	F	W	100
Dr.	Kinnear	South Africa	SU	M	B	100
Dr.	Moller	South Africa	SU	F	W	100
Dr.	Jackson	South Africa	SU	F	W	100
Prof.	Sirgel	South Africa	SU	M	W	100
Prof.	Tromp	USA	SU	M	W	100
Prof.	Tabb	USA	SU	M	W	100
Prof.	Van Der Spuy	South Africa	SU	M	W	100
Dr.	Evans	South Africa	UCT	F	W	100
Dr.	Ealand	South Africa	Wits	M	W	100
Dr.	Machowski		Wits	F	W	50[a]

a. Part time researcher - funded through various grants.

Administrative and Other Staff

Title	Surname	Position	Based at	Gender	Race
Dr.	Smith	Project Manager	SU	F	B
Ms.	Baatjies	MRC Technical Officer	SU	F	B

Ms.	Mohammed	Bookkeeper / Admin Assistant	Wits	F	B
Ms.	Jakoet	Admin Assistant	UCT	F	B
Ms.	Masangana	Laboratory Tech Assistant	Wits	F	B
Mrs.	Snyders	Senior Secretary	SU	F	B
Ms.	Durelle	Senior Secretary	SU	F	W
Ms.	Jordaan	Laboratory Technologist	UCT	F	B

3. Postdoctoral Fellows

Title	Surname	Nationality	Institution	Race	Gender	Status	% Time spent in CoE
Dr.	Haylett	South Africa	SU	W	M	In Progress	100
Dr.	Klopper	South Africa	SU	W	F	In Progress	100
Dr.	Leisching	South Africa	SU	W	F	In Progress	100
Dr.	Ley	Switzerland	SU	W	F	In Progress	100
Dr.	Mouton	South Africa	SU	W	F	In Progress	100
Dr.	Naidoo	South Africa	SU	B	F	In Progress	100
Dr.	Ngwane	South Africa	SU	B	M	In Progress	100
Dr.	Whitfield	South Africa	SU	W	M	In Progress	100
Dr.	Mishra	India	SU	B	M	In Progress	100
Dr.	Dippenaar	South Africa	SU	W	F	In Progress	100
Dr.	Reeve	South Africa	SU	W	M	In Progress	100
Dr.	Neethling	South Africa	SU	W	F	In Progress	100
Dr.	Womersley	South Africa	SU	W	F	In Progress	100
Dr.	Glanzmann	South Africa	SU	W	F	In Progress	100
Dr.	Soa Emani	Cameroon	SU	B	F	In Progress	100
Dr.	Beltran	South Africa	SU	W	F	In Progress	100
Dr.	Williamse	South Africa	SU	W	F	In Progress	100
Dr.	Malan-Muller	South Africa	SU	W	F	In Progress	100
Dr.	Meier	South Africa	SU	W	M	In Progress	100
Dr.	Magcwebeba	South Africa	SU	B	F	In Progress	100
Dr.	Kerr	South Africa	SU	W	F	In Progress	100
Dr.	Grobbelaar	South Africa	SU	W	F	In Progress	100
Dr.	Heunis	South Africa	SU	W	M	In Progress	100
Dr.	Neethling	South Africa	SU	W	F	In Progress	100
Dr.	Banda	Zimbabwe	SU	B	M	Complete	100
Dr.	Sakar	India	SU	B	M	Complete	100
Dr.	Van Der Merwe	South Africa	SU	W	M	Complete	100
Dr.	Fortuin	South Africa	SU	B	F	Complete	100
Dr.	Styger	South Africa	SU	W	M	Complete	100
Dr.	Peters	Zimbabwe	Wits	B	F	In Progress	100
Dr.	Chengalroyen	South Africa	Wits	B	F	Completed	100
Dr.	Ealand	South Africa	Wits	B	M	Completed	100
Dr.	Longwe	Malawi	Wits	B	M	Completed	100
Dr.	Anoosheh	Iran	UCT	W	M	In Progress	100
Dr.	Moosa	South Africa	UCT	I	F	In Progress	50
Dr.	Mashabela	South Africa	UCT	B	M	In Progress	100
Dr.	Mason	South Africa	UCT	W	F	In Progress	100
Dr.	Agarwal	India	UCT	I	F	In Progress	100
Dr.	Singh	India	UCT	I	M	Completed	100
Dr.	Mukherjee	India	UCT	I	M	Completed	20
Dr.	Majumdar	India	UCT	I	M	Completed	10
Dr.	Macingwana	South Africa	UCT	B	M	Completed	50

4. Graduated Students 2016

Surname	Name	Degree	Institution	Race	Gender	Nationality	% Time spent in CoE
Botha	Nicole	BSc Hons	SU	W	F	South Africa	100
De Buys	Keren	BSc Hons	SU	W	F	South Africa	100
Francois	Sydney	BSc Hons	SU	W	F	South Africa	100
Gutridge	Ashley	BSc Hons	SU	W	F	South Africa	100
Nagel	Simone'	BSc Hons	SU	W	F	South Africa	100
Okugbeni	Naomi	BSc Hons	SU	B	F	Nigeria	100
Sebate	Bibi	BSc Hons	SU	B	F	South Africa	100
Shabangu	Ayanda	BSc Hons	SU	B	F	Swaziland	100
Sparks	Anel	BSc Hons	SU	W	F	South Africa	100
Theron	Jessica	BSc Hons	SU	W	F	South Africa	100
Theys	Janice	BSc Hons	SU	B	F	South Africa	100
Zimmerman	Dominic	BSc Hons	SU	W	M	South Africa	100
Mashigo	Lethabo	BSc Hons	Wits	B	F	South Africa	100
Manemela	Nelia	BSc Hons	Wits	B	F	South Africa	100
De Wet	Timothy	BSc Hons	UCT	W	M	South Africa	100
Taylor	Kaitlin	BSc Hons	UCT	W	F	Zimbabwe	100
Trevor	Tamzyn	BSc Hons	UCT	W	F	South Africa	100
Alley	Philbe-Jeanne	MSc	SU	B	F	South Africa	100
Benecke	Rohan	MSc	SU	W	M	South Africa	100
Borrageiro	Genevie	MSc	SU	W	F	South Africa	100
Bowker	Nicholas	MSc	SU	W	M	South Africa	100
Clarke	Charlene	MSc	SU	W	F	South Africa	100
Colic	Antoinette	MSc	SU	W	F	South Africa	100
Da Camara	Ncite	MSc	SU	W	F	South Africa	100
Jacobs	Ruschca	MSc	SU	B	F	South Africa	100
Klazen	Jessica	MSc	SU	B	F	Namibia	100
Parbhoo	Trisha	MSc	SU	B	F	South Africa	100
Polson	Alma	MSc	SU	W	F	South Africa	100
Selamolela	Mosa	MSc	SU	B	F	South Africa	100
Van Rensburg	Ilana	MSc	SU	B	F	South Africa	100
Zass	Lyndon	MSc	SU	B	M	South Africa	100
Siame	Kabengele	MSc	SU	B	M	Zambia	100
Ralefeta	Ditshego	MSc	Wits		M	South Africa	100
Nthambeleni	Gadisi	MSc	Wits		M	South Africa	100
Ismail	Zaahida sheik	MSc	Wits		F	South Africa	100
Baartes	Nadia	MSc	UCT		F		100
Awoniyi	Dolapo	PhD	SU	B	M	Nigeria	100
Goosen	Wynand	PhD	SU	W	M	South Africa	100
Grobbelaar	Melanie	PhD	SU	W	F	South Africa	100
Hammond-Aryee	Kenneth	PhD	SU	B	M	Ghana	100
Kayigire	Xavier	PhD	SU	B	M	Rwanda	100
Malherbe	Stephanus	PhD	SU	W	M	South Africa	100
Mc Grath	Marieta	PhD	SU	W	F	South Africa	100
Mphahlele	Matsie	PhD	SU	B	F	South Africa	100
Neethling	Annika	PhD	SU	W	F	South Africa	100
Schlechter	Nikola	PhD	SU	W	F	South Africa	100
Viljoen	Ignatius	PhD	SU	W	M	South Africa	100
Whitfield	Michael	PhD	SU	W	M	South Africa	100
Willemse	Danicke	PhD	SU	W	F	South Africa	100

5. Current Registered Students - 2017

Surname	Name	Degree	Institution	Race	Gender	Nationality	% Time spent in CoE
Butterworth	Ciara	BSc Hons	SU	W	F	South Africa	100
De Waal	Candice	BSc Hons	SU	B	F	South Africa	100
Dlangalala	Manana	BSc Hons	SU	B	F	South Africa	100
Gabazana	Zikhona	BSc Hons	SU	B	F	South Africa	100
Hearne	Tammy	BSc Hons	SU	W	F	South Africa	100
King	Hannah	BSc Hons	SU	W	F	South Africa	100
La Fleur	Shane	BSc Hons	SU	B	F	South Africa	100
Leonard	Bryan	BSc Hons	SU	B	M	South Africa	100
Leqheka	Monkoe	BSc Hons	SU	B	M	Lesotho	100
Makhoba	Nonjabulo	BSc Hons	SU	B	F	South Africa	100
Manolas	Erin	BSc Hons	SU	W	F	South Africa	100
Minnies	Stephanie	BSc Hons	SU	B	F	South Africa	100
Moller	Andreas	BSc Hons	SU	W	M	South Africa	100
Nolan	Heidi	BSc Hons	SU	W	F	South Africa	100
Prins	Nicole	BSc Hons	SU	B	F	South Africa	100
Ramruthan	Nikitia	BSc Hons	SU	B	F	South Africa	100
Ropertz	Megan	BSc Hons	SU	W	F	South Africa	100
Van Der Merwe	Charnay	BSc Hons	SU	B	F	South Africa	100
Van Eeden	Gerald	BSc Hons	SU	W	M	South Africa	100
Young	Caitlyne	BSc Hons	SU	W	F	South Africa	100
Bain	Chané	MSc	SU	W	F	South Africa	100
Cole	Victoria	MSc	SU	C	F	South Africa	100
De Buys	Keren	MSc	SU	W	F	South Africa	100
Derendinger	Brigitta	MSc	SU	W	F	South Africa	100
Dicks	Laetitia	MSc	SU	W	F	South Africa	100
Fitzermann	Yessica	MSc	SU	W	F	Germany	100
Herholdt	Helene	MSc	SU	W	F	South Africa	100
Higgitt	Roxanne	MSc	SU	W	F	South Africa	100
Hofmeyr	Jennifer	MSc	SU	W	F	South Africa	100
Knell	Jeneva	MSc	SU	W	F	South Africa	100
Leukes	Vinzeigh	MSc	SU	B	M	South Africa	100
Mahlobo	Zama	MSc	SU	B	F	South Africa	100
Maluleke	Twananani	MSc	SU	B	F	South Africa	100
Manngo	Makhadzi	MSc	SU	B	F	South Africa	100
Manyelo	Charles	MSc	SU	B	M	South Africa	100
Mendy	Joseph F	MSc	SU	B	M	Gambia	100
Mesatywa	Pumla	MSc	SU	B	F	South Africa	100
Moore	Dannie	MSc	SU	W	F	South Africa	100
Motaung	Bongani	MSc	SU	B	M	South Africa	100
Mujuru	Nyasha	MSc	SU	B	M	Zimbabwe	100
Nagel	Simone'	MSc	SU	W	F	South Africa	100
Niemand	Nandi	MSc	SU	W	F	South Africa	100
Okugbeni	Naomi	MSc	SU	B	F	Nigeria	100
Pillay	Samantha	MSc	SU	Indian	F	South Africa	100
Sebate	Bibi	MSc	SU	B	F	South Africa	100
Shabangu	Ayanda	MSc	SU	B	F	Swaziland	100
Sieberhagen	Jeanie	MSc	SU	W	F	South Africa	100
Sparks	Anel	MSc	SU	W	F	South Africa	100
Tamuhla	Tsaone	MSc	SU	B	F	Botswana	100

Tobias	Al-Girvan	MSc	SU	B	M	South Africa	100
Tshoko	Siyanda	MSc	SU	B	F	South Africa	100
Van Schalkwyk	Talani	MSc	SU	W	F	South Africa	100
Young	Carly	MSc	SU	W	F	South Africa	100
Zimire	Darryn	MSc	SU	B	M	South Africa	100
Shaku	Moagi Tube	MSc	Wits	B	M	South Africa	100
Moseki	Moeketsi Raymond	MSc	Wits	B	M	South Africa	100
Rantsi	Tebogo Christina	MSc	Wits	B	F	South Africa	100
Maphatsoe	Masethabela	MSc	Wits	B	M	South Africa	100
Sikhosana	Nombeko	MSc	Wits	B	F	South Africa	100
Mashilo	Poppy	MSc	Wits	B	F	South Africa	100
Sewgoolam	Bevika	MSc	UCT	I	F	South Africa	100
Dinkele	Ryan	Msc	UCT	W	M	South Africa	100
Centner	Chad	MSc	UCT	W	M	South Africa	100
Arries	Jessie	PhD	SU	B	F	South Africa	100
Baatjies	Lucinda	PhD	SU	B	F	South Africa	100
Bernitz	Netanya	PhD	SU	W	F	South Africa	100
Chileshe	Josephine	PhD	SU	B	F	Zambia	100
Chirenda	Joconiah	PhD	SU	B	M	Zimbabwe	100
Chisompola	Namaunga	PhD	SU	B	F	Zambia	100
Du Plessis	Juanelle	PhD	SU	W	F	South Africa	100
Gallant	James	PhD	SU	W	M	South Africa	100
Kotzé	Leigh	PhD	SU	W	F	South Africa	100
Kunsevi-Kilola	Carine	PhD	SU	B	F	Congo	100
Maasdorp	Elizna	PhD	SU	W	F	South Africa	100
Mishra	Abhilasha	PhD	SU	I	F	India	100
Moiane	Ivânia	PhD	SU	B	F	Mozambique	100
Mutavhatsindi	Hygon	PhD	SU	B	M	South Africa	100
Nyawo	Georgina	PhD	SU	B	F	Zimbabwe	100
Oluwole	Gabriel	PhD	SU	B	M	Nigeria	100
Parbhoo	Trisha	PhD	SU	I	F	South Africa	100
Pietersen	Ray-Dean Donovan	PhD	SU	B	M	South Africa	100
Pitts	Stephanie	PhD	SU	B	F	South Africa	100
Pule	Caroline	PhD	SU	B	F	South Africa	100
Roos	Eduard	PhD	SU	W	M	South Africa	100
Schurz	Haiko	PhD	SU	W	M	Namibia	100
Scott	Chantelle	PhD	SU	W	F	South Africa	100
Steyn	Nastassja	PhD	SU	W	F	South Africa	100
Sylvester	Tashnica	PhD	SU	B	F	South Africa	100
Tshivhula	Happy	PhD	SU	B	F	South Africa	100
Uren	Caitlin	PhD	SU	W	F	South Africa	100
Venter	Rouxjeane	PhD	SU	W	F	South Africa	100
Visser	Hanri	PhD	SU	W	F	South Africa	100
Mclvor	Amanda	PhD	Wits	W	F	South Africa	100
Narrandes	Nicole	PhD	Wits	B	F	South Africa	100
Senzani	Sibusiso	PhD	Wits	B	M	South Africa	100
Papadopoulus	Andrea	PhD	Wits	W	F	South Africa	100
Van Coller	Phia	PhD	UCT	W	F	South Africa	100
Broadley	Simon	PhD	UCT	W	M	South Africa	50
Omollo	Charles	PhD	UCT	B	M	Kenya	100
Wasuna	Antonia	PhD	UCT	B	F	Kenya	50
Kipkorir	Terry	PhD	UCT	B	M	Kenya	100
Martin	Zela	PhD	UCT	W	F	South Africa	100

Reiche	Michael	PhD	UCT	W	M	South Africa	100
Masuku	Bianca	PhD	UCT	B	F	South Africa	50
Tanner	Lloyd	PhD	UCT	W	M	South Africa	50
Gobe	Irene	PhD	UCT	B	F	Botswana	100
Mabhula	Amanda	PhD	UCT	B	F	South Africa	50
Mbau	Rendani	PhD	UCT	B	M	South Africa	100

5. OUTPUTS

Articles in Peer-Reviewed Journals (Total: 90)

49/90 (54%) of publications were first- and/or last-authored by a member(s) of the CBTBR

Baartzes, N. Stringer, T. Seldon, R., Warner, D.F., de Kock, C., Smith, P.J., Smith, G.S. 2016. Synthesis, characterization and antimicrobial evaluation of mono- and polynuclear ferrocenyl derived amino and imino complexes, *J. Organometallic Chem.* doi: 10.1016/j.jorganchem.2016.02.033. **IF:2.173**
Baartzes, N., Stringer, T., Okombo, J., Seldon, R., Warner, D.F., de Kock, C., Smith, P.J., Smith G.S. (2016). Mono- and polynuclear ferrocenylthiosemicarbazones: synthesis, characterisation, and antimicrobial evaluation. *J Organometallic Chem.* 819:166-172. doi: 10.1016/j.jorganchem.2016.06.032 **IF:2.173**
Warner, D.F. 2016. Defining a diagnostic gene signature for tuberculosis. *Lancet Respir. Med*. http://dx.doi.org/10.1016/S2213-2600(16)00063-1 **IF:15.328**
Wood, R., Morrow, C., Barry, C.E. III, Bryden, W.A., Call, C.J., Hickey, A.J., Rodes, C.E., Scriba, T.J., Blackburn, J., Issarow, C., Mulder, N., Woodward, J., Moosa, A., Singh, V., Mizrahi, V., and Warner, D.F. 2016. Real-time investigation of tuberculosis transmission: Developing the Respiratory Aerosol Sampling Chamber (RASC). *PLoS One* doi: 10.1371/journal.pone.0146658 **IF:3.234**
Leinhardt, C., Lönnroth, K., Menzies, D., Balasegaram, M., Chakaya, J., Cobelens, F., Cohn, J., Denkinger, C.M., Evans, T.G., Källenius, G., Kaplan, G., Kumar, A.M.V., Matthiesen, L., Mgone, C.S., Mizrahi, V., Mukadi, Y., Nguyen, V.N., Nordström, A., Sizemore, C.F., Spigelman, M., Quire, S.B., Swaminathan, S., van Helden, P.D., Zumla, A., Weyer, K., Weil, D., and Raviglione, M. *PLoS Med.* DOI:10.1371/journal.pmed.1001965 **IF:13.585**
Djaout, K., Singh, V., Boum, Y., Katawera, V., Becker, H.F., Bush, N.G, Hearnshaw, S.J., Pritchard, J.E., Bourbon, P., Madrid, P.B., Maxwell, A., Mizrahi, V., Myllykallio, H., & Ekins, S. Predictive modeling targets thymidylate synthase ThyX in *Mycobacterium tuberculosis. Sci. Rep.* 2016; Jun 10;6:27792. doi: 10.1038/srep27792. **IF:5.228**
Kumar, M., Singh, K., Naran, K., Hamzabegovic, F., Hoft, D.F., Warner, D.F., Ruminski, P., Abate, G., and Chibale, K. 2016. Design, Synthesis and Evaluation of Novel Hybrid Efflux Pump Inhibitors for use against *Mycobacterium tuberculosis*. *ACS Infect. Dis.* doi: 10.1021/acsinfecdis.6b00111 **IF: not available**
Naran, K.*, Moosa, A.*, Barry, C.E. III, Boshoff, H.I.M., Mizrahi, V., and Warner, D.F. 2016. Bioluminescent reporters for rapid mechanism of action assignment in tuberculosis drug discovery. *Antimicrob. Agents Chemother*. doi:10.1128/AAC.01178-16 [*joint first authors] **IF:4.415**
Singh, V., Donini, S., Pacitto, A., Sala, C., Hartkoorn, R.C., Dhar, N., Keri, G., Ascher, D.B., Mondésert, G., Vocat, A., Lupien, A., Sommer, R., Vermet, H., Lagrange, S., Buechler, J., Warner, D.F., McKinney, J.D., Pato, J., Cole, S.T., Blundell, T.L., Rizzi, M., and Mizrahi, V. 2016. The inosine monophosphate dehydrogenase, GuaB2, is a vulnerable new bactericidal drug target for tuberculosis. *ACS Infect. Dis*. doi:10.1021/acsinfecdis.6b00102 **IF: not available**
Singh, V., and Mizrahi, V. Identification and validation of novel drug targets in *Mycobacterium tuberculosis. Drug Discovery Today* 2016; doi: 10.1016/j.drudis.2016.09.010. [IF=5.625] **IF:5.625**
Evans, J.C., Trujillo, C., Wang, Z., Eoh, H., Boshoff, H.I.M., Ehrt, S., Schnappinger, D., Rhee, K., Barry, C.E. III and Mizrahi, V. Validation of CoaBC as a bactericidal target in the coenzyme A pathway of *Mycobacterium tuberculosis*. *ACS Infect. Dis*. 2016; doi: 10.1021/acsinfecdis.6b00150. **IF: not available**
Singh, V., Dhar, N., Pato, J., Kolly, G.S., Korduláková, J., Forbák, M., Evans, J.C., Szekely, R.E., Rybnicker, J.L., Svetlíková, Z., Zemanová, J., Santi, I., Signorino-Gelo, F., Rodrigues L., Vocat, A., Covarrubias, A.S., Rengifo, M.G., Johnsson, K., Mowbray, S., Buechler, J., Delorme, V., Brodin, P., Knott, G.W., Ainsa, J., Warner, D.F., Keri, G., Mikušová, K., McKinney, J.D., Cole, S.T.*, Mizrahi, V.* and Hartkoorn, R.C.* Identification of Aminopyrimidine-Sulfonamides as potent modulators of Wag31-mediated cell elongation in mycobacteria. *Mol. Microbiol*. 2016; doi:10.1111/mmi.13535 [*Joint senior authors] **IF:3.761**
Majumdar, G., Mbau, R., Singh, V., Warner, D.F., Dragse, M.S., and Mukherjee, R. Genome-wide transposon mutagenesis in *Mycobacterium tuberculosis* and *Mycobacterium smegmatis*. *In*: In vitro mutagenesis: methods and protocols. Methods in Molecular Biology, Springer Science + Business Media, New York, 2017; vol. 1498, ch. 21, pp. 321-334. doi: 10.1007/978-1-4939-6472-7_21 **IF: not available**

Chengalroyen, M.D., Beukes, G.M., Gordhan, B.G., Streicher, E.M., Churchyard, G., Hafner, R., Warren, R., Otwombe, K., Martinson, N.A. and Kana B.D.* (2016). Detection and quantification of differentially culturable tubercle bacteria in tuberculosis patients. Am J Respir Crit Care Med. 194. p. 1532-1540 **IF: 13.118**

Su, H.W., Zhu, J.H., Li, H., Cai, R.J., Ealand, C., Wang, X., Chen, Y.X., Kayani, M.U., Zhu, T.F., Moradigaravand, D., Huang, H., Kana, B.D., Javid, B. (2016) The essential mycobacterial amidotransferase GatCAB is a modulator of specific translational fidelity. Nature Microbiol. 1. p. 16147. **IF: not available**

Gama, N.H., Elkhadir, A.Y., Gordhan, B.G., Kana, B.D., Darkwa, J. and Meyer, D. (2016) Activity of phosphino palladium(II) and platinum(II) complexes against HIV-1 and *Mycobacterium tuberculosis*. Biometals. 29. p. 637-50. **IF: 2.134**

Karat, A.S., Tlali, M., Fielding, K.L., Charalambous, S., Chihota, V.N., Churchyard, G.J., Hanifa, Y., Johnson, S., McCarthy, K., Martinson, N.A., Omar, T., Kahn, K., Chandramohan, D., Grant, A.D. (2016). Measuring mortality due to HIV-associated tuberculosis among adults in South Africa: Comparing verbal autopsy, minimally-invasive autopsy, and research data. PLoS One. 12:e0174097 **IF: 3.057**

Bronner Murrison, L., Martinson, N., Moloney, R.M., Msandiwa, R., Mashabela, M., Samet, J.M., Golub, J.E. (2016) Tobacco Smoking and Tuberculosis among Men Living with HIV in Johannesburg, South Africa: A Case-Control Study. PLoS One. 11:e0167133 **IF: 3.057**

Kayigire, X.A., Friedrich, S.O., Karinja, M.N., van der Merwe, L., Martinson, N.A., Diacon, A.H. (2016) Propidium monoazide and Xpert MTB/RIF to quantify *Mycobacterium tuberculosis* cells. Tuberculosis (Edinb). 2016 Dec;101:79-84. **IF: 2.952**

Karat, A.S., Omar, T., von Gottberg, A., Tlali, M., Chihota, V.N., Churchyard, G.J., Fielding, K.L., Johnson, S., Martinson, N.A., McCarthy, K., Wolter, N., Wong, E.B., Charalambous, S., Grant, A.D. (2016) Autopsy Prevalence of Tuberculosis and Other Potentially Treatable Infections among Adults with Advanced HIV Enrolled in Out-Patient Care in South Africa. PLoS One. 11: e0166158. **IF: 3.057**

Lebina, L., Fuller, N., Osoba, T., Scott, L., Motlhaoleng, K., Rakgokong, M., Abraham, P., Variava, E., Martinson, N.A. (2016) The Use of Xpert MTB/Rif for Active Case Finding among TB Contacts in North West Province, South Africa. Tuberc Res Treat. 2016:4282313. **IF: not available**

Newton-Foot M, Warren R M, Sampson S L, van Helden P D and Gey van Pittius N C. The plasmid-mediated evolution of the mycobacterial ESX (Type VII) secretion systems. BMC Evol. Biol. (2016) 16:62. **IF: 3.406**

Gallant J L, Viljoen A J, van Helden P D and Wiid I J F. Glutamate Dehydrogenase Is Required by *Mycobacterium bovis* BCG for Resistance to Cellular Stress. PLoS ONE (2016) 11:e0147706. **IF: 3.057**

Macuamule C L S, Wiid I J, van Helden P D, Tanner M and Witthuhn R C. Effect of milk fermentation by kefir grains and selected single strains of lactic acid bacteria on the survival of *Mycobacterium bovis* BCG. Int. J. Food Microbiol. (2016) 217:170-176. **IF:3.445**

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Seifert M, Georghiou S B, Catanzaro D, Rodrigues C, Crudu V, Victor T C, Garfein R S, Catanzaro A and Rodwell T C. MTBDRplus and MTBDRsl Assays: The Absence of Wild Type Probe Hybridization and Implications for the Detection of Drug-resistant Tuberculosis. J. Clin. Microbiol. (2016). **IF:3.631**

Tomasicchio M, Theron G, Pietersen E, Streicher E, Stanley-Josephs D, van Helden P, Warren R and Dheda K. The diagnostic accuracy of the MTBDRplus and MTBDRsl assays for drug-resistant TB detection when performed on sputum and culture isolates. Sci Rep (2016) 6:17850. **IF:5.228**

Miller M, Michel A, van Helden P and Buss P. Tuberculosis in Rhinoceros: An Underrecognized Threat? Transbound Emerg Dis (2016). **IF:2.714**

Theron G, Venter R, Calligaro G, Smith L, Limberis J, Meldau R, Chanda D, Esmail A, Peter J and Dheda K. Xpert MTB/RIF Results in Patients with Previous Tuberculosis: Can We Distinguish True from False Positive Results? Clin. Infect. Dis. (2016). **IF: 8.736**

Losi M, Knights A J, Mariani F, Altieri A M, Paone G, Loxton A G, Chegou N N, Kenneth J, Alma M G, Colizzi V, Walzl G, Saltini C, Boyle J and Amicosante M. QuantiFERON-TB performance enhanced by novel *Mycobacterium tuberculosis*-specific antigens. Eur. Respir. J. (2016) 47:660-664. **IF: 8.332**

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Phelan J E, Coll F, Bergval I, Anthony R M, Warren R, Sampson S L, Gey van Pittius N C, Glynn J R, Crampin A C, Alves A, Bessa T B, Campino S, Dheda K, Grandjean L, Hasan R, Hasan Z, Miranda A, Moore D, Panaiotov S, Perdigao J, Portugal I, Sheen P, de Oliveira Sousa E, Streicher E M, van Helden P D, Viveiros M, Hibberd M L, Pain A, McNerney R and Clark T G. Recombination in pe/ppe genes contributes to genetic variation in *Mycobacterium tuberculosis* lineages. BMC Genomics (2016) 17:151. **IF: 3.867**

Miller M, Kruger M, Kruger M, Olea-Popelka F and Buss P. A Scoring system to improve decision making and outcomes in the adaptation of recently captured white rhinoceroses (Ceratotherium Simum) to captivity. J. Wildl. Dis. (2016) 52: S78-85. **IF: 1.189**

Farhat M R, Sultana R, Lartchouk O, Bozeman S, Galagan J, Sisk P, Stolte C, Nebenzahl-Guimaraes H, Jacobson K, Sloutsky A, Kaur D, Posey J, Kreiswirth B N, Kurepina N, Rigouts L, Streicher E M, Victor T C, Warren R M, van Soolingen D and Murray M. Genetic Determinants of Drug Resistance in *Mycobacterium tuberculosis* and Their Diagnostic Value. Am. J. Respir. Crit. Care Med. (2016). **IF: 13.118**

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Chisompola NK, Streicher EM, Warren RM, Sampson SL. Genetic diversity in drug resistant clinical isolates of *Mycobacterium tuberculosis* circulating within Ndola district; a high HIV prevalence district of Zambia. Antimicrobial Resistance and Infection Control 2016, 6(Suppl 1):1. DOI 10.1186/s13756-016-0153-0 **IF: 2.716**

Conferences/Meetings Attended & Invited Talks/Seminars Presented (Total=108)

Invited / Plenary / Keynote Lectures (11) National and International
Mizrahi, V. Identifying vulnerable steps in the CoA biosynthesis pathway of M. tuberculosis. Plenary lecture delivered at the ASBMB Annual Meeting, EB2016, San Diego, 4 April 2016
Mizrahi, V. Targeting core metabolic pathways in *Mycobacterium tuberculosis*. Invited talk, Chemistry Department, Ben-Gurion University of the Negev, Be'er Sheva, Israel, 7 June 2016
Mizrahi, V. The IMPDH, GuaB2, is a vulnerable bactericidal drug target for TB. Plenary lecture delivered at the EMBO Conference on Tuberculosis 2016: Interdisciplinary research on tuberculosis and pathogenic mycobacteria, Institut Pasteur, Paris, 19-23 September 2016
Mizrahi, V. Global health networks and networking. Plenary lecture, Imperial-UCT Graduate Summer School, Global Health Fellows Programme, University of Cape Town, 15 June 2016.
Kana, B.D. Amidase_3 domain-containing N-acetylmuramyl-L-alanine amidases are required for cell division in mycobacteria. EMBO conference on Bacterial morphogenesis, survival and virulence: Regulation in 4D. 27th November – 1 December 2016. Estuary Island Resort, Kerala, India
Kana, B.D. Differentially Culturable Tubercle Bacteria During TB Treatment. Catalysis Bacterial Load Meeting. Bill and Melinda Gates Foundation. 10th – 11th August 2016. Seattle, USA.
Kana, B.D. The Impact of differentially culturable organisms on transmission. Bill and Melinda Gates Foundation Aerobiology Summit. 22nd – 23rd March 2016. The Maxwell Hotel, Cape Town, South Africa.
Kana, B.D. Biomimicry for Innovation. Wits University Innovator's Forum. 15th September 2016. The Wits Club, University of the Witwaterstand, Johannesburg, South Africa.
Kana, B.D. Remodelling of the mycobacterial cell surface during tuberculosis disease: Separation anxiety and multiple personality disorder in mycobacteria. South African Society of Biochemistry and Molecular Biology. 10th-14th July 2016. East London International Convention Centre, East London, South Africa.
Kana, B.D. Transitions in Academic Careers. DST-NRF Postdoctoral Forum. 13th-15th March 2016. Lagoon Beach Hotel, Cape Town, South Africa.
Tabb DL. Keynote: Quality Control for Proteomics Keynote address presented at the HUPO-PSI 2016 meeting. University of Ghent, Ghent, Belgium, 18-20 April 2016.

Invited Talks (47) National and International
Reiche, M.A., Martin, Z., Lang, D., Dhar, N., McKinney, J.D., Mizrahi, V., and Warner, D.F. Visualizing the Mycobacterial Mutasome. Cape
Mbau, R.D. Whole-genome mutagenesis to elucidate the genetic requirements for vitamin B_{12} biosynthesis and assimilation in mycobacteria. Early Career Scientist Conference, SAMRC Conference Centre, Parow, 19-20 October 2016.
Evans, J. Validation of CoaBC as a bactericidal drug target in the coenzyme A pathway of *Mycobacterium tuberculosis*. Invited talk presented at the 2016 H3D Symposium, Goudini Spa, Western Cape, 15-18 November 2016
Singh, V. The inosine monophosphate dehydrogenase GuaB2 is a vulnerable new bactericidal drug target in *Mycobacterium tuberculosis*. Invited talk presented at the 2016 H3D Symposium, Goudini Spa, Western Cape, 15-18 November 2016
Ealand, C., Mashigo, L., Mapela, L., Beukes, G., Machowski, E., Chengalroyen, M. and Kana, B. Resuscitation promoting factors are required for biofilm formation in *Mycobacterium smegmatis*. Oral presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
Shaku. TM, Chengalroyen. MD and Kana. B. Characterization of LytM-domain containing proteins in Mycobacterium smegmatis. Oral presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
Papadopoulos. A. and Kana. B Breaking down walls! How do mycobacteria remodel their cell surface? Oral presentation at the Molecular Biosciences Research Thrust, University of the Witwatersrand. 8 December 2016. **Won second prize for best oral presentation.**
Peters, J.S., McIvor, A., Gordhan, B., Martinson, N., Waja, Z. and Kana B.D. Dynamics in DCTB decline during early treatment of tuberculosis. Oral presentation at the Clinical Symposium TB Centre meeting Vanderbilt University, TN, USA. 27 April 2016
Peters, J.S., McIvor, A., Gordhan, B., Martinson, N., Waja, Z. and Kana B.D. Strain distribution of infecting M. tuberculosis populations in two socio-economically diverse South African communities. Oral presentation at the

Soweto Matlosana Collaborative Centre for HIV/AIDS & TB (SoMCAT) young researchers conference. 18 November 2016
McIvor. A., Gordhan. B., Martinson. N. and Kana. B.D. Enhancing detection of *Mycobacterium tuberculosis* by the BACTEC MGIT 960 culture system. Oral Presentation at the MRC Soweto Matlosana Collaborating Centre for HIV/AIDS and TB Conference (SoMCHAT). 18 November 2016
Ralefeta D., Machowski E. and Kana B.D. Mycobacterial DD-Carboxypetidases: Filling In The Gaps. Oral Presentation at the Wits 7th Cross Faculty Symposium. 1-2 March 2016. **Won third prize for an oral presentation from the Faculty of Health Sciences**
Senzani. S., Dhar. N. and Kana. B.D. Identification and Characterization of Mycobacterial Cell wall amidases. Oral presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016. **Won first prize for an oral presentation by a student in the Infectious Diseases Track**
Maphatsoe. M., Ealand. C., and Kana. B. D. Localization of *Mycobacterium smegmatis* DD- Cpases and cell wall remodeling enzymes. Oral presentation at the Molecular Bioscience Research Thrust (MBRT). 08 December 2016
Chengalroyen M., Said H., Beylis N., da Silva P., Padanilam X., Radebe D., Ramsamy S., Louw R. and Kana B.D. Genotypic and phenotypic heteroresistance of extensively drug resistant TB isolates. Oral presentation at the Somchat Young Researchers Conference. 18 November 2016
Narrandes. N. and Kana. B.D. Characterization of the mycobacterial electron transport chain- Implications for drug efficacy. Oral presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016. **Won first prize for an oral presentation by a student in the Molecular and Comparative Biosciences Track**
Loxton AG. Discovery of new TB Biomarker Candidates Talk presented at the TB Vaccine meeting 2016. Eurotel Victoria Hotel, Les Diablerets, Switzerland, 21 January-05 February 2016.
Whitfield MG, Streicher EM, Dolby T, Simpson JA, Sampson SL, van Helden PD, van Rie A, Warren RM. Prevalence of pyrazinamide resistance across the spectrum of drug resistant phenotypes of *Mycobacterium Tuberculosis* Talk presented at the 37th Annual Congress of the European Society of Mycobacteriology. Sheraton Catania Hotel & Conference Center, Catania, Sicily, Italy, 03-06 July 2016.
Whitfield MG, Streicher EM, Dolby T, Simpson JA, Sampson SL, van Helden PD, van Rie A, Warren RM. Prevalence of pyrazinamide resistance across the spectrum of drug resistant phenotypes of *Mycobacterium Tuberculosis* Talk presented at the 2nd Acid Fast Cape Town Meeting. Stellenbosch University, Cape Town, South Africa, 08 November 2016.
Tabb DL. Studying Bioinformatics at SUN Talk presented at the Square Kilometer Array Data Science Career Workshop. Sol Plaatjie University, Kimberley, South Africa, 07-08 September 2016.
Tabb DL. Quality Control for Proteomics Talk presented at the National Institute of Biological Sciences, Beijing, China, 20 September 2016.
Tabb DL. Publishing in a consortium Talk presented at the Phoenix Center, Beijing, China, 20 September 2016.
Tabb DL. Identification with Unbounded Databases Talk presented at the Institute for Computing Technology, Beijing, China, 21-22 September 2016.
Tabb DL. Publishing in a Consortium Talk presented at the Shanghai Jiao Tong University, Shanghai, China, 28 September 2016.
Van Helden PD. Drug Susceptibility testing: yesterday, today and tomorrow in the context of heteroresistance Talk presented at the Malaria, Tuberculosis and neglected tropical diseases: Progress in drug discovery and development. Goudini spa, Cape Town, South Africa, 15-18 November 2016.
Grobbelaar M, Sampson SL, Louw GE, Victor TC, van Helden PD, Warren RM and de Vos M . Phosphate ABC transporter system regulates the level of rifampicin resistance in *Mycobacterium Tuberculosis* Talk presented at the 37th Annual Congress of the European Society of Mycobacteriology. Sheraton Catania, Catania, Sicily, 03-06 July 2016.
Willemse D, Weber B, Warren RM, Adinolfi S, Pastore A, Williams MJ. Regulation of iron-sulphur cluster biogenesis in *Mycobacterium Tuberculosis* Talk presented at the FMHS 60th Annual Academic Year Day. Stellenbosch University, Cape Town, South Africa, 11 August 2016.
Chegou NN. Diagnostic Performance of a Seven-marker Serum Protein Biosignature for the Diagnosis of Active TB disease in African Primary Health Care Clinic Attendees with Signs and Symptoms Suggestive of TB Talk presented at the South African Immunology Society Congress. GLENBURN LODGE & SPA, Johannesburg, South Africa, 06 March-09 November 2016.
Miller M. TB in Wildlife Talk presented at the International Conservation Workshop for Arabias Biodiversity. Conservation Workshop, Sharjah, United Arab Emirates, 08-11 February 2016.
Miller M. Tuberculosis in Under-Recognized Species – Is this an Emerging Disease Threat? Talk presented at the American Association of Zoo Veterinarians Annual Conference. Sheraton Hotel Conference Center, Atlanta, USA, 16-22 July 2016.
Miller M. Infectious Disease Threats to Wild Mammals in Southern Africa: Risks at Intra- and Interspecies Interfaces Talk presented at the Mammal Research Institute 50th Anniversary Workshop. Mopani, Kruger National Park, Mopani, South Africa, 12-15 September 2016.
Miller M. IP-10 Enhances the Diagnosis of Bovine Tuberculosis in African Buffaloes Talk presented at the U.S. Animal Health Association Annual Conference. Greensboro Conference Center, Greensboro, USA, 15-20 October 2016.
Theron GDV, Reeve BW. How well do different diagnostic tests detect heteroresistance in tuberculosis patients? Talk presented at the Departmental Meeting. Lecture Hall 7, Cape Town, South Africa, 23 September 2016.

Mujuru TN. How well do different diagnostic tests detect heteroresistance in tuberculosis patients? Talk presented at the Departmental Meeting. Lecture Hall 7, Cape Town, South Africa, 23 September 2016.
Warren RM. The genetic basis of drug resistance in tuberculosis Talk presented at the Diagnosis and Management of Drug-Resistant Tuberculosis, ESCMID Postgraduate Technical Workshop. University of Cape Town Faculty of Health Sciences, Cape Town, South Africa, 18 January 2016.
Warren RM. Overview of drug resistant tuberculosis Talk presented at the Infectious Diseases Day. University of Pretoria, Pretoria, South Africa, 12 February 2016.
Warren RM. Drug Resistant Tuberculosis – lessons from South Africa Talk presented at the SACORE Meeting. Lilongwe, Lilongwe, Malawi, 01 March 2016.
Warren RM. Lights-on Light-off: clinical evaluation in South Africa Talk presented at the CPTR Workshop 2016. Washington, Washington, United States of America, 04-07 April 2016.
Warren RM. Biomolecular diagnostics, gene sequencing and whole genome sequencing Talk presented at the Tenth International Child TB Training Course. Goudini Spa, Cape Town, South Africa, 27 September 2016.
Haylett W, Neethling A. Exploring mitochondrial dysfunction in LRRK2 and Parkin cellular models of Parkinson's disease Talk presented at the FMHS 60th Annual Academic Year Day. Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, 01 August 2016.
Borrageiro G. Investigation of differential gene expression in Parkinson's disease patients:A whole transcriptome approach Talk presented at the FMHS 60th Annual Academic Year Day. Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa, 11 August 2016.
Miller M. Evaluation of serum ferritin in free-ranging black rhinoceros as a tool to understand factors affecting iron overload disorder Talk presented at the 2nd international Workshop on Iron Overload Disorder in Browsing Rhinoceros. Disney's Animal Kingdom, Orlando, USA, 21-22 January 2016.
Bibi Sebate. Targeted-resequencing of genes involved in neurological conitions in South African patients with Parkinson's disease Talk presented at the Biomedical Sciences Research Day. Lecture Hall F139, Cape Town, South Africa, 15-23 November 2016.
Bardien S. Targeted-resequencing of genes involved in neurological conitions in South African patients with Parkinson's disease Talk presented at the African Society of Human Genetics meeting. Dakar, Dakar, Senegal, 15-17 May 2016.
Bardien S. The genetics of Parkinson's disease in South Africa Talk presented at the Congress of the Neurological Association of South Africa. Central Drakensberg, Kwa-Zulu Natal, South Africa, 15-20 March 2016.
Oluwole OG. A pilot study to evaluate a targeted resequencing approach for identification of pathogenic mutations in South African Parkinson's disease patients Talk presented at the South African Association of Neuroscience Symposium. UCT Medical School University of Cape Town, Cape Town, South Africa, 09-11 December 2016.
Mouton JM, Elucidating population-wide mycobacterial replication dynamics at the single-cell level. The Acid-Fast Club, University of Cape Town, South Africa, May 2016, Oral Presentation.
Van Helden P, Drug Susceptibility Testing: Yesterday, Today and Tomorrow in the context of Heteroresistance. H3D Pioneering World-class Drug Discovery in Africa, 15-18 November 2016, Goudini Spa, Western Cape.

Posters (50) National and International
Masuku, B., Young, E., Mizrahi, V., Wilkinson, R. J., Mkhwanai, N., Koch, A. and Warner, D. F. Beyond the lab and behind the lens: An anthropological exploration of a youth-based community engagement initiative and its reflection of the lived experience of TB in Khayelitsha, Cape Town. TB2016, International AIDS Society, Durban, 16-17 July 2016
Sewgoolam, B. Koch, A., Mizrahi, V. & Warner, D.F. Investigating the fitness cost of rifampicin-resistance in mycobacteria. TB2016, International AIDS Society, Durban, 16-17 July 2016
Koch, A., Brites, D., Stucki, D., vans, J., Seldon, R., Nicol, M., Oni, T., Warner, D.F., Mizrahi, V., Parkhill, J., Gagneux, S., Marin, D., Wilkinson, R.J. The evolution of *Mycobacterium tuberculosis* in HIV co-infected individuals in an HIV/TB endemic setting. Poster presented at the EMBO Conference on Tuberculosis 2016: Interdisciplinary research on tuberculosis and pathogenic mycobacteria, Institut Pasteur, Paris, 19-23 September 2016
Sewgoolam, B., Koch, A., Mizrahi, V., Warner, D.F. Investigating the cost of rifampicin resistance in mycobacteria. Poster presented at the EMBO Conference on Tuberculosis 2016: Interdisciplinary research on tuberculosis and pathogenic mycobacteria, Institut Pasteur, Paris, 19-23 September 2016
Reiche, M., Martin, Z., Lang, D., Dhar, N., McKinney, J.D., Mizrahi, V., Warner, D.F. Recruitment and regulation of the mycobacterial mutasome. Poster presented at the EMBO Conference on Tuberculosis 2016: Interdisciplinary research on tuberculosis and pathogenic mycobacteria, Institut Pasteur, Paris, 19-23 September 2016
Ray, P., Boshoff, H., Arora, K., Tsang, P., Bayliss, N., Harrison, J., Murugesan, D., Buchanan, K., Green, S., Zucotto, F., Read, K., Scullion, P., Epemolu, R., McKenzie, C., Mizrahi V., Warner, D.F., Barry, C., Wyatt, P. Poster presented at the EMBO Conference on Tuberculosis 2016: Interdisciplinary research on tuberculosis and pathogenic mycobacteria, Institut Pasteur, Paris, 19-23 September 2016
Van der Westhuyzen, R., Moosa, A., Naran, K., Warner, D.F., Chibale, K. Pyrrolo-[3,4-c]-pyridine-1,3(2H)-diones: a novel antimycoacterial class targeting mycobacterial respiration. Poster presented at the EMBO Conference on Tuberculosis 2016: Interdisciplinary research on tuberculosis and pathogenic mycobacteria, Institut Pasteur, Paris, 19-23 September 2016

van Coller, S.J., Ioerger, T. R., Mizrahi, V., Warner, D.F. DnaE2 plays no role in starvation-induced adaptive mutagenesis in *Mycobacterium tuberculosis*. DNA polymerase meeting: from molecular function to human diseases, Biarritz, France, 4–8 October 2016
Agarwal, P., and Mizrahi, V. Growth, persistence and drug susceptibility of *Mycobacterium tuberculosis* in foamy macrophages: implications for TB drug discovery. Poster presented at Metchnikoff's Legacy: Tissue Phagocytes and Function. Napoli, Italy 12-14 October 2016
Morrow, C., Bryden, W., Silcott, D., Warner, D.F., Scriba, T., Blackburn, J., Mizrahi, V., and Wood, R. Real-time investigation of tuberculosis transmission. Poster presented at the 47th Union World Conference on Lung Health, Liverpool, 24-26 October 2016
Omollo, C; Chibale,K, Warner D. Developing synergistic combinations to restore sensitivity in drug-resistant *Mycobacterium tuberculosis*. Poster presentation at a Drug discovery Symposium on Tuberculosis and Neglected Diseases, Goudini Spa Resort, Cape Town, 15-18 November 2016
Sikhosana. N., Chengalroyen M. and Kana. B. Mycobacterium amidases: Biological function and putative role in cell wall remodelling. Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
Papadopoulos. A. and Kana. B. Characterisation Of M23-Domain Activators of Peptidoglycan Degrading Amidases in *Mycobacterium tuberculosis*. Poster presentation at the 7th Cross-faculty Postgraduate Symposium, University of the Witwatersrand. 1-2 March 2016
Papadopoulos. A. and Kana. B A novel family of proteins in *Mycobacterium tuberculosis* with putative, differential roles in bacterial cell wall degradation. Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
McIvor. A., Peters. J., Papadopoulos. A., Gordhan. B., Martinson. M., Letutu. M. and Kana. B.D. Decline in non-culturable tubercle bacteria in HIV-positive and HIV-negative tuberculosis patients during early first-line treatment Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
McIvor. A., Peters. J., Papadopoulos. A., Gordhan. B., Martinson. M., Letutu. M. and Kana. B.D. Decline in non-culturable tubercle bacteria in HIV-positive and HIV-negative tuberculosis patients during early first-line treatment. Poster presentation at the Molecular Biosciences Research Thrust Postgraduate Research Day. 8 December 2016. **Won second prize for best poster presentation.**
Ralefeta D., Machowski E. and Kana B.D. Mycobacterial DD-CArboxypetidases: Filling In The Gaps. Poster presentation at the Wits 7th Cross Faculty Symposium. 1 September 2016
Mashilo. P. and Kana. B.D. Characterization of mycobacterial peptidoglycan remodelling enzymes. Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
Mashilo. P. and Kana. B.D. Characterization of mycobacterial peptidoglycan remodelling enzymes. Poster presentation at the Molecular Biosciences Research Thrust Research Day. 8 December 2016
Maphatsoe. M., Ealand. C., and Kana. B.D. Cellular localization of low molecular weight penicillin binding proteins and other cell wall remodelling enzymes in *Mycobacterium smegmatis*. Poster presentation at the Biennial Research Day and Postgraduate Expo, Faculty of Health Sciences. 01 September 2016
Chengalroyen M., Beukes G., Gordhan B., Martinson N., Otwombe K. and Kana B.D. The detection and quantification of differentially culturable tubercle bacteria in sputum from tuberculosis patients. Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
Narrandes. N. and Kana. B.D. Characterization of the mycobacterial electron transport chain. Poster presentation at the MBRT Postgraduate Research Day. Wits Club, West Campus, university of the Witwatersrand. 8 December 2016. **Won third prize for best poster presentation.**
Mashigo. L., Ealand. C. and Kana. B.D. DacB is essential in *Mycobacterium smegmatis*. Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
Manamela. N., Kana. B.D. and Gordhan. B. DNA repair and mutagenesis in *Mycobacterium smegmatis*. Poster presentation at the Faculty of Health Sciences Biennial Research Day and Postgraduate Expo. 1 September 2016
du Plessis N, Jacobs R, Fang Z, van Helden P, Lutz M, Walzl G. TUBERCULOSIS: Investigations into the role of MDSC Poster presented at the Regulatory Myeloid Suppressor Cells: From Basic Discovery to Therapeutic Application. Wistar Institute, Philadelphia, USA, 23-26 June 2016.
Kleynhans L, Tshivhula H, Kunsevi C, Ronacher K. Changes in Endocrine and Immune Signatures during TB treatment Poster presented at the Keystone Symposium: B6, Tuberculosis Co-Morbidities and Immunopathogenesis. Keystone Resort, Colorado, USA, 28 February- 03 March 2016.
Niemand N, Weber B, Williams MJ. Investigating the function of A-type carrier proteins in mycobacteria Poster presented at the South African Society of Biochemistry and Molecular Biology (SASBMB). East London ICC, East London, South Africa, 10-13 July 2016.
Loxton AG. The Functional Response of B cells to Antigenic Stimulation during Latent Tuberculosis Poster presented at the International Conference of Immunology 2016. Melbourne Convention Centre, Melbourne, Australia, 21 August-27 November 2016.
Loxton AG, van Rensburg I. The Functional Response of B cells to Antigenic Stimulation during Latent Tuberculosis Poster presented at the B Cells at the Intersection of Innate and Adaptive Immunity (E3) - Keystone Symposia. Clarion Hotel Sign, Stockholm, Sweden, 29 May- 02 June 2016.

Salie M, Schurz H, van Helden PD, Möller M, Hoal EGl. Genetic contributions to the MHC and LRC regions of a South African population and its effect on TB vaccine efficacy Poster presented at the The American Society of Human Genetics 66th Annual Meeting. Vancouver Convention Centre, Vancouver, Canada, 18-22 October 2016.
Kreiswirth B, Rice J, Wangh L, Whitfield MG, Warren RM, Posey J, Bifani P, Marras S. Virtual sequencing of the entire pncA gene target in a single tube using Late-PCR and Lights-On/Lights-Off probes to predict PZA susceptibility Poster presented at the 37th Annual Congress of the European Society of Mycobacteriology. Sheraton Catania Hotel & Conference Center, Catania, Sicily, Italy, 03-06 July 2016.
Sylvester TT, van Helden P, Miller MA, Parsons SDC, Loxton AG. Screening of commercially available antibodies for flow cytometric analysis in African lions (Panthera leo) : A pilot study Poster presented at the FMHS 60th Annual Academic Year Day. Teaching Building, Tygerberg Campus, Stellenbosch University, Cape Town, South Africa, 11 August 2016.
Willemse D, Warren RM, Williams MJ. Truncation of Rv1460 increases sensitivity of *Mycobacterium tuberculosis* to oxidative stress Poster presented at the H3D Symposium. Goudini Spa, Cape Town, South Africa, 15-18 November 2016.
Malherbe ST, Ronacher K, Warwick J, Walzl G. Tuberculosis treatment response with 18F-FDG-PET/CT imaging Poster presented at the Western Cape Provincial Health Research Day. SUN Faculty of Medicine Health Sciences, Tygerberg, Cape Town, South Africa, 04 November 2016.
Werely C, Cloete R, Akurugu W, van Helden P, Christoffels A. Modelling the Structural and functional effects of nucleotide polymorphisms in the NAT1 drug metabolising enzyme. Poster presented at the 8th Santorini Conference Biology Prospective: Systems Medicine, Personalised Health and Therapy. European Society of Pharmacogenomics and Personalised Therapy. Petros M. Nomikos Conference Centre, Thira, Santorini Island, Greece, 03-05 October 2016.
Naidoo CC. Extensively drug-resistant M. tuberculosis strains of the F15/LAM4/KZN genotype exhibit enhanced proinflammatory cytokine induction in THP-1 macrophages Poster presented at the 2016 TB SUMMIT. The ICC, Durban, South Africa, 16-17 July 2016.
Venter R, Derendinger B, de Vos M, Naidoo S, van Helden PD, Warren R, Theron, G. DNA extracted from used Xpert MTB/RIF cartridges can be used for second-line drug susceptibility testing. Poster presented at the 2016 TB SUMMIT. The ICC, Durban, South Africa, 17 July 2016.
Leisching G, Pietersen R-D, Mpongoshe V, van Heerden C, van Helden P, Wiid I, Baker B. The Host Response to a Clinical MDR Mycobacterial Strain Cultured in a Detergent-Free Environment: A Global Transcriptomics Approach Poster presented at the Tuberculosis Co-Morbidities And Immunopathogenesis. Keystone, Colorado, USA, 29 February-03 March 2016.
Sao Emani C, Williams M, Wiid I, Van Helden P, Baker B. The role of ergothioneine in the physiology of Mycobacterium smegmatis. Poster presented at the Keystone Symposia Conference: Tuberculosis Co-Morbidities and Immunopathogenesis, Keystone, Colorado, USA, 28 February – 03 March 2016.
Derendinger B, de Vos M, van Helden PD, Warren RM, Theron G. Decreased sensitivity and increased indeterminate rates of GenoType MTBDRplus (v2.0) are associated with use of inappropriate PCR ramp rate: Implications for routine diagnostic laboratories Poster presented at the 2016 TB SUMMIT. Durban International Conference Centre, Durban, South Africa, 16-17 July 2016.
Pule C. Underlying physiological changes of drug resistant *Mycobacterium tuberculosis* Poster presented at the 2016 TB SUMMIT. Cineworld, Greenwich, London, UK, 21-23 June 2016.
Jacobs R, Walzl G, Chegou NN. Evaluation of novel host markers detected in plasma and saliva as biosignatures for the rapid diagnosis of TB disease and monitoring of the response to TB treatment Poster presented at the 5th South African Society for Immunology Congress. GLENBURN LODGE & SPA, Johannesburg, South Africa, 06-09 March 2016.
Jacobs R, Walzl G, Chegou NN. Identification of novel tuberculosis diagnostic biomarkers in plasma and saliva Poster presented at the European Respiratory Society International Congress 2016. London ExCel, London, United Kindgom, 03-07 September 2016.
Jacobs R, Walzl G, Chegou NN. Identification of novel plasma and salivary biosignatures for the diagnosis of TB disease and monitoring of treatment response Poster presented at the 8th EDCTP Forum. New Government Complex, Lusaka, Zambia, 06-09 November 2016.
Haylett W. ATPAF1 and SEPT9 are novel protein substrates of Parkin Poster presented at the 11th Annual Meeting of the Genetic Epidemiology of Parkinson's Disease Consortium and the 3rd International Parkinson's Disease Symposium. Luxembourg Centre for Systems Biomedicine, University of Louxembourg, Esch-Sur-Alzette, Luxembourg, 05-08 October 2016.
Borrageiro G. Investigation into the genetic etiology in South Africa Parkinson's disease patients Poster presented at the 20th International Congress of Parkinson's Disease and Movement Disorders. City Cube, Berlin, Germany, 19-23 June 2016.
Oluwole OG. A pilot study to evaluate a targeted resequencing approach for identification of pathogenic mutations in South African Parkinson's disease patients Poster presented at the FMHS 60th Annual Academic Year Day. Faculty of Medicine and Health Sciences, Tygerberg Campus, SU, Cape Town, South Africa, 11 August 2016.

Oluwole OG. A pilot study to evaluate a targeted resequencing approach for identification of pathogenic mutations in South African Parkinson's disease patients Poster presented at the Biomedical Science Research Day. Faculthy of medicine and Health Sciences, Tygerberg campus, SU, Cape Town, South Africa, 23 November 2016.
Willemse D., Weber B., Warren R.W., Williams M.J. Rv1460 functions as a repressor of the Rv1460-Rv1461-Rv1462-Rv1463-csd-Rv1465-Rv1466 operon in *Mycobacterium tuberculosis* (Student poster presentation, Keystone Symposium, New Developments in Our Basic Understanding of Tuberculosis (A5), Vancouver, British Columbia Canada January 14—18, 2017).
Baatjies L., Niemand N. and Williams M.J. Investigating the susceptibility of a *Mycobacterium smegmatis MSMEG_4272* conditional mutant to various compounds. (Student poster presentation, H3D Symposium 2016, Goudini Spa, Western Cape, 15 – 18 November 2016).

Products / Artifacts / Patents

Title: **Host biomarkers for immunodiagnosis and monitoring of tuberculosis disease.** Inventors: Jacobs, R, Walzl, G, **Chegou, NN,.** Applicant: Stellenbosch University, Application type: Provisional patent application, Country: South Africa, Application: **ZA 2016/02557**, Filing date: 2016/04/15, Status: **Expired, PCT Filed;**

Same patent: Country: PCT/WIPO, Application number: **PCT/IB2017/052142,** Filing date: 13/04/2017, **Status: Pending**

Progress of CBTBR Trainees (2016)

Postdoctoral Fellows who completed their fellowships in 2016

Title	Surname	Institution	Current Position
Dr	Banda	SU	Registered for an MSc in Information Technology at UCT, 2017
Dr	Sakar	SU	Unknown
Dr	Van Der Merwe	SU	Employed at Roche
Dr	Fortuin	SU	Post-doc UCT
Dr	Styger	SU	Unknown
Dr	Chengalroyen	Wits	Still working in Science, will be taking up a position at the UCT node in July 2017
Dr	Ealand	Wits	Appointed as a Researcher at the Wits node
Dr	Longwe	Wits	Unknown
Dr	Singh	UCT	Took up a position as a Research Officer in the H3D Centre for Drug Discovery and Development at UCT.
Dr	Mukherjee	UCT	Returned to India to take up a faculty position at ISER-Tirupati
Dr	Majumdar	UCT	Returned to India for personal reasons
Dr	Macingwana	UCT	Took up a faculty position at Walter Sisulu University

Postgraduate students who graduated in 2016

Surname	Name	Degree	Institution	Current Position
Botha	Nicole	BSc Hons	SU	Unknown
De Buys	Keren	BSc Hons	SU	Registered as MSc at SU / SAMRC 2017
Francois	Sydney	BSc Hons	SU	Unknown
Gutridge	Ashley	BSc Hons	SU	Unknown
Nagel	Simone'	BSc Hons	SU	Registered as MSc at SU 2017
Okugbeni	Naomi	BSc Hons	SU	Registered as MSc at SU 2017
Sebate	Bibi	BSc Hons	SU	Registered as MSc at SU 2017
Shabangu	Ayanda	BSc Hons	SU	Registered as MSc at SU 2017
Sparks	Anel	BSc Hons	SU	Registered as MSc at SU 2017
Theron	Jessica	BSc Hons	SU	Research Assistant in Psychiatry, SU 2017

Theys	Janice	BSc Hons	SU	Research Assistant, TB Host Genetics (ResisTB)
Zimmerman	Dominic	BSc Hons	SU	Unknown
Mashigo	Lethabo	BSc Hons	Wits	
Manemela	Nelia	BSc Hons	Wits	
De Wet	Timothy	BSc Hons	UCT	Registered for a PhD degree in the UCT node as an intercalated MBBCh-PhD student
Taylor	Kaitlin	BSc Hons	UCT	Registered for an MSc degree in the UCT node
Trevor	Tamzyn	BSc Hons	UCT	Resumed MBBCh studies at UCT
Alley	Philbe-Jeanne	MSc	SU	Unknown
Benecke	Rohan	MSc	SU	Unknown
Borrageiro	Genevie	MSc	SU	Registered for MBChB, SU
Bowker	Nicholas	MSc	SU	Working in UK
Clarke	Charlene	MSc	SU	Working as a Research Assistant / Technician at SU
Colic	Antoinette	MSc	SU	Working
Da Camara	Ncite	MSc	SU	Unknown
Jacobs	Ruschca	MSc	SU	Registered for MBChB at SU
Klazen	Jessica	MSc	SU	Working at Nam Water in Namibia
Parbhoo	Trisha	MSc	SU	Registered for PhD at SU 2017
Polson	Alma	MSc	SU	English teacher in Thailand
Selamolela	Mosa	MSc	SU	Registered as PhD student at Tuks
Van Rensburg	Ilana	MSc	SU	Working as English teacher abroad
Zass	Lyndon	MSc	SU	Unknown
Siame	Kabengele	MSc	SU	Unknown
Ralefeta	Ditshego	MSc	Wits	Completing a PhD at the Wits node in 2017
Nthambeleni	Gadisi	MSc	Wits	Completing an HPCSA accredication course
Ismail	Zaahida sheik	MSc	Wits	Working in Industry
Baartes	Nadia	MSc	UCT	Unknown
Awoniyi	Dolapo	PhD	SU	Joined Desmond Tutu TB Centre at SU as a Manager
Goosen	Wynand	PhD	SU	Registered as a Postdoctoral Fellow at UCT, LIIU
Grobbelaar	Melanie	PhD	SU	Registered as a Postdoctoral Fellow at SU node
Hammond-Aryee	Kenneth	PhD	SU	Moved back to Ghana, looking after family business, and seeking job opportunity in Science
Kayigire	Xavier	PhD	SU	Registered as a Postdoctoral Fellow at SAMRC
Malherbe	Stephanus	PhD	SU	PI of clinical team at SU node
Mc Grath	Marieta	PhD	SU	Housewife
Mphahlele	Matsie	PhD	SU	Working
Neethling	Annika	PhD	SU	Registered as a Postdoctoral Fellow at SU node
Schlechter	Nikola	PhD	SU	Registered as a Postdoctoral Fellow at SU node
Viljoen	Ignatius	PhD	SU	Registered as a Postdoctoral Fellow at SU node
Whitfield	Michael	PhD	SU	Registered as a Postdoctoral Fellow at SU node
Willemse	Danicke	PhD	SU	Registered as a Postdoctoral Fellow at SU node

FINANCES

The income statement, balance sheet and cash flow statement for period 1 Jan 2016 to 31 Dec 2016 have been reviewed and approved by the external auditors and will be forwarded to the Board.

Table 7: Summary of the cumulative funding for 2016

	Funding Sources			
	CoE - NRF	**Other - NRF**	**Institution**	**National / International**
UCT	R1 578 942,00	R751 736,00	R157 894,00	R15 377 607,00
Wits	R2 442 333,00	R764 748,00	R2 123 703,00	R8 095 221,00
SU	R7 276 548,00	R9 859 827,00	R1 731 452,00	R43 208 745,62