DST/NRF CENTRE OF EXCELLENCE FOR BIOMEDICAL TB RESEARCH

DST-NRF CENTRE OF EXCELLENCE

ANNUAL PROGRESS REPORT

Reporting Period

1 January 2017 – 31 December 2017

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	February 2018

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EXECUTIVE SUMMARY

1. Financial Information (Funding of the CoE)

Table 1: Cumulative NRF funding for 2017

Total DST/NRF Funding contributed to the CBTBR (3 Nodes) for 2017	R11 862 714,00
CoE Specific Funding from Hosts in 2017	
UCT	**R450 000,00**
Wits	**R1 910 843,79**
SU	**R6 217 530,00**
Funding from other sources to the CBTBR in 2017	**R103 250 548,24**
Cumulative Total funding for 2017	**R123 691 636,03**

Table 2: Breakdown of Funding – UCT – 2017

Total funding for 2017 for UCT node:	**R17 272 485,00**	
CoE funding from NRF:	**R1 578 942,00**	
Other funding from NRF:	**R515 538,00**	[1]
Funding from UCT (excluding salaries):	**R450 000,00**	[2]
Funding from other sources:[3]	**R14 728 005,00**	made up as follows:
SAMRC Unit (MMRU; Mizrahi)	R1 107 616,00	
FNIH (SHORTEN-TB) (Mizrahi)	R7 430 287,00	
Broad Institute (Mizrahi)	R389 205,00	
HHMI SIRS grant (Mizrahi)	R1 395 042,00	
SAMRC SHIP (Drug Discovery, Warner)	R808 737,00	
SAMRC Internship Scholarship (Mbau)	R200 000,00	
SAMRC Med Stud. Training Program (de Wet)	R120 000,00	
SAMRC Newton Fund grant (Warner)	R400 000,00	
University of Oslo (Warner)	R483 060,00	
US NIH (sub-award from Stanford, Warner)	R528 525,00	
US NIH U01 (Warner)	R1 865 533,00	[4]

1[1] Incentive Funding for Rated Researchers (V. Mizrahi, R100,000; D. Warner – R 40,000) Competitive Programme for Rated Researchers (D. Warner – R 228,960); SA/Zambia Research Cooperation grant (D. Warner - R71,576); Community Engagement Award (D. Warner) - R 75,000).
1[2] Faculty Research Committee grant to SAMRC Unit (V Mizrahi - R100,000); Carnegie Corporation doctoral fellowship for C. Omollo (D. Warner – R 250,000); FRC grant for emerging researchers (M Chengalroyen)
1[3] Where applicable, grant awards from external funders include indirect costs (IDC), and ZAR values are calculated based on landed e-rates

1[4] UO1 grant awarded under the NIH-SAMRC South Africa-US program for Collaborative Biomedical Research

Table 3: Breakdown of Funding – Wits – 2017

Total funding for 2017 for Wits node:	**R9 981 904,91**	
CoE funding from NRF:	**2442333.00**	
Other funding from NRF:	**1025746.00**	made up of:
Incentive Funding (Kana)[1]	80000.00	
NRF CPRR Grant	R320 000,00	
Swiss-SA (NRF/SNSF) [2]	R625 746,00	
Funding from Wits and NHLS:	**R1 910 843,79**	made up of
10% Wits Institutional Commitment	R244 233,30	
Research Incentive Funding	R33 499,78	
Research Incentive Funding (SOP)	R24 300,00	
Salaries[3]	R1 408 925,00	
TIA – WITS Seed Fund[4]	R199 885,71	
Funding from other sources:	**R4 602 982,12**	made up of
Stanford University Subcontacts[5]	R2 370 599,12	
MRC Career Development Award[6]	R1 200 000,00	
Andrea Research Grant	R8 000,00	
Edith Machowski Grant	R25 000,00	
MRC India Grant	R999 383,00	

[1] NRF Incentive Funding to BD Kana – Year 3

[2] SA-Swiss Year 1 to B. Kana

[3] Wits Salary Contribution B. Kana and C. Ealand

[4] To B. Kana

[5] Year ½ to B. Kana

[6] Year 2 MRC Career Award to C. Ealand

Table 4: Breakdown of Funding – SUN – 2017

Total funding for 2017 for SU node:	**R96 437 246,12**	
CoE Funding from NRF 2016	**R7 841 439,00**	
Funding from Instituite - SUN	**R6 217 530,00**	made up of:
CoE Specific Funding from Host Instituite	R900 380,00	
SU - Faculty contribution to salaries	R5 317 150,00	
International Funding	**R48 422 285,00**	made up of:
NIH LATE-PCR - CGDR	R1 950 000,00	
NIH Fluoroquinolone - CGDR	R260 000,00	
Hain Lifescience - CGDR	R500 000,00	
FWO - CGDR	R1 000 000,00	
NIH TRUST - CGDR	R669 500,00	
NIH OpitQ - CGDR	R299 000,00	
Yale -CGDR	R182 000,00	
UCT/SWISS - CGDR	R300 000,00	
NIH CASS - CGDR	R400 000,00	
Thermofisher - CGDR	R240 000,00	
SANBI -CGDR	R420 000,00	
FIND - CGDR	R200 000,00	
XACTII - CGDR	R75 000,00	
NIH ResisTB (6 months) - Host Genetics	R1 788 500,00	
NIH PAEDS (LEVINE)	R1 269 000,00	
EDCTP (ScreenTB project) - Immunology	R2 847 854,00	
NEXGEN (NIH) - Immunology	R1 625 000,00	
NEXGEN (NIH) -OTSUKA	R90 000,00	
NEXGEN-BMGF	R1 215 000,00	
ICIDR (NIH) - IRG	R1 495 000,00	
TBVAC - IRG	R969 931,00	
CORTIS (BMGF) - IRG	R883 805,00	
Cortis -HR	R850 000,00	
Cortis- biobanking	R90 000,00	
Report	R650 000,00	
ALERT (NIH) - IRG	R4 500 000,00	
VPM/SII - IRG	R3 200 000,00	
AERAS-BIOBANKING	R2 100 000,00	
PREDICT-EDCTP	R6 500 000,00	
PREDICT-FNIH	R5 100 000,00	
TESA II EDCTP	R2 100 000,00	
EDCTP - CLIME	R1 410 510,00	
Quidel Corporation - CLIME	R864 303,00	
Norwegian Institute of Public Health - CLIME	R15 790,00	
AAZV Wild Animal Health Fund - Animal TB	R69 836,00	
WDA small grants - Animal TB	R54 825,00	
UCSF - CLIME	R190 020,00	

CFAR-CLIME	R322 066,00	
Harvard Global Health-CLIME	R1 050 361,00	
Stanford - CLIME	R674 984,00	
National Funding	**R22 591 660,62**	made up of:
MRC TB HART - CGDR	R280 000,00	
MRC NEXT - CGDR	R400 000,00	
Harry Crossley Project funding - Host Pathogen Mycobactomics	R148 640,00	
NHLS - Host Genetics	R250 000,00	
SAMRC - Baseline	R3 106 398,00	
SAMRC Biosafety	R300 000,00	
SAMRC Equipment	R750 000,00	
SAMRC Student	R500 000,00	
SAMRC Salary	R9 002 376,00	
SAMRC Career development awards	R600 000,00	
MRC SHIP - SATBBI- Bioinformatics/IRG	R2 800 000,00	
TIA -IRG-CHEGOU	R463 214,00	
MRC SHIP - IRG	R1 500 000,00	
SAMRC SATRI Grant - PVH	R930 409,00	
MRC BAR-TB - CLIME	R1 257 378,00	
SAVF - Animal TB	R100 000,00	
MRC Flagship MalTB Redox Project - TB Drugs	R203 245,62	
Other NRF Funding	**R10 178 471,00**	made up of:
NRF - SARChI - Host Pathogen Mycobactomics	R1 566 810,00	
NRF - CSUR - Host Pathogen Mycobactomics	R330 000,00	
NRF - IRG - South Africa / Tunisia Research Cooperation Programme - Host Pathogen Mycobactomics	R203 000,00	
NRF Research career award - Iron sulphur cluster	R100 000,00	
NRF Research career award - CGDR	R300 000,00	
NRF Incentive funding - CGDR (RMW)	R80 000,00	
NRF incentive funding -CGDR (EMS)	R40 000,00	
NRF Competitive funding - CGDR (RMW)	R430 000,00	
NRF - Career Award - CGDR (EMS)	R150 000,00	
Harry Crossley	R100 000,00	
Claude Leon - CGDR (MW)	R275 000,00	
NRF Y rated - CGDR (EMS)	R98 000,00	
NRF SARChI- TB Biomarker	R2 500 000,00	
NRF RESEARCH DEV GRANT Y-RATED	R299 697,00	
NRF- CSRR- IRG	R500 000,00	
IRG Africa -collaboration	R17 000,00	
NRF Incentive funding - CLIME	R40 000,00	
NRF Competitive Programme - CLIME	R650 000,00	
NRF SARChI - Animal TB	R1 741 514,00	
NRF Incentive Funding - PVH	R100 000,00	
NRF Research career award - Host Genetics	R100 000,00	
NRF National Bioinformatics Functional Genomics Grant	R91 000,00	
NRF - CSUR - Mycobacterial physiology/Iron-sulphur cluster	R216 450,00	

NRF Bilateral Award- CLIME	R250 000,00	
Other Funding	**R1 185 860,50**	made up of:
Knowledge, Interchange and Collaboration (KIC) 2017	R10 736,00	
Travel Grant - Faculty - CLIME	R15 000,00	
Travel Grant - Division of Research and Dev - CLIME	R15 000,00	
Travel Grant - Faculty - CLIME	R12 977,00	
Travel Grant - Division of Research and Dev - CLIME	R15 000,00	
International Scientific Travel Award - Host pathogen Mycobactomics	R15 000,00	
American Association of Zoo Veterinarians Wildlife Health Fund - Animal TB	R138 988,50	
FMHS - Early Career Research Funding - CGDR	R150 000,00	
FMHS - Early Career Research Funding - CGDR	R150 000,00	
SAMRC - Student Funds - CGDR	R500 000,00	
Travel Grant - European Society for Mycobacteriology - CGDR	R13 159,00	
SANORD - Immunology	R60 000,00	
International Scientific Travel Award - Host Genetics	R15 000,00	
International Scientific Travel Award - Host Genetics	R15 000,00	
International Scientific Travel Award - Host Genetics	R15 000,00	
National Scientific Travel Award- Host Genetics	R5 000,00	
SU African Collaboration Award_CLIME	R40 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 2017 as evidenced by the fact that 122 articles in peer-reviewed journals were published, and 101 conference presentations were made, including 18 plenary/ keynote lectures, and numerous invited talks. Of the research articles published, 54 were in journals with an impact factor (IF) >2 and 39 were in journals with impact factors >5. Included in the outputs from 2017 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, 52/122 (43%) 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 6 PhD students, 7 MSc students and 20 Honours students from the CBTBR graduated or completed their training in 2017. 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 (75% female) and percentage of postdoctoral fellows (27,2% of total student complement) exceeded the SLA targets of ≥50% and ≥10%, respectively. The proportion of black students (50%) met the SLA target of ≥50%.

Progress against SLA 4 targets: The total of 1136 postgraduate students associated with the CBTBR in 2017 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

The CBTBR research has had significant impact on clinical services, the formulation of diagnostic protocols and programmatic responses to the TB epidemic. The CBTBR continues to assist with countrywide roll out of the GeneXpert through the WITS node 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. CBTBR members contributed to the characterization of the South African TB care cascade, in collaboration with policy makers, which assesses programmatic performance and gaps in the health system. A systematic review of specimen preservation products for TB diagnosis was done by CBTBR researchers and the findings are now integrated into a report published by the WHO, which detailed the lack of evidence to support the use of certain products and future research gaps.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 (including WHO, the Stop TB Partnership and funding bodies like the Bill and Melinda Gates Foundation, the NIH and the EDCTP), 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. CBTBR researchers recently found evidence of *M. bovis* infection in white and black Rhino and have subsequently been involved in formulating the response by the South African National Parks to this serious problem. 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 75% of all postgraduate students (including postdoctoral fellows) in the CBTBR in 2017 were female. This gender distribution has changed significantly from the inception of the CBTBR. Additionally, there has been increased representation of 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. CBTBR has 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 translational and clinical research, largely focused on Tuberculosis (TB) and on the quality training of students. Various research teams form this node, each with its own research niche.

Theme 1: Immunology Research Group (IRG)

A main focus of the Immunology Research Group, led by Prof. Walzl, 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 continued 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 which is led by the South African TB Vaccine Initiative (SATVI), at UCT, outside of the CoE iii) the effect of type II DM on protective immune responses at the site of disease and iv) the PredictTB clinical trial, which tests a biomarker-driven treatment shortening approach through a combination of PET/CT imaging and microbiological markers.

Diagnostic studies: Regarding the identification of biomarkers for use for novel diagnostics, earlier work done in the group identified pleural fluid IFN-γ levels as a highly sensitive and specific biomarker 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. As part of an translational approach, the node is now seeking funding for direct comparison with the 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. This area saw much activity in the group in the current reporting period. We previously identified a three-marker cerebrospinal fluid (CSF) protein signmature that performed better than any other single diagnostic modality to diagnose TB meningitis in children. The SU node obtained funding from the Technology Innovation Agency (TIA) to refine this biosignatures in a new cohort of prospectively recruited children with suspected TBM disease. The specific objectives of this project were therefore 1) to validate the diagnostic accuracy of this previously identified 3-marker biosignature and 2) to investigate alternative, more accurate candidate biomarkers for TBM. The ultimate aim of the project is to incorporate validated biomarkers into a user-friendly lateral flow assay platform, similar to tests that we are also developing for the diagnosis of adult pulmonary TB disease. Therefore, in addition to the three proteins comprising our published 3-marker signature, we evaluated the concentrations of over 40 other potentially discriminating proteins in CSF and serum samples from a new cohort of prospectively recruited children with TBM or Non-TBM, with the Non-TBM group also comprising of children with other types of meningitis including viral and bacterial meningitis. We successfully validated the 3-marker biosignature in this new cohort of children but also identified new candidate biomarkers with further improved accuracy. Furthermore, the team also identified a new, promising blood based biosignature, which showed potential as a tool for the diagnosis of TBM. Future research efforts will include the incorporation of the validated TBM CSF biosignature into a lateral flow device, while continuing to validate the blood based test in larger pediatric cohorts.

The 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 we are currently working on point of care, lateral flow-based tests to measure such signatures as part of screening approaches for active TB. The EDCTP-funded, multi-site clinical trial aims to develop a point of care device for finger prick blood to serve as a screening test for active TB. This work is being carried out in collaboration with partners in four other African countries, with three European partner institutions. The screening tool would be used by community health care workers, based on the detection of the levels of up to seven different proteins in finger-

prick blood samples from individuals who are suspected of having active TB disease. In collaboration with our partners at Leiden University Medical Centre in the Netherlands, we completed the development of this point-of-care screening test device and during the third year of the project (2018) we will see the first implementation of the diagnostic test in the field by the intended end-users (nurses and community health care workers, working at peripheral levels of the healthcare system), in the five African partner institutions that are part of the project. 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 subsequent one to two years to identify treatment outcomes and to discover host biomarkers that predict outcomes. We have used PET/CT imaging, microbiological, transcriptomic, metabolomics and serum protein assays in collaborative studies to discover biosignatures and 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, and the start of recruitement into the study took place 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 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, alternatively, 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 and forms the basis of the current biomarker-driven treatment shortening trial, Predict TB, that is ongoing in Cape Town and China. This work was published in Nature Medicine in 2016.

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 >4.400 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 co-led by Prof. Walzl and Prof Sciba at SATVI, 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 recently been submitted. This work is done in close collaboration with 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).

TB HDT: Cellular immunology: Under the theme of translation, we are pursuing investigations into the role of regulatory myeloid cell (RMC) pathways to uncover biological targets for novel host-directed therapeutic (HDT) interventions. Our main goals are to (1) Identify "druggable" myeloid-derived suppressor cell (MDSC)-associated targets at cellular, protein, soluble or gene level, (2) Design HDT compounds that could successfully modulate the immunosuppressive function and frequency of MDSC. (3) Define and assess the optimal targeting strategy (timing, dose) using in vitro and in vivo approaches. Current efforts include site of disease studies on MDSC in lungs of TB patients with corresponding assessment of the peripheral blood compartment, determination of lung- and peripheral gene expression and protein profile, evaluation of the role of MDSC in Mtb persistence and lipid accumulation, and assessment of small molecule compounds targeting lung- and peripheral MDSC in TB patients. The latter includes an EDCTP-funded study evaluating the impact of PDE-5 inhibitors on MDSC immunosuppressive function. Experimental protocols have been drawn up and collaboration with international MDSC experts have been established

TB-diabetes comorbidity: The TB/DM group focus on immune-endocrine interactions and particularly the role of Type 2 Diabetes Mellitus (T2D) on TB susceptibility. In the last year the research focussed on a National Institute of Health (NIH) funded R01 grant entitled 'Altered endocrine axis during type 2 diabetes and tuberculosis risk' which is supported under the US-SA collaborative framework. This work is done in collaboration with Dr. Blanca Restrepo from the University of Texas, Prof. Larry Schlesinger from Texas Biomedical Research Institute and Prof Katharina Ronacher, previously from the US node and now from the Mater Research Insitute at the University of Queensland, who is the prinicipal investigator on the grant. The central hypothesis is that in diabetes patients, the interplay of hormones (under neuroendocrine regulation), adipokines and insulin, and chronic low-grade inflammation potentially contribute to the compromised immune response to Mycobaterium tuberculosis (Mtb). This particular study sheds light on the interplay between the immune and endocrine systems, both in the periphery and the lung, and by doing so help to identify underlying risk factors in diabetes patients for progression to active TB. From an epidemiological point of view, we have shown that there is a marked heterogeneity in host sociodemographic and metabolic features in TB contacts from different ethnicities and continents, which contribute to the poorly-understood variation in TB risk attributed to T2D. In addition, substantial gene expression differences were identified with enhanced inflammatory responses seen in T2D, but significantly lower interferon responses compared to non-T2D. In this work, we are also performing bronchoscopy and broncho alveolar lavage to investigate cellular responses against Mtb in patients with and without T2D. We are further comparing the cellular responses at the site of the disease, the lung, to those in the blood.

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 work, the acquisition of second line drug resistance among MDR-TB patients was determined to assess the impact of 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. These findings have the potential to significantly change the MDR treatment approach.

Whole genome sequencing of members of the *Mycobacterium tuberculosis* complex: To date, we have whole genome sequenced ~2300 isolates of members of the *M. tuberculosis* 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. tuberculosis* and *in vitro* generated mutants of *M. tuberculosis* clinical isolates and laboratory strains. Clinical isolates originate mainly from the Western Cape Province of South Africa. The sequenced *M. tuberculosis* isolates are comprised of:

- Isolates with varying levels of drug resistance
- Serial patient isolates showing evolution of drug resistance (mono-resistant – MDR – pre-XDR – XDR)
- Isolates representative of a local outbreak (defined by IS*6110* RFLP as having identical fingerprints)
- Isolates showing resistance to new drugs being implemented in treatment regimens
- Isolates representative of the different IS*6110* RFLP families found in a high TB incidence setting in Cape Town

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. tuberculosis* 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. tuberculosis* strains to enable the development of clinically useful, WHO-endorsed in vitro diagnostic assays for rapid drug susceptibility testing of *M. tuberculosis*.

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* at the wildlife-livestock interface can lead to clonal expansion of the disease in a single ecosystem: We published the first whole genome sequences of *M. bovis* isolates from South Africa. *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. This work will provide essential background information to *M. bovis* control measures in both wildlife and livestock.

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 continued until October 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 was tasked with doing genotyping experiments. The student has graduated in December 2017, and will be continuing with the project for her Masters' degree in 2018. 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), while genotyping indicated that several patients were infected with resistant strains that do not harbour the canonical mutations.

Mutations in *ppe38* block PE_PGRS secretion and increase virulence of *Mycobacterium tuberculosis:* *M. tuberculosis* requires a large number of secreted and exported proteins for its virulence, immune modulation and nutrient uptake. Most of these proteins are transported by the different type VII secretion systems. The most recently evolved type VII secretion system, ESX-5, secretes dozens of substrates belonging to the PE and PPE families, which are named for conserved proline and glutamic acid residues close to the amino terminus. However, the role of these proteins remains largely elusive. Our findings show that there is much more phenotypic variation in protein secretion of *M. tuberculosis* than was previously assumed. The specific secretion defect of PE_PGRS and also PPE-MPTR proteins, the most recently evolved subgroups of ESX-5 substrates, in the *ppe38*-mutated strains also opens the door for a more holistic approach to study these proteins. Thus far, these proteins have been considered as virulence factors. Our results challenge this dogma, since blocking the secretion of these proteins increases the virulence of *M. tuberculosis* and they may therefore function as anti-virulence factors. This collaborative study between Stellenbosch University, Institut Pasteur (Paris, France), Vrije Universiteit (Amsterdam, The Netherlands), King Abdullah University of Science and Technology (Thuwal, Saudi Ariabia), and National Institute of Medical Sciences and Nutrition “Salvador Zubirán” (Mexico City, Mexico), was recently published in Nature Microbiology.

***Mycobacterium tuberculosis* transmission dynamics in a high incidence setting:** The genetic basis of virulence, transmissibility, drug resistance, persistence and the mechanisms of pathogenicity of *M. tuberculosis* are still poorly understood. Changes in the *M. tuberculosis* genome are caused by single nucleotide polymorphisms (SNPs), deletions, duplications, genetic rearrangements, and transposon insertions. Currently, genetic markers are used to identify and distinguish members of the *M. tuberculosis* complex (MTBC) from each other, to identify different strains of *M. tuberculosis* and to differentiate strains from the same lineage from each other. Here, we are using Next-Generation whole genome sequencing (WGS) to examine the evolution and outbreak dynamics of a particular *M. tuberculosis* cluster to understand strain diversity over time using a high resolution technique. By broadening our understanding of microevolution in *M. tuberculosis* we will be able to better interpret WGS data to ultimately inform TB control strategies that are currently failing. It is therefore envisaged that this collaborative study will provide new insight into *M. tuberculosis* transmission and micro-evolutionary population dynamics which will guide NGS-based epidemiological studies and transmission investigations.

Pyrazinamide resistance: Pyrazinamide resistance is largely under reported due to the technical challenges associated with the phenotypic drug susceptibility test as well as the fact that there is no approved standardized genotypic diagnostic. A systematic review was published by the group which 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 virtual sequencing method for rapid DST. Further work is planned for this novel technique using a new handheld instrument known as the MIC through a collaboration with Larry Wangh (Boston, United States of America). This study adds significant knowledge to the current understanding of drug resistance in *M. tuberculosis*. A DNA sequencing pipeline to be able

to sequence the whole *pncA* gene of *M. tuberculosis* 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. tuberculosis* 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.

The potential of using rifabutin to treat rifampicin resistant tuberculosis: The rifamycins are widely considered the most important class of anti-TB drugs, however with the introduction of the GeneXpert MTB/RIF assay as the initial diagnostic, many patients are found to be resistant to rifampicin and placed on multi-drug resistant treatment. Thus these patients are unable to be treated with rifampicin. A study from the group investigated cross-resistance between rifampicin and rifabutin, it was observed that certain *rpoB* mutations present in both a South African and Belgian cohort of rifampicin resistant patients were susceptible to rifabutin. This creates the opportunity to identify these mutations where patients could be treated with rifabutin in place of rifampicin. This holds significant value in patient management and outcomes, a randomized control trial is recommended.

Rifampicin discrepancies and "disputed" mutations: Since rifampicin is largely considered to be the most important anti-TB drug, as well as the surrogate marker for multi-drug resistant TB there are several rapid genotypic assays to determine resistance to rifampicin. The two routinely used genotypic assays are the Hain line probe assay, MTBDR*plus* and the GeneXpert MTB/RIF assay. However with two accepted routine genotypic assays, discrepancies may occur between the tests. Of course, there is also Sanger sequencing of the *rpoB* gene as well as the phenotypic drug susceptibility test available. There are reports of discrepant results between these different assays. We investigated the mechanism for these discrepancies as well as a population prevalence from a South African population based-cohort. This research identifies the commonly referred to "disputed" *rpoB* mutations to be the main mechanism for discrepancy. The "disputed" mutations are such due to some reports identifying them as resistant and others identifying them as susceptible. Following from this study, we investigated the stability of rifampicin in both liquid and solid media according to the current standard of testing. This research shows that rifampicin may have a half-life of three days, much shorter than previously reported. This may explain the "disputed" mutations that have been observed.

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, 41 patients were identified from the Western Cape Province demonstrating evolution from MDR to XDR-TB. They whole genome sequenced 200 serial isolates of *M. tuberculosis* of these patients at CDC. Preliminary data analysis of a sub-set of these isolates showed the emergence of low kanamycin resistance-conferring mutations, 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. tuberculosis* 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.

Within-patient evolution of serial isolates collected from patients in Khayelitsha receiving new and repurposed antibiotics: We will use WGS to identify genetic changes over longitudinal isolates from patients exposed to new anti-TB drugs. We will also use various phenotypic DST methods to determine the wild type and mutant distributions to calculate ECOFF values for these drugs. We will use clinical data to identify risk factors associated with drug resistance and treatment failure.

The first evaluation of the diagnostic performance of the Fluorotype MTBDR assay for the detection of *M. tuberculosis* 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. tuberculosis* 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. tuberculosis* 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*. The study has been submitted for publication.

Evaluation of the diagnostic performance of the Fluorotype MTB VER2.0: The diagnostic performance of the FluoroType MTB VER2.0 assay is being evaluated on 300 Xpert TB positive clinical specimens as well as 250 Xpert TB negative specimens. These specimens were collected at the NHLS and culture will be used as the reference drug susceptibility testing method. In addition, Genotype MTBDRplus will also be used as a method for discrepancy analysis. DNA will be extracted using the GXT12 automated instrument as well as the Fluorolyse kit.

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, the minimum inhibitory concentration (MIC) was determined for each isolate. Subsequently, Sanger sequencing of the classical INH resistance causing gene regions was done. Spoligotyping of all the original cultures as well as all the cultures from the MIC determination was done 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. Whole Genome Sequencing was done 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. tuberculosis* that cause resistance to INH.

Cough sound analysis: One of the obstacles in reducing the TB burden is delayed diagnosis, which can take several weeks or even months from the onset of symptoms. This implies an extended period of infectiousness, perpetuating the epidemic. In order to address this, we investigated the usefulness of audio analysis of coughs to be able to identify TB patients early. A small cohort of TB patients and healthy controls were recorded while coughing, and the recordings were analysed in collaboration with the Stellenbosch University Faculty of Electric and Electronic Engineering. It was found that sounds outside of the human audible spectrum may be useful for identifying TB coughs. This work is currently under review after minor amendments, for publication in Physiological Measurement.

Mycolic acids: a novel function: Mutations in the promoter region of the *inhA* gene in *M. tuberculosis* is known to cause resistance to the first-line drug isoniazid, as well as the second-line drug ethionamide. It is thought that *inhA* promoter mutations are acquired to confer additional ethionamide resistance in isolates that are already high-level isoniazid resistant due to *katG* mutations, or low-level isoniazid resistance in the absence of *katG* mutations. However, we discovered that a certain strain type present in South Africa that first acquired an *ethA* mutation, conferring ethionamide resistance, followed by a *katG* mutation and an *inhA* mutation last. This questions the role of the *inhA* promoter mutation, as it would not confer any known additional advantage to the bacilli. *inhA* promoter mutations have been shown to cause upregulation of the entire *inhA* operon, including two genes involved in mycolic acid synthesis and one involved in heme biosynthesis. In collaboration with Imperial College London, we have done preliminary 3-dimentional modeling to show that the structure of mycolic acids – which span the mycobacterial membrane – take the form of a “funnel”, suggesting that it may be used in the transmembrane transport of small molecules. We are currently investigating this possible new role of mycolic acids.

Hetero-resistance in *Mycobacterium tuberculosis:* Hetero resistance arises when the bacterium gains resistance causing mutation(s), with the wildtype/drug susceptible bacterium still present,

thereby creating a mixture of different drug resistance levels. We have identified isolates with hetero resistance to different drugs, but would be missed by molecular diagnostic tests because of detection limits. In a pilot study in collaboration with UCSF (Prof John Metcalfe), by using targeted deep sequencing, we have demonstrated the presence of subpopulations of strains that are resistant to the major first- and second-line anti-TB drugs. Furthermore, we demonstrated how subculturing influences the presence of these drug resistant subpopulations. We have expanded this collaboration to study the changes in strain population of different TB patients for the duration of treatment. We have been awarded an NIH R01 grant through the collaboration with UCSF for this study.

Theme 3: Clinical Mycobacteriology and Epidemiology (CLIME)

The CLIME group, led by Prof. Theron focuses on three areas of tuberculosis research. These include: 1) the diagnosis of TB and drug resistance, 2) the study of patient infectiousness and TB transmission, and 3) the 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 and global organisations (e.g., FIND). Some of the major projects executed by CLIME during the reporting period are: (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 (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 (iii) The longitudinal microbiome of MDR-TB patients on treatment and association with outcome (TB-BIOME), (iv) Investigating the infectiousness of TB patients and factors associated with the airborne survival of M. tb (TB-AIR), and (v) the accuracy and impact of new diagnostics for extrapulmonary TB and drug-resistance. These studies are co-funded by the NRF, SAMRC, EDCTP, and research subcontracts with organisations like UCSF, Stanford, Harvard, and FIND.

In 2017, CLIME contributed to translational research via two mechanisms. The first was the first characterization of the South African TB care cascade, in collaboration with policy makers, which CLIME members co-authored. This framework is a critical tool to assess programmatic performance and gaps in the health system. Secondly, as part of an in press publication led by CLIME members, a systematic review of specimen preservation products for TB diagnosis was done as part of a WHO process and presented at WHO headquarters. The findings were integrated into a report published by the WHO, which detailed the lack of evidence to support the use of these products and future research gaps. In 2018, it is expected that each of the in progress projects listed above will have relevance to policy.

Other significance activity in 2017 includes the growth of CLIME to 24 members, the establishment of clinical research infrastructure at Wallacedene TB clinic (in addition to two existing facilities), and the completion of an aerobiology research platform. In terms of additional research activity, CLIME members have authored manuscripts detailing "hacking" of the Xpert MTB/RIF cartridge (which permits rapid TB, first line, and second line DST all from one sputum), the use of deep sequencing methods to detect clinically-relevant microheteroresistance, a study describing the outcomes of patients diagnosed with drug-resistant TB who have minimal symptoms and were not started on treatment, and several other studies on drug-resistant TB.

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. tuberculosis* interacts with its host to cause disease. 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*. In 2017, the group published 6 papers, and produced 3 PhDs and 2 BSc Hons graduates.

Selected ongoing research:
Persisters. In 2017, the group continued efforts to isolate and characterize *M. tuberculosis* persisters. Their aim is to understand the biology of non-replicating "persister" populations of *M. tuberculosis*, which are the underlying cause of latent *M. tuberculosis* 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 using flow cytometry. This tool is currently being applied to determine whether strains with different genetic backgrounds exhibit differential persister formation (and consequently, what the mechanism thereof is). For this, they are using both naturally occurring clinical isolates and genetically engineered strains.

An existing collaboration with Prof. Wolfaardt, Director of Water Institute at Stellenbosch has been expanded to include Dr. Tobi Louw in Process Engineering at Stellenbosch University. This work aims to perform mathematical modelling of selected factors influencing biofilm formation, to gain new insights into persister bacteria within those biofilms.

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. tuberculosis* isolates and the interaction of *M. tuberculosis* with its host. We are using these methods to assess *M. tuberculosis* stress responses over time. In addition, these methods are being applied to gain a deeper understanding of the phenotypic consequences of strain variability. Together with collaborators in The Netherlands, we are also applying proteomics methods to explore the mechanisms of PE/PPE secretion and consequences thereof for host responses.

TB Drugs and drug resistance. 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). Ms. Visser successfully completed her PhD, and has identified a promising new compound with anti-TB activity This work has lead to 2 publications, with additional ones in preparation. Another student to successfully complete her PhD was Ms. Namaunga Chisompola, whose work used strain genotyping and whole genome sequencing to generate new insights into the drug resistant TB epidemic in Zambia. Alarmingly, she identified several cases of pre-XDR TB, and showed evidence for transmission of drug resistant strains.

Dr. Juanelle du Plessis, another successful PhD candidate, investigated the potential of a bacteriophage protein as the framework for novel anti-tuberculosis drugs, and published this wor. She revealed a novel mechanism for how *M. tuberculosis* is able to gain resistance to the second-line drug cycloserine. She also studied the physiological effects of various drug-resistance and compensatory mutations using *in vitro* assays and next generation sequencing technologies.

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. Two Hons students (Hannah King and Megan Ropertz), one MSc student (Victoria Cole) and one PhD student (Caitlin Uren) graduated and manuscripts from these degrees have been published or are being prepared. The group published 13 peer-reviewed articles during 2017.
Research highlights:
1. ***Human genetics of TB resistance in HIV-infected persons***. The group is recruiting participants for this key study done in collaboration with Prof Erwin Schurr (Research Institute of the McGill University Health Centre). This study is funded by the NIAID. We have identified a number of individuals who are HIV-positive and live in a high TB incidence community, but are IGRA and TST negative.

2. ***Genetic control of human anti-mycobacterial immunity***. There is a large inter-individual variability in the response to *Mycobacterium tuberculosis* infection. In previous linkage analyses, we identified a major locus on chromosome region 8q controlling IFN-γ production after stimulation with live BCG (Bacillus Calmette-Guérin), and a second locus on chromosome region 3q affecting IFN-γ production triggered by the 6-kDa early secretory antigen target (ESAT-6), taking into account the IFN-γ production induced by BCG (IFNγ-ESAT6BCG). High-density genotyping and imputation identified ~100,000 variants within each linkage region, which we tested for association with the corresponding IFN-γ phenotype in families from a tuberculosis household contact study in France. Significant associations were replicated in a South African familial sample. The most convincing association observed was that between the IFNγ-ESAT6BCG phenotype and rs9828868 on chromosome 3q ($p = 9.8 \times 10\text{-}6$ in the French sample). This variant made a significant contribution to the linkage signal ($p < 0.001$), and a trend towards the same association was observed in the South African sample. This variant was reported to be an eQTL of the ZXDC gene, biologically linked to monocyte IL-12 production through CCL2/MCP1. The identification of rs9828868 as a genetic driver of IFNγ production in response to mycobacterial antigens provides new insights into human anti-tuberculosis immunity.
The molecular mechanisms that regulate tuberculosis susceptibility and bacillus Calmette-Guérin (BCG)-induced immunity are mostly unknown. However, induction of the adaptive immune response

is a critical step in host control of Mycobacterium tuberculosis. Toll-interacting protein (TOLLIP) is a ubiquitin-binding protein that regulates innate immune responses, including Toll-like receptor signaling, which initiate adaptive immunity. TOLLIP variation is associated with susceptibility to tuberculosis, but the mechanism by which it regulates tuberculosis immunity is poorly understood. To identify functional TOLLIP variants and evaluate the role of TOLLIP variation on innate and adaptive immune responses to mycobacteria and susceptibility to tuberculosis. We used human cellular immunology approaches to characterize the role of a functional TOLLIP variant on monocyte mRNA expression and M. tuberculosis-induced monocyte immune functions. We also examined the association of TOLLIP variation with BCG-induced T-cell responses and susceptibility to latent tuberculosis infection. We identified a functional TOLLIP promoter region single-nucleotide polymorphism, rs5743854, which was associated with decreased TOLLIP mRNA expression in infant monocytes. After M. tuberculosis infection, TOLLIP-deficient monocytes demonstrated increased IL-6, increased nitrite, and decreased bacterial replication. The TOLLIP-deficiency G/G genotype was associated with decreased BCG-specific IL-2+ CD4+ T-cell frequency and proliferation. This genotype was also associated with increased susceptibility to latent tuberculosis infection. TOLLIP deficiency is associated with decreased BCG-specific T-cell responses and increased susceptibility to tuberculosis. We hypothesize that the heightened antibacterial monocyte responses after vaccination of TOLLIP-deficient infants are responsible for decreased BCG-specific T-cell responses. Activating TOLLIP may provide a novel adjuvant strategy for BCG vaccination.

3. ***TB association studies****.* Utilizing data from published tuberculosis (TB) genome-wide association studies (GWAS), we use a bioinformatics pipeline to detect all polymorphisms in linkage disequilibrium (LD) with variants previously implicated in TB disease susceptibility. The probability that these variants had a predicted regulatory function was estimated using RegulomeDB and Ensembl's Variant Effect Predictor. Subsequent genotyping of these 133 predicted regulatory polymorphisms was performed in 400 admixed South African TB cases and 366 healthy controls in a population-based case-control association study to fine-map the causal variant. We detected associations between tuberculosis susceptibility and six intronic polymorphisms located in MARCO, IFNGR2, ASHAS2, ACACA, NISCH and TLR10. Our post-GWAS approach demonstrates the feasibility of combining multiple TB GWAS datasets with linkage information to identify regulatory variants associated with this infectious disease.

4. ***Population genetics***. The group previously demonstrated that Khoisan ancestry is associated with TB susceptibility. The KhoeSan populations are the earliest known indigenous inhabitants of southern Africa. The relatively recent expansion of Bantu-speaking agropastoralists, as well as European colonial settlement along the south–west coast, dramatically changed patterns of genetic diversity in a region which had been largely isolated for thousands of years. Owing to this unique history, population structure in southern Africa reflects both the underlying KhoeSan genetic diversity as well as differential recent admixture. This population structure has a wide range of biomedical and sociocultural implications; such as changes in disease risk profiles. We consolidate information from various population genetic studies that characterize admixture patterns in southern Africa with an aim to better understand differences in adverse disease phenotypes observed among groups. We confirmed that ancestry has a direct impact on an individual’s immune response to infectious diseases. In addition, we emphasize the importance of collaborative research, especially for populations in southern Africa that have a high incidence of potentially fatal infectious diseases such as HIV and tuberculosis.

Our collaboration with Dr Brenna Henn (UC Davis) involved skin pigmentation in South African populations. This relates to TB, since many diseased individuals have been shown to be vitamin D

deficient and skin pigmentation is a main predictor of vitamin D status. Approximately 15 genes have been directly associated with skin pigmentation variation in humans, leading to its characterization as a relatively simple trait. However, by assembling a global survey of quantitative skin pigmentation phenotypes, we demonstrate that pigmentation is more complex than previously assumed, with genetic architecture varying by latitude. We investigate polygenicity in the KhoeSan populations indigenous to southern Africa who have considerably lighter skin than equatorial Africans. We demonstrate that skin pigmentation is highly heritable, but known pigmentation loci explain only a small fraction of the variance. Rather, baseline skin pigmentation is a complex, polygenic trait in the KhoeSan. Despite this, we identify canonical and non-canonical skin pigmentation loci, including near SLC24A5, TYRP1, SMARCA2/VLDLR, and SNX13, using a genome-wide association approach complemented by targeted resequencing. By considering diverse, under-studied African populations, we show how the architecture of skin pigmentation can vary across humans subject to different local evolutionary pressures.

5. ***Primary immunodeficiency disorders*** **(PIDs)**. These patients are vulnerable to infection with a wide range of microorganisms and thus provide good in vivo models for the assessment of immune responses during infectious challenges e.g. TB. Priming of the immune system, especially in infancy, depends on different environmental exposures and medical practices. This may determine the timing and phenotype of clinical appearance of immune deficits as exemplified with early exposure to Bacillus Calmette-Guérin (BCG) vaccination and dissemination in combined immunodeficiencies. Varied phenotype expression poses a challenge to identification of the putative immune deficit. Without the availability of genomic diagnosis and data analysis resources and with limited capacity for functional definition of immune pathways, it is difficult to establish a definitive diagnosis and to decide on appropriate treatment. We described the use of exome sequencing to identify a homozygous recessive variant in MAP3K14, NIKVal345Met, in a patient with combined immunodeficiency, disseminated BCG-osis, and paradoxically elevated lymphocytes. This work was published in *Frontiers in Immunology*. Laboratory testing confirmed hypogammaglobulinemia with normal CD19, but failed to confirm a definitive diagnosis for targeted treatment decisions. NIKVal345Met is predicted to be deleterious and pathogenic by two *in silico* prediction tools and is situated in a gene crucial for effective functioning of the non-canonical nuclear factor-kappa B signaling pathway. Functional analysis of NIKVal345Met- versus NIKWT-transfected human embryonic kidney-293T cells showed that this mutation significantly affects the kinase activity of NIK leading to decreased levels of phosphorylated IkappaB kinase-alpha (IKKα), the target of NIK. BCG-stimulated RAW264.7 cells transfected with NIKVal345Met also presented with reduced levels of phosphorylated IKKα, significantly increased p100 levels and significantly decreased p52 levels compared to cells transfected with NIKWT. Ideally, these experiments would have been conducted in patient-derived immune cells, but we were unable to source these cells from the patient. The functional analysis described in this paper supports previous illustrations of the importance of NIK in human immune responses and demonstrates the involvement of function-altering mutations in MAP3K14 in PIDs. The genomic approach used for this patient demonstrates its value in the diagnosis of an unusual PID and as a tool for detecting rarer mutations to help guide treatment approaches. Two additional publications described the use of WES in the the identication of PID-associated variants.

6. ***Autophagy***. Autophagy (intracellular degradation system) is a process that allows eukaryotic cells to generate nutrients under conditions of starvation by degrading damaged or obsolete organelles and proteins. In addition to this, autophagy has also been found to play a role in a number of physiological and pathophysiological processes that include regulation of the innate immune

system where it aids in the clearance of intracellular pathogens such as *Mycobacterium tuberculosis*. Autophagy begins with the formation of double-membrane vesicles called the autophagosome which engulfs cytosolic material and delivers it to lysosomes for degradation and recycling of cellular nutrients. The fusion of the autophagosomes with lysosomes creates an acidic environment filled with hydrolytic enzymes that are able to kill and degrade microbes. Recently, the SNARE-associated protein, SNAPIN, has been shown to play a crucial role in the fusion of the autophagosome and lysosome and preliminary data from our laboratory suggests that infection of macrophages with *M. tb* reduces the SNAPIN expression. We investigate the host autophagic response and molecular mechanisms involved in this vital process. Dr Craig Kinnear published two articles in this field with long-time collaborator Prof Ben Loos.

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.

Prof. Tromp has supported research groups by providing rigorous statistical and bioinformatic analyses. He has developed models using statistical learning techniques (also referred to as machine learning). These models can use cytokines levels in serum or whole-blood cultures, transcript levels (RNA-seq) or other analytes. He has developed models to predict development of TB in indivduals exposed to infection, as well as relapse and other poor outcomes in individuals with TB during treatment, and models that correlate with extent of infection according to PET/CT.

Profs. Tromp and Tabb have recruited a number of masters and doctoral students and Post-doctoral fellows who form the nucleus of bioinformaticians and biostatisticians to do research and support research projects. They have also have contributed to the establishment of the Centre for Bioinformatics and Computational Biology at Stellenbosch, to ensure that formal undergraduate curriculum in bioinformatics is established and quality of post-graduate studies is of a uniform high standard. These activities will ensure a stream of students necessary to provide future bioinformaticians to support research and to develop a pool of candidates for leadership roles in bioinformatics to drive the discipline forward in South Africa.

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*. A major theme in this team's work in exploring the regulation of this gene cluster, particularly under disease-relevant conditions. This has involved investigating the structure of the promoters controlling expression of the operon, and the interaction of the *Rv1460*-encoded transcriptional regulator with these promoters. A PhD. student involved in

the study, Lucinda Baatjies, has developed a fluorescent reporter system, which will enable monitoring of the operon's expression by flow cytometry during intracellular growth in macrophages. Ms Baatjies has also optimized an assay for investigating the immunogenicity of Rv1460, in collaboration with Dr. André Loxton (Immunology research group).

A second theme for this team involves describing the protein-protein interactions between components of the Fe – S cluster biogenesis system in mycobacteria. A PhD student in the team, Jessie Arries, has optimized the conditions for performing IP-MS experiments with several proteins in the system, namely SufB, SufC, SufD & Csd. Ms Arries has also developed a fluorescence-based mycobacterial system for evaluating protein-protein interactions, and is currently validating this system in *Mycobacterium smegmatis*. One of the major questions in Fe – S cluster assembly in prokaryotes is the source of iron used to produce the co-factor. A PhD. student in the team, Nandi Niemand, has demonstrated that a protein in mycobacteria, that is homologous to A-type carrier proteins, is able to bind iron. She has also generated a protein knock-down strain of *M. smegmatis* that will be used to explore the role of this protein in Fe – S cluster biogenesis. Finally, an MSc. student in the team, Tsaone Tamuhla, is exploring the link between iron, Fe – S cluster biogenesis and biofilm formation in mycobacteria, and has shown that iron is important for biofilm maturation.

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 Colin Kenyon. The team has four main research focus areas:

(i) **Testing 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. We have demonstrated 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. We have demonstrated that artemisinin-cholesterol does show significant effectiveness against strains of *M. tb* and in contrast to artemether, the conjugates display enhanced activities. This was published in ChemMedChem. In collaboration with Dr. Chibale we have also shown that reversed isoniazid agents have improved antimycobacterial activity. These results have been published in the journal, Bioorg Med Chem.

(ii) **Identifying 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. The ergothioneine deficient *M. smegmatis* 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. As opposed to mycothiol, it was demonstrated that ergothioneine is secreted. *M.tb* mutants have been generated and we determined that the ERG-deficient ΔegtB mutant which accumulated gamma-glutamylcysteine (GGC) was more resistant to oxidative and nitrosative stress than the ERG-deficient, GGC-deficient ΔegtA mutant. This implicates GGC in the detoxification of reactive oxygen and nitrogen species in *M. tb*, and compensatory anti-oxidative role of ergothioneine, mycothiol and GGC in mycobacteria. This work was published in the journal, BBRC.

(iii) **Identifying 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. It was further shown that the macrophage response to hypo- and hyper-virulent clinical mycobacterial strains differed dramatically and identified host candidate genes potentially related to hypervirulence, published in the journal, *Virulence*.

(iv) The following **kinase metabolic enzymes** have been cloned, expressed and purified from *Mycobacterium tuberculosis*, ribokinase (*rbks*, Rv2436), thiamine monophosphate kinase (*thil*, Rv2977c), glycerol kinase (Rv3696c), nucleoside diphosphate kinase (Rv2445c), homoserine kinase (Rv1296), acetate kinase (Rv0409), aspartokinase full-length gene as well as the b-subunit and shikimate kinase (*aroK*). All constructs have been expressed in *E. coli* with C-terminal N_6-histidine tags for ease of purification. The TEV protease site is to be included in all constructs between the C-terminal residues and the N_6-histidine tags. Preliminary enzymology has indicated that all of these kinase enzymes are functionally expressed. It is envisaged that once all the kinetic constants have been defined as well as the kinase reaction mechanisms the assays will be optimised to be run in preliminary kinase inhibitor screens.

Theme 9: Animal TB

The overall research goal of the Animal TB research program, led by Prof. Miller (NRF SARChI Chair) and Dr. Parsons, is to advance our understanding of how the *Mycobacterium tuberculosis* complex (MTBC) members affect different animal hosts and develop tools for investigating the epidemiology, pathogenesis and immunology of these pathogens in different species. This research group has been actively investigating immunological and molecular assays that can detect infection in various wildlife species as a contribution to basic comparative biological information as well as application of these tests for practical field use. The focus of this group's research in 2017 included: 1) genomic characterization of animal-adapted MTBC; 2) identification of biomarkers of *M. bovis* infection across multiple animal host species; 3) investigation of rapid methods of detection of *M. bovis* in animal samples; 4) understanding the immunology of co-infection with M. bovis and feline immunodeficiency virus in lions (natural model for human TB-HIV co-infection); and 5) epidemiology of *M. bovis* infection in wildlife in endemic areas. As a result of this research, 11 papers were published in peer-reviewed international scientific journals in 2017. Selected research projects:

1) **Genomic characterization of animal-adapted MTBC**. For this project, a master's student, Yessica Fitzermann, along with Prof. Rob Warren, Prof. Michele Miller, Dr. Sven Parsons, and Dr. Anzaan Dippenaar, investigated the relationship of the animal-adapted MTBC, *Mycobacterium mungi*, the dassie bacillus, and *Mycobacterium suricattae,* to other members of the complex. These organisms are difficult to isolate using conventional mycobacterial culture; therefore, novel techniques for in-solution DNA capture were used to obtain samples for whole genome sequencing. Using the whole genome sequences, a phylogenetic tree was developed to include the new animal isolates. The results showed that the dassie bacillus lineage is

paraphyletic with one strain clustering with *M. suricattae*. Two *M. suricattae* clades were observed and associated epidemiologically with distinct host populations. These lineages were shown to share a common ancestor with *M. africanum* lineage 6, and suggests that the dassie bacillus and *M. suricattae* lineages may have evolved due to genetic isolation within their niche. In addition, genetic markers were identified that may be related to *in vitro* growth and pathogenicity.

2) Identification of **biomarkers of *M. bovis* infection** across multiple animal host species. Since the wildlife industry and ecotourism are significant contributors to the South African economy, the presence of disease, such as bovine tuberculosis (bTB) can have a major impact. However, there is a lack of diagnostic tests. Therefore, the Animal TB Research team (including Prof. Miller, Dr. Parsons, Eduard Roos, Netanya Bernitz, Josephine Chileshe, Dr. Tanya Kerr) has been investigating blood-based assays in key species including African buffaloes, rhinoceros, wild dogs, warthogs, and lions. This research has led to identification of new biomarkers such as the cytokine IP-10, cytokine genes CXCL10, and others that can be used to develop immunodiagnostic tests. In collaboration with biotech companies, Qiagen, ThermoFisher Scientific, and MabTech, commercially available reagents have been adapted for use in wildlife species, providing more easily standardized assays for future diagnostic use. Two papers, published in *Plos One* and *Frontiers in Immunology* in 2017, highlighted the first scientific study of clinicopathologic and immunological changes in *M. bovis* infected white rhinoceros. Significantly, these assays are being discussed with the Department of Agriculture, Forests, and Fisheries for use in future policies affecting animal movement and disease control.

3) Investigation of **rapid methods of detection of *M. bovis*** in animal samples. Rapid methods of detecting pathogens in animal samples are needed to improve decision-making for disease control. The Animal TB Research group (including Prof. Miller, Dr. Parsons, Eduard Roos, and Honour's student Candice De Waal) have initiated work to explore the utility of GeneXpert Ultra, an automated platform for human TB samples, for detection of *M. bovis* in animal samples. In addition a novel in-house qPCR assay was developed to rapidly differentiate *M. tuberculosis* from *M. bovis*. Studies will continue in 2018 and expand to use of different sample types in a range of species. These techniques may provide a rapid method of screening wildlife samples in the future.

4) Understanding the **immunology of co-infection with *M. bovis*** and feline immunodeficiency virus in lions. Feline immunodeficiency virus (FIV) causes an AIDs-like disease in domestic cats and serves as an important disease model for humans. Wild felids such as African lions (*Panthera leo*) are also infected by FIV but there is limited knowledge regarding its impact on host immune status and role in susceptibility to other diseases such as TB. There is a high prevalence of feline immunodeficiency virus in African lions but the lack of diagnostic tools undermines our ability to investigate disease progression and outcomes in this species. Therefore, Honour's student Manana Dlangalala along with mentor, Dr. Tanya Kerr, worked on developing a reverse transcription polymerase chain reaction (PCR) assay for FIV in lions using RNA extracted from lion whole blood samples. They were successful in detecting cell-associated FIV in lion samples as a first step in developing a qPCR assay for measuring FIV viral load in lions. In addition, Taime (Olivier) Sylvester focused her doctoral research on identifying biomarkers of immune responses to *M. bovis* in African lions and the impact of feline immunodeficiency virus infection on the host's responses. She has developed a cytokine gene expression assay (CXCL9) which can distinguish *M. bovis* infected lions, and has used this to estimate prevalence in exposed populations. She is

also validating antibody panels for flow cytometry analysis of immune cells in lion peripheral blood. This work creates an important foundation for future studies on the immunology of lions.

5) **Epidemiology of *M. bovis* infection in wildlife** in endemic areas. In multi-host ecosystems, understanding the role of different species in transmitting and spreading TB provides a more complete picture of the impact of disease. Doctoral student Eduard Roos has been investigating the immunology and epidemiology of bovine TB in warthogs He has found that warthogs develop a robust antibody response when infected which permits detection of infection. Using an in-house serological assay, he was able to determine the bTB seroprevalence of 170 warthogs, which was 38%. This is the first TB surveillance study of warthogs in endemic areas of South Africa.
Mycobacterium bovis infection was first discovered by the Animal TB Research group in free-ranging wild dogs in the Kruger National Park (KNP) in late 2015. Since that time, additional cases have been found which has triggered implementation of large scale disease surveillance and diagnostic development research on this critically endangered carnivore. A novel wild dog interferon-gamma (IFN-γ) release assay (IGRA) was developed by master's student Roxanne Higgitt using commercially available tubes for antigen stimulation (QuantiFERON®-TB Gold) and the R&D canine IFN-γ ELISA kit. Using this assay, the infection prevalence of wild dogs in KNP was estimated to be 74% (95% CI: 63 – 83%). Additionally, 22/23 wild dog packs sampled from KNP were IGRA positive, which may indicate a high infection pressure in this species. These studies highlight the importance of understanding TB in wildlife species, their role in disease and impact on conservation strategies.

UCT Node

The research program of the UCT node comprises a highly integrated suite of 12 projects that are aimed at investigating aspects of the physiology and metabolism of *M. tuberculosis* of relevance to TB drug discovery, TB drug efficacy, mycobacterial persistence and TB transmission. The research program falls under three broad thematic areas: mycobacterial metabolism and physiology; TB drug discovery; and TB transmission. Projects 1-7 are built on areas of fundamental mycobacterial metabolism and physiology research; this thematic area has grown considerably over the past year with some exciting new projects having been initiated that take advantage of new developments in high-throughput genetic technologies for mycobacteria (Tn-Seq and CRISPRi) coupled with the establishment of advanced imaging capabilities in our and other laboratories in the Institute of Infectious Disease and Molecular Medicine at UCT (time-lapse fluorescence, confocal and super-resolution microscopy). As outlined below, the projects in this theme are of direct relevance to our work under the themes of TB drug discovery and TB transmission. Thus, projects 8 and 9 are based on the application of our capabilities in mycobacterial genetics and physiology in the area of drug discovery. Project 8 comprises 7 sub-projects, whereas Project 9 represents a new area of investigation for the UCT node at the host-pathogen interface. Projects 10-12 represent another major growth area for the UCT node focused on the topic of TB transmission. These projects form part of larger interdisciplinary studies on the aerobiology and genomics of TB transmission, funded by UCT's Flagship 1 grant from the SAMRC and a grant from the Bill and Melinda Gates Foundation (BMGF).

OVERVIEW AND HIGHLIGHTS OF PROGRESS SINCE THE LAST REPORT

Theme 1: Mycobacterial metabolism and physiology

DNA metabolism. An SOS-inducible DNA repair system has been linked to transient hyper-mutation and the development of drug resistance in *Mycobacterium tuberculosis*. Previous work has established that this "mycobacterial mutasome" comprises the specialist DNA polymerase, DnaE2, and accessory factors of unknown function, ImuA′ and ImuB. However, the molecular interactions and sub-cellular recruitment dynamics enabling mutasome function remain poorly understood. Over the past year, PhD student Michael Reiche working under the supervision of Digby Warner, constructed a panel of fluorescent strains of *M. smegmatis* to investigate expression and subcellular localization of ImuA′ and ImuB in live mycobacteria exposed to genotoxic stress. Using wide-field and fluorescence microscopy it was observed that, during prolonged genotoxic stress, single *M. smegmatis* cells exhibit an elongated cell phenotype and potential aneuploidy. Furthermore, ImuB was seen to associate with the *dnaN*-encoded β clamp in discrete foci during mutagenic DNA repair. In contrast, ImuA′ did not exhibit similar localization and instead appeared to diffuse throughout the bacillus. A mutant ImuB protein deficient in the β-clamp-binding motif failed to co-localize with the β clamp, reinforcing the inferred essentiality of the ImuB-β clamp protein-protein interaction for mutasome recruitment and induced mutagenesis. Additionally, exposure of *M. smegmatis* to the novel β clamp-targeting natural product antibiotic, griselimycin, prevented ImuB-β clamp co-localization during SOS induced mutagenesis, an observation confirmed by super-resolution, three-dimensional interferometric photo-activated light microscopy. These results establish the capacity of griselimycin to inhibit DNA replication as well as prevent DNA damage-induced mutagenesis by disrupting mutasome assembly and function. Notably, this differentiates griselimycin from other inhibitors of DNA metabolic function, which carry the often unavoidable liability of accelerating drug-resistance by inducing mutagenic DNA repair. In turn, it suggests the potential application of griselimycin as an anti-evolution agent in novel therapeutic regimens designed to protect existing TB drugs. Ongoing work is therefore aimed at establishing whether the ImuB localization and griselimycin-mediated protein inhibition observed in *M. smegmatis* is recapitulated in *M. tuberculosis*. This study has attracted significant interest as evidenced by the fact that Michael Reiche was invited to present this work as short talks at international TB conferences in New York and Sweden. A major manuscript describing the key findings will be submitted for publication in early 2018. Michael Reiche, Digby Warner and Valerie Mizrahi co-authored an invited review article in *Frontiers in Molecular Biosciences* on new opportunities for targeting DNA metabolism for TB drug discovery as part of a special issue on *The DNA Replication Machinery as Therapeutic Targets*.

A related study by PhD student Zela Martin has focused on studying the regulators on the SOS – the LexA repressor and the RecA activator as part of a collaboration with Prof. John McKinney (EPFL, Lausanne) who hosted Ms. Martin in his laboratory for a year through a postgraduate student exchange program between South African and Switzerland. Recent studies have found a considerable amount of phenotypic heterogeneity and "pulsing" in *recA* expression in single cells of mycobacteria (G. Manina and J. McKinney, personal communication). The *recA* gene is itself an SOS-regulated gene, and is unusual in mycobacteria in that it is expressed off two promoters: P2, a typical SOS-dependent promoter that is regulated in the classical RecA-LexA dependant manner; and P1, a second promoter that is regulated in a RecA-LexA-independent manner. In this study, *recA* reporter strains with the P1 and/or P2 promoter inactivated and a LexA-uninducible mutant have been used to characterize dynamics of *recA* expression in *M. smegmatis* in the absence and presence of DNA-damaging agent mitomycin C by means of single-cell time-lapse fluorescence

microscopy. The *lexA* mutants were found to be more susceptible to mitomycin C and showed significantly lower recA expression upon DNA damage compared to wildtype. Moreover, the *lexA* mutants displayed significantly slower growth rates compared to wildtype after removal of the DNA-damaging agent. However, pulsing was present in the *lexA* mutants, but pulsing amplitude was significantly lower compared to wildtype. These results suggest that LexA cleavage is not responsible for the observed pulsing. Pulsing and heterogeneity in *recA* expression is therefore likely due to a LexA cleavage-independent mechanism. Zela is in the process of transferring her technical know-how in single-cell time-lapse microscopy and imaging data analysis to other members of the UCT node whose projects are increasingly reliant on the advanced imaging capabilities that have been established in within the Faculty of Health Sciences.

Filamentation in mycobacteria. This new study by PhD student Ryan Dinkele, Intercalated MBBCh-PhD student Timothy de Wet, and Digby Warner, is predicated on the hypothesis that bacillary filamentation (DNA replication without division) is an important phenotype in the ability of *M. tuberculosis* to establish an infection and develop drug resistance, even under antibiotic treatment. In an attempt to understand the importance of filamentation in DNA-damage tolerance, Ryan's work has demonstrated potential functional redundancy in pathways leading to filamentation in *M. smegmatis* utilizing a knockout mutant in a candidate gene implicated in cell division by others. These preliminary results suggest that filamentation is a robust cellular response which may be difficult to completely eradicate. Early work in stressed, late stationary phase *M. smegmatis* has led us to uncover a characteristic and reproducible phenotype comprised of dense lipid regions (1-2 per cell) flanked by highly condensed nucleic acid. Exploring the response of *M. smegmatis* during late-stationary phase stress may shed light on growth and division regulation in Mycobacteria. In a parallel approach, Tim de Wet is developing a high-content CRISPRi screen in a study done in collaboration with Dr. Musa Mhlanga (CSIR/UCT Biomedical Translational Research Initiative) who has established capabilities for high-throughput microscopy screens of mycobacterial mutant libraries (knockout or knockdown). The recent optimisation of CRISPRi in mycobacteria by researchers in the USA, along with large-scale pooled oligo synthesis, has enabled a new form of functional genomics based on the creation of comprehensive knockdown libraries using inducible CRISPRi. Inducible CRISPRi libraries offer the benefit of simple library preparations, arraying of essential mutants (which would not be present in Tn-based libraries), and simple implementation of combinatorial screens. Over the past year, outstanding progress was made by Tim de Wet during the first year of his PhD on the design, construction, and validation of a CRISPRi-based library targeting *M. smegmatis* homologues of *M. tuberculosis* genes. Using bioinformatic identification of viable CRISPRi target sites in *M. smegmatis*, a pool of oligos targeting 2385 genes with homologues in *M. tuberculosis* with a maximum of 5 guides per gene was constructed. The sgRNA library was cloned into plasmid, capable of inducible-expression of both dCas9 and the targeting sgRNA. Design and construction of the CRISPRi library was highly successful, with every one of the targeted genes having at least one sgRNA present. The plasmid library was electroporated into *M. smegmatis*, and a pooled negative selection screen performed which identified the majority of known essential genes and validated the library and techniques. In further work, the use of CRISPRi for studying morphological impacts of gene knockdowns was validated using reporter strains and time-lapse fluorescence microscopy, for two sentinel genes involved in cell division. Having validated this powerful new approach, the next phase of this project will focus on high-throughput microscopy screening of the inducible CRISPRi library to identify mutants with impaired ability to filament in response to specific stresses. We expect this approach to revolutionise our work in other areas of mycobacterial physiology and metabolism through targeted combinatorial screens. A major manuscript describing this work is in preparation, and will be submitted by end-January 2018.

Vitamin B_{12} metabolism. *M. tuberculosis* is among a select group of prokaryotes that encodes a near complete vitamin B_{12} biosynthetic pathway. The presence of functional vitamin B12 dependent enzymes, methionine synthse (MetH) and methylmalonyl-CoA mutase (MutAB) in *M. tuberculosis*, coupled with the absence of components of the canonical bacterial B_{12} transport system, BtuCDF, suggests that *M. tuberculosis* may acquire B_{12} through de novo biosynthesis. We demonstrated B_{12} auxotrophy in a mutant strain disrupted in the alternative, B_{12}-independent methionine synthase (MetE) which argued against B_{12} biosynthetic capability but found that addition of cobalt to the culture medium rescued growth of the Δ*metE* which suggested that M. tuberculosis might be capable of making B_{12}, albeit in small amounts. Deletion of *cobF*, a methyl transferase that mediates biosynthesis of precorrin 6, in *M. tuberculosis* is among the many profound changes that occurred during evolution from its immediate precursor, *Mycobacterium canettii*. In a study led by postdoctoral fellow Gabriel Mashabela, a highly sensitive LC-MS/MS method with a detection limit of 0.69 ng/ml was used to confirm that *M. tuberculosis* lacks the ability to synthesize detectable levels of canonical B_{12} or the variant, pseudovitamin B_{12} in vitro. Furthermore, mycobacterial strains lacking *cobF* not only fail to produce detectable amounts of vitamin B_{12}, but are highly sensitive to the combination of propionate and isocitrate lyase inhibitors – an effect that was reversible by addition of B_{12} to the growth medium to activate MutAB, consistent with previous findings. In collaboration with Prof. Roland Brosch (Institut Pasteur), *M. canetti* was shown to be robust producer of B_{12}, which places the absence of *cobF* as the sole reason for the inability of *M. tuberculosis* to synthesize canonical B_{12}. Although there was no clear indication of growth stage-specific dependence of B_{12} production the levels of B_{12} detected in *M. canettii* and *M. smegmatis* increased over 10-fold upon addition of exogenous cobalt into the growth media. This result suggests that either *M. tuberculosis* produces levels of B_{12} sufficient to support growth but below the limit of detection using the current method; or *M. tuberculosis* produced a novel form of B_{12} distinct from pseudovitamin B_{12}, a hypothesis strengthened by the recent identification of alternate forms of this cofactor, such as norcobalamin. This study will be submitted for publication in early 2018.

In related studies, PhD student Terry Kipkorir is using a genetic approach to investigate B_{12}-dependent riboswitch regulation of methionine biosynthesis and cobalt acquisition in mycobacteria, and PhD student Rendani Mbau is using a Tn-Seq approach to elucidate the genetic requirements for B_{12} biosynthesis and assimilation in *M. smegmatis* with the aim of constructing the corresponding pathway in the pathogenic *M. tuberculosis*. Terry was invited to present his work on the uptake and utilization of B_{12} and the role of this cofactor in the riboswitch-dependent regulation of methionine biosynthesis in mycobacteria as a short talk at the 7th FEMS Congress of European Microbiologists in Spain.

Riboflavin biosynthesis in mycobacteria. In a promising new study led by Dr. Melissa Chengalroyen who joined the UCT node from Wits in July 2017 as a Research Officer, and Honours student, Justin Govender, we are targeting the riboflavin (vitamin B_2) biosynthetic pathway in mycobacteria in order to unravel MAIT cell (Mucosal-Associated Invariant T cell) antigen recognition during infection. MAIT cells are an abundant population of innate-like T cells in humans that are activated by an antigen(s) bound to the MHC class I-like molecule, MR1. There is strong evidence to suggest that MR1 bind ligands originating from vitamin metabolites, in particular, those derived from the riboflavin biosynthetic pathway, which have been shown to activate MAIT cells potently and selectively. A current hypothesis is that these cells could be protective against *M. tuberculosis* infection. Our working hypothesis is that generation of regulatable mycobacterial mutants disrupted

at various steps in the biosynthetic pathway will allow this to be tested. In initial experiments, three essential genes in the riboflavin pathway, *ribA2*, *ribG* and *ribH* were targeted for downregulation in *M. smegmatis* by inducible CRISPRi. Fourteen guide RNAs were tested to target *ribG* and fifteen were chosen to target *ribA2*. Screening of relevant guide RNAs revealed five efficient guides that downregulated the expression of *ribA2*, resulting in complete abrogation of growth. A single guide was effective in downregulating *ribH* whereas none of the guides targeted against *ribG* was effective in conferring inducer-dependent growth inhibition. Further testing has shown that these clones showing inducer (tetracycline)-dependent growth phenotypes can be rescued by exogenously supplied riboflavin at a minimum concentration of 4 ng/ml in the presence of growth inhibitory levels of inducer. Preliminary results suggest that FMN but not FAD can also rescue *ribA2* knockdown clones. In ongoing work, constructs for conditional CRISPRi-mediated silencing of *ribG* and *ribA2* were designed and have been electroporated into *M. tuberculosis*. The results obtained to date augur well for our ability to generate mycobacterial cell extracts that are depleted in riboflavin pathway intermediates for use in immunological assays. This study forms part of a new collaboration with Prof. David Lewinsohn (Oregon Health & Science University, USA) that was established during his sabbatical at UCT in 2017.

Theme 2: TB drug discovery

This remained a major area of interest and progress at the UCT node. As leaders in the biology of TB drug discovery, researchers at the UCT node continued to collaborate closely with medical chemists and pharmacologists on a number of projects in early-stage drug discovery, supported by a new three-year grant from the BMGF (TB Drug Accelerator program) with complementary support through a grant from the SHIP division of the SAMRC. The screening and biological profiling platform supported by the SHIP grant, and run in partnership with the H3D Centre for Drug Development at UCT, continued to provide a service to H3D, as well as large number of local and international research groups.

Biological profiling of new antituberculars, and identification and validation of new TB drug targets. In a paper published in *Antimicrobial Agents & Chemotherapy* and led jointly from the UCT node, Vinayak Singh and Valerie Mizrahi partnered with collaborators at Cornelius University in Bratislava in a study that provided compelling validation of the mycobacterial phosphoglycosyltransferase WecA, as a new TB drug target. WecA initiates arabinogalactan biosynthesis in *M. tuberculosis*, has been proposed as a target of the caprazamycin derivative CPZEN-45, a preclinical drug candidate for the treatment of TB. In this study, we described the functional characterization of mycobacterial WecA and confirm the essentiality of its encoding gene in *M. tuberculosis* by demonstrating that the transcriptional silencing of *wecA* is bactericidal *in vitro* and in macrophages. Silencing *wecA* also conferred hypersensitivity of *M. tuberculosis* to the drug tunicamycin, confirming its target selectivity for WecA in whole cells. Simple radiometric assays performed with mycobacterial membranes and commercially available substrates allowed chemical validation of other putative WecA inhibitors and resolved their selectivity toward WecA versus another attractive cell wall target, translocase I, which catalyzes the first membrane step in the biosynthesis of peptidoglycan. The biochemical assays developed in our collaborators' laboratory coupled with the mutant strain constructed in the UCT node will be useful for identifying potential antitubercular leads by screening chemical libraries for novel WecA inhibitors. In a very recent development, we were approached by a researcher based at the US Department of Agriculture with a view to collaborating on establishing the target selectivity of putative WecA inhibitors that he has developed.

In a study led by Atica Moosa and Digby Warner, also published *in Antimicrobial Agents and Chemotherapy*, subunits I (*cydA*) and II (*cydB*) of the *M. tuberculosis* cytochrome *bd* menaquinol

oxidase were deleted from *M. tuberculosis* with the aim of comparing the effects of loss of the *bd* oxidase (CydAB) itself versus the ABC-type transporter, CydDC, predicted to be essential for cytochrome *bd* assembly. The resulting mutants were hypersusceptible to compounds targeting the mycobacterial bc_1 menaquinol-cytochrome *c* oxidoreductase, and fully phenocopied the behavior of a *cydC*::*aph* mutant. Moreover, in work conducted by our collaborators, Adrie Steyn and Dirk Lamprechts (AHRI, Durban), the two *bd* oxidase deletion mutants exhibited bioenergetic profiles indistinguishable from the CydDC mutant. These results confirm CydAB and CydDC as potential targets for drugs aimed at inhibiting a terminal respiratory oxidase implicated in pathogenesis, and confirm the utility of the *cydC*::*aph* mutant as counter-screening strain for rapidly identifying respiratory inhibitors as part of the first tier of the hit triage cascade which Digby Warner and Valerie Mizrahi contributed in developing in collaboration with Drs. Helena Boshoff and Clif Barry (NIAID) at the NIAID. A manuscript describing the cascade and its application within the TB Drug Accelerator program, is in preparation.

An exciting new study led by Vinayak Singh and Digby Warner has focused on elucidating the mechanism of antitubercular action of a small molecule synthesized by Prof. Simon Teague (Kings College London). This compound, designated as “SH”, has reasonably potent bactericidal against *M. tuberculosis* in vitro and in macrophages. Spontaneous resistance to SH was found to map to *aspC*, which is annotated as encoding one of two aspartate aminotransferases in *M. tuberculosis*. The role of *aspC* in the mechanism of resistance of *M. tuberculosis* to SH was confirmed by demonstrating that integration of a single copy of *aspC* carrying the mutation identified in a spontaneous resistant mutant (V325M) in wildtype *M. tuberculosis* was sufficient to confer resistance to the same level as observed in the spontaneous mutant. The essentiality of AspC for growth of *M. tuberculosis in vitro* was confirmed by conditional knockdown mutagenesis. Transcriptional silencing of *aspC* conferred hypersensitivity of *M. tuberculosis* to SH, implicating AspC as a target for this compound. Importantly, SH was found to specifically and profoundly potentiate the activity of the second-line TB drug, D-cycloserine (DCS), which targets both alanine racemase (Alr) and D-Ala-D-Ala ligase (Ddl) that catalyse the two steps immediately downstream of the L-alanine aminotransferase step in the peptidoglycan biosynthesis pathway. Reasoning that AspC might in fact serve as the pyridoxal 5-phosphate (PLP)-dependent L-alanine aminotransferase in *M. tuberculosis*, a series of metabolite rescue experiments were performed, which supported this hypothesis: firstly, D-Ala and L-Ala supplementation partly rescued *M. tuberculosis* from SH-mediated toxicity; and secondly, PLP completely rescued *M. tuberculosis* from SH toxicity when supplied exogenously at concentrations >20μM. Together, these data point convincingly to AspC as a target for SH. Preliminary biochemical data from Dr. Helena Boshoff’s lab at the NIAID is consistent with this notion. Ongoing studies are aimed at exploring the structure-activity relationship (SAR) in this compound series using a set of SH analogues obtained from Pfizer, and at determining whether other PLP-dependent enzymes might serve as secondary targets of SH. This highly productive collaboration with Prof. Teague, which extends to the MOA elucidation of other compounds not reported herein, has been strengthened by the award of grant from the Newton Fund (UK) held jointly with Digby Warner.

In other work conducted under the auspices of the SHORTEN-TB project, UCT node researchers have elucidated the MOA of myxovalargin (MXV), a natural product of myxobacterial origin provided by our collaborating partner, Prof. Rolf Müller (HIPS, Germany). MXV was shown to have bactericidal activity against *M. tuberculosis* and to target protein synthesis, as evidenced by the mapping of resistance-conferring mutations to the *rrl* gene. Interestingly, there was some overlap of the three mutations in *rrl* conferring resistance to MXV with mutations identified in *M. tuberculosis*

isolates resistant to the oxazolidinone, linezolid (LZD), selected in vitro and/or identified clinically (Dr. Taeksun Song, personal communication). As expected, MXV showed cross-resistance to a LZD-resistant mutant carrying an a2741g mutation in *rrl*. However, MXV retained wild type activity against LZD-resistant mutants carrying a t460c mutation in *rplC*, a g2841t mutation in *rrl* or a g2270t mutation in *rrl*, suggesting that cross-resistance between LZD and MXV is limited. This work will be incorporated into a larger manuscript on the interaction between MXV and the ribosome that is being prepared by our collaborators in Germany. Another project being conducted with other collaborators from the TB Drug Accelerator consortium (Merck Research Laboratories, NIAID, Weill Cornell Medical College and University of Dundee) has focused on elucidating the MOA of a compound series that is structurally related to the second-line TB drug, *p*-aminosalicylic acid (PAS). Interestingly, however, this series is unrelated to PAS in terms of MOA, showing instead an intriguing mechanism of resistance that involves a key enzyme in the TCA cycle, which potentially implicates central carbon metabolism in the MOA.

In recognition of the high standing of the UCT node in the biology of TB drug discovery, Valerie Mizrahi was invited to write a review on the topic of new antimycobacterials and drug targets for publication in the leading microbiology journal, *Current Opinion in Microbiology*. This review, which was co-authored with Joanna Evans, will be published in mid-2018 in a special issue focusing on antimicrobials.

Hit and lead identification against high-value drug targets. In other work, we have continued to pursue *M. tuberculosis* IMPDH (GuaB2) as new target for drug discovery. This enzyme plays an essential role in de novo purine biosynthesis and was recently identified and validated by UCT node researchers (Singh *et al. ACS Infect. Dis*. 2017). Vinayak Singh and Valerie Mizrahi are contributing authors on two manuscripts on this topic which are under review at *J. Med. Chem*., and aim to submit a separate, UCT-led manuscript in early 2018. In other SHORTEN-TB work, Joanna Evans has continued to support collaborative efforts aimed at developing on-target inhibitors with whole-cell activity against the CoaBC enzyme, which she validated recently as a vulnerable and uniquely bactericidal drug target in the coenzyme A biosynthesis pathway of *M. tuberculosis* (Evans et al. *ACS Infect. Dis*. 2016). Funding to support the synthesis and evaluation of new, mechanism-based CoaBC inhibitors has been requested from the NIH through a grant application led by our collaborator, Erick Strauss, from Stellenbosch University (outcome pending).

Novel approaches to potentiating drug efficacy. Other research under this theme has focused on exploring the potential of synergistic drug combinations as a strategy for early-stage identification of novel TB drug partners, with emphasis on repurposed drugs that have limited anti-tubercular drug efficacy when employed on their own, and on elucidating mechanisms to accelerate the rate of antibiotic-mediated kill of *M. tuberculosis*, funded by a grant from “TB Gift” program at the Broad Institute of Harvard and MIT (Mandy Mason, postdoctoral fellow). This project is focused on identifying intrinsic factors of *M. tuberculosis* that affect antibiotic efficacy over time, specifically genetic components whose absence results in a decreased fitness (hypersusceptible mutants) in response to short duration treatment with RIF. Hypersusceptible mutants will be identified using a transposon sequencing (Tn-Seq) approach. Preliminary experiments were performed in the *M. tuberculosis* Δ*leuD* Δ*panCD* double auxotroph. Saturated libraries were generated (~60 %) and selection performed using a culture expansion model under minimal selection over 6 days of treatment. Mutant fitness data were generated and compared to recently published data. Work was continued with virulent *M. tuberculosis* H37Rv where eight mutant libraries were generated and sequenced. The Tn insertion density of these ranged from 58-68% indicating that these were

suitable for downstream selection experiments which are underway using three drugs with different mechanisms of action. This study is one of three projects underway in the UCT node which are based on the application of Tn-Seq – a powerful method for genome-scale identification of conditionally essential gene function – as the key analytical tool. Significant progress has been made over the past year by Mandy Mason, and PhD students, Rendani Mbau and Irene Gobe, in perfecting the methods for *M. tuberculosis* and *M. smegmatis* Tn mutant library construction, propagation, sequencing and data analysis which has poised these projects for major advances in the coming year.

Understanding drug permeation, accumulation and efficacy in *M. tuberculosis*-infected macrophages. PhD students Amanda Mabhula and Lloyd Tanner, working together with postdoctoral Gabriel Mashabela, have made steady progress on drug permeation in a macrophage infection model in order to identify disease-relevant physicochemical and pharmacological properties that drive permeation of compounds into *M. tuberculosis*-infected cells, with a view to utilizing these data to determine predictors of cellular drug distribution. This work forms part of a collaboration between Digby Warner and Dr. Lubbe Wiesner, Clinical Pharmacology, UCT).

In a new project on the cell biology of TB led by Valerie Mizrahi, postdoctoral fellow Pooja Agarwal has developed and applied a robust experimental system for investigating the growth, persistence and drug susceptibility of *M. tuberculosis* in foamy macrophages, whose function in TB pathogenesis and response to therapy remain unknown but are the subject of considerable interest. Foam cells generated by exposure of THP-1-derived macrophages to oleic acid were shown to accumulate lipid bodies in a time-and concentration-dependent manner, and to be capable of phagocytosing live *M. tuberculosis*, as confirmed by confocal microscopy. While growth of *M. tuberculosis* was significantly retarded in foamy vs. resting macrophages, no significant difference in susceptibility to a range of TB drugs was observed although marked differences in the kinetics of uptake and steady-state levels of accumulation were detected for certain drugs. Specifically, bedaquiline accumulated to a significantly higher level in foam cells likely reflecting an association with drug lipophilicity. To further explore the biology of foamy macrophages and their interaction with *M. tuberculosis*, Pooja Agarwal and Valerie Mizrahi were awarded an academic exchange grant from the Oppenheimer Fund (University of Oxford) which enabled Pooja to spend two months developing and evaluating a primary foam cell model in the laboratories of Emeritus Prof. Siamon Gordon (Oxford) and Dr. Fernando Martinez Estrada (University of Surrey). Intriguing preliminary data obtained by imaging flow cytometry using an AMNIS ImageStream instrument at Oxford revealed very striking and unexpected differences in the cellular response to infection with *M. tuberculosis* (and other bacterial pathogens) in primary foam cells *vs*. human serum macrophages, which may be highly relevant to TB pathogenesis. Plans are underway for Dr. Agarwal to return for the UK for a further three-month exchange visit in early 2018 to further pursue this exciting new line of investigation.

Theme 3: TB transmission

Over the past year, research on a UCT-based project aimed at investigating the microbiological, immunological and environmental determinants of TB transmission, led by Prof. Robin 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. Under the leadership of Digby Warner, the UCT node is responsible for the molecular and bacteriological component of this interdisciplinary project which is co-funded by the BMGF (Aerobiology program). The second paper from this collaborative, which described

the sampling of bio-aerosols from newly diagnosed TB patients for detection and enumeration of *M. tuberculosis* using the Respiratory Aerosol Sampling Chamber (RASC; described in Wood *et al. PLoS ONE* 2016) was published in *Gates Open Research* in late 2017. In this study, each of 35 newly diagnosed, GeneXpert sputum-positive, TB patients were monitored during 1 hour confinement in the RASC. Microbiological culture and ddPCR were used by UCT node researchers, Atica Moosa and Vinayak Singh, to detect *M. tuberculosis* in each of the bio-aerosol collection devices. *M. tuberculosis* was identified in bio-aerosols exhaled by the majority of untreated TB patients using the RASC. Molecular detection was more sensitive than mycobacterial culture on solid media, suggesting that further studies are required to determine whether this difference might be attributable to the presence of a significant proportion of differentially detectable bacilli in these samples.

Outstanding progress was also made over the past year on establishing methods for the detection of aerosolized tubercle bacilli, captured in liquid, without a culture step. This requires the ability to concentrate a low number of bacilli into a usable format for microscopy, and to specifically label *M. tuberculosis* to distinguish it from any other airborne microbes. To this end, PhD student Ryan Dinkele, investigated the use of the probe, DMN-trehalose, developed recently in the laboratory of Prof. Carolyn Bertozzi (Stanford University). DMN-tre is an unnatural trehalose analogue that can be incorporated into the cell envelope of metabolically active *M. tuberculosis* (and other actinobacteria) through the action of Ag85 (trehalose mycolyltransferase) enzymes. However, a key consideration regarding the utility of DMN-tre for the detection of aerosolized *M. tuberculosis* is whether – and to what extent – the extent to which its efficacy might be affected by cellular stresses. Ryan Dinkele and Sophia van Coller addressed this question through a comprehensive series of experiments in both *M. smegmatis* and *M. tuberculosis.* Their results have confirmed that DMN-tre can stain mycobacteria exposed to a wide variety of stresses and cultured under different conditions. In a recent breakthrough using a sample collected from an untreated TB patient, *M. tuberculosis* was successfully detected and visualised after direct capture without an intervening culture step, thus providing exciting proof-of-concept for this approach. Ongoing work is aimed at further refining and optimizing the microscopic visualization methodology to enable confident identification as well as quantification of *M. tuberculosis*. In addition to this, new methods that enable culture independent whole genome sequencing from liquid capture as well as sputum are being researched.

In a related study initiated in September 2017, and enabled by the award of a three-year Carnegie Corporation *Developing Emerging African Leaders* early-career fellowship to Dr. Anastasia Koch, an analytical approach that can provide high-resolution and quantitative genetic characterization of *M. tuberculosis* populations within clinical samples is being developed. This approach will be applied ascertaining whether *M. tuberculosis* genotypes in expectorated sputum are representative of those in exhaled-air samples from TB patients. Preliminary work on this project has focused on optimizing DNA extraction techniques from various samples of *M. tuberculosis* to ensure as much of the genetic diversity within a population can be captured.

Wits Node

Research at the Wits node covers identification and validation of novel drug targets for TB, with a particular focus on peptidoglycan, DNA repair and mycobacterial oxidative phosphorylation as tractable areas for the discovery of new drugs. Enzymes that remodel the peptidoglycan are essential for bacterial cell division and the Wits node has uncovered a novel class of amidases that

are essential for bacterial survival. In addition to this, the Wits node is also focused on investigation of microbial heterogeneity in TB diseased individuals, prior to the initiation of treatment and during treatment. In this regard, they have described the prevalence of differentially culturable tubercle bacteria (DCTB) in the sputum of treatment naïve individuals and in the process of studying how the prevalence of these organisms changes during treatment. In addition, the Wits node supports the rollout of molecular TB diagnostics in South African and almost 20 other countries through the provision verification and quality assurance reagents. Finally, researchers at the Wits node have been involved in the search for new TB drugs through screening of compounds/extracts from medicinal plants. Research highlights in these four thematic areas are detailed below.

Peptidoglycan remodeling: In 2017, the morphological analysis of an *M. tuberculosis* mutant defective for a cell wall amidase (*ami1*) revealed no substantive defects in cell division 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. To further investigate the role of Ami1 in growth and survival of *M. tuberculosis,* the mutant together with the parental strain was assessed for survival defects under antibiotic stress, limited nutrients conditions, acid stress conditions and oxidative and nitrosative stress conditions. The *ami1* mutant displayed reduced survival under all the conditions tested suggesting that the *M. tuberculosis* Ami1 plays a critical role in cell wall biosynthesis and shows promise as a possible drug target. Consistent with this, the mutant was defective for growth in activated murine macrophages. These data are currently being collated for a manuscript and a Ph.D dissertation.

Following the extensive study of the amidase_1domain containing proteins in *M. smegmatis*, deletion strains of amidase_2 domain containing proteins in *M. smegmatis* were created which included Δ*ami3*, Δ*ami4* and Δ*ami5* respectively. These strains, when grown in minimal and rich media, showed marginal to no differences in growth compared to the wild type and genetically complemented derivatives. Further investigation, revealed that the Ami3 knockout strain displayed increased susceptibility to cell wall targeting antibiotics and was defective for the formation of biofilms when compared to the wild type strain. Next, possible interacting partners for Ami1 were investigated using a bacterial two-hybrid assay, which identified the cell wall transglycosylase and transpeptidase PonA1 and the immune evasion and antibiotic resistance protein MmpL as possible interacting partners. Loss of Ami3 also affected cell elongation and division through destabilization of DivIVA, a critical component involved in coordinating cell wall elongation.

The peptidoglycan layer undergoes constant reconstruction by penicillin binding proteins (PBPs) in addition to other enzymes that expand, break down and modify it to allow for cell growth and division while preventing lysis. PBPs have been shown to be involved in β-lactam antibiotic resistance, particularly LMW PBPs known as D,D-carboxypeptidases (D,D-CPases), making them putative targets for new antibiotic development. The functional role of two mycobacterial D,D-CPases, designated MSMEG_6113 and MSMEG_2433 was investigated through interaction and gene knockout studies. The MSMEG_6113 partners included cell division control protein 48 (Cdc48) and penicillin binding protein B (PBPb) also known as FtsI whilst the MSMEG_2433 partners included penicillin binding protein 1 (ponA1) and ATP-binding zinc metallo-protease FtsH. The deletion mutants for the MSMEG_6113 partners were successfully generated in *M. smegmatis*. However, knockout of FtsI was only possible in a merodiploid strain, confirming the essentiality of this gene. Further functional assessment of MSMEG_6113 and MSMEG_2433 domains showed that the transpeptidase domain of the two D,D-CPases is responsible for interaction with selected protein partners. The *M. smegmatis* FtsI protein was shown to be essential for growth *in vitro* and the

Δcdc48 mutants displayed morphological defects, with a weakened cell wall that was more permeable to selected cell wall targeting antibiotics.

The peptidoglycan (PG) recycling pathways are also hypothesized to regulate β-lactam resistance in mycobacteria. To investigate this, a *M. tuberculosis* mutant unable to induce BlaC expression is currently being generated through transposon mutagenesis and phenotypic characterization of the mutant should provide a better understanding of these penicillin binding antibiotics. The role of the *murT* gene, required for amidation of the mycobacterial peptidoglycan was also investigated in both *M. smegmatis* and *M. tuberculosis.* The gene could not be deleted in both organisms by allelic exchange suggesting that *murT* plays an essential role in peptidoglycan metabolism. Using the Crispr-dcas9 methodology, a knock down mutant of *murT* in *M. smegmatis* has been generated which showed maximal growth both in nutrient rich or limited conditions.

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. Previous studies in *M. smegmatis*, highlighted that the two LytM domain-containing homologues (M23 peptidases) designated MepB1-MepB4 are dispensable for growth but have important roles in bacterial growth. Similarly, in 2017 the two M23-domain genes from the *M. tuberculosis* genome were deleted and the effect of the M23-domain gene deletion on cell wall degradation was phenotypically assessed. Growth rate analyses, cell wall-targeted antibiotic susceptibility assays, fluorescence microscopy and scanning electron microscopy revealed that deletion of the two M23-domain genes *mepA* and *nlpAL* in *M. tuberculosis* did not result in a cell separation defect or other gross morphological changes, suggesting a different role for the M23-domain factors in *M. tuberculosis* compared to *M. smegmatis*. Work towards building a MepA protein-interaction library, studying the effects of *mepA* gene overexpression and generating microarrays of the *mepA*-deletion mutant to identify pathways in which the gene may be involved are currently underway. Collectively, these observations should 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 mycobacteria. Resuscitation promoting factors (Rpfs) have previously been shown to act as growth stimulatory molecules via their lysozyme-like activity on peptidoglycan in the bacterial cell wall. In *M. tuberculosis*, Rpfs have been implicated in resuscitation from a non-culturable state and pathogenesis in the mouse model. *M. smegmatis*, encodes four distinct homologues (i.e. *rpfA*, *rpfB*, *rpfE* and *rpfE2*). A panel of *M. smegmatis* mutant strains lacking *rpf* genes individually or in combination was previously constructed at the Wits node of the CBTBR. Gene expression patterns of the *rpf* homologues in liquid culture corresponding to early- logarithmic, mid-logarithmic and late logarithmic phase revealed differential gene expression patterns for the different *rpf*-like genes that was dependent on growth phase. Gene expression appeared to be similar in pellicle biofilms assessed at 7, 14 and 28 days. In addition, assessment of individual colony morphologies on solid media showed abnormal colony formation for the mutant with a combined deletion in *rpfA* and *rpfB*. Colonies lost their ability to form serpentine cords and were also unable to form biofilms. Biofilm biomasses were reduced and could not be corrected with exogenous supplementation of Rpfs however, genetic complementation with *M. tuberculosis rpf* homologues reversed the defect, suggesting that Rpfs have to be produced endogenously. Moreover, the relative susceptibility of these defective biofilms to antibiotics and cell wall damaging agents was increased when multiple *rpf*-like genes were deleted. In collaboration with Baylor University, using LC-MS analysis the peptidoglycan composition of the parental and the Δ*rpfABEE2* mutant showed a reduced level of 4-3 cross-linked PG dimers and concomitant increased amount of 3-3 cross-linked muropeptides in the mutant strain. In addition, the level of PG-repeat units terminating in 1, 6-anhydroMurNAc

appeared to be significantly reduced. Collectively, our data demonstrate that Rpfs play an important role in biofilm formation via alterations in PG cross-linking and the production of signaling muropeptides.

Mycobacterial oxidative phosphorylaytion: M. tuberculosis has a branched electron transport chain (ETC) with two terminal oxidases i.e. the cytochrome *c* oxidase (CcO) and the cytochrome *bd* oxidase (CbO). The CcO is essential in mycobacteria and is considered the predominantly active terminal oxidase during aerobic respiration. The CbO has been shown to be important under hypoxic conditions in mycobacteria. More recent studies have highlighted an important role for the mycobacterial CbO in resistance to oxidative stress and re-routing of electron flux when bacteria are treated with ETC-targeting compounds. The CbO has thus been proposed as a promising new drug target and research at the Wits node is aimed at characterizing the role of the mycobacterial CbO under different environmental conditions. In addition, the alternative nitrate respiratory/assimilatory pathway mediated by nitrate reduction in *M. smegmatis* is also being assessed. Findings show that the CbO contributes to redox balance and when absent, leads to a more reduced intracellular environment in the organism. These and other effects are being studied further.

DNA Repair: During infection, *M. tuberculosis* encounters hostile conditions which result in the generation of host-derived reactive oxidative and nitrosative species 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. tuberculosis* 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. Previously, research at the Wits node demonstrated 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 *neiI* 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 *neiII* 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 with *neiI*, resulted in increased stalling of the replication fork during DNA replication compared to *neiII*. Collectively, the data indicate that the *neiI* homologue has a greater role together with the Nth DNA glycosylase in maintaining mycobacterial genome integrity compared to the *neiII* homologue.

Clinical microbiology: In a cross-sectional observational cohort of patients, the Wits node demonstrated that sputum from TB patients harbours drug tolerant differentially culturable tubercle bacilli (DCTB) that are unable to grow on solid media but can be recovered in liquid media supplemented with culture filtrate. However, in addition to culture filtrate dependent-DCTB, sputum from TB patients also harbored a comparably significant proportion of Rpf-independent DCTB indicating that other components, apart from Rpfs, are responsible for growth of DCTB. To further investigate this, two longitudinal cohorts have been established to determine the relative

proportions and the rate of decline in DCTB in patients with drug susceptible pulmonary TB throughout first-line anti-TB treatment and further follow up of patients to record any incidence of TB relapse disease. More recently, a third cohort of patients that are failing first line therapy and have been diagnosed with drug resistant TB are being monitored for DCTB and disseminated TB during second line therapy with two year follow ups to identify cure and relapse rates.

Culture remains the gold standard for tuberculosis diagnosis but the results can take up to six weeks hence, methods to reduce diagnosis times are urgently required, particularly in HIV-infected TB patients where the bacterial load in sputum samples is often low leading to diagnostic difficulties. A total of 120 patients were recruited for a new study at the Wits node and sputum from these patients was grown in a modified BACTEC MGIT 960 assay which was supplemented with *M. tuberculosis* H37Rv culture filtrate. Addition of culture filtrate to MGIT media did not significantly accelerated time to positivity (TTP) but greatly enhanced detection in smear negative patients with low sputum bacillary load. Further microbiological analysis indicated that the change in MGIT TTP was mainly due to accelerated growth of few viable organisms rather than resuscitating non-culturable bacteria. Our data provide compelling evidence that the addition of culture filtrate to the MGIT assay does have the potential to enhance the detection of HIV-infected TB patients who are smear-negative.

In another new project, through collaboration with Dr. Carolyn 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 is a solvatochromic derivative of trehalose that only fluoresces when taken up by live mycobacterial cells and as such offers the possibility of a low signal to noise ratio. The uptake of the dye by bacteria grown in axenic culture and sputum was measured using flow cytometry and auramine culture smear that allowed relative comparison with existing diagnostic tools. Approximately 60 samples were processed using optimized protocols for cytometry and culture smear with further confirmation using fluorescence microscopy. Labelling with DMN-Tre proved to be comparable to auramine staining but still requires some optimization before it can be rolled out as a diagnostic tool. These data were incorporated into a manuscript entitled “Rapid detection of *Mycobacterium tuberculosis* (*Mtb*) in sputum with a solvatochromic trehalose probe” and has been submitted to *Science Translational Medicine* for peer-review.

TB Diagnostics: Due to the threat of bacterial drug resistance, more sensitive, reliable and rapid molecular diagnostic methods are now available for TB diagnosis. For example, the GeneXpert MTB/RIF system is used for simultaneous identification of infection and rifampicin resistant *M. tuberculosis*. The Wits node of the CBTBR has invested substantial effort in the past to streamline 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 undertook 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. *M. smegmatis* was chosen as a host for biomimetic delivery as it is a non-pathogenic relative of *M. tuberculosis* that is known to test negative in the GeneXpert MTB/RIF and the GenoType MTBDR*plus* diagnostic assays. Nucleic acid from *M. tuberculosis* was introduced into *M. smegmatis* using standard molecular techniques that resulted in strains that contained the rifampicin resistance determining region (RRDR) specific to the *M. tuberculosis* Complex (MTBC). Introduction of the RRDR of the MTBC in the derived *M. smegmatis* strain, produced positive diagnostic signals mimicking those of the MTBC. Furthermore, *M. smegmatis* bearing the RRDR of

MTBC with single nucleotide polymorphisms mimicked the profile expected for *M. tuberculosis* strains that are clinically rifampicin resistant. As an extension of this work the methodology was tested on the *Staphylococcus aureus* GeneXpert SA Nasal Complete cartridge which is able to detect the nucleic acid sequence SCC*mec* present in methicillin resistant strains. Wild type *M. smegmatis* yielded no signal, while a strain containing artificially introduced nucleic acid produced the expected signal from the targeted region. This work was published in 2017 in J Clin Microbiol
Drug screening: In the backdrop of local and international drug development for TB disease, the Wits node has set up two collaborative initiatives to test synthetic and natural compounds for anti-mycobacterial activity. The first of these collaborations is with Prof Daniel Strand from Lunds University in Sweden and the second is with Dr. Tozama Qwebani from the Vaal University of technology (VUT). Several compounds have already been tested for VUT and the first compounds from Lunds University are expected in April 2018

Joint Research and Training activities

The 3 nodes from the CBTBR have many collaborations in place. These can be seen under the National Networking section of this report. A number of these collaborations are highlighted below.

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 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 (LIIU) 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. One meetings of the WCAFC was held in 2017 at SU.

Outside the umbrella of the CBTBR, members of Prof Warren's group (SU) and Prof Dheda (UCT – LIIU) have an ongoing collaboration to explore drug resistance in the Western Cape, and Prof Walzl's team works closely with the SATVI team, based at the IDM, UCT as well as the CIDRI team of Prof Robert Wilkinson, based at UCT.

2. EDUCATION AND TRAINING

Breakdown of postgraduate students and postdoctoral fellows in the CBTBR in 2017

Student Category	Number / Percentage	Target based on SLA4 (for Extension Phase 2014-2018)
Total number of students	136	≥ 35
% Postdoctoral fellows	27,2%	≥10%
% PhD students	32,4%	N/A
% MSc students	25,7%	N/A
% BSc (Hons) students	14,7%	N/A
% Women students*	75%	≥ 50%
% Black students*	50%	≥ 50%

***Includes postdoctoral fellows

Degrees conferred and postdoctoral fellowships completed

The CBTBR graduated 6 PhD, 7 MSc and 20 BSc (Hons) students in 2017.

Recruitment of new postgraduate students

A number of new students have joined the team during the course of 2017. At the SU node, for 2017 including the new students, 30 Postdoctoral fellows, 31 PhD students, 31 MSc students and 20 BSc (Hons) students were registered. At the UCT node a total of 6 Postdoctoral fellows, 9 PhD students and 2 MSc studentswe registered. The Wits node registered 1 Postdoctoral fellow, 4 PhD students and 2 MSc students for 2017.

Summary of recruitment of new postgraduate students

	UCT	Wits	SU	Total for 2017
Postdoc Fellows	6	1	30	37
PhD	9	4	31	44
MSc	2	2	31	35
BSc Hons	0	0	20	20

Honours and awards to staff and students

- Professor Bavesh Kana received an award from the Dean of the Faculty of Health Sciences for Excellence in Academic Service. This award was conferred upon him in November 2017, at an event to honour Faculty members.

- In July 2017, Professor Kana received Faculty Honours for notable contribution to Research

- Miss Andrea Papadopoulos was renewed for a second year of a Medical Faculty Research Endowment Fund (MFREF) by the Faculty of Health Sciences, University of the Witwatersrand towards research project operating costs.

- Mr. Moagi Shaku was appointed as a TB blogger for the online journal, Nature Microbiology Community

- Mr. Moagi Shaku won first prize for the best oral presentation in the Medical Microbiology and Virology track at the PathRed 2017 congress

- Dr. Machowski was awarded the Claude Leon Foundation (CLF) Merit Award through the WITS Research Office worth R25 000.

- Miss Poppy Mashilo was awarded merit award by the University of the Witwatersrand, 2017.

- Miss Poppy Mashilo won first prize for a poster presentation in the Infectious Disease Tract at the Molecular Biosciences Research Trust Postgraduate Research Day 2017.

- Valerie Mizrahi was awarded the 2017 SAMRC Platinum Lifetime Achievement Award for outstanding lifetime achievements in the field of health research. She was also selected as one of nine microbiologists from around the world to contribute to a *Leading Edge Voices* article on “Big Questions in Microbiology” that was published in *Cell* in May 2017.

- Valerie Mizrahi was appointed to the Editorial Advisory Board of *Genome Biology.*

- Valerie Mizrahi was appointed as an *ad hoc* member of the Keystone Symposia Scientific Advisory Board for 2018

- Valerie Mizrahi served as a Principal Investigator and BSLIII Platform Lead on UCT’s successful application to the Wellcome Trust for the creation of the Wellcome Centre for Clinical Infectious Diseases Research in Africa. This new Wellcome Centre, which is led by Professor Robert J. Wilkinson, is the only one awarded to an institution outside the UK. Digby Warner is a Collaborating Investigator in this Centre.

- Mandy Mason was awarded a Claude Leon Postdoctoral Research Fellowship for 2018-2019.

- Rendani Mbau was awarded a SAMRC Internship PhD scholarship for 2017.

- Anastasia Koch was awarded an early-career fellowship from the Carnegie Corporation’s Developing Emerging Academic Leaders in Africa (DEAL) program, UCT. This fellowship will support Anastasia as a Junior Research Fellow in the UCT node for 2018-2020.

- Charles Omollo was awarded a postdoctoral fellowship from the Carnegie Corporation’s Developing Emerging Academic Leaders in Africa (DEAL) program, UCT

- Michael Reiche won second prize in the review article category of the IDM Postgraduate Student Publication Competition 2017, for his article that was published in *Frontiers in Molecular Biosciences.* Michael also won travel awards from American Society for Microbiology, the NRF and Mycobact2017 to attend conferences in the USA and Sweden where he was selected to present short talks.

- Terry Kipkorir received a travel award from the American Society for Microbiology to attend a conference in New York in April, and from UCT to attend a conference in Europe where he was selected to present a short talk.

- Caitlin Taylor won the Mary Veenstra Prize for the best poster presentation at the Microscopy Society of Southern African 2017 conference. She also won second prize in the Nikon Small World Competition for photomicrography at this conference.

- Lloyd Tanner won the Best Poster Prize at the 2017 South African Society for Basic and Clinical Pharmacology Conference. He was also the recipient of an NRF innovation scholarship

- Amanda Mabhula was awarded a UCT Travel grant to attend the Gordon Research Conference and Gordon Research Seminar on Tuberculosis Drug Discovery and Development in Italy, June 2017.

- Timothy de Wet was awarded a Croucher Foundation Fellowship, an Institut Pasteur Fellowship and a SAMRC Clinician Scientist Scholarship. He was also awarded the Second Prize in the Oral Presentation category at the UCT Faculty of Health Sciences Postgraduate Research Day, September 2017.

- Bianca Masuku was awarded a SAHUDA-NIHSS Doctoral scholarship

- Both Bianca Masuku and Timothy de Wet reached the finals of the FameLab Competition, CSIR, December 2017

Training courses / Teaching implemented by staff and students

- Prof. Warner served as Convenor of the BMedSc (Hons) programme, Faculty of Health Sciences, UCT.

- Prof. Warner served as Convenor, *Laboratory Research Methods* module of the BMedSci(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. Mason 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 and Dr. Koch lectured in this course.

- Timothy de Wet served as a tutor for the BMedSci(Hons) Techniques course and Terry Kipkorir co-supervised students and graded lab reports for the Infectious Disease & Immunology Virology-Bacteriology practical module.

- Dr. Sophia Gessner served as co-convener of the Statistical Literacy course presented to BMedSci(Hons) students.

- Prof. Warner presented the *Tuberculosis* module in the *Defence and Disease* programme in the Department of Molecular and Cell Biology, Faculty of Science, UCT

- Prof. Warner and Dr. Saber Anoosheh hosted Dimitri Griffault, a visiting student from Poitiers University, France, during his three-month internship in the lab

- Prof Kana and Dr. Gordhan taught third year students in the Molecular Medicine degree at Wits University.

- Prof. Kana delivered lectures on Gene Manipulation and Recombinant DNA technology to Masters of Medicine students.

- Juanelle du Plessis and James Gallant delivered lectures: BSc Hons Course Training from 2017/02/01 to 2017/02/28 held at Stellenbosch University.

- Samantha Sampson and Tiaan Heunis delivered lectures: BSc Hons Mycobacteriology Module, Stellenbosch University.

- David Tabb taught the following:

    Quality control Proteomics, Moscow.
    Bioinformatics SU node, BSc Hons, 8-day course
    Annotating non-model organisms
    Chemical and Symtems Bioinformatics, UCT
    Biostatistics, UWC - IMBM, 12-day course
    Bioinformatics, UWC – Biotechnology, 3-day course
    Proteome informatics, UWC – SANBI
    ASMS Workshop, Indianapolis, USA

Online Courses

- Juanelle du Plessis attended the following: Health Care System Fundamentals - Online Course, Novartis

- N de Villiers attended the following: H3ABioNet Introduction to Bioinformatics, Distance-based learning, online.

- M. Klopper and S. Ley, attended the following: Introduction to bioinformatics from 2017/05/01 to 2017/08/31 held at FMHS, Stellenbosch University online.

- Boiketlo Sebate attended the following: Webinar with Prof Peter Donald from 2017/08/09 to 2017/08/09 – Webinar.

- Nandi Niemand attended the following: Maestro software training from 2017/07/17 to 2017/07/31, Webinar series.

- Roxanne Higgitt attended the following: Introduction to Bioinformatics - Online & FMHS from 2017/05/09 to 2017/08/04 held at FMHS, Stellenbosch University, Cape Town

Exchange Visits and Training Courses / Workshops attended

- Pooja Agarwal undertook a two-month training visit to the laboratories of Prof. Siamon Gordon (University of Oxford) and Dr. Fernando Estrada Martinez (University of Surrey) with the support of an Academic exchange grant to Prof. Mizrahi from the Oppenheimer Fund (UK). This was a highly productive visit that has led to a new, three-way collaborative research project on the role of foam cells in TB pathogenesis.
- Charles Omollo undertook a six-week training visit to the Helmholtz Institute of Pharmaceutical Sciences, University of Saarland, Saarbrucken, Germany (2017), September 9– October 22. The aim of this visit was to gain hands-on experience in research aimed at exploring the utility of natural products as anti-microbial agents. This visit was funded by a SA/Germany Binational Research Collaboration grant from the NRF (Prof. Mizrahi and Prof. Rolf Müller, co-PIs).
- Timothy de Wet attended the Institut Pasteur / Institut Curie Molecular Biology of the Cell workshop in Paris, January 2017. He also participated in the University of Hong Kong 2nd Croucher Summer Course in Advanced Imaging in October 2017.
- Ryan Dinkele participated in the University of Hong Kong 2nd Croucher Summer Course in Advanced Imaging in October 2017. He also attended the Biodefense World Summit in Alexandria, VA USA, from 26-29 June 2017, and thereafter visited the laboratories of Prof. Carolyn Bertozzi and Dr. Jason Andrews (Stanford University, USA) on 3rd July, as well as the ImageStream facility at Merck, Seattle USA, from 6-7 July.
- Pooja Agarwal attended the ISAC Flow Cytometry Workshop at Stellenbosch University, April 2017.
- Caitlin Taylor attended the FIJI Workshop (13-14 March 2017); the First Flow Cytometry Workshop (11-13 April 2017); the Confocal 880 with Fast Airyscan Technology Workshop (2-4 August 2017); AFGRICA Medical Mycology Workshop (8 August 2017); and the South African Raman Workshop (27-28 November 2017), all of which were held in Cape Town.
- Anastasia Koch visited the laboratory of Dr Vegard Eldholm, Norwegian Public Health Institute, 4 – 6 September, 2017 to discuss how to investigate heterogeneity within in *M. tuberculosis* populations in clinical samples, with a view to establishing a possible collaboration**.**
- Anastasia Koch also attended the CRyPTIC consortium annual general meeting (http://modmedmicro.nsms.ox.ac.uk/cryptic/), 6 – 7 November 2017, Dubai, UAE.
- Melissa Chengalroyen, Mandy Mason, Ryan Dinkele, Caitlin Taylor, Timothy de Wet, Pooja Agarwal attended the ImageXpress Micro confocal training workshop held at UCT in November 2017.
- Bianca Masuku attended a two-day BMJ Medical Humanities Special Issue workshop held at the Wits Institute for Social and Economic Research (WiSER) in Johannesburg, 15 – 16 September 2017.

- Dr. Machowski attended the University of the Witwatersrand course for the T4 Terminal Website interface.
- Prof Kana, Drs Ealand, Gordhan, Padyachee and Peters and Ms. Masangana and Sewcharran attended the Good Clinical Practice course over October – November. BEESA Conference Centre, 5 Sherborne Rd, Parktown.
- Mr Saku represented the Wits node at the DST/NRF CoE annual directors' forum in collaboration with the Nelson Mandela Metropolitan University, Port Elizabeth. 1st September 2017.
- Prof Warner represented the UCT node at the DST/NRF CoE annual directors' forum in collaboration with the Nelson Mandela Metropolitan University, Port Elizabeth. 1st September 2017.
- Dr L Smith, Prof Walzl, Dr Loxton, Dr Maqwebeba, Ms Moore and Ms Young represented the SU node at the DST/NRF CoE annual directors' forum in collaboration with the Nelson Mandela Metropolitan University, Port Elizabeth. 1st September 2017.
- Stephanie Pitts attended the following: Genome-wide association analysis from 2017/06/26 to 2017/06/30 held at Max Dulbruck Center for Molecular Medicine, Berlin, Germany.
- S Mboniswas and V Ndunana, attended the following: Mantoux training from 2017/06/21 to 2017/06/21 held at Faculty of Medicine and Health Sciences, Stellenbosch University.
- Nikola de Villiers attended the following: Project Management for the Research Team from 2017/05/10 to 2017/05/11 held at Research Development and Support Division, Faculty of Medicine and Health Sciences, Stellenbosch University.
- Brigitta Derendinger and Natasha Kitchin attended the following: Science Communication: A workshop on the basics from 2017/07/12 to 2017/07/12 held at Faculty of Medicine and Health Sciences, Stellenbosch University.
- Stephanie Minnies attended the following: Science Communication: A workshop on the basics from 2017/07/12 to 2017/07/12 held at Faculty of Medicine and Health Sciences, Stellenbosch University.
- Stephanie Minnies attended the following: Literature Review workshop from 2017/07/24 to 2017/07/25 held at Faculty of Medicine and Health Sciences, Stellenbosch University.
- Novel Chegou attended the following: Project management course from 2017/07/28 to 2017/07/28 held at STIAS, Stellenbosch.
- Bongani Motaung and Danielle Moore attended the following: Confocal Microscopy Course from 2017/07/03 to 2017/07/04 held at CAF, Stellenbosch University.
- Annika Neethling and Soraya Bardien attended the following: Tritateral mitochondrial workshop (UK-Egypt-SA) from 2017/01/30 to 2017/02/02 held at STIAS, Stellenbosch.
- Annika Neethling attended the following: Project management for the research team from 2017/05/10 to 2017/05/11 held at Tygerberg Campus, Stellenbosch University.
- William Haylett and Shameemah Abrahams, attended the following: Nucleic Acid Preparartion, QC and Library building for Next Generation Sequencing workshop from 2017/06/20 to 2017/06/22 held at CAF, Stellenbosch.
- William Haylett, attended the following: EMBL course: Genome Engineering: CRISPR/Cas from 2017/09/17 to 2017/09/22 held at EMBL Heidelberg, Germany.
- Thea Heinemeyer and Soraya Bardien, attended the following: Mendeley workshop from 2017/07/27 to 2017/07/27 held at Gerga 1, Stellenbosch University.
- Boiketlo Sebate, attended the following: Formating your dissertation from 2017/03/06 to 2017/03/06 held at Main campus, Stellenbosch University.

- Boiketlo Sebate attended the following: Scientific research leading to policy changing from 2017/05/12 to 2017/05/12 held at F334, Fisan, Tygerberg, SU.
- Boiketlo Sebate attended the following: Personal branding from 2017/05/23 to 2017/05/23 held at Lecture hall 5, Teaching block, Stellenbosch University.
- Boiketlo Sebate attended the following: Article writing workshop from 2017/06/01 to 2017/06/01 held at Admin B, Seminar room, Stellenbosch University.
- Boiketlo Sebate attended the following: Workshop on predicting the effects of mutations on protein structure using bioinformatics tools from 2017/09/04 to 2017/09/07 held at SANBI, University of Western Cape.
- Boiketlo Sebate attended the following: Science communication workshop held at Tygerberg Campus, Stellenbosch University.
- Boiketlo Sebate attended the following: Creating your thesis or dissertation from 2017/10/03 to 2017/10/06 held at Main campus, Stellenbosch University.
- Shameemah Abrahams attended the following: International grants: What you need to know, short information session from 2017/08/03 held at Tygerberg campus, Stellenbosch University.
- Shameemah Abrahams attended the following: How to write an abstract, 2017/06/01 held at Tygerberg campus, Stellenbosch University.
- Soraya Bardien attended the following: Library week 2017: The nuts and bolts of research from 2017/07/31 to 2017/08/04 held at Stellenbosch University.
- Soraya Bardien attended the following: Preditory publishing workshop, 2017/08/17 held at Devon valley hotel, Stellenbosch.
- Tiaan Heunis attended the following: GCP beginner's course from 2017/03/08 to 2017/03/09 held at Stellenbosch University.
- Tiaan Heunis and James Gallant, attended the following: Pathogen Bioinformatics Course from 2017/03/27 to 2017/03/28 held at University of Cape Town.
- Jomien Mouton and Tiaan Heunis, attended the following: Post-doc grant writing workshop, 2017/03/30 and 2017/04/06 held at Stellenbosch University.
- Nastassja Kriel attended the following: ISAC Flow Cytometry Workshop from 2017/04/11 to 2017/04/13 held at Stellenbosch University.
- Jomien Mouton attended the following: Bacterial Flow Forum, 2017/04/10 held at Stellenbosch University.
- Caroline Pule attended the following: RNA seq workshop, held at University of Pretoria.
- Jomien Mouton and Trisha Parbhoo, attended the following: Workshop, BD Horizon Tour, 2017/06/29 held at University of Cape Town, IDM.
- Caroline Pule attended the following: Flow Cytometry and Cell Sorting Workshop held at Stellenbosch University.
- Nastassja Kriel attended the following: Workshop on predicting the effects of mutations/nsSNP's on protein structure using Homology Modeling, Gibbs free energy calculation webservers (SDM and mCSM) and Interaction analysis from 2017/09/04 to 2017/09/06 held at University of the Western Cape.
- Nastassja Kriel and Jomien Mouton attended the following: NIH Grant Writing Workshop, 2017/09/18 and 2017/10/02 held at Stellenbosch University.
- Pumla Mesatywa attended the following: Academic Article Writing, 2017/08/11 and 2017/08/26 held at Stellenbosch University.

- Caroline Pule attended the following: H3ABioNet Introduction to Bioinformatics Course, held at Stellenbosch University.
- James Gallant attended the VU Netherlands from 2017/08/06 to 2017/10/14 in the Netherlands.
- Nastassja Kriel attended the following: Harry Crossley Grant Writing Workshop, 2017/08/31 held at Stellenbosch University.
- Jomien Mouton attended the following: EMBO Practical Course: The fundamentals of high-end cell sorting from 2017/11/20 to 2017/11/24 held at Heidelberg, Germany.
- S Boolay attended the following: Internal Auditing Course by Quality First Business Solutions from 2017/08/15 to 2017/08/17 held at Tygerberg, Stellenbosch University.
- J Theys attended the following: First Aid level 1 course from 2017/08/15 to 2017/08/16 held at Stellenbosch University.
- M Williams attended the following: Leadership Development Programme 2017 from 2017/08/24 to 2017/08/25 held at Durbanville.
- CJ Werely attended the following: Annual Biobanking Course, 2017/08/18 held at SAMRC Conference Centre, Cape Town.
- Sihaam Boolay and Janice Theys, attended the following: QFT Plus Training - Warren Fransman (Barker Medical) held at Division of Molecular Biology and Human Genetics, Stellenbosch University.
- Craig Kinnear attended the following: Diversity Workshop from 2017/04/06 to 2017/04/06 held at South African Medical Research Council.
- M Klopper attended the following: Postgraduate supervision in Health Sciences from 2017/08/16 to 2017/08/17 held at FMHS, Stellenbosch University.
- Entire SU node, Students and staff participated in a series of Interactive capacity building from 2017/08/15 to 2017/08/15 held at FMHS, Stellenbosch University.
- Charissa Naidoo and Georgina Nyawo, attended the following: H3ABioNet Introduction to Bioinformatics course, held at Stellenbosch University.
- Natasha Kitchin and Zaida Palmer, attended the following: Annual Biobank workshop, 2017/08/18 held at SA-MRC.
- Members of the SU and UCT nodes attended the following: Acid Fast Club meeting, 2017/08/22 held at Stellenbosch University.
- Members from the SU node attended the following: Annual Academic Year Day, 2017/08/30 held at Stellenbosch University.
- Natasha Kitchin, Liezel Smith and Taime Sylvester attended the following: SA WISE Personal Branding, 2017/08/07 held at Century City, Cape Town.
- Lucinda Baatjies attended the following: PowerPoint for Conference Presentations, 2017/08/17 held at Stellenbosch University.
- Michele A. Miller, Sven D.C. Parsons, attended the following: Rhino TB Management Plan Workshop, 2017/01/06 held at Skukuza, South Africa.
- Michele A. Miller attended the following: Zimbabwe Wildlife Immobilization Course from 2017/02/10 to 2017/02/18 held at Malilangwe Game Reserve, Zimbabwe.
- Michele A. Miller attended the following: Conservation Workshop for Arabia's Biodiversity from 2017/02/06 to 2017/02/09 held at Sharjah, UAE.
- Eduard O. Roos attended the following: Introduction to molecular biology: Theory and Practical from 2017/02/06 to 2017/02/10 held at School of Veterinary Medicine, University of Nambia, Nambia.

- Tashnica T. Sylvester attended the following: Honours and Masters Workshop on Time Management, 2017/02/27 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica, T. Sylvester attended the following: Science Friday - promote interdisciplinary conversations about the impact of science on society, 2017/02/10 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica T, Sylvester attended the following: PhD Focus / Information Session for all PhD students at the FMHS, 2017/03/01 held at FMHS, Stellenbosch University, Cape Town.
- Yessica Fitzermann, Roxanne Higgitt, attended the following: Pathogen Bioinformatics Course from 2017/03/27 to 2017/03/28 held at UCT, Cape Town.
- Tashnica T. Sylvester organized and attended the following: Association of South African Women in Science and Engineering Meet and Greet, themed 'Decolonizing STEM', 2017/03/08 held at Sports Science Institute, Newlands, South Africa.
- Tashnica T. Sylvester attended the following: Association of South African Women in Science and Engineering Annual General Meeting, 2017/03/08 held at Sports Science Institute, Newlands, South Africa.
- Tashnica T. Sylvester attended the following: Honors and Masters Workshop on Presentation Skills, 2017/03/24 held at FMHS, Stellenbosch University, Cape Town.
- Michele A. Miller attended the following: Rhinoceros TB for SANParks and State Veterinary Staff, 2017/04/19 held at Skukuza, South Africa.
- Netanya Bernitz and Tashnica T. Sylvester, attended the following: International Society for Advancement of Flow Cytometry (ISAC) Flow Cytometry Workshop from 2017/04/11 to 2017/04/14 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica T. Sylvester attended the following: How can scientific research translate to policy change? 2017/05/12 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica T. Sylvester attended the following: Post Graduate Workshop - CV Writing and Interview Skills, 2017/05/16 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica T. Sylvester attended the following: Postgraduate Workshop - Stress Management, 2017/05/18 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica T. Sylvester attended the following: Postgraduate Workshop - Personal Branding 2017/05/23 held at FMHS, Stellenbosch University, Cape Town.
- Michele A. Miller attended the following: Tuberculosis in South African Wildlife - Why Is It Important? 2017/05/26 held at Skukuza, South Africa.
- Tashnica T. Sylvester organized and attended the following: Mentorship and Networking Event for Women in Science, Engineering and Mathematics, 2017/06/22 held at Cape Town.
- Tashnica T. Sylvester attended the following: Navigating the student-supervisor relationship for postgraduate students, 2017/06/29 held at FMHS, Stellenbosch University, Cape Town.
- Tashnica T. Sylvester attended the following: Animal Tuberculosis: A peek into the devastating epidemic, 2017/06/20 held at Department of Science, UCT, Cape Town.
- Tashnica T. Sylvester attended the following: From Sci-Speak to street-speak, 2017/07/12 and 2017/07/26 held at FMHS, Stellenbosch University.
- Josephine Chileshe and Tanya J. Kerr, attended the following: Harry Crossley Foundation Grant Application Workshop, 2017/08/31 held at FMHS, Stellenbosch University.
- Tanya J. Kerr and Tashnica T. Sylvester, attended the following: How to manage your research project using Project Management tools - Short Information Session, 2017/10/10 held at FMHS, Stellenbosch University, Cape Town.

- Josephine Chileshe attended the following: Short Course - Introduction to Epidemiology, 2017/07/04 and 2017/10/02 held at SACEMA, Stellenbosch.
- Michele Miller, Liezel Smith and Craig Kinnear attended the following: NRF workshop 'Planning for Impact', 2017/11/28 held at Pretoria, South Africa.
- Gina Leisching, Bienyameen Baker, Liezel Smith, Nasiema Allie, Jennifer Jackson, Monique Williams, attended the following: Introductory NIH Grant writing Workshop, 2017/09/18 and 2017/10/02 held at SU FMHS, Teaching building, 4053A.
- R, Warren and M Whitfield attended the following: Meeting the challenge of drug resistant tuberculosis from 2017/03/24 to 2017/03/26 held at University of Cape Town.
- M. Whitfield attended the following: Whole Genome Sequencing Course from 2017/03/27 to 2017/03/28 held at UCT.
- M. Klopper attended the following: Basic SUNLearn Training for Lecturers, 2017/04/21 held at Stellenbosch University.
- R. Warren attended the following: Getting published 2017/05/10 held at Stellenbosch University.
- S. Ley, M. Klopper, attended the following: H3ABioNet course, 2017/08/31 held at Stellenbosch University, Tygerberg.
- R. Warren attended the following: halting transmission from 2017/06/01 to 2017/06/02 held at Cape Town.
- R. Warren attended the following: Centre for Tuberculosis Research - SAMRC presentation to the Nigerian Medical Research Council, 2017/06/07 held at Cape Town.
- S. Ley attended the following: Project specific personal training on bioinformatics for data processing and data analysis of XDR-TB whole genome sequencing data from 2017/06/08 to 2017/06/09 held at Swiss Institute of Bioinformatics, Lausanne, Switzerland.
- M. Grobbelaar attended the following: Trinity RNA-Seq workshop from 2017/06/12 to 2017/06/16, Berlin.
- Shameemah Abrahams attended the following: Introductory NIH Grant writing, 2017/09/18 held at 4053A Teaching Building, Tygerberg Campus, Stellenbosch University.
- Oluwafemi Oluwole attended the following: Predicting the effects of mutations/nsSNP's on protein, from 2017/09/04 to 2017/09/06 held at South African National Bioinformatics Institutes UWC.
- M. Grobbelaar and A. Dippenaar, attended the following: predicting the effects of mutations/nsSNP's on protein structure using Homology Modelling, Gibbs free energy calculation webservers (SDM and mCSM) and Interaction analysis from 2017/09/04 to 2017/09/06 held at SANBI, UWC.
- R. Warren attended the following: XIth International Child TB Training Course from 2017/09/11 to 2017/09/15 held at Goudini Spa, South Africa.
- M Klopper attended the following: MBHG NIH grant writing, 2017/09/18 and 2017/10/02 held at MBHG.
- Naomi Okugbeni attended the following: Mass Spectrometry-Based Proteomics Workshop from 2017/09/05 to 2017/09/07 held at Tygerberg Campus, Stellenbosch University.
- Haiko Schurz attended the following: Predicting the effects of mutations/nsSNP's on protein structure using Homology Modeling, Gibbs free energy calculation webservers (SDM and mCSM) and Interaction analysis from 2017/09/04 to 2017/09/06 held at South African National Bioinformatics Institute, University of the Western Cape.

- Craig Kinnear, Marlo Moller, attended the following: NIH Grant Writing Introductory Workshop from 2017/09/18 to 2017/09/18 held at Molecular Biology and Human Genetics, Stellenbosch University.
- Tsaone Tsamulha attended the following: Harry Crossley Foundation Grant Writing Workshop, 2017/08/31 held at Stellenbosch University.
- Danicke Willemse attended the following: Postgraduate Supervision in Health Sciences (Workshop) from 2017/08/16 to 2017/08/17 held at Stellenbosch University.
- Danicke Willemse attended the following: Catalysing Sci-speak to Street-speak at Tygerberg: Science Communication Workshop, 2017/07/26 held at Stellenbosch University.
- Lucinda Baatjies attended the following: MS Word for Large Documents Workshop, 2017/04/04 held at Stellenbosch University.
- Lucinda Baatjies attended the following: Savvy Researcher Course, 2017/05/05 and 2017/06/02 held at MRC Boardroom.
- Lucinda Baatjies attended the following: Writing a Literature Review Workshop 2017/07/25 held at Stellenbosch University.
- Lucinda Baatjies attended the following: PowerPoint for Conference Presentations 2017/08/17 held at Stellenbosch University.
- Monique Williams attended the following: FMHS Leadership Development Programme from 2017/09/07 to 2017/09/15 held at Rushlamere Conference centre.
- Hridesh Mishra attended the following: NIH Grant Writing Introductory workshop from 2017/09/18 to 2017/09/18 held at Stellenbosch University.
- R. Warren attended the following: 7th meeting of the ReSeqTB External Advisory Panel and the Workshop on a Standard Language for Reporting Next Generation Sequencing and Molecular Drug Sensitivity Tests from 2017/09/26 to 2017/09/28 held at London.
- Marisa Klopper, Anzaan Dippenaar, attended the following: NIH Grant writing 2017/10/02 held at FMHS.
- Nelita du Plessis attended the following: NIH Grant writing workshop 2017/10/12 held at Research Grants Management Office, FMHS, Stellenbosch University.
- Shameemah Abrahams attended the following: Introductory NIH Grantwriting: Part 2 2017/10/02 held at 4053A Teaching Building, Tygerberg Campus, Stellenbosch University.
- Grant Theron attended the following: EDCTP Alumni Network Launch Workshop from 2017/10/03 to 2017/10/04 held at Johannesburg.
- Charissa Naidoo attended the following: SANBio Microbiome workshop from 2017/10/23 to 2017/10/27 held at University of Cape Town.
- MG Whitfield attended the following: Whole Genome Sequencing Training from 2017/11/20 to 2017/12/01 held at University of Antwerp, Antwerp, Belgium.
- A. Dippenaar, S, Ley, L. Smith, C Kinnear, S Bardien, M Williams, M Moller, S Malherbe attended the following: Writing retreat 2017/11/07 held at STIAS.
- Ilze Louw and Ayanda Shabangu, attended the following: Flow Cytometry and Cell Sorting from 2017/06/20 to 2017/06/20 held at CAF, Stellenbosch.
- Candice Snyders and Devon Allies, attended the following: GCLP course presented by Quality First Business solutions from 2017/06/27 to 2017/06/28 held at Path Care Academy, Goodwood.
- Mpho Tlali attended the following: Basic Life Support, 2017/06/12 held at Professional Emergency Care (PEC), Plumstead, Cape Town.

- Mpho Tlali attended the following: Advanced Cardiac Life Support from 2017/06/13 to 2017/06/14 held at Professional Emergency Care (PEC), Plumstead, Cape Town.
- Nelita du Plessis attended the following: Project Management Course held at USBD (Stellenbosch).
- Liezel Smith attended the following: EDCTP Financial and Project Management Training from 2017/11/29 to 2017/12/01 held at Johannesburg.
- Liezel Smith attended the following: NIH Grant writing 2017/09/18 and 2017/10/02 held at Tygerberg Campus, Stellenbosch University.
- Liezel Smith attended the following: Project Management for the Research Team from 2017/05/10 to 2017/05/11 held at Tygerberg Campus, Stellenbosch University.
- Walzl, G. NIH grant meeting (Pediatric Diagnostics for TB). London UK, Imperial College
- Walzl, G. International Symposium on TB-DM comorbidity: challenges and opportunities, Lima, Peru
- Walzl, G. Life Laboratories site visit, The Netherlands

Conferences / Symposia Organised

- Valerie Mizrahi co-organised the 2017 Keystone Symposium on *New Developments in Our Basic Understanding of Tuberculosis* which was held in Vancouver, Canada from 14-18 January 2017. She also presented a plenary lecture at this Keystone Symposium, which was attended by a diverse group of scientists from across the world. This symposium, was preceded by a pre-meeting workshop for Global Health Travel Awardees at which Valerie presented a talk on key facets of the biology of *Mycobacterium tuberculosis*.

- Prof. Kana assisted with organization of a session entitled: Understanding the Spectrum of *M. tuberculosis* infection at the TB Infection Workshop: Building a framework for eradication. DAIDS, NIAID and HMS workshop: Hyatt Regency Dubai Creek Heights, Dubai, 27-28 September 2017.

Expert consultant/Facilitator/Rapporteur and Chairing activities

Professor Kana participated in a workshop hosted by the Human Vaccines Project in Johannesburg, 18-19 July 2017.

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 / workshops, 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.

Knowledge translation to stakeholder groups

CBTBR members were involved in numerous public awareness activities countrywide in 2017:

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

- The SU Node (Dr Whitfield – PostDoctoral Candidate) has been actively involved in promoting public engagement within the Division of Molecular Biology and Human Genetics to engage the public. Presentations promoting Science and Research were given to the following schools:

Date	School visited	No of Students present
20 April 2017	Somerset College	100
5 May 2017	Fairmont High School	120
8 May 2017	Bishops High School	27
24 May 2017	Bridge House School	52
1 June 2017	Harry Gwala Secondary School	140
25 July 2017	Rondebosch Boys High School	800
31 July 2017	Stellenbosch High School	60
3 August 2017	Westerford High School	25
22 August 2017	Rustenburg Girls High School	180
5 September 2017	Paul Roos Boys High School	40
16 October 2017	Bloemhof Girls High School	79

This platform has results in over 1500 students addressed/engaged.

- Dr Anastasia Koch jointly led the Eh!Woza public engagement project with artist Ed Young. She oversaw the successful completion of the 2017 workshop programme with 20 workshops held, and four films produced by learner participants. This pioneering public engagement project was awarded two Wellcome Trust Pubic Engagement grants (one in collaboration with WITS University for social science research around sexuality [PI: Dr Nolwazi Mkhwanazi], and the other for a collaborative project with MSF around TB and music video production [PI: Mr Ed Young]). UCT node researchers, Joanna Evans, Mandy Mason and Charles Omollo, 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.

- The Eh!Woza project has inspired the PhD project of Bianca Masuku, an Anthropology student who is based at UCT, co-supervised by Digby Warner, Anastasia Koch and Nolwazi Mkhwanazi (WiSER, WITS), and supported by a bursary from the CoE for Human Development. The title of her thesis is "*Beyond the lab and behind the lens: An anthropological exploration of a youth-based TB community engagement project in Khayelitsha, Cape Town*". The Eh!Woza project is a community engagement initiative that aims to document and engage with the problem of TB/HIV within the township of Khayelitsha where the diseases are endemic. Through inter-disciplinary collaboration this project serves as a bridge between biomedical research, youth education and the arts in order to understand how people understand and experience TB disease. Through the lens of anthropology, this research study makes use of this community engagement project to provide an ethnographic analysis of a youth-based initiative on TB working with young people between the ages of 15-17 years recruited from a Khayelitsha-based educational NGO. Exposed to high impact biomedical research and provided with filming equipment and skills, the participating youth document the story of TB within their communities using the knowledge they acquire from the

initiative. With this Bianca asks: How does Eh!woza, a youth-based community engagement project, navigate the experience of TB in the township of Khayelitsha? Bianca's research is still in progress and fieldwork has commenced following preliminary data collection from May to October 2016 and 2017. The preliminary findings of this study have revealed four key points/themes that will be explored further. These are:

a. The science-based workshops of the Eh!Woza project establish a particular understanding of TB disease oriented within a biomedical framework that neglects the experience of the disease outside of the laboratory. This revealed the limits of biomedical research in capturing and realising the social burden of the disease through the narratives of the ill. The media workshops capture both the perspectives of the youth and affected individuals within the community on the lived reality of TB illness. In doing so, they work to show what influences people's understandings of TB and the effects these have on the way the disease is experienced and navigated.
b. The manner in which the youth choose to represent themselves and their community highlights how they navigate their own position in their communities, articulating a particular voice about the role they play in creating particular understanding and narrating how disease is understood and lived within social worlds.
c. Perceptions of community members about TB as an infectious disease are influenced by the social reality of poverty and its daily constraints.
d. Engaging youth on an infectious disease such as TB through film not only creates a platform for young people to represent their own perspectives of the disease, but also exposes them to the reality of the disease in their own communities.

- Prof. Warner participated in a series of workshops in 2017 that were hosted by UCT's Office of Postgraduate Studies and aimed at equipping Postdoctoral Fellows at UCT with the skills necessary to supervise postgraduate students. Prof. Warner also served as mentor during a related workshop which was designed to develop writing skills among recent postdoctoral appointees within the University.

- On World TB Day 24th March 2017, members of the Wits node participated in the Unmask Stigma campaign aimed at building public awareness that TB today remains an epidemic in much of the world. Created and manned exhibitions on TB statistics and posters. A photo booth, microscope, posters and other props were displayed to educate students on TB. Flyers with TB information was given to passer-by's. The exhibition photographs were posted on social media to create awareness about the danger associated with TB.

- Members of the Wits node participated at the Wits Students' Pathology Society event: Pathology and Precision Medicine Week at Wits medical school. Information on the research carried out at the CBTBR and the kind of careers one could pursue with the training was provided.

- Dr. Machowski was involved in the maintenance of the CBTBR Website (www.wits.ac.za/cbtbr), Facebook page (https://www.facebook.com/CBTBR) and Twitter account (CBTBRwits). She is also involved in setting up and maintaining the Molecular Biosciences Research Thrust (MBRT; www.wits.ac.za/mbrt) website.

TB under the Microscope

"TB Under the Microscope" is a collaborative exhibition between scientists and social scientists. As part of the greater collective of 'Swallowing the World: A Multidisciplinary Curatorial Project on Tuberculosis in South Africa', the project arises from the desire to share scientific research on Tuberculosis with the broader public. Through collaboration with a number of scientific researchers from the DSTNRF Centre of Excellence for Biomedical Tuberculosis Research and the SAMRC Centre for Tuberculosis Research, the body of work consists of enlarged microscopic images of *Mycobacterium tuberculosis* – the bacteria that causes the disease, Tuberculosis. The project is made possible by the generous funding of the Wellcome Trust.

This exhibit aims to showcase the work of scientists dedicated to better understanding *Mycobacterium tuberculosis* in order to contribute to the development of better treatments and vaccines for TB. One of the major aims is to foster a space in which the work of scientists is brought 'out of the laboratory' and into the realm of the public; where TB science is made accessible and understandable to more than a few. Bringing these scientific understandings into the public realm adds another dimension to the social discussions around TB. Rather than centering the experiences of TB patients, this project explores the care and passion of researchers, humanizing the 'cold face of science'. In doing so it decenters, but does not ignore, the infection and disease inside human beings and the social experience of having TB.

These images – familiar to some, strange to most – allow the viewer to enter into another world that would not be possible without the aid of technology; an invisible world seemingly as unreachable as outer space, and just as fascinating. The images center the bacteria in such a way that it is rendered a 'subject' rather than an object of scientific research and prompt us to question; what new understandings of TB are brought into being when this 'bug' is reframed in such a way?

Through these microscopic images, one can further contemplate the dichotomy between a deadly pathogen responsible for killing 1.5 million people globally every year and its aesthetic beauty when placed outside the context of the human body. Indeed, these images lend themselves to unknown and invisible worlds, and the many truths, experiences and understandings that orbit around TB. We have thus chosen to visualize the bacteria through microscopic images in order to take the viewer on a journey, exploring the many dichotomies that emerge when these fascinating and terrifying bacteria is reframed and 'made visible' through the work of science and the passion of scientists.

FameLab 2017

In December 2017 (6th to 7th), three of our students, Timothy De Wet, Bianca Masuku and Tsaone Tamuhla were invited to participate in the FameLab heat at Science Forum South Africa (SFSA) 2017.

By taking part, they would stand a chance to represent the centre at the national semi-finals of FameLab South Africa 2018.

FameLab is one of the longest running science communication competitions in the world, with over 30 participating countries globally. It is an exciting initiative to find new voices in science, technology, engineering, maths and innovation (STEMI). Science Forum South Africa is an initiative of the Department of Science and Technology, which took place 7-8 December 2017 under the theme, “Igniting conversations about science”.

All three representatives were selected to compete in the final heat of the competition. This was a great platform and opportunity for the students to learn and showcase their projects. Well done to the team!

Values-Driven Renewal Process

In November 2016, an external professional consultant from the University of Stellenbosch Business School, facilitated and presented a strategic plan for the SU node. Walzl and his management team participated and contributed to the contents of this strategic plan, which highlights the SU nodes’ vision, mission, values and strategic objectives. This activity showed that a comprehensive approach was needed to change the culture of the node and therefore embarked on a general Values-Driven Renewal Process at the beginning of 2017. The node enlisted the company, Retha Alberts and Associates to drive this process. The aim was for the facilitators to use a scientific model to align the process with the Vision, Mission and Values of the node. These conversations centered around Transfoprmation, Decolonization, Equity, Diversity etc. Approximately 200 members from the SU node participated in these workshops. Staff and students were divided into focus groups of approximately 20 for a facilitated organizational development process that included gauging the staff’s understanding and buy-in of the vision, mission and the espoused values and their willingness and ability to demonstrate these values in their daily behavior. In addition, an assessment of the current climate and culture within the node was undertaken to gain a better understanding of the constraints and enablers that would ensure the realization of the vision and mission. The participants were asked to propose ways in which to co-create an inclusive, harmonious collegial and sustainable successful new culture and the transformational leadership required within the node. The facilitators then diagnosed and interpreted the participants’ inputs, and proposed meaningful processes (a ‘roadmap’) of capacity building interventions, that were then presented over a period of approximately 8 -12 months. The importance of taking into account and striving for diversity (i.t.o. age, race, gender, position / seniority) and using an inclusive approach, e.g. ensuring that all staff, across all divisions and functional areas were included (“all voices need to be heard”) was emphasized.

The next steps (Roadmap) in the Values-Driven Renewal Approach was the following: (i) Interactive workshops with the management team (40 individuals) to discuss “Change Readiness” – Effective crucial conversations influencing behavior and performance feedback. (ii) Interactive workshop with management to discuss Emotional Intelligence (MBTI) and this included conflict handling and team work. (iii) Individual coaching (1:1) to facilitate individual growth. This arm of the roadmap will take place in the first semester of 2018, and (iv) Interactive Embracing Diversity Workshops with all staff and students from the SU node.

BSc Honors Mentoring Project

In 2017, Prof Sampson and Dr Smith (SU node) started a mentorship program for the BSc Hons class of 2017. All Hons students (mentees) were paired up with a mentor (senior student) from the node. Mentoring is seen as a voluntary relationship between a person of lesser experience and a person of greater experience that is based on mutual trust and respect. The inception year of this program was a success and will be expanded to other new students joining the Division. Goal-setting vision, professional development and domain-specific knowledge were some of the key points that was highlighted.

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		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	Dr. Barry III, Dr. H Boshoff		TB treatment response project	USA
Prof. Ronacher, Dr. Kleynhans	SU	Prof. Restrepo	University of Texas	ALERT: Altered endocrine axis during type 2 diabetes and risk for tuberculosis	USA
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	USA

				families may have both increased fitness and increased potential for acquiring drug resistance.	
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*

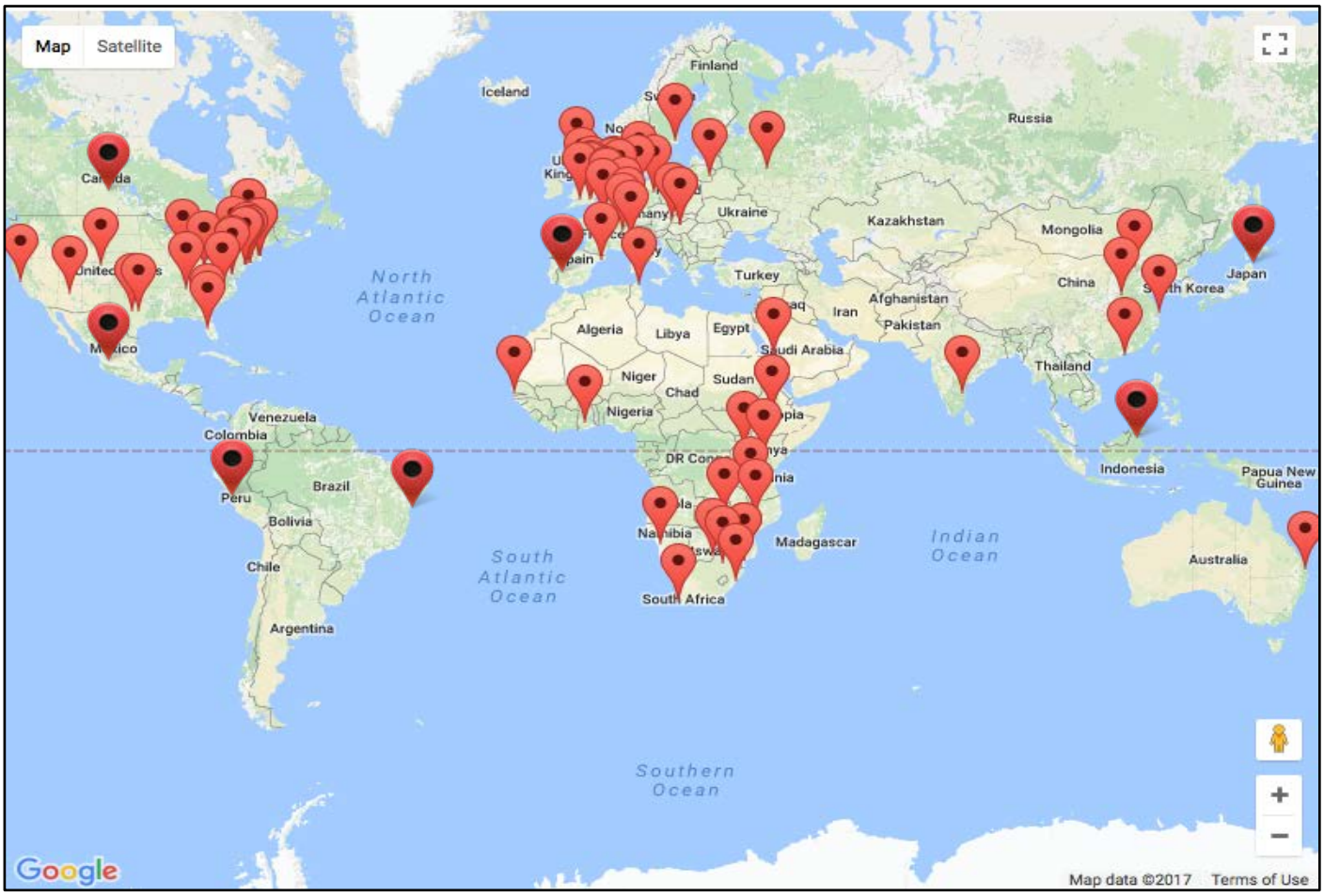
Prof. van Hoal	SU	Prof. Wilkinson	CIDRI, IDM	Human genetics of TB resistance in HIV-infected persons
Prof. Warren, Dr. Streicher	SU	Dr. Cox	UCT	Evolution of drug resistance in HIV positive and negative individuals
Dr. Smith, Prof. Warren, Dr. Streicher	SU	Prof. Dheda	UCT	Molecular epidemiology of XDR-TB
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, University of Pretoria	Ongoing collaboration on TB diagnostics in buffalo and elephants
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)

Graphic Presentation of the various National and International networks.



4. 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. Mizrahi served as external examiner of a PhD thesis submitted to the University of British Columbia, Vancouver, Canada

Prof. Warner served as external examiner of a PhD submitted to Stellenbosch University and of MSc/MTech theses submitted to Wits University, Vaal University of Technology, North-West University, UKZN, and Stellenbosch.

Prof. Warner served as external examiner of the BSc(Hons) programme in the Faculty of Health Sciences at Stellenbosch University.

Professor Kana served as an internal external examiner for three MSc dissertations from the University of KwaZulu-Natal.

Dr Gordhan served as an internal Examiner for an MSc. dissertation, Faculty of Health Sciences, University of the Witwatersrand.

The following served as Thesis Examiners for the BSc Hons Projects (SU node): Dr Caitlin Uren, Dr Shameema Abrahams, Dr Tandeka Magcwebeba, Dr Serej Ley, Dr Tanya Kerr, Prof Paul van Helden, Dr Margaretha De Vos, Prof Ian Wiid and Prof Gerard Tromp.

The following served as examiners for the BSc Hons Literature reviews (SU node): Dr Annika Neethling, Dr Nikola de Villiers, Dr Hridesh Mishra, Dr Monique Williams, Dr Bienyameen Baker, Dr Michael Whitfield, Dr Jennifer Jackson and Prof Gerard Tromp

Journal editing and reviews

Prof David Tabb, journal reviews for the following: Proteomics, Analytical Chemistry, Nature Biotech, Nature Methods, Bioinformatics, Molecular Cellular Proteomics, BMC Bioinformatics, Journal of Proteome Research

Prof. Mizrahi served on the Editorial Boards of *Current Opinion in Microbiology*; *Pathogens & Disease*, *Emerging Microbes and Infection*, *Cell Chemical Biology ACS Central Science*, *ACS Infectious Diseases* and *Genome Medicine* and was appointed to the Editorial Board of *Genome Biology.*

Prof. Warner served on the Editorial Board of *PLoS One*, and as guest editor for *mBio*.

Prof. Warner was admitted to the Faculty of F1000.

Members of the UCT node reviewed manuscripts submitted to *Science; Chemical Reviews, PLoS Pathogens*; *PNAS*; *ACS Infectious Diseases; Antimicrobial Agents and Chemotherapy; mBio*; *Tuberculosis; International Journal of Infectious Diseases; Environmental Technology; African Journal of Biotechnology; International Biodeterioration and Biodegradation; American Journal of Respiratory and Critical Care Medicine; Analytical and Bioanalytical Chemistry; Biomarkers in Medicine; DNA Repair; Expert Reviews in Respiratory Medicine; FEMS Microbiology Reviews;*

Molecular Microbiology; mSphere; Nature Communications; Lancet Infectious Diseases; Tuberculosis

Prof. Kana or Dr. Gordhan reviewed manuscripts for *eLife, American Journal of Respiratory Critical Care Medicine, Microbiology, Archives of Microbiology, ACS Infectious Diseases, South African Health Review (SAHR)*

Prof. Kana served as an editor for a special supplement on Tuberculosis Transmission in the *Journal of Infectious Diseases*

Prof. Kana served as a reviewing editor for *eLife*.

Prof. Kana edited a JID supplement.

Prof Walzl serves a Associate Editor of the journal Microbes and Infection.

Prof Walzl reviewed manuscripts for Microbes and Infection, the *American Journal of Respiratory Critical Care Medicine and Tuberculosis.*

Expert panel or committee membership

- Dr. L Smith served on the Diversity Task Team, SU Node
- Dr. L Smith served on the Animal Ethics Committee, SU Node
- Dr. L Smith served on the Research Task Team, SU Node
- Dr. M Williams served and lead the Diversity Task Team
- Prof. Mizrahi served as Interim Chair of 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 Innovative Medicines for Tuberculosis (iM4TB), EPFL, Switzerland
- Prof. Mizrahi served on the National TB Think Tank
- Prof. Warner and Prof. Mizrahi served on UCT's Institutional Biosafety Committee, with Prof. Warner serving on the Executive of this committee
- 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
- Prof. Warner served in the Africa Research Excellence Fund (AREF) College of Experts
- 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

- Mr. Timothy de Wet served as Head of Finance of the South African Medical Students Association
- Professor Kana served on the following committees:
  Wits - Chair of the School of Pathology Transformation Committee
  Wits - Faculty of Health Sciences Transformation Committee
  Wits - Health Sciences Budget Task Group
  Wits - Health Sciences Executive Committee
  Wits - Health Sciences Equipment Task Group
  Wits - Health Sciences Fundraising Task Group
  Wits - MMU Board member
  Wits – Board Member for the Sidney Brenner Institute for Molecular Biosciences
  Wits - Faculty Research Committee
  Wits - Faculty of Health Sciences Research Entity Forum
  Wits - Faculty of Health Sciences Imaging Committee
  Wits - Faculty of Health Sciences Equipment Committee
  National TB Think Tank
- Dr. Ealand and Moagi Shaku were appointed to serve on the Wits Faculty of Health Sciences 2018 Research Day Committee.
- Dr. Ealand assisted with assessment and panel interviews for MSc. research protocols in the School of Pathology
- Dr Ealand judged posters for the MBRT Research Day
- Dr Gordhan reviewed a rating application for the National Research foundation (NRF)
- Prof Walzl serves on the following SU committees:
  SU Faculty of Medicine and Health Sciences Faculty Board
  SU Senate
  SU Faculty of Medicine and Health Sciences Research Committee
  SU Research Committee
  SU Faculty of Medicine and Health Sciences Executive Heads Committee
- Prof Walzl serves on the following national and international committees:
  Executive Member of the Consortium for TB Biomarkers (CTB2)

  National TB Think Tank

  External Advisory Board member for the TB Sequel project

Selection of research funding reviews

- Prof Mizrahi served as a member, TB Program Scientific Advisory Committee of the Bill & Melinda Gates Foundation.
- Prof. Mizrahi served as a reviewer and on the Interview Panel for the HHMI/BMGF/Wellcome Trust International Research Scholars competition.
- Prof. Mizrahi served as *ad hoc* member of the Interview Panel for Fellowships and Investigator Awards from the Wellcome Trust
- Prof. Mizrahi served as a reviewer of grant applications submitted to the Wellcome Trust; AESA and the Canada 150 Research Chairs Program. She also served as a promotion reviewer for Michigan State University.
- Prof. Warner served as reviewer for international funding organizations including the Africa Research Excellence Fund (AREF) College of Experts, Aga Khan-FCT (Portugal), EDCTP, H3Africa, and the International Union against Tuberculosis and Lung Disease. He was also a reviewer for the NRF Blue Skies programme. 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.
- Dr. Evans served as peer reviewer of abstracts submitted for the 48th Union World Conference on Lung Health, Guadalajara, Mexico, 2017
- Dr. Kana assisted with reviews for grant applications for the NRF
- Dr. Ealand assisted with reviews of FRC Individual Grant Applications.

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 75% of all postgraduate students (including postdoctoral fellows) in the CBTBR in 2017 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). Dr. (Ms) Taime Sylvester is currently the Chair for SAWISE (South African Women oin Science and Engineering). She, together with Dr Liezel Smith is heading the Mentorship program at the SU node. A number of task teams have been established, with Dr Monique Williams (SU) heading the Diversity Task team and Prof Sam Sampson heading the Research Funding and Networking Task teams.

HUMAN RESOURCES

1. Core Team Members (Scientific Staff)

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	40
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.	Malherbe	South Africa	SU	M	W	100
Prof.	Sirgel	South Africa	SU	M	W	40
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.	Chengalroyen	South Africa	UCT	F	B	
Dr.	Ealand	South Africa	Wits	M	W	100
Dr.	Machowski		Wits	F	W	50[a]

a. Director of IDM, UCT
b. Director of SAMRC Centre for Tuberculosis Research

c. Director of the Perinatal HIV Research Unit (PHRU)

2. Administrative and Other Staff

Title	Surname	Position	Based at	Gender	Race
Dr.	Smith	Project Manager	SU	F	B
Dr.	Allie	Biosafety Level 3 Manager	SU	F	B
Dr.	Jackson	BSc Hons Coordinator and Lab Manager	SU	F	W
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
Dr.	Padayachee	Research Assistant	Wits	F	B
Ms.	Sewcharran	Research 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
Ms.	Lynch	Biosafety Level 3 technician	UCT	F	B
Ms	Rika	Van Dyk	SU	F	W

5. 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.	Schlechter	South African	SU	W	F	In Progress	100
Dr.	Kidzeru	Kenya	SU	B	M	In Progress	100
Dr.	Kerr	South Africa	SU	W	F	In Progress	100
Dr.	Naidoo	South Africa	SU	B	F	In Progress	100
Dr.	Willemse	South Africa	SU	W	F	In Progress	100
Dr.	Maqwebeba	South Africa	SU	B	F	In Progress	100

Dr.	Peters	Zimbabwe	Wits	B	F	In Progress	100
Dr.	Anoosheh	Iran	UCT	W	M	In Progress	100
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.	Gessner		UCT		F	In Progress	100
Dr.	Luies		UCT			In Progress	100

6. Graduated 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
Gabanza	Zikhona	BSc Hons	SU	B	F	South Africa	100
King	Hannah	BSc Hons	SU	W	F	South Africa	100
Leqheka	Monkoe	BSc Hons	SU	B	M	South Africa	100
Lucas	Tammy	BSc Hons	SU	W	F	South Africa	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
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
Trevor	Tamzyn	BSc Hons	UCT	W	F	South Africa	100
Govender	Justion	BSc Hons	UCT	B	M	South Africa	100
Campbell	Lisa	BSc Hons	Wits	W	F	South Africa	100
Padarath	Kiyasha	BSc Hons	Wits	B	F	South Africa	100
Dicks	Laetitia	MSc	SU	W	F	South Africa	100
Sewgoolam	Bevika	MSc	UCT	I	F	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
Ismail	Zaahida sheik	MSc	Wits		F	South Africa	100
Du Plessis	Juanelle	PhD	SU	W	F	South Africa	100
Steyn	Nastassja	PhD	SU	W	F	South Africa	100
Uren	Caitlin	PhD	SU	W	F	South Africa	100
Van Coller	Sophia	PhD	UCT	W	F	South Africa	100
Omollo	Charles	PhD	UCT	B	M	Kenya	100
Wasuna	Antonia	PhD	UCT	B	F	Kenya	50

7. 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	50
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	B	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
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
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	B	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

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
Sikhosana	Nombeko	MSc	Wits	B	F	South Africa	100
Mashilo	Poppy	MSc	Wits	B	F	South Africa	100
Taylor	Caitlin	MSc	UCT	W	F	Zimbabwe	100
De Wet	Timothy	MSc	UCT	W	M	South Africa	100
Dinkele	Ryan	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
Derringer	Brigitte	PhD	SU	W	F	South Africa	100
Du Plessis	Juanelle	PhD	SU	W	F	South Africa	100
Gallant	James	PhD	SU	W	M	South Africa	100
Kelbi	Lisa	PhD	SU	W	F	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
Shaku	Moagi Tube	MSc	Wits	B	M	South Africa	100
Van Coller	Phia	PhD	UCT	W	F	South Africa	100
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
Mthwalenga	Ndengane	PhD	UCT	B	M	South Africa	50
Mbau	Rendani	PhD	UCT	B	M	South Africa	100

5. OUTPUTS

Books

- Jacobs WR Jr, McShane H, Mizrahi V, Orme, I. eds. Tuberculosis and the Tubercle Bacillus (2nd edition), ASM Press, Washington D.C., 2017. doi:10.1128/9871555819569

Book chapters

- Ditse Z, Lamers MH, Warner DF. DNA Replication in *Mycobacterium tuberculosis*. *Microbiology Spectrum*. 2017 Mar 31;5(2). DOI: 10.1128/microbiolspec.TBTB2-0027-2016

- Gordhan, B.G. and Kana B.D. 2017. Microfluidics for tuberculosis diagnosis: Advances, scalability and challenges. Francesco Piraino and Seila Selimovic (ed.), Diagnostic devices with microfluidics, Chapter 8, Taylor and Francis, CRC Press

Articles in Peer-Reviewed Journals (Total:122)

52 / 122 (43%) of publications were first- and/or last-authored by a member(s) of the CBTBR

Summary of Publication outputs for 2017

Publications	**2017**
Articles in peer-reviewed journals	122
Impact factor < 2 [a]	23
Impact factor between 2 and 5	54
Impact factor > 5	39
No Impact factor at time of reporting	6
Publications with first-and/or last authored by members of CBTBR	52
Books/chapters in books	3
Non-peer-reviewed articles	2

- Park Y, Pacitto A, Bayliss T, Cleghorn LA, Wang Z, Hartman T, Arora K, Ioerger TR, Sacchettini J, Rizzi M, Donini S, Blundell TL, Ascher DB, Rhee KY, Breda A, Zhou N, Dartois V, Jonnala SR, Via LE, **Mizrahi V**, Epemolu O, Stojanovski L, Simeons FR, Osuna-Cabello M, Ellis L, MacKenzie CJ, Smith AR, Davis SH, Murugesan D, Buchanan KI, Turner PA, Huggett M, Zuccotto F, Rebollo-Lopez MJ, Lafuente-Monasterio MJ, Sanz O, Santos Diaz G, Lelièvre J, Ballell L, Selenski C, Axtman M, Ghidelli-Disse S, Pflaumer H, Boesche M, Drewes G, Freiberg G, Kurnick MD, Srikumaran M, Kempf DJ, Green SR, Ray PC, Read KD, Wyatt PG, Barry Rd CE, Boshoff HI. Essential but not vulnerable: indazole sulfonamides targeting inosine monophosphate dehydrogenase as potential leads against *Mycobacterium tuberculosis. ACS Infect. Dis*. 2017 13;3(1):18-33. doi: 10.1021/acsinfecdis.6b00103. **IF:3.600**

- Koch AS, Brites D, Stucki D, **Evans JC**, **Seldon R**, Heekes A, Mulder N, Nicol M, Oni T, **Mizrahi V, Warner DF**, Parkhill J, Gagneux S, Martin DP, Wilkinson RJ. The Influence of HIV on the Evolution of Mycobacterium tuberculosis. Molecular Biology and Evolution. 2017;34(7):1654-68. DOI: 10.1093/molbev/msx107 **IF:6.202**

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- WALTERS E, VAN DER ZALM MM, PALMER M, BOSCH C, DEMERS A, DRAPER HR, GOUSSARD P, SCHAAF HS, FRIEDRICH SO, WHITELAW AC, **WARREN RM**, GIE RP, HESSELING AC. Xpert MTB/RIF on Stool is Useful for the Rapid Diagnosis of Tuberculosis in Young Children with Severe Pulmonary Disease. PEDIATRIC INFECTIOUS DISEASE JOURNAL 2017; 36(9):837-843. **IF: 2.486**

- **WALZL G, CHEGOU NN, MALHERBE ST**, HATHERILL M, SCRIBA T, ZAK D, BARRY III CE, KAUFMANN SHE. Policy-driven interventions: tuberculosis. BMJ (British Medical Journal) 2017; 2:1. **IF: 20.785**

- WILSON CR, GESSNER RK, MOOSA A, SELDON R, WARNER DF, MIZRAHI V, SOARES DE MELO C, SIMELANE SB, NCHINDA AT, **SIRGEL FA, VAN HELDEN PD**, ET AL E. Novel Anti-tubercular 6-Dialkylaminopyrimidine Carboxamides from Phenotypic Whole-Cell High Throughput screening of a SoftFocus Library: structure activity Relationship and Target Identification Studies. JOURNAL OF MEDICINAL CHEMISTRY 2017; 60(24):10118-10134. **IF: 4.519**

- ZHOU J, CHEN L, ZHANG B, TIAN Y, LIU T, THOMAS SN, CHEN L, SCHNAUBELT M, BOJA E, HILTKE T, KINSINGER CR, RODRIGUEZ H, DAVIES SR, LI S, SNIDER JE, ERDMANN-GILMORE P, **TABB D**, ET AL E. Quality assessments of Long-Term Quantitative Proteomic analysis of breast Cancer xenograft Tissues. JOURNAL OF PROTEOME RESEARCH 2017; 16(1):4523-4530. **IF: 4.268**

- KANNAN M, BAYAM E, WAGNER C, RINALDI B, KRETZ PF, TILLY P, ROOS MR, MCGILLEWIE L, **KINNEAR CJ**, LOOS B. WD40-repeat 47, a microtubule-associated protein, is essential for brain development and autophagy. Proceedings of the National academy of sciences of the United States of America 2017; 114(44):19. **IF: 9.661**

- VAN RENSBURG IC, **KLEYNHANS-CORNELISSEN** L, KEYSER A, **WALZL G, LOXTON AG**. B-cells with a FasL expressing regulatory phenotype are induced following successful anti-tuberculosis treatment. Immunity, Inflammation and Disease 2017; 5(1):57-67. **IF: 22.85**

Conferences/Meetings Attended & Invited Talks/Seminars Presented (Total=101)

International invited/plenary/keynote addresses

- **Mizrahi, V**. Harnessing biological insight to accelerate TB drug discovery. Keynote Lecture presented at the Gordon Research Conference on Tuberculosis Drug Discovery & Development, Lucca, Italy, 25-30 June 2017.
- **Kana, B.D.** Can peptidoglycan remodeling reveal novel drug targets and probe for phenotypic complexity in sputum-derived mycobacteria? Center for Emerging and Neglected Diseases Symposium. March 31st 2017. University of California, Berkley, USA. Invited plenary lecture.
- **Kana, B.D.** Differentially Culturable Tubercle Bacteria: Possible roles in TB transmission. Aerobiology Meeting. Bill and Melinda Gates Foundation. 7th – 8th March 2017. Seattle, USA.
- **Kana, B.D.** Differentially Culturable Tubercle Bacteria (DCTB): Possible roles in TB transmission. NIH Workshop on Halting TB Transmission in HIV Endemic Settings, June 1-2, 2017, Vineyard Hotel, Cape Town, South Africa.
- **Kana, B.D.** Differentially Culturable Tubercle Bacteria (DCTB). 10th International Conference on the Pathogenesis of Mycobacterial Infections. August 23-26, Stockholm, Sweden.
- **Kana, B.D.** Peptidoglycan remodelling reveals novel TB drug targets and phenotypic complexity in sputum-derived mycobacteria. Joint annual SSM meeting, August 30 – September 01, 2017, Congress Centre Basel, Basel, Switzerland.
- **Kana, B.D.** Chaired Workshop entitled: Key Knowledge Gaps with TB. Joint annual SSM meeting, August 30 – September 01, 2017, Congress Centre Basel, Basel, Switzerland.
- **Kana, B.D.** States of Wakefulness: Mycobacterial physiology during tuberculosis infection and disease. TB Infection Workshop: Building a framework for eradication. DAIDS, NIAID and HMS workshop: Hyatt Regency Dubai Creek Heights, Dubai, 27-28 September 2017.
- **Kana, B.D.** Can peptidoglycan remodelling reveal novel drug targets and probe for phenotypic complexity in sputum-derived mycobacteria? Baylor University, Waco, Texas, USA, 2 September 2017.
- **Kana, B.D.** Can peptidoglycan remodelling reveal novel drug targets and probe for phenotypic complexity in sputum-derived mycobacteria? Université de Genève Médecine, Faculté de médecine, 4 April 2017.
- **Walzl, G.** 1st Ningxia International Clinical Pathogenic Microorganism Forum, Yinchuan, China General Hospital of Ningxia Medical University.
- **Walzl, G.** TB Vaccine Accellerator Meeting, Leiden, Netherlands
- **Walzl, G.** Centre of Exellence Director's meeting, Port Elizabeth, SA Department of Science and Technology
- **Walzl, G.** Central Plains TB Control and Treatment International Summit Forum, Zhengzhou, China
- **Walzl, G.** TB Vaccine Initiative Symposium, Les Diableret, Switzerland.
- **H. Kuivaniemi**, Tips for successful grantwriting for early-career scientist, BIOLOGICAL PSYCHIATRY CONGRESS 2017, Somerset West, Western Cape, South Africa
- **G. Walzl**, Developing treatment response biomarkers, Gordon TB drug discovery and development conference, Lucca, Italy.
- **S. Sampson,** Elucidating Population-Wide Mycobacterial Replication Dynamics at the Single-Cell Level, ASM Microbe 2017, New Orleans, USA.

National invited/plenary/keynote addresses

- **Mizrahi, V**. Harnessing biological insight to accelerate TB drug discovery. Keynote Lecture presented at the South African Immunological Society (SAIS) Conference, Gordon's Bay, 3 September 2017.
- **Michele A. Miller**, Mycobacterium bovis infection in a free-ranging black rhinoceros - application of tools to facilitate rapid diagnosis, Keynote lecture presented at the South African Veterinary Association Annual Conference, Pretoria, South Africa.
- **Sven D.C. Parsons**, The diagnostic sensitivity of selected tests for Mycobacterium bovis infection in African buffaloes. Keynote Address at the South African Veterinary Association Annual Conference, Pretoria South Africa.

International and National oral contributions

- **Mizrahi, V.** Metabolic vulnerabilities in *M. tuberculosis*: lessons from guanine nucleotide metabolism. Plenary lecture presented at the Keystone Symposia: New Developments in our Basic Understanding of Tuberculosis, Vancouver, 14-19 January 2017.
- **Reiche, M.** Martin, Z., Lang, D., Aaron, J., Chew, T., Dhar, N., Müller, R., McKinney, J.D., Mizrahi, V., Warner, D.F. SOS-dependent mutasome recruitment and griselimycin-mediated inhibition of mutagenesis in live mycobacterial cells. Invited short talk presented at the ASM Conference on Tuberculosis: Past, Present and Future, New York, 1-4 April, 2017.
- **Warner, D.F**. Phenotypic and genomic approaches to *M. tuberculosis* transmission. Plenary lecture presented at the NIAID/SAMRC/BMGF Workshop on Halting TB Transmission in HIV-Endemic Settings, Cape Town, 1-2 June 2017.
- **Warner, D.F.** A moving target: evolution of drug resistance in *Mycobacterium tuberculosis*. Invited talk presented at Turning the tide of antimicrobial resistance (TTA), Oslo, Norway, 27-28 April, 2017.
- **Warner, D.F**. Whole-genome sequencing of *M. tuberculosis* for TB transmission. BMGF Aerobiology Symposium, Seattle, USA, 7-8 March, 2017.
- **Warner, D.F.** Drug permeation and activity in Mycobacterium tuberculosis infected macrophages. Invited talk at Scientific Research Workshop of the US-SA Program for Collaborative Biomedical Research, Durban, 12 June, 2017.
- **Warner, D.F.** Mutasome targeting to limit TB drug-resistance. Invited talk at the ICGEB Workshop on Host-directed therapies in infectious disease, Cape Town, 18-21 September, 2107.
- **Kipkorir, T.,** Mashabela, G., Krishnamoorthy, G., Mizrahi, V. and Warner, D.F. Riboswitch regulation of methionine metabolism and vitamin B12 uptake in mycobacteria: a role in pathogenesis? Invited poster talk presented at FEMS 2017, 7th Congress of European Microbiologists, Valencia, Spain, 10-17 July 2017.
- **Reiche, M**., Martin, Z., Lang, D., Aaron, J., Chew, T.L., Dhar, N., Müller, R., McKinney, J., Mizrahi, V., and Warner, D.F. Invited talk presented at Mycobact '17: 10th International Conference on the Pathogenesis of Mycobacterial Infection, Stockholm, Sweden, 23-26 August 2017.
- **de Wet**, T.J., Mhlanga, M., Warner, D.F. Knocked down and out: A Comprehensive CRISPRi library targeting *M. smegmatis* genes with *M. tuberculosis* homologues. Invited talk

presented at the Genomics Discovery Initiative Annual Meeting, Philadelphia, USA, 12 October 2017.

- **Kana, B.D.** Research Careers in a Time of Uncertainty. 4th Biennial Faculty of Health Sciences Postdoctoral & Carnegie Fellows Symposium, 6 October 2017, Emoyeni Conference Center, Parktown, South Africa.
- **Papadopoulos, A.O.** and Kana, B.D. The in's and out's of mycobacterial lytM endopeptidases. CPD-accredited seminar presented at the Molecular Medicine and Haematology Wednesday seminar series, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand. 6 September 2017.
- **Shaku, T.M.,** Chengalroyen. M.D. and Kana. B.D. Characterization of LytM-domain containing proteins in *Mycobacterium smegmatis*. CPD-accredited seminar presented at the Molecular Medicine and Haematology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand. 31 July 2017.
- **Cardoso, N.** and Kana, B.D. The mycobacterial electron transport chain: *How does TB breathe*? Oral presentation at the NHLS Pathology Research and Development Congress (PathRed). 22- 24 June 2017. Received an "Honorable Mention" for the presentation in the Microbiology and Virology Track.
- Sikhosana, N., Chengalroyen M. and Kana, B.D. Mycobacterium amidases: Biological function and putative role in cell wall remodelling. Oral presentation at the 8th Cross Faculty Graduate Symposium. 25 October 2017.
- **Shaku, T.M.,** Chengalroyen. M and Kana. B.D. Characterization of LytM-domain containing proteins in *Mycobacterium smegmatis*. Oral presentation at the Pathology Research and Development Congress, National Health Laboratory Service, Johannesburg, South Africa. 22-24 June 2017. Received an honourable mention for the presentation by the adjudication panel. Won first prize for the presentation.
- **Cardoso, N.** and Kana, B. The mycobacterial electron transport chain: *How does TB breathe*? Oral presentation at the NHLS Pathology Research and Development Congress (PathRed). 22- 24 June 2017.
- **Warner, D.F.** A moving target: evolution of drug resistance in *Mycobacterium tuberculosis*. Invited talk presented at Meeting the challenge of drug resistant tuberculosis, Cape Town, 24-26 March, 2017.
- **Warner, D.F.** A moving target: evolution of drug resistance in *Mycobacterium tuberculosis*. Invited talk presented IDM/ICGEB Seminar Series, UCT, 19 April, 2017.
- **Warner, D.F.** A moving target: evolution of drug resistance in *Mycobacterium tuberculosis*. Invited talk presented in the School of Public Health, UCT, 24-26 March, 2017.
- **de Wet**, T.J., Mhlanga, M., Warner, D.F. Knocked down and out: A Comprehensive CRISPRi library targeting *M. smegmatis genes* with *M. tuberculosis* homologues. Talk presented at the HUB/IBMS/PAT Postgraduate Research Day, Faculty of Health Sciences, UCT, 27 September 2017.
- **Kipkorir, T**., Mashabela, G., Krishnamoorthy, G., Mizrahi, V. and Warner, D.F. Riboswitch regulation of methionine metabolism and vitamin B12 uptake in mycobacteria: a role in pathogenesis? Talk alk presented at the Western Cape Acid Fast Club meeting, Stellenbosch University, 22, August 2017.
- **M. Grobbelaar,** Physiological impact of the evolution of the rpoB mutation, 38th Annual Congress of the European Society of Mycobacteriology, Sibenik, Croatia.

- **B. Glanzmann,** Exome sequencing of the first reported South African X-linked primary immunodeficiency case identifies a hemizygous mutation in MSN, African Society for Immunodeficiencies (ASID) 2017 5th Biannual Congress, Livingstone, Zambia
- **R. Warren**, Simplifying the diagnosis of TB and associated drug resistance, Hain Lifescience Symposium, Geneva.
- **R. Warren**, Implementation of new tools for MDR-TB detection and control, Asian African Society of Mycobacteriology, Isfahan, Iran.
- **G. Leisching**, RNAseq Reveals Hypervirulence-Specific Host Responses to M. tuberculosis infection, 19th International Conference on Tuberculosis Therapy, Wembley, UK.
- **B. Glanzmann**, Identification of novel candidate genes for susceptibility to tuberculosis by identifying disease-causing mutations in individuals with PIDs, African Society for Immunodeficiencies (ASID) 2017 5th Biannual Congress, Livingstone, Zambia
- **E. Streicher**, Genetics of drug resistance in tuberculosis, First International Symposium on Clinical Pathogenic Microorganisms, Ningxia, China
- **S. Sampson**, Mycobacterium tuberculosis PE/PPE Proteins at the Host-Pathogen Interface, First International Symposium on Clinical Pathogenic Microorganisms, Ningxia, China
- **N. Du Plessis**, Innate immune regulation in tuberculosis: Immunosuppressive myeloid cells as targets for TB HDT, First International Symposium on Clinical Pathogenic Microorganisms, Ningxia, China
- **G. Walzl**, Innate immune regulation in tuberculosis: A REVERSE TRANSLATIONAL APPROACH, First International Symposium on Clinical Pathogenic Microorganisms, Ningxia, China
- **M. Miller**, Use of the Qiagen QuantiFERON TB Gold In-Tube System for Detection of Mycobacterium bovis Infection in Wildlife, U.S. Animal Health Association, San Diego, California, USA.
- **H. Kuivaniemi**, Genetics of abdominal aortic aneurysms, Special Symposium 'ISACB 30 YEARS OLD: The era of Repair, Replacement and Regeneration', part of the 50th Anniversary of the 1st Heart Transplant, Groote Schuur Hospital, University of Cape Town, South Africa.
- **S. Bardien**, Progress on R21 grant: Genetic etiology of Parkinson's disease in South Africa and Nigeria, Global Brain Network Meeting, Fogarty International Center, NIH, Bethesda Maryland USA.
- **A. Dippenaar**, Investigating recurrence of tuberculosis due to relapse and reinfection using whole genome sequencing, Swiss SA Bioinformatics Symposium, UCT.
- **Femi Oluwole**, Genetic screening in black South African Parkinson's disease patients for pathogenic mutations using a targeted resequencing approach, Southern African Society for Human Genetics, Durban.
- **Al-Girvan Tobias**, OXYCUTE: A bioinformatics pipeline to identify markers of oxidative damage in proteomic data, SU 61st Annual Academic year day, Tygerberg Campus.
- **N de Villiers**, Identification of novel candidate genes for susceptibility to tuberculosis by identifying disease-causing mutations in individuals with PIDs, Southern African Society of Human Genetics, Durban.
- **Roxanne Higgitt**, A canine interferon-? release assay for the detection of Mycobacterium bovis infection in African wild dogs (Lycaon pictus), FMHS Annual Academic Day, Tygerberg Campus.
- **Yessica Fitzermann**, Genetic characterisation of the dassie bacillus, Mycobacterium suricattae and Mycobacterium mungi, FMHS Annual Academic Day, Tygerberg Campus.

- **Roxanne Higgit**, A diagnostic assay for Mycobacterium bovis infection in African wild dogs (Lycaon pictus), South African Immunology Society Symposium 2017, Gordons Bay, Cape Town.
- **Netanya Bernitz**, Detection of Mycobacterium bovis infection in African buffaloes (Syncerus caffer) using QuantiFERON, South African Immunology Society Symposium 2017, Gordons Bay, Cape Town.
- **Tabb, D.** delivered a presentation at Eubic, Semmering, Austria
- **Tabb, D.** African Doctoral Academy, Cape Town
- **Tabb, D.** Square Kilometer Array, Big Data, Cape Town
- **Tabb, D.** HUPO-PSI, Beijing, China
- **Tabb, D.** Genome Web for ABRF - online
- **Tabb, D.** Russia ClinProt ProteoGenomics, Moscow, Russian Federation
- **S. Tonsing** attended the ACTG trials meeting, Washington, DC.
- **C. Abrahams** attended the ACTG trials meeting, Washington, DC.
- **G. Walzl** attended the NIH RO1 Paediatric Biomarker meeting, London, UK
- **D. Tabb** attended the American Society of Mass Spectrometry.
- **J. Du Plessis** attended the Solutions for Drug-Resistant infections (SDRI), Brisbane
- **S. Bardien** attended the 12th Annual Meeting of the Genetic Epidemiology of Parkinson's disease Consortium, Cairns, Australia.
- **M. Klopper** attended the USAID/TB CARE II meeting, Cape Town.
- **M. Whitfield** attended the DTTC seminar, Cape Town
- **N. Chegou** attended the Pathology and Development Research Congress (PathRed), Emperor's Palace, Johannesburg
- **E. Roos** attended the ESSA and ZSSA Combined Congress, Pretoria, South Africa
- **M. Miller** attended the 9th SA Veterinary & Paraveterinary & SASVEPM Congress, Johannesburg, South Africa.
- **G. Theron** attended Building a Healthy Community, One Individual at a Time meeting, Pretoria, South Africa
- **T. Kerr** attended the Stellenbosch Universtity - Postdoc Research Day, Stellenbosch.
- **M. Klopper** attended the SAMRC Early Career Scientists Convention, Cape Town.
- **M. Whitfield** attended the Stellenbosch University Postdoc Research Day 2017, Stellenbosch.
- **G. Theron** attended the 5th SA TB Conference 2018 Committee Launch.
- **J Jackson** attended the South African Clinical Research Association Regional Conference, Cape Town.
- **E. Rood** attended the 8th Annual NZG Research Symposium, Pretoria, South Africa
- **S. Bardien** attended the Southern Africa Society of Human Genetics, Durban.
- **C. Pule** attended the Leadership Development for Women in Health and Science Conference, Johannesburg.
- **J. Mouton** attended the Stellenbosch Post-doc Research Day, Stias, Stellenbosch
- **N. Kriel** attended the Annual Academic Year Day, Stellenboschg University.
- **S. Sampson** attended the Transformation Indaba, Stellenbosch.

International and National posters

- **Singh, V**., Ioerger, T. Mizrahi, V., Teague, S., Warner, D.F. Identification of AspC as primary target of a novel bactericidal compound. Poster presented at the Keystone Symposia: New Developments in our Basic Understanding of Tuberculosis, Vancouver, 14-19 January 2017.
- **Kipkorir, T**., Mashabela, G., Mizrahi, V. & Warner, D.F. Riboswitch regulation of methionine metabolism and vitamin B12 uptake in mycobacteria. Poster presented at the ASM Conference on Tuberculosis: Past, Present and Future, New York, 1-4 April, 2017.
- **Singh, V**., Ioerger, T. Mizrahi, V., Teague, S., Warner, D.F. Identification of AspC as primary target of a novel bactericidal compound. Poster presented at the Gordon Research Conference on Tuberculosis Drug Discovery & Development, Lucca, Italy, 25-30 June 2017.
- **Mabhula, A**., Mashabela, G., Njoroge, M., Tanner, L., Wiesner, L., Warner, D.F, and Chibale, K. Investigating permeation of anti-mycobacterial agents in macrophages as an in vitro model for early stage TB drug discovery. Poster presented at the Gordon Research Conference on Tuberculosis Drug Discovery & Development, Lucca, Italy, 25-30 June 2017.
- **Agarwal, P**. and Mizrahi V. Development of an assay for growth, persistence and drug susceptibility of Mycobacterium tuberculosis in foamy macrophages. Poster presented at the Gordon Research Conference on Tuberculosis Drug Discovery & Development, Lucca, Italy, 25-20 June 2017.
- **Mashabela, G**., Moosa, A., Frigui, W., Krishnamoorthy, G., Mizrahi, V., Brosch, R., and Warner, D.F. The evolution of *Mycobacterium tuberculosis* as obligate pathogen: loss of *cobF* results in vitamin B_{12} auxotrophy in *M. canettii*. Poster presented at Mycobact '17: 10th International Conference on the Pathogenesis of Mycobacterial Infection, Stockholm, Sweden, 23-26 August 2017.
- **Tanner, L.,** Mashabela, G., de Wet, T., Parkinson, C., Warner, D., Haynes, R., and Wiesner, L. An in vitro model of drug accumulation at the target site of pulmonary tuberculosis. 10th International Conference on the Pathogenesis of Mycobacterial Infections, Stockholm, Sweden, 23-26 August 2017.
- **Koch A**., Brites B., Stucki D., Evans J.C., Seldon R., Nicol M., Oni T., Mizrahi V., Warner D.F, Parkhill J., Gagneux S., Martin D.P, Wilkinson R.J. 2017. The evolution of *Mycobacterium tuberculosis* in HIV co-infected individuals in an HIV/TB endemic setting. 22nd International Bioinformatics Workshop on Virus Evolution and Molecular Epidemiology (VEME), Lisbon, Portugal 27 August – 1 September 2017.
- **Koch A.,** Brites B., Stucki D., Evans J.C., Seldon R., Nicol M., Oni T., Mizrahi V., Warner D.F, Parkhill J., Gagneux S., Martin D.P, Wilkinson R.J. 2017. The evolution of *Mycobacterium tuberculosis* in HIV co-infected individuals in an HIV/TB endemic setting. 2nd ASM Conference on Rapid Applied Microbial Next-Generation Sequencing and Bioinformatic Pipelines, Washington D.C., USA, 8 – 11 October, 2017.
- Chengalroyen, M.D., Beukes, G.M., Gordhan, B.G., Streicher, E.M., Churchyard, G., Hafner, R., Warren, R., Otwombe, K., Martinson, N., and **Kana B.D**. Detection and quantification of differentially culturable tubercle bacteria in sputum from tuberculosis patients. Gordon Research Conference on Tuberculosis Drug Development, Il Ciocco Hotel and Resort, Lucca (Barga), Italy, 25-30 June 2017.
- **Gordhan, B.G**, Rantsi, T, Padarath, K, Moolla N, Goosens, V and Kana, B.D. Targeting the base excision repair pathway to limit the emergence of drug resistant tuberculosis disease. Poster presentation at the Keystone Symposia, Antimicrobials and Resistance: Opportunities and Challenges, Santa Fe, New Mexico, USA. 30 October 2017.

- **Taylor, C**., Mizrahi, V., Warner, D.F, and Egan, T. Visualising whole-cell translational activity to investigate metabolic quiescence in mycobacteria. Poster presented at the Microscopy Society of Southern Africa 2017 Annual Conference, Bela Bela, 4-7 December 2017.
- **Tanner, L**., Mashabela, G., de Wet, T., Parkinson, C., Warner, D., Haynes, R., and Wiesner, L. An in vitro model of drug accumulation at the target site of pulmonary tuberculosis. South African Society for Basic and Clinical Pharmacology Conference 2017, 1-4 October, Bloemfontein.
- **Gobe, I**., Mizrahi, V., and Warner, D.F. Disabling the intrinsic resistome of Mycobacterium tuberculosis: elucidating hierarchies of DNA repair and mutagenesis that undermine current antibiotic efficacy. HUB/IBMS/PATH Postgraduate Research Day, Faculty of Health Sciences, UCT, 27 September 2017.
- **Mbau, R.D**., Mukherjee, R., Mizrahi, V and Warner, D.F. Whole-genome transposon mutagenesis to elucidate the genetic requirements for vitamin B12 biosynthesis and assimilation in mycobacteria. HUB/IBMS/PATH Postgraduate Research Day, Faculty of Health Sciences, UCT, 27 September 2017.
- **Masuku, B**., Young, E., Mizrahi, V., Wilkinson, R. J., Mkhwanai, N., Koch, A. and Warner, D. F. (2016). 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 Conference, Durban, South Africa. (Poster)
- **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 TB community engagement project in Khayelitsha, Cape Town. HUB/ IBMS Research Day, Faculty of Health Sciences, 27 September 2017.
- **McIvor. A.,** Gordhan B. Martinson N. and Kana. B. The use of culture filtrate enhances diagnosis of HIV-infected, sputum smear negative individuals. Poster presentation at the Molecular Biosciences Research Thrust Postgraduate Research Day. 30 November 2017.
- **Papadopoulos A.O**. and Kana, B.D. LytM endopeptidases contrast cell division regulation between slow-growing *M. tuberculosis* and rapidly-growing model organisms. Poster presentation at the Molecular Biosciences Research Thrust, University of the Witwatersrand. 30 November 2017.
- **Sikhosana. N**., Chengalroyen M. and Kana. B.D. Mycobacterium amidases: Biological function and putative role in cell wall remodelling. Poster presentation at the Molecular Bioscience Research Thrust. 30 November 2017.
- **Mashilo. P**. and Kana. B.D. Characterization of mycobacterial D,D-carboxypeptidases: protein interaction and genetic knockout. Molecular Biosciences Research Thrust, University of the Witwatersrand. 30 November 2017. **Won first prize for best poster presentation.**
- **David Tabb**, ASMS, Indianapolis, USA
- **V Cole**, Investigation of Parkin-mediated ubiquitination of Mycobacterium tuberculosis, Southern African Society of Human Genetics, Durban.
- **N. Bernitz,** Detection of Mycobacterium bovis infection in African buffaloes (Syncerus caffer) using human QuantiFERON, FMHS Annual Academic Day, Tygerberg Campus.
- **N. Bernitz,** Detection of Mycobacterium bovis infection in African buffaloes (Syncerus caffer) using QuantiFERON, South African Immunology Society Symposium 2017, Gordons Bay, Cape Town.
- **M. Grobbelaar**, Physiological impact of the evolution of the rpoB mutation, 38th Annual Congress of the European Society of Mycobacteriology, Sibenik, Croatia

- **M. de Vos,** The first evaluation of the diagnostic performance of the FluoroType MTBDR assay for the detection of Mycobacterium tuberculosis and resistance to rifampicin and isoniazid, 38th Annual Congress of the European Society of Mycobacteriology, Sibenik, Croatia
- **S. Ley**, Evolution of Extensively Drug-resistant Mycobacterium tuberculosis in Western Cape Province of South Africa: Whole Genome Sequencing of Serial Patient Isolates, 38th Annual Congress of the European Society of Mycobacteriology, Sibenik, Croatia
- **A. Dippenaar,** Point source introduction of Mycobacterium bovis at the wildlife-livestock interface can lead to clonal expansion of the disease in a single ecosystem, 38th Annual Congress of the European Society of Mycobacteriology, Sibenik, Croatia
- **M. de Vos,** Genotypic characterization of delamanid susceptibility in delamanid, 38th Annual Congress of the European Society of Mycobacteriology, Sibenik, Croatia
- **G. Leisching,** The OAS family is induced early post-infection by slow-growing mycobacteria only, 10th international conference on bacterial pathogenesis, Stockholm, Sweden
- **A. Loxton**, Phenotype and non-humoral function of B-cells during Mtb infection and disease, ACTG trials meeting, Washington, DC.
- **S. Sampson**, Elucidating Population-Wide Mycobacterial Replication Dynamics at the Single-Cell Level, ASM Microbe 2017, New Orleans, USA.
- **C. Pule**, Deciphering the physiological state of drug-resistant Mycobacterium tuberculosis strains, 48th Union World Conference on Lung Health, Guadalajara, Mexico.
- **C. Naidoo**, Respiratory and gut microbial communities are altered in patients with active tuberculosis, Exploring Human Host-Microbe Interactions in Health and Disease, London.
- **M. Moller**, PIDDGEN: A multi- disciplinary team providing molecular diagnoses of primary immunodeficiency diseases in South Africa, American Society for Humamn Genetics, Orlando, Florida

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 (2017)

Postdoctoral Fellows who completed their fellowships in 2017

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
Dr	Du Plessis	SU	Post-Doc UCT
Dr	Neethling	SU	Roche
Dr	Awoniyi	SU	Desmond Tutu TB Centre

Postgraduate students who graduated in 2017

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	Unknown
Manemela	Nelia	BSc Hons	Wits	Unknown
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

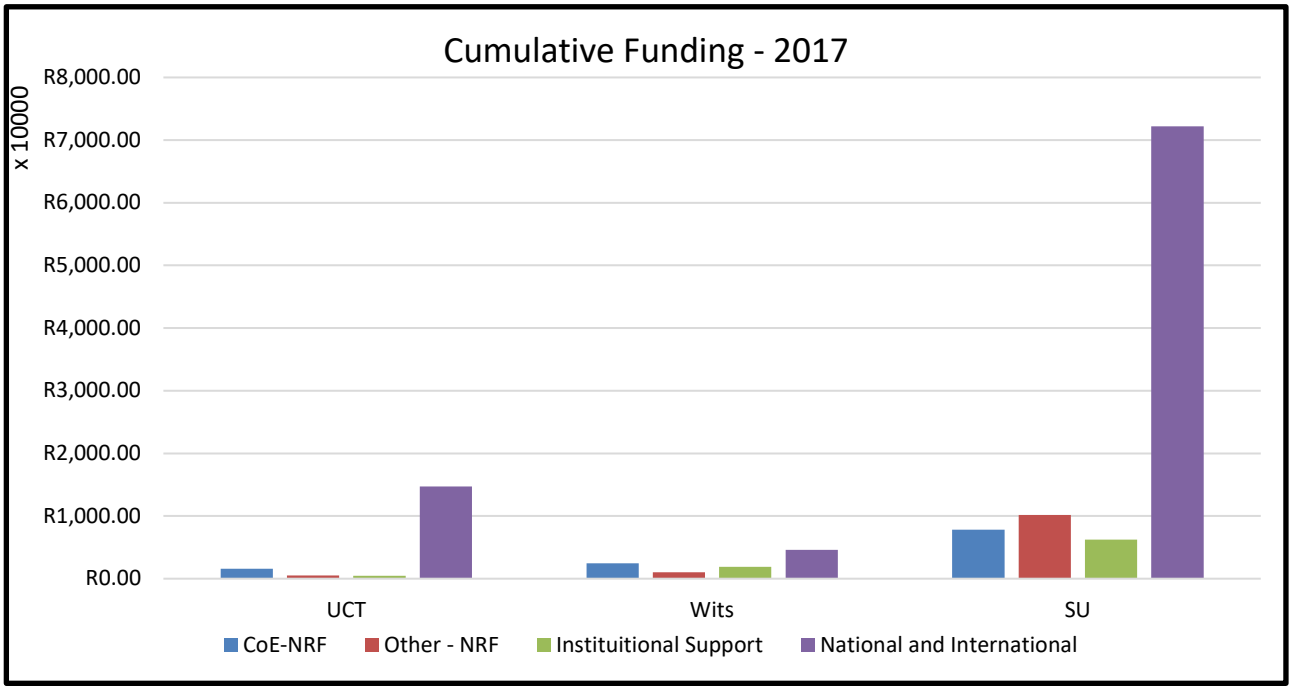
Baartes	Nadia	MSc	UCT	Unknown
Awoniyi	Dolapo	PhD	SU	Joined Desmond Tutu TB Centre at SU as a Manager
Goosen	Wynand	PhD	SU	Registered as a Postdoctoral Fellow at UCT, LIIU
Grobbelaar	Melanie	PhD	SU	Registered as a Postdoctoral Fellow at SU node
Hammond-Aryee	Kenneth	PhD	SU	Moved back to Ghana, looking 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 2017 to 31 Dec 2017 have been reviewed and is currently awaiting approval by the external auditors and will be forwarded to the Steering Committee.

Table 7: Summary of the cumulative funding for 2017

	Funding Sources					
	CoE-NRF	**Other - NRF**	**Instituitional Support**	**National and International**		**Total Income**
UCT	R1 578 942,00	R515 538,00	R450 000,00	R14 728 005,00		R17 272 485,00
Wits	R2 442 333,00	R1 025 746,00	R1 910 843,79	R4 602 982,12		R9 981 904,91
SU	R7 841 439,00	R10 178 471,00	R6 217 530,00	R72 199 806,12		R96 437 246,12
Total Income	R11 862 714,00	R11 719 755,00	R8 578 373,79	R91 530 793,24		R123 691 636,03



Data Storage, utilisation and accessibility Detail data storage and utilisation for the period. Expand on how access to this data is ensured, leading to data sharing, usage and dissemination.

All research findings from the UCT node as well as Wits and SU are published in the peer-reviewed literature and/or in theses or dissertations which are publically available through the Institutes open access policy. Where affordable, pages charges were paid to enable open access, and hence, increase visibility, of certain papers. Students and researchers have the opportunity to present their findings and national and international Symposia, conferences and workshops.

Challenges and constraints for the CoE for the reporting period.

The ongoing uncertainty regarding future funding prospects from the DST and NRF beyond the termination date of the CBTBR has impacted negatively on our momentum by discouraging the recruitment of new PhD students. While the NRF has repeatedly committed to seeing registered

postgraduate students through to completion, the main challenge with respect to sustaining PhD students in our field of research are the high running costs associated with laboratory-based TB research. In the absence of other confirmed sources of funding, we have reluctantly decided to focus our attention on seeing our existing cohort of students through to completion and to be highly selective about recruiting new students and as a result, we only recruited one new MSc student for 2018. Compounding this “shrinkage” problem was the fact that no inflationary increase was granted to the CBTBR in 2017, meaning that the 2017 grant was at least 5% lower than that received in 2016. In terms of funding allocated to the three nodes, and the pending institutional application, we request that each node should be allocated an equal amount of R10 million per annum. Due to budget constraints, we were allocated the same amount of R 11 862 714.00 with 0% increase from 2017.

We find that the online system is extremely tedious. Information that was captured in the previous year’s needs to be manually loaded again on the system. Apparently, in the past these issues were addressed to the NRF, however, nothing was done. For example, loading key personnel on the NRF system. Information include demographics, race, identity numbers etc. Another example of this inefficient online system is the linking of Researchers / key personnel’s CV’s to load the publications. The system does not recognise any duplicates and one has to manually check these peer reviewed publications. Those individuals who do not have NRF CV’s, their publications need to be added manually.

Loading of student information is another sore topic. Each student / Postdoc’s information (Copies of degree, Proof of registration and copy of identity documents together with personal details, address / email and contact numbers) need to be captured. Bearing in mind we had, for 2017, 136 Students and postdocs.

The NRF’s reporting requirements also imposed a heavy burden on the admin assistants at the Wits and UCT nodes, who were responsible for assembling all of the necessary information. In the case of the UCT node, the individual whose salary is covered in part by the CBTBR grant, is the only admin assistant in the entire node and is therefore also responsible for all student/postdoc as well as grants administration for the group, which comprised 25 personnel in 2017.

Any other relevant Information

None to report