UNIVERSITY OF PRETORIA
DEPARTMENT OF GENETICS

POST GRADUATE STUDY PROGRAMMES AND DEPARTMENTAL RESEARCH PROGRAMMES

The Department of Genetics administers three Masters and two Doctoral study programmes as detailed below. All degrees are research based and is conferred on the grounds of a dissertation / thesis. The medium of instruction is English and the dissertation / thesis must be submitted in English.

MSc: Genetics
PhD: Genetics

The majority of our registered postgraduate students are in the Genetics programmes. Masters and doctoral students in these programmes are all associated with the research programmes detailed below.

MSc(Agric): Genetics

Students registered in the MSc(Agric) programmes will be required to complete ancillary modules concurrently with their prescribed modules during their first year of study, since they have not completed an Honours degree programme. Ancillary modules will be selected from the Genetics Honours modules (700-level).

MSc: Biotechnology
PhD: Biotechnology

The Biotechnology programme is a collaborative, inter-departmental degree managed jointly by the Depts. of Genetics, Biochemistry, Plant Science, Microbiology & Plant Pathology, as well as Plant Production & Soil Science. The programme is, however, administered by the Department of Genetics. As with the Honours programme in Biotechnology, a student's choice of research programme will direct in which of the respective participating Departments they will register and conduct their research. The curriculum for any given student is therefore determined by their supervisor and the head of the department in which they register.

The Biotechnology programmes have a strong focus on molecular biotechnology and recombinant DNA technology. Students who wish to register for this programme must be able to demonstrate an advanced background in aspects of molecular genetics, biochemistry and microbiology (NQF level 6 and/or 7). Students may register to complete their Biotechnology studies in any of the participating departments and should contact the respective departments to find out more about their research programmes within the field of Biotechnology.

Biotechnology students associated with the Department of Genetics will register for the 800- or 900-level Genetics modules as set out below, and are required to fulfill all associated requirements.

◢ Masters Programme in the Department of Genetics

Admission requirements:

An appropriate BScHons or four year BScAgric degree (NQF level 8), with an overall average of no less than 60% and clear evidence of experience in advanced genetics, is a prerequisite for admission to the MSc degree. Preference will be given to applicants with the highest final grade point averages for their preceding degree and qualifying applicants may be subjected to an entrance evaluation examination. Admissions to the various MSc programmes are furthermore contingent on the availability of suitable research positions within the student's field of interest and experience, and must be personally negotiated with the research supervisor prior to registration.

International students must submit a Certificate of Evaluation, as issued by the South African Qualifications Authority (SAQA), along with their application. The Department will abide by the

recommended recognition of any prior degrees as designated on the SAQA Certificate. Persons applying with a BTech or MTech degree (or equivalent) must refer to the section in the Postgraduate Yearbook concerning *Faculty Guidelines for Consideration of BTech and/or MTech Students to Postgraduate Study*. It is furthermore compulsory for such applicants to satisfactorily pass an entrance examination and to register for at least 70 credits of coursework (at NQF levels 6 and 7) as prescribed by the Head of Department to be completed in the first year of study.

Programme Composition:
GTK 890: Dissertation 890

Total credits required: 180

- Applicants may be required to submit proof of English language proficiency; alternatively, additional modules may be prescribed by the Head of the Department, e.g. Advanced Language Proficiency 300 (EOT 300), where deemed necessary.
- The Department reserves the right to prescribe additional modules at NQF levels 6 and 7 in cases where a candidate's background in aspects of advanced genetics is deemed incomplete.
- Applicants who have a four year BSc(Agric) degree will be expected to complete additional coursework during their first year of registration for the Masters degree. In addition to the above-mentioned modules they must register for GTK702, GTK705 and MLB721 and complete the associated Advanced Techniques course, seminar and article discussions, as well as the project proposal.
- The standard period of study for a Masters degree is two years uninterrupted, fulltime study. Part-time students will only be accepted in very exceptional circumstances and depending on the supervisor, their affiliation, and the scope of the research project. The minimum registration period for an MSc is one year.
- Strict guidelines exist in the Department to oversee the progress of registered Masters students. Renewal of registration is dependent on satisfactory progress during the preceding year as assessed by their Project Committee.
- Students are required, upon submission of their dissertation, to also provide a draft article formatted for submission to an accredited academic journal.

◢ Doctoral Programme in the Department of Genetics

Admission requirements:
An appropriate Masters degree (NQF level 9), with an overall average of no less than 60% and clear evidence of experience in advanced genetics, is a prerequisite for admission to the PhD degree. Preference will be given to applicants with the highest final grade point averages for their preceding degree and qualifying applicants may be subjected to an entrance evaluation examination. Admissions to our PhD programmes are furthermore contingent on the availability of suitable research positions within the student's field of interest and experience, and must be personally negotiated with the research supervisor prior to registration.

International students must submit a Certificate of Evaluation, as issued by the South African Qualifications Authority (SAQA), along with their application. The Department will abide by the recommended recognition of any prior degrees as designated on the SAQA Certificate. Persons applying with an MTech degree must refer to the section in the Postgraduate Yearbook concerning *Faculty Guidelines for Consideration of BTech and/or MTech Students to Postgraduate Study*. It is furthermore compulsory for such applicants to satisfactorily pass an oral entrance examination and at least 70 credits of coursework (at NQF levels 6 and 7) will be prescribed by the Head of Department to be completed in the first year of study.

Programme Composition:
GTK 990: Dissertation 990

Total credits required: 360

- Applicants may be required to submit proof of English language proficiency; alternatively, additional modules may be prescribed by the Head of the Department, e.g. Advanced Language Proficiency 300 (EOT 300), where deemed necessary.
- The Department reserves the right to prescribe additional modules at NQF levels 6 and 7 in cases where a candidate's background in aspects of advanced genetics is deemed incomplete.
- The minimum period of study for a doctoral degree is two years uninterrupted, fulltime study. Most projects, however, take at least three years to complete.
- Renewal of registration is dependent on satisfactory progress during the preceding year as assessed by their Project Committee or primary supervisor.
- A doctoral degree is only conferred subject to the successful completion of a final oral on the thesis and general subject knowledge, once the thesis has been submitted and examined.
- Students are required, upon submission of their thesis, to also submit proof of acceptance of a manuscript for publication in an accredited academic journal.

Prospective postgraduate students are advised to consult the respective research programmes' primary investigators for further information regarding their research programme, available positions and financial support. More in depth details regarding admission are also available from the primary investigators.

An official application to the University of Pretoria (online or otherwise) should only be submitted once a supervisor has been identified and when he/she has agreed that there is an available position in his/her research programme.

Also consult our webpage: **http://www.up.ac.za/genetics**

Brief overview of the ongoing research programmes in the Department of Genetics

Our research programmes can generally be divided in six research focus areas, namely Animal Health, Plant Genetics and Genomics, Metagenomics, Fungal- and Insect Genetics & Evolutionary Genomics, Evolutionary & Behavioural Genetics, and Human & Medical Genetics.

ANIMAL HEALTH

Programme 1: MOLECULAR VIROLOGY OF ORBIVIRUSES

Primary Investigators: Dr Vida van Staden and Prof Henk Huismans

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Collaborators: Prof Jacques Theron (Dept Microbiology, UP), Dr Christiaan Potgieter

Members of the oribivirus genus such as African horse sickness virus (AHSV) and bluetongue virus (BTV) are responsible for some of the most important viral diseases of horses and sheep in South Africa. AHSV is the aetiological agent of African horse sickness, a non-contagious but highly lethal disease of equids. The disease is enzootic in eastern and central Africa and occurs regularly throughout sub-Saharan Africa including South Africa. Orbiviruses have double shelled virus particles with a genome comprised of 10 segments of double stranded RNA, each encoding a specific virus protein.

Nearly all virology research is driven by two main questions – how the virus life cycle causes pathogenesis or disease in its host, and how we can prevent or treat the disease. Our research is predominantly focused on AHSV, and specifically on how its molecular biology contributes to pathogenesis. Basic questions relating to virus structure and the role of the genes and proteins in virus assembly, virus replication and the induction of a protective immune response are addressed. We also investigate the contribution of the different viral components to virulence, pathogenesis and the epidemiology of disease. These findings ultimately have applications in the development of products of importance in biotechnology e.g. vaccine delivery systems and diagnostic tools.

There are nine AHSV serotypes, which are distinguished by the fact that antibodies to one serotype do not neutralise virus from another serotype. The ten dsRNA genome segments of the virus encode seven structural proteins, designated VP1 to VP7, and four non-structural proteins (NS1 to NS4). The segmented genome is enclosed in an icosahedral core particle composed of major capsid proteins VP7 and VP3 and three minor structural proteins. A diffuse outer protein layer, composed of capsid proteins VP2 and VP5, surrounds the core. The genes encoding these proteins have by now all been cloned, sequenced and expressed in prokaryotic and/or eukaryotic expression systems. The four non-structural proteins have functions related to viral replication, assembly and release of virus particles from infected cells.

Much of the current research is focused on the role of AHSV structural proteins in virus particle assembly. VP7 forms trimers, which bind onto the sub-core VP3 scaffold to form the virus core particle. However the bulk of VP7 spontaneously self-aggregates to form large crystalline-like cytoplasmic particles. These crystals are unique to AHSV, and compete with the assembly of core particles. It is not known why they form, and whether they play any role in the virus life cycle or pathogenesis. This work involves the genetic engineering of VP7, and using the modified protein as a tool to study its interaction with cellular proteins or trafficking pathways, and its role in core particle assembly and virus replication.

Another part of the research has a strong focus on the role of non-structural proteins in AHSV virulence, viral release from infected cells, induction of cell death responses in infected cells and the pathogenesis of AHS disease. We are investigating the role of host proteins, trafficking pathways and plasma membrane related events in virion release, comparatively investigating the regulation of NS3 expression in the AHSV life cycle in mammalian and insect cells, and characterising the different domains of individual proteins that determine their subcellular localisation and trafficking. A novel non-structural protein only described recently, NS4, is of special interest as it localises to the nucleus of the host cell and seems to modulate the host immune response to virus infection. Collaboration with Prof Jacques Theron (Dept Microbiology), who has recently developed a unique reverse genetics strategy for AHSV, opens many new avenues of investigation. Answers to these questions could provide opportunities for directed interference with the viral life cycle, and can thereby lead to developing improved control strategies for this debilitating disease.

Research objectives:

Research objectives have been focused on the following long-term objectives:

1. To investigate the role of some of the capsid proteins and non-structural proteins in virus assembly and replication.
2. To investigate the role of non-structural proteins in the release of virus particles from the cell and how this relates to virulence, disease and epidemiological characteristics.
3. To investigate the mechanisms of virus-induced cell death (e.g. apoptosis, necrosis and autophagy) in mammalian cells.

Programme 2: TICKS AND TICK-BORNE DISEASES

Primary Investigator: Dr Christine Maritz-Olivier

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Collaborators:

- International:

1. Towards a complete genome, transcriptome and interactome of the cattle tick *R. microplus* (2012-). Dr. Felix D. Guerrero (USDA-ARS Knipling-Bushland, US Livestock Insects Research Laboratory, Kerrville, Tx 78028, USA) & Dr. Matthew Bellgard (Director of Murdoch University's Center for Comparative Genomics, Murdoch University, Perth, Western Australia, Australia).
2. Evaluation of promising anti-malarial compounds against *Babesia* spp. Prof Eric Maréchal (Institut de Recherches en Technologies et Sciences pour le Vivant CEA-Grenoble, France).
3. Identification of subolesin interacting partners and homologous in South African mosquitoes and midges (2005-current) & Two-hybrid analysis of *Anaplasma* MSP-1 using tick cDNA libraries (2011-current). Prof. Jose de la Fuente (Instituto de Investigacion en Recursos Cinegeticos, IREC Ronda de Toledo s/n 13005 Ciudad Real, Spain and Department of Veterinary Pathobiology Center for Veterinary Health Sciences Oklahoma State University Stillwater, Oklahoma, USA)
4. Reverse vaccinology and VaxiJen-based studies for the identification of protective antigens. Prof. Irini Doytchinova (University of Sofia, Bulgaria).
5. Improvement of Bm86-and ATAQ-based anti-tick vaccines, as well as *in vivo* RNAi of vaccine candidates. Dr. A. Nijhof (Institut für Parasitologie und Tropenveterinärmedizin, Freie Universität Berlin, Germany).

- National:

1. Pfizer Pty (Ltd.): Genotyping and acaricide resistance screening of *Rhipicephlaus* ticks throughout South Africa (Dr Chris van Dijk).
2. NHLS vector control unit: Validation of akirins as sterile insect-based control measure in South African mosquitoes (Prof Lizette Koekemoer)
3. Validation of akirins as sterile insect-based control measure in African midges (Dr Wilma Fick, Department of Genetics, UP).
4. Tropical Disease unit of the Agriculture Research Council, Onderstepoort: Cattle vaccine trials, tick rearing and co-supervision of students. (Drs Latif and Mans and Mr Daniël de Klerk).
5. University of Pretoria Biomedical Research Centre (2008-current): Validating vaccine candidates in cattle trials (Drs V Naidoo and T Pulker, Ms S Meyer)
6. Medical research council (2012-): Anti-sera production and small animal research (Mr K Venter)
7. University of Stellenbosch, Proteomics centre: Gut proteome analysis using LC-MS-MS (Dr S Smit)
8. Malaria Research Program, Department of Biochemistry, University of Pretoria (2010-current): Evaluation of promising anti-malarial compounds against *Babesia* spp. (Ms I Rossouw, Prof L Birkholtz, Prof Eric Maréchal) and Expression of *Plasmodium* proteins in *Pichia pastoris* (2008) (Dr. L. Birkholtz, Ms. M. Dreyer)

Ticks rank second to mosquitoes as global vectors of human diseases, but are the most relevant vectors of disease-causing pathogens in domestic and wild animals. Ticks and tick borne diseases place a major constraint on livestock production throughout much of the developing world, nowhere more so than in Sub-Saharan Africa. Factors such as climate, host movement, animal husbandry practices, vector distribution and vector population changes, affect tick distribution and occurrence of tick-borne diseases.

The feasibility of vaccinating against at least one tick species, *Rhipicephalus (Boophilus) microplus*, has been demonstrated using the recombinant antigen Bm86 and commercially developed vaccines. This tick species has long been considered of minor importance in most of Africa, virtually absent throughout West Africa. However, in recent years it has been found that *R. microplus* has spread rapidly, infesting previously unaffected regions. Moreover, it has been found that *R. microplus* has displaced “endemic” species, *R.*

decoloratus, throughout much of its range in eastern and southern Africa, including the Limpopo province in South Africa. Therefore, given the fecundity of this species, its adaptability to different climatic zones, efficiency as a disease vector and ability to develop pesticide resistance, the full impact of its introduction to the African continent is difficult to estimate and likely to be catastrophic in the long term. The latter necessitates the development and implementation of effective control strategies to alleviate the increasing pressure this species places on livestock in Africa. Anti-tick vaccines offer the advantage of controlling both tick numbers and disrupting the tick vector-pathogen interface. Our group utilize cutting edge technologies (including transcriptome analysis, bioinformatics and immune-informatics, *in vivo* and *in situ* gene silencing, molecular biology, recombinant protein expression, protein-protein interactions, and animal vaccination trials) to identify and validate protective antigens as vaccine candidates in order to lessen the socio-economic burdens associated with ticks and tick-borne pathogens.

The tick research program is, furthermore, supported by a program focusing on the genetic diversity and current acaricide resistance status of *Rhipicephalus* ticks from endemic South African regions. Analyses for five acaricide resistance genes and eight microsatellites have been optimized and are used in a large-scale screening of *Rhipicephalus* ticks. These studies will provide us with an understanding of the parasite-host-pathogen interactions and solutions to economical viable tick control measures.

The skills developed in the tick research program have now been extended to a broader vector control program, to include *Culicoides* (a vector for bluetongue virus and African horse sickness virus), as well as an *Anopheles* species (a vector for *Plasmodium* species). Currently the focus is on the identification of transcripts vital to vector feeding and fecundity, followed by *in vivo* evaluations on vector fitness during gene silencing. Promising anti-apicomplexan compounds are furthermore, being evaluated in *Babesia* species to determine their IC50 and mode of action using cutting edge functional genomics methods and comparative genomics between other apicomplexan parasites. This research is critical for future drug design and ensuring animal health.

Research objectives and current activities:

Currently, the following focus areas are addressed in order to identify and evaluate ant-tick vaccine candidates.

- A reverse genetics approach using RNA-interference in both living ticks and in tick cell cultures. This approach allows the identification of transcripts with a lethal phenotype (i.e. possible new vaccine candidates), as well as determining the differential transcriptional response elicited in ticks after silencing a specific transcript (i.e. possible cocktail vaccine candidates).
- We aim to unravel essential processes mediated by protein-protein interactions using the yeast two-hybrid screening system. Currently, we are focussing on the existing vaccines which will not only provide insight into their biological roles, but also identify more possible tick-control points.
- We use functional genomics and immune-informatics to identify highly immunogenic proteins that are expressed throughout the lifecycle of the two most prominent cattle tick species in South Africa (*R. microplus* and *R. decoloratus*). This research have yielded some 40 promising candidates that are currently expressed and further validated as possible anti-tick vaccine candidates in cattle vaccine trials.
- *R. microplus* and *R. decoloratus* from some 160 cattle farms throughout SA has been collected and are being analysed using mitochondrial- and nuclear genes as well as microsatellites to gain insight into their genetic diversity.
- Acaricide resistance screening is conducted using PCR for the detection of resistance-induced SNPs, as well as protein docking of newly identified SNPs to evaluate their possible effects on the protein structure-function relationship.
- Promising anti-*Babesia* drugs are evaluated *in vitro* and their mode-of-action determined using transcriptome and proteome analysis.

Programme 3: EPIDEMIOLOGY OF PARASITIC NEMATODES

Primary Investigator: Dr Pamela de Waal

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Collaborators: Dr Sarah Clift (Pathology Section, Onderstepoort, UP), Prof Jaco Greeff (Dept of Genetics, UP)

The nematode parasite *Spirocerca lupi* causes spirocercosis in canids. It forms nodules in the esophagus of the dog which may become cancerous and be fatal. Anthelminthic treatment is only effective if administered soon after infestation. Most dogs remain asymptomatic until the disease progression is advanced. At this stage treatment is both risky and expensive.

Nothing is known about the genetic landscape of the *S. lupi* population. Similarly, there is very little molecular data available. Recent evidence suggests a substantial increase in the reported incidence of the disease over the last ten years. This increase may be due to an increased prevalence or to an increase in the virulence of the parasite.

Spirocerca lupi occurs globally in tropical and sub-tropical areas. The incidence of *S. lupi* is considerably higher in urban as opposed to rural areas. We have estimated an urban density in the order of 1775 dogs per km^2 in South Africa. This high density combined with the observed increased prevalence may result in a breeding ground for more virulent strains of *S. lupi*. This may in turn serve as a source of infection for wild canids, such as wild dogs, hyenas and jackals, in surrounding areas. Wild canids have much larger territories and are found in much lower densities than urban domestic canids. As such, their immune systems are naïve and contact with a more virulent strain of *S. lupi* could decimate local populations.

Based on the number of dogs infested with *S. lupi*, current reports of the incidence of the parasite determined by faecal flotation assays may be an underestimate. The sensitivity of faecal flotation assays is variable. Also, egg shedding is intermittent. Development of diagnostic tools for identification of *S. lupi,* quantification of population structure over a large region and assessment of genetic variation would greatly enhance our understanding of the dispersal and distribution of the worm. This knowledge would assist in the management and prevention of the disease.

Research objectives:

This programme aims to investigate the population structure, prevalence and genetic diversity of *Spirocerca lupi* in its primary, secondary and paratenic hosts. Specific objectives include:

- The development of diagnostic tools for specific detection;
- The development of genetic markers for quantification of genetic variation;
- Evaluation of genetic variation within and between the primary canid host, the secondary coprophagus beetle host and various paratenic hosts;
- Determining the incidence and genetic variation of *S. lupi* in wild canids, and
- Assessing prevalence and genetic diversity of *S. lupi* at the interface between urban and rural areas.

PLANT GENETICS AND GENOMICS

Programme 1: FOREST MOLECULAR GENETICS / FOREST GENOMICS

Primary Investigators: Prof Zander Myburg, Dr. Eshchar Mizrachi, Dr. Sanushka Naidoo

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Collaborators: We have an extensive network of collaborators at international institutions (University of British Columbia, Oregon State University, Ghent University, etc.) and we work closely with local forestry companies (Sappi, Mondi and others).

Forest trees are large, long-lived organisms with unique biology. Their population genetics is similar to that of humans (long life-cycles, outbreeding and large population sizes). They play important roles in environmental processes such as carbon sequestration and constitute excellent renewable resources for a diversity of wood, fiber and lignocellulose-based products. In addition to their use for pulp and paper production and for solid wood products, they are increasingly being seen as potential bio refineries for the production of novel biopolymers, fine chemicals and biofuels. With the depletion of fossil fuel reserves and the reality of accelerated global warming, large international efforts are now under way to modify the growth and wood properties of forest trees to make them more amenable to bioenergy production. Excellent progress has been made in the analysis of forest tree genomes and the development of biotechnology tools for trees. Our research programme was one of the lead participants in the recently completed international project to

sequence the *Eucalyptus* tree genome. We have also completed several transcriptome sequencing projects aimed at gene expression profiling during wood formation in individual trees and in 100s of trees at the population level. Information generated from transcriptomics, metabolomics and (in future) proteomics investigations can be integrated into a systems biology modeling of wood formation processes. These approaches can be extended further by combining the power of genomics technologies and genetic analysis of segregating populations to achieve systems genetics modeling of tree biology. Forest tree genomics and associated forest biotechnology is an exciting field of research with many opportunities for basic as well as applied research. Strategic investments by industry (e.g. Sappi and Mondi) and government (NRF, DST) agencies are creating tremendous opportunities for biotechnology innovation and for future careers in plant biotechnology.

Research emphasis:

Research in the **Forest Molecular Genetics (FMG) Programme** focuses on the molecular genetics and genomics of xylogenesis, the developmentally regulated process through which wood fibre is formed in trees and which includes processes that are fundamental to carbon fixation in plants. We are addressing important scientific questions such as the genetic control of carbon partitioning into cellulose, hemi-cellulose and lignin, the major biochemical constituents of wood fibre. As an example, we have isolated and studied the regulation of cellulose synthase (CesA) genes of *Eucalyptus* trees, the most widely grown plantation tree species in the world. CesA genes encode a multimeric enzyme complex that polymerizes activated glucose molecules into very long cellulose chains and deposit these cellulose chains into plant cell walls. Cellulose is the most abundant biopolymer on earth and we have only recently gained an understanding of the complex genetic regulation of its biosynthesis. Several FMG student projects are focused on the transcriptional regulation of cellulose and hemi-cellulose biosynthesis both in individual trees and in segregating populations (a systems genetics approach). In addition, we have a focus on molecular breeding of *Eucalyptus* trees, in which we have embarked on high-throughput genome-wide genotyping and genetic association of growth and wood properties for genomic selection of these traits. These approaches will also be used for genome mapping of disease resistance in trees as part of the Eucalyptus & Pine Pathogen Interactions (EPPI) Programme (see below).

Programme 2: EUCALYPTUS & PINE PATHOGEN INTERACTIONS

Primary Investigator: Dr Sanushka Naidoo

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Collaborators: Prof Zander Myburg, Prof Bernard Slippers, Prof Emma Steenkamp

Various fungal and bacterial pathogens pose a threat to the forestry industry as they infect *Eucalyptus* and Pine tree species. It is expected that climate changes in the near future could contribute to a more favourable environment for forest pathogens, escalating disease incidence in forestry plantations. This problem is especially important for clonally propagated species, as entire plantations could be lost due to susceptibility of the clone to a particular pathogen. One of the most desirable means of control would be the production of varieties with enhanced tolerance or resistance against the disease. Genetic engineering provides the promise of accelerating the production of commercial *Eucalyptus* and *Pinus* varieties, which will not only provide high-quality fibre, but also a high degree of resistance or tolerance to various pathogens.

The **Eucalyptus and Pine Pathogen Interactions (EPPI) programme** was initiated in 2007 with the motive of investigating the defense response of forest trees to various pathogens. *Arabidopsis thaliana* is used to model plant-pathogen interactions in eucalyptus or pine in order to understand and identify resistance mechanisms, which can be manipulated in trees in future. We undertake a genomics approach to perform gene discovery in *Arabidopsis*, *Eucalyptus* and pine.

Recent developments:

***Eucalyptus* host responses**

The recent release of the genome sequencing of *Eucalyptus grandis* is a resource that holds the promise of improving gene discovery. This, coupled with the availability of high-throughput transcriptome technologies such as mRNA sequencing provides important foundations to elucidate plant-pathogen interactions and promote gene discovery in forest tree species. Two *Eucalyptus* projects being undertaken by EPPI aim to (i)

ascertain the molecular basis of disease responses in *Eucalyptus* to a canker pathogen *Chrysoporthe austroafricana* and (ii) determine the molecular defence mechanisms of *E. grandis* against the gall wasp *Leptocybe invasa*.

Eucalyptus responses to the fungal pathogen *Chrysoporthe austroafricana*

The fungus *C. austroafricana* causes stem canker on *Eucalyptus* trees. The initial stem canker leads to stem breakage and even plant death. In South Africa tolerant species have been propagated (primarily *E. grandis* has been replaced with *E. grandis* x *E. urophylla* hybrids in subtropical regions) and thus disease incidence caused by the pathogen has been curbed. Global climate change however, is predicted to create favourable environments for such pathogens and it is expected that tolerant species or hybrids may succumb to a disease outbreak.

Previous work, using artificial inoculation techniques, has revealed *E. grandis* clones tolerant and susceptible to *C. austroafricana.* This pathosystem provides a unique model to dissect defence responses that are important to improve tolerance in *Eucalyptus*. A draft genome of *C. austroafricana* and two sibling species are now available and this will greatly enhance the understanding of this host pathogen interaction.

Eucalyptus responses to *Leptocybe invasa*

Leptocybe invasa (Hymenoptera: Eulophidae) is a *Eucalyptus* gall wasp which has become an emerging threat to the South African forestry industry. Female wasps oviposit their eggs along the leaf midribs, petioles and stems. The larvae hatch inside the tree and feed on the host tissue, resulting in the formation of coalescing galls. Susceptible trees become severely stunted. We have investigated the defence responses to the wasp in resistant and susceptible genotypes of *E. grandis* and have identified possible mechanisms that contribute to resistance in the host. Our current research is focused on confirming these observations.

Pinus patula responses to *Fusarium circinatum*

Pinus patula is highly susceptible to the fungus *Fusarium circinatum.* The pathogen infects seedlings in the nursery causing discolouration, wilting and death of seedlings. In older trees, the pathogen causes pitch canker disease. As a starting point, we are sequencing the transcriptome of *P. patula* during challenge with the pathogen to determine what potential defence responses in pine are being suppressed by the pathogen to render the plant susceptible. . The genome of *F. circinatum* was sequenced in 2010 and the availability of this genome will greatly enhance the understanding of this disease.

Programme 3: FRUIT TREE BIOTECHNOLOGY

Primary Investigator: Dr Noëlani van den Berg

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Collaborators: Prof Zander Myburg, Dr Sanushka Naidoo, Prof Dave Berger

Avocado root rot caused by *Phytophthora cinnamomi* is regarded as one of the most serious diseases of the fruit and has a large financial impact on the South African and world-wide avocado industry. Undoubtedly the most significant problem is the lack of total resistance against the disease. There are several reasons why Phytophthora root rot (PRR) is such a devastating problem on avocados. Most seedling rootstocks are extremely susceptible to the disease, some soils are poorly drained and not very suitable for production, the cultivar selection is influential and the use of chemical fungicides is not always effective. Despite the great importance of avocados in the agricultural sector, little is known about its genetics and the molecular processes underlying resistance responses, metabolic pathways and downstream signalling of the avocado-*Phytophthora cinnamomi* (*Pc*) interaction.

The search for genes conferring resistance to diseases and pests has become an important objective towards understanding plant resistance and developing genetically improved agricultural crops. An analysis of pathogen-induced genes may lead to a better understanding of the molecular processes involved in resistance, and may contribute to the development of biotechnological strategies to fight the disease. Once identified, avocado resistance genes could also be used as markers for the rapid detection of resistant traits in rootstock selections, or for the genetic improvement of susceptible avocado rootstocks via transformation.

We undertake a genomics approach to perform gene discovery in avocado. The technology platforms employed include 454 Pyrosequencing, SOLEXA digital gene expression profiling and RNA

sequencing, quantitative RT-PCR profiling, quantitative trait loci (QTL) mapping and expression QTL mapping (eQTLs).

Recent developments:
Previous research in our laboratory has generated cDNA libraries from a range of avocado rootstocks with variable tolerance against PRR. Using 454 Pyrosequencing several candidate genes have been identified which may be responsible for tolerance against *Pc*. Currently; we are analyzing the 2Mb of 454 sequences which will then be confirmed with Q-RT-PCR. We have also elucidated the role of known defence genes in avocado in response to the pathogen. The aim of this programme is to shed light on and understand the mechanisms and gene expression pathways whereby tolerant avocado rootstocks, are protected against *Phytophthora cinnamomi*.

We have set three long term objectives: 1. Understanding the avocado tolerance/resistance to Phytophthora root rot by identifying the host defence mechanisms in various rootstocks. 2. Identification of the genes that control certain defence mechanism and the development of molecular markers to aid in the selection and screening of avocado rootstocks. 3. Exploring the possibilities of genetic manipulation to develop new super-genotypes based on superior defence mechanisms.

METAGENOMICS

The **Centre for Microbial Ecology and Genomics (CMEG)** will undertake a wide variety of projects in the fields of environmental microbiology, microbial ecology, metagenomics and applied microbiology (see project areas below).

Primary Investigator: Prof Don Cowan

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Programme 1: MICROBIAL ECOLOGY

Collaborators: Dr Angel Valverde (UP), Dr Jean-Baptiste Ramond (UP), Prof Marla Tuffin (UWC), Prof Ed Rybicki (UCT), Dr Chris McKay (NASA Ames, USA), Prof Craig Cary (University of Waikato, NZ), Dr Gabriela Mataloni (Universidad Nacional de San Martín, Argentina), Dr Mary Seely (Gobabeb Research and Training Centre, Namibia), Prof David Hopkins (Heriot-Watt University, UK), Prof Diana Wall (Colorado State University, USA)

Projects in microbial ecology aim to ask (and answer) basic questions relating to the presence, function and role of microorganisms in the environment. Such questions include 'who is there?', 'what are the physiological and ecological roles of specific phylotypes?', 'how do organisms interact?', and 'how do species and communities respond to environment changes?'. The techniques used to address these questions include many of the modern molecular methods (such as phylogenetics, metagenomics and metatranscriptomics), and increasingly rely on next generation DNA sequencing.

Projects:
- Metagenomics of Antarctic cold desert ecosystems.
- Microbial ecology of Namib Desert soil ecosystems [several projects].
- Metaviromics of hot and cold desert soils.
- Prokaryotic ecology and diversity of Argentinian sub-Antarctic peat bogs.
- The microbiology of the plant root-soil interface.
- Microbial community fingerprinting of sub-Saharan African soils.

Programme 2: MICROBIAL PHYSIOLOGY AND ADAPTATION

Collaborators: Prof Marla Tuffin (UWC), Dr David Mead (Lucigen Corp., USA)

The CMEG laboratory uses a combination of genome sequencing, proteomics, transcriptomics and metagenomic library expression screening to identify genes and gene products which are responsive to

stress conditions in bacteria. Understanding metabolic responses and adaptation mechanisms not only contributes to a fundamental understanding of microbial physiology, but is directly relevant to the performance of microorganisms in industrial fermentation processes, such as in bioethanol production.

Projects

- Genomics and genome sequencing of *Geobacillus.*
- Identification of novel stress response and adaptation genes using functional metagenomics.
- Assembling and interpreting genomes of uncultured prokaryotes from multi-Gbp metagenome sequence datasets.

Programme 3: APPLIED AND INDUSTRIAL MICROBIOLOGY AND ENZYMOLOGY

Collaborators: Prof Christoph Syldakt (KIT, DE), Prof Mike Wingfield (FABI) and Prof Trevor Sewell (UCT)

Many of the basic studies outlined above lead to, or are related to, more applied research projects, where the objectives are to identify and investigate genes and gene products which may have eventual application in industry. Using classical microbiological, genomic and metagenomic methods, researchers in Prof Cowan's laboratory will target a range of novel genes (and gene products) in biotechnologically important categories.

Projects

- The structures and mechanistics of novel lignocellulosic degrading enzymes .
- Engineering fungal strains for high level protein expression.
- Structure-function studies of nitrile- and amide-converting enzymes.
- Mining metagenomes for novel carbohydrate modifying enzymes.

FUNGAL & INSECT GENETICS AND EVOLUTIONARY GENOMICS

Programme 1: MOLECULAR PHYLOGENY, GENOMICS AND EVOLUTION OF FUNGI

Primary Investigators: Prof Brenda Wingfield, Prof Bernard Slippers, Drs Martin Coetzee, Dr Albé van der Merwe, Dr Irene Barnes, Dr Magriet van der Nest and Dr Martin Kembler.

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Collaborators: Proff. Mike Wingfield, Jolanda Roux, Paulette Bloomer and Emma Steenkamp, Drs Wilhelm de Beer, Wubetu Bihon, Stephanie Slinski, Tuan Duong and Lieschen de Vos

This Programme operates under the umbrella of the Tree Protection Co-operative Programme and the NRF/DST Centre of Excellence in Tree Health Biotechnology (CTHB) of which Prof Mike Wingfield is the director. The research focus of the CTHB is the pests and diseases of native South African trees while the Tree Protection Co-operative (TPCP) which has as its focus commercial forest plantations. The research of the TPCP is supported by all the South African forestry industries and the THRIP programme of the NRF.

Our research focus is on understanding the molecular evolution and genomics of fungal tree pathogens. This includes some in depth studies of the population dynamics of these organisms as well as their phylogenetics. We are interested in answering questions such as the centre of origin of these pathogens, how they have spread and how diverse they are in both native and commercial forests. We employ all the latest molecular techniques to answer these questions and have a number of projects involving the sequencing of a number of nuclear and mitochondrial genomes. We have genome sequence for the fungi which we have the greatest focus on [these include: Fusarium *circinatum, Fusarium temperatum, Ceratocystis fimbriata, C. moniliformis, C. albifundus, Diploidia sapinea*]. These genomes are in different

stages of assembly and annotation and a number of student projects are linked to the understanding aspects of these fungi using these genomes. In addition we have a number of bioinformatics projects focused on these genomes. We anticipate that we will have access to the genomes of all the fungi we study within the next ten years.

Identification of pathogens is a crucial first step in dealing with any disease situation. This involves identification of the organisms associated with the disease and subsequently proof of causal activity (Koch's rules of proof). In some cases, identification of the causal agents of a disease is relatively simple. However, our recent experience has shown that great numbers of pathogens have been incorrectly identified. This can have a very serious impact on strategies used to reduce the impact of diseases.

Problems related to pathogen identification are commonly associated with the fact that microbes are small and have relatively diminished structure on which to base accurate identifications. In addition, there are a growing number of examples of hybridisation of pathogens, which seriously complicates identification. The relatively recent emergence of DNA based methods for comparison of microbes associated with disease has contributed enormously to accurate pathogen identification. An important component of the research in the CTHB and TPCP is to enhance pathogen identification using contemporary DNA-based methods.

Research objectives:

The research programme has the following long-term objectives.

- Study genetic diversity of specific pathogen populations in South Africa and elsewhere. This is essential if we are to develop sensible disease management strategies for these pathogens. It will also allow us to understand how these pathogens spread and evolve.
- Develop DNA sequence based phylogenies for the important fungal tree pathogens and related species. These will be used as a tool for plant pathogen identification in the field and lab situation.
- Using our knowledge of the pathogens diversity to understand its mode of action. We have produced our first AFLP map of one of the most important pathogens and hope to identify some pathogenicity related genes.
- Investigate the genes, gene regulation, gene structure and regulatory elements in fungal genomes.
- Using genomes to better understand phylogeny, pathogenicity and mating systems of these pathogens.

Programme 2: EPIDEMIOLOGY AND EVOLUTIONARY POPULATION GENETICS

Primary Investigators: Dr Albé van der Merwe, Prof Brenda Wingfield and Prof Mike Wingfield

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Collaborators: In collaboration with the Tree Protection Co-operative Programme and the DST/NRF Center of Excellence in Tree Health Biotechnology.
Dr Sanushka Naidoo (Genetics, UP) Prof Emma Steenkamp (Microbiology, UP), Prof Bernard Slippers (Genetics, UP), Dr Marieka Gryzenhout (UFS), Dr Morag Ferguson (IITA, Kenya), Dr Carlos Rodas (Smurfit Kappa, Colombia).

Epidemiology is a branch of biological science that deals with the spread and control of pests and diseases, and therefore, it is highly dependent on time and space, as well as ecological factors such as climate, niche availability, and geography. Under the Epidemiology and Population Genetics research topic we focus on the epidemiology of fungal pathogens of forestry trees in South Africa. The topic includes many aspects of genetics, such as population genetics of plants and pathogens, phylogenetics, phylogeography, evolutionary biology, as well as molecular biology of pathogenesis systems. These aspects of epidemiology are all understood in terms of climate change and evolutionary ecology. Due to the diverse nature of research under the Epidemiology banner, we collaborate with various other researchers and their programmes.

Research objectives:

- To quantify and understand the establishment and maintenance of genetic diversity in *Chrysoporthe* species and *Fusarium* species.
- To study fungal biology at the genomic level, with the aim of using this information to delimit species, discover new species, understand sexual reproduction and to estimate population genetic parameters.

On-going research projects:

- Characterization of endophytic Cryphonectriaceae from native hosts in Colombia (N.A. van der Merwe, C. Rodas, M. Gryzenhout)
- Sequencing, assembling and comparing the genomes of three *Chrysoporthe* species, namely *C. austroafricana*, *C. cubensis* and *C. deuterocubensis* (N.A. van der Merwe)
- Elucidation of the evolution of the pheromone-pheromone receptor system in *Fusarium* species (T. Kone, N.A. van der Merwe, E.T. Steenkamp)
- Characterization of the mitochondrial genomes from *Fusarium* species in order to understand uniparental inheritance, mitochondrial leakage and hybridization in this group of fungi (G. Fourie, N.A. van der Merwe, E.T. Steenkamp)
- Assembling and characterizing the whole genome sequence from *Fusarium circinatum* in terms of quantitative characters and genome synteny (L. de Vos, N.A. van der Merwe, E.T. Steenkamp)
- Quantitative analysis of a cassava viral disease complex in Tanzania (E. Masumba, N.A. van der Merwe, M. Ferguson)

Recent developments:

We recently showed that host switching of one of the major fungal pathogens of *Eucalyptus*, namely *Chrysoporthe cubensis*, may play an important role in the establishment and maintenance of population diversity. This is an important development, because *C. cubensis* and its relatives, including *C. austroafricana* from Southern Africa, have alternative native hosts in the areas where they occur. Thus, focus is shifting from considering only fungal populations on commercial forest trees, to also include populations occurring on native hosts.

Programme 3: MOLECULAR ECOLOGY AND EVOLUTION OF TREE PESTS AND PATHOGENS

Primary Investigator: Prof Bernard Slippers

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Collaborators: Prof Mike Wingfield, Prof Brenda Wingfield, Prof Jaco Greeff, Dr Sanushka Naidoo, Dr Martin Coetzee, Dr Magriet van der Nest, Dr Irene Barnes, Dr Martin Kemler, Dr Brett Hurley, Dr Jeff Garnas and others

Human society depends on plant production for development and survival. Insect pests and fungal pathogens threaten commercial plant production and native ecosystems alike, and increasingly so due to human influences on invasions and environments. Apart from their practical importance, these organisms also offer a rich opportunity to ask basic ecological and biological questions. We study a variety of fungi, oomycetes, insects and nematodes in such systems, particularly on trees. We use a range of molecular genetics and genomics tools, in combination with more traditional laboratory and field based measurements and observations. By combining these data, we aim to characterise specific species and populations of these pests and pathogens and their biological control agents, and gain an understanding of the processes that influence population diversity and changes abundance in these organisms. Such information are often directly applicable to the management of these organisms.

This programme overlaps significantly with those under the Fungal Genetics and Evolutionary Genomics section, and links to some of the other programmes listed under Plant Genetics and Genomics.

Projects:

- Ecology and evolution of insect-fungal mutualism
- Characterizing the global movement of tree pests and pathogens
- Metagenomics and function of tree microbiomes
- Cryptic species and population diversity of tree pests and pathogens
- Host jumps as a source of emerging tree diseases and pest populations

Programme 1: MOLECULAR ECOLOGY AND EVOLUTION

Primary Investigators: Prof Paulette Bloomer, Dr Michael Cunningham and Dr Thierry Hoareau

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South Africa ranks among the world's most biodiverse regions, yet only a fraction of species are known to science. We are interested in contributing to the uncovering of this hidden diversity but more importantly, in understanding the processes underlying biodiversity (at ecosystem, species and genetic levels). We are interested to know how genetic diversity contributes to speciation and population structure within species. Typical questions we ask are: What processes have driven speciation? Why do species occur where there are found today? What is a population? What is the extent of gene flow within and among populations? We use data from different disciplines to identify processes that may underlie the patterns of genetic diversity we observe and apply our findings in a variety of contexts.

Research approach and examples of current projects:
We use a number of model species to understand the evolutionary and ecological processes in selected southern African biomes:

- **Ecological genetics in terrestrial and freshwater habitats.**
  We use small mammals as models in, amongst others, arid savannah, moist savannah, fynbos and montane grassland. In addition we are studying some of Africa's most threatened species, e.g. the golden moles and wild dogs. Elusive species, such as the subterranean golden moles or small, forest dwelling suni antelope, are difficult to study through direct observation methods and genetic analyses allow us to understand their movements, breeding behaviour and gene flow on local and larger spatial scales.

  Freshwater fish represents a major component of global vertebrate biodiversity, yet these species are heavily impacted due to human influences on freshwater habitats. Our research contributes to diversity estimation and formulating guidelines for management and exploitation. Some fish species also serve as indicators of healthy freshwater systems.

- **Marine conservation genetics**.
  We aim to identify discrete populations within exploited marine resources (linefish and demersal species e.g. kob and hake) to contribute to their sustainable utilization and to understanding of marine biodiversity patterns and processes in the Benguela and Agulhas currents. We are team members in the African Coelacanth Ecosystem Programme (ACEP) which aims to understand the functioning of the Western Indian Ocean with implications for fisheries and global climate change.

- **The inference of demographic processes from molecular data**.
  We are part of the DST Centre of Excellence (CoE) in Birds as Keys to Biodiversity Conservation at the Percy FitzPatrick Institute (UCT). The CoE aims to contribute to the understanding and maintenance of biodiversity. Our specific focus is on the use of molecular markers in understanding processes that operate in populations and during speciation, e.g. how are fragmented forest bird populations connected via gene flow?; how do disruptive selection and asymmetrical gene flow drive ecological speciation?; how does colonial living in an unpredictable environment impact on local and wider scale gene flow patterns?

Programme 3: EVOLUTION OF INTERACTIONS

Primary Investigator: Prof Jaco Greeff

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Collaborators: In this focus area our group collaborates with Dr Sarah Clift, Onderstepoort, UP; Dr Pam de Waal, Genetics, UP; Prof Bernard Slippers, FABI, UP; Prof Nigel Bennett, Zoology, UP; Dr Muhammad Ahmed, Florida Museum of Natural History, USA; Prof Robin Giblin-Davis, University of Florida – Centre for Tropical Agriculture, USA; Prof. Steve Compton,

Leeds University, UK.; Prof Matthias Jakobsson and Dr Carina Schlebusch, Uppsala University, Sweden.

We are particularly fascinated in the evolution of mating systems and how interactions evolve. Our main study animals are fig trees and their wasps and the Afrikaner population (humans).

We have shown that fig wasp mothers regulate the number of sons they produce very carefully in order to minimize competition between their sons. However, if competition between fig wasp males is too intense they will evolve robust morphologies and fighting behaviour to fight even with their brothers. Going forward, we want to explore the evolution of virulence because it is claimed to be analogous to sex ratios and sibling rivalry in that competition between parasites can result in higher virulence which can be mitigated by relatedness. Currently we are quantifying the population structure and mating behaviour of parasites to get a handle on the relatedness structure of parasitic populations. For these activities we have joined forces with several researchers: Muhammad Ahmed and Bao-Li Qiu looking at *Wolbachia* in whiteflies, Robin Giblin-Davis looking at the nematodes of fig wasps, Sarah Clift and Pam de Waal looking at *Spirocerca lupi*, a nematode of dogs. In the future we hope to progress to studying virulence itself.

Studying these population genetic structures and also the mating systems of parasites forms a natural bridge with my interest in the evolution of mating strategies. We study reproductive strategies using theoretical models to predict optimal behaviour and by quantifying the effects of key parameters illustrated in models. We also describe the mating systems of unknown systems and look at the fitness effects of various strategies. Recently we considered the beneficial role of inbreeding and how it is balanced with inbreeding depression; understanding the evolution, causes and consequences of infertility in humans; and quantifying the determinants of fitness through male and female functions in several fig tree species.

In another project we have been looking at the genetic heritage of the Afrikaner population. Here we are particularly interested in racial admixture during the inception of the population and selection in the subsequent 350 years. These data have also revealed interesting links with reproductive strategies in humans.

Programme 4: EVOLUTIONARY PERSPECTIVES ON HUMAN MATE CHOICE

Primary Investigators: Dr Vinet Coetzee & Prof Jaco Greeff

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Collaborators: Prof Dave Perrett, School of Psychology and Neuroscience, University of St Andrews, UK; Prof Dave Evans, Diamantina Institute, University of Queensland, Australia; Dr Markus Rantala, Department of Biology, University of Turku, Finland; Dr Ian Stephen, School of Psychology, Macquarie University, Australia; Dr Fhionna Moore, School of Psychology, University of Abertay, UK; Prof Richard Russell, Psychology Department, Gettysburg College, US; Dr Bernard Tiddeman, Department of Computer Science, Aberystwyth University, UK; Prof Riette de Kock, Department of Food Science, UP; Dr Helen Steel, Department of Immunology, UP; and Dr Nicoleen Coetzee, Department of Psychology, UP.

Human evolutionary biology is an interdisciplinary field aimed at understanding how evolutionary forces have shaped human design, biology and patterns of behaviour. Our research programme focuses on the genetic and environmental determinants of human behaviour, particularly human mate choice. Facial attractiveness plays a crucial role in human mate choice, in that people prefer to date and marry facially attractive individuals. This preference for more attractive partners is warranted from an evolutionary perspective, given that facial attractiveness is heritable and serves as a cue to health and reproductive success.

This newly established research programme has three main focus areas. First, we aim to identify the genes that underpin attractiveness and the perception of health in the face. The second aim is to identify the environmental, conditional and cultural factors that influence attractiveness preferences between populations. Third, since most previous studies on human behaviour were conducted in Western populations, we aim to expand the current knowledge of human mate choice to include African populations.

Recent developments:
Previous work found that common Human Leukocyte Antigen (HLA) genes are associated with general health measures, but not with female attractiveness. We established facial adiposity or 'facial fat' as a robust facial cue to health and attractiveness and identified quantifiable facial measures to estimate facial adiposity. Moreover, recent work highlighted the role of facial adiposity as a crucial cue to immunocompetence. Collaborative work also indicated the role of skin colour, specifically skin blood perfusion, melanin and carotenoid pigments (yellow and red pigments obtained from fruit and vegetables) in the perception of health and attractiveness of African skin.

Research objectives:
- To identify candidate genes that plays a role in the perception of facial attractiveness.
- To identify environmental, conditional and cultural factors that affect African perceptions of an attractive weight.
- To test the role of known facial cues (identified in Western populations) in African perceptions of male and female attractiveness.

HUMAN AND MEDICAL GENETICS

Programme 1: CANCER GENETICS

Primary Investigator: Prof Lizette J van Rensburg

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One of the most important developments in genetics has been proof that cancer is essentially a genetic disease at cellular level. Today it is a well-known fact that cancer is a multistage process which results from a variety of genetic changes, some inherited, some induced by environmental exposures and some occurring by chance. Much progress has been made in recent years in the identification of genetic lesions that predispose individuals to cancer. It has been estimated that 5 - 10% of persons with common cancers are due to inheritance of a number of highly penetrant mutations and a larger number of low-penetrance variants. The completion of the sequence of the human genome and recent advances in technology now provide a means of identifying the multiple genetic variants involved in pathways that affect individual cancer susceptibility and also the somatic changes that occur in cancerous tumours. This in turn offers the potential of identifying novel and effective cancer-specific markers, and should enable the design of more efficient anticancer drugs and therapy. Molecular genetic studies of cancer in developing countries provide ideal opportunities to study the pathogenesis of cancer because of the differences in lifestyle, environment and diverse patterns of cancer that exist.

Research programme:
- **Breast cancer**

Cancer of the breast is the most common cancer in South African women. Important population differences however exist with regard to lifetime risks for breast cancer, varying from 1 in 12 in white to 1 in 49 in black women. Presently the reason for this four-fold difference in lifetime risk is incompletely understood. One of the most common inherited cancer syndromes is the hereditary breast-ovarian cancer syndrome, which is primarily attributable to two genes, BRCA1 and BRCA2. The protein products of these genes are implicated in DNA repair and recombination, checkpoint control of the cell cycle, and transcription. The estimated cumulative risk of developing breast cancer in a woman with a germ line mutation in BRCA1 or BRCA2 is as high as 84% by age 70. Identification of persons with a BRCA1 or BRCA2 germ line mutation therefore allows for early identification of other at-risk individuals who can be targeted for screening and preventative measures. By continuing to investigate an existing cohort of women with breast cancer (from high-risk families as well as women not selected for age at diagnosis or family history) this study aims to clarify what the role/impact breast cancer susceptibility genes have on the burden of breast cancer in South Africa.

Evidence is mounting that common, low- to moderate-penetrant genes may have a substantial impact through combinations with one another and with environmental factors, holding the key to a large percentage of breast cancers. Variation in these genes may contribute to breast cancer susceptibility in the general South African population. This information may inform targeting of breast cancer susceptible women (due to

mutations in target genes) for preventative treatment and/or early detection of cancer, thereby reducing the incidence and mortality of breast cancer in South Africa.

- **Colorectal carcinoma**

Colorectal cancer (CRC) is one of the most common neoplasms in Western populations but is uncommon in sub-Saharan Africa. The incidence of CRC in black South Africans is approximately ten fold lower than that of white South Africans. The objectives of this study are to investigate various genes that may be involved in the occurrence of CRC with the express purpose of determining the molecular genetic etiology of CRC. Investigation of the molecular events in CRC occurring in black South Africans (low prevalent CRC population) compared to Western populations (high prevalent CRC population) may reveal: (i) different mutations (ii) may show identical events - in lower frequency, or (iii) a different spectrum of cancer genes may be involved. Genes presently being investigated are the mismatch repair genes, hMLH1 and hMSH2, the STK11 and PTEN genes, etc.

- **Other investigations**

Various other tumour suppressor genes are currently being analysed in a number of different tumour types, such as retinoblastoma, endometrial carcinoma and renal cell carcinoma.