

Department of Biochemistry Stellenbosch University

Project portfolio



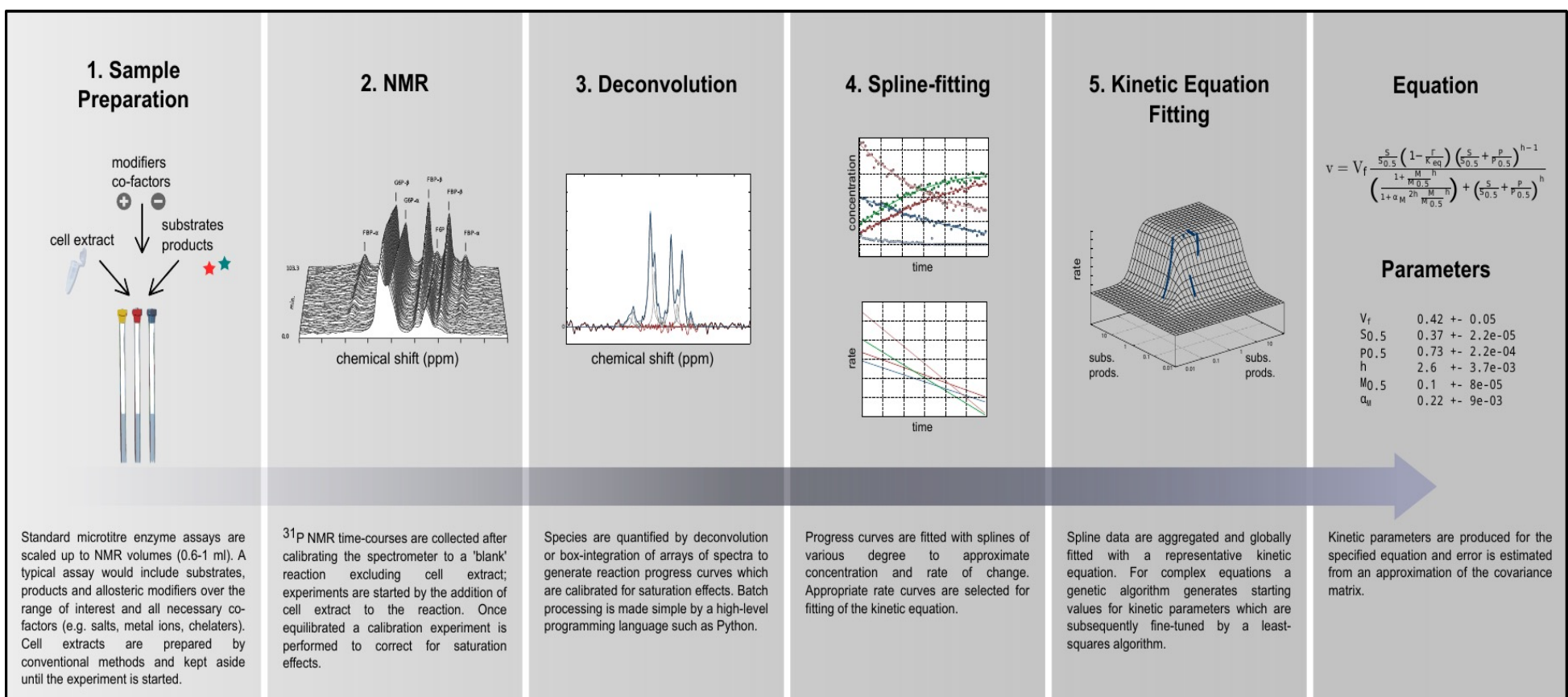
ENZYME KINETICS FOR SYSTEMS BIOLOGY



Project leader
Prof Johann Rohwer
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HIGHLIGHTS

- We construct kinetic models of metabolic pathways
- This requires enzyme kinetic parameters determined under realistic cellular conditions
- We have developed a high throughput method using NMR spectroscopy
- Using this, we can easily investigate effects of e.g. pH or macromolecular crowding



APPLICATION OF RESEARCH

- Kinetic models help us better understand emergent properties of complex cellular systems
- They can assist in drug discovery, biotechnology, crop improvement

MATHEMATICAL MODELLING TOOLS

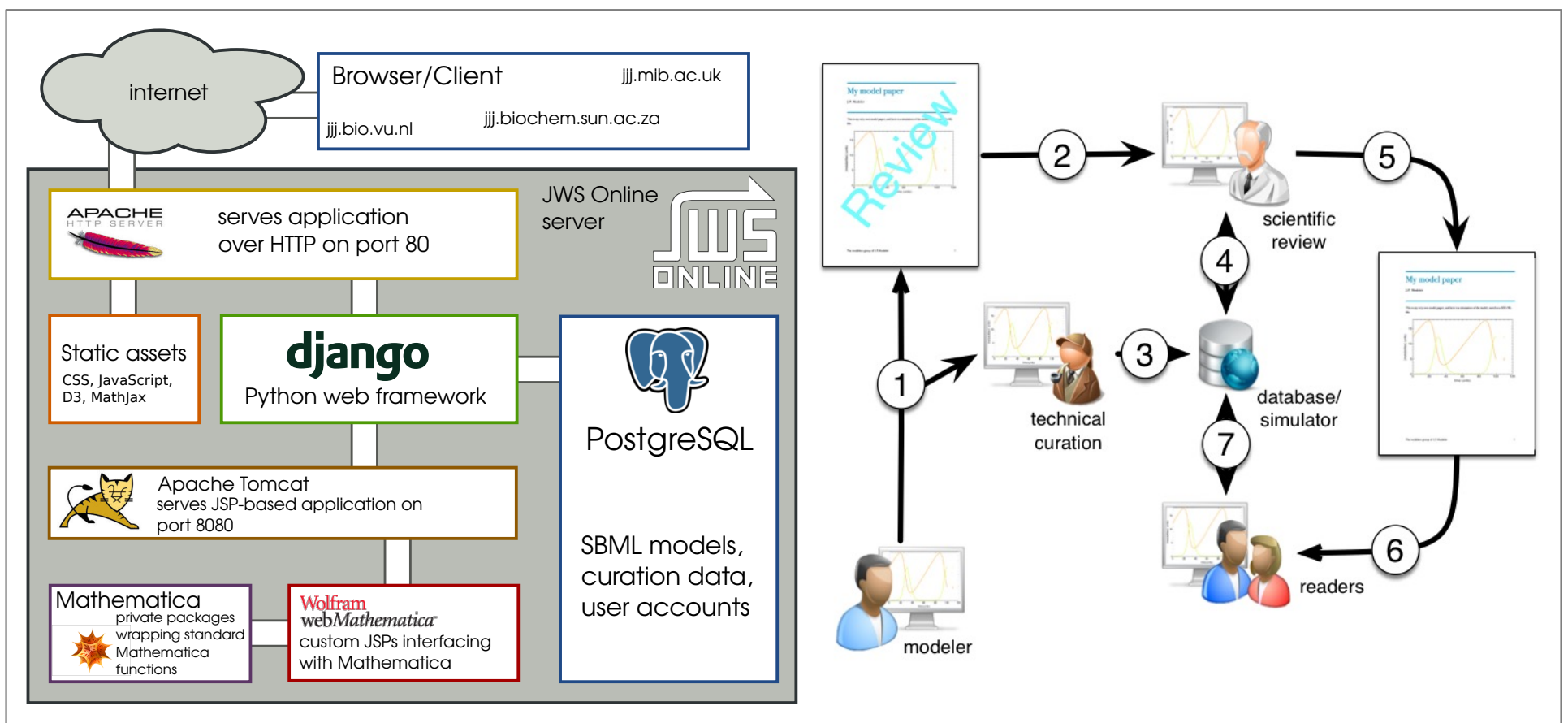
JWS ONLINE

HIGHLIGHTS

Project leaders
Dr Dawie van Niekerk &
Prof Jacky Snoep
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- Curated open-access database of published models of metabolism, signal transduction, disease, pharmacology and epidemiology
- Browser-based simulation and manipulation of models
- International collaboration with journals on published models
- Part of FAIRDOM Association for Findable, Accessible, Interoperable, and Re-usable research (fair-dom.org)



APPLICATION OF RESEARCH

- Model builder and simulation tools for research and teaching
- Simulation database for one-click figure reproduction
- Technical curation of models during peer review process

METABOLIC MODELLING

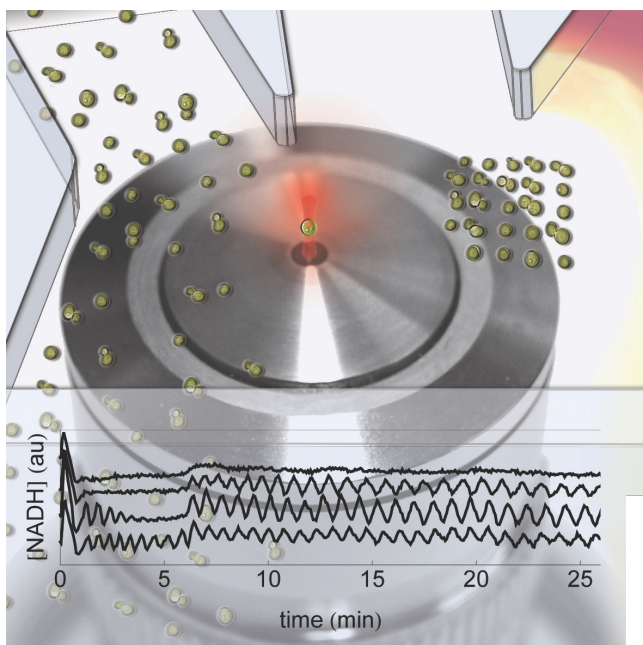
YEAST GLYCOLYTIC OSCILLATIONS



Project leaders
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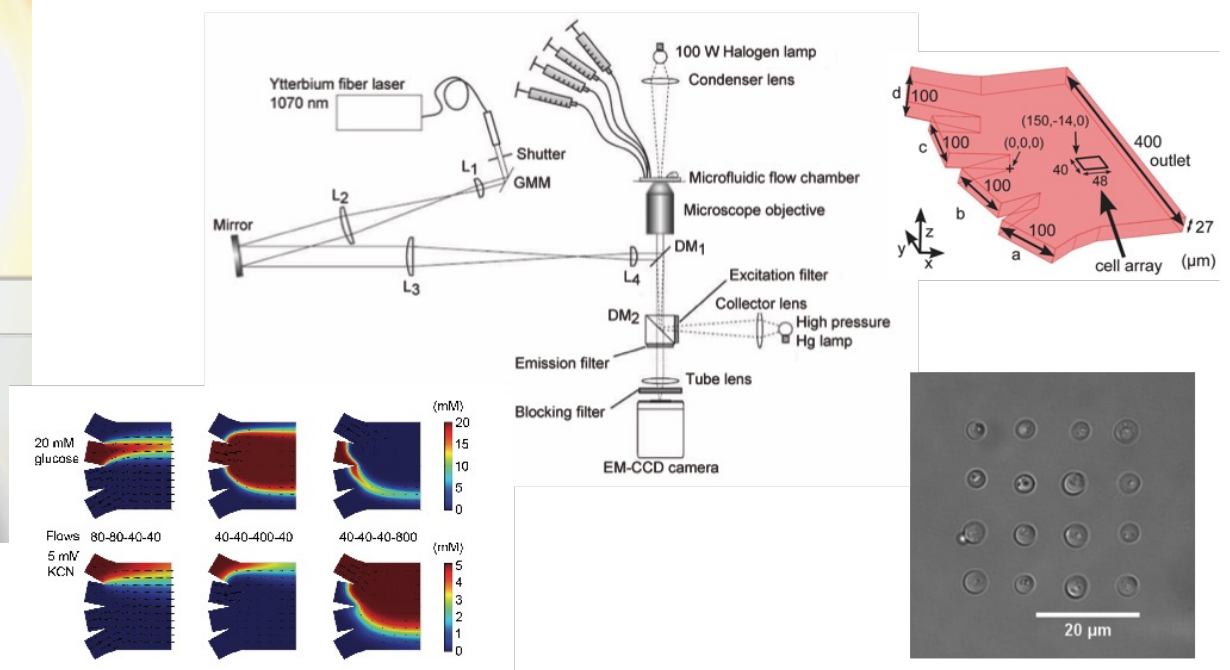
HIGHLIGHTS

- Constructed and validated detailed mathematical models of glycolysis during oscillations
- Predicted and confirmed oscillation-features in single cells
- Gaining a mechanistic understanding of phase shifts and synchronization in populations of cells



Gustavsson, van Niekerk et al. FEBS Journal 279, 2012.

Experimental setup with optical tweezers and microfluidic flow chamber.



APPLICATION OF RESEARCH

- Broadened understanding of oscillation characteristics and communication and synchronization phenomena in biological oscillators

MODELLING CELLULAR NETWORKS

REDOXIN

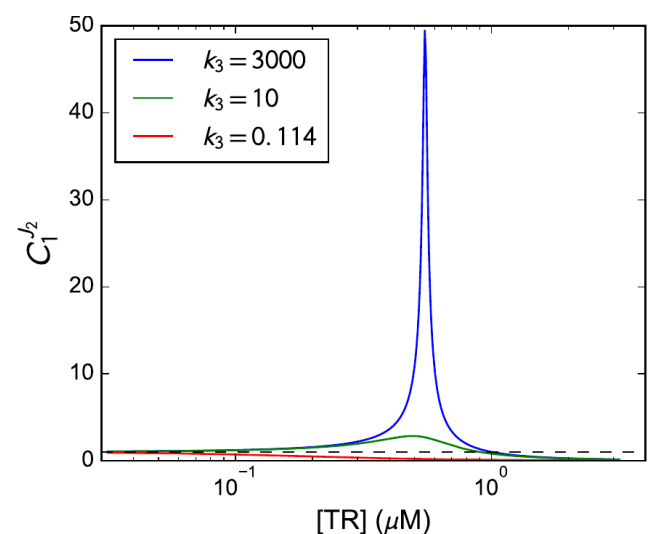
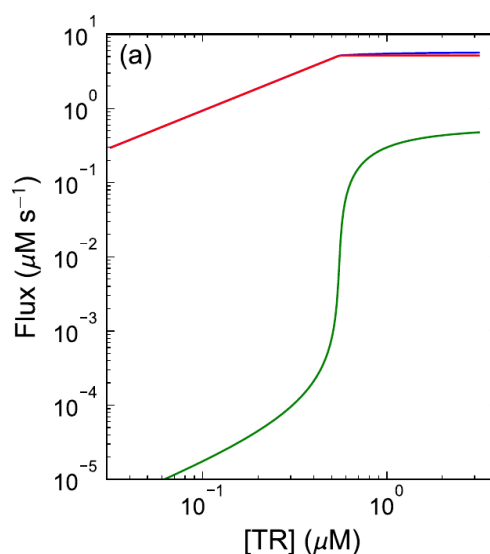
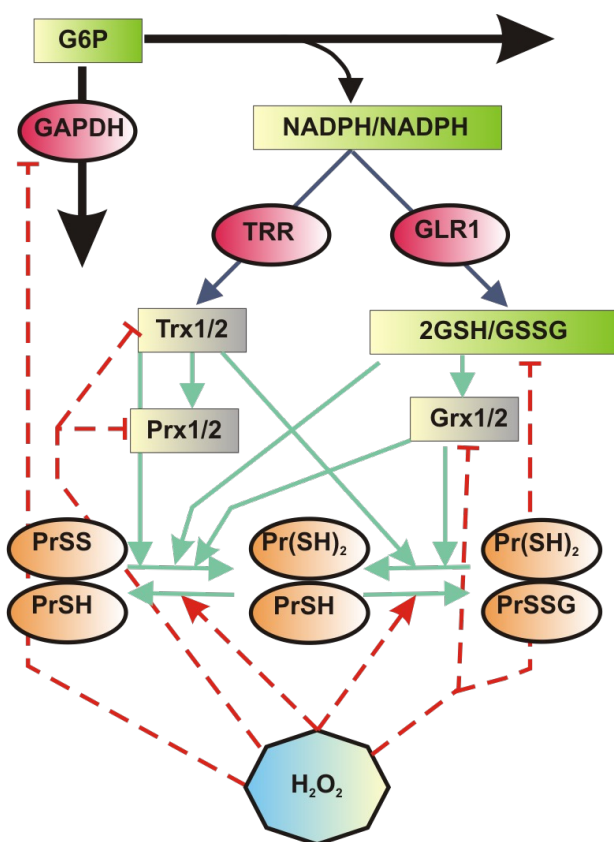


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HIGHLIGHTS

- Studying the importance of redoxin networks in regulation, antioxidant defence and signalling
- Developing quantitative measures for describing these networks in computational models
- Constructing new models, e.g. for *E. coli* and *M. tuberculosis*
- Comparing these networks, e.g. between host and pathogen

Redoxin networks display complex inter-connectivity with multiple interacting loops



They can show ultrasensitive responses, which can be quantified and understood with metabolic control analysis

APPLICATION OF RESEARCH

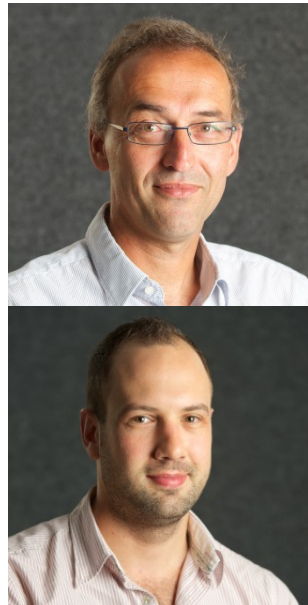
- Redoxin networks contribute to health and disease
- A thorough quantitative description of their regulation may assist the development of intervention strategies for combatting disease

MECHANISTIC MODELLING

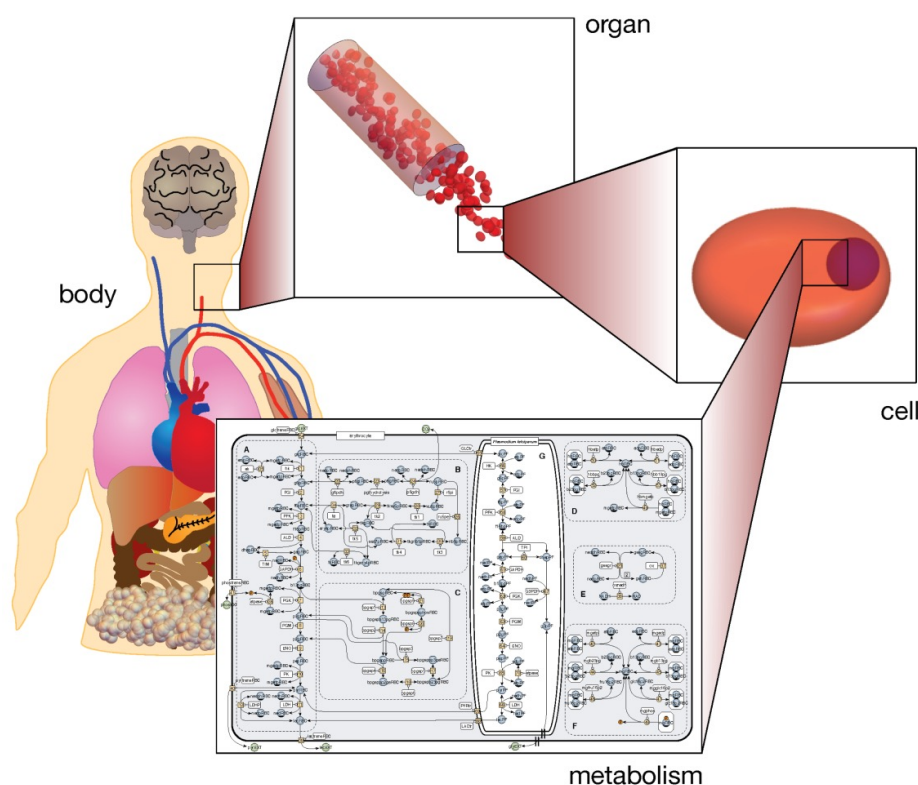
THE BIOCHEMISTRY OF DISEASE

HIGHLIGHTS

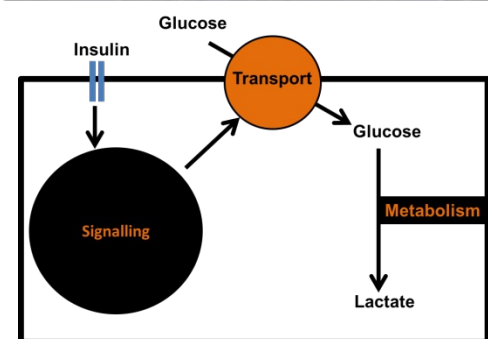
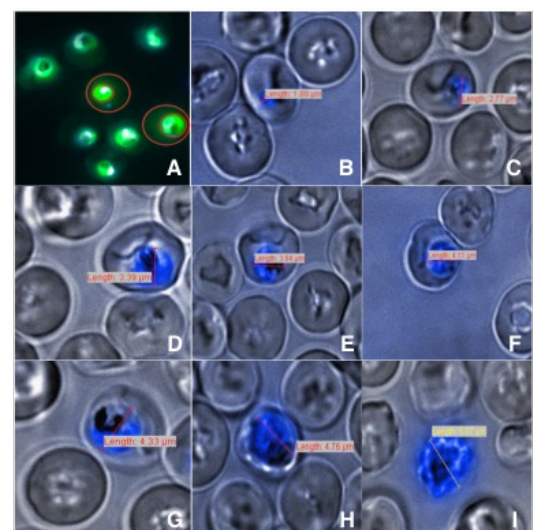
Project leaders
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- Constructed a detailed model of glycolysis in the malaria parasite and glucose homeostasis in the malaria-infected human
- Characterising kinetics of insulin signalling and glucose metabolism in type 2 diabetes
- Elucidating cholesterol metabolism in *Mycobacterium tuberculosis*
- Investigating dynamics in models of HIV disease progression



Snoep et al, Biochem. Soc. Trans. 43, 2015.



APPLICATION OF RESEARCH

- Drug target identification in malaria and TB
- Mechanistic understanding of disease pathophysiology and progression

DISEASE MODELLING

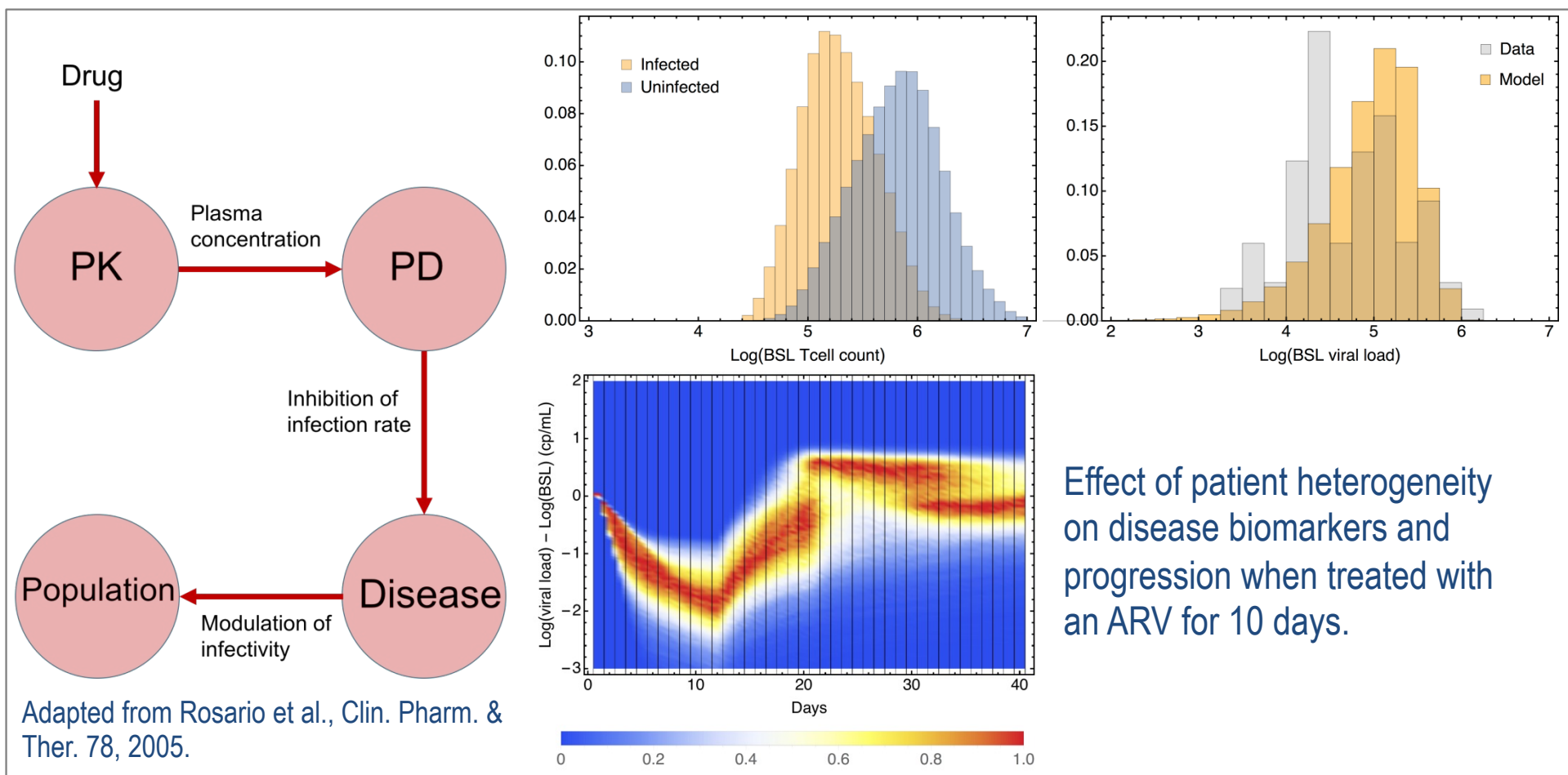
LINKING DISEASE TO PHARMACOLOGY AND EPIDEMIOLOGY

HIGHLIGHTS

Project leaders
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- Linking models of personal health and pharmacology to epidemiology (public health)
- Prediction of disease progression upon drug intervention
- Investigating clinical features and epidemiology as a result of patient heterogeneity and drug regimens



APPLICATION OF RESEARCH

- Mechanistic understanding of drug side effects and efficacy
- Informing strategies for public health

PROGESTINS AND CANCER

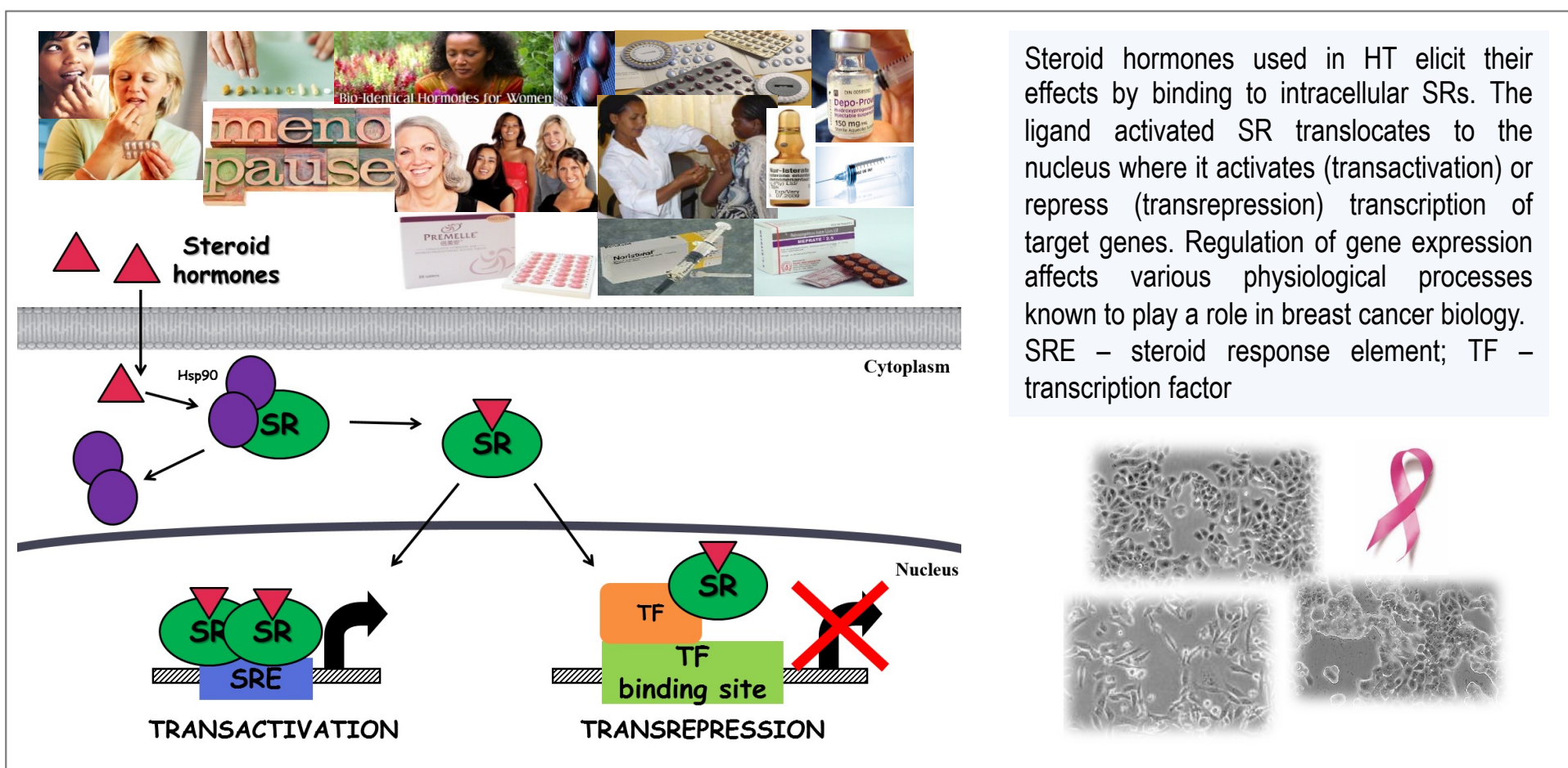
ROLE OF STEROID RECEPTOR CROSSTALK



Project Leader
Dr Donita Africander
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HIGHLIGHTS

- Hormone therapy (HT) is prescribed to relieve symptoms of menopause.
- Estrogens and progestins used in HT have been associated with increased breast cancer risk.
- Interplay between several steroid receptors (SRs), to which these hormones bind, have been implicated in breast cancer pathogenesis.
- We showed that the SR mediated effects of progestins often differ from one another and natural progesterone, suggesting that not all hormones used in HT may increase breast cancer development.



APPLICATION OF RESEARCH

- Aid in the design of new HTs that would alleviate menopausal symptoms without increasing breast cancer risk.
- The outcome of this study may influence the current implementation of health practices in South Africa.

ADRENAL SEX STEROIDS

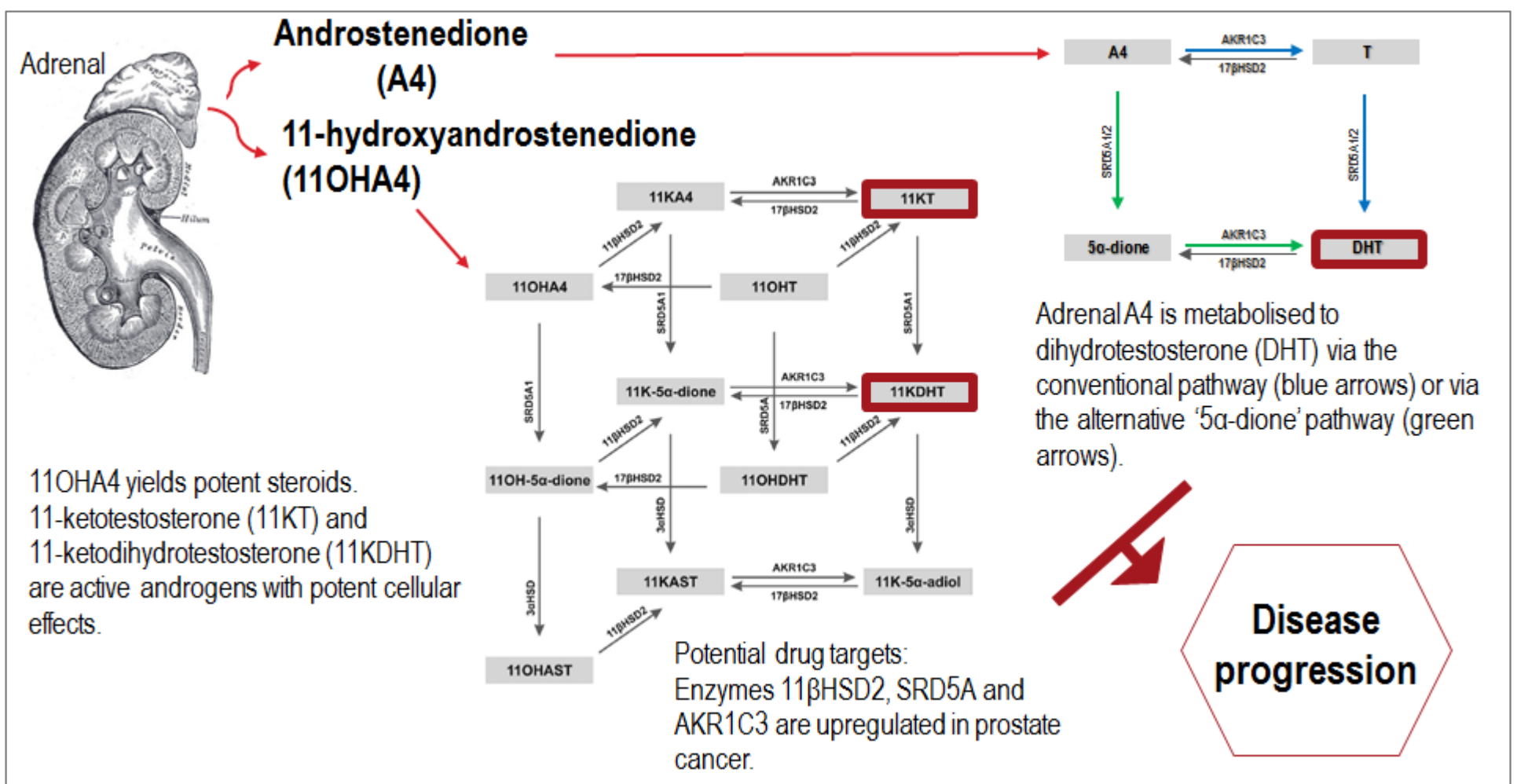
THE IDENTIFICATION IN DISEASE STATES



Project leader
Prof Amanda C Swart
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HIGHLIGHTS

- C11-oxy adrenal steroids drive disease development/progression.
- C11-oxy androgens and progesterones contribute to adrenal hyperplasia, polycystic ovary syndrome, prostate cancer, etc.
- *In vitro* cell models are utilized to investigate integrated steroid production and metabolism.
- UPC²-MS/MS enables comprehensive & accurate steroid evaluation in tissue and blood establishing steroid fingerprint profiles.



APPLICATION OF RESEARCH

- Steroid fingerprinting – identifying steroids as biomarkers in various disease states
- Drug targets – enzymes in metabolic pathways can be identified as drug targets

GLUCOCORTICOIDS AND CYTOKINES

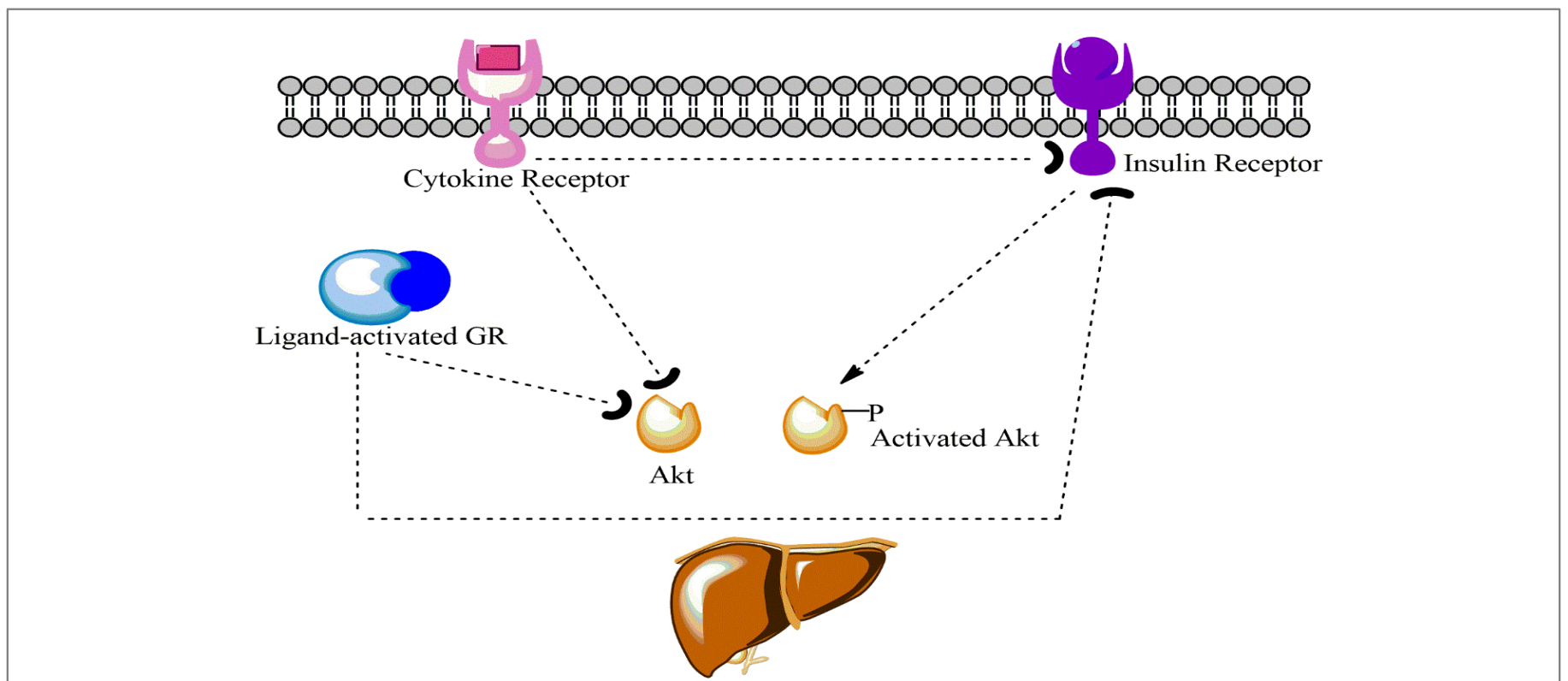
IMPLICATIONS IN INSULIN RESISTANCE

HIGHLIGHTS



Project leader
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- Investigating the role glucocorticoids together with cytokines (inflammation) have on developing insulin resistance
- These classic antagonists (GCs & inflammatory mediators) both negatively affect insulin signalling
- This project identified a possible role PAI-1, a Type 2 diabetes bio-marker and upregulated by both GCs & inflammatory mediators, in insulin signalling



APPLICATION OF RESEARCH

- This project aims to better understand the non-communicable disease Type 2 diabetes as a result of insulin resistance
- This research could contribute to designing better drugs for treating Type 2 diabetes or insulin resistance

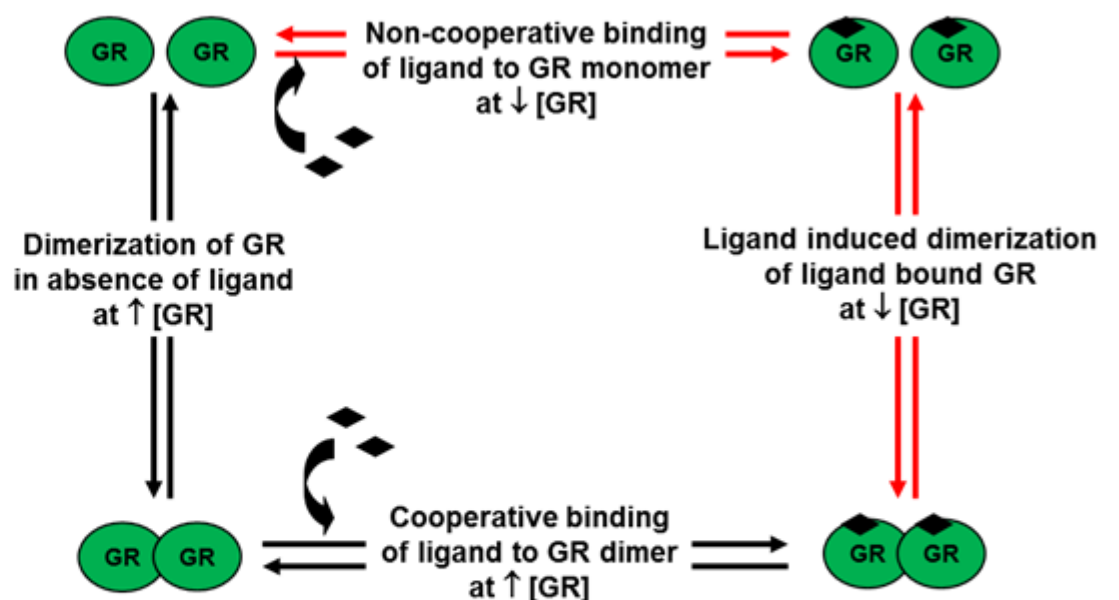
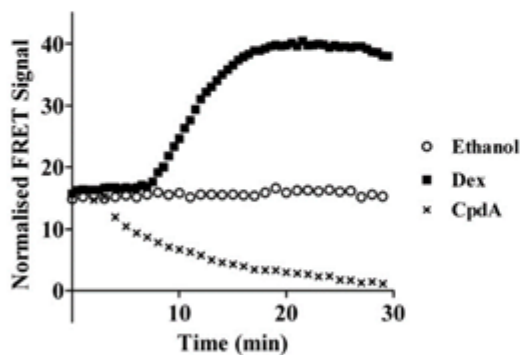
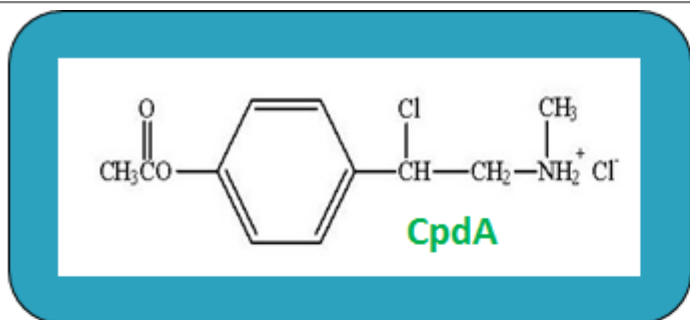
GLUCOCORTICOID RECEPTOR



Project leader
Prof Ann Louw
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THE IMPORTANCE OF BEING DIMERIZED HIGHLIGHTS

- CpdA, unlike other glucocorticoid drugs, abrogates GR dimerization
- Loss of dimerization:
 - Correlates with SEGRM activity which maintains anti-inflammatory activity while reducing side-effects
 - Correlates with loss of autologous down-regulation which maintains glucocorticoid sensitivity



CpdA, unlike dexamethasone, abrogates GR dimerization

APPLICATION OF RESEARCH

- Understanding of the implications GR dimerization could aid the search for anti-inflammatory drugs that
 - display less side-effects
 - have a reduced risk for glucocorticoid resistance

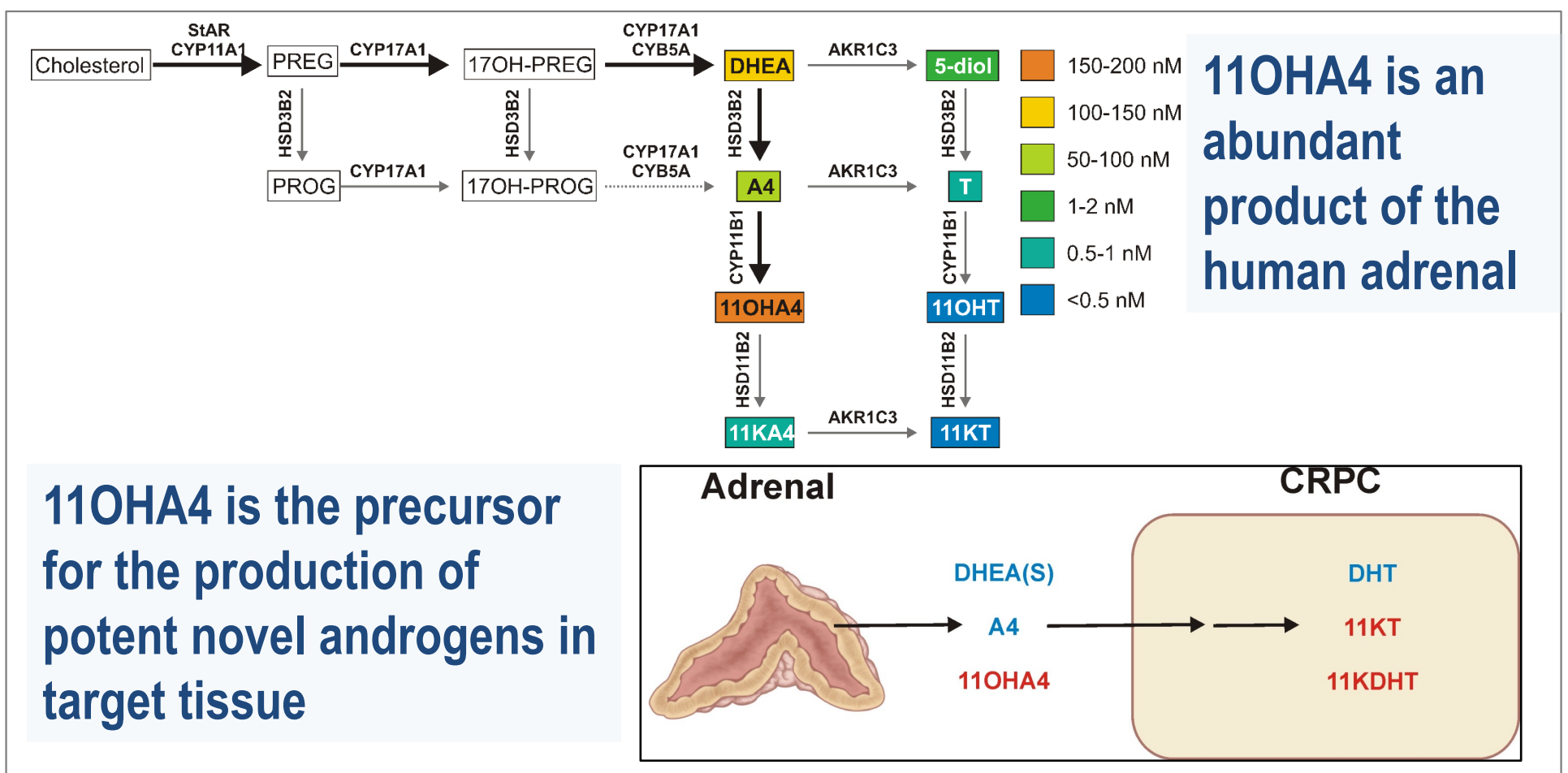
11-OXYGENATED ANDROGENS IN HEALTH AND DISEASE



Project leader
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HIGHLIGHTS

- Adrenal 11 β -hydroxyandrostenedione (11OHA4) was previously written off as a dead end product.
- Recent studies have shown that 11OHA4 is the precursor to novel 11-oxygenated androgens (e.g. 11-ketodihydrotestosterone)
- 11-oxygenated androgens are as potent as classical androgens.

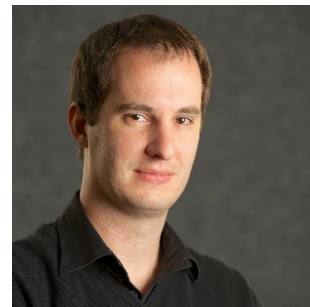


APPLICATION OF RESEARCH

- 11-oxygenated androgens have recently been implicated in disease states including Castration Resistant Prostate Cancer (CRPC), Polycystic Ovary Syndrome (PCOS) and Congenital Adrenal Hyperplasia (CAH).

UPSFC-MS/MS

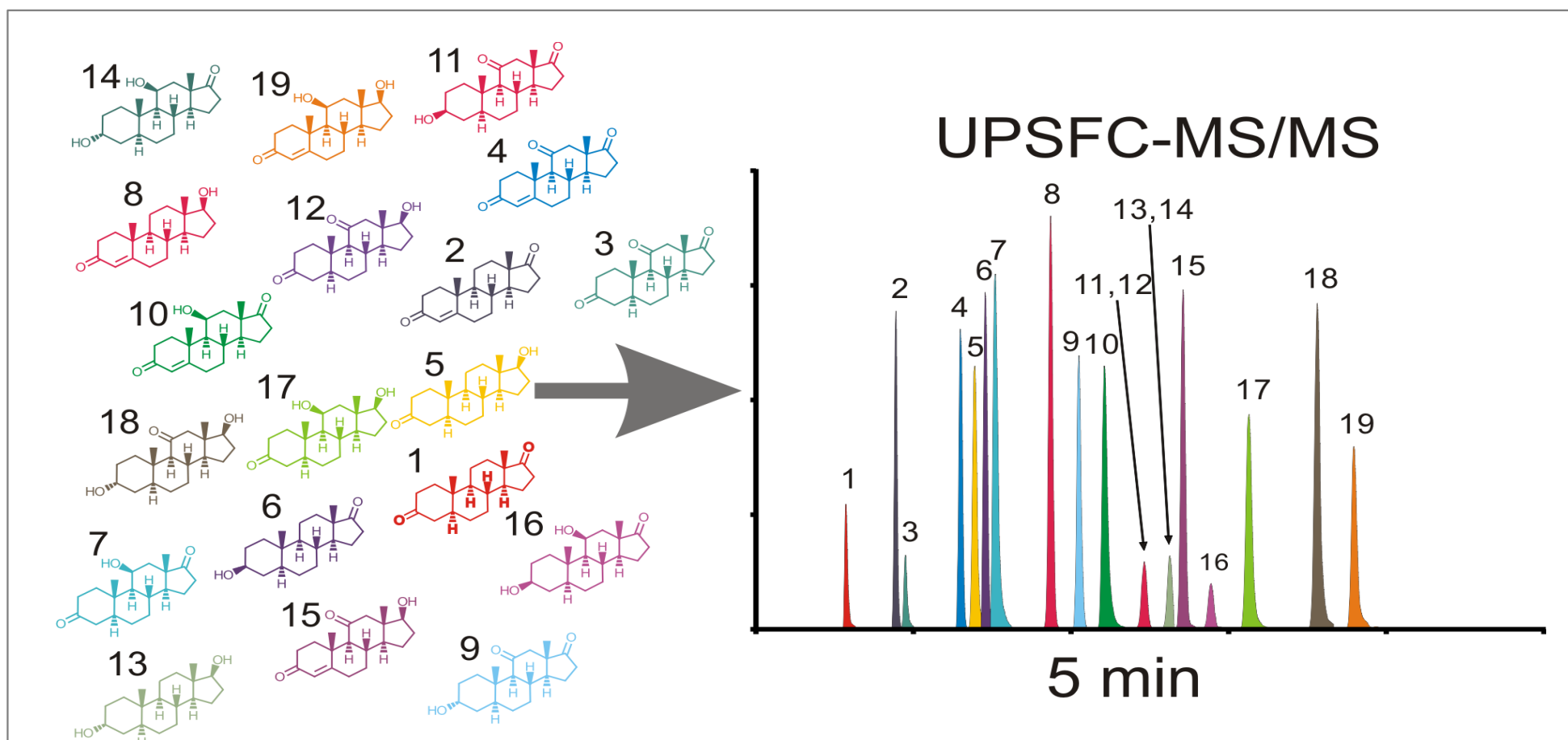
ULTRA-PERFORMANCE SUPERCRITICAL FLUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY OF STEROIDS



Project leader
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HIGHLIGHTS

- UPSFC-MS/MS combines the strengths of both GC-MS and UHPLC-MS/MS.
- UPSFC-MS/MS offers orthogonal selectivity and increased chromatographic efficiency.
- High throughput methods for the separation and quantification of multiple structurally similar steroids have been developed.



APPLICATION OF RESEARCH

- UPSFC-MS/MS has broad application in analysis of pesticides, environmental toxins and pharmaceuticals
- Ideal for the separation and quantification of steroids for
 - application in steroid-dependent disease diagnosis
 - identifying anabolic steroid abuse in sport



ROOIBOS TEA

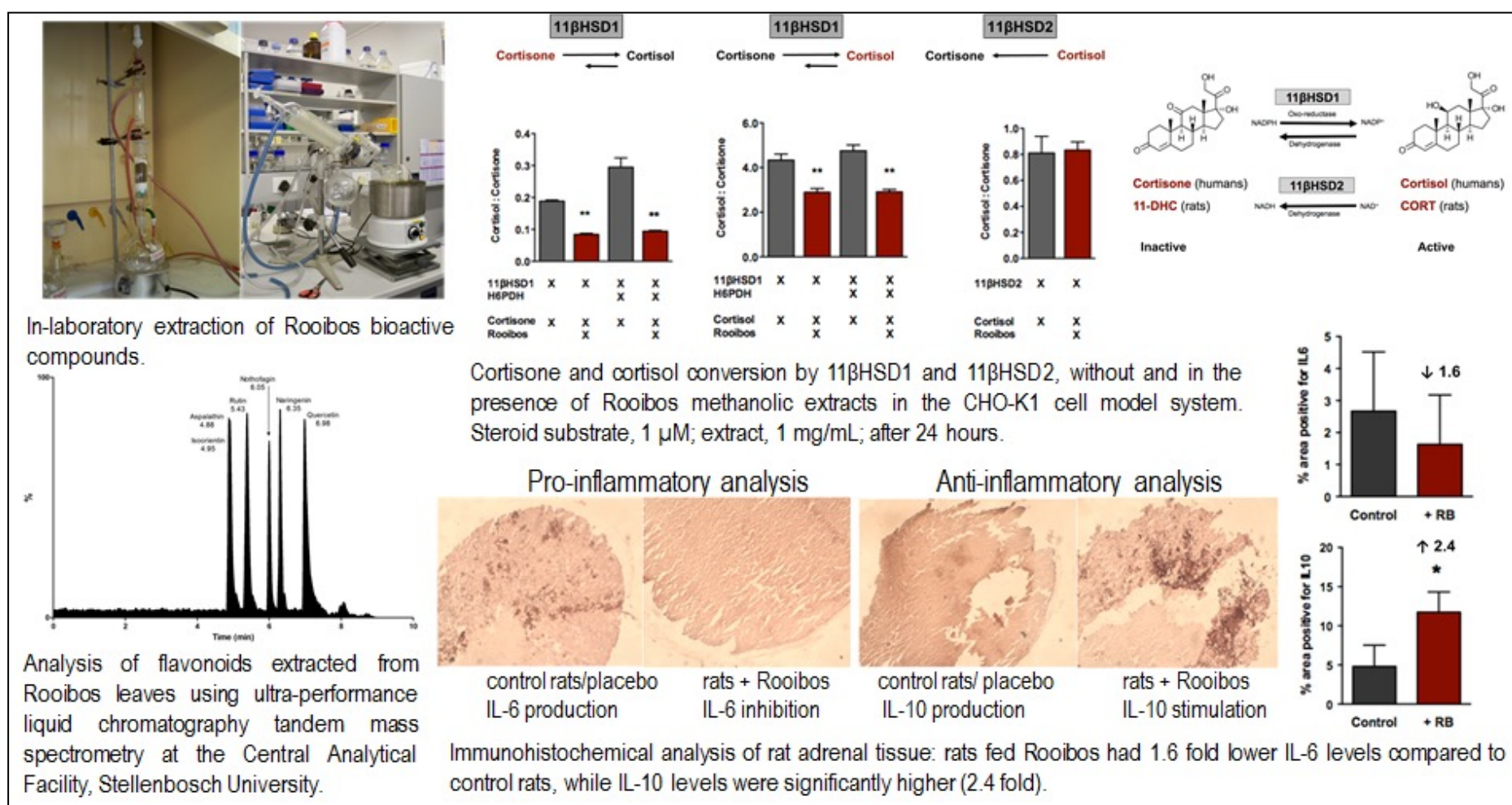
A FUNCTIONAL FOOD



Project leader
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HIGHLIGHTS

- In-laboratory extraction and UPLC-MS/MS analysis of Rooibos polyphenols.
- In cell models: Rooibos modulates steroidogenic enzymes, reducing the stress hormone, cortisol.
- Aqueous Rooibos extracts influences the immune response.
- Rooibos reduces pro-inflammatory cytokines, while increasing anti-inflammatory cytokines.



APPLICATION OF RESEARCH

- Rooibos may act as therapeutic agent for patients suffering from anxiety & the metabolic syndrome.
- Rooibos is a natural food additive with nutraceutical aspects.



HONEYBUSH TEA

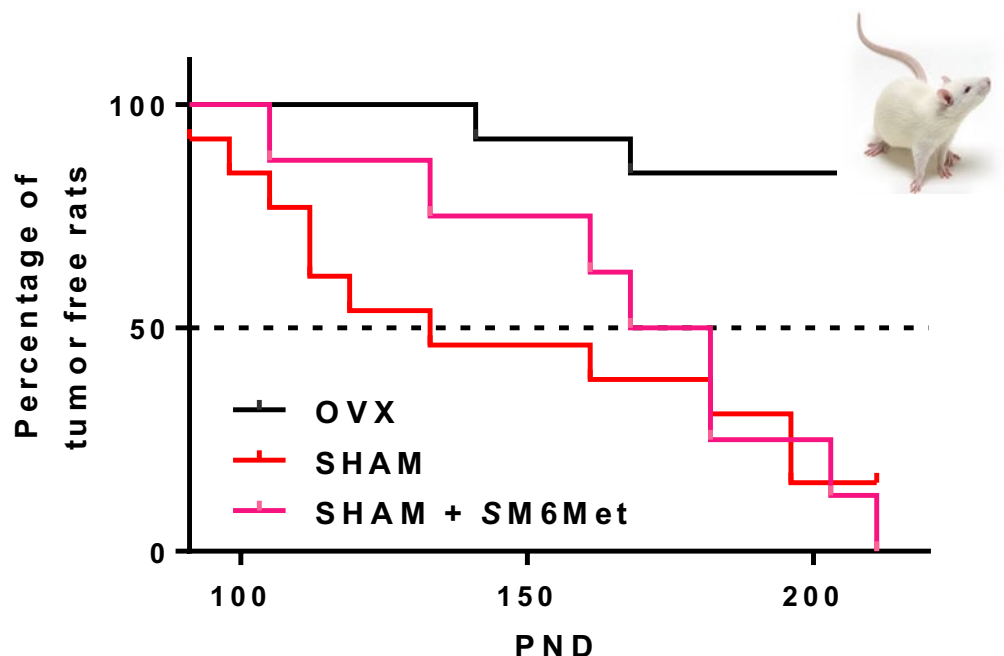
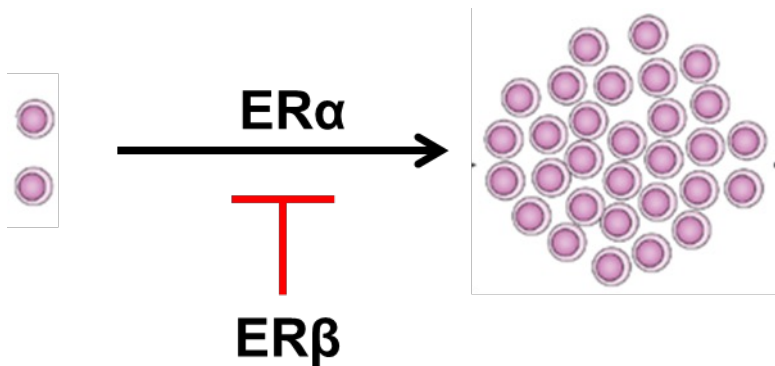
MORE THAN A CUP OF TEA



Project leader
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HIGHLIGHTS

- Honeybush tea (*Cyclopia*) extracts have phytoestrogenic potential
- Benchmarking suggests comparable potency and efficacy to commercial phytoestrogen extracts for menopausal use
- ER subtype specific effects reduces risk profile in rats
- Breast cancer chemo-preventative properties in rats



- Latency extended by **7** days
- Median latency extended by **42** days

APPLICATION OF RESEARCH

- *Cyclopia* extracts have potential as marketable phytoestrogenic nutraceuticals for women's health:
 - Relief of Menopausal symptoms
 - Chemo-prevention of breast cancer

NATURE'S ANTIBIOTICS

BIOMINING IN THE ENVIRONMENTAL PHARMACY



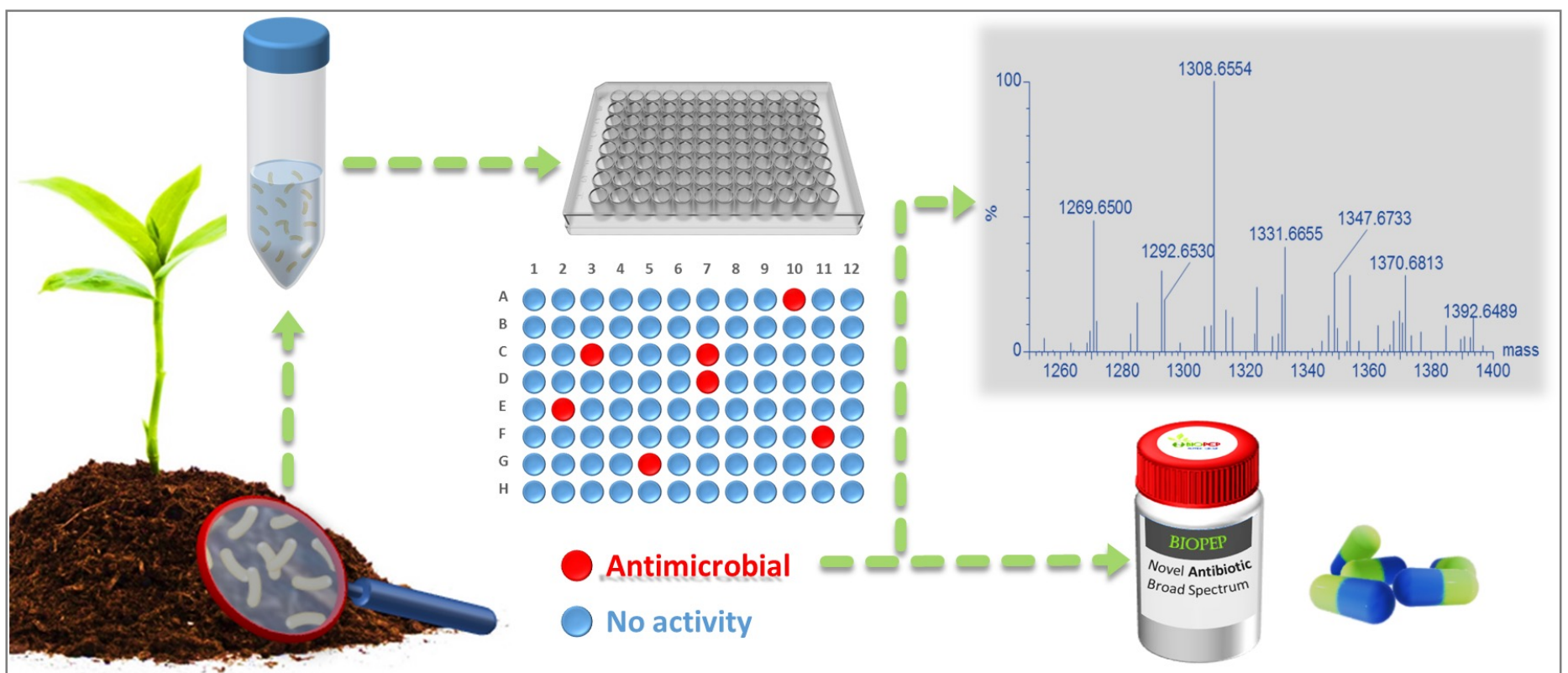
Project leader

Prof Marina Rautenbach

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HIGHLIGHTS

- The environmental microbiome holds a pharmacy of novel antibiotics that can combat the disastrous rise in antibiotic resistance
- High throughput assays combining antimicrobial activity and advanced mass spectrometry are used to identify bacterial producers and their products with anti-biofilm, -fungal and -bacterial activity
- Optimised microbial production and isolation procedures are used to obtain enough of the antibiotic compound for characterisation and development.



APPLICATION OF RESEARCH

- New antimicrobial compounds can be developed into:
 - anti-fungal/anti-bacterial creams and dressings
 - antibiotics and last resort drugs for systemic infections
 - preservatives and biocides for industrial use

TYROCIDINES

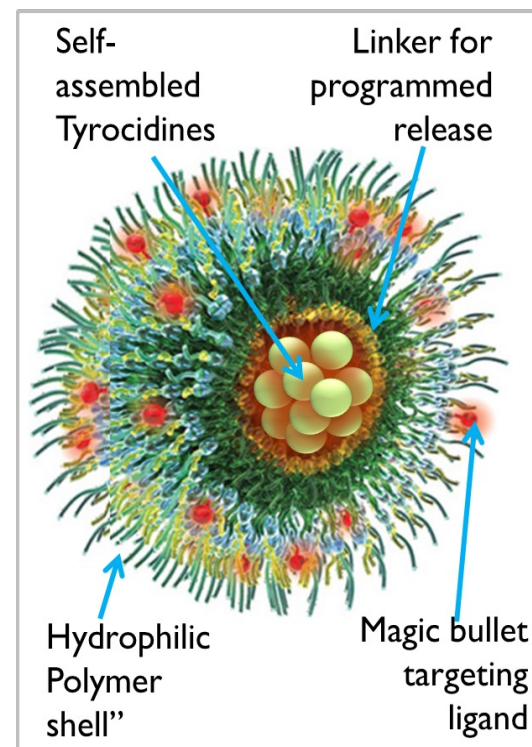
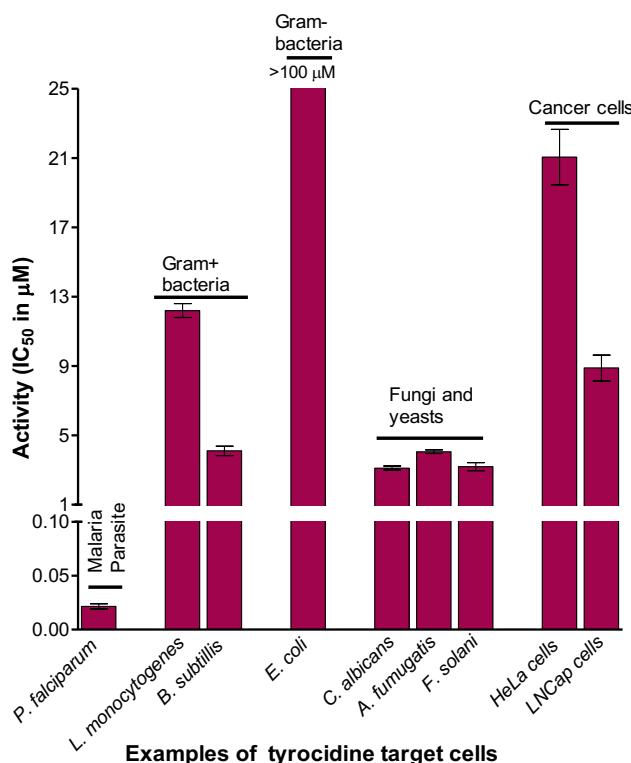
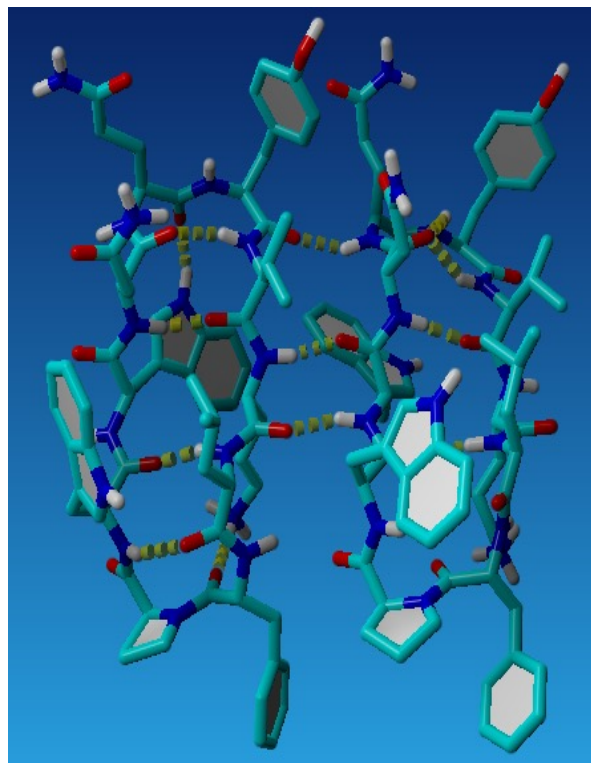
POTENTIAL ANTIBIOTICS AND DRUGS



Project leader
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HIGHLIGHTS

- Cyclic non-ribosomal antimicrobial peptides are regarded as a new antibiotic class with a very low potential for resistance
- The cyclic tyrocidines (Trcs) from *Brevibacillus parabrevis* have a broad spectrum of anti-bacterial, -fungal, -malarial and -cancer activity
- Selective activity against fungi is significantly improved in dextran formulations of Trcs
- Designer nanoparticles and micelles with Trcs have high selective activity against malaria parasites and certain cancers



APPLICATION OF RESEARCH

- The Trcs can be developed into health products:
 - anti-fungal/anti-bacterial creams and dressings
 - selective chemotherapeutic drug against cancers
 - selective last resort drug against malaria

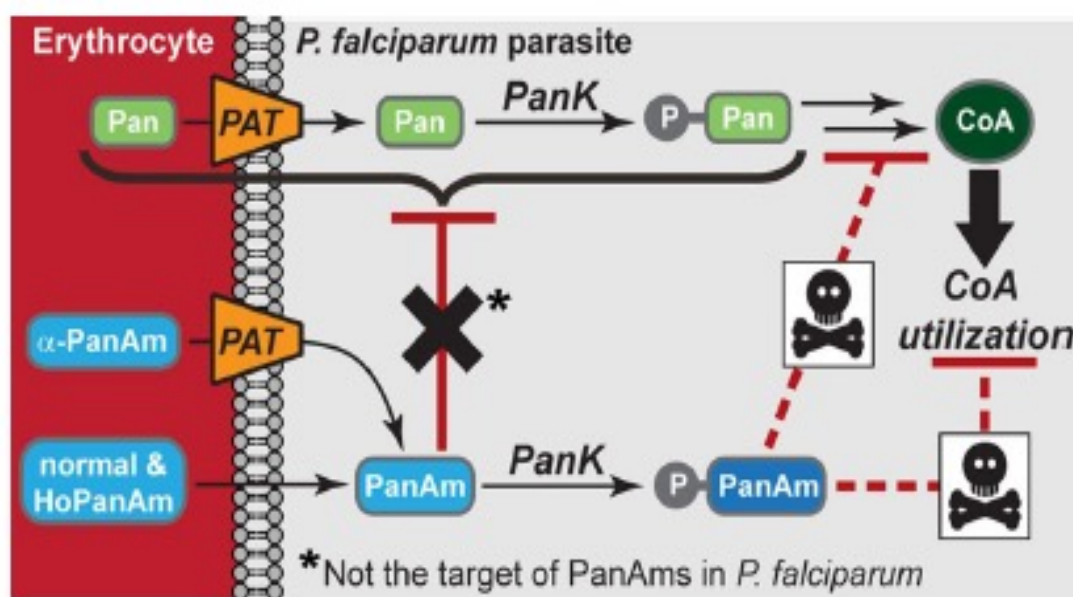
PANTOTHENATE ANALOGUES AS NOVEL ANTIMALARIALS



Project leader
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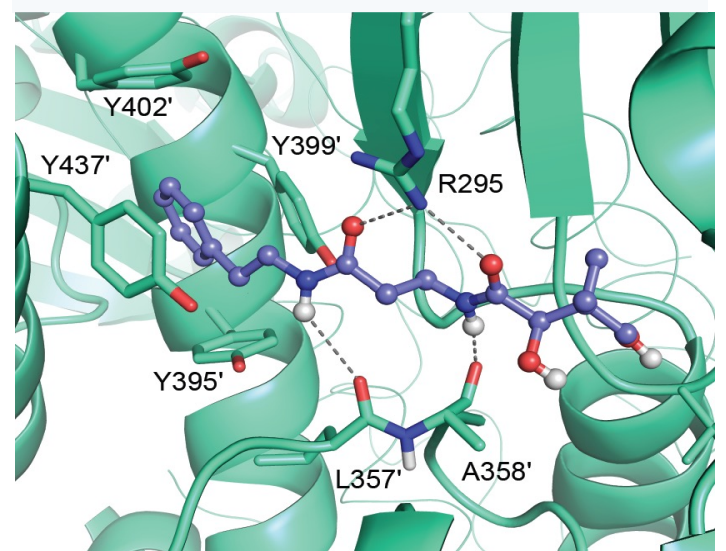
HIGHLIGHTS

- Pantothenamides (PanAms) have potent antiplasmodial activity *in vivo* with similar activity as the known antimalarial chloroquine
- PanAms target CoA metabolism overall; the specific point of inhibition is still unknown
- Mode of action studies are currently conducted in malaria causing parasites like *Plasmodium falciparum*



PanAms enter the parasite from the red blood cells either through the PAT transporter or by possible diffusion. Here they compete with pantothenate (the native substrate) for PfPanK phosphorylation and exert their effect downstream in CoA metabolism.

Model of PfPanK with N-PE-PanAm bound showing the hydrogen interactions similar to the native substrate between the ligand and residues in the active site.



APPLICATION OF RESEARCH

- PanAms are being investigated as possible new antimalarials by MMV as part of a MMV-supported projects
- These scaffolds from these compounds might be useful as agents against other diseases

ANTIMICROBIAL DRUGS

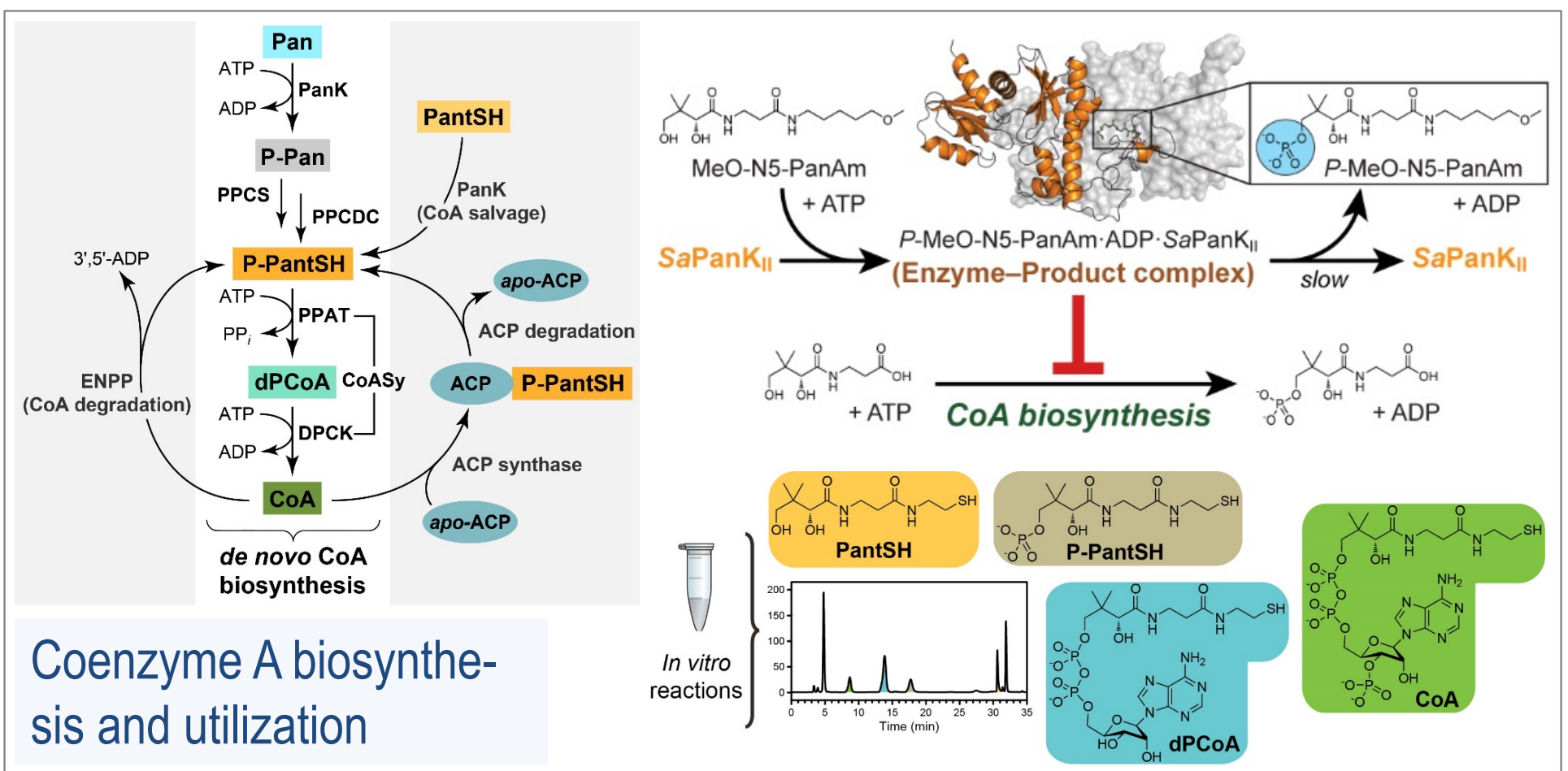
TARGETING COA BIOSYNTHESIS



Project leader
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HIGHLIGHTS

- Developing new antistaphylococcal agents
- Discovery of new compounds that can be used as tools for the elucidation of key biological processes
- Developing new analytical tools to study CoA-dependent biology
- Discovering new ways to improve cell-permeability



APPLICATION OF RESEARCH

- New antimicrobials for treatment of hospital-acquired infections caused by *Staphylococcus aureus*
- Furthering our understanding of the role of important cofactors in bacterial physiology

BACK TO NATURE

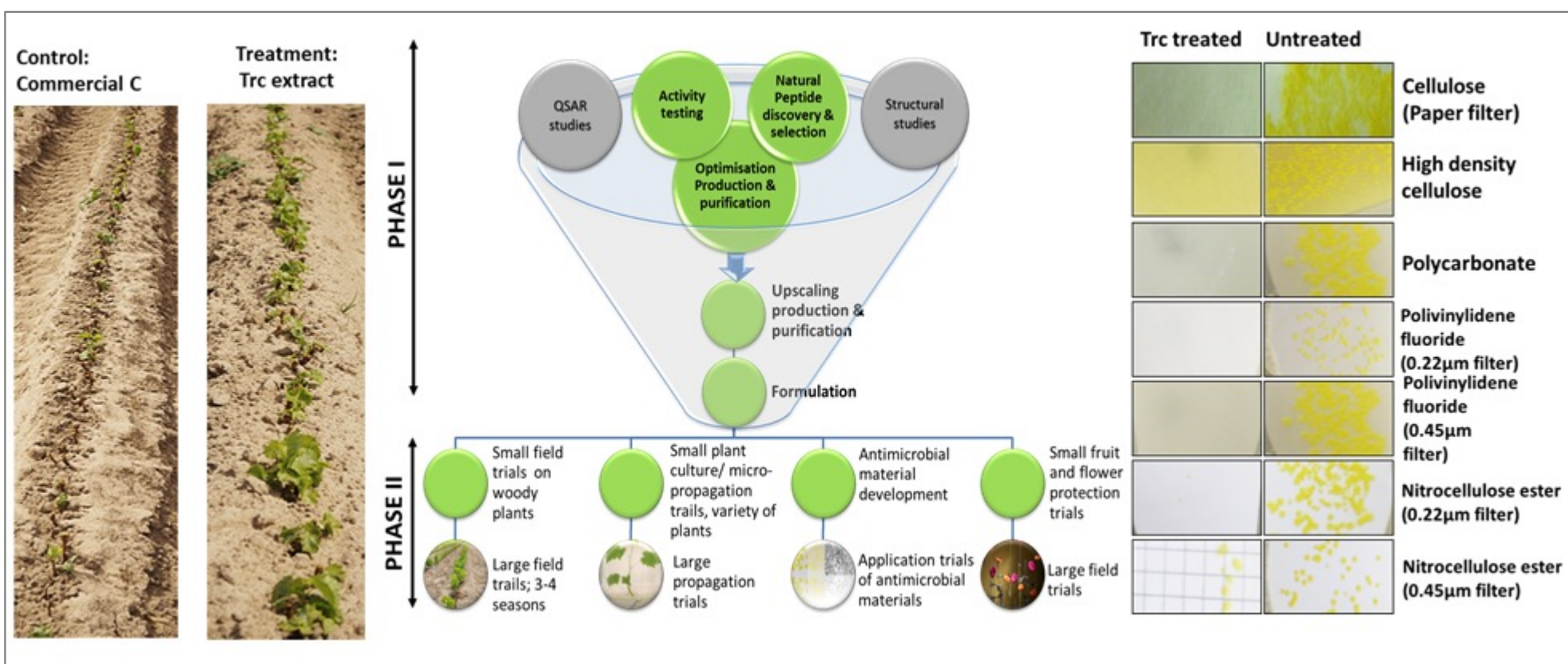
ANTIMICROBIAL PEPTIDES FROM SOIL BACTERIA



Project leader
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HIGHLIGHTS

- Non-ribosomal antimicrobial peptides (AMPs) from soil bacteria can be readily identified, produced and isolated at low cost
- The cyclic tyrocidines (Trcs) from *Brevibacillus parabrevis* have a broad spectrum of antibacterial and antifungal activity
- Trcs protect and stimulate growth of micro-propagated plants from grafts, cuttings and seeds (Patent registered: WO/2013/150394)
- Trcs have potent sterilisation activity in/on paper and a variety of polymers (Patent: PCT/IB2015/054166, WO registration pending)



APPLICATION OF RESEARCH

- Biodegradable cyclic AMPs can be utilised as
 - as green biocides in agriculture
 - as preservatives in food, beverages, cosmetics etc.
 - for producing sterilising biodegradable packaging and filters

OSTRICH PATHOGENS

DETECTION & CONTROL



Project leader
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HIGHLIGHTS

- Focus on disease causing organisms that impact production
- Determine the development of gut microbiome in chicks
- Development of tools for pathogen detection
- DNA-vaccines development and evaluation in field trials



Intensive farming conditions



Samples are taken from GIT sections

Gastrointestinal tract infections

- Cause of deaths amongst intensively farmed chicks receiving high-concentrate feed
- Treated using antibiotics
- Determine change in GIT microbiome using next generation sequencing

Mycoplasma

- Bacterial infections
- 3 ostrich-specific species identified
- Causes reduced production and downgrading of carcasses
- Treated using antibiotics
- DNA vaccine development to control infections - requires genomic information

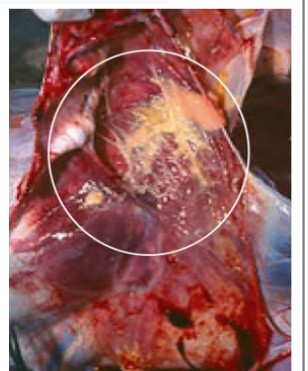
Mycoplasma associated with respiratory symptoms



Foam in eye followed by infection



Swollen sinuses



Yellow lesions on carcass

Tool development

- ELISA
- Secondary anti-ostrich antibodies
- Recombinant production of proteins
- PCR assays

APPLICATION OF RESEARCH

- Establish dietary intervention and husbandry practices to control and prevent infections
- Optimal disease management, reduced antibiotic use and subsequent improved food safety

RNA VIRUS DETECTION

POTATO PATHOGENS



Project leader
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HIGHLIGHTS

- Methods were developed for detection of *Ralstonia solanacearum*, Potato Virus Y (PVY) and Potato Leaf Roll Virus (PLRV)
- Unique variants of PVY and PLRV documented in South Africa
- Book chapters published in world authoritative books



Symptoms of Potato Leaf Roll Virus infection

Dramatic yield reduction due to infection



Determine RNA sequences of whole viruses



Identify conserved regions to develop specific primers



Develop realtime PCR methods for detection

APPLICATION OF RESEARCH

- ELISA method for *Ralstonia* detection used for testing of all South Africa seed potatoes since 1991
- More pathogenic PVY and PLRV variants identified, PCR detection methods developed for use in Sandveld Region, South Africa

PLANT MOLECULAR SYSTEMATICS

GENUS ERICA

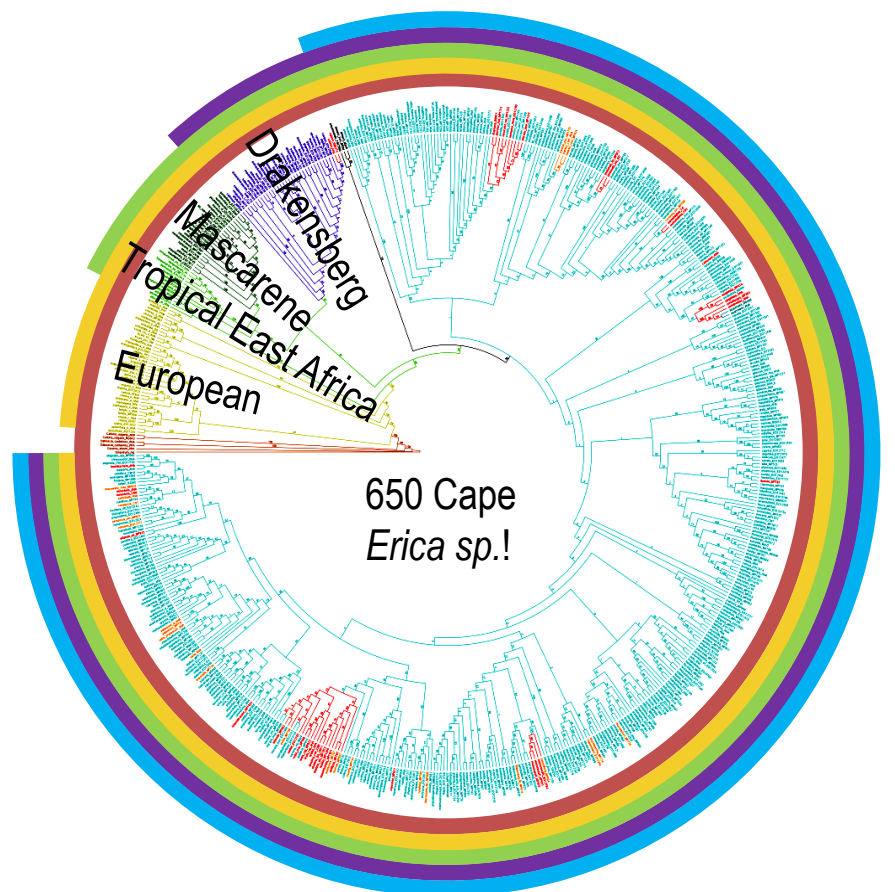


Project leader
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HIGHLIGHTS

- Major advances in DNA sequencing technology has enabled us to determine phylogenetic relationships using bioinformatic methods
- This has enabled us to make major advances in plant classification and Biogeography in Cape plant groups

Most recent project: Largest
Cape plant genus *Erica*



APPLICATION OF RESEARCH

- Documents South African plant diversity in detail, when it diversified, how many species, where did it come from and when, important for conservation

