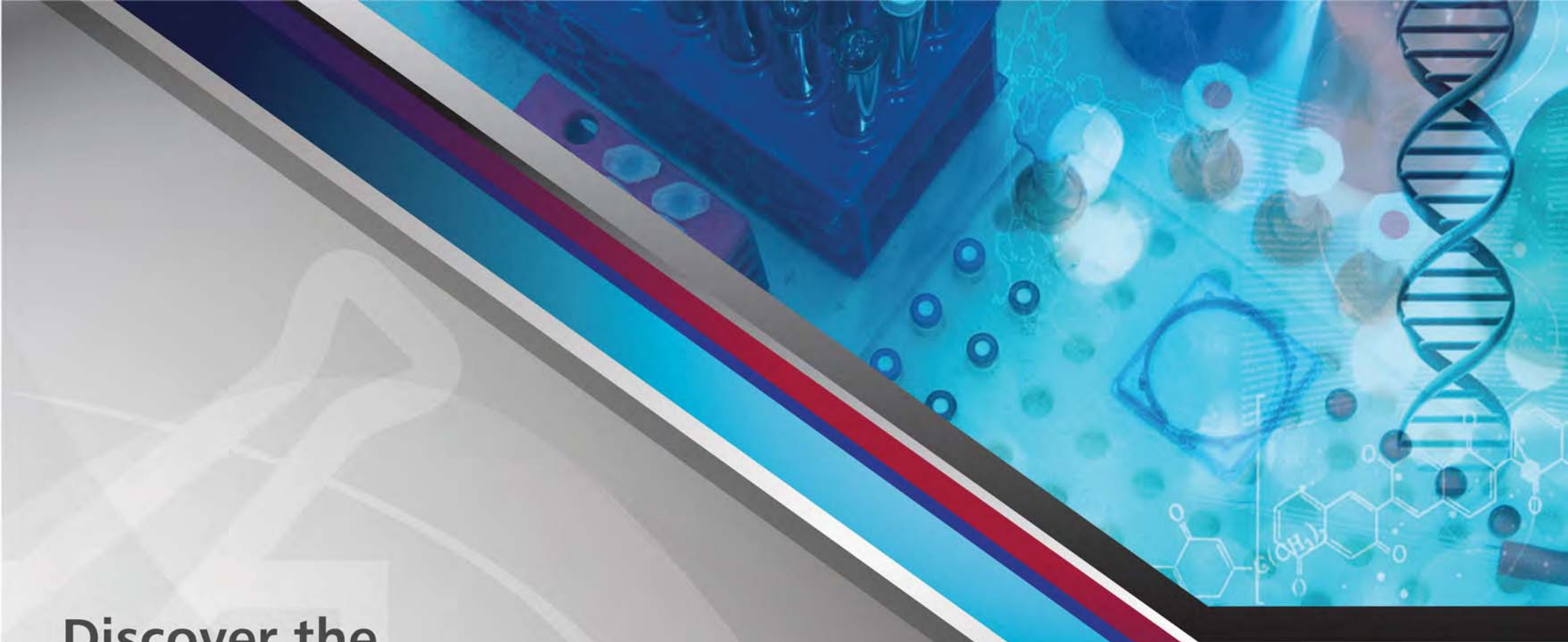


Discover the Centre of Excellence for Pharmaceutical Sciences

We set the trend for cutting edge Pharmaceutical Research and Innovation

PhaRxmaCen

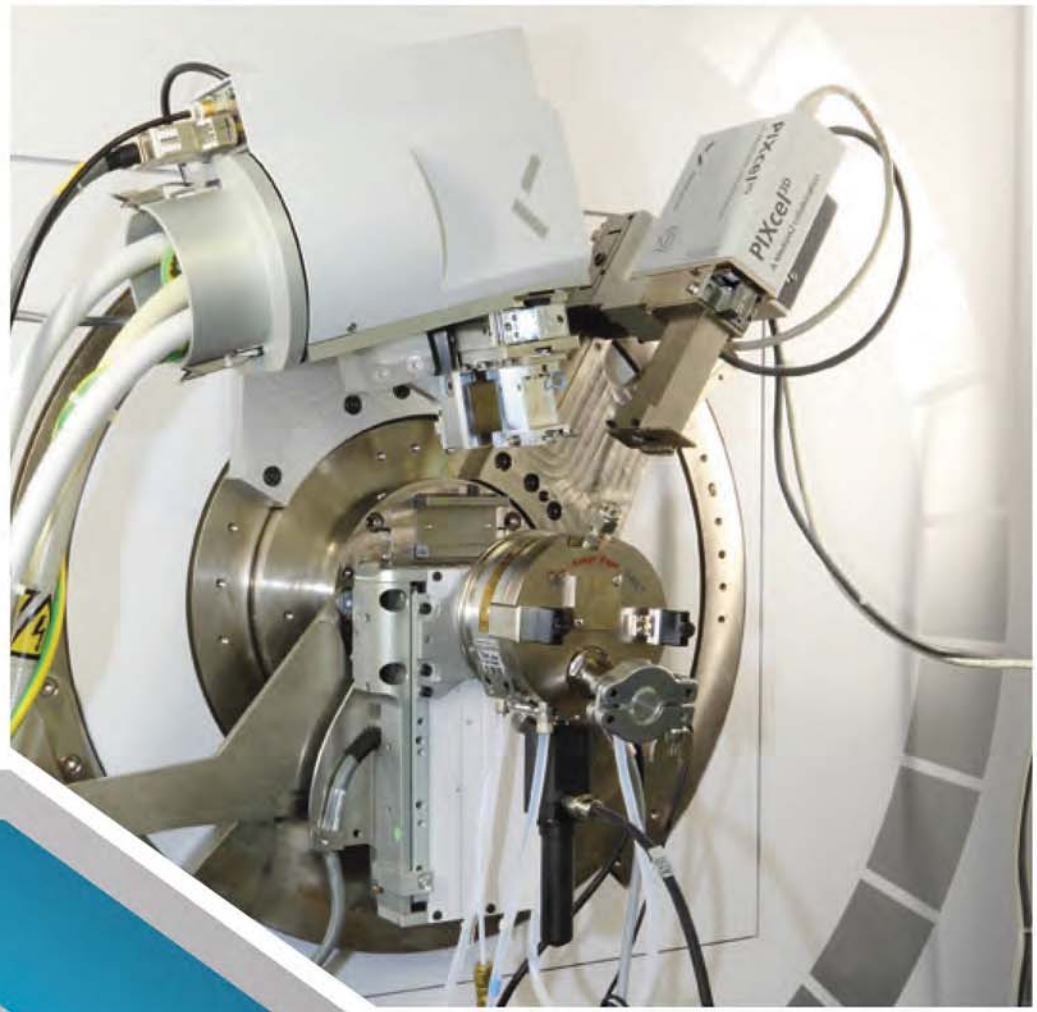
NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOM CAMPUS

It all starts here™

Pharmacen is the way to excellence

Setting the trend

Pharmacen is thé cutting edge Pharmaceutical Research and Innovation Centre in South Africa that delivers post graduate students (MSc and PhD) and post-doctoral fellows. Our mission is to continuously strive for excellence in research and to accumulate new scientific knowledge. The Centre has world-class research facilities and technologies that focus on optimal drug delivery, translational neuro-science and therapeutics.



Pharmacen is ....

A research entity with a clear focus. Our programs are linked to national priorities and have international research impact. Pharmacen currently consists of two programs, i.e. Translational neuroscience and neurotherapeutics, and Drug delivery. The main activities of Pharmacen lie within the following research and functional groups: The Medical Research Council (MRC) Flagship programme: MAL-TB REDOX, Animal models of anxiety/stress disorders (MRC unit), Novel drug design in neuroprotection, Indigenous knowledge: Phyto-chemistry and ethno-pharmacology, Biopharmaceutics and drug delivery systems, Solid-state pharmaceutical innovation and nanotechnology, Cosmeceutical research, Analytical technology laboratory, and the Laboratory of Applied Molecular Biology.

Our core business is to ...

- further develop and refine current knowledge and technologies; and
- accumulate new scientific knowledge to develop novel products and technologies.

We move aggressively and strategically to enhance existing research programmes through anticipating and addressing future needs, by developing new initiatives, as determined by community based research priorities. These include:

- Researcher and research student support operations that are caring, personal and service oriented;
- Increased external support in the form of scholarships, grants and research initiatives;
- Establish national and international academic reputation by developing distinctive research programmes and new initiatives;
- Promote, strengthen and support research as a pathway to learning, discovery, problem solving and contributing towards projects that would benefit the community; and to
- Provide world class, modern and enhanced facilities and technologies that support this research Centre's mission.

The outcomes of our research include:

- Development of human resources through capacity building;
- World-class physical infrastructure;
- Research productivity and impact;
- Researchers of stature; and
- Global community service.

Vision & Mission

Our Vision

Pharmacen will be an internationally recognised role player and the leader in drug research and development in Africa.

Our Mission

Excellence in research with the accumulation of new scientific knowledge, and to apply our research findings in the development of novel pharmaceutical products and technologies which will enable capacity building by delivering skilled post-graduates with high levels of training and experience.

Translational Neuroscience and Neurotherapeutics

The program *Translational Neuroscience and Neurotherapeutics*, seeks to build a bridge between our existing animal models and clinical application. The first priority of the programme is the development and application of validated pathological animal models of anxiety and stress-related disorders, as well as neurodegenerative disorders, for use in explorative studies into the neurobiology and treatment of these illnesses. Research within this programme comprises two primary research groups, namely (1) Animal models of anxiety/stress disorders (Medical Research Council (MRC) unit), and (2) novel drug design in neuroprotection.

The one group aims at developing in vivo animal models of anxiety and stress related disorders. This group's primary goal is to develop analogous animal models of a given human illness, in order to study the complex neurobiology of the human disorder and to identify novel targets for treatment. The other group uses the discipline of synthetic medicinal chemistry to develop novel chemical entities with possibly new pharmacological properties. This group uses computational approaches to design novel compounds, which may be of value to neurodegenerative diseases, specifically Parkinson's - and Alzheimer's diseases. This group is also involved in the chemistry and synthesis of novel antimalarial drugs, especially studying antimalarial efficacy vs. neurological profile.

The research in this programme therefore includes mainly Pharmacology and Pharmaceutical Chemistry an they are united towards a common goal, i.e. to focus on understanding the underlying neurobiology of various neuropsychiatric diseases. These endeavours culminate in selected and/or novel target identification, leading to rational drug design.

Subprogrammes

Drug Delivery

Research within Drug Delivery programme focuses on different aspects of dosage form design and the effective delivery of active pharmaceutical ingredients via different routes of drug administration, in order to optimise therapeutic outcome. These research activities cover a wide range of topics within the field of drug delivery that include evaluation of the physico-chemical properties of solid materials, the design of novel dosage forms, transdermal drug delivery, and the *in vitro* and *in vivo* characterisation of pharmacokinetics/ pharmacodynamics. Researchers from different scientific backgrounds and expertise participate in this programme by following a multidisciplinary approach in order to increase the impact of their research outputs.

The Solid-state Pharmaceutical Innovation & Nanotechnology group (SPIN) carries out research and development in all aspects of the solid-state of active pharmaceutical ingredients from optimisation and characterisation to formulation and product development. Identification of chemical drug absorption enhancers from natural origin and herb-drug pharmacokinetic interactions form the focus of this research. Our expertise also include a battery of cell culture tests to determine dermal toxicology, wound healing, efficacy testing (e.g. melanoma cell line), dermal metabolism and the testing of antioxidant properties of new formulations and actives.

In vivo bioavailability studies are conducted in the animal facility of the NWU/DST pre-clinical drug development platform to evaluate the clinical significance of the absorption enhancers and herbal products on drug delivery and to confirm the effects identified by means of in vitro techniques.

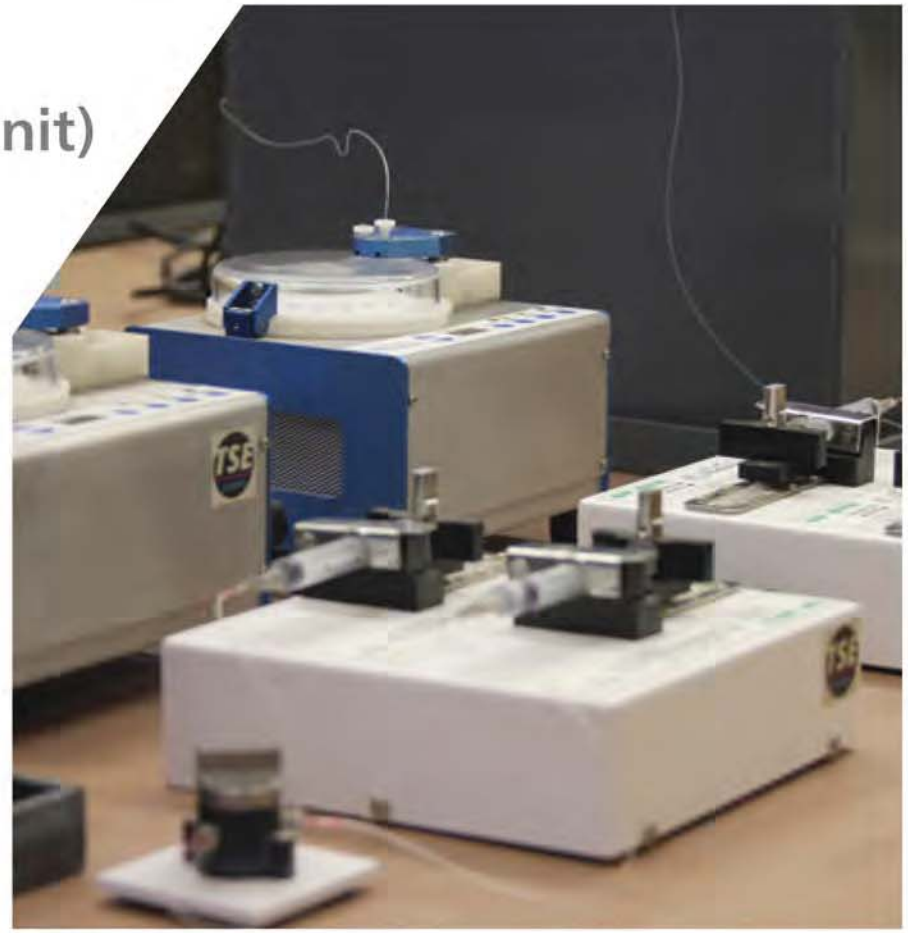
One part of our research is primarily focused on the design and evaluation of specialised solid oral dosage forms. The majority of research projects are concentrated on the development of multi-particulate oral drug delivery systems. Investigations into topical and transdermal drug delivery also form an important part of the activities of this research group.

Translational Neuroscience & Neuroprotection

Animal Models of Anxiety and Stress Disorders (SA Medical Research Council Unit)

This research group employs behavioural neuro-science and neuro-psychopharmacology to understand the deepest secrets of the brain and its afflictions, and to develop improved treatments. Attempting to understand the brain and drug action in an isolated organ experiment, or in an in vitro cell culture, presents significant translational limitations. Working with animals is equally challenging, since they do not develop "neuro-psychiatric illnesses", as observed in humans. Moreover, while they may present with stressful and adverse responses, similarly to humans, the bio-behavioural basis to their responses may be vastly different. Irrespective, through careful, methodical validation of the behavioural, biological, endocrine and pharmacological responses, it is possible to simulate a given human disorder in an animal.

Key research areas are the setting up, validation and application of translational animal models of human anxiety and stress related disorders, specifically depression, schizophrenia, post-traumatic stress disorder and obsessive compulsive disorder. Our expertise includes behavioural screening for anxiety, depression- and psychosis-like behaviours, as well as the assessment of a range of social and cognitive functions, including social interaction, short and long term memory, conditioned taste aversion, sensory-motor gating and conditioned fear. We also undertake intra-cerebral micro-dialysis and various neuro-chemical, molecular, biological and analytical assays to for example determine neuro-receptor density, cell viability, mitochondrial function, redox status, nitric oxide and immune-inflammatory markers, kynurenine metabolism, and mono-amine/non-mono-amine neuro-transmitters.

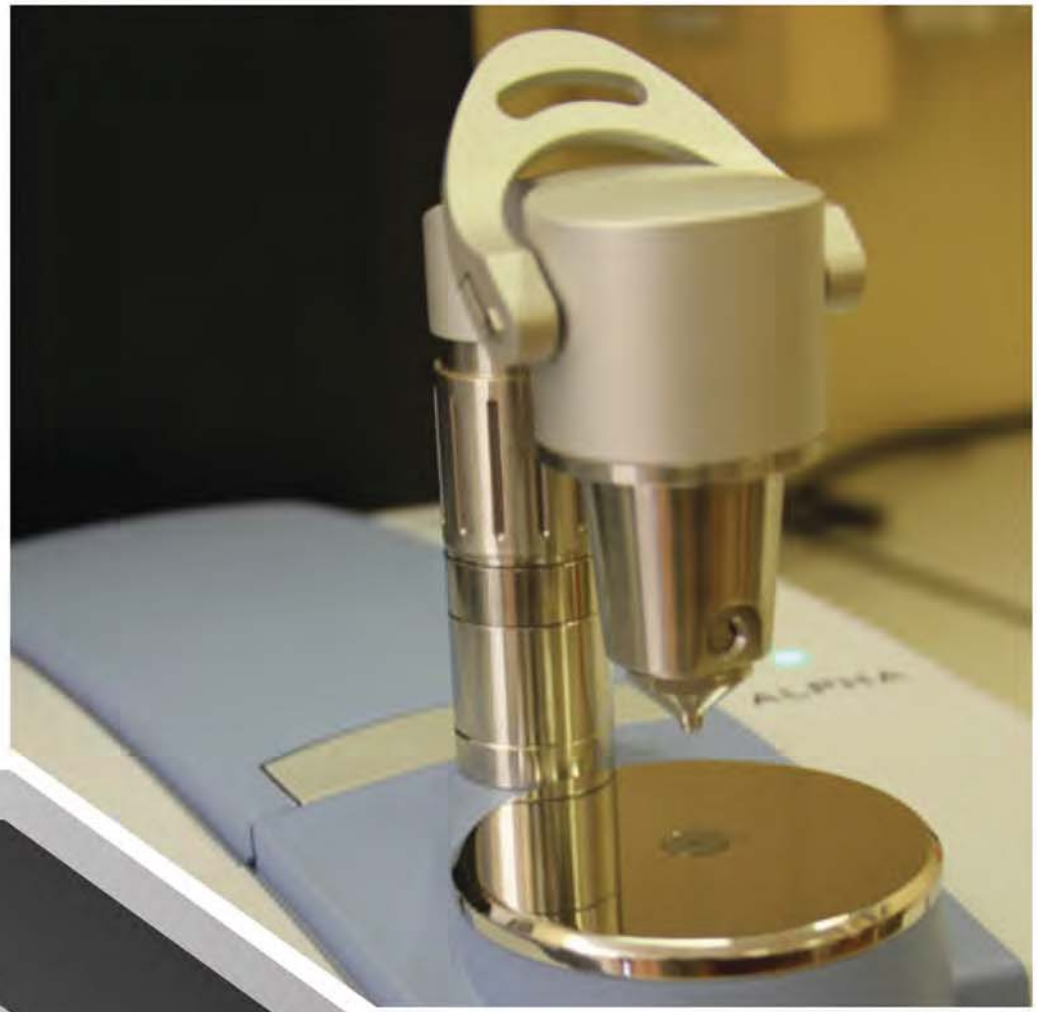


Novel Drug Design in Neuroprotection

The main focus of this research group is the design of compounds for use in the therapy of neuro-degenerative disorders, such as Parkinson's disease (PD) and Alzheimer's disease (AD), and for neuro-psychiatric diseases, such as depression. The design of novel, reversible inhibitors of the enzyme, monoamine oxidase (MAO), has been the mainstay of the group for several years, but our focus has recently expanded to include compounds with antagonistic properties at adenosine receptors, particularly the A2A sub-type. In this respect, the design of dual-target-directed drugs that block both MAO and A2A receptors, has become one of the main objectives of the group. Such compounds may prove to add value to managing PD and depression.

Another approach that is followed by our research team is drug repurposing (also called drug repositioning), which aims at identifying a new clinical use for an existing approved drug. A computational approach is followed whereby a virtual library of drugs is screened for activity at a specific target.

Our expertise includes structure based drug design, chemical synthesis, biological screening and the determination of key physico-chemical properties. Cytotoxicity studies, employing tissue cultures and in vivo efficacy testing, are also performed on promising lead compounds.



Drug Design and Mechanisms

One of the primary interests of this research group is the pharmacology of methylene blue (MB). MB possesses diverse pharmacological actions and is it attracting increasing attention for the treatment of a variety of disorders, including Alzheimer's disease, anxiety and depression. The molecular basis for MB's actions in the central nervous system (CNS) is, however, not yet well understood. Furthermore, MB is metabolised to yield N-demethylated products, which may contribute to the pharmacology and toxicology of MB. Our group aims at elucidating the mechanisms of action of MB in the CNS, particularly with regards to its anti-depressant effect, and to determine if major MB metabolites contribute towards the pharmacological profile of MB.

Another research interest of the team is the design of novel pro-drugs of L-Dopa, the direct precursor of dopamine, which is the treatment of choice for Parkinson's disease. This project attempts to overcome the poor oral bio-availability of L-Dopa and its therefore limited delivery to the brain. With the pro-drug approach, the unfavourable physico-chemical properties of L-Dopa may be masked, since an L-Dopa pro-drug may exhibit improved oral bio-availability and blood-brain barrier penetration.

Our expertise include chemical synthesis, the *in vivo* evaluation of the anti-depressant properties of compounds and the determination of key physico-chemical properties.

Translational Neuroscience & Neuroprotection

Indigenous Knowledge: Phyto-Chemistry and Ethno-Pharmacology

The majority of published research on formulated products containing medicinal plants as active ingredients, originate in China and India. While having a rich plant bio-diversity, with more than 3000 species currently being used medicinally, only a few South African medicinal plants have been successfully commercialised. Active constituents of most of the plants used in herbal medicines (including herbal African traditional medicines) have not been identified and for these medicines, whole plants are considered to be the active ingredients.

This poses a challenge for developing pharmaceutical assay methods for use in the quality control of traditional, African medicine products, due to the numerous compounds that are present within plant extracts.

The challenge arises from the fact that the theory, development and validation of these assay methods have been optimised for pure, single, pharmaceutical active ingredients. The aim and objective of medicinal plant research are to develop monographs, assays and specifications for the testing of medicinal plant extracts and medicinal plant products in order to submit dossiers for registration to the relevant regulatory authorities.

Drug Delivery
Biopharmaceutics

Absorption Enhancers and Herb-drug Pharmacokinetic Interactions

The identification of chemical drug absorption enhancers from natural origin and herb-drug pharmacokinetic interactions form the focus of our research. Many drugs, especially protein and peptide therapeutics, are exclusively administered through injection, due to their poor membrane permeability properties. Our research is focused on identifying and evaluating drug absorption enhancers that reversibly remove those barriers that impede drug bio-availability, to thereby allow effective drug delivery after oral administration. A large percentage of patients take herbal products together with conventional medicines that may lead to adverse interactions. One part of our research thus aims at identifying pharmacokinetic interactions on the level of drug absorption and metabolism, so that therapeutic failure and undesirable adverse effects can be anticipated and prevented.

Several *in vitro* techniques are available in our laboratories to evaluate drug permeation across the intestinal epithelium, including the Sweetana Grass diffusion chamber system, the everted sac system, as well as different cell culture models. *In vitro* models, such as excised pig and rat intestinal tissue and Caco-2 cell cultures, are used to screen compounds for their drug absorption enhancing effects or herb-drug interactions, and also to elucidate mechanisms of action on molecular level.

In vivo bio-availability studies are conducted in the animal facility of the pre-clinical drug development platform, to evaluate the clinical significance of absorption enhancers and herbal products on drug delivery, and to confirm any effects identified through *in vitro* techniques.

Solid, Oral Dosage Forms

Our research primarily focuses on the design and evaluation of specialised, solid, oral dosage forms. The majority of research projects are concentrated on the development of multi-particulate, oral drug delivery systems. Multi-particulate systems that are investigated for incorporation in solid, oral drug delivery systems include granulates, microspheres, beads and pellets. The beads are manufactured through extrusion spheronisation, while microspheres are prepared by means of emulsification solvent evaporation techniques. These multi-particulate systems are specifically investigated for the development of fixed dose combinations for the effective treatment of conditions requiring more than one active ingredient.

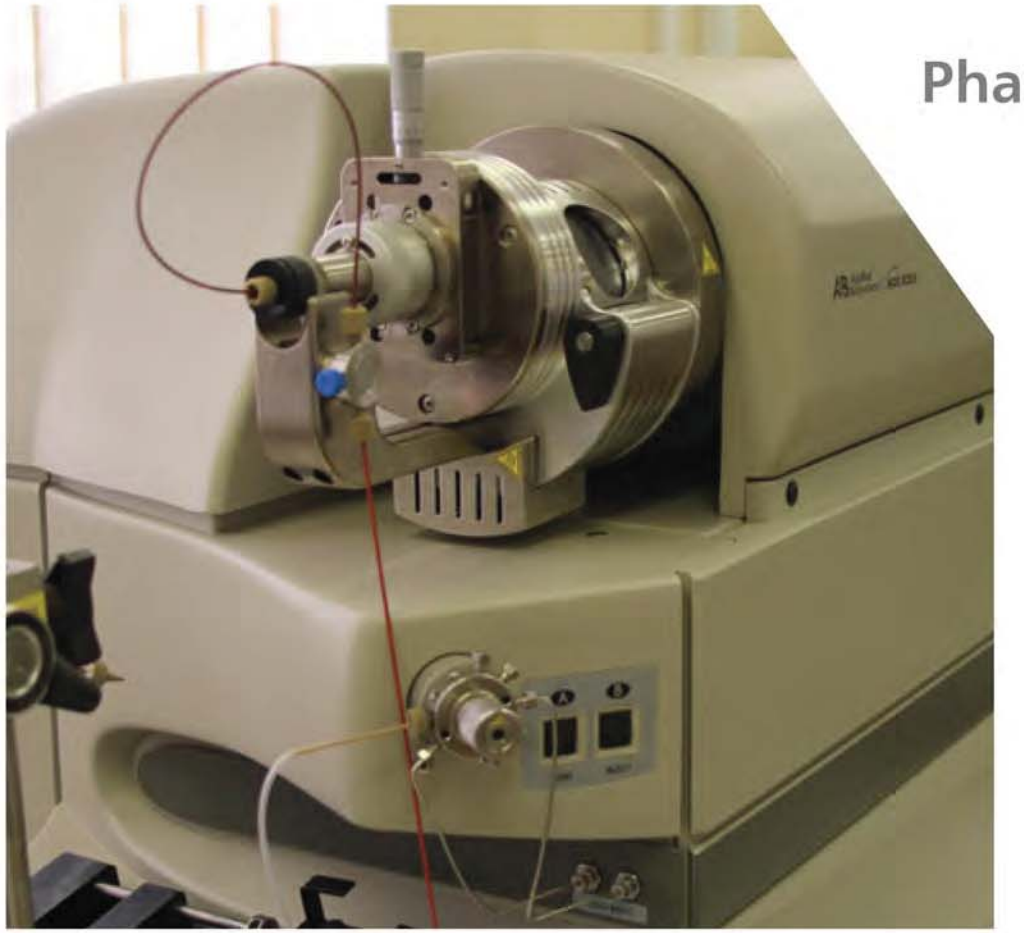
An important area of our research is the compression of particles, such as beads, into matrix type tablets to form multi-unit pellet systems (MUPS). Our formulation laboratory is equipped with a tablet press, linked to a computer capable of measuring and recording all technical aspects of the tableting process, such as compression force and ejection force. MUPS are designed to improve the stability of active ingredients combined in a single dosage form and to modify active release, according to the needs of the patient.

As part of dosage form design, polymers of natural origin are investigated as multi-functional excipients in the manufacturing of the multi-particulate drug delivery systems. Natural materials are targeted, due to their renewability and favourable toxicity profiles. The aim of this part of our research is the discovery new excipients for incorporation into novel dosage forms.

Molecular Pharmaceutics

Molecular pharmaceutics within bio-pharmaceutics and drug delivery systems deals with ways to deliver and maintain the desired amount of a therapeutic agent at the target site for a desired period of time and with cell based therapies. The development of a drug, or vaccine delivery system that can accomplish this is based on an understanding of their transport properties across biological barriers and subsequent bio-distribution, as well as the mechanisms by which they are metabolised and eliminated. These drug delivery systems are tested in cell based functional assays and/or human disease models in animals. As such, pharmacokinetic and pharmacodynamic assessments are the measure of performance of a given delivery system. The pharmacokinetics, be it at a sub-cellular/molecular level, or at organ/tissue level, require a sensitive and specific analytical method. Due to the inter-disciplinary nature of research, most projects are in collaboration with colleagues with relevant expertise. Current research involves improving the efficacy and delivery of a broad range of therapeutic agents, from small molecules to biologicals, such as proteins, anti-bodies and peptides.

Drug Delivery
Biopharmaceutics



Pharmacogenetics and Pharmacokinetics

Our research mainly focuses on the pharmacogenetics and pharmacokinetics of anti-retroviral (ARV) drugs.

Pharmacogenetics research entails investigating the genetic basis for variations in drug responses in individuals. Certain ARV drugs are metabolised by the CYP2B6 gene, which is characterised by extensive, inter-individual variability, associated with plasma concentrations outside of the therapeutic range, which impacts on the efficacy of highly active anti-retroviral treatment (HAART).

Various clinical studies on children and adults using HAART have been conducted since 2007, in which plasma, urine and saliva drug concentrations have been measured. Important metabolism aspects within the Black South African population have been investigated and population pharmacokinetic parameters have been determined.

Our areas of expertise include HPLC/MS/MS, conventional and real-time PCR methods, as well as the modelling of pharmacokinetic parameters with the non-linear mixed effects modelling (NONMEM) program.

Pharmacovigilance and the monitoring of the safety of ARVs have also recently been added to our research projects.

Drug Delivery

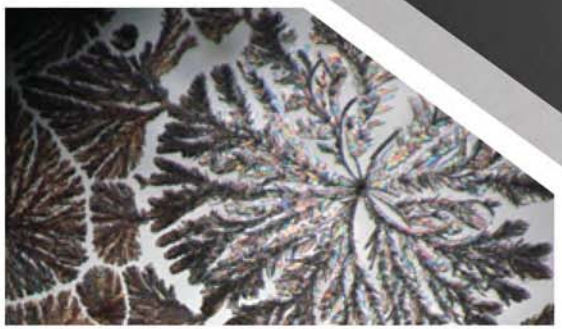
Solid-state Pharmaceutical Innovation & Nanotechnology

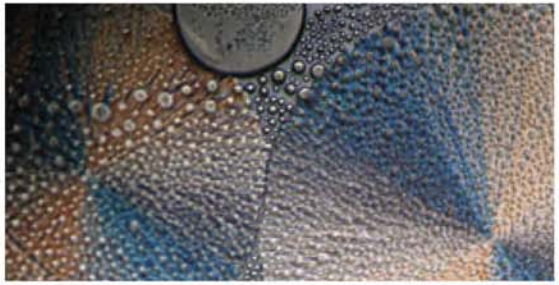
Our Solid-state Pharmaceutical Innovation and Nanotechnology (SPIN) team carries out research and development on all aspects of the solid state of active pharmaceutical ingredients (APIs), from optimisation and characterisation to formulation and product development.

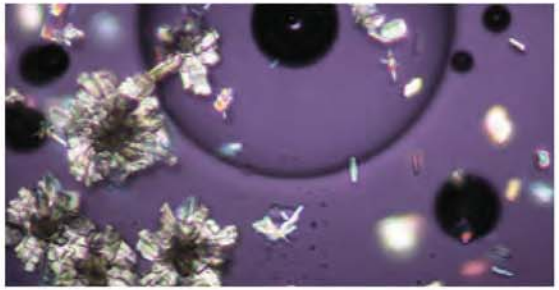
The expertise of the SPIN team includes the following: physico-chemical characterisation, optimisation of the solid-state properties of APIs and excipients, pharmaceutical polymorphs, amorphous APIs, co-crystals and co-polymers, the solubility and stability enhancement of APIs, novel uses for existing APIs, layer-by-layer nano-coating, micro- and nano-particles, dosage form formulation, product development, process development, analytical method development and optimisation, and post-graduate training.

SPIN has an international reputation for excellence in research and publishing, innovative industry related problem solving and technology transfer.


VTI-SA





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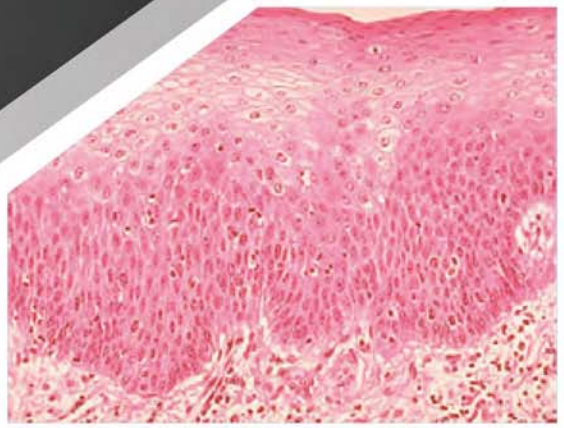



Grant JB series

Drug Delivery

Cosmeceutical Research

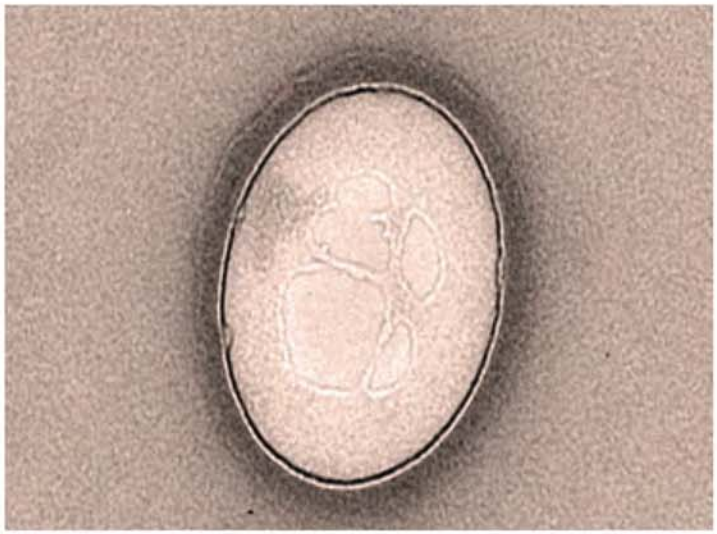
Cosmeceuticals is a term that expands the concept of cosmetics to include pharmaceutical properties. Aspects of healing, protection and the treatment of skin conditions are added to the aesthetical properties of general skin care products. The Cosmeceutical research team focuses on both topical and transdermal drug delivery. Skin care products that concern the delivery of active ingredients to the layers of the skin are also included.

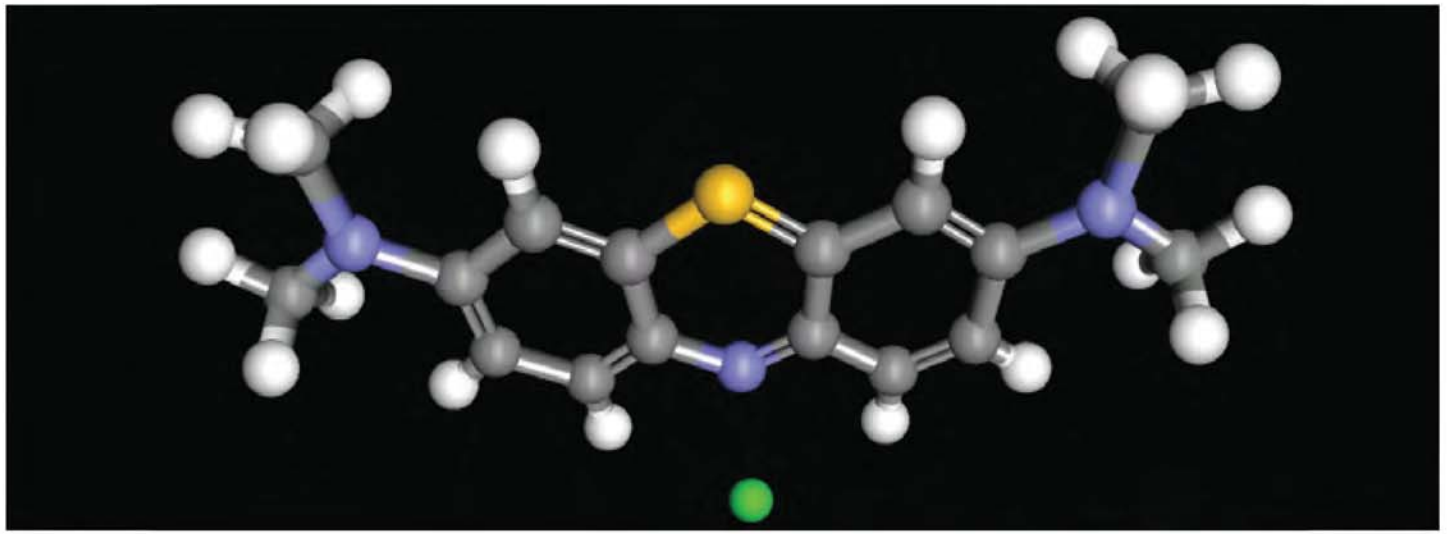
Investigations into transdermal drug delivery form an important part of the activities of our research group, including the use of penetration enhancers to increase drug permeation across the skin. We have a fully equipped, Type 2 laboratory in which we perform transdermal diffusion studies through human skin.

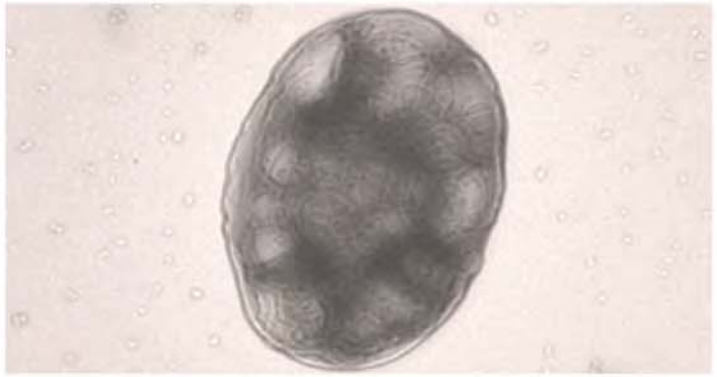
The key research areas within this research group are the formulation of high quality cosmeceutical products, the development of novel dosage forms and penetration enhancers, the determination of shelve life, the stability of cosmeceutical products and the determination as to whether drugs reach their targets through transdermal delivery.

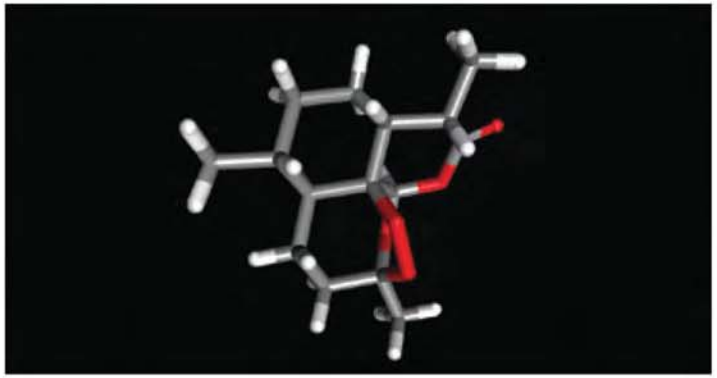
Our expertise also include a battery of cell culture tests to determine dermal toxicology, wound healing, efficacy testing (e.g. melanoma cell line), and the testing of the anti-oxidant properties of new formulations and actives. We further perform efficacy testing of preservatives, as well as chemical and physical stability testing.

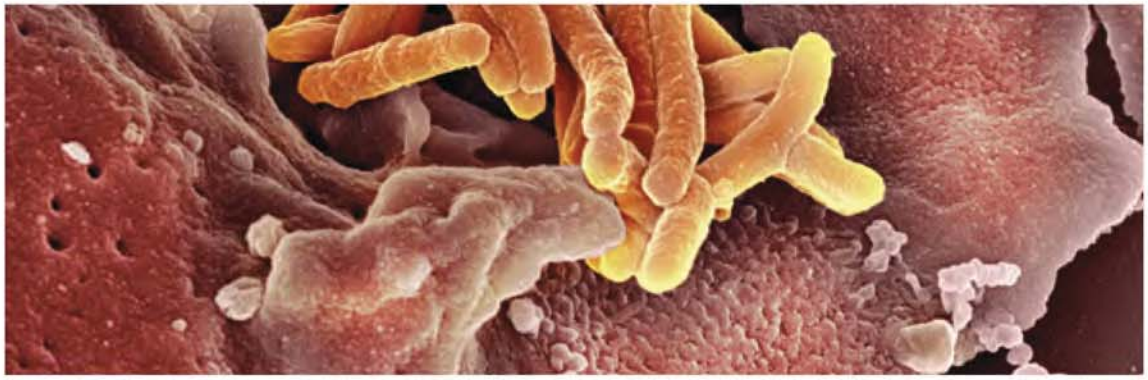
SA Medical Research Council Flagship Project: MAL-TB Redox











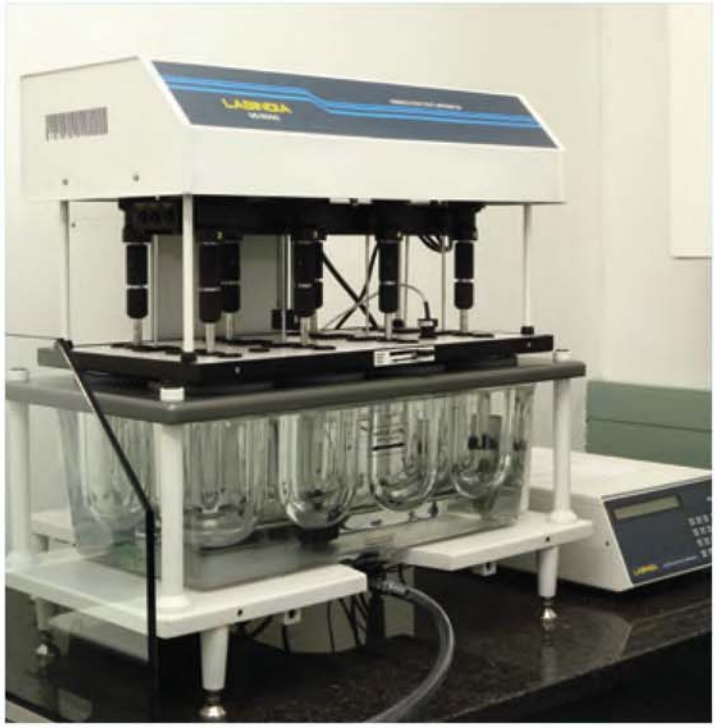
This MRC Flagship Project is directed from Pharmacen and includes research groups from South Africa, Australia and Europe. We develop rational drugs combinations for the treatment of malaria, tuberculosis, toxoplasmosis and related infections. Each drug in a combination has a different mechanism of action.

Malaria treatment is prejudiced by emerging resistance of the malaria parasite to current drugs. Novel treatments, especially of MDR and XDR TB are urgently required. Our hypothesis that a combination of an oxidant drug with a redox-active (redox)drug represents the best strategy for rapidly inducing lethal toxicity in pathogenic organisms, holds considerable potential for shortening future treatment regimens.

We therefore use the non-neurotoxic artemisinin artemisone and newer, third generation derivatives as the oxidant drugs, combined with redox drugs, such as methylene blue (MB) and clofazimine (CFZ), as well as newer, rationally designed derivatives. MB synergises the anti-malarial action of artemisinins and is strongly active against the malaria parasite, while CFZ (Lamprene) is currently being investigated by the Global TB Alliance, because of its identified activity against MDR TB. We base the third drug on quinolone, selected for its activity against the pathogens associated with each of malaria, TB and toxoplasmosis.

Considerable emphasis is placed on formulation aspects, in particular for TB. Collaborating groups ensure progress to proof of concept, and the selection of development candidate combinations.

Central Laboratory Infrastructure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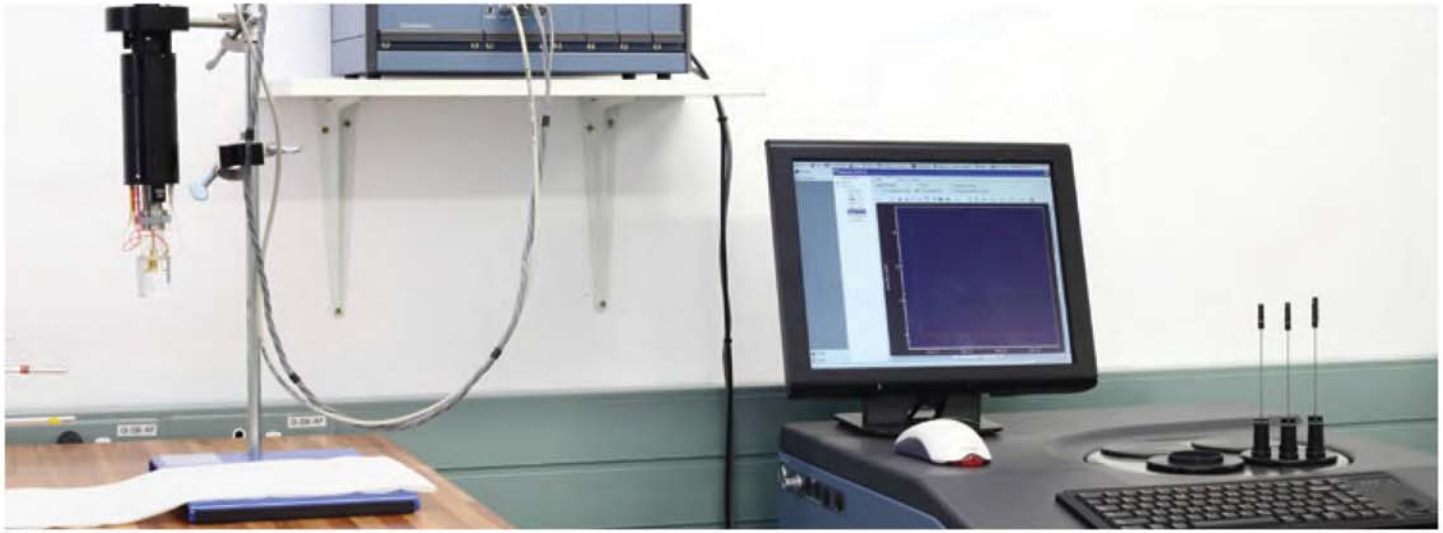
Central Laboratory Infrastructure



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