Physiology as a mature science – old challenges and new opportunities in teaching and research

Prof AM Joubert
Inaugural Address

12 June 2018

Make today matter
Welcoming

Special word of welcome to:

- Prof Duncan, Vice-Principal: Academic
- Prof Ströh, Vice-Principal: Institutional Planning
- Prof Rantloane, Deputy Dean: HS
- Prof de Jager, Dean: HS (in his absence)
- Prof Manning, Deputy Dean: Teaching and Research (HS)
- Prof van Papendorp, Former HOD - Physiology
- Deans from other Faculties
- Heads of Academic- and Clinical Departments
- Directors of Institutes, Units and Centres
- Distinguished guests, colleagues, family and friends
Please allow me to extend a warm word of welcome to you

- It is indeed a privilege to deliver my inaugural address as Head of the Department of Physiology tonight.
- In the guidelines of the University of Pretoria’s academic policy for inaugural addresses it is stated that the professor should speak on the basic principles of the discipline, its development including historical context, vision and mission for the Department and her/his own research field.
- I have therefore proposed the title of my address to be ‘Physiology as a mature science - old challenges and new opportunities in teaching and research’.
Outline of presentation

- History and exponential growth of the discipline of Physiology
- Vision and Mission
- Teaching and Learning
- Departmental Research Focus Areas:
  - Neurophysiology
  - Sport- and Exercise Physiology
  - Cellular and Molecular Physiology – Cancer Cellular Physiology
  - Applied Morphology in Pathophysiology
- The way forward…
- Acknowledgements
The word Physiology

Study of life that entails the functioning of cells, tissues and organisms

Stems from ancient Greek:
- ‘Physis’ - nature/origin
- ‘Logia’ - study of

History
Origin of Physiology as a mature science

Ancient India and Egypt
- Knowledge of ancient Egyptian Physiology/medicine
- Limited to papyrus scrolls (>3 000 years old)

Taxila (ancient India)
- First university of the world
- Gandhar (600 BC to 500 AD)
- 68 subjects
- Minimum entry age (16 years)
- Students from Babylon, Greece, Syria and China enrolled for Physiology
Physiology as a discipline

Hippocrates (460-377 BC)

- ‘Father of Medicine’
- Inaugurated Physiology centred on observation and case documenting

http://www.villakos.com/

http://www.elsevier.es/es-revista-offarm-4-articulo-la-farmacia-las-porporciones-armonicas--13116054

http://prevencionar.com.ec/2016/01/12/historia-de-la-seguridad-industrial/amp/
Leonardo da Vinci (1452-1519)

- ‘Movement is the cause of all life,’
The term Physiology

First introduced by Jean Fernel (1497-1558)

- ‘Study of nature, origins’
- First to describe the spinal canal of the human body
- Fernelius

https://en.wikipedia.org/wiki/Fernelius_(crater)
http://www.skatefins.com/spinal-canal-anatomy-and-physiology-pictures-cross-section
https://za.pinterest.com/pin/306596687105071470/
The journey of blood

William Harvey (1578-1657)

- First to fully describe circulatory system
- ‘Systemic circulation and the journey of blood through the brain and body driven by the heart’

https://www.famousscientists.org/william-harvey/
Exponential growth - discipline of Physiology

Claude Bernard (1813-1878)

- Founder of experimental Physiology
- ‘He is not merely a physiologist, he is physiology’
- Chemical- and nervous system control of digestion
- Function of the pancreas, bile secretion


https://www.everydayhealth.com/crohns-disease/treatment/can-vagus-nerve-stimulation-treat-crohns/


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Experimental physiology

Claude Bernard (1865)

‘The scientific basis of experimental medicine is physiology;..... without it no medical science is possible.... In a word, physiology must be constantly applied to medicine, if we are to understand and explain the mechanism of disease and the action of toxic and medicinal agents’


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Cell theory

Theodore Shwann (1810-1882) and Rudolf Virchow (1821-1902)

‘... the activity of an organism depends on both the individual and the collective activities of its cells’ came to light in the 1800s’

The lives of a cell

Lewis Thomas (1913-1993)

‘I have been trying to think of the earth as a single organism, but… I cannot think of it this way. It is too big, too complex, with too many working parts…. it is most like a single cell’

https://www.nap.edu/read/11172/chapter/19
https://www.rockefeller.edu/news/
History of the Department of Physiology

University of Pretoria (UP) - 1908

- Physiology taught in 1930 (Department of Animal Science)
- Faculty of Medicine
  - Founded in 1942
  - Only two lecturers

- Acting HOD: mid-2014-2015
- HOD: 2016-current

Prof G.W.H. Scheepers
1942-1943

Prof E. Janssen
1944-1945

Prof C. Brink
1947-1953

Prof B.J. Meyer
1954-1984

Prof J.J. Theron
1985-1990

Prof D van Papendorp
1990-2014

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Vision and Mission
Vision for the Department

The Department of Physiology will be internationally acknowledged for its superiority in:

- Excellence in teaching and learning and
- Research that will augment the health of the community locally and globally
Mission of the Department

To improve quality of life of students and staff

- Providing superior teaching and learning,
- Supporting career development opportunities,
- Strengthening UP’s socio-economic responsiveness

To enhance research outputs

- Building research capacity by reaching out to other disciplines/sharing research facilities, enabling transformation,
- Fostering teamwork → successful applications of external funding
- Supporting emerging-, established- and leading researchers
- Strengthening UP’s international profile
Teaching and Learning
Teaching and Learning

‘Education is the most powerful weapon to change the world’ (Mr Nelson Mandela)

- Medicine
- Dentistry
- Nursing, Occupational therapy, Physiotherapy, Radiography, Dietetics
- Communication pathology
- Biokinetics and Sport Sciences
- Human Physiology - major for two study programs (Faculty of Natural and Agricultural Sciences)
- Food science and some consumer science courses
- ~3 000 students per annum in 66 undergraduate- and postgraduate modules

‘In an academic environment, it is not about maintaining status quo, but it is about accelerating progress’ Prof S Nkomo
Number of students enrolled for all Physiology modules

2018

- Hatfield campus: 2960
- Prinshof campus: 1440
- Hillcrest campus: 840
- Postgraduates: 105
Virtual practical’s
Postgraduate students

PhD 2018 (19)

Dr Craig Grobbelaar
Thandi Mqoco
Sajee Alummoottil
Lisa Repsold
Abe Kasonga
Jenny Du Plooy
Yvette Hlophe
Keitumetse Mothibeli
Vangi Nortje
Tamarin Perks
Elsa Nolte

Dr Rivak Punchoo
Dr Morné Strydom
Dr Candice Van Wyk
Stembile Mbotwe
Marcelle Verwey
Mandie Botes
Jolene Helena
Nare Sekoba
Postgraduate students

MSc 2018 (31)

Liechka Groenewald  Tiaan Vermeulen  Mokgadi Gwangwa  Sulette De Villiers  Desireé Fraser  Travers Sagar  Karlien Balt  Monique Otto  Lorenzo Fernandes  Julien Nunes Goncalves  Tebogo Lebelo

Jandré Bezuidenhout  Robin Du Preez  Bernadette Van Heerden  Wikus Meijer  Odette Emmerson  Mary-Anne Phasha  Hildegarde Roberts  Tanya Fouché  Tebogo Ramoshayi  Amelia Cockrell  Babalwa Jobela

Wihan Scholtz  Kayla Howard  Yuvelia Pather  Nomvu Nyathi  Koketso Chauke  Morné Ferreira  Simoné Grobbelaar  Juan Jv Nieuwenhuizen  Alexis Schwulst
# Postgraduate students

## Honours 2018 (26)

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Mikateko Nxumalo</td>
<td>Melissa Bekker</td>
<td>Justine Pillay</td>
<td>Ashleigh Gruneberg</td>
<td>Daniël Joubert</td>
<td>Anél Naudé</td>
<td>Sandi Mahlangu</td>
<td>Nicola Weidhase</td>
<td>Nibha Surajal</td>
<td>Victoria Verrall</td>
<td>Tshinakaho Mudzunga</td>
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<tr>
<td>Carla Pieterse</td>
<td>Nicola Kruger</td>
<td>Angela Bona</td>
<td>Shannen Marais</td>
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Postgraduate students

Biokinetcs 2018 (16)

Sports Science 2018 (6)
Research
Departmental research focus areas

Research intensive university

- Neurophysiology
- Cellular- and molecular physiology
- Sport- and exercise physiology
- Applied morphology in pathophysiology
Division of Biokinetics and Sport Science

Impact on biokinetics and sport science practice and communities we serve

Collaborators
Sport, Exercise Medicine and Lifestyle Institute (SEMLI);
UP (Engineering, Sports Medicine, Physiotherapy, Internal Medicine)
Bone research (osteoporosis)
Angiogenesis

Study vessel formation in physiological- and pathophysiological settings

Growing microvessels in a rat aorta ring model

Microvessels – patient biopsy vascular tumour tissue/haemangioma tissue (HT), untreated (A) and following treatment with bleomycin, an anti-angiogenic chemotherapeutic

Awarded Microscopy Society of South Africa - Innovative technique
Applied morphology in pathophysiology

Erythrocytes, fibrin and platelets

Scanning electron microscopy
Laser scanning confocal microscopy
Thromboelastography

Oral contraceptives

Controls

Alzheimer’s

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Molecular mechanisms of non-communicable diseases

- Genetics: genotyping and polymorphisms
- Epigenetics: microRNA analysis
- Biochemical assays
Cancer incidence (internationally)

http://globalcancermap.com/
Breast cancer incidence (internationally)

http://globalcancermap.com/
Estrogen and its dual nature?

From *in silico*-design of 2-methoxyestradiol analogues to *in vitro* and *ex vivo* analyses and their *in vivo* detection limits in a murine model

Make today matter
Postgraduate students and research collaborators
Introduction

2-Methoxyestradiol (2ME) (endogenous 17-beta estradiol metabolite)
(anticancer effects, limitations due to low oral bio-availability)

Objective

To develop an anti-cancer drug

- Mitotic spindle - highly validated target 1
- Carbonic anhydrase (CA) IX - highly validated target 2 (membrane associated, over expressed in many metastatic cancers)

https://www.researchgate.net/figure/Colchicine-binding-site-at-the-interface-between-a-and-b-subunits-of-tubulin-The_i_fig2_335773573

CAIX docking
Materials and methods

17-Beta estradiol metabolite (2ME) as source molecule

- In silico
- Synthesis
- In vitro
- Ex vivo
- In vivo
Results - *In silico*

<table>
<thead>
<tr>
<th>Best tubulin colchicine site binding energy</th>
<th>Molecules to be synthesized</th>
<th>Best CAIX:CAII binding energy ratio</th>
</tr>
</thead>
</table>

**Modifications of estradiol 80 analogues**

- Ensemble docking
- Multiple X-ray structures
- Tubulin
- Carbonic anhydrase II and IX
- Flexibility of proteins under different conditions (simulate protein flexibility)
Results - Synthesis

Synthesis scheme of 2ME derivatives

17-Beta-Estradiol Analog Inhibits Cell Proliferation by Induction of Apoptosis in Breast Cell Lines

MICHELLE HELEN VISAGE,1 LYNN-MARIE BIRKHOILTZ,2 AND ANNA MARGARETHA JOUBERT1
1Department of Physiology, University of Pretoria, Arcadia 0028, South Africa
2Department of Biochemistry, University of Pretoria, Pretoria 0028, South Africa

Molecular docking of ESE-16 in the colchicine-binding site of tubulin

Docking, Synthesis, and in vitro Evaluation of Antimitotic Estrone Analogs

Andre Stander1,2, Fourie Joubert2 and Annie Joubert1

1Department of Physiolou University of Pretoria, Pretoria South Africa

Chem Biol Drug Des 2011
Research Article

© 2011 John Wiley & Sons A/S
DOI: 10.1111/j.1747-0289.2010.01847.x
Results - *In silico*: inhibitory constants

- Carbonic anhydrase II and IX
- Ligand-protein binding analysis $\rightarrow$ membrane-inlet mass spectrometry
- $\sim$2 times more selective for CAIX

---

**Characterization of Carbonic Anhydrase Isozyme Specific Inhibition by Sulfamated 2-Ethylestra Compounds**

Katherine H. Sippel, Andre Stander, Chingkuang Tu, Balasubramaniam Venkatakrishnan, Arthur H. Robbins, Mavis Agbona-McKenna, Fourie Joubert, Anne M. Joubert and Robert McKenna.

**Signaling Pathways of ESE-16, an Antimitotic and Anticarbonic Anhydrase Estradiol Analog, in Breast Cancer Cells**

Barond Andre Stander, Fourie Joubert, Chingkuang Tu, Katherine H. Sippel, Robert McKenna, Annie Margareththa Joubert.

**In Vitro Evaluation of ESE-15-ol, an Estradiol Analogue with Nanomolar Antimitotic and Carbonic Anhydrase Inhibitory Activity**

Barond Andre Stander, Fourie Joubert, Chingkuang Tu, Katherine H. Sippel, Robert McKenna, Annie Margareththa Joubert.

---

<table>
<thead>
<tr>
<th></th>
<th>Experimental Inhibition Constants (K)</th>
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</thead>
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<tr>
<td></td>
<td>SEE</td>
</tr>
<tr>
<td>CAII</td>
<td>$180 \pm 10 \text{ nM}$</td>
</tr>
<tr>
<td>CAIX mimic</td>
<td>$2100 \pm 220 \text{ nM}$</td>
</tr>
</tbody>
</table>
Results - Synthesis: purity

> 95% purity

2-Ethyl-3-O-sulphamoyl-1,3,5(10)16-tetraene (ESE-16)

1H Nuclear Magnetic Resonance (WITS)

Electron Impact (EI)
**Results - *In vitro*: cell proliferation**

Growth inhibitory effect of ESE-16 on MCF-7, SNO, MDA-MB-231, HeLa and MCF-12A cells
Results - signalling

Signaling Pathways of ESE-16, an Antimitotic and Anticarbonic Anhydrase Estradiol Analog, in Breast Cancer Cells

Barend Andre Stander, Frouie Joubert, Chingkuang Tu, Katherine H. Sippel, Robert McKenna, Annie Margaretha Joubert

1 Department of Physiology, University of Pretoria, Pretoria, Gauteng, South Africa; 2 Department of Biochemistry, Bioinformatics and Computational Biology Unit, University of Pretoria, Pretoria, Gauteng, South Africa; 3 Department of Biochemistry and Molecular Biology, College of Medicine, University of Florida, Gainesville, Florida, United States of America; 4 Parker College of Medicine, Houston, Texas, United States of America; 5 Department of Pharmaceutical Sciences and Therapeutics, University of Florida, Gainesville, Florida, United States of America

Research article

NOVEL ESTRADIOL ANALOGUE INDUCES APOPTOSIS AND AUTOPHAGY IN ESOPHAGEAL CARCINOMA CELLS

ELIZE WOLMARANS1, THANDI V. MQOCO1, ANDRE STANDER1, SANDRA D. NKANDE1, KATHERINE SIPPEL2, ROBERT MCKENNA3 and ANNIE JOUBERT4, *

Biomedical Research 2013; 24 (4): 525-530

Short communication: Effects of a 17-beta estradiol analogue on gene expression and morphology in a breast epithelial adenocarcinoma cell line: A potential antiproliferative agent.

Michelle Helen Visagie1, Barend André Stander1, Lyn-Marie Birkholtz2, Annie Margaretha Joubert1

1 Department of Physiology, University of Pretoria, Private Bag X323, Arcadia, 0007, South Africa
2 Department of Biochemistry, University of Pretoria, Private Bag X30 Hatfield, Pretoria, 0001, South Africa
Anti-mitogenic activity
Inhibition of tubulin polymerization

Sulphamoylated 2-Methoxyestradiol Analogues Induce Apoptosis in Adenocarcinoma Cell Lines

Michelle Visagie¹, Anne Theron¹, Thandi Mqoco¹, Warren Vieira¹, Renaud Prudent², Anne Martinez², Laurence Lafanechère², Annie Joubert¹

¹ Department of Physiology, University of Pretoria, Pretoria, South Africa, ² Institut Albert Bonniot, CRI INSERM/UJF U823, Team 3 Polarity, Development and Cancer, Rond-point de la Chantournée, La Tronche Cedex, France

Cellular & Molecular Biology Letters

Crosstalk between the Warburg effect, redox regulation and autophagy induction in tumourigenesis

Mokgadi Violet Gwangwa, Anna Margaretha Joubert and Michelle Helen Visagie
Actin network response

Actin fibre response to microtubule abrogation

- Control
- 1 μM Colchicine
- 0.2 μM ESE-16
- 0.5 μM ESE-16

2 hours

24 hours
Tyrosinated/detyrosinated tubulin

Tyrosinated and detyrosinated microtubules in response to compound exposure

1 μM Colchicine 0.2 μM ESE-16 0.5 μM ESE-16

2 hours

24 hours

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Mitochondrial response

Tyrosinated and detyrosinated microtubules in response to compound exposure

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Microtubule dynamics

Microtubule dynamics in DMSO exposed HeLa cell as control

Microtubule dynamics in HeLa cell exposed to 0.5 μM ESE-16

Microtubule dynamics in HeLa cell exposed to 0.25 μM ESE-16

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DMSO</th>
<th>C19 0.25 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time spent growing</td>
<td>73.79</td>
<td>28.58</td>
</tr>
<tr>
<td>% time spent in pause</td>
<td>26.21</td>
<td>71.42</td>
</tr>
<tr>
<td>Growth rate (μm/min ± SE)</td>
<td>14.52±1.00</td>
<td>9.79±0.64</td>
</tr>
<tr>
<td>Catastrophe frequency (μm²/μm² ± SE)</td>
<td>0.15±0.04</td>
<td>0.78±0.16**</td>
</tr>
<tr>
<td>Catastrophe frequency (min⁻¹ ± SE)</td>
<td>1.57±0.59</td>
<td>2.12±0.42*</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.001, significantly different from control values (DMSO) using a Student’s t test

(Catastrophe: switch from growth to shrinking in microtubules)
Morphology

- Smooth well-defined cell membrane
- Mitochondria
- Normal cell membrane protrusions
- Nuclear membrane

- Mitochondrion
- Normal cell protrusions

- Increased number of cell membrane protrusions
- Apoptotic bodies
- Hypercondensed chromatin
- Autophagosomes
- Distressed cell

- Apoptotic bodies
- Golgi bodies
- Autophagosomes

Molecular crosstalk between apoptosis and autophagy induced by a novel 2-methoxyestradiol analogue in cervical adenocarcinoma cells

Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition)
Autophagy

Pharmacology

Original Paper
A Novel 2-Methoxyestradiol Analogue Is Responsible for Vesicle Disruption and Lysosome Aggregation in Breast Cancer Cells

Nkandu S.D.¹, van den Bout I.², Cronjé M.J.³, van Papendorp D.H.³, Joubert A.M.³

Formula 1: Aggresome Activity Factor

\[
AAF = 100 \times \frac{M_{\text{TREATED}} - M_{\text{CONTROL}}}{M_{\text{TREATED}}}
\]

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Autophagy induced by a sulphamoylated estrone analogue contributes to its cytotoxic effect on breast cancer cells

Marcel Verwey*, Elske M. Noote, Anna M. Joubert and Anne E. Theron

*Correspondence: mverwey@sun.ac.za
# Gene ontology and protein expression

## Table of Genes and Proteins

<table>
<thead>
<tr>
<th>Gene ID</th>
<th>Gene Description</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53INP1</td>
<td>Tumor protein p53 inducible nuclear protein 1 (NM_033285)</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>BBC3</td>
<td>BCL2 binding component 3 (NM_014417)</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>MAP2K3</td>
<td>Mitogen-activated protein kinase 3 (NM_145109)</td>
<td>Activates p38</td>
</tr>
<tr>
<td>EGR1</td>
<td>Early growth response 1 (NM_001964)</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>TRIB3</td>
<td>Tribbles [NM_021158]</td>
<td>Negatively regulates AKT1</td>
</tr>
<tr>
<td>EXT1</td>
<td>Exostoses (multiple) 1 (NM_000127)</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog [NM_003014]</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>TNFRSF21</td>
<td>Tumor necrosis factor receptor superfamily, member 21</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>TNFSF15</td>
<td>Tumor necrosis factor (ligand) superfamily, member 12</td>
<td>Apoptosis facilitator</td>
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<tr>
<td>FKN</td>
<td>Fyn-related kinase [NM_002031]</td>
<td>Activates p38</td>
</tr>
<tr>
<td>MKNK2</td>
<td>MAPK kinase interacting serine/threonine kinase 2</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>DDIT3</td>
<td>DNA-damage-inducible transcript 3 (DDIT3) [NM_004083]</td>
<td>Apoptosis facilitator</td>
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<tr>
<td>BCL2L11</td>
<td>BCL2-like 11 (NM_138621)</td>
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<tr>
<td>IL24</td>
<td>Interleukin 24 (NM_006850)</td>
<td>Induces p38 and p53</td>
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<td>GADD45A</td>
<td>Iurowth arrest and DNA-damage-inducible, alpha</td>
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## Function of Selected Genes

- **TP53INP1**: Tumor protein p53 inducible nuclear protein 1 (NM_033285)
- **BBC3**: BCL2 binding component 3 (NM_014417)
- **GADD45A**: Iurowth arrest and DNA-damage-inducible, alpha (NM_019241)
- **IL24**: Interleukin 24 (NM_006850)
- **GADD45A**: Induces p38 and p53
- **BBC3**: Activates p38
- **TP53INP1**: Apoptosis facilitator

## Gene Expression

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<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53INP1</td>
<td>Tumor protein p53 inducible nuclear protein 1 (NM_033285)</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>BBC3</td>
<td>BCL2 binding component 3 (NM_014417)</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>MAP2K3</td>
<td>Mitogen-activated protein kinase 3 (NM_145109)</td>
<td>Activates p38</td>
</tr>
<tr>
<td>EGR1</td>
<td>Early growth response 1 (NM_001964)</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>TRIB3</td>
<td>Tribbles [NM_021158]</td>
<td>Negatively regulates AKT1</td>
</tr>
<tr>
<td>EXT1</td>
<td>Exostoses (multiple) 1 (NM_000127)</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog [NM_003014]</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>TNFRSF21</td>
<td>Tumor necrosis factor receptor superfamily, member 21</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>TNFSF15</td>
<td>Tumor necrosis factor (ligand) superfamily, member 12</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>FKN</td>
<td>Fyn-related kinase [NM_002031]</td>
<td>Activates p38</td>
</tr>
<tr>
<td>MKNK2</td>
<td>MAPK kinase interacting serine/threonine kinase 2</td>
<td>Tumor suppressor</td>
</tr>
<tr>
<td>DDIT3</td>
<td>DNA-damage-inducible transcript 3 (DDIT3) [NM_004083]</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>BCL2L11</td>
<td>BCL2-like 11 (NM_138621)</td>
<td>Apoptosis facilitator</td>
</tr>
<tr>
<td>IL24</td>
<td>Interleukin 24 (NM_006850)</td>
<td>Induces p38 and p53</td>
</tr>
<tr>
<td>GADD45A</td>
<td>Iurowth arrest and DNA-damage-inducible, alpha (NM_019241)</td>
<td>Activates p38</td>
</tr>
<tr>
<td>BBC3</td>
<td>BCL2 binding component 3 (NM_014417)</td>
<td>Apoptosis facilitator</td>
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</tr>
</tbody>
</table>
Proposed mechanism of action – cancer cell signalling?
Cancer cell metastasis

The effect of estrone-like compounds on migration and survival (two- and three dimensional)

Anti-migratory effect of microtubule interrupters

Development of *in vitro* three-dimensional cancer models

Cell detachment

Prof AM Joubert – Inaugural Address – 12 June 2018
Ex vivo

An estrogen analogue and promising anticancer agent refrains from inducing morphological damage and reactive oxygen species generation in erythrocytes, fibrin and platelets: a pilot study
Lisa Repsold, Ethelesia Pretorius and Annie Margaretha Joubert

Ex vivo apoptotic and autophagic influence of an estradiol analogue on platelets
Lisa Repsold, Ethelesia Pretorius and Annie Margaretha Joubert

Eryptosis: An Erythrocyte’s Suicidal Type of Cell Death
Lisa Repsold and Anna Margaretha Joubert
In vivo - screening: threshold determination in murine model

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

2-ethyl-3-O-sulphamoyl-oestra-1,3,5(10),15-tetraene-3-ol-17-one
Discussion and conclusion

Molecular crosstalk between apoptosis and autophagy induced by a novel 2-methoxyestradiol analogue in cervical adenocarcinoma cells
Anne E Theron¹, Ellie M Noote, Laurence Lafanechère² and Annie M Joubert¹

Antimitotic drugs in the treatment of cancer
Rustelle Janse van Vuuren¹ · Michelle H. Visagie¹ · Anne E. Theron¹ · Annie M. Joubert¹

Cancer Chemother Pharmacol (2015) 76:1101–1112
DOI 10.1007/s00280-015-2903-8

Review Article

Table 1 Classes of antimitotic drugs and their stages of development [25, 26, 28, 61, 65, 67, 70, 71, 83, 85, 105–107]

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Mechanism of action</th>
<th>Approved for treatment of (cancer type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used as cancer treatment regimens</td>
<td>Paclitaxel (taxol)³</td>
<td>Microtubule-stabilizing</td>
<td>Metastatic adenocarcinoma of the pancreas (in combination with gemcitabine)</td>
</tr>
<tr>
<td></td>
<td>Cabazitaxel (杰隆素)⁵</td>
<td>Microtubule-stabilizing</td>
<td>Metastatic, hormone-resistant prostate cancer (in combination with prednisone)</td>
</tr>
<tr>
<td></td>
<td>Epothilones</td>
<td>Microtubule-stabilizing</td>
<td>Metastatic or locally advanced breast cancer (resistant to taxanes and anthracyclines)</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Eribulin (E7389, ERI86526, 6)</td>
<td>Microtubule-destabilizing</td>
<td>Recurrent metastatic breast cancer (pre-treated with taxanes and anthracyclines)</td>
</tr>
</tbody>
</table>

Class | Name | Mechanism of action | Phase of clinical trials |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs undergoing clinical trials</td>
<td>Vinca alkaloids</td>
<td>Microtubule-destabilizing</td>
<td>In Clinical phase II trials as sole treatment for ovarian and lung cancer</td>
</tr>
</tbody>
</table>

Class | Name | Mechanism of action | Model |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs undergoing in vivo studies</td>
<td>Peloroside A (PLA, CHEBE:77692)</td>
<td>Microtubule-stabilizing</td>
<td>Lung and breast tumor xenograft studies in athymic nu/nu mice</td>
</tr>
<tr>
<td></td>
<td>Laulimalide</td>
<td>Microtubule-stabilizing</td>
<td>High toxicity and low tumor inhibition in human breast cancer and fibrosarcoma xenograft studies in athymic nu/nu mice</td>
</tr>
</tbody>
</table>

Class | Name | Mechanism of action | Effective in cell line |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs undergoing in vitro studies</td>
<td>Estrogen derivatives</td>
<td>Microtubule-destabilizing</td>
<td>Breast cancer (MCF-7, MDA-MB-231) and lung cancer (A549)</td>
</tr>
<tr>
<td></td>
<td>ESE-15-ol</td>
<td>Microtubule-destabilizing</td>
<td>Breast cancer cell lines (MCF-7, MDA-MB-231) and esophageal cancer (SNO)</td>
</tr>
<tr>
<td></td>
<td>ESE-16</td>
<td>Microtubule-destabilizing</td>
<td>Breast cancer (MCF-7, MDA-MB-231) and lung cancer (A549)</td>
</tr>
</tbody>
</table>
Collaboration - Grenoble, France

- 2008 - sabbatical leave
- Prof Lafanéchère - extraordinary professor
- Postgraduate student visits to Grenoble
- Co-tuelle – dual PhD degree (Grenoble and Pretoria) (2017-2018)
Collaboration - Oxford and Bath, UK

Greetings from Oxford and thanks for the great collaboration!

Manuscript accepted:
24 May 2018
Drug Design, Development and Therapy

Prof AM Joubert – Inaugural Address – 12 June 2018
Rationale for combining two key structural motifs from a steroid and colchicine with a sulfamate motif to make a non-steroidal drug candidate
Structure-based drug design
Collaboration - Istanbul, Turkey
Collaboration - University of Johannesburg
Research group highlights

- Science Trends February 6, 2018
  ‘Computer-based Technology As An Anticancer Agent In Cervical Cancer Cells’
- Cancer Association of South Africa (CANSA) Detectives
- Quest Science for SA and newspapers
- International- and national research awards - young researchers
Several Nobel Prize Medals for Physiology or Medicine followed from 1901- current

President Barack Obama (Nobel prize laureate): ‘Science is more essential for our prosperity, our security, our health, our environment, and our quality of life than it has ever been before’

‘Speech to the National Academy of Sciences Annual Meeting (27 Apr 2009).”

2002 Programmed cell death

Sydney Brenner (South Africa)  H. Robert Horvitz (United States)  Sir John E. Sulston (United Kingdom)
More highlights

- Albert Beyers Travelling Fellowship, Oxford, UK
- A.G. Oettle Silver Medal from the Cancer Association of South Africa
- Carte Blanche Medical
- KykNET
- Plenary/keynote addresses

President of the International Cell Death Society

Queens College of the City University of New York, NY, USA
External research funding
Future of cancer cellular physiology

- Strategic partnerships and collaboration
- Increase international standing; UP’s endocrine cancer initiative
The way forward....

- ‘Scarce skills techniques’ (core knowledge and application, prospects to further postgraduate careers, socio-economic contribution, work readiness)
- Postgraduate student visits and exchange
- Private sector visits to experience ‘day-to-day’ working environment
- Visiting scientist/professor programmes, extraordinary lecturers/professors
- Attract postdoctoral fellows
- High impact publications in accredited peer-reviewed journals (citations, international profile)
- Augment the health of the community of South Africa, as well as internationally
Interdepartmental- and interfaculty collaboration

Centre for Neuroendocrinology

Institute for Cellular and Molecular Medicine

Institute for Food Nutrition and Well-being

Sport, Exercise Medicine and Lifestyle Institute
International- and national collaboration
Our amazing team
Conclusion

Claude Bernard

‘It is what we know already that often prevents us from learning

Man can learn nothing except by going from the known to the unknown

Observation is a passive science, experimentation an active science’
Acknowledgements
Thank You