

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of
Health Sciences

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

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

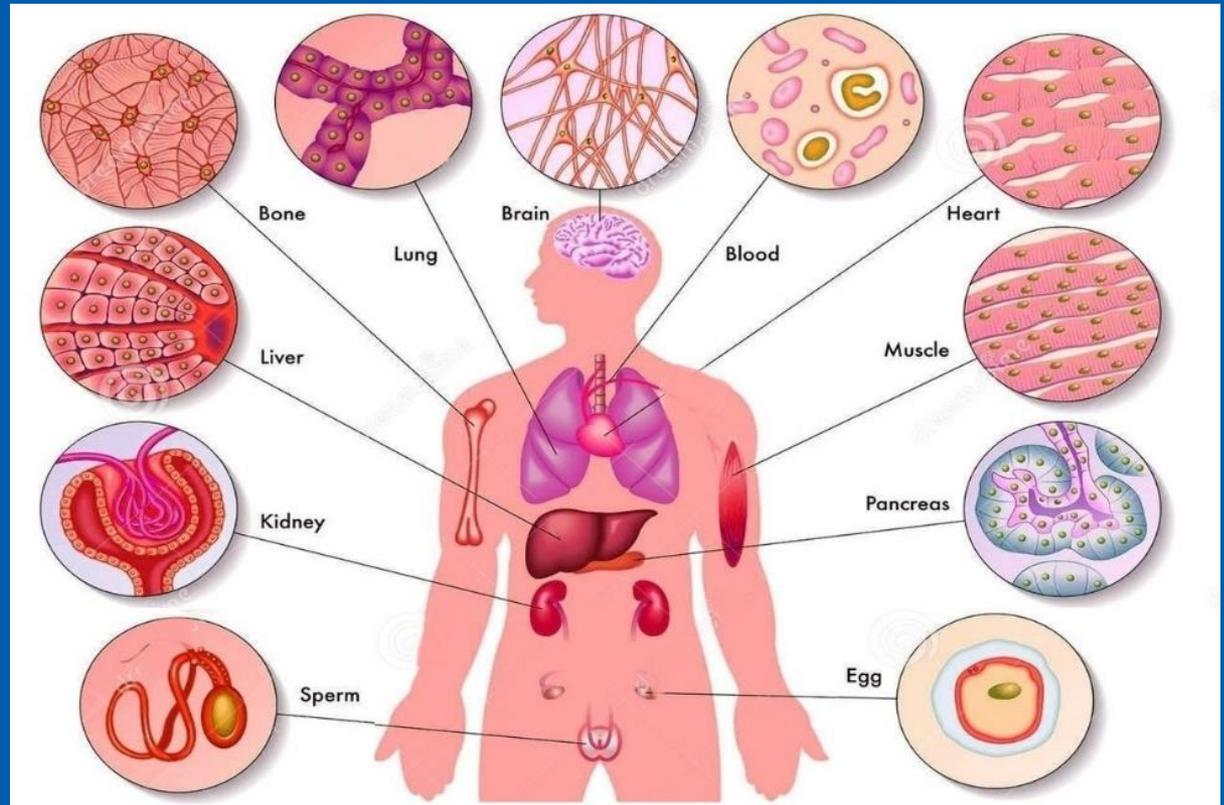
- History and exponential growth of the discipline of Physiology
- Vision and Mission
- Teaching and Learning
- Departmental Research Focus Areas:
 - Neurophysiology
 - Sport- and Exercise Physiology
 - Cellular and Molecular Physiology – Cancer Cellular Physiology
 - Applied Morphology in Pathophysiology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



<http://anatomystructure.net/diagram-of-different-cell-found-in-human-body/diagram-of-different-cell-found-in-human-body-the-diagram-of-a-human-body-anatomy-chart-body/>

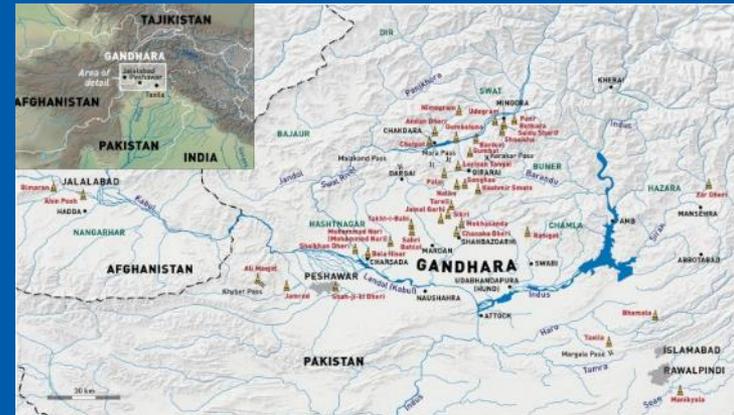
History



Origin of Physiology as a mature science

Ancient India and Egypt

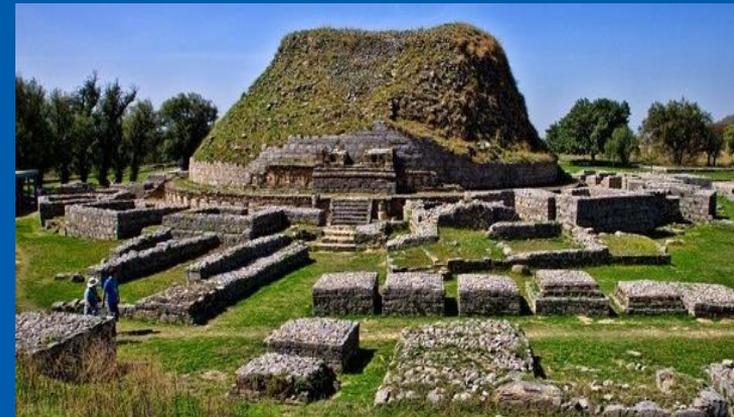
- Knowledge of ancient Egyptian Physiology/medicine
- Limited to papyrus scrolls (>3 000 years old)



<https://www.ancient.eu/image/3943/>

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



<https://travel.jumia.com/blog/pk/historic-city-taxila-1614>

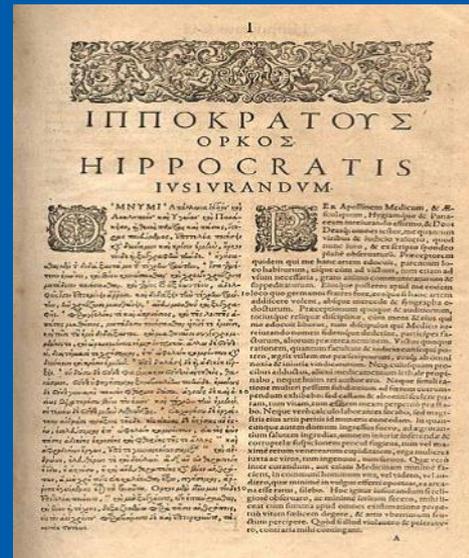
Physiology as a discipline

Hippocrates (460-377 BC)

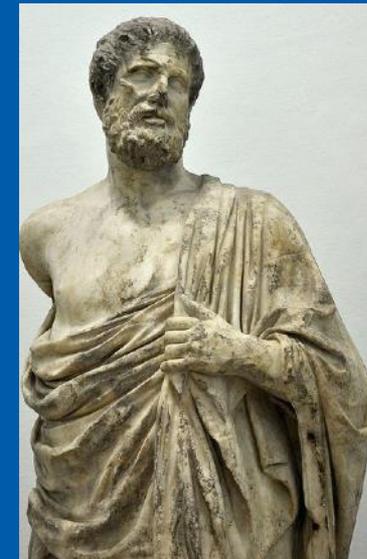
- 'Father of Medicine'
- Inaugurated Physiology centred on observation and case documenting



<http://www.villakos.com/>



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

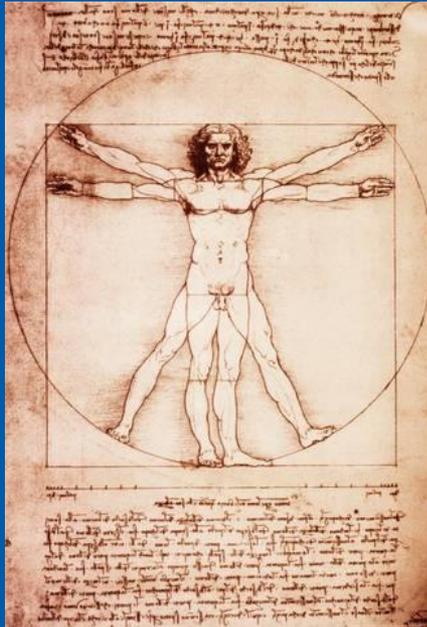


<http://prevencionar.com.ec/2016/01/12/historia-de-la-seguridad-industrial/amp/>

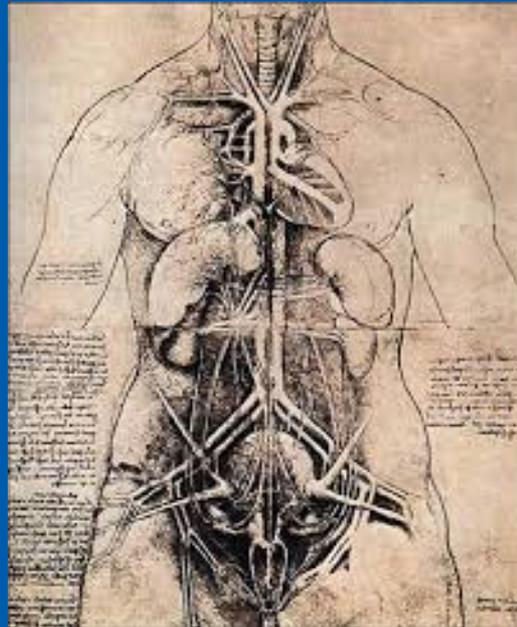
Renaissance

Leonardo da Vinci (1452-1519)

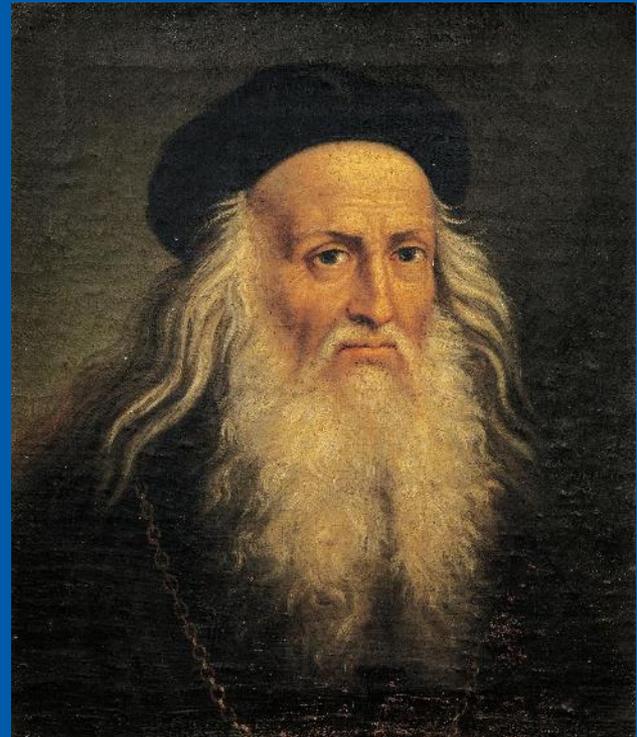
- Postgrad Med J. 1952 Oct; 28(324): 521–528.
- *'Movement is the cause of all life,'*



https://www.allposters.ca/-sp/Vitruvian-Man-posters_i2549011_.htm



<http://theleanberets.com/organic-colon-parts-2-3-summary/>

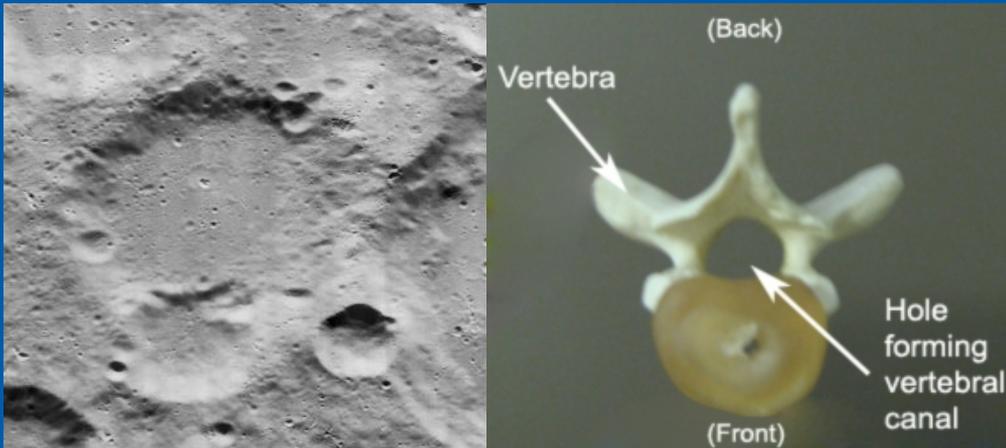


<https://news.nationalgeographic.com/2017/11/leonardo-da-vinci-genius-walter-isacson/>

The term Physiology

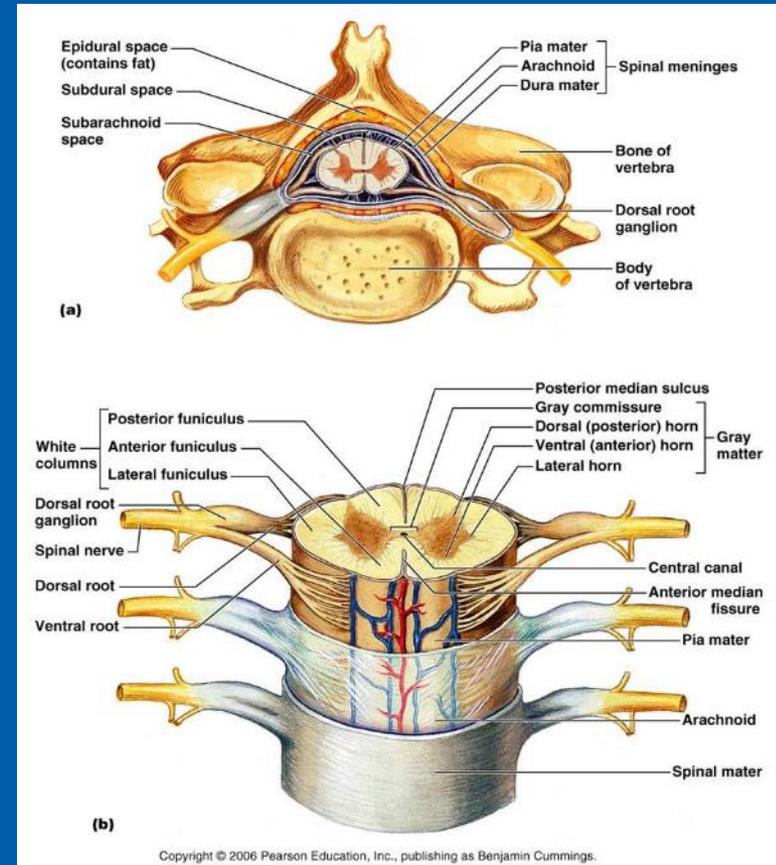
First introduced by Jean Fernel (1497-1558)

- *'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>

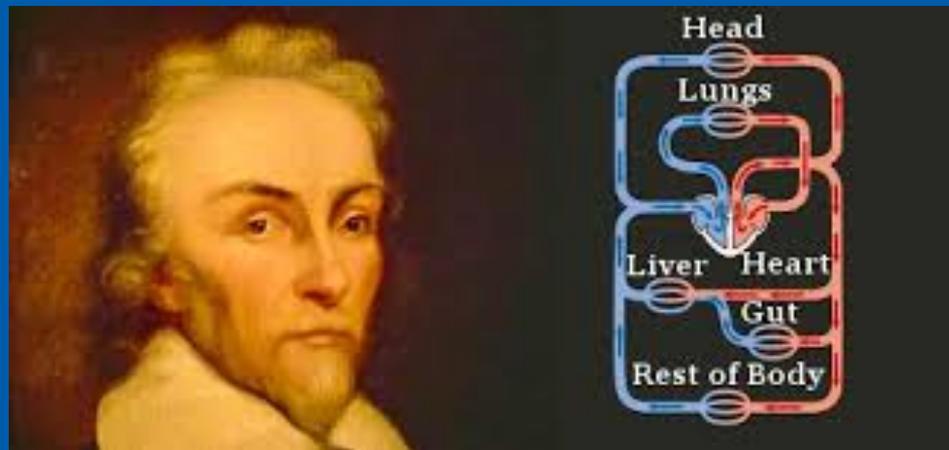


<https://za.pinterest.com/pin/306596687105071470/>

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'*

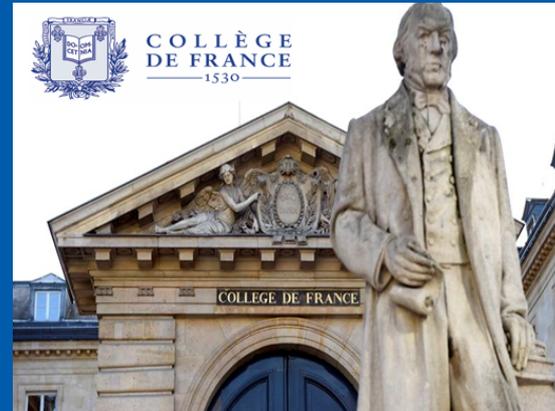


<https://www.famousscientists.org/william-harvey/>

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



<http://www.energie-rs2e.com/en/news/rs2e-director-appointed-college-france>



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

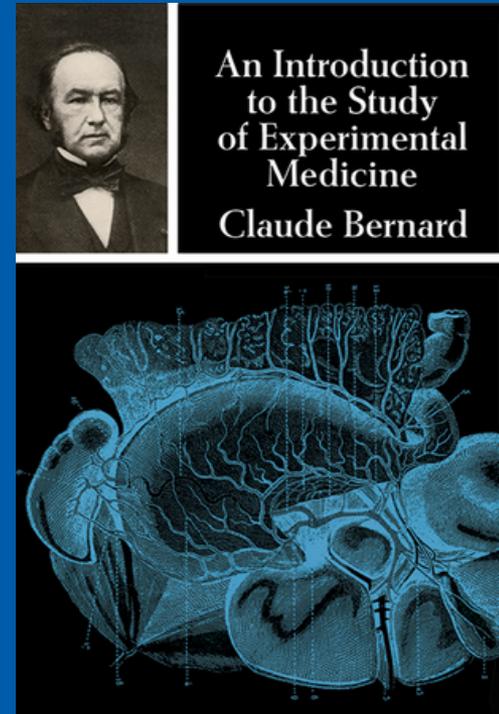


<https://www.livestrong.com/article/417469-what-causes-the-release-of-pancreatic-juice-bile/>

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'

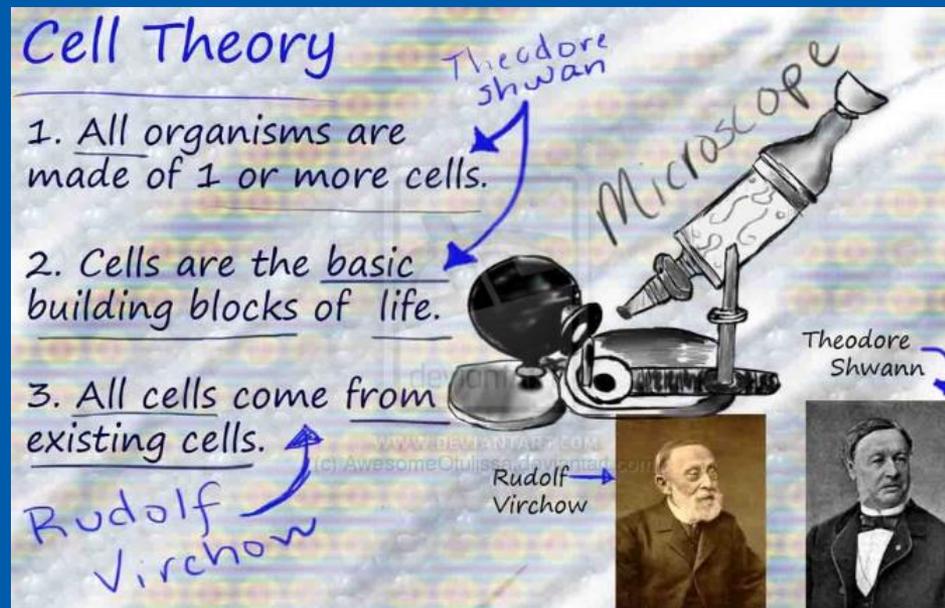


https://www.goodreads.com/book/show/1972743.An_Introduction_to_the_Study_of_Experimental_Medicine

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'

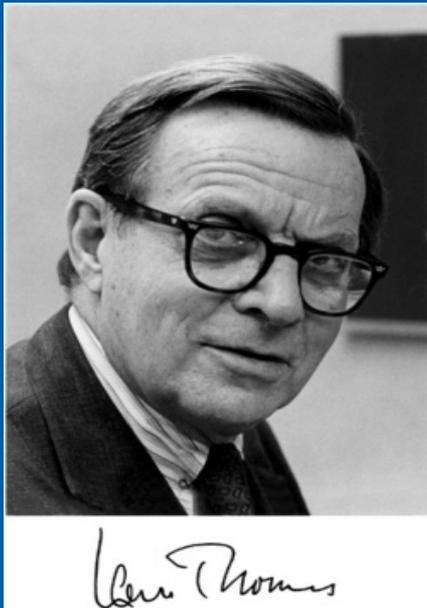


<https://socratic.org/questions/how-do-viruses-violate-the-cell-theory>

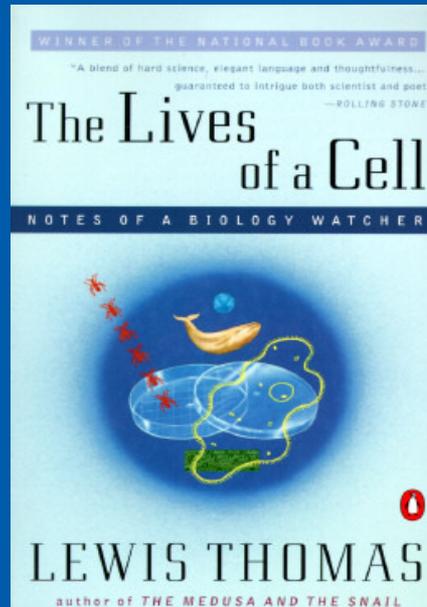
The lives of a cell

Lewis Thomas (1913-1993)

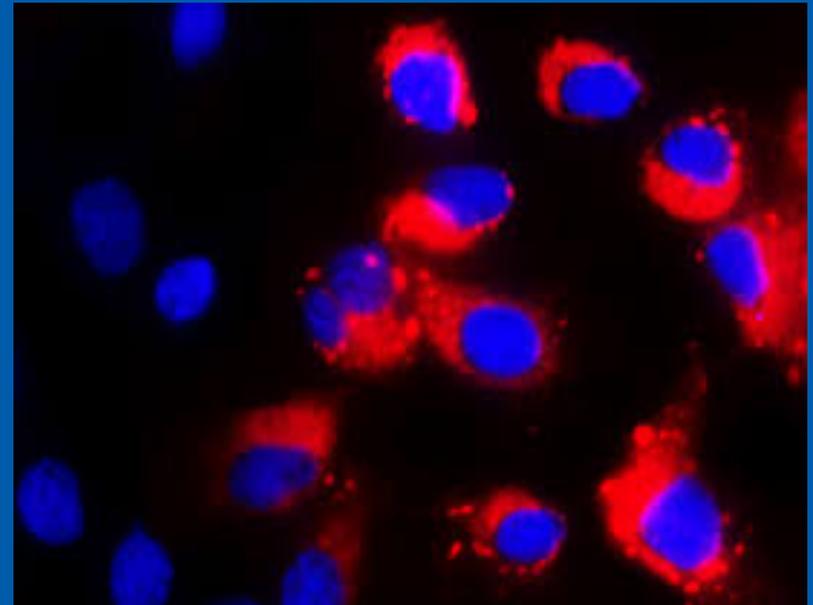
'I have been trying to think of the earth as a single organism, but... I cannot think of it this way. It is too big, too complex, with too many working parts.... it is most like a single cell'



<https://www.nap.edu/read/11172/chapter/19>



https://www.goodreads.com/book/show/294368.The_Lives_of_a_Cell



<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



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

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

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

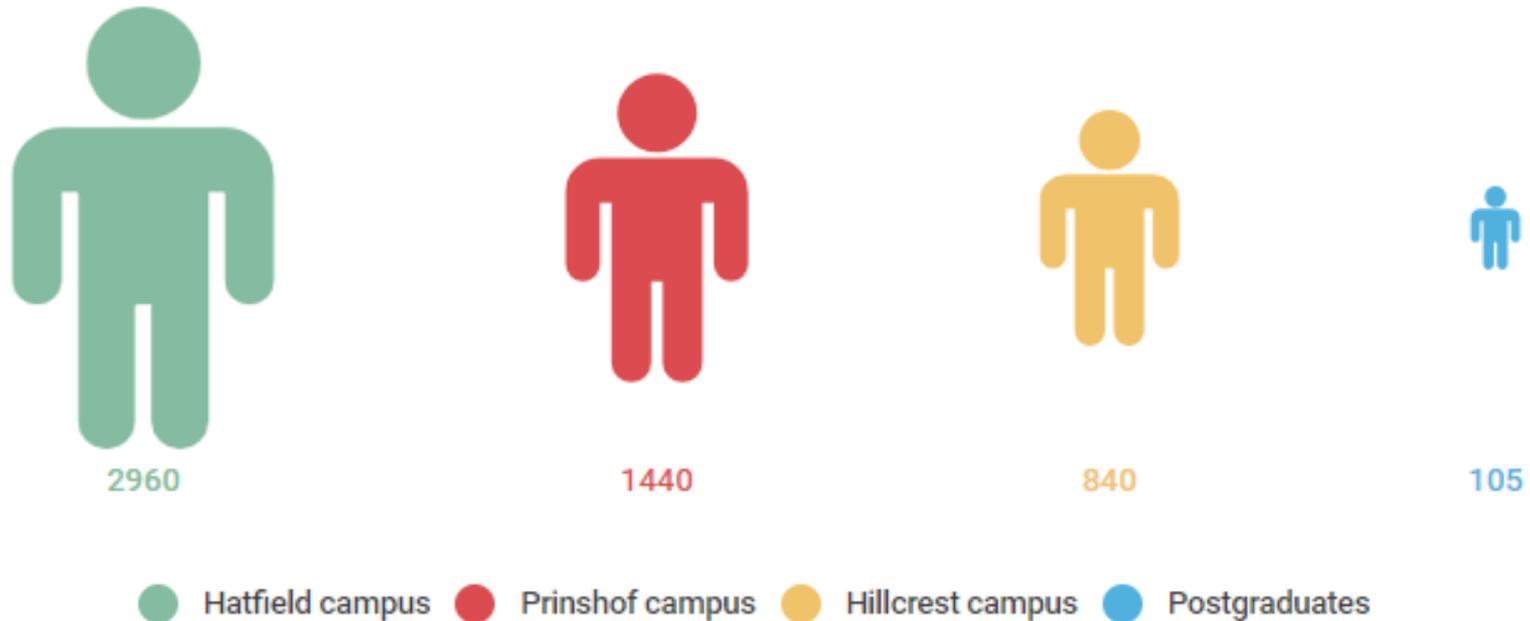
Teaching and Learning

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

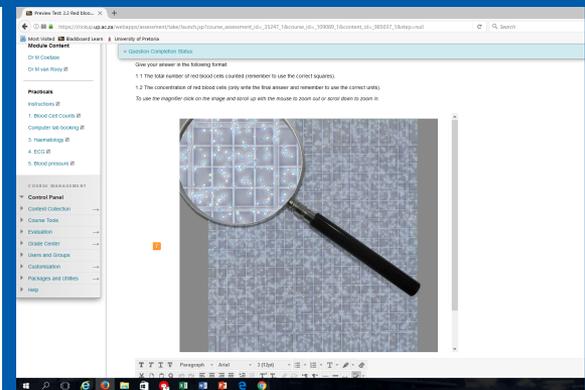
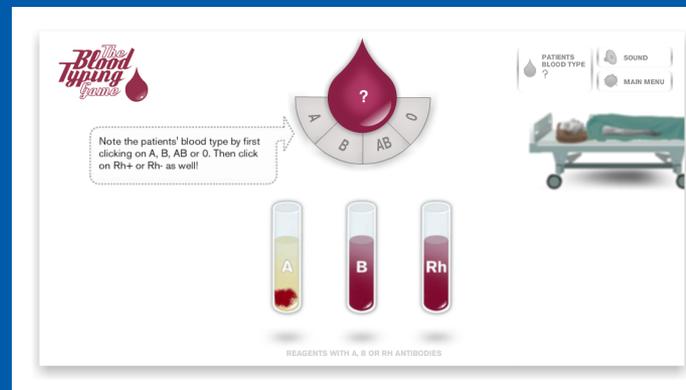
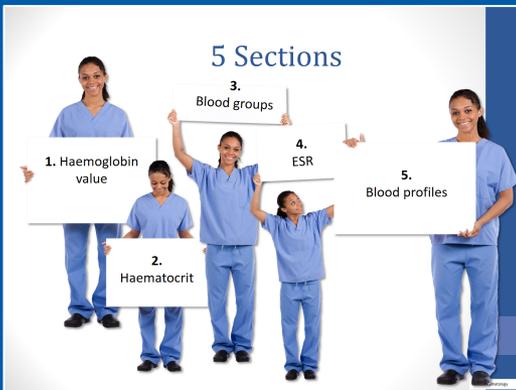
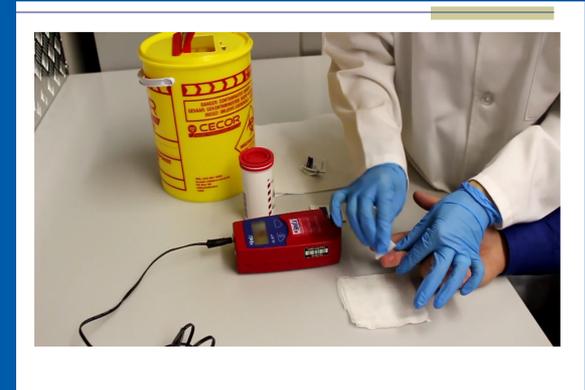
- Medicine
- Dentistry
- Nursing, Occupational therapy, Physiotherapy, Radiography, Dietetics
- Communication pathology
- Biokinetics and Sport Sciences
- Human Physiology - major for two study programs (Faculty of Natural and Agricultural Sciences)
- Food science and some consumer science courses
- ~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



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



Desiree 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



Hildegard
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)



Glory Tambwe



Shanna-lee
Bester



Sachin Bhoora



Ayanda
Mkwanzai



Tarryn
Rodomsky



Leslie Pedzisayi



Jaclyn Moneron



Amy Wium



Karen Barnes



Nonkululeko
Dhlamini



Micha
Barkhuizen



Mikateko
Nxumalo



Melissa Bekker



Justine Pillay



Ashleigh
Gruneberg



Daniël Joubert



Anél Naudé



Sandi Mahlangu



Nicola Weidhase



Nibha Surajlal



Victoria Verrall



Tshinakaho
Mudzunga



Carla Pieterse



Nicola Kruger



Angela Bona



Shannen Marais

Postgraduate students

Biokinetics 2018 (16)



Sports Science 2018 (6)



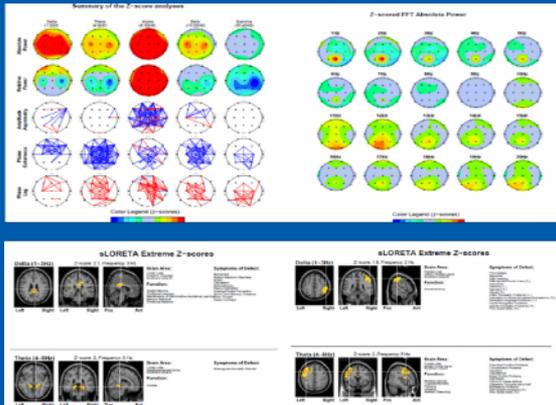
Research



Departmental research focus areas

Research intensive university

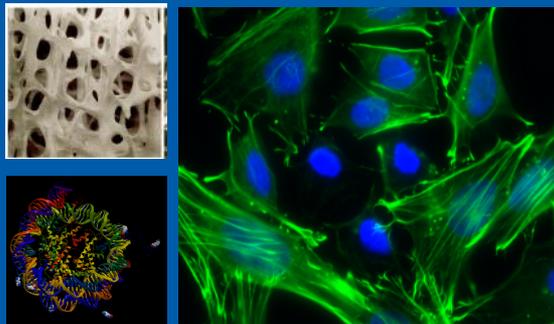
- Neurophysiology



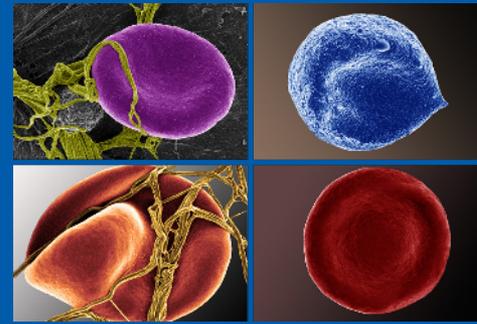
- Sport- and exercise physiology



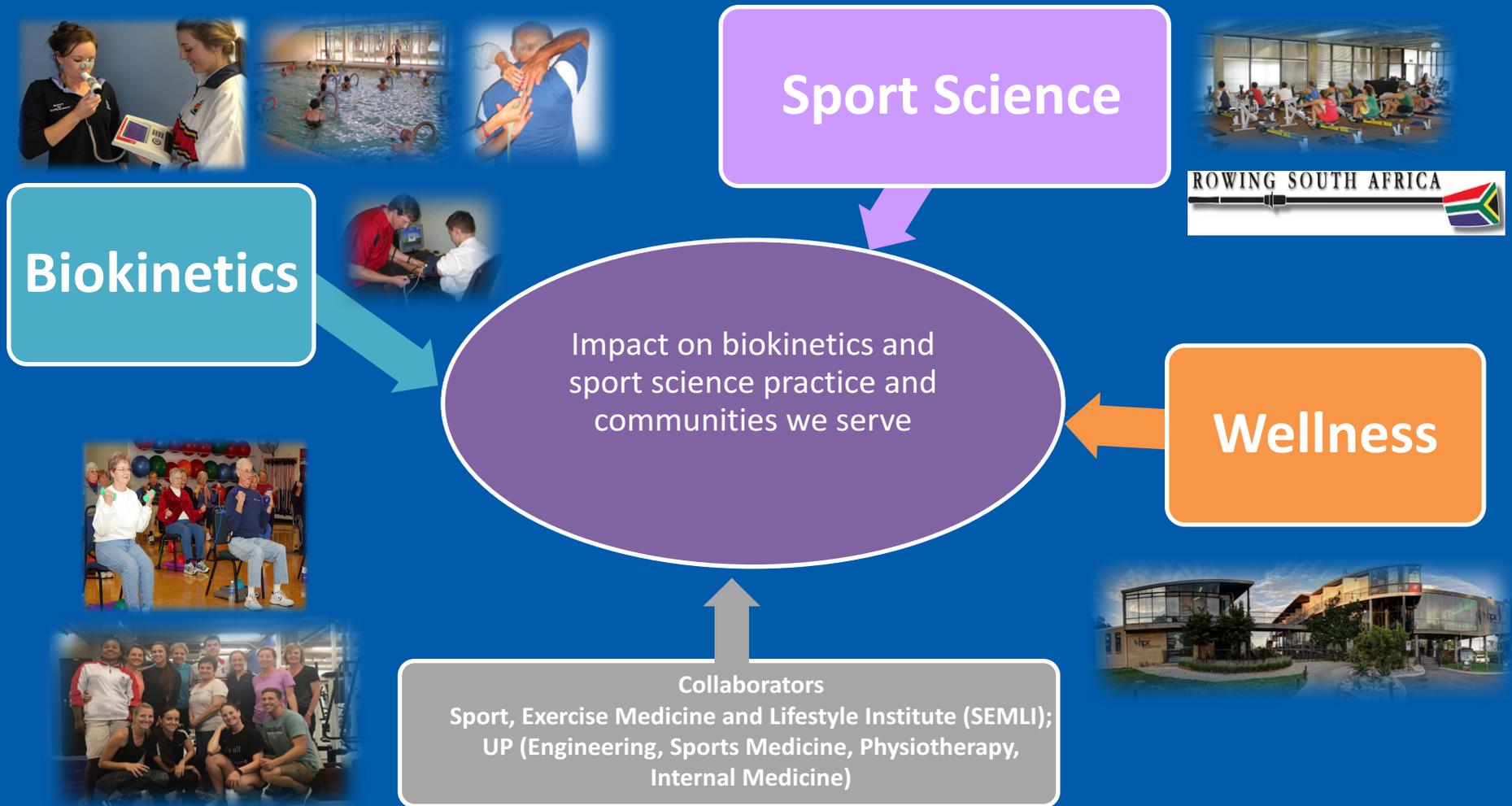
- Cellular- and molecular physiology



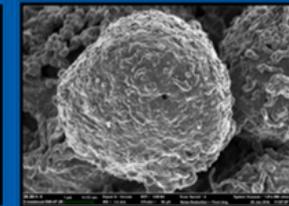
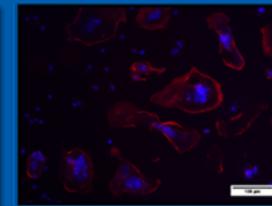
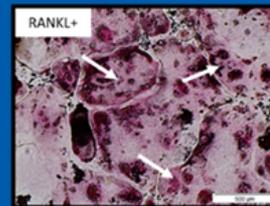
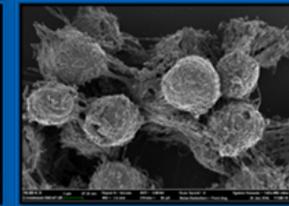
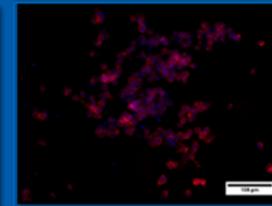
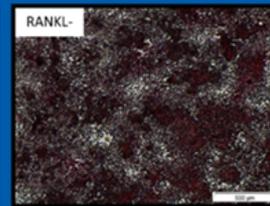
- Applied morphology in pathophysiology



Division of Biokinetics and Sport Science



Bone research (osteoporosis)



German Scientists and UP Researchers collaborating to bring new technology to the Department of Physiology



Travers Sagar kneeling in front of the research team at the Bone Lab, Universitätsklinikum Carl Gustav Carus, Dresden, Germany.

Young UP researcher receives award for excellence at international conference



Postgraduate students in the Department of Physiology receive research accolades at PSSA 2017

The 45th conference of the Physiological Society of Southern Africa was hosted at the Groenkloof Campus in 2017. The conference attracted 694 national and international delegates. Topics were of high quality and included interdisciplinary research in the field of physiology. Several researchers from the Department of Physiology were awarded accolades for their research. Ms T Jurgens (PhD student) was awarded 3rd place in the Wyndham podium competition, as well as 1st place for research methodology. Ms B van Heerden (MSc student)

was awarded 1st prize in the Johnny van der Walt poster competition category and Ms Y Pather (Hons student) was runner-up in this category. Ms S Marais (MSc student) received the best poster award. Mr T Sagar (MSc student) who also recently visited the Bone Laboratory research group in Dresden, Germany, received an accolade in the 'best publication' category for his work published in an internationally accredited peer-reviewed journal.

Food and Function - 2018

Rooibos tea extracts inhibit osteoclast formation and activity through attenuation of NF- κ B activity in RAW264.7 murine macrophages

Nutrients 2017, 9, 441

Palmitoleic Acid Inhibits RANKL-Induced Osteoclastogenesis and Bone Resorption by Suppressing NF- κ B and MAPK Signalling Pathways

PLoSone 10(4): e0125145 - 2015

Arachidonic Acid and Docosahexaenoic Acid Suppress Osteoclast Formation and Activity in Human CD14+ Monocytes, *In vitro*

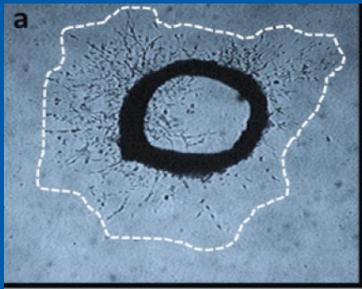
Int. J. Environ. Res. Public Health 2015, 12, 13779-13793

Commercial Honeybush (*Cyclopia* spp.) Tea Extract Inhibits Osteoclast Formation and Bone Resorption in RAW264.7 Murine Macrophages—An *in vitro* Study

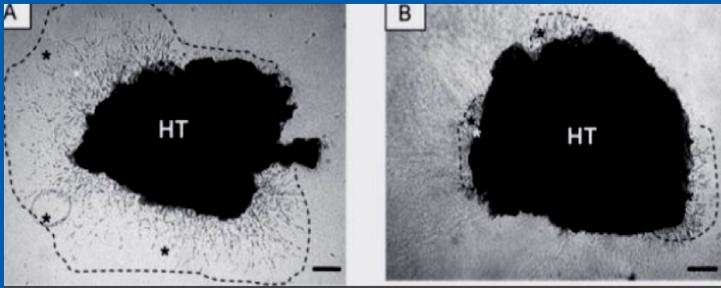
Angiogenesis



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

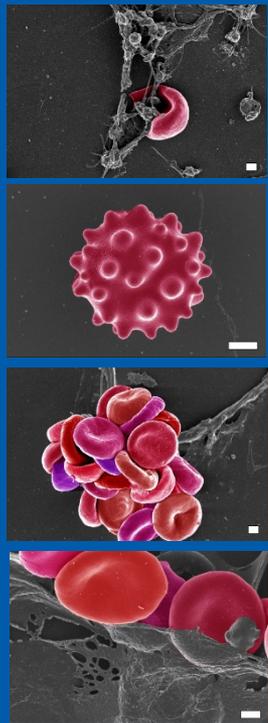


Awarded Microscopy Society of South Africa - Innovative technique

Applied morphology in pathophysiology



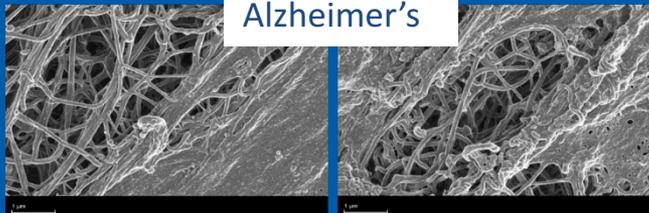
Oral contraceptives



Controls

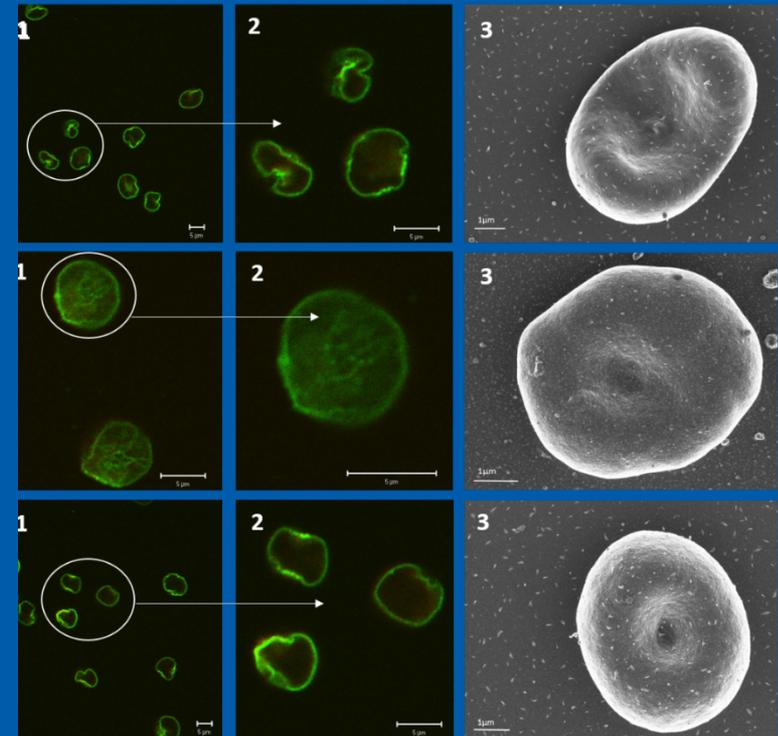


Alzheimer's



Erythrocytes, fibrin and platelets

Scanning electron microscopy
Laser scanning confocal microscopy
Thromboelastography



Molecular mechanisms of non-communicable diseases

- Genetics: genotyping and polymorphisms
- Epigenetics: microRNA analysis
- Biochemical assays



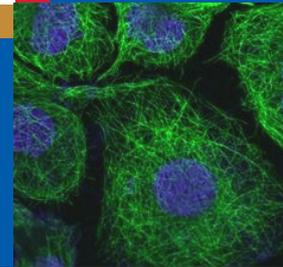
Research focus area: Cellular- and molecular physiology

Cancer cellular physiology



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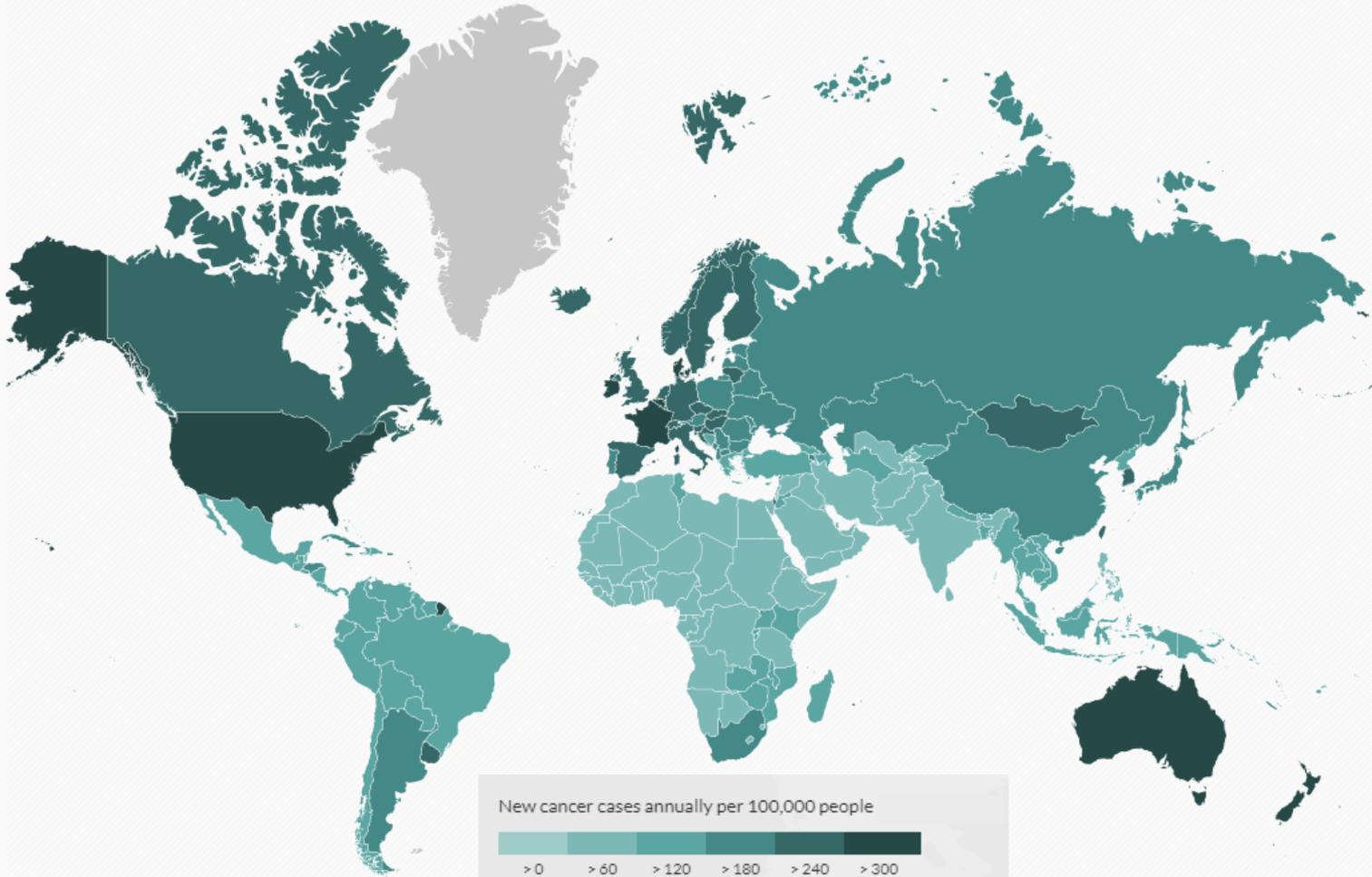
Make today matter



8 Hallmarks of Cancer



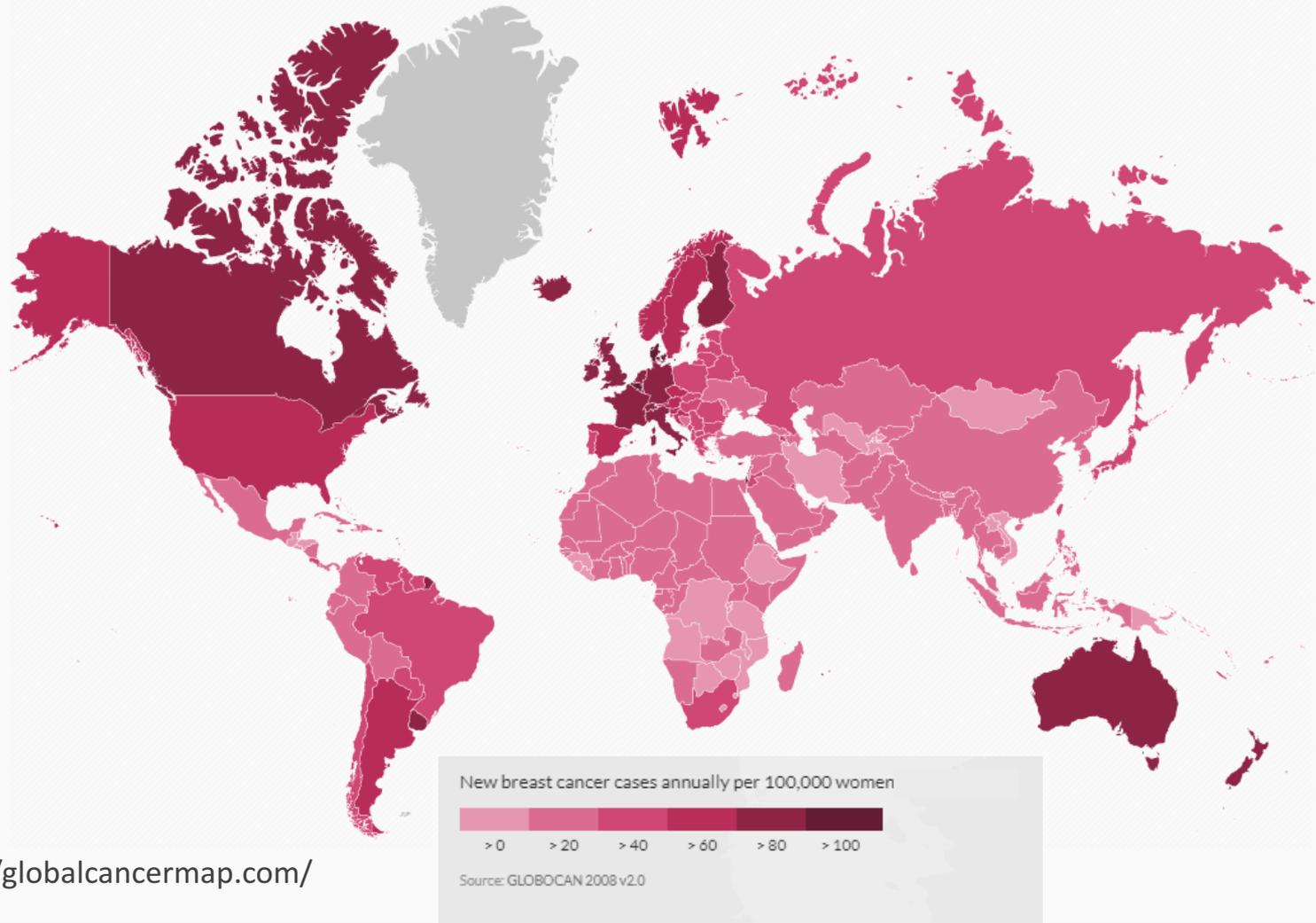
Cancer incidence (internationally)



<http://globalcancermap.com/>

Source: GLOBOCAN 2008 v2.0

Breast cancer incidence (internationally)



<http://globalcancermap.com/>

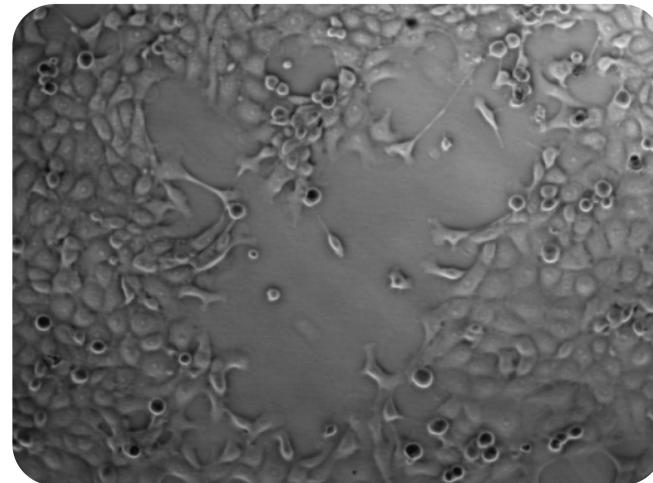
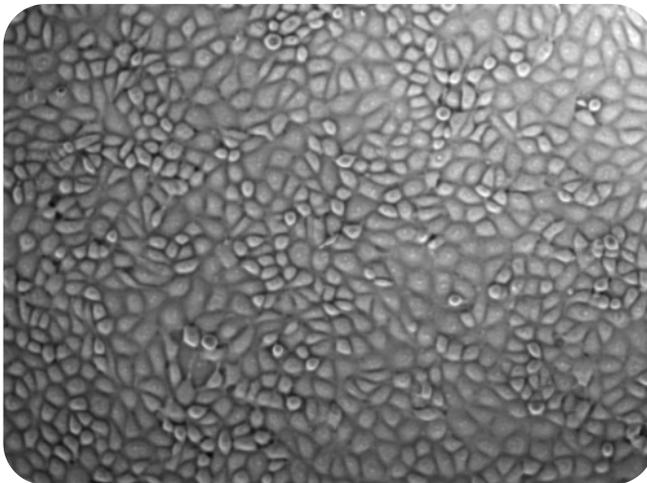
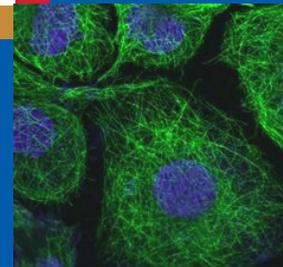
Estrogen and its dual nature?

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

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Postgraduate students and research collaborators



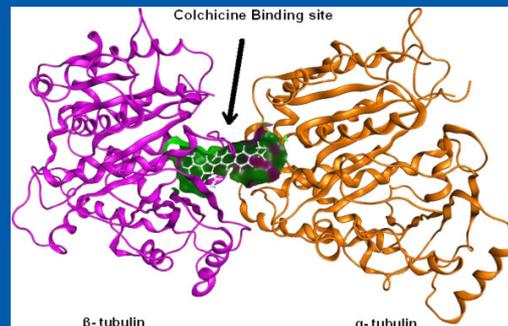
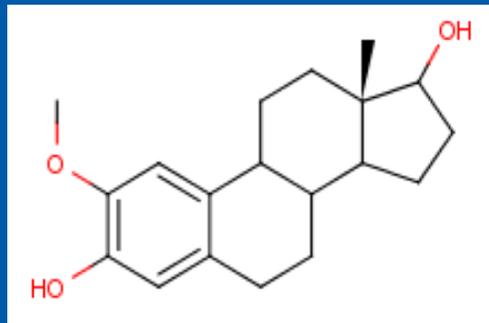
Introduction

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

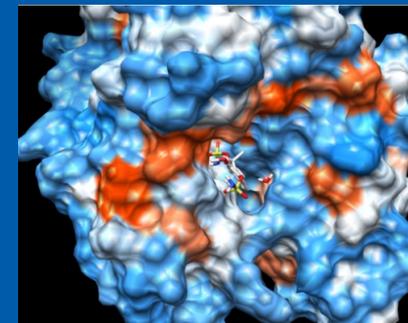
Objective

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_235773573



Materials and methods

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

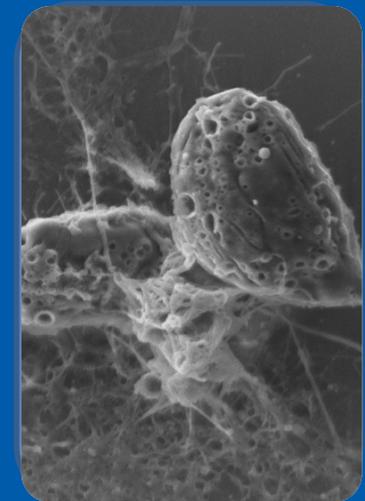
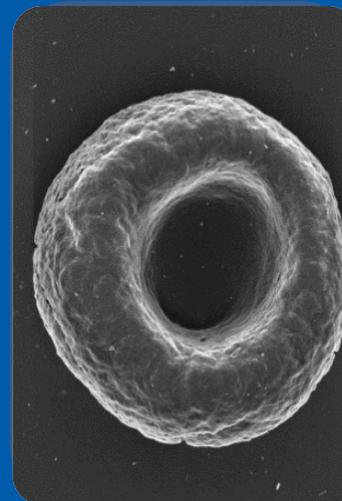
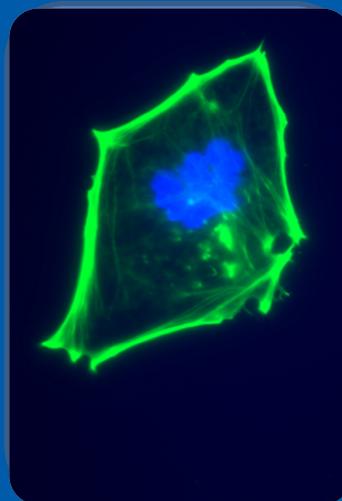
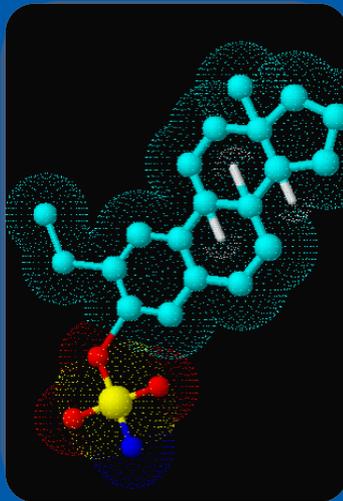
In silico

Synthesis

In vitro

Ex vivo

In vivo



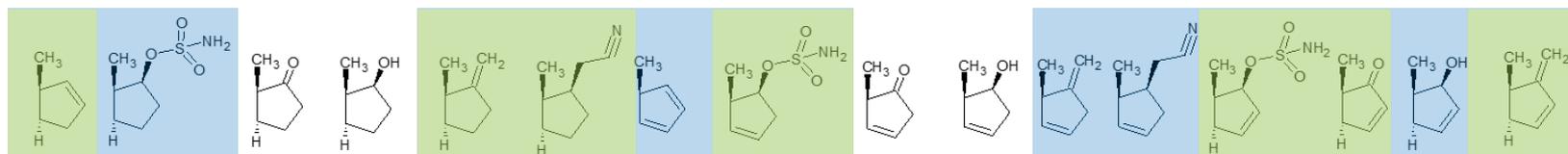
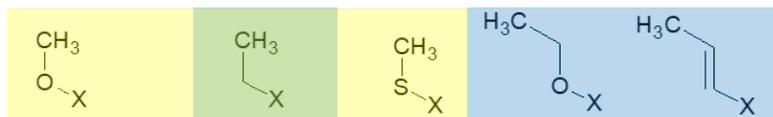
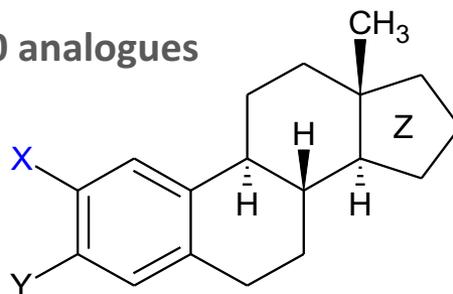
Results - *In silico*

Best tubulin colchicine site binding energy

Molecules to be synthesized

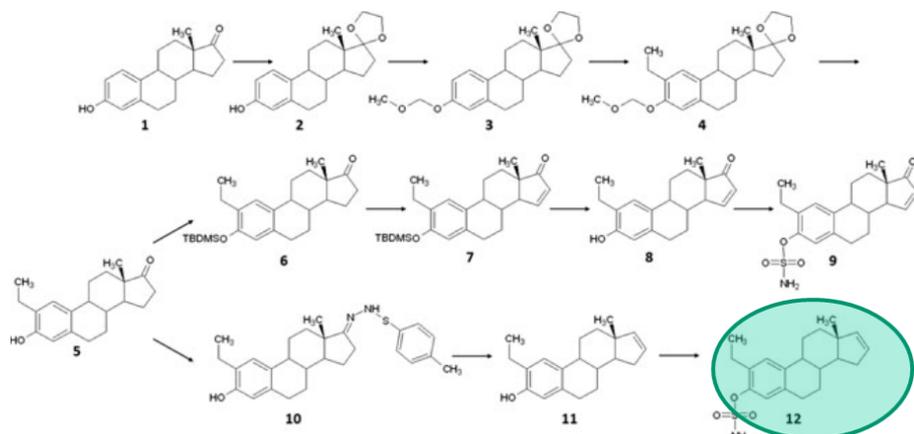
Best CAIX:CAII binding energy ratio

Modifications of estradiol 80 analogues

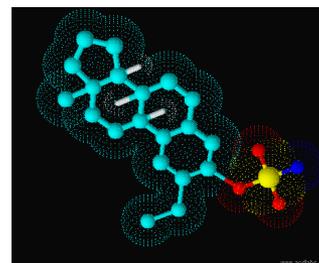


- Ensemble docking
- Multiple X-ray structures
- Tubulin
- Carbonic anhydrase II and IX
- Flexibility of proteins under different conditions (simulate protein flexibility)

Results - Synthesis



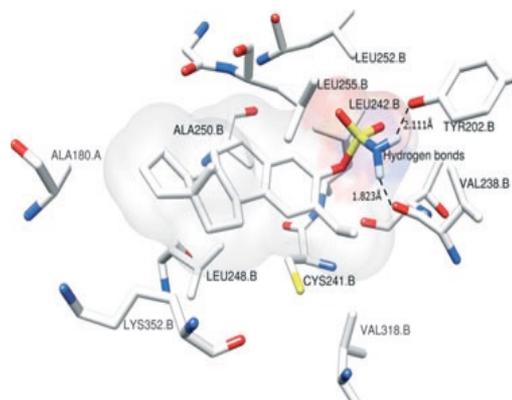
Synthesis scheme of 2ME derivatives



MICROSCOPY RESEARCH AND TECHNIQUE 77:236-242 (2014)

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

MICHELLE HELEN VISAGIE,¹ LYNN-MARIE BIRKHOLTZ,² AND ANNA MARGARETHA JOUBERT^{1*}
¹Department of Physiology, University of Pretoria, Arcadia 0007, South Africa
²Department of Biochemistry, University of Pretoria, Pretoria 0028, South Africa



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

Chem Biol Drug Des 2011

Research Article

© 2011 John Wiley & Sons A/S
 doi: 10.1111/j.1747-0285.2010.01064.x

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

Andre Stander^{1,*}, Fourie Joubert² and Annie Joubert¹

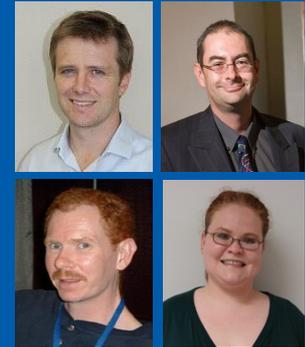
¹Department of Physiology, University of Pretoria, Pretoria, South Africa

binds along the interior surface of the microtubule, thereby interfering with the dynamics of the microtubules (4). Various agents that bind to the colchicine-binding site of microtubules are in various stages of clinical trials. These include combretastatins and its vari-



Results - *In silico*: inhibitory constants

- Carbonic anhydrase II and IX
- Ligand-protein binding analysis → membrane-inlet mass spectrometry
- ~2 times more selective for CAIX



678 *Letters in Drug Design & Discovery*, 2011, 8, 678-684

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

Katherine H. Sippel¹, Andre Stander², Chingkuang Tu³, Balasubramanian Venkatakrishnan¹, Arthur H. Robbins¹, Mavis Agbandje-McKenna¹, Fourie Joubert⁴, Annie M. Joubert⁴ and Robert McKenna^{*1}

OPEN ACCESS Freely available online



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

Barend Andre Stander^{1*}, Fourie Joubert², Chingkuang Tu³, Katherine H. Sippel⁴, Robert McKenna⁵, Annie Margaretha Joubert²

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 Baylor College of Medicine, Houston, Texas, United States of America, ⁵ Department of Pharmacology and Therapeutics, University of Florida, Gainesville, Florida, United States of America

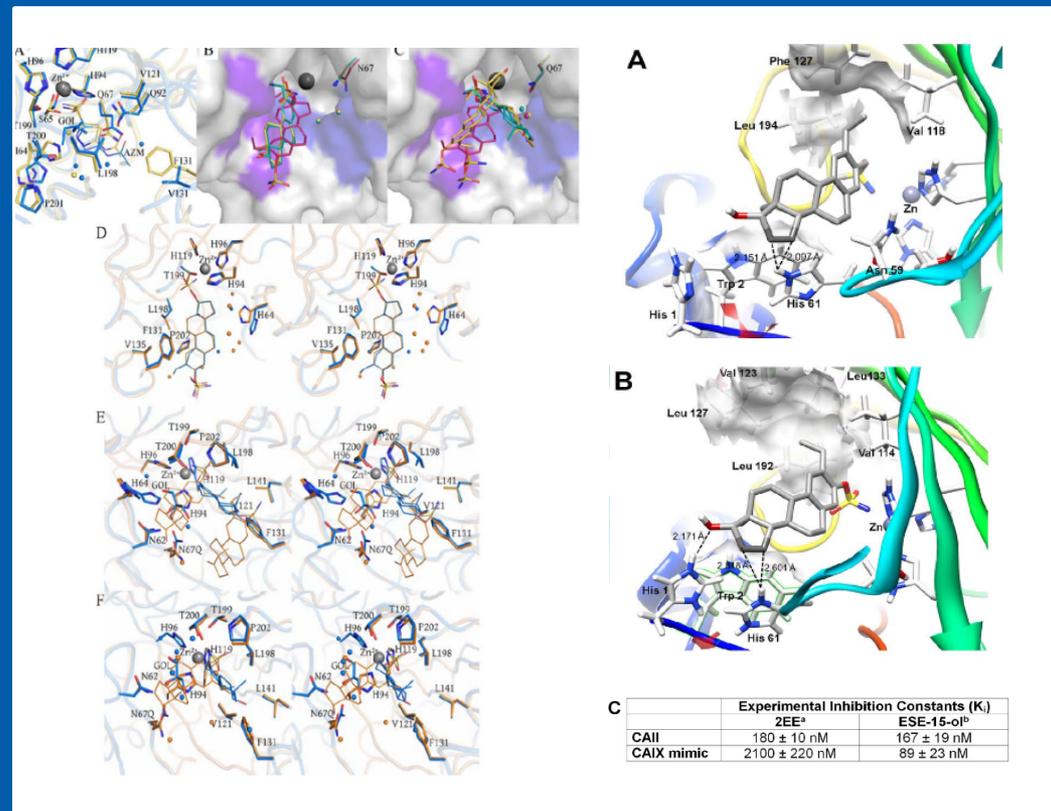
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In Vitro Evaluation of ESE-15-ol, an Estradiol Analogue with Nanomolar Antimitotic and Carbonic Anhydrase Inhibitory Activity

Barend Andre Stander^{1*}, Fourie Joubert², Chingkuang Tu³, Katherine H. Sippel⁴, Robert McKenna⁵, Annie Margaretha Joubert¹

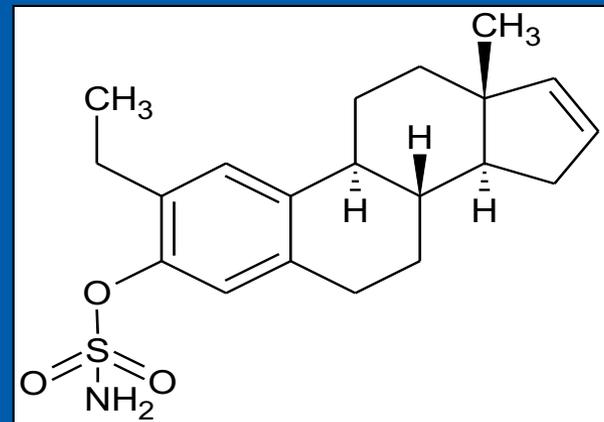
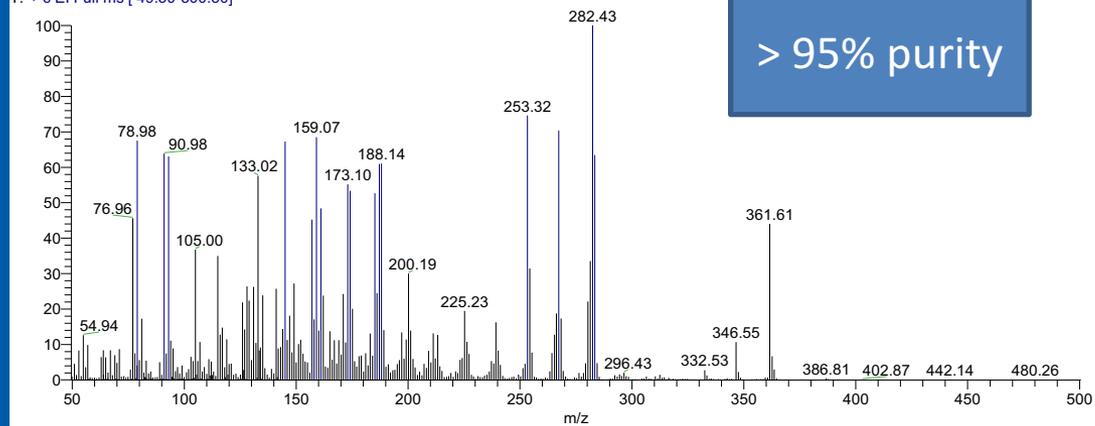
¹ Department of Physiology, University of Pretoria, Pretoria, Gauteng, South Africa, ² Department of Biochemistry, Bioinformatics and Computational Biology Unit, University of Pretoria, Pretoria, Gauteng, South Africa, ³ Department of Biochemistry and Molecular Biology, College of Medicine, University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



Results - Synthesis: purity

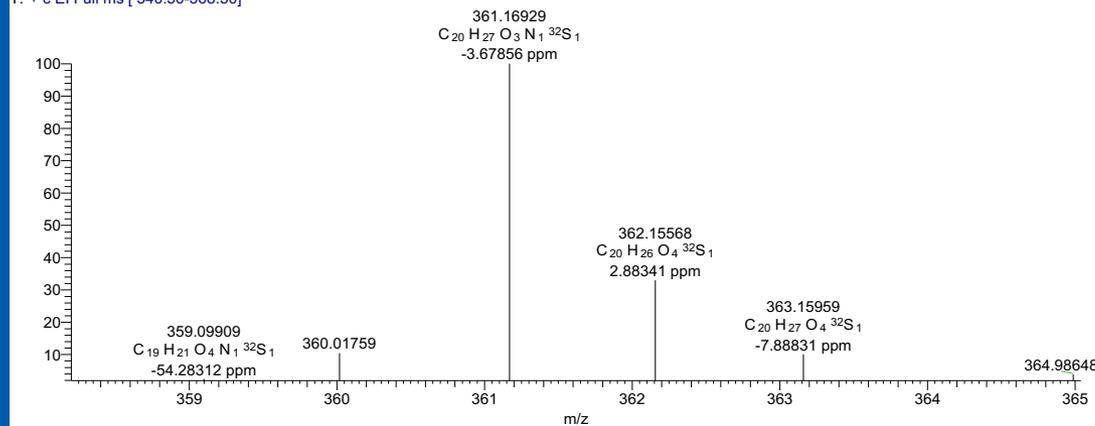


C19 #25 RT: 0.90 AV: 1 NL: 1.43E8
T: + c EI Full ms [49.50-500.50]

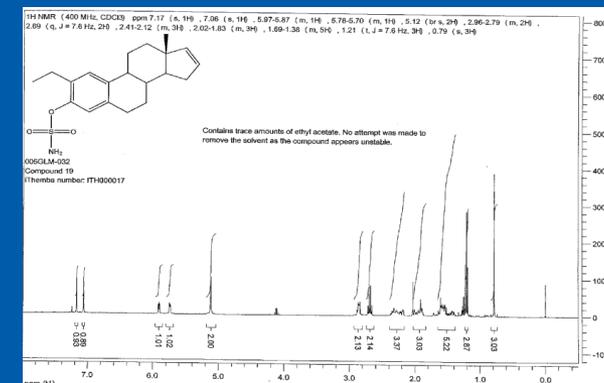


2-Ethyl-3-O-sulphamoyl-estra-1,3,5(10)16-tetraene (ESE-16)

C19_HR-c1 #159-162 RT: 2.29-2.34 AV: 4 93E5
T: + c EI Full ms [340.50-368.50]

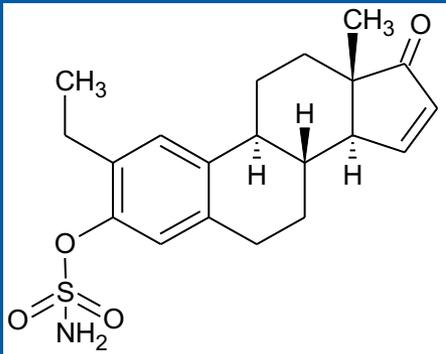


1H Nuclear Magnetic Resonance (WITS)

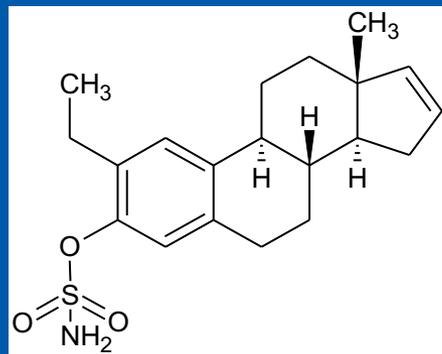


Electron Impact (EI)

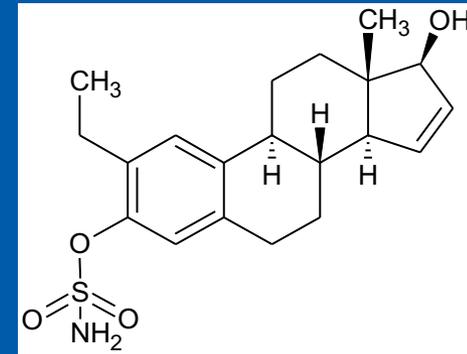
Results - *In vitro*: cell proliferation



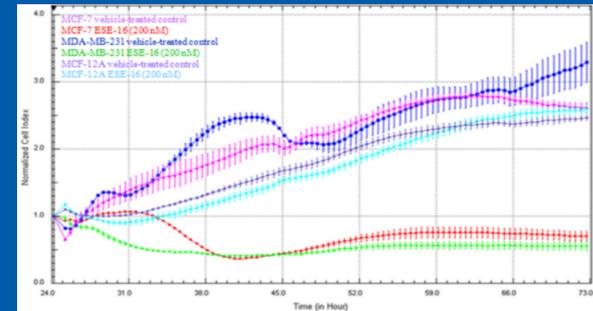
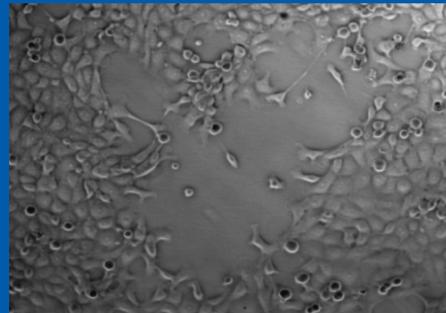
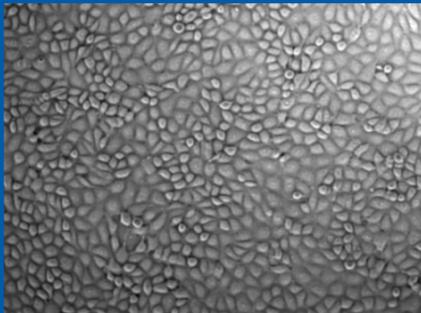
ESE-15-one



ESE-16



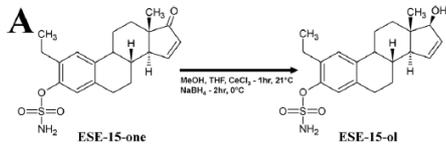
ESE-15-ol



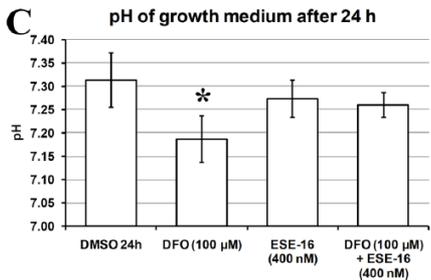
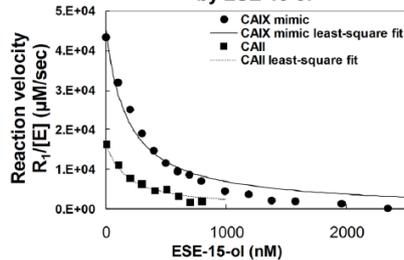
Growth inhibitory effect of ESE-16 on MCF-7, SNO, MDA-MB-231, HeLa and MCF-12A cells



Results - signalling



B CAII and CAIX Mimic Enzyme Inhibited by ESE-15-ol



Visagie *et al. Cell & Bioscience* (2015) 5:37
DOI 10.1186/s13578-015-0030-1



RESEARCH

Open Access



Influence of partial and complete glutamine- and glucose deprivation of breast- and cervical tumorigenic cell lines

Michelle Helen Visagie^{1*}, Thandi Vuyelwa Mqoco¹, Leon Liebenberg², Edward Henry Mathews², George Edward Mathews² and Anna Margaretha Joubert¹

Prof AM Joubert – Inaugural Address – 12 June 2018

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

Barend Andre Stander^{1*}, Fourie Joubert², Chingkuang Tu³, Katherine H. Sippel⁴, Robert McKenna⁵, Annie Margaretha Joubert²

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



CELLULAR & MOLECULAR BIOLOGY LETTERS
<http://www.cmbi.org.pl>



Received: 03 September 2014
Final form accepted: 29 January 2014
Published online: February 2014

Volume 19 (2014) pp 98-115
DOI: 10.2478/s11658-014-0183-7
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Research article

NOVEL ESTRADIOL ANALOGUE INDUCES APOPTOSIS AND AUTOPHAGY IN ESOPHAGEAL CARCINOMA CELLS

ELIZE WOLMARANS¹, THANDI V. MQOCO¹, ANDRE STANDER¹, SANDRA D. NKANDEU¹, KATHERINE SIPPEL², ROBERT MCKENNA³ and ANNIE JOUBERT^{1,*}

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

ISSN 0970-938X
<http://www.biomedres.info>

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.

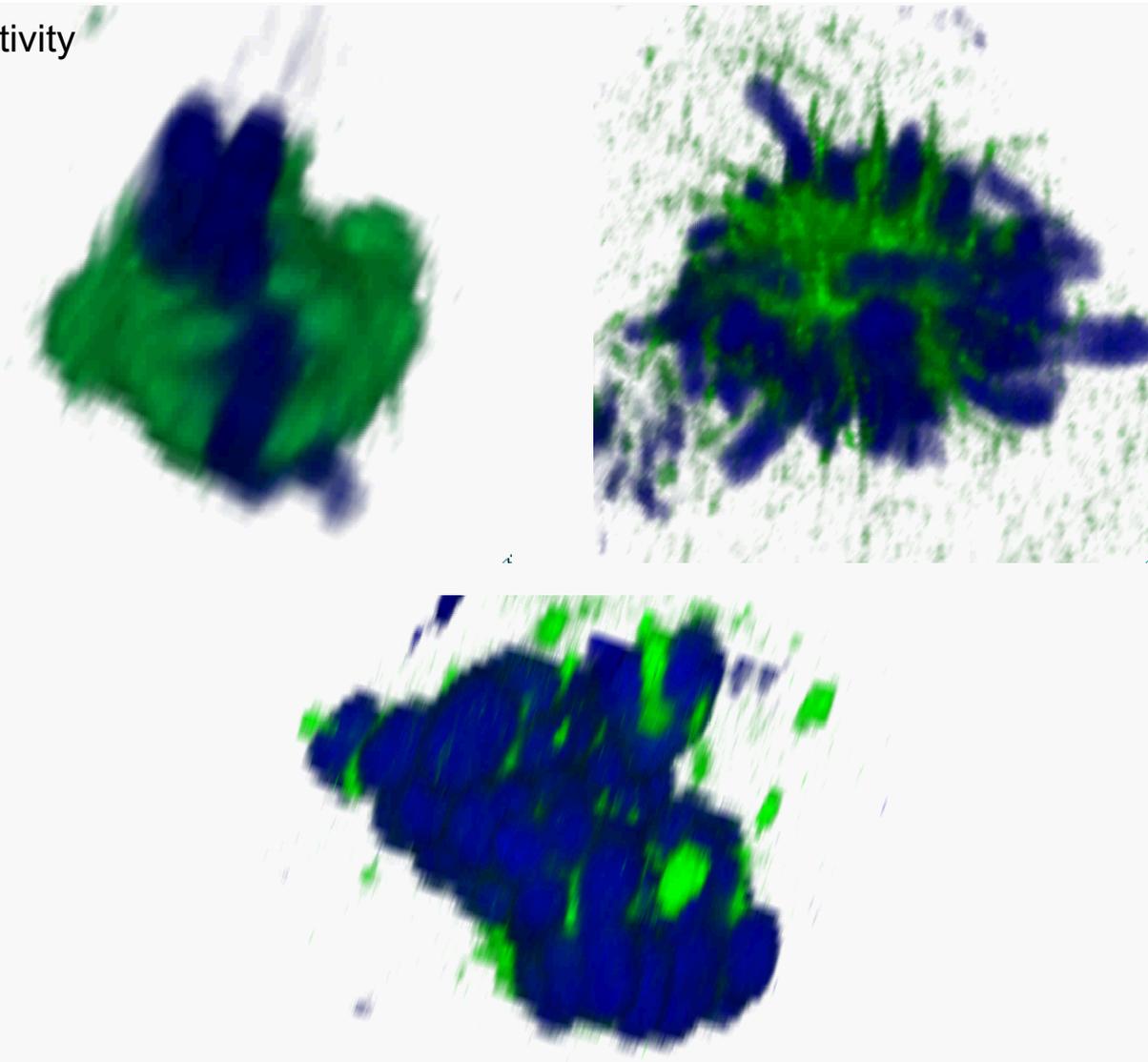
Michelle Helen Visagie¹, Barend André Stander¹, Lyn-Marie Birkholtz², Annie Margaretha Joubert¹

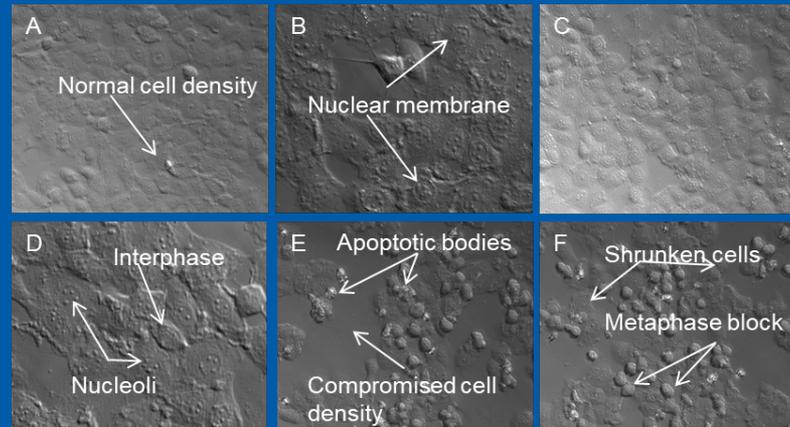
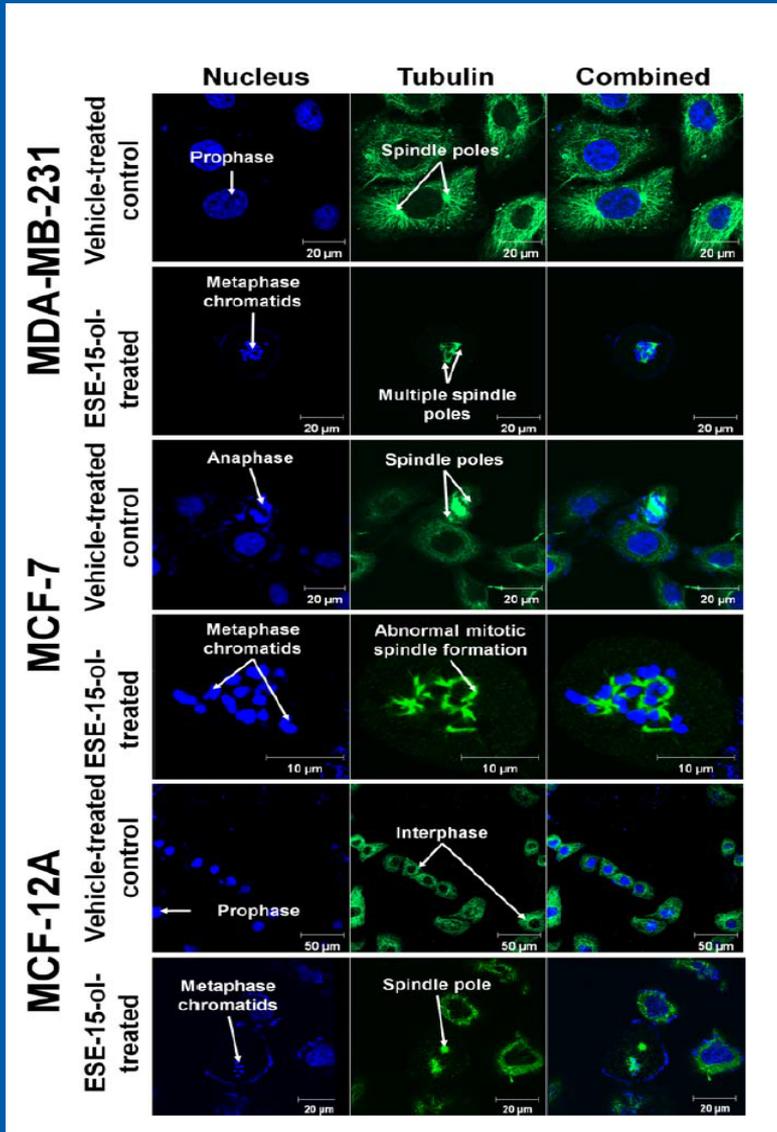
¹Department of Physiology, University of Pretoria, Private Bag X323, Arcadia, 0007, South Africa

²Department of Biochemistry, University of Pretoria, Private Bag X20 Hatfield, Pretoria, 0028, South Africa



Anti-mitogenic activity





CELL BIOCHEMISTRY & FUNCTION

CELL BIOCHEMISTRY AND FUNCTION
Cell Biochem Funct (2013)
 Published online in Wiley Online Library
 (wileyonlinelibrary.com) DOI: 10.1002/cbf.2937

In vitro changes in mitochondrial potential, aggresome formation and caspase activity by a novel 17-β-estradiol analogue in breast adenocarcinoma cells

Danielle S. Nkandeu¹, Thandi V. Mqoco¹, Michelle H. Visagie¹, Barend A. Stander¹, Elize Wolmarans¹, Marianne J. Cronje² and Annie M. Joubert^{1*}

¹Department of Physiology, University of Pretoria, South Africa
²Department of Biochemistry, University of Johannesburg, South Africa

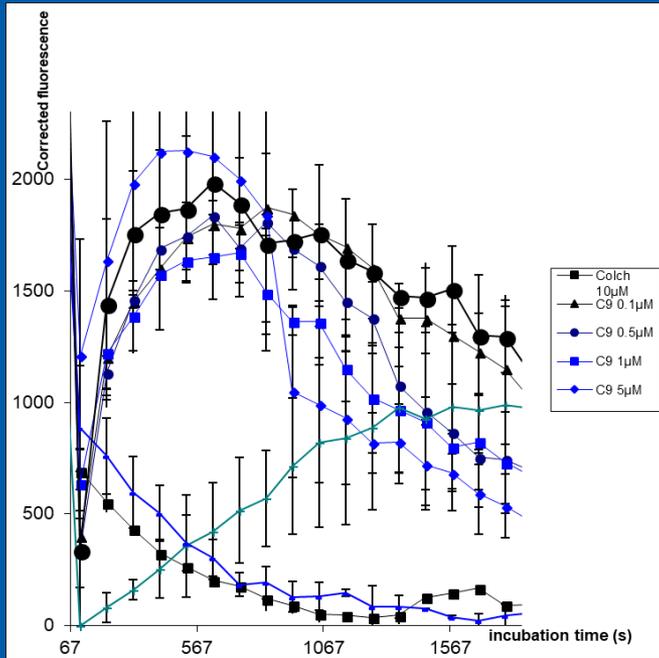
Boyd et al. *Cellular & Molecular Biology Letters* (2018) 23:10
<https://doi.org/10.1186/s11658-018-0079-z>

Cellular & Molecular
Biology Letters

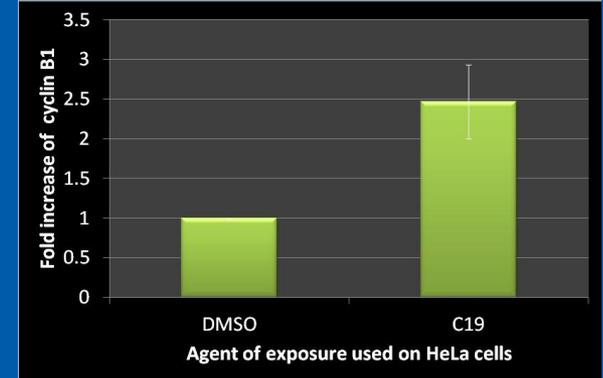
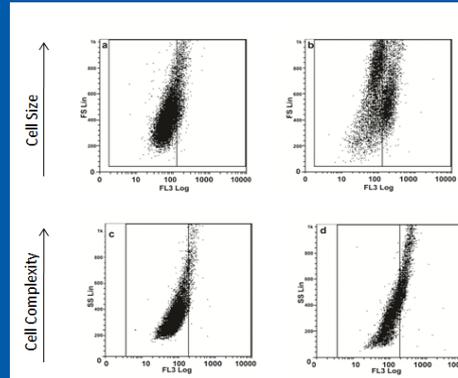
RESEARCH **Open Access**

The *in vitro* effects of a novel estradiol analog on cell proliferation and morphology in human epithelial cervical carcinoma

Laura Susan Boyd¹, Devrim Gozuacik² and Anna Margaretha Joubert^{1*}



Inhibition of tubulin polymerization



OPEN ACCESS Freely available online

PLOS ONE

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 Joubert^{1*}

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 Chantourne, La Tronche Cedex, France



Gwangwa et al. Cellular & Molecular Biology Letters (2018) 23:20
<https://doi.org/10.1186/s11658-018-0088-y>

Cellular & Molecular
Biology Letters

REVIEW

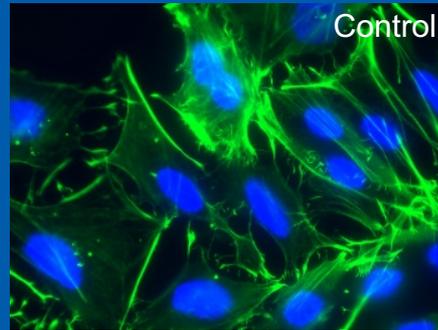
Open Access



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

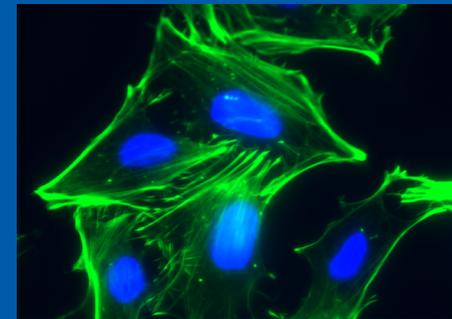
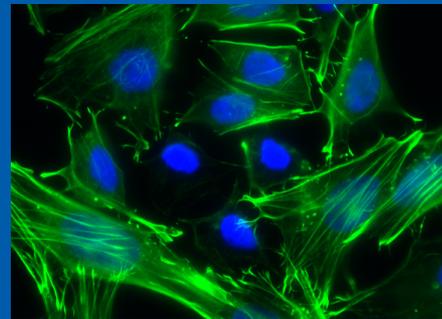
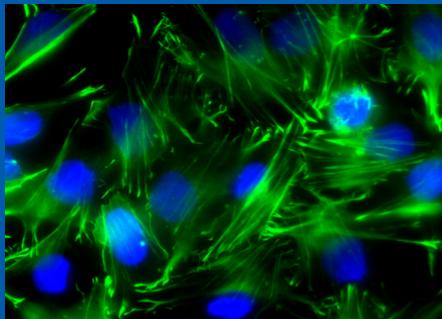


1 μ M Colchicine

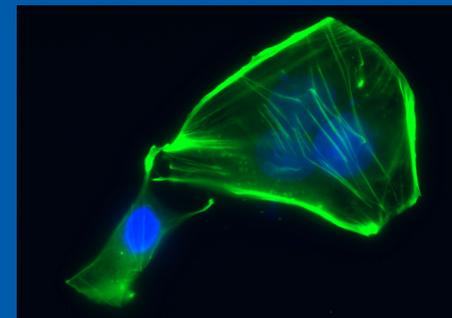
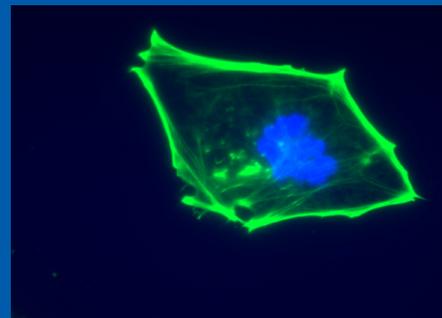
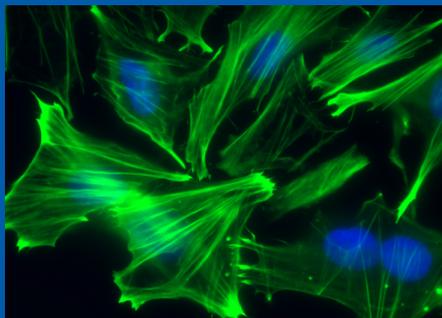
0.2 μ M ESE-16

0.5 μ M ESE-16

2 hours

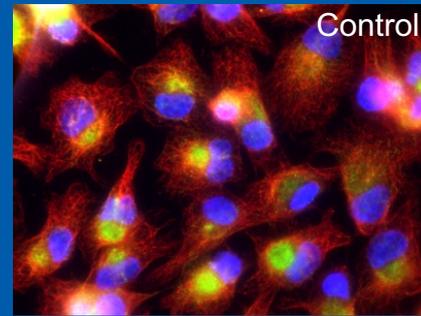


24 hours



Actin fibre response to microtubule abrogation

Tyrosinated/detyrosinated tubulin

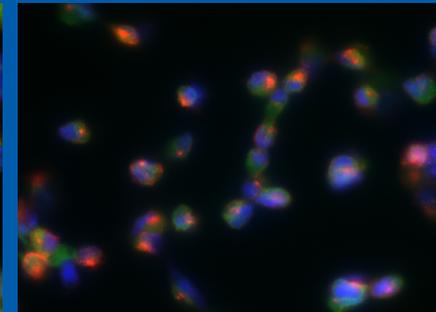
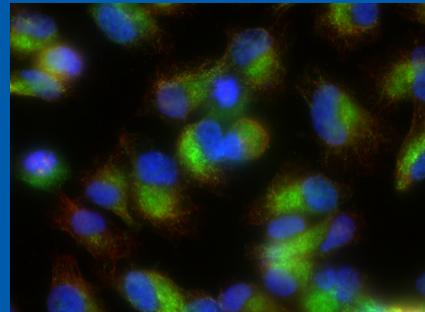
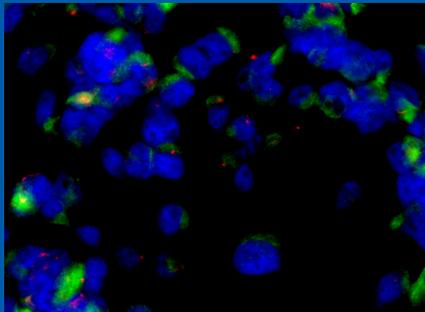


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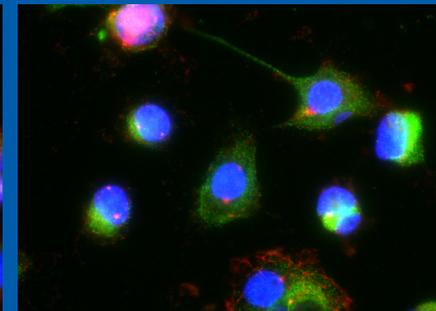
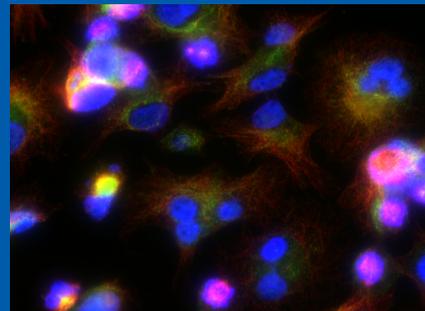
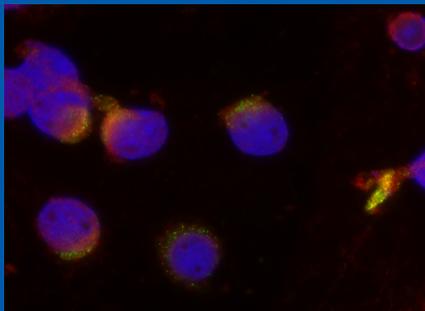
0.2 μ M ESE-16

0.5 μ M ESE-16

2 hours

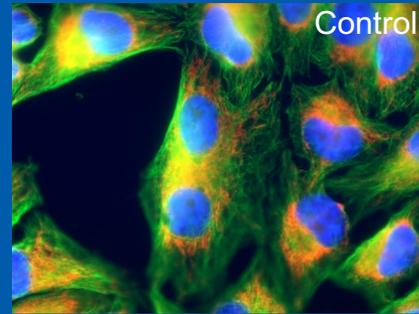


24 hours



Tyrosinated and detyrosinated microtubules in response to compound exposure

Mitochondrial response

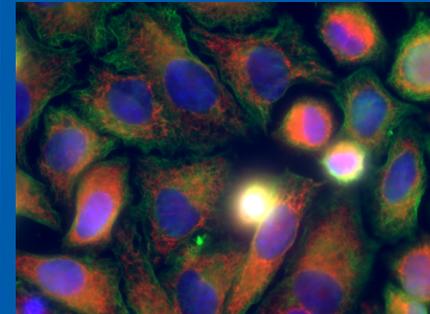
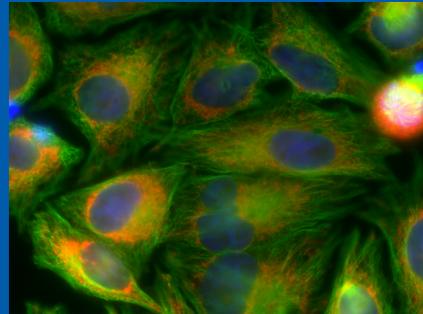
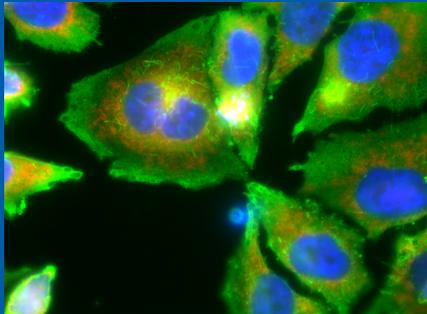


1 μ M Colchicine

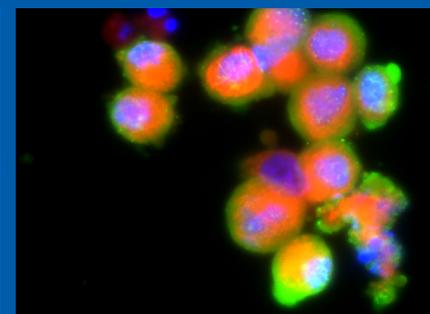
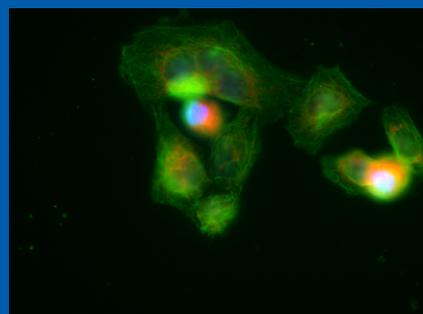
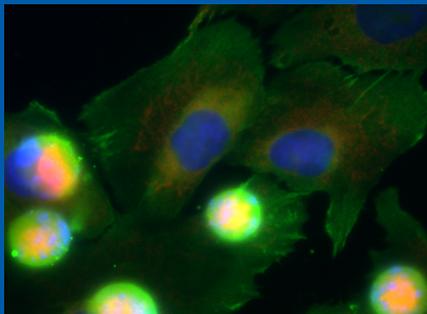
0.2 μ M ESE-16

0.5 μ M ESE-16

2 hours

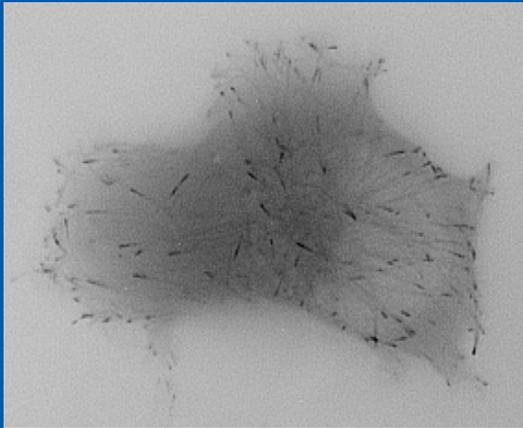


24 hours

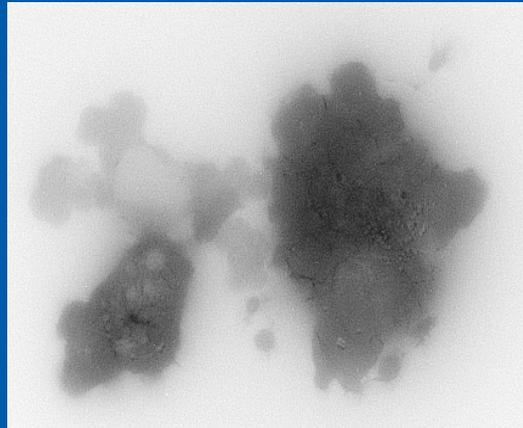


Tyrosinated and detyrosinated microtubules in response to compound exposure

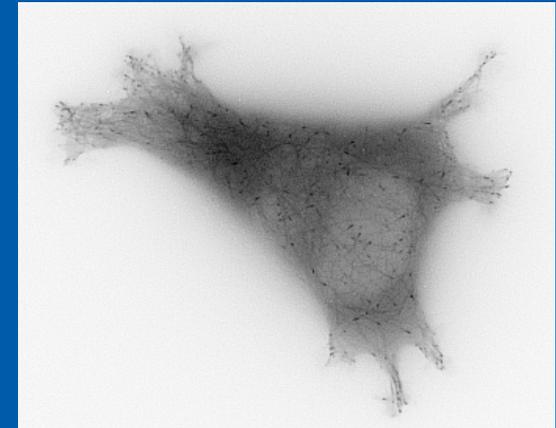
Microtubule dynamics



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

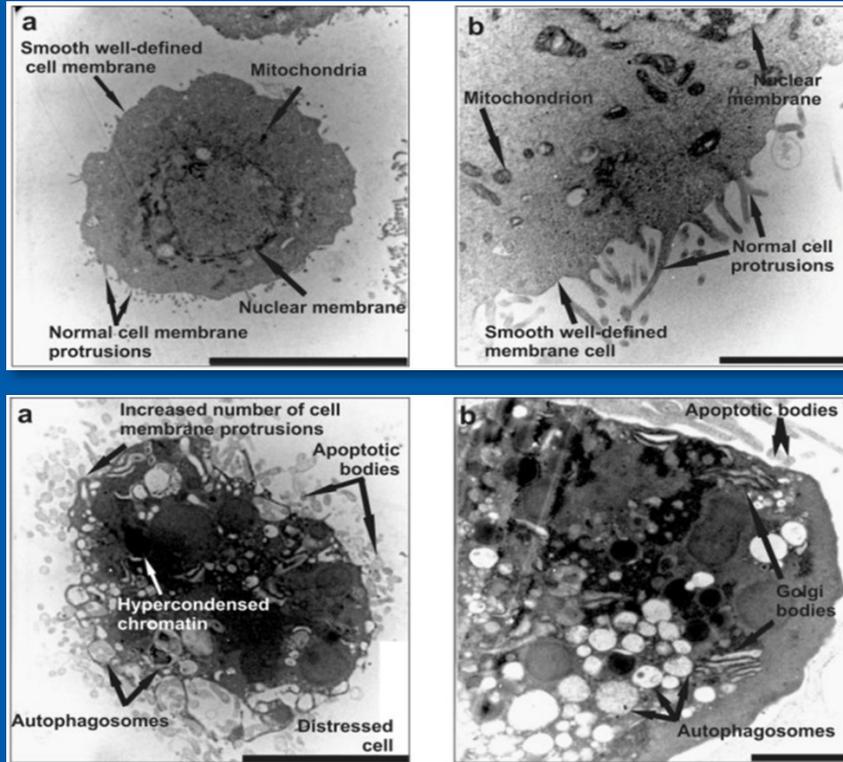
Table 1: Parameters of microtubule dynamics after 0.25 μM C19 exposure for 2 hours

Parameters	DMSO	C19 0.25 μM
% time spent growing	73.79	28.58
% time spent in pause	26.21	71.42
Growth rate ($\mu\text{m}/\text{min} \pm \text{SE}$)	14.52 \pm 1.00	9.79 \pm 0.64
Catastrophe frequency ($\mu\text{m}^{-1} \pm \text{SE}$)	0.15 \pm 0.04	0.78 \pm 0.16**
Catastrophe frequency ($\text{min}^{-1} \pm \text{SE}$)	1.57 \pm 0.59	2.12 \pm 0.42*

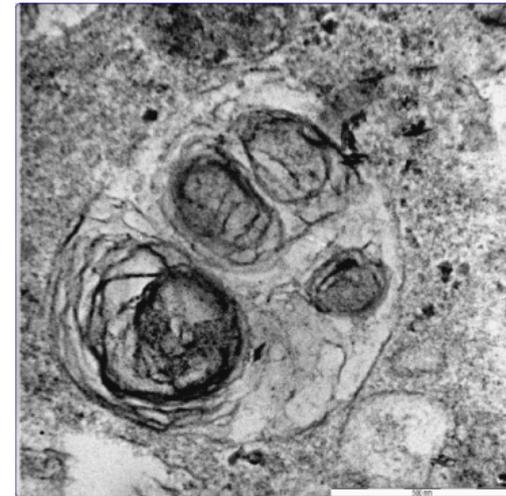
*p < 0.05; **p < 0.001, significantly different from control values (DMSO) using a Student's t test

(Catastrophe: switch from growth to shrinking in microtubules)

Morphology



CANCER CELL INTERNATIONAL



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

Theron *et al.*

BioMed Central

Theron *et al.* *Cancer Cell International* 2013, 13:87
<http://www.cancer-cell-international.com/content/13/1/87>



AUTOPHAGY
 2016, VOL. 12, NO. 1, 1–222
<http://dx.doi.org/10.1080/15548627.2015.1100356>

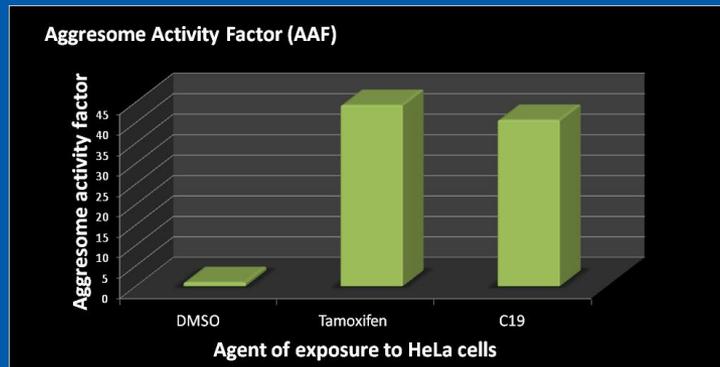
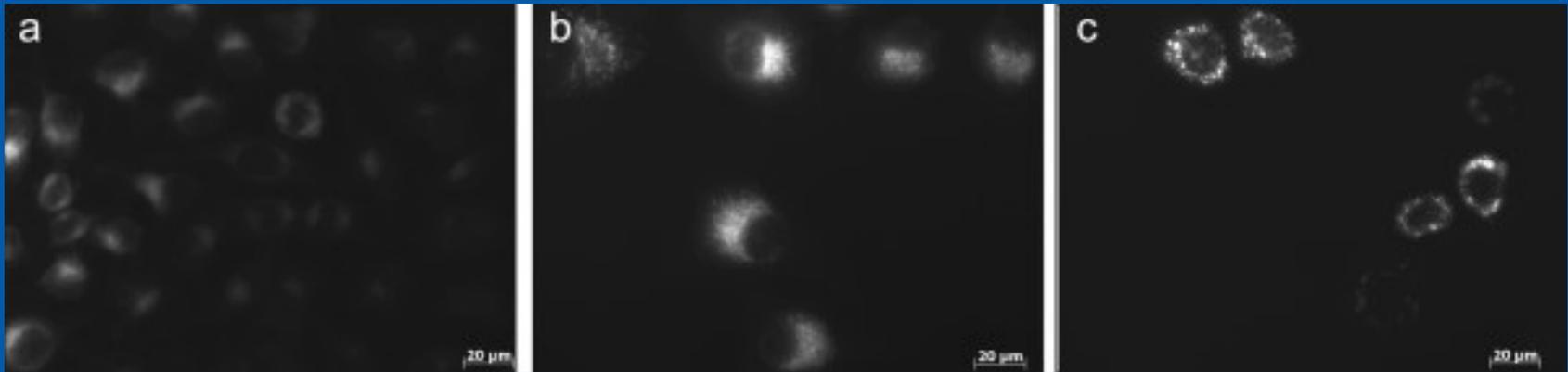
Taylor & Francis
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EDITORIAL

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



Autophagy



Pharmacology

Original Paper

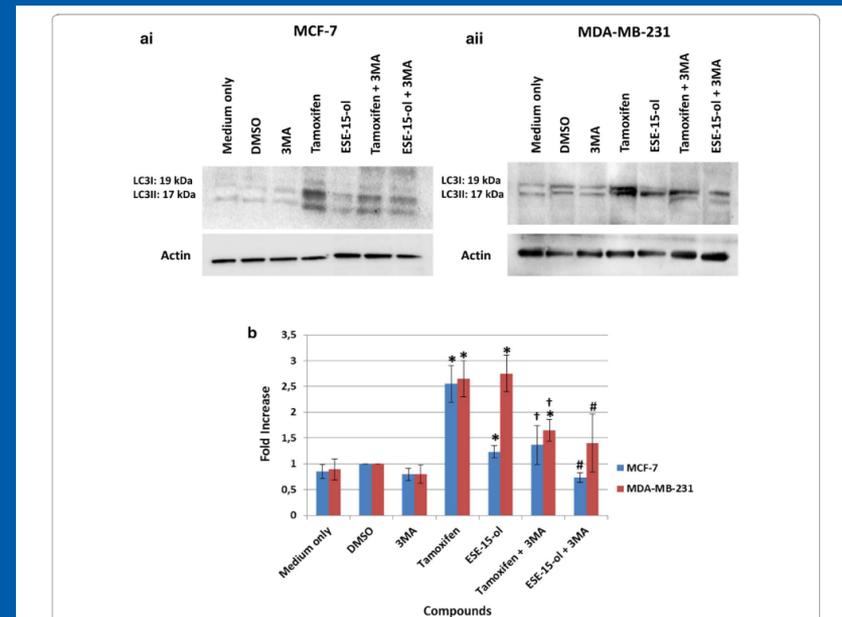
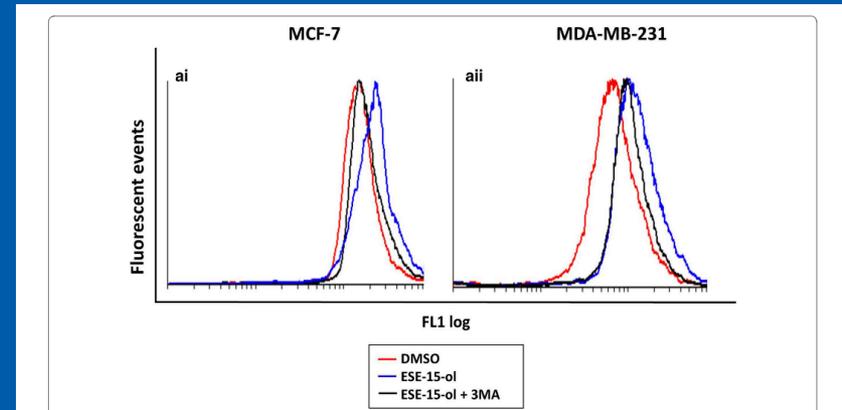
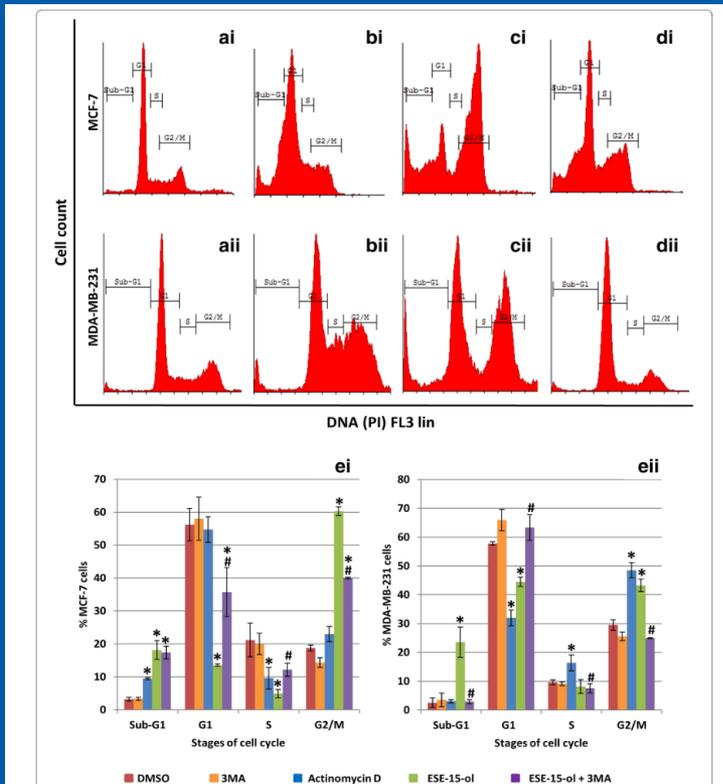
A Novel 2-Methoxyestradiol Analogue Is Responsible for Vesicle Disruption and Lysosome Aggregation in Breast Cancer Cells

Nkandeu S.D.^a · van den Bout I.^{a,b} · Cronjé M.J.^c · van Papendorp D.H.^a · Joubert A.M.^a

Formula 1: Aggresome Activity Factor

$$\text{AAF} = 100 \times \frac{(\text{MFI}_{\text{TREATED}} - \text{MFI}_{\text{CONTROL}})}{\text{MFI}_{\text{TREATED}}}$$

Autophagy



Verwey et al. *Cancer Cell Int.* (2016) 16:91
DOI 10.1186/s12935-016-0367-5

Cancer Cell International

PRIMARY RESEARCH

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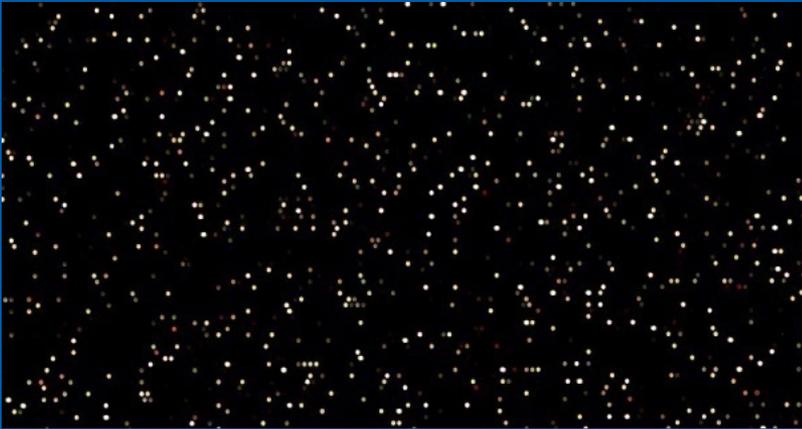


Autophagy induced by a sulphamoylated estrone analogue contributes to its cytotoxic effect on breast cancer cells

Marcel Verwey*, Elsie M. Nolte, Anna M. Joubert and Anne E. Theron



Gene ontology and protein expression



Gene	Description	Function
EGR1	Early growth response 1 [NM_001964]	Tumor suppressor, induced by E2F1
TRIB3	Tribbles [NM_021158]	Negatively regulates AKT1
EXT1	Exostosins (multiple) 1 [NM_000127]	Tumor suppressor
MAP2K3	Mitogen-activated protein kinase kinase 3 [NM_145109]	Activates p38
PTEN	Phosphatase and tensin homolog [NM_000314]	Tumor suppressor
TNFRSF21	Tumor necrosis factor receptor superfamily, member 21 [NM_014452]	Apoptosis facilitator
TNFSF15	Tumor necrosis factor (ligand) superfamily, member 15 [NM_005118]	Apoptosis facilitator
FRK	Fyn-related kinase [NM_002031]	Activates p38
MKNK2	MAP kinase interacting serine/threonine kinase 2 [NM_017572]	Tumor suppressor
DDIT3	DNA-damage-inducible transcript 3 (DDIT3) [NM_004083]	Apoptosis facilitator
BCL2L11	BCL2-like 11 [NM_138621]	Apoptosis facilitator
IL24	Interleukin 24 [NM_006850]	Induces p38 and p53
GADD45A	Growth arrest and DNA-damage-inducible, alpha [NM_001924]	Activates p38
BBC3	BCL2 binding component 3 [NM_014417]	Apoptosis facilitator
TP53INP1	Tumor protein p53 inducible nuclear protein 1 [NM_033285]	Apoptosis facilitator

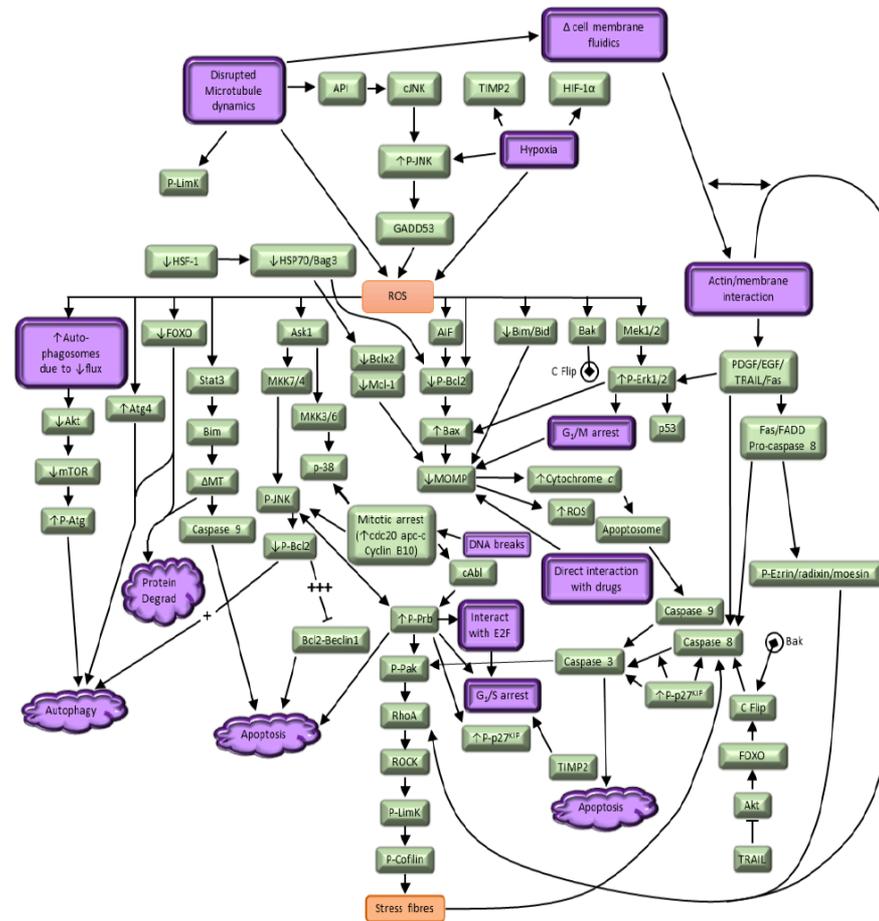
RefSeq RNA	Gene ID	Protein ID	Description	MCF-7		MDA-MB-231	
				Average Log ₂	STDEV	Average Log ₂	STDEV
Cell death							
BAX	581	Q07814	BCL2-associated X protein			0.23	0.067
EPB49	2039	Q08495	Erythrocyte membrane protein band 4.9 (dematin)	0.77	<0.001	0.63	0.115
CASP4	837	P49662	Caspase 4, apoptosis-related cysteine protease	0.32		0.32	0.001
CASP7	840	P55210	Caspase 7, apoptosis-related cysteine protease			0.23	0.06
STAT3	6774	P40763	Signal transducer and activator of transcription 3	0.23	0.062	0.46	0.071
DAB2	1601	P98082	Disabled homolog 2, mitogen-responsive phosphoprotein	0.47	0.022		
Cell cycle							
CCNB1	891	P14635	Cyclin B1			0.15	0.001
BUB3	9184	O43684	BUB3 budding uninhibited by benzimidazoles 3			0.34	0.144
Protein folding							
HSP60	3329	P10809	Heat shock 60 kDa protein 1 (chaperonin)	0.2	0.05		
HDJ-2	3301	P31689	DnaJ (Hsp40) homolog, subfamily A, member 1	0.31	0.05	-0.24	0.04
HSPA1A	3303	P08107	Heat shock 70 kDa protein 1A			0.32	0.053
Ras-related							
CSK	1445	P41240	c-Src tyrosine kinase	0.27	0.004	0.19	0.017
ARHGEF7	8874	Q14155	Rho guanine nucleotide exchange factor (GEF) 7	-0.29	0.035	-0.21	0.073
ARHGDI3	397	P52566	Rho GDP dissociation inhibitor (GDI) beta	0.24	0.008		
RASA2	5922	Q15283	RAS p21 protein activator 2			0.27	0.062
RAC1	5879	P15154	Ras-related C3 botulinum toxin substrate 1			-0.44	0.062
Ras-GAP	5921	P20936	RAS p21 protein activator (GTPase activating protein) 1			0.2	0.12
Transcription and translation							
TCERG1	10915	Q14776	Transcription elongation regulator 1 (CA150)	0.28	0.013	0.29	0.019
NASP	4678	P49321	Nuclear autoantigenic sperm protein (histone-binding)	-0.27	0.013	-0.58	0.025
RPS6KB1	6198	P23443	Ribosomal protein S6 kinase, 70 kDa, polypeptide 1			-0.12	0.011
NCOR2	9612	Q9Y618	Nuclear receptor co-repressor 2	-1.11	0.127		

doi:10.1371/journal.pone.0053853.t002

Transcription → translation??



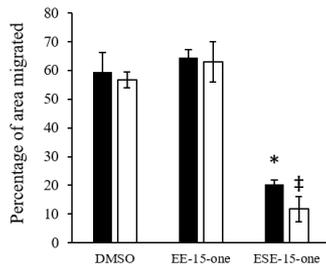
Proposed mechanism of action – cancer cell signalling?



Cancer cell metastasis

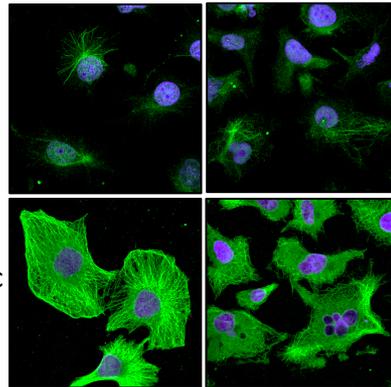
The effect of estrone-like compounds on migration and survival (two- and three dimensional)

Anti-migratory effect of microtubule interrupters

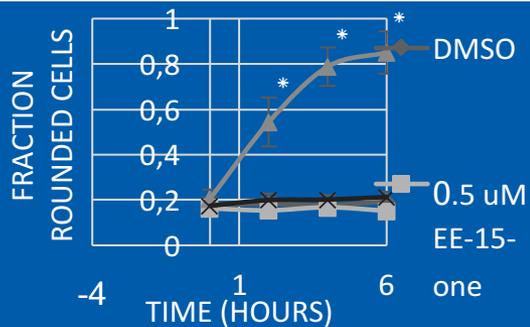
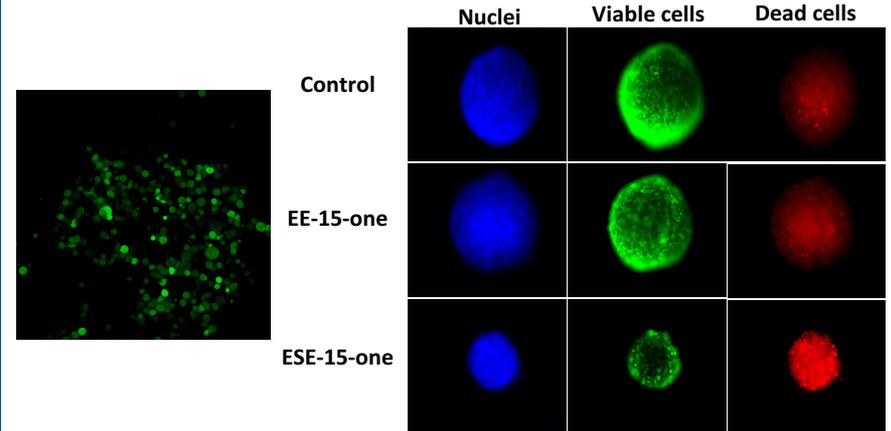


Stable
MTs

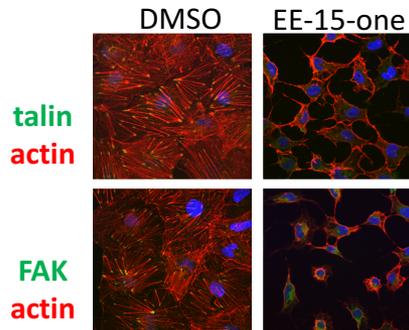
Dynamic
MTs



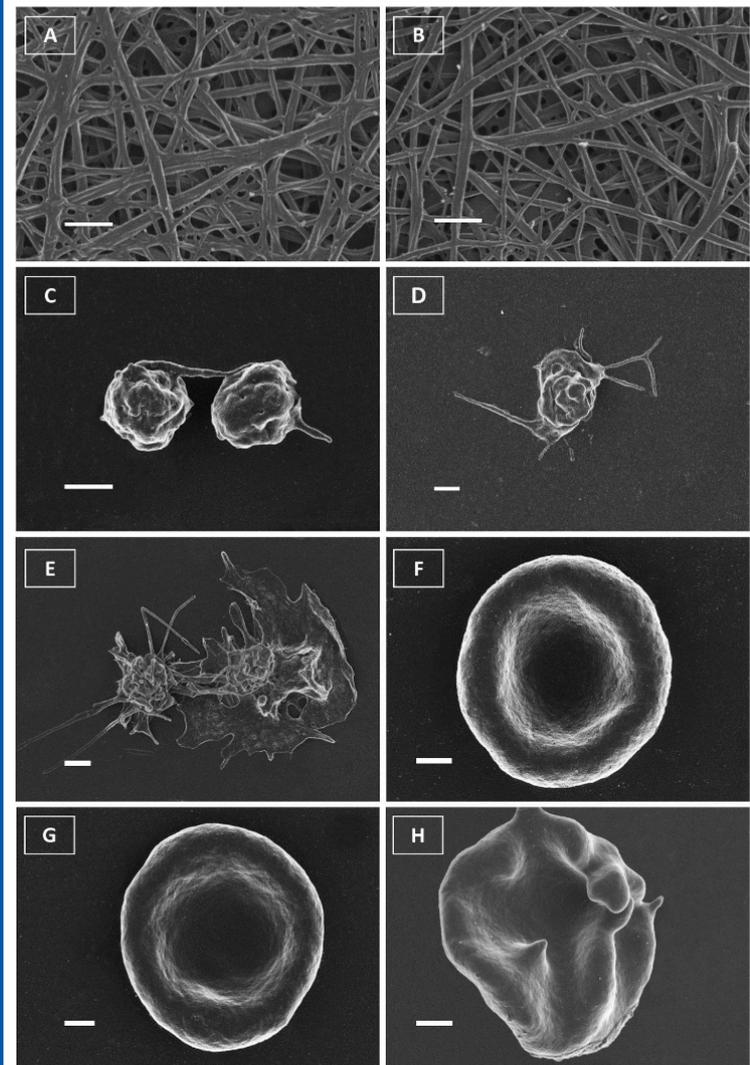
Development of *in vitro* three-dimensional cancer models



Cell detachment



Ex vivo



Repsold et al. *Cancer Cell International* 2014, **14**:48
<http://www.cancercl.com/content/14/1/48>



PRIMARY RESEARCH

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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, Etheresia Pretorius and Annie Margaretha Joubert*

Repsold et al. *Exp Hematol Oncol* (2016) **5**:18
DOI 10.1186/s40164-016-0048-z

Experimental Hematology &
Oncology

RESEARCH

Open Access



Ex vivo apoptotic and autophagic influence of an estradiol analogue on platelets

Lisa Repsold, Etheresia Pretorius and Annie Margaretha Joubert*

BioMed Research International
Volume 2018, Article ID 9405617, 10 pages
<https://doi.org/10.1155/2018/9405617>

Review Article

Eryptosis: An Erythrocyte's Suicidal Type of Cell Death

Lisa Repsold and Anna Margaretha Joubert



Discussion and conclusion

Theron et al. *Cancer Cell International* 2013, **13**:87
<http://www.cancer-ci.com/content/13/1/87>



PRIMARY RESEARCH

Open Access

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

Anne E Theron^{1*}, Elsie M Nolte¹, Laurence Lafanechère² and Annie M Joubert¹

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

REVIEW ARTICLE

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

1105

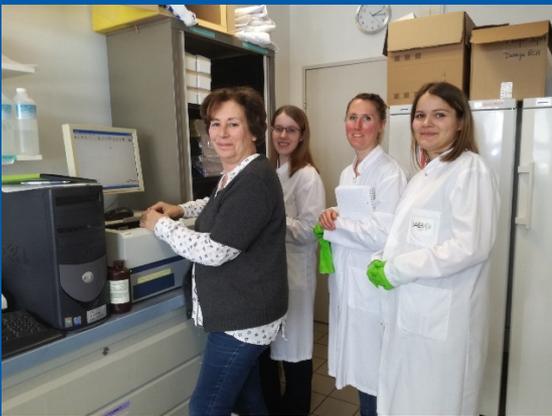
Table 1 Classes of antimitotic drugs and their stages of development [25, 26, 58, 61, 65, 67, 70, 71, 83, 85, 105–107]

Class	Name	Mechanism of action	Approved for treatment of (cancer type)
Drugs used as cancer treatment regimens			
Taxanes	Paclitaxel (taxol [®])	Microtubule-stabilizing	Metastatic adenocarcinoma of the pancreas (in combination with gemcitabine)
	Cabazitaxel (Jextana [®])	Microtubule-stabilizing	Metastatic, hormone-resistant prostate cancer (in combination with prednisone)
Epothilones	Ixabepilone (Ixempra [®])	Microtubule-stabilizing	Metastatic or locally advanced breast cancer (resistant to taxanes and anthracycline)
Vinca alkaloids	Eribulin (E7389, ER086526, 6)	Microtubule-destabilizing	Recurrent metastatic breast cancer (pre-treated with taxanes and anthracycline)
Class	Name	Mechanism of action	Phase of clinical trials
Drugs undergoing clinical trials			
Vinca alkaloids	Vintafolide (EC145)	Microtubule-destabilizing	In Clinical phase II trials as sole treatment for ovarian and lung cancer
Class	Name	Mechanism of action	Model
Drugs undergoing in vivo studies			
Non-taxoid site microtubule-stabilizing agents	Peloruside A (PLA, CHEBI:77692)	Microtubule-stabilizing	Lung and breast tumor xenograft studies in athymic nu/nu mice
	Laulimalide	Microtubule-stabilizing	High toxicity and low tumor inhibition in human breast cancer and fibrosarcoma xenograft studies in athymic NCr-nu/nu mice
Class	Name	Mechanism of action	Effective in cell line
Drugs undergoing in vitro studies			
Estrogen derivatives	ESE-15-ol	Microtubule-destabilizing	Breast cancer (MCF-7, MDA-MB-231) and lung cancer (A549)
	ESE-16	Microtubule-destabilizing	Breast cancer cell lines (MCF-7, MDA-MB-231) and esophageal cancer (SNO)

Collaboration - Grenoble, France



- 2008 - sabbatical leave
- Prof Lafanechère - extraordinary professor
- Postgraduate student visits to Grenoble
- Co-tuelle – dual PhD degree (Grenoble and Pretoria) (2017-2018)





Collaboration - Oxford and Bath, UK

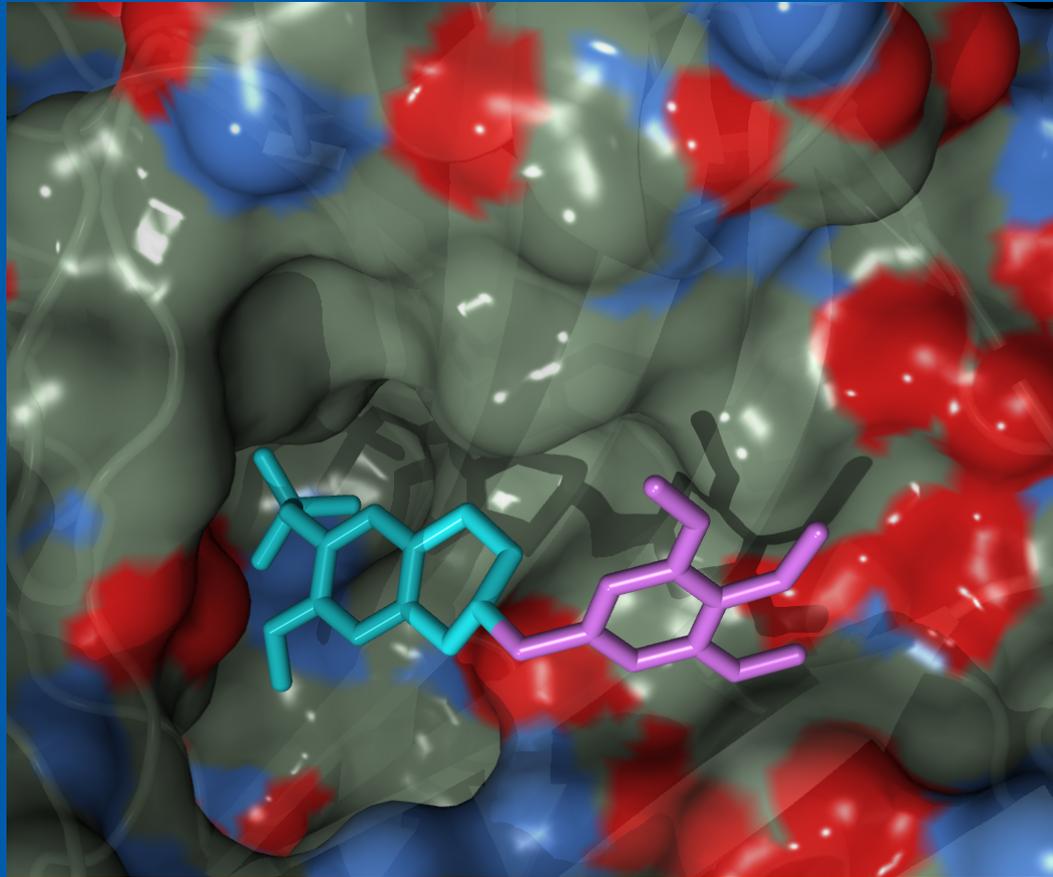


Manuscript
accepted:

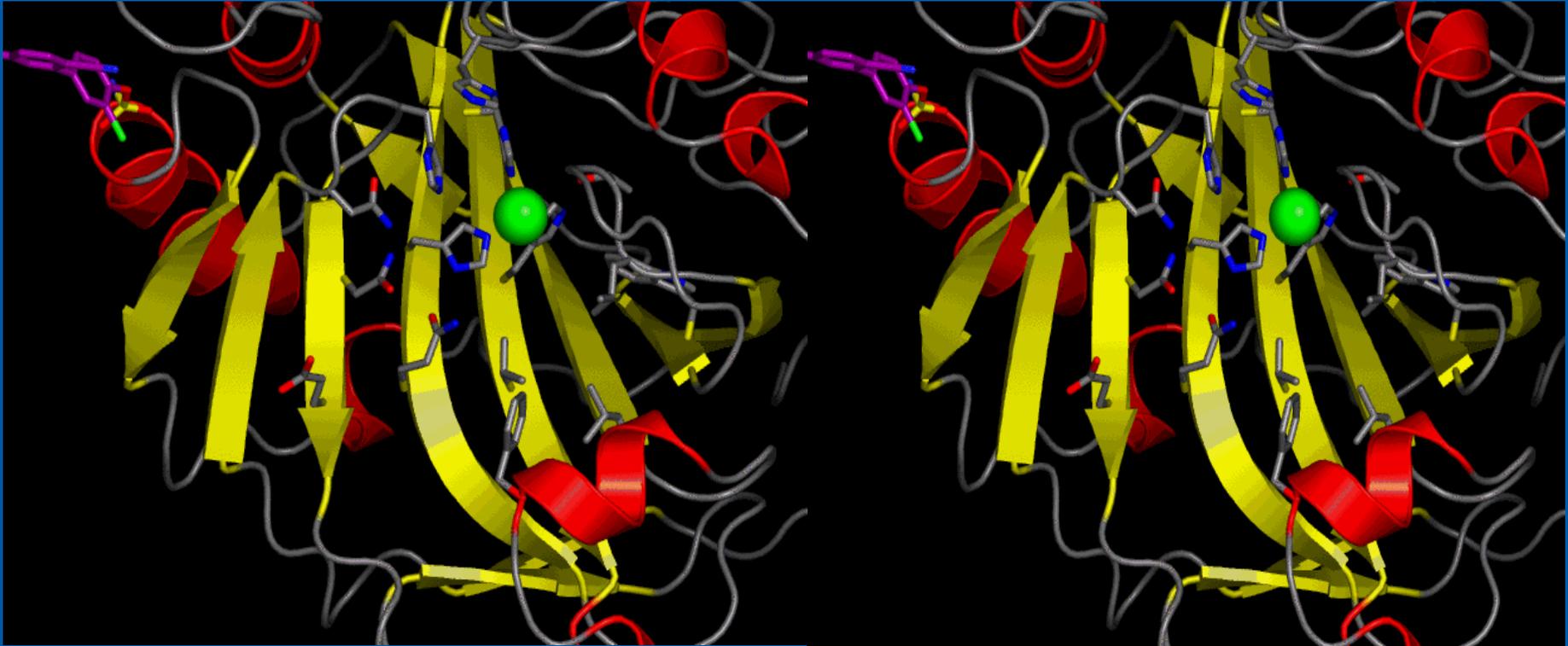
24 May 2018
*Drug Design,
Development and
Therapy*

**Greetings from Oxford and thanks for the
great collaboration!**

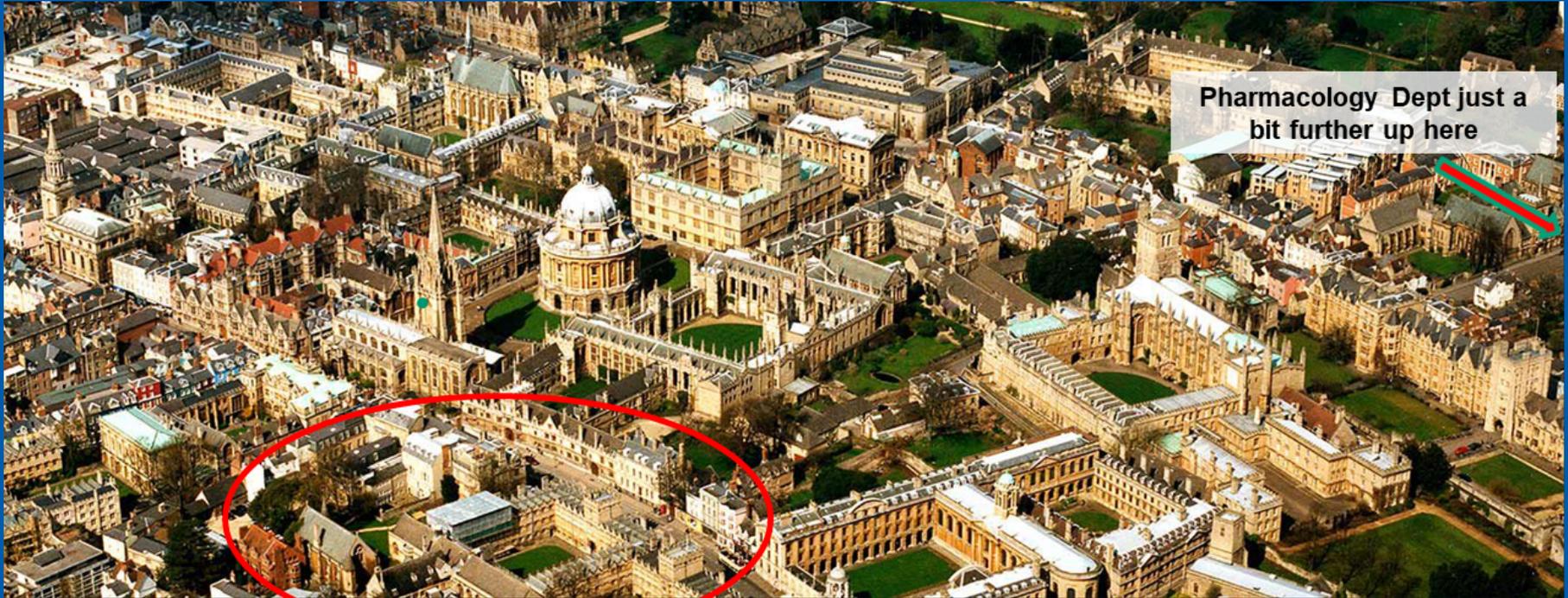
Rationale for combining two key structural motifs from a steroid and colchicine with a sulfamate motif to make a non-steroidal drug candidate



Structure-based drug design



Oxford University



Pharmacology Dept just a bit further up here

Prof Potter's College

Collaboration - Istanbul, Turkey

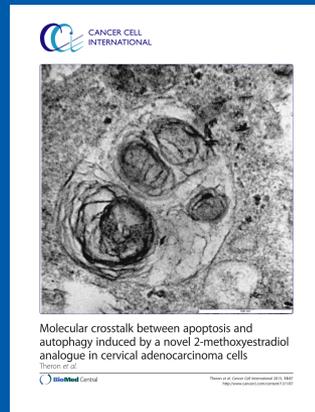
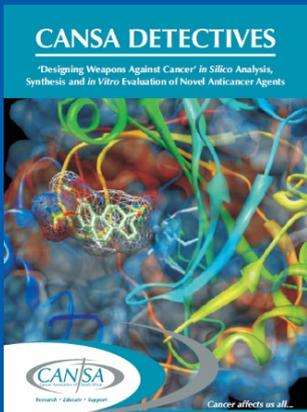


Collaboration - University of Johannesburg



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



businessmagazin.ro

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

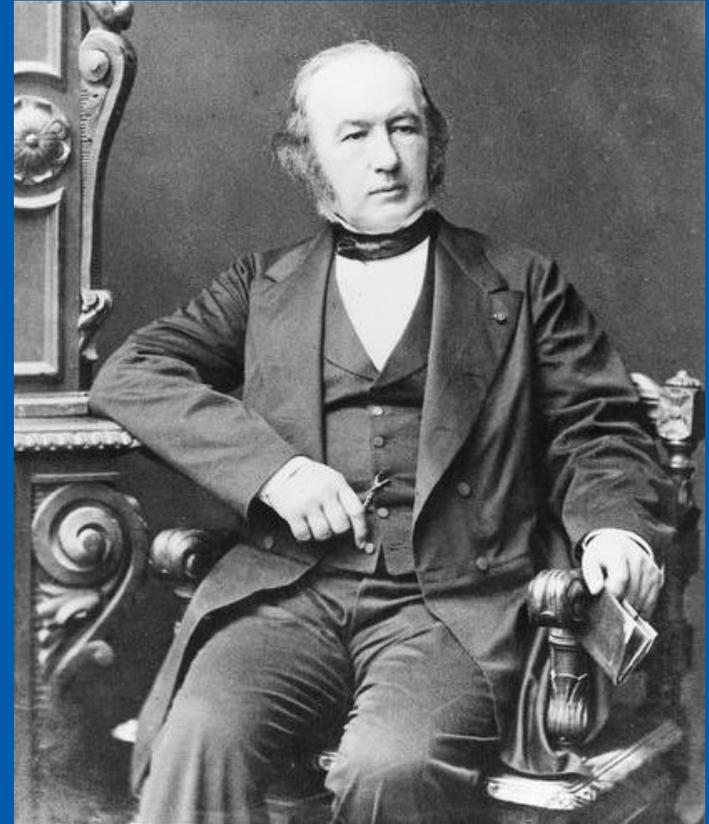
Conclusion

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'



http://www.larousse.fr/encyclopedie/personnage/Claude_Bernard/108551

Acknowledgements



Thank You

