
An oily start towards a medical biotechnology institute

Jan Verschoor

Department of Biochemistry

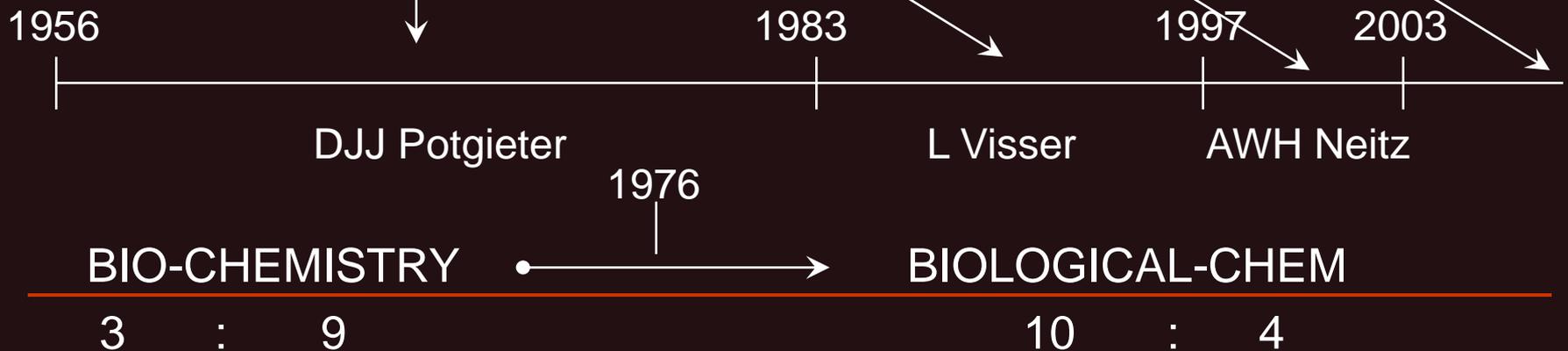
Lecture layout

- Start Department history 1976 – 2009
- Medical Current research momentum
- Biotech In the UP environment
- Oil Case study: mycolic acids in TB
- Institute The need and vision for

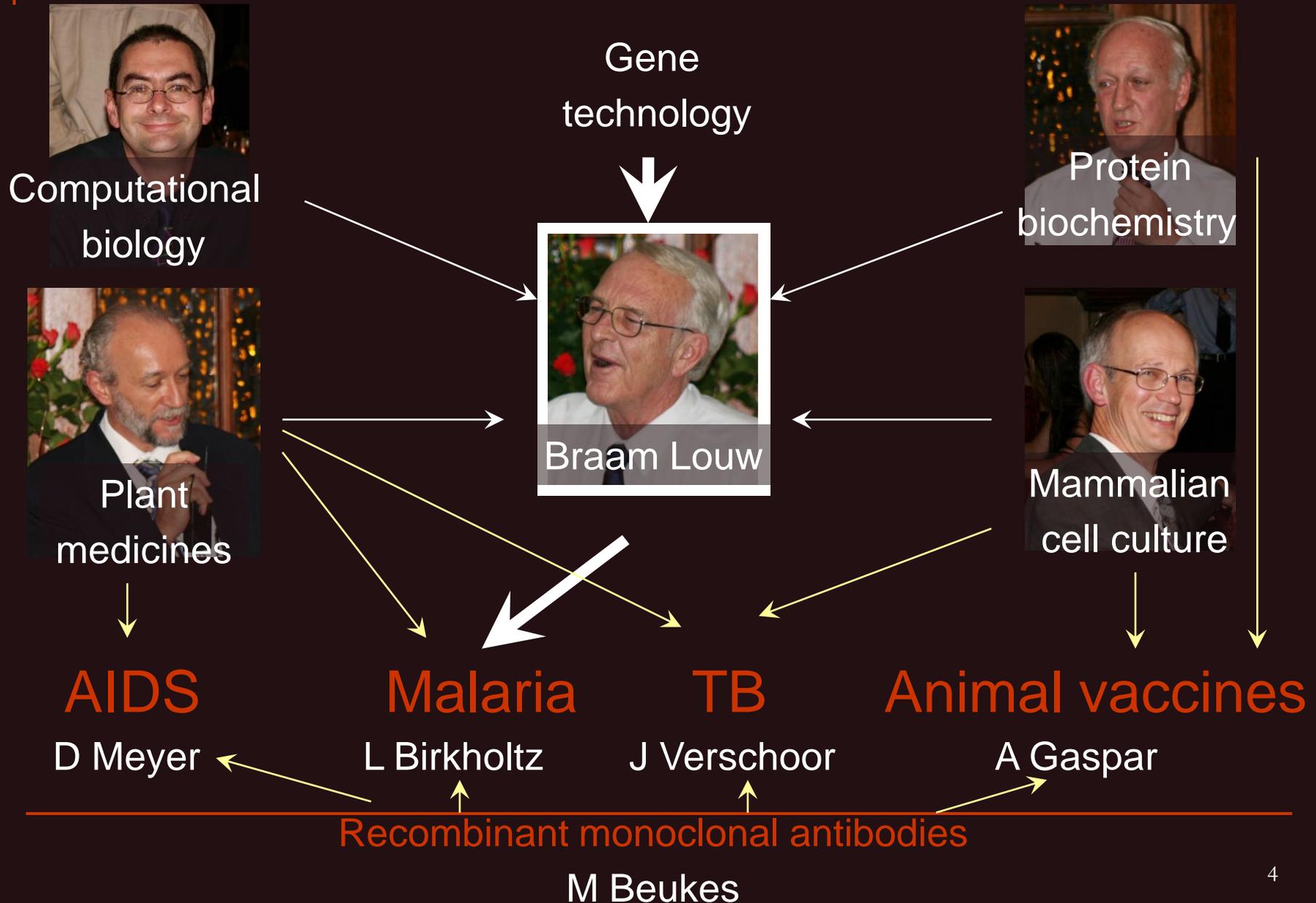
A facilitator between bench and bedside



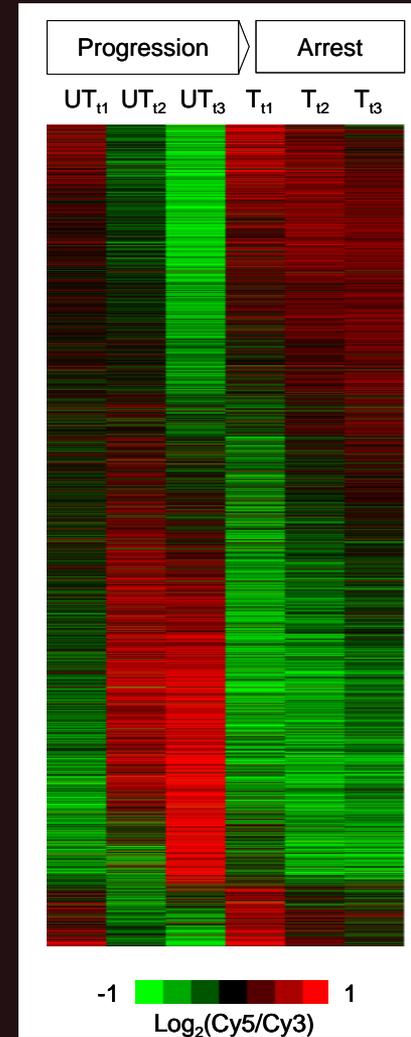
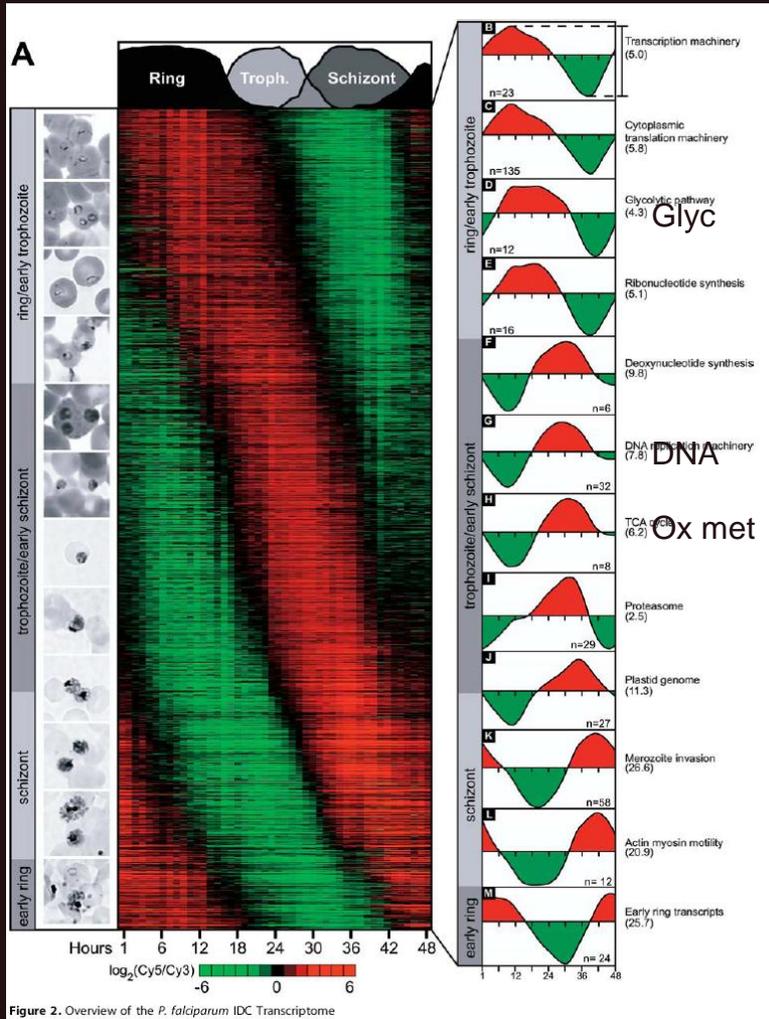
Start: Department Biochemistry 50 year history



Medical: Current momentum of the department



Biotech: in the UP environment

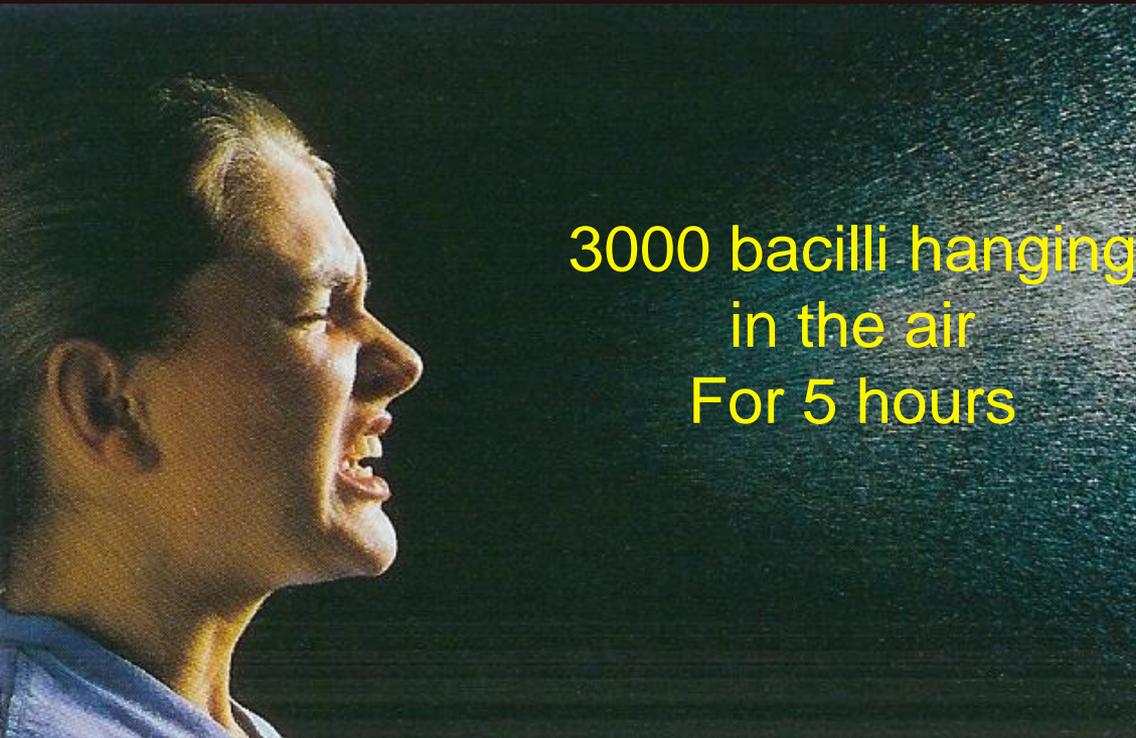


Malaria



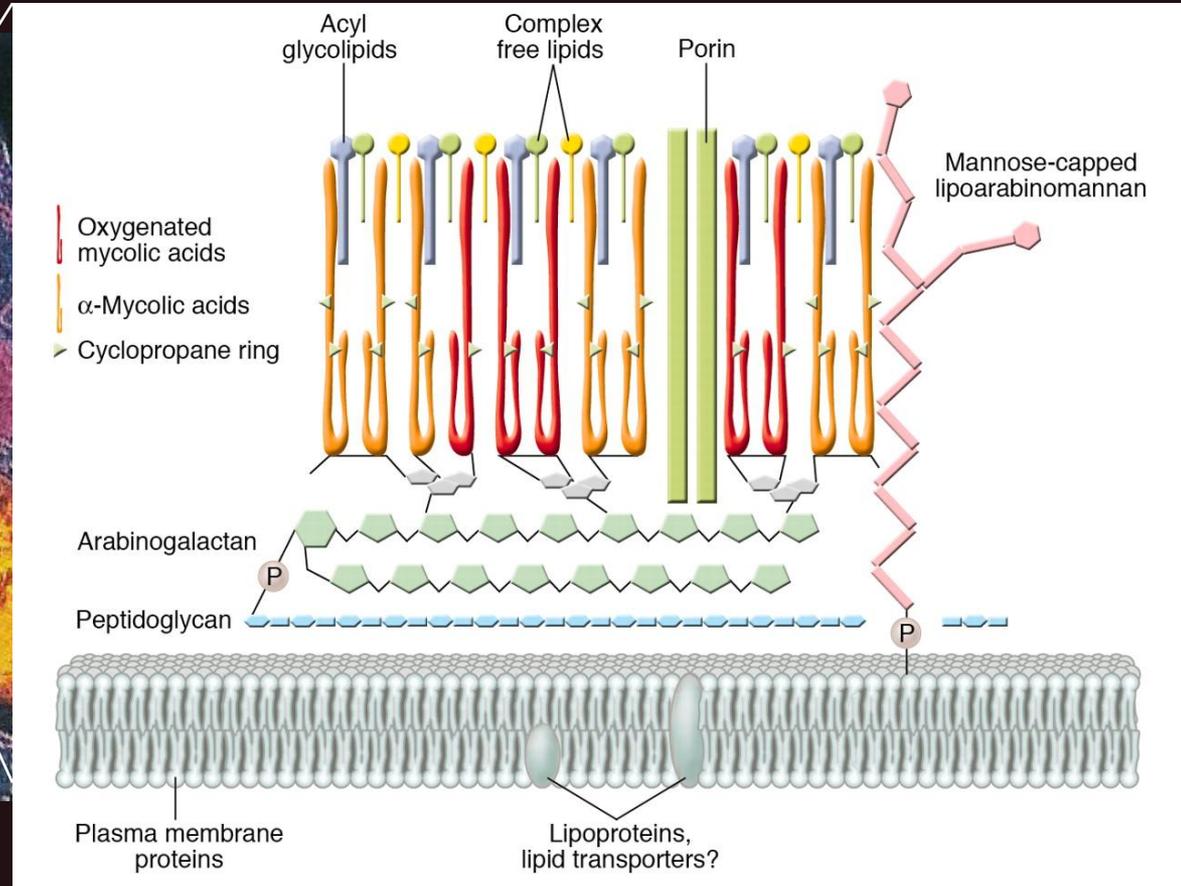
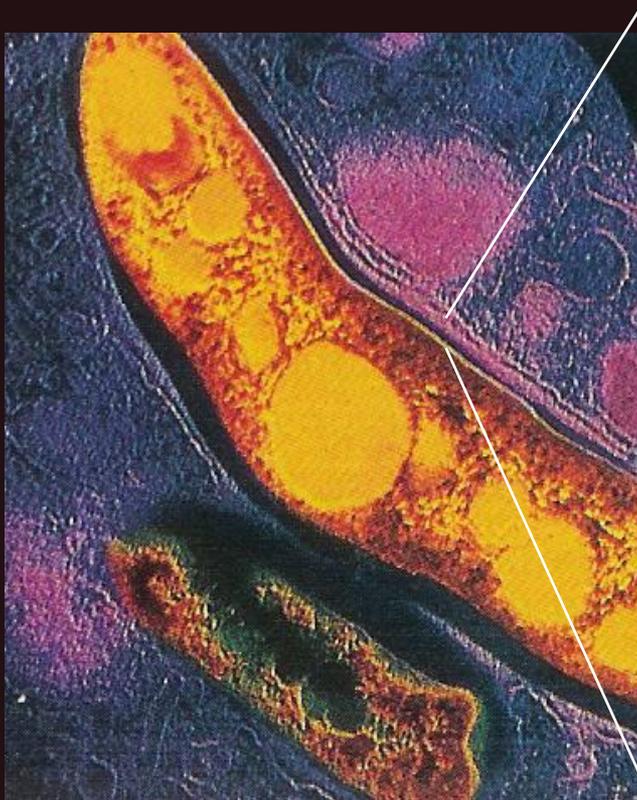
Drug
target
analysis

Oil: Case study of mycolic acids in TB



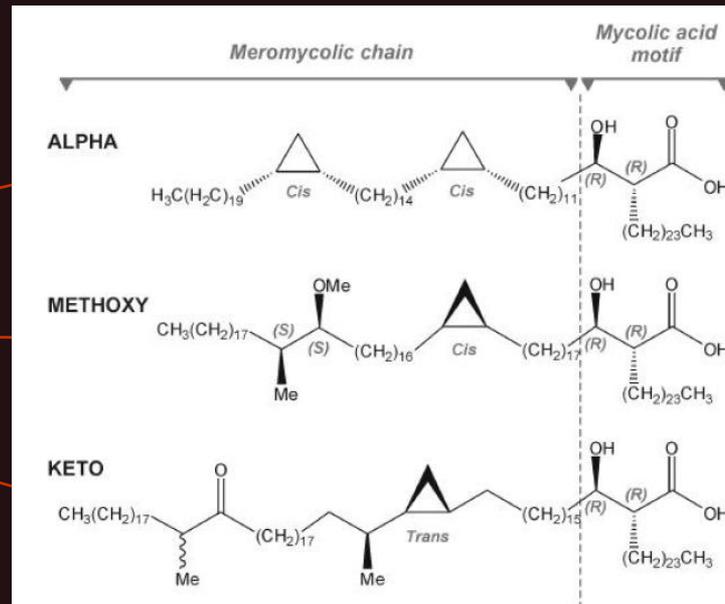
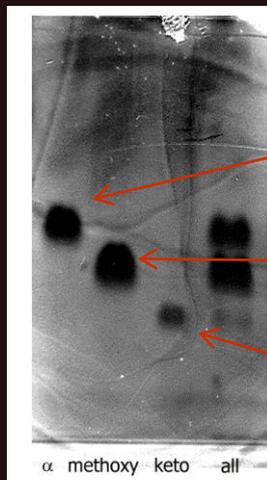
- 8-10 million infections per year
- 1.6 million deaths annually
- 33% HIV⁺ patients co-infected with TB
- Challenges: Treatment and diagnosis

Oil: The mycolic acid wax-layer of the mycobacterial envelope



Oil: Mycolic acids (MA) = Mycobacterial identikit

- Unique MA composition each for 60 different species of *Mycobacterium*!
- Mycobacterial MA molecules larger than from other species, eg *Nocardia* and *Corynebacterium*
- Three main classes of MA for *M. tuberculosis*:



Oil: Mycolic acids in innate immunity: 1994

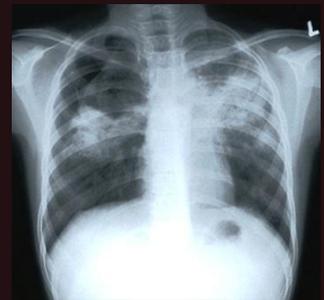
- Breakthrough, Harvard, USA: A lipid (MA) presenting role described for the CD1 protein on antigen presenting cells:
 - Stimulation of T cell immunity (and antibodies?) without needing the CD4 T helper cell¹.
 - A possibility to bolster immunity in HIV infected patients with MA².

1. Beckman *et al.* (1994) *Nature* 372: 691

2. Verschoor & Onyebujoh (1999) *Bioessays* 21: 365-366

Oil: Three research questions on MA:

- Can antibodies to MA be used as highly specific and sensitive surrogate markers for active TB, even in HIV burdened individuals/communities?
- Are MAs good immune stimulants to assist the body against immune related diseases such as arthritis and asthma?
- What is the role of MA in the establishment of TB?

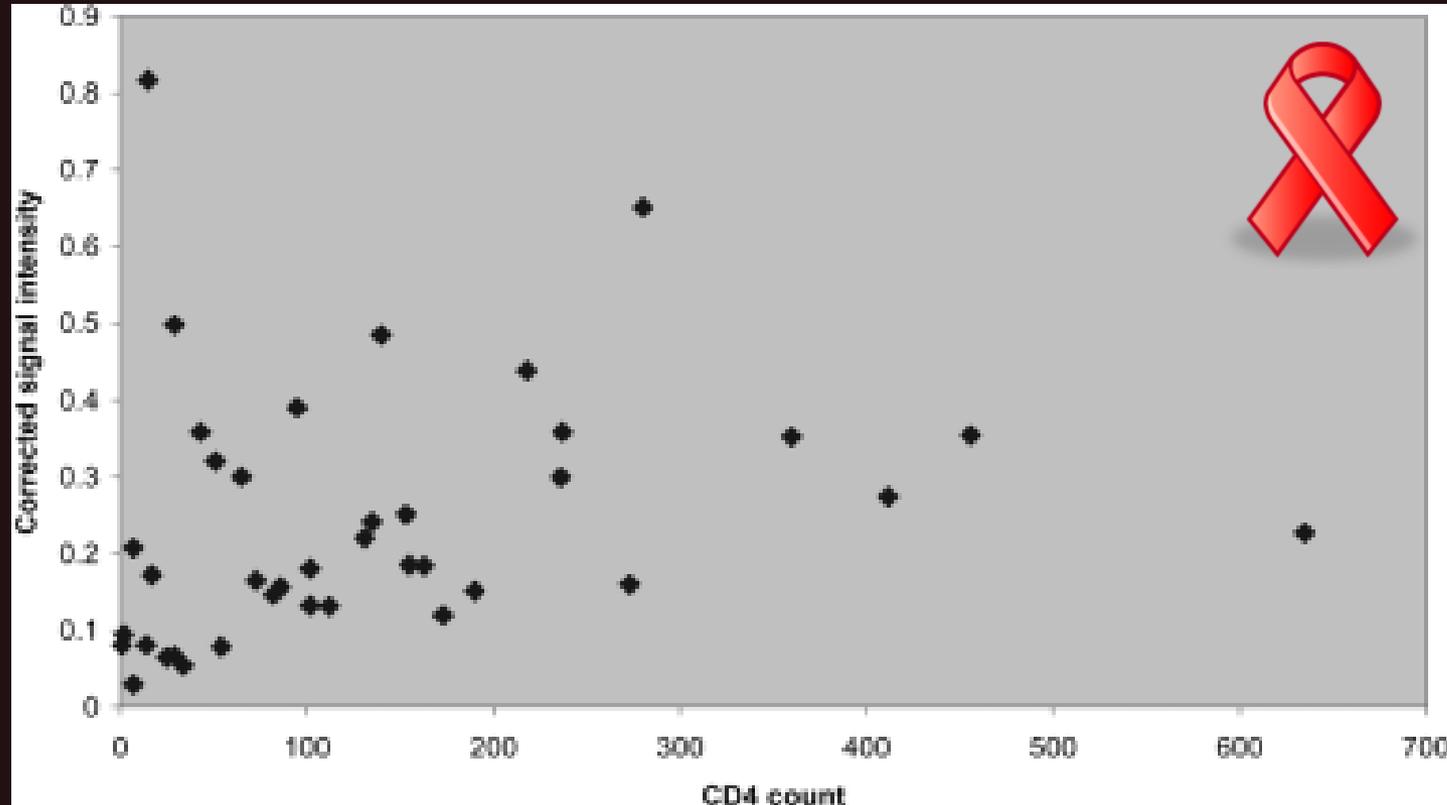


Oil: First to purify natural MA on large scale with simple method

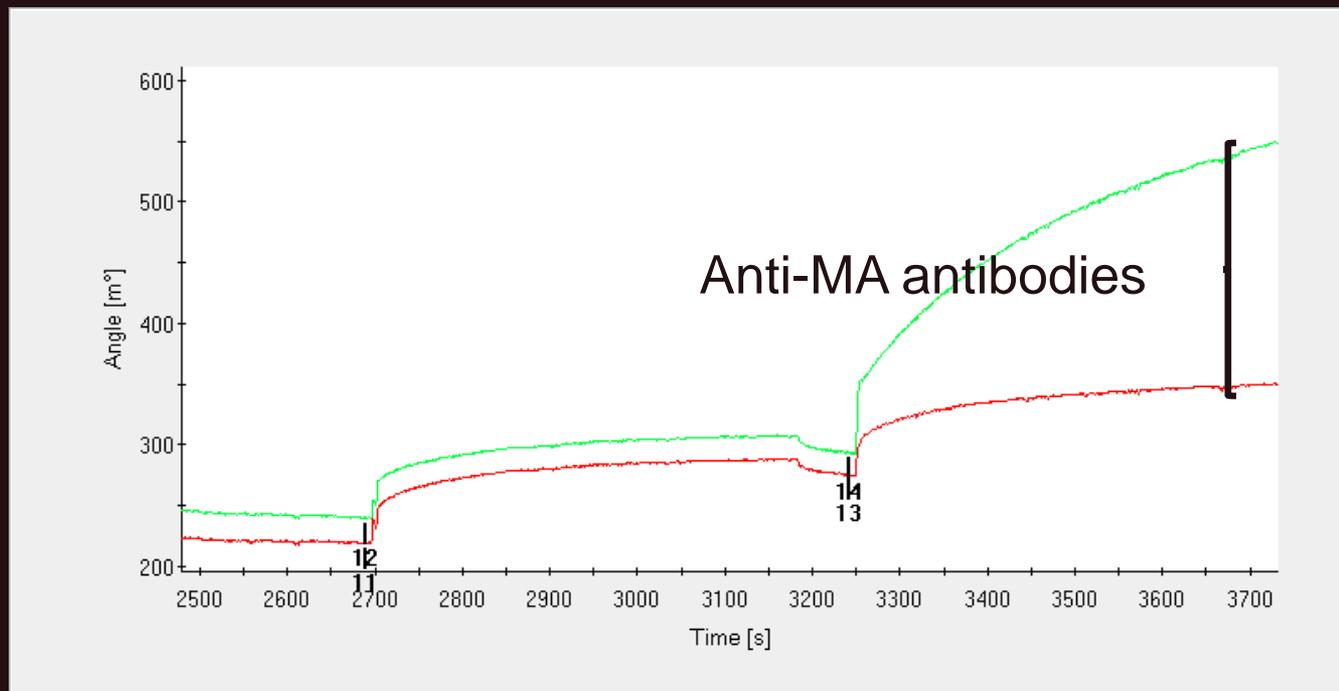
- Countercurrent distribution ideal for MA separation from a crude mycobacterial extract – The MA fraction forms different emulsion pattern visible by eye.
- HPLC confirmed purity and yield
- Stimulation of primary cultures of human PBL confirmed biological activity



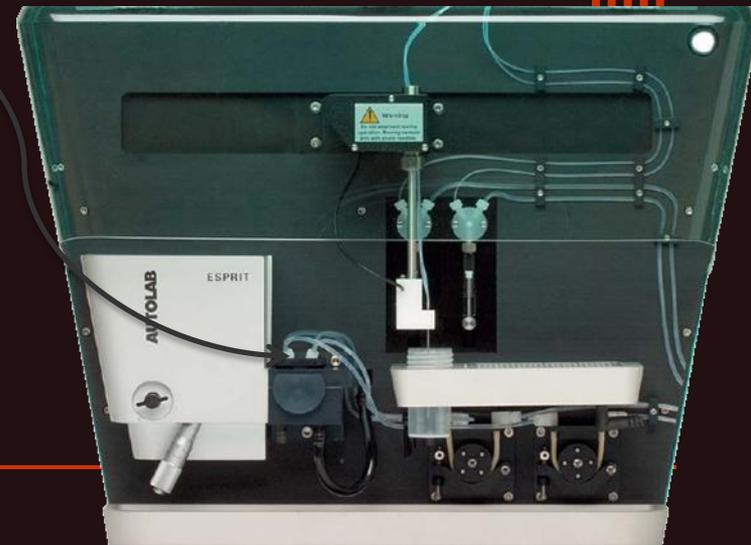
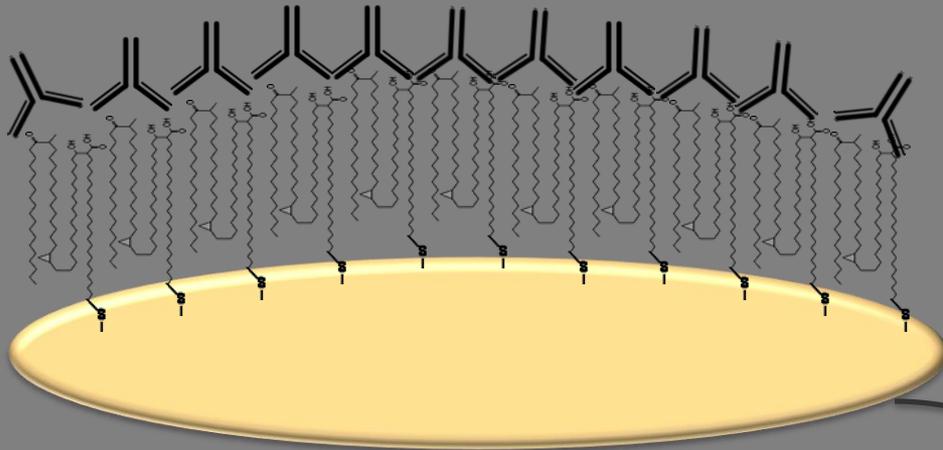
Oil: First to report anti-MA antibodies in HIV infected patients with low CD4 counts



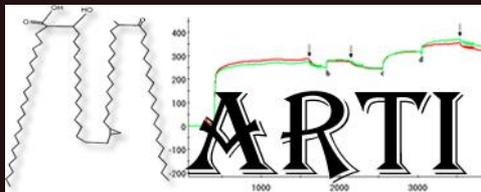
Oil: First with an anti-MA antibody TB biosensor test for TB with $>80\%$ accuracy



Oil: How MARTI Works

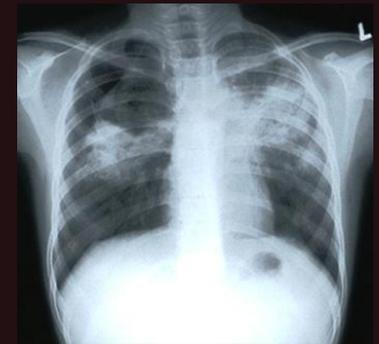
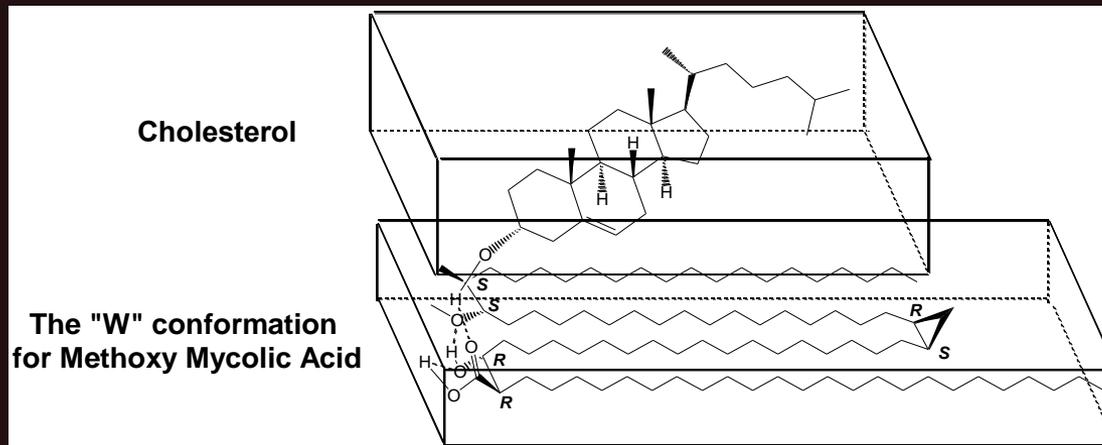


**Rapid reliable
Diagnostic Technique**



Oil: First to show MA /cholesterol similarities

- Cross-reactivity in immunoassays
- MA attracts cholesterol
- Both recognised by Amphotericin B



Oil: MA as immune stimulant: with Prof Johan Grooten



- Post-doc Dr Anne Lenaerts (1998): MA induces innate immunity in mice – patent.
- PhD students Dr Anton Stoltz, Dr Hannelie Korf (2005): MA = PAMP = induces foamy macrophage with cholesterol accumulation in mice
- Dr Hannelie Korf (2006): Reprogramming of macrophages by MA to make mice tolerant to asthma allergen challenge



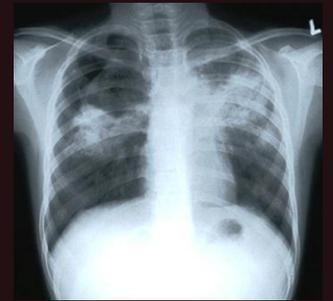
Oil: Chemical synthesis of MA: with Prof Mark Baird



- First to achieve stereocontrolled chemical synthesis of all three major subclasses of MA from *Mtb*.
 - α -MA: Al-Dulayymi *et al.* (2005) *Tetrahedron* 61:11939-11951
 - Keto-MA: Koza & Baird (2007) *Tetrahedron Lett.* 48:2165
 - Methoxy-MA: Al-Dulayymi *et al.* (2007) *Tetrahedron* 63:2571*
*First involvement of UP PhD student: Madrey Deysel

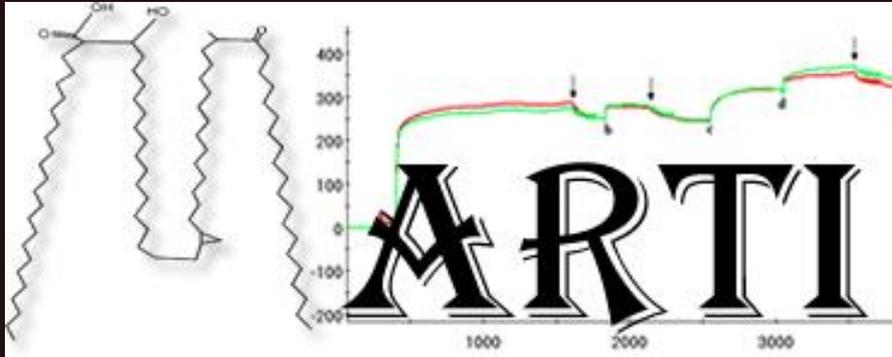
Oil: Conclusions:

- Antibodies to MA can be highly specific, sensitive surrogate markers for active TB in HIV burdened individuals/communities when performed as an inhibition test in real-time using a biosensor.
- MAs are highly specific pronounced inducers of innate immunity in mice leading to allergen tolerance
- MA induces foam cells typical of granulomas in the lungs of mice and attracts cholesterol - the main carbon diet of persistent TB bacilli.



Oil: Envisioned commercial products from mycolic acids

- A faster and more accurate test for TB diagnosis by 2012
- Adjuvants for vaccines by 2013
- Targeting of nano-encapsulated anti-TB drugs by 2014
- An asthma cure by 2015?



Diagnostics

An oily, early, slippery start for a UP medical biotech institute that strives to be

A facilitator between bench and bedside



Institute: Why a medical biotechnology institute?

- The conversion of scientific discoveries into practical applications for the improvement of health and the standard of living
- To comply with the new South African act on: *Intellectual property rights from publicly financed research and development*, January 2009
- To facilitate between academia and industry

A facilitator between bench and bedside



Institute: Who mediated between the bald and the beautiful?



**Mycolic acids purified:
Patent, thesis
and paper**

**Countercurrent
technology**

**University of Pretoria,
Prof Jan Verschoor**

**Facilitator,
Dr Ela Johannsen**

**Adcock Ingram,
Rina van der Merwe**

Medical Institute: world examples

- Yeda Research and Development Company
- Hadasit Technology Transfer Company
- University of Rochester Medical Center

Medical Biotechnology Institute: Task-list

- Enterprising medical technologies for Faculties of Natural/Agricultural, Health and Veterinary Sciences
- National and international networking: Advisory Board
- Business incubation for SMME spin-out companies
- Acquirement of technology – even through spin-in
- Liaison with NIPMO umbrella organisation

A facilitator between bench and bedside



Medical Biotechnology Institute: Task-list (2)

- Marketing of UP technologies to companies.
- Presenting confidential information to interested companies (under secrecy agreements)
- Funding of research by companies and Ministries of Trade and Industry/Science and Technology
- Patent disclosures written and submitted
- License and option agreements negotiated

A facilitator between bench and bedside



Institute: Existing building blocks

- **F** ABI – ready for NIPMO patent demand?
- **U** P Research Support – long term vision?
- **S** AMI – emphasis on entrepreneurship?
- **E** nterprise @ UP - good at logistics!
- **D** r Ela Johannsen - needs to be cloned!
- ||
- **FUSED**: An ideal Medical Biotech Institute!

A facilitator between bench and bedside



Acknowledgements: international

- Rob Benner Erasmus MC NL
 - Annemieke ten Bokum

- Mark Baird Bangor U UK
 - Juma Al Dulayymi, Gianna Toschi

- Johan Grooten Gent U BE
 - Anne Lenaerts

- Tim Niehues H Heine U GE

- David Minnikin Birmingham U UK

Acknowledgements: national

- Rina vd Merwe Adcock Ingram
- Ela Johannsen Bioflora
- Hulda Swai CSIR
- NRF, MRC, Cape Biotech, Lifelab

Acknowledgements: TB Team



+ Anton Stoltz, Cathryn Driver, Yvonne Maas, Monica Gomes,
Hannelie Korf, Mohammed Balogun, Pieter Vrey, Gilbert Siko