PHARMACEUTICALS AND INTELLECTUAL PROPERTY TRAINING SEMINAR

- 12 – 14 March 2012
- Pretoria, South Africa

BASIC RESEARCH & DEVELOPMENT

FROM MOLECULE TO MEDICINE
PHARMACON TO PHARMACOLOGY

Prof Oppel B W Greeff
MBCHB, FCFP (SA) MPharmMed, FFPM (RCP), MD
Head: Department of Pharmacology, University of Pretoria
There has never been such a rich time for innovation and the invention of new medicines ..........and we have burgeoning R&D pipelines !
• Full portfolios (mostly !)
• Highly innovative new products
• Responsible behavior (Codes of Practice)
  …..more to come …an end to DTC in the USA ?
• Considerable commitment to the health of the developing world
• Still a very profitable industry
1. Growth factors
2. Growth factor receptors
3. Adaptor proteins
4. Docking proteins/binding proteins
5. Guanine nucleotide exchange factors
6. Phosphatases and phospholipases
7. Signaling kinases
8. Ribosomes
9. Transcription factors
10. Histones
11. Molecular chaperones
12. DNA
13. Microtubules
14. Cyclins
15. Cyclin-dependent kinases
16. Cell death receptors
17. Apoptosis-effector caspases
18. Caspase inhibitors
19. CD40-CD40L

Cell Growth  Motility  Survival  Proliferation  Angiogenesis

Plasma Membrane  Nuclear Membrane  Microtubule Dynamics

RNA Translation  Gene Transcription  DNA Replication and Repair
Phosphodiesterase inhibitors

Non selective
- caffeine
- theophylline

PDE1-selective inhibitors
- Vinpocetine

PDE2-selective inhibitors
- EHNA

PDE3-selective inhibitors
- Enoximone and milrinone:

PDE4-selective inhibitors
- Mesembrine: an alkaloid present in the herb *Sceletium tortuosum*
- Rolipram: used as investigative tool in pharmacological research
- Ibudilast,

PDE5-selective inhibitors
- Sildenafil, tadalafil and vardenafil; and the newer ones, udenafil and avanafil
### Phosphodiesterases

<table>
<thead>
<tr>
<th>PDE Family</th>
<th>Characteristics</th>
<th>PDE4 Expressed in</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE1</td>
<td>Calmodulin-dependent</td>
<td>T cells (3, 7)</td>
</tr>
<tr>
<td>PDE2</td>
<td>cGMP-stimulated</td>
<td>B cells</td>
</tr>
<tr>
<td>PDE3</td>
<td>cGMP-inhibited</td>
<td>Eosinophils (7)</td>
</tr>
<tr>
<td>PDE4</td>
<td>cAMP-specific</td>
<td>Neutrophils (7)</td>
</tr>
<tr>
<td>PDE5</td>
<td>cGMP-specific</td>
<td>Macrophages (1,3,5,7)</td>
</tr>
<tr>
<td>PDE6</td>
<td>Photoreceptor</td>
<td>Mast cells</td>
</tr>
<tr>
<td>PDE7</td>
<td>High affinity, cAMP-specific</td>
<td>Airway epithelial cells (1-3, 5,7,8)</td>
</tr>
<tr>
<td>PDE8</td>
<td>High affinity, cAMP-specific</td>
<td>Endothelial cells (2,3,5)</td>
</tr>
<tr>
<td>PDE9</td>
<td>cGMP-specific</td>
<td>Fibroblasts (1-3, 5, 7, 8)</td>
</tr>
<tr>
<td>PDE10</td>
<td>cAMP/cGMP</td>
<td>Sensory nerves (1,3)</td>
</tr>
<tr>
<td>PDE11</td>
<td>cAMP/cGMP</td>
<td></td>
</tr>
<tr>
<td>PDE12</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

### PDE Family Characteristics

- **PDE1**: Calmodulin-dependent
- **PDE2**: cGMP-stimulated
- **PDE3**: cGMP-inhibited
- **PDE4**: cAMP-specific
- **PDE5**: cGMP-specific
- **PDE6**: Photoreceptor
- **PDE7**: High affinity, cAMP-specific
- **PDE8**: High affinity, cAMP-specific
- **PDE9**: cGMP-specific
- **PDE10**: cAMP/cGMP
- **PDE11**: cAMP/cGMP
- **PDE12**: ?

### PDE4 Expressed in

- T cells (3, 7)
- B cells
- Eosinophils (7)
- Neutrophils (7)
- Macrophages (1,3,5,7)
- Mast cells
- Airway epithelial cells (1-3, 5,7,8)
- Endothelial cells (2,3,5)
- Fibroblasts (1-3, 5, 7, 8)
- Sensory nerves (1,3)

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PDE4 inhibitors: Magic Shotgun?
MANAGING COMPLEXITY!
The most significant discovery of the 20th century was...
THE RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL!

1st in the early 1950’s

1960’s: Drug amendments in the USA led to the modern trial and the coming into being of the F.D.A
SOUTH AFRICA: ACT 101, 1965
MCC came into being

Not far behind the USA!
Since then: active participation by SA in International Drug Development Programmes

- SA has done 2 total developments from first-time in man (FIM) to FDA registration:
  - Triptorelin – LHRH – agonist
  - Rifapentine – the last anti-TB drug registered
- Busy with the 3rd:
  - Malaria vaccine
- China and India: NONE!
At the moment the international pharmaceutical industry is weathering the perfect storm

- Patent expiries and loss of exclusivity – Exclusivity loss estimated to be around $11 Bn per annum for 2008 – 2011

- Increasing payor pressure – Health care reforms in the US expected to put further pressure

- Generic competition from emerging markets

- Growing safety concerns - Increasing complexity and data requirements

- Brand Pharma has a perception problem – The Big Evil Pharma

- Increasing earnings pressure from the financial market
Research-based pharmaceutical companies’ based on ethical pharmaceutical sales and ethical pharmaceutical R&D only, as tabulated by PhRMA. ‘Drugs and medicine’ category based on total R&D and sales for all products of companies within the drugs and medicine sector, tabulated by Standard & Poor’s Compustat, a McGraw-Hill Division.
Productivity crisis

- Phase II clog in development pipeline
- Number of molecules entering Phase III development expected to decline
- Increasing complexity and study durations
- Industry consolidation and portfolio rationalization

In 2005, Goldman Sachs analyzed the pipeline of 17 large pharma firms and estimated that there ~180 drugs at various stages of development, targeting the market before 2009. After applying normal industry attrition rates, the output comes to <20 per annum, roughly one molecule per firm...
An unviable innovation model?

In spite of Industry’s best efforts, Cumulative success rates are still low

<table>
<thead>
<tr>
<th></th>
<th>Pre-Clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III/ File</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995 - 2000</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>37.5%</td>
<td>25%</td>
<td>12.5%</td>
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</tr>
<tr>
<td>2000 - 2003</td>
<td>13</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>68.23%</td>
<td>38.46%</td>
<td>15.38%</td>
<td>7.69%</td>
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</table>

With increasing payor pressures and shorter exclusivity periods, Pharma innovation is becoming unattractive to investors

Base data source: Bain Consulting
Example of a phase III failure: The Torcetrapib Mystery

“Pfizer spent more than $900 million testing its experiment heart pill, torcetrapib. But in December 2006 a 15,000 – patient study revealed that this chemical increased death rates (93 vs 58), forcing Pfizer to suddenly drop the project”

“What when wrong”

“Why torcetrapib failed is the biggest mystery facing the $260 billion global pharmaceutical industry”
... In spite of the considerable improvement in the early 2000s, the average development cycle continues to cross a decade...
What can be done about it – What would Einstein do?

“The significant problems we face today cannot be solved at the same level of thinking we were at when we created them”

Albert Einstein