History of clofazimine
50 years since its discovery.

Jacques H. Grosset
Discovery of clofazimine

- Lichens constituted in the 40s an important source of antimicrobiologically active products
- **Depsidones** are natural products of lichens. **Diploicin** (tricyclic diphenyl ether lactone system) obtained from the lichen *Buellia canescens*¹ was one of these products
- Derivatives from diploicin led Barry to the discovery of anilinoaposafranine, active against M.tb² but too toxic in the guinea pig
- Several structural modifications (R-substitution) mainly in the (NH) imino group (hence the name “rimino” compounds) led Barry to the synthesis of the rimino-phenazine, clofazimine (B663, Lamprene)

Chemical structure of rimino-phenazines

- **Phenazines**

- **Clofazimine**
  - *p*-chlorophenyl group
  - Isopropylimino group
  - *p*-chloroanilino group
Anti-tuberculosis activity of clofazimine (B663)
From Barry & al., Nature 1957; 179: 1013-1015

- MIC for *M. tuberculosis*: ≤ 0.25-1.0µg/ml
- In mice:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening</th>
<th>Daily intake for 14 days</th>
<th>Increase survival time (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B663</td>
<td>Protective</td>
<td>20 mg/kg</td>
<td>&gt;210</td>
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<tr>
<td></td>
<td></td>
<td>8 mg/kg</td>
<td>&gt;210</td>
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<tr>
<td></td>
<td></td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Established</td>
<td>11mg/kg</td>
<td>&gt;80</td>
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<td></td>
<td>Protective (INH-R)</td>
<td>3.3 mg/kg</td>
<td>&gt;133</td>
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<tr>
<td>Isoniazid</td>
<td>Protective</td>
<td>25 mg/kg</td>
<td>150</td>
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<tr>
<td></td>
<td>Established</td>
<td>39</td>
<td>67</td>
</tr>
</tbody>
</table>
Anti-tuberculosis activity of clofazimine (B663)
From Grumbach, Ann Inst Pasteur 1960; 99: 567-585

Pharmacokinetics:
After daily (6/7) administration of 50mg/kg of clofazimine, lung concentrations were:
- 42 µg/ml after 7 days
- 190 µg/ml after 30 days
- 567 µg/ml after 60 days

Antimicrobial activity:
20mg/kg clofazimine is as active as 5mg/kg isoniazid and their combination prevents selection of resistant mutants
The premature sunset of clofazimine

• In the guinea pig, poor activity (but very poor GI absorption)

• In the Rhesus monkey, very poor activity even at 100mg/kg (LH Schmidt, 1960). No explanation

• In humans, in Davos, Switzerland, 5-10mg/kg/day to patients with cavitary pulmonary TB was ineffective (later it was found that only 15% of the dose was absorbed)

• The spectacular activity of the 3-drug combination SM-INH-PAS totally overshadowed clofazimine in 1960!