Bio-mining the microbial treasures of the ocean
Early drug discovery and models for entering pharmaceutical pipelines

Dr. Antje Labes

Marine microbial compounds: from habitat to product

Helmholtz Centre for Ocean Research Kiel

Kiel Center for marine natural products
Natural compounds – highly potential molecules


„high potentials“ of the ocean

70% of earth’s surface
Less than 1% of microbial diversity known

New compounds
New enzymes

1967, a small symposium was held in Rhode Island, USA, with the ambitious title “Drugs from the Sea”: 
Current status of the pipeline of marine natural products

- 4 drugs approved by FDA, 1 registered in the European Union.
- Current clinical pipeline includes more than 10 in different clinical phases.
- 4 of these originate from marine microbes.
- Preclinical pipeline: continues to supply several hundred novel/year.

Mayer et al. 2010

High added value chain from habitat to biotechnological product in marine biotechnology

Classical value/risk problem?
Value/risk/scientific topics

- Discovery
- Clinical pharmacology
- Phase I and Phase II
- Phase III, PMS

Scientific topics and competences needed

Acc. to Douglas et al. 2010

Number of big pharma deals is decreasing

Adapted from Kessel, 2011

"Post-mega-merger pharmaceutical landscape"
High added value chain from habitat to biotechnological product in marine biotechnology

establishment of research platforms
re-thinking financing of early discovery

Example: Culture collections
c. 15,000 marine bacteria
c. 10,000 marine fungi
Access to diverse marine habitats
Marine habitat

Strains

Strain collections

Genomic approach

Cultivation and extraction

Gene optimization

Extracts

Purification

Compounds

Pure compounds library

Process development

Lead structure development

(aus: Imhoff et al., 2011)

WP1: Project Management and Coordination

Molecular based approach

Selected fungal strains

WP2

Genome analysis, identification of biosynthetic genes and regulators

Culture based approach

Selected marine macrobes from geographically distinct habitats

WP3

Isolation and identification of new fungal strains and optimisation of secondary metabolite production

WP4

Chemical identification and biochemical characterisation of active metabolites and substance purification

WP5

Strain improvement

WP6

In vitro bioassays for cancer targets, rational lead structure selection and in vivo efficacy determination in xenograft models

WP7

Robust and sustainable process development

WP8: Intellectual Property protection & and dissemination activities

PROF. DR. JOHANNES F. IMHOF
FP7, 265926
## Success?

Table 1: New drugs approved by the FDA CDER from 1990 to 2007 by type and discovering organization

<table>
<thead>
<tr>
<th>Drug classification</th>
<th>Pharmaceutical company</th>
<th>Biotechnology company</th>
<th>University; first transfer to a pharmaceutical company</th>
<th>University; first transfer to a biotechnology company</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original CDER classification</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>pMWE</td>
<td>62.7 (57%, 60%)</td>
<td>6.0 (1%, 2%)</td>
<td>9.1 (15%, 45%)</td>
<td>12.4(10%, 28%)</td>
<td>31 (14%)</td>
</tr>
<tr>
<td>pNWE</td>
<td>55.4 (67%, 38%)</td>
<td>15.4 (60%, 35%)</td>
<td>9.1 (15%, 45%)</td>
<td>10.0 (13%, 46%)</td>
<td>40 (19%)</td>
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<tr>
<td>NTBs</td>
<td>4.0 (13%, 2%)</td>
<td>10.8 (4%, 45%)</td>
<td>3.3 (8%, 14%)</td>
<td>10.0 (13%, 25%)</td>
<td>37 (15%)</td>
</tr>
<tr>
<td>After reclassifying 21 polypeptide and two polynucleotide NMEs as NTBs</td>
<td></td>
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</tr>
<tr>
<td>pMWE</td>
<td>1.25 (20%, 57%)</td>
<td>6.4 (14%, 14%)</td>
<td>2.7 (7%, 34%)</td>
<td>3.7 (9%, 22%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>pNWE</td>
<td>52.2 (61%, 39%)</td>
<td>9.3 (11%, 23%)</td>
<td>6.4 (10%, 45%)</td>
<td>15.9 (10%, 45%)</td>
<td>56 (24%)</td>
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<tr>
<td>NTBs (reclassified)</td>
<td>11.2 (19%, 5%)</td>
<td>20.8 (7%, 44%)</td>
<td>5.4 (9%, 26%)</td>
<td>14.7 (7%, 37%)</td>
<td>40 (18%)</td>
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<tr>
<td>All drugs (excluding NTBs classified according to review priority)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Standard</td>
<td>96.5 (50%, 27%)</td>
<td>15.2 (2%, 35%)</td>
<td>10.2 (3%, 45%)</td>
<td>13.0 (1%, 33%)</td>
<td>120 (51%)</td>
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<tr>
<td>Priority</td>
<td>14.6 (40%, 30%)</td>
<td>24.0 (1%, 65%)</td>
<td>11.2 (3%, 17%)</td>
<td>26.3 (1%, 67%)</td>
<td>121 (49%)</td>
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<tr>
<td>All drugs classified according to scientific novelty</td>
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<tr>
<td>Focused</td>
<td>95.8 (15%, 85%)</td>
<td>14.2 (1%, 32%)</td>
<td>12.0 (1%, 86%)</td>
<td>12.2 (1%, 32%)</td>
<td>154 (57%)</td>
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<tr>
<td>Scientifically novel</td>
<td>51.5 (44%, 35%)</td>
<td>28.9 (55%, 65%)</td>
<td>9.4 (15%, 45%)</td>
<td>22.2 (23%, 69%)</td>
<td>131 (47%)</td>
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<tr>
<td>Overall</td>
<td>35.6 (29%, 31%)</td>
<td>32.0 (2%, 27%)</td>
<td>6.7 (2%, 33%)</td>
<td>28.6 (1%, 49%)</td>
<td>54 (21%)</td>
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<tr>
<td>Total</td>
<td>34.7 (2%, 98%)</td>
<td>44.1 (1%, 99%)</td>
<td>20.4 (1%, 99%)</td>
<td>40.3 (1%, 99%)</td>
<td>252</td>
</tr>
</tbody>
</table>

Kellner 2010
Transfer models for early drug discovery

- Early – proof of concept
  - Broad research possibilities, public funding for basic tasks
  - Enhance academic value
  - Early onset of SME
  - New financing models, e.g. shared portfolios

- Middle – proof of relevance
  - Focussing on few tasks – transition
  - Funding cycle oriented with exit-strategy

- Question of IP models
Much of nature’s treasure trove of small molecules remains to be explored, particularly from the marine and microbial environments."

(Newman & Cragg, 2007)