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
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”:
In 1967, a small symposium was held in Rhode Island, USA, with the ambitious title “Drugs from the Sea”. The catchphrase of the symposium title has endured over the decades as a metaphor for drug development from marine natural products, though the first genuine drug from the sea was a long time coming (Molinski et al., 2009). The need for novel substances for the treatment of severe human diseases such as cancer, microbial infections and inflammatory processes, combined with the recognition that marine organisms provide a rich potential source of such substances support the intensive search for new substances from marine organisms. In the past, often algae and marine invertebrates have been investigated.
High added value products from marine organisms

„Much of nature‘s treasure trove of small molecules remains to be explored, particularly from the marine and microbial environments.“

(Newman & Cragg, 2007)

Pharmacy, Medical technology and hygiene, Cosmetics
Industrial biotechnology, Food, Plant protection
Ziconotide, a successful example

- isolated from cone snail *Conus magnus*
- ω-Conotoxin MVIIA (SNX-111)
- Prialt® against pain
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

“Post-mega-merger pharmaceutical landscape“  
Adapted from Kessel, 2011

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**Figure 1** The number of big pharma deals with biotech have fallen in all stages. Source: Burrill & Co. (San Francisco); 2010 year to date (YTD) is through September 30.
Example: Culture collections
ca. 15,000 marine bacteria
ca. 10,000 marine fungi
Access to diverse marine habitats
Marine habitat

Isolation

Strains

Strain collections

Genomic approaches

Cultivation and extraction

Modification of growth parameters

Strain optimization

Extracts

Purification

Compounds

Pure compounds library

Structure elucidation

Structures

Selection

Process development

Lead structure development

Bioassays

Bioactivity
**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 & dissemination activities

**FP7, 265926**
11 partners within MARINE FUNGI
Success?

<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><strong>Original CDER classification</strong></td>
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<tr>
<td>sNMEs</td>
<td>87.7 (75%, 60%)</td>
<td>8.8 (7%, 20%)</td>
<td>9.2 (8%, 43%)</td>
<td>11.4 (10%, 29%)</td>
<td>117 (46%)</td>
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<tr>
<td>pNMEs</td>
<td>55.4 (57%, 38%)</td>
<td>15.4 (10%, 35%)</td>
<td>9.1 (9%, 43%)</td>
<td>18.0 (10%, 46%)</td>
<td>98 (39%)</td>
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<tr>
<td>NTBs</td>
<td>4.0 (11%, 3%)</td>
<td>19.0 (54%, 45%)</td>
<td>3.1 (8%, 14%)</td>
<td>10.0 (27%, 25%)</td>
<td>37 (15%)</td>
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<tr>
<td><strong>After reclassifying 21 polypeptide and two polynucleotide NMEs as NTBs</strong></td>
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<tr>
<td>sNMEs</td>
<td>83.7 (79%, 57%)</td>
<td>6.4 (6%, 14%)</td>
<td>7.2 (7%, 34%)</td>
<td>8.7 (8%, 22%)</td>
<td>106 (42%)</td>
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<tr>
<td>pNMEs</td>
<td>52.2 (61%, 35%)</td>
<td>9.3 (11%, 21%)</td>
<td>8.6 (10%, 40%)</td>
<td>15.9 (18%, 40%)</td>
<td>56 (34%)</td>
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<tr>
<td>NTBs (expanded)</td>
<td>11.2 (19%, 8%)</td>
<td>28.4 (47%, 64%)</td>
<td>5.6 (9%, 26%)</td>
<td>14.7 (25%, 37%)</td>
<td>60 (24%)</td>
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<td><strong>All drugs (including NTBs) classified according to review priority</strong></td>
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<tr>
<td>Standard</td>
<td>90.5 (70%, 62%)</td>
<td>15.2 (12%, 35%)</td>
<td>10.2 (8%, 48%)</td>
<td>13.0 (10%, 33%)</td>
<td>129 (51%)</td>
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<td>Priority</td>
<td>56.6 (46%, 38%)</td>
<td>29.0 (23%, 65%)</td>
<td>11.2 (9%, 52%)</td>
<td>26.3 (21%, 67%)</td>
<td>123 (49%)</td>
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<tr>
<td><strong>All drugs classified according to scientific novelty</strong></td>
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<td>Follow-ons</td>
<td>95.6 (71%, 65%)</td>
<td>14.2 (11%, 32%)</td>
<td>12.0 (9%, 56%)</td>
<td>12.2 (9%, 31%)</td>
<td>134 (53%)</td>
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<td>Scientifically novel</td>
<td>51.5 (44%, 35%)</td>
<td>29.9 (25%, 60%)</td>
<td>9.4 (6%, 44%)</td>
<td>27.2 (23%, 69%)</td>
<td>118 (47%)</td>
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<td><strong>Overall</strong></td>
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<td>Orphan drugs</td>
<td>15.6 (29%, 11%)</td>
<td>12.0 (22%, 27%)</td>
<td>6.7 (12%, 33%)</td>
<td>19.6 (36%, 49%)</td>
<td>54 (21%)</td>
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<tr>
<td>Total</td>
<td>147.2 (58%)</td>
<td>44.1 (18%)</td>
<td>20.4 (8%)</td>
<td>40.3 (16%)</td>
<td>252</td>
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</tbody>
</table>

Kellner 2010
From scientific rationale to capital flow?

**Biology of marine fungi**
Understanding the complexity of a neglected group with diverse functions

**Microbial interaction**
Understanding communication at the µm-level

**Marine natural products**
Linking ecology and biotechnology
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
  - Public-private partnerships

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

- Question of IP models
Beyond venture capital

European Approach?

Hollway 2010
„Much of nature‘s treasure trove of small molecules remains to be explored, particularly from the marine and microbial environments.“

(Newman & Cragg, 2007)