Some Perspectives on Marine Biotechnology

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Contribution of Natural Products to 1355 Drugs Over the Last 30 Years

Diseases Ineffectively Treated by Current Medications: Incidence of Cancer Mortality by Site (1930 – 2016)
Emerging Diseases For Which We Have Few or No Effective Therapies

Emergent Viral Disease From Wild Animal Reservoirs (HIV, Zika, Ebola, SARS, Wuhan coronavirus etc.)
A Huge Unmet Medical Need Exists with Neurological Diseases

Alzheimer's Disease

Huntington's Disease

Parkinson's Disease

Drug Addiction

PAIN
Nineteen Approved Marine Natural Products, Derivatives or Inspired Drugs as of 2020

**Fludarabine Phosphate**
- Cancer - Leukemia

**Nelarabine**
- Cancer – T-cell acute lymphoblastic leukemia

**Cytarabine**
- Cancer – Leukemia and Lymphomas

**Vidarabine**
- Antiviral – ocular

**Prialt**
- Pain

**Aplidine**
- Cancer – multiple myeloma

**Lota-carrageenan**
- Nasal spray; reduce duration of viral colds

**Propylene glycol alginate Sulfate Sodium (PSS)**
- Cardiovascular, Hyperlipidemia

**Brentuximab vedotin**
- Polatuzumab vedotin
- Enfortum ab vedotin
- Lymphoma/Carcinoma

**Erubulin**
- Cancer – breast carcinoma

**Lovaza, Omtryg, Vascepa, Epanova**
- Hyperlipidemia

**Trabectedine**
- Cancer - sarcomas

**Protamine sulfate**
- Diabetes & heparin overdose

**Hemocyanin KLH**
- Immune stimulation with cancer vaccines
Antibody-Drug Conjugates, A Growing Class of Patient-Specific Therapeutics

Primary Mechanism of Action of ADCs: Targeted Delivery of a Cytotoxic Agent

1. ADC in plasma
2. ADC binds to receptor
3. ADC-receptor complex is internalized
4. Cytotoxic agent is released
5. Apoptosis (cell death)

Usually by proteases such as cathepsin B

What are Some of the Frontiers to Be Explored in the Coming Decade?

Exploring New Habitats, New Environmental Niches (Microbiomes) and New Classes of Marine Organisms
Exploring the Natural Product Biosynthetic “Dark Matter” of Microbial Genomes

Traditional “Top-Down” Approach

- biomass
- extraction
- bioassay
- fractionation
- analytical chemistry
- structure determination

Newer “Bottom-Up” Genome Mining Approach

- searching in genomic database
- cluster activation & compound isolation
- analytical chemistry
- structure determination

Yan et al., Nat. Prod. Rep. 2020 (advance publication)
Macromolecular Marine Biotechnology

Green Fluorescent Protein

Vent Polymerase

Phycoerythrin and Other Marine Pigments
Developing New Methodologies to Accelerate and Make More Efficient the Natural Product-Based Drug Discovery Process
New Automatic Methods in Mapping Metabolomes (Dorrestein and UCSD Community)

1. Cyanobacterial collection

2. LC-MS/MS or nanoDESI-MS/MS

3. Scoring of MS/MS of Similarity

4. Creation of MS/MS Molecular Network
Gerwick library of 3500 marine cyanobacterial extracts/fraction analyzed by LC-MS/MS

- Dereplication of known compounds
- Location of desired analogs
- New natural products

Metadata:
- Hawaii
- Curacao
- Panama-Bocas del Toro
- Panama-Coiba
- Panama-Gulf of Chiriqui
- Panama-Portobello
- Palmyra
- Papua New Guinea
- 2 Groups or more
- Library hit

Standard MS/MS Spectra
‘Small Molecule Accurate Recognition Technology’ (SMART) uses Deep Learning
Saxitoxin (orange) Embedded in HSQC Space
Comprised of 62,000 Natural Products using
SMART Deep CNN
Summarizing on a Few Frontiers in Marine Biotechnology

- Exploring new niches, especially microbiomes
- Using new approaches such as genome mining
- New marine enzymes for green chemical biology
- Developing sophisticated new tools to accelerate the discovery and development process
- Natural products research engages and trains a highly diverse workforce that is needed in government, industry and academia
Both “top-down” and “bottom-up” approaches are highly varied with much opportunity for innovation, resulting in discovery of biomedically significant molecules.

Much of the diverse biota in the world’s oceans have only been superficially sampled to date.

Borrowing of technologies from other scientific disciplines provides exciting opportunities for innovation and creativity in natural products drug discovery.

Natural products research engages and trains a highly diverse workforce that is needed in government, industry and academia.