INSIDE this issue

Conquering Cancer with Drugs from Nature’s Medicine Cabinet

A life-saving compound from nature

1

Developing Taxol

2

Overcoming nature’s scarcity

3

Too toxic for therapy

4

Antibody-targeted therapies

7

Rapamycin: it’s complicated

8

Into the deep

8

Nature’s designs: tried and still true

10
Acknowledgments
Conquering Cancer with Drugs from Nature’s Medicine Cabinet

Author, Cathryn M. Delude

Scientific Advisor, John A. Beutler, PhD, National Cancer Institute, National Institutes of Health

Scientific Reviewer, David Newman, DPhil, National Cancer Institute, National Institutes of Health

BREAKTHROUGHS IN BIOSCIENCE COMMITTEE
James E. Barrett, PhD, Chair, Drexel University College of Medicine

Aditi Bhargava, PhD, University of California San Francisco

David Brautigan, PhD, University of Virginia School of Medicine

Rao L. Divi, PhD, National Cancer Institute, National Institutes of Health

Marnie Halpern, PhD, Carnegie Institution of Washington

Tony E. Hugli, PhD, Torrey Pines Institute for Molecular Studies

Edward R. B. McCabe, MD, PhD, University of California Los Angeles

Lorraine Oman-Ganes, MD, FRCP(C), CCMG, FACMG, RBC Life Insurance Company

Sharma S. Prabhakar, MD, MBA, FACP, Texas Tech University Health Sciences Center

R. Brooks Robey, MD, FASN, FAHA, White River Junction VA Medical Center and Geisel School of Medicine at Dartmouth

Paula Stern, PhD, Northwestern University Feinberg School of Medicine

BREAKTHROUGHS IN BIOSCIENCE PRODUCTION STAFF
Managing Editor, Tyrone C. Spady, PhD, Legislative Affairs Officer, FASEB Office of Public Affairs

Production Staff, Lawrence Green, Communications Specialist, FASEB Office of Public Affairs

COVER: Many of our most potent anti-cancer therapies were discovered in or inspired by organisms that inhabit the seas, forests, and other habitats. It was not until the 1940s and after seeing the successful treatment of infectious diseases that scientists began to examine the potential of natural products to treat cancers. With new approaches to identifying anticancer compounds and new technologies for investigating the interaction of drug molecules with cancer cells, researchers supported by the National Institutes of Health and other agencies are bringing new drugs to the medicine cabinets of patients in need. Images credits: Darrin Klimek and Manuel Velasco.
Conquering Cancer with Drugs from Nature’s Medicine Cabinet

Despite a four decade “war on cancer,” this year, 1.5 million Americans will be diagnosed with a form of this broad group of diseases, and a half million will die as a result. Until the early part of the 20th Century, the standard way to treat cancer involved cutting it out, sometimes crudely. Radiation therapy, introduced in 1913, proved an effective way to treat some cancers without surgery, but it also caused tremendous collateral damage to healthy tissues. Beginning in the late 1930’s - early 1940’s, researchers were inspired by the success in treating infectious diseases with chemicals isolated from microorganisms and other natural products, such as penicillin from a fungus. Could chemicals battle cancer too? The first of such drugs, a variant of mustard gas, actually came from the battlefield and owes its origin, ironically, to the gas warfare conducted during World War I. Early on, military physicians realized that service-men exposed to mustard gas had diminished numbers of a type of white blood cell known as a lymphocyte. Scientists then deduced that this class of compounds might be useful in the treatment of cancer of the lymphocytes — lymphoma—and other blood diseases. But the treatment was too harsh and eventually fell from use. Despite this initial failure due to adverse side effects, the discovery that chemicals could be used to treat cancer was a watershed moment and foreshadowed the century of medical breakthroughs that was to come.

A life-saving compound from nature

Various folk remedies had attributed anticancer properties to plants, but virtually no scientific research had explored the use of natural compounds, from plant and other sources, to treat cancers. Then in the 1950s, researchers discovered that the Madagascar periwinkle (Catharanthus genus) contained biologically active compounds called alkaloids. Periwinkle alkaloids interfere with cell division in cancer cells, and so these compounds became the basis for a class of “vinca alkaloid” drugs, which includes vincristine and vinblastine, which are still in use today.

In 1960, the National Cancer Institute (NCI) began systematically screening other plants for similar anticancer properties. NCI-funded researchers collected a wide assortment of samples—bark, leaves, stems, seeds, roots—and tested extracts from them for anticancer activity. Extracts that either killed cancer cells or slowed the growth of tumors were sent to research laboratories for activity-guided fractionation, a process that isolates a pure compound for further study. Early in the process, the NCI plant program teamed up with the United States Department of Agriculture (USDA) for more widespread sample collection.

On a hot day in August 1962, one of the USDA’s botanists, Arthur Barclay, gathered specimens from a scraggly, slow-growing Pacific yew tree, Taxus brevifolia. This tree lives along stream banks, gorges, and ravines in old growth forests in the
Pacific Northwest. Because it is poisonous, the yew has no natural pests, and laboratory tests quickly showed that an extract prepared from it killed cancer cells. It would take years to determine what the anticancer compound was and how it worked. Finally, 30 years later in 1992, the breakthrough drug derived from the Pacific yew, Taxol, received Food and Drug Administration (FDA) approval for advanced ovarian cancer. It has since saved untold lives and extended others by many years.  

New Drug Development. Drug discovery is an iterative process. It goes back and forth between theoretical biology; the necessary, appropriate, and humane use of animal assays to determine a compound’s biological activity in the body; and medicinal chemistry to optimize the compound. Then in human studies, clinical observations test hypotheses about how a candidate drug may target cancer cells; determine its safety and effective doses; and compare its ability to shrink tumors or stop cancer progression relative to standard treatments.
years. With metastatic ovarian cancer, for example, the pendulum swung dramatically from 20 to 80 percent survival after five years.

To illustrate the significance of this breakthrough in cancer therapy, consider the case of Tia McAlpine. A 36-year-old mother of three children, Tia was diagnosed with advanced ovarian cancer in May 1982. Ovarian cancer is almost always undetected until the tumor has metastasized. Its presentation

**DRUG DEVELOPMENT PROCESS**

- **Using the in vitro laboratory assay,** 5,000-10,000 new and previously developed compounds are tested for biological activity.
- **On average,** 250 of the compounds tested possess the desired activity and are now designated as “hits.”
- **A handful of the most promising hits** are chosen for chemical modification to improve target specificity, potency, chemical and metabolic stability, water solubility, and other pharmacological parameters. Improved hits are now known as “lead compounds.”
- **A New Drug Application is filed with the FDA.**
- **Phase III clinical trials** test large numbers of patients. Before moving to testing in humans, an Investigational New Drug Application must be filed with the FDA.
- **Phase I clinical trials** consist of drug safety studies in healthy humans. III clinical trials, this portion of the drug development process is usually funded by industry and other private organizations and is distinguished by blue borders. Because this process is so rigorous, only four to seven percent of candidate drugs receive approval from the Food and Drug Administration (FDA).
nies invest the 10 or more years it takes to bring a cancer drug to the market, they like to know how the drug actually kills cancer cells, i.e. its “mechanism of action.” No one knew how Taxol worked until 1979, when research conducted by Susan Horwitz showed that it worked in a totally different manner from any other known anticancer drug.

The existing drugs either damaged DNA directly, or they interfered with tubulin, a protein that is essential for cell division, or mitosis. Tubulin chains constantly form and un-form (technically stated, they polymerize and de-polymerize) during mitosis. Vinca alkaloid drugs prevent tubulin chain formation, while Taxol does the opposite, preventing its “un-forming” or disassembly. Both of these interferences stop cell division and lead to cell death. (See the sidebar “How Some Drugs Kill Cancer Cells.”)

It had been years since researchers had discovered a new mechanism in the war on cancer. This breakthrough generated great excitement for Taxol, and catapulted it into clinical trials in the early 1980s for refractory ovarian cancer, the kind that afflicted Tia McAlpine.

Fifteen years later in 1998, Jim’s 46-year old sister Jan Ely was also diagnosed with ovarian cancer. She began Taxol immediately, went into remission, and resumed her normal life with her family. After six years she relapsed and died two years later. “Those eight years would have made a big difference for Tia and us, especially for our daughter who was ten when her mother died,” says Jim. “We tend not to realize how much progress we have made since Tia died.”

**Developing Taxol**

It took 30 years of research to make Taxol available to people like Tia. (To view a general overview of how drugs are developed, see the flowchart “Drug Development Process”) After NCI confirmed the anticancer properties of the yew sample, scientists at Research Triangle Institute in North Carolina received 30 pounds of Taxus yew bark in 1964. The researchers isolated a biologically active compound that appeared to have the chemical properties of an alcohol. It was thus named Taxol, combining Taxus with alcohol. But it was hard to purify enough of the compound from the bark to determine its structure. Stripping each yew tree produced two kilograms of dried bark, but yielded just one-half gram of Taxol—and left the tree dead. This made the compound much less attractive as a potential treatment, and by 1967, Taxol had been relegated to NCI’s back burner. The work limped slowly along however, and in 1978 researchers using a new type of laboratory mouse model of cancer showed that Taxol caused regression of mammary tumors.

Before pharmaceutical compa-
How Some Anticancer Drugs Work

Ideally, anti-cancer drugs should harm only cancer cells and spare normal cells in the body. Cancer cells differ from normal cells in many ways, but one hallmark is that they grow and divide rapidly, so many drugs target fast-dividing and fast-growing cells by disrupting steps in cell division. This disruption damages cells so badly that the cells “commit suicide”—they initiate a cell death program called apoptosis. Here are several ways that drugs derived from natural products kill cancer cells.

1) Damage DNA

DNA is usually tightly wound inside the nucleus of our cells, but it unwinds during cell division. This makes the cell vulnerable to damage.

- Calicheamicin, a drug isolated from a soil bacterium, binds to this unwound DNA and cuts apart both strands of the double helix.

2) Interrupt Cell Division (Anti-tubulin)

During cell division (mitosis), the chromosomes are duplicated, and a protein called tubulin pulls a set of chromosomes to each end of the cell so that each subsequent daughter cell will receive a complete set of chromosomes. Tubulin chains continuously assemble and disassemble (polymerizes and de-polymerizes) a tubular structure called a microtubule. When drugs prevent this assembly or disassembly, the cell undergoes apoptosis.

- Vinca alkaloids like vinblastine and vincristine, derived from a periwinkle plant, cause chaos by binding to tubulin and preventing formation of the microtubule.
- Taxol, derived from the yew tree, does the opposite. It “freezes” the tubulin, preventing the disassembly of the microtubule.
- Eribulin, a synthetic drug developed from the structure of a marine sponge compound, appears to prevent both assembly and disassembly.

3) Prevent DNA Repair

DNA damage happens during the normal course of living, so cells have developed DNA repair mechanisms to fix the nicks and mismatches that otherwise accumulate. Some anti-cancer drugs prevent these DNA repair mechanisms from functioning properly, causing cell death.

- Yondelis ( trabectedin), a drug developed from a sea squirt and approved in the USA in 2007, inhibits the transcription of genes involved in DNA repair. The accumulating DNA damage stops the cell cycle, activating apoptosis.
- Anthracyclines like doxorubicin, a class of drugs derived from bacteria, inhibit enzymes called topoisomerase II. These enzymes allow DNA loops to come apart and reunite in order to express genes or duplicate DNA for cell division. Inhibiting them prevents the DNA repair required for reuniting the loops.

Disaster was averted when researchers developed another, less environmentally destructive way to harvest a closely related compound (10-deacetylba- ccentin III) from the needles of the English yew, Taxus baccata. They chemically modified the Taxol-like compound to generate the chemical structure of Taxol. The needles were renewable since the tree could grow more of them, and clipping them did not kill the tree. Thanks to that advance, further clinical trials proceeded, and in 1994 the FDA approved the semi-synthetic version, named Paclitaxel, for refractory ovarian cancer, and then a related drug, Taxotere (docetaxel). Researchers continue to fine-tune and expand the uses of these drugs, such as for metastatic breast cancer, AIDS-related Kaposi’s sarcoma, and some lung and head-and-neck cancers. Most recently in June 2010, a semi-synthetic taxane drug, Jevtana (cabazitaxel), was approved for treating hormone-refractory prostate cancer. To fully take advan-
vantage of the power of Taxol, the drug is also being tested in a new experimental approach, discussed below, to target it more exclusively to cancer cells.

Too toxic for therapy

An unconfirmed but enticing legend holds that Alexander the Great was fatally poisoned in 323 BC by drinking water from the River Styx, the mythological river that divides life and death. The river is thought to be based on the Mavroneri River in northern Greece, where nearby soils have traces of a deadly naturally occurring compound called calicheamicin. Calicheamicin is produced by a soil bacterium and is among the most cytotoxic and potent natural substances known. Like many initially promising compounds, and in keeping with Greek tragedies, its fabled toxicity has proven to be its pharmaceutical downfall, at least temporarily.

Calicheamicin research began in the 1980s when a scientist collected a soil sample while vacationing in Texas, and his lab later isolated the compound from the Micromonospora echinospora bacterium in the sample. This compound and another, esperamycin, were the first members in a class of chemotherapeutics called enediyynes to be fully identified. These compounds damage the DNA of a cell’s chromosomes so badly that the cell is unable to repair it. This causes the cell to “commit suicide” by activating a program called apoptosis. Different agents damage DNA in different ways; calicheamicin, for example, causes breaks in both strands of DNA.

Calicheamicin killed cancer cells, researchers discovered, but was up to ten thousand times more toxic than existing chemotherapy drugs. This was also too toxic to normal cells, so the compound could not gain approval for clinical use. But what if there was a way to strategically harness this potent compound by targeting it specifically to cancer cells? Efforts to accomplish this have led to an ingenious new method for targeting drugs and may ultimately revive the promise of many anticancer compounds deemed too toxic.

Antibody-targeted therapies

Targeted drug delivery of highly toxic compounds builds upon another approach researchers were using to fight cancer: monoclonal antibodies. Antibodies are molecules made by the immune system that bind to protein “identification tags” called antigens that are found on the surface of cells. (The term monoclonal
means these antibodies are all produced by the same cloned cells, so they are identical.) Cancer cells have unique antigens that distinguish them from healthy cells. Thus antibodies that bind to the cancer antigens allow for the targeting of cancer cells rather than normal cells. Among the most widely used antibody therapies are Rituxan (for treatment of non-Hodgkin’s lymphoma), Erubitux (for colorectal cancer), and Herceptin (for metastatic breast cancer). These antibody therapies cause the immune system to attack cancer cells by triggering an immune response. Even though they have the advantage of specificity, monoclonal antibodies are only effective in treating a few cancers. Cytotoxic compounds, on the other hand, have the advantage of being much more potent, but they are not specific and decimate healthy cells, often damaging the liver, kidney, and bone marrow. So the idea of targeted drug delivery was to combine the specificity of antibodies with the cancer cell-killing power of compounds that are too toxic for patients when administered without targeting. These cancer-seeking missiles are called antibody-drug conjugates (ADC), and they essentially shepherd inactive forms of highly potent drugs into the unsuspecting cancer cell. Exposure to the internal environment of the cell then triggers the conversion of the drug to its active form.

The first attempts at employing ADCs used clinically approved drugs derived from natural products, such as vinca alkaloids and doxorubicin, a compound that Italian researchers searching for anticancer molecules in the 1950’s isolated from soil bacterium near a 13th century castle on the Adriatic Sea. Doxorubicin is the basis for drugs used in combination to treat a number of cancers. But results of these ADCs were marginal because the drugs were themselves not very potent. Then researchers proposed using the more potent but unapproved compound, calicheamicin. The calicheamicin-based ADC, called Mylotarg, was targeted to the aberrant cells in acute myeloid leukemia (AML) and was approved for patients with advanced AML in 2000.

Ten years later, however, the drug was pulled off the market because of concerns about...
safety and insufficient efficacy in patients with advanced AML. Despite the cleverness of the ADC approach, the actual execution is not a trivial task. The antibody-drug linkage has to be stable within the bloodstream so as not to release the cytotoxic compound prematurely and off-target. Further, once inside the cancer cell, the drug must be resistant to being pumped out, a trick often used by drug-resistant forms of cancer. Since the development of Mylotarg, researchers have made important advances in the design of ADCs. Mylotarg’s example showed that this new approach for targeted drug delivery could work. In 2011, the FDA approved another monoclonal antibody linked to auristatin, a drug derived from dolstatin 10, a marine natural product. This conjugate, named Adcetris (brentuximab vedotin), is approved for treating two types of lymphoma and is in clinical trials for other lymphatic cancers. Many other ADCs are now in development (see Table 1), and scientists hope that the ability to tame very potent cytotoxic compounds may rescue discarded drug candidates that failed because they were too toxic when delivered the old fashioned way.

Table 1: Antibody-Drug Conjugates Under Development

<table>
<thead>
<tr>
<th>Name of Conjugate</th>
<th>Antibody Target</th>
<th>Drug Compound</th>
<th>Natural Source</th>
<th>Mechanism of Action</th>
<th>Cancers Being Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotuzumab ozogamicin</td>
<td>CD22 (immune cell regulator)</td>
<td>Calicheamicin (ozogamicin)</td>
<td>Bacterium, <em>Micromonospora echinospora</em></td>
<td>Breaks DNA</td>
<td>Acute lymphocytic leukemia</td>
</tr>
<tr>
<td>Trastuzumab-mertansine</td>
<td>HER2 receptor</td>
<td>Maytansine derivative</td>
<td>Plant in the staff vine family, <em>Celastraceae</em>.</td>
<td>Inhibits tubulin assembly during cell division</td>
<td>Breast cancer</td>
</tr>
</tbody>
</table>

Figure 5 — Plaque for Rapamycin on Easter Island

Figure 6 — Marine sponge: natural source for Eribulin
The marine sponge, *Halichondria okadai*, is the source for the compound that was developed as the cancer drug Eribulin. This drug interferes with the tubulin molecule during cell division. Eribulin is now made synthetically and was approved in November 2010 to treat metastatic breast cancer. Image courtesy of Dennis Sabo. *Image courtesy of Richard Seaman.*
Rapamycin: it’s complicated

The natural products developed into anticancer therapies discussed so far work mainly by killing dividing cells. But other natural products with anticancer properties target different cellular processes. One of the most complex examples of this came to light from studying a compound called rapamycin. In 1965, researchers were looking for antibiotics in soil bacteria on the island of Rapa Nui (Easter Island) when they isolated this compound, which they named rapamycin after the island. At first, rapamycin was investigated as an antifungal medication, but was later approved as an immunosuppressant to prevent the rejection of transplanted organs. It also inhibits cell proliferation, and so it was developed as a cancer drug, Temsirolimus. Currently six approved drugs and three candidate drugs are derived from rapamycin, one of which is being investigated as a potential treatment in autism and Alzheimer’s disease, as well as for HIV infections.

What could account for such diverse effects from one compound? The answer lies in the importance of rapamycin’s target in the cell, which researchers named mammalian Target of Rapamycin, or mTOR. The mTOR pathway is involved in many fundamental biological processes. Among other things, it is a master regulator of cellular metabolism and coordinates cell growth and proliferation with the availability of nutrients and
oxygen. In the past decades, researchers have come to appreciate that metabolism in cancer cells differs from that of normal cells. Cancer cells consume much more glucose, and they metabolize it using a different process that produces more of the proteins, lipids, and other “building blocks” required to support rapidly growing and dividing cells. Many researchers think that shutting off this super-charged metabolism could provide an entirely new approach to anticancer therapy. Rapamycin inhibits mTOR, which suppresses some aspects of cancer metabolism and is effective against several cancers. Researchers are also developing drugs to target other points in the metabolic pathways of cancer cells. This research on cancer metabolism runs parallel to other work attacking nodes in specific cancers’ growth pathways, as discussed in the sidebar “Targeted Therapies.”

### Into the deep

If finding natural compounds growing on land is hard, imagine searching for them in deep, dark, shark-infested ocean waters. There is little folklore about medicines from the sea, probably because exploration was confined to where humans could swim or fish. But in the past 50 years, submersibles have opened up these previously inaccessible environments, and new molecular technologies are revealing the secrets in the organisms found there.

In the mid-1980s, the NCI began funding research and large-scale collection projects to systematically explore the potential of drugs from the sea. It seemed a promising place to look for new anticancer compounds, since organisms that have adapted to odd ecosystems, like high-pressure zones and sulfurous deep sea vents, have evolved novel proteins, with unusual biological activity, to survive. And because sessile marine creatures like sea sponges encounter so many different types of predators, they have concocted ingenious toxins and other defensive—or offensive—compounds to protect themselves.

The first new chemotherapeutic produced directly from the sea came from the tunicate (sea squirt) *Ecteinascidia turbinate*. That drug, Yondelis (trabectedin), inhibits the genes involved in repairing damaged DNA. Without this DNA repair process, the damage accumulates, and that triggers the cell death program, apoptosis. Yondelis was approved in the United Kingdom and Europe in 2007 for the treatment of sarcoma and is in clinical trials in the United States for breast and prostate cancers and pediatric sarcomas as well.

Eribulin, the second approved chemotherapeutic from the sea, involved a multidisciplinary, multinational drug development effort and technological tour de force requiring aquaculture, and an interplay of academic, industrial, and government labs on three continents. This effort began in 1986 when Japanese researchers isolated a compound called halichondrin from a sponge (*Halichondria okadai*) living off the coast of Japan. Like Taxol, halichondrin interferes with tubulin, the protein strands that pull the chromosomes around during mitosis or cell division, but in a unique...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Natural Source</th>
<th>Mechanism of Action</th>
<th>Cancers Being Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryostatin 1</td>
<td>Marine moss creature, <em>Bugula neritina</em></td>
<td>Modulates protein kinase C</td>
<td>Various cancers</td>
</tr>
<tr>
<td>Aplidin</td>
<td>Mediterranean tunicate, <em>Aplidium albicans</em></td>
<td>Inhibits protein synthesis and VEGFR1</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Irvalec</td>
<td>Hawaiian marine mollusk <em>Elysia Rufescens</em></td>
<td>Damages plasma membranes</td>
<td>Various cancers</td>
</tr>
<tr>
<td>Zalypsis</td>
<td>Synthetic related to Jorumycin and Renieramycins, from mollusks and sponges</td>
<td>Causes DNA double-strand breaks and other mechanisms</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>PM-060184</td>
<td>Synthetic modification of a marine-derived compound similar to Zalypsis</td>
<td>Causes DNA double-strand breaks</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Marizomib</td>
<td>Marine bacterium, <em>Salinospora tropica</em></td>
<td>As a proteasome inhibitor, prevents breakdown of proteins</td>
<td>Multiple myeloma, lymphomas, leukemias, and solid tumors</td>
</tr>
<tr>
<td>Plinabulin</td>
<td>Halimide isolated from a marine <em>Aspergillus</em> fungus</td>
<td>Disrupts established tumor vasculature</td>
<td>Non-small cell lung cancer</td>
</tr>
</tbody>
</table>
way. It binds to the microtubules formed by tubulin at different sites than other drugs, and prevents the strands from growing or decreasing in size.

Because the marine sponge that produces the compound is rare and cannot be cultured or grown in a lab, researchers looked for similar compounds in related species, as had been done to overcome a similar problem with Taxol. They found the halichondrin-like compounds in a sponge growing off the coast of New Zealand that they were able to “farm” at shallow depths, the first time this had been achieved. However, the compound was simply too huge—more than twice the size of a typical drug molecule.

This unwieldy compound also proved to be incredibly complex, with a unique chemical structure. Starting in 1987, Yoshito Kishi, a chemist at Harvard University, undertook the challenge of synthesizing halichondrin and eventually identified the biologically active part. He worked with a Japanese pharmaceutical company to synthesize this component, which they called Eribulin. The NCI entered Eribulin into clinical trials in 2002, and the FDA approved it for metastatic breast cancer in patients who were unresponsive to other therapies in November 2010. The drug is now being tested in other cancers as well.

A third, entirely different type of marine compound, bryostatin 1, was discovered in the late 1960s when G. Robert Pettit of Arizona State University, working with the NCI early collection programs, extracted it from a reddish-purple moss-like marine creature, Bugula neritina, in the phylum Bryozoa. Bryostatin 1 modulates protein kinase C, which is involved in many cellular functions. The compound appears to work synergistically with other cancer drugs but is less effective as a stand-alone therapy. It is being tested in combination with other cytotoxic drugs in a variety of cancers. Interestingly, it also appears to enhance memory and is being explored as a treatment for Alzheimer’s disease.

A variety of drug candidates, coming either directly from marine sources or modified marine-sourced chemical structures, are in the clinical development pipeline as antitumor agents. (See Table 2.) Still, of the 25,000 marine-sourced compounds that researchers have described to date, only around 20—a mere 0.1%—have reached clinical trials for human diseases, with seven approved by the FDA or its international equivalents. And so, we have only just begun the search for medicinal compounds in the sea!

Nature’s designs: tried and still true

To be sure, the development of anticancer drugs from natural products is a long and arduous journey of discovery, testing, and development. In the late 1980s, many researchers hoped that screening small synthetic molecules for anticancer properties could bring more new drugs to the market more quickly. But that approach was not very effective. Many of these small molecules failed in pre-clinical trials, while natural products and their derivatives are still inspiring new anticancer drugs. In 2007, for example, the FDA approved the first of a new class of anticancer drugs called epothilones, isolated from a gliding bacterium (Sorangium cellulosum). One drug, Ixempra
ways with the cellular processes involved in health and disease. And so, 20 years after moving away from the search for natural product-based drugs, many researchers have a renewed interest in exploring natural products, as well as complex molecules that have structural similarities to them.

Anticancer drugs based on natural products have carried much of the load during the modern war on cancer, and they have made a huge difference for millions of cancer patients. But the legions of cancer patients who still have no effective therapy mean that victory against cancer is still far off, and natural compounds are likely to continue to play important roles in the ongoing battles. With new approaches to identifying anticancer compounds and new technologies for investigating the interaction of drug molecules with cancer cells, we can hopefully bring new drugs to the medicine cabinets of patients in need.

(ixabepilone), is being used to treat breast cancer that does not respond to other therapies and works similarly to Taxol in “freezing” tubulin to prevent cell division. More recently five antitumor drugs approved in 2010 stemmed from natural product research. (See Table 3.)

As difficult as natural products may be to develop as drugs, they frequently have advantages over simpler small molecules. Their biologically active parts are complex structures that interact in more biologically relevant ways with the cellular processes involved in health and disease. And so, 20 years after moving away from the search for natural product-based drugs, many researchers have a renewed interest in exploring natural products, as well as complex molecules that have structural similarities to them.

Anticancer drugs based on natural products have carried much of the load during the modern war on cancer, and they have made a huge difference for millions of cancer patients. But the legions of cancer patients who still have no effective therapy mean that victory against cancer is still far off, and natural compounds are likely to continue to play important roles in the ongoing battles. With new approaches to identifying anticancer compounds and new technologies for investigating the interaction of drug molecules with cancer cells, we can hopefully bring new drugs to the medicine cabinets of patients in need.

(ixabepilone), is being used to treat breast cancer that does not respond to other therapies and works similarly to Taxol in “freezing” tubulin to prevent cell division. More recently five antitumor drugs approved in 2010 stemmed from natural product research. (See Table 3.)

As difficult as natural products may be to develop as drugs, they frequently have advantages over simpler small molecules. Their biologically active parts are complex structures that interact in more biologically relevant ways with the cellular processes involved in health and disease. And so, 20 years after moving away from the search for natural product-based drugs, many researchers have a renewed interest in exploring natural products, as well as complex molecules that have structural similarities to them.

Anticancer drugs based on natural products have carried much of the load during the modern war on cancer, and they have made a huge difference for millions of cancer patients. But the legions of cancer patients who still have no effective therapy mean that victory against cancer is still far off, and natural compounds are likely to continue to play important roles in the ongoing battles. With new approaches to identifying anticancer compounds and new technologies for investigating the interaction of drug molecules with cancer cells, we can hopefully bring new drugs to the medicine cabinets of patients in need.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Natural Source</th>
<th>Cancer Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Eribulin (halichondrin)</td>
<td>Halichondria okadai (marine sponge)</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>2010</td>
<td>Istatodax (romidepsin)</td>
<td>Chromobacterium violaceum (soil bacterium)</td>
<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>2010</td>
<td>Javlor (vinflunine)</td>
<td>Vinca (periwinkle)</td>
<td>Cancer of urothelial tract</td>
</tr>
<tr>
<td>2010</td>
<td>Jevtana (cabazitaxel)</td>
<td>Yew tree</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>2010</td>
<td>Mepact (mifamurtide)</td>
<td>Modified peptide from the cell wall of a bacterium</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>2011</td>
<td>Adcetris (brentuximab vedotin)</td>
<td>Antibody-drug conjugate with auristatin, derivative of dolstatin 10, from a shell-less sea mollusk</td>
<td>Hodgkin’s lymphoma and anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>2012</td>
<td>Kyprolis (carfilzomib)</td>
<td>Modification of a bacterial proteasome inhibitor</td>
<td>Multiple myeloma</td>
</tr>
</tbody>
</table>
Additional suggested reading:


Biographies:

Cathryn M. Delude, of Andover, Massachusetts, writes about science and medicine for magazines and newspapers. She has written for FASEB in the past, and her articles have appeared in Nature Outlook, AACR’s Cancer Discovery, Los Angeles Times, Boston Globe, New York Times, Scientific American, The Scientist, Proto: Dispatches from the Frontiers of Medicine, and other publications on topics including neuroscience, cancer, molecular biology, microbiology, infectious diseases, water, energy, and civil and environmental engineering. She has additionally written for the Howard Hughes Medical Institute, Harvard Health Publications, Harvard School of Public Health, Massachusetts General Hospital, Massachusetts Institute of Technology, Dana Farber Cancer Center, Stowers Institute for Medical Research, and the National Institutes of Health - Office of Science Education.

John A. Beutler, PhD, is a natural products chemist with broad interests in cancer biology and drug screening and development. He works in the Molecular Targets Laboratory of the National Cancer Institute Center for Cancer Research in Frederick, MD, and is currently pursuing the development of natural product drug candidates for brain and kidney cancer. He has published over 100 scientific papers, is Co-editor of the Review of Natural Products, and was President of the American Society of Pharmacognosy in 2010-11. His undergraduate degree was awarded by Vassar College, and his MS and PhD degrees were awarded by the Philadelphia College of Pharmacy & Science. Dr. Beutler went on to complete his postdoctoral training at Northeastern University and the University of Texas Medical School.