1. Medicines from the Sea
    a. This is a presentation meant to communicate critical gaps in our knowledge of medicines and the process of discovering a new compound and how we test for its potential medicinal use. It is by no means comprehensive but is meant to be a framework to understand some of the science behind making medicines. The presentation is most appropriate for middle to high school groups and was written to help teach students the importance of preserving biodiversity. If you have any questions, suggestions or comments you can contact the author, Raphael Ritson-Williams at raphswall@gmail.com. Raphael is a PhD student at the University of Hawaii who studies ecology, evolution and conservation of biodiversity. He is funded by STAR Fellowship Assistance Agreement # FP917660 awarded by the U.S. Environmental Protection Agency (EPA). This presentation has not been formally reviewed by EPA. The views expressed in this presentation are solely those of the author, and EPA does not endorse any products or commercial services mentioned in this publication.
2. Where do medicines come from?
    a. Ask your class. Some medicines come from scientists and labs so this is not wrong, but many of them are from microbes, plants and animals.
3. Where do medicines come from?
    a. 78% of antibacterial and 61% of anticancer agents come from natural chemicals found in land and marine organisms. There is a rich cultural tradition of using plants to cure disease and much of this local knowledge is still being studied in a discipline called ethnobotany. Many of the first medicines were traditional cures from plants.
4. Penicillin
    a. Penicillin is a common antibiotic, it was discovered from mold growing on bread. Penicillin kills bacteria, so we think it evolved so that the mold can outcompete bacteria to decompose the bread.
5. Aspirin
    a. Aspirin comes from a willow tree. The willow bark has been used for at least 2,400 years. Aspirin is an effective pain killer, anti inflammatory, and can help treat fevers. Aspirin was patented by BAYER on March 6, 1889. Aspirin is one of the most used medicines in the world.
6. Morphine
    a. Morphine comes from the sap of poppies. Morphine is an important pain killer that acts on the central nervous system to block our pain receptors. It can be addictive and can cause low blood pressure.
7. Taxol
    a. Taxol is the most used anticancer treatment today and it comes from the bark of the pacific yew tree, *Taxus brevifolia* (a type of evergreen tree). Taxol works by stabilizing the microtubule network in a cell,

these are needed during cell division, and taxol stops them from being broken down, effectively stopping cell division.

8. What is this compound?
    a. This is how we draw the structure of a compound. The number and diversity of elements are critical to how every compound works. The lines are carbon bonds, the letters represent different elements, o is oxygen, h is hydrogen, n is nitrogen. This compound is very common in everyday life; it has 8 carbons, 4 nitrogens, and 2 oxygens.
9. Caffeine
    a. Caffeine. Every one does an extraction when they drink tea or coffee. This is a simple organic chemistry technique of soaking a plant-based material (coffee beans) in an organic solvent (water) and extracting a compound of interested (caffeine and associated flavors).
10. Making a medicine: Finding new species
    a. Much of the search for novel compounds is discovering species that are new to science. Underwater this happens a lot since most species are unstudied. We focus our attention on creatures that are exposed, especially those that are stuck on the bottom and can't get up and run away. These creatures often make novel chemicals to protect them from predators. These chemical defenses can be toxic or they can taste bad. Every compound has a different way of working on cells, and this mechanism of action often determines its potential to be a novel medicine. For example compounds that stop cell division are especially important for anticancer treatments because they stop the replication of cancer cells.
11. Making a medicine: Finding new compounds
    a. When we collect these organisms we freeze them, this stabilizes most compounds. Then we extract the chemicals out of them similar to how you extract caffeine from coffee beans. Then we isolate individual compounds and test them in the lab for their potential medicinal uses.
12. Making a medicine: Clinical Testing
    a. Phase I clinical studies (25-50 people). This stage is to test how well novel compounds work in initial experiments. Researchers test clinical pharmacology of the drug, its short-term safety, and its pharmacological and pharmacokinetic effects in disease. These tests take about a year and involve about 20 to 80 normal, healthy volunteers. The tests study a drug's safety profile, including the safe dosage range. The studies also determine how a drug is absorbed, distributed, metabolized and excreted, and the duration of its action. People who participate in Phase I trials face the highest risks compared to possible benefits.
13. Making a medicine: Clinical Testing Phase II
    a. In this phase, controlled studies of approximately 100 to 300 volunteer patients (people with the disease) assess the drug's effectiveness and take about two years.

    b. These trials are randomized**.** Participants are divided into two groups. One group receives the study drug. The other group is the reference or control group. People in the control group get standard treatment (called "standard of care.") If there is no standard treatment, they may get a dummy medication (called a placebo).
14. Making a medicine: Clinical Testing Phase III
    a. This stage collects more data on a drug's effectiveness and side effects. These studies use a few thousand people and last for a year or more. In phase III trials all of the trials are randomized and the patients are blinded. With good results in Phase III trials, a manufacturer can apply for FDA approval to sell the new drug.
15. Making a medicine: Clinical Testing Phase III
    a. This is a challenging process, and most of the new compounds we find are not good medicines. It can take 10-20 years and up to $800 million for an experimental drug to travel from the source creature to the medicine cabinet.
16. Understanding Marine Biodiversity
    a. We really don't understand much of the diversity on the planet. Many new species don't even have names, and we don't know their roles in ecosystems. How many of these species have a useful medicine? We have no idea, and if we let species go extinct we will never know.
17. Marine Plants
    a. Marine algae include 4 phyla (Rhodophyta, Phaeophyta, Chlorophyta, Cyanobacteria). These primary producers convert sunlight to energy and are the foundation of food webs. They are stuck on the bottom and cannot escape predation. Many plants produce secondary metabolites for defense, anti-fouling and to stop disease. Some of these compounds have potential use for humans.
    b. Red algae are rich sources of natural products. So far 938 compounds have been isolated from red algae. Green algae have 177 isolated compounds. So far 759 compounds have been isolated from brown algae.
18. Cyanobacteria
    a. Cyanobacteria are often referred to as algae because they have similar growth forms and also conduct photosynthesis. Cyanobacteria are rich sources of natural products. So far >700 compounds have been isolated from cyanobacteria.
19. Cyanobacteria
    a. This microscopic photo shows how cyanobacteria are stacks of individual bacterial cells arranged in hair like filaments. Many cyanobacteria produce a wide range of compounds, probably because they are some of the oldest creatures on the planet.
20. Largazole
    a. Largazole was recently isolated from a cyanobacteria off of the Florida Keys close to Key Largo. It shows great promise against cancer, but it still needs to be tested in clinical trials.

21. Largazole: Mechanism of action
    a. When our cells reproduce they copy chromosomes. This is a complex process, and it involves the unwinding of DNA from being twisted around histones (the proteins in the bottom right figure). Once the double strand is unwound transcription can take place where DNA is copied into RNA. Largazole blocks the unwinding of DNA from histones. This means that DNA cannot be transcribed, effectively blocking cell replication.
22. Sponges
    a. So far sponges have been the most prolific source of marine natural products (50%). Secondary metabolites have a variety of ecological functions in sponges including chemical defenses, antifoulants, antibiotics, anti-settlement cues and photoprotective agents. Recent research is showing that symbiotic bacteria make many of these compounds when they live in the sponges.
23. Discodermolide
    a. *Discodermia dissoluta* is a deep-sea sponge that produces the compound discodermolide, which is in clinical trials as an anticancer agent.
24. Cytosar-U
    a. Isolated from a sponge, and it is used to treat leukemia.
25. Cytosar-U: Mechanism of Action
    a. During DNA replication the double helix is broken open, just like when a zipper splits. Then the protein DNA polyerase moves down one of the single strands and makes the complementary nucleic acids to make the DNA double stranded again. Cytosar-U binds to and stops DNA polymerase from working. Inhibits the process of DNA replication by blocking the active building of a complementary strand of DNA.
26. Molluscs
    a. Snails use venoms to paralyze prey allowing these slow moving snails to catch faster moving animals. Closely related slugs (snails without a shell) have many types of compounds that protect them from predators. However these toxins are often taken from their sponge or cnidarian prey.
27. Cone Snails
    a. Cone snails are predators that range from the size of a dime to a dollar bill. They are predators that use a mixture of many small compounds to paralyze their prey.
28. Prialt
    a. Prialt is a medicine that is made from a cone snail toxin. This medicine is a very strong painkiller.
29. Prialt: Mechanism of action
    a. This diagram is showing a neuron. Prialt blocks the calcium channel because it fits in these channels just like a cork in a bottle. The calcium channels are used to create chemical energy that drives the release of

the signal (neurotransmitters). If there is no signal across the synaptic cleft your brain does not receive the message that you should be in pain. Prialt blocks these calcium channels, stopping nerve impulses that would typically signal pain.

30. Fish
    a. Most fish can swim so do not have chemical defenses. However, some slow moving fish are chemically defended. The soap fish exude a thick mucus that is toxic to other fish. Puffer fish are slow moving and contain a potent toxin.
31. Tetrodotoxin
    a. Tetrodotoxin (TTX) was first found in puffer fish but is now known from over 10 phyla of organisms. Puffer fish (Fugu) is a delicacy in Japan that contains enough toxin to cause tingling of lips but not to kill people. The strength of the toxin depends on the skill of the chef, tetrodotoxin from a medium sized puffer fish could kill 30 people. It was known as a poison in Japanese culture for centuries (approx 200 AD). James Cook was poisoned (but survived) in 1774. The first experimental work on puffer fish poison was done in 1889, and the chemical structure was determined 75 years later in 1964.
32. Tetrodotoxin: Mechanism of action
    a. Tetrodotoxin is not a medicine it is used to study the function/ structure of sodium ion channels. TTX acts as a plug in sodium ion channels, much like prialt it is the perfect structure to block these critical membrane channels. The sodium ion channels drive muscle action, so blocking the sodium ion channels causes paralysis. TTX has allowed scientists to study the function and structure of sodium ion channels and nerve impulses. A single point mutation in the structure of sodium ion channels is enough to stop TTX from blocking them.
33. Blue Ringed Octopus
    a. This little octopus is about the size of a tennis ball, it uses tetrodotoxin among a cocktail of toxins to kill its prey.
34. Poison Dart Frogs
    a. Tetrodotoxin is thought to be a defense against birds and other predators that would normally eat frogs.
35. Marine Diversity
    a. Hopefully you have seen that many different animals create chemicals that could be medicines. We need to preserve biodiversity because these creatures are rich sources of novel medicines. Coral reefs are especially important habitats because they contain 30 phyla of animals. This diversity makes coral reefs a great place to discover novel medicines. Different organisms have different strategies for survival and different physiological pathways, which could contribute to the diversity of natural medicines found in marine creatures.