Tracking Marine Pollution

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(6). Next will be LIGO-India (7) and Kagra-Japan (8). Median error regions of 50 (or 6) degrees^2 can be achieved with three (or five) interferometers (4, 9). The network will be sensitive to mergers out to 400 Mpc (or 750 Mpc) for three (or five) interferometers (2, 4). Low-latency gravitational wave localization volumes can be constructed within minutes to alert the astronomers to search for the relevant electromagnetic counterpart (4).

Theorists are working out the expected electromagnetic signature from neutron star and black hole mergers; the luminosity, time scale, and spectral energy distribution. The predicted counterpart is expected to be fainter than a supernova (but brighter than a nova), last for a few hours to a few days, and have red colors (10–12). Nucleosynthesis in the neutron-rich ejecta is expected to give elements with mass numbers ranging between 120 and 200. Indeed, the majority of gold in the universe may be produced during neutron star or black hole mergers (12, 13).

Observational astronomers are mobilizing large telescopes across the entire electromagnetic spectrum. For the tiny fraction of jets (<2.5%) beamed toward us, an all-sky gamma-ray monitor (such as the Fermi and Swift space-based telescopes) detecting contemporaneous emission would be the most straightforward identification. Radio astronomers have also recently brought online a wide array of low-frequency antenna arrays to look for a contemporaneous pulse and upgraded existing facilities (e.g., Jansky Very Large Array) to improve mapping speed.

Optical astronomers have the strongest arsenal to search wide areas efficiently to look for a counterpart to all gravitational wave events. Very wide-field cameras on all sizes of telescopes are being built: Zwicky Transient Facility (35 degrees^2, 1.2 m; 2015), Dark Energy Camera (3 degrees^2, 4 m; 2012), and HyperSuprimeCam (1.8 degrees^2, 8.2 m; 2012). Opacity calculations suggest that there may be an emission peak in the infrared (12). Unfortunately, the infrared sky doesn't have wide-field instrumentation at this time. Astronomers have proposed to build the Synoptic All-Sky Infrared telescope (SASIR; 0.2 to 1 degrees^2) on the ground and the Wide-Field Infrared Survey Telescope (WFIRST; 0.3 degrees^2) in space.

The biggest challenge ahead is that the transient sky is extremely dynamic, which results in a large number of false positives (4, 14). Because of the small solid angle occupied by galaxies on the sky, spatial coincidence with nearby galaxies can reduce the false positives from hundreds to just a few (4, 14). Unfortunately, we do not know the location of half of the galaxies within the relevant horizon. Efforts are under way to complete our galaxy catalog using H-α narrow-band imaging in the optical and HI imaging in the radio. Systematic surveys are characterizing all types of transient phenomena in the local universe and have recently found multiple new distinct classes of elusive transients (15).

A complete inventory of transients and a complete catalog of nearby galaxies will empower us to find these needles in the haystack. Thus, there is a surge of excitement as the era of routine gravitational wave detection draws near—this search may prove to be the 21st-century gold rush.

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ENVIRONMENTAL SCIENCE

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Seabird monitoring studies are providing a global picture of an increasing range of marine pollutants.
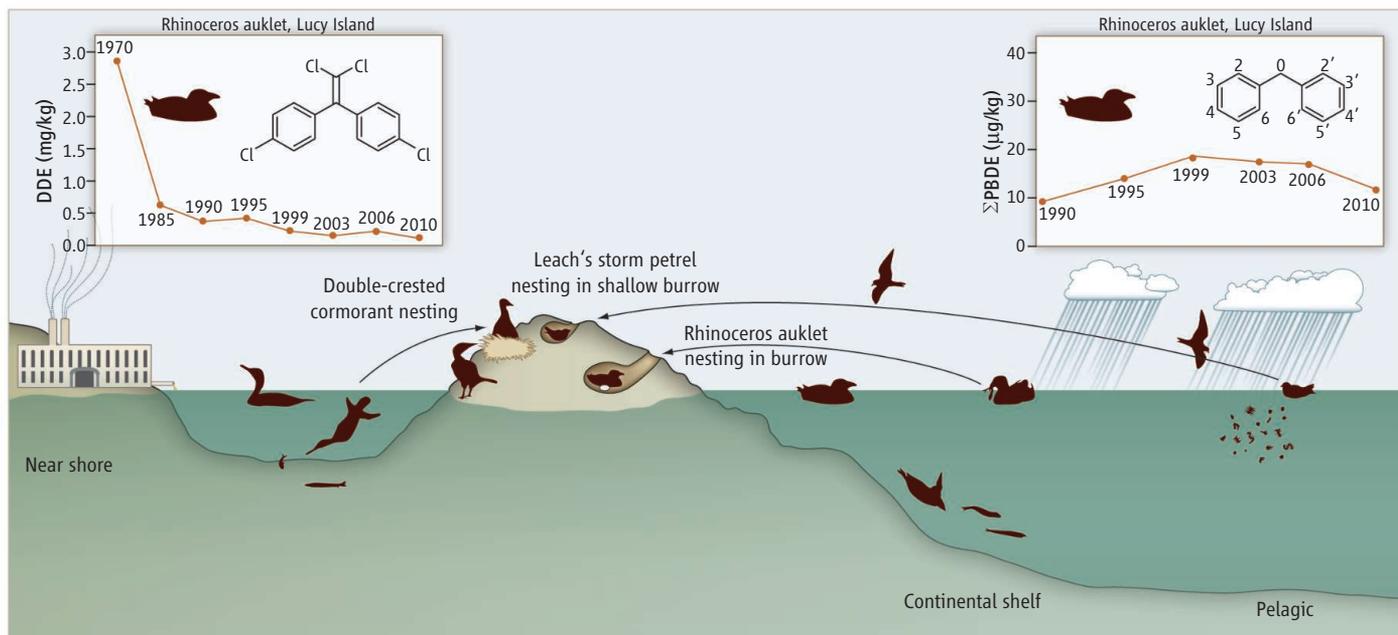
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Visit a beach almost anywhere and you will see plastic waste floating in the water and heaped above the tide lines. That debris is both a source and an overt signal of the even more pervasive contamination of marine biota by persistent chemicals. Present at ultra-trace levels but often highly toxic, chemical pollutants can be challenging to measure and understand. As the most problematic compounds biomagnify in food chains, sampling of marine top predators yields a global picture of ocean pollution.

We have come a long way since Rachel Carson's *Silent Spring* and subsequent reports of chemical contamination of even the most remote ecosystems, including effects on the survival and reproduction of coastal seabirds (1). Use of the worst chlorinated chemicals was banned or severely restricted through the 2001 Stockholm Convention. Increasing mercury levels in marine wildlife, among other reasons, led to the adoption in January 2013 of the global Minamata Convention on Mercury. But with thousands of new chemicals introduced annually, some will inevitably slip through the regulatory net to become the next persistent global contaminants. There is thus a continuing need for efficient monitoring.

Mammals, particularly pinnipeds and cetaceans, are useful sentinels for marine pollution (2). However, seabirds have several practical advantages. Variance in organochlorine concentrations in seabirds is less than in fish or marine mammals; thus, a small sample size of seabirds can provide greater statistical power in addition to reduced environmental impact and cost of sampling (3). Seabirds range widely across oceans, feeding as they move, yet return annually to breed in a single central place (see the figure). In one afternoon at a seabird colony, a biologist can sample an area of ocean that would cost millions of dollars to investigate using a scientific vessel. Nonlethal samples of blood, feathers, oils, and biopsies each provide information on dif-

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How seabirds sample the marine environment. Cormorants forage mainly on fish in near-shore environments. Auks, such as the rhinoceros auklet, feed on smaller fish and zooplankton on the continental shelf. Pelagic seabirds such as the Leach's storm petrel range across the offshore environment, feeding on zooplankton and larval fishes. They all return to breed in colonies, where they can be sampled for contaminants and tagged for tracking. As an example of the information that can be obtained, the graphs show data for two contaminants in rhinoceros auklet eggs at Lucy Island, northwest Canada: DDE, dichlorodiphenyl-dichloroethylene (a DDT metabolite), and PBDEs, polybrominated diphenyl ethers (a flame retardant).

ferent spatial and time scales (*4–7*). The lipid-rich avian egg, in particular, provides a simple matrix to measure the lipophilic chemicals that are of most concern (*8–14*).

Many studies provide a snapshot of contaminants in marine birds from locations around the globe. Some developed countries have also maintained consistent sampling efforts (*8–14*). For example, Environment Canada has monitored near-shore and off-shore habitats of three oceans and the Great Lakes since the early 1970s (*8, 9, 14*). Other countries have devised similar schemes that vary in choice of seabirds and scope (*7, 10–13*). Museum specimens have been used to examine trends from a century ago or longer—for example, affirming the rise in mercury levels associated with fossil fuel use in the 20th century (*5*).

Seabird egg monitoring documented the decline of the legacy persistent organic pollutants (POPs) such as dichlorodiphenyltrichloroethane (DDT) in coastal habitats by the early 1980s, followed by their diffusion into deep ocean environments. The POPs then persisted at lower concentrations. However, even recalcitrant chemicals such as DDT may be finally if slowly fading from marine food chains (*8*).

In the past decade, other contaminants have emerged as threats to marine biota. The most problematic of those are structurally similar to the chlorinated POPs but are substituted with bromine or fluorine. Access to eggs archived in specimen banks and advances in analytical chemistry have enabled retrospective analyses of such emerging pollutants (*8–12*). Similar to the legacy POPs, an exponential increase was followed by a reversal of trends following regulation (*8, 10*).

Contaminants accumulate in seabirds mainly through their diet. Lipophilic compounds are retained in body lipids and excreted slowly; their levels are usually higher in seabirds feeding on large fish than in those feeding on plankton. Similarly, heavier nitrogen isotopes are mostly retained in body protein and, like contaminants, enriched between prey and predator. Nitrogen isotope ratios can therefore help distinguish historical changes in contamination from changes in diet (*5–10, 14*). An increase in both nitrogen isotope ratios and contaminants over time, for instance, could indicate that the higher contamination is due to a switch in diet to more contaminated prey from a higher trophic level (*14*). Stable isotopes can also help us to understand spatial variation in contamination. For example, carbon and mercury isotope ratios demonstrated that elevated mercury levels in Alaskan seabirds originated not from upwelling or atmospheric deposition but from Yukon River sediments (*13*).

Use of miniaturized animal-borne recorders can refine the basin-scale estimates derived from isotope analysis. In one study, two species of albatross differed in accumulation of polychlorinated biphenyls (PCBs) and DDT by almost a factor of 5, despite nesting on the same atoll. Satellite tracking showed that the species with higher contamination foraged in the California Current, whereas the other species foraged off Alaska (*6*). Use of solar-powered GPS loggers with Bluetooth capability or tracked from the International Space Station could reduce battery weight and increase battery duration while eliminating the need to recapture individuals. Such technologies could track birds at meter-scale accuracy, providing more clues about the specific locations where birds derive their contaminant burdens (*15*).

Many chemical pollutants are hydrophobic and are adsorbed by plastics floating in the ocean (*4*). Seabird stomachs regularly contain hundreds of plastics; species with high plastic ingestion also have elevated contamination (*4*). If not killed directly by the garbage, seabirds with high levels of plastic may experience toxicological effects from the pollution.

The plastic not piled onto beaches or left undigested in seabird stomachs can end up circulating for decades. Likewise, toxic contaminants will tend to move toward the ocean. Long after legislation removes a chemical from commerce, that compound will continue to cycle through the ocean and be

absorbed by seabirds. It seems inevitable that there will be a need to track contaminants and assess their impact on marine wildlife long into the future.

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CANCER

Silencing a Metabolic Oncogene

Small molecules inhibit a mutant enzyme confined to tumors, supporting therapeutic approaches that can reprogram metabolism in cancer.

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Many human cancers, particularly gliomas and acute myelogenous leukemia (AML), contain mutations in the genes *IDH1* or *IDH2*, which encode two isoforms of the metabolic enzyme isocitrate dehydrogenase (*1, 2*). These mutant enzymes produce the (*R*)-enantiomer of 2-hydroxyglutaric acid [(*R*)-2HG], a molecule that inhibits histone- and DNA-modifying enzymes, thereby altering gene expression and promoting the acquisition of malignant features (*3–5*). Reports by Losman *et al.* (*6*) as well as by Wang *et al.* (*7*) and Rohle *et al.* (*8*) on pages 622 and 626 of this issue, respectively, find that inhibitors of the mutant forms of IDH1/2 suppress the growth of (*R*)-2HG–producing tumor cells (*6–8*). The findings imply that curtailing (*R*)-2HG supply normalizes gene expression and reverses malignancy.

Metabolic reprogramming in cancer has long been considered a potential source of therapeutic targets. However, much of this reprogramming reflects the enhancement of normal metabolic activities already present in nonmalignant tissue, rather than the appearance of novel activities confined to the tumor. This makes it challenging to develop strategies that impair tumor metabolism without disturbing metabolism elsewhere. By contrast, *IDH1/2* mutations are somatically acquired and elicit an entirely new function for the enzymes (so-called "gain-of-function" or neomorphic activity) that is absent outside of the tumor (*1–3*). Wild-type IDH homodimers catalyze the nicotinamide adenine dinucleotide phosphate (NADP$^+$)–dependent conversion of isocitrate to α-ketoglutarate. In tumors with monoallelic mutations in *IDH1* or *IDH2*, heterodimers containing one mutant and one wild-type subunit catalyze the reduction of α-ketoglutarate to (*R*)-2HG, a reaction that depends on NADPH (the reduced form of NADP$^+$) (see the figure) (*3, 9*). (*R*)-2HG accumulates to millimolar concentrations within the tumor (*3*). The identification of this particular metabolite as the product of mutant IDH1/2 is compelling because its (*L*)-enantiomer [(*L*)-2HG] is associated with pediatric brain tumors (*10*). These observations implicate mutant *IDH1/2*, and specifically (*R*)-2HG, as functional drivers of malignancy. More than half of "low-grade" gliomas (slow-growing but eventually lethal) and almost 10% of AML cases contain *IDH1/2* mutations, and a number of other tumors (including chondrosarcomas and cholangiosarcoma) also harbor mutations in these genes.

A key insight into the role of *IDH1/2* in cancer was that (*R*)-2HG interferes with dioxygenases that use α-ketoglutarate as a cosubstrate. These include enzymes that chemically modify histone proteins and DNA to orchestrate gene expression.

Reversing the perfect storm. Heterodimers of wild-type (wt) and mutant (mut) subunits of the metabolic enzymes IDH1/2 catalyze the production of (*R*)-2-hydroxyglutarate. Its accumulation impairs α-ketoglutarate–dependent dioxygenases, including those that modify DNA and histones (including the demethylation of 5-methylcytosine by TET-family hydroxylases and histone demethylases of the JmjC domain-containing family). This alters the epigenetic landscape, thereby blocking cell differentiation and promoting the acquisition of malignant features. Inhibitors (AGI-6780 and AGI-5198) that block (*R*)-2 hydroxyglutarate–producing IDH isoforms limit the growth of glioma- and AML-derived cancer cells.
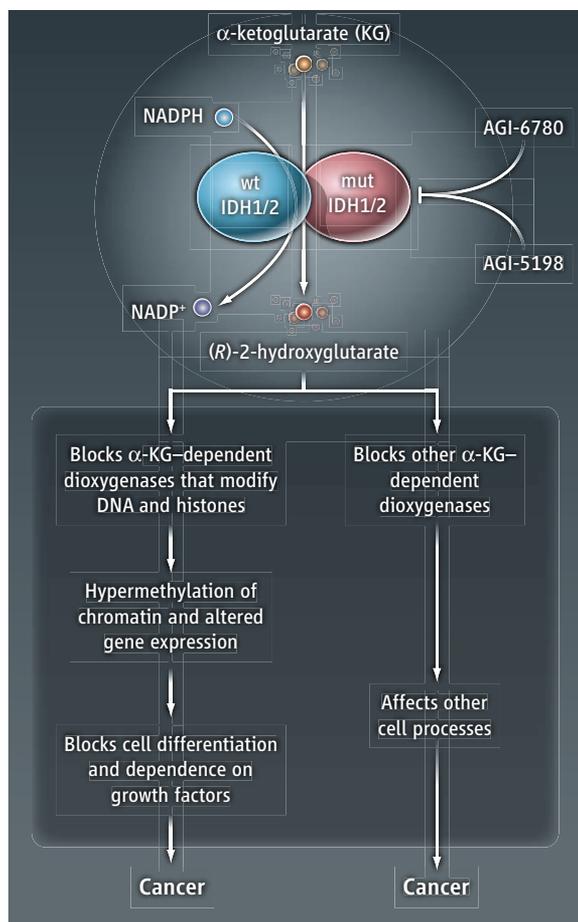
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