BRANCHING OUT

Invasive Species Management Through the Lens of Chemistry

Yu-Pu Juang and Tim Cernak

What can a chemist contribute to ecosystem health? In recent years, chemical tools for the invention of materials, pharmaceuticals, perfumes, and agrichemicals have advanced at a rapid pace. While invasive species management leans heavily on the use of chemical tools—such as herbicides for invasive plants, avicides for introduced birds, piscicides for invasive fish, or insecticides for controlling the population of exotic arthropods—few of these chemical tools have enjoyed the front-edge of modern chemical technologies. In human health, novel pharmaceuticals are driving towards high precision, efficacy, and safety. The multi-trillion-dollar pharmaceutical industry is merging artificial intelligence (AI) and automated workflows with large genomic, proteomic, and metabolomic datasets to design the medicines of the future and combat patients' diseases with surgical precision.

In comparison, the chemical tools of invasive species management are blunt-force instruments. While many innovations in the application of such pesticides have enabled precise targeting of exotic invaders through the method of application, the chemicals themselves are highly toxic to entire classes of flora and fauna. We imagine a future where stewardship of our ecosystems can enjoy the same levels of chemical precision as are enjoyed in modern medicine. We imagine a field of conservation chemistry to enable such studies.

When we zoom in to the atomic level, to understand how a chemical binds to a protein and interrupts a biochemical pathway associated with a "health" outcome, it doesn't matter if we are talking about an insect, a plant, a fungus, or an affluent human with premium healthcare coverage: the chemical technologies are the same. A One Health Pharmacy can be imagined, where the arsenal of chemical tools in the toolbox gives ecosystem stewards better treatment options. The deployment of chemicals into ecosystems has a checkered history, with countless examples of chemical pollutants driving the extinction of plants and animals, so great care must be taken. Nonetheless, invasive species management is one of the greatest ecosystem health challenges of our time, and chemists deserve a seat at the table alongside ecologists, biologists, foresters, and park stewards.

The introduction of exotic species already leads to trillions of dollars in economic losses globally. The cost of invasive species is estimated to have reached US$1.288 trillion from 1970 to 2017, based on the InvaCost database, and the costs continue to rise.[1] Invasive species impact public health. The introduction of emerald ash borer (*Agrilus planipennis*) to southeast Michigan led to a drastic decline in the population of ash trees—perhaps 100 million trees were lost in the Midwest in less than a decade. Many of these trees were prevalent in

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midwestern suburbs and urban areas, leading to a rapid loss in the air-filtering ecosystem service of this forest canopy. Donovan et al. performed a county-by-county analysis of hospital records showing that the introduction of emerald ash borer was associated with an additional 6,113 deaths attributable to illness of the lower respiratory system, and 15,080 cardiovascular-related deaths—morbidities that are linked to poor air quality.[2] In the Eastern United States, bat populations have plummeted due to the introduction of an exotic fungus, *Pseudogymnococcus destructans*, which causes white-nose syndrome and frequently kills entire bat colonies in a season. A key ecosystem service of bats is the removal of insects from the landscape, but in the absence of these winged insectivores, insect populations increased, leading farmers to apply more pesticides to their crops to deal with the foraging pests. Many such insecticides are linked to infant mortality. Sure enough, it can be shown that the reporting of white-nose syndrome to a region correlates with an increase in local pesticide application, and an overall spike in local (human) infant mortalities of 8%.[3]

The establishment of invasive species often leads to rapid declines in the populations of native biodiversity. The control of invasive species is therefore critical to local economies and to conservation. In this Branching Out essay, we discuss the control of invasive species through the eyes of chemists. The notion of chemical management tools that target specific invasive species with exquisite selectivity is intriguing and more research is needed. Precision chemicals for invasive species management do not presently exist, although targeted applications of repurposed pesticides have made great strides. This essay will explore the development of targeted molecules or formulations that could offer a precision approach in landscape stewardship. As an inspiration for such a selective approach to invasive species management, we look to modern precision medicine.

One of us (T.C.) is a professor in a College of Pharmacy who trained in synthetic organic chemistry before dedicating a decade-long industrial career to the invention of pharmaceuticals, both in big pharma and in biotech. When a human patient battles an illness, it is common to intervene with a pharmaceutical—a drug targeted to combat their disease developed through considerable research and clinical trials. One can argue that pharmaceuticals are a bandage that ignores the root cause. Fair point. Nonetheless, a major component of modern health interventions for humans is the deployment of chemical therapies, such as imatinib, oseltamivir, tirzepatide, aspirin, losartan, ivermectin, nirmeltravir, itraconazole, penicillin, sitagliptin, or atorvastatin. These chemicals have saved or extended many millions of lives. They were invented through well-funded research. Current economics make funding challenging for comparable precision invasive species management tools or for other conservation needs. However, in the future, the invention of medicines will be faster, more sophisticated, and nimbler. The pharmaceutical industry is eagerly adopting AI and automation,[4|5] allowing scientists to generate relevant protein structures in the computer as soon as a genome exists.[6] We have recently demonstrated how insecticidal targets can be explored using these tools for the invasive hemlock woolly adelgid insect.[7] This new study aims to highlight how modern drug discovery technologies can be applied to invasive species. And technologies for precision health and drug discovery are rapidly advancing in our modern data-rich, AI-guided, age of "-omics." Just as the automated assembly line of automotive manufacturing led to the mass production of cars with distinct features and properties to appeal to different customers and purposes, the continued automation of drug discovery will accelerate the invention and production of diverse molecules to serve diverse purposes. AI and the democratization of experimentation tools will make it easier for non-experts to engage in the design of molecules based on the function they are desired to have, lessening the

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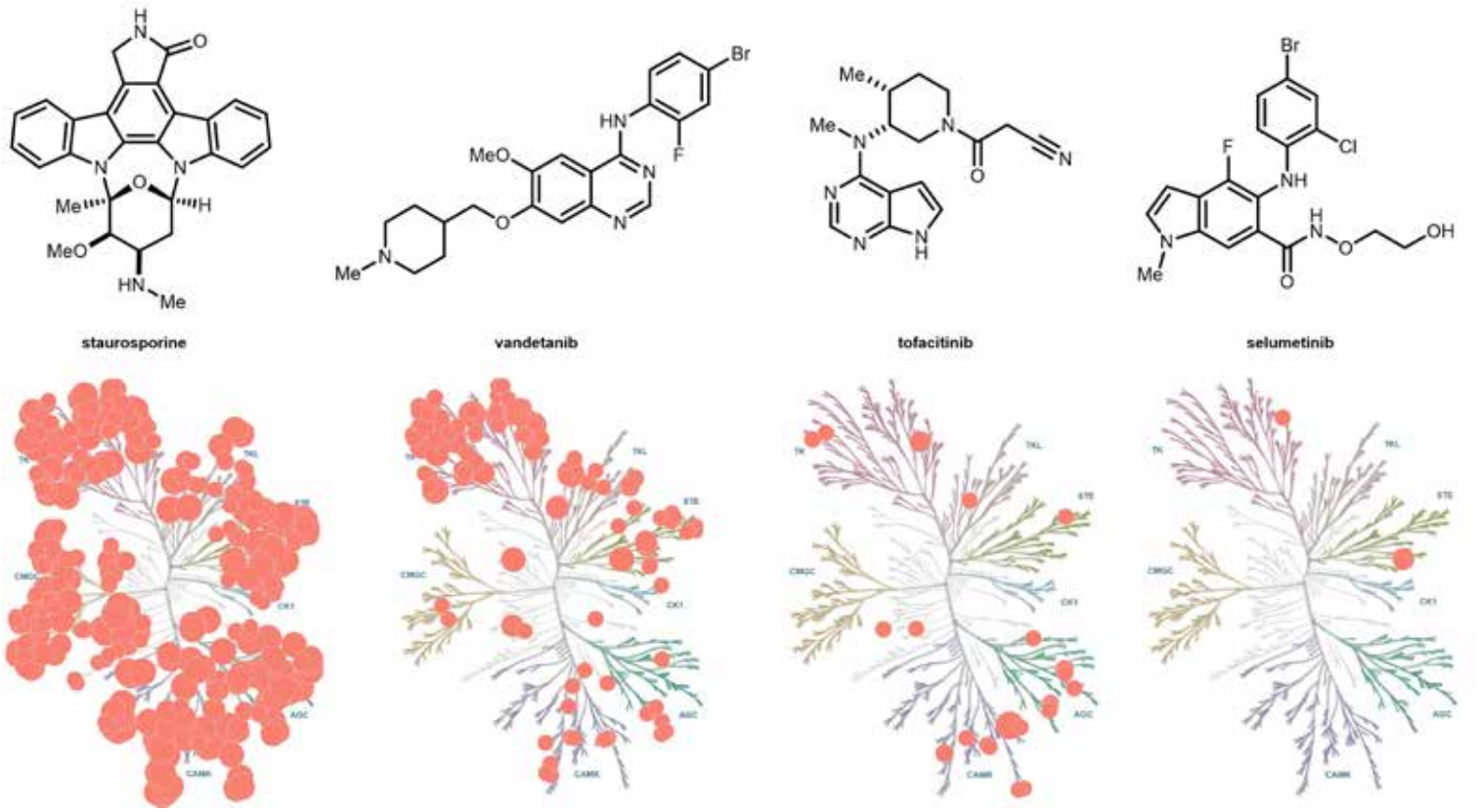
demand for expertise in atomic-level understanding and broadening participation of land stewards from the frontlines of pest-invaded landscapes.

The technologies required to achieve the utopia of precision medicine are agnostic of the patient's available healthcare coverage—and also of their species. Imagine a world where exquisitely precise "ecosystem medicines" can be deployed at scale for niche challenges such as the management of invasive species. By looking to the tools under development at the cutting edge of precision medicine for humans, we can anticipate technologies that could be repurposed for the control of exotic intruders. Kinase inhibitors employed in anticancer treatment are an instructive example of the state-of-the-art in medicine (Figure 1). Kinases are an important class of protein in biology that drive many biochemical signaling pathways by phosphorylation. There are many different kinase proteins in our bodies, and while all kinases are related because each one exists to install a phosphate group, each kinase serves a unique purpose because it phosphorylates a different substrate. There are hundreds of kinases in the body, collectively referred to as the "kinome." If we inhibit all kinases in the body, it will be lethal. Indeed, the natural product staurosporine serves just this purpose. As a pan-kinase inhibitor, staurosporine shuts down all signaling, and the bacteria that makes it surely developed this natural poison as part of its defensive arsenal. While inhibiting the entire kinome in a patient is likely to present with many toxic side-effects, selectively inhibiting a single kinase, or at least single nodes of the kinome, has formed the basis of many modern anticancer drugs because aberrant kinase signaling is associated with many

FIGURE 1. Drug-kinome interaction maps showing the evolution of precision drug targeting. Each branch of the kinome map represents an individual kinase, and the pink circles represent a binding interaction between that kinase and the drug shown, with the size of the circles indicate the binding affinity. The drugs are arrayed from oldest to newest, with vandetanib released in 2011, tofacitinib approved in 2012, and selumetinib released in 2020, while staurosporine is a natural product. The drug-kinase interaction maps were generated by KinMap[8] and with the illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

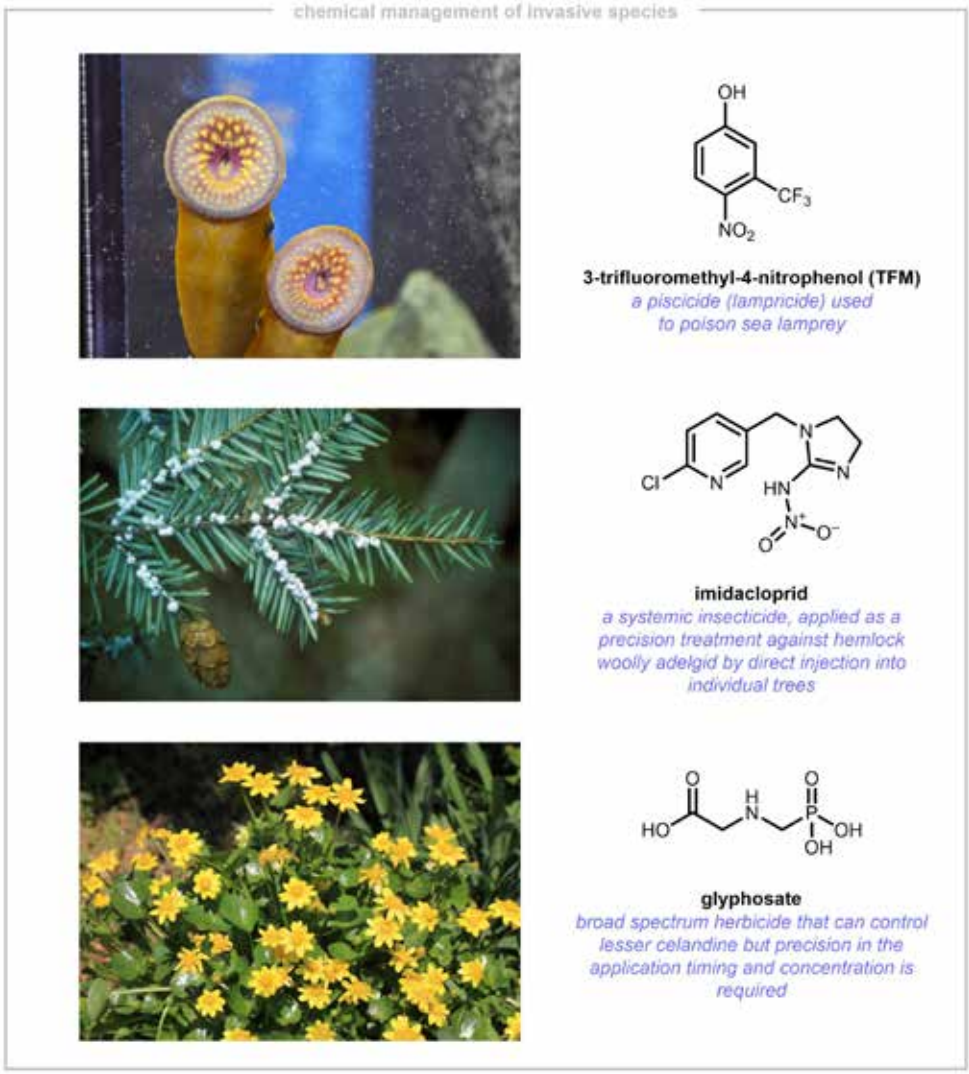


forms of cancer. The later drugs in this class, such as vandetanib and tofacitinib, are much more selective than staurosporine, but still inhibit multiple targets as can be seen in the phylogenetic tree map of the kinome where each pink circle represents the affinity of the drug of a specific kinase. While these molecules were a breakthrough in cancer therapy, side-effects were common and some of these toxicities can be linked to the inhibition of kinases other than the target kinase protein, such as tyrosine kinase inhibitor-related cardiotoxicity.[9]

Today, decades of innovations in drug discovery technologies and a drive to make safer and better medicines for cancer patients have led to a modern ability to inhibit kinases with exquisite selectivity. This is seen with the recently approved cancer medicine selumetinib, which selectively inhibits the mitogen-activated protein kinase 1 and 2 (MAPK1 and 2), and is effective against neurofibromatosis in children.[10] Increases in computational drug discovery and many other medicinal chemistry breakthroughs have made it increasingly feasible to achieve selectivity among kinases, which is no easy feat given that every single kinase is using ATP as its phosphorylation feedstock, so the molecular machinery of phosphate transfer is highly conserved across the kinome.

Having worked on the frontlines of invention of selective inhibitors for a variety of diseases, we are intrigued by an allegorical treatment of invasive species. If we imagine the spread of invasive species as a disease—invasive water hyacinth is often called "water cancer" in the Middle East—can we consider the development of selective chemical tools to address their spread? Precision application of chemicals towards the treatment of invasive species is already in practice. But the chemicals used themselves are typically broad spectrum. For instance, for nearly six decades, the piscicide 3-trifluoromethyl-4-nitrophenol (TFM) has been deployed to tributaries of the Great Lakes on an enormous scale to control the populations of invasive sea lamprey (*Petromyzon marinus*) (Figure 2).[11] While TFM shows toxicity to some fish, it more selectively kills the invasive lamprey. Critically, the lamprey are targeted at the specific point in their life cycle when they are tiny juveniles, most susceptible to

FIGURE 2. Invasive sea lamprey, hemlock woolly adelgid, and lesser celandine are controlled with chemicals. While the chemicals used are broad spectrum, innovative formulations and administration methods enable some levels of precision in conservation interventions.
SEA LAMPREY BY US FISH AND WILDLIFE SERVICE–MIDWEST REGION (CC BY 2.0), HEMLOCK WOOLLY ADELGID BY CONNECTICUT AGRICULTURAL EXPERIMENT STATION (CC BY 3.0), AND LESSER CELANDINE BY TANAKA JUUYOH (CC BY 2.0)



poison, and localized in small tributary streams to the Great Lakes, where the lamprey babies are born. The understanding of sea lamprey biology that went into this prescription makes their treatment feasible. Scientific determination of the timing of TFM deployment, including monitoring tributary water pH for optimal chemical solubility, as well as in the creation of specialized application and monitoring hardware, have been critical to the program. As such, sea lamprey populations in the Great Lakes have been controlled through chemical deployment since 1958 and ushered back a thriving fishery. While off-target toxicities to critical fish like sturgeon are observed, models have proposed that the benefits of removing sea lampreys, which feed on sturgeon, may outweigh the risks of off-target sturgeon toxicity and enable the overall population growth of this ancient fish.[12]

Another example is the deployment of the broad-spectrum systemic insecticide imidacloprid into Canadian hemlock trees (*Tsuga canadensis*) to control the devastating impact of an introduced sap-sucking insect, the hemlock woolly adelgid (*Adelges tsugae*). Here, the insecticide is applied directly to each individual tree through trunk injection, basal bark application, or localized soil drench (Figure 2). This ensures that the pesticide reaches its target and compartmentalizes it within the ecosystem. Since hemlock trees are not pollinated by insects, the impacts are only on herbivorous insects, of which hemlock wooly adelgid is a major player and driver of the decline of the majestic State Tree of Pennsylvania. As well, the control of lesser celandine (*Ficaria verna;* previously *Ranunculus ficaria*) with the broad-spectrum plant-killer glyphosate requires a precision application based on knowledge of this invasive plant's biology.[13] Applications of full-strength glyphosate will kill the tender leaves of the plant so rapidly that the invader doesn't draw the poison into its robust tuber system (Figure 3). It is only through a precision application of a diluted form of glyphosate that park stewards learned the trick to killing this yellow-flowered pest.[14]

Just as we have championed the creation of exquisitely selective pharmaceuticals for killing cancer cells inside an ecosystem of other beneficial (human) cells, we believe it will be possible to invent precision medicine for invasive species.

We must be clear-eyed about the application of pesticides in the ecosystem for the management of invasive pests. These chemicals are meant to kill various life-forms aggressively—whether rodent, bird, predator, fish, tree, shrub, flower, fungus, or otherwise—and we need to acknowledge that the chemical arsenal used to treat invasive species are some of humanity's most potent chemical warfare agents. Neonicotinoids can be used to control many invasive insect pests, and these chemicals are notorious for driving the extinction of many beneficial native insects. Nevertheless, we advocate for increased study of the development of precision chemical treatments. Just as we have championed the creation of exquisitely selective pharmaceuticals for killing cancer cells inside an ecosystem of other beneficial (human) cells, we believe it will be possible to invent precision medicine for invasive species. Someone will have to pay for it, and that is another big discussion. Regulatory, ethical, cultural, local, and Indigenous insights will be critical to the thoughtful deployment of attempts to prevent our land's iconic native species from suffering extinction at the hands of invasive species.

Today chemists are often seen as the villains of conservation. The enormous scale of deployment of the insecticide DDT, largely in the service of controlling invasive mosquitoes, led to the near-extinction of bald eagles and many other iconic birds. This classic story highlights the damage that chemicals can do to an ecosystem. When Rachel Carson showcased the devastating impacts of DDT in "Silent Spring," a propaganda campaign based on eradication of invasive fire ants was used to lobby for the continued use of DDT. We like to remember that an analytical chemist was needed to process samples from dead birds by mass spectrometry to determine

FIGURE 3. One of the authors (Y.-P. J.) applying glyphosate to freshly cut invasive honeysuckle (*Lonicera japonica*) in Southeast Michigan. Even though a broad-spectrum herbicide is used, the precise application to individual honeysuckle stems limits the chances of off-target poisoning of nearby plants. DARYL MARSHKE

that DDT was the culprit.[15] Without downplaying the poisoning of ecosystems by DDT, the need for analytical chemistry to shine a spotlight on this chemical and its metabolites showcases the need for chemistry expertise in conservation. A more recent example is the poisoning of Himalayan raptors by the drug diclofenac, which was given to cattle for pain relief. This non-steroidal anti-inflammatory drug is exquisitely toxic to the vultures that later fed on the bovine corpses and led to the near-extinction of Asian *Gyps* vultures.[16] In a remarkable showcase of the inadvertent consequences of chemical applications in the environment, the plummeting Gyps populations were associated with an estimated loss of $69.4 billion dollars and half a million human lives from the lost ecosystem service of landscape sanitation provided by vultures.[17] In modern human medicine, there are considerable guardrails in place to mitigate unintended toxic side-effects. There are robust and recent technological innovations that enable the invention of safe and efficacious precision medicines.

We advocate that the time is now for a new field of conservation chemistry, one which aims to bring the best tools of modern chemistry innovation to the frontlines of conservation. The state-of-the-art medicine with which we rid human patients of cancers with precision can teach us a complementary approach to precision invasive species management and serve as a new tool in the fight to preserve biodiversity and improve planetary health.

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