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Perspective

Think Biologically, Act Chemically

Miniperspective

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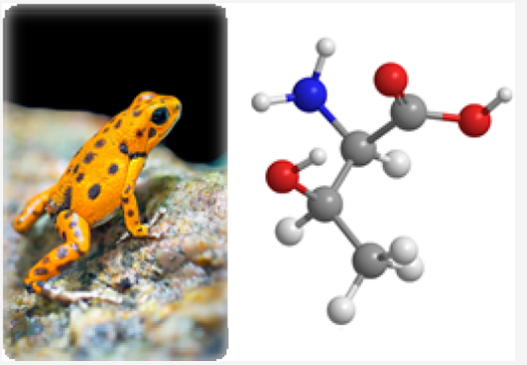
ABSTRACT: A drug is a sophisticated molecule, purposely evolved, resulting from the accumulation of knowledge learned and exploited from simpler molecules over time. Advanced molecules with increased sophistication and capability are derived from simpler, less sophisticated structures with less capabilities. Medicinal chemists do not find, stumble upon, accidentally discover, screen for, or construct drugs. We *purposefully evolve* molecules through the use of feedback cycles; we emphasize efficiency and simplicity in pursuit of multiproperty homeostasis; and we design and learn from molecular outliers. This Miniperspective illustrates inspirational themes from nature including evolution, feedback cycles, homeostasis, efficiency, and mutation. These biological themes are then exemplified in modern medicinal chemistry practices, such as design−make−test−analyze cycles (feedback), balancing molecular properties (homeostasis), defining the minimum pharmacophore (simplicity, efficiency), understanding molecular outliers (mutants), and the unifying concept of molecular evolution.



INTRODUCTION

"Think chemically, act biologically" are the words of Professor Christopher T. Walsh, recently honored[1] with a named, endowed chair in celebration of his career and a milestone birthday. As a giant in the field of mechanistic enzymology, Chris inspired a generation of scientists to understand the fundamental chemistry behind complex biological systems and enzymatic mechanisms. To "think chemically, act biologically" is to fully contemplate the mechanistic chemistry of the enzyme and then action the next appropriate biological experiment. As a leader, Chris captured this sentiment in a simple, easily understood idiom for all to consider.

As medicinal chemists, to "think chemically" comes quite readily, as we design new molecules and plan their assembly using organic chemistry. We purposefully modify the properties of our molecules by manipulating atoms and functional groups, and we enhance ligand−protein interactions by understanding and enhancing intermolecular interactions. Moreover, medicinal chemists "act biologically" to collaboratively assess the biological activity of compounds, gaining understanding of structure−activity relationships. We design *in vivo* experiments such as pharmacokinetics, efficacy, and safety studies and further our collective knowledge of human biology toward improving human health.

What if one extends the idiom and considers the opposite logic, *think biologically, act chemically*? As medicinal chemists, we *think biologically* as we seek to understand the biology of disease, organism, tissue, cell, pathway, and target. We certainly *act chemically* as we design, synthesize, and iterate molecules toward understanding and curing human disease, and as we practice, define, and extend the field of medicinal chemistry and related disciplines. Like many working in the field of medicinal chemistry, I draw inspiration from biology and related fields while engaging the interdisciplinary journey of drug discovery. This Miniperspective illustrates the sentiment of *think biologically, act chemically* with inspirational themes from nature including evolution, feedback cycles, homeostasis, simplicity, efficiency, and mutation. These biological themes are then exemplified in modern medicinal chemistry practices, such as design−make−test−analyze cycles (feedback), balancing molecular properties (homeostasis), defining the minimum pharmacophore (simplicity, efficiency), understanding molecular outliers (mutants), and the unifying concept of molecular evolution.

THE EVOLUTION OF MAN AND MOLECULES

In Darwinian evolution, heritable characteristics of biological populations change over successive generations. Natural selection preserves each slight variation of a trait if the trait is

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useful. Just as humans evolved from apes, amphibians, fish, and single cell organisms over the millennia, small molecule drugs purposely evolve over a shorter period from development candidates, chemical leads, screening hits, and sometimes molecular fragments (Figure 1).[2,3] In the forward sense, fragment and molecular hits are iteratively optimized by perturbing their structure and selecting useful traits or characteristics such as improved potency, solubility, or permeability. Just as nature propagates useful traits during species' evolution from simple organisms to more complex creatures, chemists select and propagate molecules and functional groups that advance one or more useful properties. In this way we purposely evolve our molecules toward more sophisticated capabilities found in advanced compounds such as leads and development candidates. The purposeful evolution of molecules by medicinal chemists is related to, but distinct from, metabolic pathway evolution,[4] directed evolutionary studies,[2,3] and machine learning approaches for *in silico* compound selection.

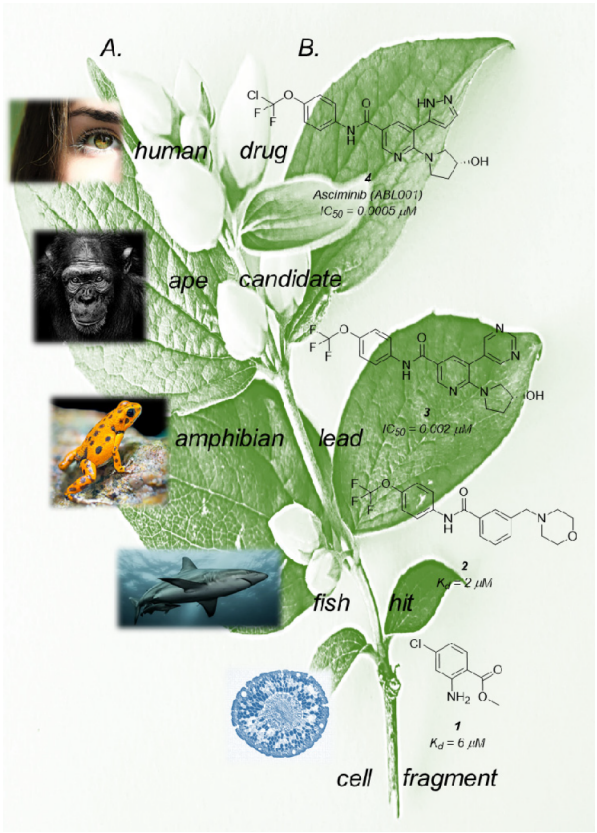

Figure 1. Evolution of man and molecules. (A) The phylogenetic tree is shown which describes the evolution of humans from apes, amphibians, fish, and unicelled organisms. (B) The "phylomolecular" tree is shown describing the evolution of the drug asciminib from the lesser evolved lead (**3**), hit (**2**), and fragment (**1**) molecules.

For example, a compound fragment hit from a screening effort may only very weakly bind to its intended target, *e.g.*, with a K_d in the weak micromolar or even millimolar range, while a traditional hit molecule may bind more tightly (*e.g.*, with a low μM K_d).[5] Further along the evolutionary path of drug discovery, a lead molecule may offer even more potency (*e.g.*, nM K_d) in addition to perhaps other capabilities such as improved solubility, permeability, cellular activity, proven target engagement, and *in vivo* pharmacodynamic effects. The lead molecule is an intermediately evolved ligand with certain capabilities, but also limitations. In comparison to the evolution of species, fish can swim, but do not walk. The limitations of the lead molecule constitute opportunities for further optimization and evolution from water onto land. For example, hERG binding, or another off-target selectivity challenge, may limit the safety of a lead molecule. A lead molecule could also suffer from poor *in vivo* potency for any number of reasons, such as weak binding, insufficient exposure, or restrictive protein binding. Further optimization for selectivity, *in vivo* potency (or other limitations) of a lead results in still a higher-evolved molecule, capable of more robust *in vivo* efficacy for example, or safety assessment. This purposeful evolution toward increased sophistication may eventually result in identification of a development candidate, often after *in vivo* properties are honed (*e.g.*, PK/PD, efficacy, initial safety, *etc.*). Even further evolution of clinical candidates is sometimes necessary to identify a drug which has demonstrated safety and efficacy in humans. Further complicating matters is the demonstration of a commercial marketplace for a successful product launch, which is beyond the scope of this Miniperspective.

The discovery of BCR-ABL1 allosteric inhibitor, asciminib,[6] beautifully illustrates molecular evolution from fragment to drug (Figure 1B). Chlorobenzoate fragment **1** was identified in an NMR conformational screen with a K_d of only 6 μM. By combining SAR from other fragments, and optimizing for affinity, hit compound **2** was identified with an improved K_d (2 μM) and a measurable GI_{50} in cells (2 μM), an important increase in molecular sophistication. Further evolution of this hit using structure-based drug design led to pyridine **3**, a molecule with greatly enhanced capabilities. Lead compound **3** is a selective kinase inhibitor, has excellent oral bioavailability and low clearance in rodents, and is efficacious in a xenograft model of chronic myelogenous leukemia. Opportunities to optimize further capabilities into the evolving molecule included an increased selectivity over the hERG channel (**3**: IC_{50} = 9.6 μM), and to improve the *in vitro* potency and *in vivo* efficacy. Thus, further molecular evolution modulating these parameters resulted in the identification of asciminib, **4**.

HOMEOSTASIS, THE BALANCE OF PROPERTIES

In human physiology as part of a normal glucose cycle, β cells in the islets of the pancreas sense an increase in glucose in the bloodstream after a meal and release insulin, a hormone which allows cells to process glucose as fuel for metabolism (Figure 2A). If glucose levels fall too low, the liver releases the hormone glucagon to raise sugar levels, avoiding hypoglycemia, possible coma, and death. If glucose levels are too high for extended periods, ketoacidosis and other long-term toxic effects of glucose in multiple organs occur. This remarkable feedback cycle safely maintains homeostatic glucose concentrations at 70−120 mg/dL for our entire life span. Challenges to this extraordinary system with poor diet and excess body mass can cause loss of homeostasis, obesity, and metabolic syndrome.

In medicinal chemistry, we also practice and exploit feedback cycles. We iterate our molecules through design−make−test−analyze cycles (DMTA, Figure 2B). These iterative feedback loops provide opportunities to optimize the properties of molecules, such as the binding potency, selectivity, and physicochemical properties. For example, after observing a positive SAR result, we select this knowledge and propagate this to future molecules in the evolution of the SAR, similar to the

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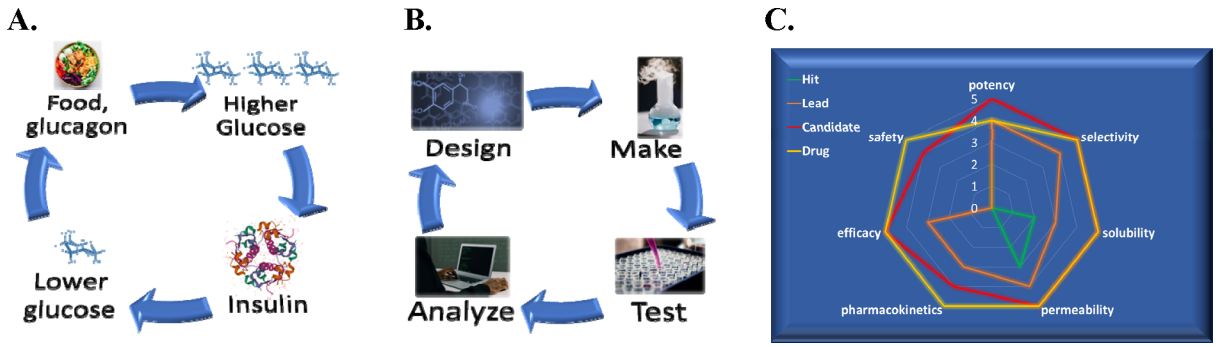

Figure 2. Feedback cycles drive homeostasis. In Figure 2A, human physiology controls blood glucose homeostasis through a hormonal feedback mechanism using insulin (PDB: 1J73)[11] and glucagon. Figure 2B depicts the medicinal chemistry feedback mechanism of design−make−test−analyze cycles to evolve molecules toward higher capability and sophistication. Figure 2C depicts property homeostasis of the evolving molecule. For example, 7 parameters commonly optimized during multiparameter optimization campaigns are shown (potency, selectivity, solubility, permeability, pharmacokinetics, efficacy). Hits, leads, candidates, and drugs are illustrated by colored lines with relative capabilities ranked from 1 to 5 (low to high; 0 = not assessed). For example, hit molecules (green line) are typically assessed in only a few of these criteria, and are less sophisticated than higher evolved molecules (leads in orange, candidates in red, drugs in yellow) which satisfy more criteria, respectively.

natural selection of useful traits in the evolution of species. After observing a negative SAR result, we learn what not to do, and select against this structural modification as it relates to the activity or property criteria. This type of less useful trait stops in the intermediately evolved ligand and does not propagate further. *Useless* traits may even become extinct! Quinone and catechol functional groups, although represented in several approved drugs, are becoming less useful functional groups for modern drug discovery because of their propensity for redox chemistry perturbing biological screening assays.[7] Through this iterative cycle of positive and negative feedback on our molecules and correlating properties (*i.e.*, potency, permeability, solubility, oral bioavailability, clearance, etc.), we achieve higher sophistication and build up additional capabilities into our ligands.

As humans evolved to regulate and balance blood sugar, in medicinal chemistry, we seek *molecular homeostasis* by balancing various molecular properties during multiparameter optimization.[8,9] As described above, chemists practice multiparameter optimization when evolving a hit molecule to a lead, and eventually to a development candidate. The optimization of potency together with physicochemical properties, selectivity, and ADME properties is commonplace toward identifying more highly evolved molecules. For example, balancing potency with enabling physicochemical properties provides safer candidate molecules, as highly lipophilic molecules tend to reside in membranes and lysosomes. In turn, higher lysosomal occupancy can lead to phospholipidosis and liver toxicity.[10] Highly lipophilic molecules also suffer from poor absorption and difficulty in formulation. Thus, mitigating high lipophilicity avoids molecular-based toxicity, dissolution and adsorption challenges, and difficulty in formulation. Just as the insulin-glucagon cycle allows for homeostatic glucose regulation, medicinal chemists equilibrate and balance the parameters of optimization to achieve molecular homeostasis.

FEEDBACK DRIVES FLUX

In enzymology, feedback inhibition regulates cellular metabolism (Figure 3A). For example, the concentration of a metabolic pathway product (*e.g.*, isoleucine) controls the activity of threonine deaminase near the beginning of the pathway (shown in orange), turning the pathway off. The "metabolic flux", the rate of turnover through a metabolic pathway, is controlled by

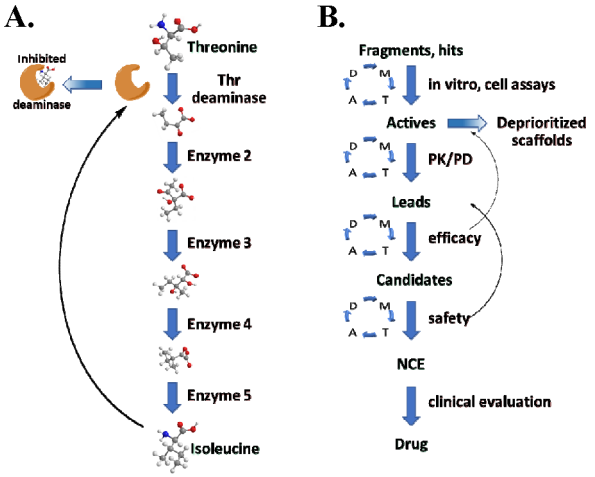

Figure 3. Feedback drives flux. Figure 3A describes feedback inhibition of the threonine-isoleucine metabolic pathway where the product of the pathway (isoleucine) inhibits its own biosynthesis (black arrow). Likewise, in Figure 3B, a typical drug discovery flowchart is shown where results from downstream assays impact the design and selection of compounds earlier in the flowchart, reminiscent of biochemical feedback inhibition.

such feedback. Thus, feedback cycles can allow for *homeostasis*, such as the physiological range of glucose in blood, and *flux*, such as the metabolic flow of products in a biochemical pathway.

In medicinal chemistry, DMTA feedback cycles allow for optimization of molecular homeostasis and can also drive *molecular flux*. This is often described in a flowchart with defined assays, time constraints, and molecular criteria for a given drug discovery project (Figure 3B). Fragment and hit molecules are assayed *in vitro*, often measuring biological activity against target, selectivity against antitargets, physicochemical properties, and *in vitro* ADME. When evolving molecules meet *in vitro* criteria, we propagate our molecules into *in vivo* assessments such as pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety experiments. Informational feedback from these assays (shown as black arrows) often informs which molecules or molecular series to select and propagate into assays and how to further evolve our molecules toward candidates. Just as products of metabolic pathways can inhibit upstream enzymes to regulate metabolic flux, molecules which perform optimally

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(or conversely poorly) in assays should change the flux of compounds through the flowchart, perhaps narrowing the selection of compounds or series propagated. Thus, just as nature drives flux through feedback cycles, medicinal chemists drive feedback and molecular flux through design−make−test−analyze cycles and flowcharts.

SIMPLICITY AND EFFICIENCY: DEFINING THE MINIMUM PHARMACOPHORE

While feedback cycles drive flux and homeostasis, nature also evolves for efficiency. A bird's feather (Figure 4A) is lightweight,

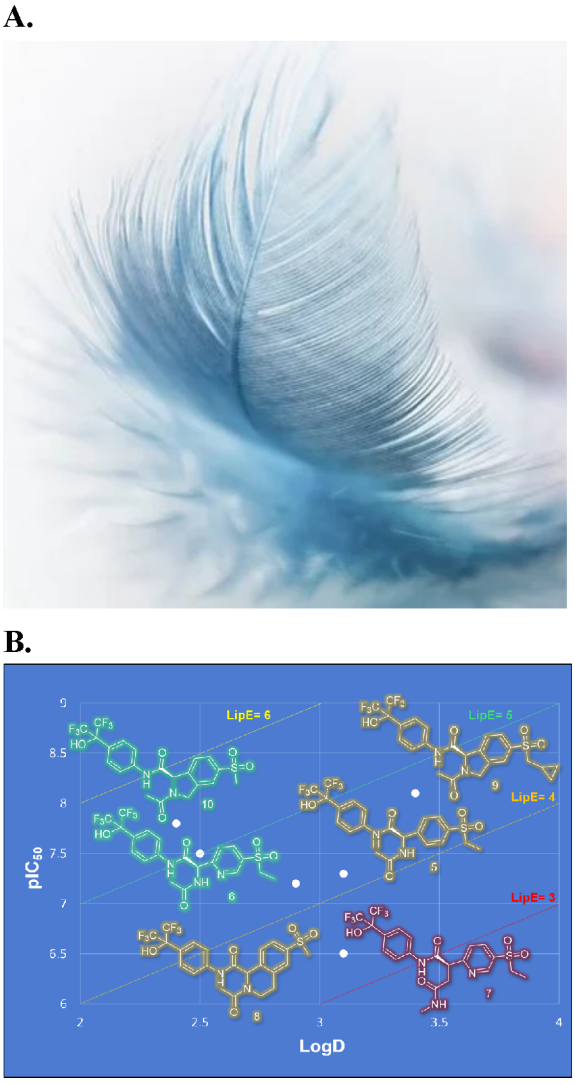

Figure 4. Simple, efficient, yet sophisticated. Figure 4A depicts feathers which are structurally simple, elegant, and yet very sophisticated. Figure 4B illustrates a typical medicinal chemistry LipE analysis by plotting pIC_{50} vs LogD to determine the lipophilic efficiency (diagonal lines). Candidates with LipE > 5 are considered highly optimized, efficient molecules.

structurally simple, elegant, and yet quite sophisticated. Feathers evolved to minimize weight and air resistance for flight, for insulation, to shed water, for defense, for camouflage and sometimes even for display. Likewise, medicinal chemists seek to discover important, lifesaving molecules efficiently, as patients are waiting for cures. Matched-molecular pair comparisons of structure−activity (or structure−property) relationships allow for efficient DMTA cycles with the fewest iterations possible.[12] Like the feather of a bird, highly evolved molecules will have minimal structural complexity yet offer maximal capability. Thus, medicinal chemists routinely *define the minimum pharmacophore* at various stages of the drug discovery effort en route to identifying more highly evolved molecules with increased capability. Pursuing minimalistic structures simplifies SAR interpretation, reduces synthetic step count, minimizes cost, and maximizes the speed of synthesis. Revisiting or challenging the minimum pharmacophore after observing an activity or property cliff is often needed to determine if previous SAR holds, and whether the same molecular features are still required to achieve the desired profile.

Medicinal chemists calculate composite parameters such as lipophilic efficiency,[13,14] to optimize the capability of our molecules while minimizing their structural complexity. It is reported widely that drugs and development candidates have a higher lipophilic efficiency (LipE)[15] a composite parameter calculated from lipophilicity and biological activity, than lesser-evolved molecules such as hits or lead molecules.[16] Often, development candidate ligands are not the most potent molecules discovered on a drug discovery project (or the most soluble or the most highly exposed), they are a compromise among multiple optimized parameters that have been carefully and purposefully balanced (*vide supra*).

The identification of AZD0284,[17] a potent and selective inverse agonist of retinoic acid receptor-related orphan receptor C2, nicely illustrates the optimization for lipophilic efficiency and molecular homeostasis (Figure 4B). Early lead-like compounds (*e.g.*, **5**, LipE = 4.2) were optimized for physicochemical properties and cellular activity by introducing heteroatoms (*e.g.*, pyridine **6**), which lowered the LogD and slightly increased the cellular potency, thus increasing the LipE (∼5). An intramolecular H-bond between the pyridine and amide proton, which stabilized the bound conformation, was key to higher potency. Compounds incapable of intramolecular H-binding had reduced activity compared to **6** (*e.g.*, **5**, **7**). Further optimization included cyclization to 6-6 fused bicyclic ring systems (*e.g.*, **8**) and 5-6 fused bicyclic systems (*e.g.*, **9**, **10**). The optimal balance of lipophilicity and potency was realized in AZD0284 (**10**), where a simple methyl group replaced the more lipophilic methylene-cyclopropyl functional group lowering the logD. This not only illustrates a successful LipE optimization, but further exemplifies molecular homeostasis, where the most potent compound (*e.g.*, **9**) was not necessarily optimal, and a balance of properties was necessary.

MUTANTS TEACH WHAT IS POSSIBLE

Genetic mutation challenges the fitness of biological populations by introducing variation. Mutant organisms possess "outlier" traits. If the phenotypic variation confers an advantage to survival, it is propagated and the species evolves. In a similar sense, "analogues" are the subject of medicinal chemistry campaigns due to the similarity of structure or property of project compounds. These like molecules possess many of the same substructures, properties, or activities as their counterparts. Like genetic mutations which challenge the fitness of populations, medicinal chemists also design, make, test, and analyze *outlier compounds*, introducing significant variation of structure. These mutant compounds more aggressively challenge the assumptions of the SAR, as well as sometimes the assumptions of medicinal chemistry as a discipline. Outlier compounds often do not advance themselves (but sometimes

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do, *vide infra*) but teach the limits of what is possible in an assay or biological study. Outlier compounds' unique properties and the knowledge that accompanies them are then incorporated into the evolving molecule.

Outlier functional groups and mutant compounds can extend our field in unexpected ways. The discovery of brigatinib[18] appropriately illustrates the concept of a molecular outlier, a mutant molecule. During the molecular evolution campaign, many iterations were examined (Figure 5B) substituting on the

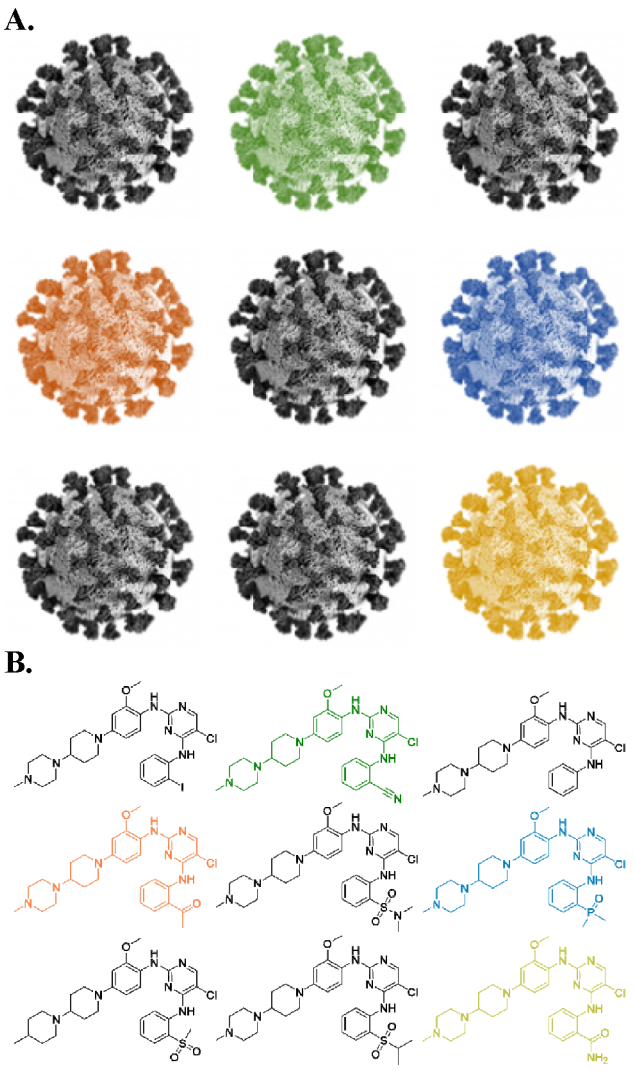

Figure 5. Mutants teach what is possible. Figure 5A illustrates the diversity of mutations (represented by various colors) across a viral species population (electron micrograph of COVID-19 shown) which challenges the fitness of individual traits. Figure 5B illustrates variation of functional groups across a population of compounds, which challenges the fitness of specific properties and functional groups. Brigatinib, a phosphine oxide shown in blue, wonderfully extends the field.

southern aniline *ortho* position. One outlier molecule (shown in blue) possessed a mutant structure, a phosphine oxide. This unique functional group is easily synthesized, chemically stable, and uniquely tetrahedral as a H-bond acceptor, has three points for derivatization, and has been overlooked by medicinal chemists as it is the first phosphine oxide exemplified in a commercialized drug. By designing, making, testing, and analyzing this molecular outlier these pioneering scientists challenged the traditional functional groups previously reported as H-bond acceptors, and graciously extended our field.

NATURE EVOLVES MOLECULES TOO

Medicinal chemists are not alone in the evolution of small molecules. Microorganisms have been practicing chemical warfare for millennia, producing potent cytotoxic and targeted compounds to exclude other organisms from encroaching their biological niche. These naturally occurring compounds and their biosynthetic pathways result from iterative biosynthetic gene cluster evolution. Thus, when discovering, modifying, and exploiting natural products for medicinal purposes, we are building on and in some cases extending, centuries of genetic and molecular evolution. The emerging fields of directed evolution and machine learning hold the promise of further evolving biologically derived molecules and *in silico* molecules, respectively, and have been extensively reviewed elsewhere.[2]

The molecular evolution of the secondary metabolite halichondrin B was initiated by nature and then continued via medicinal chemistry (Figure 6). Early Earth atmosphere

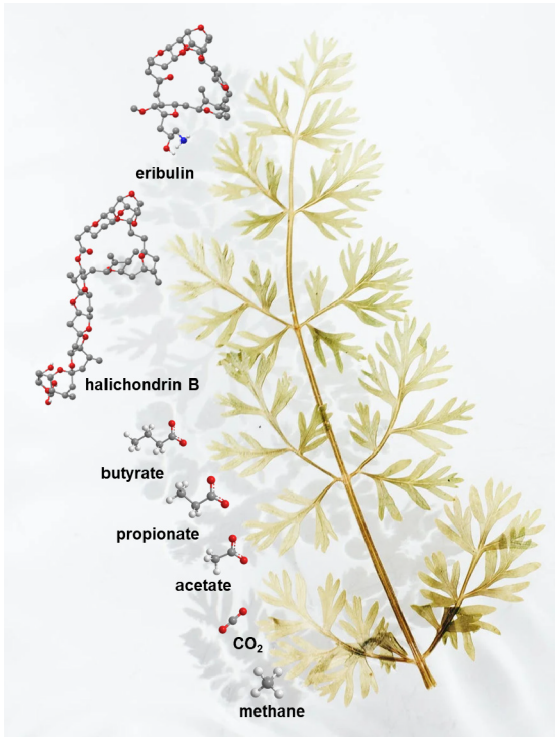

Figure 6. Extending the molecular evolution of nature.

contained methane which life eventually evolved into biomolecules such as acetate, propionate, and butyrate. These more sophisticated oxygen containing building blocks were assembled into much more complex structures by microorganisms including the polycyclic ether class of natural products.[19] The medicinal chemistry optimization effort then removed the entire Western portion of the natural product, added a basic amine, and replaced the ester moiety with a ketone. The resultant drug, Eribulin,[20] is structurally simplified by 381 Da, yet remarkably more sophisticated- no longer prone to ester hydrolysis and able to be formulated as a mesylate salt, all while maintaining potent binding on microtubules and activity in breast cancer cells.

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DISCUSSION

As nature uses feedback loops to drive homeostasis (*e.g.*, blood glucose), medicinal chemists exploit design−make−test−analyze cycles to drive molecular homeostasis in multiparameter optimization campaigns. As feedback inhibition controls metabolic pathway flux, we utilize compound flowchart feedback to control molecular flux. Just as nature exploits simple, yet sophisticated structures (*e.g.*, a bird's plume of feathers), we determine the minimum pharmacophore while maximizing the capability of our molecules (*e.g.*, LipE). And just as mutants challenge the fitness of traits in the evolving species, medicinal chemists design and evaluate outlier compounds to challenge the assumptions of what is possible and extend our field (*e.g.*, the phosphine oxide of brigatinib). Many commercialized drugs are based on naturally occurring, secondary metabolites. Although these molecules were found, sometimes derivatized, then commercialized by man, nature evolved these molecules too, over centuries.

Small molecule drugs are not found, suddenly discovered, screened for, nor constructed. "Finding" or "screening for" a drug implies that the molecules already exist physically or has already been designed *in silico*, and we just need to locate these molecules with various screening strategies or technologies. "Constructing" a drug implies an applied science, where the materials and blueprints are readily available and therefore just need to be read, understood, and resourced. These are misconceptions in modern day drug discovery. Small molecule drugs are not found, they are purposefully evolved. Highly optimized molecules result from knowledge learned and exploited from simpler, less sophisticated molecules. The challenge of small molecule drug discovery is not necessarily a screening problem, it is how best to quickly and efficiently accumulate and exploit knowledge to evolve molecules.

That multiple species share a common ancestor is generally referred to as "common descent". The human hand, the flipper of a whale, and the bird's wing all evolved from a common ancestor for adaptation to life on land, in the ocean, and in the air, respectively. Likewise in medicinal chemistry, some common scientific challenges avail themselves across multiple project contexts over time. For example, achieving hERG selectivity, optimizing for both potency and properties (*e.g.*, LipE), pursuing amide isosteres, modulating pK_a for improved permeability are just a few common medicinal chemistry challenges that most drug hunting scientists experience in their careers, often multiple times across different project contexts- reminiscent of common descent. The prudent medicinal chemistry team will see the flipper, paw, hand, wing analogies of these scientific challenges and use past experiences, knowledge, and solutions to solve current and future project challenges.

Nature inspires our field in countless ways, and only a few inspirational examples were described above. Recognize and exploit the feedback in DMTA cycles and flowcharts to achieve molecular homeostasis and to define the flux of projects. Improve the efficiency of your ligands, and synthesize your mutants, as you purposely evolve molecules. Tell these stories of common ancestral challenges to your colleagues. When we *think biologically*, we may recognize and improve how to *act chemically*, to further define and extend the field of medicinal chemistry.

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Notes

The author declares no competing financial interest.

Biography

Matt LaMarche earned his B.S. in biochemistry at the University of Notre Dame, and a Ph.D. at the University of Pennsylvania with Amos B. Smith, III. He conducted undergraduate research with Professors Chris Walsh at Harvard Medical School, and Richard Taylor at Notre Dame. His graduate studies focused on the gram-scale total synthesis, solution structure, and analogues of (+)-discodermolide. Matt began his industrial career at Millennium in 2002, then joined Novartis in 2005. Matt has led multiple NCEs into clinical study spanning therapeutic areas, including the SHP2 inhibitor TNO155 for cancer; he chaired the 2019 GRC on Natural Products. In 2020 Matt joined Sanofi as the US Head of Medicinal Chemistry, and recently assumed the role of US Site Head of Integrated Drug Discovery.

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ABBREVIATIONS

DMTA, design−make−test−analyze cycles

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