Personalized Cardiovascular Medicine and Drug Development: Time for a New Paradigm

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I am both truly delighted and most grateful for the opportunity to present this year’s Lewis A. Conner Lecture, a lecture given in memory of the American Heart Association’s first president. This lectureship recognizes Lewis Conner’s very many accomplishments, and memorializes his contributions in advancing the cause of the association.

I gave much thought to the theme of this presentation, and ultimately settled on the topic of drug development and personalized medicine. My reasons for this choice are several, including the timeliness of the topic, its relevance to the modern genome era, the confluence of current political and economic forces that threaten it, and the evolution of the historical context within which the discipline of pharmacology has developed and continues to develop. There is one additional personal reason for this choice of topic, and that has to do with the chair I hold at Harvard Medical School. This chair was established in 1781 and, with its endowment, Harvard Medical School itself. The formal title of this chair is the Hersey Professorship of the Theory and Practice of Physic. This title has recently been modernized to the Hersey Professorship of the Theory and Practice of Medicine, in view of the definition of “physic” as the “art or practice of healing disease”; however, “physic” also refers to any medicinal agent or preparation, thereby linking the chair to therapeutics, which ultimately became the field of pharmacology.

The treatment of disease before the modern era (which, for the purpose of this talk, I define as the mid-19th century) was largely based on empirical tradition and folklore, and included herbal preparations, toxins, and other natural substances, several of which ultimately became part of the formal pharmacopoeia. In the 19th century, this approach to the treatment of disease began to change, first with better definition of disease through the clinicopathological correlation of Malpighi and Osler; with the development of organic chemical synthesis and medicinal chemistry by Wohler, and, as a result, a definitive refutation of the vital force theory; and with the early work of Claude Bernard, Oswald Schmiedberg, and John Abel, whose efforts established the physiological basis for the action of drugs such as curare, chloroform, and epinephrine, respectively. These early days of modern pharmacology were predicated on the growing discipline of physiology and the availability of physiological screening tests; as such, it remained a semiempirical science, but with specific phenotype assays, such as blood pressure or pulse, that could be quantitated and analyzed. These and other assays like them were then used to determine the strength and duration of the action of a drug, and also its potential toxicity.

Beginning in the early 20th century with the seminal work of Paul Ehrlich, three principles of modern pharmacology were born. First, Ehrlich developed the concept of drug screening, which led to his identification of arsphenamine, or Salvarsan 606, as the first specific treatment for syphilis (and trypanosomiasis). With the identification of this compound, he also devised the concept of the magic bullet, a concept that permeates modern pharmacology, that is consistent with the scientific reductionism needed to identify a drug target, and that raises the collective hope of modern society ever in search of a singular, definitive treatment for every disease. Last, the specificity of this agent led Ehrlich to develop the concept of a unique, specific receptor on the spirochete through which arsphenamine exerted spirochetidal action selectively without harming the host (too much). As conceptually appealing as this Ehrlichian paradigm was, its early successes were relatively few in number. In fact, in 1940, the Brigham and Women’s Hospital house staff manual listed the hospital’s pharmacopoeia as containing merely 91 drugs, most of which had been developed using the age-old semiempirical strategy; by contrast, the current USP-National Formulary contains ~22,000 drugs and almost 6000 over-the-counter preparations.

Over the next 100 years, pharmacology and the pharmaceutical industry evolved in parallel with the fields of biochemistry and of structural and molecular biology. Receptors were no longer theoretical constructs, but macromolecules that could be isolated, cloned, sequenced, structurally and functionally characterized, and inhibited (or activated). Examples of the latter well known to this audience include the work of Lefkowitz on the β-receptor family and the work of Ondetti on the angiotensin-converting enzyme. As increasing numbers of these macromolecules were identified and

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their role in cellular and disease mechanisms characterized, they became drug targets that were subject first to semiempirical target-based screens. These screens served as the basis for defining structure-activity relationships among members of drug families, fueling the enterprise of drug development well into the 1990s. In this formalism, the actual binding site for the drug on the target need not be known (in fact, generally was not known); yet, drug action correlated with specific structural features of the parent compound and its derivatives, deepening the patent portfolios of many pharmaceutical companies and offering subtle, but on occasion clinically important, differences among drug class members.

Over the past 20 years, the confluence of three forces has changed this classical pharmacological formalism to one of rational drug design. In this construct, the tertiary structure of the drug target is known, and thus, the choice of drug (inhibitor or activator) is based on the precise lock-in-key notion of drug-drug-target interaction. The three forces that have driven the discipline in this deterministic direction include the expansion of possible drug targets with the expansion of genomic data sets, the growth of tertiary structural data sets via protein x-ray crystal structure determinations and nuclear magnetic resonance spectroscopy, and the development of virtual and real drug libraries and high-throughput technologies with which drug screening of potential targets can be effectively and rapidly performed, in vitro and in silico.

This summary of the history of pharmacology and drug development can easily leave any of us breathless with its rationality and determinism. Think of it—we have gone from purely empirical administration of a few crude preparations of natural products to patients in the 19th century to an expansive, molecular drug-target–driven pharmacopoeia that has refined our therapeutic options considerably, specifically, and with great efficacy—at least theoretically.

One would surmise that, with the growth in drug target data sets, in three-dimensional protein structural information, and in real and virtual drug libraries and high-throughput screening technologies, there should be a commensurate growth in available drugs, especially over the past 20 years. In fact, however, the number of US Food and Drug Administration (FDA)-approved drugs has been in decline: in 2000 to 2003, 90 to 100 drugs were approved annually, whereas only approximately one-fifth of that number have been approved annually over the past 6 years. Some analysts have suggested that these sobering data indicate a clear decline in the research and development productivity and innovation of the pharmaceutical industry. As Matt Ridley pointed out in a recent piece in the Wall Street Journal, “… the productivity of drugs coming out of clinical trials has been plummeting, and the cost per drug has been rocketing skyward. The more knowledge swells, the more pharmaceutical innovation fails. What’s going on?” he questions.5 Clearly, there is something amiss in the industry; productivity and innovation are in steep decline. Rather than blame this decline on regulatory forces, costs of development, etc (which are clearly important), I propose that the key problem is one of the very nature of the drug discovery process itself.

Well-accepted statistics bear out this decline: for the years 2000 to 2008, the top 10 pharmaceutical companies launched ≈1740 new projects per year, but achieved merely 35 approved (FDA and/or European Union) drugs per year, yielding a probability of success of just over 2%. The overall development time increased from 9.7 years in the 1990s to 13.9 years in this century, with 7 years on average needed for completion of the required US clinical trials. Figure 1 depicts the decrease in FDA-approved drugs over the past decade, with the most abrupt change occurring in 2002 to 2004. This change has occurred in the face of an increasing attrition rate at each stage of drug development, from phase I to postregistration.3 As a result of this serious economic challenge, the industry has curtailed its investment in comparatively risky areas of drug development, as illustrated in Figure 2 adapted from the analysis of Pammolli and colleagues.3 Two contour plots are shown that illustrate on the x axes the probability of successfully developing a drug (with a 2% reference line given in yellow) and on the y axes the average annual US sales (with a $10 million reference line given in yellow). The z axis shows the percentage distribution of research and development projects in the upper plot, and the change in the percentage distribution over the past decade in the lower plot, with positive values indicating an increase in research and development expenditure and negative values a decrease. Clearly, over the past decade, there has been a greater concentration of research and development projects funded in the least risky and most lucrative quadrant, with a decrease in projects in all other quadrants. Clearly, the industry’s financial imperative is moving it toward targets with optimal reward and minimal development risk.

There are many reasons for this decline in productivity in the pharmaceutical industry. Among these are included an increase in development time driven by a more stringent regulatory environment; an increasing need to explore novel drug targets owing to greater patent stringencies, and the fact that the “easy” targets have all been exhausted; and, as discussed above, an increase in attrition rates for developing drugs, all with a commensurate increase in research and development costs.
There is, however, one additional explanation for this decrease in productivity, which strikes at the very basis of contemporary drug development—namely, that target-based drug development oversimplifies both the complex mechanisms of chronic illnesses, and the complex perturbations of these disease mechanisms brought about by pharmacological agents. Both the pharmaceutical industry and society are ever in search of another Ehrlichian magic bullet to eliminate the suffering caused by any chronic illness, and the contemporary pharmaceutical drug development paradigm has taken this strategy to its purest form—one target whose structure is known and one drug whose action can be predicted by detailed structural knowledge of the target. Disease and pharmacology, like life itself, are, however, much more complicated than this reductionist simplicity could ever allow, and failing to acknowledge this complexity is an increasingly perilous proposition.

To explore this shortcoming in more detail, let us briefly review first the four basic preclinical strategies for identifying candidate drugs. These include phenotypic screening, which is simply the semiempiric identification of a drug without knowledge of its target; target-based screening; semiempiric modification of natural products; and the development of biologics, which are largely target-based. A recent review by Swinney and Anthony showed that, when these approaches are compared in the modern era, there are 50% more FDA-approved first-in-class drugs developed by phenotypic screening than by target-based drug screening; this outcome contrasts strikingly with follower drugs, among which there is a 2.5-fold increase in FDA-approved drugs developed by target-based drug screening than by phenotypic screening. Clearly, despite the highly rational determinism that underlies the drug target-screening paradigm, it is less effective than the phenotype-screening paradigm in discovering new, useful drugs (with the exception of when an established drug class undergoes further refinement).

Why does phenotype screening fare so well, even in the current era? Does its success suggest that we need to rethink the drive toward reductionism in drug development? In two words, the answer to this second question is most definitely. Let me give you the reasons for this conclusion. To do so, I will begin with an example well known to this audience—that of homocysteine-lowering therapies in atherosclerotic vascular disease.

The homocysteine theory of atherothrombosis was first proposed in 1969, and was based on Kilmer McCully’s analysis of autopsy specimens of young individuals who died in their second or third decades with the rare inborn error of metabolism, homocystinuria. He observed that these individuals had arteriosclerotic changes in their vasculature, which he posited might underlie the risk of developing atherosclerosis in individuals who had far lower (yet still elevated) levels of plasma homocysteine. In the subsequent 30 years, evidence from >30 epidemiological studies supported this
hypothesis, leading to the several secondary prevention trials that began in the 1990s. These trials were designed to take advantage of the benefits of B-vitamin therapy in lowering homocysteine levels, and derive from the simple reductionist paradigm that folate and vitamin B12 promote the remethylation of homocysteine to methionine, which will lower plasma homocysteine levels and, as a result, reduce the risk of a second clinical event. Unfortunately, this overly simplistic, linear, reductionist paradigm was proven to be incorrect, as virtually all of the studies completed to date failed to show any significant decrease in clinical event rates despite a significant reduction in plasma homocysteine levels with this therapy. There are several reasons for these failed trials, including the modest elevations of homocysteine that study participants had, the secondary prevention strategy implying the presence of well-established relatively irreversible structural vascular changes, and the co-occurrence of other risk factors that may have provided a greater attributable risk to a second event. In addition, however, I believe that another major limitation was that this reductionist rationale ignored the many other effects that folate, in particular, could have on vascular phenotype, some of which could offset the homocysteine-lowering benefit. Some of these effects include an increase in vascular cell DNA synthesis and proliferation, epigenetic effects through modulating DNA methylation reactions, and enhanced production of a naturally occurring inhibitor of vascular nitric oxide synthesis, asymmetric dimethylarginine.

There are countless other examples that litter the landscape of drug trial failures, many of which can, in retrospect, be attributed to neglecting the potential effects of a given therapeutic strategy that extend beyond the key target or target pathway through which the drug was developed and the clinical trial conceived. Some of these unanticipated effects are defined as “off-target” effects, intimating by terminology that the action is not one of considered importance for the disease under study. All of these “unanticipated” effects are really a reflection of the overly zealous application of Cartesian reductionism to drug development and clinical trial design. Drugs, in general, act not on single targets operating in a vacuum, but perturb a complex network of interacting proteins or metabolites to modify the dynamic output of a system that can extend well beyond the pathway in which the original target is operative. Therefore, to develop drugs in this century, one needs to move beyond the reductionist biomedical science of Occam, Descartes, Osler, and Ehrlich, and consider the complex biological system within which a drug acts holistically, in its tractable entirety. One needs to apply the principles of systems biology to pharmacology, and thereby establish the new discipline of systems pharmacology. To explore this approach in a bit more detail, consider the following brief background.

First, systems biology is the science of integrating genetic, genomic, biochemical, cellular, physiological, and clinical data to create a network that can be used to model predictively a biological event; by analogy, systems pathobiology uses the same strategy to model predictively a disease-linked event or process (pathophenome). The networks underlying these pathobiological systems are a collection of linked proteins or genes that govern the system’s biological response. The specific molecular entities can be represented as nodes, and their links (intermediates handled by two different nodes) as lines connecting the nodes, yielding a topologically complex network representation of the entire system. Theoretical examples of these complex networks are shown in Figure 3. The first point to make about these complex biological systems is that the links among the nodes are not random, as depicted in the network on the left with a Poisson distribution of links among nodes; rather, there are some nodes that are linked to many other nodes (called hubs), and others that are weakly linked to a few nodes, leading to the creation of a network that is clustered, or, as the mathematicians call it, scale-free with a power-law distribution of links among nodes, shown on the right. Scale-freeness reflects the
fact that these linkage densities are invariant with respect to the size of the system. This scale-free architecture of biological networks offers unique properties to the system, which include minimizing the transition time between states of the system; facilitating the transfer of molecular information across the system; accommodating perturbations to the system with minimal effect on critical functions; limiting the adverse effects of both biochemical and genetic errors; and providing the basis for tolerance to most genetic variants and, thereby, promoting biological diversity. Another point to make about these complex biological systems is that they manifest emergent behavior, which means that when the network is operative, it behaves in a way that cannot be predicted on the basis of knowledge of any of its component parts considered in isolation. Much like an electric circuit, comprehensive knowledge about any of the circuit elements—the resistors, capacitors, or battery—tells you nothing about how the system will respond to the application of a voltage across it unless and until you understand the wiring diagram within which this circuit element holds a place; so, too, with a complex biological system: without knowledge of where each enzyme or gene sits within the complete network, one cannot predict how the system will behave when activated or perturbed by a drug. A third point to make about scale-free complex biological systems is that they are over-determined from an engineering perspective; ie, one does not need to know every link or node within the network to understand how the system is likely to respond to perturbations. Thus, to summarize, complex biological systems comprise networks that have scale-free, or clustered, architecture; manifest emergent properties, or express behaviors that cannot be predicted on the basis of conventional reductionist science; and are overdetermined with respect to their dynamic behavior, indicating that one can predict the system’s behavior with less than complete knowledge of all of its component parts and their linkages.

Viewed from a network perspective, disease is a consequence of aberrant activity (overactivity or underactivity) of a subcomponent, or module, of a biological network. As shown in Figure 4, biological networks contain topological modules, or a collection of nodes that are contiguous one to another (interacting either physically, as identified by an analysis of the protein interactome, eg, or by common intermediates); functional modules, or a collection of nodes that work through a common functional pathway; and disease modules, which often cross functional modules. Expanding this network metaphor, we can view a drug or therapeutic agent as a perturbation of the functional dynamics of such a complex biological network. As shown in Figure 4, current drug development strategies focus on a single node in this complex network and monitor either the specific behavior of the node (enzyme, receptor) in target-based screens (in blue) or the system output as manifest by a measurable phenotypic property in phenotype screening (in red).

In view of this model of biology and disease, one can justifiably argue for the need to conceive of therapeutic strategies from a systems perspective and, in so doing, define the concept of systems pharmacology (Figure 5). In this model, a therapeutic intervention is viewed as a perturbation of the system’s dynamic behavior that is meant to correct or restore its normal function from that dysfunctional state caused by the consequences of an active disease module. Thus, systems pharmacology can be defined as the science of integrating genetic, genomic, biochemical, cellular, physiological, pathophysiological, and clinical data to create a network that can be used to model predictively the response of a diseased system to a potential therapeutic intervention.

We can think about the effect of a drug on a complex biological system in yet another way. In Figure 6A, I depict the conventional pharmacological approach to drug development with a single drug target, and a specific target function that can be monitored. Note that this target is linked to other molecules in the system, but those links and their consequences for system function following drug-target interaction are not typically considered. By contrast, in Figure 6B, I depict the systems view of drug interventions, viz, that a drug has other potential effects—either directly by interacting with other targets or indirectly by affecting other pathways in the system through system links—on overall system function. The net effect is the systems response, which reflects what truly happens in vivo, and can be viewed as the net consequence of a drug’s action in modifying several targets, some of which promote the beneficial phenotype and some of which may not. In this paradigm, one can view the off-target effect of a drug or a side effect of a drug as an emergent behavior, one that is generally not predicted with current drug

![Figure 4](http://circ.ahajournals.org/doi/fig/10.1161/CIRCULATIONAHA.111.095531) Modules in biological networks and drug development. A theoretical network of interacting nodes is illustrated in each panel, and distinctive modules within the network are highlighted. **Left**, a topological module that corresponds to locally associated nodes within the “interactome” is circled. **Middle**, a functional module in which there is a segregation of nodes of related function is shown in gray. **Right**, a disease module associated with a disease phenotype is shown in red; note that the disease module is neither part of the topological nor functional module in this network. A potential drug target is shown in blue, with target function (as assayed in conventional target-based drug development) distinguished from phenotypic function (as assayed in phenotype-based drug development). Reproduced with modification from Barabasi et al, with permission from the publisher. Copyright © Nature Publishing Group, 2011.
development strategies until after the drug is released and after many patients are exposed to it.

Using these complex systems approaches, one can learn about many drugs’ off-target actions. One example of this point is a study by Campillos and colleagues,\textsuperscript{10} who showed that ~20% of all drugs in the US Pharmacopoeia have common side effects that are indicative of their affecting common, previously unrecognized pathways. This kind of analysis, then, offers a better understanding of the universe of actions of any drug, can be used to predict potentially undesirable side effects of a drug, and can be used to identify previously unrecognized potential therapeutic actions of a drug.

Similarly, one can use a comprehensive systems pharmacology approach to understand differences among drugs of a specific class, as Xie and colleagues\textsuperscript{11} recently did for the cholesteryl ester transfer protein inhibitors. As you remember, the first of these, torcetrapib, increased high-density lipoprotein cholesterol as predicted from drug target analysis and development, but was associated with an unanticipated increase in clinical events compared with the control arm of the trial. Using a systems approach coupled with structural similarity network analysis, Xie and colleagues\textsuperscript{11} showed that in contrast to two other members of this class of agents, torcetrapib activated the renin-angiotensin-aldosterone system, likely accounting, at least in part, for these differences in outcome and supporting the development of other members of the class, such as anacetrapib.

To many in the burgeoning field of personalized medicine, identification of unique drug targets in individuals, rather than in populations, followed by development of specific inhibitors of those targets will lead to more effective, safer medicines that can be used in well-characterized disease phenotypes. A very good example of this concept is crizotinib (Xalkori), which targets a unique abnormal fusion product of the ALK1 receptor in a select group of patients with non-small-cell lung cancer (i.e., 4% of all non–small-cell lung cancers), and has been viewed as a clear proof-of-concept of the potential benefits of personalized medicine. Another example is the use of the RAF inhibitor, PLX4032 (vemurafenib), in patients with BRAF mutant melanoma. One such patient recently reported by Wagle and colleagues\textsuperscript{12} with widely metastatic melanoma had a fantastic response, with the melanoma initially melting away with this treatment; however, resistance developed as a consequence of an acquired mutation in the downstream MEK1 kinase, MEK1\textsuperscript{C121S}, a mutation that was not present before treatment with PLX4032 (Figure 7). As a result, the melanoma recurred with wide and rapid dissemination leading to the patient’s demise.

Although these examples, strictly speaking, exemplify the current view of personalized medicine, this latter example also demonstrates that personalizing drug development using conventional methods of single drug target identification is
simply inadequate because doing so fails to consider the systems context within which a personalized drug operates, with all of its potential for downstream (literally and figuratively) consequences. Understanding the control points in the network of kinases controlling melanoma growth, and using a strategy of targeting those control points and downstream nodes in the network that can serve a bypass function will be necessary to design definitive therapies for such complex diseases. We must, therefore, consider rational polypharmaceutical approaches for optimal outcome. Although this is polypharmacy to be sure, it is polypharmacy with a twist—it is systems-based polypharmacy designed for optimal system control and minimal mutational override.

Systems-based drug development, then, reflects the culmination of an iterative process. The initial conditions require that one characterize the disease module within the biological network, and use rational drug design to screen for agents that can restore system homeostasis; and iterative refinement requires characterizing the emergent properties and control nodes or points within the module, and those emergent properties that are manifestations of undesirable side effects, as well. In this way, truly rational systems-based drug design may have a hope of yielding truly personalized, effective, and safe drug therapies for complex illnesses (Figure 8).9,14

In addition to these complex systems-based changes in drug development strategy, we also need to consider complexity in clinical trial design. For example, adaptive trial designs, now prevalent in oncology, can limit the size of the study population and enhance our focus on narrowly redefined, well-characterized phenotypes for specific therapies. A straightforward example of the limitations of inadequate phenotyping is the example of pernicious anemia: hematologists point out that if all patients with anemia were treated with liver extract using conventional clinical trial design, one never would have detected a beneficial signal because the percentage of all anemic patients who have pernicious anemia is too small to detect an effect in the universe of all anemic individuals in a typical anemic study population. This almost trivial example is important because many of the phenotypes we consider in conventional cardiovascular trials are quite crude and may well mask subsets of patients who would greatly benefit from (or be harmed by) therapies that are tested in a broad population of individuals. From a mechanistic perspective, it is absurd to consider that all ST-segment myocardial infarctions are absolutely homogeneous; and we already are painfully aware that heart failure, truly a syndrome rather than a disease, has many distinct subtypes, which respond differently to the complex polypharmacy with which this syndrome is typically treated. Better phenotyping, in general, will optimize our ability to use the expansive genomic information to which we will have increasing access. In addition, it will move

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**Figure 7.** Effect of an inhibitor of mutant BRAF. PLX4032, in a patient with melanoma. A, Before initiation of treatment. B, After 15 weeks of treatment. C, after 23 weeks of treatment with relapse. D, Mechanism of drug resistance in kinase-dependent oncogene pathway, with mutation developing downstream of BRAF, in MEK, leading to recurrence of tumor. Rx indicates treatment. Reproduced with modification from Wagle et al,12 with permission from the publisher. Copyright © American Society of Clinical Oncology, 2011.

**Figure 8.** Network-based drug discovery. Reproduced with modification from Schadt et al,14 with permission from the publisher. Copyright © Nature Publishing Group, 2009.
us toward—but not to—truly personalized, individualized therapies by optimizing beneficial effects and limiting adverse events. Meeting this goal of personalized systems medicine will only be achieved by adaptive trials designed to meet the increasingly refined and personalized classifications of pathophenotype with which to explore therapeutic benefits.

Last, we need to develop a robust, viable business model through which the pharmaceutical industry can move from drug development strategies that are population-based to strategies that focus on increasingly individualized therapies. There needs to be an alignment of incentives that move the industry from conventional blockbuster drugs developed in large populations with single drug targets within which one size fits all toward smaller, better defined systems pharmacology-based molecular pathophenotypes that benefit from these well-conceived therapies with minimal risk. In so doing, we will move into a new, brighter era of therapeutics for medicine, for pharmacology, for the pharmaceutical industry, and most of all for our patients. Society should expect no less.

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