



# A Public/Private Partnership for Dual-Use Antibiotics

Pharmacogenomics offers potential new approaches to defend against both bacterial resistance and bioterrorism, but the pursuit of new antibiotic medications is not particularly attractive from a business standpoint. A public/private partnership could provide the structure for the R&D effort.

But they're not perfect. Obviously, if a bacterial pathogen is able to develop or acquire resistance to an antibiotic, that antibiotic becomes compromised, and quite possibly useless, in the treatment of infectious disease caused by that pathogen. New antibiotics must be developed to replace those that have become ineffectual.

Cases of antibiotics reaching the point of being ineffective are many. The CDC, in fact, reports that virtually all important bacterial infections throughout the world are becoming resistant to commonly used antibiotics (2). Furthermore, in her message introducing a 2000 report from the World Health Organization (Geneva, Switzerland), Director-General Gro Harlem Brundtland warned, "Now, at the dawn of a new millennium, humanity is faced with another crisis. Formerly curable diseases such as gonorrhea and typhoid rapidly are becoming difficult to treat, while old killers such as tuberculosis and malaria now are arrayed in the increasingly impenetrable armor of antimicrobial resistance (3)."

Coupled with this problem of older antibiotics outliving their usefulness is the emergence of new (at least in that they now have a name) diseases: Lyme disease, toxic shock syndrome, Legionnaire's disease — the list goes on and on. It seems that it's only a matter of time before we will need new antibiotics to replace those that currently work for these diseases.

Unfortunately, as looming as these problems are, they aren't the only ones for which we need new antibiotics. While the bacteria themselves are busy outsmarting the scientists, might it not also be the case that some scientists are busy trying to outsmart everyone — with the intention of doing evil with bacteria?

**A**s we've argued previously in these pages, pharmacogenomics is the necessary path upon which the pharmaceutical industry of the 21st century must travel. We've made a case for why it is the path to realizing new opportunities and achieving individualized medicines that will result in an overall improvement in the health of society. Now we want to argue this point from another angle — that it could lead to the provision of necessary protection from "conquering invaders," both bacterial and from bioterrorism.

One of what the Centers for Disease Control (CDC) calls "the world's most pressing public health problems (1)" — the increasing resistance to antibiotics by infectious agents — results from the rapid evolution bacteria undergo. In other words, bacteria mutate so quickly, they are, in effect, outsmarting drug developers.

Following their discovery in the 1940s, drugs that fight bacterial infections transformed medical care. It is agreed widely that the use of these so-called "wonder drugs" of the 20th century has been a major contributor to extending the life expectancy of human beings.

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**The need for dual-use antibiotics that address bacterial resistance to existing medicines and form a line of defense in the case of bioterrorism has entered the national consciousness.**

**A Business Model for Combating Bioterrorism**

In June 2002, the MIT Program on the Pharmaceutical Industry (POPI) held a workshop on “biodefense.” We brought together scientists and executives from industry, academia and some non-governmental organizations to discuss the threat posed by the possible unleashing of biological agents as part of a terrorist attack, and what ought to be done to prevent the catastrophic results.

Our discussion started with a fact recognized by all: new antibiotics are needed. This is not only because of general antimicrobial resistance — “dual-use” antibiotics that are active against many causative organisms are needed for general healthcare and biodefense. Clearly, this is a challenging scientific problem.

While this dilemma could heighten the sense of urgency, it does little to moderate the scientific difficulty of achieving success. Consider that, despite a considerable level of effort, there has been only one completely new class of antibiotics developed and introduced in the past 30 years — linezolid. And then there’s the business problem of limited market incentives.

Pharmaceutical firms that might consider developing a new antibiotic surely will use the standard ways to assess the market size. They will correctly

assume that the new drug initially would be a “third-line therapy” — withheld for cases when more familiar antibiotics fail. After all, doctors are unlikely to prescribe a new antibiotic for general healthcare use unless the existing ones aren’t working. That means a smaller market. No one would reasonably expect some new antibiotic to replace, from the outset, the ubiquitous bottles of pink amoxicillin found at some time in the refrigerator of nearly every parent of a toddler in the United States. Subsequent generations or members of a new class of antibiotics could transform the size of the market, but that takes time. And the market with respect to biodefense only comes into play in the event of an attack — a prospect that, admittedly, has a relatively low probability.

These issues frame the two big questions we want to address. The first is what characteristics of the “scientific path” can be expected to lead to promising targets for the development of new antibiotic medications? The other is how, given the likely market, should the research and development effort for a new drug be organized and financed?

It is in answering the first question that pharmacogenomics comes into play.

**The Scientific Path to New Antibiotics**

The new science and technology about which we’ve been writing in this column is where, we believe, the best hope lies for finding new antibiotics, as it seems the old way of looking for antimicrobials has failed to produce much during the past 30 years. Pharmacogenomics could be the starting point for an entire new enterprise.

The new path involves employing all the advances we’ve seen in life science in recent

years. It will mean continuing the exploration and identification of genomic and proteomic targets. Already, large commitments to genomic sequencing have resulted in the complete sequencing of 60 eukaryotic and prokaryotic genomes, and additional efforts currently are underway for more than 200 other genome sequences (4). The new path also means taking advantage of combinatorial chemistry and network biology. It will require exploiting all the technological advances that offer promise, such as high-throughput technologies and *in silico* modeling.

Who’s going to do all this? That’s the subject of the second big question. We think some new kind of public/private partnership will be required.

There’s no doubt that the assumed market limitations we described already factor into any firm’s decision-making about pursuing new antibiotic medications. On top of that risk, there are significant cost considerations. Given the staggering numbers we’ve all seen regarding the average cost of developing a new drug, what will it cost to develop a new antibiotic that is the first member of an entirely new class of antibiotics?

No one yet knows the answer to that question, though we have some initial thoughts. There won’t be amortized costs of failures in all classes of medications to factor in, so that should lower costs. Further, because the clinical endpoints are better defined, *in silico* modeling of genomic targets could make the discovery process more effective and, hence, less costly. On the other hand, one could argue reasonably that the inability to find more than one new antibiotic in three decades suggests much higher costs. Irrespective of the answer, we’re convinced that pharmacogenomics is the best

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— if not the only — available path that makes sense. The interaction of new chemistry approaches and new biological targets translates into multiple genomes of interest.

### Making it Happen

How can we ensure that the necessary forces come together to investigate the path we've identified? It became clear at the MIT/POPI workshop that the players — researchers, industry and government — have an interest in exploring the answer.

Scientists in academia want to get busy with exploration. Meanwhile, industry folks rightly express skepticism about whether the government truly appreciates the challenge and understands new costs and risks involved. They bring up questions of opportunity cost, capital investment requirements and returns on investment. Government players justifiably worry whether concerns about the small market size could be overcome so that industry will rise to the challenge. They want to determine which agents to target and ensure that the nation's defense is served. They want this to be a "public good" — available to all.

The assembled group discussed what incentives might encourage new antibiotics development. And, we wondered whether there are models for a public/private partnership, such

as Semitech in the semiconductor industry, that could lead first to a workable structure for the R&D effort and then to the desired outcome — new medicines.

These are only the beginning questions. The case for needing new antibiotics to thwart bacterial resistance has been clear for some time, and the need for dual-use antibiotics that also defend against bioterrorism now has entered the national consciousness. It was put eloquently in testimony before the U.S. House of Representatives: "In the long term, the only way to defend against bioterrorism is through a combination of constant surveillance, accurate diagnostics to identify threats as early as possible and continuous innovation to provide high-quality vaccines and drugs that can be useful against any attacks that do occur. Research related to bioterrorism is linked inextricably to that of naturally occurring infectious agents and development of new antibiotics, antivirals, diagnostics and vaccines. The research and development of technologies for biodefense should be synergistic and not duplicative (5)."

Who will take the lead in figuring out the next steps? Can we produce this century's "wonder drugs?" Will people have the chance to realize the benefits of such drugs in the natural course of their lives? The answers to these questions remain to be seen, but they all entail making sure we're biodefensive against bacteria — whether unleashed by bioterrorists or by the bacteria themselves.

### References

1. P.B. Lieberman and M.G. Wootan, "Protecting the Crown Jewels of Medicine: A Strategic Plan to Preserve the Effectiveness of Antibiotics." Report issued by the Center for Science in the Public Interest, Washington, DC, 1998.

2. H.C. Lane, J. LaMontagne and A.S. Fauci, *Nature Medicine* **7(12)**, 1271–1273 (2001).
3. World Health Organization. "Overcoming Antimicrobial Resistance." WHO Report on Infectious Diseases 2000. Available online at <http://www.who.int/infectious-disease-report/2000/index.html>.
4. See the web site of the U.S. Department of Energy Joint Genome Institute at <http://jgi.doe.gov>. See also the Genomes Online Database at <http://wit.integratedgenomics.com/GOLD/> and The Institute for Genomic Research web site at <http://www.tigr.org>.
5. U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations. At a hearing on "Creating the Department of Homeland Security: Consideration of the Administration's Proposal." Testimony of Dr. Gail Cassell, Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company. 9 July 2002. Available online at <http://energycommerce.house.gov/107/hearings/07092002Hearing629/Cassell1061.htm>. **PG**