Rationally Designed Antifungal Compounds that Evade Resistance Reported in Nature Chemical Biology by Scientific Founder of REVOLUTION Medicines

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New Leads Efficiently and Selectively Kill Pathogens in Vivo

REDWOOD CITY, Calif.--(BUSINESS WIRE)--REVOLUTION Medicines, Inc., a company focused on the discovery and development of innovative drugs derived from natural compounds, announced that progress in antimicrobial drug discovery was published today in *Nature Chemical Biology* by the company's academic founder and scientific advisory board chairman, Martin D. Burke, M.D., Ph.D., professor of chemistry, University of Illinois at Urbana-Champaign, and Early Career Scientist of the Howard Hughes Medical Institute. The paper titled "Non-toxic antimicrobials that evade drug resistance" reports on new chemical entities derived from the natural product amphotericin B, which has been used for more than 50 years as a highly effective treatment for serious fungal infections that is often accompanied by serious side effects. The novel compounds were active against fungal pathogens that cause life-threatening human diseases, effective in treating a rodent model of systemic yeast infections, and significantly less toxic to human cells than the parent natural product. Unlike many antifungal drugs used today, these molecules also evaded the emergence of drug resistance.

REVOLUTION Medicines, which reported its launch in February 2015, is developing new antifungal drugs based on these discoveries under an exclusive license from the University of Illinois. The new findings from the Burke group and colleagues at the Whitehead Institute and the University of Wisconsin build on data published previously by Dr. Burke that overturned decades of misunderstanding about the mechanisms of antimicrobial activity and toxicity to human cells. Leveraging biochemical, molecular and structural insights enabled by building block chemistry, the Burke group rationally designed new compounds that act as selective molecular sponges for the essential lipid, ergosterol, found exclusively on the surfaces of fungi, thereby killing the microbes. These novel compounds were shown to exhibit undetectable binding to the molecular counterpart in human cells, cholesterol, and to be less damaging to human cells. Notably, attempts to derive microbes that are resistant to the new compounds yielded exclusively organisms that had markedly impaired ability to cause infection *in vivo*, a sign of reduced biological "fitness." Collectively, these results demonstrate that susceptibility to resistance development is not an inevitable consequence for new drug leads designed to retain potent antifungal activity without concomitant effects on mammalian cells.

Invasive fungal infections have become more prevalent over the past three decades, due in large part to the increasing number of immunocompromised hosts and hospitalized patients with significant underlying diseases. *Candida* and *Aspergillus* are the most common causes of invasive fungal infections and, despite the introduction of broad spectrum azoles (e.g., voriconazole) and echinocandins (e.g., caspofungin), morbidity and mortality remain unacceptably high. There has also been a shift in epidemiology with an increase in *Candida* and *Aspergillus spp*. resistant to available therapies, resulting in the addition of these organisms to the list of qualifying pathogens under the GAIN Act (Generate Anti-infectives Now). There is an urgent need for new, broad spectrum, -cidal antifungal agents with a high barrier to development of resistance.

"Fungal infections pose a grave threat to patients, particularly those who are immunocompromised. This study reported promising fungicidal activity against common pathogens causing invasive infections in humans, and we are working on progressing new compounds based on these important discoveries toward clinical evaluation," said Carole Sable, M.D., chief medical officer of REVOLUTION Medicines. While at Merck earlier in her career, Dr. Sable led the development of caspofungin (Cancidas), the first echinocandin antifungal drug to be approved.

"The findings reported today validate the approach that uses biological insights to guide the introduction of important new properties into natural product backbones, in this case opening a potential path to improved therapy for patients with severe fungal infections," said Mark A. Goldsmith, M.D., Ph.D., president and chief executive officer of REVOLUTION Medicines. "With the power of our REVBLOCKS™ chemical synthesis product engine reported recently, we look forward to expanding our pipeline by redesigning additional molecules based on lessons from evolution."

The *Nature Chemical Biology* paper titled "Non-toxic antimicrobials that evade resistance" can be viewed online at http://www.nature.com/nchembio/index.html.

About REVOLUTION Medicines

The mission of REVOLUTION Medicines is redesigning evolution's products to treat serious diseases. The company discovers and develops new drugs by reconfiguring natural substances that are inherently rich with biological function as a result of natural selection. REVOLUTION Medicines' innovative product engine is based on the REVEAL™ platform, which uses evolution's lessons to inform selection of chemical scaffolds, and the REVBLOCKS™ technology, a rapid, standardized and transformative synthesis process for assembling simple chemical "building blocks" into refined natural product-like structures with optimized pharmacologic and pharmaceutical properties. The company's first leads are innovative small molecules that exploit and improve upon the properties of amphotericin B, a powerful, broad-spectrum antifungal compound found in nature that has avoided generating significant drug resistance in 50 years of clinical use. Headquartered in Redwood City, Calif. at the intersection of Silicon Valley and the birthplace of biotechnology, REVOLUTION Medicines is a private company financed by top-tier investor Third Rock Ventures. For more information, please visit www.revolutionmedicines.com.

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