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DRUG RESISTANT FUNGI *the crisis deepens*

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without causing immunoparalysis

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SPECIAL ISSUE ON INFECTIOUS DISEASES

The Quest to Conquer HIV/AIDS

by **Min Lu**

Conquering HIV/AIDS is clearly the scientific grand challenge of our day. It's the key to saving millions of lives and ending great suffering everywhere and to stopping widespread personal, political, and economic devastation throughout the developed and the developing world. The challenges to halting the epidemic are many. The crisis in Africa and now Asia has been widely covered, and the dire need for inexpensive drugs, better clinical care, and preventive education is well known. But the ultimate goal remains a vaccine, and perhaps the fiercest battles are being fought in laboratories. A common feature of successful vaccines for other infectious diseases is their ability to rapidly neutralize viruses in newly exposed individuals — before the infection can become established. Inducing neutralizing antibodies will be important for developing a preventative AIDS vaccine.

Despite heroic efforts, the successful development of a safe and effective HIV vaccine remains elusive. And there is no pharmacologic strategy in sight that can eradicate persistent HIV to bring the goal of

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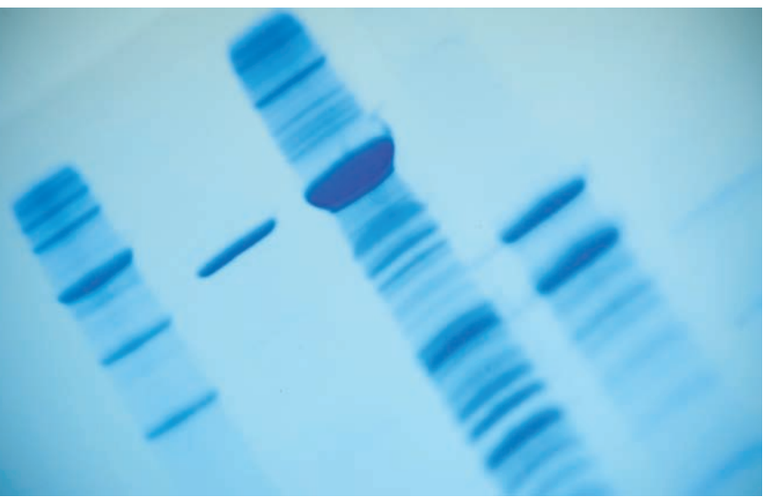

The recombinant HIV-1 gp41 protein was analyzed by SDS–PAGE and Coomassie blue staining".

— continued from front cover

an AIDS-free generation within our reach. Research in my laboratory seeks to address both of these fundamental problems. Our approach is to define the detailed molecular mechanisms that underlie HIV entry into target cells, specifically how HIV uses its envelope glycoprotein (Env) to fuse with the target cell membrane, and how to inhibit this process with specific drug candidates and virus-neutralizing antibodies.

HIV Env is located on the surface of the virion as a trimeric complex comprising three gp120 outer subunits non-covalently associated with three membrane-anchored gp41 subunits. This native Env complex is kinetically trapped in a metastable conformation, primed for fusogenic activation upon engagement with its receptors (CD4 and CCR5 or CXCR4). Thereupon the Env complex undergoes large-scale conformational changes, driven by formation of an energetically stable trimer of alpha-helical hairpins in gp41 that couples protein refolding directly to virus-cell membrane fusion, enabling viral entry. My laboratory aims to elucidate the molecular basis of each fusogenic structural transition, thereby guiding rational, structure-based efforts to design new immunogens and fusion inhibitors.

The design of immunogens able to elicit broadly reactive neutralizing antibodies is the holy grail of HIV research. The general lack of a neutralizing antibody response would seem to reflect a conformational shielding of conserved functional epitopes within the native Env complex. My laboratory has recently determined the crystal structures of two newly identified coiled-coil domains in gp41 that are metastable and may thus correspond to prefusion native form of the protein. We are currently using protein engineering to create stable recombinant soluble Env proteins for structural studies, and to correlate specific gp41-gp41 interactions with the corresponding structural, functional and immunogenic properties of the Env complex. Our long-term goal is to develop stable immunogens capable of displaying the authentic native Env trimer that is sufficiently long-lived to elicit antibodies that bind the cognate epitopes on infectious viruses.

The fusion-inhibiting drug enfuvirtide is used for salvage therapy in patients with multi-drug resistant HIV. However, its clinical use is limited by the requirement for parenteral delivery and the high cost of therapy. Despite intensive efforts over many years by researchers in academic and industrial laboratories, the search for orally bioavailable small-molecule HIV fusion inhibitors targeting gp41 has been frustrating. My laboratory has used structural and chemical biology approaches to identify a novel small-molecule fusion inhibitor that acts to stabilize the native Env complex against receptor-induced activation. Importantly, atomic-level structural information enables deriving principles that govern binding of small molecules to gp41. This knowledge in turn has provided a basis for successful lead optimization. In collaborative efforts, we are seeking to develop a potent small-molecule gp41 fusion inhibitor for the treatment and prevention of HIV infection. ■

Min Lu received his PhD in biophysical chemistry in 1990 from New York University. He did postdoctoral work at Harvard University and Massachusetts Institute of Technology. He joined Weill Cornell Medical College in 1996 as an assistant professor of biochemistry and became associate professor in 2001 and professor in 2006. He joined New Jersey Medical School as professor of microbiology and molecular genetics in 2010.