

EVOLVING NEW DRUGS WITH EVOLVA



THE THEORY OF EVOLUTION IS THE CORNERSTONE OF BIOLOGICAL SCIENCE, SO IT IS NOT SURPRISING THAT ENTERPRISING BIOTECHNOLOGISTS COULD PUT IT TO WORK IN THE SERVICE OF NEW PRODUCTS

Darwinian principles today constitute the driving intellectual force behind the technology of a number of biotech companies, guiding a wide range of clinical applications that have already been developed or are on the drawing boards. On the forefront of this technology is Evolva, a Swiss company that seeks to use the principles of natural selection to propel their drug discovery program.

According to CEO Dr. Neil Goldsmith, “as many as 61% of the world’s most important drugs derive from nature.” Since the earliest days of medicine, natural compounds, mainly from plants, have been the principle source of pharmaceuticals. These substances evolved over the course of eons to protect the plant from various environmental insults, so their beneficial effects for humans were purely serendipitous. Thus, a pivotal step in traditional drug discovery is to take a promising compound and subject it to a series of chemical modifications that will lessen unwanted side effects and increase its disease fighting capability. This may frequently turn out to be a laborious and frustrating task, calling on hundreds of hours in the chemistry lab, and large expenditures of resources. The conventional path used by the big pharma companies is to start with a molecule that has promise, because an academic institution or private company has found that it inhibits a critical step in some disease process. Then an army of analytical chemists will close in on the molecule, making a series of modifications based on their

knowledge of its physiology, biochemistry and pharmacology. Many different substitutions are made, adding and subtracting groups from the framework of the molecule. These slightly modified molecules will be subjected to tests using tissues culture cells, then moving to various species of lab animals, and finally the really promising candidates will enter clinical trials.

So the time required to produce a successful pharmaceutical product may be measured in years, which eliminates the possibility of the potential drug being brought in for crisis management during disease epidemics.

The Evolva process is quite different, and seeks to find a shortcut around this sisyphian task. It is based on building complex genetic libraries (huge collections of genes), that can carry out the synthesis of families of low molecular weight compounds with anti-viral or anti-bacterial potential. These genes, that code for various biosynthetic enzymes, can be taken from nature or developed artificially. The goal is to arm the yeast cell with the potential to escape the killing effects of exposure to the pathogenic



Scientist Thomas Tange analyzes the molecular mating step in growth media.

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<< Senior Scientist, Markus Schwab assembles yeasts for screening.
 >> Cell Biologist Julia Yakovela checks for activity on human cell compounds.



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agent. In one permutation, the yeast cells are modified in such a way that a critical protein can be “hijacked” by agents such as HIV and Ebola virus. Those yeast cells that evolve a low molecular compound that kills the virus can survive. The survivors are subjected to additional rounds of selection so that stairstep-wise, a better and better protective compound is produced.

The company has contracts for designing antivirals, immunomodulators and antibacterial compounds. These molecules could be used as protective agents against bioterrorism, or for natural epidemics. Four other collaborative programs are underway in the area of cancer therapeutics, glycosylation and production optimization.

Another program that the company has been pursuing is the development of immunomodulators, that is, drugs that work by stimulating the immune system so the host is provided with a generalized level of protection. Yet another effort is aimed at developing anti-fungal drugs. Pathogenic fungi are particularly deadly for individuals with compromised immune systems, and currently available drugs offer only limited protection.

Evolva’s program is beginning to pay off as the candidates move into pre-clinical evaluation. In animal studies, an anti-Ebola compound referred to as EV-063-4321 provided mice with 90% protection against a lethal infection. An immunomodulator, EV-009-1440, protected 50% of mice against a lethal bacterial dose. Yet another candidate, EV-075, was shown to have efficacy against influenza, Ebola and Marburg virus. These viruses, members of the family Filoviridae, are responsible for a deadly and untreatable hemorrhagic fever.

Although confined to Africa, these viruses are a source of constant concern because of their lethality and their potential for adoption for bioterrorism purposes. Indeed, in 1992, members of Japan’s psychopathic cult Aum Shinrikyo traveled to Zaire in a failed effort to obtain samples of the Ebola virus.

In preclinical studies, Evolva has demonstrated that EV-075 works synergistically with Tamiflu, and could be used in flu epidemics. Thus the Evolva technology could greatly speed the process of drug development and serve as a rapid response strategy for moving against arising worldwide health threats.

While Evolva’s approach is cleverly engineered to take advantage of a Darwinian survival program tied to the development of new small molecule compounds, a number of biotechs are using comparable strategies to isolate large protein molecules with beneficial qualities.

The most widely used approach relies on very large antibody gene libraries carried in bacterial strains. In this case, the goal is to isolate synthetic antibody molecules that bind to a target (disease-associated) protein. The genes are transferred into special viruses and their protein products expressed on the exterior of the virus. If any of these virus particles attach to a protein target, the viruses can be rescued, their population expanded and subjected to round after round of selection. During this process, the genes are heavily mutagenized to introduce new variability into the system and make the evolutionary process move even more rapidly. By moving step by step, a large protein with more and specific binding abilities can be obtained. This approach has resulted in the discovery of a number of antibody-based drugs over the years.

New screening techniques and protocols could carve years off the current daunting timelines. We may finally be witnessing an entirely new vision in drug development – faster, cheaper and much more powerful – that may reveal an undiscovered universe of disease fighting agents. **S**

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For centuries drug discovery has been a random, hit or miss proposition. In the 20th century it acquired the mantle of science, but was still based on a search for exotic substances, a combination of Indiana Jones-style exploration and serendipity. One of the most famous of these discoveries was the anti-cancer drug Taxol, isolated from the bark of the **Pacific Yew tree**. First noted in 1964, years passed before it finally became part of the chemotherapy repertoire. We may now finally be witnessing an entirely new vision in drug development; faster, cheaper and more powerful.

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