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Innovations

Resurrection Men Dig through the Drug Graveyard:
ARYx Revives Problem Blockbuster Drugs

One company's fiasco can be another's potential fortune, especially if that fiasco involves a billion-dollar drug that has been pulled from the market because of toxic side effects. Fremont, CA-based ARYx (http://www.aryx.com/) is in the drug-resurrection business, reviving other companies' failed blockbusters by reengineering their metabolic pathways. ARYx is using a process it dubs "retrometabolic drug design" to reengineer oral drugs used to treat blood clots and gastrointestinal and cardiac problems in order to reduce or eliminate liver toxicity. Drug-drug or drug-food interactions can overwhelm the liver's cytochrome P-450 oxidase enzyme system, causing drugs to accumulate in the body to toxic levels. ARYx "rehabilitates" drugs by working backward, changing the way they are metabolized and excreted in the body.

"There is a graveyard for drugs," says Dr. John S. Lazo, Allegheny Foundation Professor of Pharmacology and Director of the Drug Discovery Institute, University of Pittsburgh School of Medicine. Unexpected side effects have occasionally led to blockbuster drugs, such as Viagra, Lazo says, but they have also been the downfall of many good drugs. Pharmaceutical companies have, for various reasons, abandoned excellent drugs that had huge potential but were pulled off the market after FDA approval because of unexpected side effects. "The business model of taking a drug already there and making it better has clearly been around," Lazo says, citing thalidomide, which was reapproved, this time to treat leprosy and is now used for multiple myeloma. "Claritin/Clarinex and Prilosec/Nexium are examples of drug reengineering," he added.

Feeling a Bit Liverish?

To find drug candidates suitable for retrometabolic engineering, ARYx's selection committee reviews the literature for drugs that have large clinical market potential, are primarily metabolized by the liver (most drugs are), produce toxic side effects, and are not constrained by patents.

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ARYx chemists then create water soluble, "ideal" metabolites that are pharmacologically inert at the normal dose range of the reference drug. They chemically attach the metabolite to the drug molecule. The upshot should be a new drug with changed binding interactions that hopefully will bypass the P-450 bottleneck in the liver and be excreted through the kidneys. The metabolite is different with each program, says Pascal Druzgala, ARYx Chief Scientific Officer. ARYx's process depends on expertise, or "medicinal chemistry common sense" as well as knowledge gained from the literature about compounds with no known biological interactions to create the metabolites. Sometimes, they retroengineer a known inactive metabolite of a natural product. They also employ computational methods, although less frequently.

Metabolites are selected based on the intended pharmacokinetic properties of the target compound. Selection also depends on the size of the final molecule as a large drug will probably need a more radical biotransformation to make it inactive than a small molecule. For example, ARYx chemists designed the metabolite of ATI-2042 (a potential drug to target atrial fibrillation) so that it is negatively charged, Druzgala says, impeding its ability to interact with cation channels (potassium, sodium, calcium), and so it therefore would be inactive. They designed the metabolite for ATI-5923 (coumadin) to be hydrophilic, so that it would not interact with VitK reductase (VitK is a very lipophilic substrate for this enzyme).

The company's researchers may also tweak the half-life of a molecule while keeping or improving its prior pharmacokinetic effectiveness, thus significantly reducing or eliminating toxicity by rerouting the metabolic pathways away from the liver's P-450 enzyme pathways. Although this was the rationale for ATI-7505 (a serotonin type 4 agonist) and for ATI-5923, Druzgala notes, the main strategy for ATI-2042 was to target tissue esterases as the main metabolism pathway to shorten the terminal elimination half-life by making the compound biodegradable in muscles and organs. ATI-2042 still travels to the liver but places a substantially reduced load on the P-450 enzymes.

"From first principles, we've learned a lot about cytochrome P-450 enzymes in the last ten years," says Dr. John Lazo. "There has been a substantial increase of our understanding at a genetic level, at a cellular level, and from a biochemical level and structural level. Armed with that information, I think you can be much more thoughtful in the construction of the compound that you are going after. From that standpoint, I think ARYx's approach is appealing."

Getting Started in the Resurrection Business

The company was founded in 1997 by Dr. Peter Milner, a physician with extensive experience in biotechnology, and Pascal Druzgala, a medicinal chemist with a long-standing interest in "retrometabolic" drug design. Druzgala had been involved with similar ideas since 1982 at the University of Florida. "Originally, the soft drug concept, which originated in several parts of the country

but was popularized at the University of Florida, was advocating the use of nonoxidative metabolic systems in order to safely metabolize drugs," says Druzgala. In the last 20 years, Druzgala says, more than ten percent of FDA-approved drugs were eventually removed from circulation because of toxicity and drug-drug interactions. The entrepreneurs saw an opportunity in safety issues, the underbelly of the drug industry. They launched the company on the basis of the intellectual property of a compound Druzgala invented, ATI -2042, an analog of amiodarone, a heart arrhythmia drug that had high liver toxicity.

For the first several years ARYx was funded by family and friends (Milner's family had been in the drug business back in England). The preclinical data and IP of ATI-2042 convinced MPM Capital in 2002 to lead an investment round of $25 million with OrbiMed Advisors and Merlin BioMed. Two years later, the company received $55 million in Series D funding led by Nomura Phase4 Ventures. Currently, ARYx employs about 55 people and has 20 patents and 22 pending in the U.S. and another 75 or so foreign patents, says David Nagler, VP of Corporate Affairs. In successful revivals, timing is everything. The company is setting the stage to go public as its three drug candidates are now in phase I or II testing.

Side Effects May Include …

ATI-5923, a novel coumadin (warfarin) analog now in phase I trials, promises to prevent clotting without endangering patients. Commonly administered to prevent stroke associated with blood circulation problems, "Warfarin interacts with pretty much anything, even the food you eat," says Druzgala, causing patients to either bleed to death or suffer stroke if they go off the drug. The dose effects are unpredictable as they vary with the individual. "ATI-5923 has the same pharmacology as warfarin," says Druzgala. "It basically slows down the formation of active coagulation factors, II, VII, IX, and X. The difference is that our compound, unlike warfarin, is achiral. It is not a mixture of isomers. It is not metabolized by oxidative systems. It is rapidly metabolized by esterase. We have modified the metabolism so it takes a different metabolic pathway than other drugs, so by definition, they don't interact."

ARYx also has developed ATI-7505, now in phase II trials. ATI-7505 is an analog of Propulsid cisapride, Janssen Pharmaceutical's drug for treating gastrointestinal diseases such as gastroesophageal reflux disease (GERD) and diabetic gastroparesis, which is delayed emptying of the stomach. Propulsid commanded a $950 million market share when it was withdrawn in 2000 because it caused cardiac toxicity when administered along with antifungals or antibiotics.

The Benefits of Hindsight

Large pharmaceutical companies have tightened up their screening databases and broadened their patents after incidents of drugs slipping through pharmaceutical patents and being restructured by enterprising startups. Notably in 1996, Sepracor transformed Hoechst Marion Roussel Ltd.'s problematic antihistamine Seldane into a single isomer drug and then licensed it back to HMR as Allegra (fexofenadine/pseudoephedrine). Seldane was subsequently banned by the FDA. "It will be a matter of being very clever at identifying the best candidates, both from the chemical standpoint and from an intellectual property point of view," John Lazo says. "There are a number of compounds out there that could be reengineered for the benefit of mankind."

ARYx is not the only company in the resurrection business. For example, Jazz Pharmaceuticals in Palo Alto, CA raised $250 million in 2004, the largest second-round financing for a drug company to date. Jazz has no proprietary technology and does not plan to do R&D but rather purports to license, improve, develop, and market known compounds for neurological and psychiatric disorders. ARYx is also competing against pharmaceutical companies themselves, which are developing other drugs to meet the same market needs as the ones they abandoned.

"We do the same old lab benchwork medicinal chemistry that everybody else does," says Druzgala, "and have to establish all the same preclinical data for the FDA. We believe our advantages are that we are not attempting to create new validated targets. The big advantage we have is that we can look at an old drug with many years of research and postmarket surveillance."

ARYx's approach bypasses the long screening stages of drug discovery because it deals with known compounds brought through FDA approval—but the revamped drugs would still have to go through the most expensive parts of phase III human clinical testing and resubmission to the FDA as well as pass post-FDA extended clinical use. Even if a drug has well-characterized structure-activity relationships, redirecting its properties in a complex system, for example, fiddling with fat versus water solubility, can cause other unexpected effects, such as changes in the drug localization within the body, local toxicity of a drug, and its rate of uptake and resulting bioavailability.

The company hopes to offload the cost of the clinical phase. "We don't expect to be in partnership with the drug company that made the original drug. Our business is based on entering into a commercial partnership which will work with us under phase III trials and commercialization," says David Nagler.

Resurrection is one thing. Redemption in the market for refurbished drugs known to have a toxic history is another. It remains an open question if doctors will be willing to prescribe drugs that have a bad reputation, even if they have been revived, reworked, and renamed.

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