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Innovations

Infinity Pharmaceuticals

Back to the Future

Infinity Pharmaceuticals, of Cambridge, Massachusetts, believes there is a better way to begin drug discovery through a chemical biology approach enabled by novel chemistry. Infinity's compound collections mimic the diversity and pharmacophoric display of natural products, but without the traditional barriers associated with working with natural products—difficulties with purification, identification of active species, synthesis, analog development, and scale-up. "We're about bringing the full power of modern synthetic organic chemistry to bear on the discovery of new chemical entities," says Michael Foley, PhD, cofounder and Vice President of Chemical Technologies at Infinity.

Back to the Future

According to Foley, the company's motto in bumper sticker language would be "back to the future." "The idea is that we are creating molecules as starting points for drug discovery with the positive attributes found in natural products yet easily constructed reproducibly on a large scale," he says. These molecules are known in Infinity parlance as the *Infiniplex* library, which the company hopes will represent functionally diverse and stereochemically rich industrially scalable molecules. "In short," says Foley, "we are working on the types of molecules that are the greatest challenge for modern synthetic chemistry."

Nature may have offered up several important natural products like Taxol and rapamycin, but the inherent difficulties in analoging and synthesis often make natural products intractable starting points for drug development. According to Foley, Infinity's aim is to make med-chem-friendly molecules that rival the complexity of natural product drugs. "We can modify the building blocks around them very simply and also invert the stereocenters at our choosing," he explains. The hope is that the molecules will be tractable from a medicinal chemistry standpoint yet yield the potency and selectivity found in natural products.

Harvard Roots

Foley's familiarity with the chemistry-driven approach at Infinity stems from his graduate laboratory experience in the laboratory of Stuart Schreiber at the Harvard Institute of Chemistry and Cell Biology (ICCB). Schreiber is also an Infinity cofounder. Schreiber's vision was to create structurally diverse molecules that traditional combinatorial chemistry couldn't access. To do so required embracing tougher chemistry, explains Adelene Perkins, Infinity's Chief Business Officer. "Dr. Schreiber, through the ICCB, has perfected the technology over the past five years to take tough chemical transformations and make them robust enough to be used in high-throughput synthesis," she says. Infinity's plan is to use its novel chemistry to discover drugs, building off of the revolutions in biology and information technology that they believe will be perfected by a revolution in chemistry. Says Perkins, "The value of the IT and biology revolutions of the 1990s has not been fully realized in drug discovery because it was not matched by a parallel revolution in chemistry. Our chemical biology approach allows us to capitalize on all the work done on genomics with a technology—small molecules—that is absolutely proven."

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Also in the Harvard laboratory with Foley was Jeffrey Tong, PhD, now Senior Director, Corporate Strategy and Development at Infinity. While Foley developed technologies to create the molecules, Tong had worked on developing technologies for microarray printing that were later adapted by ICCB and Infinity to become a small molecule array screening platform. "There are major classes of protein targets that were inaccessible to current compound collections," explains Tong of the need for new drug discovery tools. "Historical chemical file collections were largely created to focus on the drug targets of interest over the last 20–30 years, things like GPCRs, ion channels, kinases, and proteases." The result has been a large collection of compounds built up around those targets. "Everyone has been mining in the same space, so we are interested in looking at other validated targets with promise," says Perkins.

Homing in on Non-Druggable Targets

According to Tong, many highly attractive targets remain off limits to drug discovery because of their intractability to current chemistries in identifying molecules with the right potency, selectivity, and pharmacokinetic properties. The fundamental synthesis-driven approach at Infinity is leading the company to close in on that gap between interesting molecules with potential clinical relevance and drug candidates. Says Perkins, "We want to create whole libraries of molecules against every protein in the body and have a recipe for how to make them again in a large-scale setting." Examples of potentially interesting targets include new and well-credentialed targets arising from the human genome sequencing projects. "There are many attractive targets for which people have failed to raise relevant chemical matter," explains Foley.

Targets cited include PTB1B for type II diabetes, hepatitis C protease, beta-secretase for Alzheimer's disease, and numerous protein-protein interactions. "Everyone in the industry would say if you had a ligand against those proteins or if you could interrupt that protein-protein interaction you would have something very special," he says. "There are probably 40 to 50 important proteins lacking a drug against them."

Three-Platform Screening Process

Once synthesized, the molecules are screened with one of three screening platforms to find matches with proteins of interest. The first is a traditional series of target-based biochemical assays. "There is nothing proprietary about these types of assays," explains Foley. "It is the targets that are unique because they have been previously unavailable for traditional drug discovery methods."

The second approach, classified by Infinity as its chemical genomics method, is the small molecule microarray. "In this approach, we use small molecule microarrays to screen our molecules against hundreds of proteins, including both tractable and previously intractable targets, in a very efficient manner that nobody, or very few, could rival in the industry," explains Foley. Infinity hopes to exploit the power of small molecule microarrays as a highly efficient method for discovery of protein-ligand interactions and, hopefully, the development of functionally relevant drug candidates.

At the moment, Infinity scientists can spot over 3000 small molecule compounds onto one glass microscope slide in a manner similar to DNA microarray technology. Miniscule amounts of labeled protein, either purified or from more complex mixtures, are passed over these glass slides. "Anything that sticks is a found protein-ligand interaction," says Foley. In March 2003, scientists generated over 1,000,000 data points with 50,000 small molecule compounds and 20 proteins. But Foley cautions that these initial assays do not provide a functional sense of what is going on. "All you know is that that protein and small molecule have an affinity for each other, but the binding of the small molecule to a protein is a precondition for directly modulating its function," he says.

The real benefit with this technology will be for proteins that are hard to purify or in limited abundance. "This is an extraordinarily efficient way to parse through a very large compound collection and get that down to a smaller number of interesting compounds and then proceed to smaller-scale functional assays," says Foley. "That is to say, we can do high-throughput screening where others could not on certain targets."

The third approach is to use chemical genetics in the form of phenotypic cell-based assays as a discovery platform to allow the molecules to interact with every protein in a disease-relevant setting. "We are using cell-based assays as a way to get our molecules in front of every protein within the cell and let nature tell us what is important," says Foley. He comments that the company's most significant milestone is a large collection of synthesized molecules that are able to perturb biological systems in a selective way in a number of high-throughput phenotypic cell-based assays. But Foley cites the difficulty in performing these assays on a large scale to make them useful for high-throughput screening. The key scientific endeavor with this technology is to make sure the detectable event observed in the population of cells is relevant to disease initiation or progression. And, it must also be linked to downstream assays like animal models or biological markers of that molecule's effect in a human being for ultimate clinical proof of concept.

The company has not yet progressed to animal or human studies. "We've got to parse through a large number of data points first," says Foley. The company hopes to have some molecules in animal models perhaps as early as this year, with the medium-term goal of having developmental candidates for human testing over the next five years.

Equal Emphasis on Informatics

Along with its chemistry and biology programs, Infinity is also heavily invested in its knowledge management competencies. Thanks to the input of cofounder Frank Moss, formerly of Tivoli and Bowstreet fame and now an Infinity Board of Directors member and part-time employee, "we have an incredible focus on informatics and information technology to make sure we are able and ready to capture meaning from all the data we are generating," says Foley. "We are employing some very leading edge computational efforts that we think are poised to be industry leading."

Infinity's vision includes mapping small molecules against all the proteins in the human body. "Obviously, the amount of information that needs to be managed in mapping near-infinite chemical space against all proteins is orders of magnitude beyond what people are used to dealing with," says Perkins of the company's heavy investment in knowledge management systems. Moss brings information industry experts to the company, "not pharma/biotech people turned informatician," says Perkins, but software professionals trained in industries where lots of information needs to be used quickly and agilely. "He has created an environment where we have an internal company of software engineers and informaticians who are all about serving our chemists and biologists with the products they need."

In its three key technology platforms, chemistry, biology, and informatics, a fundamental focus and strength at Infinity has been its ability to translate the work of the academic into utility in the industrial pharmaceutical world. The mission is single-minded: to find and develop drugs that have eluded others.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

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