

## Innovations

### Amgen redux ICOS Corporation

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Companies cannot live on pedigree alone, but it doesn't hurt to have a history of fine corporate decision-making backing you up. For ICOS Corporation (Bothell, Washington) that means a co-founder and CEO, George Rathmann, who has already directed a start-up called Amgen to billion-dollar sales, and a star-studded board of directors that includes William H. Gates III of Microsoft fame. Gates is also a major ICOS investor.

The science is a mixture of the Amgen model — proteins as drugs — and the more standard approach of using small-molecule therapeutics. “We thought we needed to do that to fully leverage the discoveries here, because a lot of the proteins that we have discovered are intracellular,” says W. Michael Gallatin, Vice President and Scientific Director.

From its beginnings in 1990, ICOS has focused on the immune system and, more specifically, cellular adhesion and signal transduction. It has reduced the risks by increasing the numbers: isolating multiple members of a given protein family to define more specific drug targets, and selecting proteins that are potential targets in multiple diseases. Some of those diseases — such as heart attack and stroke — are not usually thought of as problems of the immune system. Even more distant conceptually is a Viagra-like drug that was the focus of a huge deal recently cemented with Eli Lilly & Company.

#### Blocking adhesion

Immune cells do most of their disease-fighting in tissues. They get into tissues, and out of the

bloodstream, by attaching to adhesion proteins made by vascular endothelial cells, which line blood vessels. Once attached, the immune cells squeeze past the endothelial cells and seek out disease-causing microbes.

ICOS is attempting to block the attachment process with LeukArrest™, a humanized antibody against the immune cell integrin CD11/CD18. Although the therapy is directed at the immune system, the disease targets are not all autoimmune diseases. Instead, ICOS is using LeukArrest™ to minimize or prevent the damage that immune cells do to tissues after an interruption in blood flow. Phase II trials are underway for stroke, heart attacks, hemorrhagic shock and multiple sclerosis.

The LeukArrest™ antibody recognizes all the variants of CD11/CD18, which are found on different immune cell lineages, and it therefore has the potential to be a profound immunosuppressant.

“If you dose patients at high levels *ad infinitum* one could expect severe immunosuppression, but in the clinical setting that is not how you give the drug,” says Gallatin. “We are looking at acute inflammation or acute exacerbation. There's a pretty nice window of therapeutic utility that doesn't cause the patient to become immunocompromised.” In clinical trials, he says, “infection hasn't been a significant issue.”

For chronic disease a more specific agent is needed. One candidate is ICM-3, a humanized antibody to ICAM-3. The integrin ligand ICAM-3, discovered by ICOS researchers, is important in the interaction between T cells and antigen-presenting cells that leads to T-cell activation. ICM-3 is in phase II trials for the treatment of psoriasis, a disease in which activated T cells induce abnormal skin growth.

Next in the adhesion pipeline come two ICOS discoveries: CD11d (or Alpha d) and ICAM-5. As ICAM-5 is found predominantly on hippocampal neurons its role in neurological disease is being

explored. Alpha d is highly expressed by macrophages, including the foamy macrophages in atherosclerotic plaques. Although atherosclerosis remains a possible treatment target for the future, it will not be the subject of the first Alpha d clinical trials. “Our strategy is to identify applications with short endpoints,” says Gallatin. “For a medium-sized biotech we may not start with atherosclerosis.”

#### Large small molecules

ICOS is initially attacking adhesion molecules with antibodies, but the next line of drugs, based on a collaboration with Abbott Laboratories (Abbott Park, Illinois), may be small molecules. The design of these molecules will not be a simple task. “Unlike enzymes, cell-adhesion targets have broad points of contact,” says Gallatin. “You need to build a bigger small molecule by piecing together small molecules.”

That is just what Abbott's SAR by NMR (structure–activity relationships by nuclear magnetic resonance) technique achieves (see *Chem. Biol.* **4**, 231–232). NMR is used to detect and define the location of weak binding events; the weak binders are then linked together to make a tight-binding drug. “I won't put it forward as a panacea for all drug-targets,” says Gallatin, “but it can be very powerful.”

#### A broad approach

Of ICOS's anti-adhesion drugs, only LeukArrest™ is in multiple clinical trials. That picture is likely to change, however, as the company's resources and research expand. “We run a broader profile of clinical trials than is usual because we would rather be data driven,” says Gallatin. “I don't think there is one uniform algorithm that really substitutes for scientific empiricism.”

Once the results of the phase II trials are in, Gallatin promises the company will be “draconian” in selecting only the most promising drugs and indications for the far more extensive and costly phase III trials. “We say repeatedly that we don't

expect all of our phase II's to go forward," he says.

### The next Viagra?

In 1991, ICOS signed an agreement with Glaxo Wellcome to isolate multiple phosphodiesterases (PDEs), the enzymes that degrade cyclic nucleotides. Gallatin explains that the companies did not have a particular application in mind. "The general premise was that cyclic nucleotides are so important as general regulators of human physiology, so there were bound to be additional important enzymes."

Isolating multiple PDEs was a way to begin to understand PDE diversity, and a first step to achieving specificity. "We felt that the key for the medicinal chemist was having the tools in hand to drive selectivity to a much higher level than had been done in the past," says Gallatin.

The first drug candidate to emerge from this program is IC351 which, like Pfizer's Viagra, is a small molecule inhibitor of PDE5. Both drugs help men get erections by allowing the buildup of cyclic GMP, which causes the smooth muscle cells that line blood vessels to relax, so the blood vessels dilate. ICOS hopes that IC351 will prove superior to Viagra based on its lack of interaction with PDE6, which is closely related to PDE5. Inhibition of PDE6 by Viagra is thought to cause the blue tinge in vision experienced by some Viagra users, as PDE6 is involved in visual transduction.

IC351 is still in phase II trials, but that hasn't stopped Lilly from giving ICOS a hefty \$75 million up-front payment for the rights to 50% of any IC351 revenues. The two companies have formed an equal partnership to further develop the drug. The deal was unusual both for the size of the payment (given the early stage of IC351 testing) and for the retention by ICOS of sales rights and not just royalties.

The next candidate in the PDE program is PDE4, which has been implicated in asthma. Gallatin believes the ICOS drug will lack the

side effects of nausea and sedation seen with other PDE4 inhibitors.

### Interfering with the signals

Communication in the immune system is not all tactile; soluble messengers are also common. In 1995, ICOS scientists discovered platelet-activating factor acetylhydrolase (PAF-AH, now Pafase™), which inactivates an important inflammatory messenger. Pafase™ is in phase II trials for three inflammatory conditions including pancreatitis.

Another messenger program is focusing on chemokines, which act as chemoattractants for T cells, monocytes and neutrophils. As with LeukArrest™, an inhibitor of a chemokine should keep immune cells in the blood and out of tissues. The research approach here is, however, similar to the PDE program: ICOS has isolated multiple chemokines in a somewhat random fashion, in the hope that some of them will be interesting. Gallatin says that defining their functions using genetics and cell biology is slow, especially as many of the chemokines appear to be redundant (a fact that might complicate drug development). "It could take you a long time to do knockouts for all the possible targets, so it could be faster to do high-throughput screening to get small molecules, which can then be used as probes to define the biology."

Gallatin is particularly interested in one chemokine discovered by ICOS, dubbed macrophage-derived chemokine (MDC). MDC selectively recruits the TH2 class of T cells, which are prominent in cell-mediated reactions such as asthma. MDC's fame increased when a team at the University of Maryland at Baltimore claimed that it was the substance secreted by CD8(+) cells that can suppress HIV infection. Gallatin and others are not convinced. "I'm not personally sure that there is as significant a connection between MDC and AIDS as was originally proposed in the Gallo article," says Gallatin. "We would not consider

MDC in AIDS high on our list of clinical candidates."

Jay Levy, a chemokine researcher at the University of California at San Francisco, agrees. "Most people are finding [MDC] just isn't produced in sufficient amounts to play a clinical role," he says.

### Creative financing

ICOS has managed to keep all or most of the rights to its drugs even as the drugs advance through increasingly expensive trials, in part because of its stellar board of directors. In addition to Gates, the board includes Frank Cary (former chairman and CEO of IBM Corporation), James Ferguson (former chairman and CEO of General Foods), Alexander Trowbridge (former US Secretary of Commerce), and Walter Wriston (former chairman and CEO of Citicorp/Citibank). Their track record has no doubt made potential investors feel more secure, and allowed the use of creative financial solutions such as limited partnerships and private investments under favorable terms.

But not everyone is excited about the links between big business and biotech. DenounceNewsWire ([www.denounce.com](http://www.denounce.com)), a parody of news services such as Business Wire, used the Gates-ICOS link as inspiration for a fictional press release. The release states that Microsoft and ICOS have discovered a gene that causes a partiality for Macintosh computers, and that testing for the gene in schools is imminent. ICOS may not be pleased that it was described in the release as a company that "secretly designs, develops and markets pharmaceuticals for Microsoft Corporation's use in curbing competition." But considering that Microsoft was described as "that freight train you always dreaded in your dreams," ICOS is still faring relatively well in the land of corporate communications.

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