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Innovations

# Inhibitex, Inc: Antibody Anti-Infectives

Inhibitex's core technology may not be initially obvious, but it represents a strong potential advance in the fight against severe bacterial and fungal infection. MSCRAMM proteins, or Microbial Surface Components Recognizing Adhesive Matrix Molecules, are at the heart of Alpharetta, GA-based Inhibitex's anti-infective efforts and are the foundation of two products in clinical testing. "MSCRAMM technology involves the characterization and identification of surface proteins on pathogenic organisms that allow the adhesion of the organism to host tissues," explains Joseph M. Patti, Ph.D., Vice President of Preclinical Development and Chief Scientific Officer at Inhibitex. "We generate antibodies against these MSCRAMM proteins to prevent or interfere with the adhesion process, the first step in initiation of the host infection."

"Our mission," says CEO William D. Johnston, Ph.D., "is to develop and commercialize antibody products for severe, life-threatening infections. The reality is that since the early 1980s, the number of new antibiotics being approved by the FDA has followed a steady course downward." He adds that large pharmaceutical companies are vacating the market for new anti-infective therapies, instead focusing increasingly on chronic, larger-dollar opportunities, leaving a niche opportunity for biotech companies such as Inhibitex to meet those demands.

Inhibitex's market—at least initially—involves infections usually found in the hospital setting, such as severe staphylococcal bloodstream infections resulting from catheters and other implanted medical devices. And these infections are also becoming more commonplace outside the hospital, as with sports-related injury and infection.

From 1994 through 1998, Dr. Patti, then at Texas A&M, cofounded Inhibitex as a virtual company while pursuing the MSCRAMM/antibody research. "For the first several years we worked with collaborators in the field who had interesting concepts, ideas, and intellectual property and pulled that into the company," says Patti. Inhibitex is now a 75-person public company. In the last 12 months, the company has raised over $100 million in financing, which included an IPO in June 2004.

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–Joseph M. Patti, Ph.D., Vice President of Preclinical Development and Chief Scientific Officer

### MSCRAMMs: Targets of Opportunity

Regardless of the type of bacteria or fungus, all infectious organisms appear to possess MSCRAMM or MSCRAMM-like proteins. Although these proteins are characterized as a family, each MSCRAMM is the product of a unique gene. A common MSCRAMM, conserved among all pathogenic organisms, has not yet been identified. "However, once you understand how these organisms attach, you can apply the same developmental strategy for any organism you want to focus on," explains Patti.

The activities of MSCRAMMs have been studied for many years, although not necessarily under that acronym. For example, the MSCRAMM Inhibitex targets in both its Veronate and Aurexis antibody products, clumping factor A (ClfA), has been investigated for decades for its putative role in staphylococcal infections. "ClfA allows S*taphylococcus aureus* to specifically bind fibrinogen and/or fibrin," explains Patti. That activity causes the distinctive phenotypic clumping of *S. aureus* in plasma.

MSCRAMMs have a role in facilitating an organism's ability to initiate an infection. The current thinking is that different MSCRAMMs may be involved in different types of infections or that some predominate over others in vivo. Says Patti, "What we have done at Inhibitex is look at all the data with the goal of identifying which MSCRAMMs are important for infection, which are druggable, and which ones can you raise antibodies against or use as a vaccine."

Because most of the MSCRAMM proteins of interest have been cloned, they can be expressed in high quantities in *Eschericia coli* and studied; also, many have been crystallized, so their three-dimensional structures are known. "These proteins tend to be fairly immunogenic, so making antibodies is pretty straightforward," says Patti. The key is to find the right antibody targeting the MSCRAMM of interest. "We looked at 2,000–3,000 different antibodies against ClfA before we found one that has the totality of activity that we would like," says Patti.

### Antibody Therapies

Inhibitex has characterized many MSCRAMMs and is targeting them with antibodies via various strategies, including polyclonal and monoclonal antibodies and vaccines. "Our approach is two-fold," says Patti. "We believe these MSCRAMM proteins are viable targets both from a passive immunity stance, where we are giving

preformed antibodies to prevent infection, and as an adjunctive therapy to treat an existing infection."

Inhibitex is exploiting both modes of antibody biological activity. "The MSCRAMM attachment to human tissue is the initiation of infection," says Johnston. By bringing in an antibody that binds to that binding site on the MSCRAMM protein, the first step in infection is avoided. "That is relevant in prophylaxis but it also has relevance in a therapeutic mode because the infection is initially isolated before it goes through the equivalence of a metastatic spread through the body," he says. "You're going to be able to mitigate that spread." Antibodies also activate cellular elements of the immune system through a process called opsonization or opsonophagocytosis, in which they help clear the bacteria from the patient.

Inhibitex's two lead products independently target both prevention and therapy. Its Veronate product, now being tested in a phase III study as a means to prevent infections in very low birth-weight infants, includes antibodies selected against two MSCRAMMs—ClfA, for *S. aureus*, and SdrG, for coagulase-negative staph (CoNS), or *Staphylococcus epidermidis*. "This phase III trial is a 2,000-infant prevention study where we are administering Veronate to premature babies born prior to any transfer of maternal antibodies and who are very likely to develop some sort of infection due to their prematurity and the measures required to sustain life for those first several weeks, like catheters," says Patti. Adds Johnston, "While doctors are appropriately focusing on the immediate problems in these infants in the NICU, the data that has come out recently shows these infections lead to lifelong problems." Research from investigators in the National Institute of Child Health and Human Development Neonatal Research Network published findings in November 2004 showing that infants who had at least one infection were 40%–70% more likely to develop cerebral palsy than a baby who had no infection. Similarly, the odds of having a low Bayley score, a measure of mental development, were 30%–60% higher for a baby who had an infection. "That just adds to the critical need for the drug," says Johnston. "It is exciting to think these drugs could potentially change the course of life for these children."

Results from the phase II dose-finding Veronate trial involving 504 infants found that at a dose of 750 mg/kg, Veronate reduced the frequency of *S. aureus* infections by 63%, fungal infections by 67%, and all-cause mortality by 36%. As of January 2005, 700 infants had been enrolled in the phase III US/Canadian trial.

The company's humanized monoclonal antibody, Aurexis, targeting ClfA, recently completed a phase II trial to treat life-threatening or severe *S. aureus* infections in conjunction with antibiotics. "It used to be that these infections were found only in a hospital environment, but now we are seeing relatively normal immunocompetent people showing up at the ICU with fever and staph in the blood," says Patti. "The dramatic increase in the community-acquired staph infections is particularly worrisome."

Aurexis is directed against all *S. aureus* infections, not just methicilin-resistant *S. aureus* (MRSA). "The Aurexis antibody activity is independent of the antibiotic profile of the organism," explains Patti. "In animal models, we have demonstrated it works equally well against methicillin-sensitive and -resistant staph." Top-line data from the phase II study should be available mid-Q2.

### Other Organisms, Other Targets

"We believe the ability to target MSCRAMMs represents a platform technology," says Patti. "Accordingly, we are also looking at other medically important pathogens." This includes enterococci, particularly vancomycin-resistant enterococci (VRE), now considered the third leading cause of hospital infection behind CoNS and *S. aureus*. "We are working with Dyax to develop a monoclonal antibody with reactivity against target MSCRAMM proteins we have identified across multiple enterococcal strains," says Patti. The company is also targeting fungal infections, such as those caused by *Candida albicans*.

Inhibitex will also be studying Aurexis in an open-label trial among cystic fibrosis patients heavily colonized with staphylococci. "Staph often leads to exacerbations of the condition which result in decreased lung function and require systemic IV antibiotics," says Patti, "so we are looking at the potential of Aurexis to see if it has any impact on that heavy colonization with staph. If successful in modifying colonization, we would hope to see a reduction in exacerbations caused by the staph infection." This trial should begin in the second quarter of 2005. Inhibitex is also pursuing a vaccine program against nosocomial staphylococcal infections in partnership with Wyeth. According to Johnston, "Wyeth has had this as a goal for years but had not found an appropriate technology until our collaboration was formed."

### A New Strategy against Resistance

"We differ from the pack," explains Johnston. "When you look at clinical development, most everyone else is focused on antibiotics where they are mostly making structural modifications to improve dose timing or dosing format." He points out that since the advent of antibiotics 60 years ago, "the bugs are mutating and outrunning the chemists," leading to a reduction in the clinical efficacy of a significant number of approved antibiotics as microbes adapt through evolution. "If you look at the pressure to mutate, organisms eventually seem to develop an alternative pathway to block the cidal activity of antibiotics or find a path around it," says Johnston. Inhibitex seeks to offer an alternative strategy by focusing on antibodies. "The reason this was not done in the past is because nobody had the appropriate targets," says Johnston. "Now, we do."

If proven effective, MSCRAMM antibodies would be a valuable anti-infective strategy, particularly in cases in which resistance patterns have exhausted other options. "After examining clinical isolates from around the world, we have seen no evidence that the MSCRAMM target proteins mutate over time," adds Johnston. Although this finding may not always remain the

case, and long-term efficacy with MSCRAMM antibodies is not a guarantee, these new compounds may well prove to be a very welcome therapeutic strategy for reducing infectivity and virulence against life-threatening infection.

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