

Innovative Companies in Antibacterial Therapy

In this issue, *Pharmaceutical Innovation* presents a look at several pharmaceutical, biotech and biopharmaceutical companies developing innovative antibacterial therapeutics. Adis Business Intelligence believes that these companies represent business opportunities for acquisitions, licensing and co-marketing deals. The article is not intended to be a comprehensive evaluation and the omission of a particular company is not meant to imply any judgement with regard to its potential value as a partner.

Acambis

Acambis is a biopharmaceutical company primarily engaged in researching, developing and manufacturing vaccines for the prevention and treatment of infectious diseases. The company has a diverse portfolio of vaccine product candidates with six in clinical trials. Acambis has offices in Cambridge, UK, and Cambridge, MA. Acambis has collaborations with vaccine companies such as **Aventis** and **Baxter**.

Acambis has a technology platform for the development of novel mucosal (oral and nasal) vaccines to prevent bacterial infections. Acambis' technology can potentially overcome the problem of having a suitable delivery system and an adjuvant to induce a mucosal immune response. Most infectious agents enter the body through mucosal surfaces, yet many current injectable vaccines elicit a poor immune response in the mucosa. Mucosal vaccination can be effected by oral or nasal injectable delivery of antigens in an appropriate carrier and therefore provides protection against such infectious agents where it is most needed. Mucosal vaccination is better tolerated and is more easily and conveniently administered than conventional vaccination by injection.

Antex Biologics

Antex Biologics is a biopharmaceutical company dedicated to the production of clinical technologies and therapeutic products to identify, prevent and treat infectious diseases. The company has alliances with **GlaxoSmithKline**, **Aventis**, the US Navy and the National Institutes of Health. This development-stage

firm is working on vaccines targeting gastrointestinal and sexually transmitted infections:

- **HELIVAX** is an oral vaccine for protection against *Helicobacter pylori*, a bacterium linked to stomach cancers and ulcers;
- **CAMPYVAX** is a potential vaccine against diarrhea and gastroenteritis caused by *Campylobacter*, a food-borne pathogen;
- **ACTIVAX** for traveler's diarrhea;
- **TRACVAX** for protection against *Chlamydia*;
- **TWARVAX** for a certain type of pneumonia;
- **GONOVAX** is a vaccine that may prevent gonorrhea.

Subsidiary **AntexPharma** focuses on antibiotics to fight hospital-acquired infections.

Antigenics

Antigenics, Inc. is developing treatments for cancers, infectious diseases, autoimmune disorders and degenerative disorders, using the company's proprietary technologies to program the immune system. Antigenics' technologies include immune modulators and liposomal formulations of small-molecule drugs. Among the immune modulators are HSPs and QS-21, which activate T cells and antibodies – the two arms of the immune system that control the vast majority of cancers and infections. The CD1 receptor is the pathway through which HSPs activate cellular immune response. Drugs that interact with CD1 are expected to either downregulate or upregulate the immune system and therefore treat autoimmune diseases, cancers and infections. The CD1 antigen discovery technology is a newly recognized immunological pathway through which T cells target a variety of infectious agents, including tuberculosis and chlamydia, via the recognition of carbohydrate antigens.

AVANT Immunotherapeutics

AVANT Immunotherapeutics, Inc. was formed from the merger between **T-Cell Sciences** and **Virus**

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Research Institute in May 1998. The company is engaged in the development and commercialization of products that harness the human immune response to prevent and treat disease. AVANT's most advanced therapeutic program focuses on compounds with the potential to inhibit inappropriate activation of the complement cascade, a vital part of the body's immune defense system. AVANT is also developing a portfolio of oral vaccines aimed at protecting travelers from diseases endemic in developing areas, such as cholera and typhoid fever, as well as a proprietary therapeutic vaccine for the management of cholesterol.

Axcan Pharma

Axcan Pharma is a specialty pharmaceutical company within the field of gastroenterology in North America and Europe. Axcan markets a broad line of pharmaceutical products used in the treatment of a variety of gastrointestinal diseases and disorders. In addition to its marketing activities, Axcan carries out research and development of products at an advanced stage of development that it acquires or licenses from third parties. Helicide is Axcan's product candidate for the eradication of the *Helicobacter pylori* bacterium. Scientific studies have identified *H. pylori* as the most important known cause of peptic ulcer, a disease that affects at least 10% of the North American population at some time in their lives. Existing treatment regimens cannot prevent a high recurrence rate. Based on scientific studies, Axcan estimates that gastric and duodenal ulcers recur within a year following treatment in approximately 40% to 80% of patients. Helicide is a single-capsule triple therapy containing colloidal bismuth subcitrate, metronidazole and tetracycline. The therapy has been filed for regulatory approval in Canada and the US.

Cubist Pharmaceuticals

Founded in 1992, **Cubist Pharmaceuticals Inc.** is a global company, headquartered in Lexington, KY, with operations in Canada and the UK. Cubist is developing novel antimicrobial drugs to combat bacterial and fungal infections. Cubist is developing new class of lipopeptide antibiotics, of which the lead compound is daptomycin. Cubist is developing an injectable formulation of daptomycin (Cidecin). Multiple phase III trials are currently underway examining the safety and efficacy of Cidecin in the treatment of skin and soft tissue infection, community-acquired pneumonia in hospitalized patients and patients with certain resistant

infections. Cubist and **Emisphere Technologies** are jointly developing an oral formulation of daptomycin. Cubist has an ongoing lipopeptide program focused on the discovery of a next-generation daptomycin.

Cubist is also applying its VITA and ChemInformatics technologies to identify additional novel compounds with a broad spectrum of activity against a variety of infections. Adding to its in-house drug discovery capabilities, Cubist acquired **TerraGen Discovery Inc.** in 2000, a privately held, natural product drug-discovery company. With the acquisition, Cubist has enhanced both its antimicrobial drug discovery platform and product development engine as well as obtaining proprietary technologies and expertise in the area of small-molecule drug discovery from natural products.

In addition, Cubist has acquired worldwide rights to oral ceftriaxone. The formulation is the first orally active version of the largest-selling intravenous antibiotic worldwide, **Roche's** Rocephin.

Demegen

Demegen is a Pittsburgh, PA-based public company founded in July 1992. Demegen, taking cues from nature, has designed and patented new classes of peptides that have superior activity and less toxicity than those that occur in nature. With the acquisition of **Periodontix**, Demegen acquired a family of peptides derived from naturally occurring peptides found in human saliva – called histatins – that play a role in the body's natural defense against disease.

Demegen designs, synthesizes and screens new peptides for antibacterial and antifungal activity. With a unique mechanism of action distinct from classical antibiotics, Demegen compounds have demonstrated the capability to destroy Gram-negative and Gram-positive bacteria, including those that are resistant to current antibiotics.

Essential Therapeutics

Microcide Pharmaceuticals, Inc. changed its name to **Essential Therapeutics, Inc.** when it merged with **Althexis Company, Inc.** in October 2001. Essential Therapeutics is developing antimicrobials for the treatment of bacterial, fungal and viral infections. The company's three discovery research platforms address the growing problems of antibiotic resistance and the need for improved antifungal and antiviral therapeutics. Essential Therapeutics' cephalosporin antibiotics and efflux-pump inhibition platforms focus on developing

novel antibiotics and antibiotic potentiators (efflux inhibitors) to directly address existing bacterial and fungal resistance problems. The company's Microbial Genomics platform utilizes proprietary bacterial, fungal and viral genetics, as well as genomics tools, to discover entirely new classes of antimicrobial agents.

Genome Therapeutics

Genome Therapeutics is a leader in the commercialization of genomics-based drug discovery. The company's commercial gene discovery strategy is to identify and characterize human genes associated with major diseases and elucidate bacterial genes responsible for many serious infectious diseases. The company has several strategic partnerships. Genome Therapeutics is using genomic information to develop a new generation of genomics-based pharmaceutical, vaccine and diagnostic products. Genome Therapeutics established the PathoGenome Database, the most comprehensive commercial source of microbial genomic information available, which is now available on the internet through LabOnWeb.com. It enables researchers to search for new genes among multiple pathogens and cross-reference genomic information for the development of new anti-infective products.

ID Biomedical Corporation

ID Biomedical Corporation is a North American biotechnology company focused on the development of a proprietary gene identification system, Cycling Probe Technology, for applications in genomics and diagnostics. The company is also focused on the development of proprietary vaccines and immunotherapeutics. Using Cycling Probe Technology, ID Biomedical is developing rapid tests that identify antibiotic-resistant bacteria from culture. ID Biomedical is now licensing Cycling Probe Technology to the genomics and diagnostic industry for further product and technology development. ID Biomedical is also developing vaccines for a number of different conditions. StreptAvax, the company's lead vaccine product for the prevention of diseases caused by group A streptococcus, is in phase II clinical trials.

IntraBiotics

IntraBiotics Pharmaceuticals, Inc., founded in 1994, is a biopharmaceutical company developing novel antibacterial and antifungal drugs for the prevention or treatment of serious infectious diseases, including those related to the phenomenon of multidrug resistant

microbes and the infectious complications of neutropenia. The company's lead product candidate, iseganan, is an oral formulation (formerly referred to as Protegrin IB-367 Rinse) and is in phase II clinical trials for hospital-acquired pneumonia. Iseganan has a novel mechanism of bactericidal action and may be particularly useful in fighting bacteria that cannot be killed with currently available antibiotics.

LigoCyte Pharmaceuticals

LigoCyte Pharmaceuticals is a biotechnology company which focuses on the molecular and cellular interactions associated with inflammatory and infectious diseases. LigoCyte is developing products to block or enhance cell trafficking and signaling in fighting inflammatory and infectious diseases. The three proprietary platform technologies that LigoCyte has are: ProteoFlow, nanoparticles and M-cell directed vaccines.

M-cell directed vaccines are targeted directly to mucosal immune induction sites. The vaccine constructs can be delivered nasally or orally to the lungs, intestines and urogenital tissues. This technology is built upon LigoCyte's pioneer research in cell trafficking and cell signaling. A vaccine construct can be made using a viral adhesin protein, which targets mucosal inductive tissues through interaction with the M-cells.

Micrologix Biotech

Micrologix Biotech Inc. is a public biopharmaceutical company that researches, develops and commercializes antibiotics targeted at multidrug-resistant microorganisms responsible for the most clinically important infections and diseases. The company's current portfolio of anti-infective drug candidates is based on improved analogs of naturally occurring cationic peptides found in the host defense systems of most life forms. Micrologix currently has two drugs in clinical trials in the US: MBI-226 for preventing catheter-related bloodstream infections (phase III) and MBI-594AN for treating acne (phase II).

Whereas conventional antibiotics work on a biochemical level to interfere with a very specific mechanism essential for a microorganism's ability to function, cationic peptides kill bacterial cells through a swift physical attack on their membranes. Drug-resistant bacteria are efficiently killed, ensuring that they will have difficulty developing resistance to these compounds. Micrologix is developing proprietary recombinant DNA technologies that will allow for

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commercial-scale production of cationic peptides and provide them with a distinct competitive advantage. Micrologix is focusing on the development of two main categories of drug candidates: bactolysins and enhancins. Bactolysins are being designed to work on their own as stand-alone drugs to kill microorganisms, including sensitive and multidrug-resistant bacteria. Enhancins are being designed to work in combination with conventional antibiotics to restore antibiotic activity against resistant bacterial strains and/or extend an antibiotic's spectrum of activity.

Nabi

Nabi is a fully integrated biopharmaceutical company with a broad product portfolio and significant R&D capabilities focused on the development and commercialization of products that prevent and treat infectious and autoimmune diseases. Nabi currently has several clinical trials underway in these areas and has four marketed pharmaceutical products. Nabi has both prophylactic and therapeutic products under development to combat the growing problem of Gram-positive bacterial infections, particularly *Staphylococcus aureus*. Nabi-StaphVAX is currently in phase III pivotal trials in end-stage renal disease patients on hemodialysis. Nabi-Altastaph has completed a phase I/II trial in low-birth-weight neonates. Clinical studies of Nabi-Altastaph in preventing bacteremia in hospital intensive-care units are in the planning stages [*Pharmaceutical Innovation* 2002; 11(5): 23-25].

NewBiotics

NewBiotics, Inc. was founded in 1997 by a team of former **Genentech** and **Canji** scientists and business executives. NewBiotics develops drugs to treat cancer and infectious disease. The privately held company is applying its Enzyme Catalyzed Therapeutic Activation (ECTA) technology to develop a new generation of pharmaceuticals that transform drug resistance into therapeutic advantage. Based on an understanding of the biological and biochemical mechanisms underlying the development of drug resistance, NewBiotics intends to discover and develop novel pharmaceuticals that complement and supplement current therapeutics.

ECTA technology was developed based on the idea that cancer therapeutics and antibiotics can be developed overcoming common mechanisms of drug resistance and avoiding drug toxicity. An ECTA drug exploits the resistance enzyme by mimicking the natural substrate with which the enzyme normally reacts. After the

resistance enzyme reacts with the ECTA drug, a potent toxin is released that kills the cell. Because diseased cells overproduce the resistance enzyme, they are killed preferentially by the ECTA drug compared to normal cells. NewBiotics' lead compounds include thymectacin for the treatment of colon cancer and lamectacin for the treatment of drug-resistant bacterial infections.

Nippon Medical Research

The first Japanese biomedical venture company, **Nippon Medical Research, Inc.** (NMR), is developing an injectable antibiotic which has demonstrated excellent bactericidal efficacy and safety features in animal studies as a first-line therapy against methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The compound, WAP-8294A2, is now being further developed by NMR as an alternative to vancomycin, having a narrow spectrum of activity and being effective in a once-daily regimen. WAP-8294A2 is a major component in a complex of water-soluble depsipeptide antibiotics produced by a species of *Lysobacter*.

PowderJect Pharmaceuticals

PowderJect Pharmaceuticals is a vaccines and immunotherapeutics company headquartered in Oxford, UK, with facilities in Europe and the US. PowderJect has expertise in researching, developing, manufacturing, and marketing existing and next-generation vaccines. With a range of products sold under its Evans Vaccines and SBL Vaccin brands, PowderJect is one of the world's largest vaccines companies. The company is developing next-generation vaccines based on its proprietary delivery technology (powder injection) and a new approach – DNA vaccination – which offers the prospect of using the immune system to both protect against and treat disease. PowderJect's portfolio includes vaccines for influenza, yellow fever, travel diarrhea, cholera, tuberculosis, polio, tetanus and hepatitis B. The company's world-class biologics manufacturing facilities, which have received approximately £60 million of investment over the last four years, are among the largest in Europe and are approved by both the US and European regulatory authorities.

Sequella

Sequella, Inc. is a development-stage biotechnology company designed to facilitate the translation of concepts that exist at the lab bench into commercial therapeutics, vaccines and diagnostics that can alleviate

the global burden of infectious disease. The company, headquartered in Rockville, MD, is focusing its initial research efforts on therapeutics, diagnostics and vaccines to address the growing worldwide tuberculosis (TB) problem. The Sequella concept was conceived at a meeting held at the National Institutes of Health (NIH) to review its university granting program in TB in 1996. An increase in NIH funding of TB research from 1990–1995 resulted in new discoveries made by the TB research community, many of which had sufficient underlying basic science information to be ready for commercial development. At that time, however, a major roadblock to the development of new products for the control of TB was a lack of industry partners to take potential products forward into clinical development.

The founders of Sequella also incorporated the Sequella Global Tuberculosis Foundation, a nonprofit organization complementary to Sequella that bridges the gap between basic research and product development. The foundation helps the TB research community to identify potential products from their basic research funded by the NIH and structure proof-of-principle experiments that will capture the imagination and interest of a pharmaceutical partner. Although these two organizations are not linked financially, politically or organizationally, together they create a continuum from basic research through product development in TB. In late 2001, the Seattle-based Gates Family Foundation announced it would fund a substantial, multicomponent program being directed by the Sequella Global Tuberculosis Foundation and aimed at developing effective vaccines to protect against TB. The program, which is international in scope, will focus on translational or applied vaccine research, emphasizing efforts to develop and evaluate promising vaccine candidates through at least early-phase clinical trials and possibly into early commercial-scale production. The Gates Foundation announced that it would provide Sequella with \$US25 million over five years for several components within its TB vaccine development program.

SIGA Technologies

SIGA Technologies is a development-stage company involved in developing vaccines, novel anti-infectives and antibiotics for infectious diseases. SIGA is committed to developing products for the prevention and treatment of serious infectious diseases, based on its research in the field of bacterial surface proteins. The

company's antibiotic program addresses each of the major classes of antibiotics, a worldwide market of \$US24 billion annually. SIGA's approach is aimed at disabling or eliminating the surface proteins that bacteria use to attach to human tissue, the first step in the infection process. Since no existing antibiotics act through this mechanism, they believe this approach will be effective in addressing infections caused by drug-resistant bacteria.

SIGA is developing a novel class of antibiotics targeting Gram-positive bacteria through a partnership with **Wyeth**. The agreement with Wyeth provides for the funding of SIGA's ongoing research program in this area. SIGA's antibiotic research team has also identified novel targets to be used in the development of new classes of both Gram-negative and broad-spectrum antibiotics. Its lead program, a vaccine targeting strep throat (StreptImmune), is being developed through a partnership with the National Institute of Allergy and Infectious Diseases (NIAID).

Toyama Chemical Company

Toyama Chemical Company is a pharmaceutical manufacturer with interests across several industries, including industrial chemicals, consumer products and foods. The pharmaceutical arm is involved in antibiotics, cardiovascular drugs and other treatments. Among products in the development stage, garenoxacin (T-3811, BMS-284756), a new type of quinolone, is in phase III clinical trials. Toyama has licensed out garenoxacin to **Bristol-Myers Squibb**, and is developing it jointly with Bristol-Myers Squibb's subsidiary in Japan. The company is also developing pazufloxacin, an injectable quinolone, jointly with **Mitsubishi Pharma**. Pazufloxacin was launched in Japan in October 2002 under the tradenames Pasil and Pazucross.

Versicor

Versicor, Inc. is a biopharmaceutical company committed to discovering, developing and commercializing novel, broad-spectrum antifungal and antibiotic agents. Its lead products anidulafungin, a novel antifungal agent, and dalbavancin, a novel antibiotic for the treatment of serious Gram-positive infections, are in the advanced stages of clinical development. Versicor also has a partnered oxazolidinone project with **Pharmacia** and the VRC series, a novel bactericidal class of antibiotics emanating from internal research.

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XOMA

XOMA develops products to treat cancer, immunological and inflammatory disorders and infectious diseases. XOMA is currently building a pipeline of new anti-infectives from a human host-defense protein called BPI (bactericidal/permeability-increasing protein). BPI-derived proteins have been

shown to enhance the power of antibiotics, in some cases making resistant organisms susceptible. BPI kills bacteria, neutralizes endotoxins, enhances antibiotic activity (including activity against resistant strains), and neutralizes heparin, inhibiting angiogenesis. The lead compound opebacan (NEUPREX) is an injectable formulation of rBPI21 for systemic administration. ■

Major Pharmaceutical Conferences, April – August 2003

Date	Conference Title	Acronym	Location	Contact
28 Mar- 1 Apr 2003	Annual Meeting of the American Pharmaceutical Association	APhA	New Orleans, LA	American Pharmaceutical Association Phone: 1-202-628-4410 Fax: 1-202-628-0035.
29 Mar-4 Apr 2003	HIV Vaccine Development: Immunological and Biological Challenges		Barff, Canada	Customer Service. Phone: 800-253-0685 970-262-1230. Fax: 970-262-1525 Email: info@keystonesymposia.org
29 Mar-5-Apr 2003	55th Annual Meeting of the American Academy of Neurology	AAN	Honolulu, HI	http://am.aan.com/
30 Mar-2 Apr 2003	Annual Meeting of the American College of Cardiology	ACC	Chicago, IL	American College of Cardiology Resource Center. Phone: 800-253-4636 301-897-2694. Email: resource@acc.org
30 Mar-3 Apr 2003	Global Asthma Conference		Tel Aviv, Israel	Israel Glazer, M.D., P.O. Box 50006, Tel Aviv 61500, Israel. Phone: 97-235-140-000 Fax: 97-235-140-077 Email: asthma@kenes.com
31 Mar-3 Apr 2003	Drug Discovery Technology 2003 - European Congress - Where Sciences Meets Business		Stuttgart, Germany	http://www.drugdisc.com/ default.asp?source=septddd
1-4 Apr 2003	20th Annual General Meeting of the British Society of Rheumatology	BSR	Manchester, United Kingdom	Phone +44 (0) 20 7242 3313 Fax +44 (0) 20 7242 3277 Email: conferences@rheumatology.org.uk https://secure1.merchantservices.net/bsrcon1/
2-5 Apr 2003	Annual Meeting of the American Society for Clinical Pharmacology & Therapeutics		Washington, D.C.	ASCPT, 528 N Washington Street, Alexandria VA 22314, USA Phone: 1-703-836-6981 Fax: 1-703-836-5223 Email: meetings@ascpt.org
5-9 Apr 2003	94th Annual Meeting of the American Association for Cancer Research	AACR	Washington, D.C.	Meetings Department. Phone: 215-440-9300 Fax: 215-351-9165 Email: meetings@aacr.org
5-8 Apr 2003	13th Annual Scientific Meeting of the Society for Healthcare Epidemiology of America	SHEA	Arlington, VA	http://www.shea-online.org/ Annmtg.html#AM2003