

Expanding the therapy window for infectious disease

Intercell invests in antibody technology

Intercell AG has achieved recognition by its peers for being one of the few small European biotechnology enterprises to get its own global registration for a proprietary pharmaceutical product. In 2009, the company successfully won European, US and Australian approval for a prophylactic vaccine to treat Japanese encephalitis, a sometimes fatal viral infection.

Now the Austrian company is taking another pioneering step. This is to invest in monoclonal antibody technology for infectious disease – something that has been neglected by the pharmaceutical industry for 30 years.

On 6 May 2010, Intercell announced the signing of an agreement with Cytos Biotechnology Ltd of Switzerland to buy that company's assets in monoclonal antibody discovery (please see story on page 14).

The technology is based on the expression cloning of monoclonal antibodies from human B-cells and enables the identification of antibodies for both prophylactic and therapeutic use. Intercell is paying €15 million for the assets, which also include some preclinical, anti-infective antibody candidates discovered by Cytos. The Cytos scientists who developed the technology are moving to the Austrian company.

In separate interviews with *MedNous*, Reinhard Kandra, the company's chief financial officer, and Alexander von Gabain, its co-founder and now, strategic advisor, explained how Intercell plans to use the Cytos technology to strengthen its position in infectious disease.

Founded in 1998 as a spin-out from Vienna University, Intercell has one vaccine on the market and a pipeline of eight clinical-stage vaccines targeting bacteria or viruses that cause infectious disease. In addition it has four antibody programmes in preclinical development against infectious diseases acquired in hospitals or care homes. The company's pipeline is supported by three separate technology platforms that address different aspects of the discovery and development process. These are an antigen identification platform, a platform for developing adjuvants and a patch delivery technology.

The Cytos technology will reinforce the company's still limited portfolio of antibody products. More importantly, Intercell will be able to leverage the new asset by combining it with its own antigen identification technology.

Mr Kandra put it this way: "The nice thing is that by combining this [the Cytos assets] with our technology we will have the full tool box that you need to develop antibodies in infectious disease. We will identify the target antigens, and then find the right antibodies – rapidly."

The concept of developing monoclonal antibodies for infectious disease is not new. In fact, the first clinical trials with anti-infective antibodies go back about 30 years. But the pharmaceutical industry has invested very little money in it, and the small number of clinical trials that have been undertaken either failed or were abandoned. According to research published in *Nature Reviews Drug Discovery*, 11 clinical trials of anti-infective products were started in the 1980s compared with 59 trials of monoclonal antibodies for other indications, mainly cancer. Of the 11 anti-infective products, five advanced to Phase 2, three to Phase 3 and two went into registration. Neither application was approved.¹

In the following decade, only 13 monoclonal antibodies were tested for anti-infective diseases compared with more

than 127 for other indications. But at the end of this decade, in June 1998, the US Food and Drug Administration approved palivizumab (Synagis), a monoclonal antibody developed by MedImmune (now AstraZeneca), as a treatment for respiratory syncytial viral (RSV) infections in high-risk infants. To date, Synagis is the only anti-infective antibody on the market.

However, AstraZeneca has developed another antibody for RSV infection, motavizumab, which is under review at the FDA. This product recently encountered an obstacle. On 2 June, the FDA's Antiviral Drugs Advisory Committee voted 14 to 3 to recommend against

the licensing of motavizumab. The FDA is not obliged to follow the advice of its advisory committees but usually it does. It couldn't be immediately determined why the committee opposed a licence. But AstraZeneca said it will work with the FDA to address the issues. It noted that motavizumab was compared head-to-head with Synagis and met its primary endpoint of non-inferiority.²

Why has the pharmaceutical industry shown so little interest in developing monoclonal antibodies for infectious diseases? Cost of development is one reason. Another is competition from vaccines and antibiotics for the same markets. "The reason why no therapeutic antibodies were developed in the past for many diseases is that they seemed perfectly under control by antibiotics," Mr Kandra commented.

Intercell believes that the market situation has now changed because of a huge rise in the number of antibiotic-resistant bacteria, such as *Staphylococcus aureus* and *E. coli*. Indeed, in September 2009, the European Medicines Agency and the European Centre for Disease Prevention and Control issued a report documenting the need for new antibacterial agents. It said that each year about 25,000 patients in the

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European Union die from an infection resulting from a multidrug-resistant bacteria, and called on industry to invest in new products. But should this be new antibiotics, new antibodies, or both?

Mr Kandra and Dr von Gabain argue that monoclonal antibodies will be a good weapon against the toughest bacteria because they are modelled after natural antibodies which are the body's first line of defence against disease.

History of antibodies

Antibodies are very specific, naturally evolved molecules that recognise and eliminate disease antigens. In fact, before the first antibiotic, penicillin, was discovered by Alexander Fleming in 1928, an antibody treatment known as serum therapy was widely used against infectious diseases such as smallpox and meningitis.³ Serum therapy was derived from the sera of immunised animals. The arrival of antibiotics effectively ended this practice.

Monoclonal antibodies came onto the scene in the latter part of the 20th-century. But modern antibodies have mostly been developed for cancer and immunological diseases.

By developing monoclonal antibodies for infectious disease, Intercell is, effectively, turning the clock back. But it is doing so with new technology. The Cytos discovery platform involves the isolation of B cells, the white blood cells that produce natural antibodies, from the blood of human donors. The human antibody genes, or blueprints, are then transformed into baby hamster kidney cells, which are screened for antigen-specific antibodies. Using this technology, fully human monoclonal antibodies have been isolated within about three months.⁴

Dr von Gabain said the Cytos technology is faster and more relevant to the production of anti-infective antibodies than phage display, which is the conventional method for generating monoclonal antibodies.

"What does an antibody do? An antibody binds to an antigen. But in the infectious disease arena it often also binds with the free end on the other side; it binds to the bacteria or the virus and it binds to the complement, which is the biological entity that helps to decontaminate the bacterium or virus from the blood stream. Anti-infective antibodies interact specifically with a follow-up cascade of the immune system. But if you have an artificial antibody, even though it is built on human sequences which come out of phage display, you do not necessarily have a functional antibody," he commented.

"Phage display is not inadequate, but it takes a long time because you are not really starting up from the human repertoire, you are starting up from an abstract repertoire," he added.

The executives said that the combination of the Cytos platform and Intercell's repertoire of antigen targets will make it possible to identify candidate monoclonal antibodies that are relevant to infectious disease in three to six months. They hope to be able to move a new anti-infective antibody or antibodies into clinical development in one to

two years. Intercell's antigen identification technology has already thrown up antigens that are cross-protective against strains of the toughest bacteria. These include strains of pneumococcal bacteria, and also a large number of Group B *Streptococcus* strains, said Dr von Gabain.

A number of Intercell's clinical programmes are already partnered with large pharmaceutical companies. For example, the company has a prophylactic vaccine against *Staphylococcus aureus* in Phase 2/3 development with Merck & Co. It is also working with Merck on a preclinical antibody against *S. aureus*. Both programmes use antigens identified by Intercell. The antigens can not only be recognised by antibodies, but they also play a role in helping the bacteria acquire iron. Therefore, any antibody targeting this antigen would block a mechanism linked to the survival of the bacteria.

"We have, for the most important pathogens, like pneumococci and Group B *Streptococcus*, identified antigens that are nicely recognised by cognate antibodies but which also have pivotal functions. This is a nice, validated portfolio of antigens which we would now like to use to develop anti-infective antibodies," Dr von Gabain commented.

Antibodies for hospital infections

Intercell plans to deploy its first antibodies in a hospital, rather than a community setting. One possible target are infants borne prematurely and who are at risk of infection from Group B *Streptococcus*. At the same time, the company will be developing a number of antibodies that were acquired from Cytos and target viral infections. These products could be ready for registration before or at around the same time as the first anti-bacterial antibodies.

Intercell's antibody strategy doesn't at the moment include tuberculosis, though the company does have a prophylactic vaccine against TB in Phase 1/2.

"I think TB is not the ideal example for antibodies. But there are people who believe that if once you are diseased, maybe antibodies can help you get the disease under control. But this needs to be shown," Dr Von Gabain said.

Intercell is investing heavily in research and development. Indeed, according to Mr Kandra, it will spend all of its revenues in 2010 on research and development. "It is important for investors to know that the company's strategy is not to maximize its profit at this stage but to maximize the future value of the company by investing as much as we can afford into R&D," the executive commented.

MedNous interviewed Reinhard Kandra in Zurich, Switzerland on 20 May 2010 and Alexander von Gabain by telephone on 31 May.

Sources: 1. Anti-infective monoclonal antibodies: perils and promise of development, *Nature Reviews Drug Discovery*, March 2006. 2. Personal communication, AstraZeneca, 3 June 2010. 3. Therapeutic antibodies for human diseases at the dawn of the twenty-first century, *Nature Reviews Drug Discovery*, January 2003; The use of antibodies in the treatment of infectious disease, *Singapore Medical Journal*, 2009; 50(7). 4. Isolation of human monoclonal antibodies by mammalian cell display, *Proceedings of the National Academy of Sciences*, 2008 105.