Immunotherapies and Vaccines for Nontraditional Indications

by Lucy J. Sannes, PhD, MBA

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by Lucy J. Sannes, PhD, MBA

About the Author

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Executive Summary

The earliest immunotherapies were vaccines that stimulate the immune system’s response against infectious agents, providing protection against those diseases. Vaccines and immune globulin preparations (passive immunotherapies) have been used for many years to enhance the immune system’s response against infectious diseases. More recently, a number of monoclonal antibodies have been commercialized for treatment of cancer, and a number of active immunotherapies and vaccines that stimulate the immune response against cancer are being developed. These applications of immunotherapy focus on the benefits of the immune system when it is working correctly, and the potential beneficial therapies that may be developed by enhancing the immune response.

In contrast, sometimes a person’s immune system goes awry, either attacking the person’s own body, or overreacting or producing an exaggerated response to a foreign substance that is normally harmless to most people. In these situations, therapies are needed to suppress or modulate the unwanted immune response. Therapies that suppress or modulate the immune response are currently available. More are being developed for treatment of autoimmune diseases, treatment of allergies, or prevention of transplant rejection.

These are the most well-known applications of immunotherapies and vaccines that enhance the immune system. However, many other applications are possible. Research and development of immunotherapies for these other indications has been progressing for many years, even though this effort has not received the public attention that the work on infectious disease and cancer immunotherapies and vaccines has seen. This report discusses many of these other applications of monoclonal antibodies, therapies derived from antibodies, vaccines, and therapies that modulate the immune response for treatment of a wide range of disorders and diseases.
Some of the emerging therapies discussed in this report have been developed for treatment of diseases that are caused by the immune system including inflammatory diseases (diseases resulting from the immune response) and also disorders resulting from changes in the complement system. However, there are also other disorders included in this report that are not immune-mediated diseases or the result of the immune response. For these disorders, antibodies are being used as tools to block targeted proteins that have a role in the disease process. These antibodies may be delivered passively, or they may be generated by the patient’s own body in response to a vaccine.

Chapter 2 discusses the progress in developing immunotherapies and vaccines for treatment of Alzheimer’s disease. Several immunotherapies that target beta amyloid are in development, including both monoclonal antibodies and vaccines. The most advanced is bapineuzumab, which is in Phase III development by Johnson & Johnson and Pfizer (formerly Elan and Wyeth). In this chapter, the pathophysiology, epidemiology, and current therapy of Alzheimer’s disease are discussed. This is followed by a section that discusses why companies are developing antibodies and vaccines for treatment of Alzheimer’s disease. The next section of Chapter 2 discusses many of the emerging immunotherapies for Alzheimer’s disease that have reached clinical development. Even more emerging immunotherapies for this indication are included in a table that accompanies this section. The final section of this chapter discusses business considerations for companies that are developing immunotherapies for treatment of Alzheimer’s disease.

Similar sections are included in each of the subsequent chapters about different disease indications. Chapter 3 discusses immunotherapies that are being developed for treatment of two different addictions: nicotine and cocaine. With these immunotherapies, antibodies are either passively administered or are produced by the patient’s body in response to a vaccine. The antibodies then bind to either nicotine or cocaine, creating a large molecule that cannot be transported across the blood-brain barrier. Immunotherapies are being developed for a wide range of different neurological indications, and several of these additional indications are discussed in Chapter 4 and/or are included in a table of therapies in development that accompanies Chapter 4. These additional neurological conditions include pain, multifocal motor neuropathy, treatment of pain in dental patients undergoing third-molar extraction, treatment of ankylosing spondylitis, rheumatoid arthritis, chronic low back pain, endometriosis, the pain associated with cancer that has metastasized to the bone, blocking a protein that inhibits axonal regeneration (for treatment of stroke), and Parkinson’s disease.
Immunotherapies (including antibodies and vaccines) are also being developed for treatment of different cardiovascular disorders. These are discussed in Chapter 5. The targeted cardiovascular disorders include angina, atherosclerosis, dyslipidemia, hypertension, venous thromboembolism, and digoxin toxicity. Chapter 6 discusses the development and use of immunotherapies for hematological disorders including idiopathic (immune) thrombocytopenic purpura (ITP), paroxysmal nocturnal hemoglobinuria (PNH), and Rh incompatibility and hemolytic disease of the newborn (HDN).

Antibodies can also be used for treatment of ophthalmic diseases. As discussed in Chapter 7, Lucentis (ranibizumab) is an antibody fragment that binds to and inhibits VEGF. It is FDA approved for treatment of neovascular (wet) age-related macular degeneration. It is also in late-stage clinical development for additional ophthalmic indications. A human monoclonal antibody against VEGF, Genentech’s/Roche’s Avastin (bevacizumab), is FDA approved for treatment of colorectal cancer, non-small cell lung cancer, breast cancer, and glioblastoma. While Avastin is not approved for treatment of wet AMD, it is also used for this indication. Other examples of ophthalmic diseases for which antibodies are being developed include diabetic retinopathy and diabetic macular edema, retinal vein occlusion, and uveitis.

Chapter 8 discusses the development of antibodies for treatment of osteoporosis and other bone metabolism disorders. The most advanced of these is Amgen’s denosumab, which is a human monoclonal antibody that targets the receptor activator of nuclear factor kappa beta ligand (RANKL). Denosumab has been submitted to the FDA. Ablynx (Belgium) is developing nanobodies that target RANKL. These are in preclinical development. In addition, Amgen (with UCB Pharma) is also developing Sclerostin Ab, a humanized antibody that targets the protein sclerostin.

In addition, multiple monoclonal antibodies are being developed for treatment of type 2 diabetes. Three companies are developing antibodies that target IL-1 beta, a pro-inflammatory cytokine that stimulates the immune response. The second molecule being targeted by a monoclonal antibody in development for type 2 diabetes is the glucagon receptor. These are discussed in Chapter 9.

In addition to all of these activities in neurology, cardiovascular disease, hematology, ophthalmology, osteoporosis, and type 2 diabetes, many additional antibodies, antibody-based drugs, and other immunotherapies/anti-inflammatory drugs are being developed to treat a
wide range of indications. Several examples of those that have reached clinical development are discussed in Chapter 10, and even more are included in the table that accompanies Chapter 10.

This report also includes seven interviews with experts in the application of antibodies, antibody-derived therapies, and vaccines to the treatment of various diseases included in this study. These experts discuss the progress, challenges, and hurdles faced by researchers and companies working in this field.
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<thead>
<tr>
<th>Company</th>
<th>Product/Technology</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
</table>
| ESBATech | Antibody fragments | In development | ESBATech is a spin-out of the University of Zurich and is focusing on development of human antibody fragments for therapeutic applications. In February 2008, researchers at ESBATech and the University of Zurich published a paper entitled “Antibody-based approaches in Alzheimer’s research: safety, pharmacokinetics, metabolism, and analytical tools.” This paper includes a discussion of the potential use of antibody fragments for treatment of Alzheimer’s disease. [Lightlen P, Mohajeri MH. J Neurochem. 2008;104:859–74.]
| Genentech (part of Roche) and AC Immune | Anti-Abeta (MABT5102A) | Phase I | Humanized monoclonal antibody that binds to amyloid beta (Abeta) For Alzheimer’s disease Generated using AC Immune’s supramolecular antigen technology |
| GlaxoSmithKline | GSK933776A (933776) | Phase I | Monoclonal antibody For Alzheimer’s disease |
| JANSSEN Alzheimer Immunotherapy (Part of Johnson & Johnson) and Pfizer (Formerly being developed by Elan and Wyeth) | Bapineuzumab (AAB-001) | Phase III | Humanized monoclonal antibody For mild to moderate Alzheimer’s disease Phase III - intravenous formulation Phase II - subcutaneous formulation |

Continued
Even though pharmacological therapies have been available to aid in smoking cessation, many people who try to quit are not successful. As previously mentioned, the CDC reports that 70% of US smokers report they want to quit. The CDC also reports that more than 40% of adult smokers try to quit smoking each year. However, as demonstrated by the continued high numbers of cigarette smokers, many of these attempts to quit are not successful.

3.2. Why Immunotherapies for Addiction?

The immunotherapies currently being developed for treatment of addiction are vaccines that stimulate the body to generate antibodies against the targeted drug. These antibodies bind to the drug molecule (such as cocaine or nicotine), creating a large molecule that cannot be transported across the blood-brain barrier. Thus, these immunotherapies block the pleasurable effect of the drug molecule. However, immunotherapies do not reduce cravings for the drug and do not treat the symptoms of withdrawal. As a result, immunotherapies (if successfully developed) are likely to be most effective when used in combination with other approaches (including psychosocial approaches) for treatment of addiction.

In theory, immunotherapies for treatment of addiction could be either vaccines or passive immunotherapies such as monoclonal antibodies. As discussed in the following section, the four immunotherapies in development today are all vaccines, or active immunotherapies, that stimulate the patient’s immune system to produce antibodies that target and bind to the drug. A potential advantage of vaccines is that they may generate longer-term protection. However, it is possible that booster injections may be required to maintain the vaccine’s effect. The following section (on companies developing immunotherapies for cocaine or nicotine addiction) discusses some of the available data on how long antibodies were present following injection.

Passive immunization with monoclonal antibodies offers the theoretical advantage of a faster response to the drug, and so it might be possible to use this approach for treatment of acute intoxication or overdose. However, antibodies administered via passive immunotherapy are not likely to last as long in the bloodstream as antibodies generated in response to a vaccine.

As discussed in the following section, all of the immunotherapies for treatment of addiction that are in clinical development today are
### Table 6.4. Emerging Immunotherapies for Treatment of Hematology/Blood Disorders (cont.)

<table>
<thead>
<tr>
<th>Company</th>
<th>Product/Technology</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Apitope Technology | ATX-iF8 program    | Preclinical (as of 10/08) | Apitopes: Peptide vaccines to restore balance of the immune system; for treatment of autoimmune diseases and allergies  
|                  |                    |                 | Apitopes to prevent Factor VIII inhibitor formation identified           |
|                  |                    |                 | For hemophilia-A                                                         |
| LFB             | Anti-Rhesus D Monoclonal Antibody | Phase I | For prevention of fetomaternal alloimmunization (mother-child Rhesus incompatibility)  
|                  |                    |                 | Phase I being conducted in healthy volunteers                           |
| ThromboGenics   | Anti-VPAC          | Preclinical     | Antibody against VPAC1 (Vasoactive Intestinal Peptide/Pituitary Adenylyl Cyclase-Activating Peptide Receptor 1)  
|                  |                    |                 | VPAC is a receptor on the surface of megakaryocytes (bone marrow cells that produce platelets). Inhibiting VPAC promotes differentiation of megakaryocytes to form platelets.  
|                  |                    |                 | For treatment of thrombocytopenia (low platelet counts), a side effect of chemotherapy |

*Source: Sannes & Associates, Inc.*

### Alexion Pharmaceuticals’ Soliris (eculizumab)

Alexion Pharmaceuticals markets Soliris (eculizumab), which was approved by the FDA in March 2007 for treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. With this approval, Soliris became the first drug to be approved for treatment of PNH, a rare disorder that is discussed in Section 6.1. In June 2007, Soliris was approved in the European Union for treatment of patients with PNH.

Soliris is a terminal complement inhibitor. It is a monoclonal antibody that binds to the complement protein C5, preventing cleavage of this protein to form C5a and C5b. As discussed in Section 6.2, in patients with PNH, the red blood cells are hemolyzed (destroyed) by complement.
ESBATEch’s ESBA105

ESBATEch’s lead product candidate is a humanized single-chain (scFv) antibody fragment directed against tumor necrosis factor alpha (TNF alpha), called ESBA105. Much of the company’s development effort with ESBA105 is focused on ophthalmology indications, as discussed below. In addition, intra-articular administration of ESBA105 is being evaluated for treatment of patients with severely painful osteoarthritis of the knee (see Chapter 10).

TNF-alpha is a cytokine involved in the immune response. Multiple agents that block binding of TNF-alpha to its receptor are on the market and in development for treatment of rheumatoid arthritis and certain other autoimmune diseases. These are discussed in a separate, upcoming Insight Pharma Report titled *Immunotherapies That Suppress or Balance the Immune Response*. An agent that blocks TNF-alpha may also be useful for treatment of inflammatory conditions of the eye. ESBA105 is administered topically via eye drops and has been evaluated in a Phase I study in healthy volunteers. This study began in April 2008 and in September 2008, ESBATEch announced its successful completion.

ESBA105 is currently being evaluated for ophthalmic indications in two clinical trials. In February 2009, ESBATEch announced the start of a Phase Ib/Ila clinical study in patients undergoing cataract surgery. This is a randomized, double-blind, placebo-controlled, parallel-assignment study that is expected to include about 90 patients. Later in February 2009, ESBATEch announced the start of a Phase II study evaluating ESBA105 in patients with uveitis.

In addition, in March 2009, ESBATEch announced that ESBA105 had demonstrated efficacy in a preclinical study in a model for choroidal neovascularization (CNV). CNV occurs in patients with wet AMD and results in the formation of new blood vessels behind the retina that can bleed, leading to scarring and vision loss.

Genentech’s and Novartis’ Lucentis (ranibizumab)

Genentech, which is now part of Roche, developed Lucentis (ranibizumab). As mentioned, Lucentis is an antibody fragment that binds and inhibits VEGF and is FDA approved for treatment of wet AMD. Genentech licensed Lucentis to Novartis, which has worldwide rights outside the United States for this antibody.
Table 9.1. FDA-Approved Drugs for Treatment of Type 2 Diabetes (cont.)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Company</th>
<th>Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin and glyburide</td>
<td>Glucovance and generics</td>
<td>Bristol-Myers Squibb and generic companies</td>
<td>--</td>
</tr>
<tr>
<td>metformin and pioglitazone</td>
<td>Actoplus Met, Actoplus Met XR</td>
<td>Takeda</td>
<td>--</td>
</tr>
<tr>
<td>metformin and repaglinide</td>
<td>PrandiMet</td>
<td>Novo Nordisk</td>
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</tr>
<tr>
<td>metformin and rosiglitazone</td>
<td>Avandamet and generic</td>
<td>GlaxoSmithKline and Teva Pharmaceutical</td>
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</tr>
<tr>
<td>metformin and sitagliptin</td>
<td>Janumet</td>
<td>Merck &amp; Co.</td>
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</tr>
<tr>
<td>pioglitazone and glimepiride</td>
<td>Duetact</td>
<td>Takeda</td>
<td>--</td>
</tr>
<tr>
<td>rosiglitazone and glimepiride</td>
<td>Avandaryl</td>
<td>GlaxoSmithKline</td>
<td>--</td>
</tr>
</tbody>
</table>

(Note: Drugs in this table do not include the numerous insulins that are on the market.)

Source: Sannes & Associates, Inc.

9.2. Why Monoclonal Antibodies for Type 2 Diabetes?

Monoclonal antibodies can be used to bind and block the activity of a targeted molecule in the body that is involved in the disease process. For type 2 diabetes, two different molecules are being targeted by monoclonal antibodies that are in development: interleukin-1 beta (IL-1 beta) and glucagon receptor.

IL-1 is a pro-inflammatory cytokine that stimulates the immune response. There are two forms of IL-1: IL-1 alpha and IL-1 beta, which have similar activity and bind to interleukin-1 receptor. In 2001, the FDA approved Kineret (anakinra), a recombinant form of the interleukin-1 receptor antagonist (IL-1RA), a naturally occurring inhibitor that blocks the binding of IL-1 to its receptor.

Kineret is FDA approved for the treatment of rheumatoid arthritis and was developed by Amgen. In September 2008, Amgen licensed Kineret to Biovitrum (Sweden). While Amgen did not develop Kineret for treatment of type 2 diabetes, academic researchers at the University Hospital of Zurich, University of Zurich (Switzerland) and Steno Diabetes Center (Denmark) have evaluated Kineret in patients with type 2 diabetes. Amgen donated the Kineret used in this study. In 2007, these researchers published the results of a double-blind, parallel-group
Dr. Holz: Beyond the formatting advantage, there is potential for multiple routes of administration for Nanobodies. This differentiates them from monoclonal antibodies and other scaffolds. Most conventional antibodies are either given through the vein (intravenous route) or through the skin (subcutaneous route). But it is always by injection, which means that there is a needle attached to a syringe.

For our Nanobodies in initial clinical development (because we want to go as fast as possible into the clinic), we always consider the injection route.

Our anti-thrombotic Nanobody is administered via intravenous injection but can also be given subcutaneously in our second program, which is a little bit more convenient for patients. And, for our Nanobody program in the osteoporosis field, we have gone immediately into the subcutaneous form of administration.

In your mouth, in your throat, in your nose, and also in your lungs, you have many active proteins and enzymes that are designed to cut down other proteins that enter the nose or the mouth. This is a pretty hostile
Institute

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