Immunology: from books and bench to bedside

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The time has passed when immunology was just another basic science discipline in the first years of medical school that students needed to memorize enough to pass examinations and not to worry much thereafter depending on the specialty pursued. Nowadays, the understanding of immunological mechanisms is increasingly essential in many disciplines because most diseases have a component of inflammatory response along side the inciting agent as part of the pathogenesis of their clinical manifestations and also as part of tissue repair from damage. Besides the involvement of the immune system in diseases of other organ systems, many new immunological diseases have been recognized from deficient, exaggerated and misdirected immunological responses. The detailed knowledge of immunological mechanism of disease pathogenesis down to molecular mechanisms has been possible because of the tremendous advances in basic immunology and application of that knowledge and tools to patients.

Immunology-based therapies account for major advances in medicine (Table 1). Over a century ago when immunology was in its birth, scientists were already using killed microbes as vaccines and heterologous antibodies as antidotes. Despite rudimentary knowledge of the mechanisms of those treatments, physicians had remarkable successes and many of those treatments are still used today in refined forms. Killed microbes or parts of them are used in vaccines, which are highly successful to prevent infectious. Indeed, vaccines are the most important advance in medicine for its role in markedly preventing morbidity and mortality worldwide, particularly in children, caused by infectious diseases including poliomyelitis, measles, mumps, diphtheria, tetanus, varicella, influenza, hepatitis A and B, yellow fever, rabies and invasive bacterial infections caused by *Haemophilus influenzae*, meningococci and *Streptococcus pneumoniae*. Still, enormous challenges lie ahead such as malaria, tuberculosis and HIV infection. Since 1911, vaccines have also been successful in secondary prevention of symptoms in already established disease as in the case of IgE-mediated hypersensitivity respiratory allergies, and later, insect anaphylaxis. Vaccines prime the immune system to respond to infectious agents so that when an infection occurs, it elicits a fast and intense memory immune response that clears the infection. In the case of allergic diseases, vaccines modify the exaggerated hypersensitivity immune response to an attenuated and less damaging response.

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Table 1 - Immune-based treatments in clinical use

Drug	Type	Mechanism of Action	Indications
Vaccines	Proteins	Induce primary immune response or alter IgE-mediated hypersensitivity responses.	Prevention of infectious diseases and treatment for respiratory and insect IgE-mediated allergies.
Antiserum	Heterologous polyclonal antibody	Binding and neutralization of toxin.	Snake and insect bites and poisoning.
Glucocorticoids	Small molecules	Inhibits several inflammatory mediators.	Auto-immune and hypersensitivity disorders
Non-steroidal anti-inflammatory drugs	Small molecules	Inhibits prostaglandins.	Analgesia and inflammatory conditions.
Immunosuppressants: Calcineurin inhibitors (cyclosporine, tacrolimus)	Small molecules	Inhibits calcineurin and transcription factors in T cells.	Auto-immune diseases and graft rejection.
Immunosuppressants: DNA metabolism inhibitors	Small molecules	Methotrexate inhibits folate metabolism, azathioprine and mycophenolate inhibit nucleotide metabolism.	Rheumatoid arthritis and graft rejection.
Immunoglobulins	Polyclonal IgG purified from donors	Binding to antigen, and in high doses, inhibits autoantibodies.	Replacement in antibody deficiency, and few autoimmune diseases.
Interferons alpha, beta and gamma	Recombinant proteins	Stimulate interferon receptors.	Chronic hepatitis B and C, multiple sclerosis, and chronic granulomatous disease, respectively.
Granulocyte colony stimulating factor	Recombinant protein	G-CSF stimulates neutrophil production in bone marrow.	Neutropenia.
Interleukin 11	Recombinant protein	IL-11 stimulates platelet production in bone marrow.	Thrombocytopenia
Leukotriene antagonists	Small molecule	Inhibit binding to receptors or synthesis.	Asthma and allergic rhinitis.
Anti-CD3	Murine monoclonal antibody	Binds to CD3 and kills T cells.	Graft rejection.
Anti-IgE	Humanized monoclonal antibody	Binds to IgE and prevents binding to its receptor.	Asthma. Rheumatoid arthritis
TNFa antagonists: (Ethercept[E] and remidcade [R])	E is a fusion protein of TNFa receptor and Fc IgG1.	Binds to TNFa and prevents binding to its receptor.	and Crohn's disease.
Interleukin 1 receptor antagonist	R is a humanized monoclonal antibody Recombinant protein	Binds to IL-1 and prevents binding to its receptor.	Rheumatoid arthritis.
Interleukin 2 receptor antagonists (Denileukin diflitox [D] and basiliximab [B])	Fusion protein of diphtheria toxins A and B and interleukin 2 (D). Humanized monoclonal antibody to CD25 (B)	Binds to CD25 (IL-2Ra) bearing T cells killing them.	CD25(+) persistent cutaneous T-cell lymphoma [D], and renal transplant rejection (B).
Anti-CD52 (Alemtuzumab)	Humanized monoclonal antibody	Binds to CD52 on normal and malignant B and T cells, NK cells, monocytes, and macrophages.	Refractory B-cell chronic lymphocytic leukemia.
Anti-CD33 (Gemtuzumab)	Fusion protein of humanized monoclonal IgG4 and calicheamicin	Binds to CD33 on leukemic blasts and immature normal myelomonocytic cells.	Refractory CD33 positive acute myeloid leukemia.

TNF: Tumor necrosis factor. Sources: http://www.fda.gov/cber/label/label.htm

Besides using the etiological agents to alter immune system as therapeutic tools, many decades ago physicians were also using another immunological therapy: antibodies. Antiserum developed in animals against specific toxins and used in patients was once thought to potentially cure many diseases, but soon hypersensitivity reactions to these treatments with repeated used (e.g. serum-sickness) precluded their use in recurrent or chronic diseases. However, still today, antiserum to snake and arachnid venoms are used clinically. Advances in immunology and biochemistry of protein synthesis have allowed modification of these treatments and repeated use. Instead of polyclonal antibodies, we now use monoclonal antibodies made in animals, and in addition, amino acids are changed to those of human immunoglobulins except for the amino acids that significantly impair binding affinity to the antigen. As a result, these humanized monoclonal antibodies have 95% or more of human amino acid sequences and are less immunogenic themselves allowing chronic repeated use. Therefore, clinicians now can now treat chronic or recurrent diseases with antibodies, such as using anti-IgE to treat asthma.

Advances in basic sciences led to development of other targeted treatments. Advances in biochemistry and biophysics allow scientists to determine the three-dimensional structure of proteins and the exact binding sites between soluble ligands and their receptors, or between surface proteins. This knowledge is essential for scientists to design small molecules able to block binding and downstream signals (e.g. inhibition of binding between adhesion molecules). Advances in immunology helped us understand that soluble receptors are natural inhibitors, which are now used therapeutically (e.g. interleukin 1 and TNF alpha inhibitors). Advances in genetics led to recombinant DNA technology and synthesis of human proteins in the laboratory for therapeutic use (e.g. interleukin 2). Advances in pharmacology have improved pharmacokinetic and pharmacodynamic profile of therapeutic agents (e.g. peglated interferon). Taken together, all these advances have allowed deep and detailed understanding of immunological mechanisms in the pathogenesis of diseases, which is now being exploited to develop therapies targeting specific immunological molecules or specific immune effector functions to treat patients with allergic, infectious, neoplastic and autoimmune disorders.

It has taken several decades for the tremendous advances in basic immunology to be translated into new treatments. However, biotechnology today allows this path to be completed at a faster pace. New molecules or pathways discovered in basic science can be investigated in disease and new treatments developed in few years. Today, a large portfolio of new drug development in traditional pharmaceutical companies and new biotechnology companies involve biological agents, many designed to alter the immune system. So, the medical student today needs to develop a solid understanding in immunology to be able to properly treat patients when they finish their medical training.