

## Jeffrey Ravetch elected to Institute of Medicine

Jeffrey V. Ravetch, head of Rockefeller University's Leonard Wagner Laboratory of Molecular Genetics and Immunology, has been elected to the Institute of Medicine. Ravetch is one of 65 new members and four foreign associates whose election was announced today at the institute's annual meeting at its headquarters in Washington, D.C.

Ravetch studies the cellular and molecular mechanisms of how healthy immune cells are made to respond to specific antibodies and how a dysfunctional immune system attacks the body's own tissues. A graduate of Yale and Rockefeller Universities as well as Cornell University Medical College, Ravetch joined the faculty of Rockefeller University in 1996, and is currently Theresa and Eugene M. Lang Professor. He is the 14th current Rockefeller faculty member to be elected to the Institute of Medicine.

"Jeff's research has contributed greatly to our understanding of immunotherapy. His work is of great relevance to the fight against cancer and other devastating diseases, and this recognition of Jeff's contribution — membership to the Institute of Medicine — is very well deserved," says university president Paul Nurse.

Established in 1970 as a unit of the National Academy of Sciences, the Institute of Medicine was founded for the protection and advancement of the biomedical sciences and health professions, the promotion of research and development pertinent to health and the improvement of health care. The institute is also concerned with other areas of study as they are related to health, including the behavioral and social sciences, humanities, administration, law, the physical sciences and engineering. In pursuit of its mission, the institute conducts studies of specific problems. Institute members contribute their knowledge and professional judgment to the development of findings and the formulation of recommendations relating to public policy. With this year's election, the institute has 1,538 active members, 84 foreign associates and 70 emeritus members.

[Institute of Medicine](#)

[Other Institute of Medicine members at Rockefeller](#)

## Jeffrey Ravetch elected to American Academy of Arts and Sciences

Jeffrey V. Ravetch, an immunologist who studies how cells respond to specific antibodies, has been elected to The American Academy of Arts and Sciences, an independent policy research center that undertakes studies of complex and emerging problems. The academy announced the election this week; Ravetch, head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology, will be inducted into the academy this fall.

Ravetch's research dissects the cellular and molecular mechanisms that govern the generation of antibody specificity and the translation of that specificity into cellular responses. By identifying the genetic components that cause immune system cells to respond to specific antibodies, Ravetch hopes to gain a better understanding of how a functioning immune system protects organisms from invaders and how a dysfunctional immune system attacks the body's own tissues.

Ravetch, who is Theresa and Eugene M. Lang Professor at Rockefeller, received the American Association of Immunologists-Huang Foundation Meritorious Career Award in 2005, the Lee C. Howley Sr. Prize for Arthritis Research in 2004 and the Burroughs Wellcome Fund Award in Molecular Parasitology in 1986. He is a member of the National Academy of Sciences and its Institute of Medicine.

"Jeff's studies have revealed a great deal about antibody specificity and have helped increase our understanding of infectious and autoimmune diseases," says Rockefeller president Paul Nurse, who joined the academy in 2006. "His election to the academy is well deserved and it reflects the esteem in which he is held by his peers."

Founded in 1780 by John Adams, James Bowdoin, John Hancock and other scholar-patriots, the academy has members from diverse industries and disciplines who have made significant contributions in their fields or to society at large. Current research interests at the academy include science and global security, the humanities and culture, social policy and education. Previous generations of inductees include George Washington and Benjamin Franklin in the 18th century, Daniel Webster and Ralph Waldo Emerson in the 19th and Albert Einstein and Winston Churchill in the 20th. The current membership includes some 200 Nobel laureates and more than 60 Pulitzer Prize winners. The new class comprises 212 scholars, scientists, artists and civic, corporate and philanthropic leaders, who come from 20 states and 15 countries.

Ravetch will be honored with other elected members at a ceremony on October 11, at the academy's headquarters in Cambridge, Massachusetts.

[Science. 2008 Apr 18;320 \(5874\):373-6 18420934 \(P,S,E,B,D\)](#)

### **Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc.**

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It is well established that high doses of monomeric immunoglobulin G (IgG) purified from pooled human plasma [intravenous immunoglobulin (IVIG)] confer anti-inflammatory activity in a variety of autoimmune settings. However, exactly how those effects are mediated is not clear because of the heterogeneity of IVIG. Recent studies have demonstrated that the anti-inflammatory activity of IgG is completely dependent on sialylation of the N-linked glycan of the IgG Fc fragment. Here we determine the precise glycan requirements for this anti-inflammatory activity, allowing us to engineer an appropriate IgG1 Fc fragment, and thus generate a fully recombinant, sialylated IgG1 Fc with greatly enhanced potency. This therapeutic molecule precisely defines the biologically active component of IVIG and helps guide development of an IVIG replacement with improved activity and availability.

[J Immunol. 2008 Apr 15;180 \(8\):5670-9 18390752 \(P,S,E,B\)](#)

### **Fc $\gamma$ R1B Deficiency Leads to Autoimmunity and a Defective Response to Apoptosis in Mrl-MpJ Mice.**

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Data suggests that modulation of Fc $\gamma$ R1B expression represents a significant risk factor for the development of autoimmunity. In this study, we investigated this notion in mice that possess genetics permissible for the development of autoimmunity. To this end, Mrl-MpJ Fcgr2b<sup>-/-</sup> mice were monitored for

the development of autoreactivity. We found that FcγRIIB deficiency led to chronic B cell activation associated with increased germinal center and plasma cell accumulation in the spleen. Likewise, Mrl-MpJ FcγR2b<sup>-/-</sup> mice exhibited significant serum IgG reactivity against DNA. We further analyzed the IgG isotype contribution to the anti-dsDNA response and found increases in all subtypes with the exception of IgG3. In particular, we found large increases in IgG1 and IgG2b autoreactivity correlating with significant increases in immune complex deposition and kidney pathology. Finally, we found dendritic cells derived from Mrl-MpJ FcγR2b<sup>-/-</sup> mice greatly increased IL-12 expression upon coinubation with apoptotic thymocytes compared with wild-type controls. The results indicate that FcγRIIB is an important regulator of peripheral tolerance and attenuation of the inhibitory signal it provides enhances autoimmune disease on susceptible backgrounds. Additionally, the data indicates FcγRIIB function has a significant impact on APC activity, suggesting a prominent role in dendritic cell activity in response to interaction with particulate autoantigens.

*Annu Rev Immunol.* 2008 Apr ;26 :513-533 18370923 (P,S,E,B,D)

### **Anti-Inflammatory Actions of Intravenous Immunoglobulin.**

Falk Nimmerjahn, Jeffrey V Ravetch

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The remarkable success story of the therapeutic application of pooled immunoglobulin G (IgG) preparations from thousands of donors, the so-called intravenous IgG (IVIg) therapy, to patients with a variety of hematological and immunological disorders began more than half a century ago. Since then, the use of this primary blood product has increased constantly, resulting in the serious danger of shortages in supply. Despite its widespread use and therapeutic success, the mechanisms of action, especially of the anti-inflammatory activity, are only beginning to be understood. In this review, we summarize the clinical use of IVIg for different diseases and discuss recent data on the molecular mechanisms that might explain how this potent drug mediates its activity in vivo.

*Methods Mol Biol.* 2008 ;415 :151-62 18370153 (P,S,E,B)

### **Analyzing antibody-fc-receptor interactions.**

Falk Nimmerjahn, Jeffrey V Ravetch

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Cellular receptors for immunoglobulins (Fc-receptors; FcR) are central mediators of antibody-triggered effector functions. Immune complex (IC) binding to FcRs results in a variety of reactions such as the release of inflammatory mediators, antibody dependent cellular cytotoxicity (ADCC) and phagocytosis of ICs. Analyzing antibody-FcR (Ab-FcR) interactions in vitro is essential to determine the effector mechanisms,

binding characteristics and affinity parameters that will impact and predict antibody activity in vivo. The methods described in this chapter include the generation of ICs and soluble FcR variants, as well as ELISA and FACS-based assays to study Ab-FcR interactions.

*Biotechniques*. 2008 Feb ;44 (2):169, 171 18330345 (P,S,E,B)

### **Closing the circle. Jeffrey V. Ravetch, M.D., Ph.D. Interview by Lynne Lederman.**

Jeffrey V Ravetch

*J Immunol*. 2008 Feb 1;180 (3):1948-53 18209093 (P,S,E,B)

### **Differential Contribution of Three Activating IgG Fc Receptors (Fc{gamma}RI, Fc{gamma}RIII, and Fc{gamma}RIV) to IgG2a- and IgG2b-Induced Autoimmune Hemolytic Anemia in Mice.**

Lucie Baudino, Falk Nimmerjahn, Samareh Azeredo da Silveira, Eduardo Martinez-Soria, Takashi Saito, Michael Carroll, Jeffrey V Ravetch, J Sjeef Verbeek, Shozo Izui

Department of Pathology and Immunology, University of Geneva, Geneva, Switzerland;

Murine phagocytes express three different activating IgG FcgammaR: FcgammaRI is specific for IgG2a; FcgammaRIII for IgG1, IgG2a, and IgG2b; and FcgammaRIV for IgG2a and IgG2b. Although the role of FcgammaRIII in IgG1 and IgG2a anti-RBC-induced autoimmune hemolytic anemia (AIHA) is well documented, the contribution of FcgammaRI and FcgammaRIV to the development of IgG2a- and IgG2b-induced anemia has not yet been defined. In the present study, using mice deficient in FcgammaRI, FcgammaRIII, and C3, in combination with an FcgammaRIV-blocking mAb, we assessed the respective roles of these three FcgammaR in the development of mild and severe AIHA induced by two different doses (50 and 200 mug) of the IgG2a and IgG2b subclasses of the 34-3C anti-RBC monoclonal autoantibody. We observed that the development of mild anemia induced by a low dose of 34-3C IgG2a autoantibody was highly dependent on FcgammaRIII, while FcgammaRI and FcgammaRIV additionally contributed to the development of severe anemia induced by a high dose of this subclass. In contrast, the development of both mild and severe anemia induced by 34-3C IgG2b was dependent on FcgammaRIII and FcgammaRIV. Our results indicate differential roles of the three activating FcgammaR in IgG2a- and IgG2b-mediated AIHA.

*Nat Rev Immunol*. 2007 Dec 7; : 18064051 (P,S,E,B,D)

### **Fcgamma receptors as regulators of immune responses.**

Falk Nimmerjahn, Jeffrey V Ravetch

In addition to their role in binding antigen, antibodies can regulate immune responses through interacting with Fc receptors (FcRs). In recent years, significant progress has been made in understanding the mechanisms that regulate the activity of IgG antibodies in vivo. In this Review, we discuss recent studies addressing the multifaceted roles of FcRs for IgG (FcgammaRs) in the immune system and how this

knowledge could be translated into novel therapeutic strategies to treat human autoimmune, infectious or malignant diseases.

[Adv Immunol. 2007 ;96C :179-204 17981207 \(P,S,E,B\)](#)

### **Fc-Receptors as Regulators of Immunity.**

Falk Nimmerjahn, Jeffrey V Ravetch

Receptors for immunoglobulins [Fc-receptors (FcRs)] are widely expressed throughout the immune system. By binding to the antibody Fc-portion, they provide a link between the specificity of the adaptive immune system and the powerful effector functions triggered by innate immune effector cells. By virtue of coexpression of activating and inhibitory FcRs on the same cell, they set a threshold for immune cell activation by immune complexes (ICs). Besides their involvement in the efferent phase of an immune response, they are also important for modulating adaptive immune responses by regulating B cell and dendritic cell (DC) activation. Deletion of the inhibitory FcR leads to the loss of tolerance in the humoral immune system and the development of autoimmune disease. Uptake of ICs by FcRs on DCs and the concomitant triggering of activating and inhibitory signaling pathways will determine the strength of the initiated T-cell response. Loss of this balanced signaling results in uncontrolled responses that can lead to the damage of healthy tissues and ultimately to the initiation of autoimmune processes. In this chapter, we will discuss how coexpression of different activating and inhibitory receptors on different immune cells of the innate and adaptive immune system modulates cell activity. Moreover, we will focus on exogenous factors that can influence the balanced triggering of activating and inhibitory FcRs, such as the cytokine milieu and the role of differential antibody glycosylation.

[Eur J Immunol. 2007 Sep 26;37 \(10\):2973-2982 17899548 \(P,S,E,B,D\)](#)

### **Endoglycosidase treatment abrogates IgG arthritogenicity: Importance of IgG glycosylation in arthritis.**

Kutty Selva Nandakumar, Mattias Collin, Arne Olsén, Falk Nimmerjahn, Anna M Blom, Jeffrey V Ravetch, Rikard Holmdahl

The glycosylation status of IgG has been implicated in the pathology of rheumatoid arthritis. Earlier, we reported the identification of a novel secreted endo-beta-N-acetylglucosaminidase (EndoS), secreted by *Streptococcus pyogenes* that specifically hydrolyzes the beta-1,4-di-N-acetylchitobiose core of the asparagine-linked glycan of human IgG. Here, we analyzed the arthritogenicity of EndoS-treated collagen type II (CII)-specific mouse mAb in vivo. Endoglycosidase treatment of the antibodies inhibited the induction of arthritis in (BALB/c x B10.Q) F1 mice and induced a milder arthritis in B10.RIII mice as compared with the severe arthritis induced by non-treated antibodies. Furthermore, EndoS treatment did not affect the binding of IgG to CII and their ability to activate complement, but it resulted in reduced IgG binding to Fcγ3R and disturbed the formation of stable immune complexes. Hence, the asparagine-linked glycan on IgG plays a crucial role in the development of arthritis.

J Exp Med. 2007 Sep 24; : 17893199 (P,S,E,B,D)

## **Class A scavenger receptors regulate tolerance against apoptotic cells, and autoantibodies against these receptors are predictive of systemic lupus.**

Fredrik Wermeling, Yuning Chen, Timo Pikkarainen, Annika Scheynius, Ola Winqvist, Shozo Izui, Jeffrey V Ravetch, Karl Tryggvason, Mikael C I Karlsson

Apoptotic cells are considered to be a major source for autoantigens in autoimmune diseases such as systemic lupus erythematosus (SLE). In agreement with this, defective clearance of apoptotic cells has been shown to increase disease susceptibility. Still, little is known about how apoptotic cell-derived self-antigens activate autoreactive B cells and where this takes place. In this study, we find that apoptotic cells are taken up by specific scavenger receptors expressed on macrophages in the splenic marginal zone and that mice deficient in these receptors have a lower threshold for autoantibody responses. Furthermore, antibodies against scavenger receptors are found before the onset of clinical symptoms in SLE-prone mice, and they are also found in diagnosed SLE patients. Our findings describe a novel mechanism where autoantibodies toward scavenger receptors can alter the response to apoptotic cells, affect tolerance, and thus promote disease progression. Because the autoantibodies can be detected before onset of disease in mice, they could have predictive value as early indicators of SLE.

### Founders

#### MacroGenics, Inc.

Founded in 2000, MacroGenics is a private, venture-backed biotechnology company headquartered in Rockville, Maryland that focuses on the development, manufacture and commercialization of immunotherapeutics for autoimmune disorders, cancer and infectious diseases. In October 2007, Eli Lilly and Company (NYSE:LLY) and MacroGenics, Inc. announced a global strategic alliance to develop and commercialize teplizumab, a humanized anti-CD3 monoclonal antibody, as well as other potential next generation anti-CD3 molecules for use in the treatment of autoimmune diseases. Teplizumab is currently being studied in the PROTÉGÉ trial, a global pivotal Phase II/III clinical trial for individuals with recent-onset type 1 diabetes. The company's proprietary DART (Dual Affinity Re-Targeting) and Fc engineering technologies offer ways to improve the function of antibodies and similar molecules. For more information about MacroGenics, please visit [www.macrogenics.com](http://www.macrogenics.com).

Fc regions mediate antibody function by binding to different receptors on immune effector cells such as macrophages, natural killer cells, B-cells and neutrophils. Some of these receptors, such as CD16A and CD32A, activate the cells to build a response against antigens. Other receptors, such as CD32B inhibit the activation of immune cells. By engineering Fc regions that bind to activating receptors with greater selectivity, antibodies can be created that have greater capability to mediate cytotoxic activities desired by an anti-cancer Mab. Fc regions have also been engineered to specifically bind the inhibitory receptor, CD32B. Triggering the inhibitory receptor will provide a more effective treatment of autoimmune diseases and allergy.

MacroGenics has established a proprietary platform to engineer, screen, identify and test Fc regions with enhanced activity. In particular, the company has exclusive access to transgenic mice that express human Fc receptors. These mice can be used for *in vivo* testing of antibodies that incorporate Fc variants, especially antibodies intended for cancer therapy.



Jeffrey V. Ravetch

### Genetics of the adaptive immune response

The Laboratory of Molecular Genetics and Immunology is focussed on dissecting the cellular and molecular mechanisms governing the generation of antibody specificity and the translation of that specificity into cellular responses. Our work seeks to identify the genetic components which initiate B cell activation upon antigenic challenge, the controls which maintain tolerance both centrally and in the periphery and the mechanisms which govern the coupling of antibody specificity to effector cell response. Our entry point into this system has been through the analysis of systemic autoimmunity in murine models of disease through the investigation of the genesis and fate of the pathological antigen-antibody complexes which form in these diseases and trigger tissue damage. This complex problem has been simplified by focussing on the mechanisms by which immune complexes influence both the afferent and efferent immune responses through their interaction with a family of low-affinity surface receptors, the Fc receptors. These receptors are expressed as pairs of activation and inhibitory molecules, providing a mechanism for establishing thresholds for cellular triggering and for terminating the activation response. Each function is critical for maintaining tolerance and modulating effector cell activation. Perturbations of these pathways have revealed the central role these receptors play in appropriate immune responses.

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Photo courtesy of M. Pelletier.

## Closing the Circle

### Jeffrey V. Ravetch, M.D., Ph.D.

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I grew up in New York City during the Sputnik generation, a time when every kid wanted to be a scientist. I recall reading *Microbe Hunters* by Paul de Kruif when I was 8 or 9 years old, and decided that I, too, wanted to be a scientist and spend my life as a medical researcher. As a Yale undergraduate, working with Don Crothers in the biophysics of nucleic acids, I discovered what it really meant to do academic research in the sciences, and it was clear that was going to be my career path. Don had a wonderful attitude about science that I have tried to emulate. He believed you needed to have a killer instinct for the important problems and go after them with passion, but not be overbearing with the people around you. The environment in his laboratory was terrific, I couldn't wait to finish classes and get back to the lab. I spent four years working in Don's lab and published my first paper while I was there. I took most of my classes in chemistry, biochemistry, and biophysics, always planning on picking up biology along the way. I thought medical school was a way to get grounding in biology, so I applied to M.D./Ph.D. programs.

I chose the newly established program at Rockefeller University, and I'm still here. Rockefeller is a very special place with a wonderful tradition and great history. Each laboratory is an independent unit, free from the constraints of departments, free to pursue its own course. I moved from chemistry to bacteriophage genetics, working with Norton Zinder and Peter Model, then into molecular biology. I did a postdoc at the National Institutes of Health (NIH) with Phil Leder, got involved with structure and function of antibodies and have stayed with that problem, in one way or another, since then.

I eagerly returned to New York and started my own group at Sloan-Kettering in 1982, focusing on an obvious question, "Why do antibodies have an Fc region?", a question that many would have argued was solved by 1982. I was unsatisfied with the solution and decided to clone the receptors that bound the Fc region, in part because of the challenge of cloning genes for rare messages. Cloning of rare messages was still a big deal then, and this receptor family had no known function. The Fc receptors opened up a whole new approach to the regulation of the immune response, establishing global concepts of inhibitory signaling and balanced responses. It's been a very slow battle to get the medical community to accept the fact that antibodies work by engaging specific receptors on the cell surface, and the regulation of those receptors controls not only inflammatory processes, but tolerance pathways as well.

Sometimes choosing a research problem comes from a paradox. If IgG antibodies mediate the pathogenic effects in autoimmune diseases, why are we using high doses of IgG as a therapeutic to treat these same diseases? After 10 years of work, we have come up with an answer—differential glycosylation of IgG antibodies is an important switch controlling whether IgG is going to be a pro- or anti-inflammatory molecule. When sialic acid is incorporated into the Fc, the IgG is an anti-inflammatory molecule. When exposure to an antigen occurs, pro-inflammatory IgGs are generated that have reduced sialic acid content and can activate their Fc receptors. That leads to a new therapeutic application, fully recombinant forms of intravenous immunoglobulin that will be much more potent than the current material. It's the first extension of our basic research into a clinical program. It's exciting, it's closing the circle. There was always this childish hope that someday I could say I studied a disease, understood how it worked, developed a therapeutic, and showed how it altered the course of the disease. We're finally getting there.

I've discovered how difficult it is to translate a basic finding in the lab to a clinical experiment. The reality is that if, as an academic scientist, you want to do a clinical trial you will need to manufacture the test compound in a way that's acceptable to the FDA, and that's expensive and not usually accessible. Satisfying regulatory concerns requires significant expenditures in time and money. Where are the budgets and the infrastructures to do those experiments? Only pharmaceutical companies, and a few very special foundations, have that capacity. The majority of us have to appeal to pharmaceutical companies to take on the project. Then the questions are financial more than anything else. It prevents simple, scientific inquiry into basic questions of the human immune response. I'm pushing to recapture the academic component of therapeutic development. We can't lose the opportunity to ask questions about basic human biology. Unfortunately, I don't see government funding for research improving anytime soon. I fear that we have several years of very hard times ahead of us. As our approaches become more sophisticated and more in vivo oriented, the questions that you ask can take years. If you don't have continuity in funding, those projects can't reach fruition. Long-term approaches are in danger right now.

When I was an undergraduate at Yale, I had a double major, in molecular biophysics and biochemistry, and in English. I maintain a passionate interest in poetry, particularly modern American poetry. I'm an avid weekend gardener, an interest that has extended into the laboratory. We have a large collection of orchids we grow in the lab and enter in competitions. Last year at the New York Orchid Show, one of our orchids (*Paphiopedilum philippinense*) took best in class with two blue ribbons. I've tried to make my lab interesting and exciting, an environment you never want to leave. Everything you want in life is in your laboratory, where I'd spend all my time if I could. Scientists are still kids, curious about everything, who never really grow up.

-As told to **Lynne Lederman, Ph.D.**, a medical writer based in Mamaroneck, NY.



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Antibody Development & Production Conference*

IBC's 20th International

# Antibody Development & Production

*Approaches to Accelerate Speed to Market, Improve Manufacturability and Control Quality in Upstream and Downstream Processing*

March 12-14, 2008 • Sheraton San Diego Hotel & Marina • San Diego, CA

**Keynote Presentations:**

**From Gene to First Patient - Proposal for Standardizing Metrics when Benchmarking Process Development**  
**Wolfgang Berthold, Ph.D.**, Chief Technical Officer, Technical Development, **Biogen Idic**

**What are Therapeutic Antibodies Going to Look Like in the Future?**

**William R. Strohl**, Executive Director, Biologics Research, **Merck Research Laboratories**

**Next Generation Immunotherapeutics - Antibody-Conjugates, Antibody Fragments and Protein Scaffolds**

**Rolf G. Werner, Ph.D.**, Professor, Senior Vice President, Corporate Division **Biopharmaceuticals**, **Boehringer Ingelheim GmbH, Germany**

**Chromatography in MAb Processes - Quo Vadis**

**Greg Blank, Ph.D.**, Director, Late Stage Purification, **Genentech, Inc.**

Conveniently scheduled following IBC's 12th International **Process Validation or Biologicals**, **3rd Annual Technology Transfer for Biopharmaceuticals** and **4th Annual Outsourcing of Biopharmaceutical Manufacturing** conferences, which will be held concurrently on March 10-11, 2008.



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Priority Code: B8155BPIA