JEM Journal of Experimental Medicine 125 years

VIEWPOINT

JEM 125th Anniversary

JEM career launchpad

Anna Bigas, Ivan Zanoni, Matthew R. Hepworth, Stephanie C. Eisenbarth, Seth Lucian Masters, Jonathan Kipnis, Carola G. Vinuesa, Kim L. Good-Jacobson, Stuart G. Tangye, Sayuri Yamazaki, Claire Hivroz, Elia Tait Wojno, Ziv Shulman, and Marco Colonna

For 125 years, *JEM* has been at the forefront of biomedical discoveries, publishing outstanding contributions with an enduring legacy. Scientists now come together to celebrate the history of *JEM* and the impact that publishing in *JEM* had in launching and supporting their careers. *JEM*'s commitment for the future remains firmly to serve the scientific community and be a launching pad for young scientists' careers.

JEM's long-lasting support for developmental hematopoiesis

Anna Bigas, PhD

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Between 2012 and 2014, my laboratory published three papers in *JEM* (Ruiz-Herguido et al., 2012; Guiu et al., 2013, 2014) that represented a step forward in my career and a consolidation of the laboratory in the field of developmental hematopoiesis. In these papers, we unraveled some of the key signals for hematopoietic stem cell development in the mouse embryo. I was lucky enough to work with a very talented PhD student at that time (now a junior principal investigator at the Barcelona Centre for Regenerative Medicine), Jordi Guiu, who is an author in each of these papers. He was the force driving this research period. Also, I cannot forget the fantastic input from my long-standing colleague and co-senior author in those papers, Lluis Espinosa. For all of us, these papers were extremely important in our scientific trajectories.

There are many seminal works that have been published in *JEM* in the last 125 years, but more than highlighting a single paper, I would like to remark on the support that *JEM* has given to the field of developmental hematopoiesis. Many of the studies published in *JEM* in the last 20 years have moved this field forward (Godin et al., 1999; Ling et al., 2004; Ivanovs et al., 2011; Gao et al., 2013; Rybtsov et al., 2011; de Pater et al., 2013). I am grateful to *JEM* for this support, and I envision a bright future for the journal in the next decade continuing with this vision and ethics of scientific publishing.

JEM: At the forefront of IFN biology

Ivan Zanoni, PhD

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In 2001, I started my PhD in immunology, and in the same year, Dr. Francesca Granucci discovered that dendritic cells (DCs) respond to bacterial stimuli by producing IL-2. DCs were already well recognized as the bridge between the sensing of pathogens and activation of T lymphocytes. Nevertheless, production of IL-2 was believed to be an exclusive feature of adaptive immune cells. Puzzled by this observation, I joined Dr. Granucci's efforts to understand how the production of IL-2 by DCs affects the immune response. Inspired by, among others, a paper published in *JEM* (Grimm et al., 1983) that described the unique features of "lymphokine-activated cells" exposed to IL-2, we hypothesized that DC-derived IL-2 might be essential in controlling the functions of natural killer (NK) cells. In 2004, we pioneered in *JEM* one of the first studies on the importance of DC-derived signals in favoring the early production of IFN-γ by NK cells (Granucci et al., 2004). 15 years later, I was invited by *JEM* to write a review on the biology of type III IFNs, the latest addition to the IFN family (Broggi et al., 2020), showing that while our knowledge of the biology of IFNs expands and changes, the capacity of *JEM* to be at the forefront of innovation remains unaltered.

JEM's seminal contributions to mucosal immunology

Matthew R. Hepworth, PhD

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As #JEMLegacy takes a look back at the key contributions made by research published in *JEM* over the last 125 years, I find myself thinking of how work published in *JEM* influenced the course of my career. Like many mucosal immunologists who began their training in the first decade of this century, it was the advances in understanding mucosal tolerance that first got me excited about studying the gastrointestinal immune system; in particular, the work of Fiona Powrie demonstrating the role of regulatory T cells and IL-10 in suppressing intestinal inflammation (Asseman et al., 1999). Another notable influence on my career choices and research directions was the discovery of non-T non-B sources of type 2 effector cytokines at barrier surfaces by Fallon and McKenzie (Fallon et al., 2006), which first sparked my interest in what we now know as innate lymphoid cells (ILCs). A couple of years later, it was a discussion over a beer at a poster session over the then-emerging roles of IL-22 (Sonnenberg et al., 2010) that led to the opportunity to postdoc with Greg Sonnenberg; together, we identified new roles for ILC3 in suppressing adaptive responses to the microbiota. It was these moments of serendipity and seminal observations published in *JEM* that influenced my research; as such, I was delighted when we published the first study from my independent laboratory in *JEM* last year, in which we demonstrated a role for antigen-presenting ILC3 in regulating anti-commensal antibody responses (Melo-Gonzalez et al., 2019).

JEM's headway vision of type 2 immunity

Stephanie C. Eisenbarth, PhD

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My first paper in *JEM* was on the role of lipopolysaccharide and asthma (Eisenbarth et al., 2002). At the time, it was a heretical idea that a bacterial product could promote type 2 immunity, and so when we sent our work out to a number of journals, it was outright rejected. I was beginning to lose hope, but when we sent it to *JEM*, it got reviewed and ultimately accepted. After that, I was able to see the impact it had on the field, and personally, it resulted in invitations to speak at meetings very early in my career. It was a truly thrilling experience. Now, with more than 1,000 citations of that article, I am grateful to this day for the opportunity *JEM* provided.

Once I started my own laboratory, I began working on a new scientific area based on my clinical training—the immune response to transfused RBCs. Again, I turned to *JEM* to publish our first work (Calabro et al., 2016). Further, in surveying what was known about the immune response to allogenic RBCs, I read the work from a pioneer in the field, Nobel laureate Karl Landsteiner. Amazingly, he published numerous papers every year, at times monthly, in *JEM* from 1923 to 1928 on every aspect of RBCs (and subsequently on anaphylaxis with the same regularity until 1942; Landsteiner and Simms 1923; Heidelberger and Landsteiner, 1923; Landsteiner and van der Scheer 1925; Landsteiner and Levine 1928a; Landsteiner and Levine 1928b; Landsteiner and van der Scheer 1940; Rothen and Landsteiner 1942). It is truly an amazing body of work, laying the groundwork for the identification of antibodies. Another aspect of our work focuses on the role of DCs in antigen presentation of RBCs, as well as allergens and vaccine constituents; again, much of the early work in the DC field from Ralph Steinman was put forward in *JEM*. Therefore, *JEM* has not only had a direct impact on my scientific career, but also on informing and shaping our science by publishing new and perhaps unorthodox ideas in the immunology field (Steinman and Cohn, 1973; Nussenzweig and Steinman 1980; Inaba et al., 1992).

JEM: Found in translation

Seth Masters, PhD

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A couple of years after starting my own laboratory, we had developed a solid story outlining the first autoinflammatory disease dependent on the oft-overlooked inflammasome cytokine IL-18, as opposed to its more popular cousin IL-1β. The abstract was selected for presentation at a conference, and I knew that the editor of a prestigious journal was in the audience. I sounded them out during the following tea break, but disappointingly, the discussion was not productive. I was then approached by an editor from *JEM* and immediately had my faith in the scientific discourse renewed, as she clearly understood the data and had enthusiasm for the impact of our work. As opposed to spending months or even years going through multiple journals and rounds of revisions, our work was rapidly accepted at *JEM* (Kim et al., 2015), featuring an editorial (Borregaard, 2015). Perhaps the most important part of this for my early career was not simply the profile of the publication, but gaining confidence in the system and diffusing the pressure of rejection, which was replaced instead with the time and mental space to get on with the next project.

Although this paper was entirely based on data from model systems, it predicted the existence of a human disease; indeed, that was confirmed shortly thereafter, again in the pages of *JEM* (Standing et al., 2017). Increasingly, I suspect that this will be the major impact for *JEM* over the next decade: making fundamental insights that have characterized its legacy over the last 125 years, and demonstrating how they are manifest in human health and disease. In particular, human genetics is now at the point where it is possible to identify vanishingly rare mutations in only a single individual worldwide. The ability to underpin such studies with robust models is critical validation that characterizes many studies in *JEM*. For example, my favorite paper in recent years has been the demonstration of mutations in NLRC4 causing autoinflammatory disease in both humans and mice (Kitamura et al., 2014). Not only do such studies allow for definitive genetic diagnosis, solving often decades-long quests for clinical mysteries, but they will continue to do that every time someone is born with a similar mutation forevermore.

JEM: Fostering neuroimmunology research

Jonathan Kipnis, PhD

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Growing up scientifically as a graduate student at Israel's Weizmann Institute in the 1990s, I soon found out that *JEM* was among the leading journals publishing seminal discoveries, most of them in immunology. Neuroimmunology was my passion—a field whose holy writ was being pioneered by scientific giants, using animal EAE models to understand multiple sclerosis. To my chagrin, notwithstanding my attempts as a student, I never achieved publication in *JEM*. But in 2010, in my University of Virginia laboratory, we discovered that mice lacking T cell–derived IL-4 were cognitively impaired, suggesting that immune cell–derived molecules mediate brain processes affecting learning behavior. When this came out in *JEM* in 2010, it was then one of the few papers on psychoneuroimmunology ever published in this journal (Derecki et al., 2010). I am happy to see that that *JEM* now has a growing neuroscience audience and a distinguished status among the premier journals for the dissemination of neuroimmunology research. I look forward to seeing how *JEM* continues to influence coming generations of scientists, and to publish game-changing works for the next 125 years and more.

JEM opened the doors to a career in research

Carola G. Vinuesa, PhD

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JEM is very dear to me. It published my best work from my PhD, which opened my doors to a career in research and to the world. I have since published 10 papers in *JEM*, including 4 papers cited over 200 times. Some of these highly cited papers are not only very close to my heart, they have also contributed to the incredible honor of currently being an Institute for Scientific Information highly cited researcher, which helped attract funding (Linterman et al., 2009, 2010; Lee et al., 2011; Cañete et al., 2019). Our recent *JEM* paper was selected as one of the top 10 papers of 2019: thank you again, *JEM*!

What I like best about *JEM* is (1) they are an impressive group of highly professional, fair, responsive, fast, and flexible editors with strong principles that value good science, and (2) the journal's appreciation and understanding of the value of both human research and fundamental immunology.

My favorite *JEM* paper? The trio of papers by Weigert and Nemazee in 1993 identifying B cell receptor editing as a potent mechanism of B cell tolerance (Gay et al., 1993; Radic et al., 1993; Tiegs et al., 1993).

A challenge for *JEM* will be to come up with innovative ways to open itself to a diverse world with less travel, perhaps facilitated by scientific and academic editors based at different parts of the world.

JEM's openness to diverse ideas and approaches

Kim Good-Jacobson, PhD

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One of the most invigorating elements of being a scientist is seeing how the exploration of one seemingly simple question can lead to an array of scientific discoveries. I am particularly fond of multi-part series (Garnett Kelsoe's NP articles in *JEM* come to mind; Jacob et al., 1991; Jacob and Kelsoe, 1992; Jacob et al., 1993; Han et al., 1995; Takahashi et al., 1998; Takahashi et al., 1999). There is one series of articles, all published in *JEM*, that highlight how diversity in ideas, approaches, and expertise from scientists around the world can rapidly expand our knowledge and capability. In 1998, back-to-back articles defined CD27 as a marker for human memory B cells (Tangye et al., 1998; Klein et al., 1998), which set the foundation for later discovery of an FcRL4$^+$ subset (Ehrhardt et al., 2005). This, in turn, catalyzed studies interrogating the formation and function of memory B cells in HIV and malaria (Moir et al., 2008; Muellenbeck et al., 2013). Thus, one fundamental question—how can we define memory B cells?—provided the bedrock to ask critical questions about B cell memory and antibody dysfunction in infectious disease. Our research defining a key molecular determinant of establishing long-lived plasma cells was published in *JEM* at a key juncture of my career, between having children and establishing my independent research program (Good-Jacobson et al., 2015). Identifying the molecular regulators of antibody production, along with tackling open questions about B cell memory dysfunction, set the direction for my own independent research program. Understanding the fundamental principles governing our ability to form effective immune memory is critical for continued global health and economic security, sadly highlighted by the course of this pandemic. The current crisis has also demonstrated that established journal practices can be adapted to support the rapid advancement of science. I am optimistic that this will inspire more positive changes that support scientific progress and a diverse scientific community, while working together to push back against the darkening global landscape of science denialism.

JEM: A key venue for human immunology studies

Stuart Tangye, PhD

Leader, Immunity & Inflammation Theme; Head, Immunology & Immunodeficiency Lab; Professor (Conjoint), St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney; Garvan Institute of Medical Research, Darlinghurst, Australia

In the late 1990s, I was doing a postdoc at the wonderful DNAX Research Institute of Molecular and Cellular Biology in California. Many fundamental discoveries in basic molecular and cellular immunology had been made at DNAX in the 1980s and '90s. To be a young postdoc from Sydney working in that environment was just magic, inspirational, and influential. Toward the end of my postdoc, I was starting to think about returning to Australia for the next phase of my career. Luckily for me, in 1998, I published my first ever paper in *JEM* (Tangye et al., 1998). This paper identified specific cell surface markers (particularly CD27) that enabled detection (and subsequent isolation and detailed functional analysis) of human memory B cells. I honestly think that having achieved some measure of success during my DNAX postdoc—i.e., a first author *JEM* paper—played a very important role in my securing a research fellowship awarded by the University of Sydney, which enabled me to return to a position in Sydney in 2000. The fact that this paper went on to be highly cited, due to its importance not only in human immunology but also clinical diagnostic immunology, has allowed me to frequently refer back to this work as a key discovery in my research career—even 20+ years later.

Perhaps my favorite paper from *JEM* in the past 30 years is by Virginia Pascual, Yong-Jun Liu, and colleagues (Pascual et al., 1994). This paper elegantly delineated the stages of human B cell differentiation in secondary lymphoid tissues using a combination of flow cytometry and tracking somatic hypermutation. As a young B cell enthusiast undertaking my PhD at this time, this paper really captured my imagination and showed me that studies of human immunology could be done very well using the right approaches. Serendipitously, Yong-Jun Liu joined DNAX during my postdoc. So I was very fortunate to have Yong-Jun's significant input into my studies that were published in *JEM*.

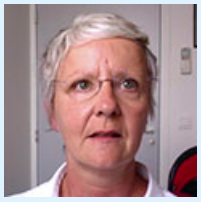
In the next decade, I really would like to see *JEM* continue to publish important papers in the area of human immunology. This has improved a lot over the past 10 years, but now with the greater emphasis on humans as an "experimental model," there need to be avenues where such papers can find an audience, even if some mechanistic aspects are incompletely deciphered.

JEM propelled my career as an independent investigator

Sayuri Yamazaki, MD, PhD

Professor and Chairman, Department of Immunology, Nagoya City University Graduate School of Medical Sciences, Japan

Regulatory T cells (T reg cells) were anergic when I was in the Shimon Sakaguchi laboratory. Thus, Prof. Steinman and I were surprised that T reg cells were expanded by antigen-presenting DCs. This finding was published in *JEM* in 2003, and is highly cited: 742 times, as of today (Yamazaki et al., 2003). It proved to be helpful in obtaining competitive grants and my current position as tenured Professor and Chairman of the Department of Immunology. The 2003 *JEM* paper impressed Prof. Akimichi Morita, Chairman of the Department of Dermatology, and he ultimately invited me to give a talk. That was the beginning of my career in Nagoya. I used to read almost all of Steinman and Kayo Inaba's *JEM* papers for my PhD as a dermatologist at Tokyo Medical and Dental University. My favorite is their legendary 1992 paper on the generation of bone marrow–derived DCs, as we used the method described in this publication to generate DCs (Inaba et al., 1992). With over 100 years of history, *JEM* will continue to publish important discoveries and impress diverse researchers in the next decade. I hope to be productive and contribute to the future legacy of the journal. Congratulations on your 125th anniversary, *JEM*!



JEM: At the core of our training

Claire Hivroz, PhD

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Beginning my career as a student in immunology in the 1980s, I was trained to carefully follow the literature. *JEM* was one of the essential scientific journals to follow, and articles published in *JEM* were and are still an integral part of my training. I have vivid memories of journal clubs discussing the latest discoveries in the field of immunology, such as Heinrich, Traunecker, and Tonegawa's "Somatic mutation creates diversity in the major group of mouse immunoglobulin kappa light chains" (Heinrich et al. 1984). Later, some articles published in *JEM* such as "Sustained signaling leading to T cell activation results from prolonged T cell receptor occupancy: Role of T cell actin cytoskeleton" by Valitutti et al. (1995) shaped the field I am working in now. It is not every day in a scientist's career that you have the privilege to publish your work in *JEM*. I was thus proud and thrilled that our work was considered for publication at *JEM* (Carpier et al., 2018). Reviews were constructive and fair, and revisions improved the scope of our study! To illustrate how *JEM* is influencing young scientists' careers, I would like to give the floor to Jean-Marie Carpier, first author of our article: "I heavily relied on research articles from *JEM* to build my knowledge in immunology. I was proud to have my PhD work published in *JEM*. It undoubtedly set me up for success, as I was awarded my first post-doctoral fellowship at Yale University the same year."

No doubt, in the next decades, *JEM* will still contribute to the diffusion of knowledge and development of talented scientists!

JEM supports female, underrepresented, and junior investigators

Elia Tait Wojno, PhD

Assistant Professor, Department of Immunology, University of Washington

JEM has been a part of my career in immunology since I was a graduate student. My work, then and now, focuses on cytokine regulation of immune responses during infection and inflammation. *JEM* has been home to seminal papers in this field that dissected IL-12 (Neurath et al., 1995) and IL-10 (Asseman et al., 1999) biology in colitis, regulation of type 2 cytokine responses (Conrad et al., 1990, Else et al., 1994, Fallon et al., 2006), Th17 responses (Langrish et al., 2005), and basic IL-4 biology (Vitetta et al., 1985), to name some favorites. I was thrilled that the first paper from my laboratory investigating regulation of basophil responses during helminth infection was published in *JEM*, after a fair and transparent review process (Webb et al., 2019). This paper led to new collaborations, speaking invitations, awards, and other professional opportunities. Today, *JEM* continues the tradition of publishing the most important work in my field and consistently elevates the cutting-edge work of female, underrepresented, and junior investigators. Here's to the next 125 years!

***JEM*: A unique place to launch a career in immunology**
Ziv Shulman, PhD
Principal Investigator, Department of Immunology, Weizmann Institute of Science, Rehovot, Israel

JEM is a remarkable journal that publishes important and exciting studies in immunology, which are always timely and informative. Many key discoveries in the field of immunology were published in *JEM* over the years, and more recent studies describe highly detailed functions of the immune system under physiological conditions and in human disease. The first study that came out of our laboratory was published in *JEM*, wherein we solved a long-standing mystery regarding the role of typical adhesion molecules in cell–cell interactions during the emergence of antibody-mediated immunity (Zaretsky et al., 2017). This first publication was very important to me during the early stages of my scientific career as an independent investigator, as it played a key role in my ability to attain grant support and enabled my participation in several scientific forums such as the EMBO Young Investigator Program. The current pandemic highlights our incomplete understanding of the immune response against pathogens, and I believe that *JEM* will take the lead in disseminating new findings that further elucidate the cellular and molecular mechanisms that endow long-lasting protection from viral infections.

***JEM*: Supporting novel discoveries for 125 years**
Marco Colonna, MD
Robert Rock Belliveau Professor, Department of Pathology and Immunology, BJC Institute of Health at Washington University, St. Louis, MO

At the National Cancer Institute of Genova, Italy, I initially pursued an idea developed as a postdoc with Jack Strominger: human NK cells recognize HLA class I epitopes shared by multiple rather than individual alleles. In 1993, I found that NK cells recognize the Bw4 epitope, the first supertype of HLA-B alleles ever discovered. I considered *JEM* a very attractive venue for this discovery because it was a prime journal in immunology that published seminal papers; moreover, *JEM* devoted considerable attention to innate immunity and NK cells, which were emerging as extraordinarily dynamic research areas. The *JEM* reviewers and editors were supportive, and this publication helped me obtain a position at the Basel Institute for Immunology in 1994 (Cella et al., 1994). There, I searched for innate receptors for HLA class I supertypes, and few years later, I found inhibitory receptors for HLA class I that are expressed on NK cells as well as DCs. I presented these findings to Ralph Steinman, who encouraged submission to *JEM*; fortunately, they were published, which bolstered my chances of becoming a tenured member (Colonna et al., 1997). While immunology has become the focus of new, outstanding journals, *JEM* remains a reference point for original discoveries, authentic advancements, and young investigators emerging in nascent areas of immunology.

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