VIEWPOINT

JEM 125th Anniversary

**JEM career launchpad**

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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

Group Leader, Cancer and Stem Cells; Scientific Director, CIBERONC; Institut Hospital del Mar d’Investigacions Mèdiques, Barcelona, Spain

Between 2012 and 2014, my laboratory published three papers in JEM (Ruíz-Herguido et al., 2012; Guíu 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 Guíu, 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, Luís 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.

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**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 allogeneic 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 1933, 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 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 animal 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.
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.

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; Tiegts 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.

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.
improved a lot over the past 10 years, but now with the greater emphasis on humans as an

Published in (Carpier et al., 2018). Reviews were constructive and fair, and revisions improved the scope of our study! To illustrate how

you have the privilege to publish your work in articles published in (Inaba et al., 1992). With over 100 years of history, the legendary 1992 paper on the generation of bone marrow

Regulatory T cells (T reg cells) were anergic when I was in the Shimon Sakaguchi laboratory. Thus, Prof. Steinman and I were surprised

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

Professor and Chairman, Department of Immunology. The 2003 JEM paper impressed Prof. Akimichi Monta, 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

In the late 1990s, I was doing a postdoc at the wonderful DNAX Research Institute of Molecular and Cellular Biology in California. Many

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 cytomtery and tracking somatic hypermutation. As a young B cell enthusiast undertaking my PhD at this time, this paper really captured

Somatic mutation creates diversity in the major group of mouse immunoglobulin kappa light chains (Heinrich et al. 1984). Later, some

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 Carpiер, 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!!
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.

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