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SPECIAL ISSUE PERSPECTIVE

JOHN F. FALLON, PhD: Fifty Years of excellence in limb research and counting

Deneen Wellik,[1]* Xin Sun,[2] and Grace Boekhoff-Falk[3]

Passion and thoughtfulness...

These are an unusual combination of descriptors perhaps, but fitting for the man to whom we dedicate this special issue on limb development, Dr. John F. Fallon. John has approached his work for more than 50 years with a combination of passion and thoughtfulness that has left indelible marks on the field and on the many scientists who have entered or passed through John's scientific universe.

John Fallon was appointed Assistant Professor of Anatomy at the University of Wisconsin-Madison on January 1, 1969, after earning the PhD degree in Biology at Marquette University and serving 2 years on active duty in the US Army Medical Service Corps. He was promoted to Professor of Anatomy in 1981 and had served as a member of the faculty for 41 years upon his retirement on December 21, 2009. During these years, John published 93 peer reviewed original research articles, 20 review articles/book chapters and 4 edited proceedings. Whereas these publications cover a range of topics from the gametes of *Nereis limbata* to the carapacial ridge of turtles, the majority of John's contributions are in the field of limb development, a passion he developed in the 1960s as a graduate student in John Saunders' laboratory at Marquette University.

John left his home in Massachusetts when he was thirteen years old and attended high school at Roosevelt Military Academy in Aledo, Illinois. During high school, he became very interested in philosophy and entered Marquette University to pursue undergraduate studies in this subject, also working as a window and awning salesman during college to pay for his education. By his senior year of college, John was completing Bachelor's degrees in both Philosophy and Zoology, and had applied, and was accepted, to pursue graduate studies in the Philosophy department at Marquette. It was also during his senior year, that John enrolled in a Cell Biology course, which was taught by Dr. John Saunders. He was riveted by Dr. Saunders' teaching style and approached Dr. Saunders after a class one day and asked whether he might work in his laboratory during his senior year. This turned out to be a career-altering event (Fig. 1).

John spent the first several months washing glassware, but he was allowed to watch, and sometimes assist, Mary Gasseling as she was performing some of the very first experiments on the function of the cell death and what would become the zone of polarizing activity in the chick limb. John was hooked! Toward the end of his senior year, he decided that he no longer was interested in pursuing philosophy, but instead wanted to turn his attention to biology. Dr. Saunders personally intervened on John's behalf to permit a change in departments for his graduate admission in Biology.

During his years under Dr. Saunders' tutelage, John was allowed to spend a few summers at Woods Hole, times that John considers transformative. He published his first paper on collaborative work done there with Dr. C.R. 'Bunny' Austin (the Charles Darwin Professor of Animal Embryology, University of Cambridge, UK) using electron microscopy, and recalls his anxiety at the first formal presentation on this work, where he talked about how jelly was released from *Nereis limbata* eggs during fertilization when the sperm makes contact with the egg. This work tested theories put forth by Drs. Alex Novikoff and Donald Costello who were both present at

[1]University of Michigan, Department of Internal Medicine, Ann Arbor, Michigan
[2]University of Wisconsin, Laboratory of Genetics, Madison, Wisconsin
[3]University of Wisconsin, Department of Cell and Regenerative Biology, Madison, Wisconsin
***Correspondence to: Deneen Wellik, Department of Internal Medicine, University of Michigan, 109 Zina Pitcher, Ann Arbor, MI 48109. E-mail: dwellik@umich.edu**

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Developmental Dynamics

the seminar, along with Arthur and Laura Colwin, international experts on fine structure of gametes. John recalls how different the environment was then, with all of the field's leaders spending time together most summers, where work and ideas were presented, discussed and argued. Back in Milwaukee, John's work in the Saunders' laboratory led to a manuscript detailing a zone of natural cell death in the posterior of the developing chick wing.

In addition to his outstanding research, John made notable contributions to his department, school and university in teaching and service. John taught many courses in the basic sciences for medical, graduate and undergraduate students. He also organized several scientific study groups, most notably the Vertebrate Development Study Group with Prof. William F. Dove that ran weekly for several years and attracted campus-wide participation. John served on a variety of University committees, including as Chair of the tenure-granting Executive Committee of the Biological Sciences Division. He also was the Assistant Dean for Graduate Studies within the Medical School from 1985 to 1991. During his time as Assistant Dean, John reinvigorated the MD/PhD program. He recruited faculty campus-wide for the program and outstanding students from all over the US. These students along with the MD/PhD educational program he put in place, constituted the solid foundation for the current NIH-funded MSTP program on the Madison campus.

John has received many awards for his scientific contributions, including being named a Fellow of The American Association for the Advancement of Science (AAAS) and the UW-WARF Harland Winfield Mossman Named Professorship. In recognition of his scientific contributions the American Association of Anatomists awarded him its highest honor, the Henry Gray Award. Following the news of his pending retirement, John was honored for his scientific contributions to limb development research at the 11th International Conference on Limb Development and Regeneration in July of 2010.

John is internationally recognized for his scientific contributions to the study of pattern formation during embryonic development and has consistently maintained federal funding. It is impossible, within the constraints of this space, to do justice to John's scientific contributions, as many of his findings have served as catalysts to move the entire limb development field forward over the course of his decades-long career. His research on limbs spans the eras of tissue manipulation in 1970s, through to the molecular and genetic studies he has published more recently. John's research consistently has been at the forefront of the field, a testament to his creativity and scientific agility at the cutting edge of a fast moving area. John also is well known and respected for his willingness to share resources and expertise. Many of his publications are results of productive collaborations that John forged with investigators both inside and outside of the field. In addition to limb development, he has made seminal contributions to the understanding of developmental mechanisms controlling skeletal patterns and epidermal specializations such as feathers, scales, and teeth. A few examples of John's contributions are highlighted below:

- In the late 1960s, John, along with Dr. John Saunders, described cell death in the developing chick limb as a part of the normal limb developmental program, a rather unusual concept at the time (Fallon and Saunders, 1968). Today, the significance of these observations is unquestioned, as elucidating the mechanisms of apoptosis has become a central pursuit in developmental biology and in fields such as cancer biology.
- John's work on defining the role of two signaling centers in the limb, the apical ectodermal ridge and the zone of polarizing activity, began in the 1970s. His extraordinary contributions were possible because of his mastery of experimental manipulations of the embryonic limb bud and macro- and microscopic analysis of the consequences of these manipulations. He worked with other leaders of the field to precisely define the tissue properties of these two signaling centers, and laid the groundwork for molecular verification of key activities emanating from these tissues (Crosby and Fallon, 1975; Fallon and Crosby, 1975a,b; Cameron and Fallon, 1977; Rowe and Fallon, 1981; Rowe and Fallon, 1982a,b; Carrington and Fallon, 1984, 1986; Todt and Fallon, 1984, 1987; Dvorak and Fallon, 1987).
- His 1982 seminal finding on the role of the AER in maintaining cell survival re-emerged in the past few years as a key piece of evidence that challenges the long-standing Progress Zone model (Rowe et al., 1982). This realization led to a flurry of exciting research on the basic mechanisms of limb pattern formation.
- Beginning in the early 1990s, John's laboratory defined many aspects of the molecular hierarchy of pattern formation in the developing limb (Coelho et al., 1991; Dvorak and Fallon, 1992; Krabbenhoft and Fallon, 1992; Ros et al., 1992, 1993; Riley et al., 1993; Savage et al., 1993). His laboratory was among the first to demonstrate that FGF is the critical limb bud outgrowth signal, a finding that has led to many subsequent discoveries of the nature of this signaling pathway (Savage et al., 1993; Fallon et al., 1994).
- In an elegant set of experiments using the chick *limbless* mutant in 1996, John's laboratory demonstrated that AER formation is tightly coupled to correct formation of a dorsoventral limb boundary (the limb edge along which the AER forms) (Ros et al., 1996). Limb buds with a bi-dorsal boundary fail in AER formation. In the same study, he presented compelling evidence that the polarity (asymmetric features) of the limb bud is determined well before the signaling centers that control proximodistal outgrowth and anteroposterior pattern become active in the early limb field.
- Beginning in 1995, John led several collaborations to define the role of *Shh* in limb development and the mechanistic relationship between *Shh* and *Gli3* in the establishment of AP limb pattern. These studies fundamentally advanced our understanding of the central role of SHH signaling pathway in AP patterning of the limb (Chang et al., 1994; Lopez-Martinez et al., 1995; Pagan et al., 1996; Ros et al., 1996;

Caruccio et al., 1999; Wang et al., 2000; Chiang et al., 2001; Litingtung et al., 2002).

- In the past 10 years, John's group, along with others, has been instrumental in identifying and characterizing the long-range (~1 Mb) enhancer that controls *Shh* expression exclusively in the posterior domain of the limb bud (Ros et al., 2003; Maas and Fallon, 2004, 2005). Notably, John's group identified mutations associated with this enhancer that are the basis of some spontaneous mutations in chick and mouse (also see review on humans by Alhituv et al. in this issue).
- John's most recent contributions include paradigm-shifting studies elucidating the nature of digit formation and patterning. This work shows that digital rays grow by recruitment of distal mesenchyme rather than elongation of a single precursor anlagen, and provides evidence that digit identities are not intrinsic to these anlage, but are instructively regulated by differential thresholds of p-SMAD1/5/8 signaling originated from the interdigital mesenchyme (Suzuki et al., 2008) also see reviews by Stricker et al. and Young et al. in this issue).
- In 2006, John's laboratory published work showing that chickens, which normally lack teeth, have retained the ability to respond to tooth-inducing signals, and propose a model in which epigenetic modification of the position of the inducing center resulted in evolutionary loss of archosaurian teeth (Harris et al., 2006). This study was featured in television programs aired by the Discovery channel.

Throughout his career John has been a dedicated reviewer of scientific papers and grant proposals. He has served on numerous NSF and NIH study sections and as Associate Editor for *The Anatomical Record* and *Developmental Dynamics*. His reviews are consistently scholarly and fair, typically providing constructive suggestions for making the author's science better. In Dr. Gary Schoenwolf's experience as Editor-in-Chief of *Developmental Dynamics*, he remarks on how John assesses manuscripts as both an editor and a reviewer: "As an editor, he is dedicated to this task, managing the review process faster than any other editor on the board. As a reviewer, he is consistently fair yet critical and kind to the author" (Fig. 2). In a conversation with Didier Stainier, who chaired a DEV1 NIH study section on which John served, Dr. Stainier remarked that John "was the voice of wisdom, who always brought us back to reality when we went off on a tangent." Dr. Stainier further remarked that John is "level headed" and "should have been chairing the study section instead of me, based on his knowledge and the respect the panel had for his opinion." The longevity of John's dedication to scientific review is remarkable: to date he has spent 28 years as an Associate Editor (18 as Associate Editor of the *Anatomical Record* and 10 as Associate Editor of *Developmental Dynamics*) and 8 years as Reviews Editor of *Developmental Dynamics*.

John has organized numerous meetings, workshops, and symposia in the field for several organizations including the American Association of Anatomists, American Society of Zoologists, and the NSF and has edited symposia volumes based on these meetings. These proceedings are considered staples in the field and are now "collectables." Assembling such proceedings is no easy task, considering the numbers of authors involved and busy schedules. Yet John always pulled it off in a gentle yet firm manner. He's a demanding taskmaster who leads by example, and authors are always eager to meet his standards and to please him with the results.

As an officer and committee member of the American Association of Anatomists, John has made enormous contributions. In fact, almost 20 years ago, he played an instrumental role on a visionary task force that made the difficult and risky decision to convert one of the Association's journals, the *American Journal of Anatomy*, into a new developmental journal called *Developmental Dynamics*. The decision was insightful and represented the first step toward raising the scientific visibility of the Association. More recently, John served as President of the Association. His main contributions were to establish a workable transition plan to move the Association from an Officer-managed organization to a new business model based on a professional manager and national office staff; and to develop mechanisms to foster the career development of young scientists. These changes substantially increased the vitality and energy of the Association. John continues his active involvement in the Association, having recently chaired the important Journal Oversight Committee. In 2007, his contributions to the Association were further recognized: he received the AAA/Wiley A.J. Ladman Exemplary Service Award.

Perhaps of all John's contributions, his life's work as a mentor to others is the one that he cherishes the most. He formally trained 23 graduate students and 12 postdoctoral fellows (Fig. 3). The impact he made on their careers is perhaps exemplified by this quote from Randy Dahn, a former graduate student: *"It's only in retrospect I realize how fortunate I was to arrive on John's doorstep as a graduate student, and to have had years of daily interactions to draw upon. My memories stay with me in the form of gentle admonishments in the back of my mind: "You will only see what your mind is prepared to see," and "Don't defend hypotheses, test them." I believe his thoughtfulness, and his respect of others' thoughtfulness, is his hallmark as a developmental biologist. To encourage perspective, he often said "No one will remember the name Fallon, or read those papers, in 50 years." In this regard, I think he was wrong. His humility was unself-conscious—he always picked up and delivered eggs for his students, and personally laundered the lab's hand towels. The only iron fist John wielded, if it can be so called, was his own example; I've since encountered nothing more effective nor instructive. For these reasons, among so many, I'm thankful to have met John."*

In addition to John's formal training record, perhaps more remarkable are his selfless efforts in mentoring scientists at all career stages outside of his own laboratory, both on the UW-Madison Campus, and at other institutions. He has spent countless

Fig. 1. The lineage. From left, Matt Harris (Fallon student), John, Dr. Saunders, and Randy Dahn (Fallon student) at International Limb Meeting in Aussois, France, May 2000.

Fig. 2. With the Editor-in-Chief. John with Dr. Gary Schoenwolff, Editor-in-Chief of *Developmental Dynamics* at the Fallon Symposium, April 2010.

Fig. 3. The legacy. John with former lab members at the Fallon Symposium, April 2010.

Fig. 4. The demonstration. Work from John and others have shown that digit 1 (thumb/big toe) is the only digit that forms independent of SHH activity. Here he is, happily showing off his SHH-independent digit.

hours critiquing the manuscripts and grant proposals of junior faculty, and talking with them about their long-term career objectives. John also attracted and welcomed numerous visiting scientists from all over the world who came to learn the techniques and approaches he pioneered. These included scientists from Spain (Dr. Marian Ros), Chile (Dr. Alexander Vargas), the US (Dr. Kerby Oberg), and Canada (Dr. Tamara Franz-Odendaal). As a testament to and example of just how deeply John cared about each and every person he mentored, Marion Ros shared this memory of her time in John's lab: "*Very special for me was the summer of 1994. I went to Madison that summer to make recombinant limbs by inserting cells expressing different constructs (N-, C-terminal, full length) of Shh to check for their activity. I went there with my family and my little daughter who was less than three months old. One of my friends had rented for us an old house that was in bad shape but that was supposed to be conditioned by the owner before our arrival. However, the owner didn't do it and just a few days before our arrival the house was a complete mess. John and Elaine, together with other friends, had worked before our*

arrival to get the house ready and they didn't mention it to us. It was by chance that we eventually found out that they had done all this for us. Elaine and John made me feel comfortable with the little baby and helped in every way you can imagine." While the impact of John's unofficial mentoring may be difficult to measure, it is noteworthy that three of the UW Madison faculty he mentored organized the John F. Fallon Symposium on Limb Development and Evolution that was held on April 15th, 2010, to honor him. More than 100 people from inside and outside the university attended the dinner and symposium held in his honor, a testament to how broad his influence has been, and continues to be, on the people around him.

John has nurtured and supported mentees' careers regardless of their choice of paths. These mentees have gone on to make contributions to science and education as professors and lecturers in universities (e.g., Dr. JoAnn Cameron-University of Illinois, Dr. Randy Dahn-Mount Desert Island Biological Laboratory, Dr. Bruce Riley-Texas A&M, Dr. Taka Suzuki-Japanese Science and Technology Agency, Dr. William Todt-Concordia College, Dr. Matt Harris, Harvard), as research directors in companies (e.g., Dr. Nick Caruccio-Epicentre Biotechnologies), and as administrators at funding agencies (e.g., Dr. Jill Carrington, NIDDK). Matt Harris, a former graduate student said this about John's contributions: *"In thinking about my time in John's lab what stands out is his thoughtful mentoring of the people in, and associated with his lab. We students were a diverse, creative lot, and in retrospect, quite rough around the edges. John recognized individual potential and shaped each student's conceptual and technical abilities using intellectual passion for science as the driving force for change. John led by example—a mold that we his students were not to form, but rather learn from and adapt our individual talents and characters to become our own scientist. I think this training is apparent in the individual advances of his students in their work while in the lab and as independent scientists. My interactions with him since I have left the lab have been as supportive, even to share his remembrances on starting his lab as I struggle with the same. One memory he shared from those early days is his panic, questioning of the prospects of the future, as he stared at a lab having nothing but a trash can and no test tubes! Looking back, it is clear that he has left quite a significant impact on science, both intellectually and in the lineage of researchers he fostered. Test tubes don't provide this type of accomplishment, it is through his innate abilities as scientist, mentor, and friend."* Another account by Sean Hasso, another former graduate student: *"It is his quiet reserve and infectious enthusiasm that inspires his students and colleagues with a sense of excitement that I have yet to see from any other scientist. I like many others owe a debt of gratitude to John for being a mentor, a colleague, and a friend."*

In 2009, John made the difficult decision to officially retire. Beginning in 2010, John transitioned to Professor Emeritus in the School of Medicine and Public Health at the University of Wisconsin-Madison, where he continues his informal mentoring and is actively working on "several more manuscripts." While we hope to continue to benefit from John's advice, wisdom and scientific insight for many years to come, it seems a fitting time to recognize the lifetime of contributions he has made to the field of developmental biology generally, and to so many members of this community individually (Fig. 4).

In closing, the authors of this introduction would like to offer our own words of thanks. While none of the three of us were formally trained in John's laboratory, we each have benefitted more times than we could possibly count on the advice, encouragement, and occasional gentle prodding from John. He has offered both his passion and his thoughtfulness to us openly and often, and we are grateful for the contributions he continues to make in our lives.

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