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IN MEMORIAM

Suzanne Eaton (1959–2019): A pioneer in quantitative tissue morphogenesis

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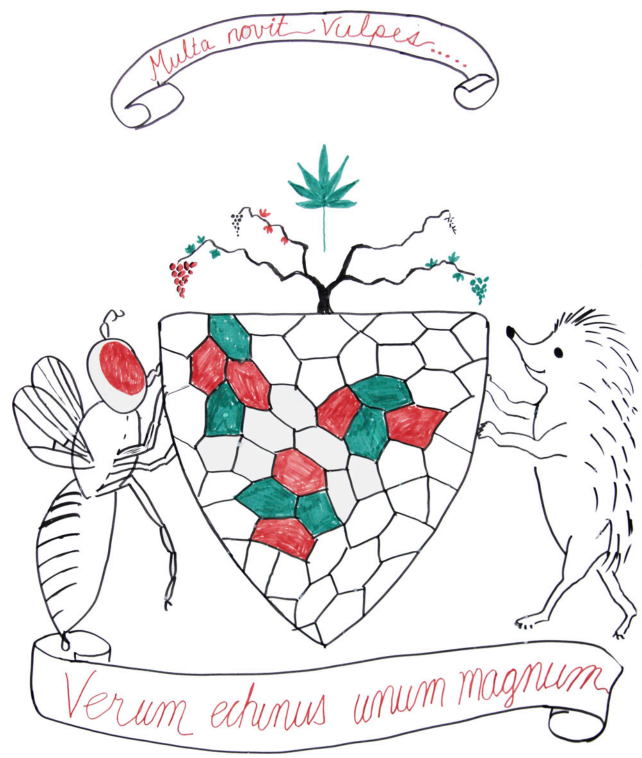
Multa novit vulpes, verum echinus unum magnum ("A fox knows many things, but a hedgehog one important thing"). This proverb was written on a poster plastered to the door of Suzanne Eaton's laboratory, together with a drawing she made (see cartoon drawing). It goes back to the ancient Greek poet Archilochus (c.680–c.645 BC) and has been included, after translation into Latin, in *Adagia*, a famous collection of Greek and Latin proverbs compiled by the Dutch humanist Erasmus von Rotterdam (1466–1536). More recently, the proverb served as the origin of the title of an essay on Leo N. Tolstoy, written by the philosopher Isaiah Berlin, called "The Hedgehog and the Fox," published in 1953. In that essay, Berlin distinguished two classes of thinkers and writers, "foxes" and "hedgehogs." While the first category includes people who are attracted by the complexity of the world, which does, however, not allow one to subsume everything under a single idea, the latter are those who relate everything to a single concept, a coherent universal principal. Is it possible, based on this distinction, to define Suzanne as a fox or a hedgehog?

Suzanne completed her PhD in 1988 at the University of Los Angeles in the laboratory of Kathryn Calame, where she identified promoter sequences and their role in transcriptional regulation of immunoglobin heavy chain and T cell receptor genes. From there, she moved to the laboratory of Tom Kornberg at the University of California, San Francisco, for her postdoctoral studies to learn more about the development of multicellular organisms, in particular of the fruit fly *Drosophila melanogaster*. In Kornberg's group, she laid down the basis of two topics that fascinated her and not only remained recurrent themes throughout her scientific career but eventually merged: signaling via Hedgehog and pattern formation and morphogenesis of the fly wing. In 1993, Suzanne moved to the European Molecular Biology Laboratory in Heidelberg, Germany, where she worked with Kai Simons to study epithelial polarity, focusing on the role of small GTPases for cell shape changes in the developing *Drosophila* wing. While in Simons' laboratory she explored the possibility that lipid microdomains play a role for genetically regulated developmental processes, thus linking two separate research areas. Strikingly, and important for her future work, this led to the discovery, published in 1999 together with Simons, that the N-terminal portion of her "old friend" Hedgehog was associated with membrane nanodomains. Already at this early stage of her career she realized the importance of the connection between these two—at first glance, separate



Cartoon drawn by Suzanne Eaton illustrating her view on the Latin proverb. The pattern carried by the hedgehog and the fly is likely to depict the rearranging cells during pupal development of the *Drosophila* wing.

fields—epithelial morphogenesis and lipid biochemistry. This was before the time when developmental biologists started to focus on the cell and its behavior as the basis for understanding developmental processes and started using novel cell biological tools that were becoming available to achieve a more comprehensive view on the role of cell polarity, cell adhesion, cell division, or cell–cell interactions on tissue formation, to mention just a few. Suzanne became one of the leaders in the fusion of cell biology with developmental biology.

In this marriage of fields, she really flourished after her move to Dresden in 2000 to build up the new Max Planck Institute of Molecular Cell Biology and Genetics. The mission of the institute was to find out "how cells form tissues." The goal was to combine not only cell and developmental biology with genetics, but also

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to include physics as a means to understand the basic principles that guide tissue formation. In that, Suzanne was in her own league because she combined in one person mathematics, physics, and cell and developmental biology, and so she became a creative and inspiring pathfinder for the project. She had not only the depth of knowledge that was required for this Herculean task but also the vision and the courage to embark on this project. As she stated in an interview published in 2013 in *JCB* (where she admitted that Mr. Spock from *Star Trek* was one of her role models): "One can take a rational approach to incomprehensible things. If you accept them, then you can think about what they might mean" (Sedwick, 2013).

Frank Jülicher became an important partner for Suzanne when he was recruited as a director to the newly established Max Planck Institute for the Physics of Complex Systems in Dresden. Since the two institutes were located some miles apart, a shuttle service was established to promote this and other collaborations. This was, to quote and extend a well-known phrase, the beginning of a beautiful friendship and very successful collaboration between Frank and Suzanne. Their work was among the first to elucidate how physical principles contribute to our understanding of developmental processes. For this, Suzanne focused again on the developing wing of *Drosophila*, initially a simple sac of a few epithelial cells, which proliferate during larval stages to give rise to a complex, three-dimensional structure that ultimately develops into the wing of the adult fly. Suzanne's group had elegantly shown how the randomly organized epithelial cells in the larval and early pupal wing epithelium undergo major rearrangements, which ultimately result in a hexagonal packing geometry. This process is under the control of the so-called planar cell polarity (PCP) genes. In their first collaborative paper (Farhadifar et al., 2007) Suzanne's and Frank's groups used a brilliant combination of theory and experiments involving imaging and laser ablation to come up with a comprehensive vertex model for how the proliferating wing achieves its shape. They analyzed how cell mechanics, adhesion, and cortical connectivity contribute to the packing geometry and morphology. They could identify two types of interacting networks, one hexagonal and solid-like and the other soft and liquid-like. Because of the liquid-like material properties, the developing wing patterns can easily be remodeled. The beauty of this analysis is that the packing geometries observed in vivo correspond to local minima of an energy function in their vertex model. Simulations showed that introducing fluctuations in line tension, which could correspond to fluctuations in adhesion and contractility, are sufficient to drive tissue remodeling. In a more recent paper (Iyer et al., 2019), E-cadherin was identified as a mechanosensitive regulator of epithelial viscoelasticity. Epithelial stress induces dissociation of E-cadherin from the cell junctions, leading to removal by endocytosis.

In subsequent work, they extended their analysis to demonstrate that shortly after prepupal stages forces, caused by contraction of the wing hinge region, exert long-range influences on the wing proper by inducing elongation of cells and thus narrowing of the wing tissue, mediated by cell shape changes, cell rearrangements, and cell divisions. Thereby, they also solved a controversial, long-debated question on the global mechanism that led to the polarization of PCP proteins along the proximo-distal axis of the wing. They demonstrated that this pattern is not specified by morphogen gradients as previously assumed but by the morphogenetic process itself and could be predicted by the vertex model. The global PCP pattern develops early and is maintained during growth (Sagner et al., 2012).

Suzanne Eaton. Photo courtesy of Max Planck Institute of Molecular Cell Biology and Genetics, Dresden.

Suzanne's second major interest, signaling by the secreted morphogen Hedgehog, goes back to her studies in the Kornberg laboratory. In a seminal paper published in 2005, she again was at the forefront of merging two scientific fields—growth control and pattern formation by morphogen gradients and circulatory lipoproteins, better known for their role in lipid transport and heart disease in humans. Her laboratory demonstrated that the association of Hedgehog and a second morphogen, Wingless, with lipoprotein particles determines their range of signaling. This work not only had an enormous impact on understanding short- and long-range spreading of morphogens but also established Hedgehog as an endocrine hormone, which coordinates the response of several tissues depending on the availability of nutrients. Moreover, she discovered a novel role for endocannabinoids as systemic inhibitors of the Hedgehog signaling pathway in human blood serum and in the hemolymph of *Drosophila* larvae (Khaliullina et al., 2015). This elicited a novel view on the role of Hedgehog and its regulator in development, but also in tissue homeostasis and cancer, not only in flies but also in mammals, where Hedgehog plays a similarly important systemic role. The fact that wing disc cells do not make the lipoproteins themselves (they are produced in the fat body) means that not only lipidated proteins but also lipids on the lipoproteins come from the systemic circulation. This opened up the interesting possibility that systemic lipoproteins could regulate cellular nutrition and lipid metabolism, and in this way they affect local signaling in a developing tissue. From there, Suzanne broadened her view on more general roles of metabolism, linking her results to yet another, distantly related research area, namely, the role of the diet for the ability of an organism (the fly) to sustain environmental changes and in particular temperature changes. At temperatures below 15°C, *Drosophila* prefers plant-based rather than yeast-based food. Plant food, which is rich in unsaturated fatty acids, modifies the lipid composition and hence the biophysical properties of cell membranes, thus allowing survival at lower temperatures (Brankatschk et al., 2018). These results open up exciting, novel perspectives of how nutrition may shape tissue function.

Looking at her oeuvre and the way she developed and expanded her various topics over the years brings us back to the question of whether we should call Suzanne a fox or a hedgehog. On the one hand, she has clearly frequently been a fox (those who pursue many ends, often unrelated and even contradictory) because she used multiple strategies and approaches to solve questions spanning a wide area of topics from molecular biology, genetics, and biochemistry to mathematics, physics, and theory. On the other hand, from her work on individual genes (or even only on parts of genes, e.g., promoters) or on proteins and lipids, she had moved in a different direction. She was looking for unity among molecular complexity. Suzanne had assembled a fascinating, completely novel mix of morphogens, metabolism, and mechanics in her pursuit of how morphogenesis works. She could therefore be considered a hedgehog (who relates everything to a single, universal, organizing principle). She was on track to cope with complexity in such a masterful way that a universal unifying principle was bound to emerge. It was also a search for beauty at the molecular level. The patterns emerging in the developing wing could be likened to beautiful knitting patterns, which are often based on mathematical structures, where each unit, even if very simple on its own, is indispensable and contributes to the beauty of the whole.

Suzanne Eaton was unique in many respects. One could say that she represented a modern Renaissance scientist in the sheer scope of her activities. She was a wife, a mother, and a brilliant piano player. She loved sports (she was a Taekwondo black belt), culture, and above all science. Science was her passion. Her all-round personality made her a master in connecting facts and findings in separate fields to come up with startling explanations. And she had this overwhelming enthusiasm that made the impossible possible. When she said, "Ha, this is so interesting," she really meant it. And she did that often! Her passion and intensity were infectious. You never left her without carrying with you a novel idea to think of, be it related to your own scientific project, to a philosophical problem, or to the last book you read. Was it not amazing how Suzanne could ask questions at seminars? She could ask questions on any subject matter and, more importantly, they were questions that you could see astonished and amazed the speaker by their precision and insight. She always hit the nail on the head with her incisive remarks!

Suzanne Eaton has been an outstanding role model for our whole community. Both her way of doing research and her compassion for others have been truly inspiring and will remain with us and enlighten us, we hope, forever.

Brankatschk, M., T. Gutmann, O. Knittelfelder, A. Palladini, E. Prince, M. Grzybek, B. Brankatschk, A. Shevchenko, Ü. Coskun, and S. Eaton. 2018. A Temperature-Dependent Switch in Feeding Preference Improves *Drosophila* Development and Survival in the Cold. *Dev. Cell.* 46:781–793.e4. https://doi.org/10.1016/j.devcel.2018.05.028

Farhadifar, R., J.C. Röper, B. Aigouy, S. Eaton, and F. Jülicher. 2007. The influence of cell mechanics, cell-cell interactions, and proliferation on epithelial packing. *Curr. Biol.* 17: 2095–2104. https://doi.org/10.1016/j.cub.2007.11.049

Iyer, K.V., R. Piscitello-Gómez, J. Paijmans, F. Jülicher, and S. Eaton. 2019. Epithelial viscoelasticity is regulated by mechanosensitive E-cadherin turnover. *Curr. Biol.* 29: 578–591.e5. https://doi.org/10.1016/j.cub.2019.01.021

Khaliullina, H., M. Bilgin, J.L. Sampaio, A. Shevchenko, and S. Eaton. 2015. Endocannabinoids are conserved inhibitors of the Hedgehog pathway. *Proc. Natl. Acad. Sci. USA.* 112:3415–3420. https://doi.org/10.1073/pnas.1416463112

Sagner, A., M. Merkel, B. Aigouy, J. Gaebel, M. Brankatschk, F. Jülicher, and S. Eaton. 2012. Establishment of global patterns of planar polarity during growth of the *Drosophila* wing epithelium. *Curr. Biol.* 22:1296–1301. https://doi.org/10.1016/j.cub.2012.04.066

Sedwick, C. 2013. Suzanne Eaton: The beautiful logic of development. *J. Cell Biol.* 202:184–185. https://doi.org/10.1083/jcb.2022pi