Andrew Ewald: Understanding cellular cooperation

Andrea Marat

Ewald takes a multidisciplinary collaborative approach to study epithelial morphogenesis

Andy Ewald moved to suburban Philadelphia from Taipei, Taiwan, with his family at a young age, becoming a lifelong Phillies, Eagles, and Flyers fan. He developed an early interest in science, encouraged by regular visits to science museums with his mother and brothers.

His first scientific mentor was his father, an engineer, who was also a skilled microscopist having also done work on the structure of cell membranes in the 1960s. Growing up, Ewald and his father had stimulating discussions about number theory, engineering principles, and astronomy, and his father was able to introduce him to astronomers and biologists.

He started out as an undergraduate in physics at Haverford College, with the intention of studying structural biophysics in graduate school. However, he became captivated during an interview at Caltech when Scott Fraser showed him a time-lapse movie of brain formation. Ewald then did his PhD thesis work with Fraser developing cutting-edge light microscopy techniques and applying them to understand the morphogenesis of early avian and amphibian embryos, highly collaborative work that benefitted from deep interactions with John Wallingford and Richard Harland.

For his postdoctoral work he wanted to focus on collective, as opposed to single-cell, migration, and he wanted to work in a mammalian system. He found his specific direction after hearing Zena Werb speak at a Gordon Research Conference; it was a career changing experience in an hour. Her talk on the regulation of lung development by metalloproteinases was stunning and led him to appreciate the information content of the extracellular matrix and the potential for proteolysis to generate new signals. He joined her laboratory to exploit the potential of 3D culture to bring together imaging, genetics, and molecular analysis to study tissue and organ formation and pathogenesis, benefiting greatly from collaborative interactions with Mina Bissell, Gabrielle Bergers, and Keith Mostov.

He branched out on his own, starting a laboratory at John Hopkins in 2008, where he continues studying epithelial morphogenesis with a very multidisciplinary approach. We contacted him to learn more.

What first drew you to study epithelial morphogenesis?

From my first days of graduate school, my goal has been to understand in molecular detail how changes in cell behavior drive changes in tissue and organ level structure and function. I thought that a truly satisfying explanation would account for how cells integrate their many inputs to make decisions and how groups of cells cooperate and compete to drive these tissue levels outcomes. I think it is fair to say that I did not fully appreciate at the time how ambitious this goal was nor how much technique development would be required. It is 19 years since I started my PhD and we are now getting to achieve these goals consistently.

"Cells are not just bags of DNA with some interesting mutations but instead social creatures living a crowded life."

What are you currently working on? What is up next for you?

My laboratory has three broad directions. In the first, we seek to understand how mammary epithelial tubes elongate, bifurcate, and polarize during normal development. We have defined the basic cell movements during each process and identified key regulators of each step (1). We are now collaborating with engineers to integrate our experimental understanding into predictive models. The second area focuses on using 3D culture and animal models to understand how the tumor microenvironment cooperates with genetic changes to affect cell behavior within intact tissues. We have demonstrated that the extracellular matrix is a potent regulator of cancer invasion (2), that activation of individual signaling nodes can drive complex tissue level behaviors (1), and that mammary cells can be induced to disseminate without losing their epithelial character (3). We are now extending these efforts by working with systems biologists to understand how information flows from DNA to protein to signaling as cells reprogram from normal to malignant phenotypes, and with oncologists to identify targets for anti-metastatic therapy. The third area focuses on understanding the metastatic process in preclinical models and in human patients. We have used 3D culture models to identify common molecular programs deployed in cancer cells during invasion across the molecular subtypes of breast cancer (4) and to show that metastasis is a collaborative process, achieved by groups of cells (5). We are collaborating with surgeons, oncologists, and pathologists to test these ideas in both archival human breast tumor samples and in live 3D cultures of primary and metastatic human tumor tissue. Across all three projects, we are continuing to deepen our interactions with both physical scientists and clinicians.

Ewald in his office. PHOTO COURTESY OF ANDY EWALD

What kind of approach do you bring to your work?

I trained across very different disciplines, and I think each contributed to my approach. From physics I bring a strong facility with cutting-edge instrumentation and a quantitative mindset that seeks to isolate and identify the key (first-order) regulators of a process. From developmental biology, I bring the framework that mutations are rarely going to invent new pathways and that disease instead most commonly results from normal processes occurring in the wrong time, wrong place, or to the wrong extent. From UCSF, I bring the conviction that cells are not just bags of DNA with some interesting

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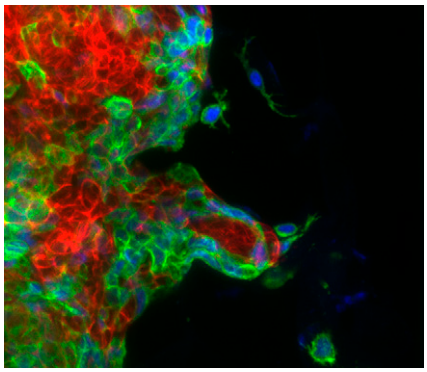

A mammary organoid was genetically engineered so that a subset of its cells (green) could inducibly express the transcription factor Twist1 (blue), while the remaining cells remain Twist1- (red). This image demonstrates that Twist1+ epithelial cells can escape from within a normal epithelial environment (3). IMAGE COURTESY OF ELIAH SHAMIR

mutations but instead social creatures living a crowded life surrounded by other cell types and information rich matrices, both responding to and modifying their microenvironment. My time at Johns Hopkins has been marked by deep interactions with diverse physicians and the experience that clinical observations really can inform our laboratory experiments. The doctors here really look to our mechanism-based research to deliver insights that can shape the next generation of diagnoses and treatments.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? What were you unprepared for?

Both Scott and Zena were outstanding role models for the two key roles of a PI in the laboratory: first, to recruit and motivate top talent and, second, to raise enough money to allow the laboratory to do ambitious, groundbreaking work. They were also both very good at shielding the laboratory from the bureaucracy and fundraising. I really got to focus on the science. I have tried to do the same for my trainees, despite the challenging climate for science in the past decade. I was least prepared for how essentially reactive I need to be as a professor, for how many key factors are beyond my control. I planned out my postdoc pretty effectively and hit every key milestone on the timing I anticipated. In contrast, some things have gone much faster than I anticipated in my independent position, others slower.

What has been the biggest accomplishment in your career so far?

Our integration of physical, biological, and clinical insights is enabling us to uncover general principles by which epithelial tissues are constructed and general mechanisms by which they are disrupted during disease processes. It has been particularly fun that our work in the mammary gland and breast cancer has had such immediate impact on researchers studying other epithelial organs and diseases. In the next stage, my goal is to get a systems level understanding of information flow in these tissues and to leverage those insights to identify targetable nodes for antimetastatic therapy. I am also very proud of my students and fellows. I genuinely believe I am training, and have trained, a cohort of scientists who will become remarkable independent investigators.

What has been the biggest challenge in your career so far?

Beginning as an assistant professor at Johns Hopkins just weeks before the economy crashed, I had to learn how to fund my laboratory in the worst climate of the past 50 yr. I survived this contraction through a combination of support from my department and Johns Hopkins, terrific productivity from my trainees, and persistence as I assembled a diversified portfolio of federal and foundation based grant support. As a first year PhD student, I was told by Rusty Lansford, then a postdoc with Scott Fraser, that the most important feature in a scientist is the ability to pick yourself up off the ground after you get knocked down. He was right.

"None of us is promised a long career, and so it is really critical to be working on topics that interest you."

What is the best advice you have been given?

Exercise. Preferably daily, at least consistently. It is an effective remedy to life's disappointments and has a really profoundly positive effect on mental and physical health.

What hobbies do you have?

When I turned 40, I decided I needed to pick something really challenging to focus on outside of work. I bought an absurdly nice mountain bike and started riding it three times a week to see how far I could progress. I am very fortunate to live less than five minutes from more than 50 miles of exceptional single-track trails and to have lots of friends who ride. I ended the summer with a 40 mile mountain bike race and really enjoy the social, physical, and mental aspects of the sport. I promise that you can't focus on reviewer three's "constructive criticism" when pedaling through a rock garden, climbing over logs, or descending steep river valleys.

What do you think you would be if you were not a scientist?

Everyone at my high school thought I would end up in law or politics. Maybe I was just argumentative. Fortunately, my twin brother Carl and younger brother Jonathan have these areas covered, and so I can focus on science.

What has been your biggest accomplishment outside of the laboratory?

My family. I am very fortunate to have met my wife, Shannon Marshall, in our very first week of graduate school at Caltech. We have been together since 1998, and I couldn't do this without her. We have two wonderful children, Eleanor, 9, and Michael, 2. Balancing our science careers with our family life keeps us very busy but also very happy and grounded.

Any tips for a successful research career?

Figure out the one question you find most necessary to answer. It should be important, it should at least potentially be answerable, and it should be something that you really want to study. Then get to work on answering it. Once you do succeed, carefully identify the next important question and then answer it, too. None of us is promised a long career, and so it is really critical to be working on topics that interest you. Don't forget to publish regularly on the way to achieving the big goals. Finally, find the right balance of internal orientation vs. responsiveness to input from others.

1. Huebner, R.J., et al. 2016. *Development.* 143:983–993.
2. Nguyen-Ngoc, K.-V., et al. 2012. *Proc. Natl. Acad. Sci. USA.* 109:E2595–E2604.
3. Shamir, E.R., et al. 2014. *J. Cell Biol.* 204:839–856.
4. Cheung, K.J., et al. 2013. *Cell.* 155:1639–1651.
5. Cheung, K.J., et al. 2016. *Proc. Natl. Acad. Sci. USA.* 113:E854–E863.

Ewald and his daughter, Eleanor, just after completing the MoCo Epic Mountain Bike ride. PHOTO COURTESY OF ANDY EWALD