

## Eugenia Piddini: Chasing how cells outcompete one another

Piddini brings a collaborative spirit to the study of cellular competition.

In the tight-knit Sicilian tradition, Eugenia Piddini lived with her parents while attending college at the University of Palermo. But her family had always encouraged her to think ambitiously about her career, and so at 25, she struck out for mainland Europe to launch her research career in cell biology, convincing the EMBL in Heidelberg to give her a PhD candidate spot. There, she studied the motor protein KIF9 and its role in cell shape changes with Carlos Dotti.

In 2002 she began postdoctoral work with Jean-Paul “J.P.” Vincent at the MRC National Institute for Medical Research in London to explore how cells integrate signals from morphogen gradients during *Drosophila* development, but an unexpected experimental detour led her into the field of cellular competition (1).

In 2010, Piddini established her own group at the Gurdon Institute at the University of Cambridge, UK. Her group has shown that cell competition takes place in adult tissues during homeostasis (2), between tumor cells and host tissue (3, 4), and in response to mechanical pressure from neighboring cells (5).

In a conversation with *JCB*, Piddini explains why cell competition could change our approach to cancer therapies and why she favors collaboration over competition in the laboratory.

### ESTABLISHING A FOOTHOLD

*How did you convince the EMBL to give you a chance at graduate school?*

It is not easy to come from the University of Palermo and go somewhere as prestigious as EMBL. But in Palermo I was surrounded by truly dedicated professors who were trying to make the most out of limited resources. I applied for the PhD program at EMBL and I was rejected. I was devastated.

Another student from Palermo, Davide Corona, who had already started a PhD there wrote to me and said, “Not everything is lost. Maybe you should just let them

know how important it is for you.” I took his advice and wrote to two PIs, saying all I wanted was a chance to be interviewed.

And there you go. I changed the course of things because they interviewed me and gave me a studentship. This was my big leap from Sicily to Heidelberg.

*How did you go from cellular integration to cellular infighting during your postdoc?*

For several years, I concentrated on the question of how cells, together with their neighbors, integrate and interpret morphogen gradients. But we realized that cells were also communicating with respect to cell survival.

I was trying to generate large patches of wing disc tissue that were devoid of *Wingless* (Wg) signaling. Other work suggested Wg was a survival signal for disc cells, so we thought that generating these patches was going to be a challenge. To our surprise, however, we generated these large patches of tissue that didn’t die in the absence of Wg signaling. We realized their death was context-dependent. Essentially, they only died if they were surrounded by cells that were still able to signal, and which could therefore outcompete them.

This was a purely serendipitous observation from an experiment I had done for a completely different reason. We were going to look at signaling output and we realized we should be looking at why the cells were still alive, instead.

*And you have pursued the phenomenon of cell competition ever since?*

I should give credit to J.P., because he gave me the freedom to pursue this observation. He had the boldness to say, “Go ahead and see what’s happening.”

Nowadays, scientific freedom is a scarcer commodity than it used to be. Projects come with tight milestones and there’s little scope for detours. I think it’s important for scientists to keep an open mind,



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Eugenia Piddini

to be on the lookout for the unexpected. This result ended up completely defining who I am as a scientist.

### SURVIVAL OF THE FITTEST CELL

*What fascinated you about cells competing?*

This was the concept that a cell is viable as long as its neighbors are in the same state. But the moment its neighbors are better, or fitter, the cell dies. It’s such a dramatic and mysterious observation. How could cells be persuaded to die, given that on their own they were viable?

The potential implications grabbed my attention, too. It means that every day in our bodies there’s a quality control mechanism making sure that things don’t go wrong. Eventually diseases do happen and organisms do age, but this was potentially an important defense against all of that.

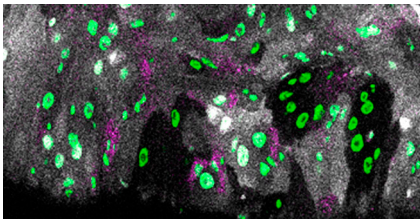
By communicating with one another, cells are able to influence decisions as to whether they survive or die. Cells make that decision, actively, all the time. They have to take into account availability of nutrients, levels of stress. But another factor is the fitness of their neighbors. I think the closest analogy would be Darwinian selection, survival of the fittest.

*Why did you choose the adult fly midgut as a model system?*

The hypothesis was that if cells have cancer-promoting mutations to become “winners,”

**“How could cells be persuaded to die, given that on their own they were viable?”**

IMAGE COURTESY OF GOLNAR KOLAHGAR, PIDDINI LAB



**Competition in the *Drosophila* midgut between loser cells (white) and winner cells (black). Dying loser cells are labeled purple.**

then they can kill their neighbors to free up space to colonize.

When I started my group, I wanted to ask whether that was true using a system that was genetically tractable and where we could generate something as close as possible to a tumor. The adult intestine of the fly is maintained by a population of intestinal stem cells. These give rise to differentiated cells, which perform the digestive and absorptive functions of the gut. It is sort of a toy, miniaturized version of our own intestine.

#### *How did you show that cell competition was important in cancer?*

Once we had a system to study competition in adult tissues, we could generate a benign tumor, much like an intestinal adenoma in humans. The gene we mutate to induce them, *APC*, is the same.

Now we could ask whether the tumor would engage in cell competition with the host and whether this was relevant to tumor growth? The results were beyond my wildest expectations. We found that cell competition was really happening between the tumor and the host, and that we could substantially reduce the tumor's growth by interfering with this competition.

Whenever we protected the host tissue from being killed using apoptosis inhibitors, the tumor was no longer able to expand, highlighting the importance of competition and local cell communication during tumor growth. Now, we aim to reproduce these observations in mouse cancer models.

#### *How does this change our view of cancer?*

It is not enough for mutations to simply provide a faster cell cycle. Cancer researchers have been focused on the idea that mutations make cells proliferate uncontrollably, and, therefore, they form a tumor. But the "therefore" is not really a given. It will not happen

unless the tumor is able to kill its surrounding host cells to free space it can grow into.

#### *How do cells communicate their fitness levels to each other?*

This is one of the most important questions we need to answer in this field. We just have pieces of the puzzle. I'd go as far as saying we have pieces of several puzzles—it's becoming increasingly clear that cells have more than one way to compete.

The effort has been to try and consolidate the information coming from mutations in *APC*, *Myc*, ribosomal mutations, or polarity genes—all of which have been shown to affect cellular competition—into one uniform pathway. But now we know that cells use more than one pathway to compete and that complicates things.

Our most recent discovery is that cells can also use purely mechanical insults to compete. Cells can become crowded as they interact with their fitter neighbors and this can cause enough stress to kill them.

#### **GLOBE-TROTTING**

##### *How do you promote cohesion among your internationally diverse group?*

We do a lot of work in teams in my lab and I think that helps keep up the morale and the motivation. People realize that they only benefit by working together. If they're not too protective about being the only one to work on their project, they realize they can really work on many more things as part of a team.

We do a lot of brainstorming sessions. One of my postdocs, Golnar Kolahgar, brought in this Magic Whiteboard™, a whiteboard you unroll and stick on the wall. It allows you to turn the whole office wall into a huge board. My lab really enjoys brainstorming in front of these boards and then, when the plan is laid out, we take a photo and send it to all of the lab members.

##### *Your husband, Rafael Carazo Salas, is also a cell biologist at the University of Cambridge. How did you solve the two-body problem?*

In 2008, he took a group leader position at ETH Zurich while I was still finishing my

postdoc, with the understanding that I would also look for positions in Zurich. Unfortunately, there were no job offers for me in Zurich. We had already been commuting for three years and did not want to live apart any longer.

So, even though he was only a year into starting his group, he made the bold decision to go on the job trail again. We have always been supportive of each other and we make each other stronger personally and scientifically. Rafael was prepared to take a toll in his career to give me a shot at being a PI. I will always be grateful for that opportunity.

##### *What do you do when not thinking about cell competition?*

I enjoy traveling a lot. My husband and I are blessed to come from two beautiful countries—Sicily and Costa Rica—so just going and visiting our families is pleasurable enough. Because I come from an island, I crave the sea. I love swimming, and I can spend hours snorkeling. It completely steals my attention. I am fully entertained looking at little creatures in their underwater life.

**"It is not enough for [oncogenic] mutations to simply provide a faster cell cycle."**

1. Vincent, J.-P., et al. 2011. *Dev. Cell.* 21:366–374.
2. Kolahgar, G., et al. 2015. *Dev. Cell.* 34:297–309.
3. Wagstaff, L., G. Kolahgar, and E. Piddini. 2013. *Trends Cell Biol.* 23:160–167.
4. Suijkerbuijk, S.J.E., et al. 2016. *Curr. Biol.* 26:428–438.
5. Wagstaff, L., et al. 2016. *Nat. Comms.* <http://dx.doi.org/10.1038/ncomms11373>



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**Piddini and her husband go snorkeling in the Maldives.**