Elise's holey relic.

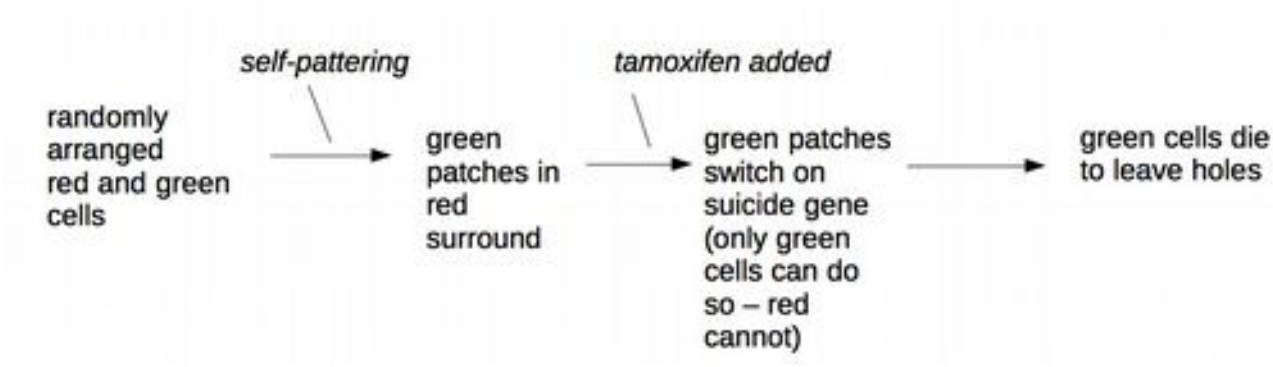
The process of embryonic development typically follows a sequence of events; patterning, followed by differentiation, followed by morphogenesis. In patterning, an initially homogenous tissue acquires internal differences so that some cells acquire a state (eg activation of signalling pathways) that others do not. This causes these cells to express different genes ('differentiation'). Often, some of these genes cause the cells to change shape or behaviour to impose a new shape on the tissue itself (for example, by bending to make a pocket in an otherwise bent cell sheet): making shape is 'morphogenesis'. After a period of growth, further sequences of patterning, differentiation and morphogenesis may follow. The earliest set up very basic anatomical features ('this is the head, this is the tail') and later ones add finer and finer details ('this is the first rib, this is the second' etc.).

One of the goals of this laboratory is to construct synthetic biological genetic modules that will drive cells that have no intrinsic developmental potential, to perform developmental acts. There are two reasons that we do this. One is to test whether embryologists' ideas on how these basic developmental events work are correct: if we really understand something, we ought to be able to use our knowledge to build it from scratch. The other is, ultimately, to make custom-tissues that may one day be used, after much safety testing, for medical purposes.

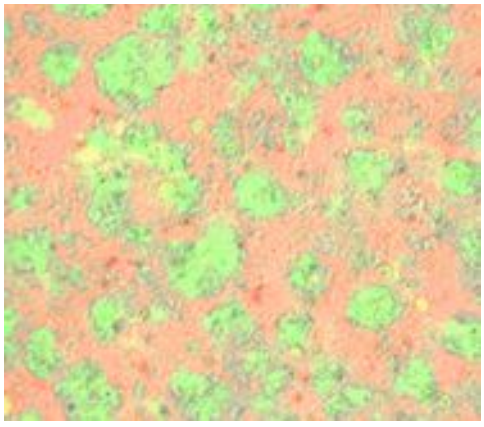
In an earlier blog (*Painting by numbers*), I described how Elise Cachat, then a postdoctoral fellow in my lab, constructed a self-patterning system that caused populations of cultured human cells to make patterns rather like the pattern of patches on a cow. This was the first step in our attempt to construct a whole patterning-differentiation-morphogenesis cycle. I am pleased to say that Elise continued to work with me and, with assistance from Weijia Liu, also of this lab, we have just published what we believe to be the first example of a synthetic patterning-differentiation-morphogenesis sequence.

Wanting to keep things as simple as possible, we chose cell suicide to be the morphogenetic mechanism. Cell suicide (elective cell death/ apoptosis) is an important part of natural development. It was responsible, for example, for eliminating the webs between your fingers or eliminating the internal reproductive plumbing of the sex that you are not. The idea is that we could use this to make a 'tissue' full of holes. Elise took as her starting point the self-patterning system we had already published, in which the pattern was demonstrated by cells expressing either the gene for a

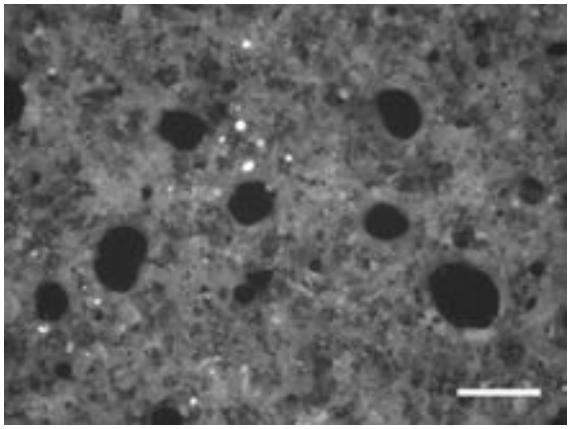
red-fluorescing protein or the gene for a green-fluorescing protein. She engineered into the cells a new gene, which would, in the presence of the drug tamoxifen, be active only in the the cells in the green state and cause these cells to kill themselves. This was the general idea:



For the key experiment (there were also many control experiments to verify the system was operating as expected), Elise allowed the system to make a pattern of green patches separated by red cells, in the absence of any tamoxifen. Then, when the pattern was made, she added that drug. The majority of the cells in the green patches quickly disappeared, leaving holes. The relic of the previously intact cell sheet had been transformed into a sieve.



An example of a red/green pattern into which cell organized themselves before the tamoxifen was given.



In a similar patterned sheet, the green cells have now killed themselves, to leave a sheet with holes (the big black circles).

Making holes may not be the most exciting example of morphogenesis, but it is a start. The work has at least provided a clear proof-of-principle that constructing genetic modules to cause cells to make 'designer tissues', by self-patterned morphogenesis, is possible. The next step will be to drive behaviours other than cell death, to make more complex and perhaps 3-dimensional shapes.

I am delighted to be able to report that Elise now has a well-earned faculty position of her own and, as a new lecturer, she is busy setting up a research group to pursue more adventures in synthetic biology, and is teaching the next generation. As always, when a brilliant post-doc earns an independent position, I am left with that strange sad-happy feeling of being sorry to lose an immensely valuable member of the lab, while being delighted to see her academic success. In this particular case, because Elise has remained in Edinburgh, I have also the consolation that I can still enjoy talking with her, and hopefully working together with her, as an independent collaborator and colleague.

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Links

Elise's paper: http://digital-library.theiet.org/content/journals/10.1049/enb.2017.0013