

## Peter Friedl: Painting a picture of cancer immunology

Friedl uses confocal and intravital microscopy to investigate the movement of T cells and cancer cells.

As a child, Peter Friedl never envisioned becoming a scientist. But curiosity and an aptitude for careful observation eventually led him to medical school and then the laboratory, where his work and career are continually evolving.

Friedl completed his MD at Bochum in Germany, then decided to indulge his burgeoning interest in immunology by joining the laboratory of Dr. Kurt Zänker at the University of Witten in Germany. Zänker sent Friedl to collaborate with Peter Noble at McGill University in Canada. There, Friedl studied T cell and cancer cell migration, fell in love with live-cell microscopy, and earned his PhD (1, 2). Since then, Friedl has leveraged the ever-advancing power of microscopy techniques to further his migration studies (3–6) and gain important insights into the different mechanisms of cellular locomotion, and the development of metastasis.

Friedl's work is the product of a creative impulse that finds its expression in long, dark hours behind a microscope. When he is not in one of his laboratories—either the Nijmegen Center for Molecular Life Sciences, Netherlands or the Rudolf Virchow Center in Würzburg, Germany—his creative impulse finds another form: oil painting. We talked with him about his career, the parallels between art and science, and his works in progress.

### TRANSGRESSION

*I understand that you're a trained physician in addition to having a PhD?*

Yes, but I wouldn't say I planned to have things turn out this way from the start. When I was seven or eight, I remember writing in a school essay that I wanted to be a bank manager, like my father. But actually, I didn't have any idea what I wanted to do. In fact, I was something of a troublemaker.

After finishing high school, I took a year off and basically did nothing. That was a very important time for me, because it helped me pull myself together, to figure out what I wanted to do. I realized that I wanted to deal with people and do something meaningful. I did a civil service year in the oncology unit in Nuremberg, and decided to go to medical school there.

*So you completed your medical studies first. What made you decide to pursue a PhD afterwards?*

While I was in medical school, I would become very caught up in questions that went beyond what we had to memorize for our classes. My imagination was always getting in the way of memorization—I kept coming up with all these theories about how things might work, and ways in which I could test my theories. I fell in love with immunology in my third year of medical school, and did an immuno-biological MD thesis in Bochum. So I thought that I should give research a try, and I decided to join the University of Witten, which is a small private university in Germany, and I worked with Dr. Zänker there.

### TRANSFORMATION

*With Dr. Zänker, you started researching cell migration—what first interested you in that topic?*

My father had just died of cancer, and immunology was my first love, so I

wanted to bridge the two subjects somehow. Studying how T cells attack a tumor fell perfectly into my personal motivation and interest. Zänker sent me over to McGill to learn cell tracking in the laboratory of Peter Noble, a physiologist, and I joined a sort of ad-hoc graduate program there; I was Noble's last graduate student. We studied T cells moving



Peter Friedl

in collagen because you can't accurately observe T cell locomotion in 2D. They are suspension cells and they float around, so standard 2D cultures don't replicate in vivo conditions very well. I remember when I did my very first movie of T cells moving in a 3D collagen gel. It was a black and white, poor quality movie, but the moment I saw it, I knew this was exactly the right thing for me.

*Is there a particular technology that you consider to have been transformative for your work?*

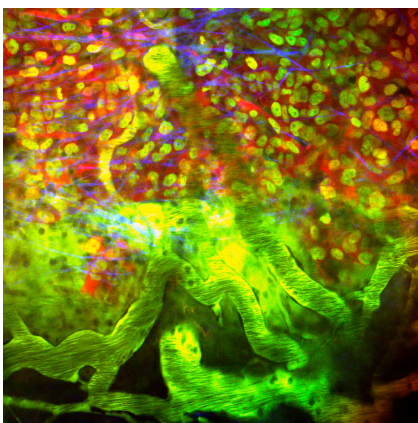
The first transformation happened when I touched a confocal for the first time. With bright field microscopy, you see the collagen matrix as a grayish, noisy background. It looks like jam. With a confocal, we saw the reflection pattern of the collagen fibers for the first time. This was totally revealing! We saw that T cells moved like little monkeys in this jungle of collagen. They never change the matrix structure, they just squeeze themselves through the gaps between fibers. Many cancer cells, on the other hand, remodel the matrix as they move, leaving behind hollow tube-like tracks.

**"We saw that T cells moved like little monkeys in this jungle of collagen."**



Various stages of Friedl's *Layers*, a work in progress. (View video compilation of *Layers* at [www.jcb.org](http://www.jcb.org))

As a graduate student at McGill, I'd accidentally made a movie of a primary tumor that gave out groups of cells that moved together, and went through the collagen while maintaining their cell-cell junctions. Of course this was difficult to publish, because we couldn't demonstrate the *in vivo* relevance of this collective movement. The dogma in the field was that cancer cells need to detach and individualize; they still are mostly thought to go as single cells through the tissue to metastasize. But, we recently published a paper where we described how invasive tumor cells remodel the extracellular matrix. They leave the main tumor mass and degrade the tissue matrix but they retain their cell-cell junctions and form a long protrusion. This collective migration creates these root-like structures: very deep, long, multicellular fingers. When our multiphoton imaging platform was finally set up, it let us image deep in actual tissues and observe tumors *in vivo*, and we observed the same phenomenon *in vivo*. It's quite striking—almost beautiful—to look at.



An artistic image created by leakage of fluorescent FITC dextran from a dyed tumor.

### *Beautiful, but a kind of a terrible beauty.*

What we are now starting to appreciate is that in many cases, cancer invasion—and probably also metastatic seeding—is a kind of wrongly tuned morphogenesis that happens in the wrong cell at the wrong time and place. It doesn't have a stop button, so it goes on and on. People have called it a non-healing wound, but you could also call it ill-fated morphogenesis. Neural tube closure, branching morphogenesis, and vascular sprouting are all collective morphogenesis processes that are subverted in cancer.

### TRANSCENDENCE

*Do you still spend a lot of time at the microscope?*

I think almost all microscopists like to stay in touch with the microscope, because watching things in real-time provides different insights from what you get when students or coworkers present images to you. So, whenever we start a new set of experiments, I tend to participate in the imaging myself, until we have the procedures ironed out. It helps me get a more intuitive understanding of the model we're using and the experiments we're running. I've also noticed that not everybody sees the same things, so my views are sometimes complementary to what my students see. I've spent so much time at the microscope that I sometimes find myself dreaming about it.

*As a microscopist, you're probably a very visual person.*

Yes, you could say that. In fact, when I'm not in the laboratory, I like to paint. For me, painting is a way of contemplation. I've never had any formal training, so it's all

autodidactic: I work by trial and error, generating colorful patterns. I tend to go layer by layer, painting over what I don't like. In the end, something is suddenly there that feels complete. I have one piece I've been working on that I've decided I will never finish. I keep painting over it; I think at the moment I'm on layer 30. Maybe one day it'll have 1,000 layers. But I've also started documenting the different stages, and playing them back as a movie, which tells a different story altogether from what's showing on the top layer right now.

*Is your art inspired by your work?*

You could look at some of it and think that's the case, maybe. I don't think of it as being particularly related.

But in a way, art and science are not so dissimilar. I've frequently observed that at some point a scientific finding will detach from the person who first made it. It transcends. It gets a new life, and different interpretations arise from different audiences; people frequently cite papers for something that was not even mentioned in the text, but that appeared in a figure. Paintings also do that; they detach from the person who made them, and get a life of their own for different observers. That is part of what makes both science and art so exciting.

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