

## CAREER DEVELOPMENT : ARTICLES

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Tony Kouzarides

### Creativity and Persistence Overcome Failure

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Tony Kouzarides tells the story of his early career as a comedy of errors. He started his Ph.D. at the [University of Cambridge](#) in the U.K. in 1981 studying the cancer-inducing potential of human cytomegalovirus. After a year of inserting part of the virus's DNA into target cells, the cells showed almost no signs of cancer. He couldn't rule out that other parts of the virus might do it, but he also couldn't publish his early results. What he could publish by the end had more to do with genetic sequencing, an area he did not want to pursue.

After a short postdoc at Cambridge sequencing cytomegalovirus, he landed a second postdoc in a lab in New York studying oncogenes. There, he spent 2 years developing an unconfirmed and unpublishable hunch. On the strength of that record, he deadpanned, he unsuccessfully applied to lead his own research group.

Finally, during the third year of his postdoc, Kouzarides read an article that sparked the connection he needed to do experiments that produced two top-tier publications. Soon after, he secured his [current position as a group leader](#) at [the Gurdon Institute](#) at Cambridge.

He calls it serendipity. Kouzarides's lifelong friend and colleague Keith Blundy says Kouzarides's secret is that "he's a fantastic people person." But there's more to Kouzarides than charisma and good luck. Kouzarides also has a strong commitment to asking what he calls the

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"right questions" and an unusual willingness to bet on his instincts.

### A FRAGILE START

The fear of a null result is sickeningly familiar to most science graduate students. But, Kouzarides says, "partly, it's almost irrelevant how well you do in your Ph.D.," because "once you do your postdoc you really have to prove yourself again."

He didn't know that yet when he was still a student, so he faced a tough decision when his first project nose-dived. His supervisor, [Tony Minson](#) in the [Department of Pathology](#) at Cambridge, says that during Kouzarides's second year, "it became apparent to him and to me that this virus was hundreds of times slower" than they had expected. Kouzarides saved his research project by arranging to work with Bart Barrell's sequencing group in Cambridge's Laboratory of Molecular Biology, where he sequenced parts of the virus's DNA. That decision was "very unusual for a student" to make on his own initiative, Minson says, but Kouzarides was "clear-thinking and independent" from the beginning. "I take no credit!" says Minson.

Kouzarides's clear-minded impulse led to some good interdisciplinary science, says Barrell, now at [the Sanger Institute](#). "It was good for Tony to come over," says Barrell, whose group consisted of sequencing specialists, "because he brought the biology over. We probably got a lot more publications out of cytomegalovirus because of him."

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## BETTING ON HIMSELF

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To capitalize on the virus-sequencing project he'd begun halfway through his Ph.D., Kouzarides did a short postdoc with Barrell. And although Kouzarides was relieved that his sequencing work was paying off in terms of publications, it wasn't what he wanted to do in the long run. "I really was much more interested in oncogenes," he says. So he arranged to do a postdoc with [Edward Ziff](#), now a biochemistry professor at New York University's Langone Medical Center.

Ziff had been working on the *c-fos* gene, which other researchers had shown was oncogenic, "but nobody knew how it worked or caused oncogenesis," Kouzarides says. "My job was to find out why." He identified a short stretch of its sequence that repeatedly coded for leucine, an amino acid. He hypothesized that these leucine repeats permitted the protein to interact with itself or other proteins necessary for cancerous replication. But there was a problem: He had no evidence that it did either.

After his second year in New York, Kouzarides says he was thinking, "Well, I've got no results, but I have a lot of publications from my first postdoc and Ph.D.," so he began applying for jobs. He was able to get a tenure-track job offer, but it was "not in the field that I was interested in. My career would have been about viruses, but I was interested in cancer." He bravely passed on the offer and went back to New York for a third year to pursue his *c-fos* project. "I was really passionate, and I really believed in this hypothesis based on no data!" he marvels now.

The decision paid off that year when he read a paper that showed that *c-jun*, another gene, had similar leucine repeats. He was able to show that the leucine repeats on *c-jun* and *c-fos* "zipped" the proteins together—evidence that C-FOS proteins could interact with other proteins involved in cancerous cell replication. Two *Nature* papers later, he was able to secure a group leader position back at Cambridge, where he's been ever since.

## ASKING THE RIGHT QUESTIONS

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In 1998, Kouzarides approached the technology arm of his major funding source, the charity [Cancer Research UK](#), about developing medical treatments from his work. His case was assigned to his friend Blundy, then a technology transfer manager at [Cancer Research Technology](#), who was charged with helping him create a commercial spinoff. Nobody was more surprised than Blundy by Kouzarides's entrepreneurialism. "I don't remember him being a commercial animal at all," Blundy says. But Kouzarides's networking skills and his willingness to let other experts handle the commercial side made the launch a smooth one. The result was Chroma Therapeutics, a drug-discovery and development company with nearly a dozen products in the pipeline today.

Now that Kouzarides's career is reasonably secure, he can afford to devote more effort to his supervisees. An important part of his job, he says, is to help new postdocs "refocus, to make sure that the path they take is the path in the right direction rather than veering off toward some nonproductive area." One wall in Kouzarides's office testifies to his success as a supervisor. It contains neatly mounted photos of grad students and postdocs celebrating holidays, lab retreats, and the first two quintennial lab reunions he's hosted. At the reunions, dozens of new principal investigators and other former members of his lab converge around him to discuss their work and catch up with one another. Kouzarides cultivates "fantastic camaraderie" in the lab, Blundy says. Kouzarides says, "We have a lot of fun together; ... it is like a big family."

Kouzarides's main piece of advice to his younger colleagues in the lab is to stop and think about the questions they are asking. "Spend as much time as you like thinking about the experiment because if you waste your time doing the wrong experiment, you might as well not do it at all," he says. "Only do the key experiments for the very important questions!" The details are best left to others. He sets the example by taking the members of his lab on an annual retreat to reflect on the state of their work and make plans for the coming year. Kouzarides remains as willing as ever to turn on a dime to pursue a new idea. "His lab is willing to drop everything and take a new direction" when a good opportunity comes up, Blundy says.

Kouzarides says it's hard to overestimate the importance of originality and independent thinking: "Formulate your own questions that haven't been addressed yet."

[Lucas Laursen](#) is a freelance science writer in Cambridge, England.

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