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Taking It Up a Notch

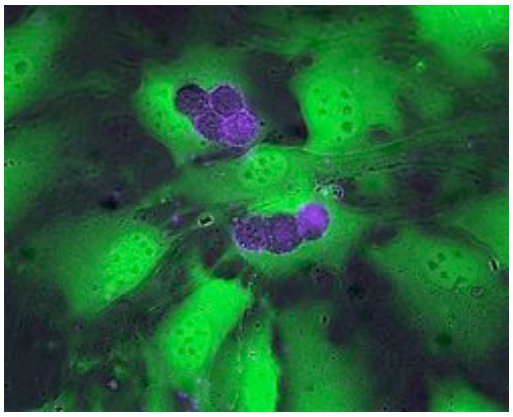
By Jim Oldfield
October 28, 2005

How do you get the cover of a prestigious international science journal? "It's partly having an image that strikes the editors, one they think speaks to an important paper in that issue, and that has the right artistic flair," according to SRI scientist Juan Carlos Zúñiga-Pflücker. Artistic flair? "Editors pick pictures based on … unscientific reasons—composition, art direction, just the way they look. They take the science and showcase it in a way that is pretty, amenable to, or easy on the eye," he says.

It's all about image, baby.

Well, not entirely. "The work has to go beyond that," he adds.

Ah, the work.



Stem cells become T cells: the moment of differentiation. Photo taken with confocal microscope by Thomas Schmitt. (Click image for large version)

Zúñiga-Pflücker's work, featured on the September 2005 cover of Nature Immunology (NI), focuses on T cell development. An essential part of the immune system, T cells orchestrate the immune response, recognizing and attacking viruses, bacteria and even cancerous cells. But T cells grow naturally only inside the thymus, a small organ in the upper chest. So scientists' ability to study their molecular development was limited until recently, when Zúñiga-Pflücker and his graduate student Thomas Schmitt created T cells in a Petri dish by mixing stem cells with a molecule called Delta-like 1. The discovery allowed scientists to study in fundamental detail, for the first time, a mysterious process.

That research breakthrough, published in Nature (a parent publication of NI and one of the most high-profile science journals in the world) is producing new science globally—more than 250 labs are now using it to study T cell creation. Understanding the molecular and cellular basis of T cell development holds the promise of clinical translation. While a ways off, successful application of this discovery—conferring boosted immunity in diseases like AIDS and cancer through controlled multiplication of T cells—would be enormous.

One lab working toward that goal, with a head start on all the others, is Zúñiga-Pflücker's, and that work took a leap forward with the discovery shown on the recent NI cover. Taken by Schmitt, the photo shows stem cells turning into healthy T cells (flush purple), supported by the Delta-like 1 molecules (glowing fluorescent green through introduction of a flourochrome and binding antibody). Zúñiga-Pflücker and student Maria Ciofani discovered that the Delta molecules, in addition to signalling and inducing the T cell creation process, actually support and sustain T cell development via another molecule called Notch.

"Notch is a pretty amazing molecule," says Zúñiga-Pflücker. "It instructs various cell types to choose a lineage when they are still pliable, plastic, or stem-like. And it does that in the immune system by telling cells to become a T cell as opposed to, say, a B cell." So that's the more understood role of Notch: it instructs cells. But what's striking and new with this finding is that Notch also instructs cells beyond their ability to adopt a lineage fate or tissue type. It tells

cells to maintain that choice through its control of receptors that keep them taking in nutrients. He says, "So [Notch] is basically what makes everything work. If you don't have the fuel, the inductive event means nothing. And that's why the paper is coming out in this high-profile journal, because it's a novel way of thinking of how this molecule instructs and maintains the choice taken by the cell."

The next step is to understand which other molecules, pathways and genes mediate T cell development. "The neat thing about science," says Zúñiga-Pflücker, laughing, "is that the work becomes more and more fundamental. You create a circuit of what's going on."

Okay, so getting the cover of a high-profile journal isn't all about pretty pictures. At least that's the image Zúñiga-Pflücker conveys.

Zúñiga-Pflücker holds a Tier 1 Canada Research Chair in Developmental Immunology. The Canadian Institutes for Health Research also supported this work, as it did for Maria Ciofani. The Canada Foundation for Innovation and Ontario Innovation Trust funded the confocal microscope that took the photograph.