

Mickie Bhatia: Embryonic stem cells come of age

Mickie Bhatia wants to tap into the therapeutic potential of human stem cells, and he's finding ways to overcome the obstacles that stand in his way.

From cloning to political controversy, human embryonic stem cells consistently capture newspaper headlines. With remarkable regenerative abilities, stem cells theoretically possess the potential to replace any diseased or damaged tissue. Governments around the world are now encouraging their top stem cell experts to conduct their research at home. In 2006, Canada succeeded in enticing 35-year-old Mickie Bhatia to stay in his native country and direct its first center for human embryonic stem cell research, the Stem Cell and Cancer Research Institute at McMaster University in Ontario.

At McMaster, Bhatia is trying to figure out what controls stem cell differentiation and what defines their environment. He's found that alterations in canonical developmental networks including the Notch, Wnt, and Hedgehog signaling pathways, alter cell differentiation (1). Swapping out one Wnt gene for another, for example, can make a pluripotent cell turn mesodermal (2). Bhatia is also trying to

find ways to distinguish between normal, pluripotent, proliferative cells and those that lead to tumors (3). These so-called cancer stem cells may be to blame for the recurrence of cancer after therapy; they drive tumor growth and spreading, and radiation treatments don't appear to harm them. Finally, Bhatia is looking to harness the power of stem cells without encountering the ethical concerns that go

hand-in-hand with embryonic stem cell research by experimenting with induced pluripotent stem (iPS) cells derived from human skin-derived fibroblasts. If iPS cells can be reliably reprogrammed, they could provide all of the advantages of embryonic stem cells, minus ethical unease. Recently, Bhatia and his colleagues optimized iPS cell generation by

creating markers that identify cells in the process of being reprogrammed (4).

How do the guidelines for using embryonic stem cell lines in Canada compare to the US?

They're not as prescriptive as the rules are in the United States. You can work with established human embryonic stem cell lines as long as appropriate consent was given to derive those lines. And unlike in the US, the rules that determine which lines can be used apply to all stem cell work. If you're doing the work on Canadian soil, you have to follow these guidelines no matter where the money comes from.

Has the recent surge in media attention on stem cells as a result of US policy changes put additional pressure on you?

I think that now the public is going to want to see results. But what isn't talked about enough is that we are actually at a very early stage of understanding. People may not understand that you can't rush things. Science moves at its own pace. And you don't want to rush it because history has told us that if you do, the science probably won't be done very well.

Are you concerned that the science is being rushed?

I'm concerned about how the data are being interpreted. Right now, our main goal with stem cells is to make other cell types. We want those cells to become progenitors of a specific lineage that could then be useful in cell replacement therapies. But we are restricted to in vitro culture, and we know that a dish is not an organism. For example, we can generate blood cells that have the right phenotype and express the right cell surface markers, but we can't make them perform [their function] (5). I think we're underestimating the amount of work that getting them to perform will require. And I worry that underestimation leads to unrealistic promissory notes and timelines that the public expects.



McMASTER UNIVERSITY

Mickie Bhatia

What do you mean by perform?

We want to get pluripotent cells to differentiate into cells like hematopoietic stem cells that we get from blood marrow donors. We've now generated cells that look identical in every measurable feature but when you engraft them into an immune-deficient mouse, they don't function how the cell markers in the dish predicted they would. The cells don't migrate to the right spot, they don't move the way they should, there's a variety of problems we've characterized. So, I don't know what the problem is but I can tell you what the failures are!

We do think that there might be some hope in using iPS cells that are derived from skin fibroblasts. First of all, by using these we can hopefully alleviate some ethical concerns. And I think these cells might actually perform a little better because they seem to have some sort of memory of their adulthood. We hope that when you transplant them into an animal, they can generate the blood system or the immune system better than embryonic cells can.

In a recent commentary, you referred to hematopoietic cells generated from embryonic stem cells as cartoons. Why?

I was trying to describe everyone's supposed improvements on the recipes to make blood cells. If I come up with a new way to get 30% blood cells [from stem cell cultures], someone might call that an improvement if before we could only come up with 20% blood cells. But if none of these methods actually

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regenerates the blood system, then that improvement doesn't matter. We need them to work in reality. But as of now, they don't. Fred Flintstone has a head, a nose, and two legs, but he can't jump out of the TV and clean your house.

Do you have more hope for embryonic stem cells than Fred Flintstone?

Oh yeah. I mean, if you take a mouse embryonic stem cell, you can generate an entire mouse. All the potential is there. Our problem is that we don't know how to tap into that potential in a dish. So I don't think that stem cells are cartoons, but rather that what we generate with our current methods are cartoons.

RISKY TERRITORY

What do you make of the promising claims made by "stem cell tourists" who have received stem cell therapies in countries where it's legal?

One of my biggest problems with stem cell tourism is that the places that offer it don't provide clear, definable, quantitative measurements of what the improvement really is. If the physicians or scientists administering these therapies in a variety of places around the world are truly getting good results, then by all means, that should be celebrated. But what you find is that observations posted on web sites are just testimonies from patients and physicians. Even from a marketing point of view, you'd think that if they were having such success, they'd want to post data showing that patients can regenerate healthy cells in their blood system, for example. And I'm not suggesting that people don't feel better like they say they do—just as a scientist, I'm a little tortured by this because as long as it's being done, I'd like the information to be shared.

Another reason why stem cell tourism really bothers me is that as director of a stem cell institute, I field a lot of calls from people who have children with terrible diseases and want to know why we aren't allowing their child to undergo these therapies. I can hear the logic combined with desperation in their voices. And it's really sad because they want to do whatever it takes to help their child—I feel like some of these places are exploiting their hopes.

Has any legal stem cell research in the US or Canada made you uneasy?

There was a concept for a period of time in which people felt that they could take human DNA from the nucleus and insert it into an enucleated egg from another species as a way to generate embryonic stem cell lines. For example, one could take a human fibroblast nucleus and insert it into a cow egg. That made me uneasy because I worry when good, creative scientists are working to sidestep policy. Very much like stem cell tourism, nobody was looking for a fundamental understanding of what was going on.

THE MEANS AND THE ENDS

Besides using embryonic stem cells in therapy, might they have another use?

It could end up that the best stem cell therapy may not require stem cells at all. We might discover new drugs that induce endogenous repair. Maybe we'll identify chemicals that target stem cells remaining in damaged tissue. If activating a signaling pathway causes pluripotent cells to become blood stem cells, perhaps a drug could be made to trigger that pathway. And if that drug could be administered to somebody who requires bone marrow regeneration, you wouldn't even need to worry about rejection.

Also, we hope that stem cells can teach us about cancer. We have evidence that many tumors don't respond to chemotherapy and/or regenerate after the tumor shrinks because there's a small fraction of cancerous cells with stem cell-like properties. So the question becomes, what is the difference between normal stem cells and cancer stem cells? By looking at both kinds of cells with this incredible self-renewal capacity, you can make cross comparisons. So far we've characterized at least 12 criteria that distinguish normal pluripotent cells from cancer cells. For example, the cancerous versions are environment independent and no longer respond to the same growth factors that regulate self-renewal in normal stem cells. Now we are trying

to develop novel bioactive compounds that will kill the cancer stem cells without harming normal stem cells. We're doing this in an automated screening process so that we can sift through thousands of molecules quickly because you can't generate 10^7 or 10^8 leukemic stem cells or normal stem cells from a patient's bone marrow.

Is there strong religious resistance to stem cell research in Canada?

Yes, I hear from concerned people all the time. And I listen carefully, answer questions, and explain how embryonic stem cells lines are generated—that human embryos used for research have been consented for destruction and also consented for research purposes. I think this two-tiered process alleviates a lot of people's fears. And, using iPS cells has relieved a number of concerns as well.

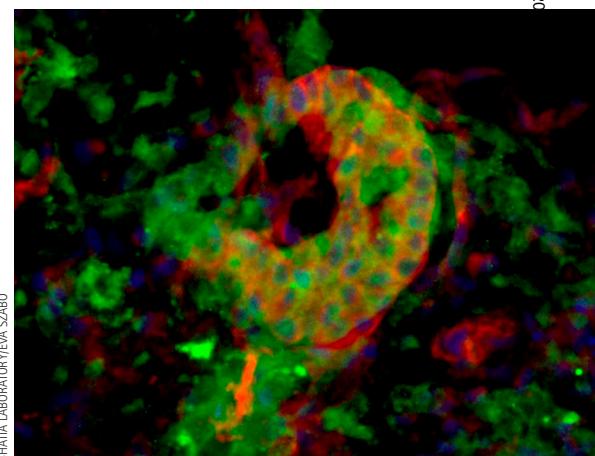
When does life begin?

Well, I don't ever want to project my opinion over another person's view. What I'm more concerned about is how to prevent life from ending and keeping the quality of life as high as possible.

"The best stem cell therapy may not require stem cells at all."

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Brachyury (red) and Frizzled (green) expression suggest that this human embryonic stem cell has differentiated into a hematopoietic cell.



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