2005 ASCI Presidential Address

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Members and guests, thank you for the opportunity to be the President of the ASCI. It has been a great experience. I want to first thank John Hawley, Executive Director of the ASCI, for all of his help through the year. Also, my officers Eric Fearon and Barbara Weber. I also appreciate the effort that the Councilors have made. It has been a pleasure to work with the AAP, particularly with Tadataka Yamada. I have learned a lot from Tachi. We had a lot of work to do, particularly picking a new executive company to run the meeting.

This year has been an amazing experience for me. I've been in the unusual position of being the president of two major societies, the ASCI and the International Society for Stem Cell Research (ISSCR). There has been a lot of hard work, and many successes. One of my missions at the ASCI was to reinvigorate the meeting by bringing the best target audience, NIH K08 holders, to the meeting. There are about 1,100 K08 holders total, and this pool is the future of the ASCI. We have 75 K08 holders at the meeting, and 40 MD/PhD students — the most junior investigators for over 5 years. I've been very happy with this excellent meeting, both on a scientific level and for the mentoring opportunities.

As I was coming up with a topic for my presidential address, I thought about my experience with the ISSCR. I have been struck by parallels between stem cells and physician-scientists. And it is for this reason that I've chosen to discuss this with you today.

A stem cell is a single cell that has the ability to make itself again, the process of self-renewal. Also, the stem cell can differentiate into tissues. But it is also important to differentiate from your mentor. It is my belief that physician-scientists, particularly through the ASCI, are capable of renewing the tradition by training more physician-scientists. Yet it is important for these new individuals to differentiate from their mentors and fully blossom into ASCI members,

and also to become mentors themselves. The ASCI represents the tree of life for physician-scientists.

In *C. elegans*, a complete fate map of early worm blastomeres has been created so that every cell division is traced to a lineage. This allows one to see the generations of cells and their progeny. We are an image of our parents, based on not only DNA, but also environmental (or mentoring) experiences. For me, I can trace my lineage through Stuart Orkin to his mentor, Philip Leder, to his mentor, Marshall Nirenberg. I guess Marshall is my great-grandfather. For me it is a pleasure to have trained physician-scientists, and one of my trainees, Nikolaus Trede, is here today. It is important for young physician-scientists to realize their family tree, embrace it, and most importantly continue the lineage. Again, the ASCI is the place for these complex genetics to take place.

Stem cells have a supportive environment called the niche. It is there that the stem cell can be kept quiescent, waiting for that breakthrough to begin self-renewal or differentiation. A young K08 holder needs to find a supportive environment — one with good mentoring, and one willing to praise you, but also one that holds you to rigor. There is no replacement for good training as a physician and a scientist. As mentors, we have to help the young student make good choices, both for their careers and for the field. The ASCI is an important organization that can give guidance.

Stem cells can be found in many organs of your body, although not all organs appear to have them. It is critical to diversify the ASCI to include and support investigators from all subspecialties. The ASCI has a preponderance of hematologists and oncologists. Why is this the case? We need to create opportunities for physician-scientists in other specialties.

Stem cells have the ability to undergo asymmetric division. One factor, Numb, is asymmetrically localized in the dividing stem cells and apportions to one of the daughter cells. As such, the sister cell changes its function. This is critical for the physician-scientist. They must listen to their mentor but the must differentiate, choosing new areas to tackle. It is this twist to the right that differentiates a young investigator from his mentor, and allows the person to develop a new area of research, acquiring with it fame and fortune, and ultimately successful induction to the

ASCI.

There is a lot of literature in the stem cell field on the concept of reprogramming, although I am not sure I believe much of it. Nevertheless, can a marrow cell be reprogrammed to all tissues? When we have a physician-scientist come to our labs in the second year of their fellowship, it is important to realize that they have just completed up to 6 years of clinical training and are often the superstar doctors of the hospitals. Yet we must reprogram them to become scientists. It will not suffice to be easy on them by choosing the easiest or most direct projects. They must be trained equally to the PhD postdocs in the lab, or later they will not compete. Physician-scientists compete for the same grant pool with other scientists. They cannot expect a break just because they are a double or triple threat. Training is very important and can never be replaced. For the K08 holders, it is important to train in the best places, giving the best chance to become ASCI members in the future.

But we also have to realize that there are many circumstances that physician-scientists are dealing with when they arrive. First, they are likely older, perhaps having done a PhD. They may have a family. They may be tired from the clinical year and have patients that still need care. They may be nervous about joining the scientific community, either for the first time or again. Be prepared. Mentor appropriately and be supportive.

Fate decisions are tough for a stem cell. Whole pathways need to be activated, and energy barriers need to be removed. I'm often struck by Waddington's model of a cell rolling down a hill to select a path. For the physician-scientist such fate decisions can be confusing. We as mentors need to provide information and help for our physician-scientists to make informed decisions. The young scientists must try to gather all the information. Also, I always say that physician-scientists need leather skin. They may be scrutinized or criticized more frequently, and need this to flow down their skin. Do not be bothered by the chairman who does not understand you. Come see an ASCI member. They will be supportive and help you realize your goals.

Chimera formation is an invaluable tool in biology, seeking to determine a cell's potential. Potential is relative. When I was in 9th grade I tried out for the high school band. I played the “Carnival

of Venice," and the conductor said, "Len, you have great potential." I made the band, and then in 12th grade, I sat first seat, first trumpet. I again had to try out, and after playing for the conductor, he proclaimed, "Len, you have great potential." At that point I understood that I had not realized my potential. More work was necessary. As a physician-scientist, as with the cell, there is confusion. When do you wear your clinic outfit? When do you worry about your science? It requires a complex decision-making process, one that the ASCI and mentors can help with.

The concept of lateral inhibition was popularized by the Notch pathway in *Drosophila*. A cell receives cues from the neighboring cells to select a particular fate. The cell with a ligand becomes one fate, and the cell with the receptor becomes another. For physician-scientists there are clearly influences on their Jives, both from the clinic and from the bench. Negotiating these two becomes very difficult, since they are under mutual repression.

Transcription factors are important intrinsically to the stem cell's identity and differentiation. It is the combinatorial code of all transcription factors that dictates cell fate, particularly for organogenesis. As physician-scientists, our academic life is determined and influenced by any number of factors, all coming together to define success, or failure. Only with a balance can the physician-scientist be successful.

When thinking about your environment for research, I'm reminded of the classic Spemann organizer transplant, in which dorsal tissue is moved onto the ventral side of a frog embryo. The ventral side, which normally makes blood, changes into another head. Two heads are thought to be better than one. It is important to have areas of collaboration. This is one of the best ways to be productive in medicine. I have had a longstanding association with my mentor, Stu Orkin. Our offices are next door to each other. For more than 10 years, we talked science every day. Our views on stem cells and their differentiation formed together, and allowed us to become a force in the hematopoiesis field. We have seen how Michael Brown and Joseph Goldstein did it. So, think it over: some form of extensive interaction with another scientist may be a benefit. Two heads are better than one, usually.

We need to be careful not to overpromise, particularly to the public. The stem cell field and the ASCI need to be careful. Certainly, bone marrow transplantation has been successful. How do

we at the ASCI measure success. The stem cell field can guide us. In reality, it is the general good and health of the nation that will determine success. I fundamentally believe that basic research translates over time to the better good. Patients do better in the long run by having physician-scientists thinking about biology and disease.

The community effect is a well-known developmental biology paradigm created by Sir John Gurdon. During embryogenesis, if a single cell is transplanted to a recipient embryo, the cell does not become an organ tissue and remains undifferentiated. If, however, more than 20 cells are transplanted together, the cells become muscle. This demonstrates that cells talk to each other and influence cell fate. For the ASCI, we have many conversations between leading physician-scientists, and this ensures that young physician-scientists go on to be successful and help society. I'm proud of my year as president of the ASCI, and of our mission. Let's continue to attract and mentor K08 holders.

Mesoderm induction is the classic reprogramming of an epithelial fate by growth factors or morphogens to become muscle, blood, or kidney. The process of ASCI induction is also an alteration of fate. Once a young investigator becomes an ASCI member, they have changed. They are expected to do well scientifically and develop new areas of biology. But they are also envisioned to help to mentor and foster the field.

Stem cells and physician-scientists are more alike that we once thought. One of my mentors told me that "the system has a way of rewarding persistence." My advice to students is to get great training and mentorship. My advice to the ASCI is to continue to embrace the K08 holders, our future. New members of the ASCI: Do your work and mentor.