

## Acceptance Lecture

The Helen Keller Prize for Vision and Research

Tuesday, May 2, 2006

7:30 pm

Riverside Hotel

Fort Lauderdale, Florida (during the ARVO meeting)

Thank you Keller (Ms. Johnson), for your kind remarks.

It is a great honor to receive the Helen Keller Prize for Vision Research.

It is a special privilege to follow in the footsteps of such distinguished previous Helen Keller Laureates. I am very gratified by the opportunity to accept the Prize in the presence of so many outstanding ophthalmologists, and many friends.

Several years ago, I was trying to promote a much deserving Assistant Professor in my laboratory, to the next rank of Associate Professor. Yuen Shing is a talented protein biochemist. Shing and I had worked together for years. He isolated and purified, with Michael Klagsbrun, the first angiogenic molecules (beginning with bFGF), while I assayed them. We followed this same “partnership” approach to discover the first angiogenesis inhibitors.

However, Harvard’s promotion committee rejected the promotion on the grounds that, “Dr. Shing is not an independent scientist.” They said, “Folkman is a co-author on his papers.”

In despair, I sought the advice of Chris Walsh who Chaired the Department of Biological Chemistry. He read over the papers and then called me, and said, “Let me have a try.”

Walsh addressed the promotion committee and said, “I do not have to prove that Shing is an independent scientist, I only have to prove that Folkman is not a biochemist. And for that, I will only need a few minutes of your time.” The promotion to Associate Professor passed unanimously.

This evening, I do not have to prove that I am not an ophthalmologist.

However, upon learning that I was to receive the Helen Keller Prize, I could not help but reflect that my affection for your specialty is because I have had a rather unique apprenticeship, extending over 30 years, in a subspecialty of experimental ocular neovascularization.

This apprenticeship began with collaborations. The first was with Arnall Patz, and this was followed by many others over the years including, Gerry Luttj, Dan Finkelstein, Lloyd Aiello, Joan Miller, Lois Smith, and Marty Friedlander, to name just a few.

And then undergraduate and graduate students came to the lab, many of whom went on to become ophthalmologists. The most recent is Lucy Shen, whose paper at ARVO this morning was on diabetic retinopathy and Rosiglitazone.

And then came outstanding post-doctoral fellows and young faculty, including: Patricia D’Amore, Bela Anand-Apté, Robert D’Amato, Tony Adamis, Richard Casey, David Shima, and others.

These ophthalmology teachers to whom I was in a sense “apprenticed,” were themselves witness to the early development of the field of angiogenesis research.

They saw how discovery of the first pro-angiogenic proteins, and discovery of the first angiogenesis inhibitors, depended critically on models of corneal neovascularization in the rabbit and mouse eye.

And they saw Robert Langer, a chemical engineer post-doc in the lab, convert the polymer of soft contact lenses, poly-hydroxy ethyl-methacrylate, into a slow-release polymer for proteins that could be implanted into the cornea.

And they saw how this *in vivo* model, used in conjunction with other bioassays, such as endothelial cell cultures, (which themselves did not exist before 1972), led to the identification today of a family of pro-angiogenic and antiangiogenic molecules. Of the more than 50 known angiogenesis inhibitors, the cornea bioassay made it possible for us to discover 12 of these over a period of 20 years, starting in 1980.

Today, it is known that at least 28 angiogenesis inhibitors are in the blood or tissues. Many of them have also been shown to be tumor suppressor proteins.

These angiogenesis regulatory molecules, fully sequenced, and in most cases, the crystal structure identified, and the gene isolated, and recombinant proteins made, caught the attention of scientists around the world.

For example, in 1971, there were only three papers on angiogenesis in the world literature, two of them from our lab, and one criticizing a previous paper of ours.

But today, more than 70 papers on angiogenesis are published every week.

This large collegial community of scientists contributed many

unexpected discoveries to angiogenesis research. Let me give just one example of what I mean by unexpected.

Scientists in São Paulo and Boston found that individuals with Down syndrome have an extra copy of the gene that results in a higher level of endostatin in their blood than the rest of us. This explains in part why these individuals are the most protected against cancer of all humans.

These individuals also have virtually no diabetic retinopathy, even though they have the same incidence of diabetes as the rest of us, and even though they are now living up to 60 or 70.

By the 1990s, the pharmaceutical and biotechnology industry began to believe that antiangiogenic drugs could be manufactured and tested clinically.

They also recognized that many non-neoplastic diseases were also dependent on angiogenesis. These include: atherosclerotic plaques, endometriosis, psoriasis, rheumatoid arthritis, uterine fibroids, benign prostatic hypertrophy, macular degeneration and diabetic retinopathy, among many others.

Today, you can write a prescription for nine different angiogenesis inhibitors in the U.S. and abroad.

But, to my mind, the most exciting clinical applications of antiangiogenic therapy have been the treatment of age-related macular degeneration, as you all know.

So, what are some future directions of the use of angiogenesis inhibitors in age-related macular degeneration, and perhaps in other diseases of ocular neovascularization, especially diabetic

retinopathy? Some predictions for ophthalmology may be inferred from progress in antiangiogenic therapy of cancer.

For example, some cancer patients can eventually become “resistant” (refractory) to angiogenesis inhibitors that suppress only VEGF, because “redundant” angiogenic proteins can be expressed (such as FGF or HGF).

Most of the angiogenesis inhibitors that have been approved by the FDA target only one angiogenic protein, (vascular endothelial growth factor). Oncologists have tried to prevent this drug resistance by adding conventional cytotoxic chemotherapy to antiangiogenic therapy. But, this may add the side-effects of conventional chemotherapy (such as bone marrow suppression), and increased thrombosis. This is mainly because cytotoxic chemotherapy increases release of tissue factor from endothelial cells, and from tumor cells.

Furthermore, the addition of an angiogenesis inhibitor may prevent repair of the endothelial damage. So, some oncologists are avoiding conventional chemotherapy and instead using antiangiogenic chemotherapy, which is low dose and frequent, and targets mainly proliferating endothelium in the tumor bed. It is also called “metronomic therapy”, and so far, has little if any thrombotic complications. Other oncologists are combining angiogenesis inhibitors, also with very low side-effects. Another approach is that some angiogenesis inhibitors are being developed that by themselves have a broader spectrum. Tarceva (erlotinib) blocks 3 angiogenic proteins, as does Sutent (sunitinib).

Endostatin has an even broader spectrum. In cancer patients who have been on endostatin every day, self-administered, for more than 3.5 years, there have been virtually no side effects. This is one reason why endostatin's derivative, Endostar is approved by China's State FDA. Caplostatin, a synthetic analogue of fumagillin, has the most broad anti-cancer spectrum of any angiogenesis inhibitor.

So, what does this have to do with treating age-related macular degeneration? I had always assumed that long-term suppression of VEGF in macular degeneration would not lead to emergence of redundant pro-angiogenic proteins, because cells in the eye don't mutate like tumor cells. However, Marty Friedlander's recent experiments suggest that we keep an open mind.

In the future, it may be necessary to use broad-spectrum angiogenesis inhibitors.

Endostatin is a theoretical possibility, because at least one report shows that in retinal neovascularization, there is a deficiency of endostatin, similar to atherosclerotic plaques. Bjorn Olsen has shown increased ocular neovascularization in endostatin-knock-out mice.

Furthermore, in the future, it may be prudent to pay attention to the biomarker proteins being developed for cancer. We have discovered that angiogenesis regulatory proteins are sequestered in platelets, and can detect even a 1 mm human tumor in a mouse (pinhead size, and invisible except with a microscope).

Could the platelet angiogenesis proteome be used to monitor recurrence of ocular neovascularization long before it would become symptomatic, or could one monitor efficacy of different therapeutics

which might drive down the biomarker long before regression of neovascularization would occur?

In other words, could ophthalmologists treat just a biomarker, and prevent ocular neovascularization? Again, we should keep an open mind. An analogy would be how we now treat infection aided by a blood biomarker, e.g., the white blood cell count. Another example is the use of cholesterol-lowering statins to prevent future myocardial infarctions without visualizing plaques.

In February 2004, Mark McClellan, the Commissioner of the U.S. FDA, announced, “Anti-angiogenic therapy can now be considered the fourth modality for cancer treatment.”

In May 2004, the U.S. National Institutes of Health announced the formation of the Trans-Institute Angiogenesis Research Program, because angiogenesis research had become the basis for research across so many Institutes, including the Cancer Institute, the Eye Institute and the Heart, Lung and Blood Institute.

In December 2005, the journal, *Nature*, published a 35-page review of the field of angiogenesis research that concluded with this interesting statement by Peter Carmeliet, “In the next decades, more than 500 million people worldwide are predicted to benefit from pro- or anti-angiogenesis treatments.”

In summing up, during the long years of laboratory work that led to the advances of which I have just given you a glimpse, I began to ponder the question, “How does one know when to keep going, or when to cut one’s losses, and start a new direction?” How does one make the decision to “persist” when the experts are insisting that the quest is futile?

There seems to be a fine line between persistence and obstinacy in research, or in creative work of any kind, thus in other professional and business activities as well. How do you know when you have crossed this line?

What happens if a long line of experiments never succeeds in the lifetime of a grant, or in the time-limit before the researcher is evaluated for tenure, or occasionally in the lifetime of the scientist?

Then, the same tenacity which we admired in the successful researcher is now blamed for the failure of the thwarted researcher, who is called: obstinate, inflexible, stiffnecked, bullheaded, "wedded to a theory," or pigheaded (the worst opprobrium of all).

The key to avoiding this fate seems to be to choose a problem that is worth persistent effort.

Edwin Land, the founder of Polaroid, put it in stronger words when he said, "My personal philosophy is not to undertake a project unless it is manifestly important and nearly impossible."

This is precisely the way angiogenesis research seemed to me when I began this long journey more than 35 years ago.

So, I am deeply grateful to the Award Committee of the Helen Keller Foundation for their confidence, and for the fact that they have put their imprimatur on the value of persistence in proving new ideas.

Thank you.