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Anti-angiogenic drugs to treat human disease: an interview with Napoleone Ferrara

Napoleone Ferrara identified vascular endothelial growth factor (VEGF) as a major regulator of blood vessel development. The antibodies that he and his colleagues created to block VEGF action also block cancer growth. Here, he discusses the work that led to the development of the anti-cancer drug Avastin (bevacizumab), and discusses the role of basic science in clinical medicine.

The formation of new blood vessels, or angiogenesis, is necessary for the development of most multicellular organisms. The new vessels allow for the perfusion of organs and tissues, including those involved in normal embryonic development, reproductive function and skeletal growth. However, promoting blood vessel development also allows tumors to obtain necessary nutrients and survival factors and to eliminate catabolic products. In 2004, Dr Ferrara's work at Genentech led to the first Food and Drug Administration (FDA) approval of the anti-VEGF antibody, under the drug name Avastin, as part of an anti-cancer combination therapy to block angiogenesis in colorectal cancer. Since then, the applications for blocking VEGF function have increased along with our understanding of normal and pathological angiogenesis.

What events led to your identification of VEGF and its crucial role in angiogenesis?

The regulation of angiogenesis has been a long-standing issue, which was very exciting to a number of investigators, not only tumor biologists but also ophthalmologists and, of course, to developmental biologists. When I started working in this field, in the early to mid 1980s, clearly a major question was 'what are the important angiogenic factors?' The idea of the existence of an angiogenic factor (or factors) is quite old. It was originally proposed in the late 1930s and people have been trying to purify such a factor for a long time.

Napoleone Ferrara is a Genentech Fellow in the Department of Molecular Oncology at Genentech (e-mail: nf@gene.com)

But none of the molecules that were initially characterized as potential angiogenic factors seemed to be important as endogenous regulators. For example, basic fibroblast growth factor (bFGF) was one of the first factors to be purified and characterized as an angiogenic factor. It was extremely potent in several in vitro and in vivo systems, but then when researchers tried to block bFGF function with antibodies, it had little effect on tumor growth. Even the knockout of the gene for bFGF did not result in any obvious defect in vascular development, so clearly something was missing. One of the lessons from these studies was the fact that although a molecule may have activity as a pharmacological agent, it does not prove that the molecule is important physiologically.

I was probably fortunate that my work was in a different field from cancer, as this gave me a fresh perspective. I worked on the pituitary gland when I was a post-doc at the University of California, San Francisco (UCSF). My interest was a group of cells in the pituitary that do not produce hormones, termed 'follicular cells'. What was intriguing to me about these cells was that there was some intimate connection between them and the vascular spaces. It looked as though the cells could potentially regulate the growth and maintenance of the vessels.

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I decided to test whether the supernatant from these cells had any mitogenic effect on endothelial cells. To my delight, I found a strong mitogenic effect. Of course, this was only the very, very first step and there was a long way to go ahead, but I ended up pursuing this idea (or dream) that the mitogenic factor that regulated blood vessel formation was isolable from that supernatant. After several years, I was finally able to purify VEGF, and sequence and clone it. That is how the discovery of VEGF happened.

When you were first looking at angiogenic regulation, you were in the field of reproductive biology. Did you immediately recognize its importance in cancer?

At that time there was reason to believe that an angiogenic factor might be important in several situations. This was supported by evidence that growth factors were important, not only in a specific tissue or organ, but that their actions had much broader implications. So, it was conceivable that a molecule that regulates physiological angiogenesis could be also potentially important in pathological angiogenesis.

Once the physiological significance of VEGF was realized, how did you use the information to develop a relevant drug?

It took several steps. We realized the importance of VEGF as a mediator of pathological

angiogenesis even before we fully appreciated its role as a physiological mediator. At the time, VEGF was an intriguing new molecule. It looked exciting, but there were already a range of angiogenic factors that were known. It was possible that VEGF was just one of many regulators of angiogenesis, such that blocking its action could have a very limited impact. So, we put a considerable amount of effort in to understanding the role of VEGF. We knocked out the VEGF gene and got a very surprising result. Even if we knocked out only one of the two VEGF alleles in mice, they died because of insufficient vascular development. This was very compelling evidence that VEGF was important. We published this in 1996, but even prior to reporting these findings we developed antibodies to human VEGF, and we were able to show that these antibodies could block tumor growth by blocking the vascularization of tumor cell lines implanted in mice.

How important is your clinical experience in your research and drug discovery?
At this point, I hardly consider myself a clinician. I have a medical background and I did some clinical training. This training gave me a biological background that allowed me to have a greater appreciation of physiology and pathology, but I cannot say that right now I can consider myself a practicing clinician.

Once you created a functional antibody with clinical application, did your work proceed in conjunction with a drug company?
Well, that was a really nice aspect. I was in an environment where I was allowed not only to do research but, at the same time, there was a strong interest in developing therapeutics.

Does your medical background influence your approach to basic science?
I truly believe it does because my research is always oriented towards some medically significant question. Even in my early work, I tried to identify angiogenic factors. This was an attempt to address questions about basic science with clinical implications.

The anti-VEGF antibody (Avastin) is now a proven anti-cancer drug but angiogenesis is involved in a lot of normal and pathological processes. Do you picture some of these drugs having other purposes in addition to treating cancer patients?
There are diseases in which anti-angiogenic therapy with VEGF inhibitors has been quite successful. In 2006, the FDA approved Lucentis (ranibizumab), an anti-VEGF antibody derived from the same murine antibody as Avastin, as a therapy for neovascular age-related macular degeneration, the leading case of blindness in the working population. In such conditions, blocking VEGF has a quite dramatic effect and almost completely inhibits the growth of vessels in choroidal neovascular membranes. Patients can even gain some visual acuity when they are treated with anti-VEGF. Other possible indications are diabetic retinopathy and retinal vein occlusion. I believe that the application of anti-VEGF therapy to eye diseases is particularly exciting.

Do you have a favorite model organism for understanding tumor biology?
We work on numerous models, utilizing mostly mouse models. We work on xenografts, as well as with genetic models. There isn't a perfect model – each model is a model of itself and it's probably in the combination and in assessing multiple models that you can hope to find something in common.

Although we have rat models and nude rat models, frankly, I don't believe they represent any step beyond mice and they are less well characterized. The mouse is still king in the area of cancer modeling. There are so many genetically modified mice available that can allow you to test many hypotheses.

Are there specific things that you must consider when using information gained from a model organism and applying it to humans?
You have to be always mindful that there is not a single model that can recapitulate the complexity of a human. There are so many variables and from these you have to choose the ones that you wish to test. So far, most of the attempts to make therapeutic predictions based on a single model have been unsuccessful. I believe that if you can combine data from multiple models, you become more likely to identify a common theme and derive some information that should be applicable to humans, keeping in mind that it is virtually impossible to fully recreate human disease in animals.

What is it like to work at Genentech?
Traditionally, Genentech has put lots of emphasis on basic research. Really, it's the closest thing to academia you can find in industry.

I must say that my job has a number of similarities to academia because I do mostly research. In addition, the opportunity to interface with a variety of groups such as development, safety evaluation, clinical, etc., makes it a particularly interesting and stimulating environment.

What do you do when you have identified a molecule that you think clearly has therapeutic potential? What is the next step?
We try to understand what the molecule does. It is important to determine what happens if you inactivate it or if you overexpress it. We then develop antagonists and other tools that allow us to test our hypotheses in in vitro and in vivo systems.

Do you have any advice for young scientists who are interested in living at this interface between research and bringing about new therapeutics?
Each situation is very different and it is difficult to generalize. I would say that 'translational research' is not a very well defined area and to many people it is not very clear what it is. I would suggest that translational research is only as good as the basic research that supports it. You can effectively translate only good basic research and that is really the foundation of any advance in medicine.

DMM greatly appreciates Napoleone Ferrara's time and willingness to share his personal story. We are grateful for the opportunity to present his story here as A Model for Life.

Napoleone Ferrara was interviewed by Kristin H. Kain, Associate Reviews Editor for DMM. This piece has been edited and condensed with approval from the interviewee.