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Napoleone Ferrara discusses Avastin™ and the future of anti-angiogenesis therapy.

Interviewed by Ulrike Knies-Bamforth and Christopher Watson

Napoleone Ferrara

Genentech Fellow, Department of Molecular Oncology at Genentech, Inc and a pioneer of angiogenesis research

Napoleone Ferrara obtained a M.D. degree from the University of Catania Medical School in 1981. He joined Genentech in 1988 after postdoctoral training at the University of California at San Francisco. At present, he is a Genentech Fellow in the Department of Molecular Oncology at Genentech, Inc. His research interests concern the regulation of angiogenesis. In 1989 he isolated vascular endothelial growth factor (VEGF). Subsequently, his laboratory has extensively investigated the basic biology and the potential clinical applications of VEGF. In 1993, Ferrara and colleagues demonstrated that inhibition of VEGF using a monoclonal antibody suppresses tumor growth in vivo. This work led to the clinical development of bevacizumab (AvastinTM), a humanized anti-VEGF monoclonal antibody, the first anti-angiogenic agent to be approved by the FDA as a anticancer agent. More recently, his laboratory has been involved in the identification of novel angiogenic factors. Dr Ferrara is author or co-author of over 200 scientific publications.

You started off as a physician. What made you pursue a career in basic research?

I studied medicine and obtained a medical degree from the University of Catania Medical School in Italy. We had no formal MD PhD programme. However, I had the opportunity to perform some research in the department of pharmacology as a part of a thesis for my medical degree. My mentor, Prof. Umberto Scapagnini, was a well-established investigator in the fields of neuroendocrinology and neuropharmacology. So, I was exposed to research during my medical school years and I developed an interest in pursuing it further.

You had a significant impact, and you still do, on the field of angiogenesis research and you have contributed a great deal to the development of Avastin, the anti-angiogenesis drug. Just for the benefit of the non-specialist reader of DDT, could you briefly explain how Avastin works?

Avastin is a recombinant humanized monoclonal antibody. It is derived from a murine anti-VEGF monoclonal antibody that had been engineered in such a way that approximately 7% of the murine residues, including the complementary determining regions (involved in antigen binding), are inserted in a human antibody framework. The purpose of humanization is to avoid the immune responses that are frequently associated with the administration of murine and sometimes chimeric antibodies. The project started with the isolation and cloning of VEGF-A in 1989. At that time, the significance of VEGF-A was virtually unknown. There were already many known angiogenic factors and it was not clear whether VEGF-A would be particularly important. A monoclonal antibody was potentially an important tool to probe the biology of VEGF-A. We were surprised to find out that an antibody that selectively targeted human VEGF-A substantially inhibited the growth of several human tumour cell lines transplanted in nude mice. Considering that these cell lines were know to produce several other angiogenic factors, it was truly unexpected that blocking VEGF alone could have such a profound impact on tumor growth.

The results of most early clinical trials of other anti-angiogenesis drugs were quite disappointing and Avastin is so far the only anti-angiogenesis drug with proven efficacy. Why do you think other anti-angiogenesis drugs failed?

Avastin targets a well-defined pathway. There is compelling pharmacological and genetic evidence that the VEGF pathway is involved in

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physiological and pathological angiogenesis. The efficacy of Avastin may also reflect the fact that, being an antibody, it has some excellent pharmacokinetic and pharmacodynamic characteristics. It's difficult to say why other agents tested failed in the clinic as the reasons vary from case to case. It is possible that a lack of mechanistic understanding may have hampered clinical development, at least in some cases.

"RNAi holds a lot of promise but there are a number of issues..that need to be resolved"

There was quite a lot of hope for the angiostatins in particular. Do you agree that they haven't quite lived up to their expectation? Or do you still think there is something that could still come out of these molecules?

To my knowledge, these molecules are still in clinical development. It has been difficult to develop them in part because they have a short half-life. Time will tell to what extent they are clinically useful.

Inhibiting VEGFA is really at the centre of the anti-angiogenesis approach. What do you think about other approaches inhibiting the VEGF, for example by using RNAi?

RNAi holds a lot of promise but there are a number of issues such as stability, bioavailability and delivery that need to be resolved. At present, it is more a research tool than a truly viable pharmaceutical. This, of course, can change. On the other hand, there are other approaches, such as small molecule tyrosine kinase inhibitors, which block VEGF receptor signalling. Some of these molecules are already in advanced clinical trials, and the results should be known sometime in the future. So there is a lot more to come in terms of VEGF inhibitors.

Going back to the early days of anti-angiogenesis research, this general approach had to undergo quite a lot of criticism and doubt. How did you overcome these obstacles?

I think that much of the doubt derived from the fact that important mediators of angiogenesis remained to be discovered. Therefore, key proof of concept experiments could not be performed. Some of the angiogenic growth factors initially identified (most notably basic FGF) held a tremendous promise in the mid 1980s. However, anti-bFGF antibodies did not result in marked inhibition of angiogenesis. Now we know that the knockout of the gene encoding bFGF has little, if any, effect on the development of the vasculature. I believe that the identification and validation of important pathways in angiogenesis made a great deal of difference.

And how do you see the future of the general approach of anti-angiogenesis therapy. Do you think there is ever a scenario in which it would be used as a mono therapy or do you think it would always be, or most likely be used in combination with chemotherapy?

It appears increasingly likely that cancer therapy is going to be combinatorial. Anti-angiogenesis drugs such as Avastin can be combined with conventional chemotherapy and possibly various targeted therapies (e.g. affecting the apoptotic machinery). This seems to be a rational approach for a complex disorder like cancer, in which mutations are frequent. It makes sense to attack the process from different angles, targeting different mechanisms.

"I think that it would be important for any scientist .. to have the opportunity to contribute ideas"

At Genentech, you were given the freedom to follow your interests and work on the VEGF. Do you think other companies should be equally generous with the scientific freedom they allow their employees?

Genentech provides a very unique environment. There are a lot of resources and technologies and also there are many extremely talented investigators. Perhaps in other companies with more focussed objectives these conditions would be difficult to reproduce. I think however that it would be important for any scientist, irrespective of the position, to have the opportunity to contribute ideas.

In the information I read about you, it says that you pursued your interest in angiogenesis in your spare time. This has proven tremendously successful. What are you now working on in your spare time?

I worked on the isolation of VEGF-A in my spare time during my first six months to a year at Genentech. Once we cloned VEGF-A in 1989, the company became interested and this became more and more my full time pursuit. In time, VEGF targeting became an important project at Genentech and this has been validated by the success of Avastin. I'm still working on angiogenesis, trying to pursue novel avenues. For example, in my lab we are exploring the idea that there could be tissue-specific angiogenic factors or pathways, which could be alternative to VEGF-A.

Can you see other applications of Avastin, apart from cancer?

There are several potential applications of Avastin outside of cancer. For example, the wet form of age-related macular degeneration (AMD) represents an important target. Lucentis, a high-affinity Fab fragment of Avastin, is now in phase III clinical trials for wet AMD. Very recently, the FDA approved Macugen (Pfizer) for the treatment of AMD. Macugen works by blocking VEGF-A. So there is evidence that anti-VEGF strategies can also be applied to treat eye diseases. Other possible indications include rheumatoid arthritis, endometriosis and psoriasis.

During the course of Avastin treatment, is there a chance for a resistance developing against Avastin?

This possibility certainly exists. In the trials that we performed, patients treated with Avastin survived longer but they eventually succumbed to the disease. On the other hand, it is possible that in patients with less advanced or severe cancer, the therapeutic impact of Avastin would be greater. It is conceivable that other angiogenic pathways may replace VEGF as the disease progresses. It would be very important to identify such pathways.

From an oncological point of view are all stages of cancer equally suitable for treatment with Avastin or are there some that would respond particularly well?

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I think the general concept is, the earlier the stage, the better the response. I would point out, however, that impressive results were obtained in previously untreated metastatic colorectal cancer patients when Avastin was given in combination with chemotherapy. Importantly, recent data indicate that Avastin prolongs survival also in patients with metastatic colorectal cancer that had been previously treated with the chemotherapy and relapsed. So there is a significant potential for Avastin to treat even advanced cancer. But there is reason to believe that early treatment would give the best results.

> "The difficulties of IRESSA should not discourage companies from developing targeted therapies"

Taking a look at cancer therapy as a whole, what to your mind is the impact of the recent withdrawal of IRESSA on the future of targeted cancer therapies?

The future still looks quite bright. Interestingly, TARCEVA, a drug known to have a similar mechanism of action as IRESSA is doing very well in the clinic. This suggests that subtle pharmacological differences or even the design of the clinical trial may have a surprisingly large impact. The difficulties of IRESSA should not discourage companies from developing targeted therapies, even though they emphasize the uncertainties and risks of drug development.

And what do you envisage being the next big breakthrough in cancer research?

This is difficult to say. There are so many areas which are being explored, angiogenesis, apoptosis, cell-cycle, that it's very difficult to anticipate at this point which one is going be the most promising or the most therapeutically relevant. Therapeutic breakthroughs could come from any of those areas.

Avastin is co-developed by Genentech and Roche. What do you think were the factors that contributed to the success of this collaboration?

Genentech markets Avastin in the USA, Roche markets Avastin outside the USA. The expertise and strength of sales force of Roche certainly have been a big plus. The interaction has been very successful. Avastin has just been approved in the European Union and I am delighted to know that the drug will be available to patients in numerous countries, including my native country.

So it is more a commercial collaboration rather than an intellectual?

In the case of Avastin, the collaboration started when the project was at a late-stage of clinical development. We continue to investigate Avastin and we work closely with Roche on the continued development of the drug, both within colon cancer and in other diseases. Additionally, in other projects the collaboration may start at earlier stages of research or development and therefore provide the ground for full-fledge scientific collaborations.

Genentech, the company, has been very successful with a number of drug approvals in the last few years, more so than many other biotech companies. What do you attribute the growth and success of Genentech to?

I attribute it to a combination of factors. A lot of basic research that went on for many years eventually paid off. The work on Avastin started 16 years ago or longer and it took many years to reach fruition. With Herceptin it was a similar story. I think it is a combination of persistence, good science and good management.

> "The work on AVASTIN started 16 years ago or longer and it took many years to reach fruition"

You have been at Genentech for almost 17 years. From your perspective, how has the biotech sector changed in that time?

I think it has matured quite a bit. Some time ago it was sufficient to have a platform but today you need much more than that. You need to have much better defined ideas, molecules and clinical plans.

And when you look at the biotech sector as a whole but also taking into consideration academia, who do you think is doing really exciting, innovative research at present?

I think there are many groups that are doing innovative research, both in academia and in industry. Just to mention a few names, Robert Kerbel, Judah Folkman, Kari Alitalo, Peter Carmeliet, and Michael Klagsbrun are doing very interesting work in academic settings. Companies like Regeneron, ImClone, Novartis and Amgen are doing or have done important work in the field.

Who or what have been the greatest influences of your career?

Initially my research interests were in the fields of neuroendocrinology and reproductive biology. I developed these interests while working with Prof. Umberto Scapagnini. During my postdoctoral fellowship in Dr Richard Weiner's laboratory at the University of California, San Francisco (UCSF), I became interested in angiogenesis in endocrine glands such as the pituitary. That was an exciting and fascinating question and in fact I made preliminary observations that eventually led to the isolation of VEGF during that period. Angiogenesis then became my major interest, being so full of biological promise and therapeutic implications.

What would you like to have accomplished at the end of your career? Which is of course a long way away but just if you can imagine something.

I believe that my lab is credited with some significant scientific discoveries in the angiogenesis field. This is rewarding. I must say, however, that the greatest satisfaction stems from the knowledge that my work has contributed to bring about some benefit to patients with serious disorders. I would love to do more. Finding other therapeutics; that would be truly fantastic.

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