

CHAPTER 6

Expert Interviews

6.1. Hubert Heinrichs, MD, PhD, Chief Medical Officer and Acting CEO, and Andrea Kottke, PhD, Head of Marketing, Antisense Pharma

Insight Pharma Reports (IPR): Please provide a brief description of what Antisense Pharma is doing in the field of cytokines. What is novel about your technology or approach? What are the benefits?

Dr. Heinrichs: Our antisense drugs specifically inhibit the synthesis of certain cytokines. Antisense molecules are small pieces of DNA that are complementary to a specific sequence in the target messenger RNA (mRNA). By binding to the target mRNA, an antisense molecule blocks the translation of the mRNA by ribosomes, and hence the target protein is not synthesized in the cell. The target of our lead compound trabedersen is transforming growth factor beta 2 (TGF- β 2). TGF- β 2 plays a pivotal role as a multimodal cytokine by regulating signal pathways that are critical to tumor progression. Immunosuppression, invasion and metastasis, proliferation and angiogenesis are simultaneously promoted by TGF- β 2 in a variety of malignant tumors.

Dr. Kottke: The multifunctional cytokine TGF- β has a prominent position among cancer targets because it exerts a whole set of effects in malignant cancer progression. Particularly at later stages of tumor progression, many tumors produce excessive amounts of TGF- β .

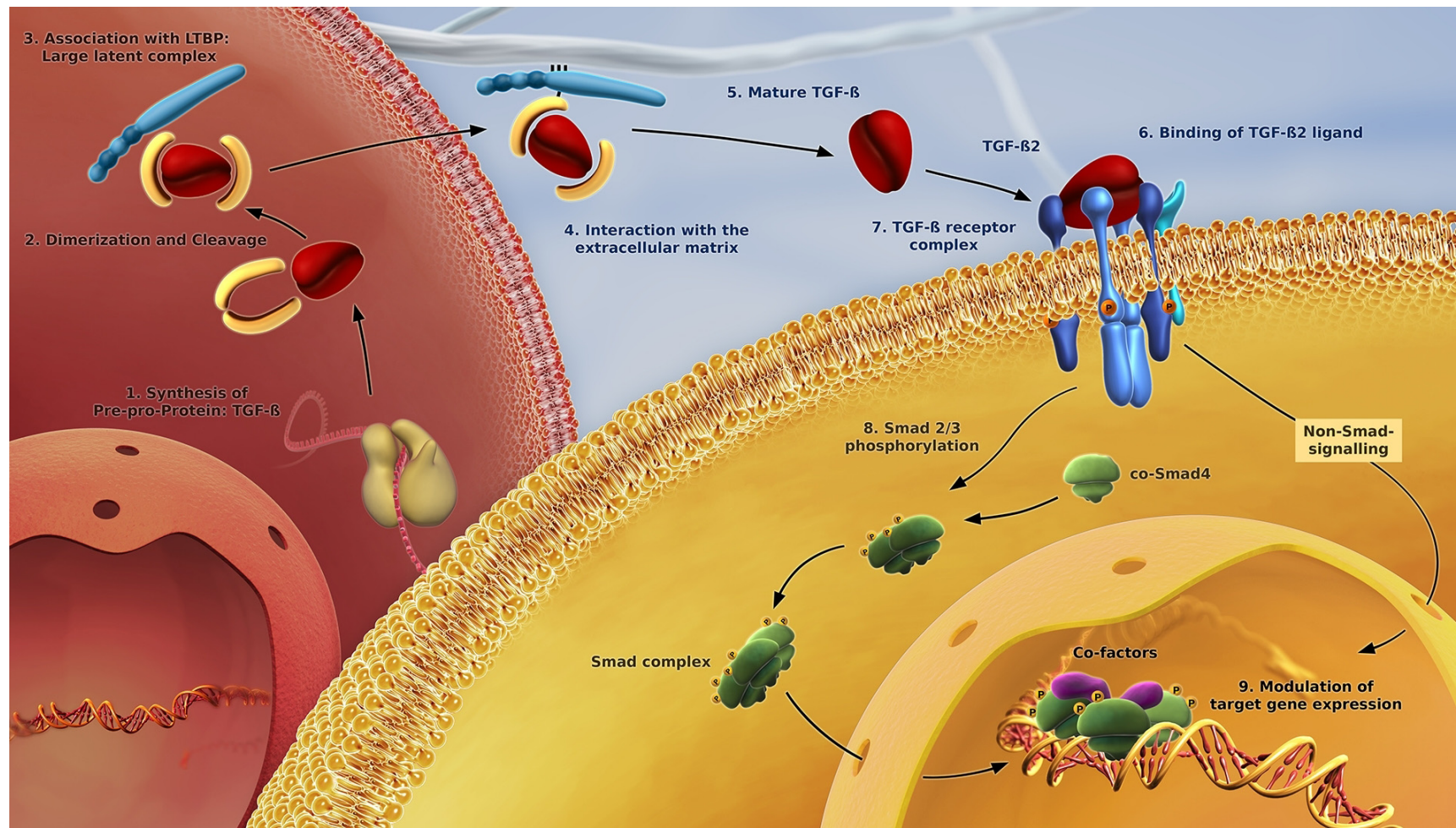
Through its effects on T cells, B cells, and antigen-presenting cells, TGF- β enables tumor cells to escape recognition and removal by the immune system. Our approach stops the synthesis of this protein and allows cancer treatment close to “its roots.”

Dr. Heinrichs: Trabedersen is currently being investigated in a pivotal international Phase III trial in high-grade glioma patients. In addition, a Phase I/II study with patients suffering from advanced pancreatic cancer or malignant melanoma showed an excellent safety profile and encouraging first signs of efficacy. Right now we are working on the design of an international Phase II/III study with trabedersen in patients with pancreatic cancer.

There are also other approaches to inhibit this target, for example by antibody-mediated neutralization. Genzyme has a human monoclonal antibody against TGF- β in development that has gone through a Phase I study. Furthermore, there is also the possibility to target the receptor that interacts with TGF- β . Eli Lilly has a small molecule that is directed against the kinase domain of receptor type I of TGF- β (ALK5) and that interrupts TGF- β signaling. To our knowledge, the Phase I studies on this molecule have been completed.

IPR: What are the benefits of blocking production of this protein versus blocking the protein or its receptors?

Figure 6.1 TGF-β2 Signaling Pathway



Source: © Antisense Pharma

Dr. Heinrichs: We can only speculate about the underlying processes that led to the clinical benefits of trabedersen we observed. However, which of the three known isoforms of the human TGF- β family, TGF- β 1, TGF- β 2, or TGF- β 3, are targeted might be an important issue because they all have different physiological functions. Our compound has the benefit that it specifically downregulates only the synthesis of the isoform TGF- β 2, whereas the tested monoclonal antibody is directed against all three isotypes. In contrast to TGF- β 2, TGF- β 1 plays an essential role in normal human homeostasis. The same concern may apply to small molecules targeting ALK5 kinase, which inhibit TGF- β -mediated signaling driven by all isoforms. In this approach severe side effects due to functional “TGF- β -knockout” have been observed in clinical trials in humans. Another aspect to be considered is that when TGF- β 2 is synthesized, chaperone molecules are associated with the newly synthesized protein. Thus, monoclonal antibodies may not be able to bind to TGF- β 2 because the epitope is masked.

Last but not least, our *in vitro* experiments revealed an 80% inhibition of TGF- β 2 in tumor cells treated with trabedersen. So it could be that avoiding a complete “knock out” of TGF- β 2 function results in very well-tolerated and effective treatment.

Our hypothesis is that it is good to be as specific as possible, in other words to inhibit the target molecule as specifically as possible. And, it is also better to prevent it from being synthesized rather than trying to neutralize it after it has been synthesized.

IPR: Please discuss your emerging drug, its clinical development to date, and what you have planned.

Dr. Heinrichs: The overexpression of TGF- β 2 and its correlation with immunosuppression in malignant brain tumors are well-known. So we started out with local trabedersen treatment in patients with high-grade glioma, namely anaplastic astrocytoma and glioblastoma patients. Since

all antisense molecules do not pass the blood-brain barrier, we decided to perform a local treatment of the tumors with convection-enhanced delivery (CED), which was first developed by NIH. The substance is administered directly to the tumor or the surrounding brain tissue by permanent, pressure-supported infusion using a special catheter/pump system. Since CED builds up a pressure gradient, a clearly higher and more homogeneous penetration volume can be achieved compared to conventional injection. In this context, Antisense Pharma developed the first portable CED application system that provides the opportunity for treatment over weeks and months [Press Release, Antisense Pharma. June 1, 2011: Antisense Pharma granted patents on medical device for application of neurotherapeutics].

We performed a Phase I/II trial that very nicely showed proof of principle with durable response and long-term survivors. We went on to do a randomized, controlled Phase II trial where we assessed two concentrations of trabedersen against standard chemotherapy. We again observed in anaplastic astrocytoma patients and in a fairly large subgroup of glioblastoma patients, durable responses, at least a doubling of the 24-month survival rate, a prolongation of the median overall survival, and a prolongation of the response versus the control treatment [Bogdahn U *et al.* Targeted therapy for high-grade glioma with the TGF- β 2 inhibitor trabedersen: results of a randomized and controlled phase IIb study. *Neuro Oncol.* 2010, doi: 10.1093/neuonc/noq142].

Dr. Kottke: Currently, we are in the middle of an ongoing Phase III trial in which we hope to confirm these results. This trial is being conducted in 15 countries around the world and enrolls anaplastic astrocytoma and secondary glioblastoma patients. Together with our drug, we supply all study sites with our innovative drug delivery system to enable an ambulant treatment of the local administration of trabedersen. We successfully developed the infusion system in-house.

A number of specifications had to be fulfilled in order to meet CED technical criteria.

Dr. Heinrichs: That is the situation with high-grade glioma. We went on to also assess patients with other solid tumors, namely pancreatic carcinoma, malignant melanoma, and colorectal carcinoma. This was a typical dose-escalation Phase I/II trial and trabedersen was systemically administered through intravenous infusion. Treatment has been completed and the data were presented at ASCO in June of this year: Trabedersen showed a very good safety profile and encouraging first signs of efficacy in solid tumors. Fifteen pancreatic cancer patients treated second-line with trabedersen achieved a median overall survival (mOS) of 6.9 months which is comparable to that of the best available chemotherapy (mOS 5–6 months, historical data). Additionally, nine patients treated second-line with a special dose showed an encouraging survival benefit: Their mOS was 13.4 months. Furthermore, one patient (a third-line treatment pancreatic carcinoma patient with liver metastases) showed complete response and is still alive after 73 months. Of course the patient numbers are very small, but they form a good basis for a confirmatory trial.

To make sure that we are on the right track, we also did a benchmarking of our data and looked at all second-line treatments for pancreatic carcinoma in the last ten years, which included 49 clinical trials. In comparison to the 49 clinical trials, the safety of our treatment was excellent, and in addition, we had the best mean overall survival data (given the small sample size we had) and the best disease control rate data. These are all good signs to perform a confirmatory trial.

Dr. Kottke: You may also be aware that there is currently no registered drug for second-line treatment of pancreatic cancer in Europe and the United States. Further promising efficacy data were also observed in stage IV melanoma patients with a mOS of 13.8 months ($n = 5$; status May 2011). The evaluation of 14 additional melanoma patients is

ongoing and still looks good. So, at this point, we see encouraging data for three different indications.

IPR: You also mentioned colorectal cancer. What did you see in this cancer?

Dr. Heinrichs: The systemic administration of trabedersen was also very well tolerated in this group and *in vitro* data demonstrate a downregulation of the target. However the patient numbers were too small to draw any conclusions about efficacy yet. As a small biotech company, we have to focus on a manageable set of indications and so one of the challenges is to set priorities. Hence, we decided to postpone further investigations in colorectal cancer and concentrate on brain tumors, pancreatic cancer, and malignant melanoma.

IPR: What are the issues or challenges that a company faces as they develop an emerging new therapy in the area of cytokines or inhibiting cytokines?

Dr. Heinrichs: One of the challenges has to do with the target itself. Like a number of other scientists and cancer experts, we are convinced that we are dealing with a valid and clinically relevant target. Unfortunately, cytokines are still more or less unknown to physicians, unlike VEGF for example. To create awareness for the clinical relevance of this target is a real challenge. Additionally, there are reservations regarding the safety of our treatment because of the negative experiences with other anti-TGF- β approaches.

Dr. Kottke: Another challenge is that cancer therapies are rather complex. The entire emerging field of immunotherapy in oncology—to which trabedersen belongs—increases this complexity even more because there are more things that are unknown than are known: T-cell regulation, natural killer cells, macrophages, and so on. We are still looking for a good molecular target or immunological marker to monitor our product's efficacy other than through clinical results such as response or survival.

Also, what is new to the entire oncology community in terms of immunotherapy is that a response takes much longer than when using

cytotoxic therapies. Usually physicians see shrinkage of the tumor almost immediately or they conclude that the (chemo)therapy did not work. Immunotherapies take much longer to work because it takes time for the immune system to kick back in again and build up a response. The FDA even issued guidelines on immunotherapy and cancer because this is important new knowledge. Also, it is a challenge for us to design trials with the right endpoint and timing. In a way we are fortunate because there have been impressive successes recently, for example, with PROVENGE in prostate cancer or with YERVOY in melanoma. So, we think that we can build on those success stories. This is part of pioneering.

Dr. Heinrichs: We have also observed, for example, that in a small subgroup of patients you see something that seems like a progression of the disease but which is later followed by a decrease in the size of the tumor and prolonged survival even without further treatment with other medications. We have seen that with our medication, and it has been also described in melanoma. This is called a delayed response. When learning about immunotherapies, it is not unusual to have to get to directly observe a phenomenon in order to better understand it.

Dr. Kottke: Another important aspect is the “launch” or implementation of our new drug delivery system. In addition to familiarizing neurosurgeons with the system, we collaborate closely with regulatory authorities concerning the development of suitable guidelines. For example, obtaining IND permission for clinical studies in the United States, the review of the study documentation by the FDA turned out to be very complex. Besides detailed documentation describing the active agent, additional data concerning the drug delivery system used to administer trabedersen directly to the tumor was requested. Among other tasks, a neurotoxicity study had to be conducted to demonstrate the safety of the administration of trabedersen directly into the brain via the drug delivery system. After the absence of potentially neurotoxic effects was successfully demonstrated, one important decision criteria was met.

Our efforts have been rewarded. Our therapeutic approach offers people affected the chance of a longer life expectancy and importantly, a better quality of life. At market launch, we would like to provide the entire set that is needed to treat the disease, the infusion system to apply the drug and the medication itself, in other words, a system that we know works.

IPR: *Are there any other issues or challenges?*

Dr. Kottke: Absolutely. Performing preclinical and clinical development on several cancer indications simultaneously is also a challenge, especially for a small company like Antisense Pharma. As already mentioned, we have to face the logistics of an international Phase III study on malignant brain tumors that is being done around the world in 15 countries. Just imagine the number of documents we have to provide in several languages. A pivotal international Phase II/III trial on pancreatic cancer is in preparation and should start in 2012.

Dr. Kottke: Besides showing efficacy and safety, the company also has to show that the drug is cost effective and that patients as well as payers have a cost benefit. So, we have to collect resource utilization and quality-of-life data so that the treatment qualifies for reimbursement from healthcare systems around the world.

Dr. Heinrichs: As you can see, most of the challenges are not directly attributable to cytokines themselves. And we do not want to sound like we only have challenges—innovation means developing new approaches and pioneer work usually means a lot of work based on new insights. Overall, we think we have a lot of opportunities.

IPR: *Is there any other early-stage work or targets that you can discuss?*

Dr. Heinrichs: We are already doing research on compounds against other cytokines but they are still very early in development. For trabedersen, we think we have preliminary data that strongly indicate that there are further cancer indications for which we see *in vitro* signs of efficacy. These are lung cancer, prostate cancer, and renal cancer, to name a few.