

Special Issue:

Transforming Growth Factor Beta (TGF- β) as a Target in Oncology

Current Pharmaceutical Biotechnology has published up-to-date reviews from more than 25 internationally renowned TGF- β experts – Antisense Pharma's founder, Karl-Hermann Schlingensiepen, entrusted with guest editor ship

Regensburg, 11th January 2012. *Antisense Pharma today announced the publication of a special issue of the journal Current Pharmaceutical Biotechnology entitled "Transforming Growth Factor Beta as a Target in Oncology". This issue provides an overview on TGF- β biology and reflects on the current status of targeting TGF- β in oncology from the perspective of basic researchers, clinicians and pharmaceutical companies.*

Traditionally, the treatment of patients with cancer has been mainly based on chemotherapy with cytotoxic agents, mostly in addition to radiation, surgery or monoclonal antibodies. Recent advances in understanding tumor biology have provided new opportunities to develop effective approaches for treating cancer patients. Intensive research on molecular pathways influencing the genesis and progression of tumors has resulted in a panoply of potential drug targets. However, the multifunctional cytokine transforming growth factor beta (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 . TGF- β supports angiogenesis and promotes metastasis. Most importantly, TGF- β potently suppresses antitumor immune response. For example, through its effects on T-cells, B-cells, and antigen presenting cells, it allows tumor cells to escape from recognition and removal by the immune system.

Current understanding of TGF- β s molecular structure, signaling pathways, role in angiogenesis and metastasis

A. Hinck and M. O'Connor-McCourt first give a comprehensive overview of recent progress in characterizing the structural features of the inter-

action of the three mammalian TGF- β isoforms TGF- β 1, TGF- β 2, and TGF- β 3 with the TGF- β receptor complex and elaborate similarities and differences between the three isoforms.

H. Ikushima and K. Miyazono then describe the elements of intracellular TGF- β signaling and the multiple factors involved in its regulation. "Which cell responses are induced or suppressed in response to TGF- β depends on the cell type and the context of TGF- β signaling," explains Professor Kohei Miyazono, M.D., Department of Molecular Pathology, Graduate School of Medicine, University of Tokyo, Japan. "In this review we consider the basic machinery of TGF- β signaling and describe several factors which make up TGF- β signaling networks. We also address major TGF- β -induced cell responses involved in several physiological and pathological conditions." Considering the resulting complex network, it is not surprising that aberrant regulation of this pathway is involved in many diseases.

L. van Meeteren, M.-J., Goumans and P. ten Dijke summarize the current understanding of TGF- β signaling in vascular development and angiogenesis and focus on recent insights on the role of the TGF- β type I receptor ALK1 and co-receptor endoglin in tumor angiogenesis. "Tyrosine kinase signaling

pathways such as those involving vascular endothelial growth factor, VEGF, are the most studied in the context of angiogenesis,” say Laurens van Meeteren, Ph.D., and Peter ten Dijke, Ph.D., Molecular Cell Biology at University of Leiden, The Netherlands. “There is however accumulating evidence that more pathways are indispensable for angiogenesis. This review highlights our understanding of TGF- β signaling in vascular development and angiogenesis and gives an update about the current progress of anti-TGF- β receptor agents targeting angiogenesis in the clinic.” **J. Buijs, P. Juárez and T. Guise** outline the role of TGF- β in bone metastasis and discuss the limitations and opportunities of current treatment approaches.

Aggressive cancer is strongly related to TGF- β overexpression. The following contributions review the specific role of TGF- β in various indications. **E. Connolly and R. Akhurst** describe the complexities of TGF- β action in the regulation of two epithelial tumor types, namely squamous cell carcinoma and breast cancer. **P. Hau, P. Jachimczak, J. Schlaier and U. Bogdahn** highlight the critical role of TGF- β 2 in high-grade glioma. The decisive role of this isoform in high-grade glioma patients was recognized early in TGF- β research.

TGF- β 2 has also an important role in two other indications reviewed in this issue. **A. Hilbig and H. Oettle** have compiled the current knowledge on TGF- β in pancreatic cancer and **A. Busse and U. Keilholz** review the effects TGF- β in malignant melanoma with special emphasis on its vital role in immunosuppression. “Human malignant melanoma is highly resistant to chemotherapy and current immunotherapeutic approaches induce long term remission only in a minority of patients. TGF- β has attracted much attention as a therapeutic target because it plays an important and pleiotropic role in melanoma progression”, comments Ulrich Keilholz, M.D., Deputy Director of the Charité Comprehensive Care Center, Berlin, Germany. “Cultured normal melanocytes and malignant melanoma express both TGF- β 1 and TGF- β 3 mRNA transcripts,

but TGF- β 2 mRNA transcripts are found only in melanoma cells. In addition, the expression of TGF- β 2 in all melanomas indicates that this cytokine is regulated independently of the TGF- β 1 and TGF- β 3 isoforms and may have a pivotal role in the development of both invasion and metastasis during melanomagenesis.”

Targeting TGF- β in oncological diseases

How can TGF- β be targeted? Generally speaking, therapeutic interventions directed against TGF- β can block excessive TGF- β production, neutralize its activity, or inhibit its receptor signaling. Several approaches are currently being developed. **S. Lonning, J. Mannick and J. McPherson** have summarized the results of experimental animal and human clinical studies on antibody-mediated neutralization of TGF- β . **L. Ling and W.-C. Lee** follow with an overview on the development of small molecules for the inhibition of TGF- β type I receptor kinase (ALK5) as a means to interrupt TGF- β -signaling. Finally, **F. Jaschinski, T. Rothhammer, P. Jachimczak, C. Seitz, A. Schneider and K.-H. Schlingensiepen** present the antisense oligodeoxynucleotide, trabedersen, for the targeted treatment of patients with tumors overproducing TGF- β 2. “We sincerely hope that this special issue provides insightful reading and contributes to increased awareness for TGF- β as a highly attractive therapeutic target in oncology,” concludes Karl-Hermann Schlingensiepen, Ph.D., M.D., founder and longtime CEO at Antisense Pharma, who was entrusted with the guest editorship of this special issue. “The results of our clinical studies with trabedersen clearly demonstrate that targeting TGF- β is a promising therapeutic option for the treatment of aggressive cancer diseases with high unmet medical need.”

Special Issue “TGF- β as Target in Oncology” – Contribution list:

- Andrew Hinck & Maureen O’Connor-McCourt: Structures of TGF- β -Receptor Complexes: Implications for Function and Therapeutic Intervention Using Ligand Traps
- Hiroaki Ikushima & Kohei Miyazono: Biology of TGF- β Signaling
- Laurens A. van Meeteren, Marie-José Goumans & Peter ten Dijke: TGF- β Signaling Pathways in Angiogenesis; Emerging Targets for Anti-Angiogenesis Therapy
- Jeroen T. Buijs, Patricia Juárez & Theresa A. Guise: Therapeutic Strategies to Target TGF- β in the Treatment of Bone Metastases
- Erin C. Conolly & Rosemary J. Akhurst: The Complexities of TGF- β Action During Mammary and Squamous Cell Carcinogenesis
- Peter Hau, Piotr Jachimczak, Jürgen Schlaier & Ulrich Bogdahn: TGF- β 2 Signaling in High-Grade Gliomas
- Andreas Hilbig & Helmut Oettle: TGF- β in Pancreatic Cancer
- Antonia Busse & Ulrich Keilholz: Role of TGF- β in Melanoma
- Scott Lonning, Joan B. Mannick & John McPherson: Antibody Targeting of TGF- β in Cancer Patients
- Leona E. Ling & Wen-Cherng Lee: TGF- β Type I Receptor (ALK5) Kinase Inhibitors in Oncology
- Jaschinski et al.: The Antisense Oligonucleotide Trabedersen (AP 12009) for the Targeted Inhibition of TGF- β 2

Additional Information

About Current Pharmaceutical Biotechnology

Current Pharmaceutical Biotechnology aims to cover all the latest and outstanding developments in molecular and pharmaceutical biotechnology. Each issue of the journal contains a series of timely, in-depth reviews written by leaders in the field covering a range of current topics in both pre-clinical and clinical areas of biotechnology. *Current Pharmaceutical Biotechnology* is an essential journal for academic, clinical, government and pharmaceutical scientists who wish to be kept informed and up-to-date with the latest and most important developments.

About Antisense Pharma GmbH

Antisense Pharma is a biopharmaceutical company located in Regensburg, Germany. The company focuses on targeted therapies for malignant tumors and is dedicated to the discovery and development of drugs based on antisense technology that specifically block the synthesis of key cancer proteins such as TGF- β 2. The company has clinical trials running that involve patients with brain tumors, advanced pancreatic carcinoma, malignant melanoma and colorectal carcinoma. Therapies for other indications are in preclinical development. The company has been honored with the German Founder’s Award and the Bavarian Innovation Award and has received the Innovation Prize TOP 100 twice.

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