TGF-β: A Prime Target for Cancer Immunotherapy

CIMT Satellite Symposium
May 7, 2014
TGF-β: A Prime Target for Cancer Immunotherapy

**Introduction**
Dr. Michael Janicot (Isarna Therapeutics, Munich)

**General role of TGF-β on the immune system**
Dr. Lalage Wakefield (National Cancer Institute, Bethesda, USA)

**TGF-β signaling in cancer**
Dr. Joan Seoane (Vall D’Hebron Institute of Oncology, Barcelona, Spain)

**Targeting TGF-β in cancer**
Dr. Michael Weller (University Hospital Zurich, Switzerland)

CIMT program: http://meeting.cimt.eu/program/
A General Role for TGF-β in the Immune System

The transforming growth factor-βs (TGF-βs) are multifunctional secreted polypeptide growth factors that arose in evolution at the same time as adaptive immunity. The TGF-β ligands and receptors are widely expressed and play important roles in maintaining adult homeostasis and coordinating responses to injury and stress.

Work in the late 1980s established that TGF-βs had highly potent immunosuppressive activity on T-cells and NK cells, and a central role for TGF-β1 in maintaining immune homeostasis was confirmed by the phenotype of the TGF-β1 knockout mouse which dies soon after weaning of an autoimmune-like inflammatory syndrome. Subsequent work established complex regulatory effects of TGF-βs on essentially every cell type of the innate and adaptive immune systems.

Broadly TGF-βs suppress the generation and/or function of effector immune cells and induce the generation of immunosuppressive cells or phenotypes. Thus in the T-cell compartment, TGF-βs have suppressive effects on Th1 and cytotoxic T-cells, while promoting the generation and activity of regulatory T-cells. In innate immunity, TGF-βs increase the suppressive activity of monocytes/macrophages by promoting polarization towards an M2 phenotype, decrease the cytotoxicity of neutrophils and NK cells, and impair antigen presentation by dendritic cells.

The majority of advanced human tumors overexpress TGF-βs and this overexpression correlates with metastasis and poor prognosis, suggesting that immunosuppressive effects of TGF-β may contribute importantly to cancer progression and resistance to existing therapies. Indeed, preclinical studies have shown that TGF-β antagonists can significantly suppress tumorigenesis and/or metastasis by mechanisms that depend on reactivation of effective antitumor immunity. Furthermore, TGF-β antagonism greatly improves the efficacy of immunomodulatory chemotherapy and of anti-cancer vaccine approaches in preclinical models. Overall, TGF-βs are emerging as important therapeutic targets in cancer immunotherapy.

Lalage Wakefield DPhil., Lab of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute, Bethesda, USA
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TGF-β: a Prime Target for Cancer Immunotherapy

Michel Janicot, Ph.D.
Isarna Ther. - Preclinical R. & D.
Chair / Introduction

May 7, 2014
Isarna Therapeutics has an unmatched commitment to developing TGF-β inhibitors that stimulate the human immune system to effectively fight cancer and other diseases. We are advancing a unique pipeline of novel oligonucleotides and combination modalities to transcend clinical response and improve patient outcomes.

(http://www.isarna-therapeutics.com)
Transforming Growth Factor beta (TGF-β)
a constellation in the ImmUniverse
Michel Janicot is head of preclinical research & development at Isarna Therapeutics.

He has over 20 years of pharmaceutical industry experience in oncology R&D. Prior to joining Isarna, he was Senior Director at Janssen R&D (Johnson&Johnson) located in Beerse, Belgium and then founded his own consulting firm (JMi ONConsulting).

He has managed large multidisciplinary teams for the worldwide preclinical and early clinical development of both small molecules and biologics drug candidates for oncology intervention. His management expertise, leadership, and strategic vision, combined with extensive experience with large pharma companies such as Johnson&Johnson and Sanofi (formerly Rhône-Poulenc Rorer), covers a large scope of the drug development process – from discovery to early clinical development.

He has a doctorate in biochemistry from the University Paris VII, France, obtained in 1988 and did a postdoctoral training at The Johns Hopkins University, Baltimore, MD (USA) from 1988 to 1992.
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General role for TGF-β in the immune system

Lelage Wakefield DPhil
Lab of Cancer Biology and Genetics
Center for Cancer Research
National Cancer Institute, Bethesda USA
Transforming growth factor-βs (TGF-βs)

- Multifunctional secreted polypeptide growth factors that arose in evolution at the same time as adaptive immunity
- TGF-β ligands (TGF-β1,2,3) are widely expressed and receptors are present on nearly every cell type
- Involved in maintaining adult homeostasis and coordinating responses to injury and stress
- Perturbations in the TGF-β pathway are a feature of many pathological states: vascular disorders, autoimmunity, fibrosis, cancer
TGF-β signaling pathway

Serine/threonine receptor kinases

TβRII  TβRI

Active TGFβ

NON-CANONICAL

RHO  ROCK

RAS  RAF  MEK  ERK

TAK1  JNK  P38  PI3K

NFκB

CANONICAL

Smad2/3

Smad2/3  Smad4

Target genes
TGF-β is an immunosuppressive cytokine

PRODUCTION OF TRANSFORMING GROWTH FACTOR β
BY HUMAN T LYMPHOCYTES AND ITS POTENTIAL ROLE
IN THE REGULATION OF T CELL GROWTH

BY JOHN H. KEHRL,* LALAGE M. WAKEFIELD,‡ ANITA B. ROBERTS,‡
SONIA JAKOWLEW,‡ MELCHOR ALVAREZ-MON,§ RIK DERYNCK,†
MICHAEL B. SPORN,‡ AND ANTHONY S. FAUCI*

From the *Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, the ‡Laboratory of Chemoprevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892; the §Servier of Internal Medicine 1, Clinica Puerta de Hierro, Madrid, Spain; and the †Department of Molecular Biology, Genentech, Incorporated, South San Francisco, California 94080
Dominant phenotype of TGF-β1 knockout mouse is an overactive immune system

TGF-β1-/- mouse dies soon after weaning from a **multifocal inflammatory disease** with hallmarks of autoimmunity


---

Runting and death of TGF-β1 KO mouse is rescued on Rag2-/- or SCID background

Mixed inflammatory infiltrates in multiple organs

Central role for TGF-β in tonically modulating and dampening immune responses in normal physiology
Cellular targets of TGF-β-driven immune suppression

- Suppression of effector cells/functions
  - CTL
  - Th1
  - B cell
  - NK
  - DC

- Induction of suppressive cells/phenotypes
  - T_{reg}
  - Th17
  - MDSC
  - M1→M2
  - N1→N2
  - Macrophages
  - Neutrophils
Effects of TGF-β on innate immune cells

Flavell et al. 2010
Effects of TGF-β on T-cells

Flavell et al. 2010
Relevance to cancer?
TGF-βs are overexpressed by many advanced tumors and correlate with metastasis and poor prognosis.

**Increased TGF-β immunostaining:**
Nearly all carcinomas, melanoma, chondrosarcoma, osteosarcoma

**Increased circulating TGF-β:**
Glioblastoma
Tumors with bone metastasis burden
Prostate cancer

*TGF-β1 in prostate CA*  
(Truong et al. Hum Pathol 1993)
Does elevated TGF-β in advanced cancers compromise anti-tumor immunity?
Anti-TGF-β monotherapy in the 4T1 mouse model of metastatic breast cancer

4T1 cancer model
- Models basal-like breast cancer
- Highly metastatic
- Poorly immunogenic
- Syngeneic to Balb/c

Anti-TGF-β antibody
- 1D11 monoclonal antibody
- Genzyme Corp
- Neutralizes all 3 isoforms of TGF-β
- Isotype-matched control antibody

Implant 40,000 4T1 cells in #4 mfp
Surgically resect primary tumor
Assess metastasis burden

Anti-TGF-β antibody (1D11) or isotype control (CON)
5mg/Kg ip 3x q wk
Most of the efficacy of anti-TGF-β monotherapy in the 4T1 model is dependent on the immune system

A. Adaptive immunity

B. Adaptive and innate immunity

Intact CD8-T-cell depleted

P=0.0006 NS

Antibody therapy

Therapeutic effect size

Intact CD8+ T-cell depleted NK cell depleted

70% 40%
Anti-TGF-β monotherapy suppresses metastasis and promotes overall survival by **reactivating or unmasking effective anti-tumor immunity**

**Tumor cells**

- Visibility to immune system
  - $\uparrow$ Rae1γ, Calr
- Sensitivity to cell death inducers and complement-mediated lysis
  - $\uparrow$ TNFSFR1A, Bsp1
- Undesirable immune modulators
  - $\downarrow$ IL-6

**Immune cells**

- Immune cell recruitment
  - $\uparrow$ NK cells, T cells; $\downarrow$ MDSCs
- Immune cell activation
  - $\uparrow$ NKG2D
- Cytotoxic effectors
  - $\uparrow$ Granzyme B, Perforin
- Cytokine production
  - $\downarrow$ IL-17 (tumor cell survival factor)
Improving efficacy by combining anti-TGF-β antibodies with immunomodulatory chemotherapy

Collaboration with Drs. Joost Oppenheim and Xin Chen (Cancer and Inflammation Program, NCI, NIH)

Cytoxan (cyclophosphamide)
Anti-TGF-β synergizes with subtherapeutic doses of cytoxan to enhance survival in the 4T1 model

A. Experimental schema

B. Survival curves (death from metastatic burden)

Chen et al. PLOS One 2014
TGF-β antibodies can enhance efficacy of anti-tumor vaccines

*Drs. Jay Berzofsky and Masaki Terabe*
*(Vaccine Branch, NCI, NIH)*
Anti-TGF-β synergistically enhances efficacy of anti-tumor whole cell vaccine

**Vaccine:** 10^5 irradiated CT26 cells sc  
**Challenge:** 10^6 CT26 cell 3 weeks post vaccination  
**Anti-TGF-β:** 3x q wk from time of vaccination

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Takaku et al., *Int J Cancer* 2010
Conclusions

TGF-β is a key immunosuppressive factor that is overexpressed by the majority of human tumors.

TGF-β antibody therapy has single agent efficacy that is largely due to reactivation of effective anti-tumor immune responses.

Combination therapy with TGF-β antagonists can enhance the efficacy of immunomodulatory chemotherapy and anti-cancer vaccines.

IMPORTANT THERAPEUTIC TARGET!
Acknowledgments

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Jay Berzofsky, MD PhD
Masaki Terabe, PhD

Lab of Molecular Immuno-regulation, CCR, NCI
Joost Oppenheim, MD
Xin Chen, PhD

Genzyme Corp, Framingham MA
Scott Lonning, DVM PhD
John McPherson, PhD
Lalage Wakefield is a Senior Investigator at the National Cancer Institute.

She has worked in the TGF-β field for 30 years, with a particular focus on mechanistic understanding of the dual role of TGF-β in breast cancer progression, and on the preclinical development of therapeutic approaches to target the TGF-β pathway in oncology. Her lab was the first to show that TGF-β antagonism could suppress experimental metastasis without the expected adverse side-effects of autoimmune disease and increased spontaneous tumorigenesis, thus demonstrating the therapeutic potential of this complex molecular target.

Her subsequent work showed that therapeutic efficacy of anti-TGF-β antibodies involved multiple cellular compartments (“death by a thousand cuts”), with the unmasking of effective anti-tumor immunesurveillance playing a critical role.

Currently the Wakefield lab is working to further improve efficacy through combination therapy and predictive biomarker development.
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CIMT program: http://meeting.cimt.eu/program/
TGF-β signaling in cancer

Joan Seoane
Vall d’Hebron Institute of Oncology (VHIO)
Vall d’Hebron University Hospital
Barcelona
Immune Cells
Inhibits T-cell proliferation
Impairs NK cell function
Impairs antigen presentation

TGF-β controls development and homeostasis

Epithelium
- Cell cycle arrest
- Apoptosis
- ECM production
- Adhesion

Fibroblasts
- ECM production
- Proliferation
- Cytokine secretion

Endothelium
- Migration
- Morphogenesis
- Proliferation
The basis of the TGF-β pathway

Type II receptor → Type I receptor → Non-Smad pathway

P38  JNK  Ras-ERK  PI3K-Akt  GTPases

Activated Smad Complex

Cell-specific DNA-binding cofactors → Co-activator or Co-repressor
The TGF-β pathway in essence in epithelial cells

- **Cytostatic Program**
  - p15Ink4b, p21Cip1, c-Myc

- **Extracellular Matrix**
  - PAI-1, uPA, Col VI-A1, ADAM19
  - Integrin α5, integrin β6

- **Paracrine Network**
  - IL11, VEGF, CTGF, Jagged1, Follistatin3
  - Angiopoietin4, IL1β, BMP4

- **Signaling Network**

- **Transcription Network**
  - Ets2, c-Jun, JunB, ATF3, Gadd45β, Pim1, Mad2, Mad4, C/EBPδ, MRG1, TRIP-Br2

- **Other Responses**
  - T-box3, MN1, Igλ, Syalyl tranf.4A
  - Sprouty 2, IAP3, UDPG-ceramide GT

- **Negative Feedback**
  - Smurf1, Smurf2, Smad7, SnoN
TGF-β-induced cell cycle arrest

Donovan et al., Breast cancer Res, 2000
Normal epithelial cells

Cancer cells lacking TGF-β receptor or Smad

Cancer cells lacking cell cycle arrest response

TGF-β

cell cycle arrest genes

other target genes

TGF-β

cell cycle arrest genes

other target genes

TGF-β

cell cycle arrest genes

other target genes

Homeostasis

Uncontrolled proliferation

Uncontrolled proliferation

Invasion

Metastasis
Escaping from the TGF-β anti-proliferative response

- Colon cancer
- Ovarian, breast, pancreatic cancer
- Pancreatic cancer, colon cancer
- Cell cycle arrest
- Other responses

TGF-β activates TβRI, TβRII, and R-Smad, leading to Smad4 phosphorylation.

Colon cancer, lung cancer
Loss of the TGF-β anti-proliferative response
Escaping from the TGF-β anti-proliferative response
The TGF-β cytostatic program

- TGF-β Receptor
- R-Smad-Smad4 complex
- Cdk2 inhibition
- Cdk4 inhibition p27 release
- Cell Cycle Arrest
- p21Cip1
- p15Ink4b
- c-myc
The TGF-β cytostatic program

TGFβ Receptor

R-Smad-Smad4 complex

p21Cip1

p15Ink4b

c-myc

Cell Cycle Arrest
Loss of the TGF-β anti-proliferative response
The TGF-β pathway in essence in epithelial cells

Cytostatic Program
p15Ink4b, p21Cip1, c-myc

Extracellular Matrix
PAI-1, uPA, Col VI-A1, ADAM19
Integrin α5, integrin β6

Paracrine Network
IL11, VEGF, CTGF, Jagged1, Follistatin3
Angiopoietin4, IL1β, BMP4

Signaling Network
BMPR-II, VDR, EphB2, RhoGEF114,
Mek4, LDLR, PGE-R4, βAR-2

Transcription Network
Ets2, c-Jun, JunB, ATF3, Gadd45β, Pim1
Mad2, Mad4, C/EBPβ, MRG1, TRIP-Br2

Other Responses
T-box3, MN1, Igλ, Syalink transf.4A
Sprouty 2, IAP3, UDPG-ceramide GT

Negative Feedback
Smurf1, Smurf2, Smad7, SnoN

Cell-specific DNA-binding cofactors
Co-activator or Co-repressor
TGF-β duality in cancer

Normal Epithelium → Adenoma → Invasive Carcinoma

Metastasis

TGF-β oncogenic response

- Immunosuppression
- Proliferation
- Angiogenesis
- Invasion
- EMT
- Metastasis
- Cancer-initiating cells
Autocrine and paracrine TGF-β signaling

TGF-β

Cancer Stem Cell (CSC)

Cancer-Associated Fibroblast (CAF)

Endothelial Cell (EC)

Pericyte (PC)

Immune Inflammatory Cells (ICs)

Invasive Cancer Cell

Local & Bone marrow-derived Stromal Stem & Progenitor Cells
Grade IV astrocytoma; Glioblastoma

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

High TGF-β is a poor prognostic factor in GBM
(Rembrandt, TCGA data base)
Cluster TCGA samples using a TGF-β signature
HYPERACTIVATION OF TGF-β SIGNALING
Regulation of the TGF-β pathway by protein ubiquitination

TGF-β

TβRII  TβRI

Smad7  Smurf

R-Smad

Ub

DNA-binding cofactors

Co-activators or Co-repressors

Pi

Smad7
USP15 promotes TGF-β activity and oncogenesis

Diagram:
- USP15
- SMURF2
- SMAD7
- Proteosomal degradation
- TGF-β
- Hyperactivation of TGF-β
- Tumor progression
- Stability

Arrows indicate the direction of the interactions:
- Blue arrows show the role of USP15 and SMURF2 in stabilizing SMAD7 and promoting TGF-β hyperactivation, leading to tumor progression.
- Red arrow indicates proteosomal degradation of SMURF2.

USP15 promotes TGF-β activity and oncogenesis through its role in stabilizing SMAD7 and inhibiting SMURF2 activity, leading to hyperactivation of TGF-β and tumor progression.
Hyperactivation of the TGF-β signaling. An oncogenic driver?
Dr. Joan Seoane  
Vall d’Hebron Institute of Oncology  
Barcelona, Spain

Joan Seoane is Director of Translational Research at the Vall d’Hebron Institute of Oncology (VHIO), leading efforts to advance cancer treatment and catalyze the transfer of new insights for the benefit of cancer patients.

His research is focused on the molecular mechanisms involved in the initiation and progression of cancer, specifically of glioma. Joan has received numerous awards including the Research Fellow Award from the Memorial Sloan-Kettering Cancer Center, the Beckman-Coulter Award from the Spanish Society for Biochemistry and Molecular Biology (SEBBM), and the Banco Sabadell Biomedical Research Award.  
He is a member of the Executive Committee of the European Association for Cancer Research (EACR) and Associate Professor at the Universidad Autónoma de Barcelona (UAB).
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Targeting transforming growth factor-β in cancer
Mainz, 7 May 2014

Michael Weller
Department of Neurology
University Hospital Zurich
Switzerland
Twelve Core Cancer Pathways

- TGF-β/SMAD Signaling
- WNT Signaling
- RAS/RAF Signaling
- PIK3/PTEN Signaling
- Hedgehog/GLI Signaling
- HIF 1α Signaling
- JAK/STAT Signaling
- NOTCH Signaling
- Control of G1/S Transition
- DNA Damage Control
- Apoptosis
- Chromatin Remodeling

B. Vogelstein, SNO Annual Meeting 2012
TGF-β signaling: a core cancer pathway
Drugs with unknown targets or indirect targeting:
- Losartan (AT1 blocker)
- Firfenidone (unknown target)
- Tranilast (unknown target)

Latent TGFβ

Active TGFβ

* Lerdelimumab (CAT-152)
* Metelimumab (CAT-192)
* Fresolimumab (GC-1000)
* 1D11
* LY2352770

SR2F (soluble TβRII-Fc)
P144, P17
IMC-TR1, IMC-MT1

SR11014
Trebedersen
Lucenix

AP11014

TGFβ mRNA

TGFβ1 gene

Pyrimidine-imidazole polynucleotide

Target gene expression

SMAD2 or SMAD3

SMAD2 or SMAD3

SMAD4

TF

Co-TFs

TRX-FOXH1B
TRX-LEF

Nucleus

Cytoplasm

Extracellular milieu

Figure 5 | Schematic representation of therapeutic approaches for blocking TGFβ signalling. Transforming growth factor-β (TGFβ) signalling can be inhibited by: sequestering ligands using soluble receptor ectodomain constructs (ligand traps) derived from TGFβ receptor type II (TβRII) or TβRII; using TGFβ-neutralizing antibodies; or with TβRII or TβRI kinase inhibitors. Furthermore, translation of TGFβ mRNA can be blocked by targeting TGFβ mRNA with antisense oligonucleotides, thus preventing the production of the ligand. Different small-molecule kinase inhibitors against TβRI have been developed to block its kinase activity. Peptide inhibitors against specific TGFβ ligands are also used. Other approaches block the transformation of TGFβ from the latent to the active form. Three molecules are shown that either affect TGFβ signalling indirectly (losartan) or that have an as-yet-identified target (tranilast and firfenidone). All of these approaches decrease the initiation of intracellular receptor signalling pathways, such as phosphorylation of downstream receptor-specific SMADs (R-SMADs), and thereby blunt the transcriptional regulation of target genes. AT1, angiotensin II type 1 receptor; co-TFs, co-transcription factors; FOXH1B, forkhead box protein H1B; LEF, lymphoid enhancer-binding factor; LSKL, Leu-Ser-Lys-Leu peptide; TRX, thioredoxin.
NovaRx Announces Results of Lucanix® Phase III Therapeutic Vaccine Trial for Maintenance Therapy in Non-small Cell Lung Cancer to Be Presented at ESMO.

SAN DIEGO, Sept. 26, 2013 /PRNewswire/ -- NovaRx Corporation announced that the results from the randomized Phase III trial of Lucanix® (belagenpumatucel-L) will be presented at the European Society for Medical Oncology 2013 annual meeting in Amsterdam. The results will be presented by Dr. Giuseppe Giaccone in "Presidential Session I: Best and Late Breaking Abstracts" on 28 September 2013.

The primary endpoint of improving overall survival in 532 patients was not met. However, in the predefined subgroup of 305 stages III/IV patients enrolled within 12 weeks of the completion of frontline chemotherapy, a median survival of 20.7 months was observed for Lucanix compared to 13.4 months for the control (HR 0.75). In a predefined subgroup of these patients with squamous cell carcinoma a median survival of 20.7 months was observed for Lucanix compared to 12.3 months for the control (HR 0.58). In another predefined subgroup of these patients who received radiation therapy prior to enrollment a median survival of 40.1 months was observed for Lucanix compared to 10.3 months for the control (HR 0.45). The endpoint was not met due to patients enrolled more than 12 weeks following the completion of chemotherapy.

About Lung Cancer
Each year lung cancer causes approximately 160,000 deaths in the USA and close to two million deaths worldwide, more than the next four most lethal cancers combined.

About Lucanix Whole Tumor Cell Vaccine
Lucanix represents a new class of tumor vaccines designed to use allogeneic whole tumor cells to stimulate the patient's own immune system to attack the patient's tumor. The cells in Lucanix have been modified to block production of transforming growth factor beta (TGF-B), which is one of the primary methods cancers use to hide from the immune system. Blocking TGF-B allows the vaccine to initiate a strong immune response, resulting in long-term clinical benefit with minimal toxicity.
Identification of TGF-β as a potent glioblastoma-associated immunosuppressant

GLIOBLASTOMA CELLS RELEASE INTERLEUKIN 1 AND FACTORS INHIBITING INTERLEUKIN 2-MEDIATED EFFECTS

ADRIANO FONTANA,²* HANS HENGARTNER,¹ NICOLAS de TRIBOLET,¹ AND ELISABETH WEBER*  

From the ¹Section of Clinical Immunology, the Neurosurgical Department, and the ²Institute for Pathology, University Hospital, Zürich; and from the ³Neurosurgical Department, University Hospital, CHUV, Lausanne, Switzerland
Biological effects of TGF-β in glioblastoma

- **Microglia**
  - Adhesion ↓
  - Cytokine synthesis ↓
  - MHC class II ↓
  - H₂O₂ and NO release ↓
  - Chemotaxis ↑
  - DC maturation ↓
  - Antigen presentation ↓

- **Macrophages**
  - Chemotaxis ↑

- **Glioblastoma**
  - Proliferation ↑ down
  - MHC class II ↓
  - MMP synthesis ↑
  - Invasion/migration ↑
  - Stem cell renewal ↑

- **Endothelial cells**
  - Adhesion ↓

- **T cells**
  - Proliferation ↓
  - Activity ↓
  - Apoptosis ↑

- **NK cells**
  - TGF-β synthesis ↑

- **Autocrine effects**
TGF-β RNA interference abrogates tumor formation in a human glioma LNT-229 xenograft model in nude mice
Friese et al. Cancer Res 2004;64:7596-7603

**Subcutaneous model**
- **Tumor volumes [mm²]**
  - Days after glioma cell inoculation
  - Control
  - TGF-β siRNA

**Intracranial model**
- **Survival [%]**
  - Days after glioma cell inoculation
  - Control
  - TGF-β siRNA
Pharmacological inhibition of TGF-β signaling in rodent glioma models

Tran et al. Neuro-Oncology 2007;9:259–270
Induction of protective immunity?

Fig. 6. Long-term survivors reject tumor rechallenge. (A) Kaplan-Meier analysis of long-term survivors rechallenged with SMA-560 cells (n = 22 per group). (B) Rejected tumor is rejected in long-term survivors. Naive animals or long-term survivors were rechallenged with SMA-560 cells in the contralateral hemisphere. Animals were sacrificed 15 days postimplantation, and the brains were harvested for histological analysis. Representative images are shown. Scale bar = 1 mm. (C) High concentration of CD3+ cells in the vicinity of the rechallenge site. Representative images are shown. Scale bar = 20 μm.
Targeted therapy for high-grade glioma with the TGF-β2 inhibitor trabedersen: results of a randomized and controlled phase IIb study


Department of Neurology, University of Regensburg, Germany (U.B., P.H.); Department of Neurology, University of Innsbruck, Austria (G.S.); Manipal Institute for Neurological Disorders, Manipal Hospital, Bangalore, India (N.K.V.); Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Raebareli, Lucknow, India (A.K.M.); Department of Neurosurgery, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India (A.S.); Department of Neurosurgery, National Institute of Mental Health and Neurosciences, Bangalore, India (A.B.); Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, Kerala, India (S.N.); Polenov Neurosurgery Research Institute, St. Petersburg, Russia (V.O.); Neurosurgery Department 6, Military Medical Academy, St. Petersburg, Russia (V.P.); Neurology Department 159, Samara Medical Hospital, Samara, Russia (I.P.); Neurosurgery Department, Rambam Medical Center, Haifa, Israel (M.Z.); Antisense Pharma GmbH, Regensburg, Germany (P.J., S.L., S.S., H.H., K.-H.S.)

This randomized, open-label, active-controlled, dose-finding phase IIb study evaluated the efficacy and safety of trabedersen (AP 12009) administered intratumorally by convection-enhanced delivery compared with standard chemotherapy in patients with recurrent/refractory high-grade glioma. One hundred and forty-five patients with central reference histopathology of recurrent/refractory glioblastoma multiforme (GBM) or anaplastic astrocytoma (AA) were randomly assigned to receive trabedersen at doses of 10 or 80 μM or standard chemotherapy (temozolomide or progabazine/lonistine/vincristine). Primary endpoint was 6-month tumor control rate, and secondary endpoints included response at further timepoints, survival, and safety. Six-month tumor control rates were not significantly different in the entire study population (AA and GBM). Prespecified AA subgroup analysis showed a significant benefit regarding the 14-month tumor control rate for 10 μM trabedersen vs chemotherapy (p = .0032). The 2-year survival rate had a trend for superiority for 10 μM trabedersen vs chemotherapy (p = .10). Median survival for 10 μM trabedersen was 39.1 months compared with 35.2 months for 80 μM trabedersen and 21.7 months for chemotherapy (not significant). In GBM patients, response and survival results were comparable among the 3 arms. Exploratory analysis on GBM patients aged ≤55 years with Karnofsky performance status ≥80 at baseline indicated a 3-fold survival at 2 and 3 years for 10 μM trabedersen vs chemotherapy. The frequency of patients with related or possibly drug-related adverse events was higher with standard chemotherapy (64%) than with 80 μM trabedersen (43%) and 10 μM trabedersen (27%). Superior efficacy and safety for 10 μM trabedersen over 80 μM trabedersen and chemotherapy and positive risk–benefit assessment suggest it as the optimal dose for further clinical development in high-grade glioma.
Future challenges

- Deciphering the contribution of selected TGF-β isoforms to tumor promotion versus host manipulation
- Defining the ideal tumor target for TGF-β inhibition
- Establishing a biomarker for TGF-β inhibition
- Identifying the ideal setting including multimodality treatment for TGF-β inhibition
Michael Weller is Chairman of the Department of Neurology at the University Hospital Zurich, Switzerland.

Dr. Weller has received several awards in recognition of his important contributions to cancer research, including the German Cancer Award in 2007. He served as the Chairman of the Neuro-Oncology Group of the German Cancer Society from 2001-2008. He is the Chairman of the Germany Glioma Network of the German Cancer Council and a member of the Board of the European Association for Neuro-Oncology (EANO).

Michael Weller was involved in major practice-changing clinical trials including the registration trial for temozolomide in glioblastoma and served as PI on the NOA-03, NOA-04, NOA-08 and G-PCNSL-SG-1 trials in Germany and the DIRECTOR and ARTE trials in Switzerland. Michael Weller has co-authored more than 500 original publications. He is a member of the editorial boards of the Journal of Clinical Oncology, Journal of Neurochemistry, Journal of Neuro-Oncology, Brain and Glia, and he was the Associate Editor Europe of Neuro-Oncology from 2006-2013.
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