TNF Superfamily Modulators – Next Generation Immunotherapy
Dr. Thomas Hoeger, CEO
Apogenix GmbH

- Founded in 2005 in Heidelberg, Germany, as a spin out from dkgz.
- Focus on next-generation immunotherapeutic drugs for treatment of cancer.
- Approach: Novel antibody-like Fc fusion proteins targeting TNF SF members.

Status of Lead Compound APG101

- Proof of concept in recurrent glioblastoma (GB) shown.
- Proof of principle and ongoing phase I in myelodysplastic syndromes (MDS).
- Mode of action ⇒ broad applicability for treatment of solid tumors.

Finance

- € 55.5m in four financing rounds.
- € 8.5m public grants.
- Upfront payment through partnering.
### Apogenix’ Pipeline 2015

#### TNF SF Inhibitors

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#### TNF SF Receptor Agonists

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PoC: Proof of concept

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Apogenix Targets TNF Superfamily Members

Checkpoint inhibitors have attracted considerable attention (e.g. PD-L1/PD-1)

Apogenix TNF SF modulators target receptor/ligand systems discovered as checkpoints for cancer immunotherapy

*APC: Antigen presenting cell
• Signaling in the TNF receptor superfamily is stimulated by receptor multimerization after interaction with the respective trimeric ligand
• Ligand members: TNF, CD95L, TRAIL, CD40L, OX40L, LIGHT etc.
**Mode of Action:**

- APG101 restores CD95 ligand-mediated immune surveillance of solid tumors and inhibits invasive cancer cell growth

**APG101:**

- Fully human Fc fusion protein
- Excellent safety profile
- Intravenous administration (30 min., once weekly)

**Clinical development:**

- Immunotherapeutic mechanism of action offers broad applicability in tumor indications
- Initial indication: Glioblastoma (brain tumor)
- Second indication: Myelodysplastic Syndromes (disease of the bone marrow)
CD95 Ligand Signaling

- Best described role of CD95L signaling is the regulation of T-cell homeostasis by “activation-induced cell death”
- Cancer cells use this pathway to stimulate their own growth and migration and to evade immune surveillance by killing immune cells

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**CD95 ligand signaling**

- **CD95 Ligand**
- **CD95 Receptor**
- Receptor Multimerisation
- Signaling

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**APG101 – CD95 ligand inhibitor**

- **CD95 Ligand**
- **APG101**
- **CD95 Receptor**
- No Signaling
Endothelial cells of solid tumors and tumor cells express CD95L
- E.g., breast, colon, renal, bladder, prostate, ovarian cancer, glioblastoma
- APG101 binds to CD95L, thereby blocking its interaction with the CD95 receptor and protecting tumor-infiltrating immune cells from apoptosis (as shown by Motz et al.)

**CD95 Ligand Inhibitor as Cancer Immunotherapy**

**CD95L positive tumors**
- Tumor cell
- Activated T Cells
- T cell death

**CD95L negative tumors**
- Tumor cell
- Activated T Cells
- T cell survival

Efficacy of APG101 Depends on the Presence of T cells

**Survival of VMDK mice in GB SMA* model**

- **median OS**
  - Vehicle: 24 days
  - APG101: 32 days

**Survival of athymic mice in GB SMA model**

- **median OS**
  - Vehicle: 20 days
  - APG101: 21 days

*SMA: Spontaneous murine astrocytoma (cells)
APG101 Inhibits Invasive Growth of Tumor Cells

- APG101 blocks invasion and proliferation of tumor cells
APG101 in GB

• Orphan drug designation in US and EU
• High unmet medical need
• Positive feedback from regulatory authorities (EMA, FDA)
• Support from global KOLs (EU: e.g., Stupp, Weller, Wick; US: e.g., Reardon, Helman, Metha)
• Sales potential > 750 Mio US$

Aggressive brain tumor: Median overall survival 15 months
Standard first-line therapy: Surgery, radiation, Temodar
No approved drug treatment in EU for second-line therapy
Annual treatment costs, e.g., for Avastin approx. 100,000 US$
Incidence US/EU: 25,000 new cases p.a.; prevalence US/EU: 33,000

Ref.: www.trajectoryscifi.com
Completed Phase II Study Design in Recurrent GB

First Line Therapy

- Surgery/Temodar/RT

Tumor Tissue

Second Line Therapy

- 56 patients
- Randomization (2:1)
- Radiotherapy (18x 2 Gray) + APG101 weekly i.v.; 400mg

Follow-up

- 28 patients
- Radiotherapy (18x 2 Gray)
- No further treatment

Centralized, blinded data analysis
(Magnetic resonance imaging, pathology)

Biomarker analysis
• APG101 provides significantly better results compared to Gliadel and TMZ in the two clinical trials that led to FDA approval in recurrent GB.

**APG101**

- **Radiotherapy + APG101**
  - HR 0.6 (95% CI 0.36-1.01); p = 0.056, n = 84

**Gliadel**

- **Gliadel (Carmustine Wafer)**
  - HR 0.83 (95% CI 0.63-1.10); p = 0.19, n = 222

**Temozolomide (TMZ)**

- **Temozolomide**
  - p = 0.33, n = 225

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Brem et al. (1995). Lancet 345: 1008

FDA Approval Letter, 2003

Treatment with APG101 significantly improved overall survival in patients carrying the newly identified CD95L epigenetic biomarker.

### Biomarker Results

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<th>Biomarker</th>
<th>APG101/RT (n=36)</th>
<th>RT (n=19)</th>
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<tbody>
<tr>
<td>CD95L low methyl. Tumors</td>
<td>16.1</td>
<td>7.3</td>
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<td>Log rank Test</td>
<td>p=0.029</td>
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<td>CpG2 methylation</td>
<td>HR 0.31 (95% CI 0.13 – 0.76); p=0.0104</td>
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Myelodysplastic Syndromes (MDS) = Disease of blood stem cells characterized by ineffective hematopoiesis, resulting in anemia, fatigue, life-threatening infections

Limited treatment options (best supportive care, e.g., blood transfusions)

Only few approved drugs for low-intermediate I classified patients

Standard of care: Transfusions; annual treatment costs at least 70,000 US$

Incidence US/EU: 35,000 new cases p.a.; prevalence US/EU >100,000

APG101 in MDS

• APG101 binds to CD95L in bone marrow of MDS patients, thereby protecting blood cell precursor cells from CD95 receptor mediated apoptosis (a.k.a. programmed cell death)
• Orphan drug designation in US
• High unmet medical need
• Peak sales potential > 800 Mio US$

http://nonbloodmedicalmanagement.blogspot.de/

June 2015

Jefferies Healthcare Conference 2015
• Myelodysplastic syndromes (MDS) are hematologic malignancies that are characterized by ineffective hematopoiesis, resulting in low red blood cell counts
• CD95 ligand has a key role in mediating hematopoietic commitment and homeostasis

CD95 ligand inhibits differentiation and development of erythrocytes in MDS patients

BFU-E*: „Burst forming unit erythrocyte
APG101_CD_003: Phase I, Pharmacodynamic / MoA study; two dose levels; 19 patients

- Study patients were treated with APG101 for a period of 12 weeks; after cessation of therapy the patients were followed for 6 months
- Bone marrow biopsies were taken before start of treatment and then every 12 weeks until week 37
The study CD_003 was designed to test the hypothesis that blocking the CD95 system in vivo using APG101 can improve erythropoiesis in low–int-1 risk MDS patients.

- Short term treatment with APG101 of transfusion dependent MDS patients who are unresponsive to EPO resulted in a remarkably reduced frequency of RBC* transfusions.
- Interim data were presented at ASH 2014.

Changes in transfusion frequency during the course of the study:

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<td>End of Study</td>
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*RBC-red blood cell
Novel Fc fusion proteins engineered on the basis of a proprietary technology platform overcome limitations of agonistic antibodies targeting the TNF-Receptor SF (Tumor necrosis factor receptor superfamily).

- Conventional antibodies have two binding sites.
- Apogenix’ compounds have six binding sites.
- Binding of Apogenix’ compounds to receptors induces a spatially well defined receptor assembly (clustering), thereby triggering a strong intracellular signal leading to, e.g., apoptosis (programmed cell death).

Defined receptor clustering leads to higher efficacy compared to antibodies.
Showcase: TRAIL Receptor Agonist APG880 (Partnered with AbbVie)

- Technology platform validated by comprehensive licensing agreement for TRAIL receptor agonist APG880 with abbvie
- Apogenix retains rights to apply its technology for other TNF-SF family members, e.g., CD40, OX40, LIGHT, ...

Binding of APG880 to receptors induces a well-defined receptor clustering, thereby triggering a strong intracellular signal leading to, e.g., apoptosis.
### Development Plan until 2019

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PoC: Proof of concept

- **Current status 2015**
- **Planned until 2019**
- **Partnered**
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