Enabling T-Cell Therapies for Solid Tumors with Oncolytic Immunotherapy

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World ADOPT Summit, London
Adoptive Cell Immunotherapies

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TILT Biotherapeutics Ltd.
Objectives and Outline

1. Overview of TILT Biotherapeutics
2. Review oncolytic virus pipeline
3. TILT’s latest preclinical results
4. Conclusion
TILT Biotherapeutics in a Nutshell

☑ Founded in 2013 by Professor Akseli Hemminki, MD, PhD, CEO
☑ Enabling T-cell therapy of solid tumors via oncolytic viruses
☑ Synergistic with all T-cell therapy strategies including TILs, CAR-T, TCR and anti-PD1 antibodies
☑ TILT technology is based on observations and data of 290 patients treated with 10 oncolytic viruses in 2007-2012 (ATAP, human data) and research conducted by Univ. of Helsinki CGTG in 2002-2016
☑ Lead product (TILT-123) is a preclinical stage TNFα/IL2 armed oncolytic adenovirus
  - Preclinical PoC is done
  - EMA Scientific Advice & ATMP classification obtained
  - First Phase I trial estimated start 2018
Current Challenges and TILT’s solution

- Adoptive T-cell therapy of humans has yielded promising results in TIL therapy of metastatic melanoma
- But it is associated with severe side effects due to pre-conditioning chemotherapy and post-conditioning IL-2
- CAR-T: good results in CD19+ leukemia, not working in solid tumors
- Checkpoint inhibitors (CPI) work in many or most tumor types, but only 10-50% of patients are benefiting
- CPI work in tumors which are inflamed (PD1L+, TIL+, neoantigen+ etc)
- CPI don’t work in tumors which are immunologically cold or immune excluded

Solution provided by TILT

- Oncolytic viruses can change cold and excluded tumors into hot inflamed tumors
- Adenovirus is the most potent stimulator of T-cells
- Adenoviruses are the perfect enabler of checkpoint inhibition in cold and excluded tumors
- TILT-123 is the only virus designed specifically for T-cell stimulation: arming with IL2 and TNFa
- Improved safety: pre-conditioning chemo and post-conditioning IL-2 not needed
Clinical Readiness After…

10 years of clinical observations, product development, and optimization

- Clinical data with oncolytic viruses
- Advancements in immunotherapy and founding of TILT
- TILT-123’s virus backbone demonstrated safe in clinic
- TILT concept and TILT-123 product patent protected
- TILT-123 preclinical PoC with TILs, CAR-T, and anti-PD1

Phase I trials

- Partner or develop ourselves

- Clinical Data from 50-80 Patients

- 2013: TILT Biotherapeutics founded
- 2014: ATAP* 290 patients treated with 10 different oncolytic viruses
- 2015: TILT technology optimized in the lab
- 2016-2017: Lead candidate: TILT-123
- 2016-2017: GMP manufacturing
- 2016-2017: Regulatory preclinical studies
- 2016-2017: Scientific Advice
- 2016-2017: Pre-IND meet

2018-2020: Phase I trials
- TILT-123+TILs
- TILT-123 + anti-PD1
- TILT-123 + CAR-T

2020-2022: Phase II
- 2023-2026: Phase III
- 2027: Launch

- Up to date, almost 10M€ in funding (equity, loan, grants) secured
- TILT is fully funded for preclinical GLP, 1 GMP Phase I batch, Phase I trial TILT-123 + TILs in EU
- Renown VC and 4-8M€ funding sought for additional Phase I trial(s)

*Advanced Therapy Access Program
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<th>PRODUCT</th>
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<th>DISCOVERY</th>
<th>PRECLINICAL</th>
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<th>PHASE I</th>
<th>KEY PROBLEMS ADDRESSED</th>
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<td>TILT-123</td>
<td>TIL, melanoma</td>
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<td>TILT-234</td>
<td>anti-PD1, melanoma / other solid tumors</td>
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<td>Recruitment and activation of T-cells to tumors</td>
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<td>Local delivery of therapeutic molecules reducing side effects</td>
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**Product description (oncolytic adenovirus):**

- **TILT-123**: Ad5/3-E2F-delta24-hTNFa-IRES-hIL2  
  (Ref: Havunen et al. 2016)
- **TILT-234**: Ad3-hTERT-CMV-hCD40L  
  (Ref: Parviainen et al. Poster. 2016)
- **TILT-321**: Ad5/3 coding for a bispecific antibody  
  (Ref: to be published)
Clinical Trial Readiness

- Scientific Advice with EMA is done, ATMP classification obtained
- GMP grade virus production of TILT-123 on-going with an experienced CMO
- Three different clinical trials (TILT-T215, TILT-T392, TILT-T401) will be started in combination with synergic technologies (TILs, anti-PD1 antibody, CAR-T cells)
TILT Biotherapeutics  - Non-Confidential  - 2017

Company and Board

- TILT was founded in 2013 by Akseli Hemminki (MD, PhD, Professor of Oncology at Univ. of Helsinki)
- Company is led by an experienced board and has a Scientific Advisory Board with world’s leading experts, as well as pre-clinical collaborations with renown research groups

**Board of Directors**

- Akseli Hemminki
  Chairman & CEO, TILT Biotherapeutics
- Timo Ahopelto
  Lifeline Ventures
- Arto Linnervuo
  Roschier Attorneys
- Veli-Matti Riihimäki
  Medical Entrepreneur and Investor

**Scientific Advisory Board**

- Brigitte Dreno (MD, PhD)
  Nantes University Hospital, France
- Viktor Umansky (PhD)
  German Cancer Research Center DKFZ
- Petri Bono (MD, PhD)
  Cancer Center at Helsinki University Central Hospital
- Tanja de Gruijl (PhD)
  University Medical Cancer Center in Amsterdam
- Inge Marie Svane (MD, PhD)
  Herlev University Hospital, Denmark
- Ramon Alemany (PhD)
  ICO Barcelona, Spain

**Pre-clinical Collaborations**

CGTG at University of Helsinki
Carl June (U Penn), leader of the field of cancer T-cell therapy
Viktor Umansky (T cell immunology, DKFZ)
Market and Oncolytic Virus Pipeline
Unmet Medical Need and Market with Significant Growth

8 million
Deaths of cancer each year (2012)

from 14 to 24 million
New cases of cancer each year (2012–2030)

$30B++
Projected market value of cancer immunotherapies in 10 years worldwide

90%
Percentage of solid tumors of all cancers

50-90%
Percentage of patients that will not respond to current T-cell therapies and checkpoint immunotherapies
Amgen’s Imlygic (T-VEC/ talimogene laherparepvec) became the first oncolytic virus to gain approval in a Western jurisdiction with FDA and EMA approvals in melanoma in 2015

Oncolytic viruses are today finding their place in immuno-oncology combination regimens

Over the past years T-cell therapy companies and oncolytic virus companies have raised over $3 billion funding

- T-cell therapy (including CAR-T, TILs) : $2,900 million
- Oncolytic viruses: $360 million

TILT has developed and protected a unique technology for combination use, enabling T-cell therapies in solid tumors via oncolytic viruses

“OUR VIEW IS ANYONE IN THE IMMUNO-ONCOLOGY SPACE SHOULD HAVE AN ONCOLYTIC VIRUS.”
Oncolytic viruses – Pipeline - Projects

- Adeno and pox (vaccinia) viruses are the most commonly used virus types.
- These projects have lead to over 200 clinical trials worldwide.
- The most studied indication is melanoma, followed by head and neck, colorectal, NSCLC, and ovarian cancers.
- Several clinical stage candidates are GM-CSF armed, preclinical stage projects are starting with arming viruses with other molecules.
- Several combination trials have been initiated with anti-PD1.
- Combination trials with T-cell approaches are rare.
Science
Clinical Observations from ATAP

- Immunological reactions seen in cancer patients
  1. Inflammation
  2. Lymphocytes redistribute from blood
  3. Accumulation of T cells in tumors

- Safety of the TILT virus backbone (Ad5/3) established in patients

Kanerva et al., Clin Cancer Res 2013.
Ranki et al., Oncoimmunology 2014.
Lead clinical product TILT-123: Ad5/3-E2F-delta24-hTNFa-IRES-hIL2

- Oncolytic platform enhances epitope presentation and local anti-immunosuppressive "danger signals"
- Viral replication occurs only in cancer cells
  - E2F promoter and 24 bp deletion in E1A limit replication to cells defective in p16-Rb pathway (cancer cells)
- Expression of TNFα and IL2 is coupled to virus replication
- Ad5/3 chimera: Ad5 fiber knob replaced with Ad3 knob
  - Improved cancer cell transduction and antitumor efficacy
Highly Optimized Construct for Safety and Efficacy

- Enhanced cancer cell transduction and killing – Ad 5/3 chimeric
- High selectivity and efficacy through 5 genetic modifications
- Safety demonstrated in humans with the TILT virus backbone
- Transduction of distant metastasis through the vasculature in humans (IV, IT)
- Armed with the most potent cytokines for combinatory use with ACT in solid tumors: IL2 and TNFa
- High local levels of cytokines produced at the tumor – no systemic exposure
- Memory response with the armed virus
The core preclinical proof in solid tumors: Can adenovirus overcome resistance of tumor to ACT?

Adoptive T-cells have higher efficacy with virus

Ad5/3-viruses delivered by IT studied in B16.OVA melanoma tumors in C57BL/6 mice with adoptive ovalbumin specific CD8+ T-cell therapy (OT-I)

Which cytokine(s) are the best for virus arming for adoptive T cell therapy in solid tumors?

Figure. Systematically administered recombinant cytokines in B16.OVA melanoma tumors in C57BL/6 mice with adoptive ovalbumin specific CD8+ T-cell therapy (OT-I).

- Close to 100% efficacy of IL-2 and TNFα in combination with OT-I demonstrated
- Favorable alteration of tumor microenvironment by IL-2 and TNFα for efficient T-cell therapy in solid tumors

Adenovirus coding for TNFa+IL2 selected as the lead into clinical trials

Figure 3. Ad5-CMV-mTNFa/Ad5-CMV-mIL2 dual virus combination together with adoptive T cell transfer. Adenoviruses coding for mTNFa and mIL2 were combined in a 1 to 1 ratio (0.5 x 10^9 VP of each virus) to treat B16-OVA tumors together with adoptive transfer of 1.5 x 10^6 CD8-enriched OT-I T-cells. Virus treatments continued every 7 days. Error bars, SE. *p<0.05, ***p<0.001.

✓ Improved antitumor efficacy with adenoviruses coding for TNFa and IL2 when compared with T-cell therapy alone or the virus alone

Curative efficacy and PoC with TILT-123

Figure 4. Syrian hamsters with established subcutaneous HapT1 tumors

Curative efficacy with oncolytic adenovirus: PoC with TILT-123

✓ Tumor rechallenge indicates memory response induced by TNFa+IL2 armed viruses: hamsters previously cured with cytokine-armed viruses resist same tumor type (HapT1) but not different one (DDT1-MF2)

Problems in T cell therapy of solid tumors

1. T-cells (the graft) don’t find their way to the tumor
2. The graft becomes anergic due to tumor immunosuppression
3. T-cell fail to propagate (no amplification signals at tumor)
4. Resistance develops via a target-negative clone
5. Pre- and post-conditioning cause severe toxicity

- **TNFa:**
  - ✓ danger signaling
  - ✓ trafficking
- **IL2:**
  - ✓ Activation
  - ✓ Propagation
  - ✓ Reversion of exhaustion

Problems in T cell therapy of solid tumors

1. T-cells (the graft) don’t find their way to the tumor
2. The graft becomes anergic due to tumor immunosuppression
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Santos in preparation.
Epitope spreading: increase in the number of "natural" anti-tumor T-cells

1. T-cells (the graft) don’t find their way to the tumor
2. The graft becomes anergic due to tumor immunosuppression
3. T-cell fail to propagate (no amplification signals at tumor)
4. Resistance develops via a target-negative clone
5. Pre and post-conditioning cause severe toxicity

- Adoptive transfer + virus injections acts act as catalyst for propagation of "other" T-cells at tumor and local lymph nodes

Other Projects
Efficacy of TILT-123 with CAR-T therapy

Large established subcutaneous ASPC1-CBG-GFP (pancreatic) tumors in NSG mice were treated with mesothelin_redirected CAR-T (SS1-BBz CAR-T) alone or in combination with intratumoral injection of TILT-123.

✓ Oncolytic Adenovirus expressing cytokines (TILT-123) enhances anti-tumor efficacy of mesothelin_redirected CAR-T Cells

✓ It is effective by enhancing T cell proliferation, persistence, function and infiltration to the tumor

✓ T cells from mice treated with the combination of O-Ad and CAR-T expressed lower levels of inhibitory molecules (PD-1, LAG3) comparing to those treated with CAR-T alone

TILT-123 with anti-PD-1-antibody

PRE-CLINICAL

Ad5-CMV-mTNFa/Ad5-CMV-mIL2 viruses delivered once by IT with 5 times of aPD1-antibody (0,1 mg/mouse every 3 days) - studied in B16.OVA melanoma tumors in C57BL/6 mice. Treatment was started 10 or 11 days after tumor engraftment.

- Data was confirmed in a repeated experiment
- A third experiment is ongoing with more controls and full dose virus and aPD1

CLINICAL

- Phase I planned with Professor Robert Andtbacka (Salt Lake City)
- Next Steps:
  - Clinical anti-PD1 partner sought
  - FDA Pre-IND meeting planned

Conclusion

- Enabling T-cell therapy of solid tumors via oncolytic viruses
- Synergistic with all T-cell therapy strategies
- TILT technology is based on 290 patients treated with 10 oncolytic viruses 2007-12 (ATAP, human data) and research conducted by Univ. of Helsinki CGTG in 2002-2016
- Lead product TILT-123 is a preclinical stage TNFα/IL2 armed oncolytic adenovirus

- EMA Scientific Advice & ATMP classification obtained
- First Phase I trial will start in 2018 with TILs (funded)
- Looking for clinical partners for 2nd and 3rd trials
THANK YOU FOR YOUR ATTENTION

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www.tiltbio.com
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<th>Reference</th>
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<tr>
<td>ATAP</td>
<td>Hemminki O et al. OncoTarget. 2015.</td>
<td>Immunological data from cancer patients treated with Ad5/3-E2F-Δ24-GMCSF suggests utility for tumor immunotherapy. Safety of the adenovirus backbone (Ad5/3-E2F-Δ24-) in humans. Ad5/3-E2F-Δ24-GMCSF (CGTG-602) was used in 13 patients with solid tumors refractory to standard therapies. The virus backbone of CGTG-602 is quite similar to TILT-123 (the only difference being the transgenes) and thus the safety data is relevant with regard to TILT-123</td>
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<tr>
<td>TILT 1 Preclin</td>
<td>Tähtinen et al. CIR. 2015.</td>
<td>Adenovirus Improves the Efficacy of Adoptive T-cell Therapy by Recruiting Immune Cells to and Promoting Their Activity at the Tumor. Can adenovirus overcome resistance of tumor to adoptive T-cell therapy? Ad5-viruses delivered by IT studied in B16.OVA melanoma tumors in C57BL/6 mice with adoptive ovalbumin specific CD8+ T-cell therapy (OT-I) → Enhanced antitumor efficacy, increased levels of TILs, enhanced maturation of APCs, epitope spreading → Proof-of-mechanism data on combining adoptive T-cell therapy with adenovirotherapy</td>
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<tr>
<td>TILT 2 Preclin</td>
<td>Tähtinen et al. Plos One. 2015.</td>
<td>Favorable alteration of tumor microenvironment by immunomodulatory cytokines for efficient T-cell therapy in solid tumors. Which cytokine(s) are the most useful for arming the adenovirus to be used as an enabling technology for adoptive T cell therapy in solid tumors? Several FDA/EMA approved cytokines studied for their capacity to favorably manipulate the effector-suppressor immune cell ratio in favor of efficient anti-tumor response in B16.OVA melanoma C57BL/6 mice → TNFa &amp; IL-2 selected due to their favorable effects</td>
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<tr>
<td>TILT 3 Preclin</td>
<td>Siurala et al. Mol Ther. 2016.</td>
<td>Adenoviral delivery of tumornecrosis factor alpha and interleukin-2 enables successful adoptive cell therapy of immunosuppressive melanoma. Can the cytokine-coding adenoviruses improve the efficacy of adoptive T-cell therapy? Ad5-virus coding for TNFa and IL2 delivered by IT injection studied in B16.OVA melanoma tumors in C57BL/6 mice with adoptive T-cell therapy (OT-I) → Improved antitumor efficacy with adenoviruses coding for TNFa and IL2 when compared with T-cell therapy alone or the virus alone</td>
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<tr>
<td>TILT 4 Preclin</td>
<td>Siurala et al. OncoImmunology. 2016.</td>
<td>Syngenic Syrian hamster tumors feature tumor-infiltrating lymphocytes allowing adoptive cell therapy enhanced by oncolytic adenovirus in a replication permissive setting. Can oncolytic adenoviruses in improve the efficacy of adoptive T-cell therapy? → Pancreatic cancer (HapT1) and melanoma (RPMI 1846) specific TILs exhibited tumor specific cytotoxic activity with the best effect seen in combination with Ad5-virus in Syrian hamsters (allowing semi-permissive replication of human adenovirus)</td>
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<td>TILT 5 Preclin</td>
<td>Havunen et al. Mol Ther Oncolytics. 2017.</td>
<td>Oncolytic Adenoviruses Armed with Tumor Necrosis Factor alpha and Interleukin-2 Enable Successful Adoptive Cell Therapy with Tumor Infiltration Lymphocytes. Can the cytokine-coding oncolytic adenoviruses improve the efficacy of adoptive T-cell therapy? Studied in vitro and vivo in human lung and ovarian cancer cell lines, Syrian hamster pancreatic cancer and leiomyosarcoma. -oncolytic activity, biologically active cytokines, dose dependent antitumor efficacy, improved curative efficacy of TIL therapy, immunological memory shown ( \rightarrow \text{Ad5/3-E2F-d24-TNFa-IRES-IL2 or TILT-123 enhance adoptive T-cell therapy by favorable alteration of tumor microenvironment} )</td>
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<tr>
<td>TILT 6 Preclin (collaboration w/ U Penn)</td>
<td>Watanabe et al. ASGCT Oral presentation. May 2016.</td>
<td>Oncolytic Adenovirus armed with cytokines enhances CAR-T cell efficacy in pancreatic tumor model. Can cytokine-coding oncolytic adenovirus enhance efficacy of CAR-T in solid tumors? Pancreatic tumor cell lines targeted by mesothelin specific CAR-T cells (SS1-BBz CAR) in combination with O-Adv; Adv-5/3-d24-IL2 or Adv-5/3-d24-TNF-IL2 ( \rightarrow ) Combination therapy of O-Adv armed with cytokine(s) and CAR-T cells is effective against solid tumors by enhancing T cell activity</td>
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<td>TILT 7 Preclin</td>
<td>Santos et al. Poster. June 2016 Manuscript in prep.</td>
<td>Safety and superiority of intratumoral administration of IL-2-armed adenoviruses compared with systemic administration of recombinant IL-2 in preclinical rodent tumor models infused with T-cells. Could TIL therapy be improved from the safety and efficacy perspective with local delivery of IL-2? Studied in B16.OVA melanoma C57BL/6 mice and HapT1 hamster tumors ( \rightarrow ) Better anti-tumor efficacy achieved with adenoviral delivery of IL-2 when compared with systemic administration</td>
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<td>TILT 8 Preclin</td>
<td>Cervera-Carrascon et al. Poster. June 2016.</td>
<td>Evaluation of PD-1 blockade in the context of solid tumor T-cell therapy enabled with tumor necrosis factor alpha and interleukin-2 expressing adenovirus. Could the anti-PD1-antibody treatment be improved with the cytokine-coding adenovirus or with the cytokine-coding adenovirus and TILs? Ad5-viruses delivered by IT studied in B16.OVA melanoma tumors in C57BL/6 mice with adoptive ovalbumin specific CD8+ T-cell therapy (OT-1) ( \rightarrow ) Positive results on the antitumor efficacy and OS, support further studies and development of combinatory treatments with Ad-viruses</td>
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| TILT 9 Preclinical | Zafar et al. Oncoimmunology. 2017. | Intravenously usable fully serotype 3 oncolytic adenovirus coding for CD40L as an enabler of dendritic cell therapy. Could DC-therapy be improved with the cytokine-coding adenovirus? Tumors treated with Ad5/3-CMV-mCD40L virus plus DCs elicited greater antitumor effect as compared with either treatment alone. Moreover, virally coded CD40L induced activation of DCs, which in turn, lead to the induction of a Th1 immune response and increased tumorspecific T cells.