Experimental oncolytic immunotherapy for individualized treatment of cancer patients incurable with routine approaches

Akseli Hemminki
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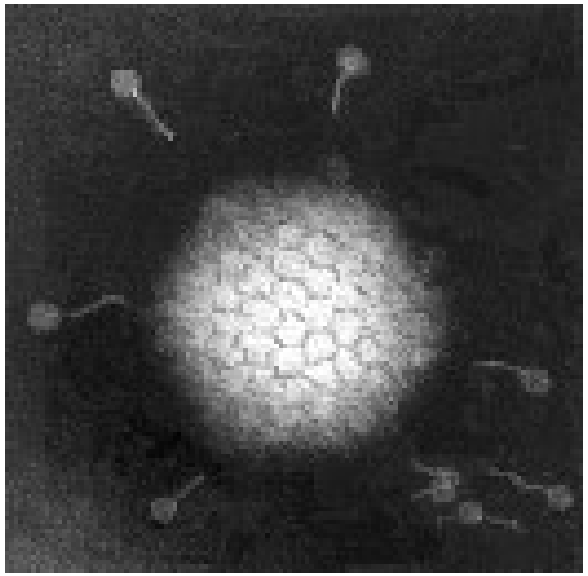

Disclaimers:

- Shareholder in Targovax ASA, a company I founded for facilitating clinical trials with oncolytic viruses
- CEO of and shareholder in TILT Biotherapeutics Ltd, a company I founded to enable T-cell therapy of solid tumors
- Consultancy for Amgen Inc
- Book author: Crossing the Valley of Death with Advanced Therapy
- Believer in immunotherapy

Tumor immunotherapy approaches

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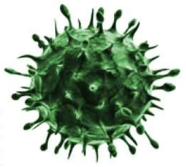
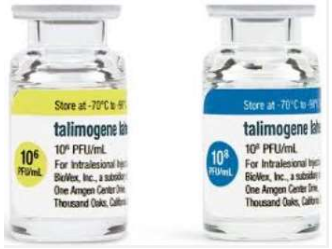
Monoclonal antibodies, immune checkpoint inhibitors

Oncolytic viruses



AMGEN

Imlygic ® HSV-virus, armed with GM-CSF



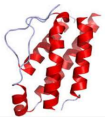
transgene

tilt BIOTHERAPEUTICS

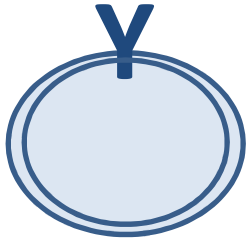
LOKON

targovax

Cytokines (eg. TNFa ja IL2)



Adoptive cell therapy



NOVARTIS

Kite Pharma

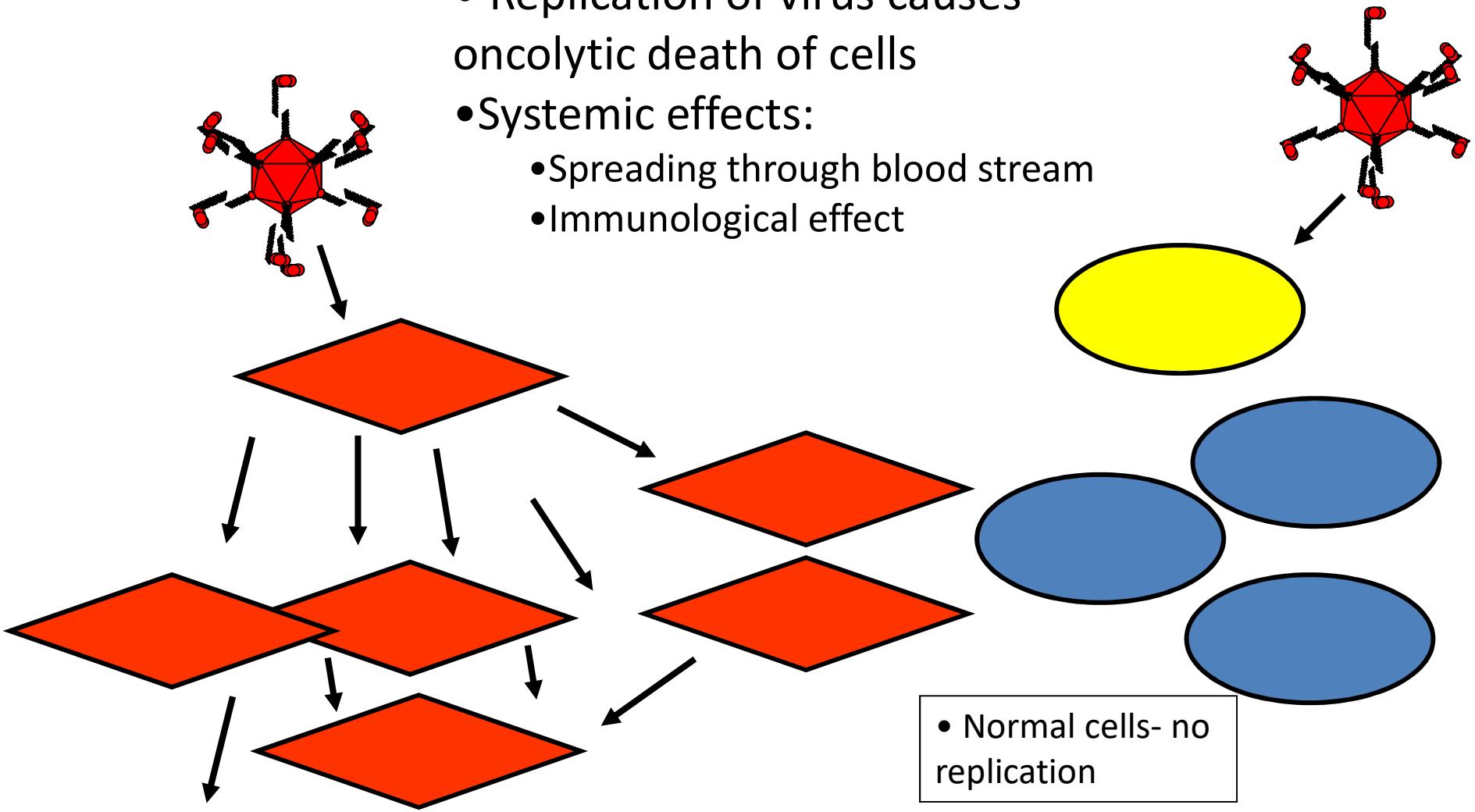
cellectis

LION Biotechnologies

JUNO THERAPEUTICS

Oncolytic viruses

- Replication of virus causes oncolytic death of cells
- Systemic effects:
  - Spreading through blood stream
  - Immunological effect

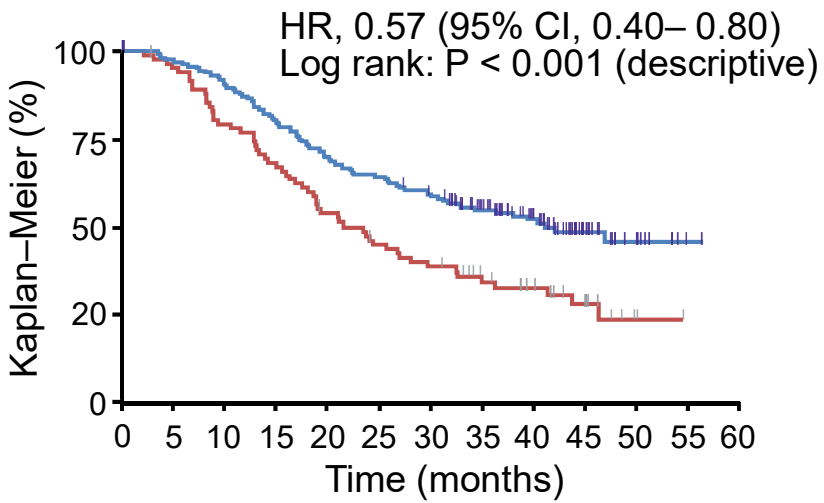


- Normal cells- no replication

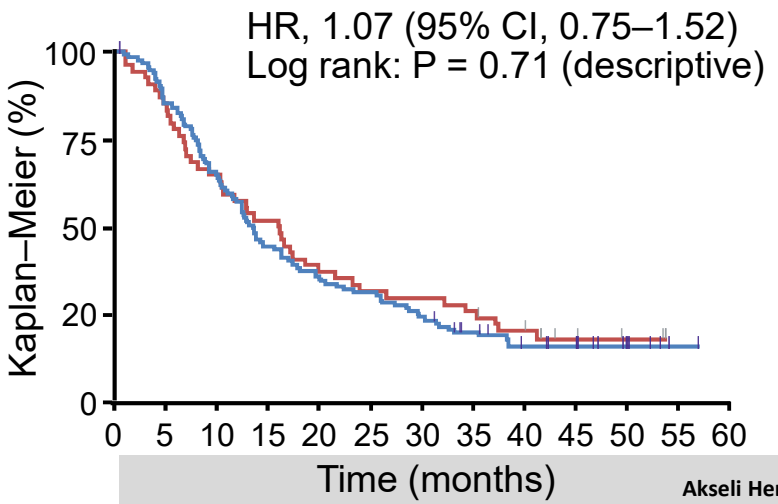
Talimogene laherparepvec (T-Vec, Imlygic) phase 3 trial (Andtbacka JCO 2015)

- 439 pts w unresected metastatic melanoma. Intratumoral T-Vec q2wk versus s.c. GM-CSF
- Adverse events: gr 1-2 fatigue, chills and pyrexia (compare to ipilimumab, anti-PD1 or vemurafenib)
- Durable response rate (CR/PR > 6mo.): 16% vs 2% (p<0.001): Better than ipilimumab
- ORR 26% vs 6% (p<0.001)
- Approved by FDA and EMA in 2015
- Promising combo w checkpoint antibodies (>50% RR, good safety, ongoing)

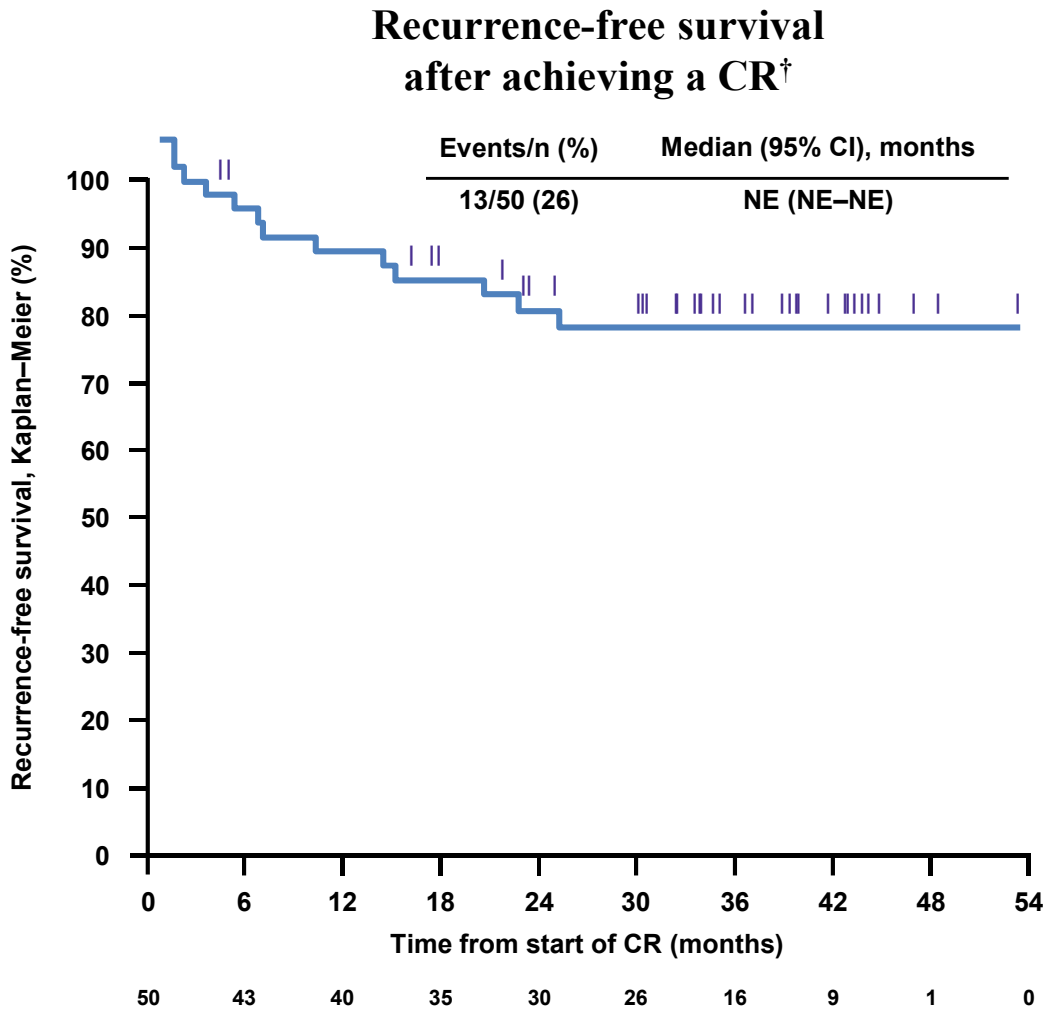
Stage IIIB/C, IV M1a



Stage IV M1b/c



Recurrence-free survival after achieving a CR with T-VEC

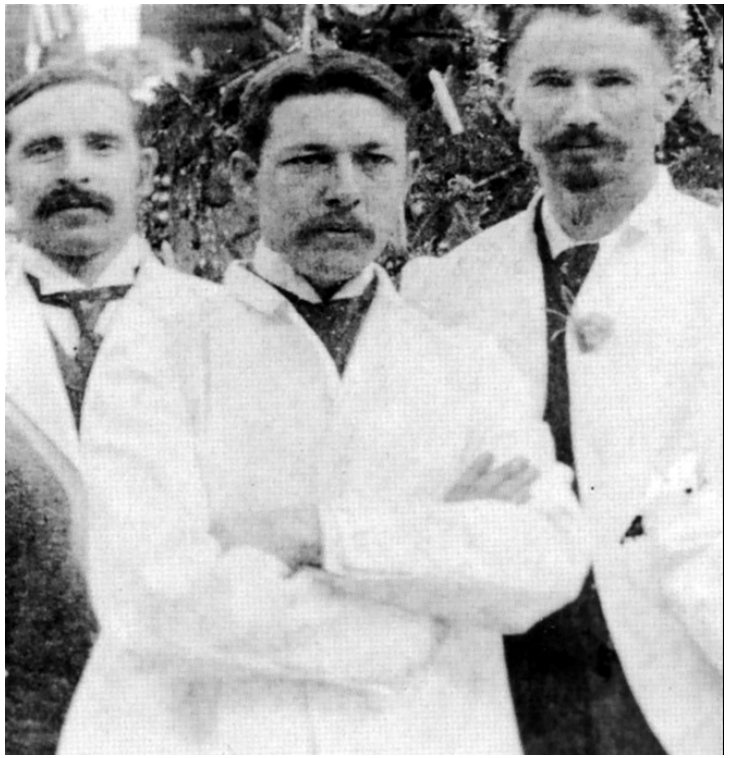


- Andtbacka RH, et al. ECC 2015:abstract 3334.

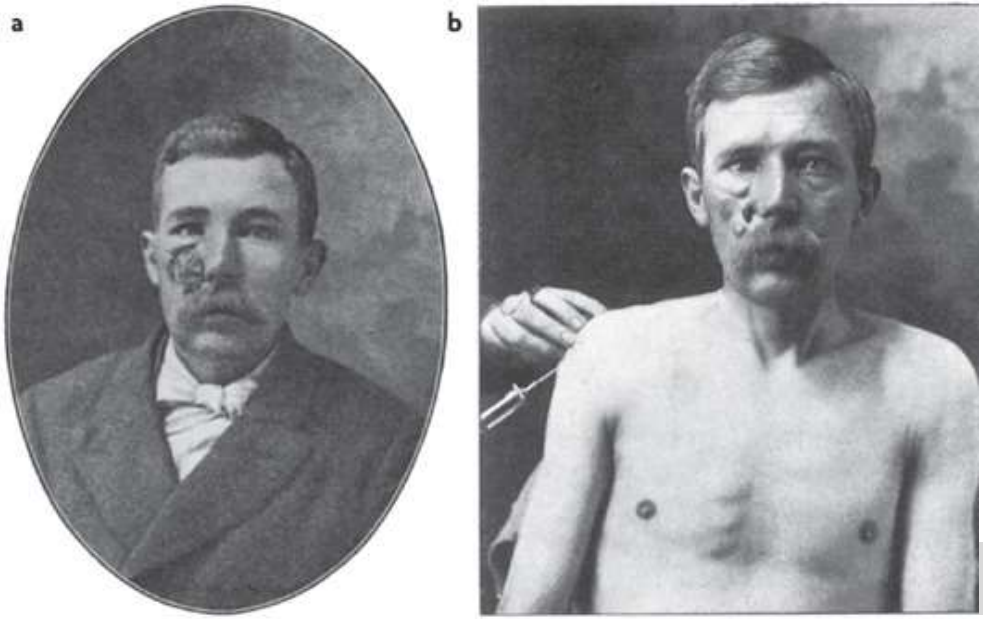
History of tumor immunotherapy

- 2600 BCE: Imhotep poultice + incision
- 1320 case reports, eg. St Peregrine Laziosi
- 1700s purposeful infection of tumors
- 1813 Vautier: cl. perfringens gangrene treats tumors
- 1891 Coley's toxin
- 1896 Tumor reductions in "flu patients"
- 1910-30 Purposeful contraction of ca pts w different viruses
- 1950 Adenovirus injections into cervical tumors
- 1977 Bacillus Calmette Guerin for bladder ca
- 2005 Oncolytic virus approved in China: Oncorine
- 2010 Cell therapy approved in US, EU: Sipuleucel-T
- 2011 Checkpoint inhibitor approved in US, EU: ipilimumab
- 2015 First oncolytic virus approved in US, EU: T-Vec
- 2017 First CAR-T cell therapy approved

William B. Coley and Coley's toxin



- Based on patient observations that bacterial infection sometimes led to tumor response
- Purposeful infection of ca patients with wild type bacteria
- Filtering of supernatant
- Mixing of different supernatants (s. pyogenes, s. marcescens)
- Dosing until fever
- MOA: TLR binding -> TNFa, IL12?
- Not accepted at the time (XRT)
- Coley's daughter founded Cancer Research Institute
- Sources: Mukherjee: Emperor of Maladies, Hemminki: Valley of Death, Tontonoz: CRI blog 2 May 2015



Situation in 2007

- We had constructed circa 30 new oncolytic adenoviruses, 100 papers published
- One patent application
- No possibility of acquiring academic funding for a clinical trial
- No company interest in our patent
- >50 000 cancer patients treated with adenoviruses globally, good safety, evidence of efficacy
- A lot of patients contacting, wanting to be treated
- Decision point: keep on treating mice or treat patients case-by-case (”Advanced therapy access program”) ?

H101 (=dl1520) phase III trial in advanced head and neck cancer

- Randomized phase III trial (N=105)
- H101 + cisplatin + 5-FU vs. cisplatin + 5-FU
- CR+PR = 79% vs. 38%, P<0.0001
- Mild tox: flu-like symptoms, injection site pain
- More than 800 patients now enrolled

Yu Curr Cancer Drug Targets 2007

Bridging the valley of death with the Advanced Therapy Access Program (ATAP)

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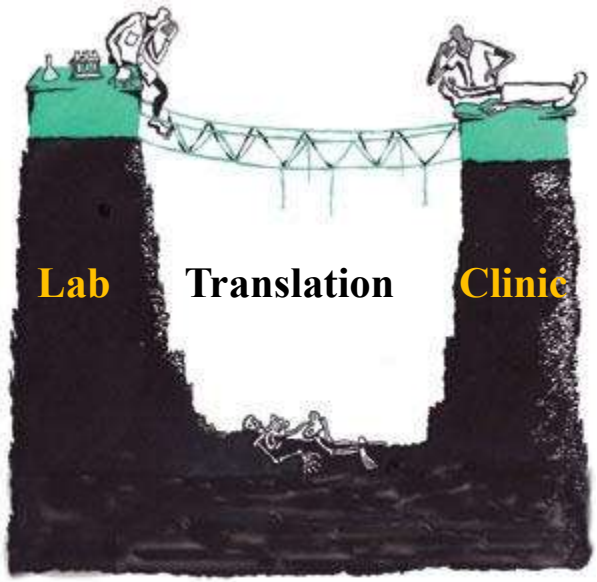
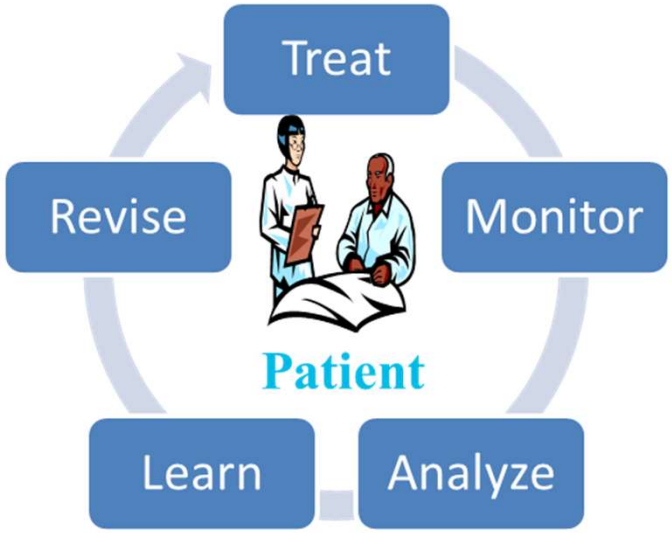


- EY 1394/2007
- FIMEA Dnro 608/2009



Maximized patient benefit

Matching the virus to the patient

Developing the best viruses into therapeutics

New virus research

Improvements in viruses

Advanced Therapy Access Program

Optimized protocol

Clinical trials

Preparations for the Advanced therapy access program (ATAP)

- Summer 2005: Finnish FDA (FIMEA) dept head suggests giving treatments instead of doing a trial if licensing is not the aim and if trials are too expensive
- Legality confirmed:
  - 2006 Finnish Medical Association
  - 2006 HUCH Institute
  - 2006 ETENE (leading ethical body in Finland)
  - 2006 HUCH local Ethics committee
  - 2006 Gene technology board
  - 2007 Ministry of Social Affairs and Health
  - 2007 FinOHTA (”Finnish NICE”)
  - 2007 Ethical Board of the Finnish Medical Assoiation
- Patient by patient gene therapy treatment used as a specific case example in a PhD thesis (Salla Lötjönen. Lääketieteellinen tutkimus ihmisillä, University of Helsinki law department 2004).
- [Legal issues in biological medicine], Lasse Lehtonen. Bio-oikeus lääketieteessä, Edita, Helsinki 2006
- Law on medical professionals 559/1994, 15§.
- World Medical Association Declaration of Helsinki article 35.
- Advanced therapy directive EY 1394/2007 (“Hospital exemption”): “treatments under the sole responsibility of the treating physician”
- National Medicolegal Department evaluation (18.4.08)
- Minister of Basic Services Paula Risikko (3/09)
- Finnish Parliament committee on Social Affairs and Health (1.4.09, HE 21/2009 vp)
- Regional Government of Southern Finland (22.12.2009).
- 1.1.2010. Finnish FDA (FIMEA) regulations based on the Advanced Therapy Directive

World Medical Association Helsinki Declaration Article 35

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with **informed consent** from the patient or a legally authorized representative, **may use an unproven intervention** if in the physician's judgement it offers **hope of saving life, re-establishing health or alleviating suffering**. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. **In all cases, new information should be recorded and, where appropriate, made publicly available.**

Differences between trials & treatments

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TRIAL

- Predetermined protocol
- Strict inclusion criteria
- Sometimes placebo included
- May involve interventions without benefit to the pt (biopsies)
- May have a sponsor with commercial interests
- Clinical trials are tightly regulated and very expensive
- May benefit society and facilitate products eventually available to millions
- May or may not benefit the pt

TREATMENT

- Pt treated case by case
- No absolute inclusion or exclusion criteria
- No placebo
- Only procedures directly relevant for pt are allowed
- Cost paid by patient, community, insurance
- Very little regulation (559/1994, 15§), except “advanced therapies” (EY 1394/2007)
- Goal is to help patient
- Limited benefit to society

Translational cancer therapy: Bench to Bedside & Back

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Industry-based: Aims at patents and product approval	Patient-based : patients get access to novel treatments; we learn how they work
New drug	New treatment
Testing in cell lines & primary tumors	Testing in cell lines & primary tumors
Testing in animal models	Testing in animal models
Toxicity and biodistribution	Understanding of tox and biodistrib
Clinical grade production	Clinical grade production
Regulatory approval: Ethics committee, Gene Tech board, National Agency of Medicines	Approval from Patient and Gene Tech board
Clinical trial	Treatment of patients with informed consent
Correlative analysis of gene transfer and preliminary efficacy	Non-interventional analysis of safety and efficacy
Conclusions	Conclusions

Personalized oncolytic adenovirus treatments in the Advanced Therapy Access Program

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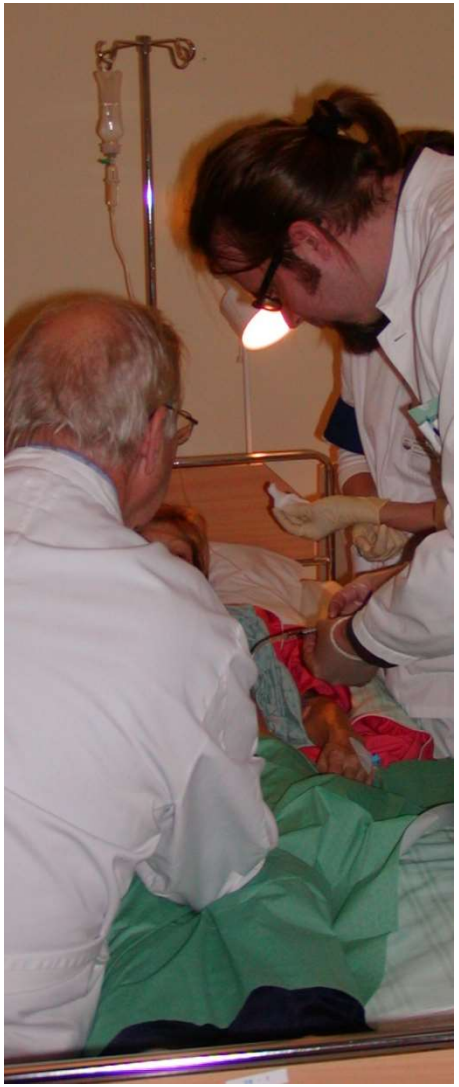
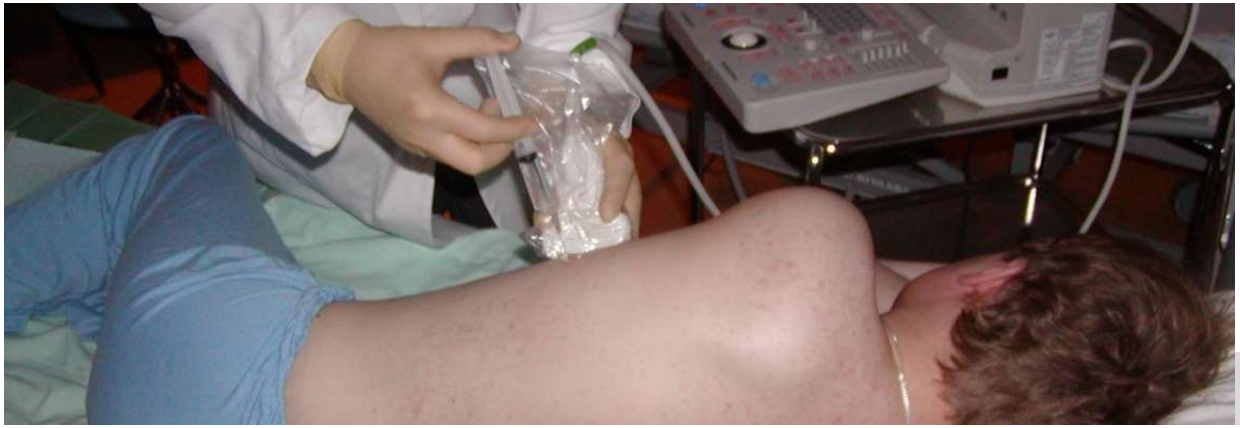
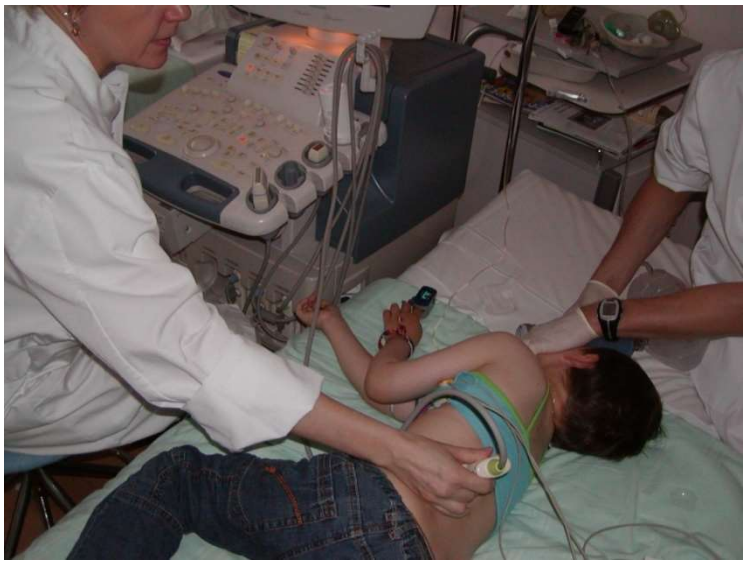
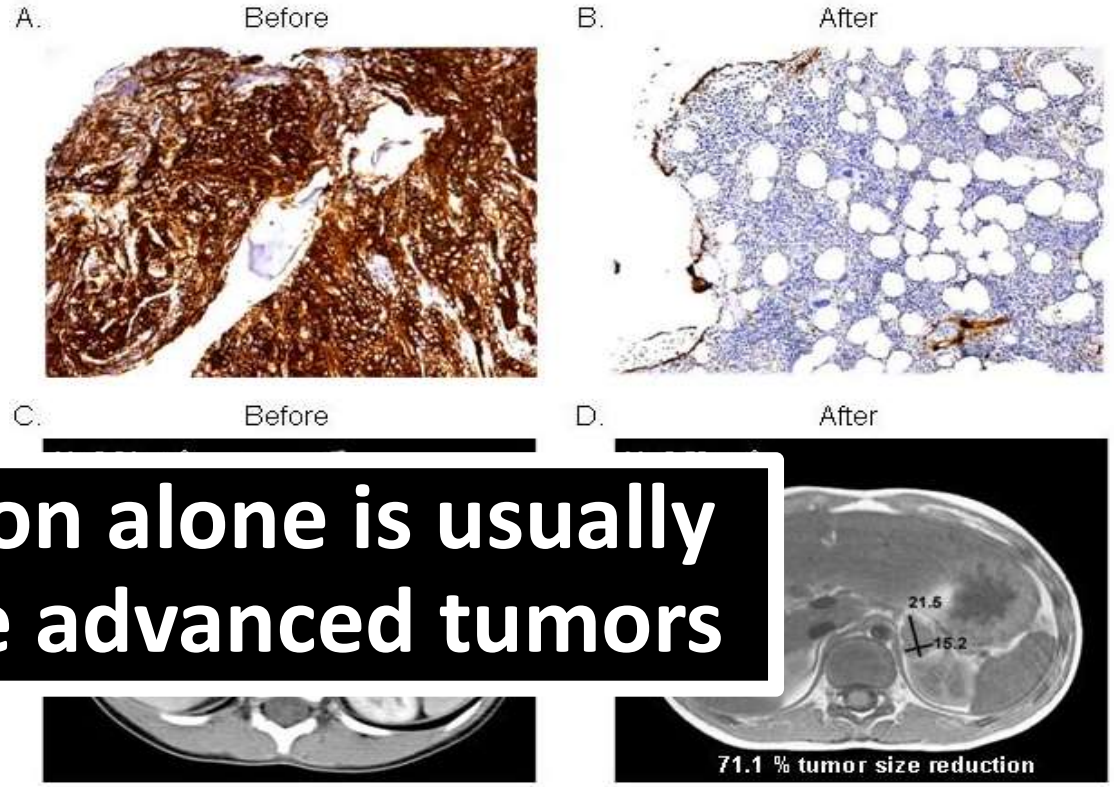


- 290 pts Nov 2007-Nov 2011. 10 different viruses
- Metastatic solid tumors progressing after routine treatments
- Production and safety regulated by FIMEA
- Side effects: gr. 1-2 flu-like symptoms, fever, fatigue, pain in all pt
- No treatment related deaths (compare to chemo, surgery)
- Disease control in pt progressing earlier (CR, PR, SD): ~ 50%
- Some patients have benefited for up to 10 yr
- Long term (>300 d) survival in 50% with best virus, best schedule



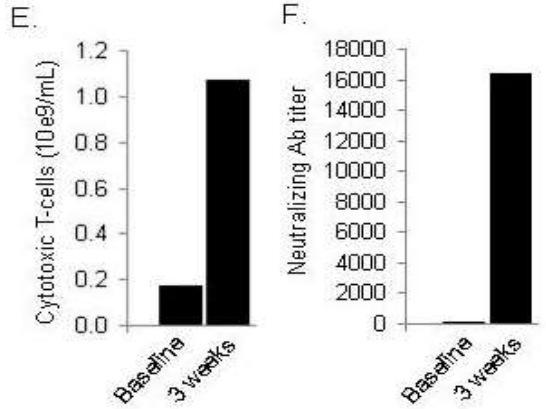


Systemic efficacy of Ad5/3-Cox2L-D24 in chemo refractory neuroblastoma



Oncolytic replication alone is usually not enough to cure advanced tumors

- 6 yr old boy, WHO 1
- Triple-modified virus was selected for intravenous efficacy
- Cox2 expression confirmed in bone marrow biopsy
- Gr. 1 stomach pain, diarrhea, flu-like symptoms, liver enzymes
- 4 wk later: complete response in bone marrow, partial response in primary



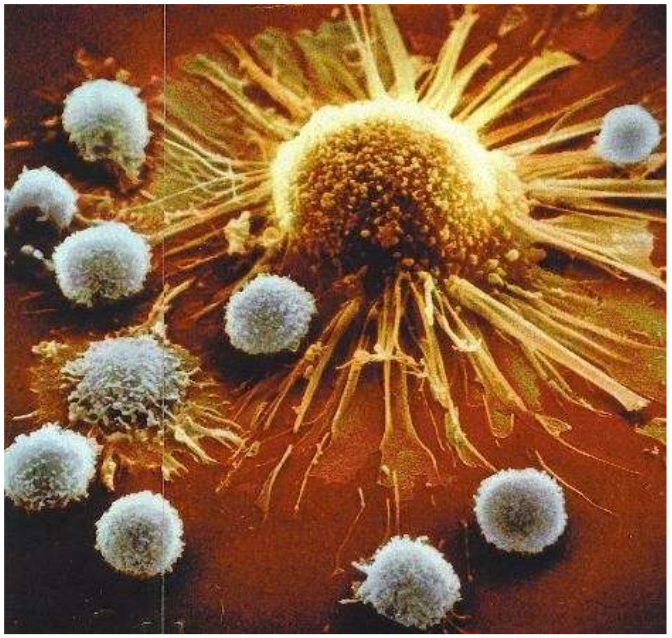
G.

Virus in blood	
Days post-treat	qPCR
0	0
1	6540
21	500

H.

Pesonen Acta Oncol 2010

Higher efficacy with a second round of treatment: role of immune response ?



atic pancreatic ca. WHO 2

mcitabine and gemcitabine chemoradiation

round of treatment with Ad5-24-RGD (Bauerschmitz Res 2002) produced response

Kanerva in preparation

75.6% tumor size reduction

GM-CSF can enhance antigen presentation and induce NK and cytotoxic T-cells

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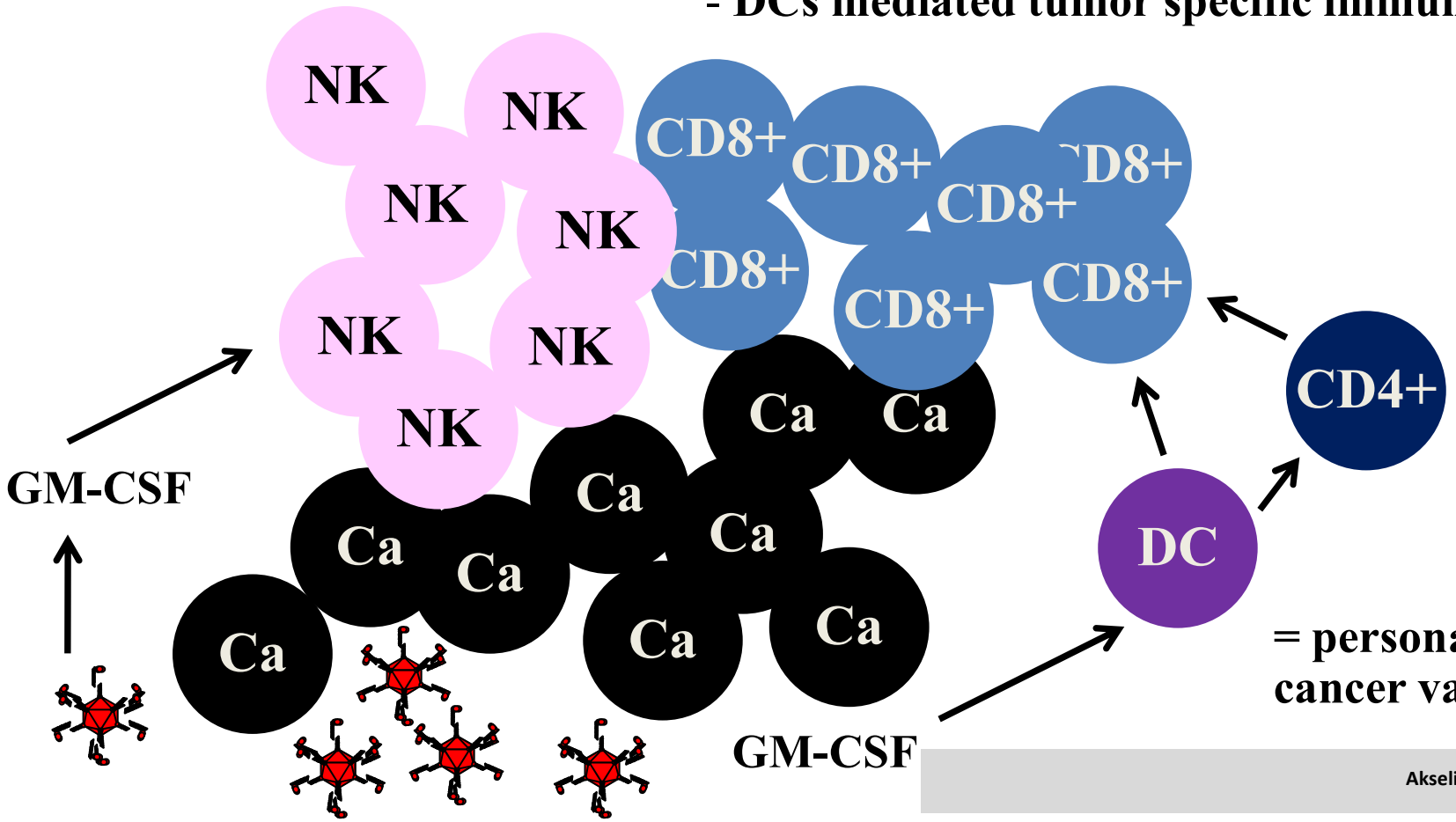
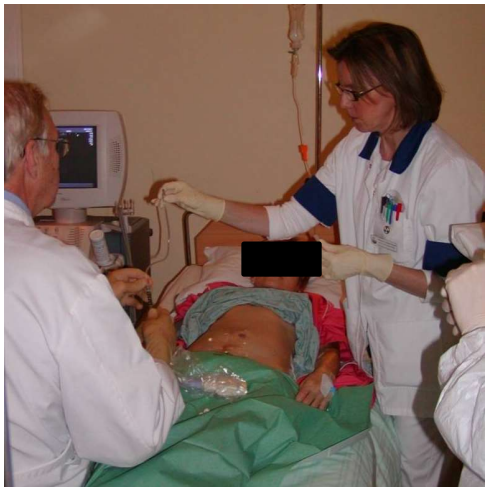
Tumor cells killed with 3 mechanisms:

- **Oncolytic effect of virus replication**
- **NK cell mediated direct cell killing**
- **DCs mediated tumor specific immunity**

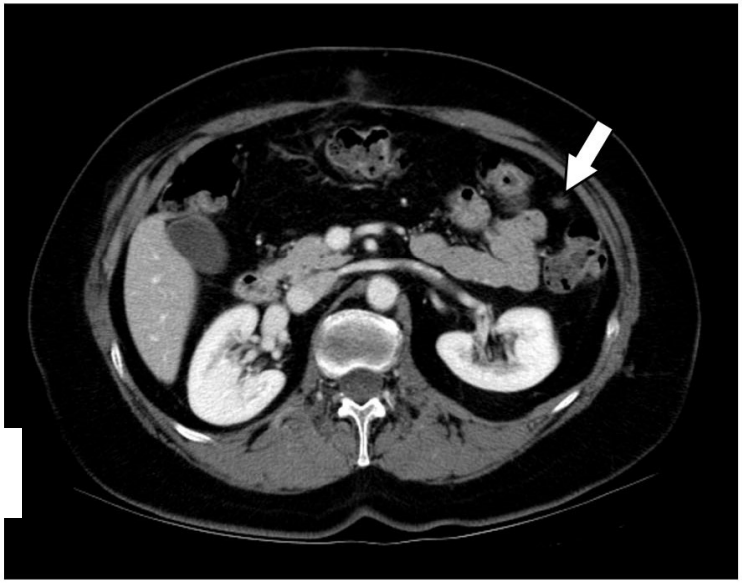


Complete response in OvCa pt with small disease burden

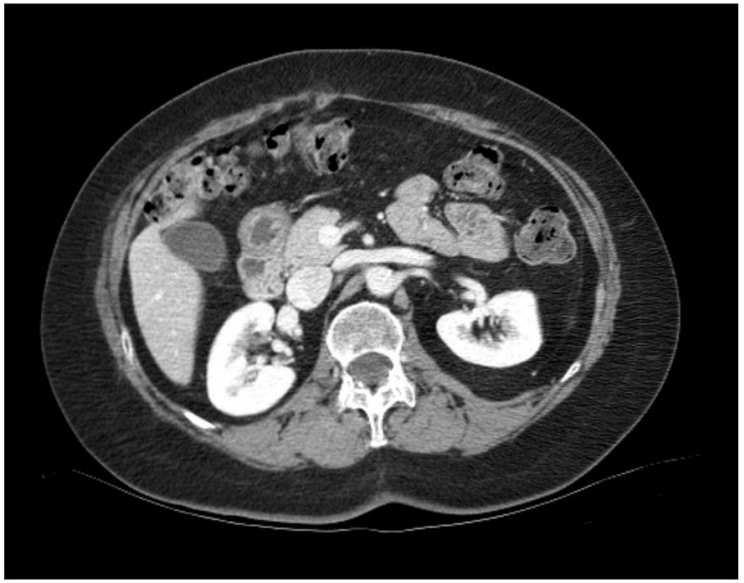
- Operation, adjuvant CEF x6, taxol+carbo x6, docetaxel, bevacizumab, topotecan, erlotinib, aromatase inhibitor
- Progressive disease, WHO 1
- Single intraperitoneal treatment with Ad5-D24-GMCSF
- Complete response (CT, markers) for 9 mo



before treatment

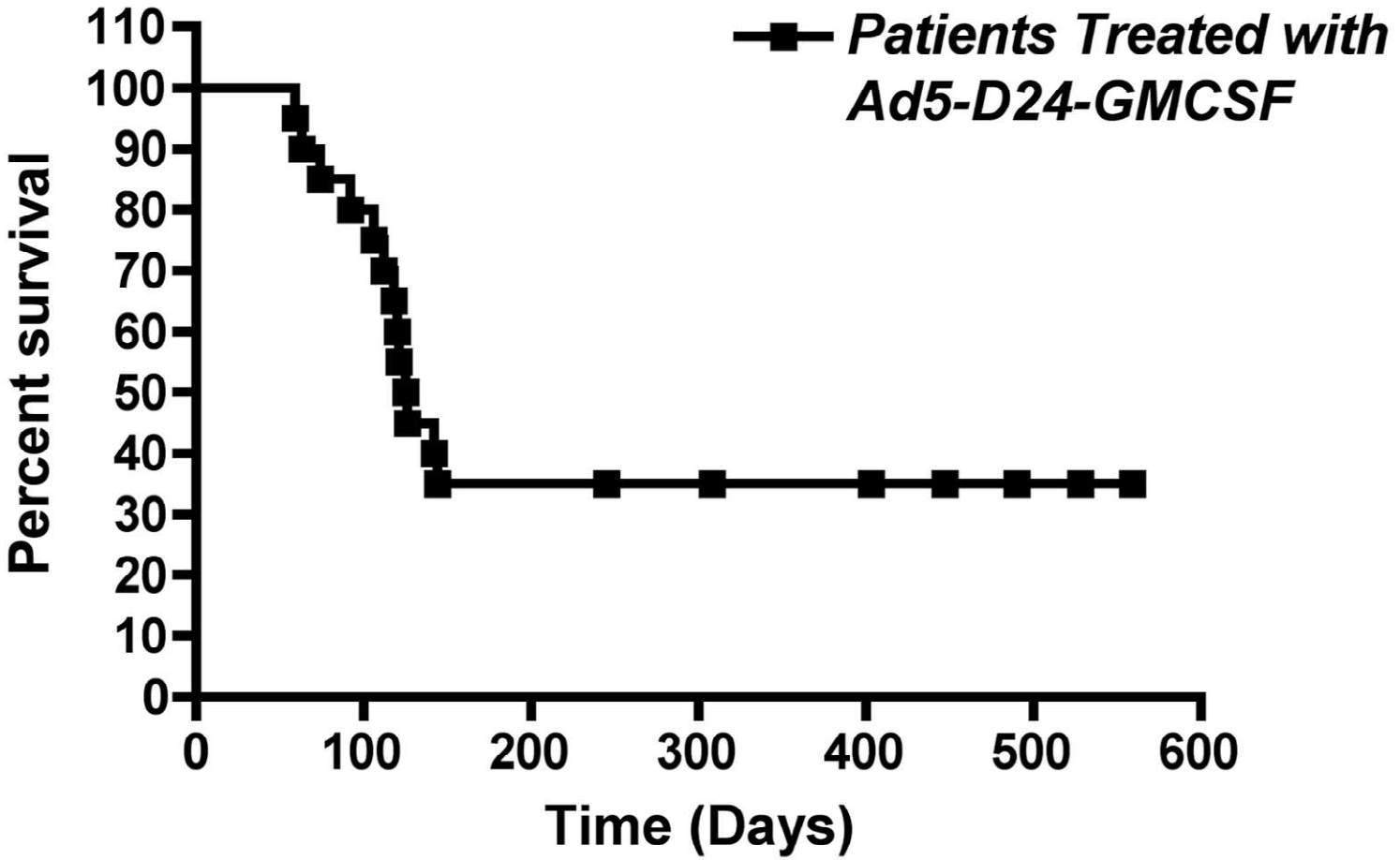


after treatment



Cerullo Cancer Res 2010

Long term survival in 1/3 of patients treated with Ad5-D24-GMCSF

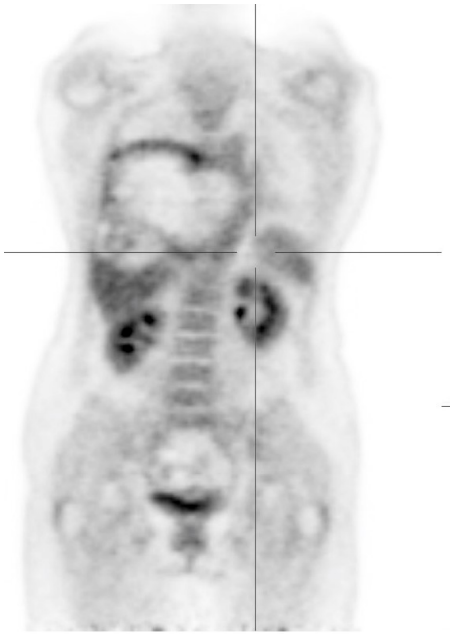


Cerullo Cancer Res 2010

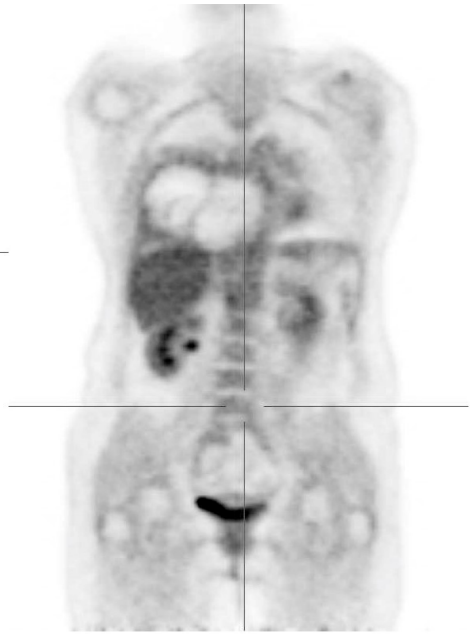
Fibrosarcoma patient S354 treated with CGTG-602 (Ad5/3-E2F-D24-GMCSF)

- 49 yr. woman with fibrosarcoma metastatic to right lung
- WHO 2, walks 500m, dyspnea, pain, fatigue gr 2
- Progressing after ifosf+dox, XRT
- Palliative care initiated
- Treated with 3x10e11 VP CGTG-602
- At 3 mo. WHO 1, walks 4 km
- At 9 mo. WHO 0
- Funeral list converted to birthday party invitations
- At 12 mo. progression -> trabectidin initiated, responding at 4 mo*
- Alive and well at 30 mo. (Sep 2013)
- Hemminki O, OncoTarget 2015

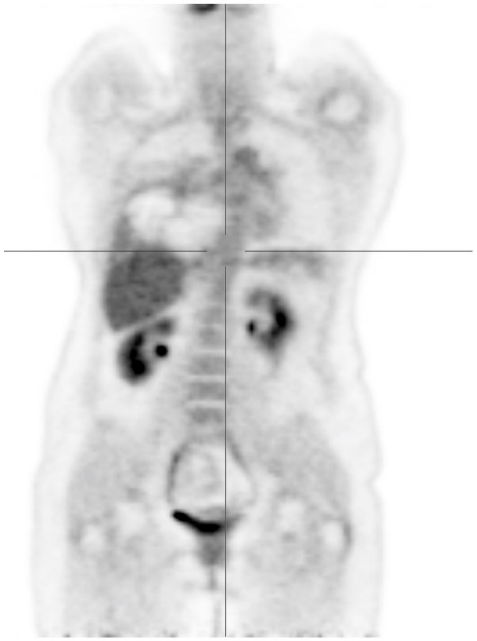
* Emerging data suggests oncolytic virus can resensitize tumors to chemo and vice versa



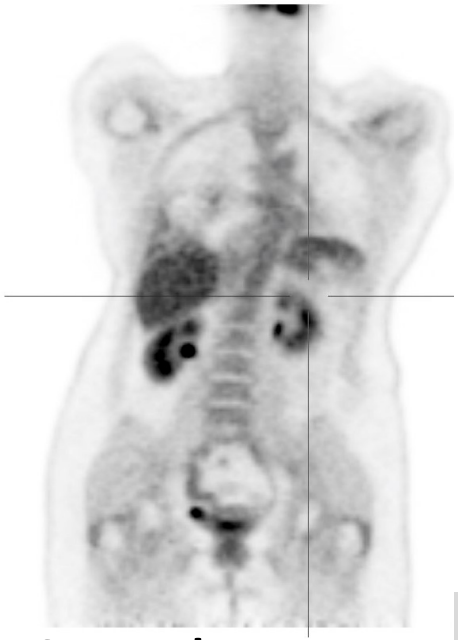
Baseline



3 months



6 months



9 months

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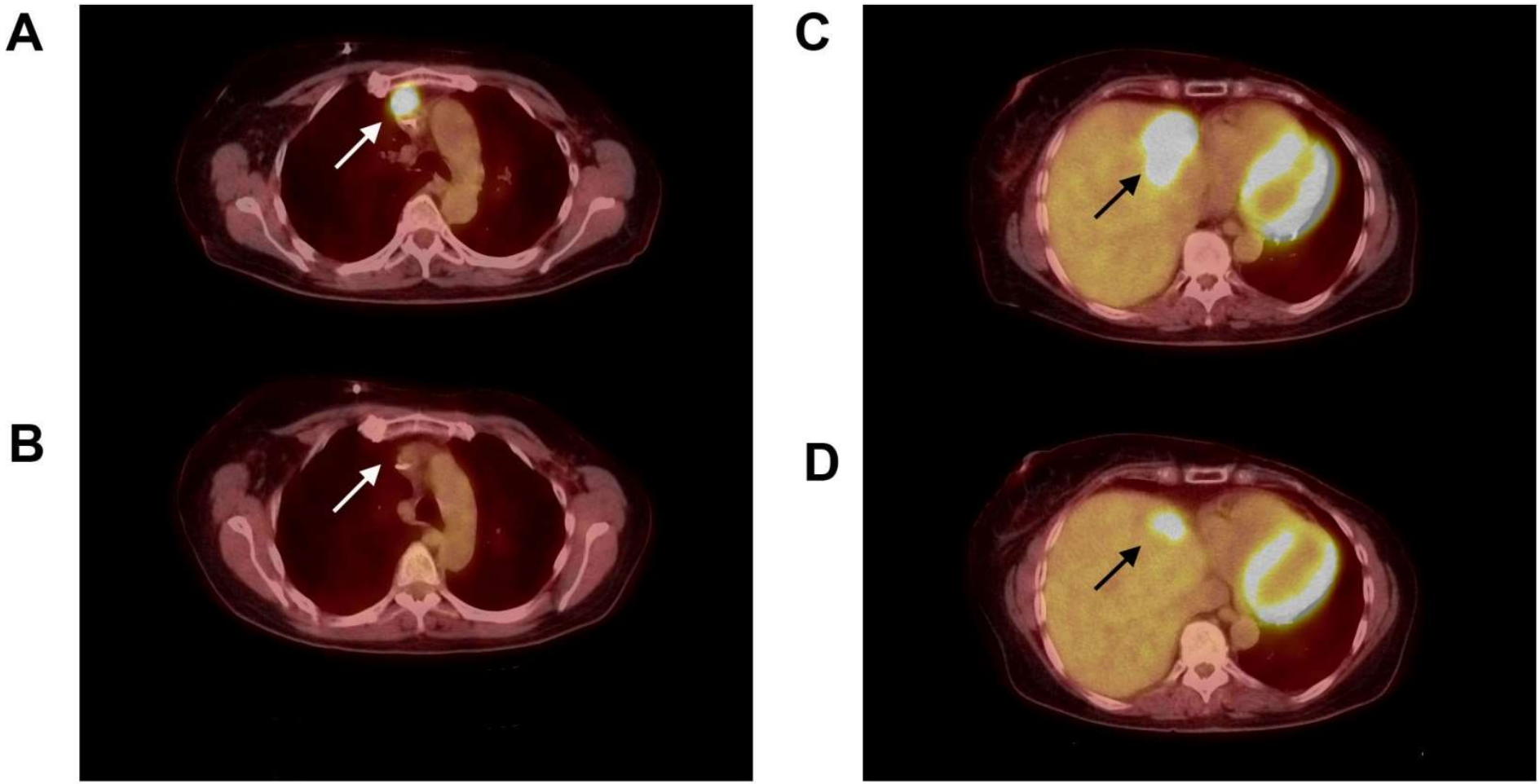
Systemic efficacy required for metastatic cancer: Anti-tumor activity in injected (right) and non-injected (left) lesions in breast cancer pt R319 treated w/ CGTG-602



Findings possible only in pts: Mechanisms of anti-tumor efficacy

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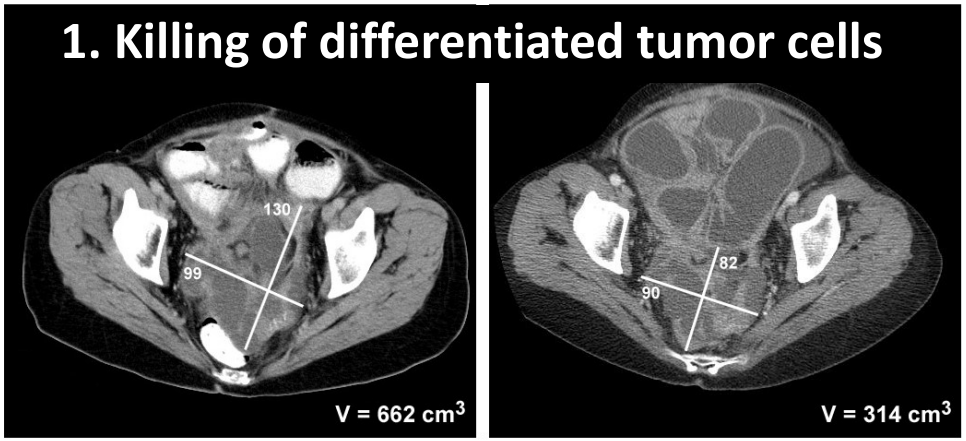
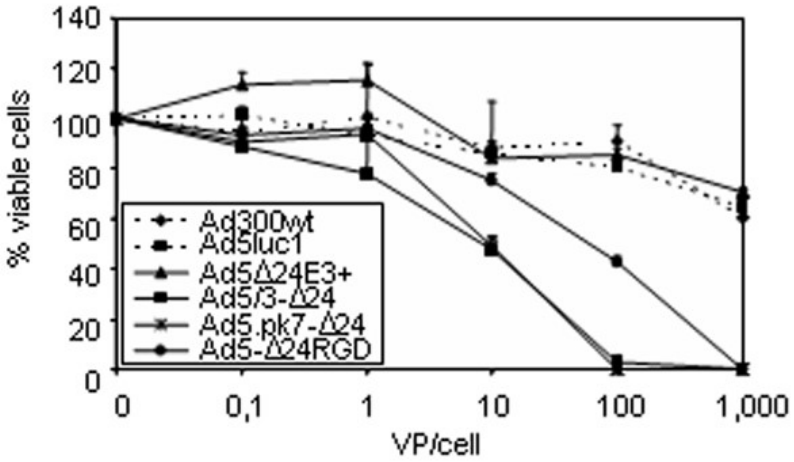
1. Killing of differentiated tumor cells



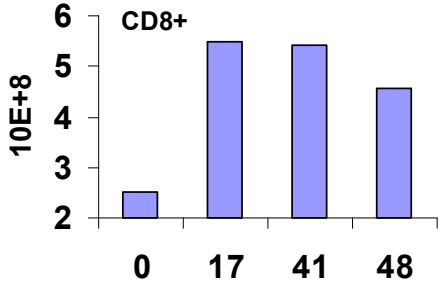
52.5% tumor size reduction

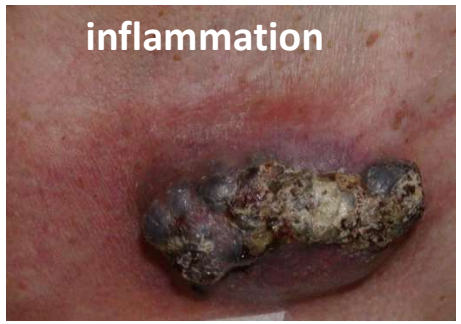
2. Killing of tumor initiating "stem" cells

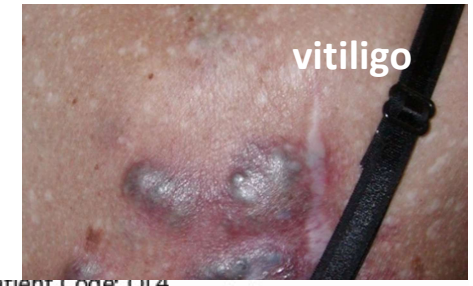


Eriksson Mol Ther 2007, Bauerschmitz Cancer Res 2008

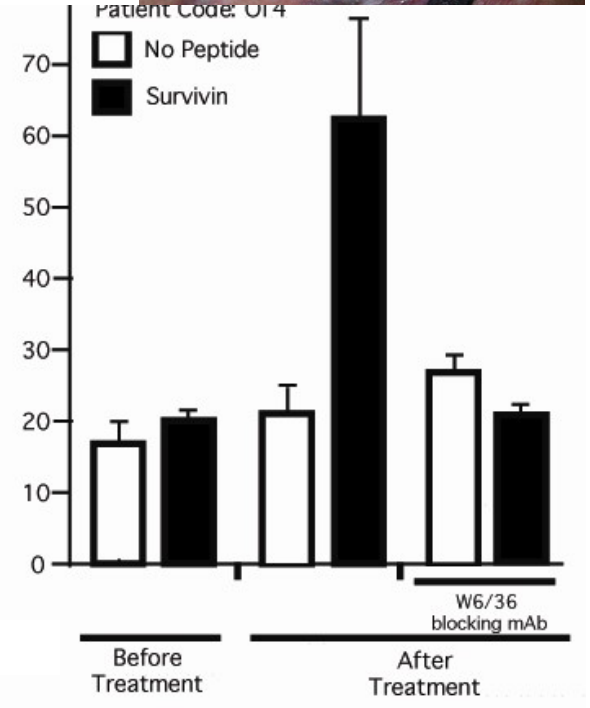
3. Induction of cytotoxic T-cells against tumors







4. Induction of specific immunity against tumor epitope (survivin)



Cerullo Cancer Res 2010

Personalized oncolytic adenovirus treatments in the Advanced Therapy Access Program

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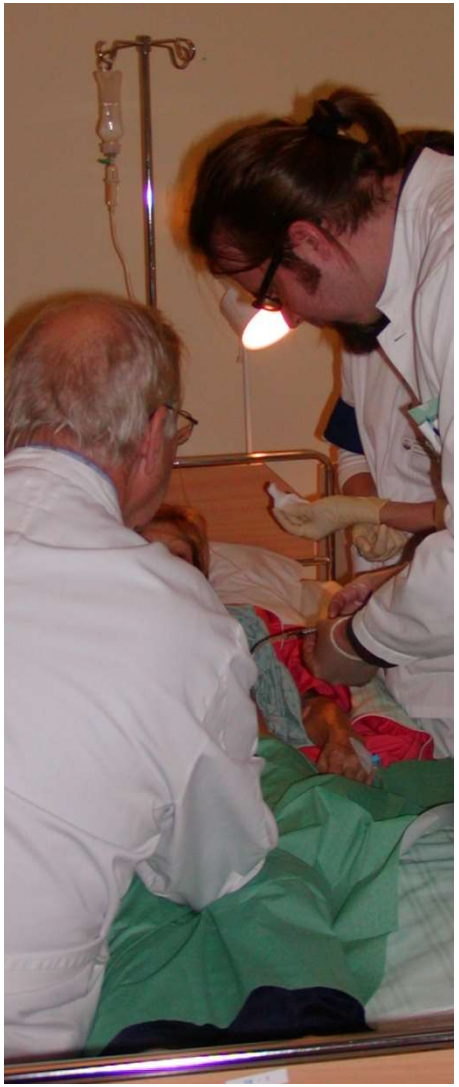
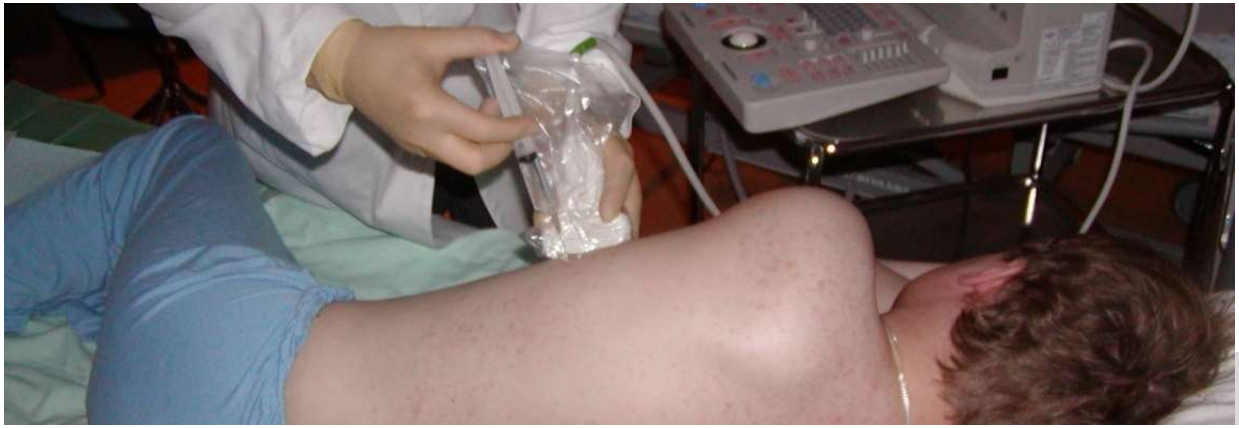


- 290 pts Nov 2007-Nov 2011.
- 10 different viruses
- Treatments were safe, no mortality
- Many patients benefited
- Fruitful interactions with regulators until…

Hemminki A: Crossing the Valley of Death with Advanced Cancer Therapy
http://www.nomerta.net/english.php



The end of the Advanced Therapy Access Program

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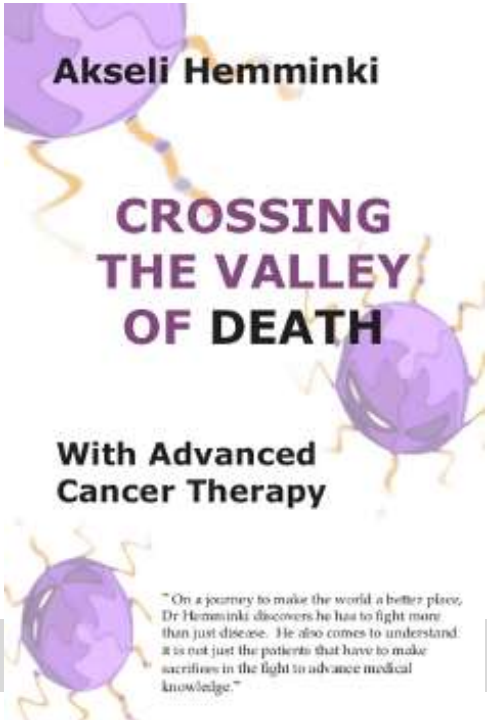
- A new Department Head at FIMEA (”Finnish FDA”) asked the police to investigate if ATAP was in fact a trial done without a trial permit
- Sponsor decided to end ATAP treatments immediately
- 2,5 years and 229 958€ of legal costs later, a 5 day trial resulted
- And the judge’s decision was …



Hemminki A: Crossing the Valley of Death with Advanced Cancer Therapy
Hemminki A: Kuoleman Laakso. Voiko syöpää hoitaa kokeellisilla menetelmillä?
http://www.nomerta.net/

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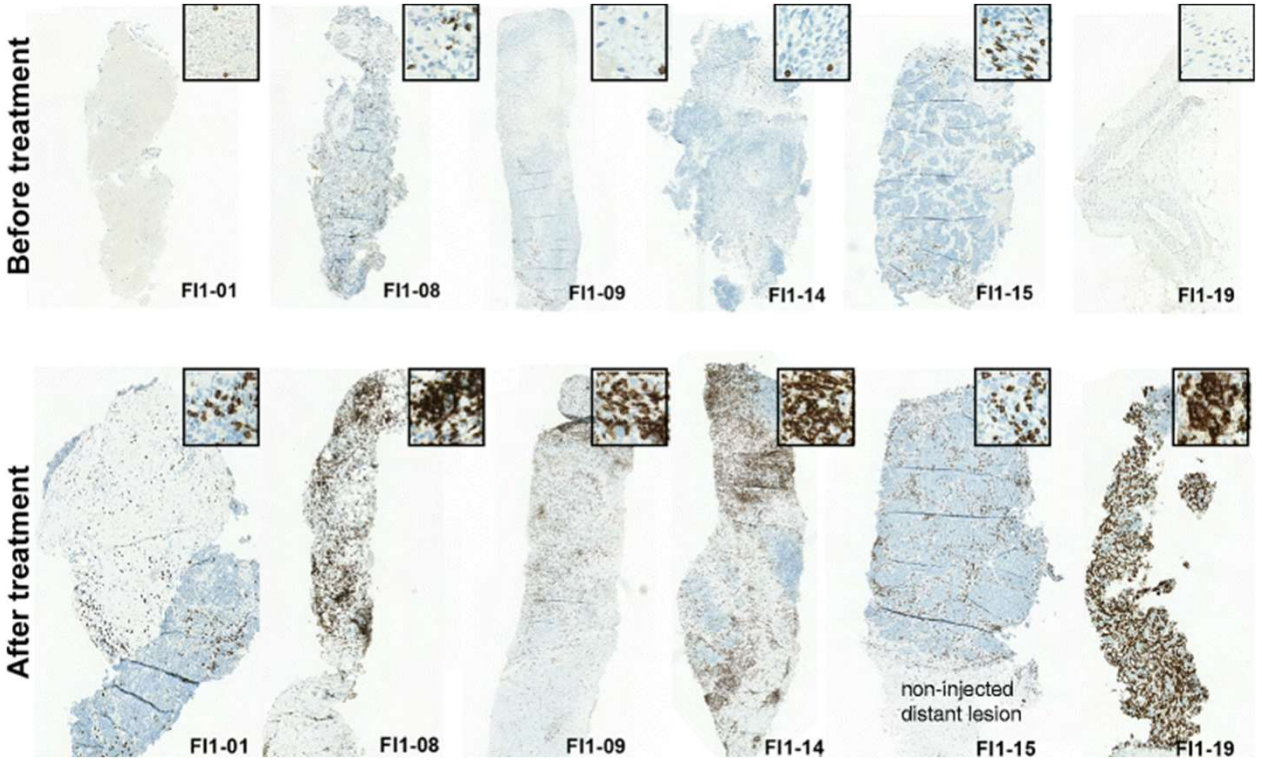
Short history of the Oncos-C1 trial



Induction of TIL in Oncos-C1
Ranki et al JITC 2016

- Virus constructed in CGTG lab in 2007, preclinical testing, patenting 2008
- Oncos Therapeutics Ltd. founded 2008
- 12 mil€ raised from eg. HealthCap and TEKES
- GMP virus production, biodistribution and toxicity testing 2010-11
- 5 rounds of ethical evaluation
- 3 rounds of evaluation by FIMEA
- *The first oncolytic virus trial approved in Northern Europe*
- Safety and efficacy as seen in ATAP
- Induction of T-cell responses

Summary

- Cancer immunotherapy has entered routine clinical use
  - BCG, TIL, CART, checkpoint antibodies, oncolytic viruses
- T-Vec (Imlygic) is the first oncolytic immunotherapy approved in US, EU
  - Also, Rigvir approved in eg Latvia 2004, Oncorine approved in China 2006
- The Advanced Therapy Access Program was a way to give patients access to experimental oncolytic virus treatments
- A lot was learned from the treatments
  - Anti-viral and anti-tumoral immunity key in efficacy
  - Several generations of new viruses developed based on human data
  - Fastest idea-to-pt time was 10 mo. (compare to 8-10 yrs typical in biotech)
  - Excellent efficacy-safety-ratio (trials needed to assess full efficacy eg. OS)
  - No issues with safety regardless of production method
  - Treatment can be personalized for each patient
  - Prognostic factors identified
- The legacy of ATAP is two biotech companies with several trials ongoing

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Acknowledgements

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tilt BIOTHERAPEUTICS

HUS

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

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The future of the advanced therapy access program?

- Costs per injection
  - Theoretical (no testing of virus preparation) 50 €
  - 2007: 900 € (produced by the University)
  - 2008: 1600 € (increase in testing, still University produced)
  - 2009: 4600 € (increase in testing, now produced by Oncos and price subvented, billed cost still 1600€)
  - 2012: 25 000 € (Full GMP now required)

-> ATAP not enrolling new patients since 11/2011

- With increased cost, is ATAP worthwhile to companies ?
- Are there physicians brave enough to do ATAP ?

Oncolytic adenoviruses: Δ24, a virus selective for a mutant p16/Rb pathway

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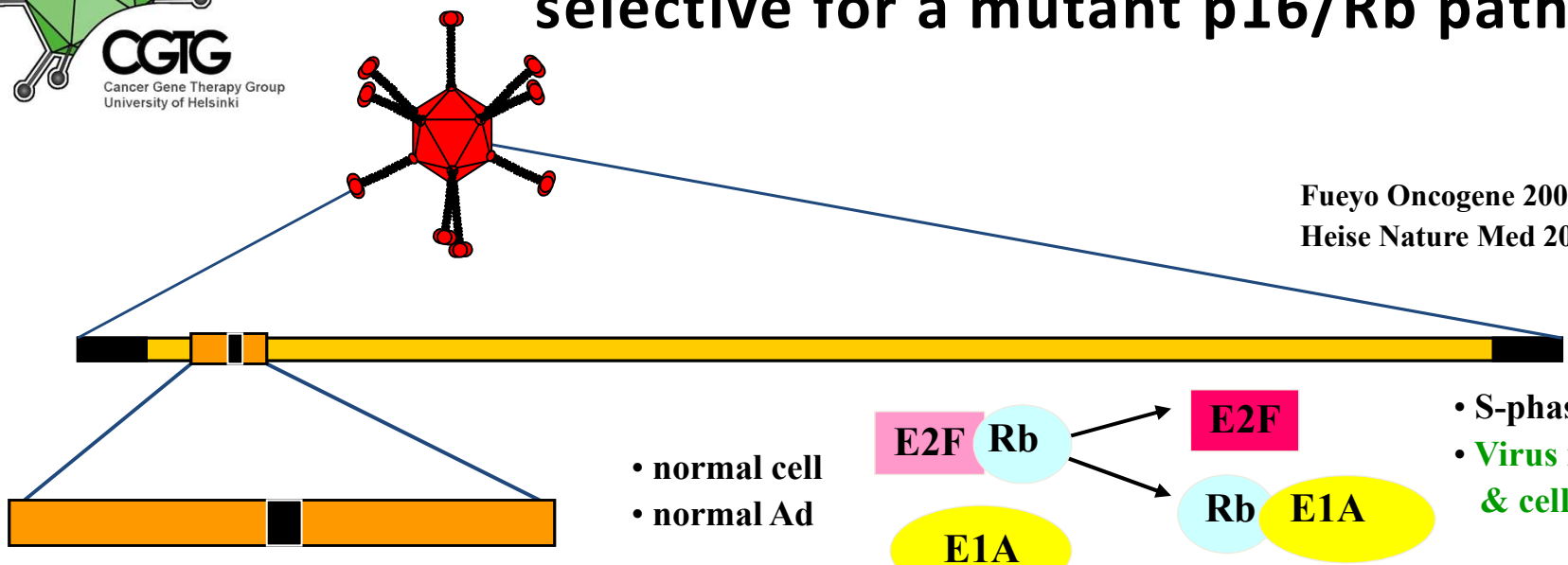

Fueyo Oncogene 2000
Heise Nature Med 2000

24 bp deletion in Rb binding site of E1A

- Replication in cells mutant in Rb-p16 pathway
- Includes all human cancers (Sherr Science 1996)