Technology offer

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A Novel Gene Therapy Approach to cancer treatment:
SuperTK1 integrated in Adeno-associated viral particles for gene therapy of human primary tumor cells

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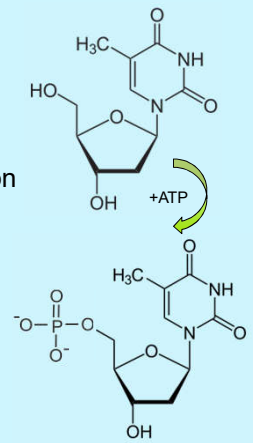
❖ What is the SuperTK1?

superTK1:

- still a human thymidine kinase 1
- aa substituted based on calculations
- in a domain essential for di- & tetramerisation
- superTK1 used has > 12-fold spec. activity
- set of improved superTKs available
- integrated in an inducible vector system
- activity high in transduced cells



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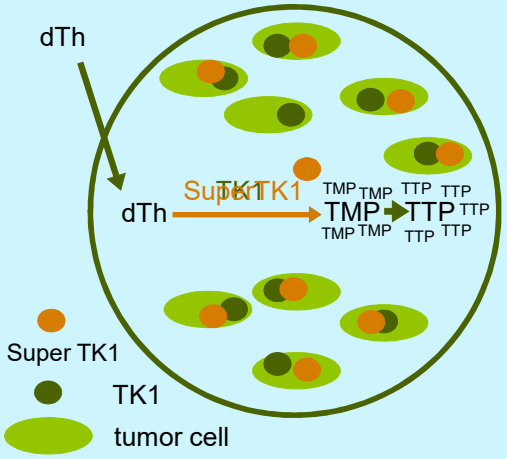
❖ How superTK1 inhibits tumor cells

illustration of the process:



- salvage pathway
- high TTP levels
- multiple effects
- high [dTh] → cytostatic in early S
- high [dTh] → cytotoxic (prolonged)
- very low [dTh] → superTK1 → boosts the effects even at very low [dTh]

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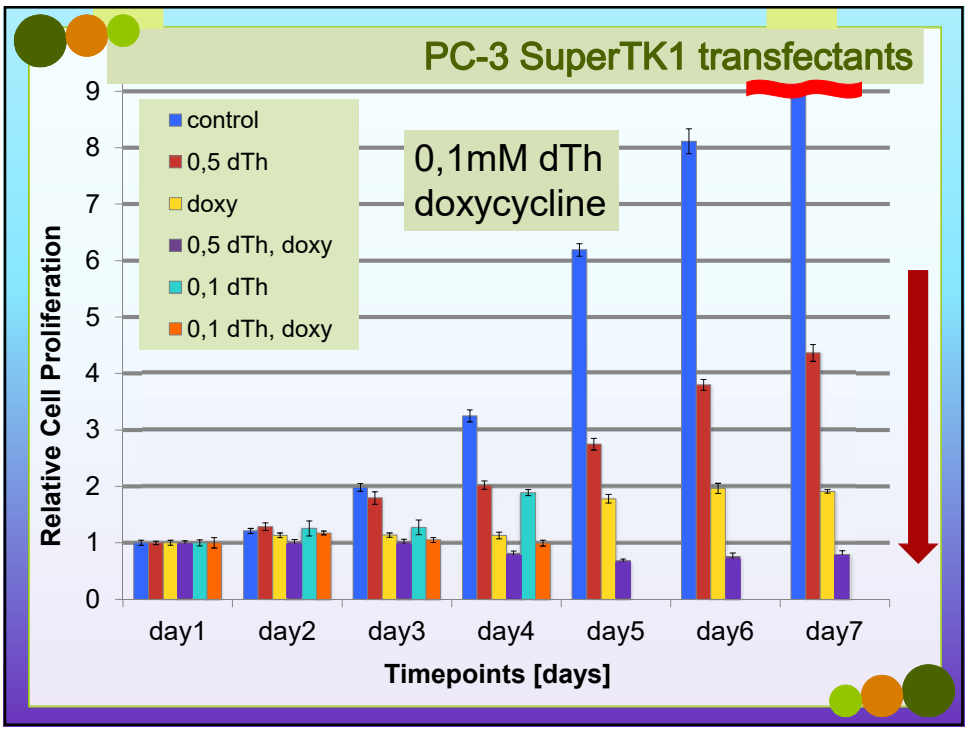
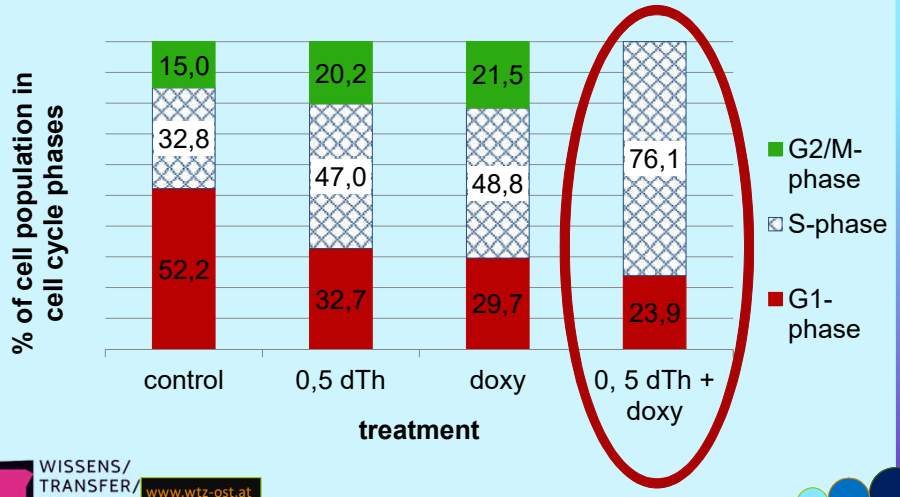


DNA profiles of PC-3 cells treated with superTK1 (FACS analysis)



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❖Why to use Adeno-associated viral particles?

- replication deficient, non-enveloped Parvoviruses
- infect cells independent of cell cycle
- infect all cancer cells evenly
- safe expression vector system
- integrate into chromosomes
- long term gene expression
- non pathogenic
- far not as immunogenic as adeno viruses

rAAVs plus superTK1

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Conclusions

BENEFITS

- treatment approach is enriching the anticancer toolbox
- using a basic cell cycle arrest that is cytostatic and cytotoxic
- a whole set of superTK1 mutants has been developed by us ➡ 5 µM dTh are sufficient for complete inhibition
- very innovative combination of molecular biology with theoretical protein engineering and gene therapy

Conclusions

APPLICATIONS

- for solid tumors of any kind of origin and location
- AAV-based transfer affects all tumor cells types equally
- “old” therapy regimens are back in contention (⬇side effects)
- repeated therapy regimens are easily possible
- method of choice for solid tumors inaccessible for surgery

Applications

Preclinical animal experiments

Using the "best" superTK1 mutant for recAAV gene therapy

- **Xenotransplants** of human primary cancer cells in **SCID mice**
- **Mamma carcinoma** (MFM233 cells)
- **Prostate carcinoma** (PC-3 cells)
- Human primary **glioblastoma** cells
- Optimization of combination therapies with **dTh alone** and with **AraC** and **5-FU**

implant cancer cells in mice (xenotransplant)

↓

grow to solid tumor to specific size (ϕ 5 mm)

↓

treatment of solid tumor with recAAVsuperTK1

Applications

Human glioblastoma

Why it is important to find new perspectives in treatment methods?

- origination of *glioblastoma multiforme*
- prognosis very bad
- therapy combinations need enhancement
- new approaches: modern promising gene therapy methods

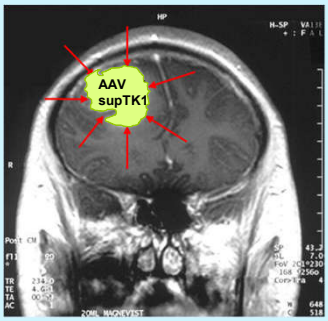

Fig.1 Coronal MRI with contrast of a glioblastoma WHO grade IV in a 15-year-old male

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