Our journey on winding road of cancer research

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Long road from bench to bedside

- **Discovery phase**
  - Design
  - Sample collection
  - Sample analysis
  - Statistical analysis

- **Validation**
  - Sample collection
  - Sample analysis
  - Statistical analysis

- **Randomized controlled trial**
  - Design
  - Ethics approval
  - Recruiting and sample collection
  - Sample analysis
  - Statistical analysis

- **Replication, validation trials and multicentre trials**

- **Healthcare systems policy changes**
  - Infrastructure and biobanking
  - High-throughput analysis development
  - Health technology assessment

- **Trial phase in clinical setting**
  - Statistical analysis

- **New immune biomarker implemented**

Funding at each stage
Long road of experimental and translational medicine in Slovenia

- CETO - Bovec 2002
What were our topics

• Biomarkers
• Preclinical testing
• Immunology
• Electroporation

• Where were/are we active
  – Organizing conferences
  – Teaching on postgraduate level
  – Journal Radiology and Oncology
What are opportunities

- Collaboration in project applications
- Scientific collaboration
- Mutual publications
- Mutual use of infrastructure
Our current open questions:
How do we make local therapy locoregional or systemic?

**Abscopal effect:** antitumor effect on distant, non-treated tumors.

- First reports were from radiation therapy
- Local therapy evokes local immune response that can be *in situ* vaccination
- This local immune response needs to be stimulated by:
  - Immunostimulation
    - IL-12
  - Overcoming the immune blockade
    - CTLA4
    - PD-1
    - Treg
Electroporation as platform technology for drug and gene delivery

- **Drug electrotransfer**
  - Primary and metastatic disease
  - Clinical application

- **Gene electrotransfer**
  - In preclinical setting
  - The first clinical studies
Electrochemotherapy – clinical
Electrochemotherapy is based on known mechanisms of action

- Direct effects on tumor cells
- Indirect effects by vascular disrupting action
Electrochemotherapy

- Effective local ablative technique
- Can we transform local effect into locoregional or systemic?
- Can we combine it with gene electrotransfer?
- Can combined treatment provide a systemic effectiveness?

Before ECT

14 days after ECT
How can we combine ECT and EGT?

- There were some previous attempts but with i.t. GET
- Can peritumoral GET of IL-12 provide boosting of the response?
ECT as *in situ* vaccination boosted with IL-12 GET

- For the abscopal effect we need
  - Immunostimulation
  - Immuno Checkpoint Blockade
- The immunostimulation can provide higher response rate and possibly also the effect on distant metastases, with influence on survival.
Proposed model of *in situ* vaccination with ECT, boosted by immunogene therapy with IL-12

Peritumoral gene therapy augments ECT and has an „Abscopal effect“

- Survival after therapy of B16F1 tumors
- Outgrowth of untreated contralateral tumors

Tumor model: B16F10
Therapeutic plasmid: pORF-mIL-12
Chemotherapeutic: cisplatin (CDDP)

Graphs showing survival and outgrowth rates after different treatments.
1 week after  2 weeks after  4 weeks after

3 months after

April 2014 – 3.5 years after treatment
Where do our roads cross

- Biomarkers for individualized treatment of patients
Department of Experimental Oncology and friends