Cancer Treatment by Alternating Electric Fields (TTFields); Physical Basis & Clinical Trial Results

Madrid, March 2015
Cancer Treatments

- **Surgical** - whenever possible, Effective mostly in Early stages, sometimes only palliative

- **Radiation** – a Physical means having a General Effect over a very wide range of Tumors, but also effects other cells

- **Chemotherapy** – Specific, restricted to cancers having certain cell Receptors and people with specific Genomes

- **Biological Therapies** – immunotherapy, etc. – Very Specific, mostly under development
Shortcomings of non-surgical Cancer Treatments

- Narrow spectrum of effectiveness (chemotherapy)
- High Toxicity - Low therapeutic index
- Severe Side Effects, even with limited Doses
- Maximum Cumulative treatment Doses
- Cancer often develops Resistance, at least to Chemotherapy
To Overcome these Limitations, a new Treatment Modality was developed

• To be able to treat a wide spectrum of Cancers – it should probably be a Physical modality

• However, the currently effective Physical modality - ionizing radiation is associated with Severe Side Effects

• To overcome this - we need a Physical modality that has a much higher Specificity to Cancer over Normal cells
The New Therapeutic Modality – *TTFields*

**TTFields - Tumor Treating Fields that are:**

- Low amplitude alternating electric fields of about 1-5V/cm, i.e. of the same amplitude as natural fields generated in the body by nerves & muscles.

- Alternating Electric fields in the Frequency range of 100 – 300 kHz range, Tuned to specific Tumors.
TTFields

*TTFields* are generated in the body by means of External “transducer arrays” positioned on the skin surface

The transducers are insulated by ceramics with $\varepsilon = 10,000$, thus their impedance at the 100kHz range is lower than that of the tissues

The fields disrupt proliferating cancer cells but -

- Have no effects on normal Non-dividing cells
- Do not Stimulate Nerves and Muscles
- Do not result in meaningful Heating
Frequency specificity and TTFields intensities

- B16F1 (Mouse Melanoma);
- MDA-MB-231 (Human Breast);
- F-98 (Rat Glioma);
- H1299 (Human Lung)

TTFields

Mechanisms of Action on Proliferating cells

First Mechanism - Dielectrophoresis
Field Distribution around living Cells

The distribution of frequency tuned Alternating Electric Fields in and around Living Cells:

Within Quiescent cells the Electric Field is **Uniform**

Actual distribution is a function of Frequency
In Contrast, within a dividing cell the electric field is Non-Uniform.

*TTFIELDS Focus* at the neck during cell division, i.e. increased field intensity.
When Dividing Cells are placed in a proper electric field, **Dielectrophoresis** Forces are generated and act on all polar & polarizable entities Disrupting Cell Structure.
Cell Destruction in TTFields

24h Time lapse microphotography of malignant melanoma cell culture
TTFields

Mechanisms of Action on Proliferating cells

Second Mechanism – Tubulin/Division Disruption
TTFields Treatment Induce Severe Spindle Damage in Cancer Cell Lines – image analysis

Disruption of Spindle Microtubules by *TTFields*

**Normal Cell Division**

Blue - DNA
Red - Actin
Yellow-Green - Tubulin

**Field Effects**
TTFields

Mechanisms of Action on Proliferating cells

Other Mechanisms
Efficacy of the combined treatment of TTFields and irradiation against U118 glioma cells

**Figure 1.** The efficacy of the combined treatment of TTFields and irradiation was evaluated based on cell counts (A) and clonogenic assay (B). Control cells (grey), irradiated cells (IR) (blue), cells treated with TTFields only for the indicated durations (TTF) (red), irradiated cells treated with TTFields (IR+TTF) (green). Student T-test was used to assess statistical significance between cell numbers and colony numbers of Control and treated cells. p values are smaller than: 0.05 (*), 0.01 (**) and 0.001 (***). Each bar represents an average of at least 3 repeats. Error bars represent standard deviation.

Results demonstrate that all 3 treatments: IR, TTFields and IR+TTFields lead to significant decrease in the number of U-118 cells. The combined treatment of TTF+IR was superior to application of TTF or IR alone with regard to both cell number and clonogenicity.
TTFields leads to the formation of aneuploid cells

A2780: Chromosomes spreads

Sky analysis

Chromosomes counts
Implementation of the *TTFIELDS* Technology
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Clinical Trials
Where to start?

About 10 years ago the choice fell on the untreatable Brain Cancer: Recurrent Grade IV Glioblastoma Multiformis or GBM

The life expectancy of these patients was, at the time, Under 6m
**TTFields** Distribution in Human Brain Model

Active Electrodes

**V/cm**
TTFields Distribution in the Brain

The NovoTTF System

TTFields-generating device with battery in shoulder bag
Recurrent GBM - Radiological Responses:
Secondary Endpoint: As Treated Overall Survival

Medians:
NovoTTF + TMZ  20.5 months
TMZ  15.6 months

Stratified Log rank p = 0.0042
Hazard Ratio = 0.67

OS12:
NovoTTF + TMZ  74%
TMZ  68%

OS24:
NovoTTF + TMZ  45%
TMZ  28%
Data Monitoring Committee Recommendation

- Based on the results of the interim analysis, the trial should be terminated early for success.
- Patients in the control arm should be allowed to cross over to the NovoTTF-100A arm prior to disease progression.
NSCLC – Extremely Promising Results

Overall Survival

- Control* OS = 8.2 months
- NovoTTF OS = 13.8 months
- 68% increase
- P<0.005

- Control 1-Year-Survival = 30%
- NovoTTF 1-Year-Survival = 57%
- 90% increase
- P<0.05

- Control 2-Year-Survival < 2%
- NovoTTF 2-Year-Survival =41%
- 20-fold increase
- P<0.001

* Control data taken from Alimta registration trial


See Also: Pemetrexed alone in patients with NSCLC previously treated with chemotherapy: median survival time = 8.3 months (Hanna et al, J Clin Oncol, 2004).
Thank You