Bilat_UKRAINIA: Summer School on European RTDI policies, instruments and participation possibilities

A succesfull story:

Electrochemotherapy, from a concept to a treatment, and the leverage by European funds

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Director of the Associated European Laboratory on the Electroporation in Biology and Medicine (LEA EBAM)

September 15, 2014 - Kiev (UKRAINIA)
26 years ago...

Experimental Cell Research 175 (1988) 15–25

Introduction of Definite Amounts of Nonpermeant Molecules into Living Cells after Electropermeabilization: Direct Access to the Cytosol

LLUIS M. MIR,* † HÉLÈNE BANOUN,† and CLAUDE PAOLETTI†

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TRANSIENT ELECTROPERMEABILIZATION OF CELLS IN CULTURE

INCREASE OF THE CYTOTOXICITY OF ANTICANCER DRUGS

STÉPHANE ORLOWSKI,* JEAN BELEHRADÈK JR.,* CLAUDE PAOLETTI* and
LLUIS M. MIR†‡
The toxicity of bleomycin on cells in culture is increased by cell electroporation.

Cell suspension was mixed with drug solution and immediately exposed to electric treatment.

Toxicity was potentiated ~1000 to 10 000 fold.

Orlowski et al. 1988
In vivo, bleomycin toxicity is also increased by tumor cells electropermeabilization.

Conditions:
8 pulses
of 100 µs and
~1300 V/cm
at a repetition frequency of 1 Hz
Electrochemotherapy: Potentiation of Antitumour Effect of Bleomycin by Local Electric Pulses

Lluis M. Mir, Stéphane Orlowski, Jean Belehradek Jr and Claude Paoletti

Electrochemotherapy of Spontaneous Mammary Tumours in Mice

Before

3 days later

« During »

30 days later

1st clinical trial, at IGR Berehradek et al. 
Cancer 1993
L’électrochimiothérapie, un nouveau traitement antitumoral : premier essai clinique

Lluís M. Mir, Michel Belehradek, Christian Domenge, Stéphane Orłowski, Bruno Poddevin, Jean Belehradek Jr, Guy Schwaab, Bernard Luboinski et Claude Paoletti

Résumé — L’électrochimiothérapie (ECT) est un nouveau traitement antitumoral qui consiste en l’application d’impulsions électriques à la tumeur quelques minutes après une injection de bleomycine. Nous rapportons ici le premier essai en clinique de ce procédé, appliqué à des patients présentant des nodules de perméation de carcinomes épidermoïdes des voies aéro-digestives supérieures. L’ECT a été bien tolérée par les patients et nous n’avons constaté aucun incident majeur. De plus, nous avons observé une nette action antitumorale.

Electrochemotherapy, a novel antitumor treatment: first clinical trial

Abstract — Electrochemotherapy (ECT) is a new antitumor treatment which consists in delivering electric pulses to the tumor some minutes after an intravenous injection of bleomycin. We report here the first clinical trial of ECT, applied to patients with permeation nodules of head and neck squamous carcinomas. ECT was well tolerated by patients, no serious incident occurred and a clear antitumor efficiency was found.
1992 – 1999
The « cryptic » electrochemotherapy

Preclinical electrochemotherapy continued:
- Villejuif FRANCE (CNRS - Institut Gustave-Roussy team)
- Toulouse FRANCE (Justin Teissié and Marie-Pierre Rols)
- Ljubljana SLOVENIA (Damijan Miklavcic and Gregor Sersa)
- Tampa FLORIDA (Richard Heller and Richard Gilbert)
- Copenhague DENMARK (Julie Gehl)


*Biomedical applications of electric pulses with special emphasis on antitumor electrochemotherapy.*

Electrochemotherapy with Bleomycin (Human Kidney Tumours)
1992 – 1999

The « cryptic » electrochemotherapy

Clinical electrochemotherapy continued:

- Villejuif FRANCE (Institut Gustave-Roussy)
- Toulouse FRANCE (Centre Claudius Régaud)
- Ljubljana SLOVENIA (Institute of Oncology)
- Tampa FLORIDA (Moffitt Cancer Center)
- Copenhague DENMARK (Herlev Hospital)
- Yamagata JAPAN (Yamagata Hospital)


Effective treatment of cutaneous and subcutaneous malignant tumors by electrochemotherapy.

ANTITUMOR ELECTROCHEMOTHERAPY

A

Before treatment

B

Gehl & Geertsen
Melanoma Research
2000

After 5 days

C

After 2 wks

D

After 8 wks
1992 – 1999

The « cryptic » electrochemotherapy

First treatments of deep-seated tumors


*A new brain tumor therapy combining bleomycin with in vivo electropermeabilization.*

*Biochemical and Biophysical Research Communications, 194, 938-943, 1993.*


*Electrochemotherapy on liver tumors in rabbits.*

*British Journal of Cancer 77, 2104-2111, 1998.*
Using hexagonal centered array of needles to treat tumors transplanted in rabbit liver
1992 – 1999
The « cryptic » electrochemotherapy

At the end of this period, limited extension of ECT use. ⇒ A loss of time?

No, since at the end of this period:
Analysis of the bases of the treatment efficacy and safety
In vivo cell electropermeabilisation tests
First experimentally validated numerical models of electric field distribution in tissues
Analysis of tissues reactions to the electric pulses
Host reactions (immune system contribution)
⇒ The credibility of ECT was reinforced

+: Electrotransfer of nucleic acids (DNA, RNA, …)
From 2000: The dissemination of the electrochemotherapy

What is needed?

1) Marketable and certified technology

=> The Cliniporator project

With the support of the European Commission (5\(^{\text{th}}\)FP)
The CLINIPORATOR project

CLINIPORATOR: a new adaptive generator for DNA electrotransfer in vivo for gene therapy

Project QLK3-1999-00484 funded by the EU commission within the 5th FP (01/02/00 to 31/07/03)

8 partners:
CO1/coord - L.M. Mir - CNRS at Villejuif (F)
• CR2 - R. Cadossi - IGEA s.r.l. at Carpi (I)
• CR3 – E. Neumann – Univ of Bielefeld (D)
• CR4 – V. Préat – Univ. Catholique de Louvain – Brussels (BE)
• CR5 - J. Gehl - Herlev Hospital at Copenhagen (DK)
• CR6 – D. Miklavcic - University of Ljubljana (SI)
• CR7 - B. Persson – University of Lund (SE)
• CR8 – J. Teissié – CNRS at Toulouse (F)
Cliniporator electrodes
“Cliniporator” electrodes: star needle array
Cliniporator power unit
The Cliniporator™
a new generator for basic and clinical applications

CE marked electric pulses generator for:
• Electrochemotherapy (HV alone)
• Electrogenetherapy (HV + LV)

Includes:
High frequency delivery
Storage of session data and of the set electrical parameters
Recording of I and U and storage of the I and U curves
From 2000: The dissemination of the electrochemotherapy

What is needed?

1) Marketable and certified technology
   => The Cliniporator project
      With the support of the European Commission (5\textsuperscript{th}FP)

2) Validated Clinical Protocols
   => The ESOPE project
      With the support of the European Commission (5\textsuperscript{th}FP)
The ESOPE project

European Standard Operating Procedures of Electrochemotherapy and Electrogenetherapy

Project QLK3-2002-02003 funded by the EU commission within the 5th FP (01/01/03 to 31/12/05)

4 cancer centers:
- CO1/coord - L.M. Mir - Institut Gustave-Roussy, Villejuif (F)
- CR3 - J. Gehl - Herlev Hospital at Copenhagen (DK)
- CR4 - G. Sersa - Institute of Oncology, Ljubljana (SI)
- CR5 - G. O’Sullivan - Cork Cancer Center (IRL)

2 other partners and 1 subcontractor:
- CR2 - R. Cadossi - IGEA s.r.l. at Carpi (I)
- CR6 - L.M. Mir - CNRS at Villejuif (F)
- SC1 - D. Miklavcic - University of Ljubljana (SI)
Final outcome of ESOPE study

(IGR, Villejuif, France; IO, Ljubljana, Slovenia; UCCC, Cork, Ireland, Herlev H., Copenhagen, Denmark)

Patients: 110 - Nodules with complete follow-up: 171

Objective Response Rate: 85%
No Response: 15%
The ESOPE clinical trial
(European Standard Operating Procedures of Electrochemotherapy)

Special issue of the European J. Cancer Supplements, vol 4, N°11, November 2006, that included:

- Results ESOPE study
- Case reports
- Standard Operating Procedures
- Reviews
From 2000: The dissemination of the electrochemotherapy

What is needed?

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2) Validated Clinical Protocols
   => The ESOPE project
      With the support of the European Commission (5\textsuperscript{th}FP)

3) Extension of technology applications
   => The Angioskin project
      With the support of the European Commission (6\textsuperscript{th}FP)
The ANGIOSKIN project

ANGIOSKIN : DNA electrotransfer of plasmids coding for antiangiogenic factors as a proof of principle of non-viral gene therapy for the treatment of skin disease

Project LSH-2004-512127 funded by the EU commission within the 6th FP (01/04/05 to 31/10/09)

9 partners:

CO1/coord - L.M. Mir - CNRS at Villejuif (F)

- CR2 - R. Cadossi - IGEA s.r.l. at Carpi (I)
- CR3 – C. Robert - Institut Gustave-Roussy, Villejuif (F)
- CR4 – V. Préat – Univ. Catholique de Louvain – Brussels (BE)
- CR5 - J. Gehl - Herlev Hospital at Copenhagen (DK)
- CR6 – M. Schoen – Univ Wurzburg/Univ Goettingen (D)
- CR7 - BioAlliance SA – Paris (F)
- CR8 - D. Miklavcic - University of Ljubljana (SI)
- CR9 – L. Skov – Gentofte Hospital at Copenhagen
From 2000 : The dissemination of the electrochemotherapy

What is needed?

1) Marketable and certified technology
   => The Cliniporator project
      With the support of the European Commission (5thFP)

2) Validated Clinical Protocols
   => The ESOPE project
      With the support of the European Commission (5thFP)

3) Extension of technology applications
   => The Angioskin project
      With the support of the European Commission (6thFP)

4) Dissemination into the clinical practice (cancer centers, Hospitals, ...)
   => The involvement of a company to deal with the regulatory agencies, health authorities... (IGEA)
The Cliniporator today
Electrochemotherapy
1st International Users’ Meeting

November 19 - 20, 2010
Bologna - ITALY
Electrochemotherapy
2nd International Users’ Meeting

March 1 - 2, 2013
Bologna - ITALY
In 2013, in Europe, 130+ hospitals use Cliniporator for electrochemotherapy of cutaneous and subcutaneous tumors (procedure reimbursed already in 7 countries)

Number of treatments per year in the EU

Clinicals trials ongoing for:

bone metastases, liver metastases, brain tumors, pancreas, colorectal cancers (endoscopic electrodes)
1st World Congress on Electroporation and Pulsed Electric Fields in Biology, Medicine and Food and Environmental Technologies
September 6-10, 2015
Portoroz, Slovenia

...we will all be there.
....we will all be there  Portorož, Slovenia – 6 to 10 September 2015

1st World Congress on Electroporation and Pulsed Electric Fields in Biology, Medicine and Food and Environmental Technologies

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Richard Heller (USA)
Damijan Miklavčič (Slovenia)
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Javier Raso (Spain)

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Vorobiev, E (France)
Xiao, C (China)
Yano, K-I (Japan)
Some clues to prepare a multilateral project

To have a **good idea** and/or new interesting/promising results

To find the « **good** » call :
- => all the words are important in the call description

To know **other** (the other) groups in your field/in complementary fields
- => interest of bilateral projects or of EU COST actions

To built the consortium in order to gather all the needed skills,
- => not necessarily all your friends... (😊 / 😞)

To involve all the other partners in the proposal writing
- => the partners must feel that the project is **their** project,
  not **your** project

To work **together**:
- => each group should organize at least 1 consortium meeting
- => organize consortium meetings on a regular bases
- => anticipate the meeting/travel costs in the previsonal budgets
- => promote the exchange of people within the consortium
Acknowledgements

Vectorology and Anticancer Therapies, UMR 8203 CNRS - Univ. Paris-Sud – IGR

- F. André, M. Breton, I. Leray, C. Calvet, J.R. Bertrand, A. Azan, T. Ragot, F. Salomone, H. Hanna

ANR (Nanopulsebiochip, IntCell, Memove, Oxylipi2)
THANK YOU FOR YOUR ATTENTION!