

## Therapeutic Perspectives of *In Vivo* Cell Electropermeabilization: Electrochemotherapy and DNA Electrotransfer for Nonviral Gene Therapy

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### INTRODUCTION

Cell electropermeabilization [1] is a new drug delivery approach as well as an efficient way to transfer DNA to cells in tissues. These two therapeutical approaches are based on the effects of the electric fields on cells and on molecules.

### DEFINITION OF ELECTROCHEMOTHERAPY

Electrochemotherapy principle [2] is the use of (i) nonpermeant molecules possessing intracellular targets, and (ii) short intense electric pulses that transiently permeabilize the cells *in vivo*. The essential role of the electric pulses is to achieve the electropermeabilization of the majority of the cells in the exposed tissue, and very short (100 microseconds) pulses can be delivered.

### DEFINITION OF DNA ELECTROTRANSFER

DNA electrotransfer is based (i) on the use of electric pulses to permeabilize the target cells, which makes possible the interaction between the DNA and the cell membrane, and therefore the internalisation of the DNA into the cells, and (ii) on the electrophoretic displacement of DNA (a highly charged molecule) under the influence of the external electric field, that approaches the DNA towards the cell membrane (therefore also favouring DNA interaction with cell membrane and its internalisation). In that case, because of the importance of the electrophoretic component in DNA uptake, longer pulses (tenths of milliseconds) seem more effective [3, 4].

### THERAPEUTICAL PERSPECTIVES OF ANTI-TUMOUR ELECTROCHEMOTHERAPY

While electrochemotherapy has already entered clinical trials, DNA electrotransfer has only been performed nowadays in animals (mice, rats, primates...). For the complete development of electrochemotherapy in clinics, a few questions must still be solved. For example, the effects on the margins of the tumours (i.e. the normal tissues located around the tumour nodule often infiltrated by tumour cells) must be analysed, in particular with respect to the dose of bleomycin and the way of administration of the drug (intratumoural versus intravenous). The comparison with present cancer treatments must now be performed. In the case of the basal cell carcinomas, electrochemotherapy efficacy appears to be similar to surgery (with the advantage

of being a less mutilating procedure). However, for other tumour types, comparison has not been yet done, in particular because electrochemotherapy cannot already be used as a first line treatment. The possibility of enhancement of the local effects, as well as the achievement of systemic effects by the combination of electrochemotherapy with immunotherapy are possibilities revealed by various preclinical trials that should be tested in future clinical trials.

### THERAPEUTICAL PERSPECTIVES OF DNA ELECTROTRANSFER FOR GENE THERAPY

DNA electrotransfer for gene therapy is a field rapidly expanding because it may constitute a real alternative to the need of viruses in the use of DNA for correcting genetic diseases. Electrotransfer in the skeletal muscle [3, 4] is really promising because it had already been shown that muscle is a secretory organ and because injections of naked DNA resulted in the expression of the injected DNA for long periods (months). However, injection of DNA results in a low and extremely variable level of the foreign gene expression. Both restrictions are palliated by the use of the electric pulses, that increase gene expression by two or three orders of magnitude and that reduce a lot its variability [3]. Consequently, the method has properties that make it appropriate for the correction of genetic diseases. In fact, expression of therapeutic genes has already been reported in animals.

### REFERENCES

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