Project Progress Summary Annex I: Project Progress Summary

Section 1: PROJECT IDENTIFICATION Information to be provided for project identification	**NOT CONFIDENTIAL**

Title of the project: Clostridial-Directed Enzyme Prodrug Therapy (CDEPT): A novel approach to Cancer Treatment

Acronym of the project: CDEPT

Type of contract		**Total project cost** (in euro)
(RS) Research and Technological Development Project		1,954,923 €
Contract number	**Duration** (in months)	**EU contribution** (in euro)
QLRT – 2000 -01737	36 Months	1,417,455 €

Commencement date:	**Period covered by the progress report**
01 December 2001	(1st December 2002 – 30th November 2003)

PROJECT COORDINATOR

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Key words (5 maximum - Please include specific keywords that best describe the project.).

Clostridium, Spore, Cancer, Prodrug, Enzyme

World wide web address (the project's www address) www.clostridia.net

List of participants Provide all partners' details including their legal status in the contract i.e.,contractor, assistant contractor (to which contractor?).

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Annex I: Project Progress Summary

Section 2: Project Progress Report **NOT CONFIDENTIAL**

(2 pages maximum.. Use short sentences. Be factual. Avoid technical terms as much as possible)

Objectives:

The overall objective is to develop a new and safe therapy for treating cancer. It is based on a bacterium that thrives in the low oxygen conditions uniquely present in solid tumours. The organism concerned, *Clostridium*, is non-pathogenic to man and is being engineered to convert a harmless chemical 'prodrug', into a potent anticancer 'drug' through the addition of enzymes. The objectives of the project are to determine and test the most effective combination of bacterial strain, prodrug, and prodrug-converting enzyme. This will involve the isolation of new enzymes and prodrugs, optimisation of enzyme production by the bacterium, and the development of non-invasive procedures to allow the treatment to be effectively monitored. To enhance the safety of the system, further defined alteration will be made to disable the host system employed.

Results and Milestones:

A more effective tumour model with greater clinical relevance has been put into place and the dose regimes for the envisaged prodrug/drug combinations have been established. Test organisms producing the lead candidate therapeutic enzyme have been created and a preliminary evaluation undertaken. To facilitate these studies, a simple and inexpensive model of cell aggregates for studying tumour colonisation by *Clostridium* has been developed. The superior sporulation and colonisation properties of the lead *Clostridium* strain has been confirmed. Moreover, the spore treatment has been shown to be entirely benign, with no measurable toxicity. To enhance the biosafety of the system, an additional target for disablement has been identified.

Evaluation of available promoter signals (the signals needed to drive production of the recombinant prodrug converting enzymes) has been completed and the most effective element identified. Studies directed at maximising the export of the therapeutic enzyme out of the clostridial delivery vehicle into the tumour mass have been initiated, with promising results. In the next phase of the programme, the most effective trans genes will be integrate into the chromosome of the *Clostridium* delivery vehicle, thereby maximising the stability of the engineered cells and obviating the need to use antibiotic resistance genes. Towards this aim, a number of genetic tools have been developed and evaluated. The most promising procedures will be now be capitalised on to generate the desired *Clostridium* strains. In parallel, the search for other more effective methods will be explored. This aspect of the project will be a priority in the coming year.

Two further novel therapeutic enzymes have been identified and their complete amino acid sequences determined. The generation and testing of novel prodrugs has continued, and a process for the manufacture of the prodrug of the lead candidate formulated for progression in the final phase of the project.

Benefits and Beneficiaries:

Cancer is a disease with a major socio-economic impact with the European Union, and elsewhere. Any small improvement of cancer treatment has major consequences in term of "saved-life", improved quality of life and reduced healthcare costs. The envisaged treatment is expected to be safe, inexpensive and easy to perform. Consequently, in addition to the European dimension it may also be easily transferred to less developed countries.

Future Actions (if applicable):

The project will build on the achievements of the first 20 months of the project through progression of the agreed objectives. In the next phase the emphasis will be on (i) optimisation of expression and secretion of therapeutic proteins; (ii) stabilisation of trans genes through incorporation into the host genome, and; (iii) evaluation of the therapeutic efficacy of the final strains in the tumour model.