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 (RS) Research and Technological Development Project		**Total project cost** (in euro) 1,954,923 €
Contract number QLRT – 2000 - 01737	**Duration** (in months) 36 Months	**EU contribution** (in euro) 1,417,455 €
Commencement date 01 December 2001	**Period covered by the progress report** (1st April 2002 – 30th November 2002)	

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

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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 strain of *Clostridium* for use in the envisaged treatment has been identified. Previously this strain has been recalcitrant to the introduction of recombinant DNA. The consortium has made a break through in this respect by devising a highly efficient means of DNA transfer. During their life-cycle, *Clostridium* form 'spores' to enable their survival during exposure to oxygen. As it is the spores that are administered in the proposed treatment, the growth conditions required to produce these spores have been optimised for the new *Clostridium* strain.

Numerous promoters (the signals needed to drive production of the recombinant prodrug converting enzymes) have been isolated a preliminary comparative evaluation undertaken, including an entirely synthetic promoter. To maximise production, the genes of 2 existing enzymes have also been chemically synthesised to incorporate signals preferred by the *Clostridium* host. This includes a gene specifying an enzyme that is far more efficient in the conversion of prodrug into drug than has currently been reported in the scientific literature.

Good progress towards the development of novel enzymes and prodrugs has been achieved. A number of environmental samples have been examined and found to contain the desired enzymes. Some of these enzyme activities have been found in *Clostridium*. Model compounds, bearing structural features desirable in the final prodrugs, have been synthesised and intermediates for the synthesis of likely prodrugs have been prepared. In the meantime, toxicity studies have been undertaken with existing prodrug/ drug combinations and more effective tumour models have been established.

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 8 months of the project through progression of the agreed objectives. In the next phase the emphasis will be on (i) testing the engineered strains in tumour models, together with existing and the novel enzymes and prodrugs; (ii) evaluating, and building in additional safety measures, and; (iii) establishing the non-evasive means of monitoring the therapeutic benefit of the treatment on tumour growth