# *Project Progress Summary* Annex I: Project Progress Summary

| Section 1: PROJECT IDENTIFICATION<br>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 2003 – 30th November 2004) |

**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:**

Our studies during this period have cleared flagged the importance of using the natural signal peptide cleavage domain in those instances where secretion of the therapeutic protein is desirable. These benefits will clearly be of use for future experiments where it is desirableto secrete the prodrug converting enzyme, and for the production of additional therapeutic molecules.

The dosing schedule for *in vivo* experiments with the lead prodrug has been further refined, and the dosage determined that can be repeatedly administered, without harmful effects. The observation that prodrug can be repeatedly administered at a relevant therapeutic dose will significantly improve the efficacy of the therpy. The most significant outcome of the reporting period has been the final selection of the *C. sporogenes* to be used. One of the candidate strains is compromised by it side-effects. Using the strain choosen, we have further been able to shown that we can reduce the dosage of prodrug from 10 days to 5, and to subsequently evaluated whether repeated treatment cycles would be possible. This would be of major interest, since it reflects the actual situation for many cancer patients treated in a clinical setting. This experiment is currently ongoing.

During this reporting period, parallel work has resulted in an even better enzyme than the current lead candidate. More significantly , a novel procedure for the synthesis of the lead prodrug, as been devised which avoids the use of a banned substance. This is a major breakthrough, as without this process the commercialisation of CDEPT using this prodrug would not be possible.

The ability to integrate genes into the chromosome still remains a major bottleneck to the project. We believe that this failure is due the fact that the frequency of transfer obtained is insufficient to detect the relatively rare integrative events that occur. Accordingly, efforts have focussed on the derivation of a conditional plasmid system, as yet with no success.

**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):**

Further progress remains hampered by our inability to integrate genes into the clostridial chromosome. In the final 3 months of the project, the progression of strategies designed to circumvent this bottleneck will be a priority. In addition, the experiments to determine whether repeated treatment cycles are possible will be completed.