

Project Progress Summary Annex I: Project Progress Summary

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| Section 1: PROJECT IDENTIFICATION | | NOT CONFIDENTIAL |
| Information to be provided for project identification | | |
| 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 (1 st December 2003 – 30 th November 2004) | |
| PROJECT COORDINATOR | | |
| Name Nigel Peter Minton | Title Professor | Address: University of Nottingham |
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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?). | | |
| <ol style="list-style-type: none"> Professor Nigel Minton (Co-ordinator – Partner 1) Centre for Biomolecular Sciences, Institute of Infection, Immunity & Inflammation, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom, Tel: (44-115) 84 67458, Fax: (44- 115) 8467951, Email: nigel.minton@nottingham.ac.uk Professor Peter Dürre (Contractor - Partner 2) Abteilung Mikrobiologie und Biotechnologie, Universitaet Ulm, D-89069, Ulm, Germany. Tel: (49-731) 5022710, Fax: (49-731) 5022719. Email: peter.duerre@biologie.uni-ulm.de Professor Jozef Anné (Contractor - Partner 3) K.U.Leuven, Rega Institute, Minderbroedersstraat 10, B-3000 Leuven, Belgium, Tel: (32- 16) 337371, Fax: (32- 16) 337340. Email: jozef.anne@rega.kuleuven.ac.be Doctor Philip Burke (Contractor - Partner 4) Building 115, Porton Down Science Park, Salisbury SP4 0JQ, United Kingdom, Tel: (44 1980) 613841. Fax: (44 1980) 613713. Email: pburke@enactpharma.com Professor Bengt Langstrom (Contractor - Partner 5) Department of Chemistry, University Hospital, Uppsala S-751 85, Sweden. Tel: (46-18) 4715381. Fax: (46-18) 4715390. Email: Bengt.Langstrom@kemi.uu.se Professor Philippe Lambin (Contractor – Partner 6) Academisch Ziekenhuis Maastricht – RTIL, Dr. Tanslaan 12, Heerlen-Maastricht, 6229 ET, Netherlands. Tel: (31-45) 5771200, Fax: (31-45) 5740277. Email: p.lambinSec@rtil.nl Doctor Myriam Sneyers (Consultancy – assistant contractor to Partner 3) Scientific and Biosafety Expert, Service of Biosafety and Biotechnology, Institute of Public Health - Louis Pasteur, Rue Juliette Wytzmanstraat, 14 1050 Brussels, Belgium, Tel: +32 26425293, Fax: +32 26425292. Email: msneyers@sbb.ihe.be | | |

Annex I: Project Progress Summary

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| Section 2: Project Progress Report | NOT CONFIDENTIAL |
| <i>(2 pages maximum.. Use short sentences. Be factual. Avoid technical terms as much as possible)</i> | |
| Objectives: | |
| <p>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, <i>Clostridium</i>, 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.</p> | |
| Results and Milestones: | |
| <p>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 desirable to secrete the prodrug converting enzyme, and for the production of additional therapeutic molecules.</p> <p>The dosing schedule for <i>in vivo</i> 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 therapy. The most significant outcome of the reporting period has been the final selection of the <i>C. sporogenes</i> to be used. One of the candidate strains is compromised by its side-effects. Using the strain chosen, we have further been able to show that we can reduce the dosage of prodrug from 10 days to 5, and to subsequently evaluate 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.</p> <p>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.</p> <p>The ability to integrate genes into the chromosome still remains a major bottleneck to the project. We believe that this failure is due to 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.</p> | |
| Benefits and Beneficiaries: | |
| <p>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 terms 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.</p> | |
| Future Actions (if applicable): | |
| <p>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.</p> | |