1. Final Scientific Activity Report - Publishable Summary

Cancer is a major disease which is responsible for approximately 23% of all deaths in the European Union. Epithelial tumours, such as those of the ovary, lung and oesophagus, have particularly poor prognosis, with only a minority of patients achieving a 5 year survival. Conventional treatments, including chemotherapy and radiotherapy, have limited efficacy and frequently cause severe side effects in the patients.

The *Apotherapy* project has brought together expertise from academic and biotechnology sectors across 7 European countries with the aim to develop and validate novel anti-cancer agents with wide therapeutic index and minimal side-effects. Specifically, the project has formulated therapeutic strategies which exploit the ability of CD40 ligand (CD40L), a TNF family member, to directly inhibit cancer cell growth and activate anti-tumor immune responses. *Apotherapy* has developed state-of-the-art adenovirus vehicles for the efficient delivery of CD40L to cancer cells, and provided extensive evidence for its efficacy in pre-clinical models. Of particular interest is the ability of CD40L therapy to enhance the activity of chemotherapeutic agents used in the clinic.

Apoptosis induced by CD40 engagement is dramatically augmented in the presence of inhibitors of the phosphoinositide 3-kinase (PI3 kinase) / Akt pathway which is frequently found activated in human tumours. Through the *Apotherapy* project, novel PI3 kinase antagonists have been developed and evaluated for their in vitro and in vivo capacity to kill tumour cells and to amplify the CD40L-mediated effects on carcinoma cell growth and metastasis. Of particular interest is the development of a new PDK1-specific inhibitor, the first of its kind, that was demonstrated to confer significant anti-tumor effects.

The *Apotherapy* project has thus developed and evaluated novel anti-cancer strategies which will be directly applicable to the clinic for the benefit of cancer sufferers. Thus, the project has led to small-scale clinical studies in patients with bladder cancer which have demonstrated the feasibility and validity of the *Apotherapy* concept and paved the way for future phase I clinical trials.