

EU FP6 Integrated Project: Adoptive engineered T-cell Targeting to Activate Cancer Killing ('ATTACK')

Abstract

Exploiting our knowledge of tumour immunology and genetic technology to treat cancer is now a realistic possibility. Already, adoptive transfer of tumour-specific T cells can successfully treat some malignancies. To extend this to other cancers and to simplify the process for clinical use, Engineered T cells (gene modified T cells artificially endowed with anti-cancer specificity) have been developed. Tumour targeting can be achieved with molecules based on T-cell receptors or on antibody fragments and the genetic constructs can also incorporate additional molecular machinery to enhance cytotoxicity, proliferation, survival, tumour homing or other features to increase anti-neoplastic activity. Partners in this IP have demonstrated key scientific aspects of these novel approaches and are now testing them in proof-of-concept clinical trials. The **ATTACK** project will optimise the technology and enhance understanding of the molecular mechanisms involved in tumour evasion of immune control to develop improved T cell mediated immunotherapy. The partners include experts in engineered T cells and authorities in key aspects of basic immunology and tumour biology. Expertise in tumour models is critical for substantiation of the activity and for testing the different targeting technologies, the effects of cell selection / expansion methodology and the survival / homing of the adoptively transferred effector T cells as well as safety of the improved methods. The **ATTACK** partners have a long record of EU based collaboration and the synergies between them combined with a co-ordinated approach will facilitate greater scientific understanding and enable delivery of optimised Engineered T-cell therapy. The partners own key patents in this and related fields and both commercial and academic partners have a strong track record of clinical trial development based on scientific and technological progress. Co-ordination will be aided by an International Advisory Board of external experts.

Partners

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Zelig Eshhar, Rehovot, Israel
Reno Debets, Rotterdam, The Netherlands
Guy Gorochov, Paris, France
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Thomas Blankenstein, Berlin, Germany
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Dorothy Crawford, Edinburgh, UK
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Stuart Naylor, Oxford (OBM), UK
Yoram Reiter, Haifa, Israel
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The specific objectives (i.e. workpackages) of the project include

1. Optimisation of T cell receptors based targeting (*lead: Rotterdam*).
2. Optimisation of Antibody based targeting (*lead: Rehovot*).
3. Evaluation of the above in realistic animal models of anti-tumour efficacy. Testing the safety of the various approaches in relevant animal models and developing methods to enhance the safety (*lead: Amsterdam*).
4. Optimisation of factors to affect the persistence and homing of T cells. These include manipulation of the host environment (eg with chemotherapy) or novel approaches to manipulate chemokines and chemokine receptors and hence allow the homing of T cells more effectively to tumours (*lead: Montpellier*).
5. Evaluation of methods for selection/expansion/ transduction of T cells and evaluating the effects of these changes in animal models (*lead: Manchester*).
6. Testing the safety of the various approaches in relevant animal models and developing methods to enhance the safety (*lead: Cologne*).

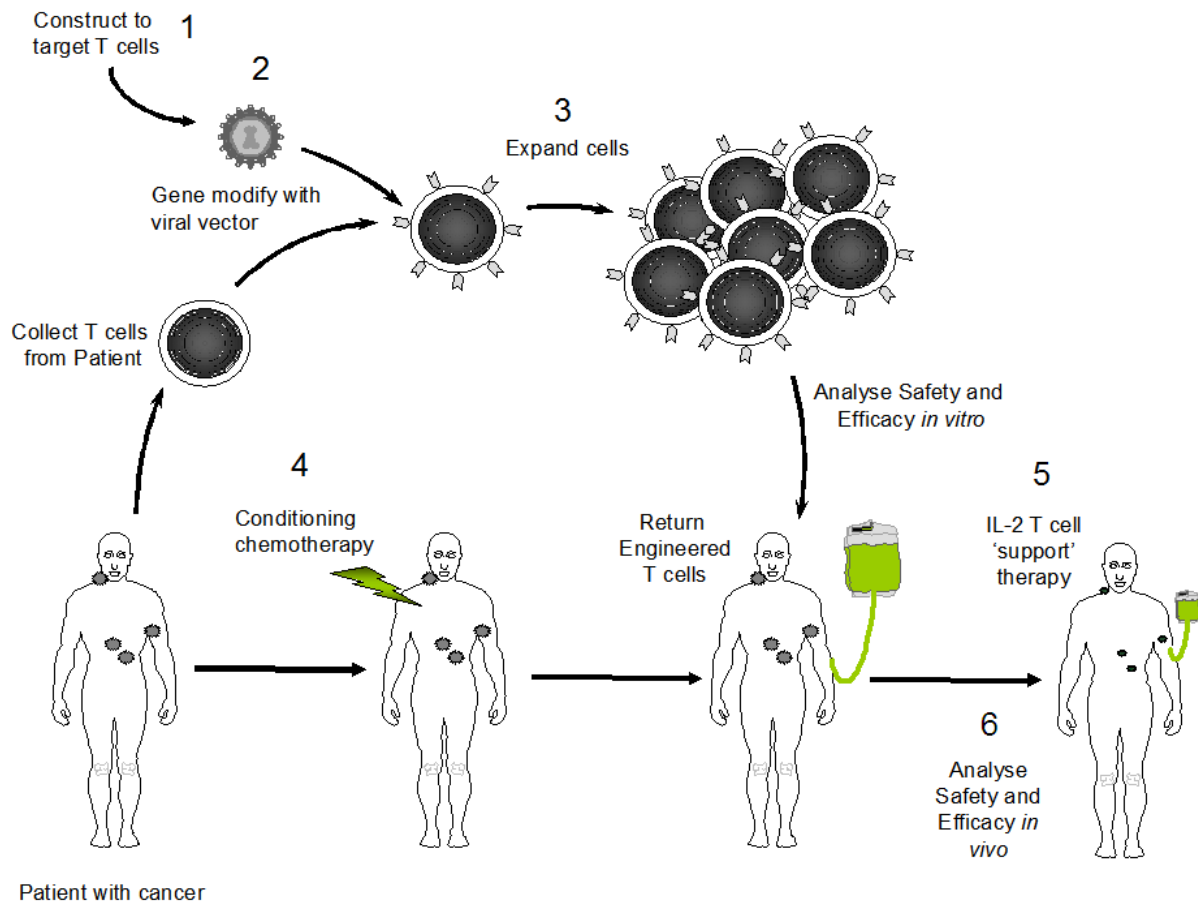


Figure 1: Overall schema for trials of engineered T cell therapy indicating potential areas of optimisation to be undertaken within the *ATTACK* project.

1. Improved constructs.
2. Improved vectors.
3. Methods to expand / select cells.
4. Manipulation of the host environment to affect homing or persistence of cells.
5. Optimisation of supportive cytokine therapy to enhance persistence / efficacy.
6. Evaluation of safety and development of novel approaches to limit risk of toxicity.