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Adoptive Engineered T-Cell Trials to Achieve Cancer Killing (ATTACK)

Contract No.: 305863; EU contribution: € 6,000,000;
Total costs: € 8,260,833.60; Starting date: 01/12/2012;
Duration: 60 months

Background and Objectives

TARGETED NUCLEIC ACID DELIVERY by genetically engineering T-cells to target tumor-associated antigens expressed on malignant cells demonstrates extraordinary efficacy in preclinical models of advanced cancer,¹ and recent results confirm the clinical effectiveness of the treatment.^{2–5} However, the use of engineered T-cells is a challenging field, and key clinical and methodological questions remain unanswered. These include:

1. Is the approach active in common epithelial malignancies, as current trials have focused on melanoma and B-cell malignancies?
2. The production of optimized genetically engineered T-cells is critical, and the number and quality of cells can clearly influence the outcome. The choice of the T-cell subset(s) may also be important as they can engraft to different extents.

The aim of ATTACK is to exploit technology for nucleic acid delivery through the clinical testing of adoptive transfer of engineered T-cells to treat cancer and builds upon previous European Union-funded preclinical projects (from the 5th, 6th, and 7th framework programs, respectively, called Chimeric Eurocell, ATTACK, and ATTRACT). The consortium, which comprises a multidisciplinary and translational research group with wide-ranging relevant expertise, will initiate two landmark studies to (1) examine activity of engineered T-cells in esophagogastric cancer as an example of a hard-to-treat common epithelial cancer, and (2) undertake a randomized phase II study to determine whether an optimized cell production system improves the current clinical response rates in patients with metastatic melanoma treated with NY-ESO-1-targeted T-cells.

Approach and Methodology

The work plan is composed of three principle scientific Work Packages (WPs).

WP1 centers upon delivery of the two clinical trials targeting NY-ESO-1. Enrolment onto each trial requires patients to be HLA-A*0201 positive and their tumor to be NY-ESO-1 and/or LAGE positive.

Trial I: A Phase II Clinical Trial to Assess the Activity of NY-ESO-1-Targeted T-Cells in Advanced Oesophago-Gastric Cancer

This trial aims to evaluate the activity of engineered T-cells to target NY-ESO-1 in esophagogastric cancer for three reasons:

1. NY-ESO-1 is considered one of the best targets for immunotherapy.⁶
2. There is preliminary clinical data in patients with both melanoma and synovial sarcoma.³

3. There is good evidence of NY-ESO-1 antigen expression in esophagogastric cancers.

Success in this trial will indicate substantial activity of adoptive cellular therapy in a common epithelial malignancy that is difficult to treat by conventional means.

Eligible patients ($N = 28$) will be pretreated with cyclophosphamide and fludarabine. Cells will be transduced and expanded using standard protocol (Fig. 1). Patients will be given IL-2 after cell infusion. If there are eight or more Response Evaluation Criteria in Solid Tumors (RECIST)-defined responses, then the treatment is showing substantial activity in this hard-to-treat disease and is worthy of future development.

Trial II: A Randomized Phase II Study in Metastatic Melanoma to Evaluate the Efficacy of Optimized Cell Production Protocols

Engineered T-cells targeting NY-ESO-1 have already shown substantial activity in metastatic melanoma,³ and we aim to test this further in a multicenter phase II study comparing standard methods of cell production (as shown in Fig. 1) (Arm 1) with an optimized method of cell production (Arm 2). The optimized production is expected to produce cells with better engraftment capability and thereby greater clinical activity. The basic clinical aspects of the trial will be similar to Trial I. A total of 42 patients will be randomly allocated to either one of these two treatment arms. The arm with the best RECIST-defined response rate will be used for future development.

WP2 focuses on GMP-compliant cell production and particularly freezing of cells for use in multicenter trials. We also aim to develop a novel automated system for cell production, which will facilitate future larger scale use and testing of adoptive engineered T-cell therapy.

WP3 is concerned with assay standardization and laboratory monitoring of the two clinical trials with the aim of determining markers of therapeutic benefit and potential predictive markers of response.

Main Findings

WP1: Clinical Trials

Trial I. Study regulatory approvals have been obtained. The trial opened to patient recruitment in the United Kingdom in October 2014. Twenty-two patients have consented to prescreening and, of these, 11 have been classified HLA-A2 positive. Four of these 11 patients have been identified as NY-ESO-1 and/or LAGE positive and thus considered eligible for the trial. The first patient is expected to be treated in Q1 2015. Karolinska University Hospital in Sweden will be the next clinical site to open to Trial I patient recruitment, followed by trial opening in the remaining European sites.

Trial II. Clinical site(s) setup is in preparation and regulatory documentation is under development.

WP2: Good Manufacturing Practice Validation and Process Development

Cellular Therapeutics Ltd. (CTL), in combination with Amsterdam Biotherapeutics Unit “GMP adoptive cell therapy manufacturing companies,” has developed the GMP manufacturing process for NY-ESO-1 T-cells with support from Adaptimmune Ltd. and Miltenyi Biotech (MILTENYI). The

FIG. 1. Standard cell manufacturing process.

ATTACK consortium has gained ethics and regulatory approval for the use in the ATTACK clinical trials. CTL, in combination with MILTENYI, has developed the naïve and central memory-derived NY-ESO-1 T-cell product (NCM-NYESO-1 T-cells) in anticipation of the phase II randomized ATTACK trial, which is aimed at answering if less differentiated NCM-NYESO-1-specific T-cells are able to engraft better compared with an unselected peripheral blood mononuclear cell-derived product and clinically how this will impact upon patient outcome.

A second aim of WP2 is development of an optimized and highly automated process for T-cell selection, activation, transduction, and expansion. Development efforts at MILTENYI now enable the automated selection of CD62L-positive cells from fresh leukapheresis, their activation with a CD3/CD28 activation reagent (TransAct), and lentiviral transduction and expansion in a novel closed, stand-alone cell processing platform named the CliniMACS Prodigy. A comparative study reveals (1) that CD62L cells are an interesting starting population for T-cell transduction experiments, and (2) that the expansion of the T-cells in TexMACS medium with IL-7 and IL-15 yields highly functional cells. The CliniMACS Prodigy process will build the basis for a “next generation” of safe and standardized clinical-scale cell manufacturing of lentiviral-transduced T-cells.

WP3: Laboratory Monitoring

To date, activities have predominantly focused upon the standardization of the research assays. The immunohistochemical detection of NY-ESO-1/LAGE antigen in tumor sections has been set up and validated, including indication of expression score. The detailed protocol has been distributed to participating clinical sites for local implementation.

The reagents and protocols for both the fluorescence correlation spectroscopy and real-time polymerase chain reaction assays for the monitoring of immune status and persistence of infused engineered cells have been received and tested at the central monitoring facilities.

Expected Outcome

Success in these trials will enable ATTACK members, and others, to carry out larger trials and potentially lead to an approved treatment for multiple cancer types.

The inclusion of a major industrial partner focused on cell therapy technology and three small and medium enterprises focused on the delivery of cell therapy will facilitate future development of this area. The project also plans to further automate and streamline cell processing to facilitate future trials and enhance European expertise and competitiveness in an important emerging market.

Major Publications

None reported yet.

Coordinator: Prof. Robert Hawkins, rhawkins@picr.man.ac.uk

Partners: The ATTACK consortium brings together 14 partners from 6 countries.

Robert Hawkins and **David Gilham**, University of Manchester, United Kingdom.

Stefan Sleijfer, **Cor Lamers**, and **Reno Debets**, Erasmus MC, The Netherlands.

Rolf Kiessling, Karolinska Institutet, Sweden.

Fiona Thistlethwaite and **Paul Lorigan**, Christie NHS Foundation Trust, United Kingdom.

Naomi Taylor, Institut National de la Santé Et de la Recherche Médicale, France.

Ryan Guest, Cellular Therapeutics Ltd., United Kingdom.

David Chao, Royal Free Hospital, United Kingdom.

Mario Assenmacher and **Andrew Kaiser**, Miltenyi Biotec GmbH, Germany.

Ton Schumacher and **John Haanen**, The Netherlands Cancer Institute—Antoni van Leeuwenhoek, The Netherlands.

Bastiaan Nuijen and **Joost van den Berg**, Amsterdam Biotherapeutics Unit, The Netherlands.

Bent Jakobsen and **Tom Hildich**, Adaptimmune Limited, United Kingdom.

Daniel Hochhauser and **Emma Morris**, University College London, United Kingdom.

Rolf Kiessling and **Roger Tell**, Karolinska University Hospital, Sweden.

Anna Mondino and **Chiara Bonini**, Ospedale San Raffaele, Italy.

Website: www.attack-cancer.eu

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Phase I/II Gene Therapy Trial of Fanconi Anemia Patients with a New Orphan Drug Consisting of a Lentiviral Vector Carrying the *FANCA* Gene: A Coordinated International Action (EuroFancolen)

Contract No.: 305421; EU contribution: € 5,380,169.75;
Total costs: € 7,002,945.20; Starting date: 01/01/2013;
Duration: 60 months

Background and Objectives

FANCONI ANEMIA (FA) is a rare inherited syndrome characterized by the early development of bone marrow failure and increasing predisposition to cancer with age. Allogeneic hematopoietic cell transplantation is the only curative therapy for hematopoietic manifestations of FA, although associated with complications arising from myeloablation, graft versus host disease, and increased

incidence of squamous cell carcinoma. The genetic correction of autologous hematopoietic stem cells (HSCs) with lentiviral vectors (LVs) has been proposed as a safe alternative for the treatment of different genetic diseases affecting mature cells from different tissues and/or committed progenitors of the hematopoietic system. One of the key features of FA that make it a unique disease for gene therapy approaches relies on the characteristic proliferation defect that is already evident in the very primitive HSCs. Thus, a marked survival advantage would be expected from corrected HSCs, potentially allowing normalization of hematopoiesis in the absence or after mild conditioning. Difficulties in the collection of sufficient numbers of HSCs from FA patients and the use of sub-optimal transduction protocols with gammaretroviral vectors limited the success of FA gene therapy trials conducted 10 years ago. The main goal of this project is to develop an efficient and safe gene therapy of FA based on two recent innovations: (1) discovery of potent HSC mobilizers, such as plerixafor, and (2) development of a new LV by members of this consortium, designated as “orphan drug” by the European Commission in December 2010.

The principal objective of this project is the development of a phase I/II gene therapy trial for FA-A patients, based on the genetic correction of plerixafor plus G-CSF–mobilized HSCs with a novel FA LV, accompanied by comprehensive and groundbreaking safety and efficacy patient-monitoring studies.

Approach and Methodology

The project is structured in six different Work Packages (WP).

WP1 aims to characterize the genetic and hematopoietic defects of FA patients to facilitate the recruitment for the clinical trials that aim (1) to collect an improved number of HSCs (WP2) and (2) to infuse gene-corrected HSCs in FA patients (WP4).

WP2 aims to implement an optimized procedure for the collection of HSCs from FA patients using an efficient HSC mobilization regimen with plerixafor combined with G-CSF.

WP3 aims to validate the efficacy and safety of clinical GMP batches of the therapeutic LV that will be used in the clinical trial.

WP4 aims to investigate the safety and the efficacy of the infusion of autologous CD34⁺ cells transduced with the therapeutic LV carrying the *FANCA* gene (the orphan drug) in FA-A patients.

WP5 carries out the actions for achieving the maximum exploitation and diffusion of EUROFANCOLEN project results.

WP6 aims the appropriate management of the project, together with an adequate dissemination and exploitation of the project results, the convenient management of intellectual property, the assurance of all ethics issues, and finally the development of a convenient gender action plan.

Main Findings

Identification of mutations in FA genes: Pathogenic mutations in 20 out of 22 FA patients have been identified.

Assessment of the safety and efficacy of plerixafor plus G-CSF–mediated mobilization of CD34⁺ cells: A clinical trial