product. Together, these data will enable further development of the therapy through clinical trials to demonstrate efficacy, and will support regulatory approval and commercial launch. Our aspiration for this therapy, should we find that it is safe and effective, is for it to become the standard of care in the EU within the next 15–20 years.

The prospective study that is collecting data and samples from women who experience severe early-onset FGR will be the first database/biobank of its kind to concentrate on this condition from when women first have a diagnosis made. The study will be a rich source of data to explore both short- and long-term maternal and neonatal morbidities of this condition. It may also generate novel biomarkers that could be used to predict prognosis of severe early-onset FGR at the time of diagnosis.

Major Publication

Spencer RN, Carr DJ, David AL. Treatment of poor placentation and the prevention of associated adverse outcomes—what does the future hold? *Prenat Diagn* 2014;34:677–684.

Coordinator: Dr. Anna David, a.david@ucl.ac.uk

Partners: The EVERREST consortium brings together 10 partners from 5 countries.

Anna David, University College London, United Kingdom.
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Richard Ashcroft, Queen Mary University of London, United Kingdom.

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Mutanome Engineered RNA Immunotherapy (MERIT)

Contract No.: 601939; EU contribution: € 5,964,250;
Total costs: € 7,794,995.47; Starting date: 01/06/2013;
Duration: 36 months

Background and Objectives

THE MUTANOME ENGINEERED RNA IMMUNO-THERAPY (MERIT) project aims to clinically and industrially validate a pioneering RNA-based immunotherapy concept that targets individually expressed tumor antigens and tu-

mor-specific mutations in patients suffering from triple-negative breast cancer (TNBC). This biomarker-guided, personalized therapy is a collaborative effort of five partners from academia and industry, funded by the European Union's Seventh Framework Programme (FP7) and led by BioNTech AG.

TNBC is an aggressive cancer that accounts for 15–20% of all breast cancer patients and is defined by the lack of estrogen receptor and progesterone receptor and the absence of HER-2 overexpression.¹ The 5-year survival rate is less than 80%.² The molecular heterogeneity across TNBCs results in a lack of common targetable molecular alterations, and thus targeted therapies frequently fail to provide clinical benefit. Encouragingly, recent studies report a high immunogenicity of TNBC tumors.³ Moreover, TNBC tumors express various numbers of specific antigens and are characterized by a moderate frequency of tumor mutations.⁴ The MERIT consortium therefore proposes to meet the unmet medical need of TNBC patients by inducing an integrated antitumoral immune response directed against both shared and mutated tumor antigens on a single-patient basis.

The major objective of the MERIT project is to assess in a phase I/II trial, the clinical safety, feasibility, and biological efficacy of a completely novel next-generation sequencing (NGS)-guided, individually engineered, and on-demand-manufactured RNA vaccine approach to treat cancer.

Secondary objectives are (1) to develop a computational medicine platform to allow for rapid identification of immunogenic shared and mutated antigens in patients with TNBC, (2) to set up an RNA vaccine warehouse of shared tumor antigens addressing >95% of TNBC patients and a manufacturing process for timely on-demand manufacturing of a personalized RNA vaccine targeting multiple tumor-specific mutations, (3) to study associated biomarkers to identify molecular and immunological signatures that correlate with clinical events following treatment, and (4) to identify synergistic compounds and optimized protocols of MERIT vaccines.

Approach and Methodology

The personalized treatment consists of (1) a vaccine containing “off-the-shelf” mRNAs selected from a presynthesized mRNA vaccine warehouse (MERIT WAREHOUSE) that encode tumor-specific antigens expressed in the respective patient's tumor and (2) a vaccine containing mRNAs engineered on-demand that encode patient-specific sequence stretches incorporating nonsynonymous mutations (MERIT MUTANOME). Before treatment, every patient's tumor will be profiled to select the suitable shared tumor antigens and identify mutations. To this end, we apply exome sequencing by NGS and qPCR in a clinical-grade processes for the rapid determination of individual tumor antigen signatures and mutations. The output of the profiling will be a patient-specific list of confirmed expressed antigens and immunogenic mutations. Based on this list, a cutting-edge platform technology will be used for the rapid design, manufacture, and release of fully tailored, pharmacologically optimized, GMP-grade RNA vaccines.

The mRNAs are administered intravenously as a nanoparticulate lipoplex formulation and are selectively delivered to splenic antigen-presenting cells (APCs). The

encoded antigens are translated into proteins that are rapidly processed and presented as peptides on the surface of APCs, which in turn leads to the induction of antigen-specific T-cell responses.

The WAREHOUSE concept is based on RNA drug products that target shared tumor-associated antigens and that are shelved in a warehouse. The novelty of this WAREHOUSE concept is that each patient will receive a tailored selection (“cocktail”) of RNAs from a pre-equipped RNA warehouse that fits the confirmed antigen expression pattern of the patient’s tumor. The MUTANOME concept is based on the identification of tumor-specific mutations by NGS and on-demand RNA manufacturing for use in individual patients to target neoantigens derived from mutated epitopes. T-cells specific for mutated antigens may be less hampered by negative thymic selection, making these antigens ideal candidates for vaccine development.

Main Findings

In the first 18 months of the project, most of the work was dedicated to (1) setting up an TNBC-specific RNA vaccine warehouse of shared tumor antigens, to (2) manufacturing the MERIT warehouse RNAs and performing stability testing, to (3) establishing a targeted screening for the presence of shared tumor antigens in patient tumors and to optimizing the clinical screening process for genome-wide tumor somatic mutations, and to (4) preparing trial documents and organizing trial operations.

Tumor-associated antigens were selected based on their selective expression profile in TNBC and their immunogenic potential. The RNA drug products were manufactured and tested in compliance with GMP regulations. The drug products are stored as independent batches; stability studies are currently conducted to determine their shelf-life.

A comprehensive set of experiments was performed to support the risk–benefit assessment of first-in-man testing and to obtain primary pharmacodynamics data in animal models.

In addition, BioNTech has developed a process for testing of MERIT WAREHOUSE target mRNA expression in tumor samples, which enables fast, accurate, and precise determination of the relative expression levels of the nine target antigens under investigation. Furthermore, we have been able to establish a clinical process to find mutations and characterize them based on expression, protein impact, and predicted immunogenicity.

Because the setup of this innovative concept of immunotherapy in a European multicenter study requires the close collaboration of the consortium with national and European regulatory agencies, a formal scientific advice from the Paul-Ehrlich-Institut (PEI) in Langen, Germany, was necessary for the preparation of the clinical trial. After the PEI agreed with the basic concept and the scientific rationale of the MERIT approach as well as with the design and procedural concept of the clinical trial, further steps were taken to start the clinical trial: clinical documents (like the Investigator’s Brochure, the Investigational Medicinal Product Dossier, the Clinical Study Protocol, the Informed Consent Form, and the patient information) were prepared and submitted for approval in November 2014.

Expected Outcome

The MERIT project aims to test a new therapeutic rationale and implement individualized medicine, along with the entire drug development process, including logistics, diagnostics, drug production, regulatory aspects, and patient management. This pioneering work takes personalized medicine from stratified medicine to the next level. Instead of searching for targets in the small common denominator shared by all patients, the MERIT approach exploits the large unique antigenic target repertoire of each single individual patient. This is a paradigm shift that opens up new opportunities to solve critical problems in current cancer drug development by addressing broad interindividual variability and intratumor clonal heterogeneity.

Successful completion of this trial may pave the way for future clinical development of a new class of immunotherapy applicable for a majority of European patients. If successful, MERIT will translate high-level scientific knowledge into innovative products directed toward more efficacious cancer immunotherapies. The MERIT project is expected to have scientific, social, and regulatory impacts.

Scientific and technological impact

Synthetic and recombinant RNAs have a huge potential as vaccines and are prime candidates to become part of the most important vaccine technology platform in the 21st century. The scientific and technological lead of RNA platforms and RNA vaccines will be further increased by MERIT. With the aim to master the regulatory, technical, and clinical requirements associated with the paradigm shifts of a rationally designed individualized therapy, the MERIT consortium may contribute strongly to contemporary medical and operational best practice.

Social and health impact

This project aims at improving survival of patients with TNBC. The applied RNA immunotherapy is expected to have a highly favorable risk–benefit ratio and thus to profoundly serve high unmet medical needs. Additionally, if proof of concept for personalized vaccines is provided for TNBC, this is also relevant for other tumor entities and potentially for personalization of medicines in general. As a versatile and easily adaptable technology blueprint, the MERIT approach will motivate analogous studies in patients with other tumors. Therapy approaches by treating physicians will be influenced by the new chances and challenges of the patient-centric tailored approach. If the current paradigm of tumor heterogeneity as a major hurdle for the efficacy of therapies is correct, personalized RNA vaccines targeting multiple shared tumor antigens and individual tumor mutations could become “game changers” that exploit unique genetic tumor alterations for the sake of patients.

Regulatory impact

Regulatory frameworks for novel concepts such as biomarker-assisted trials and individualized drugs are urgently needed. The dialog with the regulatory authorities concerning the unprecedented clinical development path for variant drug products tailored for individual use has been already initiated by the MERIT consortium partners.

Major Publications

None reported yet.

Coordinator: Prof. Ugur Sahin, ugur.sahin@biontech.de

Partners: The MERIT consortium brings together 5 partners from 5 countries.

Ugur Sahin, CEO BioNTech AG, Germany.

Laurence Zitvogel and **Fabrice André**, Gustave Roussy Comprehensive Cancer Center, France.

Kris Thielemans and **Jacques De Greve**, Vrije Universiteit Brussel, Belgium.

Thomas Kundig and **Steve Pascolo**, University Hospital of Zürich, Switzerland.

Tobias Sjöblom, Uppsala University, Sweden.

Henrik Lindman, Uppsala University Hospital, Sweden.

Website: merit-consortium.eu

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A Clinical Trial of Gene Therapy for Mucopolysaccharidosis VI, a Severe Lysosomal Storage Disorder (MeuSIX)

Contract No.: 304999; EU contribution: € 5,995,041;
Total costs: € 7,877,621.40; Starting date: 01/12/2012;
Duration: 60 months

Background and Objectives

MUCOPOLYSACCHARIDOSIS VI (MPS VI) is a rare lysosomal storage disease caused by deficient arylsulfatase B (ARSB) activity. Clinical manifestations include hydrocephalus, spinal cord compression, corneal clouding, hearing loss, coarse facial features, macroglossia, heart valve disease, cardiomyopathy, respiratory insufficiency, hepatosplenomegaly, inguinal and abdominal hernias, dwarfism/growth retardation, skeletal dysplasia, and joint stiffness. Cognitive functions are usually normal, although physical and visual impairment may limit psychomotor performance.

The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved enzyme replacement therapy (ERT) with recombinant ARSB (galsulphase; Naglazyme; BioMarin Pharmaceutical Inc.) for the treatment of MPS VI. However, current clinical evidence shows that ERT has limitations: (1) efficacy is very limited in some tissue types, (2) weekly intravenous infusions are needed to achieve disease amelioration, and (3) elevated costs make treatment inaccessible for many patients.

Gene therapy has the potential to provide a more effective, long-term solution for MPS VI: a single administration of adeno-associated viral (AAV) vectors targeting the liver can provide a lifelong source of ARSB.

Nonclinical studies in rodent and feline models of MPS VI showed that a single administration of AAV vector serotype 8 (AAV2/8) encoding ARSB converts the liver into a factory organ, which provides enzyme for systemic distribution, and results in biochemical, pathological, skeletal, and functional improvements.^{1–6} Treated MPS VI cats showed stable, within the normal range, levels of circulating ARSB activity, up to 6 years postinjection without immune responses (Ferla and Auricchio, unpublished data).

Encouraged by these ground-breaking nonclinical results, the MeuSIX consortium will conduct a multicenter phase I/II clinical trial to investigate the safety and efficacy of AAV-mediated gene therapy in patients with MPS VI. Orphan drug designation for the use of MPS VI therapeutic AAV vector has been obtained from both the EMA and the U.S. FDA.

To achieve this goal, MeuSIX has the following objectives:

1. to produce AAV2/8.TBG.hARSB vector for a gene therapy human clinical trial, according to Good Manufacturing Practice (GMP);
2. to perform nonclinical pharmacological and toxicological studies using the AAV2/8.TBG.hARSB vector;
3. to design a phase I/II clinical trial, in which the GMP vector is tested in MPS VI patients, to generate data related to pharmacokinetics, pharmacodynamics, safety, and efficacy;
4. to produce and file the documents required to obtain authorization from regulatory authorities to execute a phase I/II clinical trial; and
5. to perform a multicenter phase I/II clinical trial to investigate the safety and efficacy of AAV2/8.TBG.hARSB gene therapy for MPS VI.

In conclusion, MeuSIX has been designed to investigate the safety and efficacy of intravascular administrations of AAV2/8 in MPS VI patients. Positive results from this phase I/II study will support an eventual licensure of AAV2/8.TBG.hARSB for the treatment of MPS VI.

Approach and Methodology

The approach initially focuses on the production of GMP AAV2/8.TBG.hARSB vector and on investigation of the safety and efficacy of the vector in animals. In parallel, the consortium will generate all the necessary paperwork for the production and filing of the required regulatory documents for authorization to perform the trial, including request for protocol assistance to the EMA to appropriately develop strategies regarding the clinical aspects of the study; request for the authorization of the clinical sites to the