ConsulTech is a consulting company founded in 1992. Since then, we have been supporting biotechnology, pharmaceutical and medical technology companies as well as research institutions with the entire process of setting-up and executing proposals for R&D projects. In projects funded by the European Commission, ConsulTech supports the coordinator by resuming administrative tasks allowing coordinators and partners to fully concentrate on the scientific and technical success of the project. We solve financial and administrative issues, organise meetings, take care of the timely delivery of milestones and reports and much more.

We are partner in the **MIRACLE project** (www.miracle-fp7.eu), an FP7 ICT project dealing with the development of a device that automatically isolates and characterizes occult tumour cells. Our latest project is the **EUROCALIN project** (www.eurocalin-fp7.eu) an FP7 HEALTH project aiming at the development of a protein as a pharmaceutical including production development and early clinical trial.

MIRACLE (**M**agnetic **I**solation and molecula**R** **A**nalysis of single **C**ircu**L**ating and disseminated tumour c**E**lls on chip) is a collaborative project between 13 partners from universities, research institutions and companies from all over Europe. It is co-funded by the European Commission by 7 Mio € within the 7th Framework Programme and has started on September 1st, 2010:

Cancer remains a prominent health concern afflicting modern societies. Continuous innovations and introduction of new technologies are essential to level or even reduce current healthcare spending. As the analysis of circulating tumour cells in blood (CTCs) or disseminating tumour cells in bone marrow (DTCs) is most promising in this respect, MIRACLE aims to develop a low-cost, fully automated, integrated lab-on-a-chip (LOC) system for the isolation, counting and characterization of such occult tumour cells starting directly from clinical samples.

Traditional cancer therapy is based on the biology of the primary tumour. However, it is usually the tumour dissemination to other parts of the body that results in a negative prognosis and death. Occult tumour cells persisting in the body after primary therapy, in a dormant or low proliferative state, are responsible for disease relapse. Such cells, not detectable by current routine diagnostics, likely play a pivotal role as they may change biology and marker expression compared to the primary tumour. For this reason, the detection and characterization of CTCs and DTCs of cancer patients are believed to be of high therapeutic and prognostic importance. Already, the number of CTC is being used within clinical trials as a basis for early therapy stratification and monitoring instead of, or in comparison to, expensive and adverse radiological imaging techniques which are informative only at later follow up time points. Diagnosis and/or characterisation of occult tumour cells is believed to enable the clinician to exchange an inefficient therapy regimen at an early time point, thus addressing an individualised therapeutic approach, coined as theranostics.

Individualized monitoring of cancer metastatis is a prominent concern of clinicians and cancer biologist during cancer therapy.

The vision of MIRACLE is to develop the first automated system that can isolate viable circulating tumour cells (CTC's) from blood with high purity and perform multigene-analysis for individual CTC's. The high specificity, sensitivity & flexibility of CTC analysis will allow accurate early prognosis for metastasis and will foster fundamental studies on metastasis at single cell level.

A major challenge for occult tumour cell detection is their extremely low concentration (down to below a single cell per mL of blood or bone marrow in the midst of millions of leukocytes and even more red blood cells). Current detection methods are often based on enrichment techniques followed by cumbersome microscopic analysis of the cell phenotype. For CTC, some of these procedure steps have already been semi-automated, but the interpretation of the cell morphology requires expertise and remains subjective to a certain extent.

In contrary to standard phenotyping tests, MIRACLE aims to develop a fully automated

and integrated microsystem providing the genotype (gene expression profile) of CTCs and DTCs starting from clinical samples. This requires the integration and automation of all sample pre-processing steps including the enrichment, counting, electrochemical characterization and genotyping of the cells. This envisaged, fully-automated MIRACLE test would yield decisive results fast and cost-effective, as compared with contemporary diagnostics tests that may take days.

The MIRACLE's consortium is uniquely positioned to lead the project's main objectives to a successful outcome, well ahead of the current state-of-the-art. Combining the team's multidisciplinary and unique expertise avoids unnecessary overlap while maintaining the entire process flow from sample preparation to detection. Integrating all components into a fully operational single LOC platform will represent an immense advance for Europe to cope with interfacing and integration problems generic to microfluidic and smart miniaturized systems. More importantly, the realisation of the MIRACLE vision will revolutionise cancer diagnostics and individualized theranostics.

The MIRACLE project requires inputs from molecular biology, biosensor, micro- and nanotechnology, microfluidics as well as from system integration technology for the successful achievement of its challenging objectives. The execution of the different tasks will be carried out in parallel. It is important to note that the proposed microsystem is a generic platform using breast and prostate cancer as model system that will be demonstrated within the MIRACLE IP, but the proposed technological platform has immense application in, for example, the fields of pathogen detection, stem cell isolation as well as foetal cell isolation from maternal plasma .

As the different tasks are largely multidisciplinary, comprising both technological and biological input, the approach taken will result in the necessary cross-fertilisation between the different disciplines. Both the individual modules, as well as the integrated platform will be compared to their classical counterparts and will be evaluated using clinical samples. To achieve the challenging goals within MIRACLE, the total workload is divided into 10 work packages

Within this project, 14 partners from all over Europe work together to make this MIRACLE happen. Visit the project's homepage:

www.miracle-fp7.eu

Interuniversitair Micro-Electronica Centrum VZW, Belgium

Universitat Rovira i Virgili, Spain

Institut für Mikrotechnik Mainz GmbH, Germany

MRC Holland B.V., The Netherlands

Oslo Universitetssykehus HK, Norway

THINXXS Microtech-nology AG, Germany

ConsulTech GmbH, Germany

Kungliga Tekniska Hoegskolan, Sweden

MultiD Analyses AB, Sweden

Fujirebio Diagnostics AB, Sweden

European CanCer Organisation, Belgium

Labman Automation Ltd., United Kingdom

ICsense, Belgium

EUROCALIN is a drug development collaboration between 10 distinct companies and academic institutions across Europe and is co-funded by the European Commission under its FP7 HEALTH program with 6 Mio €.

EUROCALIN is an acronym for "EUROpean Consortium for AntiCALINS as next generation high-affinity protein therapeutics". The goal of the collaboration is to develop a potential treatment for anemia into and through the first stage of clinical evaluation. The project started in August 2011 and will continue for four years.

Anticalins® are novel, next generation therapeutic proteins designed to bind and antagonize a wide spectrum of ligands. As funded by the grant, the consortium will develop, manufacture and clinically test an Anticalin specific for hepcidin, a small peptide circulating in human blood that is considered to be a key regulator of iron homeostasis and, therefore, an important target for the treatment of multiple types of anemia. This Anticalin, called PRS-080, is the proprietary discovery of Pieris AG, an independent biotechnology company. Pieris has developed the PRS-080 molecule to the proof-of-concept stage and will oversee the consortium's progress as project coordinator.

The Disease

The therapeutic target for the PRS-080 molecule and the EUROCALIN Consortium is a disease pattern termed anemia of chronic disease (ACD). This is a condition marked by a deficiency of red blood cells or of hemoglobin in the blood, resulting in pallor and weariness. Under certain conditions (such as chronic infection, chronic immune activation, or malignancy) iron - which carries oxygen in red blood cells - is reduced in the body.

The major pathophysiological factor in ACD is retention of iron, rendering the metal ion unavailable for generation of red blood cells (erythropoiesis). Anemia in patients with chronic kidney disease (CKD) – a serious indication affecting approximately 4.5 million European patients - is often treated by administering erythropoiesis-stimulating agents (ESA) such as EPO.

Many patients with CKD and anemia can be effectively treated with ESA's. However, around 10 % of patients (~ 150,000 patients in the EU) are hypo- or non-responsive to ESA, leaving them without an effective treatment option. The important role of ESA resistance has been demonstrated by the results of clinical trials that reported an increased mortality or morbidity in patients who received high doses of ESA but did not reach the targeted hemoglobin plasma concentration. Increased mortality rates in anemic cancer patients treated with high ESA doses have recently been observed, raising yet additional safety concerns. In addition, the urgent need for new therapies to combat ACD is reflected by the fact that a large fraction (about 40-50 %) of anemic cancer patients are hypo or unresponsive to ESA therapy (~740,000 patients in the EU). Therefore, the development of alternative treatment strategies for ACD, specifically in patients with chronic kidney disease and cancer, is of utmost importance.

The exact mechanism of ACD is not fully understood but current results strongly suggest that a small protein, a peptide named hepcidin plays a very important role in regulating the iron balance in the body. Hepcidin is synthesized in the liver, enters the blood stream and binds tightly to the iron channel protein ferroprotein, which is found amongst others on the surface of reticulendothela cells. These cells store iron. If hepcidin therefore binds to ferroprotein it prevents the secretion of iron, thereby functionally reducing iron absorption. As a consequence, the body cannot effectively use iron to make new red blood cells and the number of healthy new red blood cells gradually falls.

The projects goal is to tackle ACD by binding hepcidin to the PRS-080 Anticalin. Anticalin-bound hepcidin is unable to block ferroprotein and iron can be put back into the blood system.

The project

The consortium aim to develop and produce the PRS-080 Anticalin®, a novel high-affinity, non-immunoglobulin protein derived from the

lipocalin protein family, to target and antagonize hepcidin. Hepcidin is a small peptide circulating in the human body and is thought to be a key negative regulator of iron homeostasis. The therapeutic goal of PRS-080 is to block hepcidin and thereby increase the systemic availability of iron in the circulation and, in turn, increase hemoglobin levels in patients suffering from anemia of chronic disease (ACD). ACD, the most frequent anemia found in hospitalized patients, develops in subjects suffering from infections, inflammatory and autoimmune disease, cancer and chronic kidney disease.

Anticalins are novel, non-immunoglobulin, next generation therapeutic proteins designed to bind and antagonize a wide spectrum of ligands. The PRS-080 in particular displays numerous features critical for inhibiting hepcidin-mediated hypoferremic effects, including:

- binding of the relatively small hepcidin target with high affinity and specificity within the Anticalin pocket
- favourable safety and tolerability
- adjustable half-life
- low production costs

The EUROCALIN consortium's goal is to develop a safe and effective hepcidin-specific Anticalin drug for the treatment of anemia of chronic disease (ACD).To achieve the overall goal, the consortium members will address and answer several key scientific and technical questions, which are broken down into the following specific and interdependent work packages.

In this project, 10 partner institutions (3 research institutions and 7 companies) will work together to prepare for, commence and complete initial clinical development of PRS-080, a novel Anticalin therapeutic for the treatment of anemia of chronic disease (ACD).

All partners have outstanding research and development capabilities in their respective field. Their expertise – as demonstrated by numerous publications and patent applications – will contribute to the success of the project. Visit the project's homepage for more information:

www.euroclin-fp7.eu

Pieris AG,
Germany

Antitope Ltd.
United Kingdom

ConsulTech GmbH
Germany

Coriolis Pharma
Research GmbH
Germany

Covance Inc.
United Kingdom

FGK Clinical
Research GmbH
Germany

Fujifilm Diosynth
Biotechnologies UK Ltd.,
United Kingdom

Medical University Innsbruck
Austria

Radboud University
Nijmegen
Medical Center
Netherlands

Technische Universität
München
Germany