Adipokines as Drug Targets to Combat Adverse Effects of Excess Adipose Tissue

Executive summary:

Obesity represents the major risk factor for the cardiometabolic syndrome, which is an epidemic disease that generates a severe global socio-economic burden for the public health systems. Enhanced production of proinflammatory adipocytokines by expanded adipose tissue (AT) is now considered as a key event in the pathogenesis of this syndrome. This process involves i) the systemic release of adipokines, preferentially by visceral abdominal fat; and ii) the paracrine, adipokine-mediated crosstalk between periorganic fat and different organs including skeletal and cardiac muscle. Members of the ADAPT consortium have pioneered this novel view of AT as an active endocrine organ. However, there is very limited knowledge if adipokines and their downstream signalling pathways may represent drugable targets potentially opening new avenues to combat the devastating complications linked to obesity and the cardiometabolic syndrome. Therefore, the major goal of ADAPT was to identify novel or existing adipocytokines as drug targets that could be used to reverse obesity-associated inflammation and adverse reactions related to excess fat. Specific objectives of ADAPT were to:

i) characterise the cellular origin of adipokines and to identify novel members of this family;
ii) investigate the adipokine-mediated intraorgan cross-talk between different AT cell types and to determine how adipokines regulate adipocyte lipolysis and/or fatty acid oxidation resulting in changes of fatty acid release in obesity-induced inflammation to define potential drug targets;
iii) study the inter-organ crosstalk between AT and skeletal muscle and to define the functional implications of ectopic brown fat in the protection against adipokine-induced inflammation;
iv) better understand the pathophysiological relevance of periorgan fat with emphasis on epicardial fat and its implications for altered cardiac metabolism and cardiac function;
v) determine whether new adipokines are drugable targets, to perform pharmacological evaluation and virtual screening in order to identify new chemical tools; and
vi) harmonise the existing infrastructure for clinical studies on new targets and to validate in vitro data and animal data.

The jointly executed research programme provided a number of novel findings with substantial impact both for scientific progress in the field and the future development of novel anti-diabetic drugs. These findings include:
i) the identification and characterisation of new adipokines like follistatin, FGF, TRAP, chemerin, CCL5, CTSK, INHBA and CCL20;
ii) the prediction and testing of new LXR ligands by virtual screen;
iii) an advanced analysis on the role of HSL in insulin sensitivity, resulting in the demonstration that a reduction in lipolytic capacity can reshape lipid fluxes and improve insulin sensitivity without modification of fat mass;
iv) the identification of serum amyloid A and CCL5 in the crosstalk between macrophages and fat cells;
v) the development of antibodies and ELISA assays for TRAP, a feedback signal between fatty acids and adipokines; and
vi) the clinical analysis of potential novel biomarkers like chemerin and cystatin C;

vii) the identification of PEDF as one of the most abundant proteins released by adipocytes;
viii) the description and jointly conducted analysis of DPP4 as a new adipokine potentially linking obesity to the metabolic syndrome;
ix) a detailed analysis of the role of hypoxia in adipokine production in both animal models and humans;
x) a new view on the crosstalk between preadipocytes and macrophages;
xii) novel clinical data on the analysis of cardiac mass and function in relation to abdominal and thoracic fat tissue depots, and
xiii) extensive investigations on the correlation of adipokine expression and clinical phenotypes.

Spreading of excellence was successfully carried out both in terms of public information and the generation of new knowledge presented at scientific meetings and published in high-ranking scientific journals. The ADAPT website has registered an increasing number of visits with up to 1000 visits per month. ADAPT has published more than 130 papers including 20 joint papers.

Project context and objectives:

ADAPT is a European Commission (EC)-funded collaborative project of top European laboratories focusing on AT as a major endocrine organ. The major goal of this project is to identify novel or existing adipocytokines as drug targets that could be used to reverse obesity-associated inflammation and adverse reactions related to excess fat. The multidisciplinary ADAPT consortium involves 11 partners and integrates basic and clinical science, bioinformatics, and in silico drug design. The research within ADAPT is organised in 4 tightly interacting research lines, as outlined below.

In light of substantial scientific evidence that proinflammatory adipokines are central to the initiation of pathophysiological processes related to excess fat, it must be considered as a great challenge to identify novel or existing adipokines as targets for drug design. For this purpose a multidisciplinary approach would be required that integrates expertise from diverse fields including basic and clinical science, bioinformatics, in silico drug design and the specific capacities of a large pharmaceutical company, as fullled by the ADAPT consortium. The overall concept involves four research lines that build up a stepwise strategy including (i) the identification of novel adipokines and the cellular sources and regulation of adipokine production, (ii) the analysis of intraorgan crosstalk within AT which plays a pivotal role in AT inflammation, (iii) the assessment of interorgan crosstalk with a focus on skeletal and cardiac muscle and the role of brown fat and (iv) the pharmacological and clinical evaluation of adipokines as drug targets and potential biomarkers.

The four research lines of ADAPT jointly addressed the following key topics:

RL 1 - Adipokine expression and secretion
- assessment of cell type specific adipokine production including subtypes of macrophages;
- regulation of adipokine production in the respective cell types, in particular by other adipokines and by fatty acids through lipolysis;
- discovery of novel adipokines.

RL 2 - Autocrine/paracrine role of adipokines and their link to inflammation
- understanding the communication of the different cell types within AT using adipokines;
- defining the use of adipokines by endothelial cells to remodel and re-vascularise AT in response to inflammation;
- effect of new adipokines and protective factors on the lipolytic process in AT.

RL 3 - The role of periorganic fat
- identification of specific adipokines produced by periorganic fat depots (pericardial, brown fat);
- assessment of the cross talk of the periorganic fat cells (muscle, heart) with the surrounding tissue cells (myocytes, cardiomyocytes);
- characterisation of the clinical role of epicardial fat.

RL 4 - Evaluation of drug targets
- definition of adipokines or steps in their signal transduction pathways suitable as drug targets;
- assessment of adipokine-directed antibodies or commercially available drugs models for treatment of adverse adipokine reactions;
- potential use of adipose gene expression of a particular adipokine as a predictor of adverse adipokine reactions in man.

Based on the research lines described above, the key objectives of ADAPT were to:

- characterise the cellular origin of adipokines and to identify novel members of this family;
- assess the regulation of adipokine production after dietary intervention in humans and under different controlled in vitro conditions;
- investigate the adipokine-mediated intraorgan cross-talk between different AT cell types and to determine how adipokines regulate adipocyte lipolysis and/or fatty acid oxidation resulting in changes of fatty acid release in obesity-induced inflammation to define potential drug targets;
- study the inter-organ crosstalk between AT and skeletal muscle and to define the functional implications of ectopic brown fat in the protection against adipokine-induced inflammation;
- better understand the pathophysiological relevance of periorgan fat with emphasis on epicardial fat and its implications for altered cardiac metabolism and cardiac function;
- determine whether new adipokines are drugable targets, to perform pharmacological evaluation and virtual screening in order to identify new chemical tools;
- harmonise the existing infrastructure for clinical studies on new targets and to validate in vitro data and animal data.

Project results:

WP 1.1 - Cellular origin of adipokines in AT

Objective
The main objectives of WP1.1 were to identify the cellular origin of adipokines and to broaden our knowledge on the diversity of products secreted by AT by using novel methods to detect and identify these factors.

Tasks and detailed achievements in WP1.1
Task 1: Cell source of adipokines within human adipose tissue (INST, GSK)
Human abdominal subcutaneous AT was obtained from overweight women undergoing plastic surgery. INST collected the native various cell populations from the stroma-vascular fraction and the mature adipocytes. A survey of transcript expression of adipokines was performed for each cell type using pangenomic Deoxyribonucleic acid (DNA) microarrays and reverse transcription-real-time polymerase chain reaction (rt-PCR). In parallel, isolated cells were maintained ex vivo in basal culture medium for 24 hours and their Conditioned media (CM) were collected and analysed to identify previously defined and novel adipokines using a shotgun proteomic approach (NanoLC/ESI LTQ-Orbitrap MS/MS).

Task 2: Novel methods for identification and detection of adipokines secreted from human AT (GDC, INST, CHAR, MHH)
INST used NanoLC/ESI LTQ-Orbitrap MS/MS for proteome coverage with maximum sensitivity and dynamic range of 24h culture media from different human AT cell types. GDC established an integrated proteomic platform using two complementary technics, i.e. 1DE-LC-ESI-MS/MS and 2DE-MALDI-MS, to allow comprehensive characterisation of the human adipocyte secretome (adipokinome). MHH developed new protocols to recover and detect complex large-size and lipophilic molecules by microdialysis in human AT. The relevance of adipokine secretion in/from AT with respect to insulin resistance and other metabolic abnormalities in obesity and diabetes has been investigated in prospective human clinical studies. CHAR and INST completed the studies.

WP 1.2 - Regulation of adipokine production
Objective
The main objectives of WP1.2 are to determine the factors influencing in vivo the secretion of adipokines, to investigate the relationship between adipokine expression/secretion and insulin sensitivity and to elucidate the mechanisms underlying the modulation of adipokine production in vivo in response to hormones, lipolytic products and hypoxia.

Tasks and detailed achievements in WP1.2
Task 1: Influence of obesity and fat distribution on adipokine secretion (INST, CHAR)
INST and CHAR compared SAT and VAT gene expression according to obesity, visceral fat accumulation, insulin resistance, and presence of the metabolic syndrome. CHAR recruited 56 women who were divided into 4 groups (lean, overweight, obese and metabolic syndrome). Anthropometric measurements, euglycemic hyperinsulinemic clamp, blood analysis and computed tomography scans were performed. Paired samples of subcutaneous and visceral fat were obtained and whole AT was used for gene expression analysis of macrophage-specific markers and adipokines by RT-qPCR (CHAR, INST). INST performed DNA microarray analysis on a subset of 8 patients per group.

Task 2: Determination of the regulation of adipokine expression and production at different time points in a multiple phase dietary intervention programme (CHAR, INST)
A multiple phase weight loss program composed of an energy restriction phase with a 4-week very-low-calorie diet and a weight stabilisation period composed of a 2-month low-calorie diet followed by 3-4 months of a weight maintenance diet has been performed at CHAR on 48 obese subjects. A thorough phenotypical characterisation was performed at each time point, including euglycemic hyperinsulinemic clamp and subcutaneous AT biopsy. INST and CHAR measured AT adipokine and inflammatory marker gene expression using DNA microarrays, evaluated adipokine secretion from biopsy-derived explants of the whole AT using LUMINEX technology, and quantified and quantitation of AT macrophage numbers. Messenger ribonucleic acid (mRNA) levels of the respective adipokines were also measured using microfluidic cards (CHAR, INST). Plasma levels of adipokines were measured in the entire group.

Task 3: Effects of AT lipolysis on adipocyte and stroma-vascular cell secretory activities (INST, KI, SU, GSK, PHYS)
INST conducted a series of in vitro experiments on human adipocytes and macrophage cell lines. Lipolytic challenges were performed on human hMADS adipocytes with an appropriate lipolytic agonist and the resulting conditioned-media were used to treat human THP1 macrophages. The activity of Hormone-sensitive lipase (HSL) and Adipose triglyceride lipase (ATGL) were knocked down using small interfering (siRNA) or inhibited using specific molecules in human hMADS adipocytes. KI generated CM from human mature adipocytes stimulated with different lipolytic agonists and conditioned medium from human AT explants incubated under basal (unstimulated) conditions. KI also obtained from UPMC conditioned medium from human subcutaneous AT macrophages to be tested for effects on the function of differentiated human fat cells. Finally, INST addressed the AT inflammatory profile and secretory capacity in HSL heterozygous mice (HSL+/-) and mice treated with a HSL inhibitor.

Task 4: Effects of hypoxia on adipocyte and stromal-vascular cell secretory activities (INST, UPMC)
INST tested hypoxic culture conditions (1% oxygen) on human subcutaneous AT mature adipocytes, maintained in fibrin gels or in sealed microchambers, and immunoselected macrophages (CD34-/CD14+ cells). Impact of the hypoxic conditions was studied on adipocyte metabolism (free fatty acid and glycerol release, glucose uptake and lactate release). Expression level of selected genes was measured by RT-qPCR in macrophage and adipocytes. UPMC assessed the effect of hypoxia on WAT gene expression in vivo using a model in which rats were progressively submitted to reduced barometric pressure in hypobaric chambers, until reaching the equivalent of 5500 m altitude. Quantitative RT-PCR-based gene expression analysis was performed in epididymal WAT, after 1 and 3 weeks of hypobaric exposure. UPMC also explored the effect of chronic hypoxia on AT macrophage accumulation as well as potential association with liver injuries (i.e NASH and fibrosis) in a clinical study with obese subjects.

WP 2.1 - Intraorgan crosstalk: Role of adipokines in AT inflammation

Objective
The main objective of WP2.1 is to investigate the adipokine mediated intraorgan cross-talk between AT cells. The subtypes of residing and infiltrating macrophages are explored. Their ability to produce common or subtype specific adipokines and interaction with residing fat cells is investigated. For endothelial cells cross-talk with the mature fat cells as well as their ability to induce angiogenesis of adipose tissue are studied. The cross-talks between preadipocytes, adipocytes and other adipose tissue cells (including macrophages) have been extended.
Tasks and detailed achievements in WP2.1

Task 1: Characterisation of the different macrophages in adipose tissue and their adipokine cross-talk with fat cells (INST, UPMC, KI, MAB, CHAR)

First partners (INST, UPMC, KI) pursued the generation of CM from adipose tissue cells used for macrophages, adipocytes and preadipocytes cultures. This has been extended to other adipose cell types as endothelial cells and mast cells. A protocol to isolate these very fragile mast cells from human adipose tissue has been developed by UPMC. CHAR also explored the methodology for quantification of adipose tissue macrophages and their subtypes in needle biopsy-derived samples of subcutaneous adipose tissue by flow cytometry (see D10). Moreover, INST prepared CM from human native subcutaneous adipose tissue macrophages that were applied to human mature adipocytes and their effects on adipocyte lipolysis and insulin-mediated up-regulation of lipoprotein lipase and fatty acid synthase as well as CCL20 expression were studied. Adipose tissue macrophage-CM did not modulate the basal or the stimulated lipolytic activities or the insulin-mediated up-regulation of LPL and FAS. It increased the adipocyte expression of CCL20 (Duffaut et al., 2010).

UPMC pursued the analysis of macrophages in adipose tissue depots by immunohistochemistry focusing on WAT fibrotic area. UMPc showed that both M1 (stained with CD40 surface markers) and M2 (stained with CD163 and CD206) types are located in fibrotic bundles found in human adipose tissue both located in omental and subcutaneous depots. Lymphocytes and mast cells were co-localised in these bundles. Adipocytes located in these fibrosis areas were of smaller size than adipocytes located in the parenchyma. These results suggest that these inflammatory cells might contribute directly or indirectly to fibrosis development and to adipocyte biology. The work on the characterisation of fibrotic depots in human WAT and association with inflammatory cells and obesity phenotypes was published (Divoux et al., Diabetes 2010). In addition, the work showing that weight loss induced by gastric surgery rapidly modifies the activation state of adipose tissue macrophages in obese subjects towards a less pro-inflammatory profile (i.e. decrease of CD40+ and increase of CD206+ cells counts after weight loss) was also published (Aron et al, JCEM 2009).

The adipocyte macrophage media crosstalk was addressed in the model of gastric surgery. Adipose tissue explants were prepared from 20 obese subjects before and 3, 6, 12 months after the surgical procedure and from lean subjects. This task was finalised for the following activities:

- The completion of analysis regarding the implication of adipokines in fat cells’ crosstalks and biology. Exploring preadipocyte genes induced by human macrophage media (WP2.1 task 3) revealed a strong upregulation of several mediators; as CCL5/Rantes, InhibinbetaA, and CXCL2, which was deeper explored (see task 2) for its interaction with endothelial cells. UPMC showed that CCL5 significantly triggers monocyte adhesion and transmigration to/through WAT endothelial cells perpetuating WAT inflammation. CCL5 protected macrophages from free cholesterol apoptosis allowing their lipid scavenging function to clear necrotic adipocytes, a process dependent on ERK and AKT pathway activation. This work shows that CCL5 is important in mediating adipocyte-macrophage cross talks (Keophipath, ATVB, 2010).

- The search of new targets involved in inflammation. UPMC and KI combined microarray analysis from lean and obese subjects (160 subjects) and from isolated adipocytes vs. SVF as well as from differentiated adipocytes with or without macrophage media. Bioinformatic analysis showed that a series of genes strongly expressed in isolated adipocytes are downregulated with obesity and in presence of inflammation.

- The impact of adipose tissue medium on inflammatory cell phenotype evaluated by UPMC and INST. INST studied the impact of CM of subcutaneous mature adipocytes on subcutaneous adipose tissue macrophage phenotype. Real time PCT experiments showed that adipocyte-derived secretions increased the expression of IL-6, MCP-1, MMP-9, TGFbeta and IL10. However this experiment did not alter the expression of VEGF-A and LYVE-1 (Bourlier et al., Plos One, 2012). UPMC showed that CM of adipose tissue obtained in obese subjects also induced a pro-inflammatory activation of blood monocyte-derived macrophages, characterised by a striking increase in IL1? and NLRP3 inflammasome gene expression.

Mabtech has developed new technologies (ELISpot and FluoroSpot) that enable sensitive measurement of secretion of a large number of pro-inflammatory (e.g. TNF-a, IL-1b, IL-6, IL-12, GM-CSF) as well as anti-inflammatory (IL-10, TGF-b) cytokines at the single cell level. With these techniques and using monocytes as a model for tissue macrophages it has been possible to define several functionally distinct subsets of cells as characterised by their cytokine secreting profiles (Smedman et al., Scand. J. Immunol. 2011). The same techniques have been demonstrated to work for the ex vivo analysis of macrophages derived from adipose tissue and will be used to provide a quantitative and qualitative characterisation of macrophages isolated from obese and lean subjects. In collaboration with KI, Mabtech has also developed new monoclonal antibodies against the TRAP protein which will enable a similar investigation of this protein. The same methods will also be applied for studying the cross-talk between adipose and immune cells where e.g. the effect of conditioned medium from adipocyte cultures on monocytes and macrophages and their secretion of pro- and anti-inflammatory
cytokines is investigated.

Task 2: Adipokine-mediated cross talk between vasculature and adipose tissue cells (INST, UPMC, CHAR, KI)
INST isolated the capillary endothelial cells (CD34+/CD31+) from the human subcutaneous adipose tissues from patients with distinct body mass index by the immunoselection/depletion method and their expression of various genes (angiogenic factors and receptors, adhesion molecules and chemokines, growth factors) are studied by real time PCR. CHAR explored the methodology for quantification of adipose tissue cells (incl. macrophages) in needle biopsy-derived samples of subcutaneous adipose tissue by flow cytometry (see task 1 and D10).

Similar studies were performed on endothelial cells isolated from paired biopsies from subcutaneous and visceral adipose tissues from obese patients. Visceral adipose tissue endothelial cells compared to subcutaneous ones were characterised by enhanced expression of inflammatory markers and angiogenic receptors (CCL20, CXCL8, ICAM-1) as well as angiogenic receptor (VEGFR2, Leptin Receptor and neuropilin 1 and 2) and senescent markers (IGFBP3). Immunohistochemical approaches showed also increased activation (ICAM1) and senescent state (gammaH2AX) of endothelial cells from visceral adipose tissues compared to subcutaneous ones (Villaret et al., Diabetes, 2010). KI has generated the recombinant TRAP proteins and variants thereof which are used in studies of adipocytes and endothelial cells. Methods for TRAP crosstalk between macrophages and fat cells are developed in collaboration with INST and it was shown that TRAP is expressed by human adipose tissue macrophages (Lang, Int J Obes, 2011). KI has identified SEMA3c as a fat cell-derived adipokine that stimulates extracellular matrix production from resident preadipocytes. In contrast to studies in mice, INST has shown that recombinant human SEMA3C has no effects on human endothelial cell proliferation. A joint manuscript from KI and INST detailing these as well as other findings is currently under preparation.

Task 3: Adipokine-mediated crosstalk between preadipocytes and macrophage subtypes (INST, UPMC, CHAR, KI)
Native progenitor cells population (CD34+/CD31- cells) is studied in vitro by INST. Media are tested to identify a minimal culture condition allowing the differentiation of the native progenitor cells into adipocytes. Several adipocyte differentiation markers, well described in mouse preadipocyte cell lines, are studied to identify true human adipocyte differentiation markers andpreadipocyte markers. In addition, CHAR explored the methodology for quantification of adipose tissue progenitor cells characterised by combination of CD markers CD 34+/CD31- and lymphocytes CD3+/CD4+ and CD3+/CD8+ in needle biopsy-derived samples of subcutaneous adipose tissue by flow cytometry (see also Task 1 and D10). Response of progenitor cells to dietary intervention was explored in a preliminary clinical study.

UPMC pursued the analysis of the experimental model using primary human preadipocytes cultured with secreted factors from monocyte-derived and adipose-tissue macrophages. These conditions lead to inflammatory preadipocytes with diminished adipogenesis and a profibrotic phenotype. Human inflammatory preadipocytes produce many inflammatory molecules and profibrotic mediators. In the previous 18-month report, UPMC showed that one of these players, inhibin beta A, has a mediating role in the production of profibrotic proteins by preadipocytes in contact with an inflammatory microenvironment (Keophiphath, Mol. Endoc 2009). Importantly in a collaborative work between INST, UPMC and a C Danis' group in Nice, they confirmed that Inhibin beta is also induced by obese adipose tissue and is expressed in several adipose cell types as macrophages (MolEndocrinol. 2009). This work published in Diabetes conferred additional role to the dimer of Inhibin beta Ai.e. Activin A and showed that this adipokine represents also a novel crucial player controlling self-renewal of human adipose progenitors. Activin A appears to be a critical mediator of inflammation secreted by macrophages and inflammatory preadipocytes accumulated in adipose tissue of obese subjects. To support this hypothesis, INST showed that ATM-derived factors and most specifically TGF?1 induced a myofibroblast-like phenotype of AT progenitor cells. Such an effect appeared to be mediated, at least in part, through the induction of INHBA/activinA expression by the progenitor cells. Moreover, native human AT progenitor cells exhibited an increased expression of myofibroblast markers including Snail and Slug, with obesity (Bourlier et al., Plos One, 2012) UPMC also pursued the bioinformatic analysis of the transcriptomic profile of the human preadipocytes treated by macrophages isolated from obese adipose tissue. Amongst the most over-expressed genes, were found genes corresponding to the functions chemokine signalling pathways with CXCL2 (see above) and ‘cytokine-cytokine receptors’ with G-CSF as a new candidate which role in adipose tissue biology remains to be deciphered.

WP 2.2 - Role of adipokines in the release of fatty acids from the inflamed adipose tissue

Objective
The main objectives of WP2.2 were to define how adipokines regulate fatty acid turnover (lipolysis and oxidation) including the molecular mechanisms involved and whether fatty acids influence adipokine secretion/function. In addition, a main task was to evaluate novel drug targets in human and animal models.
Tasks and detailed achievements in WP2 2

Task 1: Interactions between Tumour necrosis factor (TNF)-alpha, CIDEA and LXR's (KI, SU, INST, MED)

During the last year, KI has together with INST been able to establish that LXR interacts directly with CIDEA. MED has developed a fragment-based in silico analysis to design potentially isoform-selective LXR agonists and antagonists and has identified several novel molecules which are potential non-selective LXR blockers. SU has generated a transgenic mouse model over-expressing human CIDEA selectively in adipose tissues. These animals have now been subjected to a detailed phenotypic analysis following either regular chow or high fat diet. These assessments have demonstrated that CIDEA Tg-animals have somewhat higher insulin-sensitivity, which is in agreement with observational data in humans. SU has identified different human CIDEA isoforms, the role of which is currently under investigation. As reported previously, KI has together with INST studied the role of twist1, a transcription factor that regulates the expression and secretion of inflammatory adipokines (including TNF-alpha) in human adipocytes. These studies have now proceeded with a micro-array analysis of human adipocytes over expressing twist1. This has enabled the identification of novel twist1-regulated genes, which has been confirmed by ChIP and ChIP-seq analysis performed in collaboration with the SciLife laboratory at KI.

Task 3: Feed-back signals between fatty acids and adipokines (KI, SU, MAB)

As reported previously, using non-selective antibodies, KI has developed an ELISA assay for uncleaved TRAP to study samples from human adipose tissue and serum. KI has performed a clinical study on TRAP as a human adipokine and the results were recently published. This study demonstrated that TRAP is secreted in vivo from human adipose tissue and its secretion is fully accounted for by macrophages in the tissue. In addition, secretion rates are strongly influenced by the size and number of fat cells (increased secretion rate among those having hypertrophy-few but large fat cells). However, TRAP secretion is not related to the rate of adipocyte lipolysis. The transgenic TRAP mice that were generated for in vivo studies did not breed sufficiently enough, possibly because of attenuated fertility. We have therefore not been able to finalise the phenotypic assessments in these animals and have consequently chosen another in vivo approach. In preliminary experiments we have injected recombinant TRAP directly into subcutaneous fat tissue depots of wt mice. We found that there was a marked increase in adipogenesis at the place of injection in comparison with the contra lateral side where only vehicle was administered. These studies demonstrate that TRAP stimulates adipogenesis in vivo.

To investigate the influence of fatty acids released by lipolysis on AT inflammation at a cellular level, INST has conducted a series of in vitro experiments on human adipocytes and macrophage cell lines. In brief, lipolytic challenges were performed on human hMADS adipocytes with an appropriate lipolytic agonist and the resulting conditioned-media were used to treat human THP1 macrophages. GSK has provided pharmacological tools for these studies, as well as Standard operating procedures (SOPs) for cultivating human THP1 monocytes/macrophages. The activity of HSL and ATGL, another lipase essential in the lipolytic process, were knocked down using siRNA or inhibited using specific molecules in human hMADS adipocytes. In THP1 cells, the involvement of the TLR4 signaling pathway was assessed using the specific inhibitor TAK-242. mRNA levels of interleukins and pro- and anti-inflammatory cytokines were determined in THP1 cells by RT-qPCR. Secretion of inflammatory and anti-inflammatory cytokines was measured in the collected THP1 cell media using ELISA. The levels and composition of FAs released by differentiated hMADS adipocytes under different conditions of lipolytic activation were determined using enzymatic methods and gas chromatography. Cellular triglyceride content was assessed using enzymatic methods and specific fluorescent staining. INt has investigated the influence of lipolysis on AT inflammation and the implication of TLR4 in vivo using WT or TLR4-mutated mice fed a high fat diet and treated or not with an HSL inhibitor. Immune cell numbers were quantified by flow cytometry analyses. Insulin sensitivity was studied by in vivo tolerance tests.

WP 3.1 - The crosstalk between adipose tissue and skeletal muscle cells

Objective

The main objectives of WP3.1 are to elucidate the critical targets in skeletal muscle cells that interact with adipokines released from adipose tissue and lead to insulin resistance in muscle. Adiponectin is a major adipokine in this respect. The gene targets of fatty acids in muscle cells are also of particular significance. The assessment of a role for brown fat in adipokine-induced inflammation is also to be determined.

Tasks and detailed achievements in WP3.1

Task 1: Provision of CM and studies of effects on insulin action in human muscle cells (GDC, INST, UPMC)

GDC, INST and UPMC generated CM from a variety of different cell sources and studied the crosstalk and signalling pathways of these media (see D18 for detailed description). Specifically, CM have now been obtained and characterised from mature adipocytes, and from macrophages, endothelial cells, progenitor cells and lymphocytes from adipose tissue of patients with distinct BMI (UPMC). Further, CM have also been prepared from a variety of tissue explants including epi- and pericardial fat, perivascular fat, and subcutaneous and
visceral abdominal fat (GDC). Together with KI, GDC has studied in detail the functional implications of chemerin and its receptor ChemR23 (CMKLR1) in human skeletal muscle cells (see D19 for details). Overall, we show for the first time pro-inflammatory signalling of chemerin in human skeletal muscle and a critical role of ERK1/2 for the induction of insulin resistance. Proteomic analysis of CM revealed PEDF (pigment epithelium-derived factor) as one of the most abundant proteins released by human adipocytes. In a recent study, GDC showed that PEDF secretion is inversely regulated by insulin and hypoxia. PEDF induces insulin resistance in adipocytes and hSKMC and leads to inflammatory signalling in hSMC. Because of these diverse actions, PEDF is a key adipokine, which could have an important role in diabetes and obesity-related disorders.

Task 2: Role of adiponectin in adipose tissue crosstalk function (GDC, CHAR)
At this stage, the work towards D22 (due month 48) includes the proteomic analysis of the adipocyte secretome in the absence and presence of adiponectin, based on the methodology described in WP1.1 (see also D3). Besides several other proteins, GDC identified PEDF as being regulated by adiponectin and released by human adipocytes at high concentrations (see also task 1). GDC has started to characterise the functional impact of the novel adipokine DPP4 for skeletal muscle insulin resistance. This will probably result in a novel deliverable to be provided in month 48.

In a set of other studies the antilipolytic effect of adiponectin was investigated: in isolated adipocytes obtained from surgical biopsies adiponectin was shown to inhibit, in physiological concentrations, spontaneous as well as catecholamine-induced lipolysis (published in 2010, see below). This effect tended to be lower in obese individuals. The role of AMPK is being studied. Furthermore, in an ongoing study, the antilipolytic action of adiponectin is being investigated in isolated adipocytes derived from paired samples of visceral and subcutaneous fat in lean and obese subjects and the action in the two fat depot compared.

Task 3: Modulation of gene regulatory targets in skeletal muscle cells by adipokines and fatty acids (GDC, KI)
GDC observed a strong upregulation of the fatty acid transporter CD36 in skeletal muscle cells treated with CM that was paralleled by increased fatty acid uptake and lipid accumulation. Protein levels of the transcription factor myogenin were increased by oleic acid alone, while incubation with palmitic acid (PA) + CM nearly abrogated myogenin protein abundance. However, myogenic transcription factor MyoD and the glucose transporter GLUT4 remained unaltered. Mitochondrial integrity was impaired by CM- and FA-treatment, with the most profound defects induced by co-application of PA+CM. Consequently, FA oxidation was nearly abolished in the presence of PA+CM. Our data indicate an increased synergistic lipotoxic risk emerging from adipokines and FA specifically PA, which may be mediated via CD36 (for details, see D20).

Task 4: Significance of ectopic brown fat within skeletal muscle for leanness and thus low inflammation levels (SU, GDC)
By the signal sequence trap method, about 120 secreted proteins have been identified in cultured brown adipocytes. Of these 27 have been studied in more detail and could be considered potential paracrine signals. One example is chemerin, which is well expressed and its expression is increased after high fat diet but decreased by cold exposure. Chemerin expression in brown adipose tissue correlates positively with body weight after high fat diet treatment. Expression of the chemerin receptor CMKLR1 is decreased by both treatments. Further studies are ongoing concerning other selected adipokines from brown adipocytes, such as lipocalin 2, adrenomedullin, lumican, Niemann Pick type c2. Several of these proteins have been proposed to be associated with obesity, insulin resistance and inflammation. CM from brown adipocytes have been generated by a SOP in a special medium (hunger medium without FCS and insulin) in order to allow its testing on skeletal muscle cells. In addition, white adipocytes from the same source were cultured and conditioned medium generated under the same conditions as a positive control. Effects of these media are currently being investigated on skeletal muscle cells. Preliminary data indicate that both CM from brown and white adipocytes affect insulin signaling in skeletal muscle cells to the same extent.

WP 3.2 - Epicardial fat and its implications for altered cardiac metabolism and cardiac function

Objective
It is the overall goal of WP3.2 to investigate the secretory function of epicardial fat and to elucidate the pathophysiological role of this fat depot for cardiomyopathy associated with obesity and type 2 diabetes. In this context, experimental studies aim to assess the crosstalk between epicardial fat and cardiomyocytes, whereas clinical studies aim to show if this fat depot is critically related to cardiac structure and function and can be mobilised by dietary intervention.

Tasks and detailed achievements in WP3.2
Task 1: Analysis of adipokine expression and secretion from epicardial fat and crosstalk with cardiomyocytes using the guinea pig model (GDC, KI)
GDC in collaboration with INST has used the guinea pig model and applied a High-fat diet (HFD) to induce insulin resistance and cardiac dysfunction. CM generated from epicardial and subcutaneous adipose tissue explants were subjected to cytokine profiling using antibody arrays. Eleven factors were differentially secreted by epicardial adipose tissue when compared to subcutaneous adipose tissue. Furthermore, secretion of 30 factors by epicardial adipose tissue was affected by HFD-feeding (for details, see D25). In cardiomyocytes, CM from epicardial adipose tissue of HFD-fed animals increased SMAD2-phosphorylation, decreased SERCA2a expression, and reduced insulin-mediated phosphorylation of Akt-Ser473 versus CM from subcutaneous adipose tissue and standard diet-fed animals. Finally, CM from epicardial adipose tissue of HFD-fed animals as compared to CM from the other groups markedly reduced sarcomere shortening and cytosolic Ca(2+)-fluxes in cardiomyocytes (for details, see D27). GDC has extended this work to human epicardial fat from control and type 2 diabetic subjects. It was found that activin A is substantially upregulated in type 2 diabetics and may play an important role in the dysregulation of cardiac function under these conditions (Greulich et al, Circulation, in revision).

Task 2: Clinical studies on epicardial fat (MHH, UPMC)

MHH has continued the analysis of cardiac mass and function in relationship to abdominal and thoracic fat tissue depots in much more detail. In a cross-sectional analysis, we now published our findings on the indirect relationship between myocardiocyte lipid accumulation (MTG -myocardiocyte triglycerides) and physical fitness. As MTG are increased in subjects with insulin resistance, positively correlated to increased left ventricular remodelling, and negatively correlated to diastolic function, they may contribute to obesity-associated heart failure in the long run (Utz et al, Heart 2011). Weight loss as achieved by hypocaloric diets low in carbohydrate or fat content reduced MTG in our study population but this reduction was not associated with changes in cardiac function (paper submitted). This finding does not speak against our hypothesis, because cardiac size and performance in this population with no overt signs of diabetes and heart disease were clearly altered, but only to a modest degree. We now published the weight loss data in this cohort in detail (Haufe et al, Hepatology 2011). Interestingly, whereas pericardial adipose tissue is reduced by weight loss, epicardial fat mass did not change. Thus, our previous notion of a stronger correlation between pericardial adipose tissue and visceral adipose tissue is supported by this responsiveness towards weight loss. For epicardial adipose tissue, the relationship to visceral adipose tissue is much smaller. Weight loss significantly reduced left ventricular mass, which is the hallmark of early obesity-associated cardiac changes (Haufe et al, Hypertension 2012). Whereas the reduction of left ventricular mass was independent of the macronutrient composition of the diet, and only partly associated with hemodynamic changes, we found that the increased intake of n-3 polyunsaturated fatty acids is a predictor of left ventricular mass reduction. Furthermore, we have reevaluated FABP4 as candidate adipokine of obesity-associated heart failure and found that subjects with the highest tertile of circulating FABP4 are prone to increased cardiac mass and reduced longitudinal contractility as determined by cardiac MRI. These data in principal confirm the in vitro data for FABP4 (paper submitted). Other candidate adipokines are now analysed in our study population together with GDC. Further details on the heart can be found in deliverable 29.

WP 4.1 - Pharmacological evaluation and identification of drug targets

Objective

The main objectives of WP4.1 are to:
- determine whether the new adipokines identified in the course of this project are potentially druggable and represent a starting point for pharmacological intervention;
- identify adipokine receptors and signalling pathways to find other points for classical pharmacological interventions taking advantage of the bioinformatics analysis;
- perform virtual screening to identify potential new chemical tools.

Tasks and detailed achievements in WP4.1

Task 1: Bioinformatic analysis of new adipokines and their potential receptors identified

This task was completed month 18 and delivered a confidential pathway analysis of adipokines analysed within ADAPT (see D30).

Task 2: Provision of new animal models to study in vivo the influence of inflamed adipose tissue on whole body metabolism (PHYS, SU, INST, UPMC)

Different animal models have been investigated to study the influence of inflamed adipose tissue on whole body metabolism. All these studies used overexpression or inactivation of specific genes that could play a role in metabolism. In depth analysis of several metabolic parameters were monitored in these animal models including glucose and lipid homeostasis, inflammation of adipose tissue and body weight. Major outcomes have been reported in D31.
Task 3: Influence of adipokine overexpression and antibody blockade in rodent models (GSK, PHYS, SU, INST, MAB)

The identification of novel proteins of interest coming from proteomic studies has brought a number of candidate targets. Further analysis and filtering has led to the selection of 13 targets for which Adenovirus and/or blocking Antibodies to be used for target overexpression or neutralisation will be prepared in anticipation of in vitro/in vivo experiments. Very recently, a panel of adenovirus tools has been prepared by GSK for the partners within ADAPT.

SU, in collaboration with colleagues in Cambridge, has evaluated the metabolic effects of novel adipokines by measurement of whole body metabolism in animals with an ablation of the adipokine gene. Two studies have been performed, one with mice lacking the gene for the TGFbeta superfamily member BMP8b. The KO animals demonstrate an obese phenotype and show a reduced ability to recruit brown fat thermogenesis in a cold environment, indicating a role for BMP8b in energy balance. For mice lacking the gene for lipocalin-like prostaglandin D synthase, energy expenditure in a cold environment remains markedly dependent upon carbohydrate oxidation, rather than switching to fat oxidation, indicating a role for the gene in substrate selection.

GSK and PHYS worked together to investigate the impact of a pharmacological inhibition of Stearoyl-CoA Desaturase1 (SCD1), an enzyme that catalyses the biosynthesis of monounsaturated fatty acids from saturated fatty acids, on metabolic parameters in the rat. GSK993 is a potent and orally available SCD1 inhibitor. In Zuckerfa/fa rats, GSK993 exerted a marked reduction in hepatic lipids as well as a significant improvement of glucose tolerance. Furthermore, in a diet-induced insulin resistant rat model, GSK993 induced a very strong reduction in Triton-induced hepatic Very Low Density Lipoprotein-Triglyceride production. In addition, following a hyperinsulinemic–euglycemic clamp in GSK993-treated animals, we observed an improvement in the whole body insulin sensitivity as reflected by an increase in the glucose infusion rate. Taken together, these findings demonstrate that the pharmacological inhibition of SCD1 translates into improved lipid and glucose metabolic profiles and raises the interest of SCD1 inhibitors as potential new drugs for the treatment of insulin resistance. However, particular, attention should be focused on the impact of SCD1 inhibition in the skin. Indeed, we observed that SCD1 inhibition caused some atrophy of sebaceous and meibomian glands due to depletion of wax esters in the skin and the eyelid. Therefore, future development of SCD1 inhibitor for chronic treatment will require careful determination of the therapeutic window between the dose that confers the metabolic effects and the dose that confers these side effects.

GSK and PHYS explored the effect of Liver X receptor (LXR) activation on reverse cholesterol transport (RCT) in a hamster model (a species expressing CETP) using an LXR agonist identified by GSK, GW3965. Overall, GW3965 failed to improve both dyslipidemia and liver steatosis. However, after (3)H-cholesterol labelled macrophage injection, GW3965 treatment significantly increased the (3)H-tracer appearance by 30% in plasma over 72 h, while fecal (3)H-cholesterol excretion increased by 156% (P < 0.001). This study allowed to show that despite a lack of beneficial effect on circulating lipids, LXR activation promotes macrophage-to-feces RCT in dyslipidemic hamsters. These results emphasise the use of species with a more human-like lipoprotein metabolism for drug profiling. Both tasks 4 and 5 have been successfully completed and the corresponding deliverables (D34 and D35) have been reported.

WP 4.2 - Clinical evaluation of adipokines as a drug target

Objective

In WP4.2 the consortium aims to evaluate adipokines as identified and described in other WPs as possible drug targets. This includes the detailed examination of the regulation of these adipokines under different clinical situations. Several groups of the consortium are active in clinical research, and one main goal of WP4.2 is to harmonise the existing infrastructure for clinical studies on new targets or compounds.

Tasks and detailed achievements in WP4.2

Task 1: Further improving the existing infrastructure for clinical studies (CHAR, INST, MHH, KL, UPMC)

Most of the work related to this task has been already reported in the 2nd periodic report (including deliverables 36 and 37, and milestone 8). All partners have cooperated during the second half of the funding period on the basis of common SOPs and clinical databases. Further progress was made in sharing extensive details regarding formats of microarray data (UPMC, INST, CHAR, MHH).

Task 2: Correlation of adipokine expression and clinical phenotypes (MHH, CHAR, INST, UPMC, KL)

UPMC explored monocyte subtypes in obesity in more detail. Indeed systemic low-grade inflammation in obesity is not only related to circulating adipokines, but also to CD16+ subpopulations of monocytes (namely, CD14+CD16+, and CD14dimCD16+). Both monocyte subsets were increased in obese subjects, with a significant enrichment of the CD14dimCD16+ subpopulation in obese diabetics. The percentage of CD14dimCD16+ monocytes and glycemia was positively correlated, independent of fat mass. Weight loss led to a sharp decrease of this subpopulation, and fat mass changes strongly determined the change. A diminution of the CD14+CD16+...
subpopulation was also observed during weight loss and was associated with a decrease in intima-media thickness (Poitou C et al, ATVB 2011). In another cohort of normal-weight women and obese women who were followed over 2 y after Roux-en-Y gastric bypass, multiplex proteomics was used to assay 27 cytokines and growth factors in serum. Most of these factors were found expressed and dysregulated in obese adipose tissue by ADAPT partners. Concentrations of IL-9, IL-1-RA, IL-10, IF-inducible protein 10, macrophage inflammatory protein 1, MCP-1, IL-8, RANTES, and VEGF were elevated in obese subjects. IL-10 was further elevated in diabetic obese patients, whereas eotaxin was increased only in diabetic patients. After surgery, many factors showed a biphasic pattern of variation, decreasing sharply at month 3 before rising back to pre-surgical values at month 6; these changes closely tracked similar changes in calorie and carbohydrate intake. These coordinated changes suggest an early influence of energy and carbohydrate intake, whereas a long-term reduction in body weight might prevail in regulating circulating cytokine concentrations (Dalmas at al, Am J Clin Nutr 2011).

KI has assessed the secretion of inflammatory cytokines in subcutaneous adipose tissue from healthy lean women. These studies demonstrated that TNF, but none of the other factors, correlated significantly with adipose tissue morphology, i.e. secretion was increased in subjects with adipocyte hypertrophy characterised by the presence of few large adipocytes (Arner E et al, NEJM 2010). These results demonstrate that TNF and local inflammation may play a role in adipogenesis and adipose plasticity also in normal-weight conditions. KI together with GDC identified DPP4 as a novel adipokine and the expression was assessed in different clinical cohorts (Lamers D et al, Diabetes 2011). DPP4 expression was increased in obesity and the metabolic syndrome and correlated positively with fat cell size. In addition, in vitro experiments demonstrated that DPP4 attenuated insulin sensitivity in human adipocytes and myocytes. Taken together, our results suggest that increased DPP4 expression in obesity may be a contributing mechanism promoting insulin resistance. Finally, KI has also studied the expression of Zinc-alpha2-glycoprotein (ZAG) and could demonstrate that it is a catabolic marker in conditions of both voluntary and involuntary weight loss (Rydén M et al, J Intern Med 2011). However, the functional role of ZAG in human adipocytes is controversial and remains to be established.

CHAR pursued the multiple period dietary intervention design (energy restriction phase with a 4-week very low-calorie diet and a weight stabilisation period composed of a 2-month low-calorie diet followed by 3 months of a weight maintenance diet). In a close collaboration with INST, associations between various characteristics of SAT and clinical parameters such as adiposity, insulin resistance and other indices of metabolic syndrome were analysed. Plasma leptin appeared as the only variable that could be associated with the diet-induced improvement of insulin sensitivity (paper submitted). Adrenergic regulation of lipolysis in SAT was found to vary with respect to the dietary phase. However, no association between the time-course of lipolysis regulation and that of insulin sensitivity was found (Koppo K et al, AJP 2011). Gene expression response (for a large number of genes including adipokines, macrophage-specific markers, lymphocyte markers) to this dietary protocol was compared between abdominal and gluteal SAT. We did not find differences between the two depots before the diet. The general pattern of the diet-induced response was similar for a majority of genes (except for leptin and adiponectin). Thus, these results do not support the often cited “protective” role of gluteal adipose tissue (manuscript in preparation). CHAR and INST studied in a cross-sectional design paired samples of abdominal subcutaneous (SAT) and visceral (VAT) adipose tissue in 56 subjects. A similar distinct regulation of adipocyte-derived and macrophage-derived genes with respect to obesity and insulin resistance was found in SAT and VAT (Klimcakova et al, JCEM, 2011). Expression of macrophage-specific genes increased with increasing adiposity and insulin resistance in both, SAT and VAT (Klimcakova et al, Diabetologia 2011). In both fat depots, macrophage gene expression was higher in obese subjects with metabolic syndrome when compared with obese subjects without metabolic syndrome. These results support the opinion that SAT is as important as VAT in the pathogenesis of obesity-related metabolic disorders.

MHH together with INST analysed gene expression differences in SAT of lean and obese, normotensive and hypertensive subjects. The original hypothesis that SAT gene expression differs widely between obese normotensive and hypertensive subjects was not confirmed, only two differentially expressed genes were found. MHH also analysed FABP4. FABP4 blood concentrations correlated positively with body fat mass and insulin resistance, and were reduced by dietary weight reduction. In contrast, FABP4 gene expression was not related to obesity, and not changed by weight loss. Thus, other mechanisms than transcriptional regulation influence the amount of secreted FABP4 in obesity (manuscript submitted). MHH has established a dietary intervention which modulates fat and carbohydrate intake in a cross-sectional manner over two week periods without changing body weight and body composition. In a first analysis, we determined plasma ADMA in lean and obese subjects during the dietary intervention. Although suggested differently by other authors, neither obesity, nor a fat rich diet increased circulating ADMA. Similarly, neither diet had any influence on DDAH1 and 2 gene expression in SAT. DDAH is the principle enzyme for ADMA degradation (Engeli S et al, NMCD 2011). We are currently analysing other adipokines and genes within the framework of this experimental approach. Finally, MHH analysed the influence of different kinds of body fat distribution on the value of bioelectrical impedance analysis. This technique is widely used, and we clearly showed that the precise determination of body fat mass by BIA is influenced by body shape. These findings are important for future studies of adipokines when precise phenotyping is of relevance (Haas V et al, EJCN 2011).
Potential impact:

The ADAPT project aims to improve the health of European citizens, to increase the competitiveness and innovative capacity of European health-related industries and business, while addressing obesity and its associated complications, a global health issue and an emerging epidemic. ADAPT is focused on translational research with the ultimate goal to develop and validate new therapeutic approaches. The impact of the ADAPT Consortium rests on its ability to provide advances to combat the cardiometabolic syndrome, especially by clarifying the relationships between adipose tissue inflammation and insulin resistance, the identification of novel adipokines, the analysis of interorgan crosstalk and the evaluation of adipokines as drug targets to prevent the devastating consequences of excess fat accumulation.

The final goal of the ADAPT consortium was the identification of novel targets in the crosstalk between adipose tissue and other organs. This will contribute to development of new strategies for characterisation and diagnosis, and in a longer perspective development of new drugs for treatment and/or prevention of the metabolic syndrome. The result will have a great potential impact on combating this syndrome, which is a crucial intermediate step between obesity and the associated risk of type 2 diabetes, hypertension, and cardiovascular diseases. In view of the rapidly-developing obesity epidemic, combating the metabolic syndrome will lead to improvement of the health of the European populations.

Health impacts in Europe

The results from ADAPT will contribute to the development of a fundamentally new understanding of these pathophysiological mechanisms in order to enable us to design drugs that reduce or reverse adipokine-mediated adverse interactions and the obesity-associated inflammatory drift. The design of new drugs and their ultimate approval for use in Europe will take a further six to ten years but they will then have the potential to make an important new contribution towards dealing with one of the most serious health problems facing Europe.

The prevalence of obesity has risen up to three-fold in the last two decades. Half of all adults and one in five children in the WHO European region are overweight. Of these, one third is already obese, and numbers are increasing fast. Overweight and obesity contribute to a large proportion of non-communicable diseases, shortening life expectancy and adversely affecting the quality of life. In 2005 it was estimated that there were more than one million deaths in the European Region due to diseases related to excess body weight annually. This trend is particularly alarming in children and adolescents, thus passing the epidemic into adulthood and creating a growing health burden for the next generation. The annual rate of increase in the prevalence of childhood obesity has been rising steadily and is currently up to ten times higher than it was in 1970.

Obesity also strongly affects economic and social development. Adult obesity and overweight are responsible for up to 6% of health care expenditure in the European region; in addition, they impose indirect costs (due to the loss of lives, productivity and related income) that are at least two times higher. Overweight and obesity most affect people in lower socioeconomic groups, and this in turn contributes to a widening of health and other inequalities. There is a need for new approaches to both prevention and treatment, which include the type of approaches and medium to long-term therapeutic outcomes that have been made possible by the advances made by ADAPT.

Contributions of ADAPT to solve the societal problems associated with obesity

The ADAPT objectives are complementary in their approach to the search for a better understanding of the development of the metabolic syndrome in relation to obesity and adipose tissue inflammation. The project has generated novel fundamental knowledge by studies on animal models, but also directly applicable knowledge in humans by studies of human samples, of human integrative physiology and human populations. These two types of knowledge together are necessary to envisage development of new drugs for treatment or prevention of the Metabolic Syndrome.

Adipokines have been recognised as key players in the initiation of insulin resistance and the metabolic syndrome and they are of great potential significance both as biomarkers and drug targets. By understanding the complex intra- and inter-organ crosstalk and the specific role of adipokines ADAPT has generated an essential platform for evaluating adipokines as drugable targets. Further, the identification of novel adipokines represents an essential step beyond the current state-of-the-art and may open new avenues for drug design targeted to combat the Metabolic Syndrome and its complications.
Reinforcement of European competitiveness

Another strong potential impact is the reinforcement of European competitiveness at both the scientific and economic levels within the field of adipose tissue biology and related drug design. ADAPT has created this partnership of 7 academic research groups and 3 European biotech companies and one large pharmaceutical company as active dedicated members, including some of the world leaders in the fields of Metabolic Syndrome, insulin signalling, adipose tissue biology, inflammation and cytokine function and biotechnology for the first time. Having these partners collaborating within the frame of a single European collaborative Research and development (R&D) project has led to:

- Increase in the scientific competitiveness: Well-experienced scientific leaders are linked in the ADAPT consortium, and some of whom have already cooperated in previous projects. The consortium of research groups, laboratories, clinical departments, and companies will further develop the quality of the research pursued, and leverage these European teams further on towards worldwide leadership on essential components of adipose tissue inflammation and the specific role of adipokines and their exploitation for development of diagnostics and drug targets.

- Progression of economic competitiveness: The ADAPT consortium contributes to achieve the Lisbon objectives defined in March 2000 at the Lisbon European Council where the Heads of State and Government set the Union the goal of becoming by 2010 the most competitive and dynamic knowledge-based economy in the world, capable of sustainable economic growth with more and better jobs and greater social cohesion. The ADAPT consortium aims at driving more innovation towards European SMEs, and has an important position in this move; thus, the synergistic interaction between three SMSs specialised in different fields of drug design and a large pharmaceutical company with an established programme targeted towards treatment of the metabolic syndrome provides a platform for successful joint economic programmes. New innovations and target development programs emerging from the ADAPT research will therefore increase the cooperation between European biotech companies themselves, between academic and industrial partners, as well as between biotech companies and worldwide pharmaceutical industries.

Innovation and industrial impacts

The potential industrial impacts will follow on from the pharmacological and clinical evaluation of adipokines as drug targets and potential biomarkers. The ADAPT consortium is strongly focused on identifying and developing innovations, at different levels:

- Developing new technologies and tools: The complementarities of the partners and the breadth of the research into adipose tissue biology and adipokine function, from the molecular biology addressing the mechanistic level to the clinical level, will give the ADAPT consortium opportunities to further develop the technologies and tools in new settings and contexts. The concerted approaches are expected to lead to the identification and development of novel technologies for such areas as expression profiling, screening assays, bio-informatics, statistical methods, characterisation of new animal models, etc.

List of websites: http://www.adapt-eu.net

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