

1. Publishable summary

1.1. Summary description of the project context and the main objectives.

Obesity is one of the most serious and fast-growing health problems in the European Union, and a leading cause of diabetes. The main barrier for approval of an anti-obesity drug is the safety requirements that led to marketing prohibition of almost all anti-obesity drugs approved in the latest period of time such as sibutramine or rimonabant. This situation has led to a situation on which one of the most relevant causes of morbid-mortality in humans is almost devoid of effective pharmacotherapeutic alternatives. There is an urgent need for new drugs against obesity that is reflected in the EU VII FP research call for projects under the topic HEALTH-2007-2.4.3-6: *Nutritional signals and the development of new diabetes/obesity therapeutic agents. This project will focus on the effects of alternative compounds which improve carbohydrate/lipid metabolism or modify body weight, and could be used in the development of new therapeutics in the treatment of hyperglycaemia and hyperlipidemia.*

To be successful, any research proposal has to discover novel or improved treatments in the shortest possible timeframe. The FP VII project REPROBESITY (www.reprobesity.eu) proposed to overcome the barriers around obesity by discovering

- a) new indications of existing drugs with proven safety profiles as anti-obesity therapies. Since a relevant clinical end-point for an anti-obesity drug is its ability to reduce abdominal fat, the project has focused on approaches targeting directly abdominal fat cells. This is accomplished by a new specific technology that allows ex-vivo monitoring by flow cytometry techniques of adipose cells responses to libraries of approved drugs. This technology developed by VIVIA Biotech, is followed by target selection and pharmacological validation performed by a team of European Community researchers specialized on top quality preclinical studies in obesity.
- b) phenotypes and biomarkers that identify subsets of patients with safe and efficacious responses to drugs.. The biomarker project intend to establish if we can obtain a way or identify the responding patients to a given therapy against obesity, since the experience with formerly approved drugs indicates that its utility is limited to a restricted set of patients. A new phenotype and/or biomarker may identify responsive patients with good safety profiles.

1.2 Work performed since the beginning of the project and the main results achieved so far.

The work performed during the second reporting period has allowed the consortium to:

- a) Develop for the first time an effective technique for the reprofiling of existing drugs using both, ex vivo samples of human adipose tissue and human cells engineered to express selected pharmacological targets to identify both, new drug indications and new chemical entities. This approach has allowed the filing of 9 industrial patents derived of project's outcomes.
- b) Develop a new technique of combinatorial cytomic biomarkers capable of identify the contribution of pathological conditions (i.e. obesity) and environmental factors (i.e. consumption of carbohydrates), to an abnormal cellular response (i.e. reactive oxygen species production, expression of the insulin receptor, expression of the glucose transporter or expression fo the fatty acid transporter) that may account for the pathological consequences of obesity (i.e. metabolic syndrome, diabetes etc..).
- c) Identify the pathophysiological role of biochemical signalling pathways on obesity. This information is useful to develop new therapeutic alternatives. These targets include known receptors such as GLP-1 receptor, peroxisome proliferator receptors, cannabinoid CB1 receptors, β 3-adrenergic receptors, as well as several orphan receptors, including GPR55, GPR119, etc....
- d) Patent and development of new chemical entities interacting with these targets, one of them being ready for clinical trials in humans.

1.3 Expected final results and their potential impacts and use (includind socio-economic impact and the wider societal implications of the project so far).

Because of the high efficiency of reprofiling techniques, as well as the exploration of new relevant pharmacological targets for developing drugs against obesity, we expected to have several safe candidates with anti-obesity properties at the end of the research period. These molecules will be suitable to enter into clinical trials. These drugs will have a safe profile since they will be identified among drugs already tested in clinical studies in humans. Thus, their toxicological profile and the adverse reactions associated with its administration will be already known because they were previously tested on indications different from complicated obesity. If obtained, the impact of such therapy will be extremely relevant because of the dramatic increase on obesity prevalence among the European population and the lack of safe drugs for its treatment. Alleviation the socio-economical burden of obesity-derived pathologies will be one of the most efficacious achievements in the pursuit of a healthy European Society. In addition, the development of new chemical entities optimized from known drugs is another alternative that has led to the identification of candidates suitable for clinical trials. Finally, the strategy of combinational therapies (i.e. the combination of two different known drugs, with synergistic effects on adipocyte biology) has led to the development of a patent for combinational therapy that serves as a proof of concept for further developments.

Overall Reprobesity main objective has been achieved. The consortium has filed 9 industrial patents, having one suitable candidate to progress towards clinical trials whose exploitation is being addressed by VIVIA Biotech, the SME that was the focus of the development of the present project.

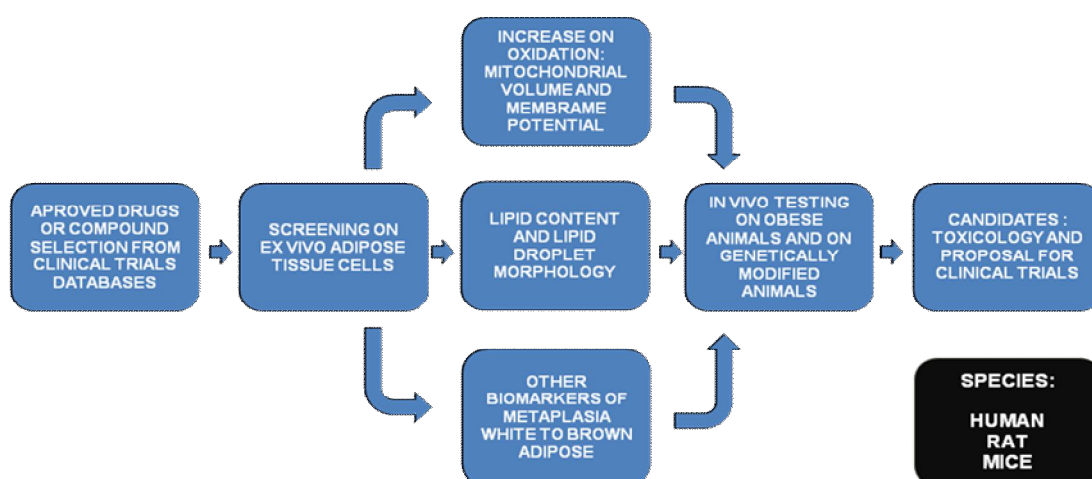


Figure 1. Screening procedure of the REPROBESITY project. The use of phase 1-approved drugs on ex vivo human adipocytes allows the concurrent evaluation of safety and efficacy.