THE SARCOB PROGRAM : A FRENCH CONSORTIUM FOR DEVELOPING DRUG CANDIDATE AND NUTRACEUTICAL TARGETING SARCOPENIC OBESITY

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Introduction

Sarcopenia, the age-related muscle mass and strength loss may occur together with a fat mass increase, leading to sarcopenic obesity (SO). SO patients show increased cardiometabolic risk. Our objective was to set up a "SARCOB" consortium associating companies and academic laboratories to develop a drug candidate and a nutraceutical formulation for treating SO. The SARCOB program comprises three main workpackages.

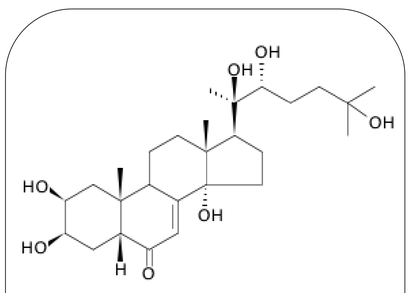
Phytoecdysones are plant secondary metabolites analogues of insect molting hormones. The most common phytoecdysone, 20-hydroxyecdysone (20E), is pharmacologically active on mammals. It has beneficial effects on several cardiovascular parameters It increases muscle mass and strength and prevents adipose tissue development (Poster of Foucault et al.) in rodents and humans.

Phytoecdysones, as attractive candidates for developing SO treatments were therefore used to formulate a new nutraceutical combination and to select putative drug candidates against sarcopenic obesity.

Partners

The Sarcob consortium was initiated in 2012 and is ending in 2014. It comprises five academic laboratories : Université Pierre et Marie Curie (Institut de Myologie; Laboratoire BIOSIPE, Centre de Recherche des Cordeliers-Laboratoire de Nutriomique), AgroParisTech and INRA Clermont Ferrand and two companies Biophytis and Metabrain Research; Biophytis being the program lead.

Phytoecdysones main effects



20-Hydroxyecdysone

Phytoecdysones effects in animal models

Reference	Animal model	Dose (mg/kg)	Length (days)	Results
Syrov *et al.* 2000	Immature and impuberal male rats. (70 - 80 g) intact or castrated and mature (210 - 220 g).	20E: 5 mg/kg vs (methylandrostenediol and nerobol	10 days	Significant increased of total muscle weight in intact and casted rats . Nerobol induced a higher increase compare to 20E in intacts or casted rats. Significant increase of the contractile proteins in intact and casted rats. The level was comparable to Nerobol.
Wu *et al.* 2001	Rat myocardial infarction	0.5, 5, and 50 mg/kg	7 days	serum creatine phosphokinase, glutamic-oxalacetic transaminase, and lactic dehydrogenase, were reduced dose dependantly. Infarct size was decreased and coronary blood flow, capillary vessel diameter, and VEGF expression were increased at 5 mg kg-1. .
Toth *et al.* 2008	Wistar male Rat (300-400g)	5 mg/d/kg	8 days	Significant increase of the size (cross sectional area) of different fiber types in a muscle specific manner.
Gorelick Feldman *et al.* 2008	Male Sprague-Dawley Rat (213-230g)	50 mg/kg. vs methandrostenolone	28 days	Significant increase of muscle strength. The level was equivalent to methandrostenolone.
Kizelsztein *et al.* 2009	C57BL/6 mice under High Fat Diet	10 mg/kg BW	13 weeks	Weight gain reduction Total fat mass reduction by 41 %. Fat free/fat mass ratio was significantly improved
Esposito *et al.* 2009	Wistar Rat. High protein diet	60 mg/kg	24 days	Signifiant increase of gastrocnemius weight. Slight increase of the lean body mass. No androgenic activity.
Fedorov *et al.,* 2009	Rats with Chronic Cardiac Failure	20mg/kg	60 days	Decreased lethality. Improved blood and heart cathecholamine levels.
Seidlova-Wuttke *et al.* 2010	Ovariectomised (ovx) rats	55 mg/kg BW	12 weeks	Reduction of total fat mass development by 23 %
Seidlova-Wuttke *et al.* 2010	Ovariectomised (ovx) rats.	170 mg/kg BW	12 weeks	Decrease of paratibial fat mass accumulation
Lawrence 2012	Male mice C57BL6J 21 months	5 mg/kg	28 days	Significant increase of fiber sizes (cross sectional area) in the *triceps brachii* (41%) and *plantaris* (+30%) . Contraction-induced phosphorylation of AMPK significantly greater in 20E-treated mice .
Foucault *et al.* 2012	C57BL/6 mice under High Fat Diet	5 mg/kg BW	3 weeks	Reduction of total fat mass development by 40 %.

Main clinical studies

Reference	Length	Volunteers	Dose	Main criteria	Secondary criteria
Simakin, et al. 1988	10 days Intense physical exercice	78 swimmers and athletes (52 placebo and 26 verum)	75 mg 20E+ 30 g protein (*Rhaponticum* extract)	Total muscle mass increase (+ 6.5 %)	Fat mass loss
Gadzhieva et al., 1995	20 days Intense physical exercice	20 athletes 17-25 years	30 mg 20E 30g protein (*Rhaponticum* extract)	Physical work capacity increase (+ 13%)	muscle mass increased (+3%)
Azizov et al.,1997 and 1998	20 days Intense physical exercice	44 athletes, 18-28 years	30 mg 20E (*Rhaponticum* extract)	Physical work capacity increase (+ 12%)	Reduction of malonyldialdehyde levels in urine (-57%). Blood coagulation factors increased II; V; VII and X by respectively 9, 0.7; 5 and 0.5 %
Seidlova-Wuttke et al., 2012	3 months No dieting or physical exercice program	39 overweight subjects (18 placebo and 21 verum). 50-70 years	100 mg 20E (Spinach extract)	Fat (- 7.6 %).	Bodyweight reduction (- 1.3 %). Waist circumference (- 3.1 %). Muscle mass increase (+2.9 %). C-reactive protein (-38%) Total cholesterol (- 17%) Triglycerides (- 37%)
Foucault et al., in preparation	3 months : hypocaloric dieting then weight loss maintenance (6 weeks/phase)	60 obese subjects (28 placebo and 30 verum) 18-65 years	40 mg 20E (Quinoa extract)	Abdominal fat mass (- 2,8 %)	Tendancy to bodyweight reduction in the maintenance phase (- 0,8%) Mean adipocyte diameter (- 4,3 %) Fasting glycemia in the dieting phase (- 3.7 %) LDL cholesterol in the dieting phase (- 8 %)

Workpackages: First Results

Workpackage	Goals	Main Results	Poster #
WPA	- Set up of cellular and *in vivo* rodent models mimicking sarcopenic obesity . - Identify the molecular receptor mediating phytoecdysones effect on muscle.	-Murine (C2C12), and human (primary and immortalised) muscle cell lines as well as adipocytes myocyes co-cultures were developed as tools for assaying candidate molecules effects on proteosynthesis. - Aged mice show mild signs of muscle alterations. Wistar or GOTO-KAKIZAKI (GK) rat, depicted reduced total lean body mass, muscle weight and lipid infiltrations in muscle . - Phytoecdysones molecular receptor in muscle cells has been identified.	- Guelzim et al. Poster N°184 Mouveaux et al. Poster N° 210
WPB	Develop a 20-hydroxyecdysone based nutraceutical formula and assay it in a suitable *in vivo* rodent model.	A new nutraceutical formula was developped and will be soon assayed on animal models. Metabolization of 20E was better characterized in rat and mice and the main metabolites were identified.	Foucault et al. Poster N° 187
WPC	Generate new chemical 20E derivatives and with natural products and metabolites use them to select the best candidates through the C2C12 screening cascade. Candidates will be further tested in the suitable *in vivo* rodent model.	Candidate molecules passed the main screening cascade steps and are ready to be assayed as drug candidates in the suitable sarcopenic obesity rodent model	Raynal et al. Poster N° 185

Conclusions

The SARCOB consortium delivered very promising results. A small set of phytoecdysones derivatives passed all the screening cascade steps and are ready to go for further development.

Several sarcopenic rodent models were assayed and the best one will be used to characterize candidates molecules selected through the screening cascade. Likewise, the new nutraceutical formula with 20-hydroxyecdysone will be assayed *in vivo.*

The molecular receptor mediating phytoecdysones effects in muscles cells has been identified. It will allow a further characterization of the selected molecules as sarcopenic obesity drug candidates.

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