sigma-tau

R&D in Cardiovascular and Metabolic Diseases

RESEARCH IS THE FUTURE

Contents

sigma-tau is a leading, all Italian capital, international pharmaceutical group that invests in the research, development and marketing of innovative and effective treatments to improve patient well-being and quality of life.

sigma-tau Group has headquarters in Pomezia (Rome, Italy), and subsidiaries in France, Switzerland, the Netherlands, Portugal, Germany, the UK and the USA, as well as in Spain and Sudan where the Group operates two production facilities. It has over 2500 employees and an extensive network of licensees worldwide.

sigma-tau was founded in Italy in 1957 and achieved a global turnover of € 665 million ($ 920 million) in 2007.

sigma-tau SpA consistently invests 16% of its annual turnover in R&D. **sigma-tau**'s 400 **R&D** staff are currently running 43 **R&D** projects. A total of 14 NCEs and 12 known molecular entities in 30 different indications are at various stages of development. In addition, research into the carnitine compounds is ongoing in several therapeutic areas.

These efforts have been paralleled by an intensive intellectual property strategy. **sigma-tau** filed 240 priority patent applications from 1998 to 2007, making **sigma-tau** one of the most active Italian pharmaceutical companies pursuing intellectual property protection.

The **sigma-tau SpA Research Center**, Pomezia (RM), with over 24000 m^2 of laboratory and approximately 300 scientists, represents the corporate **R&D** structure.

Prassis - Istituto di Ricerche sigma-tau SpA, Milan, represents **sigma-tau**'s center of excellence in cardiovascular discovery research, specializing in the genetic and molecular mechanisms of cardiovascular disorders.

In addition, **sigma-tau** is a majority shareholder of **Tecnogen SpA**, Piana di Monte Verna (CE), a biotechnology R&D company, manufacturing clinical grade monoclonal antibodies and recombinant proteins.

sigma-tau's **R&D** activities have been further strengthened by the creation of **sigma-tau Research Switzerland S.A.**, Mendrisio - CH, a new site which coordinates **R&D** activities on selected projects with clinical development and chemical & analytical capabilities.

The **R&D** organization is completed by **sigma-tau Research Inc.**, Gaithersburg (MD) - USA, which operates in the field of the clinical development of **sigma-tau** products in the United States.

The Burden of Cardiovascular and Metabolic Diseases 4

The WHO states that cardiovascular diseases are currently the number one cause of death in the world. In 2005, an estimated 17.5 million people died from cardiovascular diseases, representing 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million due to stroke. If current trends continue, an estimated 20 million people will die from cardiovascular diseases by 2015.

The economic toll from cardiovascular diseases is equally devastating, leading to billions of dollars lost due to healthcare costs and reduced productivity from the disabling and fatal outcomes related to diabetes, hypertension, stroke, valvular heart disease, and heart failure.

sigma-tau has focused its research activities on the treatment of major cardiovascular diseases such as myocardial infarction, heart failure, hypertension and diabetes which, due to their high prevalence, increasing incidence and currently unmet medical needs, represent a significant social and economic burden for patients and healthcare systems around the world.

Myocardial Infarction

Myocardial Infarction, also known as a heart attack, is the leading cause of death of all cardiovascular disorders.

Approximately one million Americans suffer a heart attack each year and four hundred thousand of them die as a result of it.

Hypertension

In 2000 more than a quarter of the world's population was hypertensive and this number is expected to climb to 29% or about 1.56 billion people worldwide by 2025 (Lancet, Jan 2005).

Heart Failure

Heart failure is a frequent complication of myocardial infarction and hypertensive disease. Almost 1 in 3 people aged 55 will develop heart failure during their remaining lifespan. Heart failure continues to be a fatal disease with only 35% of patients surviving 5 years after the first diagnosis.

Diabetes & Metabolism

Diabetes is the fourth leading cause of death in most developed countries with 195 million people world wide suffering from diabetes. The WHO estimates that more than 365 million people will suffer from diabetes by the year 2030.

The majority of diabetic patients on current therapies will develop micro-vascular complications such as neuropathy, nephropathy and retinopathy. Associated diseases are a life-threatening burden, particularly in type II diabetes. These include dyslipidemia, atherosclerosis and other features of the metabolic syndrome, leading to problems such as stroke and myocardial infarction.

Renal Disease

Over half a million people in the US and Europe suffering from end-stage renal disease (ESRD) require dialysis with over 30,000 patients requiring renal transplants each year. Diabetes and hypertension are leading causes of end-stage renal disease requiring either renal dialysis or transplantation.

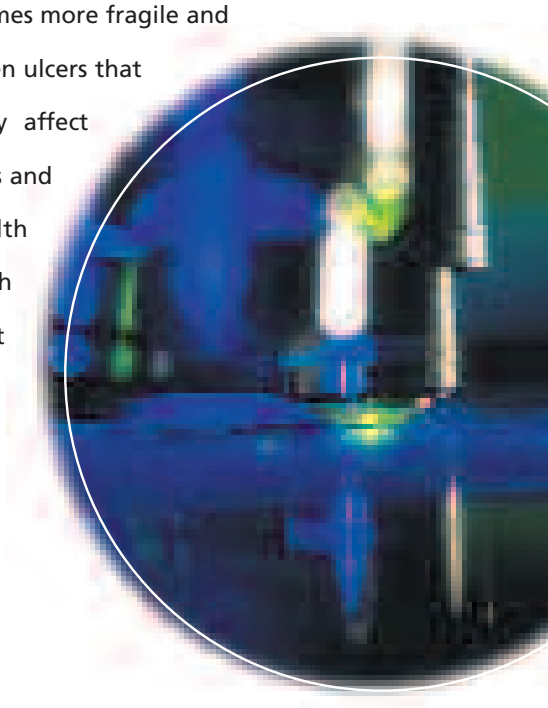
Peripheral Arterial Disease (PAD)

This is characterized by the narrowing of the arteries, reducing blood flow to the legs, arms, brain and other organs and is caused by atherosclerosis . People with PAD are at high risk for heart attack and stroke. While PAD is common - about 10 million people in the United States are affected - only about one in four is diagnosed and receives treatment.

Intermittent claudication is often a symptom of severe atherosclerotic disease and the most prominent symptom of PAD , shown by about a third to a half of these patients.

Venous Stasis Ulcers

This condition is due to the build up of extra fluid in the limbs which, in turn, makes it difficult for the blood to feed cells. The tissue becomes more fragile and a stasis dermatitis develops which may evolve in open ulcers that heal slowly. Chronic venous leg ulcers commonly affect patients with congestive heart failure, varicous veins and other conditions. They represent a major health problem affecting approximately 500,000 people each year in the US, a similar number in Europe and impact significantly on quality of life and medical expenses.

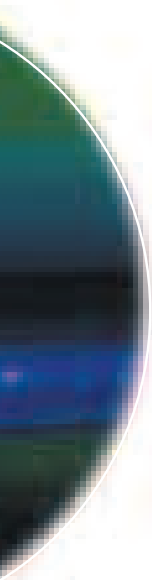


SIGMA-TAU R&D IN CARDIOVASCULAR & METABOLIC DISEASES

sigma-tau's investment in the research of innovative treatments for cardiovascular & metabolic diseases is extensive and ongoing. It has been actively researching the metabolic role of Carnitine in cardiovascular disease for over 30 years. **sigma-tau**'s objective is to provide an integrated approach to the future management of cardiovascular diseases through research into various therapeutic approaches.

sigma-tau's R&D pipeline in cardiovascular & metabolic diseases covers a wide range of closely related medical conditions.

sigma-tau has recognized the need not only for new and effective treatments but more importantly, a need for new approaches to the research and treatment of these highly interrelated and complex disorders.



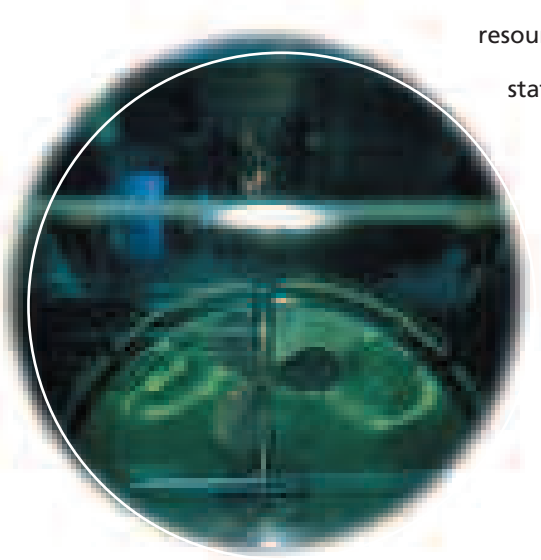
As a result, **sigma-tau** has invested in various therapeutic approaches which include:

- new pharmacological targets (Istaroxime, Teglicar)
- genetically associated defects (Rostafuroxin)
- essential metabolic defects (Carnitine compounds)

sigma-tau's ultimate objective however is to improve the patients' quality of life, independent of the nature of the pharmaceutical solution (synthetic drug, biotechnology product or metabolic compound).

sigma-tau has been actively researching the essential metabolic role of Carnitine in a wide spectrum of cardiovascular and metabolic diseases for over 30 years.

Carnitine has a fundamental biological role as a transporter of long-chain fatty-acids across the mitochondrial membrane. Approximately 99% of the body's Carnitine resources are located in skeletal and cardiac muscle and Carnitine deficiency states have been shown to cause functional defects of the heart.



On the basis of their distinct and multiple pharmacologic attributes, affecting myocardial and peripheral muscle energetics and function, various carnitine compounds are currently being studied in conditions such dialysis in heart failure (HF) patients, peritoneal dialysis and intermittent claudication.

Cardiovascular & Metabolic Pipeline

Cardiovascular Diseases		
• Luso-Inotropic agents	Heart Failure (HF)	Discovery
• Ouabain & Adducin antagonists	Hypertension & other cardiovascular indications	Discovery
• Thymosin β4[a]	Myocardial Infarction	Pre-IND
• Thymosin β4[a]	Wound healing & Venous Stasis Ulcers	Phase II
• Istaroxime[b]	Heart Failure (HF)	Phase II
• Rostafuroxin	Hypertension & other Cardiovascular indications	Phase II
• Statins/Omega-3 PUFA	Cardiovascular prevention	Phase III
• Propionyl-L-Carnitine	Intermittent Claudication	NDA submitted
Metabolic Diseases		
• CPT1 inhibitors	Diabetes/Obesity	Discovery
• PED/PLD1 interaction inhibitors	Diabetes	Discovery
• PPAR agonists	Diabetes	Discovery
• Teglicar	Diabetes	Phase II
Dialysis		
• L-Carnitine[c]	Peritoneal Dialysis	Phase II
• Propionyl-L-Carnitine	Dialysis in HF patients	Phase II

a Co-developed with RegeneRx Biopharmaceuticals Inc. (USA);
b Out-licensed to Debiopharm S.A. (CH);
c Developed by Iperboreal Pharma S.r.l. (I).

Luso-Inotropic agents

Project objective: development of new luso-inotropic agents on the basis of their ability to selectively inhibit Na+/K+ -ATPase and stimulate sarcoplasmic reticulum Ca2+ (SERCA2) pump without increasing cardiac oxygen consumption.

Ouabain & Adducin antagonists

Project objective: development of new antihypertensive drugs focusing on the identification of two main genetic-molecular targets underlying essential hypertension in a sub-set of patients:

- Adducin;
- Endogenous ouabain (EO).

CPT1 inhibitors

Project objective: design & discovery of selective and reversible inhibitors of the hepatic carnitine palmitoyltransferase-1 (CPT-1) isoform.

One selected compound (Teglicar - ST1326) is currently undergoing phase II studies.

A structurally similar compound with interesting improved characteristics (ST2425) has also been identified.

Central inhibition of CPT1 in the hypothalamus is being studied as a possible pharmacological target for food-intake modulation for the treatment of obesity. Teglicar has been identified as the lead compound.

PED/PLD1 interaction inhibitors

Project objective: design and screening *in vitro* and *in vivo* of a series of potential PED/PLD1 interaction inhibitors capable of enhancing insulin sensitivity.

ST4000, a selected hit compound, has shown activity in insulin resistant animals over-expressing PED.

PPAR agonists

Project objective: design and screening *in vitro* and *in vivo* of a series of potential PPAR α-dominant dual agonists.

ST2518, a molecule with a fibrate-related structure, has shown strong activity in decreasing in hyperglycemia in animals while improving lipid profile, with no increase in body weight and no evidence of oedema risk.

Thymosin β4

Thymosin β4 (Tβ4) is a 43 amino acid peptide currently under co-development by **sigma-tau** and RegeneRx. Clinical trials are being planned in patients with venous stasis ulcers. Interest in Tβ4 has recently been raised as a result of data obtained in myocardial infarction mouse models.

Istaroxime

Istaroxime is an innovative and novel lusitropic and inotropic (luso-inotropic) agent, which improves myocardial efficiency. Istaroxime acts as a calcium cycling modulator via the inhibition of Na+/K+ -ATPase and activation of SERCA ATPase. The overall hemodynamic and biochemical profile supports Istaroxime's role as a novel treatment option in Heart Failure.

Istaroxime is currently in phase II in decompensated HF patients.

Licensed-out to Debiopharm S.A. (CH).

Analogs/derivatives are being evaluated.

Rostafuroxin

Rostafuroxin is a digitoxygenin derivative devoid of any cardiac activity, which selectively interferes with the Na+/K+ pump correcting its functional abnormalities without interfering with other receptors involved in blood pressure regulation or hormonal homeostasis.

Na+/K+ pump hyperactivity is related to certain genotypes involving ouabain and adducin genes. This opens the possibility to identify potentially responsive patient subgroups.

Rostafuroxin has been studied in patients with mild essential hypertension, namely:

- Phase II pilot study vs. placebo 4wk treatment: clinically significant reduction in BP at 1mg and 5mg;
- Phase II db study vs. Losartan (46/23pts) 3 months treatment at 0.5 mg: similar rate of responders;
- Phase II db dose-finding, cross over study (440 pts): recently concluded.

Omega-3 PUFA and Statins

Recent large epidemiological trials have shown the beneficial effect of statins and Omega-3 PUFA in preventing cardiovascular morbidity and mortality (CTT, Lancet 2005; GISSI Prevenzione, Lancet 1999). Currently the CV morbidity and mortality preventive potential of Omega-3 PUFA is being studied in HF (GISSI-HF), in high risk patients (RISCHIO PREVENZIONE) while its putative anti-arrhythmic (AF) protective effect is being studied in the forωard trial and will be assessed in post-CABG patients (OPERA trial).

A new formulation combining Omega-3 PUFA and micro-encapsulated statins has been developed in cooperation with GP-Pharm (Spain) with the objective of:

- maintaining the clinical benefits of both drugs;
- potentiating their effects, synergistically;
- improving patient compliance.

Following an EMEA recommended registration path, bioequivalence studies are being performed to compare the new formulation with the concomitant administration of the single drugs.

PUFA *PolyUnsaturated Fatty Acids;* ***AF*** *Atrial Fibrillation;* ***CABG*** *Coronary Artery Bypass Grafting*

Propionyl-L-Carnitine (PLC) in Intermittent Claudication (IC)

Propionyl-L-Carnitine is an L-Carnitine derivative preferentially taken up by peripheral muscles, where it enhances mitochondrial energy production and replenishes the intracellular coenzyme-A pool. In addition, it has also been described as potentiating microcirculation blood flow.

Propionyl-L-Carnitine is currently being studied in a phase II/III double-blind trial in patients with IC who undergo a concomitant supervised physical training program.

Teglicar

sigma-tau's extensive research history in mitochondrial pharmacology has led to the investigation of new targets for the treatment of metabolic disorders in which energy metabolism plays a significant role, such as in hepatic gluconeogenesis.

Teglicar is a selective inhibitor of hepatic carnitine palmitoyltransferase 1 (CPT1), a mitochondrial enzyme. CPT1 blockade leads to the inhibition of fatty acid β-oxidation, ketone body formation and gluconeogenesis. Teglicar is currently undergoing phase II clinical trials in diabetic patients.

L-Carnitine in Peritoneal Dialysis (PD)

Peritoneal Dialysis is used in approximately 11% of all end stage renal disease (ESRD) patients in the US and EU.

L-Carnitine is currently undergoing studies as an osmolar agent, in order to reduce the glucose content of dialysis bags. In particular, nocturnal bags may be the most suitable for L-Carnitine replacement. Reduction of the glucose content and/or its substitution with a more biocompatible osmolar agent could help maintain the integrity of the peritoneal membrane.

This project is in phase II and it is object of an agreement between **sigma-tau**, Iperboreal Pharma and Baxter.

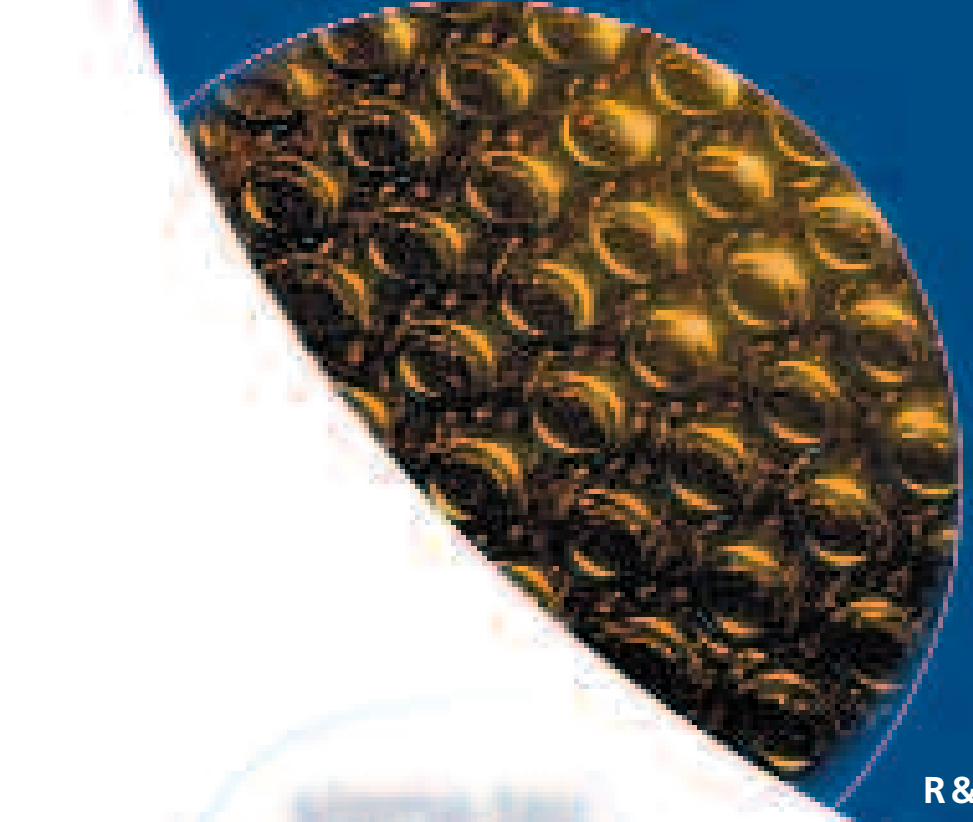
Propionyl-L-Carnitine (PLC) in Dialysis in HF patients

Two PLC doses (3 and 6 mg/kg) have been studied in dialysis patients with left ventricular hypertrophy (phase II).

The study primary end-point is a quality of life score (KDQ).

Cardiac function is evaluated ultrasonographically as a secondary end-point.

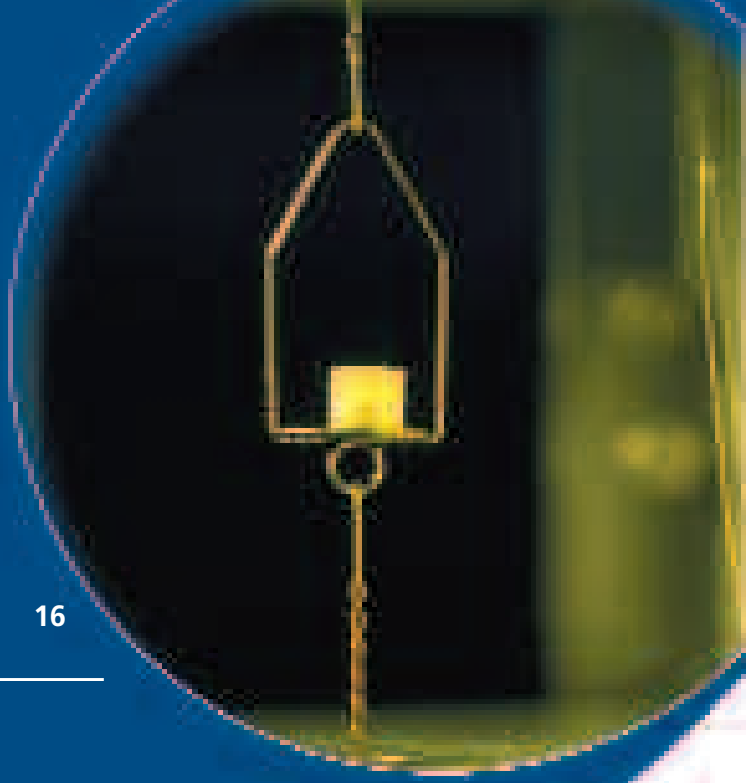
Data suggest some degree of activity that needs to be characterized in further studies.



R&D Partnerships

sigma-tau has established important research partnerships with internationally renowned research centers and organizations:

- **Endocrinology and Oncology Institute**, National Research Council, Naples, Italy
- **Dept. of Internal Medicine**, University of "Tor Vergata", Rome, Italy
- **Center for Biomolecular Sciences**, University of St. Andrews, North Haugh, St. Andrews, Scotland
- **Dept. of Nephrology**, Bergamo Hospital, Italy
- **University of Oklahoma Health Science Center**, Oklahoma City, OK, USA
- **Ohio State University**, Columbus, OH, USA
- **University of Utah Health Science Center**, Salt Lake City, UT, USA
- **University of Florida**, Gainesville, Gainesville, FL, USA
- **Northwestern University Division of Cardiology**, Chicago, IL, USA
- **Loisiana State University Health Science Center**, Shreveport, LA, USA
- **The Winters Center for Heart Failure Research**, Houston, TX, USA
- **University of Alabama, Division of Cardiovascular Disease**, Birmingham, AL, USA
- **University of Iowa Hospitals and Clinics**, Iowa City, IA, USA
- **New Orleans Center for Clinical Research (NOCCR)**, New Orleans, LA, USA
- **Massachusset General Hospital**, Harvard Medical Center, MA, USA
- **Colorado Health Sciences Center**, Colorado, USA
- **University of California at Los Angeles**, CA, USA



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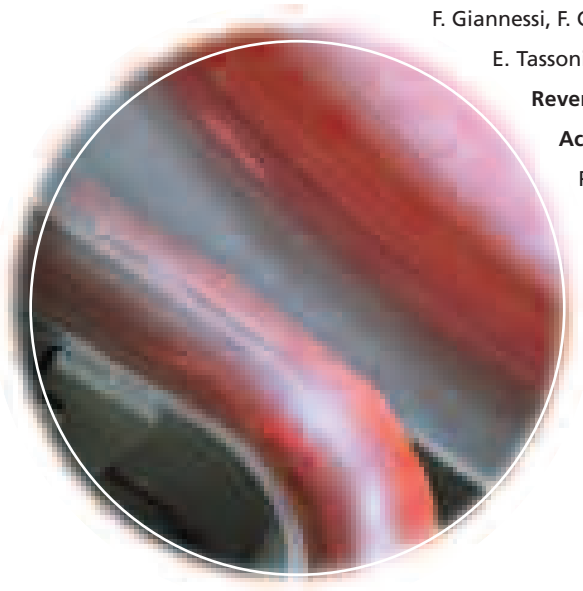

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