sigma-tau

R&D
in Oncology

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 Cancer 4

The Unmet Medical Needs

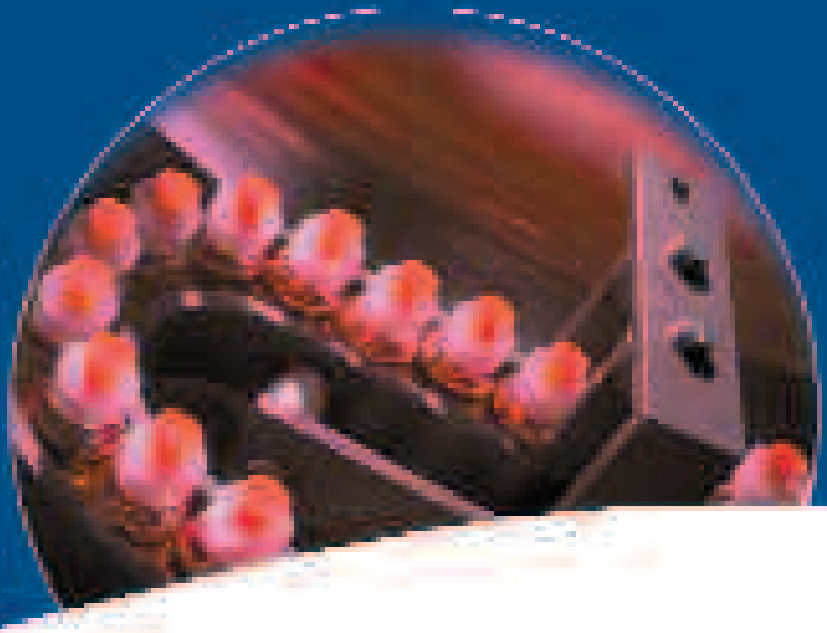
In 2005, 7.6 million people died of cancer out of 58 million deaths worldwide. The WHO projects cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015, and 11.4 million dying in 2030.

In recent years, increased research and development has given hope to many cancer patients, extending life-expectancy and saving lives for some of the most prevalent and intractable cancers. Unfortunately, despite significant investment, a lot remains to be achieved, with treatments still offering only limited hope for many cancer patients.

Cancer treatment can often be extremely debilitating for patients and calls for intensive commitment from family members. Research into more effective and well tolerated supportive treatments, to improve the quality of life of patients and long-term survivors, is of increasing importance.

Oncology Market

The size of the Oncology market has more than doubled in the past five years, with global sales reaching $35 billion in 2006. The market is now growing at around 20% and is expected to reach $62 - 70 billion in 2010. This increasingly competitive environment will ensure that only the most effective and well tolerated treatments make it to market.



sigma-tau's investment in the research of innovative cancer treatments is extensive. Its objective is to provide an integrated approach to the future management of cancer patients through various therapeutic options: cytotoxics, differentiating agents, immuno-therapeutics and supportive care.

sigma-tau's R&D oncology pipeline highlights the diversity of this approach, with active projects in:

- **Wide range of therapeutic approaches** using critical mechanisms of action related to tumor growth and spread, including cyto-differentiation and apoptosis modulation, signal transduction inhibition, immuno-modulation and cytotoxic potentiation, anti-metastatic and antivascular agents; and supportive care;
- **Advanced technologies** (chemotherapeutic and biotechnology products);
- **Variety of therapeutic indications** including melanoma, glioma, high incidence solid tumors;
- **Different stages of development**, with a wide basic and exploratory research effort (synergizing with a long standing expertise in fine chemistry research to identify lead compounds for validated pharmacological targets) as well as a significant involvement at the clinical level.

Oncology Pipeline 6

Project/Product	Description	Indication	Status
• Antimetastatic agents[a]		Various tumors	Discovery
• Cytodifferentiating and proapoptotic agents		Various tumors	Discovery
• Cytotoxics		Various tumors	Discovery
• Targeting therapy (HSP90[a])		Various tumors	Discovery
• DN30[b]	Anti-C-Met Antibody	Various tumors	Pre-IND
• SST0001[a]	Heparanase Inhibitor	Multiple Myeloma Advanced Metastatic Cancers	Pre-IND
• Adarotene	Chemotherapy Enhancer	Various tumors	Phase I
• Namitecan	Topo I Inhibitor	Various tumors	Phase I
• PAGRIT®	Radioimmuno-Therapy kit	Glioma & NHL	Phase I
• IART®	Radiotherapy kit	Breast Cancer	Phase II
• Gimatecan[c]	Topo I inhibitor	Solid Tumors (NSCLC, CRC, Brain etc)	Phase II
• ALC	Acetyl-L-Carnitine	CIF (Cancer-Induced Fatigue)	Phase II
• Thymosin α1[d]	Immunotherapy	Melanoma/Hepatocarcinoma	Phase III
• Leuprolide[e]	GnRH agonist	Prostate Cancer	Phase III
• ALC	Acetyl-L-Carnitine	CIPN (Chemotherapy-Induced Peripheral Neuropathy)	Phase III

a property of sigma-tau Research Switzerland S.A. (CH);

b managed by sigma-tau Research Switzerland S.A. (CH);

c out-licensed to Novartis Pharma A.G. (CH);

d co-developed with SciClone Pharmaceuticals International Ltd. (USA);

e co-developed with GP-Pharm (E).

Discovery Projects

sigma-tau pre-clinical oncology projects are aimed at reinforcing the therapeutic approaches currently in clinical development.

Antimetastatic agents*

New heparins (devoid of anti-coagulant activity) - heparanase inhibitors: SST0001

The aim of the project is to inhibit the heparanase enzymatic activity which is able to disrupt heparan sulphate proteoglycans (HSPGs) thus altering extracellular matrix (ECM) and basement membrane (BMs). ECM and BM are key to the integrity and functional state of tissues.

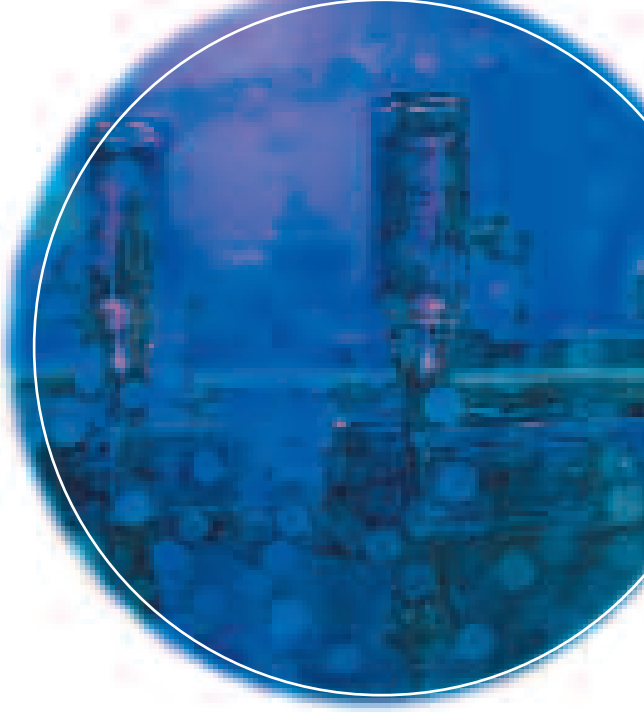
Heparanase is preferentially expressed in metastatic cell lines and specimens of human breast, colon, lung, prostate, ovary, pancreas and liver tumors.

Heparanase-inhibiting molecules reduce the incidence of experimental metastasis by more than 90% (Vlodavsky et al., Nature Medicine; 1999, 7: 793).

SST0001, selected for development, shows strong anti-heparanase activity, without anticoagulant effects, and inhibits metastasis formation in various metastatic tumor animal models. It also shows activity in human multiple myeloma models.

IP expires in 2021.

**Property of sigma-tau Research Switzerland S.A.*



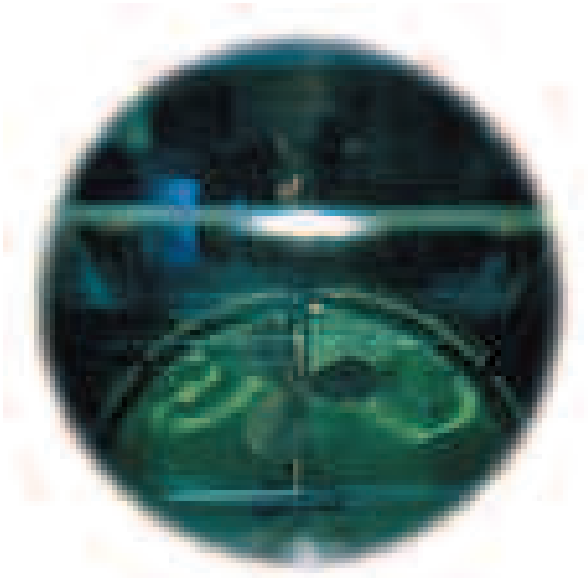
Cytodifferentiating & proapoptotic agents

Chemotherapy enhancers: Adarotene

Apoptosis is recognized to be an important phenomenon in antitumor drug-induced tumor cell killing and susceptibility to apoptosis of tumor cells is a determinant of efficacy of chemotherapy.

Synthetic retinoid related molecules (RRM's), which are reported as potent inducers of apoptosis, represent an emerging class of potentially useful agents. Whereas the biological effects of natural retinoids are mediated by the retinoid receptors, the proapoptotic activity of RRM's seems to be independent of retinoid receptors.

Indeed, RRM's exert growth-inhibitory activity and induce apoptosis in retinoid-resistant cells, and these cellular effects cannot be blocked by RAR-antagonists.



Within this project, a novel atypical retinoid, Adarotene, was selected by sigma-tau as a potent proapoptotic molecule for clinical development.

Cytotoxics

Camptothecin derivatives: Gimatecan, Namitecan

sigma-tau has developed a strong expertise in the area of camptothecin derivatives, from discovery to product development.

This has led in the recent past to the identification of a number of compounds that were considered for development. One of these, Gimatecan is currently in phase II and has been the object of a development and licensing agreement with Novartis.

The research for new camptothecin derivatives is based upon the following main criteria:

- activity on a wide panel of experimental tumors *in vivo*;
- stability of the ternary complex;
- antitumor activity on different resistant tumors (i.e. BCRP and/or MDR; positive or in unidentified mechanism driving the tumor to be resistant);
- superior therapeutic index vs currently available compounds.

Namitecan, another drug within this class, has been moved by **sigma-tau** into clinical testing.

Targeting therapy

New Histone Deacetylase Inhibitors (HDACi)

Rationale of the project

- Use of chemical original ST molecular backbone to generate HDACi;
- Use of a "complex and integrated screening method" to identify new HDACi with a different molecular-pharmacological profile respect to the known HDACi;
- Identification of molecules active on HDAC which possess additional molecular mechanism on pathways regulating apoptotic signal;
- Identification of new orally active molecules.

Status of the project

3 new compounds have been selected for their HDAC *in vitro* inhibition, anti-proliferative potency and in *in vivo* antitumor activity.

Tumor Homing

This project is based upon the tumor-specific delivery of novel camptothecin-RGD peptides conjugates with the aim of:

- reducing systemic toxicity of the camptothecin derivatives;
- improving the therapeutic index of camptothecin by delivering new RGD-camptothecin derivatives to tumor tissue overexpressing αvß3/αvß5 integrin.

Currently one molecule has been selected, showing:

- high specificity against cells expressing the molecular targets;
- antitumor activity on human ovarian cancer expressing αvß3/αvß5 integrins.

HSP90 inhibitors*

Heat Shock Protein 90 (HSP90) is a constitutively expressed molecular "chaperon" that guides the normal *folding*, intracellular disposition and proteolytic turnover of many "client" proteins, which are key regulators of cancer cell growth and survival. HSP90 typically interacts with its clients in a cyclical, interactive fashion driven by multiple rounds of ATP hydrolysis.

The objective of the project is the lead identification of new HSP90 ATPase binding site inhibitors.

To date, the primary screening has allowed the selection of three molecules, which are currently under *in vivo* investigation.

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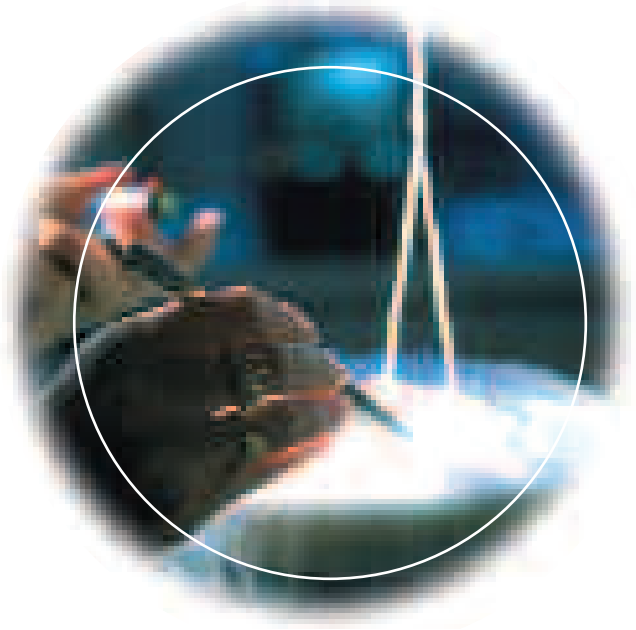
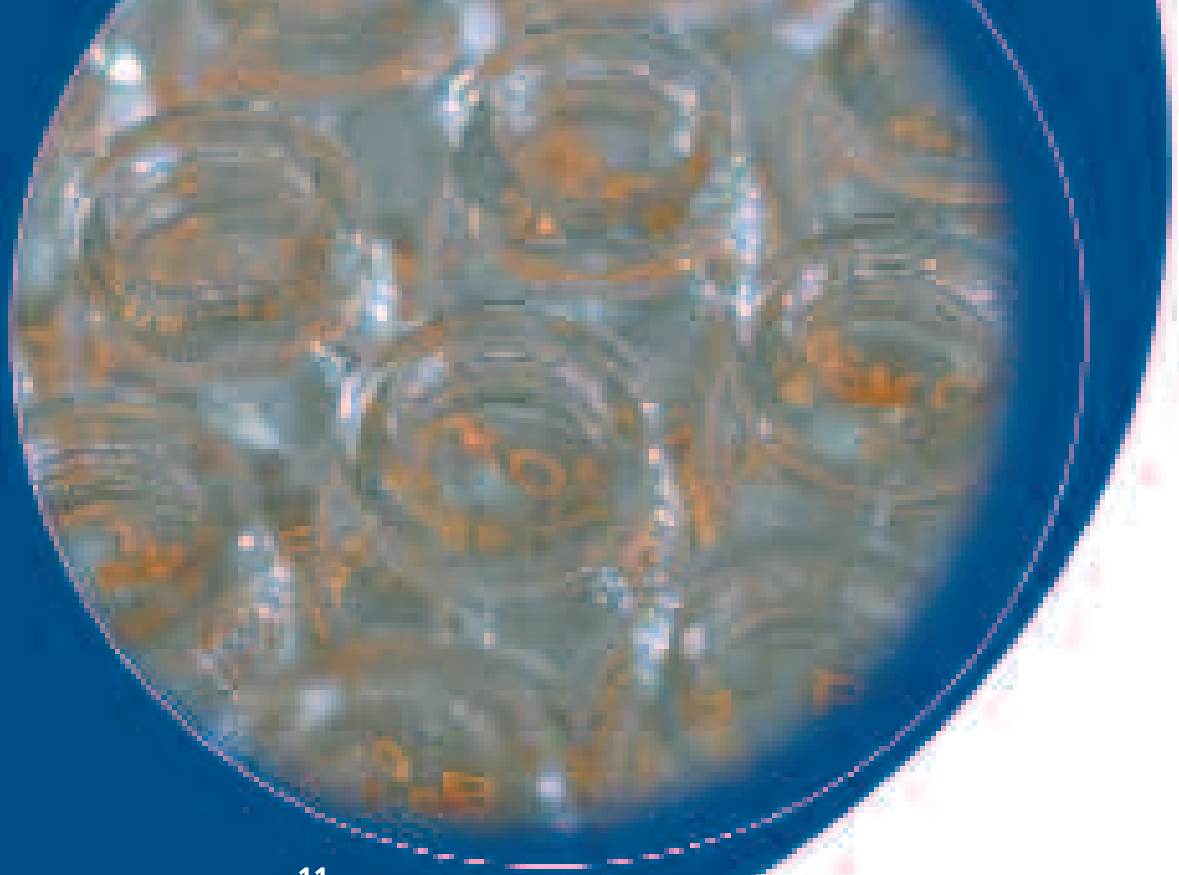




Products in Clinical Development

DN30*

DN30 is a monoclonal antibody directed vs the c-Met protein.

c-Met is the hepatocyte growth factor receptor (HGFR) encoded by the protooncogene MET.

Upon HGF stimulation, c-Met induces several biological responses that lead to invasive growth.

Abnormal c-Met activation in cancer correlates with poor prognosis, where aberrantly active c-Met triggers tumor growth, angiogenesis and metastasis.

Silencing c-Met can then interfere with these processes leading to cancer cell growth and spread inhibition.

sigma-tau Research Switzerland S.A. has in-licensed DN30 with a peculiar shedding activity, as well as other anti c-Met antibodies, and is currently carrying on the development of the antibodies for clinical use in therapy and diagnosis.

**Managed by sigma-tau Research Switzerland S.A.*

SST0001*

The objective of this project is to identify compounds exhibiting inhibition of heparanase enzymatic activity: this enzyme disrupts heparan sulphate proteoglycans (HSPGs) thus altering extracellular matrix (ECM) and basement membrane (BMs). ECM and BM are key to the integrity and functional state of tissues.

Heparanase is preferentially expressed in metastatic cell lines and specimens of human breast, colon, lung, prostate, ovary, pancreas and liver tumors.
Heparanase-inhibiting molecules reduce the incidence of experimental metastasis by more than 90% (Vlodavsky et al., Nature Medicine; 1999, 7: 793).

SST0001, selected for development, shows strong anti-heparanase activity, being devoid of anticoagulant effects, and with the ability to inhibit metastasis formation in various metastatic tumor animal models and activity also in human multiple myeloma models.
IP expires in 2021.
**Property of sigma-tau Research Switzerland S.A.*

Adarotene (ST1926)

Adarotene is a retinoid derived compound which has shown proapoptotic abilities in pre-clinical models of hematological as well as solid tumors (i.e. ovarian ca.) inducing a DNA damage response and affecting the modulation of cancer cell survival pathways.

When used in combination with other anticancer agents, Adarotene has shown a significant synergistic effect in most of the combinations and models tested.

A phase I study in solid tumor (ovarian ca.) has been started. A new formulation study is being undertaken to optimize patient exposure.

Namitecan (ST1968)

It's an injectable camptothecin derivative showing:

- High or superior therapeutic index when compared to Irinotecan and Topotecan (i.v. treatments);
- Improved pharmacological profile vs. Irinotecan and Topotecan;
- Impressive activity against several tumor xenograft models;
- Activity on a DX, Paclitaxel and DDP-resistant tumor xenografts;
- Activity on a tumor cell line expressing a topo 1 mutation;
- A peculiar PK/PD profile because its impressive prolonged half life in tumors and lack of metabolism.

Namitecan is currently in Phase I.

PAGRIT®

(Pre-targeted Antibody Guided RadioImmunoTherapy)

PAGRIT® is based upon stepwise administration of different reagents (Mab; Avidin and Biotin) to optimize radioisotope tumor targeting.

Inventors: G. Paganelli et al. (European Institute of Oncology, Milan - Italy).

Technology is property of **sigma-tau**.

Current plans are aimed at evaluating PAGRIT® for the treatment of tumor expressing specific targets like tenascin (e.g. glioma; non Hodgkin's lymphoma).

Status: Phase I.

Data generated on the basis of an Investigator's IND showed significant effect in glioma patients. However, on the basis of pilot clinical evidence, development is being focused on NHL patients.

IART®

(Intraoperative Avidination for Radionuclide Treatment)

IART® is based upon intraoperative administration of avidine for optimizing tumor targeting of biotinylated radioisotope systemic post-operative treatment.

Inventors: G. Paganelli et al. (European Institute of Oncology, Milan - Italy).

Technology is property of **sigma-tau**.

Status: Phase II.

Phase III clinical studies will be focused on Stage I/II breast cancer patients undergoing surgery and adjuvant radiotherapy.

Gimatecan

Based on a cooperation with the National Cancer Institute of Milan and the University of Milan, **sigma-tau R&D** has identified and started to develop Gimatecan, a novel second generation oral topo-I inhibitor.

sigma-tau granted a patent and know-how license to Novartis, which acquired the rights to further develop and commercialize the drug worldwide.

Gimatecan is currently in Phase II.

Acetyl-L-Carnitine (ALC) in Cancer-Induced Fatigue

ALC is the object of another clinical development program for the treatment of fatigue in patients with breast cancer undergoing chemo/radiotherapy in the adjuvant setting.

Proof-of-concept data have been generated by some investigators, using L-Carnitine, showing a significant effect in non-anemic patients undergoing several chemotherapy regimens.

An early phase II trial is currently ongoing in several US centers on patients with radiotherapy-associated fatigue following surgery and chemotherapy for potentially curable breast cancer.

Thymosin alpha 1 (Tα1)

Tα1 affects the activity of immunologic cells (e.g. NK, cytotoxic lymphocytes) as well as that of a number of immunological mediators (e.g. cytokines, surface-marker proteins as MHC-1) that may play a role in fighting cancer.

These phase III trials in melanoma and hepatocarcinoma are part of an agreement with SciClone Pharmaceuticals International Ltd.

Tα1 is also being studied for the treatment of interferon resistant HCV patients. A phase III program is in place in cooperation with SciClone.

Leuprolide

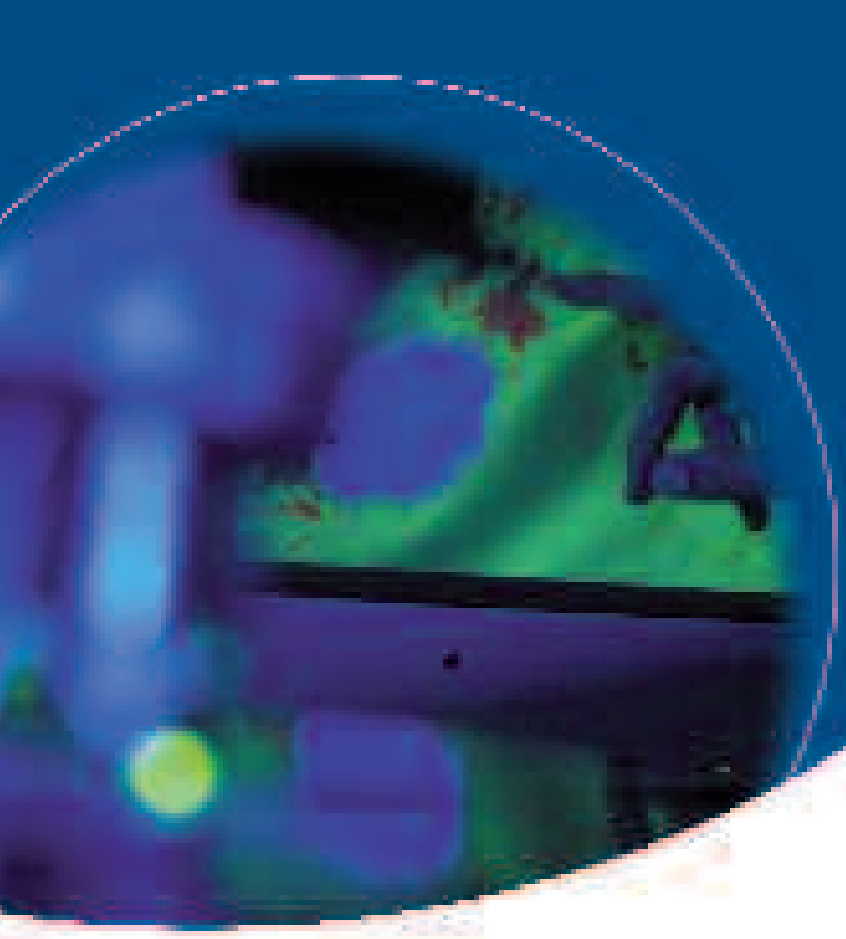
A phase III program currently ongoing in Europe and US, in cooperation with GP-Pharm (Barcelona, Spain), to develop innovative 1 and 3 month slow release formulations of Leuprolide for the treatment of hormone-sensitive prostate cancer.

Acetyl-L-Carnitine (ALC) in Chemotherapy-Induced Peripheral Neuropathy (CIPN)

ALC is the object of a comprehensive clinical development plan for the treatment of CIPN, which is a frequent and potentially severe side effect of taxanes, platinum-based cytotoxics and vinca alkaloids.

Proof-of-concept data have been generated by various investigators, showing a significant decrease in incidence and severity of CIPN with ALC.

Phase III trials are currently ongoing in patients with taxanes/platinum-induced, as well as vincristine-induced, peripheral neuropathy.



sigma-tau has various Immuno-Oncology projects under development with Tecnogen, the group's biotechnology R&D center.

Tecnogen Immuno-Oncology Projects

Product	Phase	Therapeutic target	Active Product Ingredient	Goal
• IART®	Phase II	Breast cancer	Avidin & Clinical Grade Manufacturing	Process Development
• PAGRIT®	Phase I	Glioma & NHL Avidin	Monoclonal Antibodies & Clinical Grade Manufacturing	Process Development
• PTX3	Pre-IND	Aspergillosis	Recombinant PTX3 & Clinical Grade Manufacturing	Process Development

All projects are carried out in close cooperation with sigma-tau S.p.A. Immunology R&D Area

Tecnogen S.p.A., located in Piana di Monte Verna (Caserta), Italy, is a biotechnology Research & Development company, an innovative addition to sigma-tau's R&D organization.

Tecnogen is authorized by the Italian Health Authorities to manufacture clinical grade monoclonal antibodies and recombinant proteins.

R&D Partnerships

sigma-tau has an extensive network of collaborations with national and international academic institutions, NGOs and other pharmaceutical and biotechnology companies.

sigma-tau has established important research alliances and collaborations with leading oncology research centers and organizations such as:

- **National Cancer Institute of Milan,** Italy
- **European Oncology Institute of Milan**, Italy
- **Dept. of Agroalimentary Sciences,** University of Milan, Italy
- **Dept. of Industrial Organic Chemistry,** University of Milan, Italy
- **Institute Ronzoni,** Milan, Italy
- **Institute for Pharmacological Research "Mario Negri",** Milan, Italy
- **Consorzio Mario Negri Sud,** S. Maria Imbaro (CH), Italy
- **Southern European New Drug Organization (SENDO),** Milan, Italy
- **Center for Advanced Biotechnologies,** Genoa, Italy
- **Department of Biomedical Sciences and Biotechnology,** School of Medicine, University of Brescia, Italy
- **Oncology Center,** Aviano, Italy
- **Biotechnology Institute,** National Research Council, Rome, Italy
- **Department of Anatomy,** School of Medicine, University of Bari, Italy
- **Dept. of Pharmacology,** University of Naples, Italy
- **Dept. of Pharmacology,** University of Salerno, Italy
- **Dept of Chemistry,** University of Zurich, Switzerland
- **Dept. of Medicine,** Brown University, RI, USA
- **Dana Farber Cancer Center,** Boston, MA, USA
- **Wistar Institute,** Philadelphia, PA, USA
- **Department of Pathology**, University of Alabama at Birmingham, Birmingham, AL, USA
- **Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives Faculté de Médecine**, Univ de Nantes, Nantes, FR

sigma-tau Group has acquired the exclusive US rights to Defibrotide, an investigational drug from Gentium (Villa Guardia, Italy). Defibrotide is currently under clinical development in Venous Occlusive Disease (VOD), a severe and fatal complication of conditioning therapy used in bone marrow transplantation.

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Gimatecan

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Pharmacokinetic of the novel oral camptothecin Gimatecan in patients with advanced or metastatic soft tissue sarcoma

Presented at AACR-NCI-EORTC San Francisco, October 22-26, 2007

E. Badaloni; W. Cabri; A. Ciogli; R. Deias; F. Gasparrini; F. Giorgi; A. Vigevani; C. Villani

Combination of HPLC "inverted chirality columns approach" and MS/MS detection for extreme enantiomeric excess determination even in absence of reference samples. Application to camptothecin derivatives

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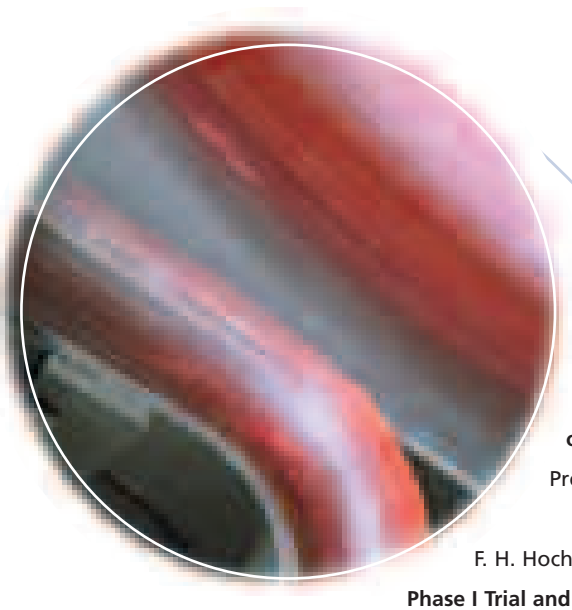

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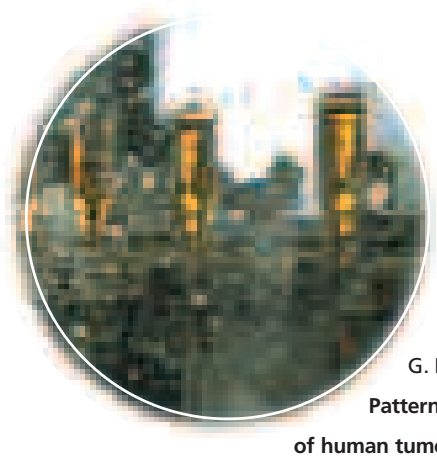

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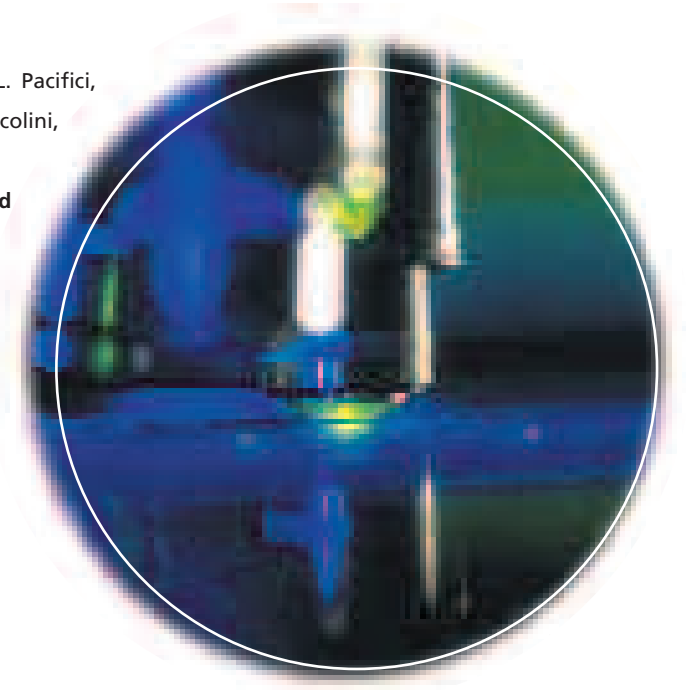

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Thymosin α1

"Thymosins in Health and Disease"
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