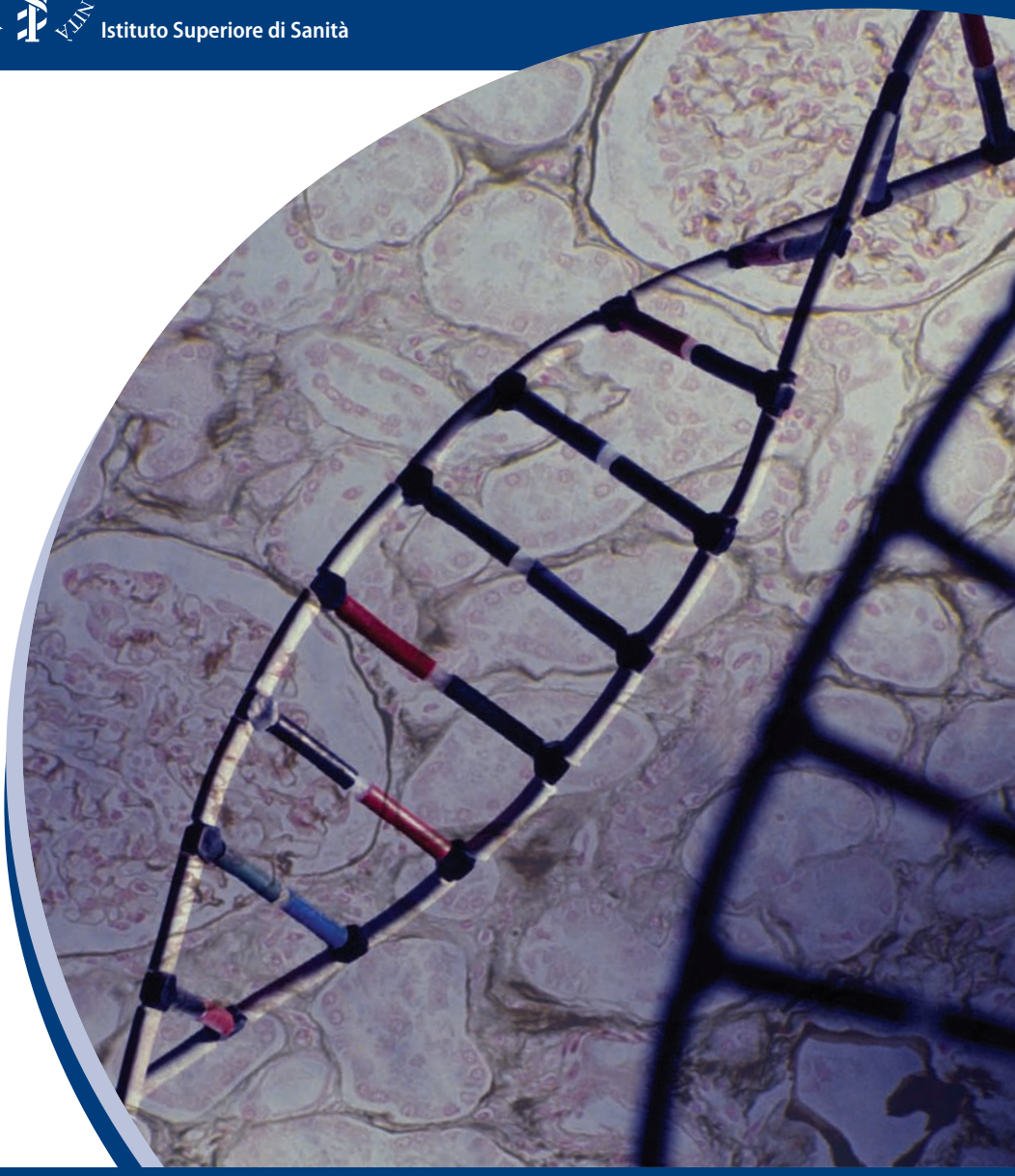
Istituto Superiore di Sanità



ISS: *your* biomedical research partner in Italy

INTELLECTUAL PROPERTY & INDUSTRIAL LIAISONS

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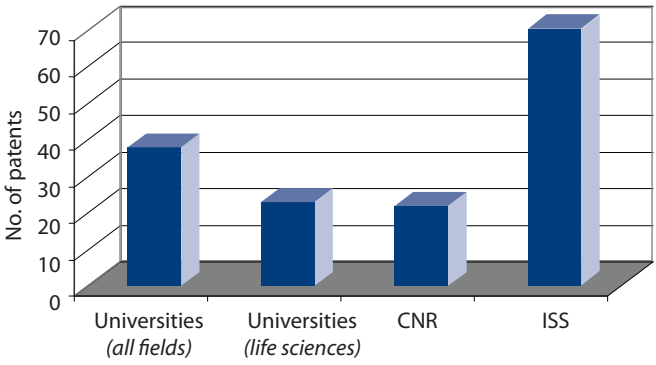
PARTNERING WITH ISS

ISS innovation

The Istituto Superiore di Sanità (ISS) is an engine for biomedical innovation in Italy. Under the leadership of its President, Prof. **Enrico Garaci** and on the wave of the patent law introduced by the Minister of Economy **Giulio Tremonti** in 2001, in the last 5 years the ISS Intellectual Property (IP) portfolio has skyrocketed from less than a dozen dormant patents to **68** actively marketed patent families.

Enrico Garaci

A number of patents that is three times that of the Department of Life Sciences of CNR (*National Research Council* in Italy) and almost double the average of an Italian university of the NETVAL (*Network per la Valorizzazione della Ricerca Universitaria*): 61 universities, 80% of teaching staff.



ISS (*2008*) *vs* Universities (*2007*) and CNR (*2008*)

The current IP portfolio comprises patent families, some granted, others in various stages of national and international prosecution, for *animal health* (2), *biomarkers* (6), *biomedical devices* (2), *biopharmaceuticals* (10), *cancer stem cells* (2), *cell-based therapies* (5), *diagnostics* (4), *DNA/RNA-based therapies* (7), *drug delivery systems* (3), *food technology* (1), *research reagents* (1), *re-styled drugs* (4), *software* (3), *vaccines & vaccine technologies* (18).

The IP portfolio is actively managed to achieve partnering with industry within the 30-month deadline for national/regional phase entry. At this time, patents with strong strategic potential and/or industry interest enter the national/regional phases in at least the three major markets (Europe, USA, Japan).

Filings that by such deadline are still orphans of industry partners are abandoned. This patent turnover strategy aims at making space for new filings while keeping patenting costs down. Patent preparation & filing is mandated, selectively by areas of expertise, to firms experienced in biomedical research in Italy, Europe and USA.

Science at ISS

ISS is at the heart of one of the largest bioscience areas in Italy and Europe, the Latium Region, where the majority of public and private research institutions are located. With its 7800+ scientists, Latium accounts for more than 23% of total research in Italy.

ISS is in downtown Rome, adjacent to "Sapienza", the largest university in Europe, to CNR and to numerous hospitals with active biomedical research departments. As the main technical-scientific organ of the Italian National Health Service and of the Ministry of Welfare/Health, its main funding source, ISS combines biomedical research with institutional consulting, training and regulatory control for the protection of public health. Its role in Italy is equivalent to the role of the US NIH and part of the role of the FDA, CDC, USDA, combined.

Research at ISS spans all fields of healthcare research with specific excellence in many areas, such as cancer research, poverty related diseases, vaccines, infectious diseases, dendritic cell research, neurosciences, and several other ones.

ISS is organized in the following Departments, Centres and Technical services:

Departments

- Cell Biology and Neurosciences
- Environment and Primary Prevention
- Food Safety and Veterinary Public Health
- Haematology, Oncology and Molecular Medicine
- Infectious, Parasitic and Immune-Mediated Diseases
- Technology and Health
- Therapeutic Research and Medicines Evaluation

Centres

- Centre for Immunobiologicals Research and Evaluation
- National AIDS Centre
- National Blood Centre
- National Centre for Chemical Substances
- National Centre for Epidemiology, Surveillance and Health Promotion
- National Transplant Centre

Technical services

- Service for Biotechnology and Animal Welfare
- Service for Data Management, Documentation, Library and Publishing Activities

Technology transfer at ISS

ISS research produces innovative technologies with commercial value.
The Intellectual Property & Industrial Liaisons Management moves technologies from the Lab to the marketplace to benefit society and the economy.
We accomplish this by developing and managing an array of partnerships with the private sector including licensing, collaborative research, sponsored research and European funded research consortia. In addition, we ensure that inventions receive proper intellectual property protection, and we serve as the ISS resource on industry relations.
We license cutting-edge technologies to companies (including start-ups) that have the financial, R&D, manufacturing, marketing, and, especially, managerial capabilities to successfully commercialize ISS inventions.

PATENTS UNDER ADVANCED DEVELOPMENT

- AIDS vaccines *(phase II, phase I, preclinical)*
- Omeprazole in cancer therapy *(phase II)*
- NNRTI in cancer therapy *(phase II)*
- Indinavir in cancer therapy *(phase II)*
- Dendritic cell-based cancer vaccines *(phase I)*
- Candida vaccine *(IND filing stage)*
- Fungal vaccine *(IND planning stage)*
- Cancer Stem Cells *(drug screening platform)*
- Colorectal tumor-associated antigen COA-1 *(pre-clinical)*
- RNAi of thymosin β4 for nervous tissue regeneration *(pre-clinical)*
- MicroRNA based therapies for cancer, cardiovascular and hematological diseases *(pre-clinical)*
- Acute lymphoblastic leukemia drug targets *(pre-clinical)*
- Novel multiple sclerosis treatments *(pre-clinical)*

Partnering with industry

ISS has an increasingly successful track record in partnering with industry, both large and small: out of 68 active patent families, 19 (28%) are the subject of licensing or options to license agreements. The international pharmaceutical and biotechnology industries are the primary targets of our technology marketing efforts.
Below there are selected cases of industry partnering. These cases are generating, or have posed the basis for, royalty streams back to ISS research:

Inflammatory Bowel Disease treatment
a novel way of treating IBD using a cholera toxin B
Dept. of Infectious, Parasitic and Immune-Mediated Diseases.
Licensed to SBL Vaccin AB (Sweden)

Proton Pump Inhibitors as anti-neoplastic agents
a novel use of PPI in cancer therapy
Dept. of Therapeutic Research and Medicines Evaluation.
Option to license by Astrazeneca Ltd. (UK)

NNRT inhibitors and RNAi in cancer therapy
novel use of NNRTIs, and a related RNAi approach to antagonize cell proliferation and induce cell differentiation
Service for Biotechnology and Animal Welfare.
Licensed to Fluofarma (France)

SGF for prevention of chemotherapy induced depletion of blood cells
a novel use of SGF in cancer therapy
Dept. of Haematology, Oncology and Molecular Medicine.
Licensed to IOM Ricerche (Italy)

Glucan-based vaccines and anti-glucan mab
a novel broad spectrum vaccine and therapeutic antibody for fungal diseases
Dept. of Infectious, Parasitic and Immune-Mediated Diseases.
Licensed to Novartis (Switzerland)

Peptide-based vaccine adjuvants
novel human vaccine adjuvants
Dept. of Infectious, Parasitic and Immune-Mediated Diseases.
Licensed to Alba Therapeutics (USA) and Novartis (Switzerland)

SAP-2 based vaccine against Candida infections in women
a novel vaccine for vulvovaginal infections
Dept. of Infectious, Parasitic and Immune-Mediated Diseases.
Licensed to Pevion Biotech (Switzerland)

Monoclonal antibodies to *E. coli*
for diagnostic use in livestock
Dept. of Food Safety and Veterinary Public Health.
Licensed to Biomerieux (France) and Dynax (USA)

Method of making T cells refractory to HIV superinfection
novel method for intracellular immunization
National AIDS Centre.
Licensed to MolMed (Italy) and Takara Bio Inc. (USA)

BENEFITTING FROM ISS TALENT

Benefits from collaboration with ISS talented scientists

- ISS has a 2000+ scientists skilled in all areas of advanced biomedical research.
- It has a sophisticated research infrastructure at par with peer international institutions.
- Its position at the centre of a vast Italian biomedical research network ensures that almost every research need can be satisfied directly or through network collaborations.
- It has significant collaborations with scientific and healthcare organizations in Europe, USA, Asia, and active partnerships and collaborations in Africa.
- ISS enjoys an international leadership position in several research areas such as, among others, AIDS vaccine research, fungal vaccines research, cancer vaccines, cancer research and cancer stem cells, CNS disorders, etc.
- ISS increasing participation in European research consortia testifies to its competitive research edge in many different fields.

EU-FUNDED CONSORTIA WITH ISS

A-CUTE-TOX, ADIPAR, ADRI, AEEC INFECTIONS, ALAVLSI, ALLIANCE-O, ALPHA RISK, ANIM, ALL.SEE, AQUAMAX, ARBAO-II, ARTRADI, AVIP, BIOPALMAR, BIOSAFEPAPER, BSETRANSMISSIONTOPR, CANCERANDMSI, CASCADEVIROLOGY, CCLATINAMERICA, CHEMORES, CHILD-INNOVAC, CJD MARKERS, CLOSTRIDIA, COCOON, CO-EXTRA, COHERENT, CPDW, CREATE, DC-THERA, DEMOWATERCOLI, DENDRITOPHAGES, DEVANI, DRESP2, EACCAD, EATRIS, ECHINORISK, ECRIN-PPI, EDCTP, EDEN, EMF-NET, EMPRO, EPRDOSRECONSTRUCTION, EPREMED, EQUAL, ERA-AGE, E-RARE, ERRICCA 2, ERYTHRON, EUROCAN+PLUS, EUROCLOT, EUROGLIA 2002, EUROPHEN, EUROSIDA 2005-2009, EUROVOLTE, EVENT, FLUARRAY, FLUMODCONT, FLUPAN, FLUSAFE, FN-ALPHA AND HBV VACC, FURAN-RA, GAP, GEHA, GENINCA, GENOMEUTWIN, GENUS CLOSTRIDIUM, HALE, HELLODOC, HOMITEB, HORIZONTAL-HYG, IMECS, INNATE DEFENSE, INTERPHONE, INVADE, INVADERS, LONG-DRUG, MAESTRO, MARE, MED-VET-NET, MICROBEARRAY, MILD-TB, MUVAPRED, NEAT, NEOTIM, NETTOX, NEUROPRION, NeuroproMiSe, NEW HIV TARGETS, NOTE, OCHRATOXINA-RISK ASS, OPTIMOILS, OSIRIS, PANFLUVAC, PCM PRION, PECO/COPERNICUS, PERIAPT, PNC-EURO, POLYMOD, PREDICT-IV, PREGVAX, PRIOMEDCHILD, RADNA, RADON EPIDEMIOLOGY, REPROTECT, SAFE FOODS, SAFEFOODERA, SALM-GENE, SCARLET, SEAFOODPLUS, SEAS, SIGMAL, SIMBAG-FEED, SMART-PIV, SOUL, STARFLAG, STOP LATENT, StopLATENT-TB, STRATFEED, STREP-EURO, TEDDY, TRICHIPORSE, TRUEFOOD, TSELAB, UNIFIED, VIAV, VIRGIL, VIROBATHE, VITAL, VIVAXNIS.

Core research skills, labs and areas of excellence

AIDS vaccine research: over a decade-long period of R&D on AIDS vaccines, ISS has built a comprehensive and all-inclusive vaccine development platform from discovery to development, regulatory affairs, clinical research organization management, clinical testing and GMP manufacturing. Its National AIDS Centre coordinates **AVIP**, a large leading HIV vaccine research project funded by the European Commission.

Animal modelling: ISS is a 3R policy (reduction, refinement and replacement) compliant institution committed to eliminating unnecessary use of animal models in research. Animal models are however indispensable to study life threatening diseases and hence ISS built over the years animal modelling expertise and facilities to respond to research needs in a variety of disease areas.

Behavioral neuroscience: ISS has an active program in behavioral neuroscience research focused on the development of animal models for selected disorders such as Down's and Williams' syndromes, depression, uni- & bi-polar disorders.

Cancer biobank: ISS is building a core tissue bank facility as a repository of patient-specific cancer biopsies for use in research, including cancer stem cell research.

Cancer Stem Cells (CSC): ISS is emerging as one of the leading research institutions worldwide in CSC research. Its CSC drug discovery platform is being increasingly engaged for the high throughput screening of both novel and commercial chemotherapeutic agents.

Cancer vaccines: ISS has a mature program for cell-based therapies, stemming from a long-lasting expertise in the field of tumor immunology and immunotherapy. It has recently launched a validated GMP facility, **FaBioCell**, dedicated to manufacturing cell products for clinical trials, both for ISS use and as a service to third parties.

Degenerative neurological diseases: ISS is one of the leading institutions in Europe for research in a number of degenerative neurological diseases, such as Creutzfeldt-Jakob disease, Bovine Spongiform Encephalopathy, Alzheimer and Multiple Sclerosis. Its Dept. of Cell Biology and Neurosciences coordinates **NeuroproMiSe**, a large research project funded by the European Commission to study neuroinflammatory diseases and multiple sclerosis.

Emerging RNA-based therapeutic approaches: RNAi and miR technologies, together with viral vectors delivery systems, are embedded and actively used over a broad range of ISS research activities, with applications, among others, for cancer therapy, cardiovascular, blood disorders and nervous tissue regeneration.

Environmental risk evaluation platform: advanced techniques are used to study health risks posed by chemical, physical and biological agents, and their effects on human health and on environment. Target substances are persistent toxic pollutants, pesticides & biocides, carcinogens, materials used in cosmetics, food & toy industries, waste and water quality.

Food safety and technology: food-transmitted diseases, antibiotic and chemical residues in meat and fish, the impact of nutrition on neurodegenerative processes and obesity, food allergies (such as coeliac disease) are some of the areas of historical research of the food safety and technology groups at ISS.

Fungal infections: the Dept. of Infectious, Parasitic and Immune-Mediated Diseases has built, over decades of research, a formidable platform for antigen discovery & selection and pre-clinical testing of novel fungal vaccines and for the screening and testing of the efficacy of new antifungal agents.

Genomics & proteomics: ISS is building up genomics & proteomics skills and facilities by teeming up with the world leaders in the field. High throughput equipment for liquid handling, microarrays, forward & reverse proteomics are increasingly being used in the study of genes and protein functions.

Medical devices: ISS has comprehensive skills in the fields of radiotherapy, radiation protection from ionising and non-ionising radiation , environmental pollutants, biomaterials, certification of a variety of medical devices such as stents, cardiac valves, prosthesis and implants, telemedicine techniques & equipment.

Oncology research platforms: cancer research at ISS is deeply entrenched across a variety of platforms and by groups in different departments and centres. Skills and resources range from discovery platforms over a variety of cancer research fields and approaches, to preclinical and clinical testing, including phase I clinical trial testing and regulatory affairs.

Pharmacological research platform: ISS has a comprehensive pharmacological research platform which includes molecular pharmacology, pharmacokinetics and pharmacogenetics, design and synthesis of new compounds, preclinical studies, and the coordination of large-scale clinical trials. Therapeutic areas cover, among others, cancer, child's health, cardiovascular, metabolic, endocrine and neurodegenerative diseases, aging, and HIV/AIDS drugs.

Phase I clinical testing: ISS is the regulatory agency in Italy for approval of phase I clinical studies. It has henceforth assembled in-house skills, including regulatory and clinical trial management for the conduction of phase I studies in all areas of clinical research.

Regulatory expertise: ISS is the technical-scientific consultant for AIFA, the Italian Drug Agency, and to EMEA, the European Drug Agency. Its multidisciplinary team of regulatory experts is vested with the mission to inspect GMP facilities for clinical and commercial production, validate assays and tests, evaluate IND dossiers for drugs & biologicals, monitor phase I trials and after-launch use.

Translational cancer research platform: ISS, in alliance with major Italian cancer research institutions (universities research hospitals, research charities), is promoting, within the European Advanced Translational Research Infrastructure in Medicine initiative (**EATRIS**), the establishment of a translational cancer research platform aimed at accelerating the translation of research results to the clinic.

Veterinary public health: ISS has historically been the reference scientific body for animal health in Italy, combining research with regulatory expertise. Its scientists are involved in the study of pathogenesis and epidemiology of bacterial and viral diseases of livestock and companion animals. They provide technical-scientific and regulatory consultancy for drugs & biologicals to the Italian Ministry of Welfare/ Health and EMEA, the European Drug Agency.

MANY WAYS TO WORK WITH ISS

The Intellectual Property & Industrial Liaisons Management serves as a focal point to foster productive relationships between ISS scientists and the private sector.

THERE ARE MANY WAYS FOR INDUSTRY TO WORK WITH ISS SCIENTISTS

License ISS intellectual property

Through technology licensing, industry helps translate new discoveries into commercially viable products and processes. Terms of licenses are negotiated on a case by case basis and are usually complemented with collaborative research agreements to further develop the licensed intellectual property.

Collaborate with ISS scientists

Collaborative research agreements are an excellent way for companies (and for other research institutions) to leverage their research activities with those of ISS, especially for the generation of new intellectual property. Collaborative research agreements at ISS are usually at arm's length in relation to both costs and intellectual property ownership, with the two partners deciding on how to share costs and IP.

Sponsor research at ISS

A company may sponsor research at ISS when capabilities and interests match. This provides companies with an excellent way to leverage their research activities. ISS rich portfolio of expertise, infrastructures and scientific network can offer an incredible boost to a company's research effort.

Join forces with ISS for grant applications

Research funding is a perennial need for both research institutions and small companies. ISS, by virtue of its scientific prestige and skills, is an excellent partner when applying for grants from national, international and European sources.

Partner with ISS for clinical trials

ISS has extensive clinical trials conduction expertise. It is a valuable and skilled partner especially for phase I clinical trials projects.

Outsource to ISS the GMP production of cell-based therapies

FaBioCell, the GMP facility for the production of cell-based therapies, has been built to service the needs of organizations, public and private, in the field of immuno-therapy. Together with the GMP production service, ISS provides regulatory expertise on issues relating to the use of cell-based products for immunotherapy.

EXAMPLES OF SUCCESSFUL R&D COLLABORATIONS

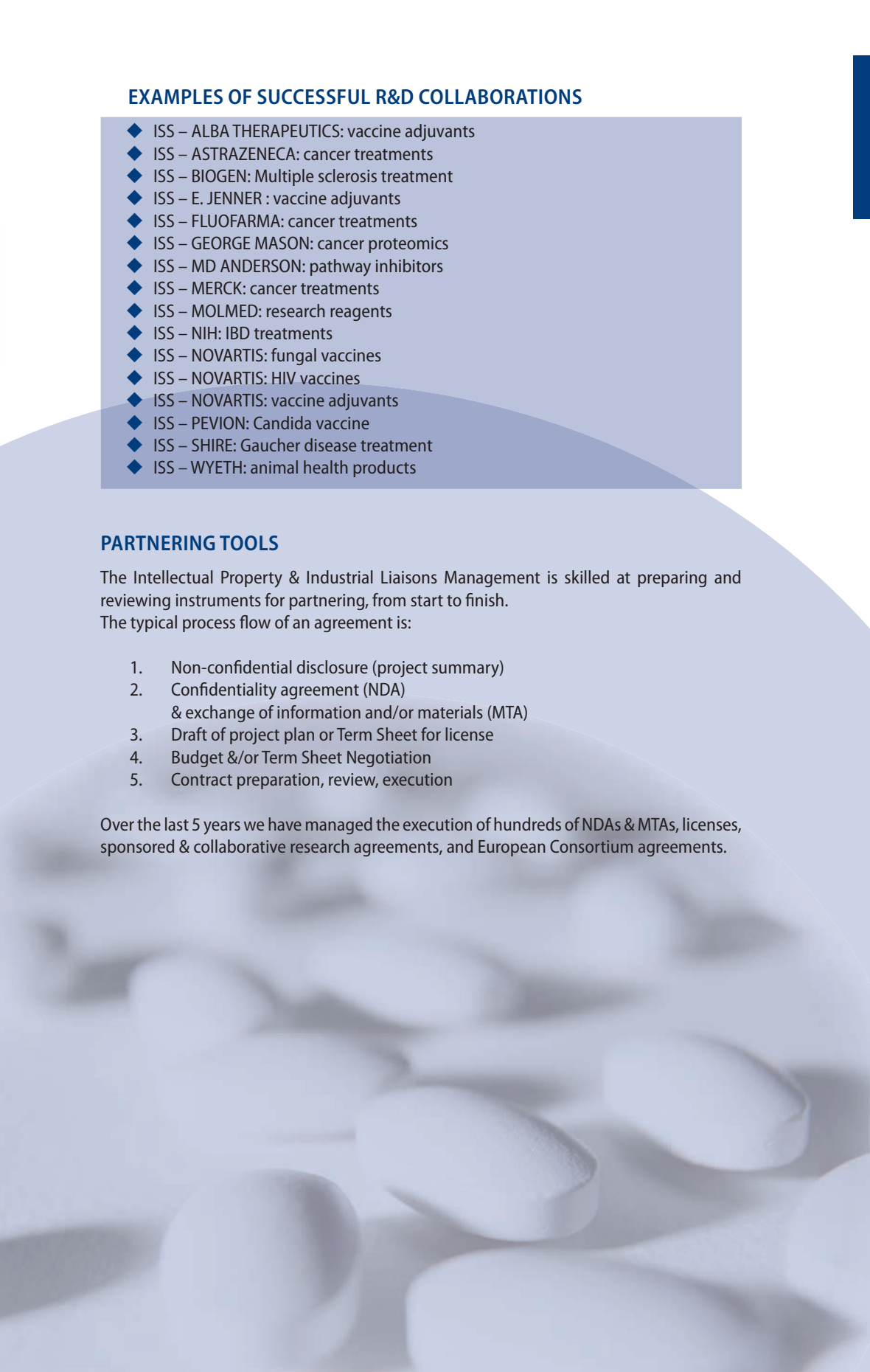
- ISS – ALBA THERAPEUTICS: vaccine adjuvants
- ISS – ASTRAZENECA: cancer treatments
- ISS – BIOGEN: Multiple sclerosis treatment
- ISS – E. JENNER : vaccine adjuvants
- ISS – FLUOFARMA: cancer treatments
- ISS – GEORGE MASON: cancer proteomics
- ISS – MD ANDERSON: pathway inhibitors
- ISS – MERCK: cancer treatments
- ISS – MOLMED: research reagents
- ISS – NIH: IBD treatments
- ISS – NOVARTIS: fungal vaccines
- ISS – NOVARTIS: HIV vaccines
- ISS – NOVARTIS: vaccine adjuvants
- ISS – PEVION: Candida vaccine
- ISS – SHIRE: Gaucher disease treatment
- ISS – WYETH: animal health products

PARTNERING TOOLS

The Intellectual Property & Industrial Liaisons Management is skilled at preparing and reviewing instruments for partnering, from start to finish.
The typical process flow of an agreement is:

1. Non-confidential disclosure (project summary)
2. Confidentiality agreement (NDA)
   & exchange of information and/or materials (MTA)
3. Draft of project plan or Term Sheet for license
4. Budget &/or Term Sheet Negotiation
5. Contract preparation, review, execution

Over the last 5 years we have managed the execution of hundreds of NDAs & MTAs, licenses, sponsored & collaborative research agreements, and European Consortium agreements.



FREQUENTLY ASKED QUESTIONS (FAQS)

How can I find out which technologies are available for licensing?

- Visit our index of available technologies at: http://www.iss.it/ipil
- Request our technology email alerts at: ipil@iss.it or cozzone@tin.it

What if I am interested in an area of research with no particular technology listed?

- We will scout in-house to match you with group(s) doing work in your area of interest.

How does ISS choose a licensee?

- ISS seeks licensees that are most able to bring a technology to the market. The criteria we use to qualify a licensee are:
  - R&D capabilities
  - Financial resources
  - Management commitment
  - Experience in relevant markets.

How long does it take ISS to negotiate a license?

- Every license is different. The time depends upon the complexity of the transaction. It can take up to 3 months. Sometimes longer.

How much does a license cost?

- Our licensing fee structure is in line with that of other peer research institutions. The cost of a license is based on:
  - The market value of the technology
  - Common benchmarks in the relevant sector
  - Additional development costs involved in bringing the technology to market
  - The scope of the field of use or geographic region.
- The financial terms include:
  - A license issue fee, nonrefundable and due upon execution of the license
  - A running royalty fee, based on a percentage of sales
  - A minimum annual royalty fee
  - Other financial terms appropriate to the technology and market, such as milestone payments.
- We endeavor to find win-win solutions and are experienced in working with small companies and start-ups. We can consider accepting equity as part of a licensee's financial commitment.

What other requirements are in ISS licenses?

- We are committed to ensuring that our licensed technologies are commercialized so that the public ultimately benefits. ISS licensees must meet mutually agreed-upon performance requirements that reflect diligent progress towards commercialization.

What is the typical length of a license?

- ISS licenses usually run for the life of the patent although other terms are available.

Can I get an exclusive license from ISS?

- Licenses may be exclusive, exclusive for a particular field of use or geographic region, or nonexclusive.

Will ISS allow me to sublicense?

- Generally yes, if you have an exclusive license.

Will ISS assign all patent rights to my company?

- No, ISS retains patent ownership of its technologies. Your company will be granted a license to use the technology.

Is ISS technology ready for immediate commercialization?

- It depends on the technology. If it is a therapeutic of biological product, it usually takes years to develop it into a commercial product.

Are licenses available to non-Italian companies?

- Yes, although, as an Italian public body, ISS has a preference for Italian companies.

The most up-dated information
on ISS Intellectual property portfolio is in a separate sheet.

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