

4. BIOTECH AND BIOINFORMATICS INNOVATION SYSTEMS IN SLOVENIA AND FRIULI-VENEZIA GIULIA (ITALY)

Best practices in Slovenia

Analysis of biotechnology, biomedicine and bioinformatics sector in Slovenia

According to OECD reports the growth of biotech companies in last decade was significant all over Europe and globally. In Slovenia, there were 27 active biotech companies in 2017. These were the companies that dedicate at least 75% of their total R&D expenditure in biotech.

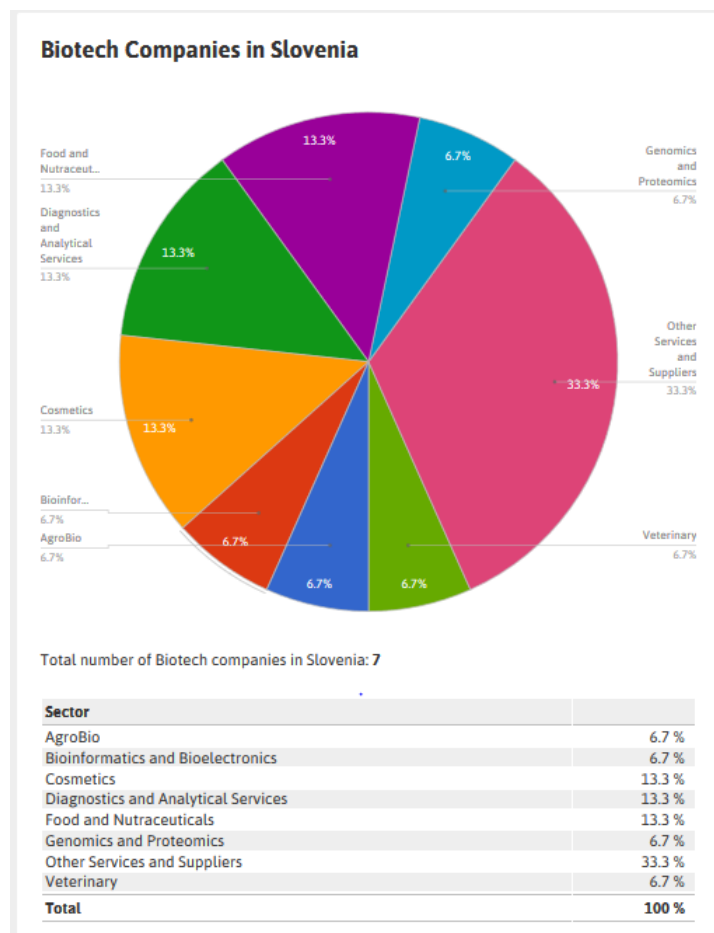


Figure 1: Biotech Companies in Slovenia ([Source](#))

Biotechnology companies in Slovenia

A small sample of biotech companies addressed by the TRAIN project shows that there is a great diversity and variety of biotech products/services that companies produce such as:

- a) services/products related to confocal microscopy, scientific research in neuroglia and technologies for the production of hybrid cells for use in cancer therapy through immunomodulation (Celica)
- b) production of bacteriophages and plasmid DNA and recombinant proteins production of biomolecules, stability studies, contract analytical testing, manufacturing of active pharmaceutical ingredients or drug substances and drug products (API/DS/DP), preparation of virus and cell banks, development and scaling up manufacturing processes (Jafra)
- c) validation/verification of analytical procedures (HPLC, GC, dissolution) for assay, related substances, degradation products, residual solvents, cleaning validations (swabs and eluates), analytics of cell-free DNA and liquid biopsies, analytics and development of GMO organisms and cell lines. (Labena)
- d) strain development through directed evolution and synthetic biology, fermentation process, development of downstream processing steps in development of bioprocess technologies, chemical synthesis processes (i.e. new methodologies), fine tune key bioprocess parameters, producing ingredients for rare disease treatments, new antibiotics based on resistant bacteria, new processes for vitamins production and other molecules for pharmaceutical, food, agriculture and chemical industry (Acies bio)
- e) small genomics research i.e. research with bacteria, viruses, fungi (Omega)

Slovenian biotech and bioinformatics ecosystem

In the scope of the regional specialization Slovenia formed so called Strategic Research and Innovation Partnerships in 2016 where companies, research organisations and education institutions closely collaborate with developing new products and services including in sectors such as biomedicine, biopharmaceuticals, cancer therapies, active healthy living and translational medicine as well as in bioTech related sectors such as bioinformatics, sensorics, advanced materials and technologies (robotics, plasma, nano technologies), biotech in agriculture, environmental biotech and other areas of biotechnologies.

Similar to Friuli Venezia Giulia, in Slovenia the sectors of biomedicine, diagnostics, medical informatics (eHealth) and bioinformatics were recognised as strategic areas of the national economy of the future. Stakeholders in these areas of biotechnology are working together in two platforms.

There is a [Strategic Innovation Partnership](#) platform in Health and Medicine, consisting of 57 member partners of which 26 are SME's, 3 start-ups, 3 large companies, 14 research organisations including 3

universities and 4 national research institutes, a developmental bank, 2 university hospitals and a technology park.

Interests of bioinformatics and e-health are in part also represented in the [Strategic Research and Development Platform](#) - Smart Cities and Communities.

Priority fields of collaboration for partners from business, academia and research are in Smart devices, sensors and tele-healthcare; Smart treatment; Digital healthcare; Smart integrated healthcare and patient care system.

Technology park Ljubljana also established a platform [Healthday.si](#) to accelerate innovation in Medtech companies and strengthen collaboration with the healthcare sector including insurances, hospitals and technology transfer offices mentioned.

Funding biotech and bioinformatics in Slovenia

Numerous instruments are available for research and products/services development in Slovenia for research and industry purposes in biotech and bioinformatics such as government and European union supported funding through various institutions and business angels and other resources as credits, venture capital investments and grants.

- ❖ [Slovenian Investment Bank](#)
- ❖ [The Entrepreneurship Fund](#)
- ❖ [Business Angels of Slovenia](#)

Project resource: [Analysis of biotechnology sector in Slovenia](#)

A Slovenian Biotechnological case: ACIES BIO d.o.o.

[Acies bio](#) (ACIES BIO, biotehnoške raziskave in razvoj, d.o.o.) is a small size R&D based company operating in the areas of agrobiotechnologies, food biotechnology, synthetic chemistry.



Acies Bio Ltd. was founded in 2006 by a small group of visionary scientists and has since grown to 50+ including microbiologists, molecular biologists, chemists and bioprocessing specialists, of which over a third with a Ph.D.

Company's core products/services are strain development through directed evolution and synthetic biology, fermentation process development for scaling up in industrial use, development of downstream processing steps in development of bioprocess technologies, chemical synthesis processes (i.e. new methodologies), fine tune key bioprocess parameters in its pilot scale bioreactors and a corresponding scale in DSP development (scaling up production facilities). Amongst the R&D

based products are ingredients for rare disease treatments, new antibiotics based on resistant bacteria, new processes for vitamin production and other molecules for pharmaceutical, food, agriculture and chemical industry. The company operates in Europe, Asia and in the USA. They developed a unique business model based on the creation of joint ventures with their clients, extensive research collaboration (through their own facility with pilot fermentation equipment suited for technology demonstration collaborations) and R&D partnerships (acting as co-investors in technology development and co-ownership in the new IP and technology).

Acies Bio's business development process is business- industrial clients oriented (problem solving) and scientific-academia (research) based company. Company's R&D process is collaborative (with domestic and foreign research institutes) and defined ahead with their clients; depending on the type and nature of R&D project they enter different phases of development, sometimes also as investors.

Acies Bio owns facility with pilot fermentation equipment which is uniquely suited for technology demonstration collaborations. Acies Bio has successfully completed numerous FP7 and H2020 projects ([TIRCON](#), [TOPCAPI](#), [Whey2Value](#), [CIPKeBiP](#), [TRIH](#)) with significant contribution to final project success. All this makes Acies Bio a premier partner for collaborative project proposals, related to food, feed and agro biotechnology and synthetic chemistry.

Acies Bio's products are compatible with the TRAIN project interests in the domains of agritech, foodtech and biomedicine. Collaboration with academia is well established and it led in the past to company's great business results. Company has extensive experience in processes of technology transfer IP protection in the field of biotechnology, including registration of patents in China. Company is located in Technology park Ljubljana.

Best practices in Italy

Analysis of biotechnology, biomedicine and bioinformatics ecosystem in Friuli Venezia Giulia

The health sector is one of the Smart Specialization Strategies (S3) of Friuli Venezia Giulia (FVG), defined by the Regional Administration after an Entrepreneurial Discovery Process (EDP), launched by CBM in 2014, regarding biomedical, biotechnological, and bioinformatics sectors.

The results of the EDP justified the adoption of the "Smart Health" as a key strategic specialization for Friuli Venezia Giulia in line with the S3. The number of private companies and the quality of public research institutions, including research hospitals, operating in the field of healthcare (*Smart Health*), located in the regional territory with a high networking capacity, are the primary elements ensuring an economic success.

In the regional territory there are about 150 companies operating in the worldwide markets with a good turnover potential. The core business of the companies is focused on one or more of the technological and innovation development roadmaps and priorities: 30% focus on biomedical and in vivo diagnostics, 17.5% on in vitro diagnostics, 20% on e-health, 17.5% on innovative therapy, and 15% on AAL. Approximately 90% are SMEs, with 30 innovative high-tech start-ups. The yearly turnover of the sector is more than 900M euro and the number of employees amounted to more than 5.000.

In addition to this strong industrial context, FVG has several international scientific research excellences such as:

- 3 universities: Trieste, Udine, and the International School for Advanced Studies (SISSA) of Trieste
- 2 National Research Council institutions (CNR): "Istituto Officina dei Materiali" (IOM) and Institute of Crystallography (IC)
- 6 international research institutions: International Centre for Genetic Engineering and Biotechnology (ICGEB- Trieste), International Centre for Theoretical Physics (ICTP- Trieste), Elettra-Sincrotrone Trieste (synchrotron and free-electron laser light), National Laboratory of Biotechnology Universities Consortium (LNCIB- Trieste), the Italian Liver Foundation (FIF - Trieste), and the Callerio Foundation (Trieste).
- 2 academic medical center hospitals: Trieste and Udine, both certified by the Joint Commission International
- 2 Scientific Research and Healthcare Institutes (IRCCS): Ospedale Infantile Burlo Garofolo of Trieste – Child Hospital – and Centro di Riferimento Oncologico (CRO) of Aviano (Pordenone) – Oncological Hospital.
- 4 science and technological parks: AREA Science Park of Trieste, Science and Technology Park Luigi Danieli of Udine, Technology Park of Pordenone, and InnovaFVG of Amaro
- 1 public organization providing services to senior citizens, specifically focusing on those who are disabled: Azienda pubblica per i Servizi alla Persona (ITIS, Trieste)

All of these research institutes foster the creation of spin-offs in FVG.

By a Regional Law 3 of 02/20/2015, the Regional Administration officially acknowledged the Smart Health Cluster FVG and entrusted CBM - identified as Innovation District by Regional Law 3 of 02/20/2015 - with the task to foster the development of MedTech, Biotechnology, IT-HealthCare, and Ambient Assisted Living (AAL) industries.

In line with S3, CBM promotes an open and inclusive network of actors and contributes to a regional business ecosystem in the following technological and innovation development roadmaps and priorities:

- ❖ Biomedical technologies and in vivo diagnostics
- ❖ In vitro diagnostics

- ❖ Medical informatics (IT HealthCare) and bioinformatics
- ❖ Innovative therapy

All of these technological innovations have to be integrated with advanced manufacturing technologies, such as big data, predictive analytics, virtualized processes, modeling and simulation, data security, cloud technologies for healthcare, high-performance computing, and IoT technologies, and with sensor systems in order to offer innovation for monitoring and managing illness and improving wellness.

As a matter of fact, one of the main goals of the regional policy is fostering innovation in active aging and citizens' well-being in order to reduce chronic diseases and their costs. FVG is one of the oldest regions in Europe with 26% of people over 65 (Trieste 28%), where the health sector should focus on the transition from "reactive medicine" (meeting patients' needs) to "proactive medicine".

The roadmaps and the technological priorities in the FVG region in the health sector are focused on:

1. Biomedical technologies and in vivo diagnostics - The development of *medical devices*, including *diagnostic imaging systems*, for the development of new products for *advanced biosensors* and for *prosthetics*; creation of *biomaterials and bioreactors* for regenerative medicine field and development of advanced instrumentation in the field of *nanotechnologies*;
2. In vitro diagnostics - The development of innovative technology platforms for *human diagnostics and clinical evaluations* of patients, for *food diagnostics* (quality, traceability and safety), and for *veterinary and environmental diagnostics* in the health sector and the development of "Omic" technologies;
3. Medical informatics and bioinformatics - The integration of informatics technologies into the development of new systems and software solutions for hospital informatics; social and health informatics; informatics for bio-imaging; informatics for medical laboratories; informatics for blood, tissue, and cell banks; and informatics for personalized medicine. The development of advanced manufacturing technologies, such as big data, predictive analytics, virtualized processes, modeling and simulation, data security, cloud technologies for healthcare, high-performance computing, and Internet of Things (IoT) technologies, and with sensor systems in order to offer innovation for monitoring and managing illness and improving wellness.
4. Innovative therapy - The development of biopharmaceuticals; biosimilars; bio-materials (e.g. for oncological, cardiovascular, metabolic, respiratory, neurodegenerative, and inflammatory diseases). Advanced biotechnological platforms for the production of drugs aimed at the treatment of rare diseases; technologies for cell therapies, gene therapies, and small molecules for personalized therapy; probiotics, prebiotics, symbiotic, and bioactive supplements as proactive, health-promoting foods; and advanced services to support the productions mentioned above, such as in silico methods for molecular modeling and drug toxicity;

5. Ambient Assisted Living (AAL) - The design of technological solutions to make the personal living environment active, intelligent, and cooperative, products, and services related to telemedicine, telecare, home automation, health aids, and wearable devices, as well as other products and services for the prevention of diseases and disabilities in older adults and the welfare of citizens.

An important facilitator of the Cluster Smart health FVG is [BioHighTech NET](#). In 2016, 36 BioHighTech companies (micro, small and medium size) set up an enterprise business network focused on the biomedical, biotechnologies and bioinformatics sectors.

As Italy has one of the highest number of researchers per capita, it is very prolific scientifically. This is aided by the fact that Italian researchers are second in the EU regarding attracting funds according to study by Centro Studi Assobiotec (2018). Trieste (along with Udine) is at the forefront of this trend in FVG and its impact will strengthen further being selected by Euro science as the European Science Capital for 2020. However, due to the low amount of public investments and low number of patent applications to European patent office, the technology transfer in Italy is to be strengthened. Emerging innovators are funded by national as well as private institutions and mechanisms.

Funding for biotech and bioinformatics

Investment and resources opportunities in Italy were well presented by Fabio Bianco, a Chief Scientific Officer at the Bio4Dreams organisation from Italy. There are over 7000 drugs under development currently in Italy, majority related to cancer. A rapid growth in drugs development is in part also due to big increase in outsourcing of services for drug development in the past ten years were outsourcing of R&D grew to 80%. Increased growth of biotech companies in Italy's is also attributed to outstanding ecosystem and to the reputation of the key clinical centers in the areas of oncology, haematology, immunology, neurology, hepatic disease and rare disease.

This vibrant research and development community of over 49 public/private centers of excellence has highest scientific results in the world and is second best in Europe for attracting research funds outside of Italy as domestic public funding in R&D amounts "only" to the 1.3% GDP (in 2017) and private venture capital investment is significantly lower than in Germany, United Kingdom, France or Switzerland and Denmark (amounting to "only" 46 MEUR in 2015). Italy scores significantly lower with the number of patents submitted to the European Patent Office by the OECD countries.

To accelerate the transfer of research to valuable products the National Operational Program on Research and Innovation assigned 1,2 billion EUR into R&D in key areas of research including in the priority area of health and green chemistry. Italy also prepared a National Industry Plan 4.0 where 13 billion EUR of public funds is invested in industry growth along with the 24 billion EUR private investments during 2015-2020 period. Other support measures were introduced by the government in the recent past to accelerate needed investments into R&D and economy growth such as Italy's start up act with measures of reducing costs for setting up companies, easier compensation of VAT, more flexible labour remuneration system, tax incentives for corporate and individual investments, internationalisation and start up hubs and smart start -up initiatives with financing schemes for innovative start-ups and friendly visa policy for entrepreneurs to name a few.

The Innovation Scenario: Italy

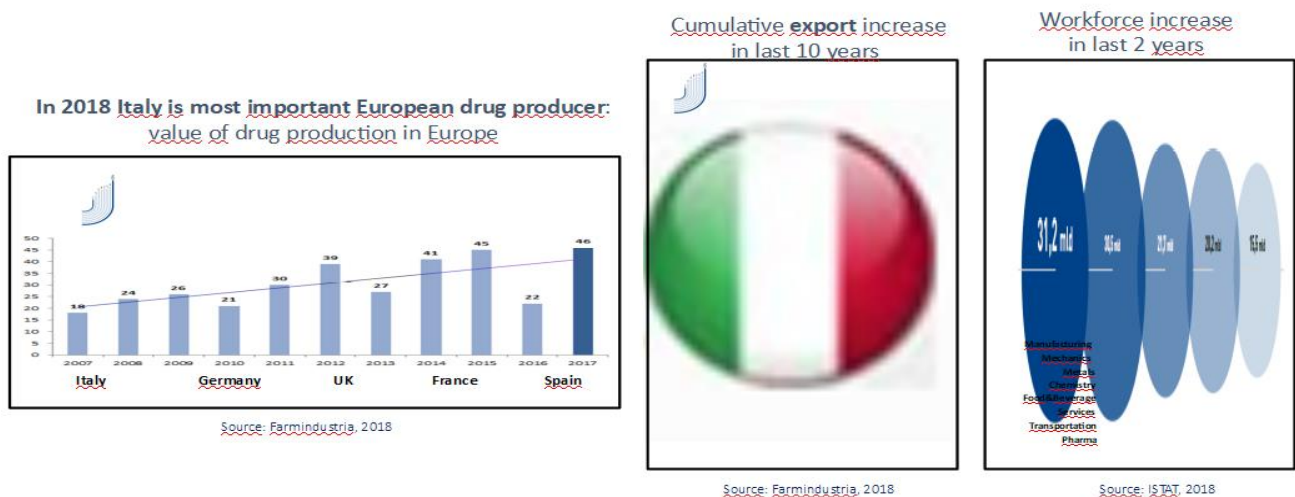
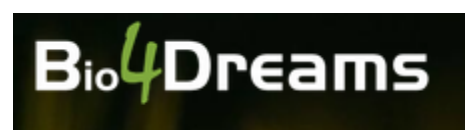


Figure 2: Investments and resources opportunities in Italy (Provided by Bio4Dreams)

The objective of investing in innovation is to make a better value from investment into research by stimulating more entrepreneurial culture, gain managerial experience also for scientists and researchers, improve knowledge of global markets, link scattered hubs and resources and create a more risk prone culture and stimulate bigger spending and investments into R&D also by the private sector. Venture capital is modestly developed in Italy and the interest is to link it better with the research organisations, incubators and accelerators.

[Bio4Dreams](#) life sciences incubator was created as a part of this initiative to accelerate technology transfer from research organisations in life sciences to the global markets.

The platform assists with the R&D based life sciences project evaluations, intellectual property issues and market analysis and preparation of business plans and assists with launching companies and with fundraising for business growth by enabling



better interactions with innovation hubs and technology transfer offices on the one hand, funds, companies and other incubators and accelerators on the other.

A biotechnological case in Friuli Venezia Giulia: The VivaBioCell S.p.A

[VivaBioCell S.p.A](#) is an Italian biomedical company based in Udine that operates in the development and marketing of devices and instruments to be used for the manufacture of advanced therapy medicinal products.

Founded in 2007 as a spin-off of the University of Udine, it was acquired in 2015 by the US company NantCell, and thus became part of the [NantWorks LCC group](#).



VivabioCell S.p.A. offers innovative solutions to support the development and production of ATMP in a strong, controlled and efficient manner. The company is currently certifying NANT 001, a bioreactor capable of automating the process of cell expansion in a closed system, which is currently performed in cleanrooms.

VivaBioCell SpA, thanks to the experience gained over the years and the relationships established over time, is also a facilitator for the adoption of advanced therapies in various markets, in particular in the European and US markets, ensuring the protection of the intellectual property at both the clinical and the manufacturing level.

The idea that gave life to VivaBioCell SpA, comes from a research conducted for the Italian Space Agency, aimed at the evaluation of the expansion of adult stem cells in particular conditions of microgravity and exposure to radiation, through the use of a "closed" automated tool that is able to ensure sterility.

The company was established on the initiative of Professor Francesco Curcio and accompanied during the establishment and initial phase by BIC Incubatori Fvg. The company has been able to gather around it important partners such as TOR - Tissue Organ Replacements srl, spin-off of the University of Udine and vehicle company of the founders, Friulia Sgr (Fund Aladdin Ventures), Allegro Srl (Luxembourg investment fund operating on behalf of Assicurazioni Generali), Banca Popolare di Cividale and ZIP (Zanchi investments and shareholding).

At the beginning VivaBioCell S.p.A. focused research on issues related to bone regeneration, dedicated to the field of dentistry and maxillofacial surgery. In the period between 2007 and 2011 the company evolved its strategy in the elaboration and formalization of an automated system for the production of a "combined" cellular product in line with the European regulations established by the EMA for medicinal products for advanced therapies. (ATMP - Advanced Medicinal Therapy Product). At the same time, the success obtained in preclinical studies carried out on animals on one way, and the need to identify the coverage of the financial needs of the company on the other, led to the activation of a commercial service aimed at pathology of canine arthrosis by autologous stem cells

from adipose tissue. This direct experience has led to the identification of an opportunity for treatment of arthritis in humans.

In 2014, VivaBioCel S.p.A won the Altran Italia award for technology transfer and the first prototype of NANT 001 was developed, a device that works as a "GMP in a box" that automates the process of cell expansion in a closed system. The company, in the same year, initiated contacts with research centers and companies of great international importance, which would be fundamental for the upgrading of NANT 001, that is to say the Spanish clinic ITRT (European leading clinic for the musculoskeletal system therapies through expanded MSC) and with NantWorks.

2015 has been a pivotal year for the company, since it has been acquired by NantWorks Group, owned by the doctor - American entrepreneur Patrick Soon-Shiong, based in Los Angeles, California. Thanks to the acquisition, the development activities of the bioreactor system have been boosted, targeting applications both for the therapy of osteoarthritis and in synergy with the NantWorks activities in the new field of immunotherapies.

Nantworks LCC is in fact an "umbrella organization" at the center of an ecosystem of companies operating in the field of immunotherapies for the fight against cancer and precision medicine and personalized medicine. Group companies include: NantHealth, NantOmics, NantBioScience, NantCell, NantKwest, NantPharma, NantMobile, NantStudio, NantCapital and NantCloud.

The commercial launch of NANT 001 has taken place in May 2018, at the World Advanced Therapies & Regenerative Medicine Congress 2019 in London, and has raised a lot of interest and confirming itself as a solution with a high degree of innovation compared to the solutions offered by its competitors.

Currently VivaBioCell S.p.A. is engaged in the launch of the industrialization of the "NANT" technology platform aimed at making the new therapies accessible to a large number of patients. In fact, there are more and more cell drugs that have shown in the main characteristics of safety and efficacy, but whose adoption is braked above all by the prohibitive costs of "labor-intensive" manufacturing processes.

VivaBioCell is committed to its region in the creation of an "ecosystem for advanced therapies" involving networks of companies, research centers, clinical centers, investors, etc. It is in fact a fundamental step for the development and diffusion of advanced therapies and the consequent progress of medicine.