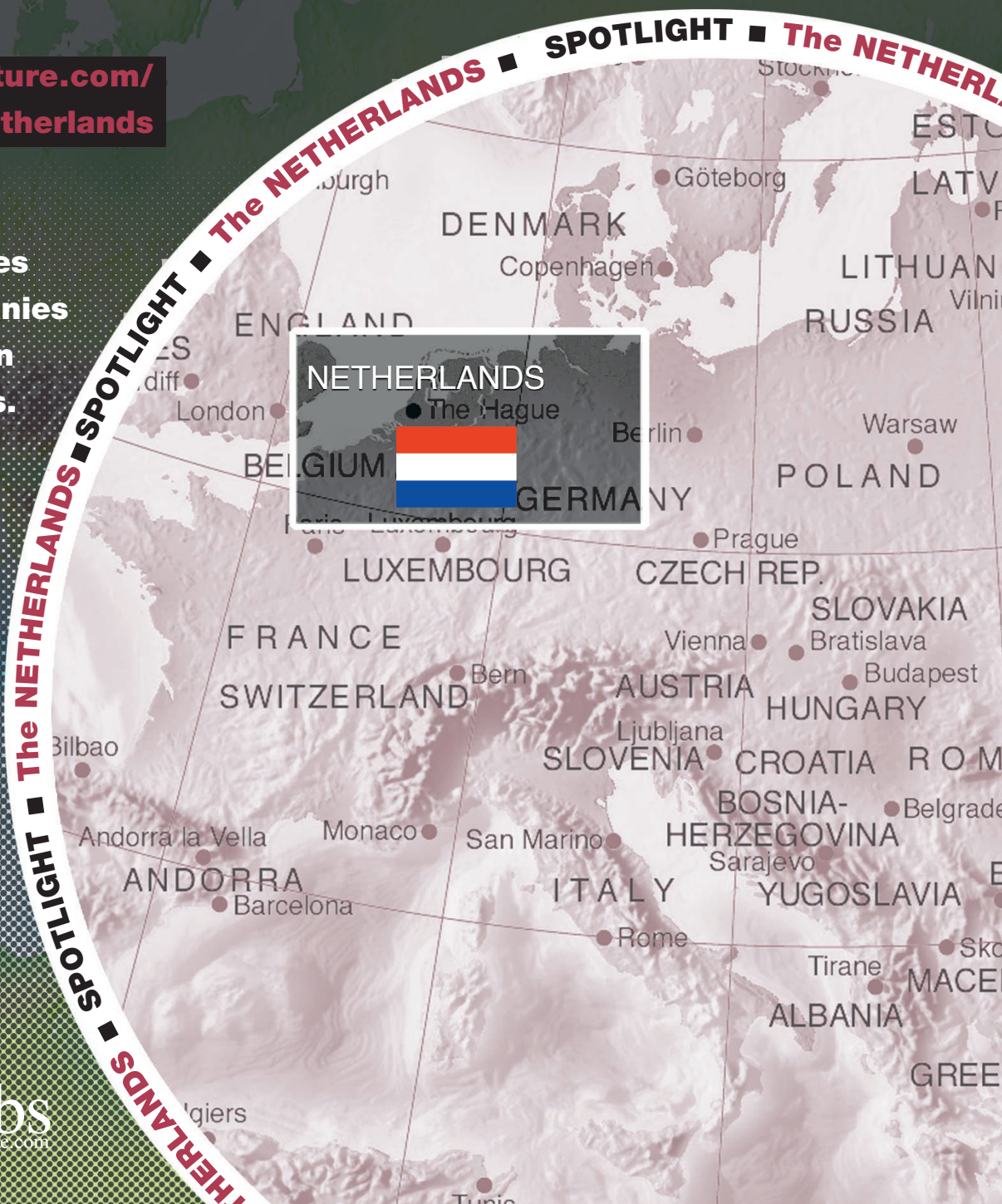


SPOTLIGHT ON The NETHERLANDS

IN THIS SECTION we will take you on a tour of some of the main areas within The Netherlands' Scientific Community. We will introduce you to various universities, institutes and companies showing their strengths and specialities .

<http://helix.nature.com/spotlight/thenetherlands>

This is part of a continuing series profiling companies and institutes in specific regions.



Promising new developments in the Netherlands



Only a few years ago, the Netherlands was one of the leading countries in European biotechnology. Nowadays it occupies seventh place in the European ranking because biotechnology has grown more quickly in other countries. However, The Netherlands has a relatively positive climate for biotechnology. In a recent policy paper the Dutch cabinet expressed the intention to 'stimulate the development of biotechnology in a considered way'. Although the debate on biotechnology is growing, public opinion is favourable to the technology. Combined with a broad scientific knowledge base this result is a good foundation for new growth in Dutch biotechnology. Several organisations are taking action to stimulate further growth.

The Netherlands has a good public scientific base in medical and healthcare biotechnology. Eight Dutch universities are involved in research in this area. These and other universities are also conducting a vast amount of research in related areas like molecular cell biology, virology, immunology and pharmacology. However, the number of commercial pharmaceutical companies remains limited. In recent years, though, the numbers of Dutch biotechnological companies in healthcare and pharmaceuticals has started to grow and there are now about 50. Many started recently in areas such as genetherapy, the development of platform technologies, diagnostics, sequential analysis and the production of monoclonal antibodies.

Stimulated by the subsidies provided by the Dutch government, plant bio(techno)logical and other agricultural research has grown in every field. The main focus for this research is the Wageningen University and Research Centre, especially in genomics research. In addition, there are about 30 Dutch branches of large life sciences companies involved in crop improvement. Research for these smaller companies is usually done by specialised institutes and companies.

The development and application of biotechnology in animal breeding is relatively small in The Netherlands compared to plant biotechnology. Two research networks and two research schools are working on food biotechnology in The Netherlands. In addition, large food and food ingredients companies are conducting research in food biotechnology with industry and the scientific community work together.

Clusters of biotechnological activity

Commercial biotechnology in The Netherlands is clustered around the centres of scientific research. Leiden was one of the first strongholds with its Bio Science Park near to the university and its focus on biotechnology and medicine. Several biotechnology companies were formed around the Rijksuniversiteit Groningen. Other companies in Groningen are working in environmental biotechnology, such as bioremediation.

The Graduate School and Research Center BioCentrum Amsterdam is another important centre with research in biomolecular sciences and biotechnology. Amsterdam and its surroundings is home to a number of biotechnological companies and the Wageningen region has a world-renowned reputation in agricultural research. Wageningen University and Research Centre has nine separate institutes. These centres conduct research in agriculture, nutrition, nature and the rural area. In this region there is also some commercial biotechnological activity. In Lelystad a new BioScience Park has opened recently. This park is targeted to agricultural and pharmaceutical companies.

Public attitude

Public attitudes to biotechnology are more positive than in other European countries. Although people have some concerns, most are convinced that the benefits of biotechnology are high and the risks low. They expect to benefit from this science within the next five years. Applications with clear benefits can count on support in The Netherlands. Most Dutch people believe biotechnology will produce new medicines. There is also widespread support for biotechnology to replace chemicals in agriculture, to produce bioplastics and to clean environmental pollution.

Governmental attitude

During a conference organized by the American embassy at the beginning of 2000, three Dutch cabinet ministers declared their support for biotechnology funding. The joint message was a powerful new signal about the benefits and possibilities of biotechnology. In

September, five ministers presented the Integral Policy Paper on Biotechnology on behalf of the cabinet. This policy paper shows the intention of the cabinet to 'stimulate the development of biotechnology in a considered way'. Considered means that possible risks have to be acceptable in relation to the benefits of a biotechnological application. More concrete proposals of the cabinet are the banning of antibiotic resistance markers in crops, a public debate on biotechnology and food as well as measures to stimulate research and business in biotechnology. There should be a parliamentary debate on the policy paper next year.

Stimulating business

During the last decades of the Twentieth Century the government did not stimulate biotechnology as strongly as in other industrialised countries. However, earlier this year the Dutch Ministry of Economic Affairs presented the Actionplan Life Sciences directed at creating new business in biotechnology. This Actionplan is based on the answers to fundamental policy questions like: What makes a region successful in developing life science business? This question was addressed by many authors¹⁻⁷, and the emerging key success factors were:

- Local availability of factors such as knowledge, information and tools
- Local availability of market pull factors such as large established industry nearby, which will act as the main customers of new small companies
- Presence of seed and venture capital
- Presence of a stock exchange for floating
- Good fiscal regulations for young companies
- Physical support facilities
- Human resources of sufficient quality and quantity

In a recent report⁸, commercialisation of life sciences in the Netherlands was compared to that in six other regions in the world. The results are represented in the table opposite.

From this comparison, several recommendations resulted:

- The Ministry of Economic Affairs should:
 - Bring money, knowledge, entrepreneurs and coaching together
 - Involve local governments
 - Provide independently managed seed funding
 - Involve a charismatic biotech manager
 - Universities should:
 - Let role models give entrepreneurial courses
 - Increase awareness about patents and their possibilities
 - Let scientists be entrepreneurial
 - Consider life sciences enterprise fellowships

Factor	Boston	Cambridge	Quebec	München	Belgium	Netherlands	Sweden
Science base	*****	*****	*****	*****	*****	*****	*****
Culture	*****	****	***	**	.	.	**
Capital	*****	****	****	***	**	**	**
Environment	*****	***	****	***	**	**	**
Incubators	*****	***	****	****	**	.	.
Management	*****	****	***	.	.	**	.

The result of this study was that the Dutch government designed a programme to overcome the distance between the Netherlands and regions such as Boston, USA and Cambridge, UK. Government involvement can be extremely beneficial for the development of new entrepreneurship in high tech. In Germany, where the government has a very generous policy on the support of start-ups in biotechnology, 450 new companies were created in life sciences since 1985, and the market capitalisation of German biotechnology rose from DM 4 billion in 1999 to DM 18 billion in 2000. The Dutch Ministry of Economic Affairs dedicated Dfl 100 million (approx. Euro 45 mln) for the period 2000-2004 to stimulate entrepreneurship in life sciences.

This Actionplan Life Sciences is now named BioPartner because people involved want to be a partner in the creation of new life sciences business. The money will be used in five instruments, aiming at the creation of new start-ups:

- BioPartner Network is dedicated to the stimulation and facilitation of entrepreneurship in life sciences in general in the Netherlands
- BioPartner First Stage Grant is a subsidy that can be obtained by a research organisation together with an employee. This employee can then dedicate up to two years to transferring a promising idea into a business plan
- BioPartner Facilities Support is designed as a revolving fund; the money provided can be used to buy equipment or facilities in an earlier stage than would be possible otherwise. The money earned by using the equipment in contract research should provide for paying back the loan
- BioPartner Centers will be built in at least five towns; they will provide adequate housing, support, permits, facilities and so on for at least 10 start-ups in life sciences
- BioPartner Start-up Ventures gives seed money (for equity) to starters in life sciences, provided that other private investors invest similar amounts.

These five instruments should result in at least 75 new start-ups in life sciences on top of those that would have emerged without government support. The programme came into operation in the

middle of 2000 and the first clients will have received their money by the end of 2000. In addition to the Dfl 100 million of the Actionplan Life Sciences, the Dutch government will also provide research subsidies. In 2001 the Dutch government will decide on extra subsidies for genomics research.

Masterclass Biobusiness

Another initiative to stimulate business in the Netherlands was taken by Niaba, the Netherlands' Biotechnology Industry Association. This year, the association organized its third annual Masterclass Biobusiness in close co-operation with de Baak, Management Education Centre of VNO-NCW, one of the major Dutch employer's organisations.

This Masterclass offers biotechnological knowledge as well as managerial and entrepreneurial skill to everyone who wants to approach biotechnology in a more entrepreneurial way. It has already proven to be attractive and useful to many scientists. It will enhance the chance of success of biotech start-ups and make employees of larger companies more business-minded. Niaba and BioPartner have started talks to explore ways to organise the next Masterclass in 2001.

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 Niaba, drs. R.T.A. (Rob) Janssen, tel. +31 70 327 04 64, e-mail janssen@niaba.vnci.nl

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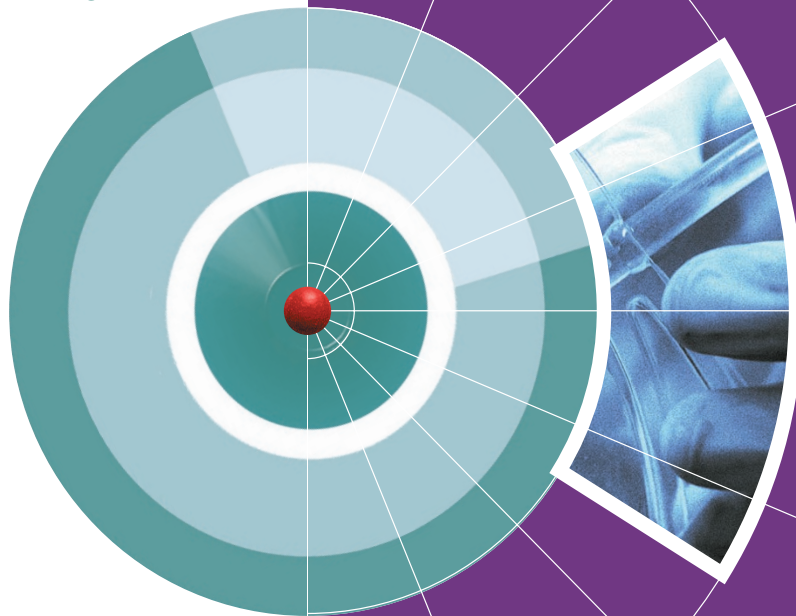
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Crucell n.v. is a Netherlands based biotechnology company, which was formed through the merger between IntroGene B.V. and U-BiSys B.V. in June, 2000.

Crucell is listed on Euronext (Amsterdam) and on the Nasdaq National Market under ticker symbol "CRXL".



Brief history

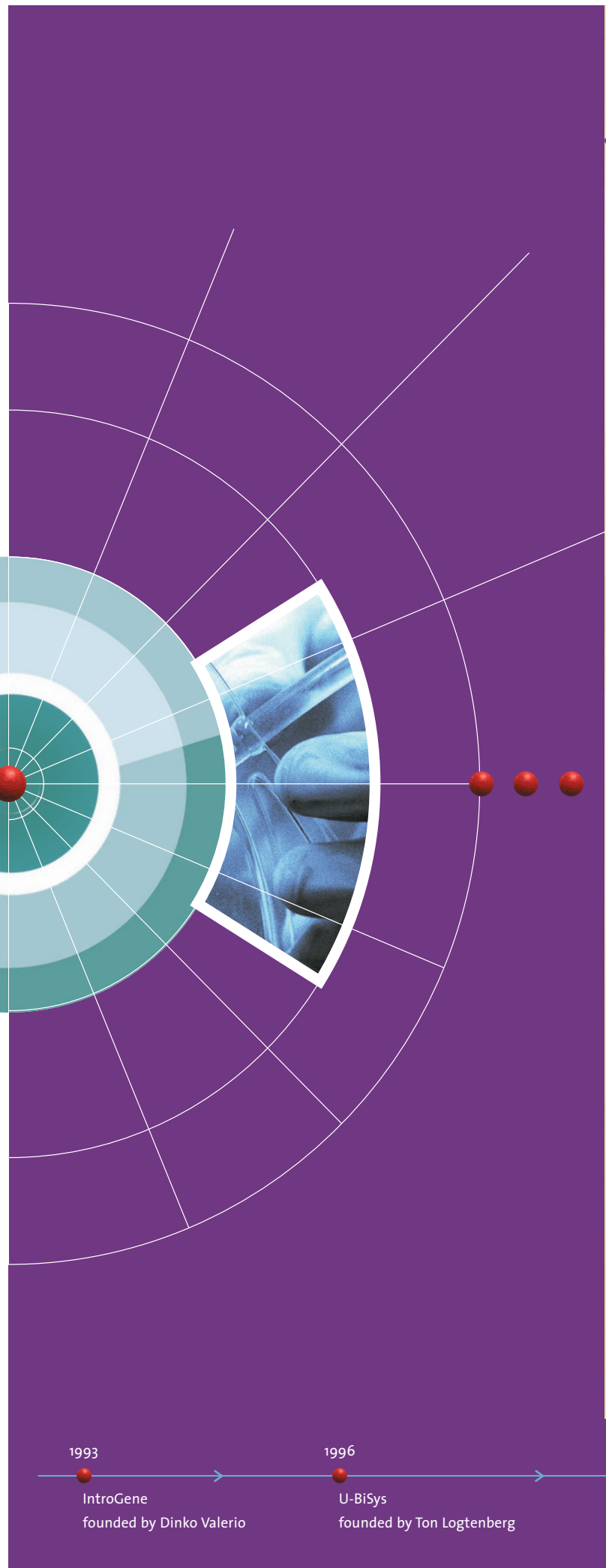


1993

IntroGene
founded by Dinko Valerio

1996

U-BiSys
founded by Ton Logtenberg



→ The Company

Crucell's two widely applicable technologies

Crucell has two widely applicable technologies: its human cell line expression platform, **PER.C6**, and its phage antibody-display library and related subtraction, selection and engineering technology, called **MAbstract**.

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Crucell's partners

Crucell has licensed its PER.C6 technology in the area of vaccines and gene therapy to 13 blue-chip pharmaceutical companies including **Merck & Co., Inc.**, **GlaxoWellcome**, **Novartis** (through its wholly-owned subsidiary, Systemix), and **Pfizer/Warner-Lambert**.

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Crucell has the ability to address all phases of human biopharmaceutical development from identifying drug targets through to commercial production. Our strategies focus on establishing PER.C6 as the production cell line of choice, discovering drug targets and developing therapeutic monoclonal antibodies, developing and commercializing own products and expanding the application of the two technology platforms through collaborations and strategic alliances.

Research focus

Our research activities related to human antibodies focus on the area of discovery and development of tumor-specific antibodies, angiogenesis, chronic inflammation and antibodies for vaccination strategies. Furthermore our research focusses on development of PER.C-flu, an influenza vaccine using the PER.C6 platform. In the area of gene therapy, we are developing our own products in the areas of cardiovascular disease and cancer.

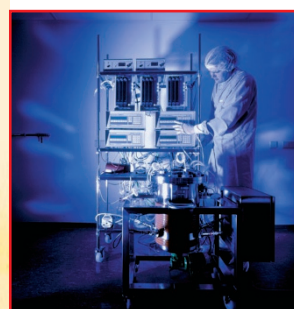
Crucell currently employs approximately 115 people in its facilities in Leiden, Utrecht and Leuven (Belgium). We are actively seeking entrepreneurial, enthusiastic and highly skilled researchers and technicians to strengthen our teams in order to achieve the ambitious goals we have set for the future.

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PER.C6

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30 June 2000

IntroGene and U-BiSys merge to form Crucell

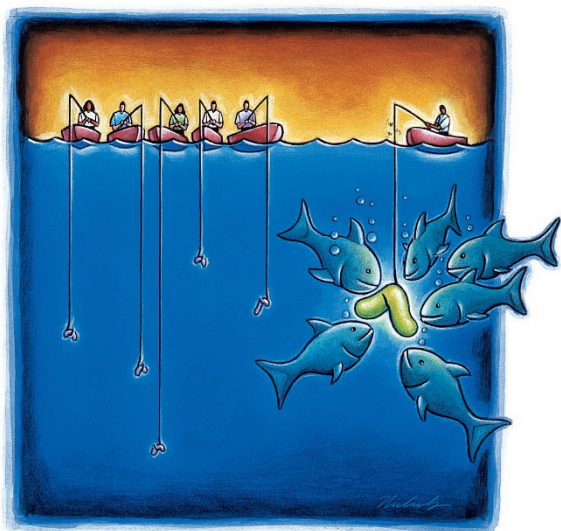
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SP10

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BioMed City Groningen

BioMed City Groningen is a virtual community of Life Science companies, knowledge institutions, and local authorities in the Northern Netherlands, with the aim of stimulating the Life Sciences in the region. BioMed City Groningen functions as the co-ordination point for all developments in the Northern Netherlands with regard to the Life Sciences, and ensures that the diverse activities in this field are appropriately counselled and coached. Its operations may vary from encouraging start-up firms to creating special facilities and arranging that the mutual networks of the larger-scale companies and knowledge institutions are well integrated. Companies such as: Cordis (J & J), Invitrogen, Pharma Bio Research, DSM Biologics, Yamanouchi, Intracel, Fresenius, and many others all participate in the Life Sciences network in the Northern Netherlands.

Facts and Figures

In the domain of the Life Sciences, the knowledge base in the Northern Netherlands is extremely comprehensive, and is primarily formed by the University of Groningen and the University Hospital. The knowledge base is a source of new development and also a source of well-educated personnel. The faculties of Natural Science and Medicine educate a total of almost 4,000 students in very diverse disciplines. The institutes of higher professional education in the Northern Netherlands educate a total of more than 3,000 students in the domain of the Life Sciences.

The University Hospital in Groningen (Academisch Ziekenhuis Groningen, AZG) provides almost 1100 beds and has a staff of 5,500. Approximately 26,000 patients are admitted to the hospital each year.

Research focus

Neuro-imaging:

The University of Groningen and Groningen University Hospital have decided to establish an integrated neuro-imaging centre that meets the highest international standards for brain research. New developments in data acquisition, visualisation methods, mathematical modelling, and image analysis emphasise the need for an integrated environment that allows the combined registration of neuronal signals. The objective is to create a neuro-imaging unit that will become one of the world's leading institutions in the area of dynamic brain research.

Genotyping:

The Northern Netherlands contains a large founder population (the term 'founder population' has been coined to denote a population with a common gene pool) of about 3 million people. Groningen University Hospital is the major reference centre of the catchment area comprising this particular population. This allows researchers in Groningen to study disease-related genomic profiles. To support this, a genome-screening facility has been established. The integrated system has enough capacity to determine 6 million genotypes per year. This is currently being combined with an infrastructure attuned to acquiring and processing relevant patient (and related normal control) samples. These can be used both for the identification of gene sequences related to increased disease sensitivity and for assessing genomic profiles related to (in)sensitivity to the toxicity of (new) medicines.

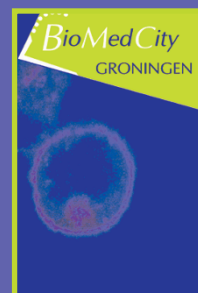
Facilities:

To support the Life Sciences as much as possible, special buildings have been reserved in the medical complex – the University Hospital and the Faculty of Medicine – to simulate the exchange of information between companies, researchers, and clinics to a maximum extent.

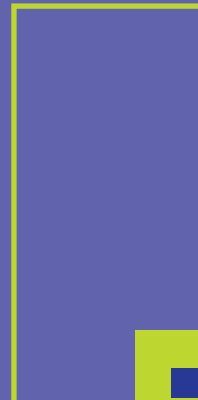
At the same time, facilities have been created at the Zernike Science Park – near the Faculty of Mathematics and Natural Sciences – for a similar exchange between companies and research groups such as GBB, MsC, BioMaDe (nanotechnology), etc.

In addition to tangible facilities such as laboratory space and business sites specially oriented towards the Life Sciences, BioMed City Groningen can also mediate in attempts to obtain investment and R&D subsidies, risk finance, and suchlike.

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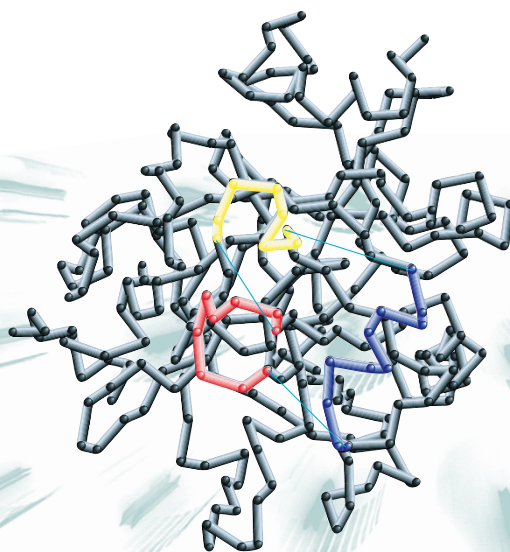
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SP12

THE BIO SCIENCE PARK | LEIDEN



The Leiden area is rapidly becoming a nodal point for medical and scientific research. The presence of the Leiden University, the Leiden University Medical Center (LUMC) and an increasing number of joint ventures between business and academic/scientific research bodies creates a dynamic atmosphere that encourages the exchange of information and the optimal use of the latest technology.

The Leiden Bio Science Park has become, since its establishment twelve years ago, one of the most successful Science Parks in the Netherlands. It currently accommodates over sixty innovative knowledge-intensive companies with a wide range of specializations, including biotechnology, medical technology and space technology.

The Bio Science Park forms an international high-tech industrial and research-based cluster, providing an excellent environment for the growth of innovative large and small-scale firms. For example: Centocor Europe, Fokker Space, Nalco Chemical, Zeneca Mogen, Pharming, Introgene, OctoPlus, TNO and the Centre for Human Drug Research. And nearby engineering companies like Jacobs Engineering and Heerema.

In the Bio Science Park, scientific research is combined with commercial activities. The Academic Business Centre facilitates co-operation between academic institutions and the business community at both national and international level.

The Bio Science Park's high standard of research is maintained through close association with the neighbouring Leiden University, internationally acclaimed for exceptional education and research. The Leiden University is not only the oldest established university in Europe, but also one of the most respected.

For additional information about the Bio Science Park please call the Bio Science Park Office phone 31-71-5167114 fax 31-71-5167119 E-mail: M.Martens@leiden.nl



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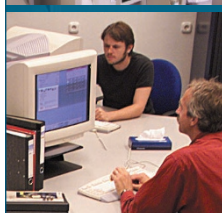
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