

## Healthcare industry BW

### Bracco Imaging: specialist in diagnostic imaging

**In future, small bubbles will allow the identification of pathological alterations at a very early stage. Molecular imaging methods developed by Bracco Imaging S.p.A. use a new ultrasound contrast agent. The German subsidiary of the company, Bracco Imaging Deutschland GmbH, based in Constance, develops and sells contrast agents.**

Bracco's company history began 80 years ago in an Italian pharmacy that sold drugs from Merck in Darmstadt. Some years later, the company started to develop and market contrast agents. Today, Bracco is one of the market leaders in this specialist area.

The latest developments are contrast agents that are able to identify molecular markers in vivo and assign them to their anatomical location. Molecular imaging allows the identification of diseases long before the first symptoms are visible. This enables therapy to be started immediately and that therapy can be accurately matched to the requirements of the patients.



Dr. Christian Greis is in charge of clinical development at Bracco. (Photo: Keller-Ullrich)

“The development and application of contrast agents is based on very specific requirements. The agents have to be tested in comprehensive preclinical and clinical tests before they can be launched on the market,” said Dr. Christian Greis, head of clinical development at Bracco. “In economic terms, our products unfortunately have a “flaw”, in that in contrast to therapeutic agents, contrast agents are not used continuously. This means that only a few packages are sold for individual diseases. However, the development costs are as high as those for therapeutic agents and the toxicological and clinical testing programmes are equally as comprehensive.

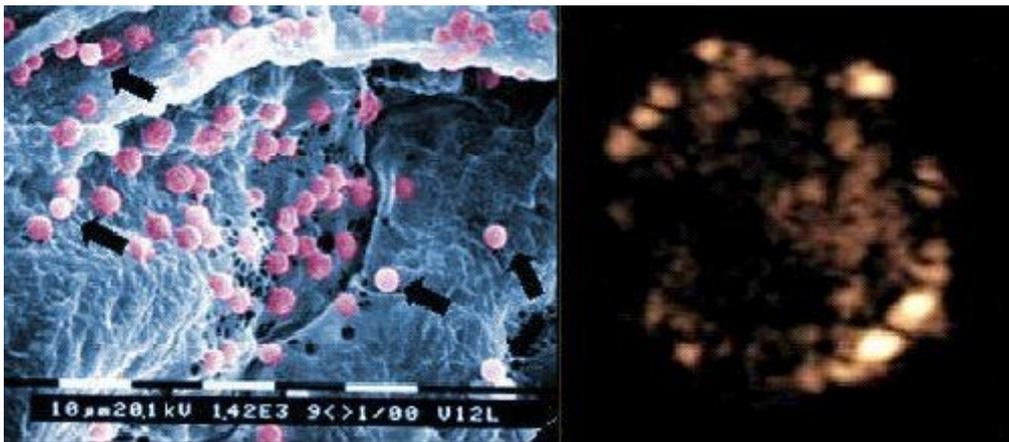
Over 300 million euros have to be invested for the launch of a contrast agent; this sum does not include the costs for production and marketing. The contrast agent manufacturers are thus very interested in earning this money prior to the product’s patent protection expiry after 12 years. That is why care has to be taken to not only develop products but also convince patients, physicians and insurance companies of the benefit of the contrast agents. “The prevention of diseases at an early stage helps to save large amounts of money because high-maintenance patient care is very expensive,” said Dr. Greis.

“From an economic point of view, the money is best invested into effective prevention and diagnostics,” said Greis, highlighting tuberculosis X-ray screenings that have led to excellent prevention and to the virtual eradication of a previously very common disease.

## “Histology” on living organs

Tumours are mainly diagnosed on the basis of newly formed tissue and blood supply (vascularity). Large blood supply usually means that the tumour is very aggressive. “This is true in many cases, but is only part of the truth,” said Dr. Greis explaining that the new methods and state-of-the-art knowledge of human genes enables physicians to identify tissue alterations at a molecular level. Pathological cells can thus be identified long before they have developed into incurable tumours.

It is particularly difficult to differentiate tumours from inflammatory processes and also the different stages of tumours. Depending on their stage of development, the tumours behave very differently and tumour-stage specific therapies have to be put in place.



Microbubbles of a highly-specific contrast agent. (Photo: Bracco)

Tumours can only be definitively identified with tissue biopsies. Pathologists regularly use molecular antibodies to identify the nature of a tumour and thus predict its biochemical properties and the receptors that are important for effective therapy. However, it is difficult to obtain tissue specimens from small tumours. Moreover, biopsies can only be taken if the tumour has already been diagnosed and its location in the body determined.

“We are using molecular imaging methods in the body to determine whether the detected tumour is malignant, the phase the tumour is in and what kind of tumour it is,” said Dr. Greis. The early detection of a tumour would enable its specific treatment and also largely save the healthy tissue surrounding it. The method is also suitable for inflammatory diseases such as rheumatism or for degenerative diseases such as Alzheimer’s.

## Identifying the right target

The method aims to identify degenerate cells in the body as soon as they have escaped the control of the body, and before a clinically manifest tumour develops and leads to metastases in the entire body. “It is quite a challenge to find the right marker molecules,” said Dr. Greis. Like pathologists investigating tissue samples for particular properties, the researchers at Bracco are also looking for characteristic molecular features that indicate the presence of degenerate cells and use contrast agents to make such cells visible.

Bracco already markets the technology to carry out such investigations. The company offers micromarker kits for research laboratories with microbubbles and everything else the researchers

need to couple their own targets to the bubbles and test them in animal experiments. "This facilitates cooperative ventures in that the laboratories do not have to give away information on the antibodies they are working with," said Dr. Greis.

VEGFR2 is such a molecule. It is a growth factor receptor that plays an important role in the vascularisation of developing tumours. A contrast agent that binds specifically to this target is currently being tested in animal experiments and will enter clinical development as soon as positive results have been obtained.

However, the clinical application of such molecular contrast agents depends on the right molecules and effective technology. That is why device and contrast agent manufacturers are working closely together. "Ultrasound is a very interesting imaging method, particularly for removing the necessity for screening and controls during and after therapy, because it is patient-friendly, cheap and flexible," said Dr. Greis. The contrast agent contains small bubbles which oscillate when exposed to sound waves and can be identified even at the smallest concentrations. "We need the right technology, the right target and need to correctly apply both during the development of the tumour as well as during the treatment and aftercare of the patients," said Dr. Greis. Preparations have begun and it is expected that the first human trial will begin within the next year.

## Diagnosics and therapy

The development of such highly-specific contrast agents does not only focus on an efficient detection method. The developers also have the vision that it might be possible to fill these bubbles with drugs and use them as drug delivery systems. Ultrasound might then also be used to release the active substances at the site of the tumour. This is no longer pure utopia. The drug delivery bubbles have already been successfully tested in animal experiments and it has been shown that it is possible to treat malignant diseases in a targeted manner or repair damage that occurs after cardiac infarction for example. "100 years ago when Paul Ehrlich was looking for effective syphilis treatments, the researcher dreamt of a magic bullet with which he could kill the disease-causing agent. Maybe, the specific ultrasound bubbles will soon become the tool Ehrlich was dreaming of," said Dr. Greis.

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