# PROMET reviews 2008

## European research on minimal residual disease in prostate cancer achieves new milestones

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**The specific targeted research project "Prostate cancer molecular-oriented detection and treatment of minimal residual disease" (PROMET) is approaching its last year of research activity. What has been achieved and where does the consortium stand?**

The project PROMET aimed at elucidating the mechanisms and the signature of minimal residual disease in prostate cancer and to develop novel therapeutic approaches to prevent the development of minimal residual disease to overt metastasis.

The concept was to explore, in close collaboration amongst basic scientists, clinical researchers and partners in the industry, the genetic pathways involved in minimal residual disease using functional genomics and expression profiling as technology platforms, advanced experimental models of minimal residual disease utilising bioluminescence, multiphoton microscopy, nanotechnology and optoacoustic technology for detection and treatment. The goal was to identify at least two signal transduction targets and to evaluate novel technologies for diagnosis of the presence of minimal residual disease and to seek novel therapeutic strategies for the treatment of this disease in prostate cancer.

Based on genetic and proteomic profiling, high throughput analysis of clinical samples and experimental *in vitro* and *in vivo models* of prostate cancer **potential markers of the presence of minimal residual disease** could be determined that are currently being evaluated in retrospective clinical sample sets and prospectively in lymph nodes of patients undergoing radical prostatectomy. These results will be compared to high end imaging modalities.

Interestingly, many of these potential markers are stem cell related, suggesting that so called cancer stem cells/cancer stem cell-like cells or early progenitor cells might be involved in the process of minimal residual disease and allow the disseminated cancer cells to survive for a long period of time in the host environment to then resurge as the seed of overt metastases.

By means of iTRAQ proteomics two potential proteins of interest as potential markers have been isolated and are currently being evaluated and validated in different clinical sample sets. Taken together the data the consortium has generated demonstrates that **differential gene and protein expression** of minimal residual disease exists. There is good preliminary evidence to suggest that minimal residual disease can be recognised and possibly targeted with such marker genes.

The development of different animal models addressing different issues of the problem of minimal residual disease using bioluminescence and thus significantly and drastically decreasing the number of experimental animals required for experiments has allowed insight into the mechanisms and the gene expression involved. **Experimental models** developed cover hormone-sensitive prostate cancer developing osteoblastic bone metastases and dormancy, which did not exist for prostate cancer research until now and are important additions to the prostate cancer researchers armamentarium.

In addition we have established a dorsal chamber metatarsal model for multiphoton fluorescent microscopy detection and quantification of micrometastases *in vivo* allowing to study the cellular mechanisms of homing, extravasation and implantation.


*Participants of the recent PROMET meeting in Bad Wildbad in Germany*

promet

PROstate cancer Molecular-oriented detEction and Treatment of minimal residual disease

In close collaboration with the industry (Fukuda Denshi) we **developed a novel optoacoustic instrument** that allows to alternately record optoacoustic and ultrasound imaging and improved the hardware by decreasing reconstruction artifacts by different algorithms and displacement compensated averaging (DCA). These proposed methods are computationally inexpensive and make real-time imaging possible.

Furthermore, we have been able to demonstrate that functionalised gold nanoparticles work as contrast agent for optoacoustics. Also in collaboration with the industry (Berthold Technologies) we have improved the sensitivity of CCD cameras for the detection of minimal residual disease, allowing a decrease in the detection threshold to approximately 100 cells in vivo.

The research groups involved are the Department of Urology, (M.G. Cecchini and G.N. Thalmann) and the Institute of Applied Physics (M. Frentz), University of Berne, Switzerland, Department of Urology, Leiden University Medical Center, the Netherlands (G. van der Pluijm and R. Pelgers), Department of Urology, University of Scheffield, United Kingdom (C. Eaton and F. Hamdy), Department of Urology and INSERM, University of Lyon, France (P. Clézardin and M. Colombel) and the Deutsches Krebsforschungszentrum Heidelberg (K. Ackermann and W. Pyerin). The SMEs involved are tp21 GmbH, Saarbrücken, Germany, Med Discovery SA, Geneva, Switzerland (L. Barki and C. Kündig), Fukada Denschi AG, Switzerland (Dieter Schweizer), Berthold Technologies GmbH & Co. KG, Bad Wildbad, Germany (M. Hennecke) and Apoxis (during first project year).

Project website: **http://www.fp6-promet.net**.