Translationale Forschung im internationalen Netzwerk – die Sichtweise der EORTC

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Technical University of Munich, Klinikum rechts der Isar, Germany

Translation

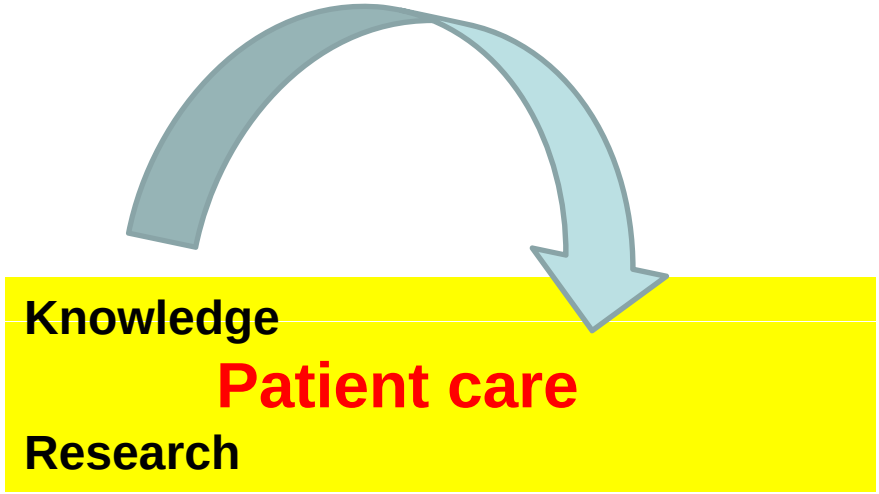
1) The act or process of translating, especially from one language into another.
2) The state of being translated.
3) A translated version of a text.
4) *Physics:* Motion of a body in which every point of the body moves parallel to and the same distance as every other point of the body.
5) *Biology* : The process by which messenger RNA directs the amino acid sequence of a growing polypeptide during protein synthesis.

The American Heritage® Dictionary of the English Language, Fourth Edition, updated in 2003.

Translational, **translatory** *adj* - relating to uniform movement without rotation

Translational research – definition (NIH)

Translational research is the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease.



EORTC, Brussels

European Organisation for Research and Treatment of Cancer

History

The **EORTC** was founded as an international organization under Belgian law in **1962** by eminent oncologists working in the main cancer research institutes of the EU countries and Switzerland.

It was named

Groupe Européen de Chimiothérapie Anticancéreuse (GECA),

and became the

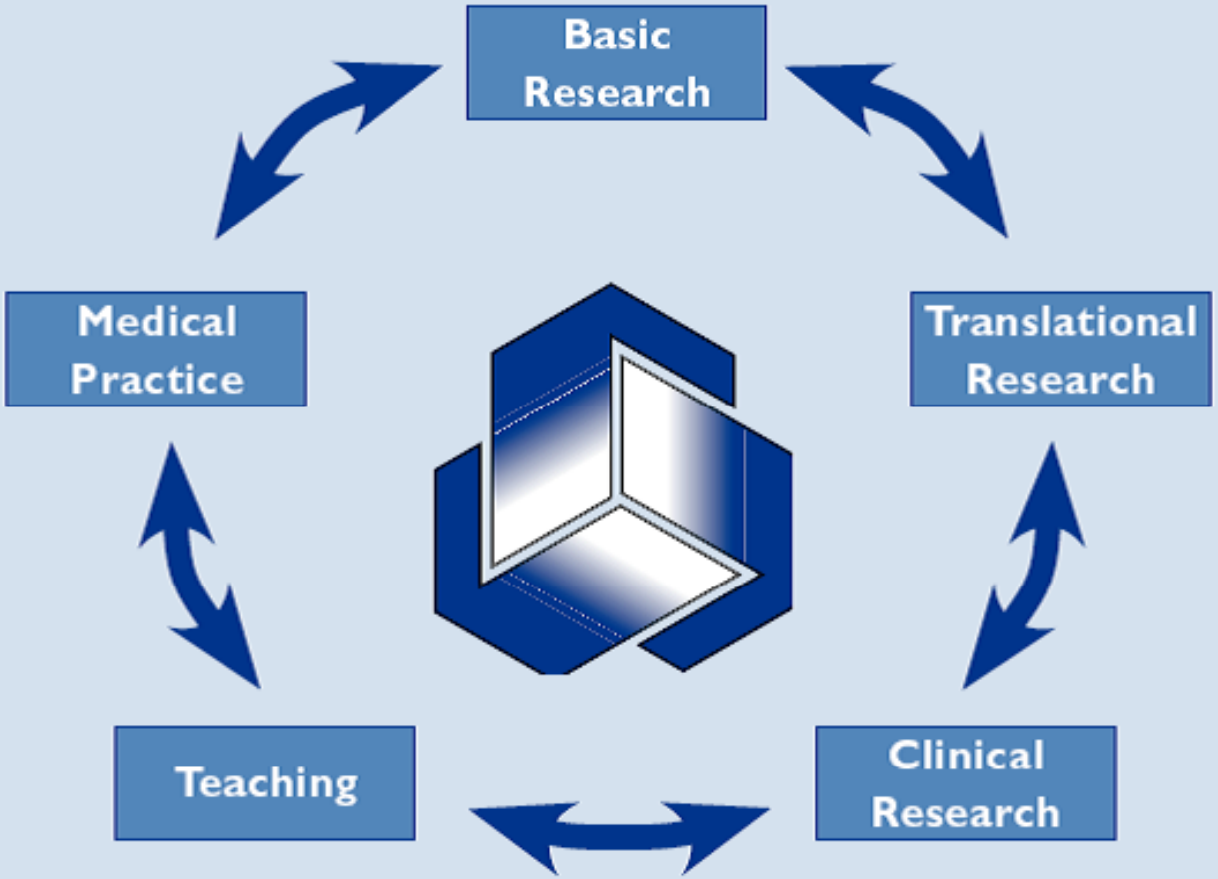
European Organisation for Research and Treatment of Cancer (EORTC) in 1968.

European Organization for Research and Treatment of Cancer (EORTC)

Private and not for profit organization

- **Main mission: promote and conduct research to improve cancer care**
  - **Core activity: conduct clinical trials**
    - **International**
    - **Multidisciplinary**
    - **Develop new treatments**
    - **Define new standards of care**
    - **Large academic trials**

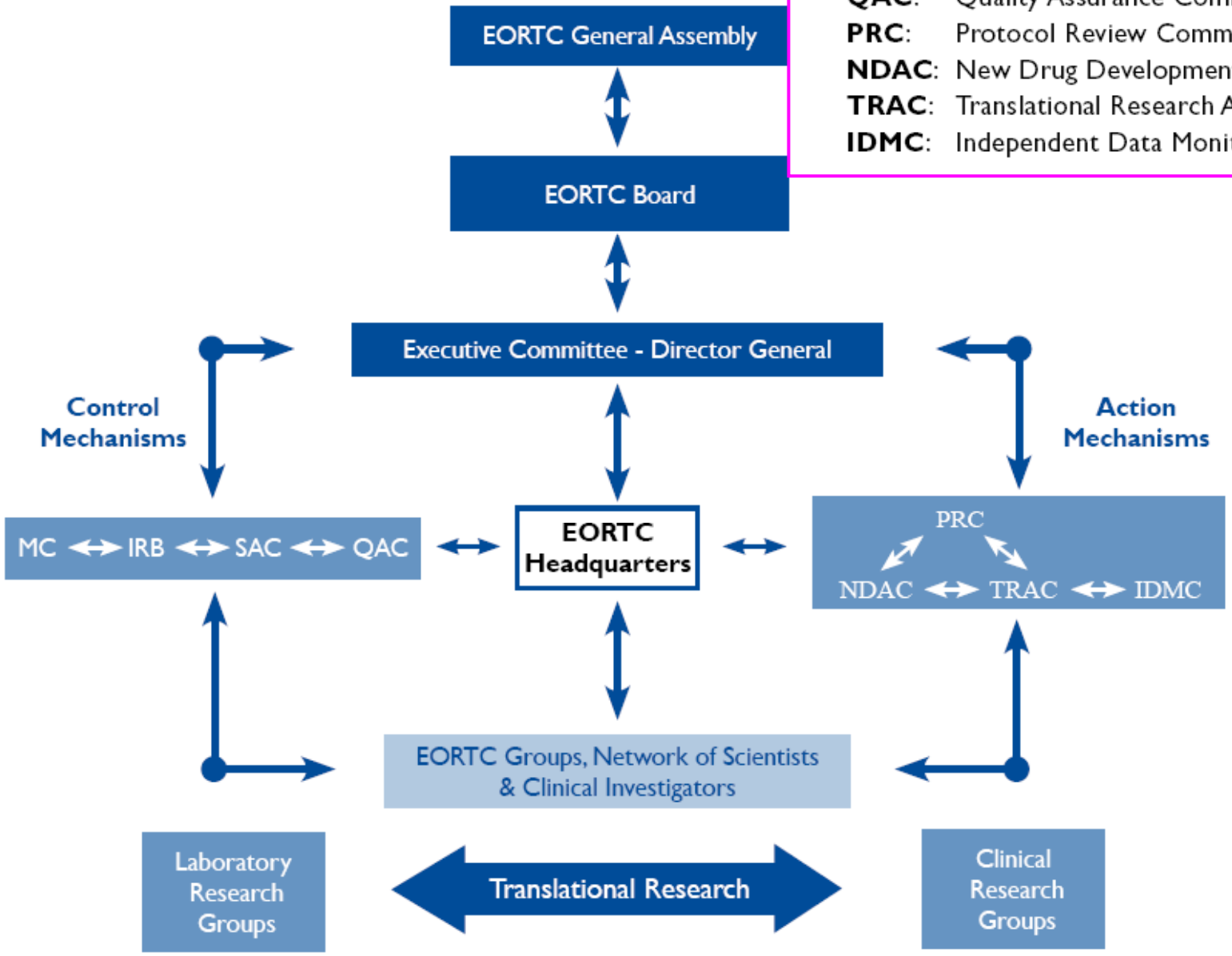
MEDICAL PRACTICE AND RESEARCH ARE INTERDEPENDENT



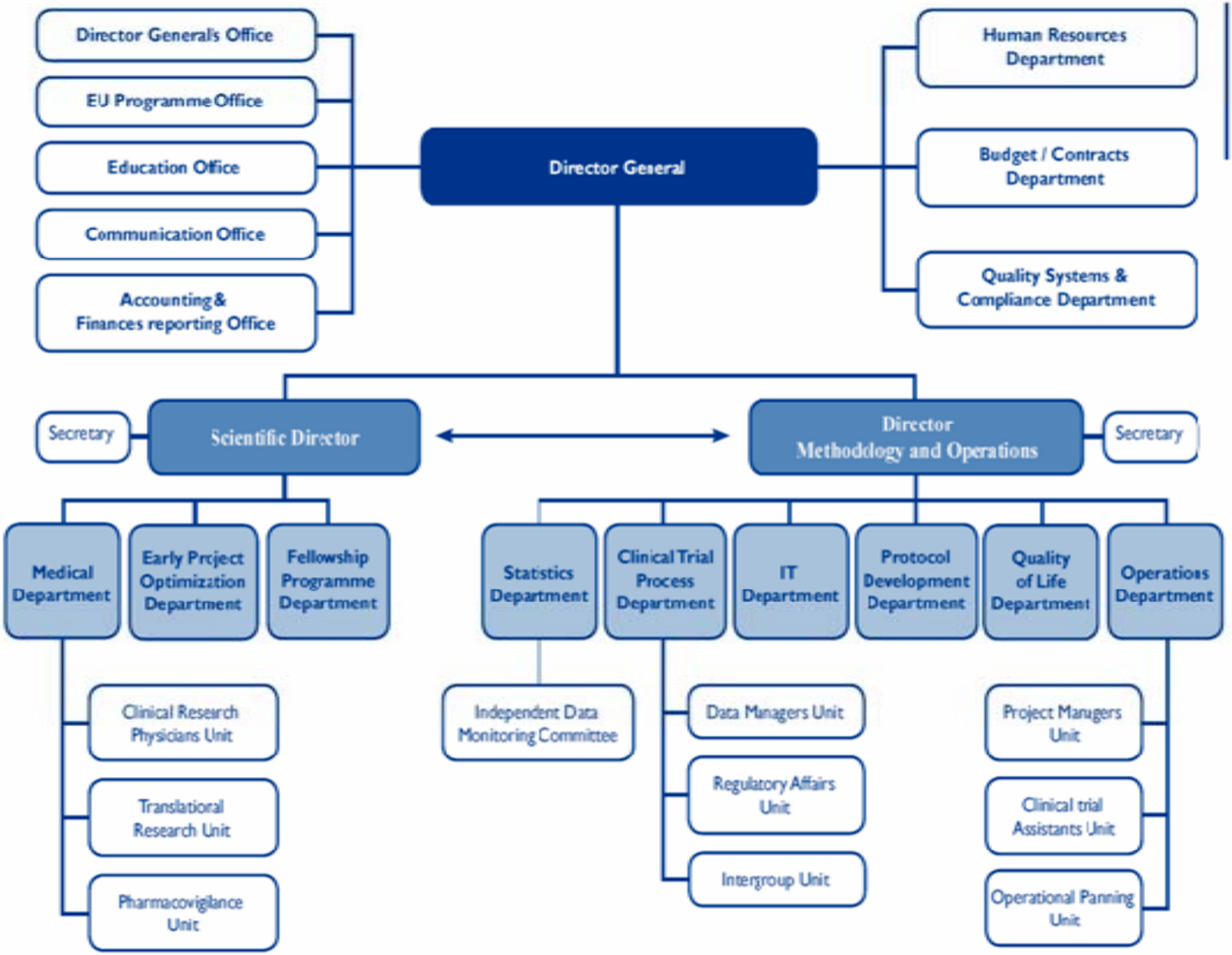
Structure of the EORTC

EORTC COMMITTEES:

MC: Membership Committee
IRB: Institutional Review Committee
SAC: Scientific Advisory Committee
QAC: Quality Assurance Committee
PRC: Protocol Review Committee
NDAC: New Drug Development Committee
TRAC: Translational Research Advisory Committee
IDMC: Independent Data Monitoring Committee



EORTC Headquarters: Organisational Charts



14th EORTC President

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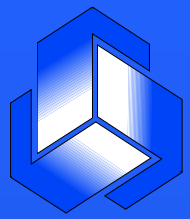
EORTC Group Chairs

Brain Tumour Group	M. J. van den Bent, Rotterdam (NL)
Breast Cancer Group	H. Bonnefoi, Bordeaux (FR)
Children's Leukaemia Group	Y. Bertrand, Lyon (FR)
Gastrointestinal Tract Cancer Group	M. Lutz, Saarbrucken (DE)
Genito-Urinary Cancer Group	T. de Reijke, Amsterdam (NL)
Gynaecological Cancer Group	N. Reed, Glasgow (GB)
Head and Neck Cancer Group	J. Vermorken, Antwerp (BE)
Infectious Diseases Group	J. Maertens, Leuven (BE)
Leukaemia Group	T. de Witte, Nijmegen (NL)
Lung Cancer Group	P. Baas, Amsterdam (NL)
Lymphoma Group	To be appointed
Melanoma Group	A. Spatz,Villejuif (FR)
Quality of Life Group	N. Aaronson, Amsterdam (NL)
Radiation Oncology Group	K. Haustermans, Leuven (BE)
Soft Tissue and Bone Sarcoma Group	J.Y. Blay, Lyon (FR)
PathoBiology Group	M. Schmitt, Munich(DE)
Pharmacology and Molecular Mechanisms Group	N. Zaffaroni, Milan (IT)

EORTC Task Force Chairs

Cancer in the Elderly U. Wedding, Jena (DE)
Cutaneous Lymphoma S. Whittaker, London (GB)



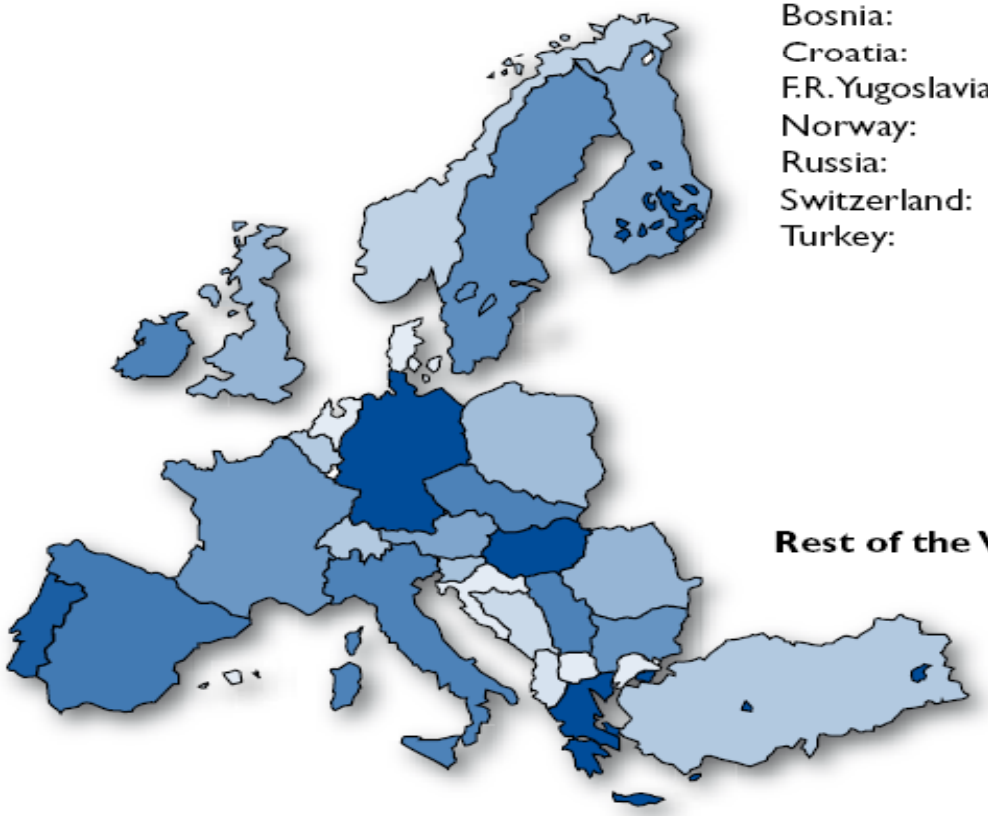
- Network of more than 200 institutions from 31 different countries
- +/- 2,000 collaborators (clinicians, pathologists, researchers,....)
- More than 5,000 patients are entered into EORTC trials each year (database of more than 140,000 patients)
- 30,000 patients being followed-up
- +/- 80 trials open to patient entry

In 2007, a total of 3,913 new patients were entered in EORTC trials by Group members. An additional 1,560 patients from other research groups were treated as part of the intergroup study scheme managed by the EORTC Headquarters.

Accrual of patients in EORTC clinical studies from 2003 - 2007: 22,672 patients

European Union:

Austria:	244
Belgium:	2,704
Bulgaria:	8
Cyprus:	72
Czech Republic:	43
Denmark:	268
Finland:	16
France:	4,061
Germany:	1,606
Greece:	1
Hungary:	71
Italy:	2,009
Latvia:	23
Luxemburg:	8
Poland:	665
Portugal:	364
Republic of Ireland:	48
Romania:	9
Slovak Republic:	240
Slovenia:	150
Spain:	534
Sweden:	156
The Netherlands:	4,496
United Kingdom:	2,892



Non-EU Countries:

Bosnia:	3
Croatia:	140
F.R. Yugoslavia:	185
Norway:	218
Russia:	16
Switzerland:	487
Turkey:	376

Rest of the World: 559

CANCER CLINICAL RESEARCH

Multidisciplinary team effort

- Surgery
- Radiotherapy
- Medical Oncology
- Pathology
- Immunology
- Infectious Diseases
- Genetics
- Psychology
- Health economics
- Other disciplines

Further clinical **progress in cancer treatment** will be accomplished mainly

- through the conduct of **translational research** projects, efficient drug development, and the execution of large, prospective, randomized, multicenter cancer **clinical trials**.

- by development, conduct, coordination, and stimulation of **laboratory and clinical research** in Europe to improve the **management** of cancer and related problems by increasing survival but also patients' quality of life.

The new EORTC

Network of Core Institutions (NOCI)

Core Institutions

- Leuven (BE)
- Rotterdam (NL)
- IGR (FR)
- Nijmegen/Arnhem (NL)
- NKI/AMC (NL)
- Bordet/Erasme (BE)
- Leiden (NL)
- Lyon (FR)
- Berlin (DE)
- Leeds (UK)
- Dijon (FR)
- Royal Marsden (UK)
- Warsaw (PL)
- Lausanne (CH)
- Aarhus (DK)
- Oslo (NO)
- Madrid (ES)
- Ljubljana (SL)

ADVANTAGES FOR PATIENTS TO PARTICIPATE IN CLINICAL TRIALS

- Better follow-up
- Better care
- Better outcome
- Assured of benefit at least from the standard treatment in a randomized setting

EORTC
Laboratory Research Division

- Pharmacology and Molecular Mechanisms and Functional Imaging
- Pathobiology

Tumor Bank

Aims

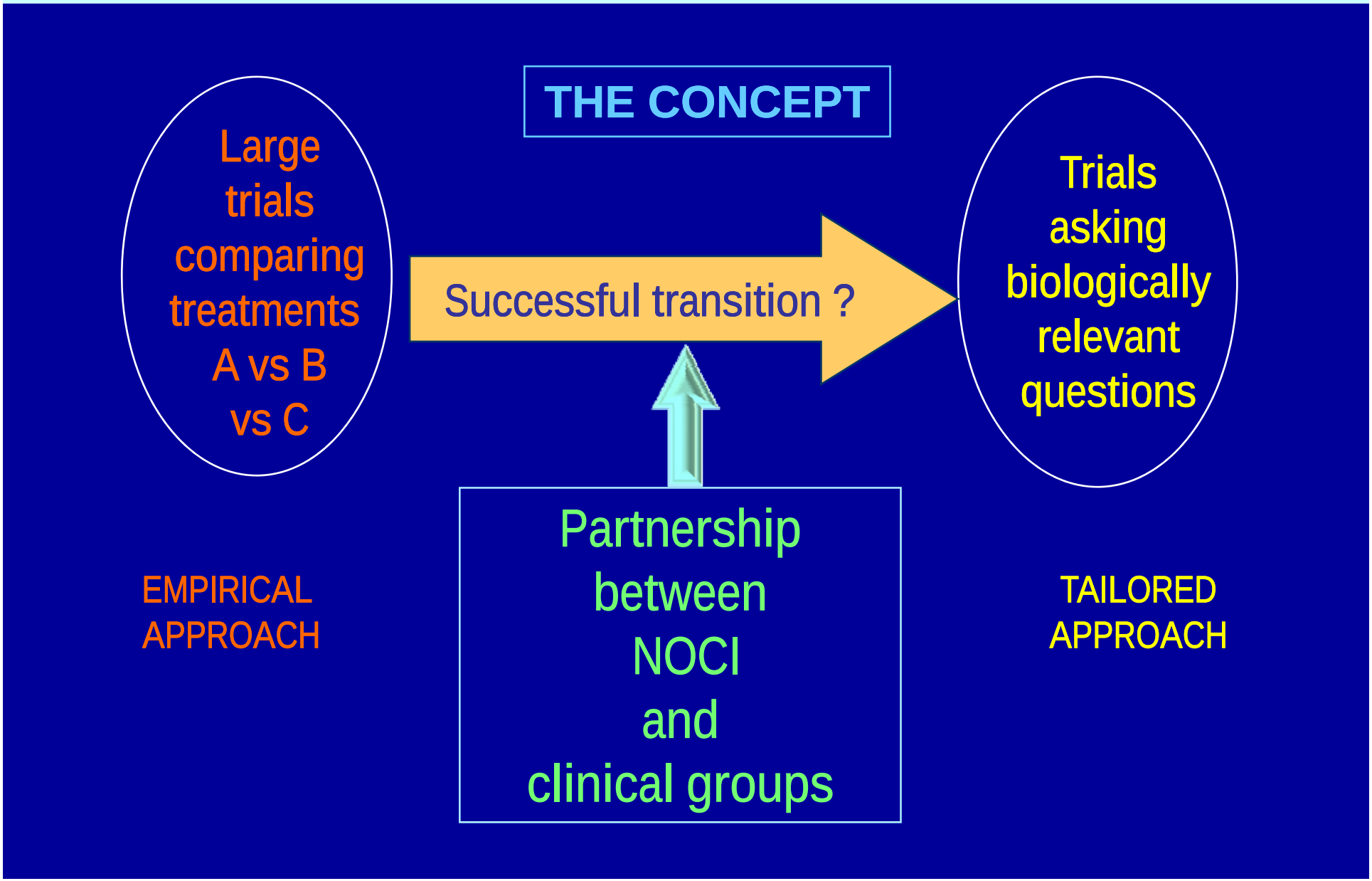
- **Create Tumor Bank**
  - **Physical tumor bank**
  - **Virtual tumor bank**
  - **Legal issues related to tissue research**
  - **Access and use**
- **Facilitate translational research and harmonize pathology review across EORTC trials**

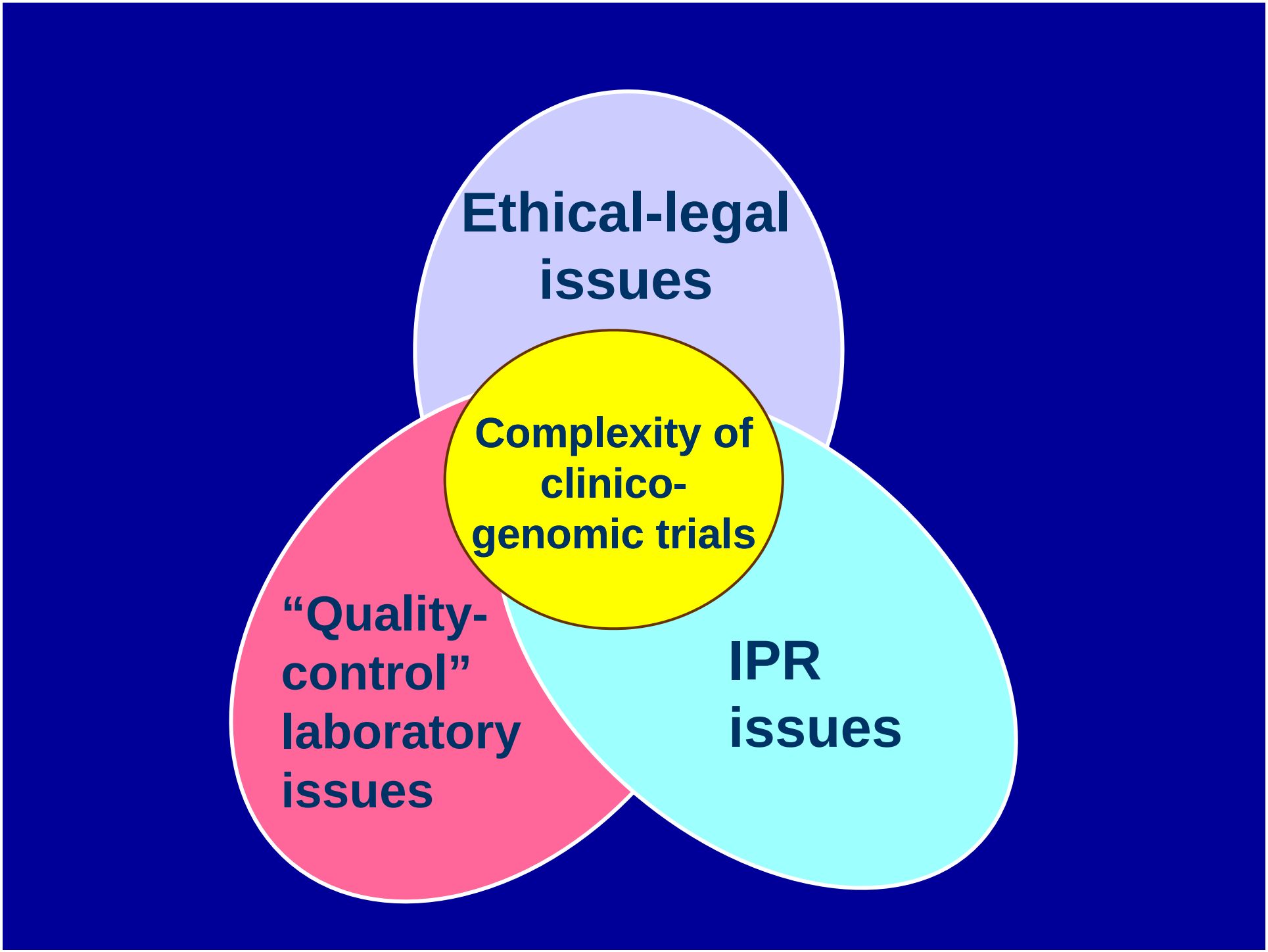
EORTC SCIENTIFIC STRATEGY

High priority trials = ?

- Randomized phase III trials aiming at answering a question which directly contributes to define new standards of care
- Randomized phase III trials with a strong targeted translational research component that may permit a fundamental advance in the understanding of a particular disease.

EORTC 2007 – 2010 : BUILDING A COMPETITIVE ORGANIZATION WITH AN "ADDED VALUE"




Ethical-legal issues
Complexity of clinico-genomic trials
“Quality-control” laboratory issues
IPR issues

EORTC
European Organisation for Research and Treatment of Cancer

TRANSBIG

MINDACT

(**M**icroarray **I**n **N**ode negative **D**isease may **A**void **C**hemo**T**herapy)

A prospective, randomised study comparing the 70-gene expression signature with common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in node-negative breast cancer. (EORTC Protocol 10041 – BIG 3-04)

Trial Coordinators:

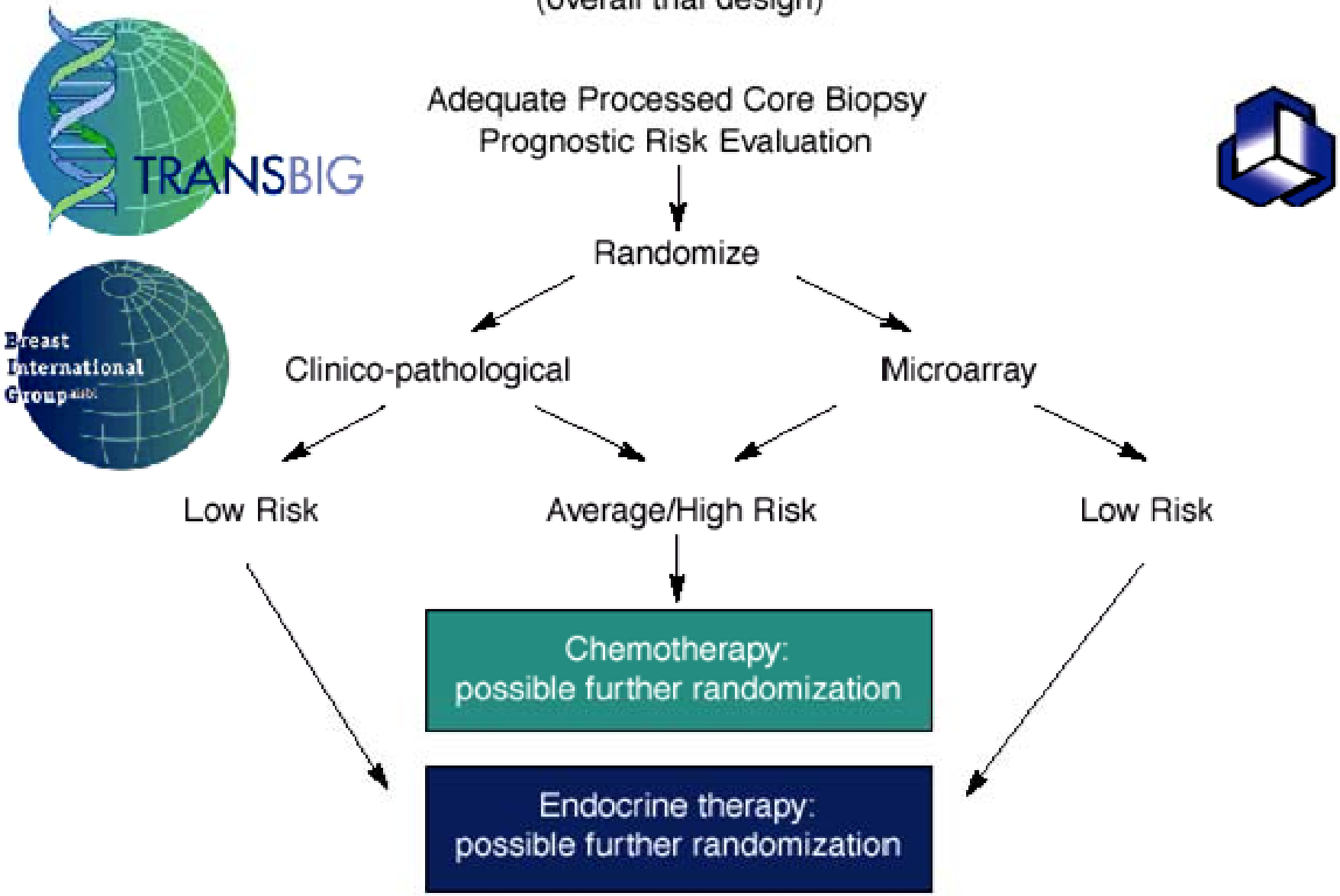
Fatima Cardoso - Institut Jules Bordet, Brussels

Martine Piccart - Institut Jules Bordet, Brussels

Emiel Rutgers - The Netherlands Cancer Institute-Antoni Van Leeuwenhoekziekenhuis, Amsterdam

EORTC/TRANSBIG MINDACT TRIAL: node negative women

(overall trial design)



Current status of the trial

Countries in which the trial is activated

COUNTRIES	DATE OF ACTIVATION
- Belgium	08/02/2007
- The Netherlands	22/03/2007
- Spain	29/05/2007
- France	25/06/2007
- Slovenia	20/08/2007
- Germany	25/02/2008
- UK	23/04/2008
- Italy	25/07/2008
- Switzerland	02/10/2008

Total accrual: Screening phase: 1459 patients (last update 15/09/2008)
Patients enrolled: 595 patients

National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

The Trial Assigning IndividuaLized Options for Treatment (Rx) (TAILORx)

TAILORx will examine whether genes that are frequently associated with risk of recurrence for women with early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment.

VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

Lyndsay Harris, Herbert Fritsche, Robert Mennel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

Table 1. Summary of Guideline Recommendations

Recommendations for the Use of Tumor Markers in Breast Cancer	
Specific Marker	2007 Recommendation
uPA and PAI-1 as a marker for breast cancer (Note: This topic is new to the guideline)	uPA/PAI-1 measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer. IHC for these markers is not accurate, and the prognostic value of ELISA using smaller tissue specimens has not been validated. Low levels of both markers are associated with a sufficiently low risk of recurrence, especially in hormone receptor–positive women who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit. Furthermore, CMF-based adjuvant chemotherapy provides substantial benefit, compared with observation alone, in patients with high risk of recurrence as determined by high levels of uPA and PAI-1.

N ⊖ d e
Negative
Breast
Cancer III

NNBC3-Trial

Trial design
Prospective, randomised, open label, multicenter phase III

GBG
GERMAN BREAST GROUP

Current Status: Open to accrual

Randomized study comparing 6x FEC with 3x FEC followed by 3x Docetaxel in highrisk node-negative patients with operable breast cancer: Comparison of efficacy and evaluation of clinico-pathological and biochemical markers as risk selection criteria.

German
Breast Group

N⊖de
Negative
Breast
Cancer III

Coordinating Centers (Germany)

Halle

Hamburg

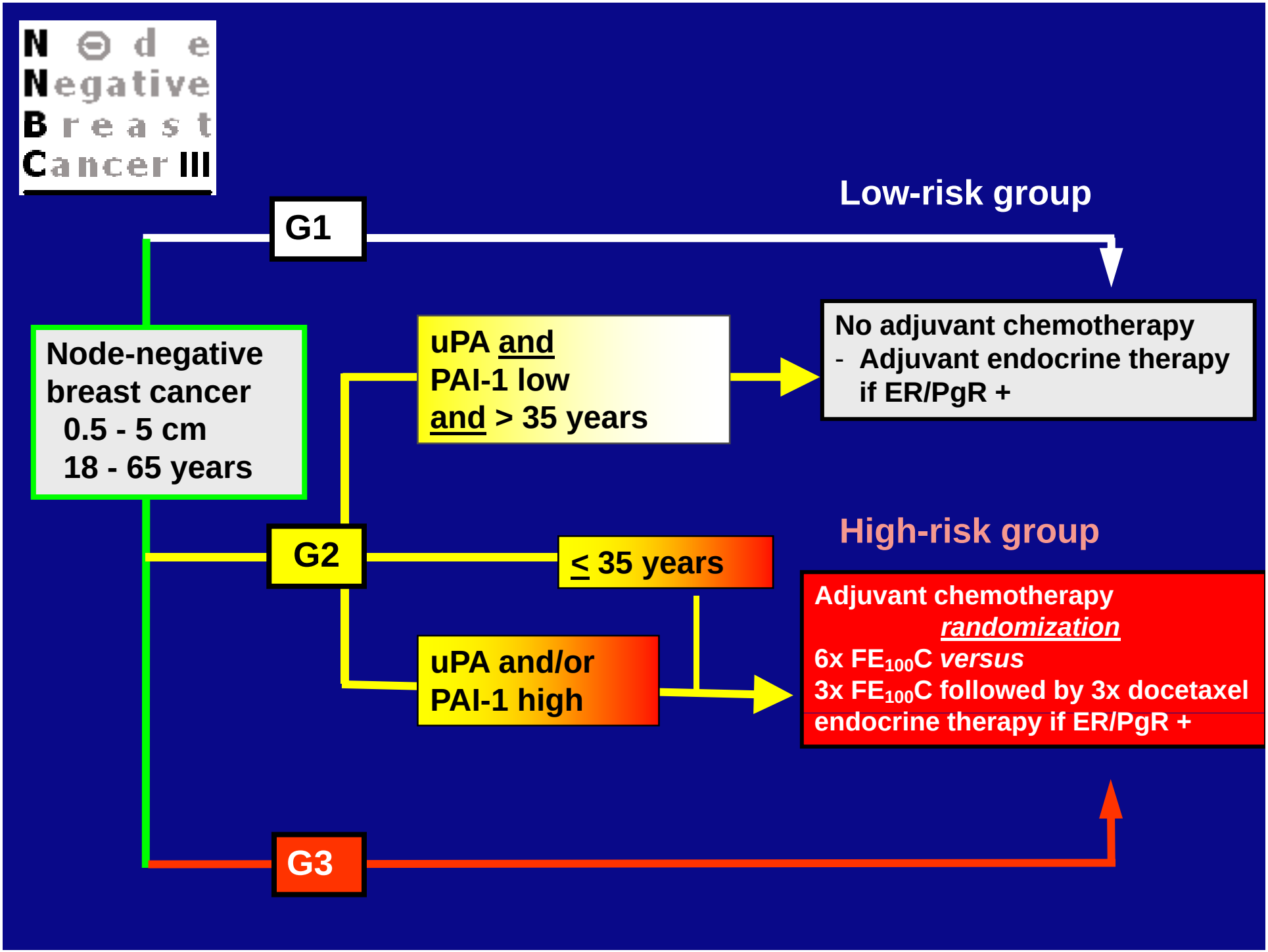
Universitätsklinikum
Hamburg-Eppendorf

Munich

Frauenklinik und Poliklinik der
Technischen Universität
München
Klinikum rechts der Isar
Direktorin: Prof. Dr. M. Kiechle

Participating countries:

Germany
France
Slovenia
Italy
The Netherlands


Node Negative Breast Cancer III
Low-risk group
G1
Node-negative breast cancer
0.5 - 5 cm
18 - 65 years
uPA and PAI-1 low and > 35 years
No adjuvant chemotherapy
- Adjuvant endocrine therapy if ER/PgR +
G2
≤ 35 years
High-risk group
uPA and/or PAI-1 high
Adjuvant chemotherapy
randomization
6x FE100C versus
3x FE100C followed by 3x docetaxel
endocrine therapy if ER/PgR +
G3

Identification of tumor biomarkers for

- disease detection
- differential diagnosis
- prognosis
- predicting response to therapy
- monitoring minimal residual disease
- and measuring tumor burden

through

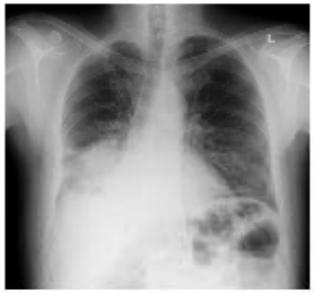
- analysis and/or molecular profiling of DNA, RNA, and protein from tumor tissue or bodily fluids

CHEMORES

TUMOUR CHEMOTHERAPY RESISTANCE

CHEMORES is an EU funded research collaboration involving clinicians and scientists at 17 universities, organizations for cancer research and research-oriented biotechnology companies in eight European countries. The purpose of the project is to improve cancer treatment by obtaining increased knowledge on mechanisms of chemotherapy resistance.

Cancer represents one of the most serious health problems in Europe. It is estimated that the two diseases that are studied in CHEMORES, lung cancer and melanoma, caused over 350,000 deaths in Europe in 2002. An important contributing factor in cancer mortality is the fact that the most common types of cancer do not respond well to systemic chemotherapy in the advanced stages. Increased understanding of the underlying processes will contribute to the development of predictors of both therapy response and toxicity, and in the end more efficient and personalised therapy.



NEWS

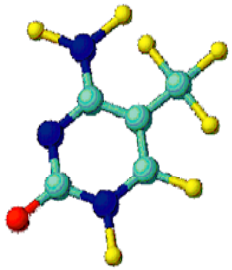
The CHEMORES integrated project started in February 2007 with a kick-off meeting at Karolinska Institutet in Stockholm, Sweden. The website is now up and running and our ambition is to give easily accessible information about the project to researchers, clinicians and interested members of the general public. Please feel free to e-mail us questions or comments at chemores@ki.se.

Sixth Framework Programme

Specific Targeted Research Project (2004 – 2006)

DNA-methylation based risk assessment in breast cancer

Coordinator: J.A. Foekens, Erasmus MedicalCenter, Rotterdam, The Netherlands



M. Schmitt	**Munich, Germany**
N. Brünner	**Copenhagen, Denmark**
C.G.J. Sweep	**Nijmegen, The Netherlands**
S. Maier	**Berlin, Germany**
F. Spyratos	**St. Cloud, France**
T. Cufer	**Ljubljana, Slovenia**
M.J. Duffy	**Dublin, Ireland**
S. Eppenberger-Castori	**Basel, Switzerland**

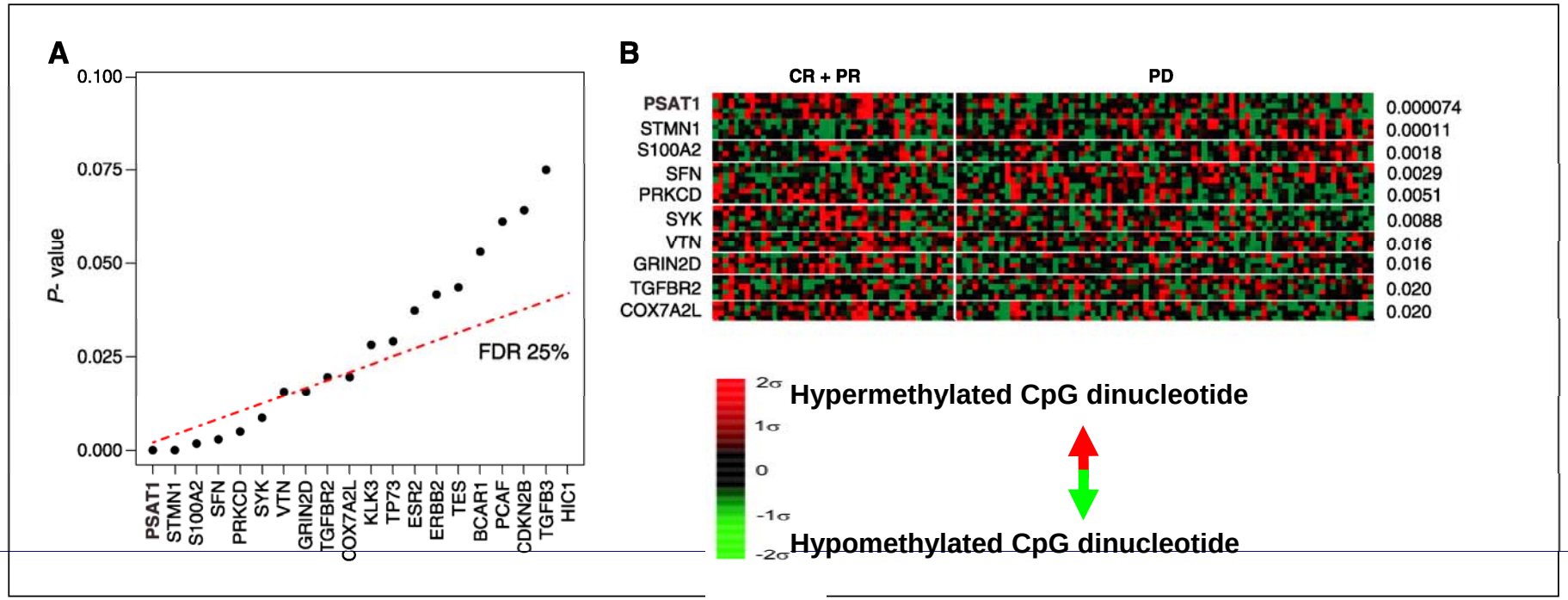
- By genome-wide DNA-methylation screening identify new therapeutic targets
- Develop prognostic and predictive DNA-methylation markers
- Confirm findings at the mRNA level
- Confirm findings at the protein level
- Confirm findings in clinically relevant subgroups of breast cancer patients
- **Achievements expected are**

  Improvement of patient prognosis by development of better therapeutic approaches based on new targeted therapies and better therapy selection

Cancer Research 2005; 65:4101-4107

Association of DNA Methylation of Phosphoserine Aminotransferase with Response to Endocrine Therapy in Patients with Recurrent Breast Cancer

John W.M. Martens,[1] Inko Nimmrich,[2] Thomas Koenig,[2] Maxime P. Look,[1] Nadia Harbeck,[3] Fabian Model,[2] Antje Kluth,[2] Joan Bolt-de Vries,[1] Anieta M. Sieuwerts,[1] Henk Portengen,[1] Marion E. Meijer-Van Gelder,[1] Christian Piepenbrock,[2] Alexander Olek,[2] Heinz Höfler,[4,5] Marion Kiechle,[3] Jan G.M. Klijn,[1] Manfred Schmitt,[3] Sabine Maier,[2] and John A. Foekens[1]



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EUROPEAN JOURNAL OF CANCER XXX (2007) XXX–XXX

ELSEVIER

available at www.sciencedirect.com

journal homepage: www.ejconline.com

DNA-methylation status of the homeodomain transcription factor PITX2 reliably predicts risk of distant disease recurrence in tamoxifen-treated, node-negative breast cancer patients – Technical and clinical validation in a multi-centre setting in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) pathobiology group

Sabine Maier[a,1], Inko Nimmrich[a,1], Thomas Koenig[a], Serenella Eppenberger-Castori[e], Inga Bohlmann[a], Angelo Paradiso[g], Frédérique Spyratos[f], Christoph Thomssen[j], Volkmar Mueller[d], Jörg Nährig[c], Francesco Schittulli[g], Ronald Kates[b], Ralf Lesche[a], Ina Schwope[a], Antje Kluth[a], Almuth Marx[a], John W.M. Martens[i], John A. Foekens[i], Manfred Schmitt[b], Nadia Harbeck[b,h,*]

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2007.14.1697
VOLUME 26 · NUMBER 30 · OCTOBER 20 2008

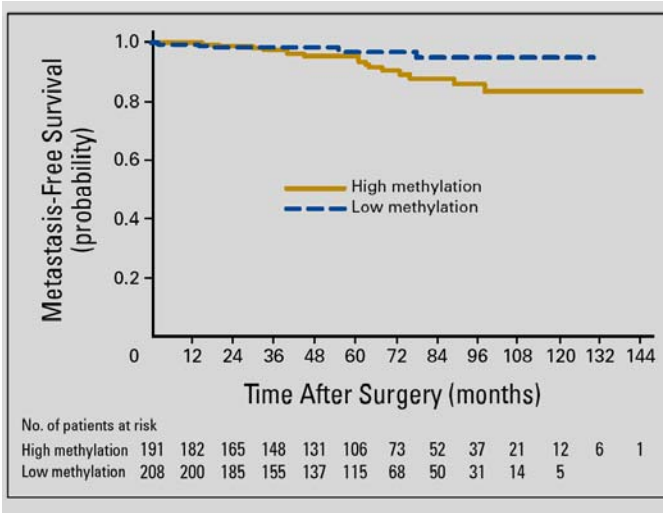
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Study Using Paraffin-Embedded Tumor Tissue Testing *PITX2* DNA Methylation As a Marker for Outcome Prediction in Tamoxifen-Treated, Node-Negative Breast Cancer Patients

Nadia Harbeck, Inko Nimmrich, Arndt Hartmann, Jeffrey S. Ross, Tanja Cufer, Robert Grützmann, Glen Kristiansen, Angelo Paradiso, Oliver Hartmann, Astrid Margossian, John Martens, Ina Schwope, Antje Lukas, Volkmar Müller, Karin Milde-Langosch, Jörg Nährig, John Foekens, Sabine Maier, Manfred Schmitt, and Ralf Lesche

From the Departments of Obstetrics and Gynecology and Pathology, Technical University of Munich, Munich; Epigenomics AG; Charite Hospital, Humboldt University, Berlin; Institute of Pathology, University of Regensburg, Regensburg; Department of Visceral, Thoracic, and Vascular Surgery, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden; Department of Gynecology, University Hospital Hamburg Eppendorf, Hamburg; Institute of Pathology, University of Erlangen, Erlangen, Germany; Institute of Clinical Pathology; University Hospital, Zurich, Switzerland; Institute of Oncology, Ljubljana, Slovenia; Clinical Experimental Oncology Laboratory, National Cancer Institute, Bari, Italy; Halitus Instituto Medico, Buenos Aires, Argentina; Department of Medical Oncology, Erasmus Medical Center, Rotterdam, the Netherlands; and Albany Medical College, Albany, New York.



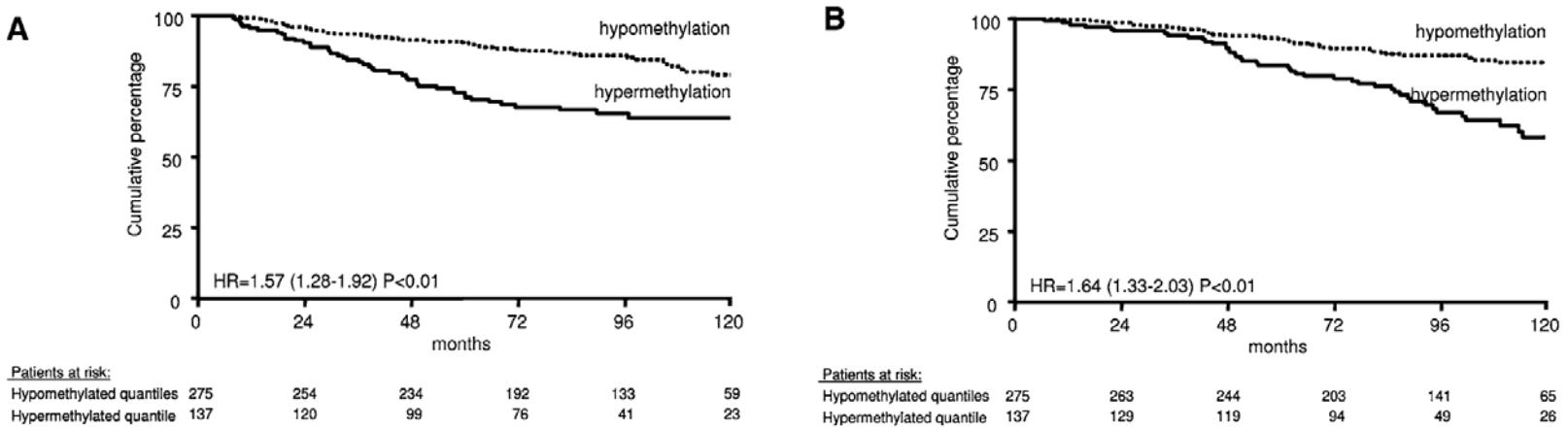
Breast Cancer Res Treat
DOI 10.1007/s10549-007-9800-8

PRECLINICAL STUDY

DNA hypermethylation of *PITX2* is a marker of poor prognosis in untreated lymph node-negative hormone receptor-positive breast cancer patients

Inko Nimmrich · Anieta M. Sieuwerts · Marion E. Meijer-van Gelder · Ina Schwope · Joan Bolt-de Vries · Nadia Harbeck · Thomas Koenig · Oliver Hartmann · Antje Kluth · Dimo Dietrich · Viktor Magdolen · Henk Portengen · Maxime P. Look · Jan G. M. Klijn · Ralf Lesche · Manfred Schmitt · Sabine Maier · John A. Foekens · John W. M. Martens

2008; 111:429-437



DNA Methylation Markers Predict Outcome in Node-positive, Estrogen Receptor-positive Breast Cancer with Adjuvant Anthracycline-based Chemotherapy

Oliver Hartmann[1], Frédérique Spyratos[4], Nadia Harbeck[2], Dimo Dietrich[1], Anne Fassbender[1], Manfred Schmitt[2], Serenella Eppenberger-Castori[3], Vincent Vuaroqueaux[3], Florence Lerebours[4], Katrin Welzel[1], Sabine Maier[1], Achim Plum[1], Stephan Niemann[1], John A. Foekens[5], Ralf Lesche[1], John W. M. Martens*[5]

[1] Epigenomics AG, Berlin, Germany
[2] Dept. OB&GYN, Technical University Munich, Germany
[3] Stiftung Tumorbank, Basel, Switzerland
[4] Centre René Huguenin, St. Cloud, France
[5] Erasmus MC, Rotterdam, The Netherlands

Clinical Cancer Research, 2008, in press

Breast cancer 76 gene signature (Rotterdam)

Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer

Yixin Wang, Jan G M Klijn, Yi Zhang, Anieta M Sieuwerts, Maxime P Look, Fei Yang, Dmitri Talantov, Mieke Timmermans, Marion E Meijer-van Gelder, Jack Yu, Tim Jatkoe, Els M J J Berns, David Atkins, John A Foekens

Lancet 2005; 365: 671–79

See **Comment** page 634

Interpretation The identified signature provides a powerful tool for identification of patients at high risk of distant recurrence. The ability to identify patients who have a favourable prognosis could, after independent confirmation, allow clinicians to avoid adjuvant systemic therapy or to choose less aggressive therapeutic options.

Multicentric validation study (Munich, Nijmegen, Bari, Ljubljana)

Published Ahead of Print on February 27, 2006 as 10.1200/JCO.2005.03.9115

VOLUME 24 · NUMBER 11 · APRIL 10 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Validation of a Gene Expression–Based Prognostic Signature in Lymph Node–Negative Primary Breast Cancer

John A. Foekens, David Atkins, Yi Zhang, Fred C.G.J. Sweep, Nadia Harbeck, Angelo Paradiso, Tanja Cufer, Anieta M. Sieuwerts, Dmitri Talantov, Paul N. Span, Vivianne C.G. Tjan-Heijnen, Alfredo F. Zito, Katja Specht, Heinz Hoefler, Rastko Golouh, Francesco Schittulli, Manfred Schmitt, Louk V.A.M. Beex, Jan G.M. Klijn, and Yixin Wang

- **In a training set of 115 tumors, we identified a 76-gene signature consisting of 60 genes for patients positive for oestrogen receptors (ER) and 16 genes for ER-negative patients.**
- **The gene profile was highly informative in identifying patients who developed distant metastases within 5 years.**

Functional class	76-gene signature
Cell death	TNFSF10, TNFSF13, MAP4, CD44, IL18, GAS2, NEFL, EEF1A2, BCLG, C3
Cell cycle	CCNE2, CD44, MAP4, SMC4L1, TNFSF10, AP2A2, FEN1, KPNA2, ORC3L, PLK1
Proliferation	CD44, IL18, TNFSF10, TNFSF13, PPP1CC, CAPN2, PLK1, SAT
DNA replication, recombination, and repair	TNFSF10, SMC4L1, FEN1, ORC3L, KPNA2, SUPT16H, POLQ, ADPRTL1
Immune response	TNFSF10, CD44, IL18, TNFSF13, ARHGDIB, C3
Growth	PPP1CC, CD44, IL18, TNFSF10, SAT, HDGFRP3
Cellular assembly and organisation	MAP4, NEFL, TNFSF10, PLK1, AP2A2, SMC4L1
Transcription	KPNA2, DUSP4, SUPT16H, DKFZP434E2220, PHF11, ETV2
Cell-to-cell signalling and interaction	CD44, IL18, TNFSF10, TNFSF13, C3
Survival	TNFSF10, TNFSF13, CD44, NEFL
Development	IL18, TNFSF10, COL2A1
Cell morphology	CAPN2, CD44, TACC2
Protein synthesis	IL18, TNFSF10, EEF1A2
ATP binding	PRO2000, URKL1, ACACB
DNA binding	HIST1H4H, DKFZP434E2220, PHF11
Colony formation	CD44, TNFSF10
Adhesion	CD44, TMEM8
Neurogenesis	CLN8, NEURL
Golgi apparatus	GOLPH2, BICD1
Kinase activity	CNK1, URKL1
Transferase activity	FUT3, ADPRTL1