Translationale Forschung im internationalen Netzwerk – die Sichtweise der EORTC

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**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.


**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.
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
14th EORTC President

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Brain Tumour Group
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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**

<table>
<thead>
<tr>
<th>European Union:</th>
<th>Non-EU Countries:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria: 244</td>
<td>Bosnia: 3</td>
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<tr>
<td>Belgium: 2,704</td>
<td>Croatia: 140</td>
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<td>Bulgaria: 8</td>
<td>F.R. Yugoslavia: 185</td>
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<td>Cyprus: 72</td>
<td>Norway: 218</td>
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<td>Finland: 16</td>
<td>Turkey: 376</td>
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<td>France: 4,061</td>
<td>Rest of the World: 559</td>
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<td>Germany: 1,606</td>
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<td>Greece: 1</td>
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<td>Hungary: 71</td>
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<td>Latvia: 23</td>
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<td>Republic of Ireland: 48</td>
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<td>Slovak Republic: 240</td>
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<td>Slovenia: 150</td>
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<td>Spain: 534</td>
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<td>Sweden: 156</td>
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<tr>
<td>The Netherlands: 4,496</td>
<td></td>
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<tr>
<td>United Kingdom: 2,892</td>
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</tr>
</tbody>
</table>
## 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
EORTC
Laboratory Research Division

- Pharmacology and Molecular Mechanisms and Functional Imaging
- Pathobiology
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
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”

THE CONCEPT

Large trials comparing treatments A vs B vs C

Successful transition?

Partnership between NOCI and clinical groups

Trials asking biologically relevant questions

EMPIRICAL APPROACH

TAILORED APPROACH
Ethical-legal issues

Complexity of clinico-genomic trials

"Quality-control" laboratory issues

IPR issues
MINDACT
(Microarray In Node negative Disease may Avoid ChemoTherapy)
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/TRANSGBIG MINDACT TRIAL: node negative women
(overall trial design)

Adequate Processed Core Biopsy
Prognostic Risk Evaluation

Randomize

Clinico-pathological
Low Risk

Average/High Risk

Microarray
Low Risk

Chemotherapy: possible further randomization

Endocrine therapy: possible further randomization
Current status of the trial

Countries in which the trial is activated

<table>
<thead>
<tr>
<th>COUNTRIES</th>
<th>DATE OF ACTIVATION</th>
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<tbody>
<tr>
<td>Belgium</td>
<td>08/02/2007</td>
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<td>The Netherlands</td>
<td>22/03/2007</td>
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<tr>
<td>Spain</td>
<td>29/05/2007</td>
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<td>France</td>
<td>25/06/2007</td>
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<td>Slovenia</td>
<td>20/08/2007</td>
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<td>Germany</td>
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<td>UK</td>
<td>23/04/2008</td>
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<td>Italy</td>
<td>25/07/2008</td>
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<tr>
<td>Switzerland</td>
<td>02/10/2008</td>
</tr>
</tbody>
</table>

Total accrual: Screening phase: 1459 patients (last update 15/09/2008)
Patients enrolled: 595 patients
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.
American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

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

Table 1. Summary of Guideline Recommendations

<table>
<thead>
<tr>
<th>Specific Marker</th>
<th>Recommendations for the Use of Tumor Markers in Breast Cancer</th>
<th>2007 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>uPA and PAI-1 as a marker for breast cancer (Note: This topic is new to the guideline)</td>
<td>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 patients. Without 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.</td>
<td></td>
</tr>
</tbody>
</table>
**NNBC3-Trial**

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

**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.
Coordinating Centers (Germany)

Halle

Hamburg

Munich

Participating countries:

Germany
France
Slovenia
Italy
The Netherlands
Node-negative breast cancer
0.5 - 5 cm
18 - 65 years

G1

No adjuvant chemotherapy
- Adjuvant endocrine therapy
  if ER/PgR +

uPA and PAI-1 low
and > 35 years

High-risk group

G2

< 35 years

Adjuvant chemotherapy
randomization
6x FE_{100}C versus
3x FE_{100}C followed by 3x docetaxel
endocrine therapy if ER/PgR +

uPA and/or PAI-1 high

G3

Low-risk group
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 is an EU funded research collaboration involving clinicians and scientists at 17 universities, organizations for cancer research and research-oriented high-technology 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.

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.

DNA-methylation based risk assessment in breast cancer

Coordinator: J.A. Foekens, Erasmus Medical Center, 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
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,3 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. Foekens1
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\textsuperscript{a,1}, Inko Nimmrich\textsuperscript{a,1}, Thomas Koenig\textsuperscript{a}, Serenella Epenberger-Castori\textsuperscript{e}, Inga Bohlmann\textsuperscript{d}, Angelo Paradiso\textsuperscript{g}, Frédérique Spyrratos\textsuperscript{f}, Christoph Thomssen\textsuperscript{l}, Volkmar Mueller\textsuperscript{d}, Jörg Nährig\textsuperscript{c}, Francesco Schittulli\textsuperscript{g}, Ronald Kates\textsuperscript{b}, Ralf Lesche\textsuperscript{a}, Ina Schwope\textsuperscript{a}, Antje Kluth\textsuperscript{a}, Almuth Marx\textsuperscript{a}, John W.M. Martens\textsuperscript{i}, John A. Foekens\textsuperscript{i}, Manfred Schmitt\textsuperscript{b}, Nadia Harbeck\textsuperscript{b,h,*}
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, Inke Nummrich, Arndt Hartmann, Jeffrey S. Ross, Tanja Cafer, Robert Grützmann, Glen Kristiansen, Angelo Paradiso, Oliver Hartmann, Astrid Margossian, John Martens, Ina Schwepe, Antje Lukas, Volkmar Müller, Karin Milde-Langosch, Jörg Nahrig, John Fockens, Sabine Maier, Manfred Schmitt, and Ralf Lesche
DNA hypermethylation of *PITX2* is a marker of poor prognosis in untreated lymph node-negative hormone receptor-positive breast cancer patients

Inko Nimrhirch · Anleta M. Sleuwers · Marion E. Meljer-van Gelder · Ina Schweppe · Joan Bolt-de Vries · Nadia Harbeck · Thomas Koenig · Oliver Hartmann · Antje Kluth · Dino 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 Hartmann¹, Frédérique Spyrotos⁴, Nadia Harbeck², Dimo Dietrich¹, Anne Fassbender¹, Manfred Schmitt², Serenella Eppenberger-Castori³, Vincent Vuaroqueaux³, Florence Lerebours⁴, Katrin Welzel¹, Sabine Maier¹, Achim Plum¹, Stephan Niemann¹, John A. Foekens⁵, Ralf Lesche¹, 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 Sienwerts, 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

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)

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

• 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.

<table>
<thead>
<tr>
<th>Functional class</th>
<th>76-gene signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell death</td>
<td>TNFSF10, TNFSF13, MAP4, CD44, IL18, GAS2, NEFL, EEF1A2, BCLG, C3</td>
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<tr>
<td>Cell cycle</td>
<td>CCNE2, CD44, MAP4, SMC4L1, TNFSF10, AP2A2, FEN1, KPNA2, ORC3L, PLK1</td>
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<tr>
<td>Proliferation</td>
<td>CD44, IL18, TNFSF10, TNFSF13, PPP1CC, CAPN2, PLK1, SAT</td>
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<tr>
<td>DNA replication, recombination, and repair</td>
<td>TNFSF10, SMC4L1, FEN1, ORC3L, KPNA2, SUPT16H, POLQ, ADPRTL1</td>
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<tr>
<td>Immune response</td>
<td>TNFSF10, CD44, IL18, TNFSF13, ARHGDIB, C3</td>
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<td>Growth</td>
<td>PPP1CC, CD44, IL18, TNFSF10, SAT, HDGFPR3</td>
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<tr>
<td>Cellular assembly and organisation</td>
<td>MAP4, NEFL, TNFSF10, PLK1, AP2A2, SMC4L1</td>
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<tr>
<td>Transcription</td>
<td>KPNA2, DUSP4, SUPT16H, DFKZP434E2220, PHF11, ETV2</td>
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<td>Cell-to-cell signalling and interaction</td>
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<td>Survival</td>
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<td>Development</td>
<td>IL18, TNFSF10, COL2A1</td>
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<td>Cell morphology</td>
<td>CAPN2, CD44, TACC2</td>
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<td>Protein synthesis</td>
<td>IL18, TNFSF10, EEF1A2</td>
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<td>ATP binding</td>
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<td>HIST1H4H, DFKZP434E2220, PHF11</td>
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<td>Colony formation</td>
<td>CD44, TNFSF10</td>
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<td>Adhesion</td>
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<td>Kinase activity</td>
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<tr>
<td>Transferase activity</td>
<td>FUT3, ADPRTL1</td>
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