

SEMMEWEIS UNIVERSITY
REGIONAL AND INSTITUTIONAL
COMMITTEE OF SCIENCE
AND RESEARCH ETHICS
Üllői st. 93., Budapest, H-1091
Phone: (36-1) 215-5038 Fax: (36-1) 215-6228
Mailing address: H-1450 Budapest, P.O.B. 9/41.

TUKEB No: 69/2008.
Protocol: -

Dr. Zsolt Tulassay
Professor
2nd Department of Internal Medicine

Budapest

Subject: Research entitled „Diagnostic assessment of inflammatory bowel diseases and colorectal cancer biomarkers determined by gene expression analysis”

Dear Professor!

Semmelweis University Regional and Institutional Committee of Science and Research Ethics (TUKEB) made a following decision at the Committee session of 2 June 2008:

The Committee found the research plan appropriate from both the scientific and ethical point of view and found the material and personal conditions of the institution suitable for the above research.

The Committee has made the decision according to Act CLIV of 1997 on health and Decree No. 23 of 2002 (May 9) of the Minister of Health on human medical research.

Budapest, 16th June 2008.

Sincerely yours,

Dr. Péter Sótonyi
Professor
Chair of TUKEB

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TUKEB No: 202/2009.
Protocol: -

Dr. Béla Molnár
senior research fellow, investigator
2nd Department of Internal Medicine
Cell Analysis Laboratory

Budapest

Subject: Research entitled „Examination of the epigenetic and gene expression effects of aging in gastrointestinal diseases”

Dear Investigator!

Semmelweis University Regional and Institutional Committee of Science and Research Ethics (TUKEB) made a following decision at the Committee session of 26 October 2009:

The Committee found the research plan appropriate from both the scientific and ethical point of view and found the material and personal conditions of the institution suitable for the above research.

The Committee has made the decision according to Act CLIV of 1997 on health and Decree No. 23 of 2002 (May 9) of the Minister of Health on human medical research.

Budapest, 8th December 2009.

Sincerely yours,

Dr. Péter Sótonyi
Professor
Chair of TUKEB

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Phone: (36-1) 215-5038 Fax: (36-1) 215-6228
Mailing address: H-1450 Budapest, P.O.B. 9/41.**

Committee members participated at the Committee session of 26 October 2009.:

Chair: **Prof. Dr. Péter Sótonyi** chair
(Department of Forensic Medicine, Faculty of Medicine, Semmelweis University)

Secretary: **Dr. Ágnes Dósa** physician-lawyer
(National Institute of Forensic Medicine)

Members:

György Hrehuss engineer laic member of the Committee

Dr. László Imrei head physician otolaryngologist
(Bethesda Children's Hospital)

Dr. István Pálfi head physician internist
(Ferenc Flót Hospital)

Dr. Szuchovszky Gyula lawyer associate member of the Committee

**Medical Research Council
Committee of Science and Research Ethics (ETT TUKEB)
Secretariat of the Medical research Council
H1051 Budapest, Arany János u. 6-8.**

Case number: **23970-1/2011-EKU (767/PI/11.)**
Official in charge: **Dr. Alfréda Temesi,**
Head of Department ETT TUKEB Secretariat
Contact: + **36-1-795-1197 (land line)**
Mobile phone: + **36-30-795-1197**
Enclosure: **2**

Re: Request for the competent specialized authority's position submitted by Dr. Béla Molnár, Semmelweis University, Faculty of Medicine, Department 2 of Internal Medicine (H-1088 Budapest, Szentkirályi u. 46.)

POSITION OF THE COMPETENT SPECIALIZED AUTHORITY

Concerning the request of the authorization of the research project titled "Examination of tissue markers for the early detection and differential diagnosis of colorectal cancer ID RD001431" submitted to this Committee by Béla Molnár, M.D., I take the following position in my capacity of competent specialized authority at the Committee session of 25 October 2011.

After due consideration of the supplements to the research plan sent to us, I hereby

grant professional and ethical authorization

for the research places listed in the attached enclosure.
The conditions of the study have been met.

The competence and jurisdiction of this specialized authority is established by section 23(8)a) of Decree 323/2010, (27 December) Korm. of the Government on the (Hungarian) National Public Health and Medical Officer Service and on the designation of a competent pharmaceutical authority.

According to Section 44(9) of Act CXL of 2004 on the general rules of administrative proceedings and services, the position of the specialized authority is not open to appeal, however the client may exercise its right to recourse by submitting an appeal in respect of the merits of the case.

JUSTIFICATION

Béla Molnár, M.D. submitted an application to the competent specialized authority for the assessment of the research plan and granting authorization on the bases Decree 235/009 (20 October) Korm. of the Government (hereinafter: The government Decree) on the rules governing authorization procedures of biomedical research, clinical trials with investigational medicinal devices intended for clinical trials.

I have examined the application and established that according to the Points a)-n) of section 7 of the Government Decree the application fulfils the following requirements:

Points a)-n) of Section 7: fulfilled.

I have taken the position set up in the operative part based on the decision of the Medical research Council Committee of Science and Research Ethics (ETT TUKEB) made at its session of 25 October 2011, in accordance with the position dated 20 December 2011 enclosed.

I inform the applicant that the specialized authority's resolution is only valid with this enclosure.

Dated: 3 January 2012

Round Seal of the Medical Research Council, Committee of Science and Research Ethics, Budapest

Signature of Dr. Zsuzsa Schaff, Academician, Professor, Chair of ETT TUKEB: signed

**Secretariat of the Medical Research Council
Committee of Science and Research Ethics (ETT TUKEB)**

H1051 Budapest, Arany János u. 6-8.

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**ENCLOSURE to the specialized authority's
position No. 767/PI/11., 23970-1/2011-EKU**

**PROFESSIONAL AND ETHICAL OPINION to the research project "Examination of tissue
markers for the early detection and differential diagnosis of colorectal cancer ID
RD001431"**

Having examined the supplements to the research plan, the Committee gives its consent to the
research from both professional and ethical aspects.

Dated: 3 January 2012

Round Seal of the Medical Research Council, Committee of Science and Research Ethics, Budapest

Signature of Dr. Zsuzsa Schaff, Academician, Professor, Chair of ETT TUKEB: signed

the expression of target genes will be compared to endogenous control, fold change values will be determined by ddCT method. Correlation analysis between RT-PCR results of differentially isolated RNA samples will be done using “linear correlation” option of the STATISTICA software.

Risk of the intervention:

During the project, the patients will not have any side effects. Complications slightly occur during colonoscopy with biopsy sampling. The endoscopic examination applied in the study is the same as routinely done, a little difference is that additional biopsy will be taken for molecular analysis. Sampling after CRC operation does not increase the risks and side effects of the surgical intervention. In case of complication, the required treatments can be done at 2nd Department of Internal Medicine or Department of Transplantation and Surgery, Semmelweis University.

Participants:

Institutes participating in the study:

1. Cell Analysis laboratory, 2nd Department of Internal Medicine, Semmelweis University (H-1088, Budapest, Szentkirályi str. 46)
2. Department of Transplantation and Surgery, Semmelweis University (H-1082, Budapest, Baross str. 23)
3. Roche Diagnostics Ltd., Germany (Nonnenwald, 82372 Penzberg, Germany)

The planned research will be done at Cell Analysis laboratory, 2nd Department of Internal Medicine and at Roche Diagnostics Ltd.

Persons participating in the study:

Physicians (Prof. Dr. Zsolt Tulassay, Dr. Béla Molnár, Dr. Ferenc Sipos, Dr. Kinga Tóth, Dr. Katalin Leiszter, Dr. Árpád Patai, Dr. Andrea Schöller), biologists (Dr. Orsolya Galamb, Sándor Spisák, Gábor Valcz, Alexandra Kalmár), biostatistician (Dr. Barnabás Wichmann) and assistants (Gabriella Kónyáné Farkas, Anita Nagy, Jánosné Dojcsák) of 2nd Department of Internal Medicine, Semmelweis University, physicians of Saint Emeric Hospital (Dr. Miklós Máté, Dr. András Bálint), physicians of 2nd Department of Surgery, Semmelweis University (Prof. Dr. Pál, Ondrejka, Dr. Gábor István), physicians of Department of Transplantation and Surgery, Semmelweis University (Dr. Antal Péter, Dr. Dénes Görög), and medical doctors, biologists, statisticians and ethical executives of Roche Diagnostics Ltd. will participate in the study.

**Medical Research Council
Committee of Science and Research Ethics (ETT TUKEB)
Secretariat of the Medical research Council
H1051 Budapest, Arany János u. 6-8.**

Case number: **23970-2/2011-EKU (767/PI/11.)**
Official in charge: **Dr. Alfréda Temesi,**
Head of Department ETT TUKEB Secretariat
Contact: + **36-1-795-1197 (land line)**
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Enclosure: **2**

Re: Request for the competent specialized authority's position submitted by Dr. Béla Molnár, Semmelweis University, Faculty of Medicine, Department 2 of Internal Medicine (H-1088 Budapest, Szentkirályi u. 46.)

POSITION OF THE COMPETENT SPECIALIZED AUTHORITY

Concerning the request of the authorization of the research project titled "Examination of tissue markers for the early detection and differential diagnosis of colorectal cancer ID RD001431" submitted to this Committee by Béla Molnár, M.D., I take the following position in my capacity of competent specialized authority at the Committee session of 25 October 2011.

After due consideration of the supplements to the research plan sent to us, I hereby

grant professional and ethical authorization

for the research places listed in the attached enclosure.
The conditions of the study have been met.

At the same time I withdraw the decision No. 23970-1/2011-EKU (767/PI/11.).

The competence and jurisdiction of this specialized authority is established by section 23(8)a) of Decree 323/2010, (27 December) Korm. of the Government on the (Hungarian) National Public Health and Medical Officer Service and on the designation of a competent pharmaceutical authority.

According to Section 44(9) of Act CXL of 2004 on the general rules of administrative proceedings and services, the position of the specialized authority is not open to appeal, however the client may exercise its right to recourse by submitting an appeal in respect of the merits of the case.

JUSTIFICATION

Béla Molnár, M.D. D.Sc. submitted an application to the competent specialized authority for the assessment of the research plan and granting authorization on the bases Decree 235/009 (20 October) Korm. of the Government (hereinafter: The government Decree) on the rules governing authorization procedures of biomedical research, clinical trials with investigational medicinal devices intended for clinical trials.

I have examined the application and established that according to the Points a)-n) of section 7 of the Government Decree the application fulfils the following requirements:

Points a)-n) of Section 7: fulfilled.

I have taken the position set up in the operative part based on the decision of the Medical research Council Committee of Science and Research Ethics (ETT TUKEB) made at its session of 25 October 2011, in accordance with the position dated 4 April 2012 enclosed.

I inform the applicant that the specialized authority's resolution is only valid with this enclosure.

Dated: 4 April 2012

Round Seal of the Medical Research Council, Committee of Science and Research Ethics, Budapest

Signature of Dr. Zsuzsa Schaff, Academician, Professor, Chair of ETT TUKEB: signed

**Secretariat of the Medical Research Council
Committee of Science and Research Ethics (ETT TUKEB)**

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**ENCLOSURE to the specialized authority's
position No. 767/PI/11., 23970-2/2011-EKU**

**PROFESSIONAL AND ETHICAL OPINION to the research project "Examination of tissue
markers for the early detection and differential diagnosis of colorectal cancer ID
RD001431"**

Having examined the supplements to the research plan, the Committee gives its consent to the research from both professional and ethical aspects.

Dated: 4 April 2012

Round Seal of the Medical Research Council, Committee of Science and Research Ethics, Budapest

Signature of Dr. Zsuzsa Schaff, Academician, Professor, Chair of ETT TUKEB: signed

Disease history of patients involved in the study will be separately stored for 10 years from the beginning of the study, in strictly anonymized manner.

Statistical methods applied in the study:

Quantitative and qualitative parameters of RNA samples from different sample types and different RNA isolation techniques will be compared using Student's T test, ANOVA and Tukey HSD test (determination of significance, P values).

For relative quantification of gene expression, the expression of target genes will be compared to endogenous control, fold change values will be determined by ddCT method. Correlation analysis between RT-PCR results of differentially isolated RNA samples will be done using "linear correlation" option of the STATISTICA software.

Risk of the intervention:

During the project, the patients will not have any side effects. Complications slightly occur during colonoscopy with biopsy sampling. The endoscopic examination applied in the study is the same as routinely done, a little difference is that additional biopsy will be taken for molecular analysis. Sampling after CRC operation does not increase the risks and side effects of the surgical intervention. In case of complication, the required treatments can be done at 2nd Department of Internal Medicine or Department of Transplantation and Surgery, Semmelweis University.

Participants:

Institutes participating in the study:

1. Cell Analysis laboratory, 2nd Department of Internal Medicine, Semmelweis University (H-1088, Budapest, Szentkirályi str. 46)
2. Department of Transplantation and Surgery, Semmelweis University (H-1082, Budapest, Baross str. 23)
3. 1st Department of Pathology and Experimental Cancer Research, Semmelweis University (H-1088, Budapest, Üllői str. 26)
4. 2nd Department of Surgery, Semmelweis University (H-1125, Budapest, Kútvölgyi str. 4)
5. Roche Diagnostics Ltd., Germany (Nonnenwald, 82372 Penzberg, Germany)

The planned research will be done at Cell Analysis laboratory, 2nd Department of Internal Medicine using PCR kits developed and sent by Roche Diagnostics Ltd. Besides 2nd Department of Internal Medicine, Semmelweis University,

Department of Transplantation and Surgery, Semmelweis University and 2nd Department of Surgery, Semmelweis University will be involved in sample collection. Pathological evaluation of tissue samples will be done at 1st Department of Pathology and Experimental Cancer Research, Semmelweis University.

Persons participating in the study:

Physicians (Prof. Dr. Zsolt Tulassay, Dr. Béla Molnár, Dr. Ferenc Sipos, Dr. Kinga Tóth, Dr. Katalin Leiszter, Dr. Árpád Patai, Dr. Andrea Schöller), biologists (Dr. Orsolya Galamb, Sándor Spisák, Gábor Valcz, Alexandra Kalmár), biostatistician (Dr. Barnabás Wichmann) and assistants (Gabriella Kónyáné Farkas, Anita Nagy, Jánosné Dojcsák) of 2nd Department of Internal Medicine, Semmelweis University, physicians of Saint Emeric Hospital (Dr. Miklós Máté, Dr. András Bálint), physicians of 2nd Department of Surgery, Semmelweis University (Prof. Dr. Pál, Ondrejka, Dr. Gábor István), physicians of Department of Transplantation and Surgery, Semmelweis University (Dr. Antal Péter, Dr. Dénes Görög), and medical doctors, biologists, statisticians and ethical executives of Roche Diagnostics Ltd. will participate in the study.

Sponsor of the study:

Roche Diagnostics Ltd., Germany (Nonnenwald, 82372 Penzberg, Germany). The sponsor company (Sponsor) will provide all equipments (reagents for molecular biological analyses, laboratory consumables, devices) and send to Cell Analysis Laboratory of 2nd Department of Internal Medicine. During the study, anonymized medical data of the patients involved in the project will be sent for Roche Diagnostics Ltd.

References

- 1., Galamb O et al. Reversal of gene expression changes in the colorectal normal-adenoma pathway by NS398 selective COX2 inhibitor. Br J Cancer. 2010;102(4):765-73.
- 2., Spisák S et al. Applicability of antibody and mRNA expression microarrays for identifying diagnostic and progression markers of early and late stage colorectal cancer. Dis Markers. 2010;28(1):1-14.