3rd INTERNATIONAL CONFERENCE «PERSONALIZED MEDICINE AND GLOBAL HEALTH»

Theme: Paving the way of Personalized medicine in Kazakhstan in the era of innovative technologies

September 15, 2017
Astana, Republic of Kazakhstan
EDITORIAL BOARD

Ilesanmi Adesida
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Dear Friends and Colleagues,

It is my pleasure and honor to welcome you to the 3rd International Scientific Conference on “Personalized Medicine & Global Health”. Nazarbayev University in collaboration with NLA continues its tradition of hosting the international scientific community in Astana, Kazakhstan.

The Conferences held during the previous years, brought together exceptional researchers and scientists to discuss the emerging trends in personalized medicine. I am excited that this 3rd International Conference, will among others, showcase research initiatives undertaken by Kazakhstan’s younger generation of scientists. The conference is structured around plenary sessions, keynote lectures, and poster presentations, thus providing a multidisciplinary forum for researchers, clinical doctors, policy makers, and representatives of healthcare systems.

I welcome you to Nazarbayev University and hope that the scholarly deliberations during the conference will inspire you to identify new scientific directions and inquiries. Please take advantage of this opportunity and enjoy being a part of this important dialogue.

Sincerely Yours,

Ilesanmi Adesida
Provost of Nazarbayev University

Astana, Kazakhstan
Dear Friends and Colleagues!

On behalf of the Organizing Committee, it is my great pleasure to welcome you to Astana and to the 3th International Scientific Conference on “Personalized Medicine & Global Health” hosted by the Center for Life Sciences of National Laboratory Astana at Nazarbayev University, Astana, Kazakhstan.

The conference aims to promote international cooperation in the field of biomedicine and global health, to generate ideal conditions to transform achievements from multi-omics technologies, bioinformatics and systems biology in a new medical platform for preventive and precision medicine in society.

Through this conference, we would like to engage with all of you in an open and constructive dialogue about the innovative advances in genomic medicine, the creation of scientific foundations of healthy aging, the development of international cooperation in innovative research directions in the field of biomedicine.

We hope that you will enjoy the Conference and that your interaction with your colleagues from different institutes will stimulate a creative exchange of ideas and will be personally rewarding.

Sincerely Yours,

Zhaxybay Zhumadilov

Director-General of National Laboratory Astana, Nazarbayev University

Astana, Kazakhstan
### THE 3rd INTERNATIONAL SCIENTIFIC CONFERENCE ON “PERSONALIZED MEDICINE & GLOBAL HEALTH”

<table>
<thead>
<tr>
<th><strong>Organizer</strong></th>
<th>Center for Life Sciences, National Laboratory Astana, Nazarbayev University</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date</strong></td>
<td>September 15, 2017</td>
</tr>
<tr>
<td><strong>Venue</strong></td>
<td>Nazarbayev University</td>
</tr>
<tr>
<td><strong>Website</strong></td>
<td><a href="http://nla.nu.edu.kz">http://nla.nu.edu.kz</a></td>
</tr>
</tbody>
</table>

**Organizing Committee**

**Chairman:** Ilesanmi Adesida, Provost, Nazarbayev University

**Co-chair:** Zhaxybay Zhumadilov, Director General, National Laboratory Astana, Nazarbayev University

**Members of organizing committee**

- Ainur Akilzhanova
- Ulykbek Kairov
- Ainur Akhmetova
- Ulan Kozhamkulov
- Saule Rakhimova
- Dauren Yerezhepov
- Zhannur Abilova
- Askhat Molkenov
- Maxat Zhabagin
- Almagul Kushugulova
- Samat Kozhakhmetov
- Zhazira Bukina

**Coordinators**

Members of the Council of Young Researchers:

- Ainur Akhmetova: Tel: +7 (7172) 70 93 18 Email: ainur.akhmetova2@nu.edu.kz
- Maxat Zhabagin: Tel: +7 (7172) 70 92 89 Email: maxat.zhabagin@nu.edu.kz
### SESSION 1 – Envisioning the Future of medicine

**Moderators:** Almaz Sharman, Richard Barker, Ilia Stambler

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Venue</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 - 9:10</td>
<td><strong>OPENING SESSION</strong></td>
<td>Nazarbayev University, Conference Hall 1022, Block C3</td>
<td>Zhaxybay Zhumadilov, MD, PhD, D.M.Sci, Professor, Director General of National Laboratory Astana</td>
</tr>
<tr>
<td>9:00 - 9:05</td>
<td><strong>Welcome &amp; Introduction</strong></td>
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<tr>
<td>9:05 - 9:10</td>
<td><strong>Welcome note</strong></td>
<td></td>
<td>Ilesanmi Adesida, Provost of Nazarbayev University</td>
</tr>
<tr>
<td>9:10 - 9:50</td>
<td><strong>SESSION 1 – Envisioning the Future of medicine</strong></td>
<td></td>
<td>Richard Barker, MD, PhD, Professor, Oxford University, Oxford, United Kingdom</td>
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<tr>
<td></td>
<td><strong>Keynote speech:</strong></td>
<td></td>
<td>1. Translating precision medicine into a longer healthier lifespan (opening speech, 20 min)</td>
</tr>
<tr>
<td>9:50 - 9:55</td>
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<td></td>
<td>2. GHI - a unique programme to catapult Kazakhstan into the era of precision medicine (20 min)</td>
</tr>
<tr>
<td>9:55 - 10:15</td>
<td><strong>SESSION 1 – Envisioning the Future of medicine</strong></td>
<td></td>
<td>Ilia Stambler, PhD, Chief Science Officer of “Vetek” Association – The Senior Citizens Movement (Israel). Chair of the Israeli Longevity Alliance and executive committee member of the International Society on Aging and Disease, Rishon Lezion, Israel</td>
</tr>
<tr>
<td>10:15 - 11:00</td>
<td><strong>SESSION 1 – Envisioning the Future of medicine</strong></td>
<td></td>
<td>Valery Benberin, D.M.Sci, Professor, Corresponding Member of National Academy of Sciences of Kazakhstan, Head of the Medical Center of the President’s Affairs Administration of Kazakhstan, Astana, Kazakhstan</td>
</tr>
<tr>
<td>11:00 - 11:20</td>
<td><strong>SESSION 1 – Envisioning the Future of medicine</strong></td>
<td>Nazarbayev University, Hall, Block C3</td>
<td>Almaz Sharman, MD, PhD, Professor. The President of the Academy of Preventive Medicine of Kazakhstan and the co-founder of HealthCity network of clinics, Almaty, Kazakhstan</td>
</tr>
</tbody>
</table>

**Keynote speech:**
- Solutions for medical and social problems of active longevity of the population of Kazakhstan
- Artificial Intelligence and Healthcare: COPD Case
11.20 - 11.25  |  Question & Answer from the audience

11.25 - 11.45  |  Massimo Pignatelli  
MD, PhD, Professor. Dean of School of Medicine, Nazarbayev University, Astana, Kazakhstan  
**Keynote speech:** Precision Medicine in Cancer: molecular profiling and targeted treatment

11.45 - 11.50  |  Question & Answer from the audience

11.50 - 12.00  |  Group photo of conference participants

**PRESS CONFERENCE/ROUND TABLE**

**Moderator:** Zhaxybay Zhumadilov  
**Venue:** Nazarbayev University, Room1011, Block C3

12:00 - 12:30  |  Translational engine of biomedical science into clinical practice

12:30 - 14:00  |  Lunch / Poster presentation  
**Venue:** Nazarbayev University, Hall, Block C3

**SESSION 2 – Innovative technologies in precision medicine**

**Moderators:** Massimo Pignatelli, Ainur Akilzhanova

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Title</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00</td>
<td>Gulnara Svyatova</td>
<td>Fetal genome increases the risk of pre-eclampsia in pregnancy, results of the InterPregGen study of EC 7FP “Genetic study of pre-eclampsia in Central Asian and European populations”</td>
<td>Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>14:10</td>
<td>Question &amp; Answer from the audience</td>
<td></td>
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<tr>
<td>14:15 - 14:25</td>
<td>Ainur Akilzhanova</td>
<td>Metabolomic analysis reveal potential metabolites and biological pathways involved in aging and obesity in Kazakh population</td>
<td>Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>14:30</td>
<td>Question &amp; Answer from the audience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14:45</td>
<td>Yergali Miyerbekov</td>
<td>Prognostic value of TNFα gene 308G&gt;A polymorphism in patients with sepsis</td>
<td>National Scientific Center of Surgery after A.N. Syzganov, Almaty, Kazakhstan</td>
</tr>
<tr>
<td>14:45</td>
<td>Question &amp; Answer from the audience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14:55</td>
<td>Asylkhan Rakhyzmhan</td>
<td>Intravital two-photon microscopy: application to the immune system</td>
<td>German Rheumatism Research Center, Berlin, Germany</td>
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<tr>
<td>14:55</td>
<td>Question &amp; Answer from the audience</td>
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<tr>
<td>Time</td>
<td>Speaker</td>
<td>Topic</td>
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<tr>
<td>15:00</td>
<td>Bibigul Ilyassova MD, PhD, Associate Professor. National Scientific Center of Surgery after A.N. Syzganov, Almaty, Kazakhstan</td>
<td>The impact of the results of the morphological study of the liver in the posttransplant period on the tactics of immunosuppressive therapy</td>
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</tr>
<tr>
<td>15:10</td>
<td>— Question &amp; Answer from the audience</td>
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<tr>
<td>15:15–15:25</td>
<td>Saule Rakhimova MD, C.B.Sci. Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan</td>
<td>Genetic variants of CYP2C9 and VKORC1 in LVAD patients</td>
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<tr>
<td>15:25</td>
<td>— Question &amp; Answer from the audience</td>
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</tr>
<tr>
<td>15:30–15:40</td>
<td>Yingqiu Xie PhD, Assistant Professor. School of Science and Technology, Nazarbayev University, Astana, Kazakhstan</td>
<td>PTEN/ARF as molecular markers of personalized cancer treatment</td>
<td></td>
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<tr>
<td>15:45</td>
<td>— Coffee Break/ Poster presentation</td>
<td>Venue: Nazarbayev University, Hall Block C3</td>
<td></td>
</tr>
<tr>
<td>16:10</td>
<td>Ulykbek Kairov PhD, Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan</td>
<td>A novel approach for determining the optimal number of independent components for reproducible cancer transcriptomes data analysis</td>
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<tr>
<td>16:20</td>
<td>— Question &amp; Answer from the audience</td>
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<tr>
<td>16:25–16:35</td>
<td>Amin Zollanvari PhD, Assistant Professor. School of Engineering, Nazarbayev University, Astana, Kazakhstan</td>
<td>An Analytical Perspective on Challenges and Future Trends in Genomic Data Analysis</td>
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<tr>
<td>16:35</td>
<td>— Question &amp; Answer from the audience</td>
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<tr>
<td>16:40–16:50</td>
<td>Ulan Kozhankulov MD, C.M.Sci. Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan</td>
<td>Whole genome sequencing of Kazakhstani M. tuberculosis strains with different drug susceptibility</td>
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<tr>
<td>16:50</td>
<td>— Question &amp; Answer from the audience</td>
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<td></td>
</tr>
<tr>
<td>16:55–17:05</td>
<td>Yuliya Mironova C.B.Sci. Perkin Elmer, Moscow, Russia</td>
<td>Modern solutions from Perkin Elmer for Next-generation sequencing</td>
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</tr>
<tr>
<td>17:05</td>
<td>— Question &amp; Answer from the audience</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 17.10 | **SESSION 4 – Microbiome Research and Global Health**  
Moderators: Almagul Kushugulova, Adil Supiyev |
|-------|--------------------------------------------------|
| 17.10-17.20 | **Luca Vangelista**  
*PhD, Associate Professor, School of Medicine, Nazarbayev University, Astana, Kazakhstan* | Engineering human microbiota for disease prevention and therapy |
| 17.20-17.25 | **Question & Answer from the audience** |
| 17.25-17.35 | **Samat Kozhakhmetov**  
*C.B.Sci. Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan* | The gut microbial diversity of Kazakhstan centenarians |
| 17.35-17.40 | **Question & Answer from the audience** |
| 17.40-17.50 | **Adil Supiyev**  
*MD, MPH, PhD. Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan* | Determinants of acute coronary syndrome and stroke in Kazakhstan: case-control study |
| 17.50-17.55 | **Question & Answer from the audience** |
| 17:55-18:05 | **Azliyati Azizan**  
*Ph.D, Associate Professor. School of Medicine, Nazarbayev University, Astana, Kazakhstan* | Extremophiles from unique ecosystems of Kazakhstan as potential producers of novel antibiotics |
| 18.05-18.10 | **Question & Answer from the audience** |
| 18.10-18.20 | **Summary / Comments** |
| 18.20-18.30 | **Chairs Closing Comments**  
*Zhaxybay Zhumadilov* |
| 19.00-21.00 | **Dinner** |

*All poster presenters are required to be next to their posters during poster session!*
### List of poster presentations

<table>
<thead>
<tr>
<th>Poster №.</th>
<th>Full Name</th>
<th>Title</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP 01</td>
<td>Abilova Zhannur</td>
<td>Association between HRYR2 mutations with ventricular tachycardia in Kazakh population</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 02</td>
<td>Adilbayeva Altnai</td>
<td>Collagen triple helix repeat containing-1 (CTHRC1) regulates the cell migration via focal adhesions in rheumatoid arthritis</td>
<td>School of Science and Technology, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 03</td>
<td>Adilgozhina Gulsim</td>
<td>Cytoprotective effect of bee keeping products</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 04</td>
<td>Akhmetova Ainur</td>
<td>Preparation of HALOPLEX cardiogenetic panel for targeted sequencing of heart rhythm disorders</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 05</td>
<td>Akilzhanov Kenes</td>
<td>New method of noninvasive surgical treatment of patellofemoral arthritis</td>
<td>Semey State Medical University, Semey, Kazakhstan</td>
</tr>
<tr>
<td>PP 06</td>
<td>Alikeyeva Elmira</td>
<td>Risk factors for unfavorable outcomes of TB in HIV-infected patients</td>
<td>National Research Center of Phthisiopulmonology, Almaty, Kazakhstan</td>
</tr>
<tr>
<td>PP 07</td>
<td>Babenko Dmitriy</td>
<td>Tendency of lab methods used in colorectal cancer research during last 20 year: Text-mining approach</td>
<td>Karaganda State Medical University, Karaganda, Kazakhstan</td>
</tr>
<tr>
<td>PP 08</td>
<td>Bekbayev Sultan</td>
<td>Analysis of microtubule targeting drugs and mitotic slippage</td>
<td>School of Science and Technology, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 09</td>
<td>Bulanin Denis</td>
<td>Identification of therapeutic targets for chemotherapy-resistant colon cancer stem cells</td>
<td>School of Medicine, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 10</td>
<td>Cainelli Francesca</td>
<td>Personalized diagnosis of Gaucher disease in Kazakhstan</td>
<td>School of Medicine, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 11</td>
<td>Kairov Ulykbek</td>
<td>Laboratory of Bioinformatics and Computational Systems Biology at Center for Life Sciences, National Laboratory Astana, Nazarbayev University</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 12</td>
<td>Karabekova Aizhan</td>
<td>Determination the main gene mutation of orphan neurological diseases in children</td>
<td>Atchabarov Research Institute of Applied and Fundamental Medicine, Asfendiyarov</td>
</tr>
<tr>
<td>PP 13</td>
<td>Li Yelena</td>
<td>Recovery of neurological function of ischemic stroke by administration of conditioned medium from adipose-derived perivascular stem cells</td>
<td>National Center for Biotechnology, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 14</td>
<td>Mach Yana</td>
<td>Identification of Hrb27C as a novel regulator of the Hippo pathway using a <em>Drosophila</em> genetic screen</td>
<td>School of Science and Technology, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 15</td>
<td>Madiyarova Meruyert</td>
<td>Bio-impedance analysis results in residents of the Esil district of Astana</td>
<td>University Medical Center, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 16</td>
<td>Mansurova Dzhamilya</td>
<td>Polymorphism of CYP2C19 gene in patients with CHD</td>
<td>Semey State Medical University, Semey, Kazakhstan</td>
</tr>
<tr>
<td>PP 17</td>
<td>Molkenov Askhat</td>
<td>New High Performance Computing platform for Bioinformatics Research</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 18</td>
<td>Mussina Dariga</td>
<td>Estimation of the state of screening program on early detection of prostate cancer within the framework of the National screening program in Pavlodar region</td>
<td>Semey State Medical University, Semey, Kazakhstan</td>
</tr>
<tr>
<td>PP 19</td>
<td>Nurmoldin Shalkar</td>
<td>Molecular fingerprinting of metabolom for various diseases</td>
<td>Atchabarov Research Institute of Applied and Fundamental Medicine, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan</td>
</tr>
<tr>
<td>PP 20</td>
<td>Salimbayeva Damilya</td>
<td>The spectrum of mutation in PAH gene among Kazakhs with phenylketonuria</td>
<td>Republican Medical Genetic Consultation, Scientific Center of Obstetrics, Gynecology and Perinatology, Almaty, Kazakhstan</td>
</tr>
<tr>
<td>PP 21</td>
<td>Sarsenova Madina</td>
<td>The study of the therapeutic effect of growth factors and synovium-derived mesenchymal stem cells incapsulated in heparin-conjugated fibrin hydrogel on osteochondral defects in rabbits</td>
<td>National Center for Biotechnology, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 22</td>
<td>Supiyev Rakhim</td>
<td>Current numerical techniques for prediction of blood hemolysis</td>
<td>School of Engineering, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 23</td>
<td>Toishibekov Yerzhan</td>
<td>Embryo development of handmade cloned Kazakh argali (ovis ammon collium) embryo using frozen-thawed fibroblast cells</td>
<td>Institute of Experimental Biology, Almaty, Kazakhstan</td>
</tr>
<tr>
<td>PP 24</td>
<td>Toleubekova Lyazzat</td>
<td>Challenges in management of patients with amyotrophic lateral sclerosis (als)</td>
<td>School of Medicine, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 25</td>
<td>Tursynbek Nurislam</td>
<td>Identifying a 229-gene signature to discriminate anaplastic astrocytoma from glioblastoma using meta-analysis of multiple microarray datasets</td>
<td>School of Science and Technology, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 26</td>
<td>Umbayev Baurzhan</td>
<td>Biocompatibility of new thermoreversible poloxamer 407-based hydrogels</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 27</td>
<td>Yerezhepov Dauren</td>
<td>Metabolic profile of breast cancer patients in Kazakhstan</td>
<td>National Laboratory Astana, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 28</td>
<td>Zhalgas Aidana</td>
<td>The role of biosensors for tuberculosis detection</td>
<td>School of Engineering, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
<tr>
<td>PP 29</td>
<td>Zhanzak Zhuldyz</td>
<td>Thalidomide affects macrophage activation and leishmania major survival</td>
<td>School of Science and Technology, Nazarbayev University, Astana, Kazakhstan</td>
</tr>
</tbody>
</table>
SPEAKERS

Richard Barker, MD, PhD, Professor.
Oxford University, Oxford, United Kingdom

Richard is an internationally respected leader in healthcare and life sciences.
He is Founding Director of New Medicine Partners, a global firm assisting public and private sector organisations to accelerate the development and adoption of precision medicine. He also founded the Oxford-UCL Centre for the Advancement of Sustainable Medical Innovation (CASMI), a major UK academic initiative aimed at bringing biomedical advances more rapidly and affordably to patients. He is chairman of the South London Health Innovation Network and of the corresponding Genomic Medicine Centre. He also chairs Image Analysis, a UK company using MRI to quantify the impact of therapy on disease and is a board member of Celgene, a major US-based biotherapeutics company.

His 30-year business career in healthcare has spanned biopharmaceuticals, diagnostics and medical informatics – both in the USA and Europe. The senior roles he has held include: Director General of the Association of the British Pharmaceutical Industry, General Manager of Healthcare Solutions for IBM, Chief Executive of Chiron Diagnostics and head of McKinsey’s European healthcare practice.

Ilia Stambler, PhD.

Chief Science Officer of “Vetek” (Seniority) Association – The Senior Citizens Movement (Israel). Chair of the Israeli Longevity Alliance and executive committee member of the International Society on Aging and Disease. Rishon Lezion, Israel.

Ilia Stambler, PhD, is Chief Science Officer of “Vetek” (Seniority) Association – The Senior Citizens Movement (Israel). He received his PhD at the Department of Science, Technology and Society, Bar Ilan University, Israel. His research has focused on the historical and social implications of aging and life extension research. He is also involved in mathematical modeling of aging and aging-related diseases (https://ec.europa.eu/eip/ageing/commitments-tracker/a3/quantified-longevity-guide-qlg_en). He is the author of A History of Life-extensionism in the Twentieth Century and Longevity Promotion: Multidisciplinary Perspectives (www.longevityhistory.com). He is actively involved in advocacy for aging and longevity research (www.longevityforall.org), and is Chair of the Israeli Longevity Alliance (http://www.longevityisrael.org/) and Executive committee member of the International Society on Aging and Disease (http://www.isoad.org/). His papers have appeared in Progress in Neurobiology, Aging and Disease, Cancer Detection and Prevention, Rejuvenation Research, Current Aging Science, Global Aging, Mechanisms of Ageing and Development, Frontiers in Genetics, Geroscience, and other journals.
Valery Benberin, D.M.Sc, Professor.

Corresponding Member of National Academy of Sciences of Kazakhstan, Head of the Medical Center of the President’s Affairs Administration of Kazakhstan, Astana, Kazakhstan.

Professor Valery Benberin currently works as a Head of the Medical Center of the President’s Affairs Administration of the Republic of Kazakhstan. He is the President of Eurasian Association of Gerontology, Geriatrics and Anti-Aging Medicine as well as the President of Gerontology and Geriatrics Society of Kazakhstan.

He received his MD from Almaty State Medical Institute (Kazakhstan) in 1978. He started his career as a cardiologist at the Kazakh Cardiology Research Institute. In 1988 he completed PhD at the Institute of Clinical Cardiology of the Academy of Medical Sciences of the USSR in Moscow. He got his Doctor of Medical Sciences degree in 2005. He has been working at the Presidential Medical Service for more than 20 years. He has published over 200 papers.

Research interests: Gerontology, Personalized medicine, Anti-aging medicine, Genomics and metabolomics, Pharmacogenetics, Cardiology, Immunology.
Almaz Sharman, MD, PhD, Professor.

The President of the Academy of Preventive Medicine of Kazakhstan and the co-founder of HealthCity network of clinics, Almaty, Kazakhstan.

Native of Kazakhstan and a citizen of the United States, Dr. Sharman has 30 years experience in the fields of biomedical science, clinical research, and healthcare management. As a researcher Dr. Sharman designed a methodology for integrated population-based HIV testing which was implemented in several developing countries and has become a standard methodology for the international demographic and health surveys. HIV testing data generated by using this methodology was recently used by UNAIDS to lower the estimate of the number of people afflicted by HIV in the world by 7 million cases. A multinational study of the anemia prevalence among women and children implemented under his leadership has led to successful anemia control and prevention and reproductive health programs in several countries. In the United States, Dr. Sharman was involved in university teaching as Associate at the Johns Hopkins University’s Bloomberg School of Public Health.

During the last several years, Dr. Sharman concentrated on healthcare management and academic medicine. He was founding CEO of the National Medical Holding (NMH), a pioneering project initiated in Kazakhstan’s capital city of Astana with six state-of-the-art hospitals. His initiatives to introduce international standards of quality care and advanced technologies at NMH have led to the Joint Commission accreditation and successful implantations of heart ventricular assistance device, heart transplantation and other innovative technologies. Since 2010, Dr. Sharman’s primary focus has been on establishments of Academic Healthcare System at Nazarbayev University with the goal of integration of patient care with biomedical research and education.

Dr. Sharman is current member of the American Public Health Association and President of Kazakhstan Academy of Preventive Medicine, a non-governmental organization serving as a platform for advocacy and collective action in addressing public health challenges and opportunities in Kazakhstan. He also co-founded HealthCity, a network of private centers for personal medicine.

Dr. Sharman designed symptomaster.com, a technology product that helps patients to assess more than 100 symptoms and to make informed decisions about their health. He also developed zdrav.kz, an extensive medical database of more than 1000 diseases and conditions. He also participated in the development of medintel.kz, an interactive decision support tool for doctors allowing to expand a differential diagnosis using artificial intelligence technology.
Massimo Pignatelli, MD, PhD, Professor.

Dean of School of Medicine, Nazarbayev University, Astana, Kazakhstan.

Massimo Pignatelli earned his MD summa cum laude from the University of Bologna, Italy, and his PhD from University College, London. He spent most of his academic career in UK as Senior Lecturer and Reader at Imperial College London and at the University of Bristol, where he was Professor of Pathology and Head of Clinical Sciences.

In 2011 Massimo moved to the University of Glasgow School of Medicine, where he served as Head of the School of Medicine (which includes Medicine, Dentistry, and Nursing). He also held the St. Mungo-Notman Chair of Pathology. He is a noted and well-published physician-scientist whose research focuses on epithelial adhesion molecules and particularly on their exploitation as biomarkers for tissue diagnosis, prognosis, and response to treatment.

Since November 2013 he is the Founding Dean of Nazarbayev University School of Medicine in Astana (Kazakhstan).
Gulnara Svyatova, MD, D.M.Sci, Professor.

Head of the Republican Medical Genetic Consultation, Scientific Center of Obstetrics, Gynecology and Perinatology of the Ministry of Health of Kazakhstan, Almaty, Kazakhstan.

The Professor of medicine; Head of Republican medical genetics Departments, Scientific Center of Obstetrics, Gynecology and Perinatology; the Chief specialist in medical genetics of Ministry of Public Health, President of Republican Association of medical geneticists of Kazakhstan.

The scientific and practical interests: Medical-genetics consulting, prenatal and neonatal screening, prenatal diagnostics, molecular genetics, populations genetic.

The Initiator of prenatal and neonatal screening in Kazakhstan, Author of informatics System “National Genetic Register of Republic of Kazakhstan” for monitoring of congenital malformations, National coordinator of InterPregGen Project the European Union Seventh Framework Programme “Genetic studies of Pre-eclampsia in Central Asian and European populations”, Head of “Miras” Biobank of DNA in Kazakh population.

Author of 450 scientific publications, 6 Monographs.

Married, have 2 children, 2 grandchildren.
Ainur Akilzhanova, MD, PhD, D.M.Sci, Associate Professor.

*Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan.*

MD, PhD, DMSci, Associate Professor (Medicine), Chief research scientist, Head of Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Nazarbayev University.

Ainur Akilzhanova is a medical doctor (internal medicine), graduated Semipalatinsk State Medical Academy (SSMA), Kazakhstan in 2000 (Honorary Diploma). She made her Ph.D. (Candidate of Medical sciences, 2004) in cardiology and worked as Assistant in the Department of Therapy of SSMA during 2001-2006. In 2006-2009 years she trained and worked in Department of Molecular Pathology, Division of Tumor and Diagnostic pathology, Atomic Bomb Disease Institute, Graduate School of Biomedical Sciences, Nagasaki University, Japan as a Research Scientist, then as postdoctoral fellow. After coming back to Kazakhstan she defended degree of Doctor of Medical Sciences (2010, Genetics and Public Health). Since 2009 Dr. Akilzhanova worked as Leading research scientist in National Center for Biotechnology of Republic of Kazakhstan and from August 2011 she has been invited to Center for Life Sciences, Nazarbayev University, Astana, as Chief research scientist, Director Department for Organization and Development of Genomic and Personalized Medicine.

Dr. Akilzhanova made her PhD (Medical Sciences) at Nagasaki University, Japan in 2009-2014 and awarded by PhD degree and medal for successful completion of JSPS RONPAKU PhD Program in 2014.

**Research interests:** genomic research in biomedicine, molecular, genomic and personalized medicine, public health and health care, methods of next generation sequencing and basics of bioinformatics and analysis of sequence data. Studies in recent years devoted to developing ways to translate the results of genetic and genomic research for human health, application of sequencing technologies in clinical research.


Ainur Akilzhanova awarded by President of Kazakhstan Nursultan Nazarbayev Scholarship, 1998-1999; by The First Semipalatinsk Nagasaki Medical Award, August 29, 1999 (Nagasaki University School of Medicine); by the Grant of Ministry of Education, Culture, Sports, Science and Techniques of JAPAN - JAPAN SOCIETY FOR THE PROMOTION OF SCIENCE - JSPS RONPAKU (Dissertation PhD) Program 2010-2014, PhD defense was in 2014; Grant of Austrian Academy of Science, Joint Excellence in Science and Humanities JESH program, June-August 2016; by two certificates of Ministry of Education and Science of Kazakhstan “Кұрыміт грамотасы” in 2016 and 2017.
Yergali Miyerbekov, D.M.Sci, Professor.

National Scientific Center of Surgery after A.N. Syzganov, Almaty, Kazakhstan.

Yergali Miyerbekov, MD, D.M.Sci., Professor, anesthesiologist. He obtained doctoral degree after research and training in Union Scientific Center of Surgery (Moscow). Currently he works in National Scientific Center of Surgery after A.N. Syzganov. Also he is a Head of Department of Anesthesiology&Reanimatology in Kazakhstan-Russian Medical University and President of NGO “Federation of Anesthesiologists&Intensive Care Specialists”. He is the author of over 250 scientific works and 2 monographs.

Scientific interests include the study of genetic factors of venous thrombosis predisposing and prognostic value of gene polymorphism in patients with septic complications.
Asylkhan Rakhymzhan, PhD.

*German Rheumatism Research Center, Berlin, Germany*

Dr. Rakhymzhan earned his BSc/MSc in Chemical and Biological Physics from Novosibirsk State University (NSU) (Novosibirsk, Russia) and his PhD from NSU in close collaboration with TU Braunschweig (Germany). In 2011-2013 he worked as a Junior Research Associate in the Institute of Chemical Kinetics and Combustion, Russian Academy of Sciences, Novosibirsk, Russia. Since 2013 he is a Postdoctoral Fellow of German Rheumatism Research Center (DRFZ), Berlin, Germany.

**Grants and Awards:** President’s Award for Excellence at CYTO 2017, Boston, USA; Grant for Young Scientists 2012 (Russian Foundation for Basic Research); DAAD (German Academic Exchange Service) PhD student Scholarship, 2009-2010; Schlumberger Company Scholarship, 2011; Scholarship for Young Scientists ICK&C, Novosibirsk, Russia, 2011.
Bibigul Ilyassova, MD, PhD, Associate Professor.
National Scientific Center of Surgery after A.N. Syzganov, Almaty, Kazakhstan.

Bibigul Ilyassova- gastroenterologist-hepatologist, clinical pharmacologist, Associate Professor, PhD, currently is Head researcher of Kazakh National Scientific Center of Surgery named after A.N. Syzganov, gastroenterologist-hepatologist of Center of Hepatopancreatobiliary surgery and Liver Transplantation and Professor of Clinical Pharmacology Faculty of Kazakh Medical University of Continuous Education.

Bibigul was born in Pavlodar, Kazakhstan on 15th of August 1968. She graduated from Semey State Medical University in 1992 as a doctor and got Clinical Ordinatura “Clinical Allergology And Immunology” in 1994 from Almaty State Medical University, also she had an 3 months of Clinical Immunology with course of Hepatology and Good Clinical Practice in NHO Nagasaki Medical Center in 2008 and 1 month Internship in Berlin, Germany. Has 23 years of working experience in a medical and scientific sphere.


Bibigul in a recent 3 years was an author of 22 articles,1 monographies and 4 methodical recommendations, such as: “The effect of the short course of the recombinant interleukin-2 (rIL2) in patients with liver cirrhosis causes by HBV and HCV infection” and “The Effect of Autologous Hematopoietic Stem Cells (AHSCT) in Patients with Primary Biliary Cirrhosis (PBC) resistant to the Drug Treatment” in 2012. Also she is a member of Kazakh Association of Study Of Liver from 2010, Manager of research of Clinical Effectiveness of BIO-C- Immun+ in 2011, Expert of “F36” drug testing, Researcher of Multicenter randomize postregistered research of “Essencialle” drug in 2015 and Manager of Research of “Hepanorm” drug. Married, has who sons.
Saule Rakhimova, MD, C.B.Sci.
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Leading Researcher, Department of Genomic and personalized Medicine, Center for Life Science, PI “National Laboratory Astana”.

She graduated Akmola State Medical Academy, Astana in 2000 Internal Medicine, and in 2001 Internship – therapeutist (physician). Since 2004 S. Rakhimova finished a few training programs: Genomic medicine and Bioinformatics: Application to clinical practice (Schneider Children`s Medical Center, Tel-Aviv, Israel), Next Generation sequencing on Illumina platform (Seoul National University, GMI, Seoul, Republic of Korea), Genetics of endocrine disorders in children (SUNY Downstate University, NY, USA).

Major projects: Genome-guided personalized anti-thrombotic therapy for patients at high risk of thrombosis and bleeding; Genomic and transcriptomic profiles of esophageal cancer.; Mapping of eco-social and genetic factors determining susceptibility of tuberculosis of the population of the Republic of Kazakhstan; Genetic architecture of Kazakhs etc. Her scientific interests: Pathogenetic aspects in oncology, monogenic diseases, new methods for detection of single nucleotide polymorphism, application of sequencing technologies in clinical research and genomic and personalized medicine. Publications: more than 30 publications, methodical guidelines, 2 certificate of state registration to objects of copyright (copyright certificates). H-Index: 3/2, i10-index: 2.
Yingqiu Xie, PhD, Assistant Professor.
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Yingqiu Xie obtained his doctoral degree from Chinese Academy of Sciences, Beijing, China through Molecular Genetics research. After his postdoctoral training University of Maryland School of Medicine and Wadsworth Center, New York Dept. of Health he held research appointments in genetics at University of Miami School of Medicine. Currently he is Assistant Professor, Department of Biology School of Science and Technology, Nazarbayev University. His present research activities at NU include genetics of cancer.

Ulykbek Kairov, PhD.
Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan

Ulykbek Kairov is head of Bioinformatics and Systems Biology lab at the Center for Life Sciences, National Laboratory Astana, Nazarbayev University. His research work over the last 10 years has focused on bioinformatics and systems biology approaches and methodologies for analysis and interpretation of multidimensional biomedical data from the high-throughput genomic platforms such as microarrays and next-generation sequencing as well as developing of new bioinformatics techniques and methods. He is a leading researcher and PI’s of several research projects in cancer transcriptomics, Kazakh genomics, bacterial genomics and development of new bioinformatics methodologies.

Amin Zollanvari, PhD, Assistant Professor.
School of Engineering, Nazarbayev University, Astana, Kazakhstan.

Dr. Zollanvari received Ph.D. in Electrical Engineering from Texas A&M University, College Station TX, in 2010. He held a postdoctoral position in Harvard Medical School and Brigham and Women's Hospital, Boston MA (2010-2012) and then joined the Department of Statistics at Texas A&M University as an Assistant Research Scientist (2012-2014). He is currently an Assistant Professor in the Department of Electrical and Computer Engineering at Nazarbayev University. He has 10 years of experience in genomic signal processing and has authored numerous articles in prestigious journals such as Bioinformatics, BMC Bioinformatics, BMC Systems Biology, IEEE TSP, IEEE TIT, IEEE SPL, etc. Dr. Zollanvari has served as reviewer for 10+ international journals focused on signal processing and/or bioinformatics and is currently serving as the lead guest editor for a special issue of Cancer Informatics on “Signal Processing Applications in Genomics”. His research interest includes bioinformatics, high-dimensional signal processing and machine learning.
Ulan Kozhamkulov, MD, C.M.Sci.
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Ulan Kozhamkulov is Leading Research Scientist of the Laboratory of Genomic and Personalized Medicine, Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan. He graduated from Kazakh State Medical University in Almaty, Kazakhstan, 1992-1998.

He obtained his scientific degree in phthisiology (TB) at the National TB Center Republic of Kazakhstan in 2006. In 1999-2006 he participated in scientific programs: “Drug resistance of *M.tuberculosis*” and collaboration work with Institute of chemical science “Development of new active, non-toxic anti-TB drugs based on new β-aminopropioamidoxime derivatives”.

In 2007-20011 years he worked at National Center for biotechnology, Astana, Kazakhstan as a senior researcher. He participated in projects for estimation of drug resistance and biodiversity of *M. tuberculosis* in Kazakhstan based on DNA sequencing of genes associated with drug resistance and MIRU-VNTR genotyping method. He also gained experience in Clinical Microbiology department of Hebrew University (Jerusalem, Israel) within collaboration project 2007-2008.

In 2012-2014 he trained and worked in Mycobacteriology Lab of Wadsworth Center, New York State Department of Health, USA as a Postdoctoral Fellow within Fogarty fellowship program. In 2014 Ulan Kozhamkulov joined the Center for Life Sciences at Nazarbayev University as a leading researcher of the Department of Genomic and Personalized medicine.

**Research interests:** Phthisiology (Tuberculosis), clinical and laboratory diagnostics aspects of tuberculosis (TB), molecular mechanisms of drug resistance of *Mycobacterium tuberculosis*, development improved assay for Pyrazinamide Drug Susceptibility testing, molecular epidemiology, molecular biology in medicine, methods of next generation sequencing.

**Publications:** more than 100 national and international articles and abstracts in conferences, 7 inventions, 3 guidelines for TB laboratory diagnostics.
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*PerkinElmer, Moscow, Russia.*

PhD, Biophysics, Lomonosov Moscow State University.

Position: Product Manager at “Pribori Oy” Company with 10 years of experience in the company.

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Luca Vangelista, PhD, Associate Professor.  
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Dr. Vangelista obtained his PhD in Molecular Biology (awarded by the University of Heidelberg) at the European Molecular Biology Laboratory (EMBL), Heidelberg, Germany in 1998. In 1998-2002 he was a Postdoctoral Fellow at the International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy. He later joined the San Raffaele Scientific Institute and University of Milan, Milan, Italy as a Senior Scientist (2003-2007), then a Group Leader (Protein Engineering and Therapeutics) (2008-2014). Since 2015 he is Associate Professor of Nazarbayev University School of Medicine in Astana (Kazakhstan).

Dr. Vangelista has extensive experience in molecular, structural and cellular biology, biochemistry, microbiology, immunology, virology, biocomputing, protein design and engineering and expression strategies. He has coordinated worldwide research networks for a number of years with success attested by 43 peer-reviewed publications, 2 patents and 3 book chapters, several research grants awarded and numerous international congress communications.
Samat Kozhakhmetov, C.B.Sci.

*Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan*

Samat Kozhakhmetov graduated from Kazakh State Agro-technical University with B.Sc. degree in Biotechnology in 2005. Later, in 2008 Samat has defended his thesis on Biological properties and bacteriocins production of Bifidobacteria at the National Center for Biotechnology, Astana, Kazakhstan. In 2011 Samat Kozhakhmetov was appointed as the Head of the Laboratory of Genetics and Biochemistry of Microorganisms at the National Center for Biotechnology. In 2012 Samat Kozhakhmetov joined the National Laboratory Astana (Center for Life Sciences) at Nazarbayev University as a senior researcher of the Human Microbiome Lab. As seen in many of his publications, his major research interests cover many aspects including metagenomic research and microbiology.

Samat Kozhakhmetov is a full member of the Kazakhstan Association of Human Microbiome Research.

Adil Supiev, MD, MPH, PhD.

*Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan.*

Adil Supiev specializes in the area of epidemiology and public health. He acquired his medical degree at First Pavlov State Medical University, Saint Petersburg, Russia; Ph.D. from Institute of Bioregulation & Gerontology, NW Branch of Russian Academy of Medical Sciences, Saint Petersburg, Russia and received MPH degree from Emory University, Atlanta, GA. His main research interests focus on social determinants of health, non-communicable diseases, markers and biomarkers of ageing and adolescents’ health.
Azliyati Azizan, Ph.D, Associate Professor.  
School of Medicine, Nazarbayev University, Astana, Kazakhstan.

Dr. Azizan obtained her MSc in Microbiology in 1987 and PhD in Biochemistry and Molecular Biology at the University of Tennessee, USA in 1995. She later joined the Shriners Hospital on the campus of the University of Florida (USF) in Tampa, Florida, USA as a Research Fellow Bioscientist. Dr. Azizan’s first academic appointment started when she joined the USF College of Public Health (COPH) in 2001 as an Assistant Professor with the Department of Global Health conducting research on Infectious Disease topics and teaching several courses for the Masters of Public Health (MPH) program. At USF, Dr. Azizan mentored many doctoral (Ph.D.) and masters level students and served as Academic Advisor for many MPH (Masters of Public Health) students. Dr. Azizan joined the Nazarbayev University School of Medicine (NUSOM) as an Associate Professor in January 2015, and lectures in several courses in the Medical Degree (MD) program and is the co-Course Lead for the Medical Microbiology course and the Block Lead for Basic Science Block. For the MPH program at NUSOM, Dr. Azizan teaches several courses and is the co-Director of this new MPH program. Apart from serving as a member on several NUSOM and NU committees, Dr. Azizan also is an Academic and Research Advisor for several students from the MD and MPH programs. Dr. Azizan is a member of the American Society for Microbiology, the American Public Health Association and the International Papillomavirus Society (IPVS).

Research Interests and projects. Dr. Azizan is currently involved in research related to natural product drug discovery and the current project involves characterization of novel antibiotic as treatment options for multidrug resistant bacterial pathogens including MRSA. This project involves active collaboration with Dr. Lyudmila Trenozhnikova and Dr. Vladimir Berezin from the Institute of Microbiology and Virology (IMV) in Almaty, Kazakhstan. Currently funded from two sources for a total of over $150,000 (from NU and from the International Science and Technology Center (ISTC)), this project which started from over ten years ago continues to be developed, and also includes characterization of extremophile extracts with anticancer activity in collaboration with Dr. John Beutler at the National Cancer Institute of NIH in the USA.
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ASSOCIATION BETWEEN hRYR2 MUTATIONS WITH VENTRICULAR TACHYCARDIA IN KAZAKH POPULATION

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Key words: Arrhythmia, ryanodine receptor, sequencing, ventricular tachycardia, mutation

Introduction: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disease characterized by polymorphic or bidirectional ventricular arrhythmias (VA) triggered by physical or emotional stress in young people with a structurally normal heart.

Materials and methods: Patients with arrhythmia – ventricular tachycardia were involved into research. Diagnosis was verified in National Research Cardiac Surgery Center, Astana. Target areas of hRYR2 gene including the most important 45 exons were amplified with PCR and directly sequenced.

Results: Genetic variants of hRYR2 gene in two catecholaminergic polymorphic ventricular tachycardia (CPVT) patients and 14 ventricular tachycardia (VT) patients were screened. Total number of VT patients whose mutation in hRYR2 gene screened was 35 people. Also genetic analysis was carried out for relatives of patient who had been observed to carry mutation in hRYR2 gene. New mutations in CPVT patients (c.A13892T; p.D4631V) and new mutation in one VT patient (c. G5428C; p.V1810L) was detected. Both variants are located in phylogenetic conservative areas of hRYR2 gene and seems to be pathological according to MutationTaster and PolyPhenII prediction programs. Also three well-known synonymous polymorphisms rs3765097, rs2253273 and TMPESP 1237 664 067 in studied group were detected. Moreover mutation (c.C7511T; p.T2504M) was found which previously was detected in arrhythmogenic right ventricular dysplasia patient. This variant is located in phylogenetic conservative areas of hRYR2 gene and assessed as pathological (points by MutationTaster D (0.99) and by PolyPhenII D (0.99)).

Conclusion. This research is useful to evaluate necessity of genetic screening and reliable genetic consultation for ventricular rhythm disorder patients in order to predict and prevent sudden cardiac death.

CRIMEAN HEMORRHAGIC FEVER IN SOUTH KAZAKHSTAN

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Key words: Congo-Crimean hemorrhagic fever, natural hearth, tick-borne infection, thrombocytopenia

Introduction: Congo-Crimean haemorrhagic fever (CCHF) continues to be an urgent health problem in the southern regions of Kazakhstan, the most acute situation is in the South Kazakhstan region (SKO). Thus, the incidence rates in the SKO in 2009-2016 varied from 0.9 to 0.21 per
100 000 population and in 2016, the growth rate was observed to 0.54, that is 2.3 times more compared with 2015. The mortality rate of patients in different years was 16-36%, in 2015 - 33.3%. Such high mortality rates are associated with insufficient registration of confirmed cases of CCHF.

**Methods:** analysis of medical documentation of patients with CCHF, their laboratory survey by ELISA, PCR.

**Results:** According to the standard definition of CCHF in Kazakhstan, the diagnosis is established in patients who have obtained positive blood test results in PCR, ELISA with detection of Ag, IgM and IgG. The aforementioned fact of understating the diagnosis is confirmed by the results of the CCHF monitoring carried out in SKO. For example, in 2015, the number of residents bitten by mites was 4070 people, 135 of whom (3.3%) were hospitalized in the period of observation with various symptoms to infectious hospitals, where they were laboratory tested according to the algorithm. 127 of them (94%) had a fever, respectively, they were all regarded as "probable case of CCHF", and ribavirin was treated with a therapeutic purpose. Some patients developed hemorrhagic syndrome which corresponded to moderate and severe forms of the disease and in 33 cases immunized plasma, blood components, haemostatic drugs were used. However, laboratory confirmation was obtained only in 6 patients. Accordingly, the number of registration cases decreased from 127 to 6. The phrase "Viral haemorrhagic fever, unspecified" (A-99), existing in ICD-10, unfortunately does not find its application in Kazakhstan.

**Conclusion:** At present, the complex epizootic and epidemiological situation of the CCHF in South Kazakhstan Oblast is preserved. The high incidence of mortality from CCHF is affected by low incidence rates associated with infrequent laboratory confirmation of infection. If there is a typical clinical picture, thrombocytopenia, leukopenia and negative results of PCR, IFA, the formulation "Viral haemorrhagic fever, unspecified" should be used in patients in natural foci of CCHF.

**SENTIEL EPIDEMIOLOGICAL SYRVELLANCE FOR INFLUENZA AND ARVI IN THE CITY SHYMKENT OF THE SOUTH KAZAKHSTAN REGION IN THE EPIDEMIC SEASON 2015-2016**

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**Key words:** Sentinel epidemiological surveillance, virus, influenza, ARVI

**Introduction:** In 2014 in the Republic of Kazakhstan, in accordance with the recommendations of WHO and UNAIDS, sentinel epidemiological surveillance of influenza (SES) was introduced. We estimated the SES system for influenza in the conditions of the Shymkent city infectious hospital during the epidemic season 2015-2016.

**Methods:** Retrospective analysis of the effectiveness using of the standard definition of the case of severe acute respiratory infection (SARI) on the medical records of inpatients; Determination of the etiological structure of influenza by the laboratory PCR method.

**Results:** In the 2015-2016 epidemic season started from November to June, 5431 people were hospitalized with a diagnosis of acute respiratory infections in the city infectious diseases hospital. Among those hospitalized with ARVI SARI diagnosis was diagnosed in 588 cases, the largest number of them in January, February, December and March. According to the rules of SES, some of them were centrally examined in the virological laboratory using the PCR method, a total of 235 analyzes, of which 103 viruses were detected in 103 samples, that is, 44% of the patients examined. In 92.2% of cases (95 patients) type A, subtype H1N1, and in 7.8% (in 8 patients) - type A, subtype
H3N2 were detected. The greatest number of laboratory detection of influenza cases among the surveyed was in January and February 2016, in a smaller number - in December 2015. Among the surveyed SARI in March-June 2016, the influenza virus was not detected laboratory-wide. When compared with the 2014-2015 epidemic season, The number of hospitalized patients with ARVI diagnosis was 5963, of which SORI was 517, 174 were screened by laboratory, 174 were detected in 56 cases; type A - 33 cases (H3N2), which was 59%; type B - 22 cases (39%). In 1 case, it was not possible to verify the type of virus detected.

**Conclusion:** The introduction of sentinel surveillance in Shymkent city of the South Kazakhstan region was an effective measure for monitoring the epidemiological situation of influenza in vulnerable groups of population. A high frequency of viruses of type A, H1N1 - in 92.2% of cases and type A, H3N2 - in 7.8% of cases was established in December - February 2015-2016 years.

**COLLAGEN TRIPLE HELIX REPEAT CONTAINING-1 (CTHRC1) REGULATES THE CELL MIGRATION VIA FOCAL ADHESIONS IN RHEUMATOID ARTHRITIS**

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**Key words:** rheumatoid arthritis, synoviocytes, migration, focal adhesions, CTHRC1

**Introduction:** Among other clinical symptoms rheumatoid arthritis is characterized by increased pathological cell migration and invasion, leading to the formation of hypertrophied synovium (also termed pannus). The exact mechanism of such increased cell motility remains largely unknown. We identified the Collagen Triple Helix Repeat Containing-1 (CTHRC1) as a promigratory biomarker of rheumatoid arthritis involved in the pathological migration of cells into the inflamed joints. CTHRC1 is an evolutionarily conserved secreted protein containing collagen like-motif with 12 Gly-X-Y repeats which was first discovered in injured rat arteries implicating a role in vascular remodeling. Here we studied the regulation of arthritic synoviocytes motility via upon treatment with CTHRC1, and its effects on cellular focal adhesions that are a part of the cellular migration machinery.

**Methods:** Activated synoviocytes were isolated form patients with rheumatoid arthritis (RA). Focal adhesion complexes were immunostained for vinculin and actin in RA-synoviocytes and murine NIH 3T3 cells. Further cells were treated with 100 ng/ml exogenous recombinant CTHRC1 and WNT5A. Focal adhesions were counted in immunostained cells as well as in living cells using time-lapse microscopy.

**Results:** We found that CTHRC1 regulates cell migration and adhesion in cells via focal adhesions. The subset of focal adhesions in the cell front provides the forward traction forces for the migrating cell and focal adhesion assembly and turnover is essential for productive forward movement. CTHRC1 induced the distribution of focal adhesions from the leading edges of the cells to the center. The prevalence of mature focal adhesions over young nascent focal contacts was apparent. In murine fibroblasts CTHRC1 facilitated the rapid turnover of focal adhesions leading to an increase in migration rate in samples treated with a combination of CTHRC1 and WNT5A.

**Conclusions:** The novel circulatory biomarker CTHRC1 acts as a WNT5A signaling moderator for activated synoviocytes and controlled synoviocyte invasiveness via assembly and disassembly of focal adhesion contacts. Thus, CTHRC1 is a promising diagnostic marker for early pannus formation.
CYTOPROTECTIVE EFFECT OF BEE KEEPING PRODUCTS

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\textbf{Key words:} Cytoprotective effect, bee keeping products, MTT assay.

\textbf{Introduction:} Inhaled air may contain particles or organisms which would be pathogenic. The respiratory pathway is a prime site for exposure to pathogens and toxic substances. When these offensive agents infiltrate the superficial barriers, the body’s immune system responds in an orchestrated manner. Therefore, the main purpose was to investigate cytoprotective cytotoxic effect of bee keeping products.

\textbf{Methods:} Cytoprotective activity of bee keeping products (honey, propolis, homogenate of drone maggots, pollen basket, pollen ball, and royal jelly) were studied using rabbit’s alveolar macrophages in MTT assay (Sigma Aldrich). Bee keeping products were diluted with saline in 1:10 and 1:100 ratios; thereafter, incubated with alveolar macrophages for 2 hours. The viability of cells in the control was taken as 100%.

\textbf{Results:} Homogenate of drone maggots and royal jelly diluted in 1:100 ratio showed cytoprotective effect with 141.5 \% and 158.2 \%, respectively. Alveolar macrophage cell count in diluted honey, homogenate of drone maggots, pollen basket, pollen ball, and royal jelly in 1:10 ratio was higher in comparison to control by 36.4 ± 7.6\%; 100.4 ± 8.4\%, 44.4 ± 9.1\%; 67.2 ± 11.3\%; 86.8 ± 9.9\%, respectively. Propolis did not show significant cytoprotective effect as well as cytotoxic effect.

\textbf{Conclusion:} Diluted honey, homogenate of drone maggots, pollen basket, pollen ball, and royal jelly upon addition to the incubation medium in a 1:10 dilution increased survival of cells, compare to control. Homogenate of drone maggots and royal jelly showed the highest cytoprotective effect.

PREPARATION OF HALOPLEX CARDIOPHOTONIC PANEL FOR TARGETED SEQUENCING OF HEART RHYTHM DISORDERS

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\textbf{Key words:} Arrhythmias, targeted sequencing, HaloPlex cardiogenetic panel

\textbf{Introduction.} Next generation sequencing allows laboratories to detect genetic changes in target genes associated with specific disorders effectively and quickly. Today, Agilent Technologies offers two panels with pre-selected content – HaloPlex Cardiomyopathy and HaloPlex Arrhythmia, that consist of 34 and 21 genes, respectively. However, these cardiogenetic panels do not consider all genes associated with rhythm disorders.
Aim of the project: To create the new HaloPlex cardiogenetic panel of sequencing that consists of 96 genes associated with arrhythmias using HaloPlex (Agilent Technologies) technology for differential diagnostics of heart rhythm disorders.

Materials and methods. SureDesign Online Design software (Agilent Technologies) was used to create HaloPlex cardiogenetic panel for targeted sequencing of 96 candidate genes. DNA-libraries for 90 patients with cardiac arrhythmias were prepared using HaloPlex Custom Panel Tier 1 kit (Agilent Technologies) according to the manufacturer’s protocol ‘HaloPlexTarget Enrichment System for Illumina Sequencing’, v.D3. December 2012. The protocol is optimized for digestion of 225 ng of genomic DNA. Enrichment Control DNA was used as a control. Quality and quantity of 90 samples were estimated using Qubit 2.0 and 2% Agarose gel. Human Genome version 19, GRCh37, February 2009 for Illumina platform was applied for preparation of final design.

Results. New HaloPlex cardiogenetic panel for targeted sequencing of 96 genes associated with rhythm disorders was developed using SureDesign Online Design software (Agilent Technologies). Developed panel was downloaded and all targets were estimated using UCSC Genome Browser. Size of the target region was 463.767 kbp, length of reads – 150 bp. 19958 amplicons were created by the software to cover all target regions. 99.46% of all target regions were covered successfully. To prepare DNA libraries of candidate genes firstly DNA samples were fragmented by restriction enzymes, then probe library was hybridized to both ends of target fragments to create circular DNA molecules. 90 samples were indexed with different indexes. Circular DNA molecules were joined together in the ligation reaction. Then, target fragments were PCR-amplified and sent for sequencing.

Conclusion. 90 DNA-libraries were prepared using created HaloPlex cardiogenetic panel. All samples were sequenced on Illumina HiSeq2000 platform. Bioinformatic analysis of obtained sequencing data is being conducted.

EVALUATION OF KNEE FUNCTIONAL STATUS AND PAIN AFTER MINIMALLY INVASIVE SURGICAL TREATMENT OF PATELLOFEMORAL ARTHRITIS USING WOMAC SCORE (QUESTIONNAIRE)

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Key words: Patellofemoral arthritis, Patellofemoral pain syndrome, WOMAC, Noninvasive surgical treatment, Arthroscopy

Patellofemoral osteoarthritis in the healthy middle-aged population is a challenging problem. Patellofemoral arthritis/arthrosis (PA) refers to the presence of degenerative changes under the kneecap (patella) with variable manifestations from the symptoms of pain in the anterior part of the knee to serious difficulties with climbing and movement along the stairs. WOMAC index or Western Ontario and McMaster Universities Osteoarthritic Index (WOMAC) is used to assess the course of disease or response to treatment in patients with knee or hip osteoarthritis. Initially developed in 1982, the WOMAC has undergone multiple revisions. WOMAC measures of three subscales on a scale of 0-4. [None – 0, Mild – 1, Moderate – 2, Severe – 3, Extreme – 4]. It measures total of 24 items and offers 5 responses for each item measured. Recall period for items is 48 hours. Three subscales are 1) Pain severity during various positions or movements, 5 items; 2) Severity of joint stiffness , 2 items; 3) Difficulty performing daily functional activities, 17 items.
WOMAC can be considered to have face and content validity. It also appears to be responsive to change following surgical and nonsurgical interventions for knee OA and chondral defects.

**Objective:** To evaluate outcomes of application of newly developed method of minimally invasive surgical treatment of PA using WOMAC score (questionnaire).

**Materials and methods:** We have developed a new method for minimally invasive surgical treatment of PA using arthroscopic instrumentation. The knee pain and functional status were evaluated by WOMAC scales. WOMAC consists of a questionnaire which is aimed to assess three items – pain, joint stiffness and difficulty in physical activity. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

**Results.** This is a prospective study of 14 consecutive knees in 14 patients who were treated by our developed noninvasive surgical method. The minimum follow up was 3 months (mean 10.2 months; range, 3–18 months). Preoperative radiographs showed IWANO stage 2 and 3 (patellofemoral joint space narrowing and degenerative changes). The mean age of the patients was 60.1 years (range, 46–81 years). The subjective outcome was based on the WOMAC score. According to the WOMAC score, the scores improved considerably by 2.34 points with respect to pain and by 1.63 points with respect to function 3 month after surgical treatment. The majority of patients experienced improvement in their patellofemoral symptoms. However, the clinical outcome was better in comparison to other surgical procedures. After the short follow up, our method of minimally invasive surgical treatment of the patellofemoral arthritis would be recommended to larger number of patients.

**NEW METHOD OF NONINVASIVE SURGICAL TREATMENT OF PATELLOFEMORAL ARTHRITIS**

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**Key words:** Patellofemoral arthritis, Patellofemoral pain syndrome, Noninvasive surgical treatment, Arthroscopy

Patellofemoral arthritis/ arthrosis (PA) refers to the presence of degenerative changes under the kneecap (patella) with variable manifestations from the symptoms of pain in the anterior part of the knee to serious difficulties with climbing and movement along the stairs. Patellectomy was one of the first surgical procedures performed for PA. However, awareness of the importance of the biomechanical role of patella led to the development of alternative surgical procedures. The emergence of diagnostic and surgical technologies using arthroscopic instrumentation has opened up new opportunities for improving the diagnosis and treatment of knee joint lesions.

**Objective:** To develop and test a new method of minimally invasive surgical treatment of PA.

**Materials and methods:** We have developed a new method for minimally invasive surgical treatment of PA using arthroscopic instrumentation. The pain syndrome was assessed using a visual analogue scale of pain (VAS visual analogue scale). Statistical analysis was performed using SPSS software (SPSS, 21.0, Chicago, IL, USA).

**Results.** We have developed a new method of surgical treatment of patellofemoral pain syndrome using arthroscopy with modification. Treatment and monitoring of patients is carried out on the basis of the trauma department Pavlodar city clinic №1. 14 patients (8 females, 6 males, average age 59.1 ± 7.3 years) were surgically treated by our developed method (patent application No. 2017 / 0102.1), as well as 5 patients by method arthrotomy (3 females and 2 males, average age
Clinical signs of the postoperative period were monitored. Follow up period is 3-6 month. Patients were asked to determine the extent of their pain with VAS, in which the "0" level was represented by the absence of pain and the "10" level was worse when the patients experienced severe pain. Night pain, walking pain, and climbing stairs were determined based on VAS as follows: no pain or negative (0 points) mild pain or +1 (1-4 points), moderate pain +2 (4-7 points), And severe pain +3 (7-10 points). Patients on admission had moderate to severe pain (VAS 7.59 ± 1.87). After applying the treatment developed by us, there was a significant reduction in the pain syndrome in the knee joint at discharge (VAS 3.43 ± 1.91, p <0.001) and 3 months after surgery (VAS 2.18 ± 1.34, p <0.01).

Conclusion. Thus, the method of minimally invasive surgical treatment developed by us allows maximum atraumatic removal of intraarticular growths at significant PA stages, as well as reducing the thickness of the patella, which leads to preventing the progression of degenerative-dystrophic changes.

METABOLOMIC ANALYSIS REVEAL POTENTIAL METABOLITES AND BIOLOGICAL PATHWAYS INVOLVED IN AGING AND OBESITY IN KAZAKH POPULATION

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Keywords: metabolomics analysis, metabolites, Kazakh population

Introduction: The determination of metabotype variations can be used to predict disease risk and diagnosis, understand molecular pathophysiology, interpret the understanding of environmental and lifestyle influences, develop and evaluate drug efficacy, toxicity, and adverse reactions. In this study metabolic differences among adults living in Kazakhstan are assessed to identify and characterize the metabolic profiles.

Methods: To perform the tasks, metabolom study of plasma was conducted among 74 Kazakh nationality study participants. The study was carried out on a platform based on tandem technology of ultra-high liquid chromatography and mass spectroscopy (Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy). The necessary logarithmic transformation and ANOVA variance analysis, a two-sample Welch t-test, were performed to determine the bio-compounds that differed significantly between the experimental groups.

Results: The study was conducted in order to identify metabolic differences in human plasma collected from obese and non-obese subjects from Kazakhstan. Subjects were further stratified by age (young <45y, old ≥45y) as well as gender. As a result of 74 participants, 853 different biochemical indicators of the main pathways for the metabolism of amino acids, pethids, nucleotides, carbohydrates, cofactors and vitamins, xenobiotics, lipid and energy metabolism were identified. These results demonstrate alterations in various putative metabolic pathways in older participants in research compared to younger subjects. Metabolic differences included changes in metabolites related to: fatty acid utilization (medium-chain, long-chain, polyunsaturated, and branched-chain free fatty acids ); steroidogenesis (steroid hormone metabolites: pregnenolone...
sulfate, 21-hydroxypregnenolone monosulfate and others); carnitine-conjugated lipids (laurylcarnitine, myristoylcarnitine, palmitoylcarnitine, and palmitoleoylcarnitine); secondary carnitine metabolism (acylcarnitines); inflammation and oxidative stress (monohydroxy-, dihydroxy- fatty acids and eicosanoids).

**Conclusion:** The changes in several known metabolites and various prospective metabolic pathways in the group older than 45 years are found compared to a group of young people. Metabolic differences included changes in metabolites associated with the metabolism of fatty acids, steroidogenesis (steroid hormone biosynthesis), secondary carnitine metabolism, inflammation and oxidative stress. Finally, for future studies, since there is a strong lipid signature in this dataset, it may be of interest to consider our complex lipid panel for quantitative assessment of complex lipid-related changes.

**IMPACT OF CYP2C9 AND VKORC1 GENES POLYMORPHISM TO THE THERAPEUTIC DOSE OF WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION**

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**Key words:** atrial fibrillation, warfarin, gene polymorphism

**Introduction.** For many years warfarin was the drug of choice for the prevention of thromboembolic complications in patients with AF. But warfarin therapy has some difficulties, including a narrow therapeutic window and the need for continuous laboratory monitoring. In the last decade, many scientific studies have been devoted to the impact of the genetic characteristics of the patient, in particular, CYP2C9 and VKORC1 gene polymorphism, on warfarin therapy.

**Methods.** We examined 50 patients with AF of Kazakh nationality who underwent genetic testing to study the relationship between gene polymorphisms and the therapeutic dose of warfarin.

**Results.** Among the studied patients the most common genotype of the CYP2C9*2 gene was the "wild" CC genotype - 74% (n = 37) and 26% (n = 13) of patients had heterozygous CT genotype. Also 92% of the patients were carriers of the "wild" AA genotype of CYP2C9*3 gene. For patients with the CC genotype of the CYP2C9*2 gene the daily dose of warfarin was 3.88 ± 0.3 mg, and for patients with CT genotype - 3.22 ± 0.5 mg (p = 1.02). The dose of warfarin for carriers of the "wild" AA genotype of CYP2C9*3 gene was 3.79 ± 0.27 mg, and for carriers of the heterozygous AC variant - 3.59 ± 0.35 mg (p = 0.74). So, there was no statistically significant difference in the average therapeutic dose of warfarin in patients with different genotypes of CYP2C9*2 and CYP2C9*3. Among the studied patients the most common genotype of the VKORC1C1173T gene was heterozygous CT genotype - 56%, the TT genotype was in 38% of patients and wild genotype (CC) 6% of patients. When analyzing the dose of warfarin, depending on the polymorphism of the gene VKORC1C1173T, it was established that in the carriers of the "wild" CC genotype the dose of warfarin was 6.25 ± 1.56 mg, which is almost 2 times higher than in homozygous carriers of the mutant allele TT - 2.99 ± 0.29 mg (p <0.05).

**Conclusions.** The patients of Kazakh nationality with the mutant allele of the VKORC1C1173T gene needs in lower therapeutic doses of warfarin.
RISK FACTORS FOR UNFAVORABLE OUTCOMES OF TB IN HIV-INFECTED PATIENTS

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Key words: tuberculosis, HIV infection, co-infection, unfavorable outcomes

Introduction: Tuberculosis and HIV infection announced by the World Health Organization (WHO) as global interrelated public health problem. In the world in 2015 identified 10.4 million cases of TB, one in eight of them was HIV-infected. In 2015 tuberculosis caused 35% of deaths among HIV-infected people. In Kazakhstan as of 31.12.2016 on the account with an active form of tuberculosis consisted 857 HIV-infected patients. In 2016 17.9% in the structure of all causes of death for people living with HIV in Kazakhstan had TB. Identifying risk factors of unfavorable outcomes of tuberculosis it is necessary to minimize their impact on the outcome of tuberculosis and determination of the correct tactics of management for each TB/HIV co-infection case.

Methods: We conducted a retrospective analysis of "case - control study" where selected 743 new cases of TB registered 2013 - 2015, which were divided into two groups: the test - cases with an unsuccessful outcome of tuberculosis and control of a favorable outcome. TB outcomes were included: "failure of treatment", "treatment gap" and "died" in the course of treatment for any reason. The outcome "cured" or "treatment completed" refers to prosperous outcomes. The study group consisted of 229 patients (30.8%) with TB/HIV, in the control group – 481 patients (64.7%), 33 patients (4.4%) with outcomes that not indicated, they were excluded from the study.

Results: Statistically significant connections adverse outcomes of tuberculosis were found with the following factors: patient age 18–29 years (p=0.041), absence of spouse (p=0.05), alcoholism (p=0.027), generalized forms of tuberculosis (p=0.002), bacterial excretion (p<0.005), multi-drug resistance (p<0.005), the CD4 cell count is less than 50 (p<0.005) and duration of HIV infection from three years or more (p=0.01).

Conclusions: The impact of the identified risk factors on the outcomes of tuberculosis in HIV infection largely can be minimized in the amplification of the control measures for TB and HIV that will reduce the number of deaths of patients co-infected with TB/HIV.

B-AMYLOID RESULTS IN ELEVATED ROS AND CYTOKINES LEVELS IN SENESCENT HUMAN ASTROCYTES

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Introduction: Aβ accumulates in the brain with age and its elevated concentrations cause neuroinflammation leading to dementia through production of neurotoxic molecules such as reactive oxygen species (ROS), nitric oxide, pro-inflammatory chemokines and cytokines. Neurons are the main source of Aβ and individual astrocytes may not produce high levels of Aβ; however, during long development period of neurodegenerative diseases, astrocytes may still contribute to
overall Aβ production due to their abundance in the brain. Astrocytes turn to senescence in response to oxidative stress and exhaustive replication expressing p16, p21, p53, 53BP1, G1 cell cycle arrest and telomere shortening and accumulate in aged brain producing high levels of cytokines and chemokines in the brain of patients suffering from neurodegenerative diseases. However, the effect of Aβ production on pro-inflammatory proteins in the brain is still unclear. The aim of this study therefore was to investigate the mechanisms of cytotoxic actions of β-amyloid peptide in senescent astrocytes.

Materials and methods: Human astrocytes were aged by multiple passaging of cells in vitro then senescent and young astrocytes were treated with β-amyloid oligomers. Astrocyte senescence was confirmed by SA-β-galactosidase staining method. The effect of β-amyloid on normal and senescent astrocytes was assessed by monitoring ROS levels, IL-6 and ERK1/2 activity and analyzed in MesoScale Discovery (MSD). N-acetyl-L-cysteine (NAC) was used as oxidative stress inhibitor.

Results: Human astrocytes reached a replicative senescence after 15-20 population doublings. β-amyloid was shown to induce increased ROS production in both, young and senescent astrocytes compared to untreated cells, however with significantly higher ROS levels in young astrocytes compared to senescent cells. NAC was shown to inhibit oxidative stress in all treatment groups. Furthermore, senescent astrocytes showed five-fold higher IL-6 levels in comparison with young astrocytes after β-amyloid treatment. Incubation of cells with selective inhibitor of p38 MAPK (10 μM/24 hours) suppressed Aβ1–42 induced activation of p38 MAPK but didn’t affect JNK activity.

Conclusion: Our findings from this study suggest that senescent astrocytes are more susceptible to cytotoxic actions induced by β-amyloid rather than young astrocytes.

POLYMORPHISMS GENES IL10 AND IL17A IN PREDISPOSITION TO CHRONIC VIRAL HEPATITIS AND LIVER CIRRHOSIS IN KAZAKH POPULATION

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Key words: IL17A; IL10; Single Nucleotide Polymorphism; Chronic Viral Hepatitis; Liver Cirrhosis.

Introduction: Nowadays chronic viral hepatitis B, C and their complications such as cirrhosis and hepatocellular carcinoma are important problem of health care. We study association of variations in the genes encoding cytokines IL10 and IL17A and chronic viral hepatitis B and/or C leading to cirrhosis in Kazakh population.

Methods: The retrospective case-control study of 862 patients of Kazakh nationality was conducted. 100 patients had both liver cirrhosis and chronic hepatitis, 341 patients had only chronic viral hepatitis. The control group included 421 HBV- and HCV-negative donors without liver disease. SNPs rs8193036, rs2275913 and rs1800872 was measured by TaqMan, using genotyping DNA by Real-time PCR of peripheral blood cells.

Results: Data analysis for IL17A polymorphism showed odds ratio close to 1.0 with a confidence interval overlaps 1.0 and statistical significance p>0.4 for all comparison groups. For IL10 rs1800872 polymorphism in the cirrhosis group OR was 1.56 (95% CI: 1.11-2.19), p=0.01 in comparison with control group A allele; for group of chronic viral hepatitis in comparison with control group A allele OR was 1.44 (95% CI: 1.14-1.82), p=0.002.

Conclusion: Association of SNP rs8193036 and rs2275913 in IL17A gene with cirrhosis of viral etiology and/or chronic viral hepatitis B and/or C was not found. Gene polymorphism cytokine
IL10 rs1800872 is the risk factor for chronic viral hepatitis B and/or C and further progression to the liver cirrhosis in the Kazakh population.

TENDENCY OF LAB METHODS USED IN COLORECTAL CANCER RESEARCH DURING LAST 20 YEAR: TEXT-MINING APPROACH

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Key words: Colorectal cancer, Pubmed, text mining, R statistics

Introduction: Colorectal cancer (CRC) is one of the most common cause of cancer death. Investigation of CRC has evolved significantly in the past 20 years. Many lab methods are used to understand mechanism of cancer developing, progression.

A large number of publications about CRC have accumulated now and text mining (TM) has emerged as a potential solution to leverage and exploit large amount of information reported in scientific publication. Here, TM approach was used to extract key words associated with lab technique used in CRC investigation.

Methods: Rentrez r package was used to get PMID number associated with colorectal cancer for 1997-2017. In-house script in the R environment is used to extract title, abstract, date and to create data table. To form pull of unique nouns and adjectives cleanNLP r package with implemented coreNLP library (Stanford) were used from which terms associated with lab methods were chosen manually. In the next stage, in-house script were used to extract these terms from each title and abstract.

Results: Pubmed search via rentrez allowed finding 147253 publications associated with colorectal cancer for 1997-2017. There were 513 words/terms associated with PCR, 482 – immunologic with using antibody and interleukins, 26 – chromatography, 21 - with next-generation sequencing, 19 – immunohistochemistry, 11 – electrophoresis, 8 – blotting, 5 – hybridization and 3 – for FISH methods.


Conclusion: These data showed that modern lab techniques are actively and widely used, with the exception of hybridization. This method has been replaced with sequencing.

RECOMBINANT VACCINIA VIRUS INTERFERON INHIBITOR B18R: COMPONENT OF EPIGENETIC REPROGRAMMING COCTAILS

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Key words: epigenetic reprogramming, interferon, inhibitor, B18R, refolding

Introduction: The B18R protein of Vaccinia virus binds to type I interferons and inhibits activation of interferon-mediated signal transduction. For a number of reasons related to the use of
virus-based vectors for epigenetic reprogramming, the B18R has become a ubiquitous component of cocktails of factors which are added to primary cell cultures to achieve the epigenetic reprogramming. Little information has been published on the obtaining of the recombinant B18R. Market prices for the B18R are very high, e.g. USD579 for 50 µg (ThermoFisher Cat# 34-8185-81).

We developed a procedure for bacterial expression, refolding and purification to produce the biologically active B18R. The method allows producing of milligram quantities of the recombinant B18R which is biologically active as it allows replication of the RNA-vectors in the primary human fibroblasts (HFF).

**Methods:** Gene for the B18R with 6His-tag was produced de novo. Synthetic gene was cloned into expression plasmid pET28c. The B18R was extracted from inclusion bodies using sodium lauroyl sarcosinate (SLS) as a solubilizing agent. Protein was subject to oxidative refolding in the presence of CuSO₄. SLS was removed using anion-exchange chromatography on Q-sepharose. Polishing purification was done using immobilized metal affinity chromatography. Thus produced B18R was added to HFF cultures which were transfected with autonomously replicating RNA (RNA-replicon) which produces GFP during intracellular replication.

**Results:** Autonomously replicating RNAs are incapable of replication in primary cells (such as HFF) because of the development of strong interferon-mediated response. Transfection of HFFs with RNA-replicon does not lead to GFP expression if the culture is maintained in plain medium w/o interferon inhibitors. Upon addition of 500 ng/ml of the B18R into culture media, >90% of cells preserve GFP-fluorescence during serial passages. Again, if the B18R is omitted, these cells quickly loss fluorescence indicating the elimination of the RNA-replicon.

**Conclusion:** The bacterially expressed protein B18R requires refolding to become biologically active. The B18R helps stably maintain autonomously replicating RNAs in primary cell cultures.

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**Cianobacteria Bioactive Compounds**

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**Key Words:** microalgae, cyanobacteria, biologically active compounds, qualitative and quantitative analysis, natural protectors

**Introduction:** In the conditions of the deteriorating ecological situation, the search for new preparations of natural biologically active compounds (BAC) is important. It is known that many species of microalgae accumulate in the cells and secrete metabolites with high biological activity in the process of vital activity.

**Methods:** We extracted the natural compounds produced by the prospective blue-green microalgae and carried out a chromatographic qualitative and quantitative analysis of extracts from their biomass and culture fluid of interesting cyanobacteria.

**Results:** Analysis of the data showed that cyanobacteria in biomass accumulate significant amounts of significant industrially structural types of BAC: alkaloids - from 0.26% in Pseudoanabaena sp. up to 0.32% for Anabaena constricta, triterpenoids - from 1.93% for Anabaena laxa to 4.51% for Amorphonostoc paludosum and phenols - from 3.44% for Pseudoanabaena sp. to 4.61% for Anabaena laxa. Cyanobacterial culture fluid was characterized by a lower content of...
metabolites: alkaloids - from 0.18% in Anabaenopsis sp. up to 0.24% in Pseudoanabaena sp.,
Triterpenoids - from 0.11% in Anabaena sp. up to 0.35% for Anabaena constricta and phenols -
2.71% for Anabaenopsis sp. up to 3.53% from Anabaena sp.

Conclusion: Thus, it was established that the studied cyanobacteria species were
characterized by a relatively high content of alkaloids, triterpenoids and total phenols, and the
culture of Anabaena laxa was characterized by a relatively high content of total alkaloids and
phenols. Present data can be useful for the study of biological activity of present bioactive
compounds and can be recommended for the development of natural protectors, that is a very
promising strategy for addressing a number of practical problems of health.

ANALYSIS OF MICROTUBULE TARGETING DRUGS AND MITOTIC SLIPPAGE

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Key words: microtubule-inhibiting drugs; cancer treatment; mitotic slippage

Introduction: Microtubule (MT) inhibiting drugs are widely used in cancer treatment due to
their ability to interfere with cell proliferation, cell cycle and cause cell death. MT drugs have a
striking effect on cell cycle via mitotic arrest, this often leads to a mitotic slippage, when a cell fails
to divide and forms a polyploid multinucleated cell, the phenomenon is not widely described. Some
sources reported that Taxol treated cells acquire micronuclei after the mitotic slippage, however
further information is mostly unknown. Thus, in this work we investigated MT-targeting drugs’
effects on cancer cells describing the process of mitotic slippage and identified mitostatic, cytotoxic
doses and concentration ranges, where mitotic slippage was common.

Methods: In order to define how human cancer cells (A549, HaCaT, U118, PC-3 and
HT1080) respond to different MT-inhibiting agents (Nocodazole, Taxol, and Vinorelbine), they
were visualized for 72 hours by time-lapse microscopy (on EVOS FL Auto 2) with 10 minutes
intervals and analyzed using FIJI ImageJ software.

Results: We identified particular drug concentrations for each cell line that correspond to a
mitostatic concentration, where at least half of cells divided after significant delay (more than
three-fold, in comparison with normal mitosis), and a cytotoxic concentration, where more than half
of mitotic cells died. The ratio between cytotoxic and mitostatic concentrations are 10-30 fold for
Taxol and Nocodazole and 30-300 fold for Vinorelbine. There was no direct correlation between
dose, drug type, or cell line and duration of mitotic arrest. In this range we frequently observed
mitotic slippage, characterized either by the absence of cytokinesis, or as a result of incomplete
cytokinesis when daughter cells fused with each other. After the mitotic slippage, cells commonly
had multiple nuclei (>3) and never form single large nucleus as reported elsewhere. The size and
number of the nuclei in the post-slippage cells did not depend on the drug type or concentration.

Conclusion: Mitotic slippage is a common outcome of mitotic arrest by anti-MT drugs
applied in a concentration above mitostatic threshold. Viability of the cells after mitotic slippage
requires further elucidation.
GENES OF PREDISPOSITION TO MISSEB ABORTION IN KAZAKH POPULATION

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Key words: missed abortion, genetic polymorphism

Introduction: Missed abortion (MA) in early stages of pregnancy occurs in 10-15% miscarriages and are caused by chromosomal abnormalities in the fetus, parental chromosomal anomalies, maternal thrombophilic, anatomic, endocrine, and immunological disorders (Branch et al., 2010). Application of genetic association studies focusing on pre-selected gene of predisposition with potential pathological effect to MA show limitations to the small study size and ethnic heterogeneity.

The aim of the study – to investigate the input of genetic polymorphism of folate metabolism’s genes (MTHFR, MTRR, MTR), fibrinolysis system of hemostasis (PLANH-1) in pathogenesis of MA in Kazakh population

Materials and methods: There were examined 102 women with MA in the first trimester of pregnancy (basic group) and 105 women with normal reproductive anamnesis (control group). All tested women were Kazakhs and comparable in age and somatic anamnesis. The SNP polymorphisms of rs1801131 and rs1801133 of MTHFR, rs1801394 MTRR, rs1805087 MTR genes, rs7242 of PLANH-1 gene were analyzed by PCR-real time method.

Results: Comparative statistical analysis revealed a statistically significant differences by decreasing the frequency of the genotypes 1298CC (MTHFR) and 66GG (MTRR) in basic group from 20,6±4,0 and 18,6±3,9 to 9,5±2,9 and 5,7±2,3 in control group (p<0.05, $\chi^2=4,9; 8,1$). Significant changes in the frequency of rs7242 PLANC-1 were found (p<0.05, $\chi^2=4,1$). The most important contribution in MA was determined for unfavorable genotypes 1298CC (MTHFR) and fibrinolysis system of hemostasis 4G/4G (PLANC-1). It was found that the carriage of haplotypes with 2 and more homozygous weak genotypes of MTHFR, MTRR, MTR and PAI-1 genes increase the risk of MA in 2,0 to 8,3 times.

Conclusion: We observed the significant genetic input of functionally weak genotypes 677TT and 1298CC (MTHFR), 66GG (MTRR), 2756GG (MTR) and 4G/4G (PAI-1) in MA in Kazakh population, suggesting that this genotypes cause hyper coagulation and endothelial dysfunction, which leads to disruption of normal trophoblast’s differentiation and invasion.

MIR-155-5P DOES NOT PLAY A ROLE IN THE PATHOGENESIS OF RADON INDUCED LUNG CANCER

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Keywords: miRNA, lung cancer, biomarker, miR-155-5p, radon

Introduction: Lung cancer is one of the leading lethal diseases worldwide. Radon is the second main factor in lung cancer progress after smoking. At the same time, there is no clear insight of the molecular mechanism of this process. Furthermore, many efforts focused on development of
non-invasive biomarkers, which would promote to early diagnostics. In accordance with the last-mentioned, the purpose of this study was to estimate the value of plasma miR-155-5p level as a response indicator to radon exposure in lung cancer pathogenesis.

**Methods:** The relative expression levels of miR-155-5p have been examined in lung cancer patients, who reside in the areas with increased doses of natural radon emission versus lung cancer patients and healthy individuals in the regions with normal radon levels. Thereby, 3 groups were formed – lung cancer with increased radon, lung cancer and healthy individuals’ blood samples collected from normal radon rates. Radon concentrations were measured in all regions, where samples were collected. Measurement of radon activity was conducted according to the Rapid Measurement Method of radon. Total RNA from blood samples was extracted and used to detect miR-155-5p expression by qRT-PCR. The $2^{-\Delta\Delta Ct}$ method was used to quantify the relative miRNA amount.

**Results:** In the given study, miR-155-5p has been associated with lung cancer but not with increased levels of radon. Plasma miR-155-5p level was higher in more than 2 times in the lung cancer patients’ groups compared with healthy control (P<0.01). No other statistically significant differences were found in the expression level of plasma miR-155-5p between patients diagnosed with lung cancer exposed to radon and healthy control (P= 0.7). There was a twofold increase in the profile of miR-155-5p in patients who were not exposed to radon compared to lung cancer patients living in areas with a high radon concentration in the air (P< 0.05).

**Conclusion:** Thus, this miRNA expression levels correlate with lung cancer, but cannot be employed as a reference for radon induced lung cancer.

**DISTRIBUTION OF HLA CLASS I AND II ALLELES IN KAZAKH PATIENTS WITH CHRONIC MYELOID LEUKEMIA**

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**Key words:** HLA (Human Leukocyte Antigens), chronic myeloid leukemia (CML), DNA, blood

**Introduction:** Associations between HLA (Human Leukocyte Antigens) alleles and the development of chronic myeloid leukemia (CML) have never been studied in Kazakhstan. The aim of the study was to determine the rate of frequency of HLA class I and class II alleles in Kazakh chronic myeloid leukemia (CML) patients.

**Methods:** The study was conducted on the blood samples of 3,657 Kazakh participants at the Scientific-Production Center of Transfusiology, Astana, Kazakhstan. The participants were consisted of two groups. In the main group, there were 47 patients with CML (23 males and 24 females) with average age 47 years (11-69 yrs). In the control group, there were 3,621 healthy blood donors (2,136 males and 1,485 females) with average age 41 years (18-64 yrs). The HLA typing method consisted of three stages: DNA isolation, amplification, detection. From whole blood, genomic DNA was isolated by a proteinase method. HLA-typing (HLA-A, -B, Cw, -DRB1 and -DQB1) for both groups was conducted by low-resolution Polymerase Chain Reaction (PCR).
Results: The current study shows that HLA-B*41 (OR=5.39; 95% CI= 2.08 – 13.99; p<0.01), *47 (OR=8.69; 95% CI= 1.08 – 70.01; p<0.01), *73 (OR=6.51; 95% CI= 0.83 – 51.13; p<0.05), HLA-DRB1*09 (OR=2.38, 95% CI=1.00-5.68, p<0.05) alleles positively associated with CML. On the other hand, HLA-A*01 (OR=0.28; 95% CI= 0.09 – 0.91; p<0.05), HLA-C*02 (OR=0.13; 95% CI= 0.02 – 0.95; p<0.05), *06 (OR=0.42; 95% CI= 0.18 – 0.98; p<0.05), DRB1*12 (OR=0; 95% CI= 0; p<0.05) alleles negatively associated with CML development. 

Conclusions: Four alleles at the HLA-B and HLA-DRB1* loci appear to be linked with CML development and four alleles at the HLA-A, HLA-C and HLA-DRB1 appear to be associated with CML protection within the Kazakh population. Additionally, this study adds useful information to study a variety of diseases associated with HLA antigens including CML and other oncohematological disorders.

BIO-IMPEDANCE ANALYSIS RESULTS IN RESIDENTS OF THE ESIL DISTRICT OF ASTANA

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Key words: Bio-impedance, Tanita, visceral fat rating, bone mass, metabolic age, phase angle, personalized medicine.

Introduction: On 28th July 2017 (World Hepatitis Day), 124 residents of the Esil district of Astana were tested for viral hepatitis B and C and informed about associated liver diseases. Of these, 73 (55 females and 18 males) also underwent bioelectrical impedance analysis.

Methods: Bio-impedance analysis was made according to a standard protocol on an advanced segmental multi frequency BIA analyser Tanita MC 780 MAS portable (Tanita Corporation, Tokyo, Japan). The instrument is equipped with eight tactile electrodes which are incorporated in steel foot pad and in hand grips. The subject was asked to stand in bare feet on the metal foot plate of the analyser, gently holding the hand grip with the arms straight and hung down in neutral standing position, without skin to skin contact.

Results: Mean age of males was 43.7 years (min 21, max 78) and of females 41.89 (min 13, max 71); mean BMI was 26.69 in males and 24.83 in females. 61.1% of males were obese or overweight compared with 43.6% of females. Body fat percentage was high or increased in 50% of males and in 23.6% of females. 5.5% of males had increased muscular mass compared to 12.7% of females while the remaining had good or low muscular mass. Visceral fat rating was excessive in 33.3% of males compared to only 3.6% of females. Bone mass was reduced in 66.6% of males and in in 71% of females across all ages. Extracellular/Total body water ratio was >40 in 55.5% of males and in 83.6% of females. The metabolic age was higher than the chronologic one in 44.4% of males and in 23.6% of females. Physique rating showed medium and large frame obesity in 50% of men and 23.6% of women.

Conclusions: These results show a worrying percentage of obesity in males and reduced bone mass in both genders and highlight the importance of bio-impedance analysis in the era of personalized medicine.
PERSONALIZED DIAGNOSIS OF GAUCHER DISEASE IN KAZAKHSTAN

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Key words: Gaucher disease, rare disease, early diagnosis, genetics

Introduction: Gaucher disease (GD) is a very serious autosomal recessive genetic disease caused by loss-of-function mutations in the gene encoding lysosomal glucocerebrosidase, which leads to accumulation of glucosylceramide in many tissues, including spleen, liver, kidneys, lungs, brain and bone marrow. The prevailing form (type 1) presents with hepatosplenomegaly, anemia, thrombocytopenia, skeletal or lung involvement. Type 2 (acute neuronopathic disease) is an infantile lethal form and type 3 is a more chronic neuronopathic form. Due to the elevated number of mutations of the glucocerebrosidase gene (GBA), the clinical expression of Gaucher disease varies enormously. However patients with at least one N370S (c.1226A > G, p.N409S) allele do not develop primary neurologic disease and patients heterozygous for the L444P (c.1448T > C, p.L483P) mutation have severe disease with neurologic complications. N370S/N370S predicts type 1 disease while L444P/L444P predict neuronopathic types 2 or 3. Pre-symptomatic or prospective interventions or the use of therapies with significant risk require accurate risk-benefit analyses based on the prognosis for individual patients.

Methods: From January 2016 to August 2017 three new patients have been diagnosed with Gaucher disease at the National Referral Center for Maternity and Child Health. Blood samples were collected on Whatman paper cards, genetic analysis (DNA extraction, PCR and sequencing of all coding exons and flanking intronic regions of the GBA) was conducted and genotypic-phenotypic correlations were made.

Results: The presence of “severe” mutation L444P in a single copy was found in two patients (one of them carrying also the N370S mutation) while the third patient displaced unique genotype L444P/L444P. The findings are predictive of neuronopathic type 3 disease in one patient (L444P/L444P), visceral disease with greater risk for early onset of Parkinson disease in the second (compound heterozygosis L444P). Unfortunately the third patient with compound heterozygosis N370S/L444P died.

Conclusions: Accurate and early diagnosis is critical, as most patients with types 1 or 3 will benefit from enzyme replacement therapy that may prevent development of irreversible complications.

DETERMINATION OF HER-2/NEU ONCOPROTEIN LEVEL IN THE SERUM OF BREAST CANCER PATIENTS

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Key words: breast cancer, HER2/NEU oncoprotein, patient serum, ELISA

Introduction: Human epidermal growth factor receptor 2 (Her2) is the tyrosine kinase growth receptor encoded by Her2 proto-oncogene. Her-2/neu markers are considered an unfavorable prognosis factor, and its high expression is indicative of high metastatic tumor
capacity. Expressed Her2 protein undergoes dimerization, resulting in degradation of intracellular and extracellular domain of receptor and extracellular domain releases into intercellular environment. Thus, the extracellular domain of the Her-2/neu receptor circulating in the bloodstream can be detected and measured in the serum. This feature formed the basis for the development of immunoassay systems for detection of soluble Her-2/neu in serum. The screening study of population can be carried out using enzyme linked immunosorbent assay, which is based on the expression and offers high sensitivity and high specificity of detection.

**Methods:** The "sandwich" version of ELISA was performed on the basis of monoclonal antibodies specific for the recombinant protein of extracellular domain of the Her-2/neu receptor.

**Results:** Serum samples from 12 patients with benign changes in mammary glands (the first group) and 49 breast cancer patients with 1-3 stages of the disease (the second group) were used in this study. In the first group, the average level of Her2/neu in serum was 8.5 ng/ml (ranging 5-12.5 ng/ml), while in the second group this indicator was 55 ng/ml (ranging 17.5-92.5 ng/ml). The broad range of oncological marker variation in the second group is attributable to cancer stages (1 through 3). Thus, the average concentration of the oncoprotein in patients at cancer stages 2 and 3 was - 72.5 ng/ml compared to patients with 1 stage where the mean was - 29.5 ng/ml.

**Conclusion:** Identification of circulating extracellular domain of Her2/neu oncoprotein in serum is a non-invasive tool for early prognosis of breast cancer. Developed ELISA on the basis of monoclonal antibodies could help choose an appropriate treatment strategy and manage patients health condition after treatment.

**IDENTIFICATION OF THERAPEUTIC TARGETS FOR CHEMOTHERAPY-RESISTANT COLON CANCER STEM CELLS**

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Current first-line chemotherapy generally consists of cytotoxic agents. While these agents may initially control disease by effectively debulking tumors, the tumors invariably recur due to the ability of cancer stem cells (CSCs) to survive and repopulate the tumor mass. To identify potential molecular targets in 5-fluorouracil (5-FU) refractory colon CSCs, we developed 5-FU resistant cell lines over a period of a year. Here we show that 5-FU maintains colon CSCs in an undifferentiated state in vitro. While untreated control cells passed in parallel progressively acquired a differentiated morphology comprising crypt–villus structures, cells treated with an IC50 dose or escalating doses of 5-FU organized in round colonies with defined edges. Cells from these chemoresistant colonies exhibited a high nucleus-to-cytoplasm ratio and prominent nucleoli, features of pluripotent stem cells. Chemoresistant cells showed a reduced proliferation rate with respect to their counterparts. While immunofluorescence analysis revealed chemoresistant cells expressed a panel of pluripotency markers, flow cytometric analysis indicated a change in CD antigens associated with tumorigenicity and pluripotency in chemoresistant cells as compared to untreated cells. These results suggest colon CSCs, while under the selective pressure of chemotherapy in vitro, are likely to display an adaptive plasticity resembling fate reprogramming. Three-dimensional growth in Matrigel revealed untreated cells were able to arrange themselves in a ring around a well-defined central lumen. Conversely, chemoresistant cell-derived organoids had
poorly defined or no central lumens. While untreated cells generated fast-growing, well-differentiated tumors, resistant cells generated slow-growing, moderately differentiated tumors in vivo. Finally, a large number of genes were screened in cells from both groups using Real-Time PCR arrays. Through this analysis, we identified molecular targets that might assist in the development of therapeutic strategies which will counteract the mechanisms of chemoresistance.

THE IMPACT OF THE RESULTS OF THE MORPHOLOGICAL STUDY OF THE LIVER IN THE POSTTRANSPLANT PERIOD ON THE TACTICS OF IMMUNOSUPPRESSIVE THERAPY

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Key words: Liver transplantation, rejection, recurrent liver disease, immunosuppressive therapy

Analysis of the results of liver transplantation showed an improvement in survival rates. This is due to the improvement of surgical and anesthetic methods of post-transplant management, relapses and other complications after transplantation. Long-term immunosuppression is required to avoid severe acute and chronic rejection and graft loss. With the current immunosuppression protocols, the risk of acute rejection requiring additional therapy is 10–40% and the risk of chronic rejection is below 5%. However, the development of histological lesions in the graft in long-term survivors suggest atypical forms of graft rejection may develop as a consequence of under-immunosuppression.

Material and methods: For 5.5 years, a biopsy was performed in 28 patients who has abnormal rates of liver function after liver transplantation, among them 19 women, 9 men including 1 child of 6 years. The cause of terminal liver disease in these patients in 35,7% was viral hepatitis D, in 21,4% - primary biliary cirrhosis, 17,85% were paiters with hepatitis B virus, 14,2% were patients with hepatitis C virus and 10,7 % - patients with autoimmune hepatitis.

Results. The result of a morphological study of the liver showed that in most cases, 50% in patients with changes in biochemical parameters, acute and chronic rejection is diagnosed. Biliary complications were found in 10.7% of cases. Recurrent liver diseases were confirmed in 17,9 % of patients after liver transplantation. Among patients in 3.6% of cases confirmed cholangitis. 7.1% of patients were diagnosed with liver steatosis.

Conclusion. Morphological diagnosis is crucial for the diagnosis of complications in the posttransplantation period and provides a personalized approach to the therapy of patients who underwent liver transplantation

THE STUDY OF POLYMORPHISM OF TGF-BETA1 IN PATIENTS WITH CIRRHOSIS CAUSED BY CHRONIC HEPATITIS C

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Key words: Transforming growth factor-β1 (TGF-β1), liver cirrhosis

TGFβ1 along with PDGF, VEGF, Angiotensin II, MCP-1, TNF, belongs to peptide ligands, which reinforce of signal transduction of fibrogenesis. TGFβ1 operates through receptor serine/threonine kinase and involves Smads and Src kinases The aim of the present study was to identify potential markers of cytokines genes associated with the susceptibility to HCV infection.

Material and methods: This prospective study was performed on 120 patients having chronic hepatitis C, 53 of them are women and 67 are men, and on healthy donors 70 people. Patients were divided into groups: 1 group - with chronic hepatitis C without cirrhosis - 40 people, 2 group - with cirrhosis in the outcome of hepatitis C Class A (Child-Pugh) -35 people and group 3 with diagnosis of cirrhosis Class B and C - 45

Results: The results of the study of polymorphism of TGF-β1 in patients with hepatitis C showed that clinically significant chronic HCV infection in the Kazakh population is associated with homozygous inheritance of the G allele of the 25 codon of the TGFβ1 gene. The development of cirrhosis is associated with the more frequent inheritance of the GG 25 homozygous genotype of the (P <0.05).

Conclusion: The functionally relevant TGF-β1 polymorphism may play a role in the clinically significant chronic HCV infection in the Kazakh population. In chronic hepatitis C, there is a significantly low incidence of the allele C of the 25 codon of the TGFβ1 gene. The development of hepatic cirrhosis is associated with a more frequent inheritance of the homozygous genotype GG 25 of the codon of the TGFβ1 gene.

ASSESSMENT OF LACTOSE INTOLERANCE AMONG THE KAZAKH POPULATION

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Lactase insufficiency (lactose intolerance) is a condition that is characterized by the inability of the child's organism or adult person to digest lactose because of inadequate lactase enzyme production in the intestine. Genotyping of polymorphisms -13910C / T and -22018G / A of LCT lactase gene is considered as a genetic test in Finland and other European countries. T-allele in position -13910 bp. and the G-allele at position 22018 bp The lactase gene (LCT) is associated with lactose intolerance syndrome, as they are mutant variants of the wild-type alleles -13910C and -22018A. Lactose intolerance is controlled as an autosomal dominant trait and is related to a population that traditionally practices domestication of cattle and in populations where dairy products form the bulk of the daily diet. Intolerance to lactose and milk can lead to a decrease in calcium intake and, thus, an increase in risk factors for osteoporosis.

The aim of our study is to estimate the frequency of lactose intolerance and to determine the genetic polymorphisms associated with the syndrome of lactose intolerance among the population of Kazakhstan.

Materials and methods: The study included school children of NIS of Semey and students of ENU, Astana, Kazakh nationality, aged 15 to 20 years. All participants were questioned regarding symptoms of intolerance to dairy products, a lactose tolerance test were done. Buccal epithelium
was taken and genomic DNA was extracted from buccal epithelium cells. Polymorphism of the LCT-13910C/T and -22018G/A lactase gene was determined by PCR and direct sequencing. An analysis of the phenotype-genotype association was conducted to assess the frequency and characteristics of the syndrome of lactose intolerance among Kazakhs.

Results. The study included 90 people. All participants were tested for tolerance to lactose. 27.8% (25/90) of participants demonstrated lactase resistance, expressed as an increase in blood glucose after taking lactose, whereas 72.2% (65/90) showed a slight increase in glucose in the blood, indicating an inadequate function of the enzyme lactase. The mean blood glucose concentration and standard deviations for both lactase persistence and lactose intolerance to (0 min) and after taking lactose (20, 40, 60 and 90 minutes) were higher when measured after 20 minutes. For patients with lactase persistence, the mean difference for blood glucose after lactose intake was 2.02×0.8 mmol/L, whereas for patients with lactase deficiency, the glucose difference level was 0.7×0.35 mmol/L. DNA samples from all 90 subjects were genotyped for the polymorphisms -13910 C/T and -22018G/A of the LCT gene. Polymorphism-22018G/A did not correlate with the preservation of lactase, which makes polymorphism -13910 C/T the only SNP associated with lactase in the population of the Kazakh population. Analysis of the phenotype-genotype association made it possible to calculate lactase persistence and lactase deficiency rates and their relationship to the corresponding alleles of the -13910C/T polymorphism of the LCT gene. Thus, 25 (27.8%) of the total number of 90 participants had a mutant type T-allele and demonstrated an increase in glucose level after consumption of milk (persistence of lactase), while 65 (72.2%) were carriers of the wild-type C-allele and not showed changes in blood sugar levels after consumption of milk (lactase deficiency). In 24.4% (24/90) of the examined subjects, the CT/TT genotype was identified at position 13910 bp upstream of the LCT gene sequence, whereas the wild type CC genotype was detected in 75.6% (68/90) subjects. The CT/TT genotype corresponds to lactase persistence, and CC is a wild-type genotype that corresponds to lactase deficiency, was found in 63.3% of those surveyed who showed symptoms of lactose intolerance. Thus, 65 (72.2%) patients had lactose intolerance syndrome and wild type CC genotype was detected in 75.6% (68/90). Associations of the phenotype of lactose intolerance with genetic variants of polymorphism -13910 C/T of the LCT gene were noted.

A NOVEL APPROACH FOR DETERMINING THE OPTIMAL NUMBER OF INDEPENDENT COMPONENTS FOR REPRODUCIBLE CANCER TRANSCRIPTOMES DATA ANALYSIS

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Keywords: Transcriptome, Independent Component Analysis, reproducibility, cancer

Introduction: Independent Component Analysis (ICA) is a method that models gene expression data as an action of a set of statistically independent hidden factors. The output of ICA depends on a fundamental parameter: the number of components (factors) to compute. The optimal choice of this parameter, related to determining the effective data dimension, remains an open question in the application of blind source separation techniques to transcriptomic data.

Methods: fastICA algorithm accompanied by the icasso package have been used to improve the independent components estimation and to rank the components based on their stability. ICA was applied to each transcriptomic dataset separately. For each analysed transcriptomic dataset, we
computed M independent components (ICs), using pow3 nonlinearity and symmetrical approach to the decomposition. In our analysis, we used Docker with packaged compiled MATLAB code for fastICA together with MATLAB Runtime environment, which can be readily used in other applications and does not require MATLAB installed.

**Results:** Here we address the question of optimizing the number of statistically independent components in the analysis of transcriptomic data for reproducibility of the components in multiple runs of ICA (within the same or within varying effective dimensions) and in multiple independent datasets. To this end, we introduce ranking of independent components based on their stability in multiple ICA computation runs and define a distinguished number of components (Most Stable Transcriptome Dimension, MSTD) corresponding to the point of the qualitative change of the stability profile.

**Conclusions:** We propose a new approach of ICA application to cancer transcriptomics data with a possibility of prioritizing components with respect to their reproducibility that strengthens the biological interpretation.

**RECOMBINANT NANOPARTICLES DECORATED WITH A NEAR-INFRARED FLUORESCENT PROTEIN FOR IN VIVO IMAGING**

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**Key words:** nanoparticles, recombinant, infrared fluorescent protein, IVIS spectrum

**Introduction:** Viral capsids are naturally occurring nanoparticles which have prospects of utilization in an *in vivo* imaging and targeted delivery. Hepatitis B virus capsid protein (HBcAg) self-assembles into spherical particles with a diameter of 32 nm. Each particle is composed of 240 protein subunits. We developed HBcAg particles decorated with the near-infrared fluorescent protein (NIRFP). Each particle (HBcAg/NIRFP) carries multiple moieties of the NIRFP. The HBcAg/NIRFP particles were injected into mice central bloodstream to study biodistribution.

**Methods:** Genes for the HBcAg and NIRFP were constructed *de novo* and the HBcAg was fused to the NIRFP using a molecular design (termed SplitCore) which allows inserting of the NIRFP into surface-exposed loops of the HBcAg so that multiple moieties (240 molecules) of the fluorescent protein are presented on a surface of the HBcAg/NIRFP particle. The gene for the HBcAg/NIRFP fusion protein was placed into an *E.coli* expression plasmid. Upon bacterial expression the HBcAg/NIRFP particles were purified using gradient ultracentrifugation. The integrity of the particles was confirmed by measurement of sizes using a dynamic light scattering and electron microscopy. Mice were injected into tale veins with 50-100 micrograms of the HBcAg/NIRFP particles to study the biodistributions using the IVIS Spectrum.

**Results:** Particles with floating density 1.12 g/ml were obtained by lysing the biomass of the *E.coli* expression strain and subjecting the lysate to ultracentrifugation in sucrose gradient. Dynamic light scattering (DLS) showed presence in the preparation of nanoparticles with uniform size distribution (hydrodynamic radius 21 nm). Electron microscopy revealed abundance in the preparation of nanoparticles with sizes completely compatible with the results of the DLS. Upon injection of mice with a solution of the HBcAg/NIRFP particles the nanoparticles’ biodistribution was studied using IVIS Spectrum in vivo Imaging System (PerkinElmer). The biodistributions shown varying time patterns with increasing accumulation in organs of reticuloendothelial system.

**Conclusion:** Viral nanoparticles decorated with the infrared fluorescent protein are efficient tools to visualize the biodistributions.
GENETIC AND BIOCHEMICAL DETERMINANTS OF HOMOCYSTEINE CONCENTRATION IN THE KAZAKH POPULATION

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Numerous studies have shown the role of homocysteine (HC) as a risk factor for cardiovascular disease, which plays a major role in the pathogenesis of atherogenesis and thrombus formation. A high level of HC leads to a 3-fold increase in the risk of cerebrovascular disease, and cancerogenesis.

**Aim:** To determine the biochemical and genetic markers of the metabolism of folic acid and homocysteine among the Kazakh population.

**Material and Methods.** 110 practically healthy persons (61 men and 49 women, the average age of 37.9 ± 16.1 years), Kazakh nationality were recruited to study the determinants of homocysteine concentration. All participants gave their written consent to participate in the study. The concentration of folate, vitamin B12, creatinine, albumin, total homocysteine (tHCY) in the blood was determined. Genomic DNA was isolated from blood. For the genotyping of C677T / MTHFR, the TaqMan PCR method was used. Statistical analysis was performed using the SPSS 19.0® program (SPSS, Tokyo, Japan).

**Results.** The level of folic acid in the blood serum in the group of Kazakh participants ranged from 0.7 to 13.5 μg / l. 72 (65.4%) of 110 had a low level of folic acid in the serum (<3/6 μg / l). The level of OGC plasma in the group of Kazakhs ranged from 5.5 to 41.1 μmol / l. Multiple regression analysis, taking into account gender and age, showed that the level of creatinine and albumin did not correlate with the concentration of HCY plasma. The level of vitamin B12 in the serum showed a relative correlation with the level of HCY (β = 0, p = 0.076). The concentration of folic acid significantly correlated with the concentration of HCY (β = -0.26, p <0.01). The frequency of the C677T / MTHFR genotypes was 41.8% for CC, 44.5% for CT, and 13.7% for TT. The level of oocyte plasma in the Kazakhs with the TT genotype was significantly higher than in the participants in the study with the genotype CC and CT (19.5 ± 1.8 μmol / l vs. 9.7 ± 0.5 μmol / L, p <0.001). After leveling the group by sex and age, the concentration of oGT in carriers of the TT genotype was twice as high as in the subjects with the CC and CT genotypes. Concentration of serum folate independently correlated with the level of HCY (p = 0.007), with the genotype of the CT of the C677T / MTHFR gene, the level of oocytes increases by a factor of 2 in comparison with the genotypes of the CC and CT. **Thus,** the determinants of hyperhomocysteinemia among the Kazakhs are the folic deficiency state, the genotype of the TT C677T / MTHFR. Effective replacement of folate levels will reduce the concentration of homocysteine. It is necessary to study polymorphisms of other genes involved in the regulation of homocysteine metabolism to identify possible additional genetic determinants of hyperhomocysteinemia.

DETERMINATION THE MAIN GENE MUTATION OF ORPHAN NEUROLOGICAL DISEASES IN CHILDREN

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55
**Key words:** genetic markers, orphan diseases (OD), Leigh syndrome, Dravet Syndrome, epilepsy.

**Introduction.** Rare or orphan diseases (OD) are diseases which affect a small number of people compared to the general population and specific issues are raised in relation to their rarity. Most rare diseases are genetic, and thus are present throughout the person's entire life. Many OD appear early in life, so that we to determine spread of the orphan neurological diseases in children under 3 years old. Children's early ages are seen neuromuscular diseases: spinal muscle atrophy, myasthenia, myopathies, and mitochondrial diseases.

The main goal of this investigation is to determine of genetic markers of the following orphan diseases with myopathy and myoclonic signs in children of Kazakh population: spinal muscle atrophy; Leigh syndrome; GM1 and GM2-gangliosidosis; Dravet Syndrome.

Spinal muscular atrophy (SMA) involves the loss of nerve cells called motor neurons in the spinal cord and is classified as a motor neuron disease; Genes are involved: SMA, TYPE I, II, III; Leigh syndrome is an under-recognized inherited neurometabolic disorder that affects the central nervous system; NDUFS8, COX10; GM1 and GM2 - gangliosidosis is an inherited disorder that progressively destroys nerve cells (neurons) in the brain and spinal cord. HEXA, HEXB; Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI), is a type of epilepsy that begins in the first year of life with frequent and/or prolonged seizures; SCN1A.

**Methods.** For detection of SNP polymerases (SMA (SNP-13); Leigh syndrome (SNP-15); GM1; GM2 – gangliosidosis (SNP-15); Dravet syndrome(SNP- 4)) we will use the TaqMan® OpenArray® Real-Time PCR Plates (Life Technologies, USA) by QuantStudio 12K Flex.

**Results.** We plan to determine spread of the orphan neurological diseases with myopathy and myasthenia based on genetic and clinical signs in Kazakh child population We plan to define clinically relevant mutations of the genes responsible for the spinal muscle atrophies (SMN1, 2), GM1, 2 –gangliosodosis 1 и 2 types (GLB1, HEXA, HEXB), Leigh syndrome (NDUFS8, COX10), Dravet syndrome (NDUFS8, COX10).

**Conclusion.** Kazakhstan can start a production of the specific medication for the enzyme replacement therapy. Collected data will be highly interesting and importance for the wide spectrum of the specialists and scientists. We will develop a system improving a children’s health quality of our country.

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**RNA-VIRUS WITH NONCYTOPATHIC REPLICATION – NOVEL VECTOR FOR EPIGENETIC REPROGRAMMING**

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**Key words:** epigenetic reprogramming, viral vector, noncytopathic replication

**Introduction:** Efficiency of obtaining of induced pluripotent stem cells (iPSCs) depends critically on the technique used to deliver reprogramming factors (transcription factors such as the Sox2, OCT4, Klf1, c-Myc). Currently the most effective systems for the production of iPSCs utilize viral vectors. Alphaviruses (gen. Alphavirus, fam. Togaviridae) comprise a genus of RNA-viruses that provide high levels of proteins from genes cloned into the viral genome, and the alphaviruses do not alter the genome of the host cell. iPSCs obtained using the Alphavirus vectors syngeneic with the donor and suitable for medical use. A cDNA of the full-length genome of a model alphavirus, the Venezuelan equine encephalitis virus (VEE) was constructed. This cDNA was used
to rescue the virus from the cDNA copy. Mutations were introduced into the cDNA to make the replication noncytopathic. Mutant virus has a stable noncytopathic phenotype, grows to high titers and provides synthesis of recombinant proteins.

**Methods:** cDNA VEE strain TC-83 was constructed from 9 DNA fragments; each fragment was produced de novo, by synthesis from oligonucleotides. Viral RNA was synthesized in vitro and transfected into cell cultures (BHK-21, CHO, HEK293). Site-directed mutagenesis and cloning of foreign genes into the cDNA was done by PCR-mediated genetic engineering. Virus titers were determined using the Reed-Muench method.

**Results:** Wild-type VEE (VEEwt) was found to be cytopathic. 100% death of an infected monolayer occurred within 48 hours upon infection. Mutations were introduced into the VEE genes for non-structural protein nsP2 and the capsid protein. Mutant virus (VEEmut) exerts no cytopathicity and accumulates to high titers (>10⁸ FFU/ml). Genes of heterologous proteins (GFP, puromycin acetyltransferase, reprogramming factors) were placed under control of the viral subgenomic promoter which resulted in the high-level production of these proteins in infected cells.

**Conclusion:** The obtained mutant RNA-virus genome is a promising vector for use in novel systems for epigenetic reprogramming and production of induced pluripotent stem cells.

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**THE ANTIMICROBIAL ACTIVITY OF HONEY KAZAKHSTAN REGIONS**


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**Key words:** Honey, antimicrobial activity, zone of inhibition, propolis

**Introduction.** Honey is a multi-component solution with antibacterial properties. The antimicrobial activity of honey is associated with the low pH, high osmolality, the presence of hydrogen peroxide, methylglyoxal, the presence of flavonoids.

**Material and methods.** The samples for study the antimicrobial activity were taken from different regions of Kazakhstan. There are monophlore (cotton, sunflower, akkuray, acacia, capers, {Allium mutans}) and polyphlore honey (meadow, steppe and mountain herbs), 4 samples of propolis, 2 samples of pollen, royal jelly and homogenate of drone maggots.

For the investigation were used the 10% aqueous solutions of samples. The antimicrobial activity was determined in vitro by the agar diffusion method on solid medium with test-strain (*Staphylococcus aureus*) ATCC 29213. The 100 ul of control/sample was added to each well. Penicillin antibiotic and distilled water were taken as a control. Zones of inhibition of test microbe growth were measured, including the diameter of the well (8 mm).

**Results.** In the experiment, 10% concentration {Allium nutans} honey showed the greatest antimicrobial effect among monophlore and polyphlore honey samples, its zone of inhibition were equal to 12,0 mm. Good value were determined for the extract of homogenate of drone maggots (14,2 mm) and royal jelly bees (10,2 mm). High antimicrobial effect were showed by poplar propolis, the diameter of its zone oppressions an average 17,0 mm, which is comparable to the result of control (penicillin-17.3 mm at 1mk/ml concentration). The antimicrobial properties of propolis linked to the presence of flavonoids.

**Conclusion.** Thus, best antimicrobial effect is showed by poplar propolis of all samples.
WHOLE GENOME SEQUENCING OF KAZAKHSTANI M.TUBERCULOSIS STRAINS WITH DIFFERENT DRUG SUSCEPTIBILITY

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Key words: M.tuberculosis, whole genome sequencing, drug resistance

Despite the effective anti-tuberculosis chemotherapy, TB remains one of the leading infectious diseases in many countries, including Kazakhstan.

The whole genome sequencing of 20 M.tuberculosis clinical isolates from TB patients with different drug resistance (8 MDR, 4 XDR, 2 mono-resistant, 1 poly-resistant, 5 susceptible) were performed by NGS platform Roche 454 GS FLX+.

Bioinformatics analysis was performed and showed that relative indicators of coverage of the 20 M.tuberculosis strains were high enough and sufficient for further analysis. Alignment of received sequences was performed separately for each of the twenty clinical isolates. On average, among all isolates 97.8% sequences was mapped to the reference strain M.tuberculosis H37Rv that composed 4334396 nucleotide bases. Most of the studied isolates of M. tuberculosis (18) are Beijing family strains (East Asian), only two isolates belongs to families T (Euro-American) and MANU-1 (Indo-Oceanic). International «Tuberculosis Drug Resistance Mutation Database» was analyzed to study the genetic loci involved in the resistance to basic anti-TB drugs. As a result of the analysis the most common mutations in genetic loci associated with drug resistance to basic anti-TB drugs were selected. Genetic mutations in genes associated with drug resistance of M.tuberculosis were analyzed and found 18-27 genetic variants. All detected genomic variants with single nucleotide polymorphisms, insertions, deletions for each clinical isolates of M.tuberculosis indicating the description of the gene and protein, the positions on reference genome H37Rv, deep coverage of gene were prepared. Three main groups for comparative bioinformatic analysis were chosen – susceptible, MDR and XDR. 1018 genomic loci were identified as a common for all three study groups. The major parts of these genomic variants are found in “core” genes that necessary for mycobacteria life-sustaining activity. Several genomic variants have been detected in four genes PE_PGRS24, PPE24, PPE5, PE_PGRS56 which are typical for MDR and XDR isolates and belong to genes of protein family PE/PPE specific for species of Mycobacteria only.

The mutations specific to MDR and XDR groups of M.tuberculosis isolates can be one of the additional virulence factors that may provide an advantage in host-pathogen interaction and require further investigation.

DISRUPTION OF HP1-KAP1 INTERACTION LEADS TO FORMATION OF LARGE NUCLEAR BODIES AND DECREASES HP1 MOBILITY IN THE NUCLEUS

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Key words: SUMOylation, BAP, BirA

Introduction: Posttranslational modifications are playing crucial roles in cellular mechanisms. SUMOylation is a reversible posttranslational modification of target proteins by the attachment of a small ubiquitin-like protein. The consequences of SUMOylation are widely variable, depending on the physiological state of the cell and the attached SUMO isoform. Accumulating recent findings have revealed a prominent role of SUMOylation in molecular pathways that govern senescence and ageing. It has been proven the link between SUMO attachment events and cellular processes that influence senescence, including promyelocytic leukaemia (PML) nuclear body, telomere function and reactive oxygen species (ROS).

Methods: The biotin ligase BirA was fused to the protein of interest, and the Biotin Acceptor Peptide (BAP) was fused to SUMO to make the detection of its biotinylation possible by confocal microscopy.

Results: KAP1 protein which mediates transcriptional control by interaction with the Krüppel-associated box repression domain found in many transcription factors was proposed to be involved in gene silencing via its recruitment of HP1 to particular sites in the genome. This simple model predicts that loss of the KAP1-HP1 interaction would weaken HP1 binding to chromatin, resulting in its higher intranuclear mobility. We used the HP1BD fragment of KAP1 as a dominant negative tool to test this prediction. Contrary to our expectations, we observed a decrease in HP1 mobility upon the disruption of the interaction between endogenous KAP1 and HP1. Moreover, large nuclear HP1-containing domains were formed under these conditions. Despite previously reported association between HP1 and PML bodies known to be highly enriched in SUMOylated proteins, we found no colocalization of PML with these HP1 domains. We conclude that the interaction between HP1 and KAP1 preserves HP1 in a more mobile and homogeneously distributed state in the nucleus.

Conclusion: We demonstrated that disruption of the KAP1-HP1g interaction leads to formation of remarkable matrix-associated nuclear domains that are enriched in HP1g and not identical to PML bodies. Overall, this part of the work illustrates how the identification of SUMO-modified proteins in proximity to a protein of interest could provide fresh clues revealing additional insights into the biology of these proteins.

RECOVERY OF NEUROLOGICAL FUNCTION OF ISCHEMIC STROKE BY ADMINISTRATION OF CONDITIONED MEDIUM FROM ADIPOSE-DERIVED PERIVASCULAR STEM CELLS

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Key words: Perivascular stem cells, stroke, conditioned medium, neurological recovery

Introduction: Perivascular stem cells (PSCs) are a rare population of multipotent progenitor cells with the capacity to self-renew and differentiate into mesenchymal and neuroectodermal
lineages. Indeed, recently it has been shown that PSCs play an important role in repairing of the nervous tissue during cerebral ischemia, as they can differentiate into neurons and glial cells in the hippocampal subgranular zone of experimental animals. Thus, these data indicate that PSCs can be promising candidates for treatment of ischemic stroke. In this regard, the purpose of our study was to examine the effect of conditioned medium derived from PSCs on recovery of neurological function after ischemic stroke in rats.

**Methods:** Rat PSCs were isolated from subcutaneous adipose tissue by a FACS Aria cell sorter using antibodies against CD146 and CD34 and expanded in α-MEM supplemented with 10% fetal bovine serum. The conditioned medium was collected after incubation with PSCs (passage 3) for 24 hours. Adult male Wistar rats were subjected to 2 hours of middle cerebral artery occlusion (MCAO) followed by femoral vein injection of 150 µg protein from PSC-derived conditioned medium or an equal volume of vehicle phosphate-buffered saline 24 hours (PBS) later. For neurological recovery evaluation, a walking beam test was carried out. Animals were trained prior to MCAO, and neurological deficits were evaluated at 1, 7, 14 and 28 d after IV injection of the conditioned medium. Neurogenesis was evaluated with histological method.

**Results:** It was observed that intravenous injection of conditioned medium of PSCs improved neurological outcome but did not reduce the ischemic lesion of the brain. Histological analysis revealed that conditioned medium treatment increased neurogenesis and attenuated microglia infiltration in stroke rats compared with PBS-treated controls. In addition, number of blood capillaries was significantly increased along the ischemic boundary zone of the cortex and striatum in rats treated with conditioned medium of PSCs.

**Conclusion:** Thus, our results suggest that intravenous administration of conditioned medium of PSCs can improve functional recovery and enhance neurogenesis and represents a novel treatment for ischemic stroke.

**IDENTIFICATION OF HRB27C AS A NOVEL REGULATOR OF THE HIPPO PATHWAY USING A DROSOPHILA GENETIC SCREEN**

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**Key words:** cancer, Hippo, YAP, TAZ, Yorkie, hnRNP, Hrb27C, Drosophila

**Introduction:** Cancer is one of the leading causes of human death across all countries of the world despite all recent advances in global medicine. Thus, identification of new genetic factors that contribute to cancer initiation and progression is an important issue for the development of new therapeutic strategies. The YAP and TAZ oncoproteins have been recently identified as important drivers of several types of human cancer, including liver cancer. YAP and TAZ in mammals and Yorkie (Yki) in Drosophila are the effectors of the Hippo tumor suppressor pathway, a key component of animal organ growth control. However, mutations in the known Hippo pathway components are rare and cannot explain the widely observed hyperactivation of YAP and TAZ in human cancers.

**Method:** In order to identify new regulators of YAP and TAZ activity, we used the fruit fly Drosophila melanogaster to screen for suppressors of tissue overgrowth and Yki activation.
Results: In our screen, we identified mutations in the hnRNP (heterogeneous nuclear Ribonucleoprotein) Hrb27C that strongly suppressed the tissue defects induced by ectopic expression of aPKC. We discovered that the mechanism of this suppression is due to the requirement of Hrb27C in regulating Yki activity and ultimately cell proliferation. We conclude from our genetic studies that Hrb27C is a new regulator of the Hippo signaling pathway and that it is required for Yki-driven overgrowth.

Conclusion: Our findings are both novel and significant. First, neither Hrb27C nor its human homolog DAZAP1 have been linked to the Hippo pathway before. Second, DAZAP1 is implicated in oncogenesis through a process called alternative splicing. Third, the expression levels of DAZAP1 correlate with poor prognosis in liver cancer patients. Further investigation of the interaction between DAZAP1 and YAP and TAZ would shed new light on the mechanisms behind the hyperactivation of YAP and TAZ in cancers and has a potential to promote the development of novel anti-cancer therapy.

DISTRIBUTION RISKS INVOLVING PSYCHOLOGICAL DEPENDENCE AMONG ADULTS IN PRIMARY HEALTH-CARE SYSTEMS IN KAZAKHSTAN

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Background: Epidemiological, clinical, social, and psychological research has suggested that dependence is not confined to chemicals alone among adults who utilize social and psychological services provided by primary health care organizations in Kazakhstan. The present study utilized the concept of social epidemics to examine risk of psychological dependence in this population.

Methods: Patients seeking routine primary care (N = 121, predominately male, M age = 30 years, predominately indigenous nationality) were recruited into the study and completed a clinical interview. The interview included sociodemographic questions, questions designed to identify the risks of dependence, and level of psychological health.

Results: The most common addiction was workaholism (73.6%), followed by TV addiction (58.7%), sexual addiction (48.8%), and relationship addiction (41.0%). Rates of chemical addictions were lower: alcohol (12.4%), other drugs (4.0%), and tobacco (12.4%). General tendencies toward psychological dependence was detected in 40% of the respondents.

Conclusion: In order to understand the breadth of dependence among patients, a comprehensive assessment of risk of dependence that extends beyond alcohol and other drugs is required.

POLYMORPHISM OF CYP2C19 GENE IN PATIENTS WITH CHD

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Key words: polymorphism of CYP 2C19 gene, clopidogrel, IHD, stent thrombosis

Introduction: The consequence of insufficient suppression of increased activity of platelets can be a repeated cardiovascular event. The most important determinants of the difference in the
effectiveness of clopidogrel use between patients are two variants of the genotype with loss of function in the CYP2C19 gene (*2 and *3), which encodes the cytochrome P450 2C19 enzyme.

Methods: The study included 34 patients with ischemic heart disease, after a recent myocardial revascularization with stenting. Pharmacogenetic testing for the determination of allelic variants (polymorphisms) of the CYP2C19 gene was carried out by polymerase chain reaction (PCR) in RealTime mode using "DNA-EXPRESS-BLOOD" reagents sets "Liteh", Moscow. Statistical processing was performed using the SPSS program: descriptive statistics, Student's t-test for independent samples, Chi-square, ROC analysis.

Results: A total of 34 patients were examined, with an average age of 61.7 (cf. 11.4) years. Male 23 (67.6%) at the age of 55.5 (compare off 8.9) years, women 11 (32.4%) at the age of 61.2 (compare off 6.9) years. Kazakh nationality 23 (67.6%), the European race - 11 (32.4%). In the history: PCI with stenting, reception of DAT (aspirin with clopidogrel). Stents with drug coating 28 (82.4%), without drug coating 6 (17.6%). According to the diameter of the stents to 2.75 mm 14 (41.2%), 3 mm and more than 20 (58.8%). For recurrent coronary events: there is no event 18 (52.9%), stent thrombosis 6 (17.6%), recurrent angina 10 (29.4%). A weak positive correlation was found between the development of stent thrombosis from genetic manifestations (r=0.35, p=0.43). Genetic testing was performed: 1 - wild type 21 homozygote (61.8%), 2 - heterozygous 11 (32.4%), 3 - homozygous mutation 2 (5.9%). All patients are divided into groups by nationality and genetic changes. The differences found in the groups are not significant (p = 0.140). The statistical significance of genetic testing for the prediction of stent thrombosis has been revealed (OR 6.708 CI 95% (1.355-33.209), p=0.02).

Conclusion: Polymorphism CYP2C19*2(G681A) has a prognostic value in the development of stent thrombosis in patients after myocardial revascularization against the background of DAT ASA and clopidogrel (OR 6.708 CI 95% (1.355-33.209), p=0.02).

ASSESSMENT OF RISK FACTORS FOR METABOLIC SYNDROME AMONG NIS SCHOOLCHILDREN IN SEMEY: INTERVIEW OF SCHOOLCHILDREN AND THEIR PARENTS AND ANTHROPOMETRY

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Metabolic syndrome (MS) is a whole bunch of risk factors for cardiovascular diseases (CVD) and type 2 diabetes, including abdominal obesity, dyslipidemia, intolerance to glucose and hypertension. A number of studies have shown that MS have a persistent ability to move from childhood and adolescence to adulthood. The feasibility of identifying risk factors for MS in children and adolescents is relevant for the timely prevention of the CVD and its complications.

The purpose of this work is to assess risk factors for metabolic syndrome among NIS schoolchildren in Semey according to the questioning of children and their parents.

Material and methods. This is a cross-sectional study. Schoolchildren, 8-9-10 grades, studying at the NIS of Semey and their parents were interviewed. Anthropometric measurements were done in all children: height, body weight, body mass index (BMI), WC, hip circumference (HC), ratio of WC/HC. BMI was calculated and assessed using percentile tables for a given age and each sex (WHO, 2007). Normal BMI between the 15th and 85th percentiles, BMI within the 85-97th percentile is estimated as excess body weight, over 97th percentile as obesity. The type of distribution of the subcutaneous fat layer was evaluated by the index of the waist circumference (WC) normalized by the height: WCn=WC(cm)/height(cm). At WCn values exceeding the indices
of the 97th centile, an abdominal-visceral type of obesity was noted, with indices less than these values being a gluteo-femoral type.

Results. The study included 100 children aged 13 to 17 years, 49.0% boys and 51.0% girls. In 15.0% of children, the BMI exceeded 85%, with a BMI of > 97% in 7.8%, which is in line with obesity, and in 7.2% of children BMI was 85-97%, indicating increased body weight. Among the overweight girls predominated, and boys were more obese. The nutrition of all children was irrational, hypercaloric, unbalanced in nutrients. Thus, the excess of solid fats was detected in 57.2%, digestible carbohydrates - 31.0%. In 4.3% of children the excess of kilocalories was due to easily assimilated carbohydrates in drinks, i.e. these children consumed daily juices and/or sweet fizzy drinks up to 1-2 liters. In 7.5% of children, the hypercaloric diet was determined by frequent visits to fast food restaurants with food intake in them, amounting to 50-75% of the daily calorific value. 50.8% of children had insufficient fiber intake in the form of vegetables and fruits, fish dishes. Unsaturated fatty acids (i.e., fish dishes and vegetable oils) were missing in the diet of children, and 40.1% of children lacked dietary fiber (vegetables, fruits). The lifestyle of overweight children was characterized by increased school load and reduced motor activity. Thus, decreased motor activity was observed in 60.7% of children with signs of obesity and in 40.4% of children with excessive body weight. Children with obesity spent 4.6 ± 1.4 hours a day in front of the TV and/or computer, and children with an overweight of 3.9 ± 1.1 hours, which further aggravated hypodynamia and caused psycho-emotional overexertion. The heredity of children was burdened by diseases that are part of the metabolic syndrome (obesity, hypertension, diabetes mellitus type 2). The analysis showed that the burdened heredity for obesity in the family was detected in 70% of children; on the maternal line 2 times more often than on the line of the father. The relatives of children had hypertension: in the first line of maternal relationship in 23.8%, on the paternal line in 19.3%; type 2 DM was found in 1.6% of the maternal line, and 2.1% in paternal line. More than half of the mothers of the examined children (63.7%) had a complicated course of pregnancy, and 38.5% had complications in childbirth. Almost every fifth child (22.3%) was on artificial feeding. Thus, the studied schoolchildren are characterized by risk factors for the development of metabolic syndrome.

ACTIVATION OF CELL AGEING PATHWAYS WITH NOVEL SMALL MOLECULES FOR CANCER TREATMENT

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Introduction: Many frontline cancer therapies function by directly or indirectly causing DNA damage and thus cell death. In their most simple form these drugs target a physiological differentiating feature of cancer cells: they tend to be more actively proliferating than normal cells. This causes well-known side-effects that result from the death of highly proliferative normal cells, notably in the gut and immune system. Recent trend in cancer research has been the development of treatment that kills cancer cells without also damaging the normal cells in the patient - a concept known as the therapeutic window. New approach therefore is p53 tumour suppressor gene and its frequent loss in cancer. Although many cancer cells have deactivated G1 checkpoint they may still retain a residual G2 checkpoint involving ATR/p38MAPK/MK2. Work using transgenic mice has recently demonstrated that genetic disruption of the p38/MK2 pathway specifically sensitzes p53-null mouse cells to DNA damaging agents. That could be due to p53-null cells in the presence of
Ablation of p38/MK2 pathways lose both G1 and G2 DNA damage checkpoint function, and enter mitosis despite the presence of DNA damage, where they die by "mitotic catastrophe".

Materials and methods: Cancer cell lines were purchased from ATCC and treated with DNA damaging agents in the presence and absence of both p38 and MK2 inhibitors (SB203580 -10uM and MK2/3 - 1uM). DNA damaging agents were used at the following concentrations: Doxorubicin (10uM), Cisplatin (200uM) and Etoposide (5uM).

Results and Conclusion: DNA damaging agents produced a profound effect on the cell cycle profile of these cell lines in a manner that is consistent with the degree of cell viability that is seen using the viable cell assay. Given the relatively modest effects of the p38/MK2 inhibitor drugs on cell viability at the concentrations used, no major shift in cell cycle was seen following treatment with these drugs. This further confirms the expected result that these inhibitors do not affect the cell cycle directly in themselves, but may do so subtly in conjunction with DNA damage.

BIOCOMPATIBILITY OF NEW THERMOREVERSIBLE POLYOXAMER 407-BASED HYDROGELS

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Key words: Poloxamer 407, hydrogel, rats, blood

Introduction: Poloxamer 407 is a hydrophilic non-ionic surfactant of the more general class of copolymers known as poloxamers. These smart polymers are sensitive to the temperature and therefore, change their microstructural features in response to changes in temperature. They are the most studied, most used and safest polymers in drug administration systems and biomaterials. They present in their structure a very sensitive balance between hydrophobic and the hydrophilic groups and a small change in temperature can create new adjustments. A poloxamer molecule can be modified using ATRP (Atom Transfer Radical Polymerization). This method allows the synthesis of polymers with precisely controlled functionalities, topologies, and compositions. This research examines the biocompatibility of novel polymers modified using the ATRP method.

Methods: Polymeric hydrogels were implanted in dorsal subcutaneous pockets in rats. At 10 and 30 days, animals were sacrificed and the gels and surrounding tissues were removed. Sectioning, paraffin embedding, and Trichrome Masson staining were performed.

Results: Using the ATRP method we obtained two Poloxamer 407 polymers with hydrophobic glycidyl methacrylate and hydrophilic N-acryloyl-6-aminohexanoic acid. Analyses of local tissue response were carried out 10 to 30 days after the subcutaneous implantation of Poloxomer 407 and its derivatives with hydrophobic glycidyl methacrylate and hydrophilic N-acryloyl-6-aminohexanoic acid in laboratory rats. Histological analyses showed no symptoms of acute inflammatory reaction or rejection. A loose fibrous capsule formed on the skin surface after 10 days. There were evidence of isolated lymphocyte cells and an increase in blood flow through the vessels. The results obtained indicate that local tissue reaction due to the implanted hydrogels was highly insignificant.

Conclusion: The results indicate that the polymer hydrogels obtained are biocompatible and can be used for new wound dressing development.
FEEDBACK BY ADOLESCENTS REGARDING SEXUALLY TRANSMITTED INFECTIONS

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Key words: sexually transmitted disease, education, young people

Introduction. Sexual contact transmits more than 30 different types of microbes. Annually, more than 340 million new cases of sexually transmitted infections (STIs) are registered in the world. One out of every 12 teenagers is infected with STIs; the incidence among young people is in 4 to 5 times higher than in the general population. Education of young people plays an important role in the prevention of STIs and feedback of teens helps to improve this work. The purpose of this study is to analyze the children’s feedback about prevention of STIs and take steps to educate the young people in prevention of STIs.

Methods: A cross sectional investigation was carried out by conducting peer interviews. The questionnaire contained questions about sexually transmitted infections and their prevention.

Results: 96 children were tested: female (52%), male (41%), 7% did not specify gender. The age of respondents was 17 years (42%), 16 years (36%), 15 years (10%), 18 years (5%), 19 years (1%) and 6% did not specify the age. According to high schoolers, parents should participate in sexual education of children (55%), specialists (23%), their own answer (13%), mass media (4%), did not answer 5%. Respondents believe that sexual education of children should begin from 15-17 years (37%), 12-14 years (29%), 2-3 years (11%), do not know (9%), 7-8 years (7%), 18 years (5%), when the child asks (2%). Students’ knowledge about contraceptive methods: condoms (93%), hormone tablets (54%), intrauterine device (43%), sterilization (23%), hormonal patches and spermicides 13% each. 74% of respondents do not have sexual life, 26% do. Children know that HIV-infection is transmitted through sexual intercourse (94%), syphilis (66%), genital herpes (31%), chlamydia (25%), gonorrhea (24%). 50% of respondents believe that they can have sexual relations over the age of 18 years, from 15 to 18 years (42%), under 12 years (5%), from 12 to 14 years (3%).

Conclusion: Thus, the answers of young people demonstrate problems in the sexual education of teens and in the prevention of STIs, for which education regarding prevention proves necessary.

PROGNOSTIC VALUE OF TNFα GENE 308G>A POLYMORPHISM IN PATIENTS WITH SEPSIS

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Key words: sepsis, tumor necrosis factor, TNFα gene polymorphism

Introduction. Peritonitis and abdominal sepsis may lead to mortality in 50-70% cases. Mortality predicting scales are very useful to determine the rate of death probability in septic patients (pts). But there are no such scales for predicting the rate of sepsis occurrence in pts after urgent abdominal surgery. Tumor necrosis factor (TNF) is critical to the immune response to
infection. The TNFα gene is also highly polymorphic. The TNFα -308G>A polymorphism is the most comprehensively studied genetic variation in immune response.

**The aim** of study is to evaluate the tumor necrosis factor (TNF) gene polymorphism as a predictor of septic complications in pts after urgent abdominal surgery in Kazakh population.

**Methods.** After local ethic Committee approval and informed concern total 152 pts all Kazakh underwent urgent abdominal surgery were studied. We studied frequency of septic complications after surgery and level of sepsis marker procalcitonin (PCT). The -308G>A polymorphism of TNFα gene was analyzed by PCR-real time method. The statistical analyses was performed with PLINK programme.

**Results.** 49 (32.2%) pts had septic complications after surgery (group 1), 103 (37.8%) pts had no complications (group 2). PCT level was increased in both groups: 4.17±0.4 ng/ml vs. 3.74±0.5 ng/ml (p>0.05). We have revealed pathological homozygous genotype AA of TNFα gene in group 1 in 68.6±6.62% of pts and 9.9±3.36% in pts of group 2 (p<0.05). Heterozygous AG genotype was in 19.7±9.45% in group 1 and 38.5±6.7% in group 2 (p<0.05). Genotype GG have 13.5±9.05% of pts in group 1 and 53.9±6.93% of pts in group 2 (p<0.05).

**Discussion.** Considering high PCT level in both groups of pts we assumed that pts initially had systemic inflammatory response syndrome (SIRS). Revealed prevalence of unfavourable genotype AA of TNFα gene in patients with septic complications after surgery let us to suggest its role in development of septic complications after surgery. Genotype AA of TNFα gene can be settled as early prognostic criteria of high risk for development of septic complications in surgical pts and may substantiate early aggressive prevention of septic complications in surgical pts to decrease mortality.

**EXOSOMES DERIVATION FROM PERIVASCULAR STEM CELLS**

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**Key words:** Exosome, perivascular stem cells, regeneration, cell therapy

**Introduction:** Exosomes have recently been highlighted as a new strategy for using in cell therapy because they are fundamental in the processes of cell growth, differentiation, invasion and angiogenesis by regulating cell-to-cell and cell-to-extracellular matrix interactions. Recently literature data shows that perivascular stem cells-derived exosomes secrete proteins include growth factors, cytokines and hormones or other soluble mediators which have therapeutic functions in a paracrine manner. In this regard, the purpose of this study was to isolate exosomes from adipose-derived perivascular stem cells.

**Methods:** Perivascular stem cells (PSCs) were initially cultured in exosome-production media containing α-MEM supplemented with exosome-free fetal bovine serum. When cells reached a confluence of 80%, extensive washes in PBS were performed to remove any possible residue of FBS. The cells were transferred in exosome-production medium and the culture split into two subcultures maintained for 48 hours. Exosomes were isolated by differential centrifugation at 300g for 10 minutes, 2,000g for 20 minutes, 10,000g for 30 minutes to eliminate cells and debris. Obtained supernatants were depleted of residual floating cells and cell debris by filtration with 0.22 µm, followed by two consecutive steps of ultracentrifugation at 100,000g for 90 minutes, including a washing step in PBS, to precipitate exosomes. The protein concentration was measured by Nanodrop. Morphological and ultrastructural characteristics of exosomes were studied using transmission electron microscopy (TEM).
Results: Our results show that yield of proteins in exosomes after 48 hours cultivation of $1 \times 10^7$ PSCs was reached 1.5 mg/ml. Furthermore, TEM revealed that exosomes have a round-shaped form and their size ranges from 80 to 120 nm which characterize exosomes of adult stem cells.

Conclusion: Thus, our study demonstrate that exosomes for the first time were successfully isolated from PSCs. Derived exosomes from PSCs can be used as a novel immunomodulatory therapeutic agent for regenerative processes.

ESTIMATION OF THE STATE OF SCREENING PROGRAM ON EARLY DETECTION OF PROSTATE CANCER WITHIN THE FRAMEWORK OF THE NATIONAL SCREENING PROGRAM IN PAVLODAR REGION

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Key words: prostate cancer, National screening program, early detection

Introduction: Prostate cancer (PCa) is the second most common cancer in men worldwide and it is one of the leading causes of death of elderly men from malignant tumors in Kazakhstan. In the structure of morbidity among all malignant neoplasms, PCa occupies the 6th ranked place (5%). Since 2013, a screening program for the early detection of premalignant and tumor states of the prostate gland is being phased in the Republic of Kazakhstan.

Methods: A database of IT named automated control system “Polyclinic” from the Pavlodar branch of the Republican Center for Electronic Health, a database of cancer patients from the Pavlodar Regional Oncology Dispensary have been analyzed. The main indicators for data collection have been determined: plan, performance from the plan, detectability of diseases, the number of detected cancers within the framework of the National Screening Program (NSP), share of cancer in the early and at the late stage etc.

Results: In Pavlodar region from 2013 to 2016, 443 new cases of PCa have been identified. Within the framework of (NSP) in 4 years 39675 men were examined for early detection of this pathology, 1034 patients were identified including 91 new cases of PCa. The proportion of newly diagnosed cases of PCa in the NSP from the total number of newly diagnosed cases of PCa in Pavlodar region was 20.4%; under this program the detectability of precancerous and tumor states of the prostate was 2.6%, and the detectability of prostate cancer was 0.3% (according to the European standards, the proportion of the detected cases of PCa among the target group is 0.08%). The share of detected cases of PCa at an early stage was 86.8%, the late stage was 13.2%.

Conclusion: Despite the low detectability of this pathology, it is advisable: 1) to continue the screening for early detection of precancerous and tumor states of the prostate, 2) to identify barriers and develop educational programs among the population, 3) to improve the effectiveness of the screening program.

DAMAGE-INDUCED MUTATION CLUSTERS IN B. SUBTILIS

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Key words: mutagenesis, bacterial genome, mutation clusters, bioinformatic analysis

Introduction: Multiple studies on different biological systems showed the presence of the non-random distribution of mutations in the genome. Particularly, mutations are located in a limited space of the genome forming a cluster or hotspots, while the remaining genomic area remains virtually intact. Whole-genome sequencing of chemically mutagenised gram-negative E.coli showed a strikingly non-uniform pattern of mutations distribution, which was arranged in clusters in several sequenced E.coli genomes. We used this strategy to extend study in gram-negative bacteria to gram-positive ones to determine whether this phenomenon is more universal and not confined only to E.coli. Use of next-generation sequencing approach and bioinformatic tools allowed analyzing several mutagenised B.subtilis genomes.

Methods: Mutagenesis in gram-positive Bacillus subtilis subsp. subtilis str. 168 using alkylating agent ethyl methanesulfonate was induced. Five randomly picked single colonies were taken for the analysis of mutation distribution through Ion Torrent PGM sequencing platform. Data analysis was conducted through bioinformatic pipeline using programs and tools as Cutadapt, Samtools, BWA, VarScan and IGV.

Results: Whole-genome sequencing of several mutagenized B.subtilis genomes through Ion Torrent PGM showed a non-random dispersion of mutations caused by the EMS treatment. Variant calling showed high number of G-to-A and C-to-T transitions that were asymmetrically distributed throughout the genomes in the form of mutation clusters of different length. The “stretch” of one mutation type was switched to the “stretch” of another mutation type. The pattern of such “stretches” and “switches” of C-to-T and G-to-A coordinated mutations was similar to the pattern observed in the work on gram-negative E.coli.

Conclusion: In the current study the use of a whole-genome sequencing approach allowed to analyze several EMS-mutagenised B.subtilis genomes. Observed asymmetrical mutation pattern in the EMS-treated gram-positive B.subtilis indicates not only the universality of the phenomenon of mutation clusters, but also the effectiveness of next-generation sequencing in detecting non-uniform mutation distribution pattern on the genomic scale.

OMICS TECHNOLOGY IN MEDICINE – METABOLOMICS ANALYSIS OF PLASMA IN DIFFERENT DISEASES

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Key words: Metabolome, OMICS technology, HPLC-MS, human diseases, biomarker.

Introduction: Metabolomics, rapidly evolving field of measuring all endogenous metabolites in a cell or body fluid, provides a functional readout of the physiological state of the human body. Most importantly, genetic variants associated with a specific metabolite level, and with a defined disorder, might provide access to the underlying molecular disease-causing mechanisms.

The main goal of this research is identifying metabolically interpretable genetic factors predisposing to manifestation and progression of various diseases.
Methods: We conducted metabolic studies by the case-control design. There was conducted an isolation of polar and non-polar metabolites from blood plasma, which were further separated into the HILIC bond column by HPLC-MS with the TOF (time-of-flight) detector. The processing of the obtained data was carried out on the public software PCDL Metlin Metabolite Database, XCMSonline. Statistical processing of data was carried out on MetaboAnalyst 3.0.

Results: There was revealed a difference in the spectra and in the amount of metabolites in various pathologies. We have investigated the following diseases: thyroid cancer, childhood food allergy and rheumatoid arthritis. There was revealed difference in the metabolic spectrum in children diagnosed with congenital food allergies in comparison with their parents. Specific biomarkers, such as L-methionine, 3-hydroxy-trimethyl lysine, etc., have been detected in patients diagnosed with thyroid cancer. Fingerprinting analysis of metabolites by free access software revealed differences between the case and control cohorts and also demonstrated notable discrimination between the RA and RA-OP cohorts.

Conclusions: As a result of our research we want to determine specific metabolically interpretable and reliable genetic factors along with metabolic pathways, which might be shared or differed between case and control groups and might provide insight into the extent to which the process of pathological changes occurs and progresses. All over the world, research on the problems of aging is carried out for this purpose and preventive diagnostics, and the prevention of the development of diseases will help healthy longevity.

BASAL METABOLIC RATE IN HEALTHY PEOPLE AFTER WEIGHT LOSS: A RANDOMIZED CLINICAL TRIAL

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Key Words: Basal metabolic rate, Body mass index, Weight loss.

Introduction: The body spends more own life energy per unit time when it has a high basal metabolic rate (BMR). Aim of the study was to evaluate the impact of body mass index (BMI) on BMR in adult healthy people.

Methods: An open prospective clinical randomized controlled trial including 140 adult healthy people (aged 35-65 years) was performed. The healthy people were divided in two groups: Main group (n=80) had BMI 31.8±0.6 kg/m2; Control (n=60) had BMI 25.3±0.5 kg/m2. Then Main group followed a fast weight loss method during 4-week. Primary endpoints were weight loss over a 4-week period, BMR (kcal/day) was measured using a Tanita-SC330S Body Composition Analyzer (Tanita Corp., Tokyo, Japan).

Results: In Main group BMR was equal to 1879.6 ± 48.4, in Control group 1494.4 ± 52.2 (P<0.0001). At 4 weeks, people in Main group weight lost 8-15 kg (15% from baseline) was due to reduction of fat mass only, BMI decreased to 24.6±0.4 kg/m2 (P<0.0001) and BMR decreased to 1350.5±48.4 or on 30% from baseline (P<0.0001). Regression analysis showed that every 1 kg fatty overweight deprives 45 kcal/day of total daily energy expenditure of the body.

Conclusions: People with a larger body mass burn more calories, since the metabolic rate is directly related to the total body mass. A decrease in body fat mass reduces BMR that could increase lifespan in people. Further investigations are required.
POTENTIAL ENERGY OF HUMAN LIFESPAN AND IMPACT OF FATTY OVERWEIGHT FOR THE LIFESPAN

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Key Words: Human Lifespan, Energy expenditure, Overweight.

Introduction: The body spends more own life energy per unit time when he has a high basal metabolic rate (BMR). Aim of the study was to account how much potential energy has human body during his life and how changes lifespan in people with overweight.

Methods: Math and scientific data methods are used. The body deprives in average 50 kcal/day of total daily energy expenditure for each 1 kg fatty overweight. In people with overweight BMR is 20-30% more compared to non-overweight [Schutz Y, et al., 2001]. According to thermodynamics principles $E_{LS} = E_K + E_P + U$, or $E_{LS} = TMR \times T_{LS}$, where $E_{LS}$ – lifespan potential energy expenditure, $E_K$ – system kinetic energy, $E_P$ – system potential energy; $U$ – thermal energy. TMR – total metabolic rate (kcal/day), where TMR = BMR + AMR, where BMR is Basal metabolic rate, and AMR is Active metabolic rate (kcal/day). $T_{LS}$ is lifespan in days. $E_K$ is directly correlated with body mass and TMR. The higher the body mass and TMR, the higher the body kinetic energy expenditure, and the lower the LS.

Results: In average TMR for human body equals to about 2300 kcal/day. If an average human potential lifespan is 120 years [Goldsmith ThC et al., 2014], that is 43800 days, then $E_{LS} = TMR \times T_{LS} = 2300 \times 43800 \approx 109.5$ million kcal, or 458.4 million Joule (1 kcal = 4.186 kJ). It is equal to a small nuclear explosive with more 100 tons of TNT equivalents. LS human potential energy is equal to the small nuclear explosion energy.

The body deprives about 2.2 million kcal (50 kcal/day × 43 800 days) on each 1 kg of fatty overweight for lifespan which is 2% of lifespan energy expenditure. If now person has overweight + 10-20 kgs, then he losses 20-40% of his LS.

Conclusions: The potential energy of human LS is equal to the small nuclear explosion energy. Human lifespan is shortened on 2% for each 1 kg of fatty overweight. In average, overweight people loss 20-40% of his LS.

GENETIC VARIANTS OF CYP2C9 AND VKORC1 IN PATIENTS WITH LVAD.

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Key words: LVAD, warfarin, CYP2C9, VKORC1.

Introduction: Warfarin mostly used as oral anticoagulant in many pathological conditions such as deep vein thrombosis, heart valve prosthetics, blood vessels stenting and especially Left Ventricular Assist Device (LVAD).
Key enzyme of the warfarin biotransformation is CYP2C9, from cytochrome P450 system, and target for the action of warfarin is vitamin K epoxide reductase complex subunit 1. Therefore, allelic variants of the CYP2C9 and VKORC1 genes are most important in the dosage of warfarin. It should be noted that the genetic component of warfarin metabolism varies in different ethnic groups. The aim of our work was to study CYP2C9 and VKORC1 polymorphisms in Kazakh patients with implanted LVADs.

Materials and methods: Patient recruitment was carried out in the National Research Cardiac Surgery Center, Astana. We include in study patients with LVAD who signed confirmed informed consent. Venous bloods of 100 patients (93 males, 7 females) were collected. Genomic DNA was isolated with Wizard® Genomic DNA Purification Kit (Promega), CYP2C9 (rs1799853, rs1057910, rs28371686) and VKORC1 (rs8050894, rs9934438, rs9923231) genotypes were determined by allelic discrimination using TaqMan assays on Fast Real-Time PCR System (Applied Biosystems).

Results: Among our patients with LVAD were found different allelic variants of VKORC1 gene. Only 12% (12/100) had a wild-type allele of three polymorphisms, 37 patients had a homozygous variant with 3 polymorphisms (rs8050894, rs9934438, rs9923231) and 2 polymorphisms (rs9934438, rs9923231) - 20% (20/100) and 17% (17/100) respectively. Other remaining patients had different heterozygous combinations of VKORC1 polymorphisms. The genotyping results of CYP2C9 showed prevalence in patient’s wild-type of allelic variant for all polymorphisms. Variants of heterozygous allele were determined in 8% (8/100) for 1 polymorphism (rs1799853) and in 7% (7/100) for another polymorphism (rs1057910).

Conclusion: Thus, in patients with LVAD were identified various genetic variants in VKORC1 and CYP2C9. Patients with homo- and heterozygous mutant allelic variants need to reduce the dose of warfarin to achieve a target INR in comparison patients with wild type.

INTRAVITAL TWO-PHOTON MICROSCOPY: APPLICATION TO THE IMMUNE SYSTEM

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Key words: germinal center reaction, intravitral imaging, spectral unmixing, multiple sclerosis (MS), neuronal dysfunction, fluorescence life-time imaging (FLIM-FRET)

Introduction: Immunity is a highly balanced system with two complementary strategies, innate and adaptive. Unlike the innate component, the adaptive immune response creates immunological memory after an initial reaction to a specific pathogen. One of the key processes forming the immune memory is germinal center (GC) reaction, the basis of vaccination. Optimizing the GC response to different vaccine antigens (HIV, influenza etc) can give us a unique tool for development of effective prophylactics against such diseases in the global context. The GCs are dynamic sites of antigen-specific B cells, T follicular helper cells and the resident follicular dendritic cells. Unlike current intravitral techniques with observation of typically 3 to 4 fluorophores, we demonstrate simultaneous detection of seven cellular and tissue compartments in popliteal lymph nodes of live mice that is necessary to study the GC mechanisms in vivo.
The functional dynamics and cellular sources of oxidative stress are central to understanding MS pathogenesis but remain elusive, due to the lack of appropriate detection methods. We employ NAD(P)H fluorescence lifetime imaging to detect functional NADPH oxidases (NOX enzymes) in vivo to identify inflammatory monocytes, activated microglia, and astrocytes expressing NOX1 as major cellular sources of oxidative stress in the central nervous system of mice.

**Methods:** Both fluorescence intensity and FLIM experiments were performed using two-photon laser-scanning microscope (LaVision BioTec, Germany). In order to a defined model of germinal center reaction in the popliteal lymph node, we immunized mice with NP-CGG and transferred into the recipient C57Bl/6 mice labeled five types of cells. The detection of the fluorescence signals was accomplished either with photomultiplier tubes or with a 16-channel parallelized TCSPC detector (FLIM-X16, LaVision BioTec, Germany).

**Results:** Using our approach, we simultaneously excite and detect seven fluorophores expressed indistinct cellular and tissue compartments, plus second harmonics generation from collagen fibers in lymph nodes. This enables us to visualize the dynamic interplay of all the central cellular players during germinal center reactions. While current *in vivo* imaging typically enables recording the dynamics of 4 tissue components at a time, our strategy allows a more comprehensive analysis of cellular dynamics involving 8 single-labeled compartments.

**Conclusions:** This work demonstrates the unique versatility of intravital NAD(P)H-FLIM as a marker-free method to investigate mechanisms of oxidative stress in inflammatory pathologies, underscoring its intriguing potential for biomedicine as well as clinical research. In the future, the design of transgenic mice combining a larger spectrum of fluorescent proteins will reveal the full potential of our method.

**OSTEOPHILIC POLYMER AND MESENCHYMAL STEM CELLS IN BONE REGENERATION**

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**Key Words:** osteoporosis, mesenchymal stem cells, ATRP synthesis, targeted cell delivery

**Introduction:** Mesenchymal stem cells (MSCs) are an attractive stem cell source for transplantation. MSCs can easily differentiate into osteoblasts and have positive effect on the bone regeneration in osteoporotic bone fracture. Age-related alterations shift bone metabolism to induced osteoclastic activity and reduction of osteoblasts that consequently result in progressive bone loss. In this case transplantation of osteoblast precursor cells, mesenchymal stem cells, may be an option.

**Methods:** For the targeted delivery of MSCs to bone we have synthesized a novel osteophilic polymer. The primary active sites of the polymer are bisphosphonate functional groups that target hydroxyapatite molecules (HA) on the bone surface. NHS groups on the other end of the molecule allow polymer to bind to the cell surface components. Coating of MSCs with the polymer allowed the cells to bind specifically to HA component of bone and localize the cellular repair functions to areas of injured bone. Osteoporotic condition in rats was experimentally induced by bilateral ovariectomy and confirmed via measuring bone density and histological assessment. Ulna fracture model was performed in 4 groups (5 animals each) and each group received different solution
(Polymer in PBS, MSCs in PBS, MSCs+Polymer in PBS). Group 1 served as a control. Injections were administrated locally at the site of the fracture every week during 1 month.

**Results:** Previous in vitro studies showed that polymer can be stably attached to cell surface for at least 4 hours and to bone fragments in vitro for at least 3 hours, confirming the bone targeting potential of the polymer. The polymer was not shown to be cytotoxic by cell viability assay (Luminescent Cell Viability Assay) and did not affect further differentiation of MSCs into osteocytes. Micro-CT morphometry analysis revealed significantly improved bone mass indicators up to 34%. Histological assessment showed formation of the young bone tissue from immature cells at fracture zone.

**Conclusion:** Osteophilic polymer was found to be an effective approach to navigate MSCs to the bone tissue and induce fracture regeneration in osteoporotic condition.

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**THE SPECTRUM OF MUTATION IN PAH GENE AMONG KAZAKHS WITH PHENYLKETONURIA**

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**Keywords:** Phenylketonuria, mutation

**Introduction:** Phenylketonuria (PKU) is inborn amino acid error etiologic factor is mutation in phenylalanine hydroxylase gene (PAH gene). It described over 500 mutations in PAH gene. The frequency and spectrum of mutations have ethnic characteristics.

**Methods:** We studied DNA of 34 Kazakh patients with PKU from unrelated families. DNA was isolated with salt standard method. At first we make molecular genetic study of most frequent mutations in PAH gene (R158Q, R252W, R261Q, R408W, P281L, IVS14+5G>T, IVS10-11G>A and IVS12+1G>A) by PCR. If mutations were unidentified, we searched more rare mutations in PAH gene by direct automated sequencing.

**Results:** The informative value of kit for 8 common mutations in PAH gene for Kazakhs was 35.2%. After automatic direct sequencing, we obtained following range of mutations in Kazakhs: R243Q (0.265), R408W (0.147), P281L (0.088), IVS4+5G>T (0.044), IVS10-11G>A (0.029), V230I (0.029), IVS12+1G>A (0.029), A300S, W187X, I65N, R243L, R158Q, IVS2+5G>A, Y387H, IVS10-14C>G, V399=, c.326e>G by 0.015. The frequency of unidentified mutations after automatic direct sequencing decreased from 0.648 to 0.221. Most common mutations in PAH gene by type were missense (60.3%), then splice (11.8%) and nonsense (1.5%). Most mutations in PAH gene were located in E7 region (36.8%), than E12 (14.7%), I10 and I4 (4.4%), E3, E6 and I12 (2.9%), E5, E8 and E11 by 1.5%.

**Conclusion:** We established a preliminary range of mutations in PAH gene in Kazakhs patients with PKU in Kazakhstan. Using the kit for 8 common mutations in PAH gene for Kazakhs is not informative, because these mutations are more common in European populations that depends on with ethnic characteristics of the spectrum of mutations. We analyzed the types and locations of mutations in PAH gene in Kazakhs. Ethnic features must consider for choosing a panel of mutations, for sequencing of the most significant regions of PAH gene and molecular genetic diagnosis of PKU patients and their families, including direct and indirect prenatal diagnosis of PKU.
THE STUDY OF THE THERAPEUTIC EFFECT OF GROWTH FACTORS AND SYNOVIAL-DERIVED MESENCHYMAL STEM CELLS INCAPSULATED IN HEPARIN-CONJUGATED FIBRIN HYDROGEL ON OSTEOCHONDRAL DEFECTS IN RABBITS

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Key words: Mesenchymal stem cells, growth factors, synovium, osteochondral defect, heparin-conjugated fibrin hydrogel

Introduction. Restoring of knee and hip joints osteochondral defects are still unsolved problem in traumatology and orthopedics. Because of the limited regeneration ability of cartilage and bone tissues after trauma or disease it leads to progressive loss of joint mobility or total loss ability to work, which in some cases even leads to disability.

Methods of stimulating the subchondral bone such as arthroplasty are used to create controlled microdamages in bone. However fibrous cartilage emerged after this does not reproduce the structural organization and functions of native hyaline cartilage.

The purpose of present study was to investigate the effect of synovial mesenchymal stem cells (MSCs), chondro- and osteoinductive growth factors (TGF-β1, BMP-4) and heparin-conjugated fibrin (HCF) hydrogel on regeneration of osteochondral defects in rabbits.

Methods. MSCs were isolated from synovium of Flemish giant rabbits. MSCs were characterized by CFU-assay, multi lineage differentiation and immunocytochemistry assays. HCF hydrogel was prepared by activating heparin and conjugating the activated heparin with fibrinogen to prepare heparin-conjugated fibrinogen. Osteochondral defects (4 mm in diameter) were performed under general calypsal anesthesia (5 mg/kg) using a kit for mosaic chondroplasty. HCF hydrogels containing MSCs and/or growth factors were examined in 7 combinations. Regeneration of osteochondral defects in control and experimental groups were analyzed macroscopically and histologically 90 days after HCF hydrogels implantation.

Results. In vivo studies revealed that application of HCF hydrogel with MSCs to the osteochondral defect formed fibrous cartilage tissue. Implantation of HCF hydrogel with MSCs and/or one of the growth factors (TGF-β1 or BMP-4) improved regeneration, however complete repair of cartilage layer and subchondral bone tissue was not observed after 90 days. Combined administration of synovial MSCs, BMP-4 and TGF-β1 encapsulated in HCF hydrogel completely restored osteochondral defect with hyaline-like cartilage and the subchondral bone tissue forming.

Conclusion. Thus, our study showed that combined application of synovium-derived MSCs, TGF-β1 and BMP-4 encapsulated in HCF hydrogel significantly promote regeneration of osteochondral defects in rabbits and will be a promising tissue engineering technique for cartilage and bone regeneration.

INFLUENCE OF DIFFERENT VITRIFICATION SOLUTIONS ON THE SURVIVAL OF SHEEP OVARIAN TISSUE

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Key words: ovarian tissue, vitrification, fetal calf serum (FCS)

Introduction: Over the past decades, advances in cryopreservation techniques and protocols for ovarian tissue is rapidly becoming a more widely offered technique by many medical centers and veterinary medicine around the world. Several studies of ovarian tissue cryopreservation of livestock animals have reported the feasibility of applying both slow freezing and vitrification methods. Vitrification is a fairly recent alternative method of cryopreservation and, compared slow freezing, is quicker and cheaper.

Methods: Ovarian tissue from 8 endangered Chuyi breed were transported to the laboratory at 36°C, dissected into smaller pieces (2.0x1.2x1 mm) in the L-15 with 5% FCS. The pieces were equilibrated sequentially (5%, 10% and 20% 10 min each) in six vitrification solution (VS): VS1: 20% DMSO + 20% EG + 0,5 М Sucrose; VS2: 20% DMSO + 20% PROH + 0,5 М Sucrose; VS3: 20% EG + 20% PROH + 0,5 М Sucrose; VS4: 20% DMSO + 20% EG + 0,5 М Sucrose + 10% FCS; VS5: 20% DMSO + 20% PROH + 0,5 М Sucrose + 10% FCS; VS6: 20% EG + 20% PROH + 0,5 М Sucrose + 10% FCS, then were vitrified by using the super-cooling ultra-rapid vitrification (SCURV) method in the Vit-Master™ (MTG, Germany). After thawing the pieces were equilibrated sequentially in the solution 0,75 М Sucrose + 10% FCS+ L-15 (10 min, 37°C) than L-15 + 10% FCS (15 min, twice), and the media for in vitro culture TCM-Hepes supplemented 10% ESS, 100 μg/mL penicillin-streptomycin, 50 μg/mL gentamicin and 2 mM L-Glutamine, 5 μg/mL FSH, 5 μg/mL LH.

Results: The viability assay was performed by light microscopy after hematoxylin and eosin staining of tissue sections after 7 days in vitro culture. The highest percentage of viable follicles was observed in the groups VS4 and VS5. The normal primordial, primary and secondary follicles in these groups were 58±3.3, 37±1.9, 29±1.6 and 52±3.1, 30±2.2, 25±1.4 respectively, but was significantly different from fresh control (98.2±1.1) (P < 0.05).

Conclusion: Using a solution containing VS4 and VS5 were the most efficient for vitrifying sheep ovarian tissue.

INVESTIGATION OF THE EFFECT OF PRP AS A NATURAL SUPPLEMENT ON DIFFERENTIATION OF PSCS INTO MSCS

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Key words: Platelet-rich-plasma, differentiation, pluripotent-derived mesenchymal stem cells.

Introduction. Platelet-rich-plasma (PRP) of peripheral blood contains valuable natural growth factors, such as: PDGF, TGF, PDAF, VEGF, EGF and presents a suitable alternative to xenogeneic supplements for ex vivo propagation of mesenchymal stem cells (MSCs). Currently, for differentiation of MSCs from pluripotent stem cells (PSC) a fetal bovine serum (FBS) as a cell culture supplement is commonly used with FGF, PDGF, EGF. Replacement of the FBS with PRP to support the cell growth may reduce risks of transfer xenogeneic infection. Hence, differentiation using PRP presents a promising alternative for generation of pluripotent-derived MSCs (PDMSCs). In this regard, the aim was to study the effect of PRP lysate as the natural supplement on differentiation of PSCs into MSCs.

Methods. Karyotypically normal and homogeneous PSCs were maintained in xeno-free and feeder-independent conditions. Pluripotent characteristics of PSCs were assessed with alkaline
phosphatase staining, immunofluorescence and RT-PCR analysis. Isolation of PRP from healthy donor was performed using PRP kit (Neogenesis, Korea). PRP lysate preparation was conducted using freeze-thawing cycles and ultracentrifugation. For MSCs differentiation, PSCs were cultured in E8 xeno-free medium (Gibco, USA) supplemented with PRP lysate for period of 11 days. For the control, the same cells were cultured in complete E8 xeno-free medium. After differentiation, the obtained PD-MSCs were characterized using morphological and immunofluorescence analysis.

Results. Our results demonstrated that PRP lysate is able to induce the differentiation of PSCs to MSCs. The first morphological changes of PSCs were appeared on the 8-th day. In these cells the lack of expression of the transcription factor Oct-4 was identified on the 11-th day. The data of immunofluorescence analysis showed the expression of MSC markers, including membrane glycoprotein - CD105, which was detected on the 11-th day of differentiation. Moreover, it was revealed that generated PD-MSCs had spindle-shape cell morphology, which is characteristic of the normal MSCs, and high proliferation potential.

Conclusion. Our preliminary data shows that the use of PRP lysate as the natural supplement of important growth factors have significant potential for reproducible, cost-effective generation of biocompatible and immunomodulatory PD-MSCs for clinical cell therapy.

RECOMBINANT ADHESIVE PROTEIN WITH PROSPECTS FOR USE AS STICKY MATRIX IN TISSUE ENGINEERING

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Key words: adhesive protein, biocompatible glue, tissue engineering.

Introduction: Proteins which provide adhesive (sticky) properties and biocompatibility are of high demand for the use as medical glues and as matrixes for the in vitro modeling of tissues. Highly impressive adhesive proteins are the “mussel foot proteins” (MFPs) which reside in the mussels’ byssus. The MFPs are sticky because of the presence of large mass fraction of an unusual amino acid 3,4-dihydroxyphenylalanine (DOPA). Recombinant mussel adhesive protein (Fp-131) was produced in a system which provides conversion of tyrosine residues to DOPA residues.

Methods: Gene encoding the protein Fp-131 was assembled from synthetic oligonucleotides. Synthetic gene was cloned into the pET28/32 plasmid for bacterial expression and co-expressed with a recombinant tyrosinase. Metal affinity chromatography was used to purify the Fp-131. Presence of the DOPA was revealed in a reaction with the nitroblue tetrazolium (NBT-test). To test the absence of cellular toxicity the Fp-131 was used to cover surfaces which were manufactured to suppress a monolayer adhesion (suspension culture treated Greiner flasks). The Fp-131-treated surfaces were tested to support proliferation of the adhesion-depended cell lines (BHK-21, CHO, HEK293).

Results: The protein Fp-131 has on both ends a repeating 10 amino-acids-long motif from the MFP-1 and the central part of the Fp-131 corresponds to the MFP-3. The expression product also has a 6His-tag. To provide co-translational conversion of the tyrosine residues to DOPA residues we developed a double-transformed expression strain in which the Fp-131 and a recombinant tyrosinase from bacterium Verrucomicrobium spinosum are simultaneously produced. The Fp-131 was purified and shown to have DOPA moieties in the NBT-test. Adhesion strength of the Fp-131 was 2.5 MPa which is a significant increase compared to the strengths of the common surgical fibrin blues. The Fp-131 covers surfaces of culture vessels and provide adhesive matrix in which various cell types readily proliferate.
Conclusion: Recombinant adhesive proteins have prospects for use as matrixes for tissue and organ engineering.

EVALUATION OF POLYMORPHISM OF MTHFR AND F5 GENES IN PATIENTS WITH IMPLANTED LEFT VENTRICULAR ASSIST DEVICES (LVAD)

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Key words: Chronic heart failure, implanted left ventricular assist devices (LVAD), polymorphism, MTHFR, F5

Chronic heart failure (CHF) is a global phenomenon, and the overall incidence and prevalence of the condition are steadily increasing. Medical therapies have proven efficacious, but only a small number of pharmacological options are in development. The main strategic direction in the effective treatment of severe forms of CHF to date is surgical treatment, implantation of left ventricular assist devices (LVAD) and heart transplantation. The field of mechanical circulatory support has seen immense growth since the early 2000s, and LVADs have transitioned over the past decade from large, pulsatile devices to smaller, more-compact, continuous-flow devices. Carrying out constant antiaggregant and anticoagulant therapy is associated with a risk of bleeding and thrombosis in the post-operative period. It is necessary to conduct complex genetic, pharmacogenetic and functional studies, including the use of modern molecular technologies to predict the clinical course and outcomes of this category of patients.

Aim of study is to study the polymorphisms of the MTHFR and F5 genes in patients with implanted LVADs for the further prediction of thrombosis development.

Material and methods. The study included patients with CHF who were implanted with LVAD on the basis of the National Scientific Cardiosurgical Center (n = 52), Astana. The control group consisted of practically healthy persons, without cardiovascular pathology, comparable in sex, age (n = 95). Genomic DNA was isolated from the blood using commercial kits. To study polymorphisms rs1801133 rs1801131 of the MTHFR gene and rs6025 gene F5, a real-time polymerase chain reaction method with allelic discrimination with TaqMan probes was used.

Results. The C677T MTHFR C/C, C/T, T/T genotypes occurred at a frequency of 44.2%, 42.3%, 13.5%, respectively, in patients with LVAD, and 57.9%, 30.5%, 11, 6%, respectively, in the control group. The genotypes A1298C MTHFR were distributed as follows: A/A, A/C, C/C - 53.8%, 38.5%, 7.7%, respectively, in the group of patients with LVAD and 30.5%, 63.1% , 6.3%, respectively, in the control group. Individuals with the 677TT genotype had a 1.3 fold higher risk of developing thrombosis (OR = 1.71, 95% CI = 1.21-2.43, p <0.01 codominant model), whereas individuals with the 677CT or TT genotype had a 1.2 fold increased risk (OR = 1.55, 95 % CI = 1.11-2.16, p <0.01). The allele frequency of T MTHFRC677T was 25.2% in patients with LVAD and 30.2% in the control group. Individuals with genotypes of 1298AC + CC had a 1.2 fold decrease in the risk of thrombosis (OR = 0.68, 95% CI = 0.49-0.95, p <0.05), which may indicate a protective role of this polymorphism. The allele frequency with MTHFR A1298C was 33.7% in the group of patients and 27.3% in the control group. The distribution of the r56025 genotypes of the F5 gene did not reveal mutant variants among the examined groups, the wild type of CC was found in 98.1% of the study group and 99.5% in the control group.
CURRENT NUMERICAL TECHNIQUES FOR PREDICTION OF BLOOD HEMOLYSIS

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Key words: Blood Stream, Computational Fluid Dynamics, Hemolysis, Granular Kinetic Theory.

Introduction: Cardiovascular Diseases, the common name for various Heart Diseases, are responsible for nearly 17.3 million deaths annually and remain the leading global cause of death in the world. It is estimated that this number will grow to more than 23.6 million by 2030, with almost 80% of all cases taking place in low and middle income countries. Surgical treatment of these diseases involves the use of blood-wetted devices. However, blood can be damaged when flowing through these devices due to the lack of biocompatibility of surrounding walls, and most prominently, the excessive exposure of blood cells to shear stress for prolonged periods of time. This extended exposure may lead to a rupture of membrane of red blood cells, resulting in a release of hemoglobin into the blood plasma (hemolysis). Therefore, regions of high shear stress and residence time of blood cells must be considered thoroughly during the design of blood-contacting devices.

Method: In-vitro experiments have proven to be costly, time-intensive and ethically controversial. On the other hand, simulating blood behavior using Computational Fluid Dynamics (CFD) is considered to be an inexpensive and promising tool to predict blood damage in complex flows. Nevertheless, current state-of-the-art CFD models of blood flow to help predicting hemolysis are still far from being fully reliable for design purposes. Previous work have demonstrated that prediction of hemolysis can be improved when using a multiphase model of the blood instead of assuming the blood as a homogeneous mixture.

Results: The attempt of this study is to develop and validate a numerical model based on Granular Kinetic Theory (GKT) for solid phases that provides an improved prediction of blood cells segregation within the flow in a microtube. Simulations were based on finite volume method using Eulerian-Eulerian modeling for treatment of three-phase (liquid-red blood cells and platelets) flow including the GKT to deal with viscous properties of the solid phases.

Conclusion: Preliminary results show that the improved segregated model leads to a better prediction of spatial distribution of blood cells. Simulations were performed using ANSYS FLUENT platform.

FETAL GENOME INCREASES THE RISK OF PRE-ECLAMPSIA IN PREGNANCY, RESULTS OF THE INTERPREGGEN STUDY OF EC 7FP “GENETIC STUDY OF PRE-ECLAMPSIA IN CENTRAL ASIAN AND EUROPEAN POPULATIONS”

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Keywords: GWAS study, pre-eclampsia, fetal genome, InterPregGen, deCODE, GOPEC, ALSPAC.
**Introduction:** Pre-eclampsia (PE) affects up to 5-10% of pregnancies and has serious complications: fits, stroke, liver and blood problems and can leads to the death of mother and baby. The problems in identifying genetic aspects of PE are the limited statistical power due to the small study size and ethnic heterogeneity. To solve this problem, InterPregGen study was established, which involved teams from the UK, Iceland, Finland, Norway, Kazakhstan and Uzbekistan. The aim of study was to investigate the genetic basis of PE in European and Central Asian populations.

**Methods:** GWAS meta-analysis tested 7,476,169 sequence variants in 2,658 offspring of preeclamptic pregnancies and 308,292 controls of European descent from Iceland (deCODE cohort) and the UK (GOPEC and ALSPAC cohorts). DNA samples were analysed by Illumina HumanOmni 2.5-8 v1.1 BeadChips (2,400,000 snps) at the Sanger Institute (UK) and deCODE Genetics (Iceland). We carried out QC using PLINK. Cases and controls were imputed together with IMPUTE2 (impute_v2.3.0) and SHAPEIT23 using the pre-phasing workflow against the 1000 Genomes Phase 1 reference panel.

**Results:** Our results of the European descent from Iceland deCODE and the UK GOPEC and ALSPAC cohorts were published in Nature Genetics, 49, 1255–1260, (2017). The first genome-wide significant susceptibility locus (rs4769613; P = 5.4x10^-11) was discovered in 4380 cases and 310,238 controls. The locus is near the gene encoding Fms-like tyrosine kinase 1 (FLT1), providing biological support since an isoform (sFlt-1) of placental origin is implicated in the pathology of preeclampsia. The strongest association is in pregnancies where preeclampsia developed in the late gestation and offspring birth weights exceeded the 10th centile. An additional nearby variant, rs12050029, associates with preeclampsia independent of rs4769613. DNA from a further 4,220 babies from pree-clamptic pregnancies in Kazakhstan and Uzbekistan is currently being analysed in an extended study to reveal the same changes near sFlt-1.

**Conclusion:** InterPregGen study discovered sequence variants in the fetal genome that increases the risk of PE. The new insights from this study could form the basis for more effective prevention and treatment of PE and improve the outcome of a pregnancy for a mother and a child.

Research leading to these results was conducted as part of the InterPregGen study, which received funding from the European Union Seventh Framework Programme under grant agreement no. 282540.

**THE ROLE OF THE FRAGILE X SYNDROME IN THE DEVELOPMENT OF PREMATURE OVARIAN FAILURE AND IVF INEFFICIENCY**

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**Key words:** Fragile X syndrome, FXS, POF

**Introduction:** Fragile X syndrome (FXS) is a rare genetic disease associated with mental retardation and autism or autism spectrum disorder, females with premature ovarian failure (POF), and older males with progressive development of intention tremor and ataxia with or without dementia.

**Methods:** DNA was used by standard isolation of lymphocytes from peripheral blood of 30 women with reproductive disorders. Molecular genetic analysis was performed by PCR method with electrophoresis on the 310 Applied Biosystem by using the TP-PCR Primers test system (AbbottMolecular).
Results: The national composition is represented by Kazakhs - 17 (56.7%), Russians - 6 (2 %) and other nationalities - 7 (23.3%). 11 women (36.7%) have somatic diseases such as chronic pyelonephritis, chronic bronchitis, etc. Analysis of pregnancy outcomes revealed severe reproductive disorders. The average number of pregnancies per 1 surveyed woman is only 0.7 ± 0.09; the average number of births is 0.34±0.04; the average number of spontaneous early miscarriages is 0.36 ± 0.04.

The average number of children was 0.33±0.06. 20(66.7%) of women have infertility (13 women have primary infertility and 7 have secondary). 25 programs of embryo transfer were carried out for the surveyed women. 20 programs (80%) of them were ineffective, pregnancy was confirmed only for 4 (20%) cases, which in 100% resulted in spontaneous early miscarriages. Studied women altogether have 10 children (30% of them with undifferentiated forms of mental retardation).

18 of the subjects (60±5.6%) have a normal number of CGG-repeats; premutation in 7 cases (23.3±4.4%); in the gray zone - 5 (16.7±4.2%). Full mutation of the FMR1 gene was not detected.

Conclusion: The high frequency of premutation and the high risk of having children with mental retardation confirm the recommendations of ASOG that it is necessary to carry out molecular genetic test for the first ineffective attempt of IVF and for egg donors.

A REAL-TIME MULTIPLEX PCR ASSAY FOR THE DETECTION OF SALMONELLA ENTERITIDIS

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Key words: salmonellosis, Salmonella, Enteritidis, real-time PCR, multiplex

Introduction: Salmonellosis is an infectious disease caused by various serotypes of Salmonella. Salmonella enterica serotype Enteritidis and Salmonella enterica serotype Typhimurium are implicated in majority of Salmonella infections in Kazakhstan. For epidemiological studies, strain identification is necessary and such investigations have traditionally relied on biochemical and serological methods. Alternative method, such as real-time PCR can be used as an effective and reliable tool for detection of Salmonella. The aim of the study is to develop a real-time multiplex PCR assay for the detection of the S. Enteritidis serotype.

Methods: A total of 75 Salmonella enterica serotype Enteritidis and serotype Typhimurium strains were isolated at the Infectious diseases hospital (Astana, Kazakhstan) during 2016-2017. The isolation of DNA from inactivated bacterial cultures was carried out by phenol-chloroform extraction. The quantitative DNA content was carried out on a spectrophotometer (Nanodrop 1000) and evaluated by electrophoresis in a 1% agarose gel. Sequence-specific TaqMan probes and primers for the invA and sefA genes were designed using FastPCR 6.5 and Beacon Designer 8.0 software. All primer sequences were tested for complementarity using the database http://blast.ncbi.nlm.nih.gov/Blast.cgi. Real-time PCR was performed on a CFX96 (Bio-Rad) instrument. The fluorescence detection was set up after each annealing step and the results were analyzed using CFX Manager 2.1 software (Bio-Rad).

Results: The proposed assay is based on a duplex real-time PCR using competing TaqMan probes that are complementary to the nucleotide sequence of S. Enteritidis. The invA gene target is used for Salmonella detection, while sefA gene target sequence is specific for S. enteritidis. InvA
gene is known to be involved in the cell invasion in *Salmonella* and serves as an internal amplification control, while *sefA* gene encodes the fimbrial antigen SEF14 that is specific for *S. enteritidis*. All 75 *Salmonella* strains were positive for the *invA* target sequence. Fifty-one strains were positive for the *sefA* target sequence of *S. Enteritidis* (100% inclusivity, 95% exclusivity).

**Conclusion:** A duplex real-time PCR assay was developed for the detection of *S. Enteritidis*. The inclusivity and exclusivity were between 100 and 95% analyzing 75 bacterial strains.

**EMBRYO DEVELOPMENT OF HANDMADE CLONED KAZAKH ARGALI (OVIS AMMON COLLUM) EMBRYO USING FROZEN-THAWED FIBROBLAST CELLS**

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**Key words:** argali, nuclear transfer, embryo

**Introduction:** Nuclear transfer has the potential to preserve genes from critically endangered wildlife species where few or no oocytes are available from the endangered species, and where cryopreserved cell line have been conserved in cryobanks. The purpose of this study was to investigate the developmental ability of embryos reconstructed with transfer of cryopreserved somatic cell from the Kazakh argali to enucleated domestic sheep oocytes.

**Methods:** Frozen–thawed fibroblasts were diluted with DMEM at a concentration of 2 × 10⁶ cells mL⁻¹. Fibroblasts were incubated at 5% CO₂, 37°C in DMEM + 20% (v/v) fetal bovine serum (FBS). A fibroblast monolaye after 21 to 22 days of incubation were incubated for 7 to 10 min in presence of Dulbecco’s phosphate buffered saline + 0.25% trypsin, then were washed with DMEM by centrifugation at 300 g for 10 min. The cumulus cells of aspirated oocytes from ovaries were removed by pipetting in 1 mg mL⁻¹ hyaluronidase in HEPES-buffered TCM-199; zonae pellucidae were removed by incubation in 2 mg mL⁻¹ pronase in HEPES-buffered TCM-199+2% cattle serum (T2) for 1 min. The cumulus cells of aspirated oocytes from ovaries were removed by pipetting in 1 mg mL⁻¹ hyaluronidase in HEPES-buffered TCM-199; zonae pellucidae were removed by incubation in 2 mg mL⁻¹ pronase in HEPES-buffered TCM-199+2% cattle serum (T2) for 1 min. Bisection was performed by hand under a stereomicroscope using a microblade in 5 μg mL⁻¹ cytochalasin B in TCM-199+20% cattle serum (T20). Fusions were performed 24-28 h after start of maturation with a single DC pulse of 100 V, each pulse for 9 μs. One cytoplast was attached to one fibroblast in 500 μg mL⁻¹ phytohemagglutinin dissolved in T2. In the fusion chamber, covered with fusion medium (0.3 M mannitol, 0.1 mM MgSO₄, 0.05 mM CaCl₂, and 0.01% PVA). Successfully fused embryos were activated 1 h after the end of fusion by incubation in 2 μM calciumionophore (Sigma) in T20 for 5 min followed by -h incubation in microdrops of culture medium containing 2 mM 6-dimethylaminopurine. After successful reconstruction, 79 nuclear transferred and activated embryos were cultured with WOW's in trigas (5% O₂, 5% CO₂, 90% N₂) in Submarine incubation system for 7 days.

**Results:** All except for 15 embryos cleaved; 35 (44.3%) developed to compacted morula, and 15 (18.9%) of them to the blastocyst stage.

**Conclusion:** Argali embryos developed from reconstruction using their frozen-thawed fibroblasts combined with domestic sheep's cytoplasts, however, in vitro developmental ability to the blastocyst stage was limited.
ANTIOXIDANT AND ANTI-INFLAMMATORY PROPERTIES OF PLANT EXTRACT FROM LIMONIUM GMELINII

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Keywords: blood–brain barrier, Endothelial cells, Astrocytes, ROS, P-selectin, Limonium Gmelinii

Introduction: Disruption of the blood–brain barrier (BBB) plays key role in the development of neurological dysfunction in acute and chronic cerebral ischemia. Numerous studies have demonstrated that ischemia and reperfusion initiate oxidative stress and inflammatory cascade in the BBB that contribute to further damage of neurons. Thus, agents targeting cell adhesion molecules expression, ROS production and activation of pro inflammatory cytokines may have therapeutic value. It has been reported previously, that reach with polyphenols extract of a plant Limonia Gmelinii exerts a wide range of therapeutic action. Here, we studied its antioxidant and anti-inflammatory potential in relation to the cells forming BBB.

Methods: Human primary astrocytes and mouse bEnd3 line of CECs (ATCC) were applied in this research as following: the cells were pretreated with extract of L. gmelinii followed by TNF-α or H2O2 exposure. We quantified ROS generation, NADPH activation, P-selectin expression and activity of ERK1/2 in the cells using quantitative fluorescence, confocal microscopy and western blotting.

Results: We have demonstrated that in astrocytes TNF-α induces overproduction of ROS, activation of NADPH oxidase and ERK1/2 phosphorylation. In CECs, exposure by TNF-α or H2O2 exerts similar effects; in addition TNF-α triggers accumulation of P-selectin on the surface of the CECs. In turn, pretreatment with extract of L. gmelinii suppresses induced by TNF-α and H2O2 oxidative stress and proinflammatory responses in both cell types.

Conclusion: Our results demonstrate that extract from Limonium gmelinii possesses antioxidant, astro- and vasculoprotective properties and can neutralize proinflammatory effect of TNF-α.

CHALLENGES IN MANAGEMENT OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Keywords: personalized medicine, amyotrophic lateral sclerosis, multidisciplinary approach

Introduction: Amyotrophic lateral sclerosis (ALS) represents one of the most unfavorable progressive forms of motor system neurodegeneration, with the involvement of upper and lower motor neurons. Dysphagia and dysarthria together with the atrophy and fasciculations are common
features in patients with ALS resulting from the degeneration of lower motor neurons in the brain stem and spinal cord. These symptoms have a significant impact on quality of life and overall life expectancy of the affected individuals. Most recent evidence highlights the survival of patients up to a decade, whereas the life expectancy given the presence of progressive respiratory failure ranges between 2 to 4 years after disease onset. Given the significant functional, behavioral and motor decline, it appears of vital importance to manage these patients by adapting a multidisciplinary holistic approach in order to address the underlying needs of the affected individuals and their families. There is strong evidence, which support the initiation of palliative care services at the early stages of the disease.

**Methods:** This report is based on the case of a 52-year-old female patient with ALS who has been treated as an inpatient at the National Scientific Center for Oncology and Transplantology, Astana, Kazakhstan. We are focusing on the challenges that arise whilst managing a patient with progressive motor neuron disease and supporting our recommendations with the recent evidence obtained from a search of the PUBMED, Cochrane database, American Academy of Neurology and peer-reviewed journal articles.

**Results:** The results of this study, which combined systematic literature review and case-based discussion, have shown to clearly support the idea to implement multidisciplinary approach for successful management of patients with ALS. Multidisciplinary team would ideally include neurologists, respiratory nurse specialists, psychologist, and district general nurses, speech therapists, GPs, social care workers, palliative care consultants and pharmacists. These specialists will help with symptom control and provide psychological and social support of the affected individuals, thus helping to achieve the goal of personalized, patient-centered care.

**Conclusion:** Based on the literature data and the results of our observation, there is no doubt that a multidisciplinary approach is required to manage patients with ALS. It is necessary to estimate the number of patients suffering from ALS in Kazakhstan, their quality of life and nutritional needs and to ensure their access to comprehensive palliative care services.

**IDENTIFYING A 229-GENE SIGNATURE TO DISCRIMINATE ANAPLASTIC ASTROCYTOMA FROM GliOBLASTOMA USING META-ANALYSIS OF MULTIPLE MICROARRAY DATASETS**

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**Keywords:** Glioblastoma Multiforme; Anaplastic Astrocytoma; Predictive Meta-analysis; Microarrays

**Introduction:** Gliomas are the most common type of primary malignant brain tumors and are graded into I to IV according to their increasing malignancy. Classification of Grade III (anaplastic astrocytoma) and IV (glioblastoma multiforme) is important not only because of the difference in the survival time of patients but also because of the significant guidance provided for therapeutic decisions.

**Results:** In this study, we conducted a predictive meta-analysis of multiple Affymetrix U133 microarrays to identify a set of signature genes that can distinguish glioblastoma multiforme from anaplastic astrocytoma. Our classifier, which was based on the nearest shrunken centroids,
contained 229 genes and achieved an accuracy, sensitivity, specificity, and J index of 75%, 78.5%, 74.1%, and 52.6%, respectively, using a dataset cross-validation procedure. Based on the identified gene signature, we found 13 pathways, most of which have been already linked in a number of sporadic studies to high-grade gliomas.

**Conclusion:** The results of this study can be potentially used: (1) to shed light on the molecular mechanisms underlying the formation of malignant gliomas; and (2) to match malignant glioma individuals with treatment strategies based on their gene expression profiles.

**PERSONALIZATION OF IVF TREATMENT USING AMH**

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**Keywords:** IVF; anti-Mullerian hormone; individualization; ovarian reserve; Age; live birth rates

**Introduction:** The main objective of individualization of treatment in IVF is to offer every single woman the best treatment tailored to her own unique characteristics, thus maximizing the chances of pregnancy and eliminating the iatrogenic and avoidable risks resulting from ovarian stimulation. Personalization of treatment in IVF should be based on the prediction of ovarian response for every individual. The starting point is to identify if a woman is likely to have a normal, poor or a hyper response and choose the ideal treatment protocol tailored to this prediction. Although anti-Mullerian hormone (AMH) level is known to predict ovarian reserve, there is conflicting evidence regarding the association between AMH and clinical pregnancy or live birth (LB).

Our aim is to establish if there is any association between AMH and LB considering the effects of age and other relevant confounding factors in predicting LB.

**Methods:** 400 in-vitro fertilization (IVF) cycles were retrospectively analyzed in IVF department of National research Center of Maternity & Child Care. From the database, data regarding the women's age, AMH level, IVF/intracytoplasmic sperm injection, the factors of infertility, protocols, median AMH level and live birth rates (LBRs) were compared between the groups with and without LB in four age groups. The influences of age and AMH in predicting LB were analyzed.

**Results:** There were no significant differences in any of the confounding factors analyzed between the groups with and without LB. In the higher two age groups, median AMH levels in the group with LB were higher than that in the group without LB. The odds of having a LB was significantly higher in the younger three age groups, and when AMH level was >20 pmol/l. AMH was not found to be the IVF outcome defining factor in younger women, but was relevant in those above 35 years. Older women with significantly higher AMH level had significantly higher LBR than their peers with low AMH level.

**Conclusion:** Personalized IVF offers several benefits; it enables clinicians to give women more accurate information on their prognosis thus facilitating counselling. AMH does have a role in counselling women when predicting live birth from IVF, although age of women plays a major role in determining success from IVF treatment.
ENGINEERING HUMAN MICROBIOTA FOR DISEASE PREVENTION AND THERAPY

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Key words: Commensal bacteria, vaccine, therapy, microbicide, HIV, CCL5, CCR5

Introduction: Bacteria living with us in commensalism at mucosal districts constitute a whole living kingdom, namely the human microbiota. Commensal bacteria have several beneficial effects and several strains have been identified to possess direct proactive interaction with the human immune system and metabolism, and more complex effects on behavior and the central nervous system. The overall protective effect exerted by the microbiota could therefore be potentiated by genetically engineering specific bacterial species for the delivery of prophylactic or therapeutic recombinant proteins. Among the diverse applications of this strategy, the engineering of anti-HIV live microbicides based on the genetic modification of lactic acid bacteria to express recombinant HIV protein blockers has been extensively investigated. Reported in detail here is the production of lactobacilli secreting recombinant human CCL5 variants acting as extremely potent HIV entry inhibitors.

Methods: Following rational design of CCL5 mutants, recombinant lactobacilli were generated to secrete CCL5 mutants that, after semi-purification from supernatant, were tested for anti-HIV activity. Successful mutations were integrated in CCL5 via iterative cycles of engineering, semi-purification and activity testing, leading to the production of the most potent HIV inhibitors to date.

Results: The dual use of engineered lactobacilli (as CCL5 mutants screening platform and as lead microbicides) led to the selection and initial development of potent anti-HIV live microbicides based on the expression and secretion of CCL5 variants with potentiated CCR5 binding affinity. Aside HIV, these CCL5 variants (either as lactobacilli-secreted live therapeutics or as purified proteins) could be used against a wealth of inflammation-related pathologies where the CCL5:CCR5 axis is of major relevance, including cancer, atherosclerosis and inflammatory bowel disease.

Conclusion: The successful generation of potent CCR5 antagonists based on CCL5 engineering via the use of recombinant commensal bacteria constitutes a paradigmatic example of how microbiota engineering could enhance human health protection.

STUDY OF THE TUMORIGENICITY OF HUMAN ADIPOSE MÉSENCHYMAL STEM CELLS

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Key words: Adipose mesenchymal stem cells, tumorigenicity

Introduction: Mesenchymal stem cells (MSCs) derived from adipose tissue, bone marrow, cord blood, and other tissues, have recently attracted much attention as potential therapeutic agents in various diseases due to their differentiation quality. The adipose tissue is more accessible and safe for the donor to isolate mesenchymal stem cells (MSC). In vitro, adipose mesenchymal stem
cells (AMSC) can be differentiated into cells such as adipocytes, chondrocytes, and osteocytes. All of this ability, with their strong immunosuppressive effects, makes AMSCs attractive candidates for cell therapy. The objective of this study was to assess the capacity of AMSC to contribute tumor pathogenesis by supporting tumor microenvironments and increasing tumor growth in experimental mice models in vivo.

Methods: The culture of MSC was derived from the adipose tissue provided by the Research Institute of Traumatology and Orthopedics (Astana, Kazakhstan). Cell cultivation took place at 37°C with a content of 5% CO2 in a complete AlphaMEM medium. Nude mice (Swiss Nu/Nu strain), provided by the Department of Experimental Radiation Oncology Breeding Core, The University of Texas MD Anderson Cancer Center. An experiment group of four weeks Nude mice were injected by 3 mln AMSC the control group was injected with 3 mln tumorigenic myeloma cells of the MDA-MB-231 in 200 µl phosphate saline buffer subcutaneously.

Results: Surveillance was carried out every 5-7 days. The control group had large tumors with metastases and according to the institutional protocol, the group was exposed to euthanasia with inhalation of carbon dioxide after 26 days. Tumors were not observed in the lymph nodes and parenchymatous bodies in the experimental group mice. According to the evaluation criteria, tumorigenicity in the experimental group of tumor development was not found, whereas in the control group the development of tumors was 100%. The latent period of tumor formation in the control group was 10 days.

Conclusion: In the course of the experiment, it was found that mesenchymal stem cells derived from human adipose tissue have not tumorigenic potential and can be considered in research for regenerative medicine.

THE ROLE OF BIOSENSORS FOR TUBERCULOSIS DETECTION

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Key words: Tuberculosis; Multi-Drug Resistant Tuberculosis (MDR-TB); Biosensor

Introduction: One of the main reasons of death from contagious diseases in the world is Tuberculosis (TB). Its main cause is pathogenic bacterium which is named the Mycobacterium Tuberculosis. The efficient way to control TB is to rapidly diagnosis and early treatment. Eastern European and central Asian countries continue to have the highest levels of multi-drug resistant tuberculosis (MDR-TB). Among new cases, the proportions with MDR-TB were highest in Belarus, Estonia, Kazakhstan, Kyrgyzstan, the Republic of Moldova, the Russian Federation. The objective of this review is to evaluate currently available biosensing techniques that are either already in use or under development for detection of TB. A comparison will also be made with conventional multistep techniques.

Methods: Biosensors are devices that transform biochemical reactions of isolated enzymes, nucleic acids, organelles, tissues with specific chemical compounds into an optical, thermal or electrical signal, which can be more easily determined and quantified. The primary
benefits of biosensors over regular diagnostic techniques can be stated as follows: (1) Technical advantage: single step detection. (2) Ease of use: many of the designed biosensors are worked out with user-friendly interfaces. (3) Quick response: typically a few minutes for most biosensors enabling rapid and better control over the measurement.

**Results:** a) Electrochemical and electrical biosensors are among the most popular biosensors that are used today in detection of not only TB but also many other diseases. The mechanism of detection relies on specific changes in electrical signals at a surface-functionalized electrode by either chemical reactions or physical interactions. It has main two types of biosensors. 1) Electronic nose-based biosensors: they are designed to recognize changeable substances produced by TB in liquid medium; 2) Nanowire-based biosensors: they are most conspicuously depicted by silicon nanowires that run as field effect transistors.

b) The second type of biosensors is Optical biosensors. 1) Fibre-optic biosensors: optical fiber-derived devices which use optical field to measure biological species such as cells, proteins, and DNA. 2) Surface plasmon resonance-based biosensors Breathalyzer biosensors: have been developed to diagnose pulmonary TB in patients. Typically, in these types of sensors the patients are asked to cough in a masked structure containing a collection tube after administration of a nebulized dose of saline.

**Conclusion:** TB remains one of the major unresolved global health problems, especially in the developing parts of the world. Most of the biosensors discussed in the present review are still at the developmental stage and lack clinical validation with real TB samples from patients. All sensor methods have their own merits and potential problems with respect to sample preparation, requirement of skilled personnel to handle the sample, sensitivity or cost.

**THALIDOMIDE AFFECTS MACROPHAGE ACTIVATION AND LEISHMANIA MAJOR SURVIVAL**

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**Key words:** Leishmaniasis, thalidomide, macrophage activation, cytokines

**Introduction:** Leishmania parasites are the causative agents of leishmaniasis, group of vector-borne parasitic diseases endemic worldwide. Once inoculated into the organism, Leishmania parasites are rapidly uptaken by macrophages. Macrophages are primary resident cells for their proliferation: they can either phagocyte or allow parasite growth. That is why proper activation of macrophages is crucial in disease fate. Macrophage activation is divided into two classes: classical (M1) and alternative (M2) that induce parasite killing and its survival, respectively. Classical activation is mediated by pro-inflammatory cytokines which cause macrophages to produce toxic molecules to kill intracellular parasites. In contrast, alternative activation is induced by anti-inflammatory cytokines that lead to parasite survival in infected cells. Thalidomide is reported to stimulate immune response and enhance cellular phagocytic activity by selectively inhibiting M2 pathway. Here, thalidomide was examined as potential drug to have suppressive effect on intracellular replication of L.major within infected macrophages in-vitro.

**Methods:** To observe macrophage activation, Raw264.7 cells were cultured. After 24hr incubation of cells in 37°C, 5% CO₂ incubator, thalidomide treatment of different concentration was done. Supernatant and pellet were collected for ELISA, RT-PCR, qPCR and WB tests. To observe pathogen survival, Raw 264.7 cells were cultured in chamber slides and infected with L. major at
1:10 ratio. After 24hr incubation, thalidomide treatment was done. Giemsa staining was applied to slides and intracellular amastigote forms of *L. major* were counted.

**Results:** In this study thalidomide’s effect on proper macrophage activation and parasite survival was analyzed. It was found that thalidomide can a) up-regulate pro-inflammatory M1 macrophages (IFN-γ, TNF-α, iNOS); b) down-regulate anti-inflammatory M2 macrophages (IL-10 and Arg-1); c) decrease intracellular amastigotes of *L. major*. Thalidomide shows inhibitory effect on alternative activation of macrophages and induces M1 polarization of macrophages, thus making them resistant to *L. major* infection.

**Conclusion:** Results highlight thalidomide’s potential contribution to a new drug development towards leishmaniasis in the future.

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**EXTREMOPHILES FROM UNIQUE ECOSYSTEMS OF KAZAKHSTAN AS POTENTIAL PRODUCERS OF NOVEL ANTIBIOTICS**

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**Introduction:** Antimicrobial resistant pathogens that cause healthcare-associated infections (HAI) pose serious challenges to healthcare Institutions. ESKAPE bacterial pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) are drug resistant HAI bacterial pathogens that pose the most threat globally and in Kazakhstan. Thus, there is an urgent need for discovery of new and efficacious drugs. Actinomycetes bacterial strains are the main producers of currently used antibiotics, including streptomycin, tetracycline, lincomycin, and others. Microorganisms that exist in extreme environment such as high salt or alkalinity known as extremophiles include Actinomycetes species. The goal of this study is discover novel antibiotics from Kazakhstan against ESKAPE pathogens from actinomycetes grown in extreme conditions by selecting active extracts for antibacterial activity. This will be followed by further analysis for chemical characterization and compound identification.

**Methods:** Soil from extreme environments of Kazakhstan was collected and cultured for isolation of pure cultures of Actinomycetes species. Pure strains of Actinomycetes were then cultured in modified Bennett’s broth containing either high salt or high pH to mimic extreme environment in soil. Antimicrobial compound was extracted with butanol and tested for activity against *S. aureus* and *E. coli*. After this screening, disk diffusion assay was performed to assess the inhibitory activity of the extracts against hospital strains of ESKAPE pathogens.

**Results:** A total number of 5936 strains were isolated from variants of modified Bennett’s agar; from these, 2019 strains of extremophile actinomycetes were further isolated into pure culture (756 strains from Northern Kazakhstan and 1263 strains from Southern Kazakhstan). Of these, 415 actinomycetes strains were chosen and analyzed based on their ability to show antibacterial inhibitory activities. Zones of inhibition for *A. baumanii*, *S. aureus*, and *E. faecium* were detected when these organisms were grown in the presence of some of these extracts.

**Conclusion:** From screening a few hundred extremophile strains, we identified some interesting candidate extracts with putative antibacterial activities against several Kazakhstan hospital strains of ESKAPE pathogens. Initial chemical characterization of the extracts was...
performed using HPLC and showed promising results. These extracts are being further investigated for their specific therapeutic potential as novel antimicrobial.

THE EFFECT OF MEDICINAL PLANTS ON PROLIFERATION OF HUMAN SW620 COLORECTAL CANCER CELLS

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Keywords: Colorectal cancer, medicinal plants, SW620

Introduction: Colorectal cancer is currently one of the most common malignancies and the third leading cause of cancer-related deaths worldwide. Mortality is attributed to invasion and metastasis, with only 12.5% five-year survival rate for patients with distant metastasis. Chemotherapy is routinely used for cancer treatment. However, it is accompanied by a number of undesired side effects that can put the patients under further strain. Therefore, research interest is drawing its attention towards alternative treatments with less toxic side effects. Medicinal plants have a wide spectrum of pharmacological properties such as anti-carcinogenic, anti-inflammatory, anti-oxidative, anti-bacterial, etc. Medicinal plants as natural reservoirs of various secondary metabolites possess chemoprotective potential in anticancer therapies. In this study, we investigated the effect of five medicinal plant (Celandine (Chelidonium majus), Fenugreek (Trigonellafoenum-graecum), Sanguisorba officinalis, Chaga mushroom (Inonotus obliquus), Carum carvi) extracts on viability of human metastatic colon cancer cells in comparison with two common chemotherapy drugs, 5-fluorouracil and oxaliplatin.

Methods: Human colon cancer cells from lymph node metastasis (SW620) were cultured in both high-glucose and low-glucose DMEM supplemented with 10% FBS for glucose starvation prior to administration of inhibiting agents, and grown at 37°C under 5% CO2. The cytotoxicity of 0.5% and 1% aqueous plant extracts, 5-fluorouracil (250μg/ml), and oxaliplatin (250μM) was determined by Alamar Blue® cell viability assay.

Results: Among all plant extracts and chemotherapy drugs, SW620 cells were more sensitive to fenugreek seeds at 1% concentration, as demonstrated by 1.3 and 1.2-fold reduction in cell viability compared to the effect of oxaliplatin and 5-fluorouracil, respectively. Fenugreek inhibited cell growth in a dose-dependent manner, with less profound difference in anti-cancer activity at a concentration of 0.5%. The response of cancer cells to Carum carvi and to Chelidonium majus was similar to the response to conventional chemotherapeutic drugs. Water extracts of Sanguisorba officinalis and Inonotus obliquus did not have significant effect on proliferation of cancer cells. Glucose starvation before the experiment revealed increased resistance of SW620 cells to an inhibiting agent.

Conclusion: Our results prove the prospects of using medicinal plants as an alternative to or in combination with chemotherapy, especially in multidrug-resistant cancer types.

AN ANALYTICAL PERSPECTIVE ON CHALLENGES AND FUTURE TRENDS IN GENOMIC DATA ANALYSIS

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Predictive modeling of patient risk of a disease using “big” genomic data have great potential to improve healthcare. Big data can be big either in terms of sample size, number of variables, or both. Although a large sample size introduces various issues in terms of storage and computational needs, another subtle problem is raised once we face a large number of variables, namely, how to learn from a large number of variables (high-dimensional observations) and a relatively small sample size?

Classical statistical learning techniques have been fashioned for situations in which the sample size ($n$) is much larger than the number of variables ($p$). This is in large part due to the classical notion of statistical consistency, which guarantees the performance of a statistical technique in situations where the number of measurements unboundedly increases ($n \to \infty$) for a fixed dimensionality of observation (fixed $p$). In a finite sample operating regime, this implies that in order to expect an acceptable performance from a statistical technique, we need to have many more sample points (subjects) than variables (genes or SNPs) – a scenario that is exactly the opposite to what we currently face in genomics.

Two mathematical–statistical machineries that are potentially capable of constructing techniques for analyzing high-dimensional observations are based on: (1) shrinkage and sparsity assumption; and (2) high-dimensional asymptotics ($n \to \infty, p \to \infty, \frac{p}{n} \to J > 0$). Despite remarkable progress in these areas, many practitioners still utilize classical methods for analyzing high-dimensional datasets. This state of affairs can be attributed to: (1) a lack of knowledge about existing methods developed using these machineries; (2) the ready-to-use computational and statistical software packages that are well developed for classical techniques; and (3) the number of existing methods developed using these machineries is comparably much less than classical large sample techniques. The third issue introduces various research opportunities to develop statistical and signal processing techniques suitable for high-dimensional data analysis. As a simple example to judge the current state of affairs in statistical learning consider the fact that we do not know yet the estimator of the mean vector with minimum quadratic risk for a multivariate Gaussian distribution when the number of variables is as small as three, let alone thousands of variables!
<table>
<thead>
<tr>
<th>A</th>
<th>33, 36, 39, 51, 52, 55, 58, 62, 70, 77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdrakhmanova S.</td>
<td>47</td>
</tr>
<tr>
<td>Abilmazhynova A.</td>
<td>39</td>
</tr>
<tr>
<td>Abilova Zh.</td>
<td>33, 36</td>
</tr>
<tr>
<td>Abuova G.</td>
<td>33, 34</td>
</tr>
<tr>
<td>Abzhanova E.</td>
<td>41, 82</td>
</tr>
<tr>
<td>Abzhaparova B.</td>
<td>51</td>
</tr>
<tr>
<td>Acs A.</td>
<td>71</td>
</tr>
<tr>
<td>Adarichev A.</td>
<td>35</td>
</tr>
<tr>
<td>Adilbayeva A.</td>
<td>35</td>
</tr>
<tr>
<td>Adilgozhina G.</td>
<td>36</td>
</tr>
<tr>
<td>Aimbetova A.</td>
<td>46</td>
</tr>
<tr>
<td>Akhmadeyeva Zh.</td>
<td>85</td>
</tr>
<tr>
<td>Akhmerova D.</td>
<td>52</td>
</tr>
<tr>
<td>Akhmetova A.</td>
<td>36, 58</td>
</tr>
<tr>
<td>Akhmetova A.</td>
<td>57</td>
</tr>
<tr>
<td>Akilzhanov K.</td>
<td>37, 38</td>
</tr>
<tr>
<td>Akilzhanova A.</td>
<td>33, 36, 39, 51, 52, 55, 58, 62</td>
</tr>
<tr>
<td>Akpanova D.</td>
<td>40</td>
</tr>
<tr>
<td>Alaei A.</td>
<td>41</td>
</tr>
<tr>
<td>Alikeyeva E.</td>
<td>41</td>
</tr>
<tr>
<td>Alimbetov D.</td>
<td>41, 63</td>
</tr>
<tr>
<td>Altynbekova G.</td>
<td>61</td>
</tr>
<tr>
<td>Amirbekov A.</td>
<td>68</td>
</tr>
<tr>
<td>Andossova S.</td>
<td>70</td>
</tr>
<tr>
<td>Apsalikov B.</td>
<td>42</td>
</tr>
<tr>
<td>Aringazina A.</td>
<td>41</td>
</tr>
<tr>
<td>Asanova E.</td>
<td>81</td>
</tr>
<tr>
<td>Askarova Sh.</td>
<td>41, 63, 64, 72, 82</td>
</tr>
<tr>
<td>Atavlieva S.</td>
<td>80</td>
</tr>
<tr>
<td>Atkins M.</td>
<td>60</td>
</tr>
<tr>
<td>Aukenov N.</td>
<td>42</td>
</tr>
<tr>
<td>Azizan A.</td>
<td>88</td>
</tr>
<tr>
<td>B</td>
<td>36, 57</td>
</tr>
<tr>
<td>Babenko D.</td>
<td>43</td>
</tr>
<tr>
<td>Baidildinova G.</td>
<td>36, 57</td>
</tr>
<tr>
<td>Baimukasheva D.</td>
<td>47</td>
</tr>
<tr>
<td>Baltabekova A.</td>
<td>43</td>
</tr>
<tr>
<td>Barillot E.</td>
<td>53</td>
</tr>
<tr>
<td>Baymakhanov B.</td>
<td>51</td>
</tr>
<tr>
<td>Begimbetova D.</td>
<td>44</td>
</tr>
<tr>
<td>Bebkayev S.</td>
<td>45</td>
</tr>
<tr>
<td>Bekbossynova M.</td>
<td>33, 36, 70</td>
</tr>
<tr>
<td>Bekenenova A.</td>
<td>48</td>
</tr>
<tr>
<td>Berezin V.</td>
<td>88</td>
</tr>
<tr>
<td>Berezina G.</td>
<td>46, 78, 79</td>
</tr>
<tr>
<td>Berikova E.</td>
<td>41</td>
</tr>
<tr>
<td>Berkinbayev S.</td>
<td>40</td>
</tr>
<tr>
<td>Bersimbaev R.</td>
<td>46</td>
</tr>
<tr>
<td>Bexeitov Y.</td>
<td>35</td>
</tr>
<tr>
<td>Birzhanbekov N.</td>
<td>51</td>
</tr>
<tr>
<td>Bobrova X.</td>
<td>44</td>
</tr>
<tr>
<td>Brook A.</td>
<td>63</td>
</tr>
<tr>
<td>Bulanin D.</td>
<td>50</td>
</tr>
<tr>
<td>Bulgakova O.</td>
<td>46</td>
</tr>
<tr>
<td>Burkibayev Zh.</td>
<td>47</td>
</tr>
<tr>
<td>C</td>
<td>48, 49</td>
</tr>
<tr>
<td>Cainelli F.</td>
<td></td>
</tr>
<tr>
<td>Cantini L.</td>
<td>53</td>
</tr>
<tr>
<td>Czerwinska U.</td>
<td>53</td>
</tr>
<tr>
<td>D</td>
<td>69, 70</td>
</tr>
<tr>
<td>Davis T.</td>
<td>63</td>
</tr>
<tr>
<td>Doskhanov M.</td>
<td>51</td>
</tr>
<tr>
<td>Dukenbayeva B.</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>49</td>
</tr>
<tr>
<td>Eskendirova S.</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>67</td>
</tr>
<tr>
<td>Fabbro E.</td>
<td></td>
</tr>
<tr>
<td>Ferghatova A.</td>
<td>52</td>
</tr>
<tr>
<td>Francipane M.</td>
<td>50</td>
</tr>
<tr>
<td>G</td>
<td>77</td>
</tr>
<tr>
<td>Gafarova D.</td>
<td></td>
</tr>
<tr>
<td>Gajewski K.</td>
<td>60</td>
</tr>
<tr>
<td>Gazizova A.</td>
<td>35</td>
</tr>
<tr>
<td>Ghahramany G.</td>
<td>83</td>
</tr>
<tr>
<td>Goto Y.</td>
<td>87</td>
</tr>
<tr>
<td>Greco A.</td>
<td>53</td>
</tr>
<tr>
<td>Guelly C.</td>
<td>36</td>
</tr>
<tr>
<td>Gulayev A.</td>
<td>36, 57</td>
</tr>
<tr>
<td>H</td>
<td>60</td>
</tr>
<tr>
<td>Halder G.</td>
<td></td>
</tr>
<tr>
<td>Hauser A.</td>
<td>71</td>
</tr>
<tr>
<td>I</td>
<td>67</td>
</tr>
<tr>
<td>Ibrayev S.</td>
<td></td>
</tr>
<tr>
<td>Ilyassova B.</td>
<td>50, 51</td>
</tr>
</tbody>
</table>

Third International Scientific Conference

**PERSONALIZED MEDICINE & GLOBAL HEALTH**

Astana, Kazakhstan
September 15, 2017
Imanbaev E. .......................... 52
Imangali N. .......................... 41
Islamov M. .......................... 86
Issabekov I. .......................... 48
Issabekova A. ......................... 74, 89
Izgutdina A. .......................... 49

Marchenko Y. .......................... 88
Maslina J. .............................. 62
Massabayeva M. ........................ 42
Masoud A. .............................. 44, 63, 64
Maukayeva S. .......................... 65
Mechold U. .............................. 58
Mills G. ................................. 60
Mills R. ................................. 60
Miyerbekov Y. .......................... 65
Molkenov A. .......................... 53, 58
Mossakowski A. ......................... 71
Mott-Pavie V. ............................ 60
Mukhlis S. .............................. 59, 66
Murata H. .............................. 72
Musagaliyeva A. ........................ 40
Mussina D. .............................. 67
Myngbay A. .............................. 35

Nabavi S. ................................. 83
Nakisbekov N. .......................... 68
Niesner R. ............................... 71
Nikolayeva L. ............................ 88
Nugmanova R. ........................... 67
Nurgaliiev D. ............................ 49
Nurozhin T. .............................. 36, 57
Nurkenov T. .............................. 82
Nurmoldin S. ............................ 68

Ogay V. ................................. 59, 66, 74, 75, 89
Ogryzko V. .............................. 58
Olgazyhev F. ............................. 59, 64, 72
Orazova S. ............................... 44
Oshakbayev K. ............................ 69, 70
Ospanova D. ............................. 40

Panzilt K. ............................... 36
Parkhomchuk D. .......................... 67
Pashimov M. ............................. 65

Radbruch H. ............................. 71
Ramagambetov E. ........................ 74
Rakhimova S. ........................... 58, 70, 77
Rakhymzhan A. .......................... 71
Ramanculov E. ........................... 58, 67, 80
Ramilyeva I. ............................ 47
<table>
<thead>
<tr>
<th>Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reshetina N.</td>
<td>51</td>
</tr>
<tr>
<td>Robin Ch.</td>
<td>58</td>
</tr>
<tr>
<td>Rojas-Solórzano L.</td>
<td>78, 86</td>
</tr>
<tr>
<td>Russell A.</td>
<td>72</td>
</tr>
<tr>
<td>Sadvakasova G.</td>
<td>61</td>
</tr>
<tr>
<td>Sadyrbekov D.</td>
<td>64</td>
</tr>
<tr>
<td>Sadyrbekova A.</td>
<td>79</td>
</tr>
<tr>
<td>Safarova Y.</td>
<td>64, 72</td>
</tr>
<tr>
<td>Saliev T.</td>
<td>44</td>
</tr>
<tr>
<td>Salimbayeva D.</td>
<td>73, 78</td>
</tr>
<tr>
<td>Sansores-Garcia L.</td>
<td>60</td>
</tr>
<tr>
<td>Saparbayev S.</td>
<td>41</td>
</tr>
<tr>
<td>Sarina N.</td>
<td>49</td>
</tr>
<tr>
<td>Sarsenova M.</td>
<td>74</td>
</tr>
<tr>
<td>Seisenbayeva A.</td>
<td>74, 81</td>
</tr>
<tr>
<td>Seikulov Y.</td>
<td>69, 70</td>
</tr>
<tr>
<td>Sekenova A.</td>
<td>75</td>
</tr>
<tr>
<td>Sergazy Sh.</td>
<td>36, 57</td>
</tr>
<tr>
<td>Shagyrova Zh.</td>
<td>76</td>
</tr>
<tr>
<td>Shalakhetova T.</td>
<td>82</td>
</tr>
<tr>
<td>Shoaib M.</td>
<td>58</td>
</tr>
<tr>
<td>Shramko A.</td>
<td>64</td>
</tr>
<tr>
<td>Shustov V.</td>
<td>54</td>
</tr>
<tr>
<td>Steins M.</td>
<td>58</td>
</tr>
<tr>
<td>Suleimenov A.</td>
<td>77</td>
</tr>
<tr>
<td>Suleimenov M.</td>
<td>45</td>
</tr>
<tr>
<td>Supiyev R.</td>
<td>78</td>
</tr>
<tr>
<td>Suraganova Y.</td>
<td>62</td>
</tr>
<tr>
<td>Svyatova G.</td>
<td>46, 65, 78, 79</td>
</tr>
<tr>
<td>Sypabekova M.</td>
<td>86</td>
</tr>
<tr>
<td>Tarlykov P.</td>
<td>67, 80</td>
</tr>
<tr>
<td>Toishibekov Y.</td>
<td>74, 81</td>
</tr>
<tr>
<td>Toishybek D.</td>
<td>81</td>
</tr>
<tr>
<td>Tokanova A.</td>
<td>55</td>
</tr>
<tr>
<td>Toleubekova L.</td>
<td>82</td>
</tr>
<tr>
<td>Trajanoski S.</td>
<td>36</td>
</tr>
<tr>
<td>Trenozhnikova L.</td>
<td>88</td>
</tr>
<tr>
<td>Tsy A.</td>
<td>41, 63, 64, 82</td>
</tr>
<tr>
<td>Turgambayeva A.</td>
<td>41, 82</td>
</tr>
<tr>
<td>Turganbekova A.</td>
<td>47</td>
</tr>
<tr>
<td>Tursynbek N.</td>
<td>83</td>
</tr>
<tr>
<td>Tursynhanova A.</td>
<td>77</td>
</tr>
<tr>
<td>Tyan O.</td>
<td>82</td>
</tr>
<tr>
<td>U</td>
<td></td>
</tr>
<tr>
<td>Umbayev B.</td>
<td>63, 64, 72</td>
</tr>
<tr>
<td>Urasova M.</td>
<td>57</td>
</tr>
<tr>
<td>Utepova G.</td>
<td>84</td>
</tr>
<tr>
<td>V</td>
<td></td>
</tr>
<tr>
<td>Vajta G.</td>
<td>81</td>
</tr>
<tr>
<td>Vangelista L.</td>
<td>85</td>
</tr>
<tr>
<td>Vergun S.</td>
<td>48</td>
</tr>
<tr>
<td>Vorobjev I.</td>
<td>45</td>
</tr>
<tr>
<td>W</td>
<td></td>
</tr>
<tr>
<td>Winkler T.</td>
<td>71</td>
</tr>
<tr>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Yenin Y.</td>
<td>51</td>
</tr>
<tr>
<td>Yerezhepov D.</td>
<td>58</td>
</tr>
<tr>
<td>Yermekova M.</td>
<td>81</td>
</tr>
<tr>
<td>Z</td>
<td></td>
</tr>
<tr>
<td>Zauatbayeva G.</td>
<td>85</td>
</tr>
<tr>
<td>Zhabayeva D.</td>
<td>46</td>
</tr>
<tr>
<td>Zhalbinova M.</td>
<td>70</td>
</tr>
<tr>
<td>Zhalgas A.</td>
<td>86</td>
</tr>
<tr>
<td>Zhanaspayev M.</td>
<td>38</td>
</tr>
<tr>
<td>Zhanazak Z.</td>
<td>87</td>
</tr>
<tr>
<td>Zhetpisbayev B.</td>
<td>59</td>
</tr>
<tr>
<td>Zhiburt E.</td>
<td>47</td>
</tr>
<tr>
<td>Zholamanova A.</td>
<td>88</td>
</tr>
<tr>
<td>Zhumbekova M.</td>
<td>89</td>
</tr>
<tr>
<td>Zhunusova M.</td>
<td>89</td>
</tr>
<tr>
<td>Zhussupova G.</td>
<td>82</td>
</tr>
<tr>
<td>Zhylkibayev A.</td>
<td>49, 85</td>
</tr>
<tr>
<td>Zinovye A.</td>
<td>53</td>
</tr>
<tr>
<td>Zollanvari A.</td>
<td>83, 89</td>
</tr>
</tbody>
</table>