NatureCleanSkin research project

Development of new methods of complex diagnostics of metagenomes* and microbiomes of throat, intestine, blood and skin of psoriatic patients, and also their corrections for achievement of long and steady remission.

Mikhail Peslyak,
Antipsoriatic Association "The Natural Alternative"

Nikolay Korotky
Pirogov Russian National Research Medical University

Total research consists of two consecutive stages:

**Stage1 (NIR1).** Metagenomes of whole blood and skin phagocytes at psoriatic disease.

**Stage2 (NIR2).** Metagenomes of whole blood, metagenomes and microbiomes of throat and gastrointestinal lavage water and permeability of small intestine at psoriatic disease. Development and approbation of new technique for treatment of psoriatic disease based on correction of throat and/or gastrointestinal microbiomes.

* Metagenome is a complex of all nhDNA (non-host DNA, that is, non-human here) contained in a biomaterial. nhDNA is a bacterial, archean, fungal, helminthic, viral, phage, etc. DNA.

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Psoriatic and normal skin

Growth of height of dermal papillae leads to increase in thickness of dermo-epidermal area. Arrows show direction of intensive proliferation of epidermal cells.
<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Number of examined</th>
<th>% with PD</th>
<th>Years</th>
<th>Patients in year on 100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1984</td>
<td>6 617 917</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China, Taiwan</td>
<td>2006</td>
<td>23 000 000</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>1974–1981</td>
<td>670 000</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2005</td>
<td>1 344 071</td>
<td>2.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>2003</td>
<td>2 238 000</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>2006</td>
<td>4 109</td>
<td>2.9</td>
<td>2005</td>
<td>230 #</td>
</tr>
<tr>
<td>Japan</td>
<td>2010–2011</td>
<td>128 000 000</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1985</td>
<td>10 576</td>
<td>1.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>2005–2009</td>
<td>2 161 832</td>
<td>1.45</td>
<td></td>
<td></td>
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<tr>
<td>Portugal</td>
<td>1994</td>
<td>1 037</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russia*</td>
<td>2004</td>
<td>~2 - 4</td>
<td></td>
<td>2009-13</td>
<td>216</td>
</tr>
<tr>
<td>Spain</td>
<td>1998</td>
<td>12 938</td>
<td>1.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>2013</td>
<td>12 711</td>
<td>2.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>1998–2010</td>
<td>–</td>
<td>1.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>2009</td>
<td>7 520 293</td>
<td>1.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>1987–2002</td>
<td>7 533 475</td>
<td>1.52</td>
<td>1996-7</td>
<td>140</td>
</tr>
<tr>
<td>USA</td>
<td>1971–1974</td>
<td>20 749</td>
<td>1.43</td>
<td>1991</td>
<td>60</td>
</tr>
<tr>
<td>USA</td>
<td>2004</td>
<td>27 220</td>
<td>2.2</td>
<td>1970-2000</td>
<td>78,9 #</td>
</tr>
<tr>
<td>USA</td>
<td>2009</td>
<td>2 573</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Region</th>
<th>Population</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of PD population in Russia and other</td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>countries of former USSR (top assessment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moscow and Moscow Region</td>
<td>17 000 000</td>
<td>680 000</td>
</tr>
<tr>
<td>Other regions of Russia</td>
<td>125 000 000</td>
<td>5 000 000</td>
</tr>
<tr>
<td>Countries of former USSR (except Russia)</td>
<td>150 000 000</td>
<td>6 000 000</td>
</tr>
<tr>
<td>% of PD population in world (on average)</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Population of all countries of world</td>
<td>7 300 000 000</td>
<td>146 000 000</td>
</tr>
</tbody>
</table>

PD - psoriatic disease
Skin immune systems and psoriasis

Film (2014) (~ 10 min).
(link)

Immunology in the skin

Miriam Merad, Mount Sinai School of Medicine, New York

James G. Krueger, The Rockefeller University, New York
Mature dendritic cell present 
unknown Y-antigen to T lymphocyte

Psoriatic derma

Mature dendritic cell maDC-Y

TL-Y

Y-specific T-lymphocyte

Key event of adaptive immune response is 
constant in each psoriatic plaque.

Y-antigen = 
unknown antigen

What chemical structure ?
Why has appeared in psoriatic derma?
## Versions of origin of unknown antigen

<table>
<thead>
<tr>
<th>Non-Host</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Host</td>
<td>A</td>
</tr>
<tr>
<td>Resident</td>
<td>-</td>
</tr>
<tr>
<td>Non-resident from external environment</td>
<td>B</td>
</tr>
<tr>
<td>Non-resident from within (for example from blood flow)</td>
<td>C</td>
</tr>
</tbody>
</table>

**Version B.** Numerous researches have shown its insolvency.

**Version A.**
The main version from authors of local models of pathogenesis. Numerous attempts to prove its solvency have not resulted in success yet.

**Version C.**
The main version from authors of systemic models of pathogenesis. The known facts do not contradict it. It will be checked within this project.

**Version D.**
Antigen has host origin, but is not resident. It is improbable. It was not checked.

Blood flow

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? Version C - the main version from authors of systemic models of pathogenesis. The known facts do not contradict it. It will be checked within this project.
<table>
<thead>
<tr>
<th>Version</th>
<th>Unknown antigen is</th>
<th>Status of version</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Autoantigens from resident skin cells</td>
<td>The main version from authors of local models of pathogenesis. N-model (Nestle F. et.al. 2009-12); GK-модель (Guttman-Yassky E, Krueger JG et al. (2010-11); TC-model (Tonel G. et al. 2009) GL-model (Gilliet M, Lande R, 2008-10) Numerous attempts to prove version A solvency have not resulted in success yet. But they proceed.</td>
</tr>
<tr>
<td>B</td>
<td>Fragments of chemicals or bacteria, fungi, viruses or proteins cosecreted by them coming on or to skin from external environment.</td>
<td>In 20th century this version existed, but numerous researches have shown its insolvency.</td>
</tr>
<tr>
<td>C</td>
<td>Fragments of chemicals or bacteria, fungi, viruses or proteins cosecreted by them. Come to psoriatic skin from other organs (for example in blood phagocytes).</td>
<td>The main version from authors of systemic models of pathogenesis. BF model. Barbara Baker and Lionel Fry (2006-7), Imperial College, London, UK. Y-model. Peslyak M. Y., Korotkii N.G. (2005-12). Moscow, Russian Federation. The known facts do not contradict this version. Within this project the main hypotheses of Y-model will be checked.</td>
</tr>
<tr>
<td>D</td>
<td>Autoantigens from non-resident host cells. Come to skin from other organs (for example fragments of blood phagocytes).</td>
<td>It is improbable. It was not checked.</td>
</tr>
</tbody>
</table>
PG structure and PsB

**Peptidoglycan (any)**

- **MDP** – muramyl dipeptide
- **Glycan chain**: GlcNAc, MurNac
- **Peptide moiety**: D-iGln, L-Lys, D-Ala

**Interpeptide Bridge**: IB

**PsB** – bacteria presumed psoriagenic

<table>
<thead>
<tr>
<th>PsB - bacteria presumed psoriagenic</th>
<th>Interpeptide Bridge</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Str. pyogenes</td>
<td>(L-Ala)2-3 or (L-Ser)-(L-Ala)</td>
<td>#, KEGG</td>
</tr>
<tr>
<td>Almost all from Streptococcus sp.</td>
<td>(L-Ala)1-3 or (L-Ser)-(L-Ala)</td>
<td>#, KEGG</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>(L-Ala)2-3</td>
<td>#, KEGG</td>
</tr>
<tr>
<td>Many from Leuconostoc sp.</td>
<td>(L-Ala)2 or (L-Ala)-(L-Ser) or (L-Ser)-(L-Ala)1-2</td>
<td>#, KEGG</td>
</tr>
<tr>
<td>Many from Weissella sp.</td>
<td>(L-Ala)2-3 or (L-Ser)-(L-Ala)</td>
<td>#</td>
</tr>
<tr>
<td>Some from Bifidobacterium sp.</td>
<td>(L-Ala)2-3 or (L-Ser)-(L-Ala)</td>
<td>#</td>
</tr>
</tbody>
</table>

# - scientific works

KEGG - Kyoto Encyclopedia of Genes and Genomes

Y-antigen = part(s) of interpeptide bridge IB-Y
Species of Gram+ bacteria with interpeptide IB-Y bridges IB-Y. IB-Y = (L-Ala)-(L-Ala) or (L-Ser)-(L-Ala). (KEGG database).

<table>
<thead>
<tr>
<th>Streptococcus sp.</th>
<th>Species from other genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus agalactiae</td>
<td>Streptococcus pseudopneumoniae</td>
</tr>
<tr>
<td></td>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Streptococcus anginosus</td>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td></td>
<td>Enterococcus silesiacus</td>
</tr>
<tr>
<td>Streptococcus constellatus</td>
<td>Streptococcus salivarius</td>
</tr>
<tr>
<td></td>
<td>Eubacterium sulci</td>
</tr>
<tr>
<td>Streptococcus cristatus</td>
<td>Streptococcus sanguinis</td>
</tr>
<tr>
<td></td>
<td>Lactococcus garvieae</td>
</tr>
<tr>
<td>Streptococcus dysgalactiae</td>
<td>Streptococcus suis</td>
</tr>
<tr>
<td></td>
<td>Lactococcus piscium</td>
</tr>
<tr>
<td>Streptococcus equi</td>
<td>Streptococcus thermophilus</td>
</tr>
<tr>
<td></td>
<td><em>Lactococcus raffinolactis</em></td>
</tr>
<tr>
<td>Streptococcus galloyticus</td>
<td>Streptococcus uberis</td>
</tr>
<tr>
<td></td>
<td>Leuconostoc carnosum</td>
</tr>
<tr>
<td>Streptococcus gordonii</td>
<td>Streptococcus vestibularis</td>
</tr>
<tr>
<td></td>
<td>Leuconostoc citreum</td>
</tr>
<tr>
<td>Streptococcus infantarius</td>
<td></td>
</tr>
<tr>
<td>Streptococcus iniae</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus intermedius</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus lutetiiensis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus macedonicus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus mutans</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pantholopis</td>
<td></td>
</tr>
<tr>
<td>Streptococcus parasanguninis</td>
<td></td>
</tr>
<tr>
<td>Streptococcus parauberis</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pasteurianus</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
</tr>
</tbody>
</table>

They have PG-Y peptidoglycan (such as at Streptococcus *pyogenes*), are named PsB and presumed psoragenic.

Almost all strains of these species have peptidoglycan similar to *Str.pyogenes* peptidoglycan. Therefore these species are presumed psoragenic. Formation of interpeptide bridges is provided by various murMN-genes. It is possible to determine everything by KEGG database (brought in it) strains of bacteria which have genes providing secretion of both enzymes i.e. and like murM and like murN. DB KEGG is replenished - 2018.
NatureCleanSkin project
"Long and steady remission for psoriatic patients"

Stage 1
NIR1
Metagenomes of whole blood and skin phagocytes at psoriatic disease.

Stage 2
NIR2
Metagenomes of whole blood, metagenomes and microbiomes of throat and gastrointestinal lavage water and permeability of small intestine at psoriatic disease.
Development and approbation of new technique for treatment of psoriatic disease based on correction of throat and/or gastrointestinal microbiomes.

Stage 3
Introduction
Complex diagnostics and treatment of psoriatic disease and other chronic dermatosis by Y-technique.

Diagnostics.
Check of hypotheses.

Diagnostics and treatment.
Check of hypotheses.
Development and approbation of Y-technique.

Introduction of diagnostics and treatment by Y-technique.
### Patients, biomaterials and WMS tests *

<table>
<thead>
<tr>
<th>Group</th>
<th>NIR1</th>
<th>NIR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP - Healthy persons (control group)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>PP - Psoriatic patients (diagnostics)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>PP - Psoriatic patients (diagnostics and treatment)</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

#### Biomaterials for WMS tests

<table>
<thead>
<tr>
<th>Type</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagocytes of psoriatic skin</td>
<td>30</td>
</tr>
<tr>
<td>Whole blood</td>
<td>40 108</td>
</tr>
<tr>
<td>Throat swabs**</td>
<td>68</td>
</tr>
<tr>
<td>Intestinal lavage waters**</td>
<td>108</td>
</tr>
<tr>
<td>Total biomaterials</td>
<td>70 284</td>
</tr>
</tbody>
</table>

* WMS test - whole metagenomic sequencing of biomaterial for definition of all DNA.
** Cultural test are in addition carried out.

Phagocytes: Neu - neutrophils, Mo - monocytes, DC - dendritic cells;
Stage 1

NIR1
Metagenomes of whole blood and skin phagocytes at psoriatic disease.

Novaseq 6000

WMS-tests: 70

Patients: 30 PP and 10 HP

Duration: 12 months

Diagnostics. Check of hypotheses.
Stage 1. Order of participation of psoriatic patients (PP) and healthy persons (HP).

Stage 1-1. Selection and preparation.
Informing, questioning, collection of data on PPC (PP - candidates for participation) and HPC (HP - candidates for participation). Selection of PPC having minimum health problems (besides psoriatic disease). Selection of HPC without any health problems. Among taken to participation presence of PP with wide range of PASI is necessary (from weak to heavy). The decision on primary selection is made by Organizing project committee. For each of participants IEMC (integrated electronic medicine card) is formed. Consultation of dermatologist. Control blood tests. The final decision on inclusion of PPC and HPC in Program is made by dermatologist.

Stage 1-2. Definition and studying of whole blood metagenomes and PAMP-nemia.
Consultation of dermatologist (for determination of urgent health of PP and HP and for purpose of dates for intake of biomaterials). Definition of whole blood metagenomes (WMS test) and concentration of nhDNA. Definition of PAMP-nemia. Search of correlations between PASI and characteristics of whole blood metagenomes and PAMP-nemia. Statistical analysis and assessment of results. Summing up stage 1-2.

Stage 1-3. Definition of metagenomes of phagocytes of psoriatic skin. Complex studying of metagenomes of whole blood and phagocytes of psoriatic skin.
Definition and studying of metagenomes of phagocytes of psoriatic biopsy (WMS test). Complex studying of metagenomes of whole blood and phagocytes of psoriatic skin, search of interrelations. Statistical analysis and assessment of results. Summing up Stage 1.

* Metagenome is a complex of all nhDNA (non-host DNA, that is, non-human here) contained in a biomaterial. nhDNA is a bacterial, archean, fungal, helminthic, viral, phage, etc. DNA.
Question 1. Does severity of psoriatic disease correlate with concentration of any nhDNA in whole blood and/or with level of PAMP-nemia?

Norm

Mild psoriasis

Severe psoriasis

Blood flow

Blood phagocytes

nhDNA, LPS, PG (including PG-Y) and other non-host material endocyted by blood phagocytes
NIR1
Stage 1-3

Question 2. Does nondegradated nhDNA come from blood into psoriatic skin?

All skin phagocytes endocytose nhDNA, LPS, PG (including PG-Y) and other non-host biomaterial of resident origin (i.e., from any microorganisms living on skin and in skin).

Blood flow

Non-resident skin phagocytes.
(bigger size - convention).

Blood phagocytes
in norm are not attracted in skin

Blood phagocytes intensively are attracted to inflammatory skin

Stage 1-3

RSP - Resident Skin Phagocytes
(smaller size - convention)

NhDNA, LPS, PG (including PG-Y) whether also other non-host biomaterial comes to psoriatic skin from blood flow in blood phagocytes?
Stage 1. Two main questions.

Question 1. Does severity of psoriatic disease correlate with concentration of any nhDNA in whole blood and/or with level of PAMP-nemia?

Question 2. Does nondegraded nhDNA come from blood into psoriatic skin? If so, which part of whole blood metagenome is found in metagenome of phagocytes of psoriatic skin and in what concentration?

Repeated researches at expense of contractor under more rigid control.

Contamination level in WMS-tests was higher than admissible?

Concentration of nhDNA of non-resident origin has appeared higher than level of contamination?

Preparation and realization of Stage 2 (NIR2).

Additional researches.
Definition of GRS (genetic risk score) for psoriatic patients. Search of correlations between PASI and combined parameters: GRS and concentration of any nhDNA in whole blood.
Correlations are found?

Brainstorming.
Content updating of Stage 1-3 taking into account received results.

Brainstorming.
Content updating of Stage 2 taking into account received results.
Stage 1 (NIR1).
What novelty consists in?

**New idea:**
New model of pathogenesis of psoriatic disease (PD).

**New methods of research**
*(at PD and for control group of healthy):*
For the first time will be

- concentration of nhDNA (non-host DNA) in whole blood and in phagocytes of psoriatic skin is defined;
- whole blood metagenome is defined (to species and strains);
- metagenome of phagocytes of psoriatic skin is defined (to species and strains);
- complex studying of these two metagenomes is executed;
- PAMP concentration - the main bacterial and fungal markers (LPS, PG and 1,3-beta-glucan) in plasma and whole blood lysate is defined;
NIR2
Metagenomes of whole blood, metagenomes and microbiomes of throat and gastrointestinal lavage water and permeability of small intestine at psoriatic disease. Development and approbation of new technique for treatment of psoriatic disease based on correction of throat and/or gastrointestinal microbiomes.


Duration: 24 months

Patients: Stage 2-2 - 68 PP, Stages 2-3, 2-4, 2-5 - 40 PP

WMS-tests: 284

Novaseq 6000
Order of psoriatic patients (PP) participation in Stage2 (NIR2)

2-1 Stage 2-1. Preparation and selection.
Informing and Questioning. Decision on participation in Stage2 is made by Project committee. Participants of Stage1 (NIR1) are accepted to participation in Stage2 out of competition (G1 group). EMC (electronic medical card) formation.

2-2 Stage 2-2. General diagnostics, definition of whole blood metagenome, definition of metagenomes and microbiomes of throat and intestine lavage waters.
Consultations (dermatologist, specialist in intestine lavage, otolaryngologist, stomatologist, gastroenterologist). Inspections (ultrasonography, allergens tests, etc.). OVA test of small intestine macromolecular permeability. Definition of whole blood metagenome (WMS test) and definition of nhDNA concentration. Definition of metagenomes and microbiomes of throat and intestine lavage waters (WMS tests).

Solution of experts concilium on basis of all Stage 2-2 results. Selection of G3 Group. Recommendations to PTS.

Not admission for some PP to Stage 2-3

PTS - Preliminary Treatment Stage
Consultations, inspections and courses of preliminary treatment. Purpose - maximum decrease of influence or full elimination of diseases at which intestine lavage is rather contraindicated and risk factors of emergence and support of SIBO.

Solution of experts concilium on basis of all inspections and PTS results.

2-3 Stage 2-3. Medical. Appointment and compliance of personal regime (PR). Carrying out PCT.
Formation PR including individual unloading diet (IUD) and individual constant diet (ICD). Personal course treatment (PCT) with IUD, intestine lavage and phagotherapy. Working off mechanisms of self-checking health control and compliance of PR.

PP continues to comply PR (including ICD), carrying out self-checking, keeps diary. If necessary consults at experts remotely (Internet, phone). Duration of stage 2-4 makes 2 months.

PP continues to comply personal regime. Cultural and metagenomic diagnostics of microbiome of intestine lavage waters. Diagnostics of small intestine permeability by OVA-testing. Assessment of PD condition.
Stage 2 (NIR2). Main questions.

- **Question 1.** Does severity of psoriatic disease correlate with concentration of any nhDNA in whole blood and/or with level of PAMP-nemia?

- **Affirmative answer on this question is received within Stage 1 (30 PP and 10 HP).** Within Stage 2 statistical importance of this answer as a result of necessary diagnostic tests of new group will be increased (68 PP at Stage 2-2).

- **Question 3.** Specific changes in the parietal intestinal microbiome and increased permeability of small intestine are the main causes of excess intake of specific bacterial products in blood in psoriatic disease?

- **NIR2. Stage 2-2.** Answer will be received. How? - See next slide.

- **Question 4.** Does stable correction of parietal small intestinal microbiome lead to a long-term remission of psoriatic disease?

- **NIR2. Stages 2-3, 2-4 and 2-5.** Answer will be received. How? - See slide through one.

nhDNA - non-host DNA,
PAMP - Pathogen-associate molecular patterns (in particular LPS and PG)
Question 3. Specific changes in the parietal intestinal microbiome and increased permeability of small intestine are the main causes of excess intake of specific bacterial products in blood in psoriatic disease?

Answer will be received after:

a) complex studying of metagenomes of whole blood, intestine lavage waters and throat swab

b) studying of small intestine permeability by OVA test.

SP1. Hyperpermeability of intestinal walls

SP2. Growth of populations of Gram(-) TLR4-active and Gram+ NOD2-active bacteria (including psoriagenic PsB) in small intestine.

SP3. Disturbance of production and/or circulation of bile acids.

SP4. PAMP-nemia. Increased kPAMP-load on blood phagocytes. Increased kPAMP level in blood. The major kPAMP are PG and LPS.

SP4.1. (PG-Y)-nemia.

SP5. Overload and/or disorders of detoxication systems at intestine (SP5.1) and in hepatobiliary system (SP5.2.)

SP6. Tonsillar PsB-infection

SP = subprocess;
Question 4. Does stable correction of parietal small intestinal microbiome lead to a long-term remission of psoriatic disease?

PP takes **Y-diagnostics course** (stage 2-2) by results of which **Y-treatment course** is formed. Y-treatment course consist of PCT (personal course of treatment) and PR (personal regime). PP carries out PCT (stage 2-3), and then within 2 months follows PR, including complying ICD (individual constant diet) (stage 2-4).

Control inspections of all PP (stage 2-5) will allow to give exact answer to Question 4.
John Pagano regime

- It is based on hypotheses stated in the middle of XX century by Edgar Cayce
- In practice it is developed by doctor naturopath John Pagano in 1977-86 in USA
- It is published in 1991 in his book "Healing Psoriasis - the Natural Alternative"
- Has helped to recover to thousands patients with psoriasis or eczema
- It was repeatedly reported at conferences of dermatologists and has received scientific justification
- This book in English was repeatedly republished
- This book is translated on 7 European and into Japanese and repeatedly on them was republished
Popularity of John Pagano regime (according to book "Healing Psoriasis: The Natural Alternative").
Original editions and translations.

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Dr. John’s healing psoriasis cookbook

French
2010, 2013

Italian

Japanese
2005

Finnish
2013

Spanish
2015

Bulgarian
2011

Czech
2012

Russian

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This book at Amazon.com

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Jonh Pagano
1930 - 2012

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One Cause, Many Ailment.
Leaky Gut Syndrome.

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John Pagano
1930 - 2012

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Original editions and translations.
Comparison of Pagano regime ("Healing Psoriasis: The Natural Alternative") and Y-techniques.

<table>
<thead>
<tr>
<th>Components</th>
<th>Pagano regime</th>
<th>Y-technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultations and inspections</td>
<td>No</td>
<td>Yes, Y-diagnostics</td>
</tr>
<tr>
<td>Preliminary treatment</td>
<td>No</td>
<td>Yes (PTS - preliminary treatment stage - by appointment)</td>
</tr>
<tr>
<td>Treatment Course</td>
<td>Regime only</td>
<td>Personal course of treatment (PCT) on basis of consultations and inspections results as initial component Y-treatments course. Development of Personal Regime (PR) which should be complied during Y-treatments course.</td>
</tr>
</tbody>
</table>
| Medicines                   | Dietary supplements and herb teas | As a part PCT (but not only):  
  - Phagotherapy (oral and nasal)  
  - Other antimicrobial medicines (by appointment)  
  - Prebiotics and probiotics (by appointment) |
| Internal detoxication        | Colono-therapy |  
  - Intestine lavage (as a part PCT (but not only))  
  - Enterosorbents  
  - Fruit unloading diets (as a part of PCT, but not only)  
  - Water (1,2-1,6 liter per day, besides other liquid food)  
  - Natural laxatives (by appointment) |
# Comparison of Pagano regime and Y-techniques (continuation)

<table>
<thead>
<tr>
<th>Component</th>
<th>Pagano regime</th>
<th>Y-technique</th>
</tr>
</thead>
</table>
| **Constant Diet**          | Pagano diet   | • ICD (individual constant diet) on basis of Pagano diet, and also taking into account sensitivity to solanaceous, tests for hidden celiac, food-borne allergens, requirements of low-microbial diet and individual preferences.  
  • Compliance of schedules of meal and water. |
| **External treatment**     | Natural       | • Natural  
  • Gels with phages                                                       |
| **Procedures**             | Manual therapy of backbone (by appointment) |                                                                             |
| **Physical exercises**     | Yes, in fresh air | • Complex of yoga exercises                                                  |
| **Correct thinking and behavior** |               | • Aiming at recovery,  
  • PD (psoriatic disease) exception from image  
  • Confidence in positive take and auto-suggestion  
  • Patience and persistence  
  • Communication with patients, successfully completed Y-treatments course  
  • Support of relatives |

*Internet link.*
Components of Y-treatment course

<table>
<thead>
<tr>
<th>Stages</th>
<th>Days</th>
<th>Phages</th>
<th>Other antimicrobial medicines and probiotics</th>
<th>Intestine lavage</th>
<th>Enteroxorbents</th>
<th>Procedures and physical exercises</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2-3. Personal course of treatment (PCT).</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>By appointment</td>
<td>5 procedures</td>
<td>-</td>
<td>Individual Unloading (IUD)</td>
</tr>
<tr>
<td>Stage 2-4. PP continues to comply personal regime (PR).</td>
<td>60</td>
<td>-</td>
<td>+</td>
<td>By appointment</td>
<td>By appointment</td>
<td>+</td>
<td>Therapy of backbone (by appointment).</td>
</tr>
<tr>
<td>Stage 2-5. Final. Control inspections.</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Individual Constant (ICD)</td>
</tr>
</tbody>
</table>

What is intestine lavage? Internet link.
Lavage SIBO-test. Integrated washout of parietal microbiome. Lavage waters as biomaterial for studying of intestine microbiome.

<table>
<thead>
<tr>
<th>Name and method of research</th>
<th>Biomaterial. Injection/collecting</th>
<th>Microbiome Test</th>
<th>Notes. Advantages (+) and Weakness (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine lavage is carried out with SES (saline enteral solution).</td>
<td>Intestine lavage waters. Injection by drink. Collecting - during defecation in sterile container.</td>
<td>Supernatants isolation. Cultural and metagenomic.</td>
<td>There were tests. (+) Biomaterial contains parietal microbiome of all small intestine (integrated washout). (-) biomaterial contains microbiome of all digestive tract. (-) There are no data on normal microbiome. (-) There are no data about SES as transport medium.</td>
</tr>
<tr>
<td>Prakshalana is carried out with SES or physical solution.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is intestine lavage? Internet link.

What is Prakshalana? Internet link.

Lavage SIBO-test will be main way of assessment of parietal intestine microbiome within Stage2 (at stages 2-2 and 2-5).
Factory phage complexes for phagotherapy

Phage complexes of Mikrogen production to which Enterococcus sp. and Streptococcus sp. can be sensitive.

- Bacteriophage streptococcal (Perm);
- Intesti-bacteriophage (Perm);
- Intesti-bacteriophage (Nizhny Novgorod);
- Piobacteriophage polyvalent cleared (Ufa);
- Piobacteriophage complex liquid (Nizhny Novgorod);
- Sekstaphage (piobacteriophage polyvalent) (Perm).

At detection of bacteria, resistant to factory phage complexes, selection and production of individual phage complex is possible. Cooperation with Federal State Unitary Enterprise NPO Mikrogen and LLC Mikromir is supposed.

In more detail about these phages. Internet link.
Stage 2 (NIR2). What novelty consists in?

**New idea**
New model of pathogenesis of psoriatic disease.

**New research methods**
*(in addition realized in Stage 1 - NIR1):*

Will be
- Metagenome of intestine lavage waters is defined (to species and strains) *(for the first time)*;
- Throat swab metagenome is defined (to species and strains);
- Whole blood metagenome is defined (to species and strains) *(for the first time)*;
- Complex studying of these three metagenomes is executed. It will allow to define in metagenomes of intestine lavage waters and throat swabs the most significant part - which defines PAMP-load in blood flow *(for the first time)*;
- Lavage SIBO-test. Intestine lavage waters as biomaterial containing parietal intestine microbiome are used *(for the first time within reseach)*;
- Cultural and metagenomic testing of the same biomaterials is executed (lavage waters and throat swab) that will allow to compare and to mutually add results, will increase their reliability.

**New Y-technique = Y-diagnostics + Y-treatment**
Y-diagnostics includes consultations and inspections of PP by new methods. On basis of Y-diagnostics results Y-treatment course is formed. Y-treatment course consist of PCT (Personal Course of Treatment) and PR (Personal Regime). PCT includes intestine lavage and phagotherapy of small intestine microbiome, PR includes ICD (individual constant diet) *(for the first time within research).*