WHAT ARE THE PROSPECTS OF AN “IGRA-SKINTEST”?

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Conflicts of interest:

I am employed by Statens Serum Institut who produce and distribute RT-23 Tuberculin, BCG Danish and develop the C-Tb specific skin test.

SSI also hold IPR on the use of ESAT-6 and other immunodiagnostic antigens used in IGRA tests.

I have no personal financial involvement in the IPR, sales and distribution of SSI TB products.
OVERVIEW OF CURRENT TRENDS IN NEXT GEN. IGRA DEVELOPMENT

T-SPOT. TB
TB Testing Just Got Easier
# OVERVIEW OF SKIN TEST PRODUCTS

<table>
<thead>
<tr>
<th></th>
<th>C-Tb (SSI, DK)</th>
<th>DIASKINTEST (Pharmstd, Ru)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development</td>
<td>Phase III</td>
<td>On market (Ru, Ukr, Kazak)</td>
</tr>
<tr>
<td>Composition</td>
<td>rdESAT-6 + rCFP10</td>
<td>rESAT-6:CFP10</td>
</tr>
<tr>
<td>Expression system</td>
<td>Lactococcus</td>
<td>E. Coli (his-tag?)</td>
</tr>
</tbody>
</table>

![Diagram of protein structure](image-url)
Pharmstd. Russia
Marketed since 2010
4 articles in Russian on Pubmed
Scattered posters/abstracts
http://www.diaskintest.ru/
Comparative results of skin testing using tuberculosis allergen recombinant (CFP-10-ESAT-6) and Quantiferon-GIT in Children and Adolescents with TB infection
L. Slogotskaya, Scientific and Clinical anti tuberculosis Center of Moscow Government Health Department

Diaskintest-screening method in mass examination of the child population for tuberculosis in Russia
V.A. Aksenova, 1st Moscow medical academy
DIASKINTEST-SCREENING METHOD IN MASS EXAMINATION OF THE CHILD POPULATION FOR TUBERCULOSIS IN RUSSIA

- Use of Diaskintest is high

<table>
<thead>
<tr>
<th></th>
<th>Total number of &lt;17 yr olds screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2012</td>
</tr>
<tr>
<td>Tuberculin</td>
<td>602,292</td>
</tr>
<tr>
<td>Diaskintest</td>
<td>460,917</td>
</tr>
</tbody>
</table>

- Consistent outcome year to year
- Association with likelihood of infection
- No comparative data
- No prospective data (PPV)
COMPARATIVE RESULTS OF SKIN TESTING USING TUBERCULOSIS ALLERGEN RECOMBINANT (CFP-10-ESAT-6) AND QUANTIFERON-GIT IN CHILDREN AND ADOLESCENTS WITH TB INFECTION

- Comparative study of Diaskintest and QFT in 6-17y olds
  - 163 Local TB (X-ray, clinical diagnosis, response to Tx)
  - 47 LTBI (?)

- Pooled analysis

- DIASKINTEST results
  - Mean induration 16.2mm
  - 90.7% positive Local TB
  - 51.1% LTBI

- Quantiferon results
  - Mean IFN-g release 7.63IU/ml
  - 92.6% positive Local TB
  - 53.2% LTBI

<table>
<thead>
<tr>
<th></th>
<th>QFT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Diaskintest</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>174</td>
</tr>
</tbody>
</table>

Comparable performance

Fig 2: A comparison of the QFT-GIT results (INF-γ level, IU/ml) and size of induration (mm)
SPECIFIC SKIN TEST, C-Tb

• Developed by SSI
• rdESAT-6 + rCFP10
• IGRA like performance
• Similar to RT-23 for end user
C-Tb, CLINICAL DEVELOPMENT PHASE I

**Safety (TESEC-01)**
- 42 healthy adults (negative controls)

- Few and mild AEs
- No sensitization

6 or 12 weeks apart

**Dose Finding (TESEC-02)**
- 38 adult TB patients

- Mild AE’s mainly transient itching
- 0.1 ug dose optimal
- Read test after 2-3 days
- Phenol preservation can be used

(Arend, Tuberculosis 2007; Lillebaek, Tuberculosis 2008; Bergstedt, Plos One 2010; Aggerbeck, Plos One 2013)
C-Tb, CLINICAL DEVELOPMENT PHASE II

Specificity (TESEC-03)
- 147 BCG vaccinated adults

BCG vaccinated controls

Induration size (mm)

Number of participants

HIV negative

HIV positive

N=146

N=95

<table>
<thead>
<tr>
<th></th>
<th>HIV negative</th>
<th>HIV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=146</td>
<td>N=95</td>
</tr>
<tr>
<td>C-Tb</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>112</td>
<td>77</td>
<td>66</td>
</tr>
<tr>
<td>QFT</td>
<td>112 (77)</td>
<td>69 (70)</td>
</tr>
</tbody>
</table>

Sensitivity (TESEC-04)
- 146 adult TB patients no HIV
- 95 adult TB patients with HIV

HIV- TB patients

Induration size (mm)

Number of participants

Table 4: C-Tb versus QFT

<table>
<thead>
<tr>
<th></th>
<th>HIV negative, N=146</th>
<th>HIV positive, N=95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QFT pos</td>
<td>QFT neg</td>
</tr>
<tr>
<td>C-Tb pos</td>
<td>91</td>
<td>12</td>
</tr>
<tr>
<td>C-Tb neg</td>
<td>21</td>
<td>9</td>
</tr>
</tbody>
</table>

McNemar's test: p=0.8774
Agreement: 0.71

HIV positive, N=95

<table>
<thead>
<tr>
<th></th>
<th>QFT pos</th>
<th>QFT neg</th>
<th>QFT ind</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Tb pos</td>
<td>58</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C-Tb neg</td>
<td>11</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

McNemar's test: p=0.6464
Agreement: 0.80

(Arend, Tuberculosis 2007; Lillebaek, Tuberculosis 2008; Bergstedt, Plos One 2010; Aggerbeck, Plos One 2013; Hoff & Dheda, in prep.)
C-Tb, MULTICENTER PHASE III TRIALS

**TESEC-06**
- Confirmation of diagnostic accuracy, adults
  - Exposure gradient
    - TB patients,
    - Close Contacts
    - Occasional Contacts
    - Un-exposed Controls
  - 950 Adults and children at all age groups

**TESEC-05**
- Confirmation of diagnostic accuracy: adults, children and HIV infected
  - TB suspects
  - Endemic controls
  - 1175 at all age groups (including 600 children and 300 HIV infected)

**TESEC-07**
- C-Tb injected alone or concomittant with PPD
  - 450 Adult Confirmed TB patients
  - HIV neg and HIV pos

Clinical documentation prepared for registration
Full scale production process ready for tech transfer
We are seeking a partner for product finalization and marketing
TESEC-06: VISIT 1, SCREENING

- Informed consent
- Medical history
- BCG, HIV status etc.
TESEC-06: VISIT 2, INCLUSION AND RANDOMIZATION

Hospital Universitario Lucus Augusti
TESEC-06: VISIT 2, C-TB AND PPD INJECTIONS

• Injections
• Marking of injection site

Agencia de Salut Publica de Barcelona
• Double reading of injection sites
• Recording of AEs
Hospital Vall d’Hebron

Hospital Universitario Lucus Augusti
TESEC-06: VISIT 4, 28 DAYS FOLLOW-UP

- Double reading of injection sites
- Digital images
- Recording of AEs
- Safety blood tests
TESEC-06: 13 TRIALS SITES, A LOT OF WORK FOR MANY DEDICATED PEOPLE
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- Keetran Dheda, UCT, ZA
- Joan Cayla, PHA BCN, SP

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