Results from Phase III, placebo-controlled, 2:1 randomized, double-blind trial of tableted TB vaccine (V7) containing 10 μg of heat-killed *Mycobacterium vaccae* administered daily for one month

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Tuberculosis

• 33% of people carry TB bacteria = 2.5 billion
• Every second, a person becomes ill with TB
• Every year 10 mln people develop TB and 2 mln die
• Drug-resistant TB poised to become global pandemic
• Less than 3% of drug-resistant TB is treated today
State-of-the-art: immunology of TB – a great deal of information gathered but…

can't see the forest through the trees

Th-1 cells = IFN-γ, IL-2, GM-CSF, IFN-α, TNF-α, IL-12, IL-18
Th-2 cells = IL-4, IL-5, IL-13
Th-17 cells = IL-6, IL-17, IL-22, TNF-α
Treg cells = IL-10, TGF-β
B cells = IFN-α, IL-1β, IL-12
Monocytes = IL-8, IL-18, TNF-α
When this vast knowledge was applied to immunotherapy of TB… it failed…

It also resulted in negative attitude toward immunotherapy

- IL-2 (increased bacterial load)
- IL-12 (no effect)
- GM-CSF (clearance not confirmed)
- IFN-γ (irreproducible, no effect)
- IFN-α (negative outcome)
- anti-TNF-α (negative outcome)
- Thalidomide (negative outcome)
- Corticosteroids (irreproducible, negative effect)
Paradoxes of Tuberculosis

• 1/3 of world population (~2.5bln) have latent *M. tuberculosis*
• Yet only about 10 Million people (0.004%) develop TB
• *M. tuberculosis* is in symbiotic relationship with the host
• In some cases it’s even beneficial (asthma, cancer)
• *M. tuberculosis* is not cytopathogenic in vitro
• Mycobacterial virulence depends on host’s immune response
• Disease occurs when the homeostasis is broken
• Disease coincides with immune activation, i.e., inflammation
• “Weakened” immunity in TB is a myth
Robert Koch (1843-1910), discoverer of *Mycobacterium tuberculosis* and tuberculin immunotherapy. Portrait made in 1890 - the year he announced tuberculin therapy. The large scale clinical trial and misinterpretation of the results by Virchow had tarnished his reputation.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Extra-pulmonary TB N=707 (%)</th>
<th>Pulmonary TB N=1010 (%)</th>
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<tbody>
<tr>
<td>Cured</td>
<td>15 (2.1)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Improved</td>
<td>385 (54.5)</td>
<td>365 (36.1)</td>
</tr>
<tr>
<td>No change</td>
<td>298 (42.1)</td>
<td>586 (58)</td>
</tr>
<tr>
<td>Died</td>
<td>9 (1.3)</td>
<td>46 (4.6)</td>
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</tbody>
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Box of “defatted” tuberculin vaccine of Georges Dreyer (1924) sold by CSL. Of special interest is the quantity of antigen – only 10 nanograms per dose. The principle of Dreyer’s vaccine is similar to Koch’s description of tuberculin
The portrait rendition of Li Shi Chen (1518-1593). He is the author of most comprehensive Chinese pharmacopoeia Pên Ts’ao Kang Mu describing earliest recorded TB immunotherapy based on ingestion of heat-inactivated tubercle bacilli derived from sputum.
History of *Mycobacterium vaccae* discovery

M. vaccae was first isolated from cow’s milk and dung by Bonicke & Juhasz in 1964.

Cynthia and John Stanford – discoverer of M. vaccae activity against TB in 1970’s.
1964 Discovered in cow’s milk and dung in Austria
1972 John Stanford re-discovered during BCG vaccination in Uganda
1990’s 55 trials in 20 countries for TB, asthma, cancer, etc.
2001 Approved for adjunct therapy of TB in China
2010 Stanford et al., shown efficacy of oral capsule formula
2010 Manufactured tableted form of heat-killed *M. vaccae*
2011 Clinical II trials in patients with DS-TB, MDR-TB, and HIV/TB
2013 Results published in 2 peer-reviewed journals
2014 $100K grant from Grand Challenges Canada
2014 Initiated Phase III trial in Ukraine and Mongolia
2015 Received biologic drug approval in Mongolia
Various other species of mycobacteria used in TB

*M. tuberculosis* (RUTI, delipidated fragments (Archivel Farma, Spain) - discontinued
*M. bovis* (standard live or killed BCG vaccine) used in Russia and China
*M. chelonae* or “turtle vaccine” (Laves-Arzneimittel GmbH, Germany – discontinued)
*M. microti* has been tested in UK and used widely in Czechoslovakia – discontinued
*M. phlei* (Sanum-Kehlbeck, Germany) manufactured in China as a homeopathic “Utilin S”
*M. w* or *M. indicus* developed as leprosy vaccine (Immuvac, Cadila Pharmaceuticals, India)
*M. smegmatis* (Institute for the Control of Pharmaceutical and Biological Products, China)
*M. habana* – TB vaccine candidate (IPK, Cuba)
*M. vaccae* – injectable formula sold in China under Vaccae® brand name (Longcom, China)
*M. vaccae* (V7) in tableted oral form (Immunitor Inc., Canada)
Injectable TB vaccine containing heat-inactivated *M. vaccae* manufactured by Longcom (Anhui, China):

positive outcome in ~30-34% cases; requires about 6 months to achieve that.
Oral form of *M. vaccae*

V7 is tableted form of *M. vaccae* developed and manufactured by Immunitor company since 2010.
Randomized, placebo-controlled phase II trial of heat-killed *Mycobacterium vaccae* (Longcom batch) formulated as an oral pill (V7)

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One-month Phase II trial was conducted in 43 sputum smear-positive patients with pulmonary tuberculosis randomized into treatment (n = 22) and placebo (n = 21) arms to investigate the safety and efficacy of an orally-administered therapeutic TB vaccine (V7) containing 10 μg of heat-killed *Mycobacterium vaccae* provided by Longcom company. Immunotherapy and control groups comprised 8 newly diagnosed (1stDx TB; 18.6%), 6 re-treated (RTB; 14%), and 29 multidrug-resistant (MDR-TB; 67.4%) cases distributed at 5:4:13 and 3:2:16 ratios, respectively. Both arms received conventional TB drugs administered under directly observed therapy. The average weight gain in V7 arm was modest, but statistically significant (0.6 kg; p = 0.004), while placebo patients lost 0.1 kg (p = 0.77). Except defervescence and increased lymphocyte percentage, other secondary endpoints such as erythrocyte sedimentation rate (ESR), leukocyte counts and hemoglobin content were not significantly affected. In control patients only one secondary endpoint, ESR, has improved. After one month mycobacterial clearance in sputum smears was observed in 31.8% (p = 0.03) and 9.5% (p = 0.83) of patients on V7 and placebo. However, the difference between outcomes in two arms was below significance threshold (p = 0.07). Thus, larger population of patients with prolonged follow-up is required to support these preliminary findings.

Randomized, placebo-controlled Phase II trial of heat-killed *Mycobacterium vaccae* (Immodulon batch) formulated as an oral pill (V7)

Aim: A 1-month Phase II trial was conducted in 41 patients with pulmonary TB who were randomized into treatment (n = 20) and placebo (n = 21) arms to investigate the safety and efficacy of an orally-administered therapeutic TB vaccine (V7) containing 10 μg heat-killed *Mycobacterium vaccae* provided by Immodulon Therapeutics Ltd (London, UK). Materials & methods: Both arms received conventional anti-TB therapy administered along with a daily pill of V7 or placebo. The subject population had four categories of TB: drug-sensitive TB; retreated TB; drug-resistant TB; and TB with HIV distributed in V7 and placebo arms at 9:4:7:6 and 14:1:6:8 ratios, respectively. Results: The mycobacterial clearance in sputum smears was observed in 72.2% (p < 0.0001) and 19% (p = 0.03) of patients on V7 and placebo, respectively. The average weight accrual among V7 recipients was 2.6 kg (p = 0.002) versus -0.2 kg (p = 0.69) in the control group. Except reduction in fever and increased lymphocyte counts, the changes in other secondary end points, such as hemoglobin, erythrocyte sedimentation rate and leukocyte counts, were not statistically different, although the proportion of patients responding favorably to V7 was invariably higher compared with placebo (p = 0.002). In control patients, no difference from baseline levels was noted except decreased hemoglobin content (p = 0.02). Conclusion: Oral *M. vaccae* was safe and has potential as an adjunct immunotherapy, targeting mucosal immunity, to improve efficacy and shorten treatment duration of TB chemotherapy.
Outcome of one-month Phase III placebo-controlled trial

TB bacteria clearance rate in %

Response rate to V7 or Placebo
Faster, Better, Cheaper

1. Shortens treatment duration down to 1 month (FASTER)
2. Three-times more effective than TB drugs (BETTER)
3. Reduces cost of treating TB by at least 100-fold (CHEAPER)
Thank you!

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