Acknowledgements

We acknowledge the contribution of Ms N. Makino in the preparation of the manuscript. We thank Ms Y. Harada for her technical support and the Japanese Red Cross Society for kindly providing blood from healthy donors. We also thank Professor William R. Jacobs, Jr, Howard Hughes Medical Institute, for providing the plasmids, pYUB854 and phAE87. This work was supported in part by a Grant-in-Aid for Research on Emerging and Re-emerging Infectious Diseases from the Ministry of Health, Labour, and Welfare of Japan.

References

Andersen P & Doherty TM (2005) The success and failure of BCG-implications for a novel tuberculosis vaccine. *Nat Rev Microbiol* **3**: 656–662.

Bardarov S, Bardarov S Jr, Pavelka MS Jr, Sambandamurthy V, Larsen M, Tufariello J, Chan J, Hatfull G & Jacobs WR Jr (2002) Specialized transduction: an efficient method for generating marked and unmarked targeted gene disruptions in *Mycobacterium tuberculosis*, *M. bovis* BCG and *M. smegmatis*. *Microbiology* **148**: 3007–3017.

Charles C & Shepard MD (1960) The experimental disease that follows the injection of human leprosy bacilli into foot-pads of mice. *J Exp Med* **112**: 445–454.

Clements DL, Lee BY & Horwitz MA (1995) Purification, characterization, and genetic-analysis of *Mycobacterium tuberculosis* urease, a potentially critical determinant of host-pathogen interaction. *J Bacteriol* **177**: 5644–5652.

Dockrell HM, Young SK, Britton K *et al.* (1996) Induction of Th1 cytokine responses by mycobacterial antigens in leprosy. *Infect Immun* **64**: 4385–4389.

Dye C, Watt CJ, Bleed DM, Hosseini SM & Raviglione MC (2005) Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* **293**: 2767–2775.

Granelli-Piperno A, Golebiowska A, Trumpfheller C, Siegal FP & Steinman RM (2004) HIV-1-infected monocyte-derived dendritic cells do not undergo maturation but can elicit IL-10 production and T cell regulation. *Proc Natl Acad Sci USA* **101**: 7669–7674.

Grode L, Seiler P, Baumann S *et al.* (2005) Increased vaccine efficacy against tuberculosis of recombinant *Mycobacterium bovis* bacille Calmette-Guérin mutants that secrete listeriolysin. *J Clin Investig* **115**: 2472–2479.

Hashimoto K, Maeda Y, Kimura H, Suzuki K, Masuda A, Matsuoka M & Makino M (2002) *Mycobacterium leprae* infection in monocyte-derived dendritic cells and its influence on antigen-presenting function. *Infect Immunity* **70**: 5167–5176.

Honerzu Bentrup K & Russell DG (2001) Mycobacterial persistence: adaptation to a changing environment [review]. *Trends Microbiol* **9**: 597–605.

Job CK (1989) Nerve damage in leprosy. *Int J Lepr Other Mycobact Dis* **57**: 532–539.

Kai M, Maeda Y, Maeda S, Fukutomi Y, Kobayashi K, Kashiwabara Y, Makino M, Abbasi MA, Khan MZ & Shah PA (2004) Active surveillance of leprosy contacts in country with low prevalence rate. *Int J Lepr Other Mycobact Dis* **72**: 50–53.

Kaufmann SHE (2005) Introduction. Rational vaccine development against tuberculosis: "those who don't remember the past are condemned to repeat it". *Microbes Infect* **7**: 897–898.

Kaufmann SHE (2006) Envisioning future strategies for vaccination against tuberculosis. *Nat Rev Immunol* **6**: 699–704.

Kaufmann SHE & McMichael AJ (2005) Annulling a dangerous liaison: vaccination strategies against AIDS and tuberculosis. *Nat Med* **11**: S33–S44.

Maeda S, Matsuoka M, Nakata N, Kai M, Maeda Y, Hashimoto K, Kimura H, Kobayashi K & Kashiwabara Y (2001) Multidrug resistant *Mycobacterium leprae* from patients with leprosy. *Antimicrob Agents Chemother* **45**: 3635–3639.

Maeda Y, Gidoh M, Ishii N, Mukai C & Makino M (2003) Assessment of cell mediated immunogenicity of *Mycobacterium leprae*-derived antigens. *Cell Immunol* **222**: 69–77.

Makino M & Baba M (1997) A cryopreservation method of human peripheral blood mononuclear cells for efficient production of dendritic cells. *Scand J Immunol* **45**: 618–622.

Makino M, Shimokubo S, Wakamatsu S, Izumo S & Baba M (1999) The role of human T-lymphotropic virus type 1 (HTLV-1)-infected dendritic cells in the development of HTLV-1-associated myelopathy/tropical spastic paraparesis. *J Virol* **73**: 4575–4581.

Makino M, Maeda Y, Fukutomi Y & Mukai T (2007) Contribution of GM-CSF on the enhancement of the T cell-stimulating activity of macrophages. *Microbes Infect* **9**: 70–77.

McDermott-Lancaster RD, Ito T, Kohsaka K, Guelpa-Lauras CC & Grosset JH (1987) Multiplication of *Mycobacterium leprae* in the nude mouse, and some applications of nude mice to experimental leprosy. *Int J Lepr Other Mycobact Dis* **55**: 889–895.

Miyamoto Y, Mukai T, Takeshita F, Nakata N, Maeda Y, Kai M & Makino M (2004) Aggregation of mycobacteria caused by disruption of fibronectin-attachment protein-encoding gene. *FEMS Microbiol Lett* **236**: 227–234.

Miyamoto Y, Mukai T, Nakata N, Maeda Y, Kai M, Naka T, Yano I & Makino M (2006) Identification and characterization of the genes involved in glycosylation pathways of mycobacterial glycopeptidolipid biosynthesis. *J Bacteriol* **188**: 86–95.

Mochida-Nishimura K, Akagawa KS & Rich EA (2001) Interleukin-10 contributes development of macrophage suppressor activities by macrophage colony-stimulating factor, but not by granulocyte-macrophage colony-stimulating factor. *Cell Immunol* **214**: 81–88.

Orme IM, Roberts AD, Griffin JP & Abrams JS (1993) Cytokine secretion by CD4 T lymphocytes acquired in response to *Mycobacterium tuberculosis* infection. *J Immunol* **151**: 518–525.

Reyrat JM, Berthet FX & Gicquel B (1995) The urease locus of *Mycobacterium tuberculosis* and its utilization for the

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demonstration of allelic exchange in *Mycobacterium bovis* bacillus Calmette-Guérin. *Proc Natl Acad Sci USA* **92**: 8768–8772.

Schaible UE, Sturgill-Koszycki S, Schlesinger PH & Russell DG (1998) Cytokine activation leads to acidification and increases maturation of *Mycobacterium avium*-containing phagosomes in murine macrophages. *J Immunol* **160**: 1290–1296.

Sendide K, Degmane AE, Reyrat JM, Talal A & Hmama Z (2004) *Mycobacterium bovis* BCG urease attenuates major histocompatibility complex class II trafficking to the macrophage cell surface. *Infect Immun* **72**: 4200–4209.

Setia MS, Steinmaus C, Ho CH & Rutherford GW (2006) The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis* **6**: 162–170.

Stoner GL (1979) Importance of the neural predilection of *Mycobacterium leprae* in leprosy. *Lancet* **2**: 994–996.

Verreck FA, de Boer T, Langenberg DM, Hoeve MA, Kramer M, Vaisberg E, Kastelein R, Kolk A, de Waal-Malefyt R & Ottenhoff TH (2004) Human IL-23-producing type 1 macrophages promote but IL-10-producing type 2 macrophages subvert immunity to (myco)bacteria. *Proc Natl Acad Sci USA* **101**: 4560–4565.

Wakamatsu S, Makino M, Tei C & Baba M (1999) Monocyte-driven activation-induced apoptotic cell death of human T-lymphotropic virus type 1-infected T cells. *J Immunol* **163**: 3914–3919.

World Health Organization. (2006) *Fact Sheet No. 104*, Rev March, http://www.who.int/mediacentre/factsheets/fs104/en

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第83回総会ミニシンポジウム

I. ワクチン研究の現在と将来

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キーワーズ：改良BCG，弱毒結核菌，成分ワクチン，DNAワクチン，感染曝露前（予防）ワクチン，感染曝露後（治療）ワクチン

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3. Present and future of TB vaccine development research
   Peter ANDERSEN (Statens Serum Institute, Copenhagen, Denmark)
4. Comments and directions in research and development of TB vaccines
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全世界で約20億人（全人口の3分の1）が結核菌（*Mycobacterium tuberculosis*）に既感染，すなわち，無症候性潜伏感染し，毎年920万人が結核を発病，170万人（後天性免疫不全症候群合併23万人を含む）が死亡している（http://www.who.int/tb/en/）。今後10年間に，少なくとも8000万人が結核を発病，2000万人が死亡することが推定されている。

日本（2006年）では年間2.6万人（罹患率人口10万対：20.6）が結核を発病し，2.3千人（死亡率：1.8）が死亡し，日本においても結核対策は重要な課題である。Robert Kochが1882年に「結核菌」を発見，爾来，120年余が経過した現在でも，国内外を問わず，結核は人類に甚大な健康被害を提供し続けている。

結核対策における世界的課題として，①薬剤耐性結核菌の出現や蔓延および②HIV-結核菌の重複感染がきわめて重要である。これらの課題を克服する科学的戦略は「安全で有効な結核ワクチン」である。現行結核ワクチンであるbacillus Calmette-Guérin（BCG）は乳幼児結核に有効であるが，潜在性結核菌感染を基盤とした多くの成人肺結核や内因性再燃結核に対するBCG接種の有効性は疑問視されている。

世界保健機関（WHO）は2015年までに現行BCGを凌駕する新規結核ワクチンの開発を目指している。新規結核ワクチンの開発戦略は「予防・治療：感染曝露前（予防的）や感染曝露後（治療的）ワクチン」，「ワクチン製剤：改良型BCG，弱毒結核菌，成分ワクチンやDNAなど遺伝子ワクチン」，「接種方法：Primeや Prime-boostワクチン」などの視点から進捗しており，前臨床試験，さらに，第1相など臨床試験で評価され，有望なワクチン候補が開発されつつある。

第83回日本結核病学会総会（石川信克会長）において，ミニシンポジウム「ワクチン研究の現在と将来」を企画し，世界の第一線で活躍されている気鋭の結核ワクチン研究者が結核ワクチン開発の現況や将来展望を発表した。ミニシンポジウム「ワクチン研究の現在と将来」が会員諸氏に有用な情報を提供，そして，研究室から臨床に迅速・効率的に"橋渡し（Translation）"し，究極的に人類に甚大な健康被害を提供し続けている結核の制圧に寄与することを祈念している。

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(Received 16 Jul. 2008)

1. 新しい結核DNAワクチン

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1998年，アメリカ合衆国疾病対策予防センター（Centers for Disease Control and Prevention：CDC）およびAdvisory Council for the Elimination of Tuberculosis（ACET）は新世代の結核ワクチン開発の必要性を発表した。しかしながら，BCGワクチンに代わる結核ワクチンは欧米でも臨床応用には至っていない。結核ワクチンは，DNAワクチン，リコンビナントBCGワクチン，サブユニットワクチンに大別される。DNAワクチンは予防ワクチン効果の切れ味ではほかより優れていることが多く，安定性・経済的にも優れている。われわれはBCGワクチンをはるかに凌駕する1万倍強力な結核予防ワクチン効果を示す新しいDNAワクチン（HVJ-エンベロープ/HSP 65＋IL-12 DNAワクチン）を開発した。

〔マウス〕の結核感染系ではBCGワクチンをはるかに凌駕する新しい結核ワクチンはきわめて少ない。われわれはプライム・ブースター法を用い，HSP 65 DNA＋IL-12 DNA（HVJ-エンベロープベクター）のワクチンはBCGワクチンよりも1万倍強力な結核予防ワクチンであることを世界に先駆けて明らかにした。このワクチンは，結核菌由来のHSP 65蛋白抗原特異的な，CD8陽性キラーT細胞およびinterferon：IFN-gamma産生T細胞の分化も増強した。肺の結核病理像の改善効果も示した。さらに生体内において，CD8陽性T細胞とCD4陽性T細胞の両者がこの結核予防ワクチンに必要であることを明らかにした。

〔治療ワクチン〕さらに，このワクチンは治療結核ワクチン効果も示した。すなわち結核菌をあらかじめ投与したマウスにおいてHVJ-エンベロープ/HSP 65 DNA＋IL-12 DNAワクチンを3回治療投与すると，コントロール群に比較して有意差をもって肺・肝・脾の結核菌数の減少を認めた。多剤耐性結核菌や超薬剤耐性結核（XDR-TB）に対しても治療ワクチン効果を示した。欧米では治療ワクチンは未開発である。モルモット（結核菌吸入感染系）の系でもこのワクチンはBCGより有効であった。〔新しいヒト生体内抗結核免疫解析モデルSCID-PBL/hu〕を用いてもワクチン効果を示した。

さらに，〔ヒト結核感染モデルに最も近いカニクイザル〕（Nature Med. 1996）を用い，HSP 65 DNA＋IL-12 DNAワクチンの強力な有効性を得た。カニクイザルに3回ワクチン接種後4週間後にヒト結核菌を経気道投与し，1年以上経過観察した。リンパ球増殖反応・サイトカイン（IFN-gamma，IL-2等）産生の増強および胸部X線所見・血沈，体重の改善効果が認められた。さらに，生存率改善・延命効果も認められた。DNAワクチン投与群は50%の生存率であり，コントロール群は生存率0%であった。さらに，サルの系でプライム-ブースター法を用いて，より強力なワクチン開発を行った。その結果，BCGワクチン・プライム-DNAワクチン・ブースター法を用いた群は100%の生存率を示した。一方，BCGワクチン単独群は33%の生存率であった。成人に対して切れ味の鋭い強力な新しい結核ワクチンが切望されているが，BCGワクチンは乳幼児でほぼ全員に実施されていることよりHSP65 DNA＋IL-12 DNAワクチンが強力な成人ワクチンとなることが示唆された。WHO STOP TB VACCINE Meetingでこのワクチンはきわめて高い評価を受けた。さらに，このワクチンを鼻粘膜または気道内ワクチンとして投与を試みつつある。さらに，カニクイザルの系で治療ワクチン効果およびプライムとブースターの期間を長期間とって，プライム-ブースター法を研究中である。（共同研究者：当臨床研究センター 喜多，井上，坂谷 各博士，金丸，橋元，西田，仲谷，高尾，栖原，岸上 各研究員，R.Gelber博士，B.Tan博士，中島俊洋博士，長澤鉄二博士，吉田栄人博士，松本真博士，金田安史博士，D.McMurray博士，厚生労働科学研究費補助金の支援による）

We have developed a novel tuberculosis (TB) vaccine; a combination of the DNA vaccines expressing mycobacterial heat shock protein 65 (HSP 65) and interleukin 12 (IL-12) delivered by the hemagglutinating virus of Japan (HVJ)-envelope and -liposome (HSP 65＋IL-12/HVJ). This vaccine provided remarkable protective efficacy in mouse and guinea pig models compared to the BCG vaccine on the basis of C.F.U of number of TB, survival, an induction of the CD8 positive CTL activity and improvement of the histopathological tuberculosis lesions. This vaccine provided therapeutic efficacy against multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) (prolongation of survival time and the decrease in the number of TB in the lung) as well as protective efficacy in murine models. Furthermore, we extended our studies to a cynomolgus monkey model, which is currently the best animal model of human tuberculosis. This novel vaccine provided a higher level of the protective efficacy than BCG based upon the assessment of mortality, the ESR, body weight, chest X-ray findings and immune responses (IFN-γ, IL-2, IL-6 produc-

tion, and lymphocyte proliferation of cynomolgus monkey). All monkeys in the control group (saline) died within 8 months, while 50% of monkeys in the HSP 65+IL-12/HVJ group survived more than 14 months post-infection (the termination period of the experiment). Furthermore, the combination of HSP 65+IL-12/HVJ and BCG by the priming-booster method showed a synergistic effect in the TB-infected cynomolgus monkey (100% survival). In contrast, 33% of monkeys from BCG Tokyo alone group were alive (33% survival). Furthermore, this vaccine exerted therapeutic efficacy in the TB-infected monkeys. These data indicate that our novel DNA vaccine might be useful against *Mycobacterium tuberculosis* for human clinical trials.

References

1) Okada M, Kita Y, Nakajima T, et al.: Evaluation of a novel vaccine (HVJ-liposome/HSP 65 DNA+IL-12 DNA) against tuberculosis using the cynomolgus monkey model of TB. Vaccine. 2007 ; 25 : 2990−3.

2) Nakano H, Nagata T, Suda T, et al.: Immunization with dendritic cells retrovirally transduced with mycobacterial antigen 85A gene elicits the specific cellular immunity including cytotoxic T-lymphocyte activity specific to an epitope on antigen 85A. Vaccine. 2006 ; 24 : 2110−9.

3) Yoshida S, Tanaka T, Kita Y, et al.: DNA vaccine using hemagglutinating virus of Japan-liposome encapsulating combination encoding mycobacterial heat shock protein 65 and interleukin-12 confers protection against *Mycobacterium tuberculosis* by T cell activation. Vaccine. 2006 ; 24 : 1191−204.

4) Kita Y, Tanaka T, Yoshida S, et al.: Novel recombinant BCG and DNA-vaccination against tuberculosis in a cynomolgus monkey model. Vaccine. 2005 ; 23 : 2132−5.

5) Miki K, Nagata T, Tanaka T, et al.: Induction of protective cellular immunity against *Mycobacterium tuberculosis* by recombinant attenuated self-destructing *Listeria monocytogenes* strains harboring eukaryotic expression plasmids for antigen 85 complex and MPB/MPT51. Infect Immun. 2004 ; 72 : 2014−21.

2. BCG vaccine trials in South Africa

South African Tuberculosis Vaccine Initiative, University of Cape Town Gregory HUSSEY

The South African Tuberculosis Vaccine Initiative, located within the University of Cape Town, has been involved in a number of BCG vaccine trials over the last few years and in this presentation I will highlight results from some of our studies.

A randomized trial comparing the efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis disease in infants and young children

Intradermal BCG vaccine is currently recommended by the World Health Organization (WHO). Prior to this study, no randomized trial comparing the relative incidence of tuberculosis following intradermal as opposed to percutaneous BCG vaccination had been conducted. 11680 South African newborns were randomized to receive Tokyo 172 BCG vaccine via either the percutaneous (n=5775) or the intradermal (n=5905) route within 24 hours of birth and then followed up for 2 years to document and investigate adverse events and suspected tuberculosis (TB) disease. The cumulative incidence of tuberculosis over two years of follow up was 6.13% [95.5 %CI : 5.52−6.79%] in the intradermal group and 6.49% [5.86−7.18%] in the percutaneous group. No significant differences were found between the routes in the cumulative incidence of adverse events. Our results suggest that the WHO should consider revising its policy of preferential intradermal vaccination to allow national immunization programs to choose percutaneous vaccination if that is more practical.

Determining BCG-induced immune correlates of protection against childhood tuberculosis disease

This study aims to determine what we can measure in the blood of a BCG-vaccinated baby to tell us whether that infant has either been protected, or not protected, against future tuberculosis disease. Defining these "immune correlates" is critical for studies of new tuberculosis vaccines. 5675 infants, routinely vaccinated with BCG at birth were enrolled. Blood was collected, processed and cryopreserved at 10 weeks of age, and the infants were followed for at least 2 years. 45 infants developed culture-positive lung tuberculosis over this period (i.e., not protected by BCG). 91 infants did not develop tuberculosis disease despite exposure to adults with tuberculosis in the households (i.e., protected by BCG). We are now in the process of retrieving blood products stored at 10 weeks of age, to compare BCG-induced immunity in the 2 groups. Our comprehensive approach to analysis includes: determining cytokine levels in plasma, evaluating cytokine expression and the memory phenotype of specific T cells, determining specific T cell proliferative and cytokine-producing capacity, assessing the pattern of mRNA expression, and determining whether BCG-induced antibody production patterns may correlate with protection. Results will be presented.

The effect of BCG strain and route of administration on the immune responses caused by the vaccine in infants

At present, we do not know whether BCG strain or route of administration determine efficacy. We evaluated antigen-specific immunity after percutaneous or intradermal administration of Japanese BCG or intradermal administration of Danish BCG. Ten weeks after vaccination of neonates, percutaneous Japanese BCG had induced significantly higher frequencies of BCG-specific IFN-gamma (-producing CD4+ and CD8+ T cells in BCG-stimulated whole blood; significantly greater secretion of the T helper 1-type cytokines IFN-γ, tumor necrosis factor (TNF)-alpha and interleukin (IL) 2; and significantly lower secretion of the T helper 2-type cytokine IL-4; and greater CD4+ and CD8+ T cell proliferation than did intradermal Danish BCG. Thus, BCG strain and route of vaccination confer different levels of immune activation, which may affect the efficacy of the vaccine.

Immune response to BCG vaccination in HIV-infected newborns

We have evaluated the risks and benefits of BCG vaccination in HIV-infected infants. However, we do not know whether BCG does protect HIV-infected children against the disease; rather BCG may itself cause disease in this population. Sequential BCG-induced immune responses were determined in 22 HIV-positive infants compared with that in 25 healthy infants born to mothers not infected with HIV and in 25 HIV-negative infants born to HIV-positive mothers. Results will be presented in the near future.

References

1) Hawkridge T, Scriba TJ, Gelderbloem S, et al.: Safety and immunogenicity of a new tuberculosis vaccine, MVA85A, in healthy adults in South Africa. J Infect Dis. 2008; 198: 544-52.
2) Soares AP, Scriba TJ, Joseph S, et al.: Bacillus Calmette-Guérin vaccination of human newborns induces T cells with complex cytokine and phenotypic profiles. J Immunol. 2008; 180: 3569-77.
3) Hussey G, Hawkridge T, Hanekom W: Childhood tuberculosis: old and new vaccines. Paediatr Respir Rev. 2007; 8: 148-54.
4) Moyo S, Hawkridge T, Mahomed H, et al.: Determining causes of mortality in children enrolled in a vaccine field trial in a rural area in the Western Cape Province of South Africa. J Paediatr Child Health. 2007; 43: 178-83.
5) Hatherill M, Hawkridge T, Whitelaw A, et al.: Isolation of non-tuberculous mycobacteria in children investigated for pulmonary tuberculosis. PLoS ONE. 2006; 1: e21.
6) Mahomed H, Kibel M, Hawkridge T, et al.: The impact of a change in bacille Calmette-Guérin vaccine policy on tuberculosis incidence in children in Cape Town, South Africa. Pediatr Infect Dis J. 2006; 25: 1167-72.
7) Murray RA, Mansoor N, Harbacheuski R, et al.: Bacillus Calmette Guérin vaccination of human newborns induces a specific, functional CD8+ T cell response. J Immunol. 2006; 177: 5647-51.
8) Davids V, Hanekom WA, Mansoor N, et al.: The effect of bacille Calmette-Guérin vaccine strain and route of administration on induced immune responses in vaccinated infants. J Infect Dis. 2006; 193: 531-6.

3. Present and future of TB vaccine development research

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Tuberculosis (TB) kills 2-3 million people every year. The current tuberculosis (TB) vaccine *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) is the most widely used vaccine worldwide, but it does not prevent the establishment of latent TB or reactivation of pulmonary disease in adults. The development of subunit vaccines has now reached the point where single antigens as well as poly-protein fusion molecules have been evaluated in animal models and found to provide efficient protection against tuberculosis. The most advanced of these vaccines such as the fusion between ESAT6/TB 10.4 and Ag85B are now in clinical trials. Currently the focus is on evaluating the influence of different adjuvants, live delivery systems, routes and prime-boost regimes for optimal expression of immunity in the lung, boosting of BCG and maintenance of immunological memory. Subunit vaccines can be used to boost BCG immunity either administered together (Tandem administration), shortly after BCG (early boost) or in adolescence when BCG immunity starts to wane (Late boost). A late BCG boost would frequently be administrated post-exposure to latently infected individuals and ongoing efforts are focused on understanding the impact this would have on existing vaccines and for the design of efficient booster vaccines.

References

1) Dietrich J, Billeskov R, Doherty TM, et al.: Synergistic

effect of bacillus Calmette-Guérin and a tuberculosis subunit vaccine in cationic liposomes: increased immunogenicity and protection. J Immunol. 2007; 178: 3721-30.
2) Andersen P: Vaccine strategies against latent tuberculosis infection. Trends Microbiol. 2007; 15: 7-13.
3) Dietrich J, Andersen C, Rappuoli R, et al.: Mucosal administration of Ag85B-ESAT-6 protects against infection with *Mycobacterium tuberculosis* and boosts prior bacillus Calmette-Guérin immunity. J Immunol. 2006; 177: 6353-60.
4) Dietrich J, Lundberg CV, Andersen P: TB vaccine strategies — what is needed to solve a complex problem? Tuberculosis (Edinb.). 2006; 86: 163-8.
5) Agger EM, Rosenkrands I, Olsen AW, et al.: Protective immunity to tuberculosis with Ag85B-ESAT-6 in a synthetic cationic adjuvant system IC31. Vaccine. 2006; 24: 5452-60.
6) Doherty TM, Andersen P: Vaccines for tuberculosis: novel concepts and recent progress. Clin Microbiol Rev. 2005; 18: 687-702.
7) Andersen P, Doherty TM: The success and failure of BCG. Implications for a novel tuberculosis vaccine. Nat Rev Microbiol. 2005; 3: 656-62.
8) Andersen P, Doherty TM: TB subunit vaccines — putting the pieces together. Microbes Infect. 2005; 7: 911-21.
9) Dietrich J, Aagaard C, Leah R, et al.: Exchanging ESAT6 with TB 10.4 in an Ag85B fusion molecule-based tuberculosis subunit vaccine: efficient protection and ESAT6-based sensitive monitoring of vaccine efficacy. J Immunol. 2005; 174: 6332-9.

4. Comments and directions in research and development of TB vaccines

Aeras Global TB Vaccine Foundation, Bethesda, Maryland, USA Jerald C. SADOFF

The 83rd Annual Meeting Mini-symposium

RESEARCH AND DEVELOPMENT OF VACCINES AGAINST TUBERCULOSIS

Chairpersons: [1]Kazuo KOBAYASHI and [2]Isamu SUGAWARA

Speakers:

1. Novel DNA vaccines against tuberculosis: Masaji OKADA (Clinical Research Center, National Hospital Organization Kinki-chuo Chest Medical Center)
2. BCG vaccine trials in South Africa: Gregory HUSSEY (South African Tuberculosis Vaccine Initiative, University of Cape Town, Cape Town, South Africa)
3. Present and future of TB vaccine development research: Peter ANDERSEN (Statens Serum Institute, Copenhagen, Denmark)
4. Comments and directions in research and development of TB vaccines: Jerald C. SADOFF (Aeras Global TB Vaccine Foundation, Bethesda, Maryland, USA)

Mycobacterium tuberculosis is one of the most successful bacterial parasites of humans, infecting over one-third of the population of the world as latent infection without clinical manifestations. Over 9.2 million new cases and nearly 1.7 million deaths by tuberculosis (TB) occur annually (http://www.who.int/tb/en/). TB poses a significant health threat to the world population. Global tuberculosis control is facing major challenges today. In general, much effort is still required to make quality care accessible without barriers of gender, age, type of disease, social setting, and ability to pay. Coinfection with *M. tuberculosis* and human immunodeficiency virus (TB/HIV), and multidrug-resistant (MDR) and extensively drug-resistant (XDR)-TB in all regions, make control activities more complex and demanding. Treating and preventing TB is challenging, even in developed countries where there is a modern health care system and infrastructure. Current treatment regimens last six to nine months, and erratic or inconsistent treatment breeds MDR (490,000 new cases/year) and even XDR-TB (40,000 new cases/year), which means that this pandemic could become even more difficult to control throughout the world. TB is a leading cause of death among people who are also infected with HIV, according to the World Health Organization. One-third of the 33.2 million people living with HIV also suffer from TB. The coinfection causes 230,000 deaths annually worldwide. Without proper treatment, approximately 90 percent of people living with HIV die within two to three months of contracting TB (http://www.stoptb.org/wg/tb_hiv/default.asp). The goal of this symposium is to understand the current situation of research and development of novel TB vaccines and the future perspective.

To win the fight against TB, a comprehensive approach is needed that includes new and more effective vaccines as well as improved diagnostics and treatment. The bacillus Calmette-Guérin (BCG) vaccine, created in 1921, is the only existing vaccine against TB. Unfortunately, it is only partially effective. It provides some protection against severe forms of pediatric TB, namely disseminated and meningeal tuberculosis occurring in the first year of life, but is unreliable against adult pulmonary TB, which accounts for most of the disease burden worldwide. Although BCG is the most widely administered vaccine in the world, there have never been as many cases of TB on the planet. There is therefore an urgent need for a modern, safe and effective vaccine that would prevent all forms of TB, including the drug-resistant strains, in all age groups and among people with human immunodeficiency virus (HIV).

Strategies for the research and development (R&D) are included 1) pre-exposure (prophylactic) and 2) post-exposure (therapeutic) vaccines. Based on the preparation, there are 4 types, such as 1) improved BCG, 2) attenuated *M. tuberculosis*, 3) subunit/component vaccines, and 4) DNA vaccines. Speakers have presented and discussed "R&D of novel vaccines against TB" better than current BCG.

To control TB and overcome the issues, such as drug-resistant TB and HIV-TB coinfection, we hope the presentation in the Mini-symposium promotes a more adventurous approach to develop a novel, effective and safe TB vaccine.

References

1) Kaufmann SHE: Robert Koch, the Nobel prize, and the ongoing threat of tuberculosis. N Engl J Med. 2005; 353: 2423–6.

2) Young DB, Perkins MD, Barry CE III: Confronting the scientific obstacles to global control of tuberculosis. J Clin Invest. 2008; 118: 1255–65.

3) Skeiky YAW, Sadoff JC: Advances in tuberculosis vaccine strategies. Nat Rev Microbiol. 2006; 4: 469–76.

Key words: Improved BCG, Attenuated *Mycobacterium tuberculosis*, Subunit/component vaccines, DNA vaccines, Pre-exposure (prophylactic) vaccines, Post-exposure (therapeutic) vaccines

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