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Beyond BCG: boosting strategies with viral vector vaccines

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Introduction

Mycobacterium tuberculosis (*Mtb*) is the causative agent for tuberculosis disease (TB). In 2013 9M people (1,1 HIV+) developed TB and 1,5M (360 000 HIV+) died from it. There were also registered 480 000 MDR-TB cases, three times higher than in 1990. HIV-TB coinfection and the increase of drug resistances have become a concern towards controlling the disease.

However, it's not all bad news. From 1990 to 2013 the mortality rate and prevalence have decreased a 45 and 41% respectively, and 37M lives were saved from 2000 to 2013 due to prevention programms and TB treatment.

Vaccination

The Bacille Calmette-Guérin (BCG) is the only vaccine available for preventing TB. The countries with the highest TB burden have a BCG vaccination policy. BCG only confers partial protection in children. Thus, in order to maximize the protection range a secondary boost is needed.

Viral vector vaccines as boosters of BCG immunization are an attractive approach. Replication-deficient variants of pathogenic virus such as the modified vaccinia virus (MVA) and adenovirus (Ad) are the most clinically advanced viral vectors.

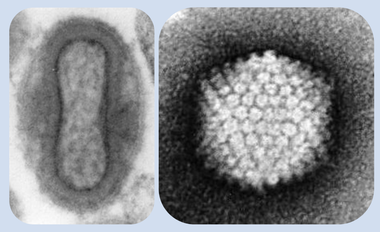
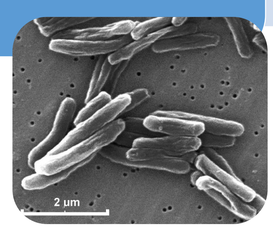


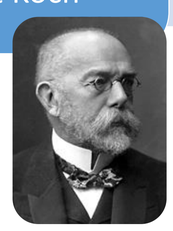
Image 1: Vaccinia virus and Adenovirus

DISCOVERY → ERRADICATION

1882 — Discovery of *Mtb* by Robert Koch



1890 — Development of tuberculine by Robert Koch



1921 — Development of BCG by Calmette and Guérin

1990 — Inclusion of BCG in the Expanded Program on Immunization

1993 — Inclusion of TB as Global Emergency by The WHO

2015 — 16 TB vaccine candidates in pipeline

Immune response to *Mtb*

The immune response required against *Mtb* is cell-mediated with T lymphocytes and mononuclear phagocytes (MP). The T-cell response is biased to the Th1 pole. The CD4+ and CD8+ T-cells both secrete INF-γ and TNF-α, that will activate the MP, whereas CD8+ also produce perforins, granulysins and granzyms that will harm the bacilli. The Th17 response is involved in the early defense and adaptive immunity against TB, it also may be a Th1 recruiter and therefore help accelerate the bacterial clearance. However, if maintained for long periods can induce pathology due to inflammation. The induction of long-lived memory T-cells is paramount in terms of control of the bacilli, this may be the major problem in the production of a TB vaccine.

Vaccine ID	Target indication	Delivery system	Notes about delivery system	Antigen	Antigen function	Mass (kDa)	Development phase	Outcomes
MVA85A/ AERAS-485	Preventive - Preexposure	Modified Vaccinia Virus Ankara (MVA)	Replication-deficient viral delivery system	Ag85A (Rv3804c)	Mycolyl transferase surface protein (virulence factor)	35.7	Phase I	Safety ✓ Immunogenicity ✓ Efficacy ✗
Ad5Ag85A	Preventive - Preexposure	Recombinant adenovirus serotype 5 (Ad5)	Replication-deficient viral delivery system	Ag85A (Rv3804c)	Mycolyl transferase surface protein (virulence factor)	35.7	Phase IIb	Safety ✓ Immunogenicity ✓ Efficacy ✗
AERAS-402	Preventive - Preexposure	Recombinant adenovirus serotype 35 (Ad35)	Replication-deficient viral delivery system	Ag85A (Rv3804c)	Mycolyl transferase surface protein (virulence factor)	35.7	Phase IIb	Safety ✓ Immunogenicity ✓ Efficacy ✗
				Ag85B (Rv1886c)	Fibronectin binding protein surface protein	34.6		
				TB10.4 (Rv0288)	ESAT-6 family protein	10.4		

CONCLUDING REMARKS

- In order to control and eventually eradicate TB there is a need for better diagnostics, treatments and an efficacious vaccine.
- In every trial conducted to date MVA85A, AdAg85a and Ad35/AERAS 402 have proved to be safe and immunogenic, but not efficacious.
- Concerns on adenoviral vectors regarding the potency for dampening the immune response due to the induction of neutralizing antibodies have been overcome
- Further investigation is required.

References

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