

Table of contents

Chapter I: Introduction

1. Tuberculosis: origins, evolution and interventions.....	1
1.1. Preface	
1.2. The Bacillus Calmette-Guérin vaccine	
1.3. Tuberculosis origins and evolution	
1.4. Tuberculosis epidemiology	
1.5. Diagnosis and treatment strategies	
1.6. Tuberculosis infection outcome and risk	
2. <i>M. tuberculosis</i> interplay with the host innate immune system.....	11
2.1. Airway epithelial cells as first innate immunity sensors	
2.2. Phagocytosis by alveolar macrophages	
2.3. <i>M. tuberculosis</i> elimination mechanisms	
2.4. <i>M. tuberculosis</i> survival mechanisms	
2.5. Early recruitment of inflammatory neutrophils	
2.6. The counteracting functions of innate myeloid subsets	
2.7. Delayed triggering of adaptive immunity	
3. Adaptive immune responses for protection against tuberculosis.....	27
3.1. Central role of CD4 ⁺ T cell responses	
3.2. Inflammatory response balanced by Treg cells	
3.3. CD8 ⁺ T cell protective immune responses	
3.4. Non-conventional T cell immunity support	
3.5. The role of B cells and antibodies	
3.6. Granuloma formation and infection control	
4. Tuberculosis stages and antigenic variation.....	39
4.1. <i>M. tuberculosis</i> -host mutual adaptation to latency	
4.2. Immunodominant antigens	
4.3. Latency-related antigens	
4.4. Resuscitation-related antigens	
4.5. Lipid antigens	
5. Tuberculosis vaccines.....	47
5.1. BCG revaccination strategy	
5.2. Alternative strategies to BCG vaccination in development	
5.3. Live attenuated recombinant vaccines	
5.4. Whole-cell and fragmented-cell vaccines	
5.5. Protein-based subunit vaccines and adjuvants	
5.6. Viral-based subunit vaccines	
5.7. DNA-based subunit vaccines	
6. Experimental animal models of mycobacterial infection.....	59

Annexe

Review: Bruffaerts N., Huygen K., Romano M., DNA vaccines against tuberculosis
Expert Opin Biol Ther 2014;14(12):1801-13

Aim of the work.....	64
Chapter II: BCG/pDNA coadministration in the mouse model.....	65
Increasing the vaccine potential of live <i>M. bovis</i> BCG by coadministration with plasmid DNA encoding a tuberculosis prototype antigen	
Bruffaerts N., Romano M., Denis O., Jurion F., Huygen K.	
<i>Vaccines</i> 2014, 2(1), 181-195	
BCG/DNA vaccine intradermal co-immunization increases B and T cell responses against <i>Mycobacterium tuberculosis</i> antigens in BALB/c mice	
Bruffaerts N., Kim J.O., Denis O., Jurion F., Vandenpoel C., Huygen K., Romano M.	
Manuscript for submission	
Chapter III: BCG/pDNA coadministration in the pig model.....	89
Increased B and T cell responses in <i>M. bovis</i> BCG vaccinated pigs co-immunized with plasmid DNA encoding a prototype tuberculosis antigen	
Bruffaerts N., Pedersen L.E., Vandermeulen G., Préat V., Stockhofe-Zurwieden N., Huygen K., Romano M.	
Manuscript accepted by <i>PLoS ONE</i>	
Chapter IV: Plasmid DNA vaccines encoding <i>Mycobacterium tuberculosis</i> stage-specific antigens	120
Immunogenicity of tuberculosis stage-specific DNA vaccines co-expressing Ag85A, PPE44 and latency-related antigens from the DosR regulon	
Bruffaerts N., Jurion F., Vandenpoel C., Franken K.L., Ottenhoff T.H., Huygen K., Romano M.	
Manuscript for submission	
Chapter V: Discussion.....	144
List of abbreviations.....	158
List of figures.....	161
References.....	162
Acknowledgements.....	195
Summary in French.....	196