

TABLE OF CONTENT

TABLE OF CONTENT	5
ACKNOWLEDGEMENT	7
SUMMARY	8
RÉSUMÉ	9
RÉSUMÉ (large public)	10
LIST OF ABBREVIATIONS	11
PREFACE	13
1. INTRODUCTION	15
1.1 BASIC PRINCIPLES OF INNATE AND ADAPTIVE IMMUNITY	15
1.2 T CELL DEVELOPMENT	16
1.2.1 T CELL DIFFERENTIATION	16
1.2.2 TCR GENE ASSEMBLY AND SOMATIC RECOMBINATION	22
1.2.3 TCR:pMHC RECOGNITION	23
1.2.4 DIVERSITY OF THE TCR REPERTOIRE	27
1.3 CANCER IMMUNOTHERAPIES	28
1.4 YELLOW FEVER VACCINATION AS A MODEL OF OPTIMAL IMMUNOGENICITY IN HUMANS	31
1.4.1 YELLOW FEVER VIRUS VACCINE (YF-17D)	31
1.4.2 HUMAN IMMUNE RESPONSE TO YF-17D VACCINATION	32
1.4.3 YELLOW FEVER AS A MODEL	35
2. PROJECT NETWORK OVERVIEW AND AIMS OF THESIS	38
3. RESULTS	41
3.1 AXIS 1: TRAV12-2 bias and TCR:pMHC studies	41
3.1.1 TRAV12-2 bias in the immunodominant response to YFV	42
3.1.2 Fishing out new A2/LLW-specific clonotypes using an optimized multimer staining procedure	57
3.1.3 Detailed description of the soluble TCR:pMHC production process	66
3.1.4 in vivo analysis of the TRAV12-2 bias using the transgenic ABAbDII mouse model	80
3.1.5 Characterization of potential superagonist variants of the A2/LLW epitope	92
3.1.6 CONCLUDING REMARKS	114
3.2 AXIS 2: Longitudinal analysis of the human immune responses to YF-17D vaccination	115
3.2.1 Characterization of all major immune cell populations following primary and booster YF-17D vaccination (aims a and b)	118
3.2.2 Analysis of A2/LLW-specific effector and long-lasting memory CD8 T cells in the early response to YF-17D (aim c)	172
4. ONGOING WORK AND PERSPECTIVES	176
5. CONCLUDING REMARKS	180
6. MATERIAL AND METHODS	181
6.1 Clinical studies: design, population and ethics statement	181
6.2 Biobank: Peripheral blood collection and processing	181
6.3 Viral load quantification	182
6.4 Plaque reduction neutralizing test (PRNT)	182
6.5 Generation and maintenance of T cell clones	182
6.6 Generation of T cell lines	183
6.7 TCR repertoire and clonotype analysis in A2/LLW-specific CD8 ⁺ T cell clones ...	183
6.8 TCR sequencing and analysis of the A2/LLW-specific T cell line	183

6.9 ⁵¹ Chromium release assays	184
6.10 Flow cytometry.....	184
6.10.1 Flow cytometry: list of reagents	186
6.10.2 Intracellular cytokine staining assay.....	188
6.10.4 Data processing and statistical analysis	188
6.10.5 Bioinformatics analysis of broad datasets.....	188
6.11 NTamer staining and dissociation kinetic measurements	189
6.12 Sizing scan.....	189
6.13 Combinatorial peptide library (CPL) scans	190
6.14 Protein expression, refolding and purification	190
6.15 Crystallization, diffraction data collection, and model refinement.....	191
6.16 Measuring the thermal stability of HLA-A*0201–peptide complexes	192
6.17 In silico TCR:pMHC analyses: Modeling the TCR:pMHC complex and Molecular Dynamics (MD) simulations	192
7. REFERENCES.....	194
APPENDIX 1: European Journal of Immunology – Cover 2/18.....	224
APPENDIX 2: T cell receptor alpha variable 12-2 bias in the immunodominant response to Yellow fever virus	225
APPENDIX 3: Human stem cell-like memory CD8 T cells establish early in the acute response to Yellow Fever virus vaccination	240
CURRICULUM VITAE	278