

Contents

Contents	13
I General introduction	23
II Research objectives	27
I The beneficial role of the immune system	29
1 SmartFACS: a new deconvolution tool	31
1 Immune cell types	31
1.1 Immunosurveillance	32
1.2 Myeloid cells	34
1.3 Innate Lymphoid Cells (ILCs)	35
1.4 B cells	35
1.5 T cells	36
2 Convex optimization	38
2.1 Convex sets and functions	38
2.2 Projection onto a convex	39
2.3 The projected gradient algorithm	41
2.4 Generalized version of the projected gradient algorithm	42
2.5 Nesterov's acceleration method	43
2.6 Subdifferential	45
2.7 Extrema with equality constraints	45
2.8 Extrema with inequality constraints	47
3 Aim	48
4 Results	49
4.1 Mathematical model	49
4.2 The reference matrix K	72
4.3 Comparison with other methods	76
5 Discussion	79
2 Immunotherapy: the anti-PD1 treatment	81
1 Oncogenesis	81
2 Immunotherapy	83
2.1 Systemic administration of recombinant cytokines	83
2.2 Adoptive transfer of T cells and CAR-T therapy	83

CONTENTS

2.3	Vaccines against cancer	85
2.4	Monoclonal antibodies, including immune checkpoint inhibitors	88
2.5	Combination of treatments	90
3	Anti-PD1 therapy	91
3.1	The anti-tumor immune response	91
3.2	Mechanism of action of PD-1/PDL-L1 in immune resistance	92
3.3	Anti-PD1 and anti-PD-L1 therapy	94
3.4	Comparison anti-PD1 versus anti-PDL1	98
3.5	Adverse events	99
3.6	Primary resistance to anti-PD1/PDL1 therapy	100
3.7	Acquired resistance to anti-PD1/PDL1 therapy	105
3.8	Predictive Biomarkers	106
3.9	Strategies for overcoming resistance	107
3.10	Therapeutic combinations and ongoing studies	109
3.11	Mouse model of bilateral tumors	109
3.12	Interest for myeloid cells in anti-PD1 therapy	111
4	Aim	112
5	Results	113
5.1	The bilateral tumor mouse model	113
5.2	Pre-treatment tumor environment analysis using bulk RNA-sequencing	115
5.3	Mice responding to anti-PD1 therapy display an increased expression of myeloid cells associated to PD-L1	124
5.4	IFN γ -dependent expression of PD-L1 in mice responding to immunotherapy	130
5.5	Presence of tumor-reactive CD8 $^{+}$ T cells expressing high levels of Tim3	134
6	Materials and methods	138
7	Discussion	144

II The deleterious role of the immune system as a cancer (chronic myeloid leukemia) 147

3	Stochastic modeling of chronic myeloid leukemia	149
1	Hierarchical organization of the blood system	149
2	The different types of leukemia	151
3	Chronic myeloid leukemia	151
3.1	Incidence	151
3.2	Genetic cause of CML	152
3.3	Symptoms and disease phases	154
4	Treatment of chronic myeloid leukemia	155
4.1	Previous treatment	155
5	Monitoring chronic myeloid leukemia	157
5.1	Hematologic response	158
5.2	Cytogenetic response	158
5.3	Molecular response	159
6	Novel approaches and technologies for monitoring molecular response	160

6.1	qPCR from genomic DNA	160
6.2	Digital PCR	162
7	Stopping treatment	163
7.1	Motivation	163
7.2	Imatinib discontinuation	164
7.3	Second-generation TKI discontinuation	166
7.4	Studies on dose reduction	167
7.5	Second TFR attempt	167
7.6	Criteria for TKI discontinuation	168
7.7	Predictors of successful TKI discontinuation	169
8	Branching processes	171
8.1	Continuous-time Markovian branching processes	171
8.2	Continuous-time Markovian multitype branching processes	172
9	Markovian trees	173
9.1	Phase-type distribution	173
9.2	Transient Markovian arrival process	174
9.3	Markovian binary trees	175
10	Approximate Bayesian Computation	178
10.1	ABC rejection method	179
10.2	ABC population Monte Carlo	180
11	Aim 1	183
12	Results part 1	184
12.1	Model parameters for hematopoiesis	184
12.2	Model parameters for CML	189
12.3	Markovian Binary Tree model for CML	190
13	Simulations of CML patients	195
14	Aim 2	199
15	Results part 2: inference on the initiation of the leukemia	200
15.1	Population Monte Carlo ABC - continuous parameter case	200
15.2	Population Monte Carlo ABC - discrete parameter case	202
16	Numerical results with simulated data	205
16.1	Validation of the method	207
16.2	Sensitivity analysis	208
16.3	Results for real patient data	211
17	Aim 3	214
18	Results part 3	215
18.1	Treatment modeling	215
19	Study of treatment discontinuation with our model	219
20	Discussion	228
4	Publications & other projects	231
5	Overall conclusion and future research	247

III Annexes	253
A Annexes	255
1 Supplementary figures of chapter 3	255
1.1 Validation of the ABC-PMC method	255
1.2 Sensitivity analysis	256
1.3 Results for real patient data	259
Bibliography	261