TABLE OF CONTENTS

LIS	ST OF FIGUERS	6
LIS	ST OF TABLES	7
LIS	ST OF ABBREVIATIONS	8
1.	INTRODUCTION	11
2.	LITERATURE 2.1. CD4+ T helper cells: differentiation, function, and regulation	12
	2.1. CD4+ T helper cells: differentiation, function, and regulation	12
	2.1.1. Immune system – an overview	12
	2.1.2. CD4+ T cells – lymphopoiesis and activation	12
	2.1.3. Classification of CD4+ T helper cell lineages	12
	2.1.4. Cross-regulation between T helper cell lineages	14
	2.1.5. CD4+ T helper cell heterogeneity and plasticity 2.1.6. Heterogenous T-bet+ GATA-3+ Th2/1 hybrid cells	15
	2.1.6. Heterogenous T-bet+ GATA-3+ Th2/1 hybrid cells	16
	2.2. Th2 response in GI nematode infections	16
	2.2.1. Heligmosomoides polygyrus – model for chronic helminthiasis	16
	2.2.2. Immune response in GI nematode infections	17
	2.2.2.1. Importance of CD4+ T cell response 2.2.2.2. CD4+ T cell response in human helminthiasis	18
	2.2.2.2. CD4+ T cell response in human helminthiasis	18
	2.2.3. Regulation of anti-nematode Th2 response by Th1 cytokines	19
	2.2.3.1. Cross-inhibition by Th1 cytokines and type 1 infections	19
	2.2.3.2. Differential resistance across inbred mice lines	19
	2.3. Memory phenotype CD4+ T cells	19
3.	MATERIAL AND METHODS	2
	3.1. MATERIAL	2′
	3.1.1. Laboratory equipment	2
	3.1.2. Laboratory plasticware	2′
	3.1.3. Reagents	2′
	3.1.4. Growth factors, inhibitors, and stimulators	22
	3.1.5. Cytokines and neutralizing antibodies for in vivo administration	22
	3.1.6. Buffers and media	22
	3.1.7. Single cell preparation	22
	3.1.8. Flow cytometry (buffers)	23
	3.1.9. Flow cytometry (antibodies, dyes, and other reagents)	23
	3.1.10.Software	24
	3.2. METHODS	24
	3.2.1. Infection model, in vivo treatments, and samplings	24
	3.2.1.1. Ethics statement	24
	3.2.1.2. Mice and parasites	24
	3.2.1.3. H. polygyrus infection	24
	3.2.1.4. In vivo treatments	24
	3.2.1.4. In vivo treatments 3.2.1.5. Intermediate blood and fecal sampling	25
	3.2.2. Parasitological assays	25
	3.2.2.1. L4 migration assay	25
	3.2.2.2. Parasite egg counting from feces	25
	3.2.2.3. Adult worm counting	25
	3.2.2.4. Female worm fecundity analysis	25
	3.2.3. Assessment of immunological parameters	25
	3.2.3.1. Preparation of single cell suspensions	25
	3.2.3.2. Isolation of lymphocytes from peripheral blood	26
	3.2.3.3. Generation of bone marrow derived dendritic cells	26
	3.2.3.4. Detection of parasite specific CD4+ T cell responses	26
	3.2.3.5. Polyclonal stimulation for detecting intracellular cytokines	26
	3.2.3.6. Cell staining for flow cytometry	2
	3.2.3.7. Flow cytometric analysis	



4.

3.2.3.8. Statistical analysis	27
RESULTS	28
4.1. IFN-γ rises in an age-dependent manner in naïve and H.p. infected	••
BALB/c mice	28
4.1.1. IFN-γ competent cells increase with age in uninfected BALB/c mice	
4.1.2. Rise in age is associated with increased effector/memory like	••
T cells at steady state	.29
4.1.3. Age-dependent rise in IFN-y is maintained post Hp infection	30
4.2. Mature mice accumulate more Th2/1 cells and display poor	
parasite control	31
4.2.1. Mature mice display increased frequencies of Th2/1 hybrid cells	31
4.2.2. Higher Th2/1 bias in mature mice correlates with poor	
parasite control	32
4.2.3. Intestinal IFN-γ competence positively correlates with	
worm fecundity	32
4.2.4. Early Th2 responses in H.p. infected adult vs. mature mice	33
4.3. Early blocking of type 1 cytokines leads to increased parasite control	34
4.3.1. Early IFN-γ/IL-12 blocking leads to restricted generation of	
Th2/1 cells	34
4.3.2. Diminished Th2/1 response correlates with higher resistance.	
4.4. Early exposure to IFN-γ promotes Th2/1 cells and leads to poor resistance	37
4.4.1. Early IFN-γ treatment leads to expansion of local and	
systemic Th2/1 cells	37
4.4.2. More Th2/1 cells correlate with poor parasite control	~~
in IFN-γ treated mice 4.5. IFN-γ promotes the overall systemic GATA-3+ T cell response	38
4.5. IFN-γ promotes the overall systemic GATA-3+ T cell response	39
4.6. Differential IFN-γ availability dramatically affects the	
parasite specific (PS) responses	41
4.6.1. PS IFN-γ producing cells rise in an age-dependent manner	41
4.6.2. Experimental manipulation of early IFN-γ availability alters	
the production of PS IFN-γ	42
4.7. Increased mucosal IFN-γ availability promotes the fitness of	
developing larvae	43
4.7.1. IFN-γ treatment leads to an early rise in IFN-γ competent	
Th2/1 cells in small intestine	43
4.7.2. Higher mucosal IFN-γ competence correlates with increased	
capacity of L4 migration in IFN-γ treated mice	45
4.8. Susceptible C57BL/6 mice are characterized by higher steady	40
state Th1 accumulation and extensive generation of Th2/1 cells	46
4.8.1. More rapid accumulation of Th1 cells is seen at steady state	46
in C57BL/6 mice	40
4.8.2. IFN-γ competent C57BL/6 mice are populated by	46
more Th2/1 cells post H.p. infection compared to BALB/c mice 4.8.3. C57BL/6 mice harboring more Th2/1 cells display poor	40
4.6.5. C57 BL/6 fillice flatborning more ffiz/1 cells display poor	47
parasite control	•′
1.6.4. Early 1112/1 bias in Co7 bb/o filice is associated with increased	48
L4 migration capacity	
SJL mice	49
SJL mice	, 5
resistant and susceptible strains	50
resistant and susceptible strains	
early IFN-γ availability	51
4.9.1. Early restriction of IFN-γ availability leads to poor Th2/1 response	_51

	4.9.2. Early blocking of IFN-γ leads to lowered mucosal IFN-γ competence	_52
	4.9.3. Diminished PS IFN-γ production seen upon early blocking of IFN-γ	53
	4.9.4. Pronounced innate type 2 responses are seen in IFN-γ	
	restricted mice	54
	4.9.5. More efficient parasite control is seen in IFN-γ restricted mice	54
	4.9.6. Ameliorated small intestinal pathology in IFN-γ restricted mice	55
5.	CONCLUSION AND PERSPECTIVES	<u></u> 57
	5.1. Conclusion	57
	5.2. Perspectives	57
6.	DISCUSSION	59
	6.1. Age-dependent bias in favor of IFN-γ and poor resistance in mature mice	
	6.2. Cross-inhibition of effective anti-nematode immunity by type 1 cytokines	
	6.3. IFN-γ availability and Th2/1 bias in inbred mice with differential resistance	60
	6.4. Determination of larval fitness by L4 migration assay	
	6.5. Experimental manipulation of early IFN-γ availability	61
	6.6. Type 2 promoting effect of IFN-γ in nematode infection	
	6.7. Role of IFN-γ in ameliorating small intestinal immunopathology	
	6.8. Implications of our findings on epidemiological models.	
7.	ZUSAMMENFASSUNG	64
	SUMMARY	66
9.	BIBLIOGRAPHY	67
10	LIST OF PUBLICATIONS	84
11	. ACKNOWLEDGEMENTS	85
12	. DECLARATION OF INDEPENDENCE	86