

Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS – I)

Ströbel P. et al. Journal of Pathology. 2007; 211:563-571

Inhalt

1. Thymome, Thymuskarzinome (TC)

2. Thymusphysiologie

3. AIRE in Thymomen

1. Thymome, TC

- Seltene maligne epitheliale Tumore des Thymus – häufigste im vord. Mediastinum
- Inz.: 0,13/100.000 Personenjahre
- Manifestationsalter – Gipfel bei 50 Jahren
- Symptome: Husten, Pneumonie, Druck auf der Brust, Muskelschwäche (Myasthenia Gravis)
- Thymome mit MG: **30-44%**
- MG mit Thymomen: **10-15%**
- Therapie: Thymektomie (z.B.: VATS)

Thymomklassifikation vs. Staging

WHO Klassifikation: histologische
Einteilung (A, AB, B1, B2, B3, C)

Modifizierte Masaoka – Koga- Staging
System (I bis IV) -> bester Marker für
Prognose und Therapie

2. Thymusphysiologie

Funktion: T-Zell Reifung (pos. – neg. Selektion)

Vor.: spezielle **reticuloepitheliale Zellen** in Cortex und Medulla (Stroma)

Cortex: Ammenzellen (BTS), Dendritische Zellen, Makrophagen -> Körnerkugeln

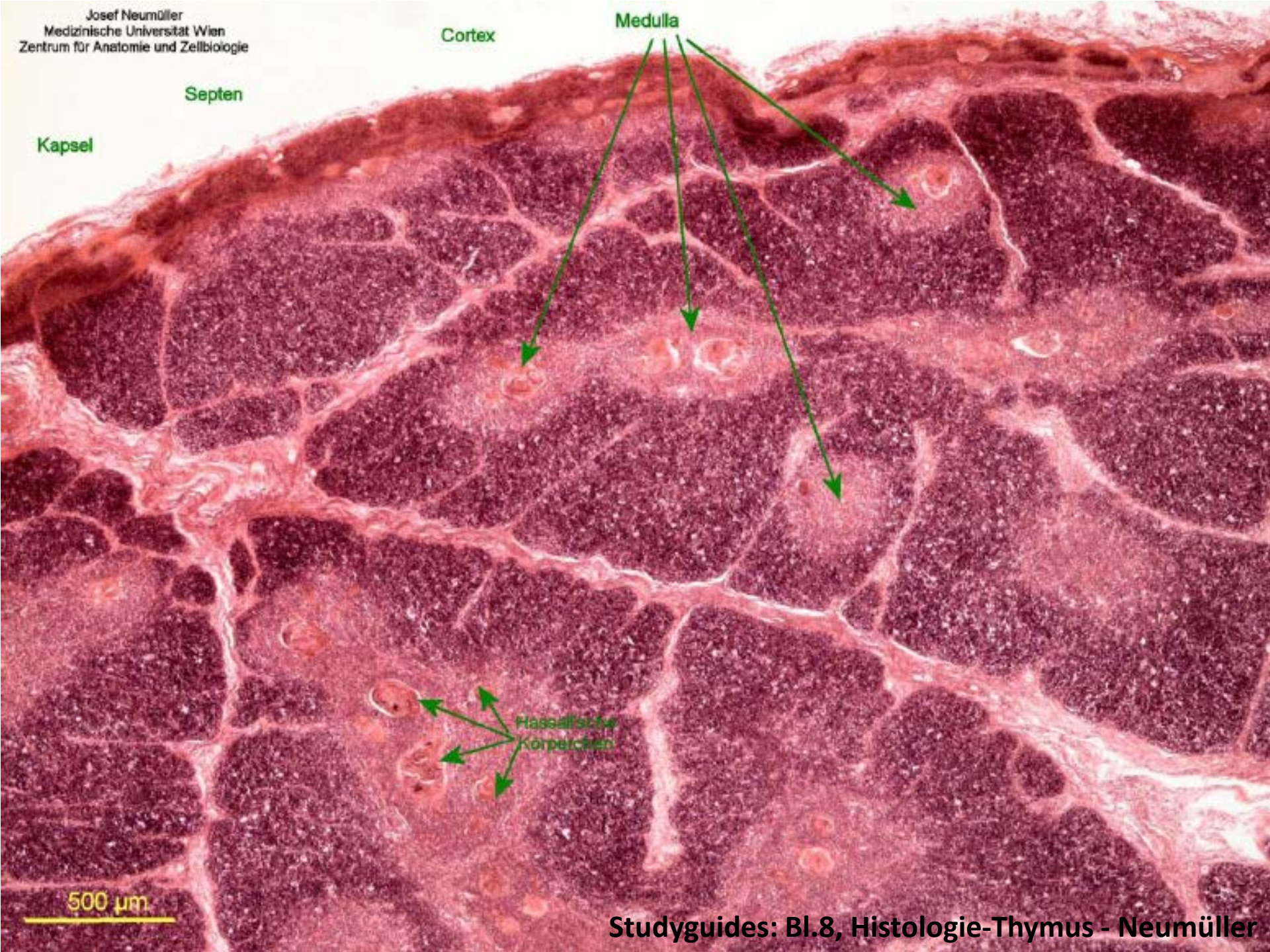
Medulla: Dendritische Zellen, Makrophagen, Hassal'sche Körperchen

Cortex

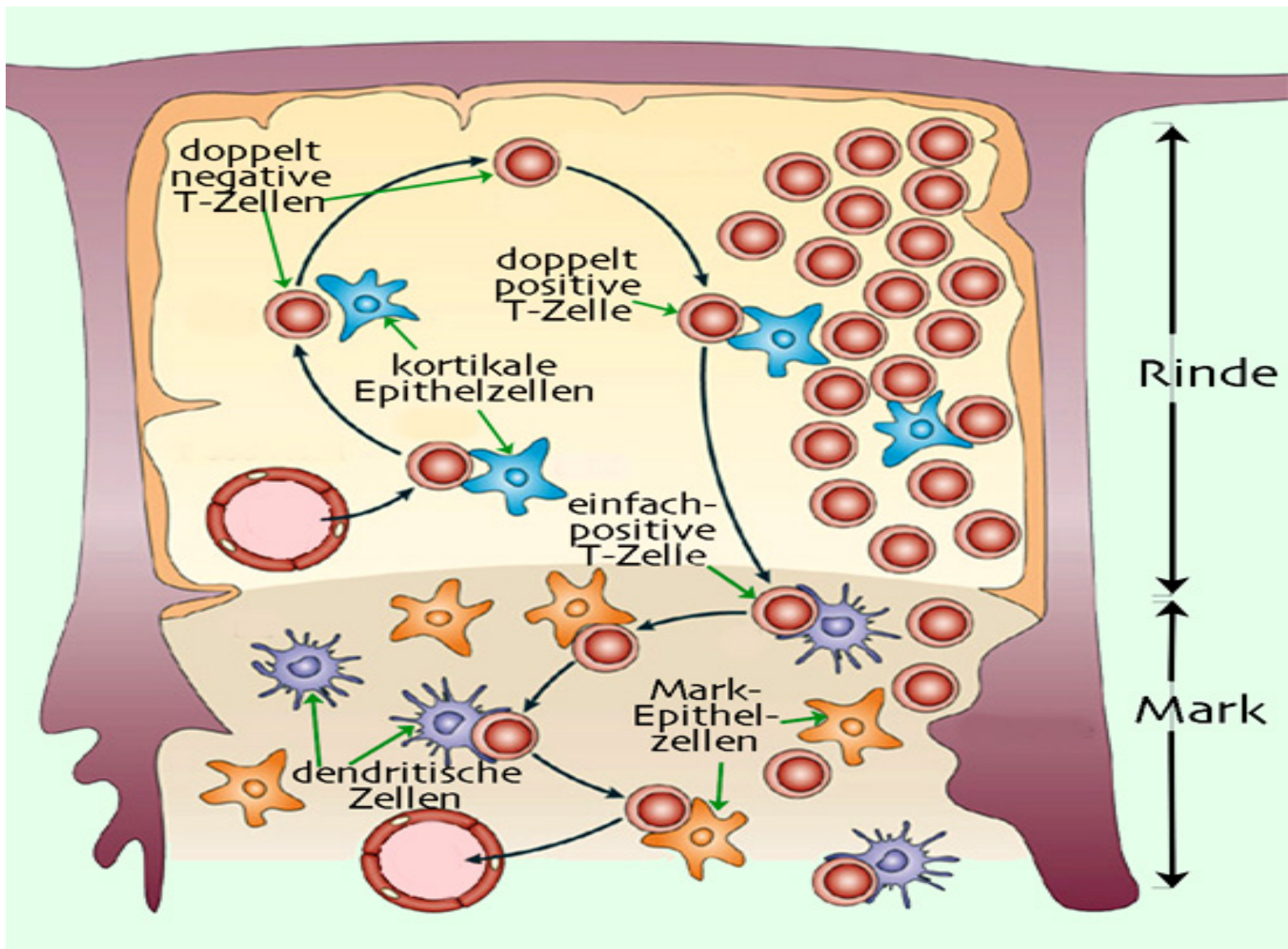
Medulla

Septen

Kapsel



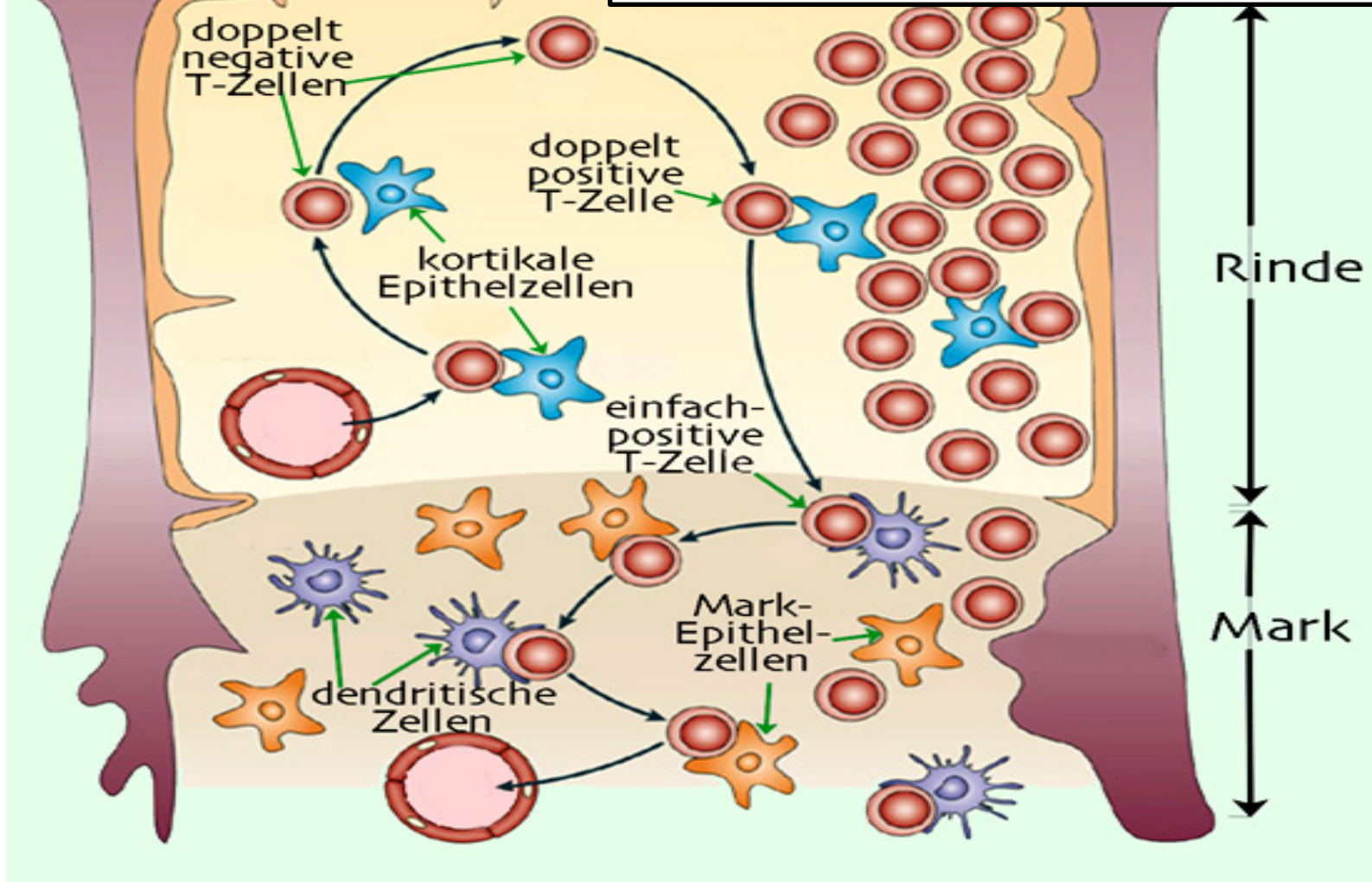
500 µm



Reifung und Selektion (positiv in der Rinde, negativ im Mark) von T-Zellen im Thymus

Nach: Klein et al, Nature Reviews Immunology 2009; 9, 833-44

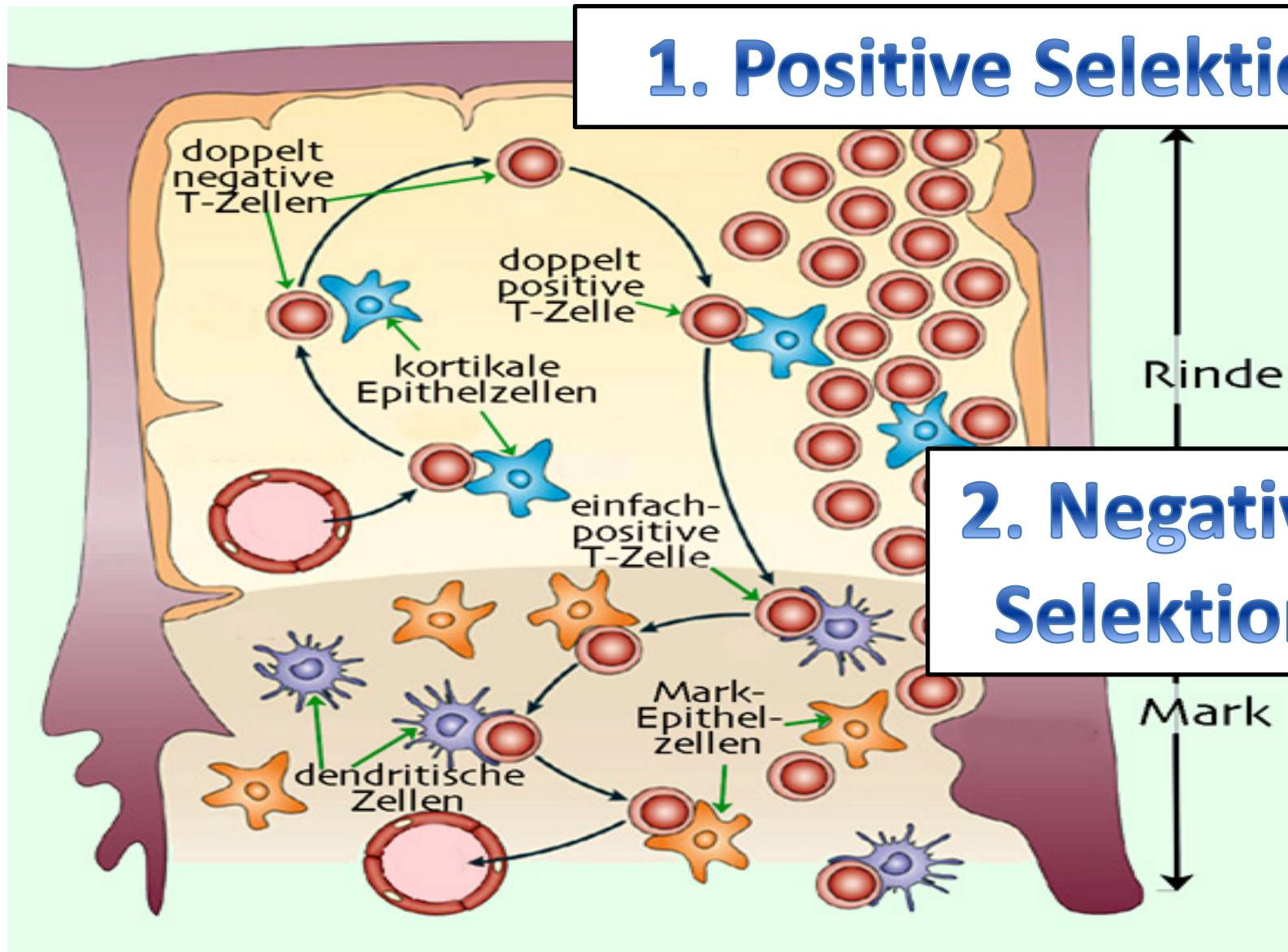
Positive Selektion



Reifung und Selektion (positiv in der Rinde, negativ im Mark) von T-Zellen im Thymus

Nach: Klein et al, Nature Reviews Immunology 2009; 9, 833-44

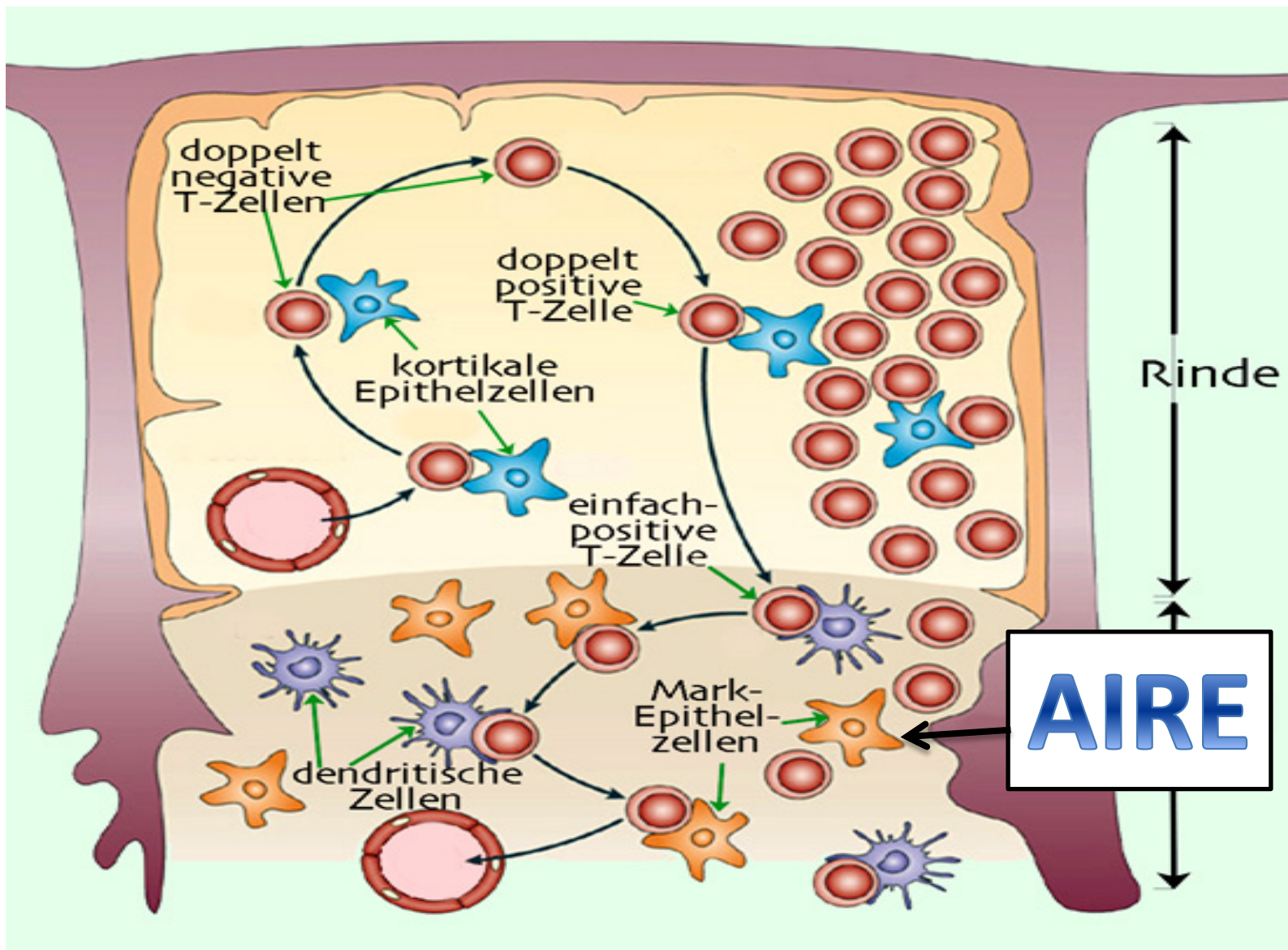
1. Positive Selektion



2. Negative Selektion

Reifung und Selektion (positiv in der Rinde, negativ im Mark) von T-Zellen im Thymus

Nach: Klein et al, Nature Reviews Immunology 2009; 9, 833-44



Reifung und Selektion (positiv in der Rinde, negativ im Mark) von T-Zellen im Thymus

Nach: Klein et al, Nature Reviews Immunology 2009; 9, 833-44

3.AIRE in Thymomen

Methodik:

- Immunhistochemie (IHC)
- ELISA
- RT-PCR

Studienpopulation

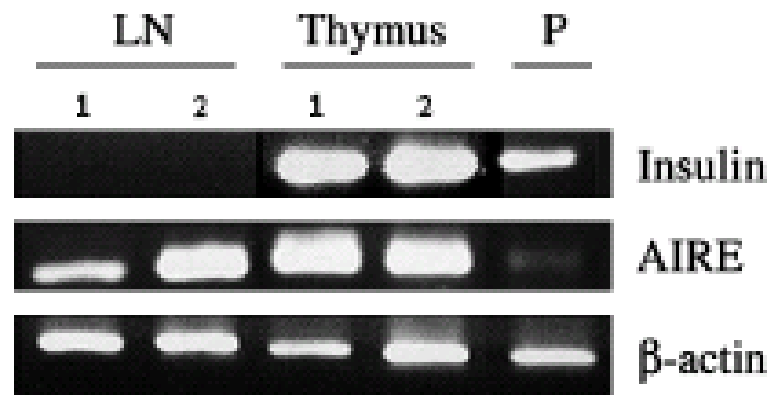
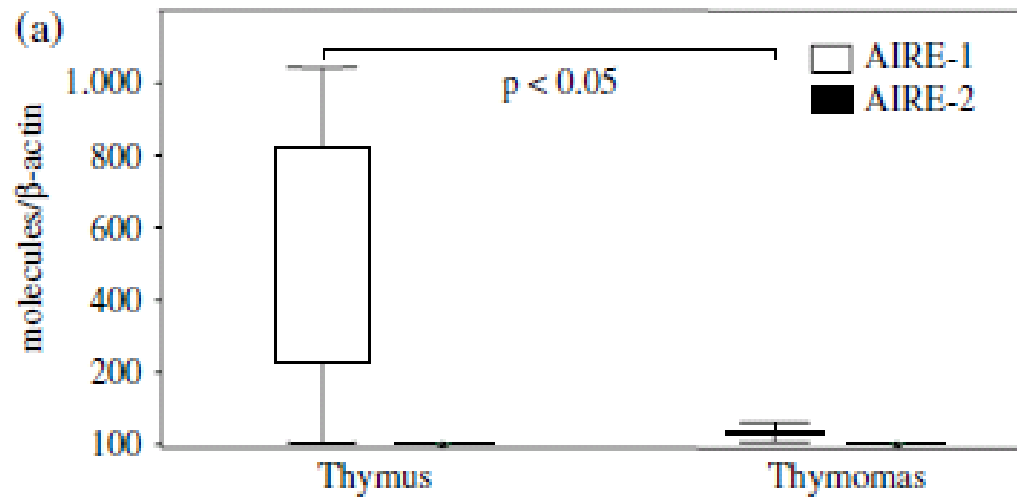
Table 1. Demographics of patients included in this study

Case No	Sex (M/F)	Age	Diagnosis	MG (yes/no)
1–21	10/11	35–88	Type A thymoma	6/15
22–69	16/32	18–89	Type AB	20/28
70–215*	61/85	29–87	Type B thymomas	93/53
216–260	15/30	15–45	TFH	45/0
261–270	2/8	35–75	Control thymuses	0/10

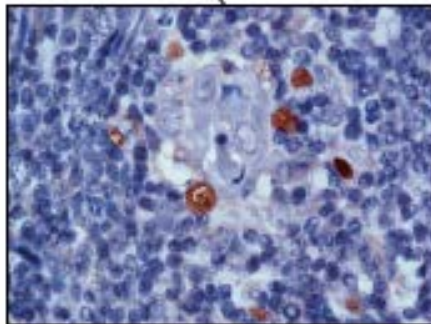
* Paraffin blocks for the preparation of a multi-tissue array were available in 171 of the 215 thymoma cases.

MG: myasthenia gravis; TFH: thymic follicular hyperplasia.

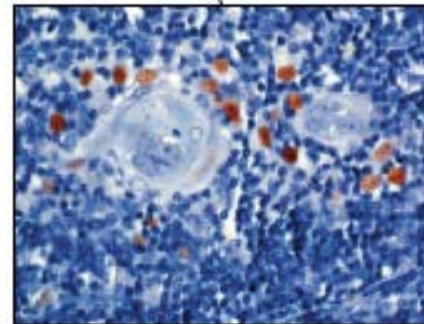
AIRE in Thymomen?



Thymus



Type B1



Type A



Type AB



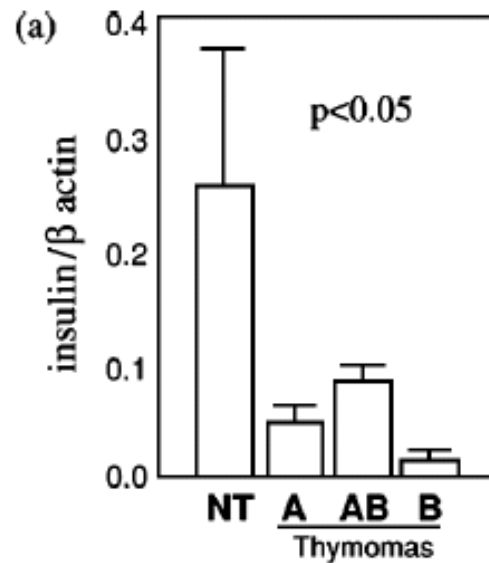
Type B2

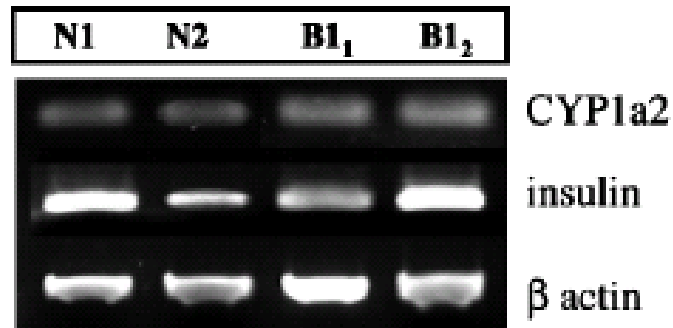
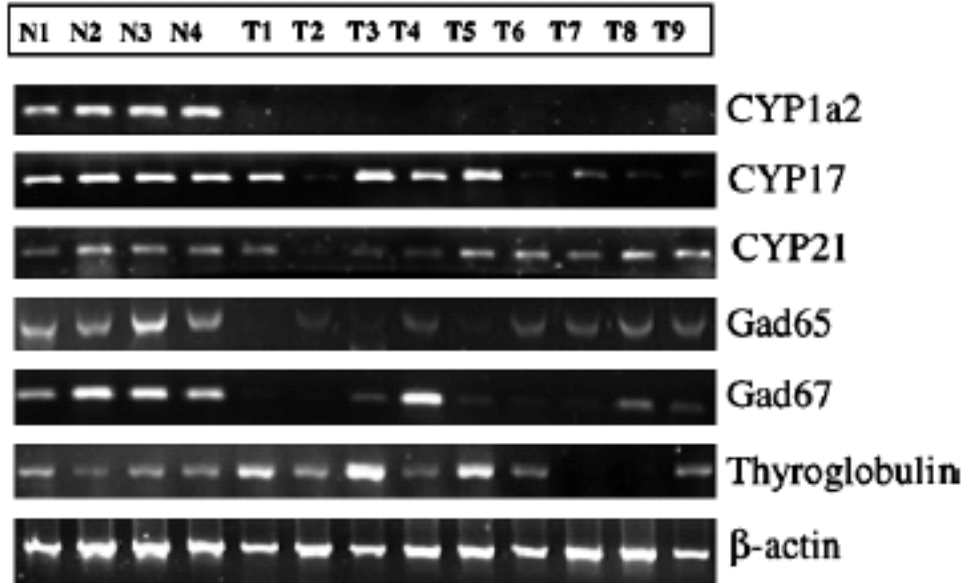


Autoimmune polyendocrinopathy syndrome type I (APS-I)

- **AIRE – Defizienz**
- Neuroendokrinen Autoimmunerkrankungen:
M.Addison, Hypoparathyroidism.,
Hypogonadism., Autoimmunhepatitis,
Candidiasis,...
- Typ. AB: Insulin, CYP 1A2, CYP 17,....

Thymome – AIRE neg. APS – I AIRE neg. Thymome vs. APS – I





Tumour type	No	MG (%)	Autoimmune diseases other than MG	
			Among MG+ cases	Among MG- cases
A	21	6 (29)	1 SLE, 1 SC	2 PRCA, 1 PV
AB	48	20 (42)	1 PV, 1 SD	1 PRCA, 2 SLE
B				
B1	17	12 (71)	—	1 RA, 1 IDDM
B2	85	51 (60)	2 aT, 1 IDDM	3 SLE, 1 aHep, 3 aT
B3	44	30 (68)	1 RA, 1 IDDM, 1 ED	—
Total	215	119 (55)	10	15

aHep = autoimmune hepatitis; aT = autoimmune thyroid disease; ED = ectodermal dystrophy; IDDM = type I diabetes; PRCA = pure red cell aplasia; PV = pemphigus vulgaris; RA = rheumatoid arthritis; SC = sarcoidosis; SD = scleroderma; SLE = systemic lupus erythematosus.

Autoimmune disease	Autoantibodies against	Incidence in thymomas		Incidence in TFH		Incidence in healthy people
		Number of Ab-pos/tested	Number of disease pos	Number of Ab-pos/tested	Number of disease pos	Number of Ab-pos/tested
Collagen disorders	Nuclei (ANA) (27)	8/27	0	2/8	0	3/30
	ENA	0/27	0	0/8	0	0/30
	dsDNA	0/27	0	0/8	0	0/30
	Centromeres (28)	0/28	0	0/8	0	0/30
	Nucleoli	2/28	0	0/8	0	3/30
Rheumatoid arthritis	CCP	1/28	0	2/8	0	0/30
Vasculitis	Granulocytes:					
	pANCA	1/28	0	0/8	0	0/30
	cANCA	1/28	0	0/8	0	0/30
Autoimmune liver						
Autoimmune hepatitis	Nuclei (ANA)	8/27	1	2/8	0	3/30
	SMA	3/27	0	1/8	0	3/30
	Actin	1/27	0	1/8	0	0/30
	LKM1	1/27	0	0/8	0	0/30
	LP/SLA	0/28	0	0/8	0	0/30
	APS-1	CYP1A2	0/28	0	0/8	0
	CYP2A6	1/28	0	0/8	0	0/20
	CYP2B6	1/28	0	0/8	0	0/20
Organ specific						
Thyroiditis	Thyroperoxidase	5/28	2	1/8	0	2/30
	Thyroglobulin	4/28	1	1/8	0	1/30
Addison's disease	Adrenal cortex	3/25	0	2/7	0	0/30
Diabetes mellitus type 1	Islet cells	0/24	0	0/3	0	0/30
	GAD65	3/29	1	1/8	0	1/30
	Insulin	0/28	0	0/8	0	0/30
Myasthenia gravis	AchR	16/27	15	8/8	8	0/30
	HMF (striational Ab)	17/27^a	11	0/8	0	2/30
	Fibrils	15/27	9	1/8	0	0/30
CAG/PA	Parietal cells	1/27	1	1/8	0	3/30
Natural autoantibodies						
Infectious/parainfectious	Sarcolemma	7/27	0	3/8	0	8/30
	Vascular	0/27	0	0/8	0	0/30
Anti-cytokine antibodies						
	IFN- α 2 (neutralizing)	24/38^a	0	0/34 Ref 41	0	0/70 Ref 41
	IFN- ω (neutralizing)	20/38^a	0	0/34 Ref 41	0	0/70 Ref 41
	IL-12	22/38^a	0	0/34 Ref 41	0	0/70 Ref 41

Conclusio

1. Mehrheit der Thymome ist AIRE neg.; Ausnahme B1 Thymome **ABER** Thymus Remnants und Lymphknoten sind pos.
2. Kein Unterschied bei AIRE neg. oder pos. Thymomen hinsichtlich Autoimmunerkrankungen
3. Obwohl AIRE neg. keine APS –I oder spezifische Antigene
4. 100% von APS-I Anti-Cytokin pos. (v.a. IFN); ~60% der Thymome pos.
5. Welche Rolle spielt AIRE in der Immunologie und T-Zell Reifung (Periphere Wirkung?)