Thrombotisch Thrombozytopenische Purpura

Innovative Therapie mit Antikörpern

3. Seminar der
TTP-Selbsthilfegruppe in der DHG
Mainz, 08.04.2006

Dr. med. Georg Heß

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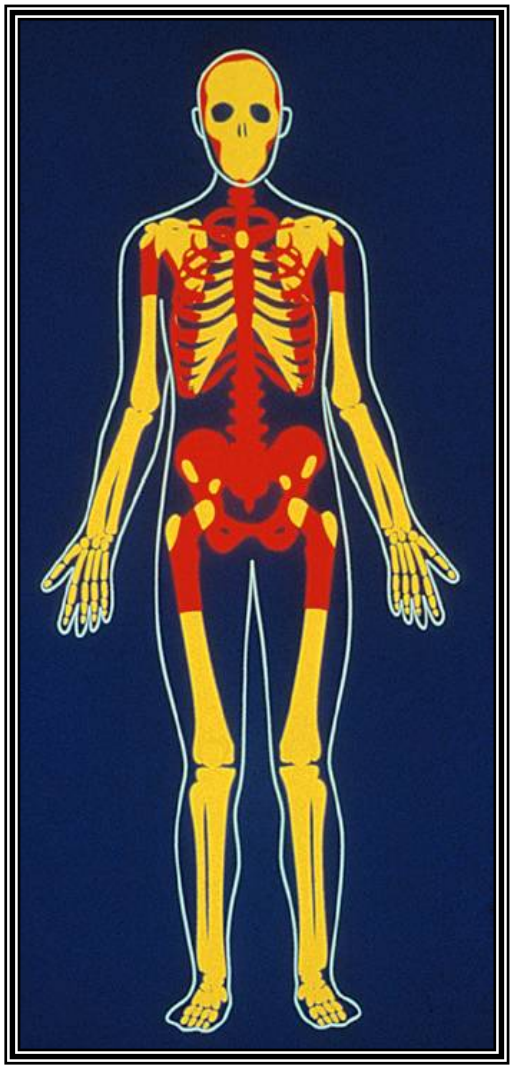
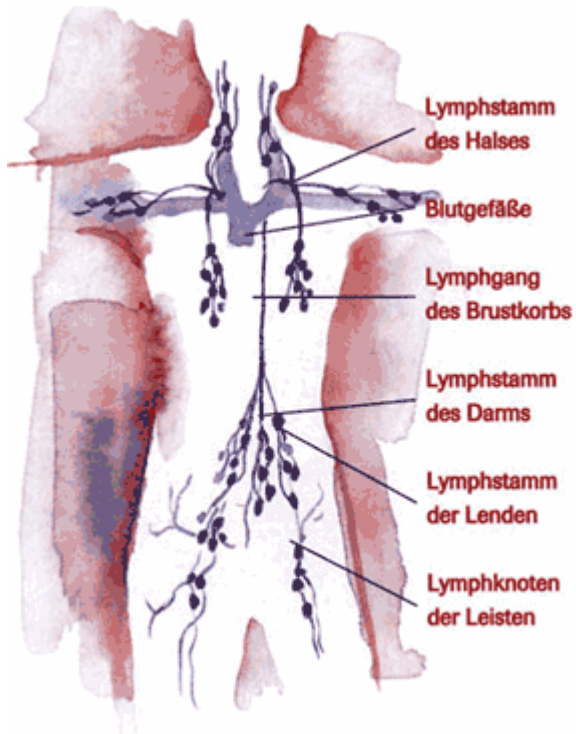
Das Knochenmark

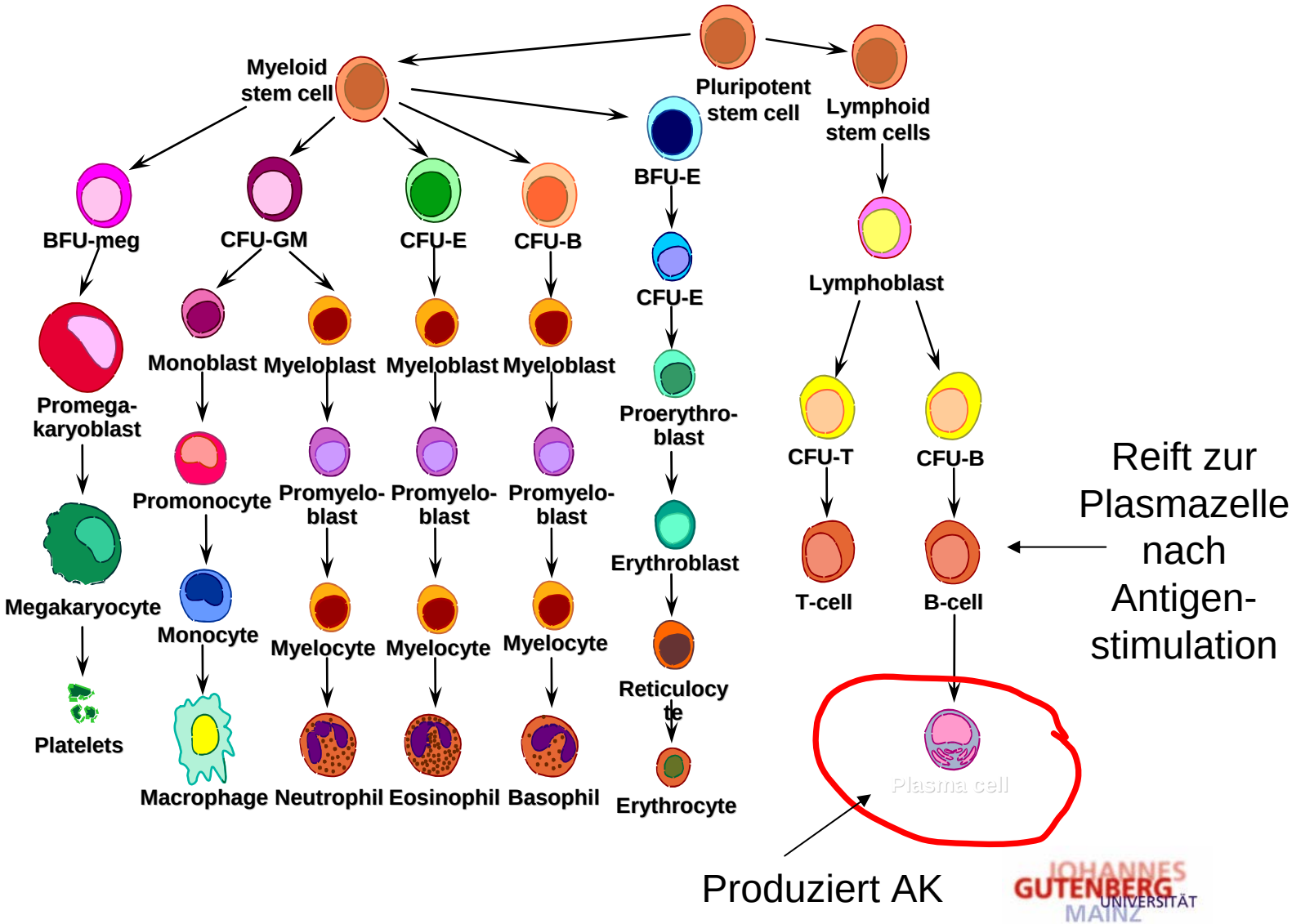


- Knochenmark
  - Rotes Mark
    - Hämopoetisch aktiv
    - Volumen ca. 1500 ml
    - Bei Geburt in allen Knochen aktiv
    - Bei Adulten hauptsächlich im Becken, Sternum, Rippen und Wirbelkörpern
  - Inaktives gelbes Mark
    - Reserve mit hämopoetischer Kapazität

Lymphsystem



Aufbau des zellulären Immunsystems



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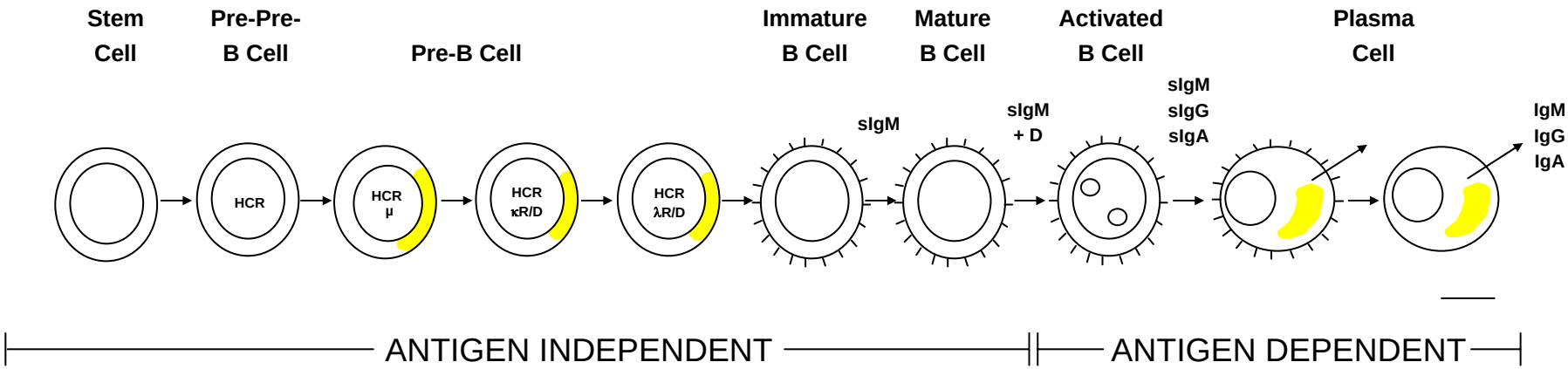
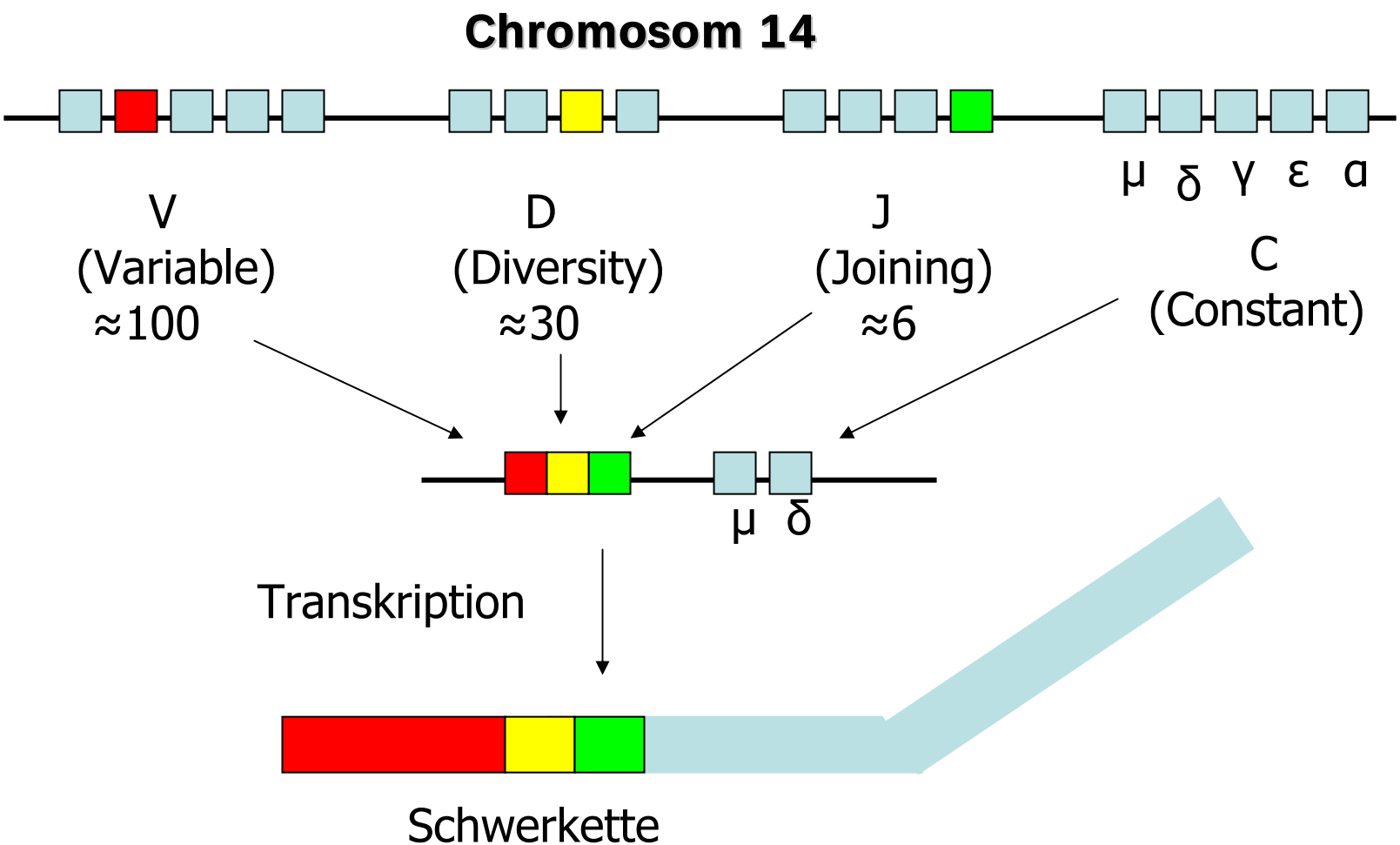
Entwicklung von T- und B-Lymphozyten



CD20 expression

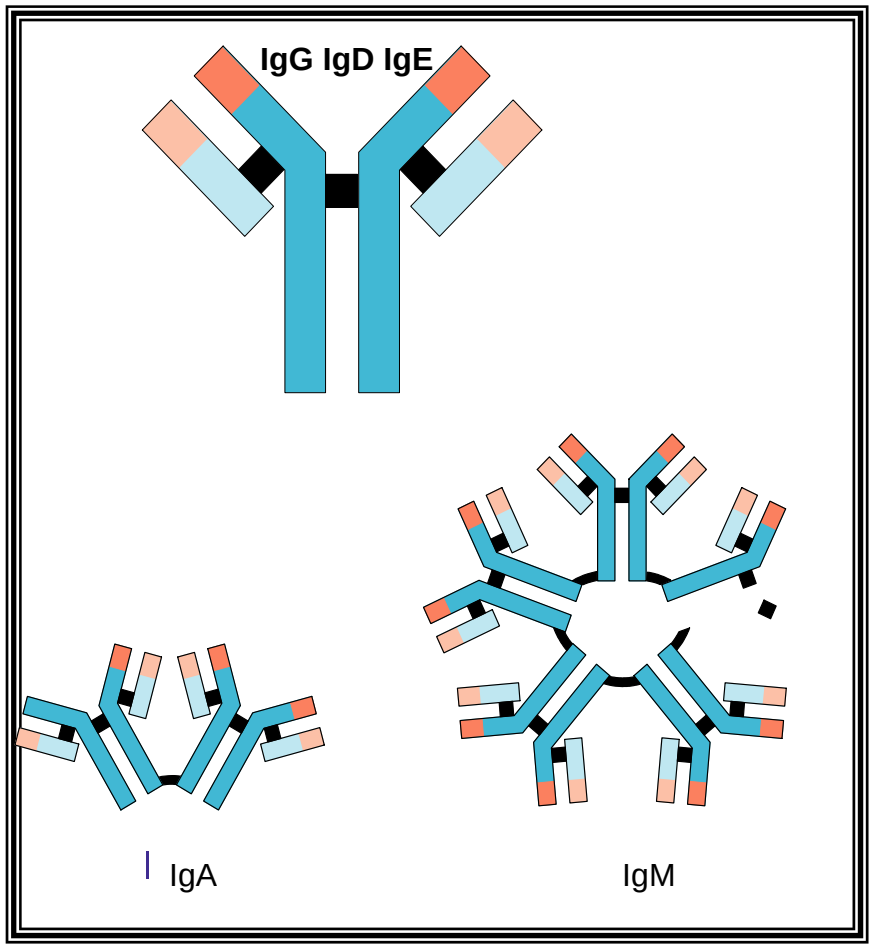
Neoplasias: Precursor B-cell leukemias	B-Cell lymphomas/CLL	WM/ Myeloma

Schwerketten-Gen-Rearrangement



Antikörper-Struktur

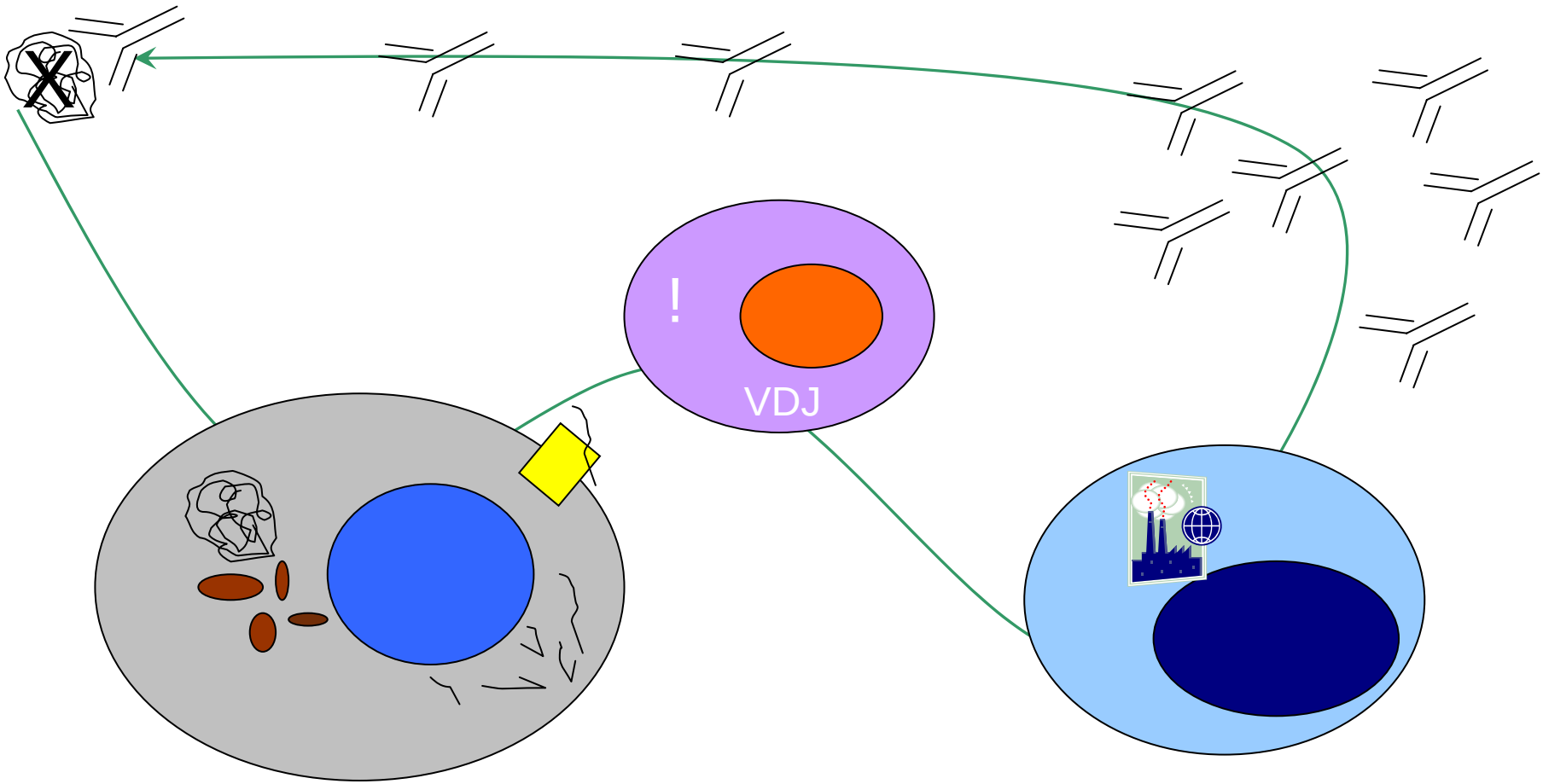
IgG, IgD, and IgE

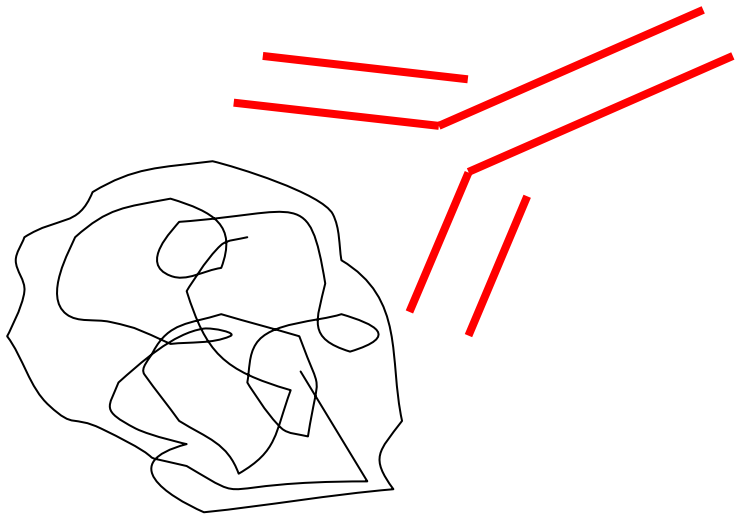


- Immunoglobulin-Struktur
  - **Klasse richtet sich nach Schwerkette – z.B. IgG γ Kette**
  - **IgG, IgD und IgE sind monomere Immunoglobuline**
  - **IgA: dimeres Immunoglobulin**
  - **IgM: pentameres Immunoglobulin**
  - **4 Subklassen von IgG**
  - **2 Subklassen von IgD, IgE, IgA und IgM**
  - **IgM erster Antikörper bei Immunantwort**

Autoimmunität

- In der Regel durch Antikörper vermittelt, die sich gegen körpereigene Strukturen richten
- Autoimmunerkrankungen
  - Lupus erythomatodes
  - M. Basedow
  - U.v.m.
- Kreuzreagierende Antikörper auf Infektionen

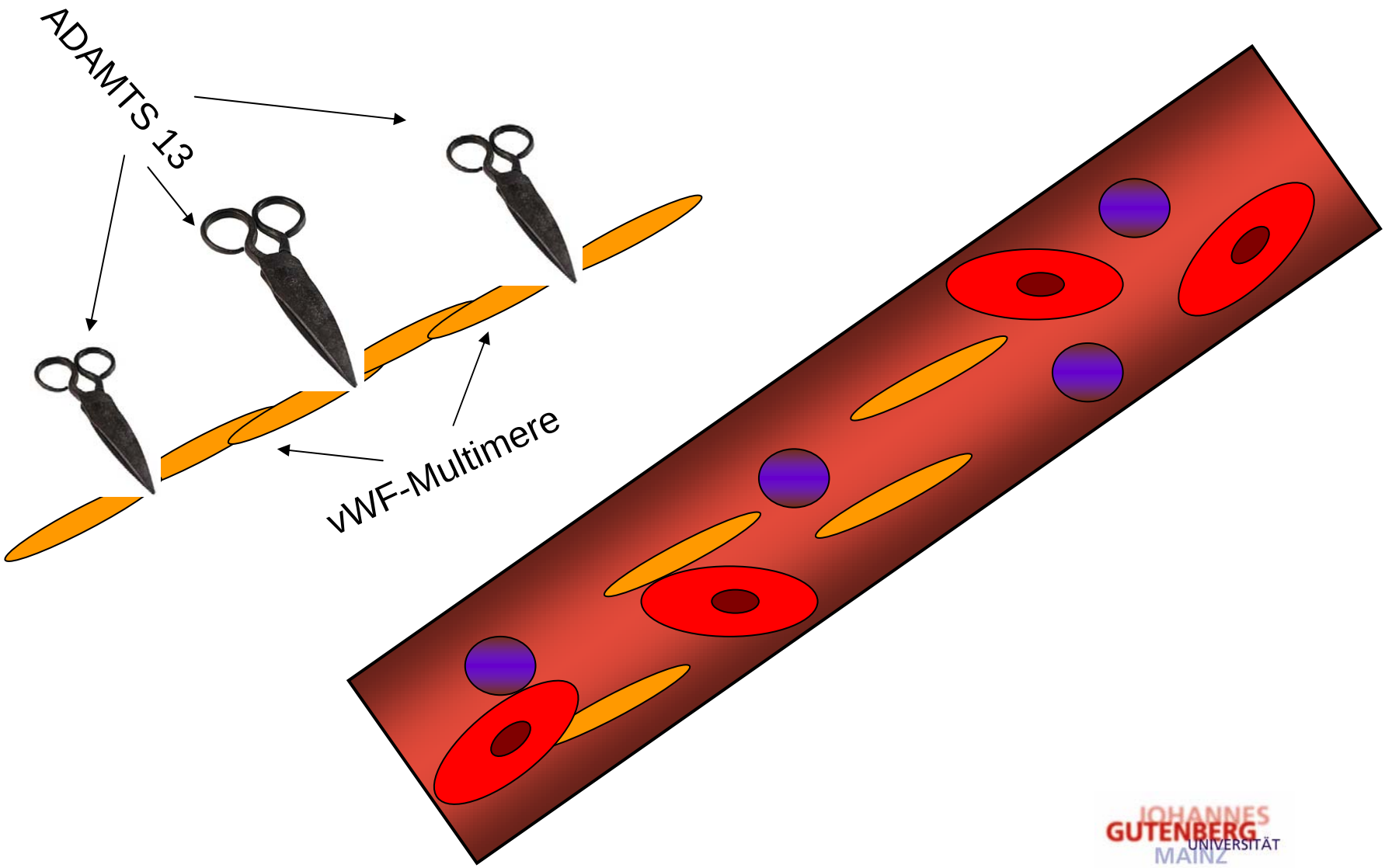




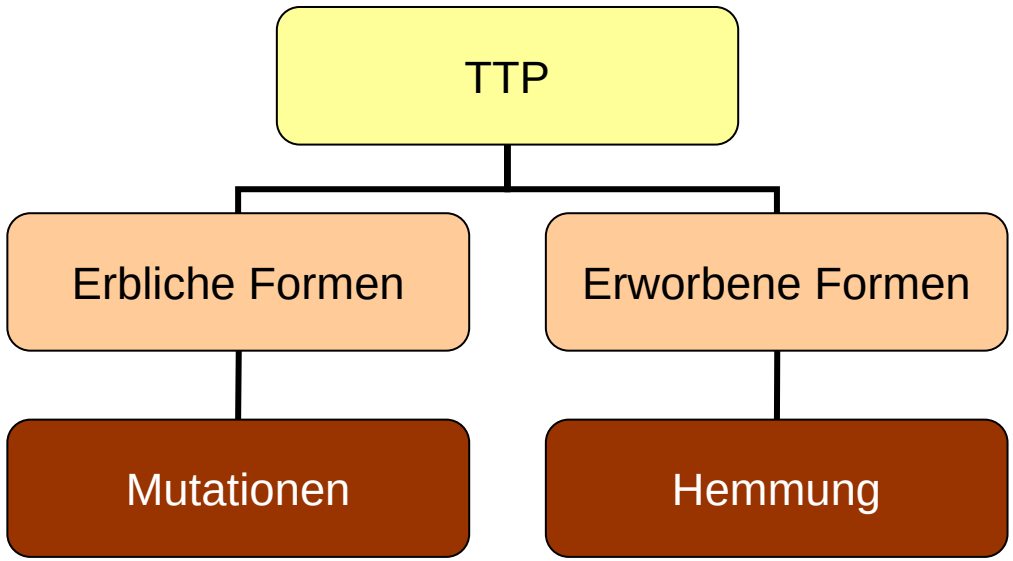
Normalerweise:
spezifisch für ein nicht körpereigenes Eiweiss

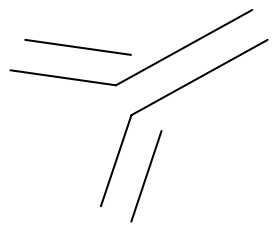
Aber: gelegentlich Kreuzreaktionen
z.B. Parvo B 19 – Pure red cell Aplasia
DM Typ I
Etc.

TTP – Pathophysiologie – Normale Situation



TTP - Pathophysiologie





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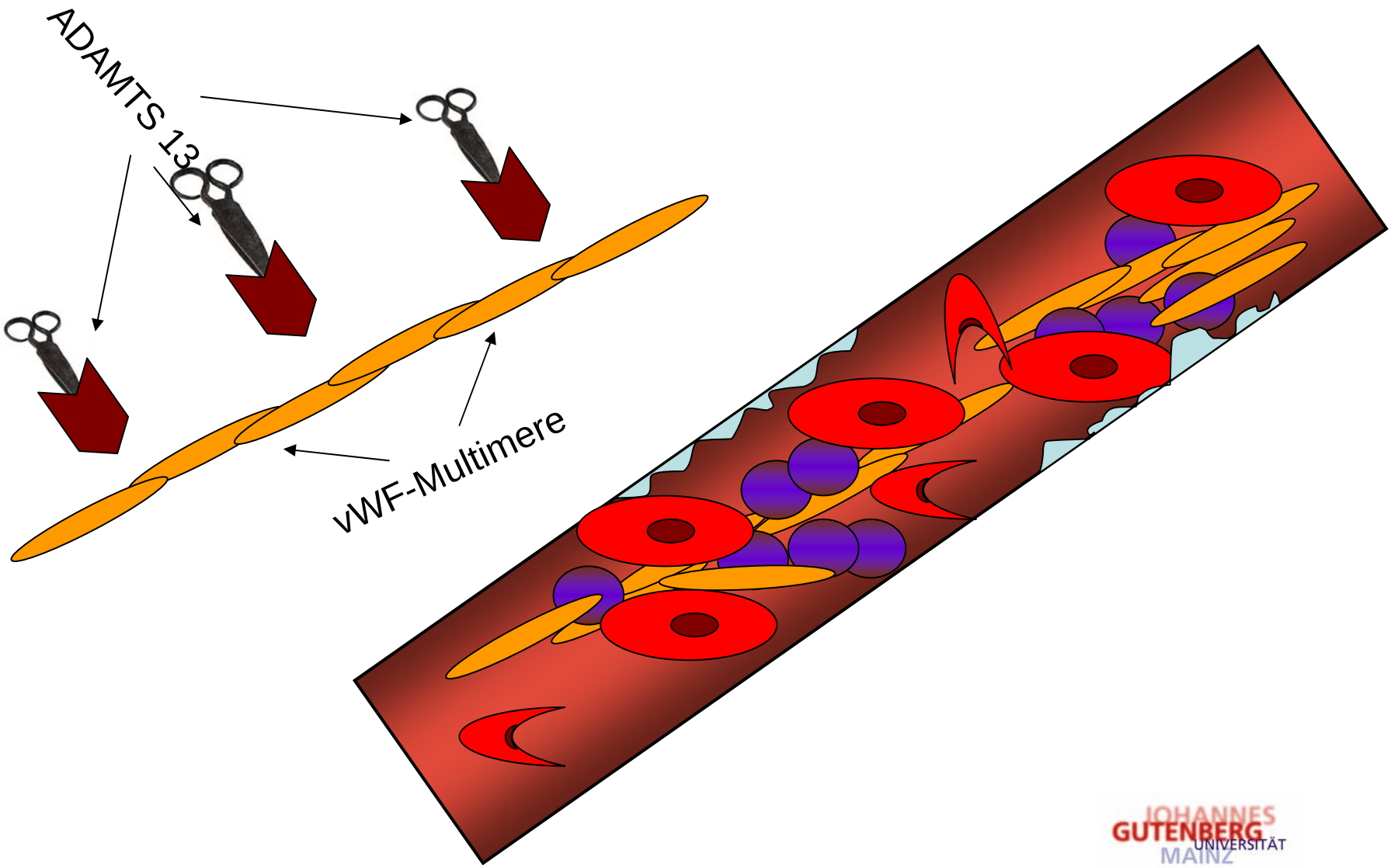
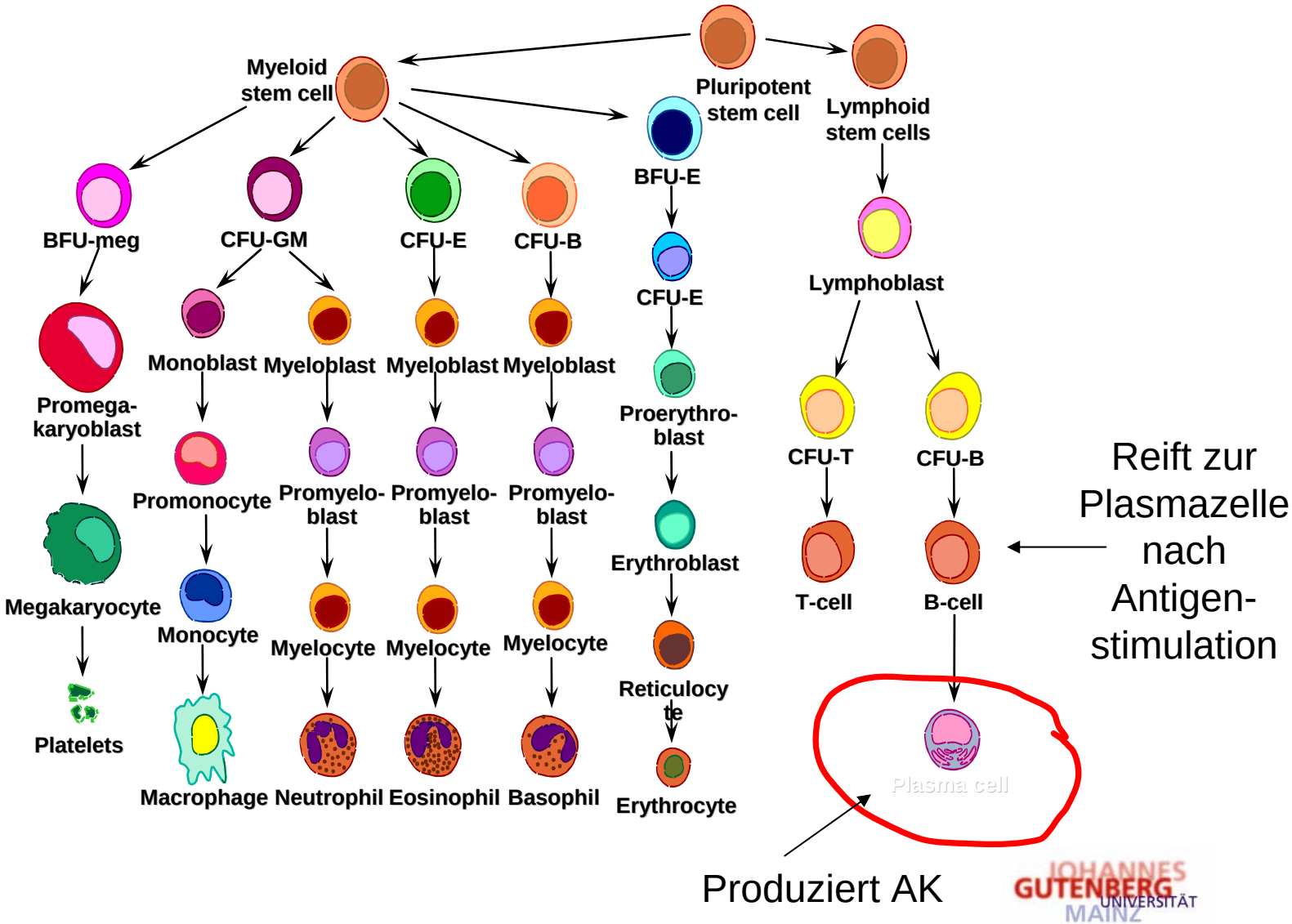
TTP – Pathophysiologie



Aufbau des zellulären Immunsystems



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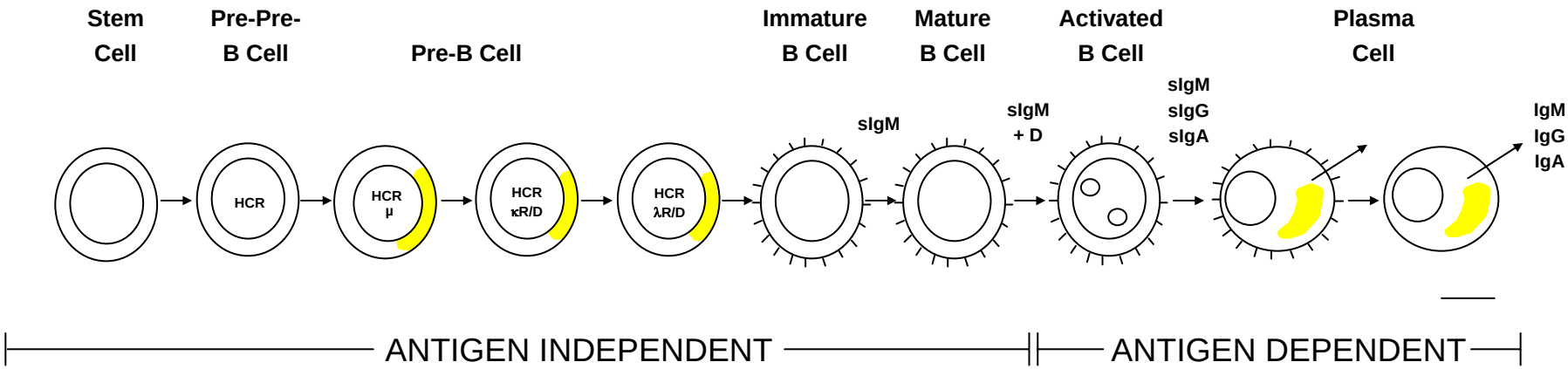
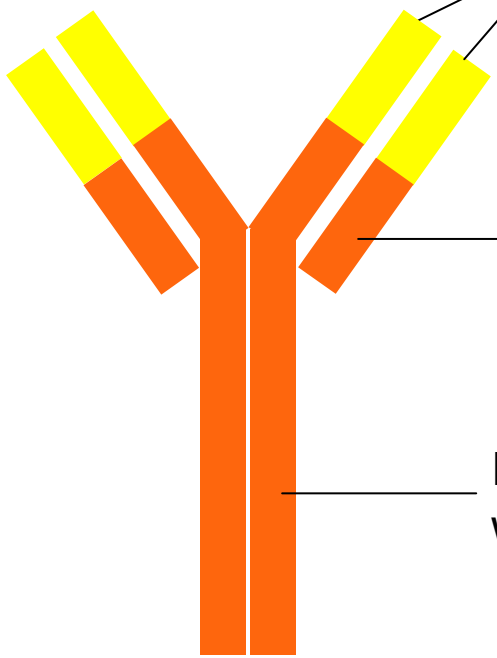


CD20 expression

Neoplasias: Precursor B-cell leukemias	B-Cell lymphomas/CLL	WM/ Myeloma

Rituximab: Maus/Humaner Chimärer monoklonaler Antikörper



Murine variable regions bind specifically to CD20 on B cells

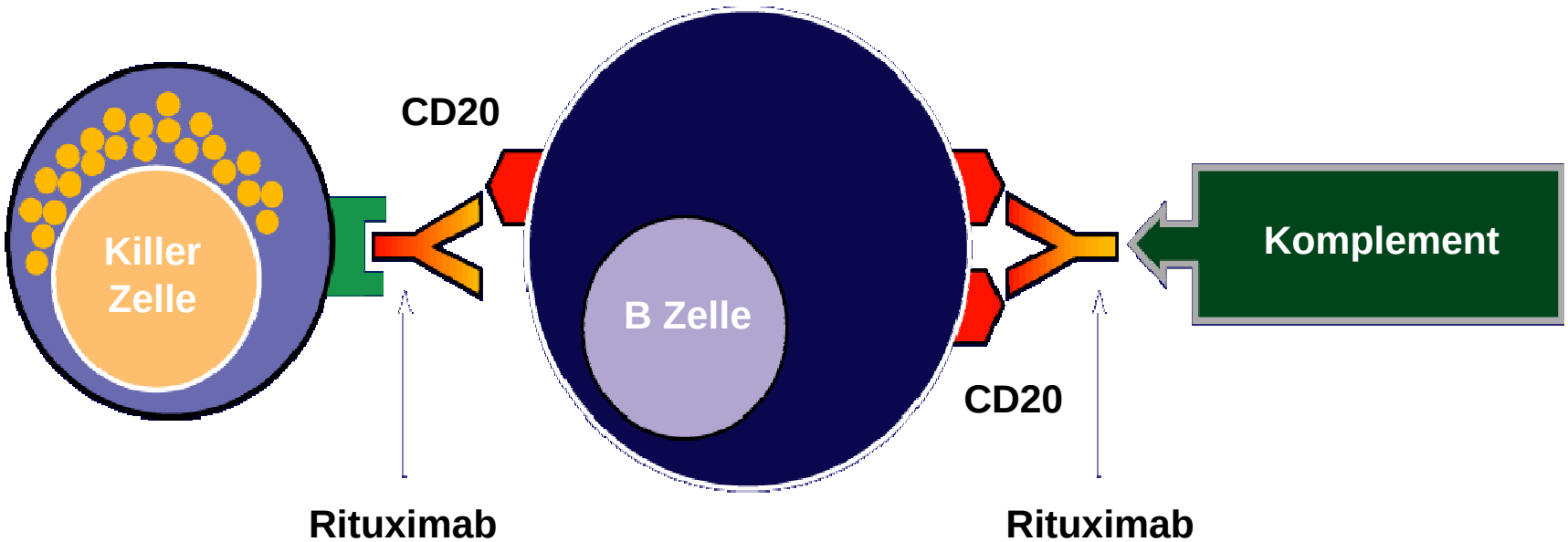
Human kappa constant regions

Human IgG_1 Fc domain works in synergy with human effector mechanisms

Chimeric IgG_1

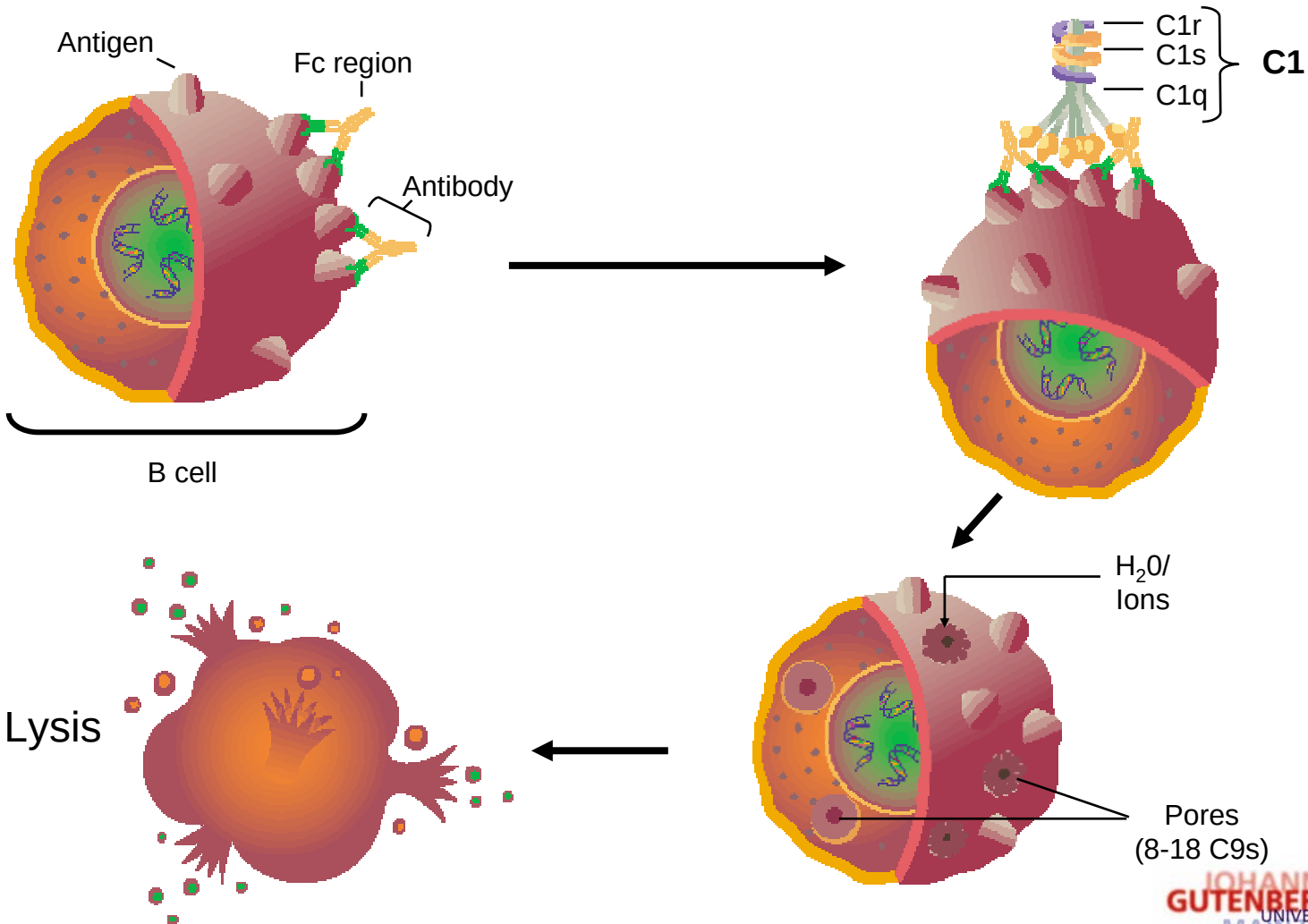
Adapted from Rybak et al. *Proc Natl Acad Sci USA.* 1992;89:3165.

Interaktionen mit Abwehrzellen



Adapted from Male et al. *Advanced Immunology*. 1996;1:1.

CDC



Inhibitor - Stellenwert

of inhibitory anti-ADAMTS13 antibodies in this context. We found that patients with no detectable inhibitory anti-ADAMTS13 antibodies usually displayed a more rapid and durable response to treatment. By contrast, patients with detectable inhibitory anti-ADAMTS13 antibodies had a delayed improvement in ADAMTS13 activity and platelet count recovery, and required significantly higher volumes of plasma to achieve durable complete remission. This worse prognosis was related to treatment refractoriness and episodes of flare-up that occurred during intensive treatment or during treatment tapering. The results of our large study are in

The mechanisms of flare-up observed in TTP yet remain totally unknown. Some authors reported that infections during

The prognostic value of inhibitory anti-ADAMTS13 antibodies titre remains more controversial (Table II). Previous

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Brief report

Rituximab prevents recurrence of thrombotic thrombocytopenic purpura: a case report

Miriam Galbusera, Elena Bresin, Marina Noris, Sara Gastoldi, Daniela Belotti, Cristina Capoferri, Erica Daina, Paolo Perseghin, Friedrich Scheiflinger, Fadi Fakhouri, Jean-Pierre Grünfeld, Enrico Pogliani, and Giuseppe Remuzzi

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder of small vessels that is associated with deficiency of the von Willebrand factor–cleaving protease, ADAMTS13. The presence of anti-ADAMTS13 autoantibodies is considered a factor predisposing to relapses. Despite close monitoring and intensive plasma treatment, in these patients acute episodes are still associated with substantial morbidity and mortality rates, and the optimal therapeutic option should be prevention of relapses. This study was conducted in a patient with recurrent TTP due to high titers of ADAMTS13 inhibitors, who used to have 2 relapses of TTP a year. The study compared the standard treatment plasma exchange with rituximab. Results documented that plasma exchange had only a small transient effect on ADAMTS13 activity and inhibitors; on the contrary, prophylaxis with rituximab was associated with disappearance of anti-ADAMTS13 antibodies, a progressive recovery of protease activity, and it allowed the patient to maintain a disease-free state during a more than 2-year follow-up. (Blood. 2005;106:925-928)

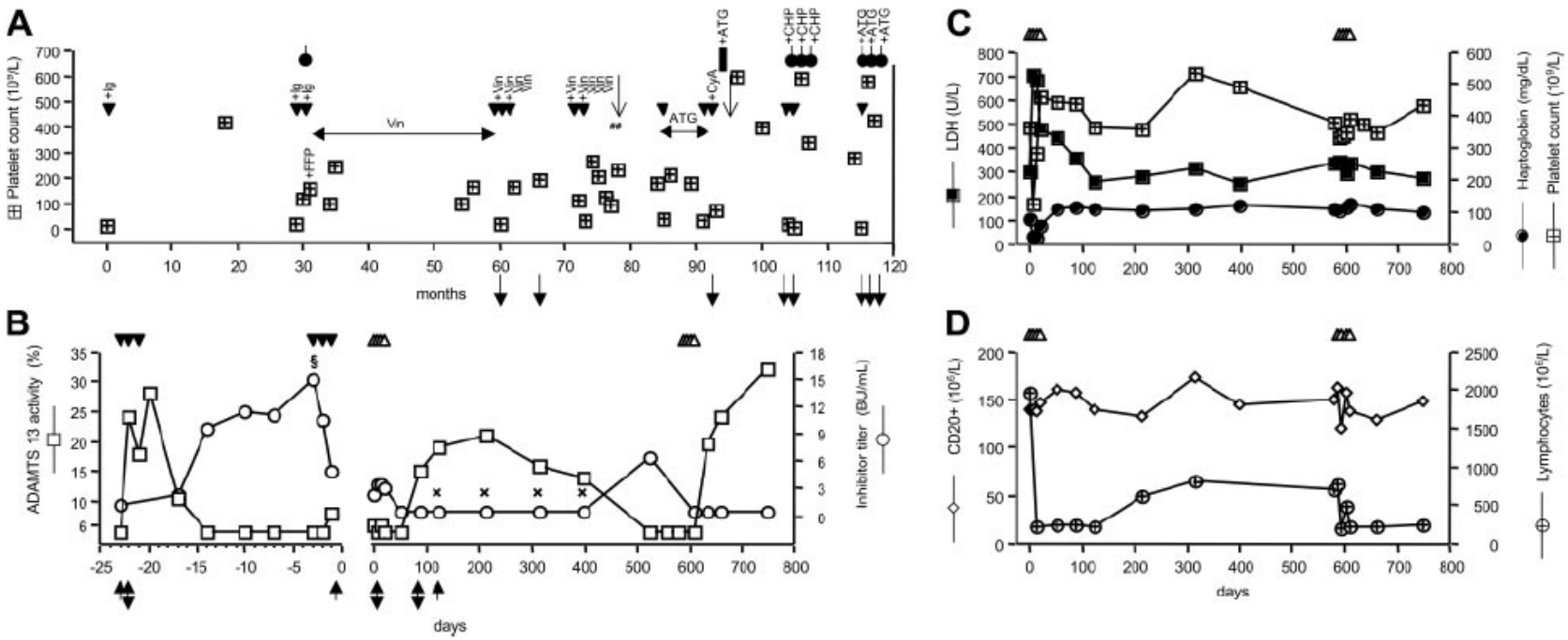

Figure 1. History of the patient, ADAMTS13 activity, and inhibitors and laboratory parameters. (A) Timeline history of the patient. Treatments: plasma exchange (▼); immunoglobulins (Ig); corticosteroids (circles with vertical lines); fresh frozen plasma (FFP); vincristine (Vin); antiplatelet agents (ATG); cyclosporine A (CyA); cyclophosphamide (CHP); plasma exchange, vincristine, antiplatelet agents, and corticosteroids (#). Filled rectangle indicates splenectomy; ↓, TIA; filled down arrow, ADAMTS13 activity less than 6% (normal range, 50%-150%), ADAMTS13 inhibitors present; and (⊞), platelet count. (B) ADAMTS13 activity (□) and anti-ADAMTS13 inhibitor titer (○) in the 2 courses of plasma exchange (▼), during rituximab (△) treatment and in the follow-up period. § indicates IgG titer, 1:1600; IgM, negative. ✖: IgG titer, negative; IgM, negative. The upward-pointing filled arrowhead indicates time of sampling for immunoblot (see Figure 2A); and the vertical double-headed arrow, time of sampling for VWF multimer analysis (see Figure 2B). (C) Platelet count (⊞; normal range, 140 × 10^9/L-440 × 10^9/L), LDH (■; normal range, 240 U/L-460 U/L), and haptoglobin (●; normal range, 49 mg/dL-246 mg/dL). (D) Lymphocytes count (⊕; normal range, 1.000-5.000 × 10^6/L) and CD20 count (◇; normal range, 5%-15% of lymphocytes count).

Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient thrombotic thrombocytopenic purpura: a study of 11 cases

Fadi Fakhouri, Jean-Paul Vernant, Agnès Veyradier, Martine Wolf, Gilles Kaplanski, Raynald Binaut, Manfred Rieger, Friedrich Scheiflinger, Pascale Poullin, Benjamin Deroure, Richard Delarue, Philippe Lesavre, Philippe Vanhille, Olivier Hermine, Giuseppe Remuzzi, and Jean-Pierre Grünfeld

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease that occurs mainly in young adults. Acquired cases are usually a result of antibodies directed against ADAMTS13 (a disintegrin-like and metalloprotease [reprolysin type] with thrombospondin type 1 motif 13), a protease that cleaves the von Willebrand factor multimers. Prognosis has been improved by plasma therapy, but some acute severe forms are refractory to this treatment and achieving a sustained remission is still a challenge in chronic relapsing forms. We therefore conducted a multicentric open-label prospective trial to test the efficacy of rituximab, an anti–B-cell monoclonal antibody, as a curative and prophylactic treatment in patients with TTP as a result of anti-ADAMTS13 antibodies. Six patients were included during an acute refractory TTP episode. Five patients with severe relapsing TTP and persistent anti-ADAMTS13 antibodies were prophylactically treated during remission. All patients received 4 weekly infusions of rituximab. The target of treatment was to restore a significant ADAMTS13 plasma activity (> 10%). Treatment with rituximab led to clinical remission in all cases of acute refractory TTP. In all patients, anti-ADAMTS13 antibodies disappeared, and a significant (18%-75%) plasma ADAMTS13 activity was detected following treatment. Tolerance of rituximab was good. Rituximab is a promising first-line immunosuppressive treatment in patients with acute refractory and severe relapsing TTP related to anti-ADAMTS13 antibodies. (Blood. 2005;106:1932-1937)

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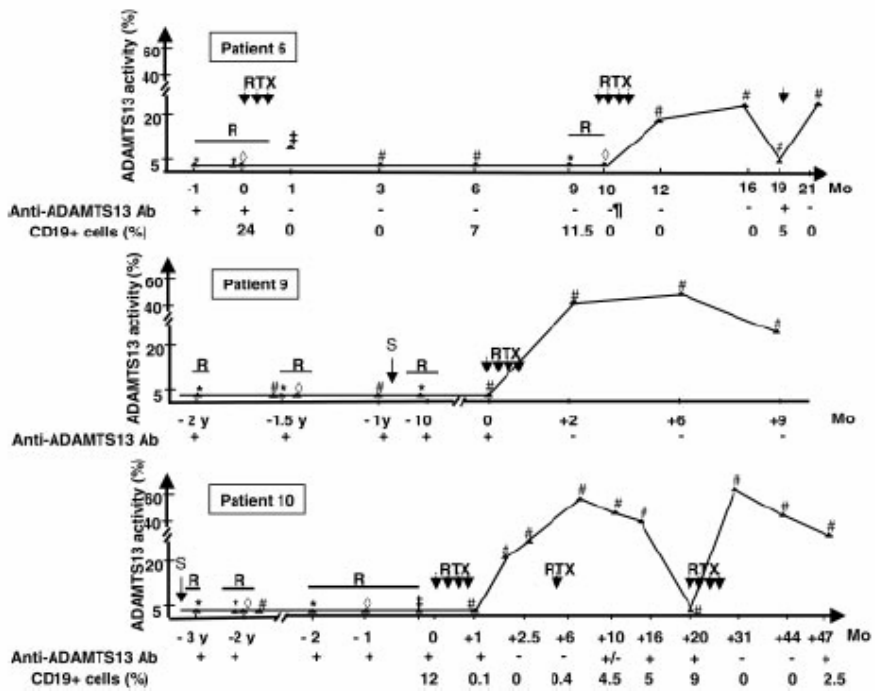
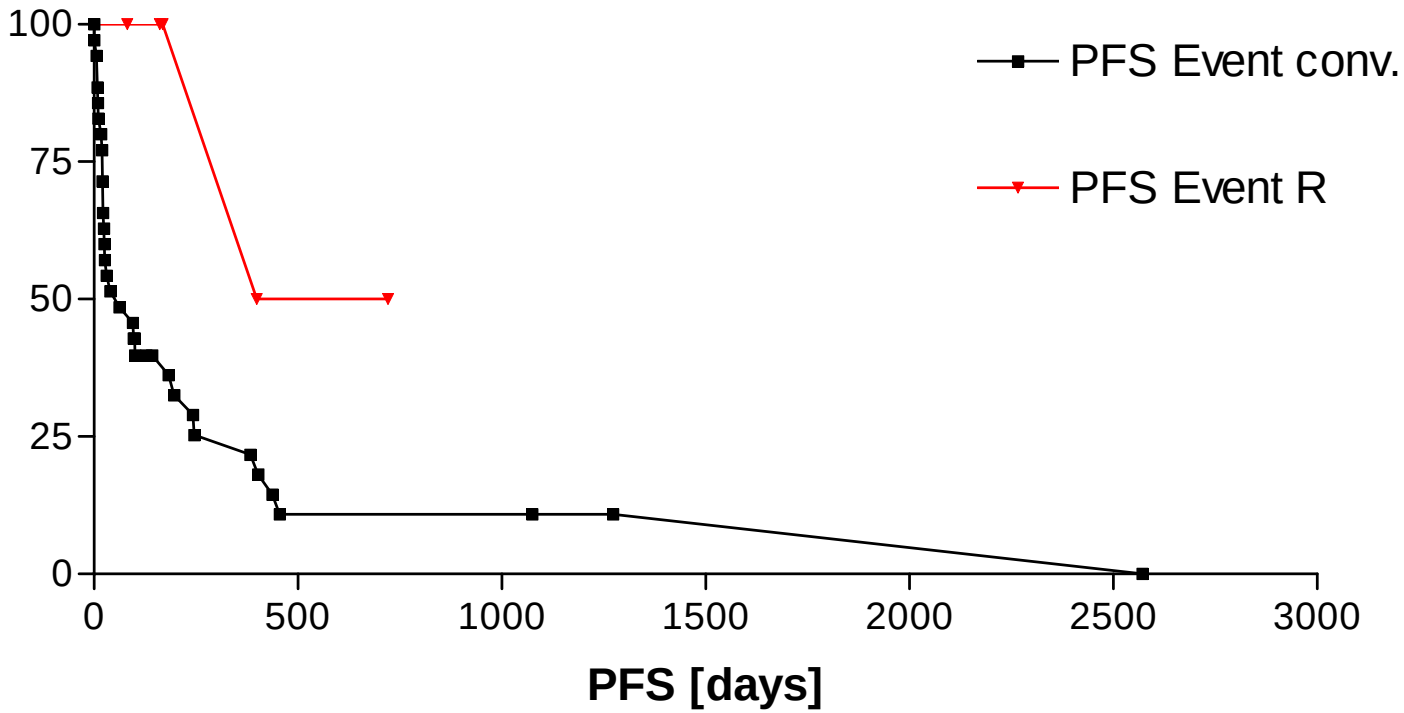


Figure 1. Time course of ADAMTS13 plasma activity in 3 patients for whom sequential measurements of ADAMTS13 plasma activity over several years are available. ADAMTS13 activity was measured during (1) a disease relapse before (*) and during plasma exchange (◇) or infusions of fresh-frozen plasma (‡) and (2) remission (#). R indicates relapse; RTX, rituximab; S, splenectomy; and Ab, antibody. Anti-ADAMTS13 antibodies were detected using the ELISA test. Sequential measurements of CD19$^+$ cells are not available for patient 9. The length of the solid bars indicates the duration of TTP relapse.

Eigene Daten

patient #	age	sex	diagnosis	lines of treatment	kind of treatment	rituximab treatment
1	51	f	AIHA	2	p,s,i	YES
2	33	m	AIHA	7	s	NO
3	59	f	AIHA	4	s,c,r	YES
4	74	f	AIHA	2	s	NO
5	71	m	AIHA	1	s	NO
6	35	f	AIHA	2	p,s,c,i,r	YES
7	74	m	AIHA	1	s	NO
8	54	f	AIHA	1	s	NO
9	83	m	AIHA	1	s,i	NO
10	75	f	TTP/HUS	1	p,s	NO
11	31	f	TTP	3	p,s	NO
12	46	m	TTP	9	p,s,c,i,r	YES
13	36	f	TTP	3	p,s,c,r	YES
14	58	f	TTP	2	p	NO
15	25	m	TTP	1	s	NO
16	77	f	TTP	3	p,s,r	YES
17	63	m	TTP	2	p,s	NO
18	21	f	TTP	4	p,s,r	YES
19	30	m	TTP	2	p,s	NO
20	68	f	TTP	5	p,s,c,r	YES
21	32	m	TTP	1	p,s	NO
22	63	f	TTP	2	p,s,c	NO
23	29	f	TTP	4	p,s,c,i,r	YES

TTP PFS R vs non R



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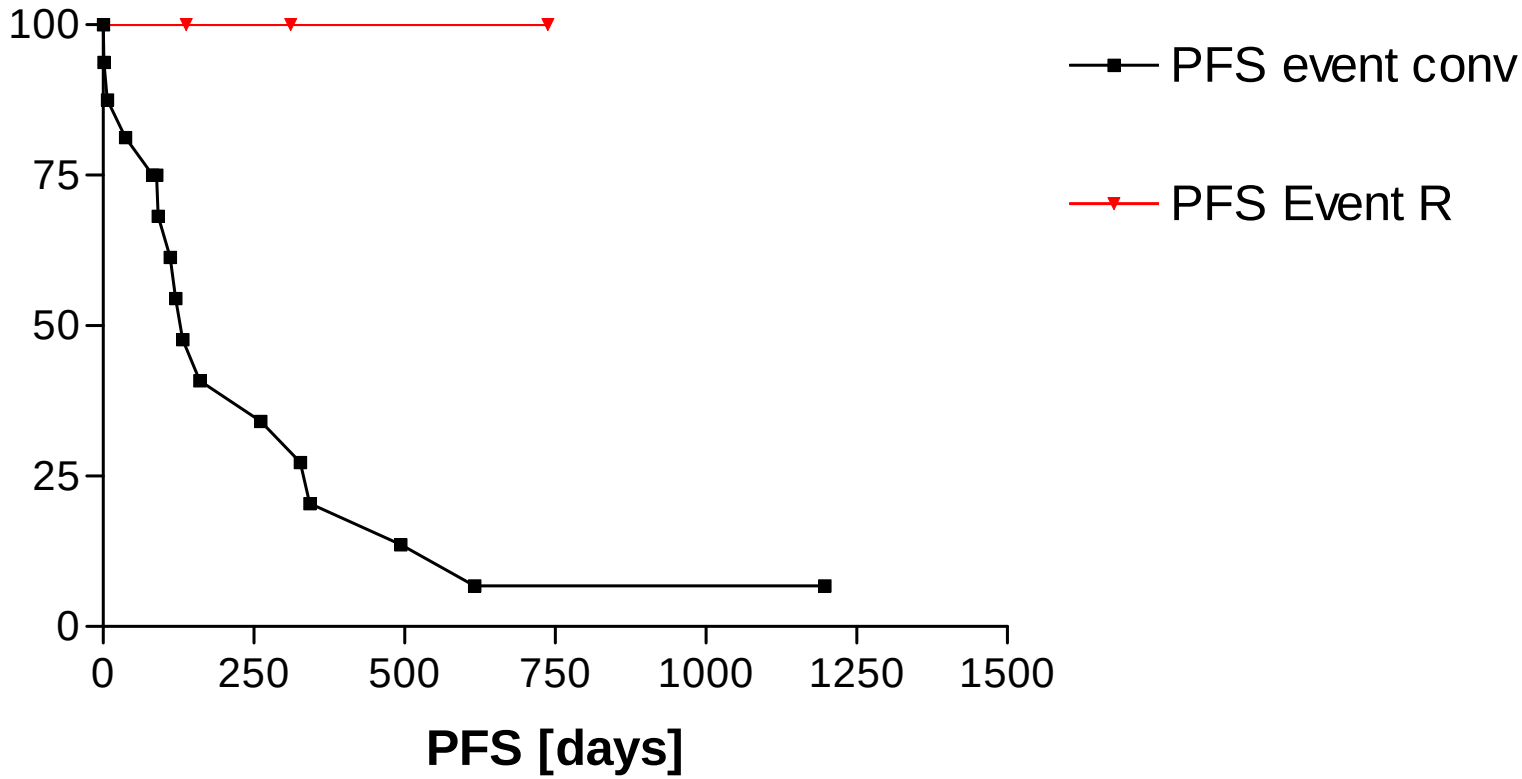
100
75
50
25
0
0
250
500
750
1000
1250
1500
PFS [days]
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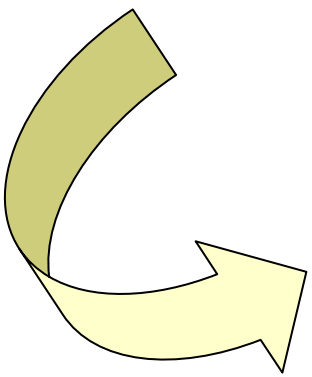
Studienkonzept – Mainz - Hamburg

Beginn: Sommer 2006

Rezidiv
oder
Refrakärer TTP



R R R R R R R R

Steroide

Plasmapherese

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Nebenwirkungen von Rituximab

- Akut:
  - Schüttelfrost, Fieber, allerg. Reaktionen
  - In der Regel mild, selten schwere Reaktionen

- Dauer
  - Mittlerweile Daten für die Langzeitanwendung vorhanden
  - Keien erhöhte Infektanfälligkeit

Zusammenfassung

- Nicht heriditäre Form der TTP häufig durch Auto-AK gegen ADAMTS-13 ausgelöst: INHIBITOR
- Plasmapherese führt zur Reduktion der Proteinmenge, vermindert aber nicht die Zahl der Produzenten
- B-Zellen, die zu Plasmazellen ausreifen sind für die Produktion des AK verantwortlich
- Auslöschung der Produzenten durch B-Zell-spezifischen monoklonalen Antikörpber: Rituximab
- Erste Daten für Wirksamkeit
- Prospektive Prüfung angestrebt

FRAGEN ?

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