

Rituximab – Wirkweise, Nebenwirkungen und potentieller Einsatz bei der TTP

4. Seminar der
TTP-Selbsthilfegruppe in der DHG
Mainz, 02.06.2007

Dr. med. Georg Heß

Inhibitor - Stellenwert

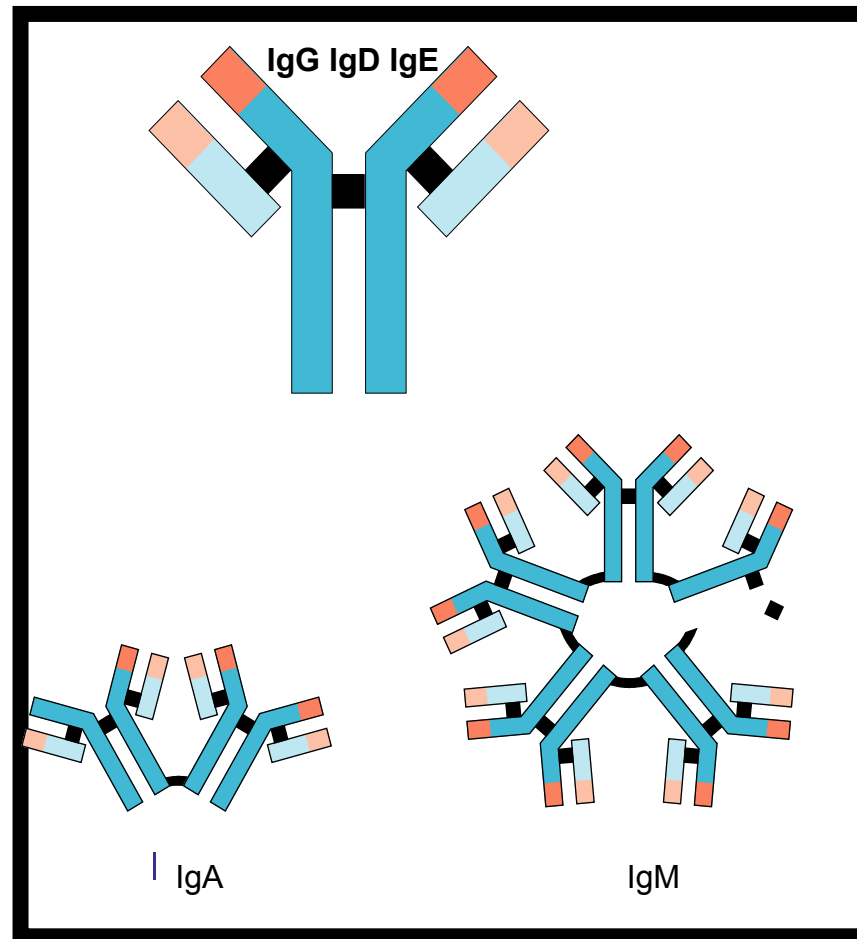
of inhibitory anti-ADAMTS13 antibodies in this context. We found that patients with no detectable inhibitory anti-ADAMTS13 antibodies usually displayed a more rapid and durable response to treatment. By contrast, patients with detectable inhibitory anti-ADAMTS13 antibodies had a delayed improvement in 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

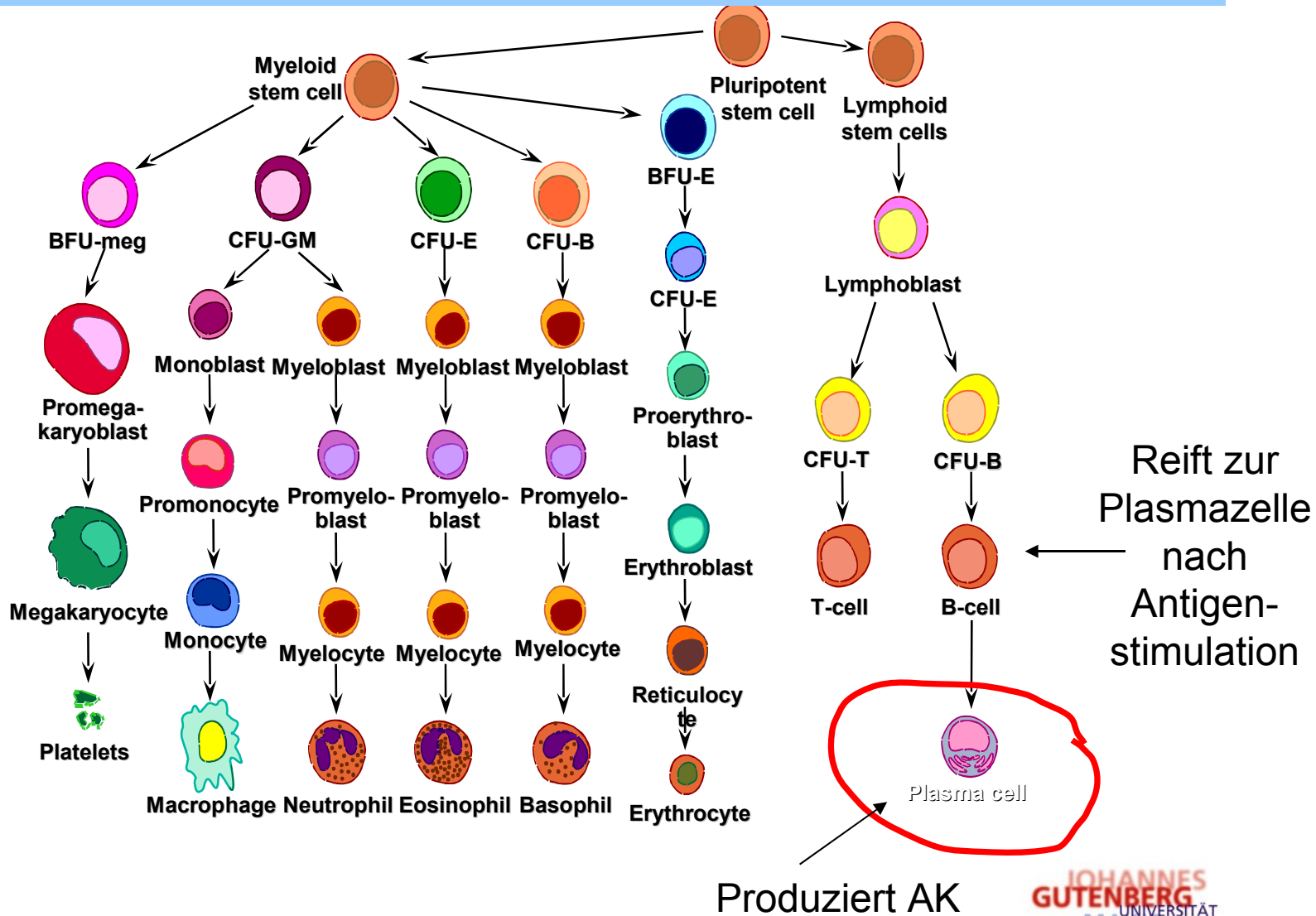
The prognostic value of inhibitory anti-ADAMTS13 antibodies titre remains more controversial (Table II). Previous

Antikörper-Struktur

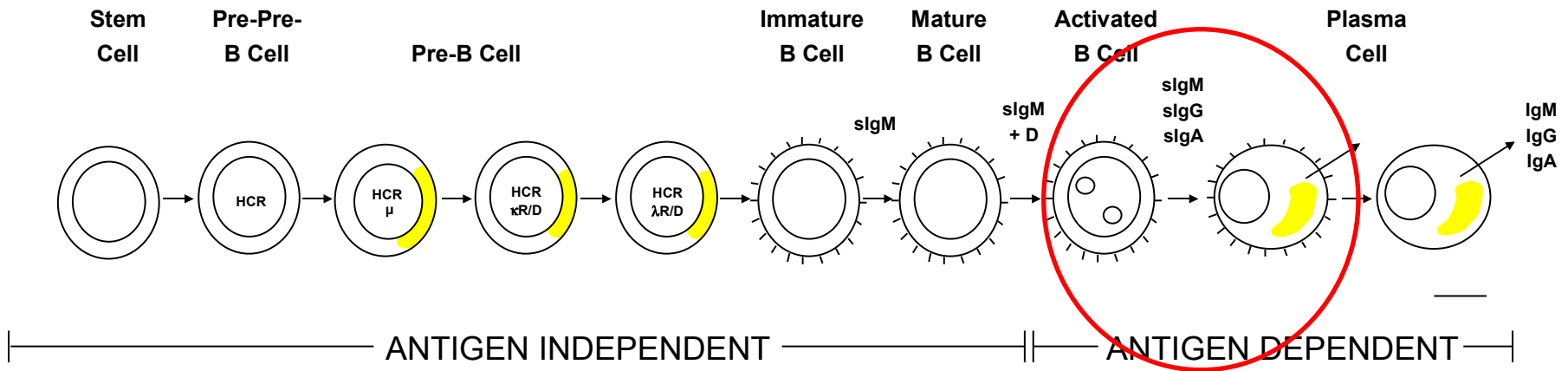
IgG, IgD, and IgE



Aufbau des zellulären Immunsystems



Entwicklung von B-Lymphozyten

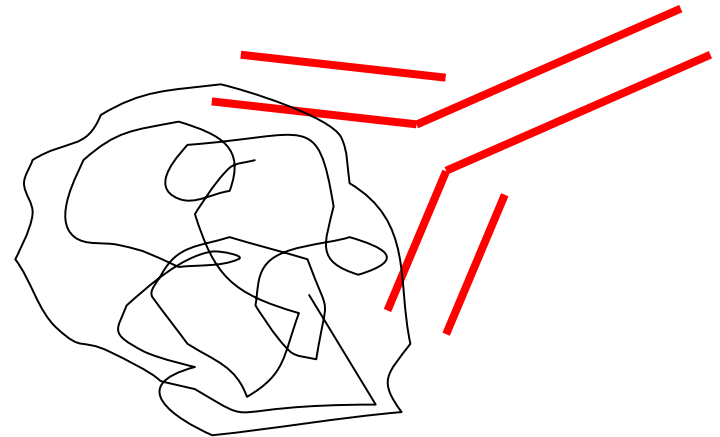


CD20
expression



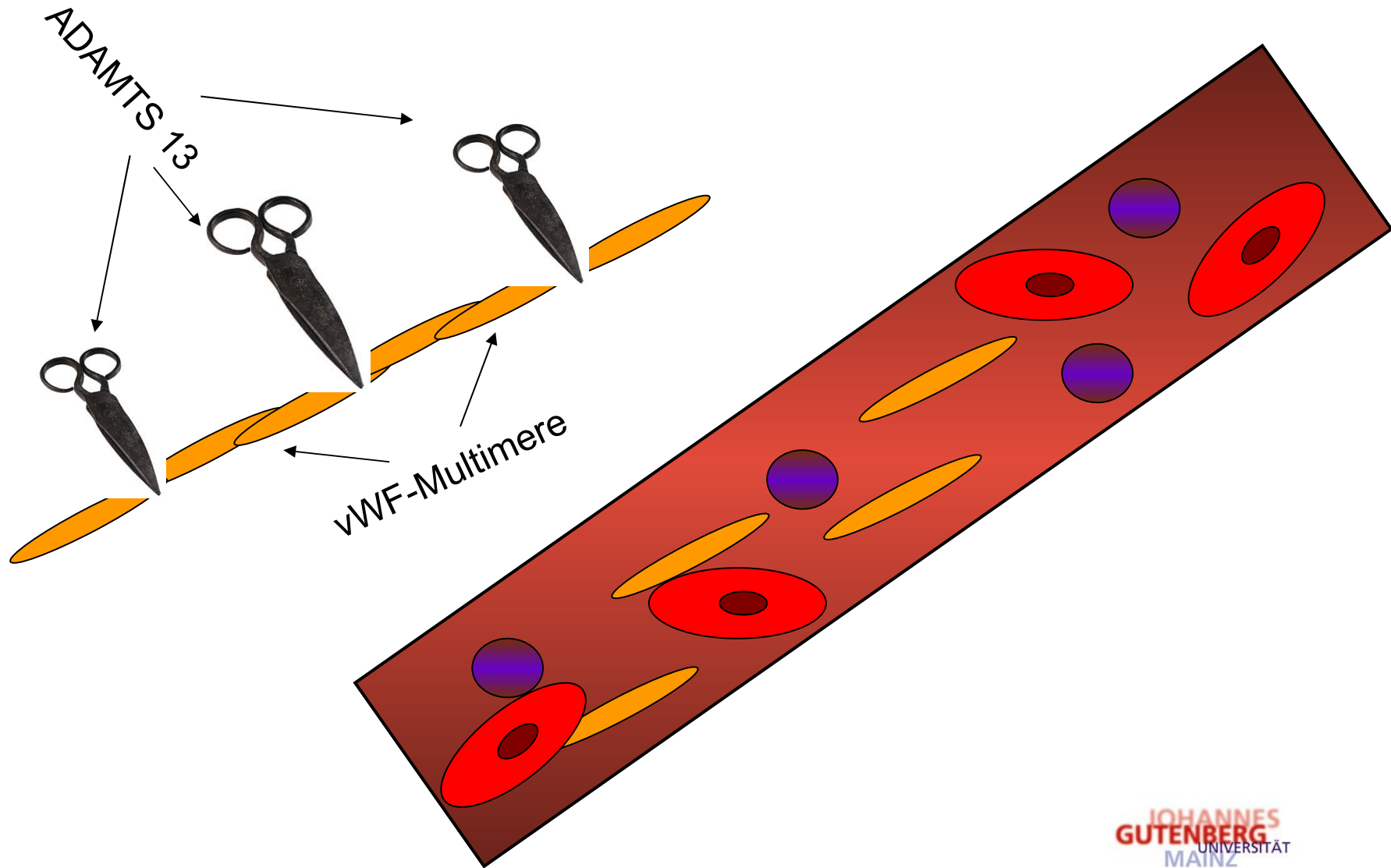
Autoimmunität - Antikörper

- Normalerweise: spezifisch für ein nicht körpereigenes Eiweiß
- Bei Autoimmunerkrankungen: Antikörper , die sich gegen körpereigene Strukturen richten
- Autoimmunerkrankungen
 - Lupus erythematodes
 - Diabetes mellitus Typ I
 - M. Basedow
 - U.v.m.
- Kreuzreagierende Antikörper auf Infektionen

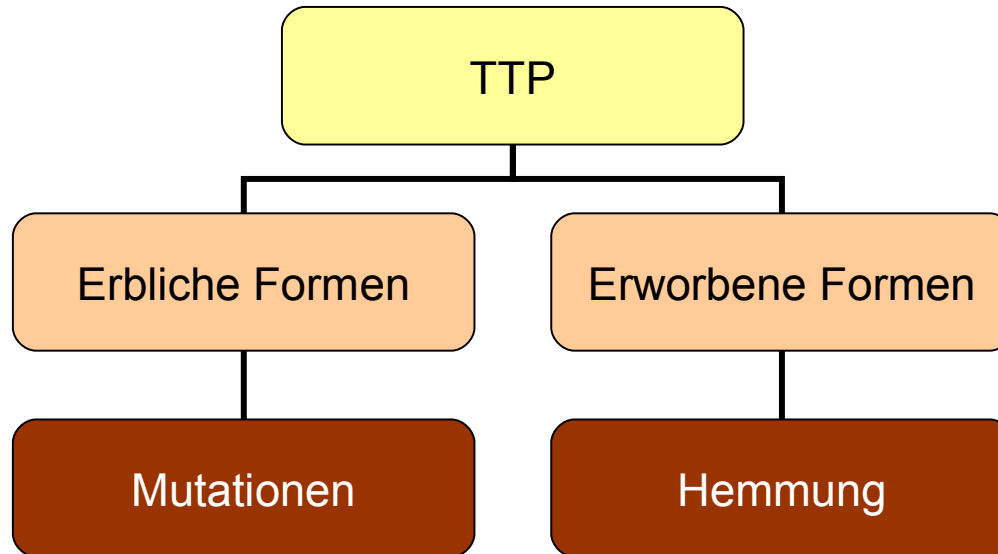


TTP und Antikörper

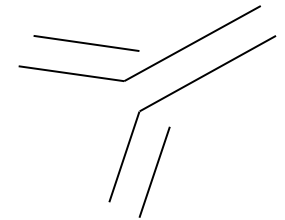
TTP – Pathophysiologie – Normale Situation



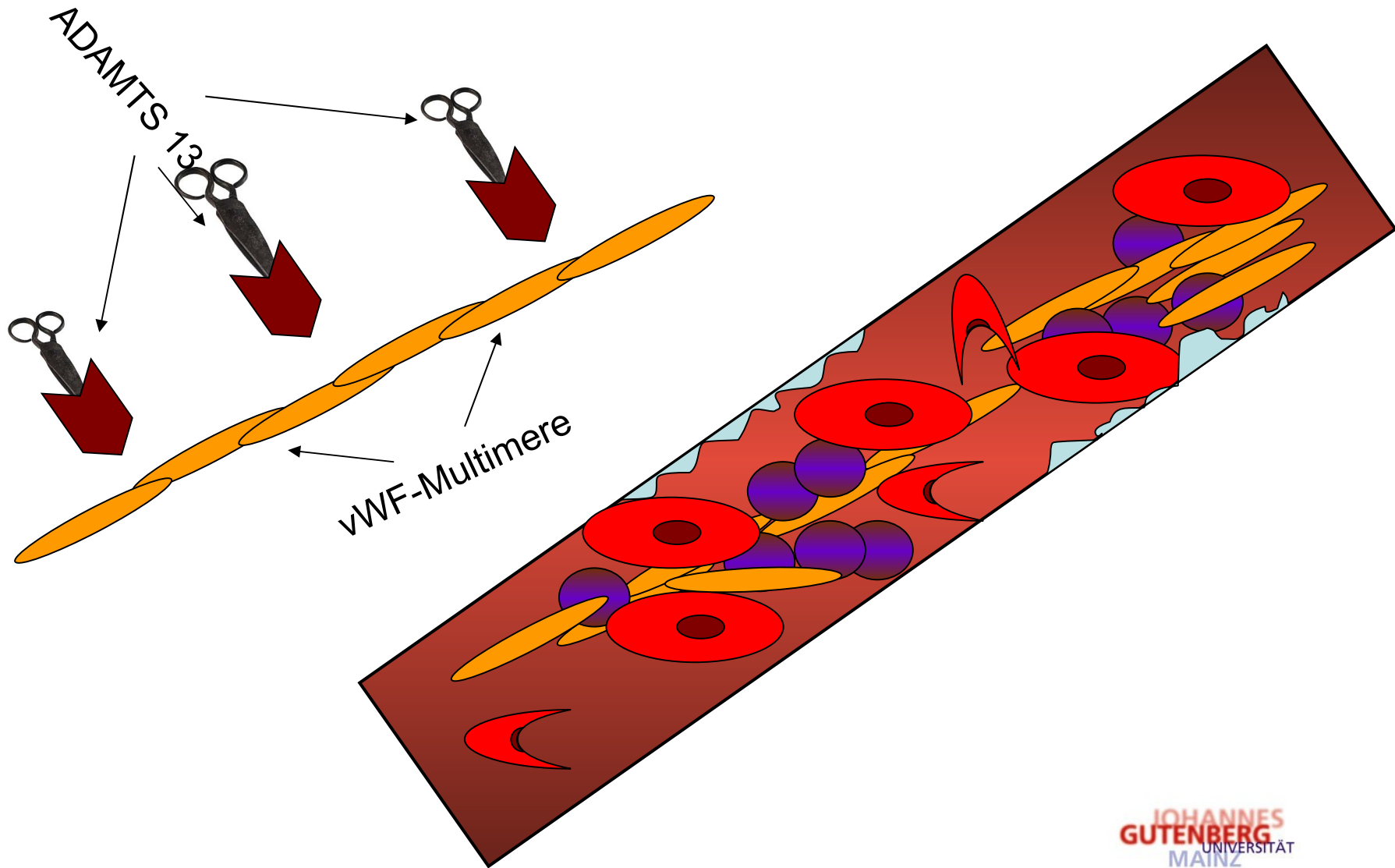
TTP - Pathophysiologie



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TTP – Pathophysiologie



Strategien zur Elimination des Inhibitors

Physikalische Entfernung

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Plasmapherese

Problem: Nachschub....?

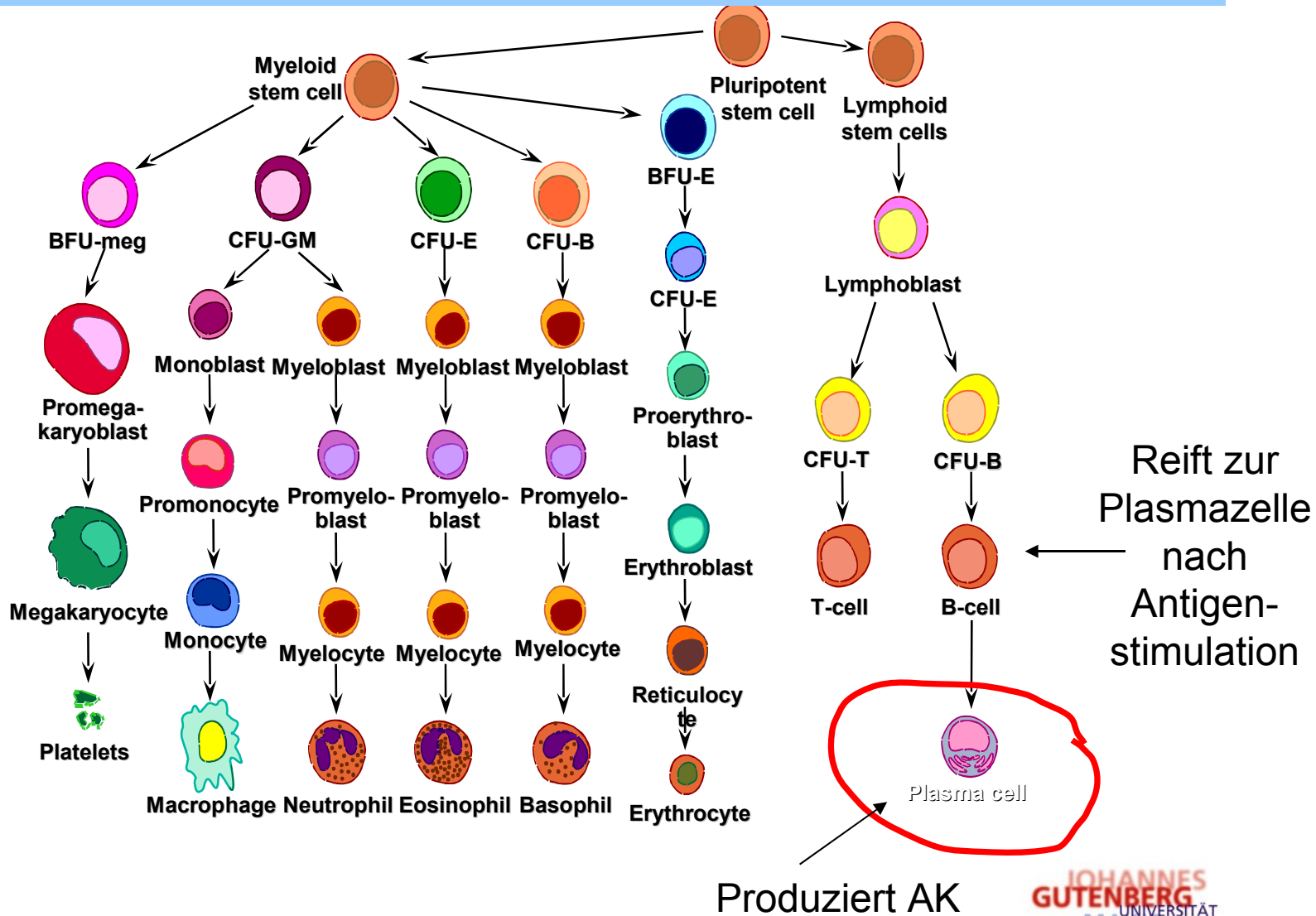
Hemmung der Produktion

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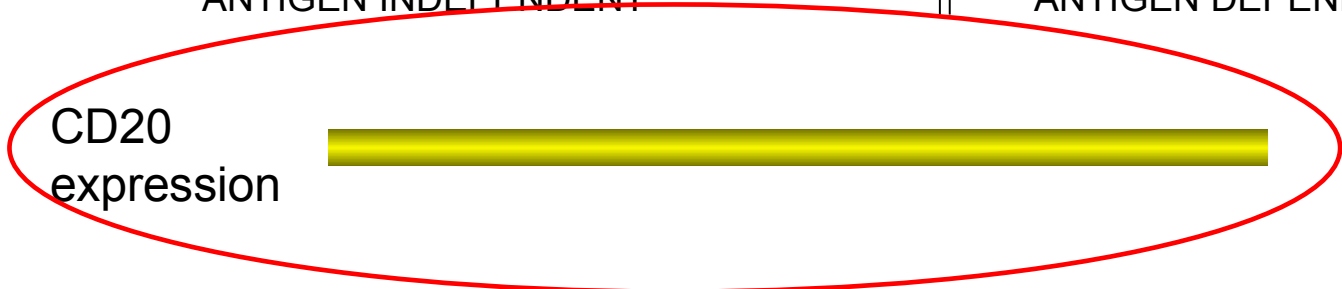
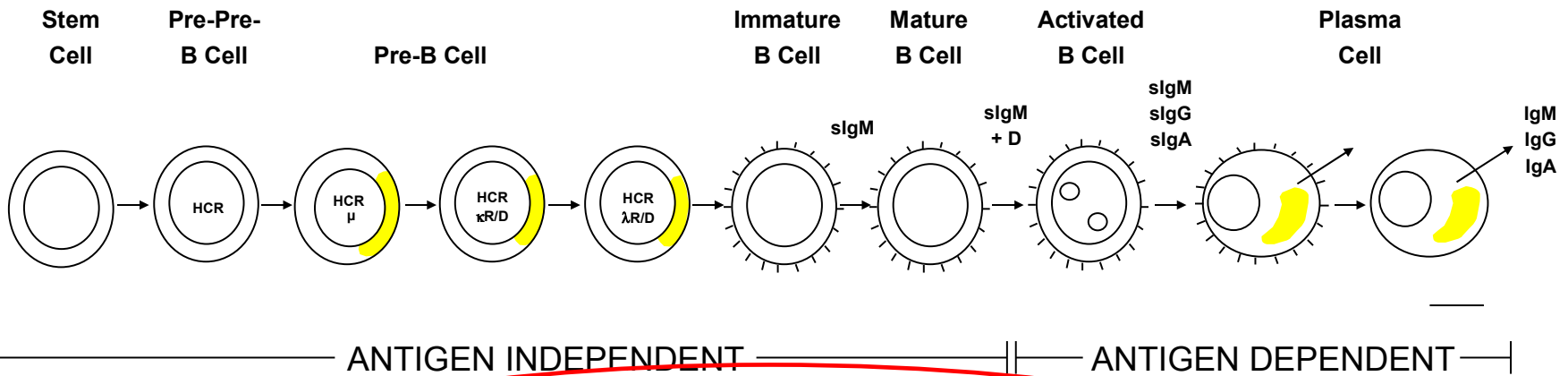
Plasmazellelimination
bzw. von Vorläuferzellen

Problem: wirkt nicht sofort
wg zirkulierendem AK

Aufbau des zellulären Immunsystems



Entwicklung von T- und B-Lymphozyten



Neoplasias: Precursor B-cell leukemias	B-Cell lymphomas/CLL	WM/ Myeloma
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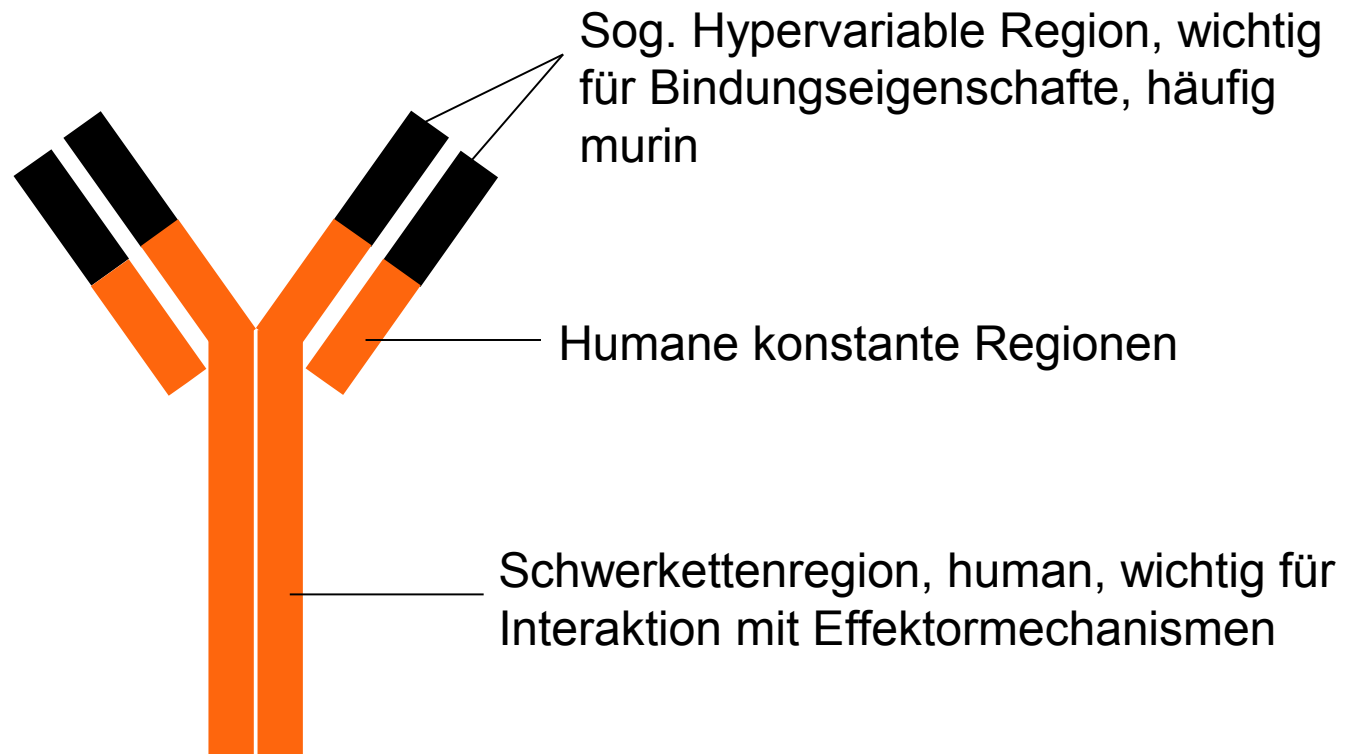
Mögliche Substanzen zur Elimination von B-Zellen

- Steroide
- Zytostatika
- Antikörper

Voraussetzungen für den Einsatz therapeutischen Einsatz von AK

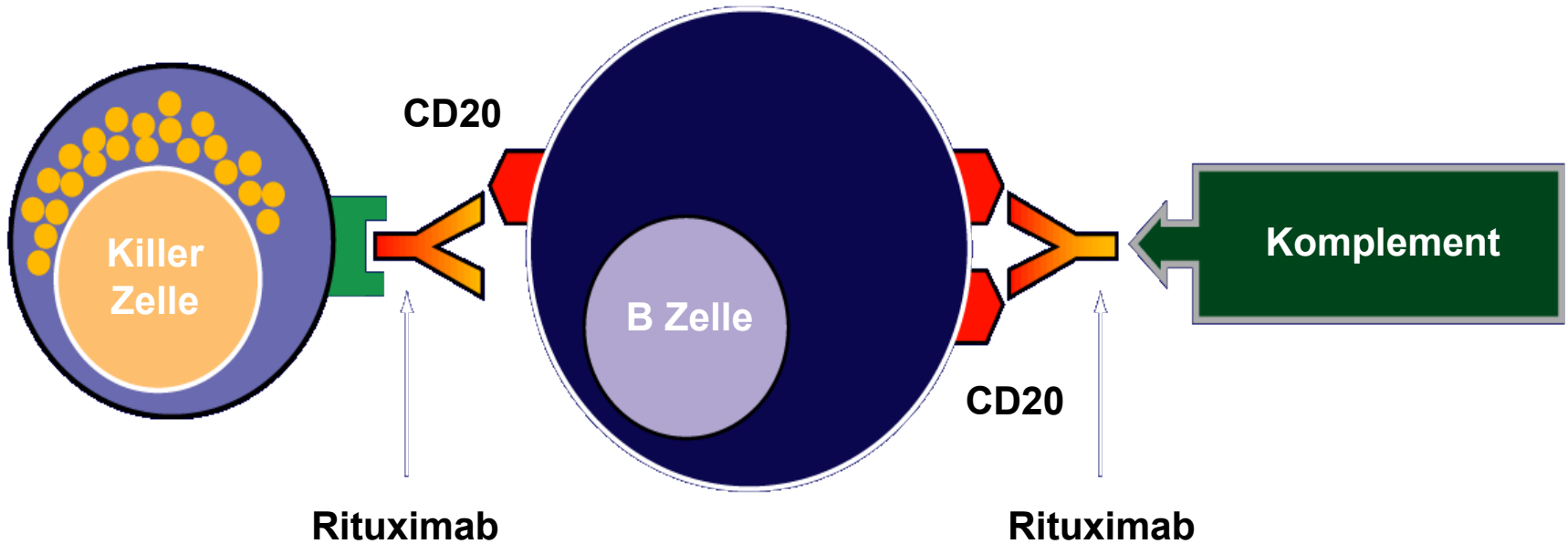
- Spezifität der Zielstruktur
 - Idealerweise nur auf der zu zerstörenden Zelle
 - Nicht als lösliches Eiweiß
 - Nicht auf anderen/lebenswichtigen Organen vorhanden
 - Stabil auf der Oberfläche der Zellen vorhanden

Rituximab: Maus/Humaner Chimärer monoklonaler Antikörper

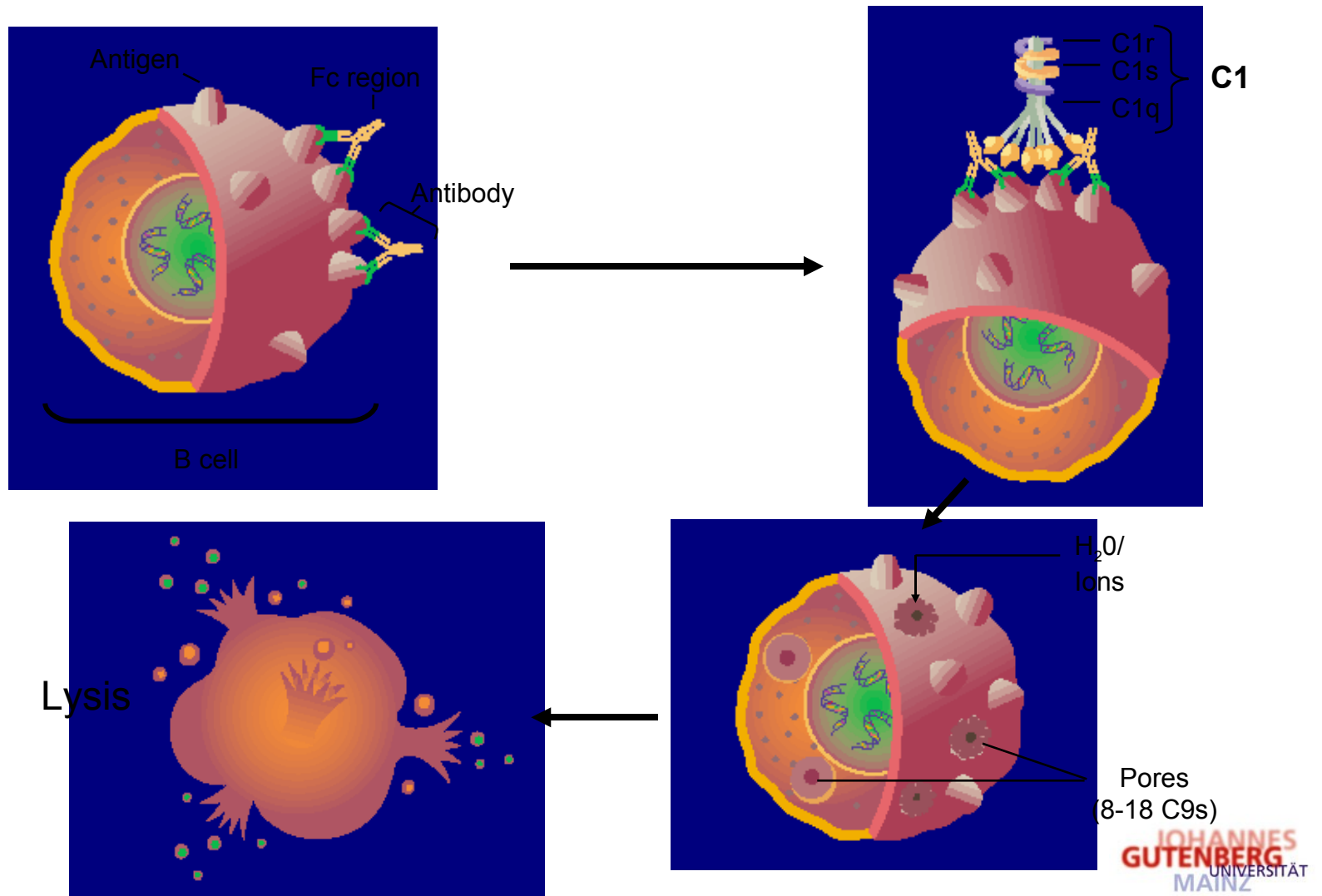


Chimeric IgG₁

Interaktionen mit Abwehrzellen



CDC



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 Scheifflinger, 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 substan-

tial 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 ef-

fect 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)

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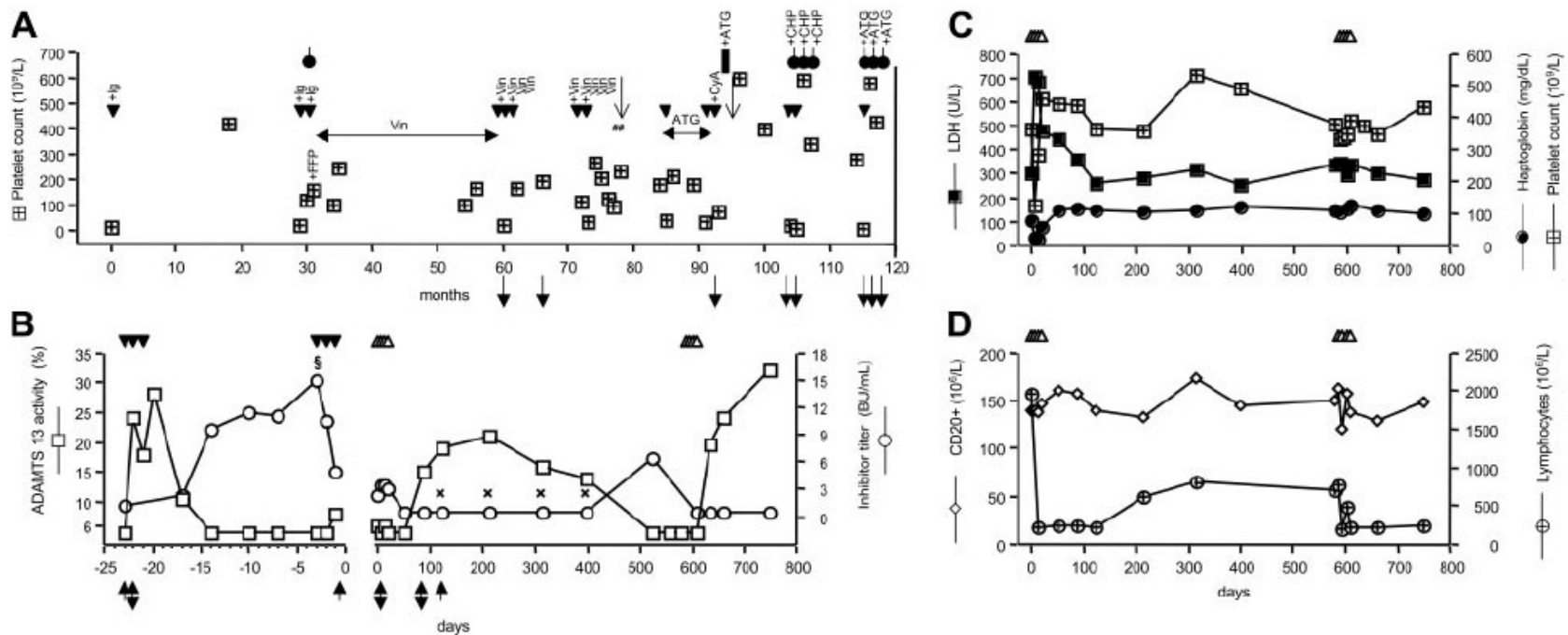


Figure 1. History of the patient, ADAMTS13 activity, and inhibitors and laboratory parameters. (A) Timeline history of the patient. Treatments: plasma exchange (▼); immunoglobulins (Ig); corticosteroids (circles with vertical lines); fresh frozen plasma (FFP); vincristine (Vin); antiplatelet agents (ATG); 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 × 10⁹/L-440 × 10⁹/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 × 10⁶/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 Scheifflinger, Pascale Poullin, Benjamin Derouere, 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

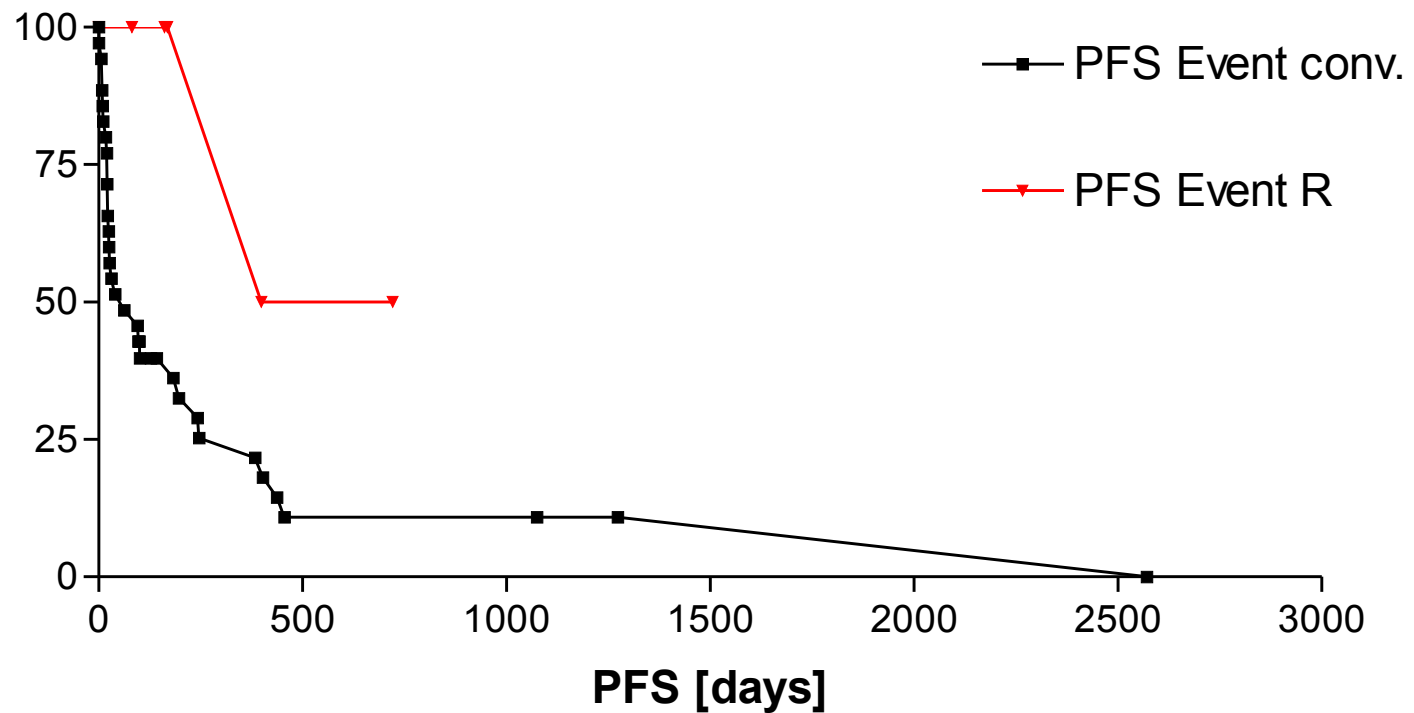
multicentric open-label prospective trial to test the efficacy of rituximab, an anti-B-cell monoclonal antibody, as a curative and prophylactic treatment in patients with TTP as a result of anti-ADAMTS13 antibodies. Six patients were included during an acute refractory TTP episode. Five patients with 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)

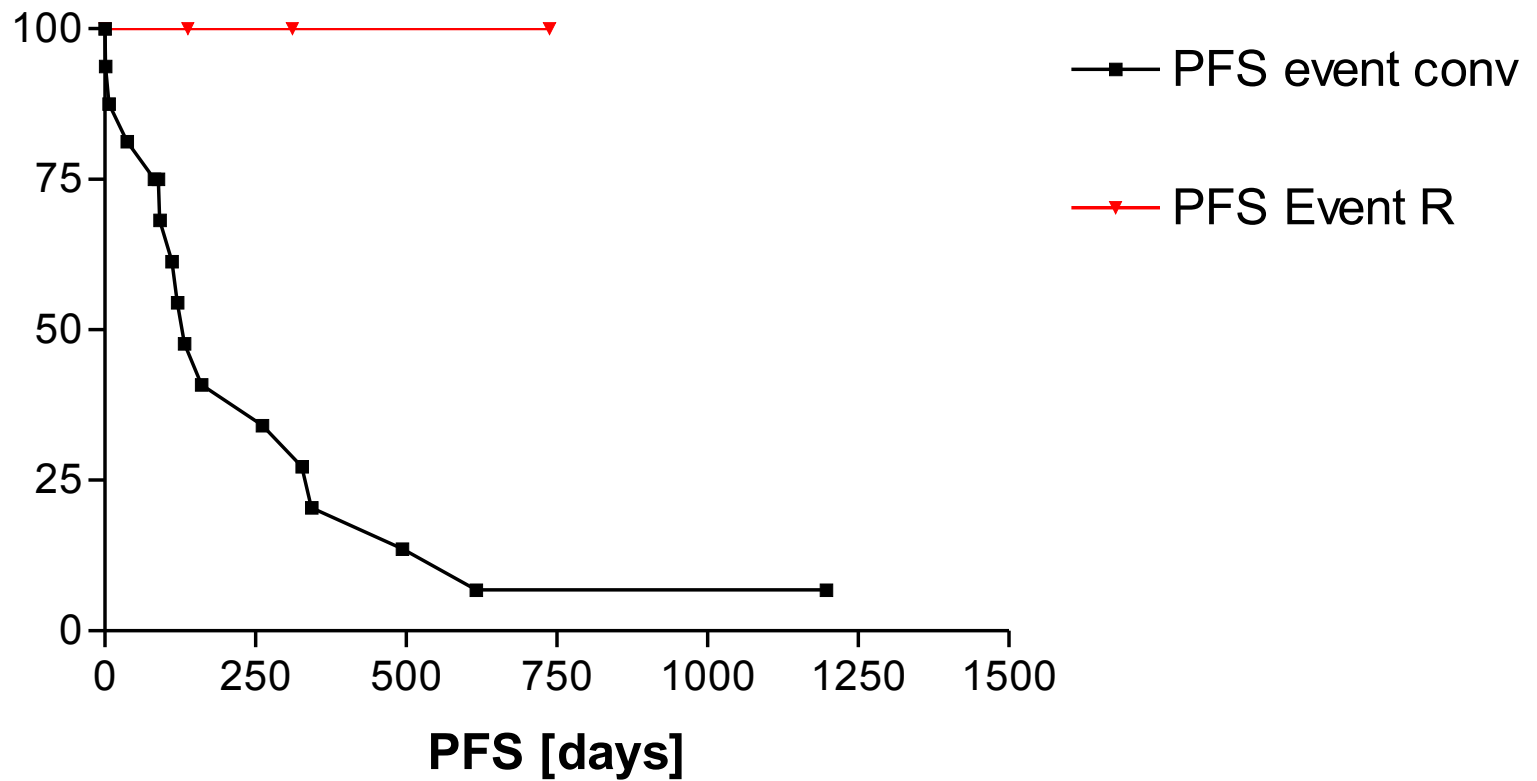
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Eigene Erfahrungen

TTP PFS R vs non R

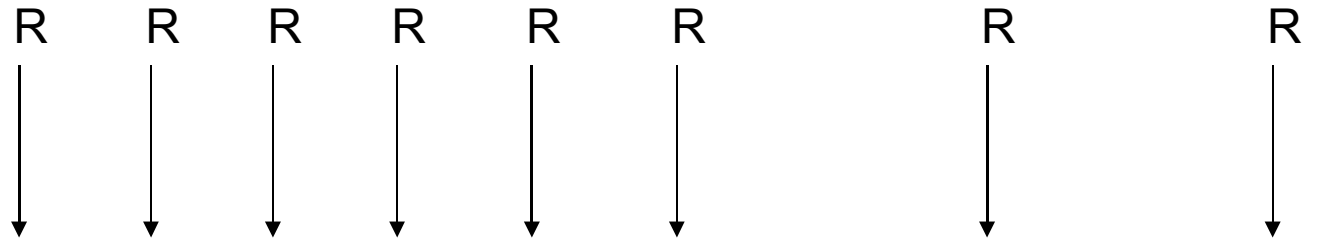
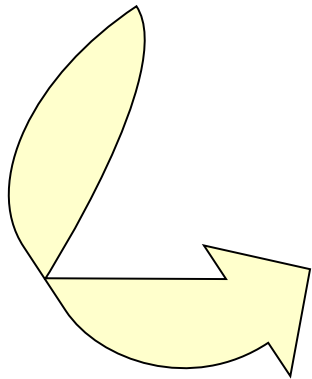


AIHA



Mögliches Studienkonzept

Rezidiv
oder
Refrakärer TTP



Steroide

Plasmapherese



Nebenwirkungen - Zytostatika

- Schädigung aller schnell teilenden Gewebe: Zytostatika sind **NICHT SELEKTIV**
 - Große Wachstumsfraktion bei normalen Zellen bei Knochenmarkzellen, Haarfollikelzellen, Intestinalschleimhaut: deshalb hier die typischen Zielgewebe für Nebenwirkungen
 - Knochenmark
 - Infektionen, Blutungen, Anämie
 - Schleimhäute
 - Verminderte Nahrungszufuhr
 - Schmerz, Infektion
 - Leber bei hepatischer Exkretion
 - Niere bei renaler Exkretion
 - Reproduktionsorgane
- Zusätzlich häufig spezifische Nebenwirkungen

Nebenwirkungen von Rituximab

- USA: VITAMIN R
- Akut:
 - Schüttelfrost, Fieber, allerg. Reaktionen
 - In der Regel mild, selten schwere Reaktionen
- Dauer
 - Mittlerweile Daten für die Langzeitanwendung vorhanden (bis zu 40-50 Infusionen/Patient)
 - Keine erhöhte Infektanfälligkeit
 - Ggf. Rate an viralen Reaktivierungen (Gürtelrose) höher

Zusammenfassung

- Nicht hereditäre 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 Antikörper: Rituximab
- Erste Daten für Wirksamkeit
- Prospektive Prüfung angestrebt

FRAGEN ?

