NIKKISO

時間 jikan
time

気 ki
energy

喜 yorokobi
joy

希望 kibou
hope

Apheresis in Ulcerative Colitis with

Immuno·pure®

Innovations for Human Care.

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Apheresis in Ulcerative Colitis and IBD

What do we know so far?

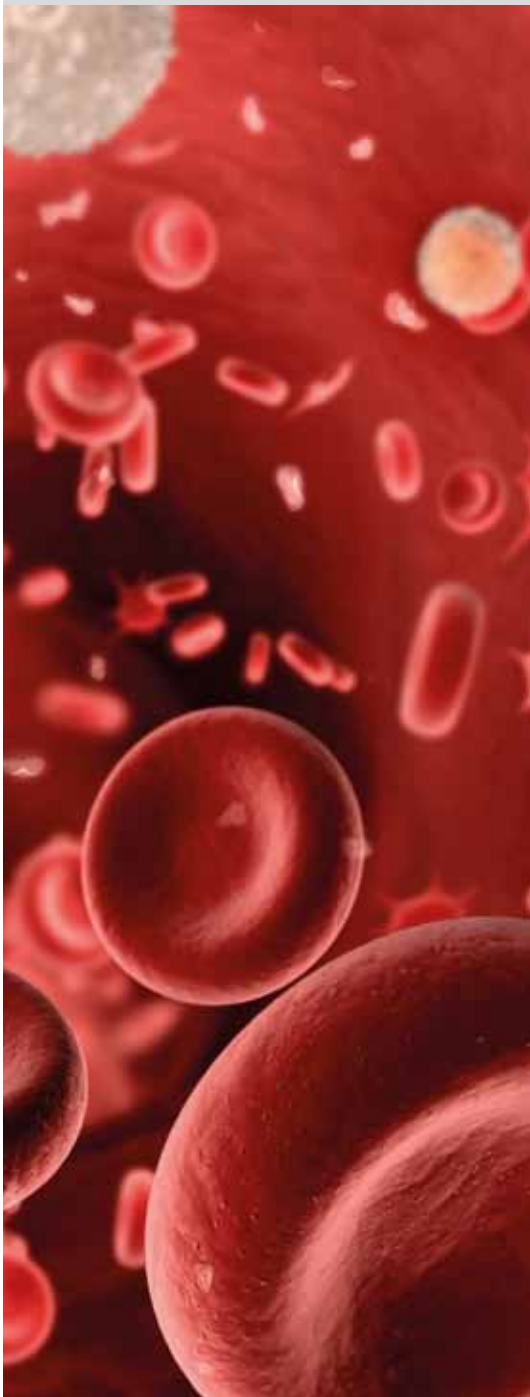
History of Apheresis

Apheresis by means of centrifugation as a method for treating patients with IBD was begun in the early 1980's on patients suffering from Crohn's disease (CD).
Initial results were very promising, however they were also associated with large volume plasma exchanges and high costs. This led to a concept for using a less complex procedure to eliminate leukocytes in patients suffering from Crohn's disease, which was also published by Bicks et al. in 1985 (1).
At the end of the 1980's, centrifugation was replaced by adsorption as a method of eliminating leukocytes. This also gave rise to an increase in clinical expectations in relation to adsorption apheresis in terms of therapeutic success with IBD patients.
For this reason, two apheresis systems for treating patients with colitis ulcerosa and Crohn's disease were developed in Japan and were also tested in clinical trials.
Clinical studies showed that apheresis can be used as a safe and effective alternative treatment or complementary treatment to previous therapeutic options (2, 3).
Both procedures seek to eliminate inflammatory cells, with one technique focusing on the adsorption of granulocytes and monocytes, while another concentrates on lymphocyte adsorption.

Apheresis today

Nonetheless, apheresis only enjoys limited acceptance as a treatment for IBD, a fact that deserves particular mention in the light of continuing high levels of medical need in relation to available alternatives in IBD.
The critical fact is that a definitive statement cannot be made concerning the effectiveness of the treatment from a gastroenterology perspective, despite the existence of numerous studies, even including controlled studies. In addition, the apheresis procedure is relatively expensive and restrictions exist in the local reimbursement systems operated in the various countries. Unfortunately, a recently published study by Sands et al. in 2009 (4) also failed to produce positive evidence of the effectiveness of apheresis.
All of these facts have led to limits on the use of apheresis in IBD.

Nonetheless, a critical question needs to be asked:
Is this limitation in regard to the use of apheresis justified in the light of the continuing medical need in IBD?



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Immunopure®

A novel device with selective adsorptive characteristic.

Rationale

Recent studies have shown that granulocytes, monocytes and platelets (5, 6) play an important role in the local inflammatory process of the gut's mucosa.
Therefore the reduction of tissue infiltration by inflammatory cells and the prevention of transmigration of pro-inflammatory peripheral blood cells to the site of inflammation is indicated.

Immunopure®

- is a novel medical device based on polyarylate beads
- has a length of 185 mm, diameter of 59 mm, total weight 537 g, total volume of 350 ml and priming volume of 139 ml
- will be used once a week over 5 weeks with 30 ml/min by using a hemoperfusion pump (LPM-01) and with heparin anticoagulation
- was tested in vitro and in animals investigations to realize the adsorption characteristic and the safety first
- was investigated in a first clinical trial in 10 patients with refractory active ulcerative colitis (Tab 01, 02) with promising results

Immunopure® Study in patient with active ulcerative colitis (UC)

- Design:
  open prospective single-center pilot study
- Objective:
  to provide data about the safety, tolerability and technical performance of Immunopure® in patients with moderately to severely active UC.
- Patients:
  10 patients with moderately to severely active UC who have failed to achieve long-term remission with steroids and/or immunosuppressants

Summary

It can be stated that - as intended - platelets, monocytes and granulocytes were effectively reduced during the treatment.

In contrast, lymphocytes were only moderately depleted, while red blood cells were not influenced by Immunopure®.

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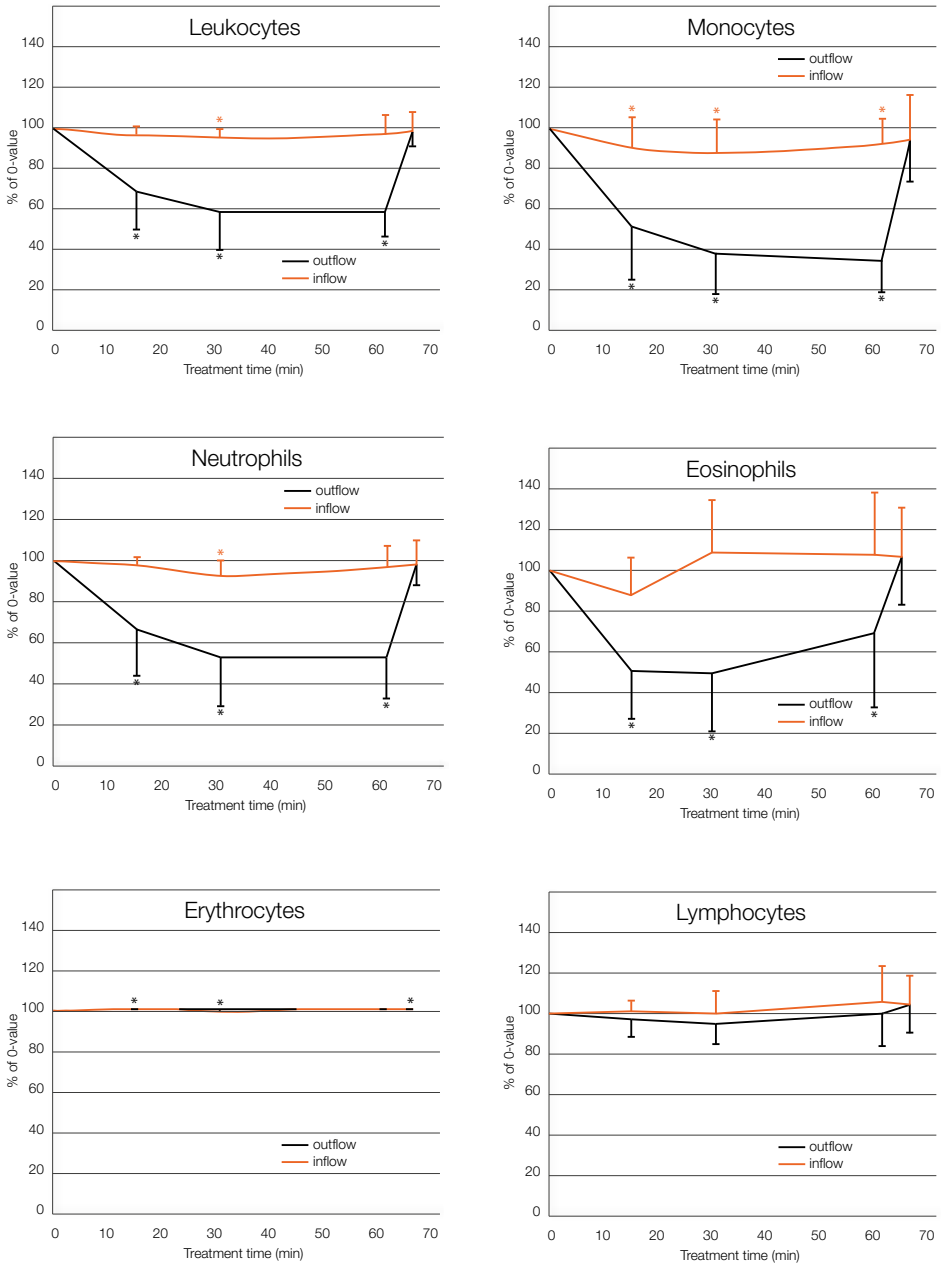
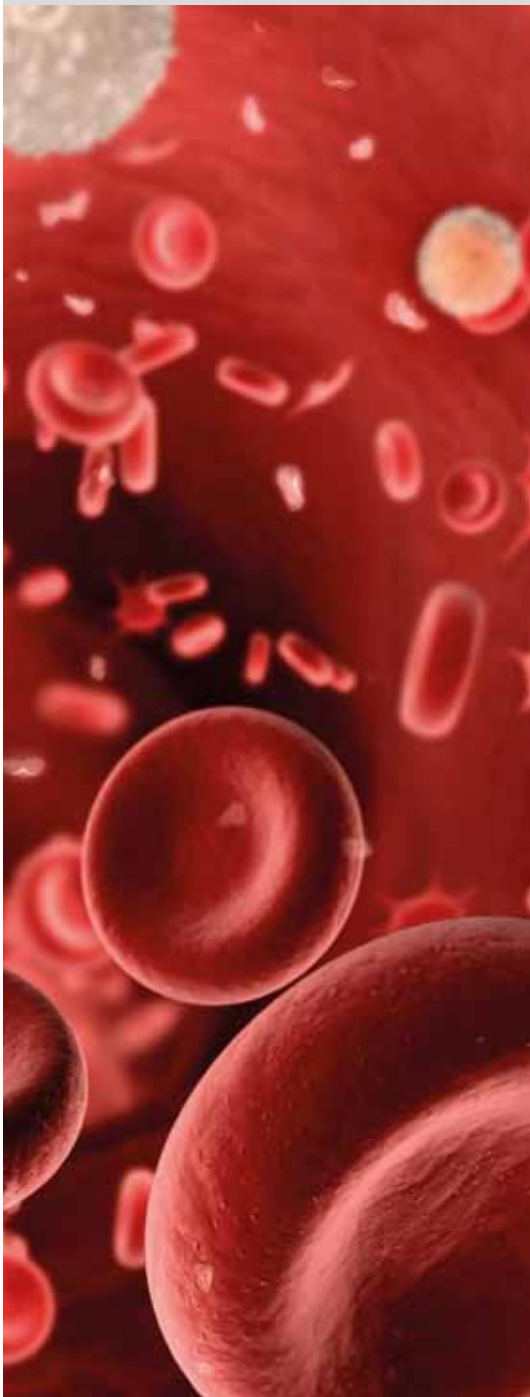
Adsorption characteristic of Immunopure®



The platelets were strongly reduced to 20.3 % in the outflow line (to 98.9 % in the inflow line) already after 15 min, however, platelet numbers recovered to 92 % after the treatment.

Fig. 1: Blood count graphs - intra-treatment impacts: Comparison of start (0 min) vs. 15, 30 and 60 min-values of one treatment session (10 patients, 50 treatments, Mean ± SD, absolute counts are expressed as % of 0-value (100 %)).



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First clinical study data with Immunopure®

The clinical efficacy is judged by the Clinical Activity Index (CAI, according to Rachmilewitz) score of all patients who were enrolled into the study (intent-to-treat population).
According to the definitions of clinical remission and clinical response (remission: CAI ≤ 4, response: CAI drop ≥3 or CAI ≤ 4) the remission and response rates are reflected by table 01.

No.	CAI/Inclusion	CAI/week 6	CAI/week 10	Final
1	10	5	2	remission
2	10	9	1	remission
3	10	11	8	non-responder
4	8	10	(5)*	non-responder
5	10	0	0	remission
6	7	2	0	remission
7	7	4	4	remission
8	6	1	1	remission
9	9	3	4	remission
10	8	0	0	remission

Tab. 01: Course of the Clinical Activity Index (CAI) of the intent-to-treat population.

** prednisolone therapy*

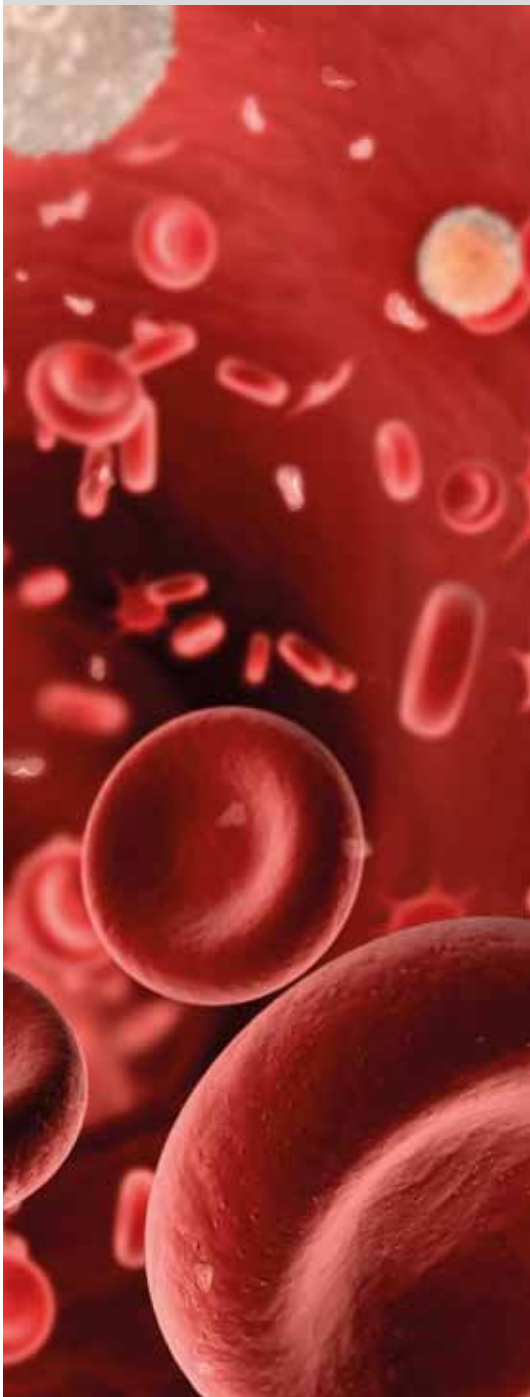
The endoscopic scores were determined using the Endoscopic Index (EI, according to Rachmilewitz). Remission according to the endoscopic score means EI < 4. Accordingly, 4 patients (44.4 %) developed remission, the same patients who had CAI remission. In 1 patient with clinical remission no endoscopic investigation was performed, and 5 patients did not show remission according to the endoscopic score (55.6 %, 3 of them had a clinical remission according to improvements in CAI score).

Endoscopic Score	Final evaluation Number of patients	Percentage
Per-Protocol Population	10	
Remission	4	44.4
No endoscopic examination	1	-
Non-responder	5	55.6

Tab. 02: Endoscopic score: remission and non-response rates of the per-protocol population

Conclusion

- It was shown that platelets, monocytes and granulocytes were effectively reduced during the treatments by Immunopure®.
- The apheresis treatments with Immunopure® assured a high degree of safety in the first clinical trial. All measured safety parameters remained substantially unchanged, both during intra-treatment and inter-treatment periods.
- The clinical efficacy based on this preliminary data judged by means of the Clinical Activity Index (CAI) and Endoscopic Index (EI) according to Rachmilewitz appears to have with Immunopure® a new and successful therapeutic option in the treatment of patient suffering from Ulcerative Colitis.



Important inflammatory cells in IBD - any news?

The role of thrombocytes in inflammation.

Gut inflammation is mediated by cells of the innate as well as adaptive immune systems, with the additional contribution on non-immune cells, such as epithelial, mesenchymal and endothelial cells and platelets (5).
Whereas the role of leukocytes in inflammatory bowel disease are well known recent publications could give us more understanding about the platelets in IBD (5, 6, 7).
Crohn's disease and ulcerative colitis are associated with abnormalities of platelet number and function.
In the peripheral circulation the state of platelet activation is typically increased and inflammatory bowel disease-involved mucosa frequently contains platelet aggregates within mucosal microthrombi.

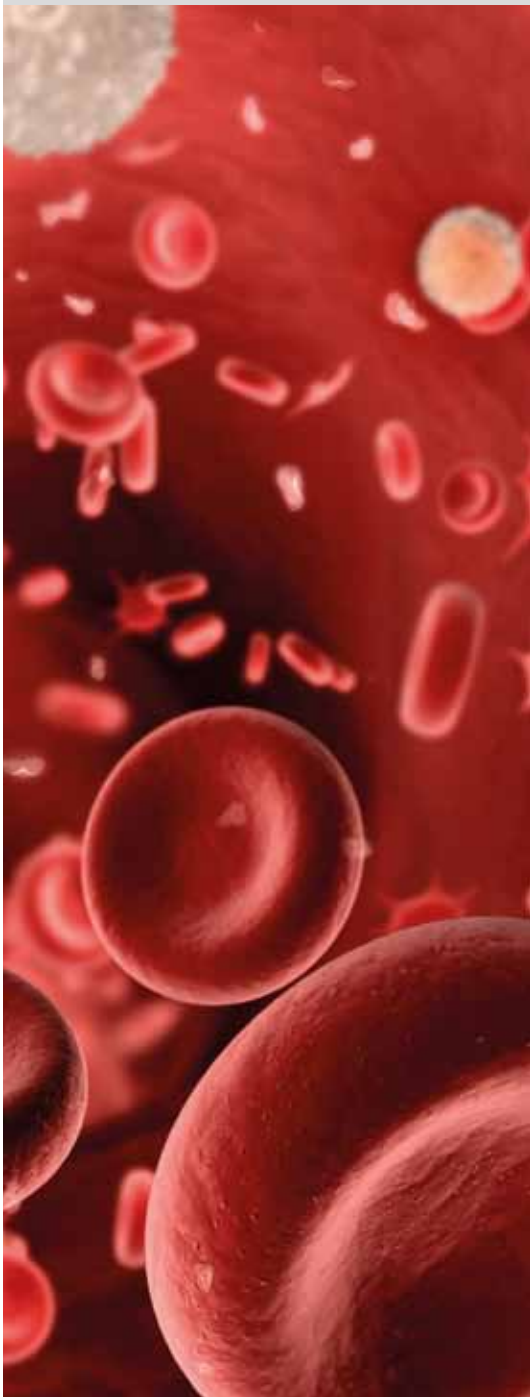
In addition to their traditional role in hemostasis platelets can also function as potent proinflammatory cells. This is related to the nature of platelets to stimulate inflammatory processes by secretion of biologically active molecules (6), see Table 03.
Beside the role of leukocytes in the pathogenesis of IBD even the platelets seems to be a key driver in the inflammatory process by secretion of several mediators.
Once seen as mere participants of the coagulation cascade, platelets have gained a new status as important components of localized inflammatory responses (8).

Bhatt et al. (9) summarized the need of targeting this cell type for therapeutic strategies for CD and UC. The adsorptive device *Immuno.pure*® seems to be effective in adsorption of leukocytes and platelets as well.

Immuno.pure® offers a new opportunity by targeting potential inflammatory cells in IBD: leukocytes and platelets.

Mediator	*Biological Action*
Histamine	Regulation of vascular permeability (10)
PGE2-PGD2	Vasodilatation (10)
PDGF	Vasoconstriction, SMC proliferation, chemotaxis, Leukocyte activation (10)
Thromboxane A2	Vasoconstriction, proinflammatory (10)
Serotonin	Vasoconstriction, SMC proliferation, chemotaxis (10)
bFGF	Angiogenesis (11)
VEGF	Angiogenesis (12)
Adenine nucleotides	Neutrophil activation and degranulation (13)
Heparanase	Extracellular matrix degradation (13)
TGF-ß	Fibrobalst proliferation, wound repair, immunosuppression (14)
PF-4	Chemotaxis, leukocyte adhesion (15)
ß-thromboglobulin	Chemotaxis, leukocyte activation and adhesion (15)
RANTES	Chemotaxis , T-cell activation, leukocyte adhesion (16)
MIP-1alpha	Chemotaxis (16)
PAF	Chemotaxis, platelet activation (15, 16)
MCP 3	Chemotaxis, leukocyte activation (16)
GRO-alpha	Chemotaxis, leukocyte activation (16)
12-HETE	Chemotaxis (17)
sCD40L	Proinflammatory, prothrombotic, immunoregulatory (18)
IL-1ß	Proinflammatory (19)
IL- 7	Immunoregulation (20)

Tab. 03 Mediators produced by Thrombocytes (Danese et al. 2004)



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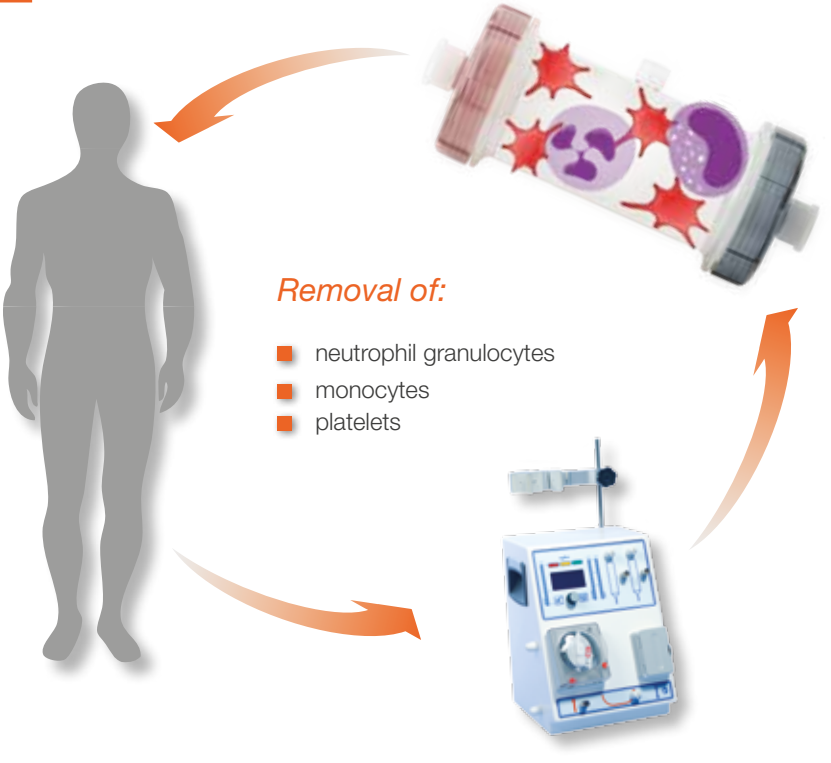
How to perform apheresis with Immunopure®?

Treatment

- five treatment sessions (once a week over five weeks)
- 30 ml / min (for 60 min)
- heparin - anticoagulation
- venovenous procedure



Removal of:

- neutrophil granulocytes
- monocytes
- platelets

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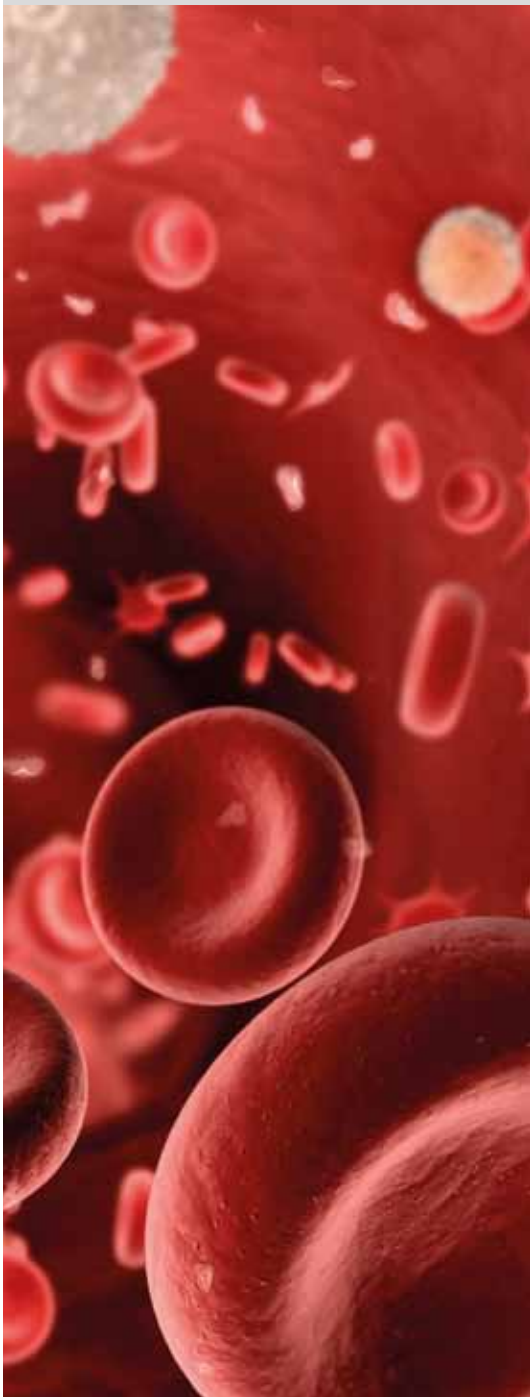

Do you want to know more?

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