

Recipients of Adacolumn® Travel Grants to the 3rd congress of ECCO – IBD 2008 in Lyon

We are happy to announce that the following persons have been chosen for the Adacolumn Travel Grant to 3rd Congress of ECCO – IBD meeting in Lyon 2008.

- **R.N. Katarina Pihl Lesnovska,**
Linköping University Hospital, Sweden
- **R.N. Leana Sits,**
Tartu University Hospital, Estonia
- **R.N. Joy Christina Hult,**
Rigshospitalet, Denmark
- **R.N. Siv Hege Bærøyd,**
Stavanger University Hospital, Norway
- **R.N. Kaisa Siirilä,**
Oulu University Hospital, Finland



We would like to take this opportunity to thank everyone who applied for this grant.

The grant recipients were selected by the scholarship committee: Professor Robert Löfberg, Sophiahemmet, Stockholm, Sweden and

Dr. Tarja Ruuska, Tampere University Hospital, Finland.

The recipients are asked to write a short report within one month of the congress. Some of these reports will be published in the Adacolumn Newsletter and on our website.

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New Publications

- Adsorptive Depletion of Elevated Proinflammatory CD14⁺CD16⁺DR⁺⁺ Monocytes in Patients With Inflammatory Bowel Disease. Hanai, et al. Am J Gastroenterol 2007;102:1-7.**
Proinflammatory monocytes suppressed by treatment. The proportion CD 14⁺ CD 16⁺ DR⁺⁺ monocytes in peripheral blood is increased in active IBD, compared to healthy controls and to quiescent IBD. The percentage of proinflammatory of CD 14⁺ CD 16⁺ DR⁺⁺ monocytes was significantly reduced by GMA apheresis with Adacolumn.

- Therapeutic leukocytapheresis for inflammatory bowel disease. Saniabadi, et al. Transfus Apher Sci 2007; 37(2):191-200.**
Increase in regulatory T-cells after treatment. This review highlights how the peripheral blood leukocyte population is affected by Adacolumn apheresis. In addition to the decrease of CD14⁺ and CD16⁺ monocytes, an increase of regulatory CD4⁺ T-lymphocytes is seen after treatment.

If you are interested in reading these recently published articles, please write your name, hospital, department and address in this Order Form and fax it to +46 8 545 286 69, or e-mail us at: reprints@otsuka.se.

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On action and reaction: Granulocyte – Macrophage Adsorption (GMA) apheresis with Adacolumn®

In addition to the reduction of pro-inflammatory leukocyte populations through the Adacolumn® treatment, the contact of the column's surface carriers with the blood seems to trigger a multitude of physiological reactions in the body, including an increase in regulatory T-cells¹. Therefore, one of the most interesting topics in GMA research today, is the progress in understanding its Mode of Action – which, as well, could be followed by a Mode of Reaction.

A new anti-inflammatory cell population

Typically, about 65% of granulocytes, 55% of monocytes and only 2% of lymphocytes from the blood passing the column are adsorbed in the Adacolumn. However, the levels of these cell populations in the patients' peripheral blood do not fall below the normal range. Instead, the absolute number of naïve neutrophilic leukocytes in the peripheral circulation increases. This is due to the release of less mature leukocytes from the bone marrow. The immature cells do not show the same features in their cytoplasm nor in their surface antigen constellation as the older cells that have been removed. This difference is crucial to inflammation.

Decreased pro-inflammatory capacity

Studies on peripheral blood sampled before and after treatment with Adacolumn® have shown that peripheral blood leukocytes capacity to produce inflammatory cytokines is noticeably decreased after the treatment. In addition, a down-modulation of L-selectin expression was observed². L-selectin, also known as CD62L, acts as an anchor for leukocytes assisting the entry of cells into the tissue at the site of inflammation.

A variety of surface antigens of the cell populations at outflow are changed after the treatment. The observed changes include a reduction of the inflammatory cytokines TNF-alpha, IL-1-beta, IL-6, and IL-8, and the chemokine receptor CXCR3. Furthermore, an increase in the anti-inflammatory mediators IL-1 receptor antagonist (IL-1ra), hepatocyte growth factor (HGF), soluble TNF-alpha-receptors sTNF RI and RII, as well as IL-10 has been observed.

Increase of regulatory T-cells

In addition to the known increase in CD10-negative granulocytes, a remarkable increase in de-novo-lymphocytes (CD4⁺CD25⁺ T-cell subsets) ►

Dear newsletter readers.

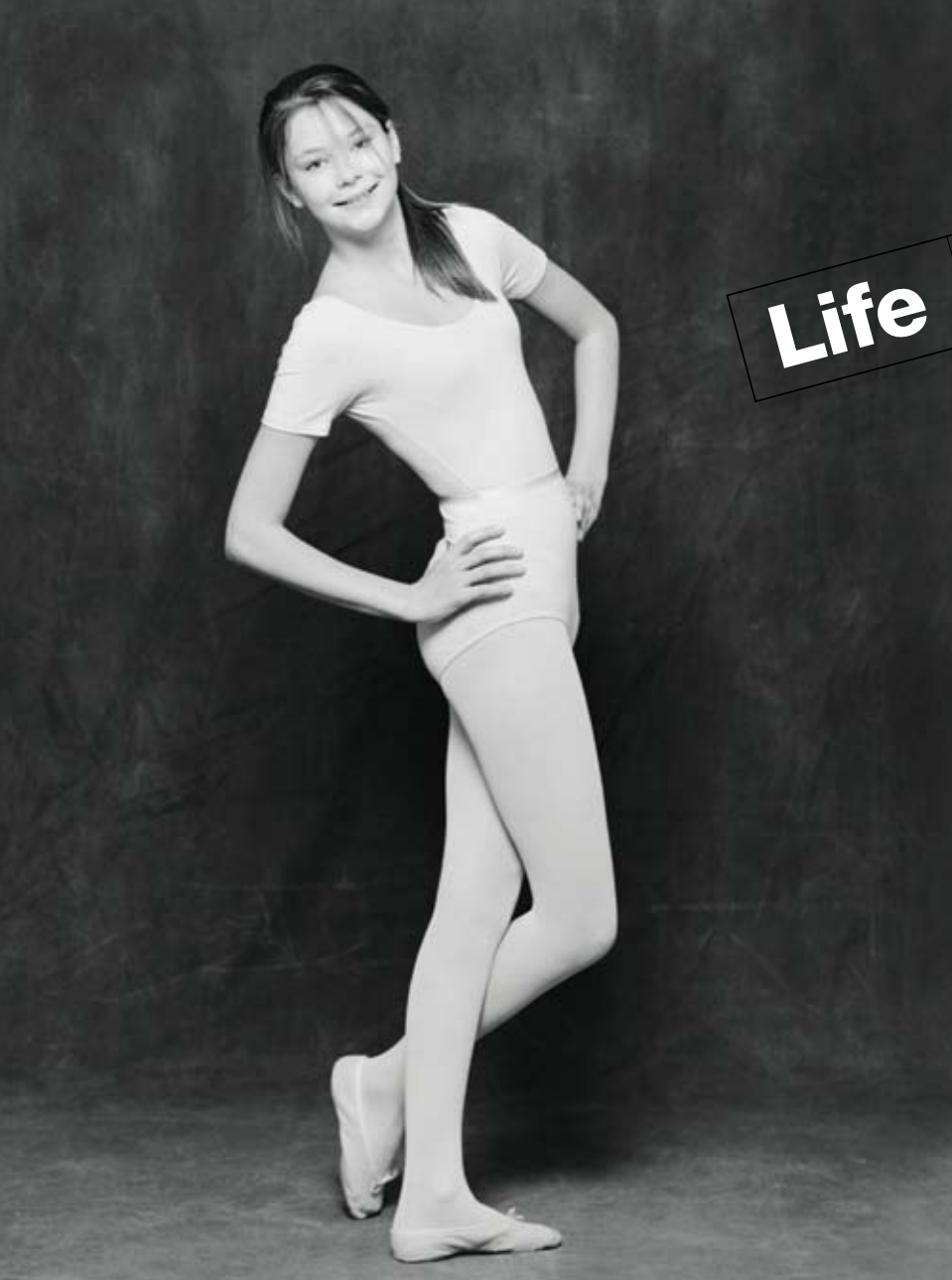
The darkest time of the year has arrived. But with the festive season comes candle lights and decorations, helping us getting into the Christmas spirit. This newsletter will be the last one of the year. Inside you will find an essay about the Adacolumn mechanism written by our Medical manager, Dr. Raphael Gruber. Also, despite of the busiest time of year, R.N. Kiikeri and Dr. Pukitis have kindly contributed with reports from the UEGW congress in Paris.

Instead of sending Christmas gifts to all of our friends, we have donated to Save the Children in Sweden and Finland this year. (Rädda Barnen & Pelastakaa Lapset Ru).

Finally, we would like to take this opportunity to express a sincere thank you for all the support we have had during 2007. We are looking forward to a fruitful corporation next year as well. We wish you all the very best for the Christmas holidays, and happy reunions with families and friends, wherever you are in the world!

Mari Liljefors

Marketing Director



Life Maximised

Background of Adacolumn® (GMA)

Selective leukocyte removal using Adacolumn®

The complete Adacolumn® system are medical devices approved for use in the EU and Japan since 1999. Venous blood is passed from one of the patient's arms via a simple venipuncture through the column, where granulocytes and monocytes/macrophages are removed. The blood is subsequently returned to the patient's body through a second venipuncture in the other arm.

Leukocytes in IBD

Several families of leukocytes are essential for the clinical appearance of IBD. Extravasation of a large number of granulocytes and macrophages into the mucosa plays a major role in the release of proinflammatory cytokines, reactive oxygen derivatives, and degradative proteases that nurture the ongoing inflammatory reactions.⁵

- ▶ can be found. These regulatory T-cells are a specialized subpopulation of T lymphocytes that act to suppress activation of the immune system.³

Regulatory T-cells and remission with Adacolumn

In IBD, "Regardless of the particular defects, the initial disease processes are channelled into a final common immunopathologic pathway comprised of either a Th1-type T cell-me-

diated inflammation (Crohn's disease) or a Th2-type T cell-mediated inflammation (ulcerative colitis)."⁴

It is plausible that the recent observations on regulatory T-cells are connected to the observed maintenance of clinical remission in IBD after GMA. More specifically, the long-term effect could depend on the mode of reaction in the body to an altered configuration of immunocompetent cells in the peripheral

blood. How this happens is virtually not yet understood, but is nevertheless a clinical reality for many IBD patients. It is one of the most intriguing areas of research relating to the mode of (re)action in Adacolumn® (GMA). ■

Dr Raphael Gruber, MD, European Medical Manager for Adacolumn®, Otsuka Pharmaceutical Europe Co. Ltd.

References: **1.** Yokoyama Y, et al. Demonstration of Low-Regulatory CD25 (High+) CD4 (+) and High-Pro-inflammatory CD28 (-) CD4 (+) T-Cell Subsets in Patients with Ulcerative Colitis: Modified by Selective Granulocyte and Monocyte Adsorption Apheresis. *Dig Dis Sci* 2007; 52: 2752 – 31. **2.** Saniabadi AR et al.: Adacolumn, an adsorptive carrier-based granulocyte and monocyte apheresis device for the treatment of inflammatory and refractory diseases associated with leukocytes. *Therapeutic Apheresis and Dialysis* 2003; 7 (1): 48 – 59. **3.** Specific bibliography available on request. Please do contact the author. **4.** Strober W, et al. The fundamental basis of inflammatory bowel disease. *Journal of Clinical Investigation* 2007; 117 (3): 514 – 21. **5.** Kruijs W et al.: Open label trial of granulocyte apheresis suggests therapeutic efficacy in chronically active steroid refractory ulcerative colitis. *World J Gastroenterol* 2005; 11 (44): 7001 – 6.

Report from UEGW in Paris 2007

By Reetta Kiikeri, Registered Nurse, Turku University Hospital, Finland

I received the Adacolumn Travel Grant to United European Gastroenterology Week (UEGW) this year. The congress took place 27th–31st October, Paris, France where I attended the three-day traditional part of the congress.

New guidelines for IBD-care

The general consensus in IBD-treatment regime seems to be changing. The traditional "step up"-model is giving way to a new "top down"-model. Both models have their supporters and opponents. Some gastroenterologists in Europe are now using the "top down" treatment.

The idea in "step up" is to start with the mildest possible medication and proceed to stronger medications if required. This means treating IBD with first 5-ASA, then corticosteroids and lastly immunomodulators, such as methotrexate, azathioprine, infliximab

and adalimumab.

In the new "top down" treatment the stronger immunomodulators is used immediately as the disease is diagnosed. After remission has been attained, the treatment proceeds with milder treatments, such as 5-ASA. The idea is to produce rapid remission, and thus improve the patients' quality of life and avoid side effects of medications such as those associated with a long-term corticosteroid use.

Regular cancer examinations of IBD-patients

The constant inflammation in the bowel and use of immunomodulators and corticosteroids gives an increased risk of cancer for IBD-patients. The general consensus was that IBD-patients do need to be examined regularly, especially older patients and long time sufferers.

Scandinavian colleagues dinner

In addition to lectures Otsuka Pharma invited the doctors and nurses from the Nordic countries to a dinner. We shared the experiences with IBD-patients with our fellow colleagues and noted the differences and similarities in our patient care.

All in all, I am really pleased and grateful to have been able to attend the UEGW congress. I received a lot of useful information, new contacts and a well needed break from the hard work we all do at the hospitals. Special greetings to Veikko and Heikki from Finland and the Norwegian nurses from Stavanger. It was nice to meet you! ■

Adacolumn® Travel Grant report from 15th UEGW, Paris 2007

By Aldis Pukitis MD, PhD. Gastroenterology Center, Paul Stradin Clinical University Hospital, Riga, Latvia

Paris was selected as 15th UEGW hometown this year. I visited this global, international event as Adacolumn Travel Grant stipendiate and participated in the UEGW Postgraduate Teaching Programm for the first time. I returned back to my hometown loaded with many new impressions from the Congress and autumn time in Paris. In this regard, I would like to share my jottings from the congress abstract book pages. One of the fields of my interest is development of granulocyte/monocyte apheresis technology, since we started Adacolumn treatment in Latvia from 2004.

We have gathered some experience before and it was excellent possibility for me to obtain new ideas.

New data were demonstrated in the Poster Session (Takeda S, UEGW, 2007) showing that granulocyte/monocyte apheresis removes CD14⁺ CD16⁺ from peripheral blood for steroid naive patients. It suggests that granulocyte/monocyte apheresis influences the inflammation by disrupting the adhesion and transmigration mechanisms of the circulating monocytes. Mucosal IL-8-mRNA expression in related with ulcerative colitis activity and it was

significantly decreased in patients, who received granulocyte/monocyte apheresis (Matsuda R, UEGW, 2007). Mucosal immunology study for IBD patients during granulocyte/monocyte apheresis was performed by Swedish group from Karolinska Institutet (Hjalmarsson E, UEGW, 2007).

New data were demonstrated regarding US and MR diagnostics in Crohn's disease. Early US findings of terminal ileum and caecum can be useful markers for differential diagnosis in appendicitis and may avoid unnecessary appendectomies (in 50% of Crohn's disease cases). Real time



► histology is now reality with endoscopy techniques for detecting of early neoplasia in longstanding ulcerative colitis. Videocapsule endoscopy in a recent meta-analysis of clinical trials, showed superiority over all other techniques to assess intestinal lesions in patients with already established diagnosis of Crohn's disease. The concept of mucosal healing underlines the role of endoscopy in the assessment of IBD and is recognized as important endpoint of IBD therapy. Above mentioned and some more targeted IBD topics were professionally discussed in the Postgraduate

Course where majority of participants were experienced doctors from all over the world.

I would like to thank the Adacolumn Committee for the high evaluation selecting me as a Travel Grant recipient.

With Christmas greetings and best wishes for all of you, your families and friends in the forthcoming year 2008. ■

