(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/001209 A1

(51) International Patent Classification[7]: G01N 33/569

(21) International Application Number: PCT/NO02/00218

(22) International Filing Date: 19 June 2002 (19.06.2002)

(25) Filing Language: Norwegian

(26) Publication Language: English

(30) Priority Data:
20013192 25 June 2001 (25.06.2001) NO

(71) Applicant (for all designated States except US): MEDINNOVA SF [NO/NO]; Rikshospitalet, N-0027 Oslo (NO).

(72) Inventor; and
(75) Inventor/Applicant (for US only): OLAUSSEN, Richard, W. [NO/NO]; Blåbærstien 13F, N-1450 Nesoddtangen (NO).

(74) Agent: KRISTIANSEN, Ewy; Bryns Zacco AS, P.O. Box 765, Sentrum, N-0106 Oslo (NO).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/001209 A1

(54) Title: METHOD FOR MONITORING THE RATE OF T-CELLS RECENTLY EMIGRATED FROM THE THYMUS

(57) Abstract: The chemokine receptor CCR9 is reported to be predominantly expressed by thymocytes as well as by circulating gut-homing and resident T cells in the small intestinal mucosa. Its ligand TECK (thymus-expressed chemokine) is produced by thymic and small intestinal epithelium. Here we report that the relative fraction of circulating CCR9$^+$ naive T cells (mostly CD4$^+$) declines with age, from approximately 15 % of all T cells at birth to around 1 % in adults. The proportion of CCR9$^+$ T cells negative for the classical gut homing marker $\alpha4\beta7$, was much higher in childhood than in adults. Therefore, circulating CD3$^+$CD45RA$^+$CCR9$^+$ cells have most likely left the thymus quite recently. Establishing a phenotypic marker for recent thymic emigrants may provide a powerful tool in the clinical assessment and follow-up after hematopoietic stem cell transplantation and during antiretroviral treatment of HIV-infected patients.

Method for monitoring the rate of T-cells recently emigrated form the thymus.

Introduction

The present invention relates to an in vitro method for monitoring the rate of T-cells, and a kit comprising antibodies for monitoring T-cells.

The human G protein-coupled receptor GPR-9-6/CCR9 was described by Zaballos et al. [1] as the receptor for the thymus-expressed chemokine (TECK). TECK is apparently produced only by thymic dendritic[2] and epithelial[3] cells, and by enterocytes of the small intestine[3,4]. CCR9 expression on circulating memory cells is reported to define a gut-homing subset[5], in agreement with the finding that most T cells in the small intestinal epithelium and lamina propria express CCR9[4,6]. Little is known about the regulation of CCR9 with age. In mice, $CD8^+$ thymocytes, as well as $CD8^+$ cells in peripheral lymphoid organs, constitute, a $CCR9^+CD69^{low}CD62^{high}$ subset that decreasingly migrates towards TECK with increasing age[7]. In humans, recently emigrated thymocytes can be identified among circulating cells by TCR-rearrangement excision circles in episomal DNA[8], but no applicable phenotypic marker has to our knowledge been described. Here, we report that most $CCR9^+$ T cells in children are of the naive ($CD45RA^+$) phenotype. This population is much lower in adults and markedly reduced in recently thymectomized children. Therefore, we postulate that circulating $CD45RA^+CCR9^+$ T cells mainly represent recent thymic emigrants. The method of the present invention is an excellent tool in determining the extent of immunefailure in different diseases and monitoring the effect of treatment.

Study Design

Peripheral blood from pediatric patients (n = 20 , 4 months-18 years) and adult healthy volunteers (n = 9, 27-59 years) was used. The study was approved by the regional ethical committee, and written informed consent was obtained from parents (or children more that 12 years old). Blood was collected for this study only when venous puncture was carried out for diagnostic or follow-up purposes of their ailments. The patients did not receive immunosuppressive treatment and were not afflicted with known immune dysfunctions. E.g., constipation, neurosis, epilepsy, migraine or temporomandibular joint ankylosis. Blood was also obtained from five children 1 week (age at investigation: 5 years), 6 weeks (age: 4 months), 11 weeks (age: 3 months), 3 years (age: 4 years), and 4 years (age: 4 years) after thymectomy which was carried out in connection with cardiac surgery.

Heparinized blood was separated with Lymphoprep (Nycomed Pharma, Oslo, Norway) and subjected to double- or triple-color immunofluorescence staining with two or three incubation steps. The following antibody reagents were used: mouse anti-CD3-FITC (fluorescein isothiocyanate), mouse anti-CD4 (IgG1; SK3 and SK4), mouse anti-CD8 (IgG1, SK1), mouse anti-CD45RA-FITC, mouse anti-CD3-PerCP (peridinin chlorophyll) (all from Becton Dickinson, San Jose, CA), mouse anti-CCR9 (LS 129 3C3, IgG2b; courtesy of Dr. Paul Ponath, LeukoSite Inc, Cambridge, MA), mouse anti-$\alpha 4\beta 7$ (Act.1, IgG1, courtesy of Dr. Andrew I. Lazarovits, Ontario, Canada), goat anti-mouse IgG2b-PE (phycoerythrin), (Southern Biotechnology Associates, Birmingham, AL) and goat anti-mouse IgG1 PE/Cy5 (PE / indodicarbocyanide) (Caltag Laboratories, Burlingame, CA). Controls were isotype- and concentration-matched antibodies of irrelevant specificities. Acquisition was carried out on a FACScan or FACS Vantage SE Flow cytometer equipped with the Cell Quest analysis programme (Becton Dickinson, San Jose, CA). SPSS for Windows, release 9.0.1 (Chicago, IL) was used for statistical analyses of the compiled flow-cytometric data.

FIGURE LEGENDS

Figure 1

Variation of $CCR9^+$ naive T cells in relation to age. The upper right quadrant of diagram A through G represents $CCR9^+$ naive T cells as defined by the CD45RA marker. *A-F:* After 1 year of age, the proportion of this subset shows a decrease that levels out in adulthood. The same subset is strikingly reduced in a thymectomized patient (*1C*). *G*: The $CCR9^+$ naive T cell population was quite low in a 59-year-old blood donor compared with that of a 51-year-old subject. This accords with a steeper decrease of naive T cells from about 60 years of age and onwards as reported by others[8]. *H-I:* A higher percentage of $CCR9^+$ T cells negative for the gut homing marker α4β7 is seen in a child compared with that of an adult.

Figure 2

Compiled flow-cytometric data in relation to age of study subjects.

A: percentage of $CCR9^+$ cells among all T cells decreases with age.

B: When a natural log transformation of the same data is plotted versus age, a linear relationship appears. C, D: Comparable data for $CCR9^+$ $CD45RA^+$ T cells.

Figure 3

Compiled flow-cytometric data for CCR9+naïve T cells (A) and CCR9+a4b7-T cells (B) in normal (o) and thymectomized (▼) subjects in relation to age. Data from Figure 2C for ages under 10 years old and, in addition, data from the thymectomized patients. The time from thymectomy was 6 and 11 weeks, respectively, for the patients located in the lower left corner, and 4 years in the 4 year-old-patient with the lowest value. The respective times for the other 4-year-old and the 5-year-old patient were 3 years and 1 week.

Results and discussion

Figure 1 shows expression of CD45RA and CCR9 on $CD3^+$ gated cells (Figure 1A-1G). Except for data from a thymectomized patient (Figure 1C), $CD45RA^+CCR9^+CD3^+$ cells constituted a relatively large fraction (~15 %) during the first year of life, declining to ~5 % by adolescence and to ~1 % in adults. The age-dependent decrease of $CD3^+CD45RA^+CCR9^+$ cells parallels the age-dependent thymic involution[9] (see below), and circulating $CCR9^+$ naive T cells might therefore represent recent thymic emigrants. According to Campbell et al[10], the most mature medullary thymocytes migrate poorly towards TECK, although the CCR9 expression of those cells was not examined. No age-dependent relationship was observed for the $CD45RA^-$ $CCR9^+$ T cell population.

The mean fluorescence intensity was lower for $CD45RA^+$ cells than for $CD45RA^-$ cells (data not shown), in agreement with data from Zabel et al.[5], and the CD4:CD8 ratio among the naive $CCR9^+$ population was 2.5:1 (data not shown). This last result differed from the reported $CD8^+$ predominance in murine CCR9-expressing cells found in peripheral lymph nodes[7].

Figure 1C displays data from a 3-month-old patient 11 weeks after thymectomy; a marked reduction of the $CD45RA^+CCR9^+$ T cell population was observed compared with that present in umilical cord blood (Figure 1A) and the 1-year-old donor (Figure 1B); another 4-month-old patient showed the same marked reduction 6 weeks after thymectomy; and in a 4-year-old patient thymectomized a few days after birth the population was reduced by 75% relative to age-matched controls (data not shown). Conversely, no decrease of the $CCR9^+$ naive T cell population was seen 1 week after thymectomy in a 5-year-old patient, and only a tendency towards reduction was seen 3 years after thymectomy in another 4-year-old patient (3.1% as compared to a median of 4.1% in age matched controls). Patient age, extent of (subtotal or total), and time after thymectomy could all contribute to the observed results. Remnants of thymic tissue might be functional and over time exert a compensatory regeneration of thymocytes. Thus, TCR-rearrangement-excision-circle studies of thymectomized patients more than 3 years after thymectomy showed that new T cells were produced although at a slightly reduced level[8].

Figure 1H and Figure 1I show that the classical intestinal homing receptor a4b7 was absent on approximately 50% of the CD3+CCR9+ cells in an 8-year-old donor but occurred on most CD3+CCR9+cells of a 47 year-old donor. Similar data are compiled in Figure 3B for a total of three children and three adults. CCR9+ on circulating T-cells has been associated with homing to the small intestine [4,5]. However, according to our results described above, the CCR9+a4b7-cells could rather be derived from the thymus. A two-fold reduction was seen for the CCR9+a4b7+ T-cells as opposed to a four-fold reduction among the CCR9+a4b7- T-cells from 5 to 47 years (data not shown). This suggested a link between the two cell populations but would only partially account for the findings with respect to CCR9+a4b7- cells and ageing. In fact, CCR9+a4b7- T-cells could also be recent thymic emigrants. Also notable in this context, the relative proportion of CCR9-expressing T cells decreased rapidly over the first 10 years of life, whereafter there was a more gradual decline (Figure 2A). The adapted curve assumed the shape of a power function of the form $y = ax^b$, and others have used this model function to describe the involution of the thymus cortex[9]. The natural log-transformed percentage variable had a normal distribution; when this variable was plotted against age (Figure 2B), a significant inverse correlation appeared (Pearsons $r = -0.79$, $P < 0.01$). Figure 2C shows that the rapid initial decline was confined to the $CD45RA^+$ population of $CCR9^+$ T cells (based on 18 donors); and a plot of the natural log-transformed percentage variable versus age (Figure 2D) again showed a significant negative correlation ($r = -0.86$, $P < 0.01$).

In conclusion, the inventors have observed a significant age-related decline of ciculating $CCR9^+$ T cells restricted to $CD45RA^+$ cells. The $CD3^+CCR9^+CD45RA^+$ population was consistently reduced dramatically after thymectomy, until after a variable period it again appeared to be increased, probably because of a compensatory mechanism. We therefore suggest that this naive T cell population represents recent thymic emigrants. The method of the present invention provides a convenient tool for monitoring the rate of T-cells recently emigrated from the thymus (RTEs) by e.g. monitoring responses to antiretroviral treatment in HIV-infected patients[8] or assess the extent of infection in said patients or to assess the regeneration of T cells after transplantation e.g. in heamatopoietic stem cell transplantation[11] or in patients suffering from autoimmune diseases. The effect on thymic function of cancer patients and in cancer related suppression after chemotherapy or irradiation as well as T cell reconstitution, can also be studied and easily monitored[12] by the method of the present invention. The present invention relates also to a kit comprising at least one type of antibody, which can be conjugated to e.g. fluorochrome for monitoring recently emigrated T-cells.
The method of the present invention has also a range of application in scientific work e.g. by studying the relation between cancer and RTEs deficiency, the relation between age and the share of RTEs or in the field of autoimmune diseases.

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Patent claims

1.
A method for monitoring T-cells, characterised in that specifically binding molecules are used to detect newly formed T-cells in that a specific binding between said newly formed T-cells and said specifically binding molecules is obtained by contacting said newly formed T-cells with a combination of specifically binding molecules, and wherein detection of this or these specific bindings is carried out instrumentally.

2.
The method according to claim 1, characterised in that said T-cells are human T-cells.

3.
The method according to claims 1-2, characterised in that said T-cells are from blood and/or bone marrow or other tissue.

4.
The method according to claims 1-3, characterised in that said specifically binding molecules are antibodies and/or molecules derived from antibodies.

5.
The method according to claims 1-4, characterised in that detection is carried out using a flow cytometer.

6.
The method according to claims 1-5, characterised in that said specifically binding molecules are used against cell markers on said T-cells, wherein said specifically binding molecules are against T-cell markers selected from the group(s) comprising: CD3, CD2, CD7 and/or CD4 or CD8 in combination with said specifically binding molecules against the cell marker CCR9 and additional said specifically binding molecules against at least one of the cell markers CD45RA or $\alpha 4\beta 7$.

7.
The use of a combination of antibodies and/or other specifically binding molecules which provide a specific binding between newly formed T-cells and antibodies and/or other specifically binding molecules for monitoring T-cells.

8.

A kit, characterised in that it comprises a selection of antibodies and/or specifically binding molecules capable of binding specifically to newly formed T-cells.

9.

A kit according to claim 8, characterised in that it comprises a selection of said antibodies and/or other specifically binding molecules, wherein said antibodies and/or specifically binding molecules are against the cell markers according to claim 6.

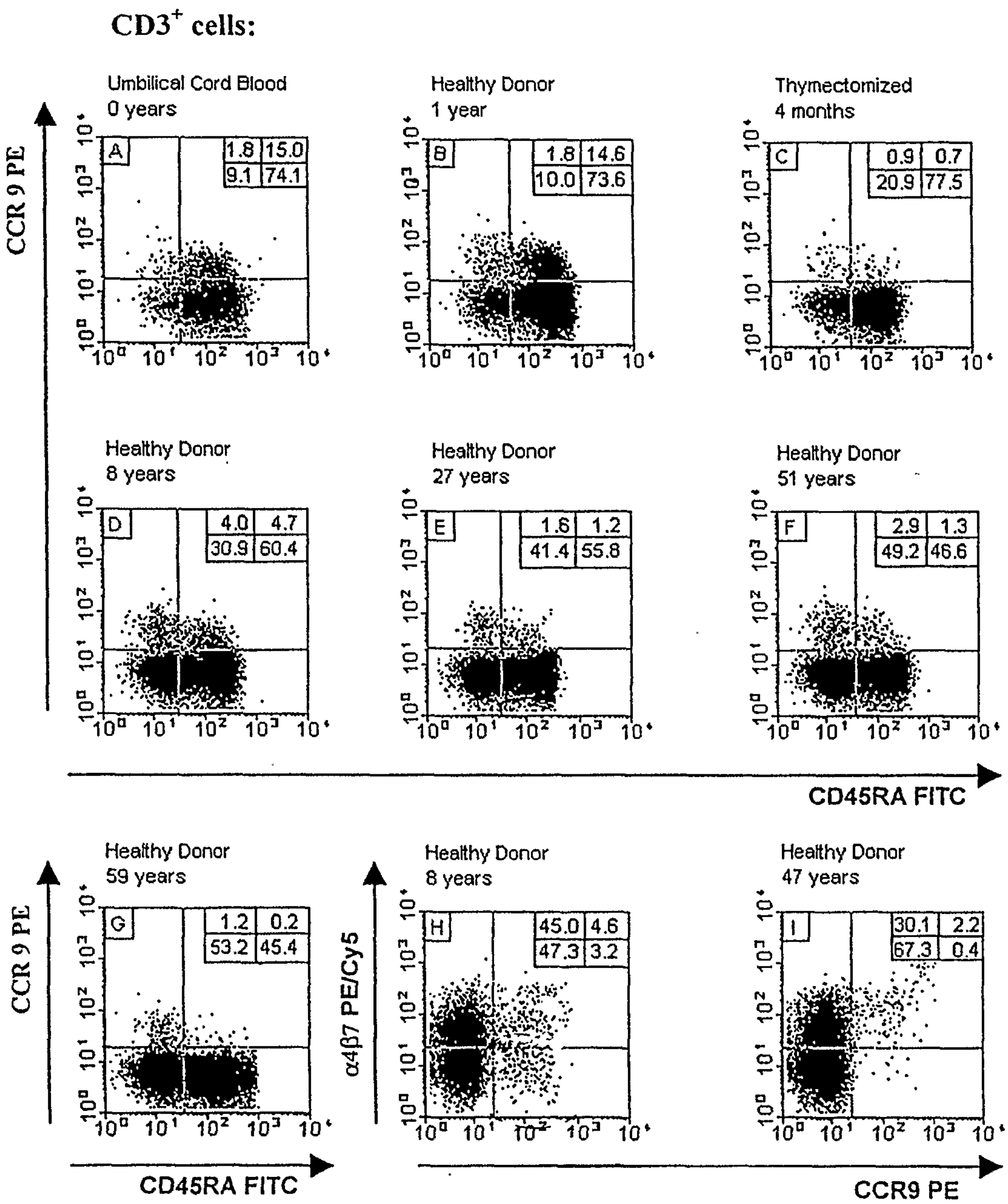
CD3⁺ cells:
Umbilical Cord Blood
0 years
A
1.8 15.0
9.1 74.1
Healthy Donor
1 year
B
1.8 14.6
10.0 73.6
Thymectomized
4 months
C
0.9 0.7
20.9 77.5
Healthy Donor
8 years
D
4.0 4.7
30.9 60.4
Healthy Donor
27 years
E
1.6 1.2
41.4 55.8
Healthy Donor
51 years
F
2.9 1.3
49.2 46.6
CCR 9 PE
CD45RA FITC
Healthy Donor
59 years
G
1.2 0.2
53.2 45.4
Healthy Donor
8 years
H
45.0 4.6
47.3 3.2
Healthy Donor
47 years
I
30.1 2.2
67.3 0.4
CCR 9 PE
CD45RA FITC
α4β7 PE/Cy5
CCR9 PE

Fig. 1

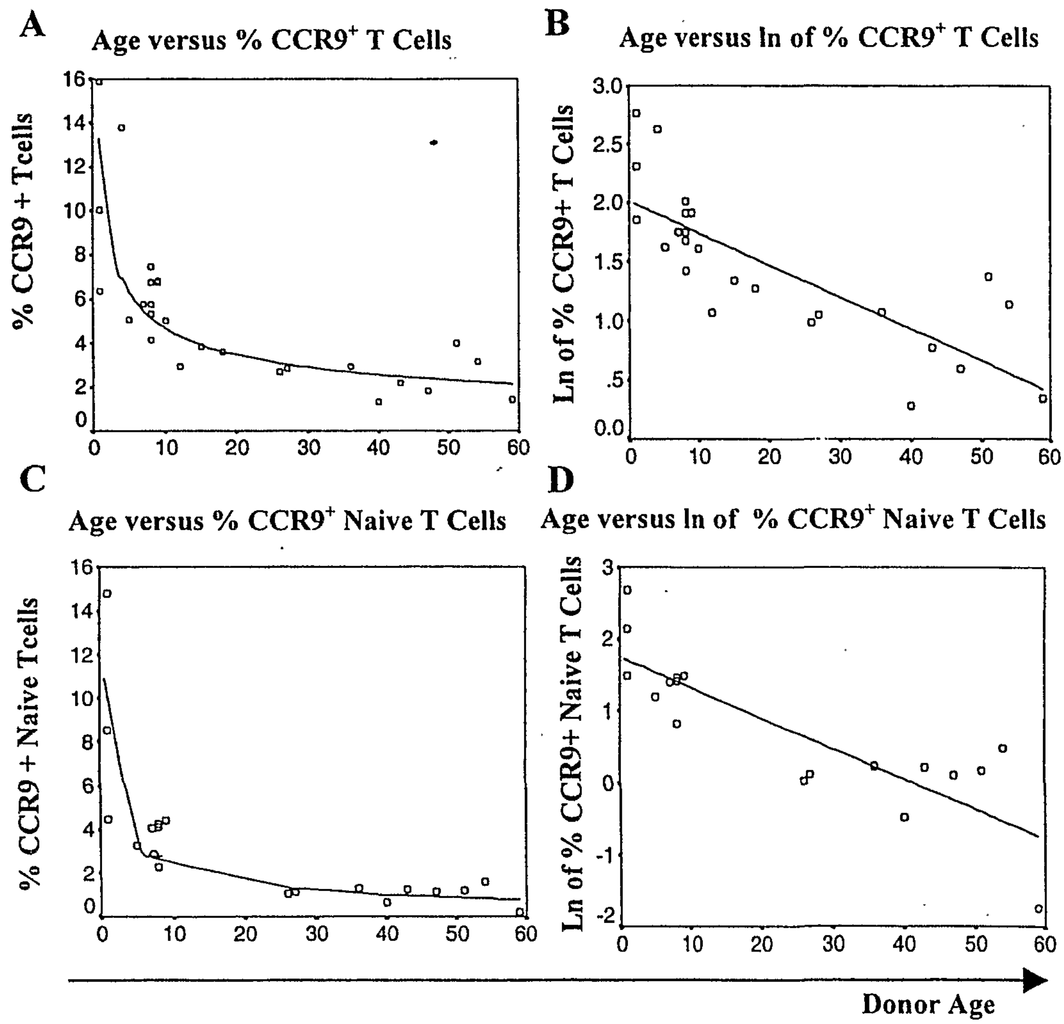
A
Age versus % CCR9+ T Cells
% CCR9 + Tcells
B
Age versus ln of % CCR9+ T Cells
Ln of % CCR9+ T Cells
C
Age versus % CCR9+ Naive T Cells
% CCR9 + Naive Tcells
D
Age versus ln of % CCR9+ Naive T Cells
Ln of % CCR9+ Naive T Cells
Donor Age

Fig. 2

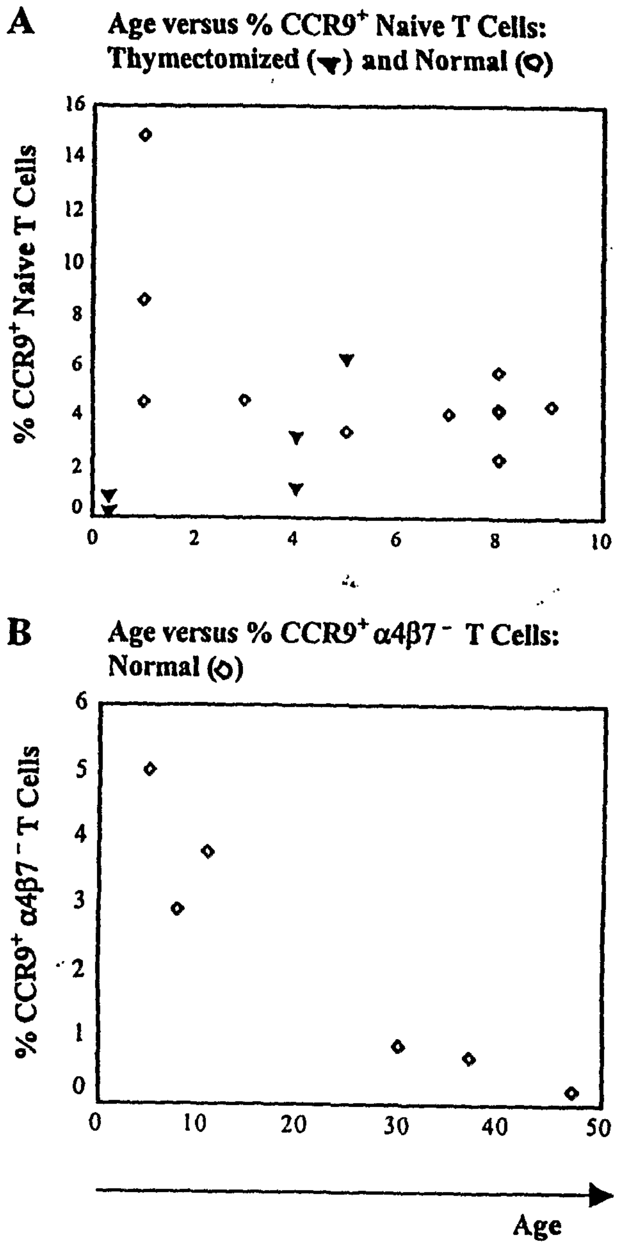
A
Age versus % CCR9+ Naive T Cells:
Thymectomized (▼) and Normal (◇)
% CCR9+ Naive T Cells
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
B
Age versus % CCR9+ α4β7 - T Cells:
Normal (◇)
% CCR9+ α4β7 - T Cells
6
5
4
3
2
1
0
0
10
20
30
40
50
Age

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 02/00218

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 33/569

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01N, C07K, C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI-DATA, EPO-INTERNAL, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	The Journal of Immunology, Volume 166, 2001, Gregory D. Sempowski et al: "Effect of Thymectomy on Human Peripheral Blood T Cell Pools in Myasthenia Gravis", page 2808 - page 2817	1-5,7-8
Y		6,9
	--	
X	Transplantation, Volume 69, no. 2000, Heitger A et al: "Requirement of Residual Thymus to Restore Normal T-Cell Subsets After Human Allogeneic Bone Marrow Transplantation", page 2238 - page2239, see spec. figure 1	1-5,7-8
Y		6,9
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
22 October 2002	23 -10- 2002

Name and mailing address of the ISA/	Authorized officer
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Nature, Volume 396, December 1998, Daniel C. Douek et al: "Changes in thymic functionwith age and during the treatment of HIV infection", page 690 - page 695	1-5,7-8
Y		6,9
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X	New England Journal of Medicine, Volume 332, no. 3, 1995, Crystal L. Mackall et al: "AGE, Thymopoiesis, and CD4+ T-Lymphocyte regeneration a chemotherapy", page 143 - page 149	1-5,7-8
Y		6,9
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X	PNAS, Volume 97, no. 8, 2000, Richard D. McFarland et al: "Identification of a human recent thymic emigrantphenotype", page 4215 - page 4220	1-5,7-8
A		6,8
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Y	Blood, Volume 97, no. 4, February 2001, Laura Carramolino et al: "Expression of CCR9 Beta-chemokine receptor is modulated in thymocyte differentiation and is selectively maintained in CD8+ T cells from secondary lymphoid organs", page 850 - page 857	6,9
A		1-5,7-8
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Y	J. Exp. Med., Volume 190, no. 9, November 1999, Brian A. Zabel et al: "Human G Protein-coupled Receptor GPR-9-6/CC Chemokine Receptor 9 Is Selectively Expressed on Intestinal Homing T Lymphocytes, Mucosal Lymphocytes, and Thymocytes and Is Required for Thymus-expressed Chemokine-mediated Chemotaxis", page 1241 - page 1254	6,9
A		1-5,7-8
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 02/00218

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	The Journal of Immunology, Volume 165, 2000, Konstantinos A. Papadakis et al: "The Role of Thymus-Expressed Chemokine and its Receptor CCR9 on Lymphocytes in the Regional Specialization of the Mucosal Immune System 1", page 5069 - page 5076	6,9
A		1-5,7-8
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A	WO 0053635 A1 (LEUKOSITE, INC.), 14 Sept 2000 (14.09.00)	1-9
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INTERNATIONAL SEARCH REPORT
Information on patent family members

30/09/02

International application No.
PCT/NO 02/00218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0053635 A1	14/09/00	AU 3522600 A	28/09/00
		EP 1157043 A	28/11/01
		US 6329159 B	11/12/01
		US 2002119504 A	29/08/02

patsnap

专利名称(译)	监测最近从胸腺移出的t细胞的比率的方法		
公开(公告)号	EP1407271A1	公开(公告)日	2004-04-14
申请号	EP2002733632	申请日	2002-06-19
[标]申请(专利权)人(译)	梅迪诺瓦公司		
申请(专利权)人(译)	MEDINNOVA SF		
当前申请(专利权)人(译)	MEDINNOVA SF		
[标]发明人	OLAUSSEN RICHARD W		
发明人	OLAUSSEN, RICHARD, W.		
IPC分类号	G01N33/53 G01N33/48 G01N33/569		
CPC分类号	G01N33/56972		
优先权	20013192 2001-06-25 NO		
外部链接	Espacenet		

摘要(译)

据报道趋化因子受体CCR9主要由胸腺细胞以及在小肠粘膜中循环肠道归巢和驻留T细胞表达。其配体TECK（胸腺表达的趋化因子）由胸腺和小肠上皮产生。在这里，我们报告循环CCR9 +幼稚T细胞（主要是CD4 +）的相对分数随着年龄而下降，从出生时所有T细胞的约15%到成人中的约1%。对于经典的肠道归巢标记物α4β7而言，CCR9 + T细胞的比例在儿童时期比在成人中高得多。因此，循环CD3 + CD45RA + CCR9 +细胞最近很可能离开胸腺。为最近的胸腺移民建立表型标记可以为造血干细胞移植后和HIV感染患者的抗逆转录病毒治疗期间的临床评估和随访提供有力工具。