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— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

[Continued on next page]

(54) Title: METHODS AND COMPOSITIONS RELATED TO T-CELL ACTIVITY

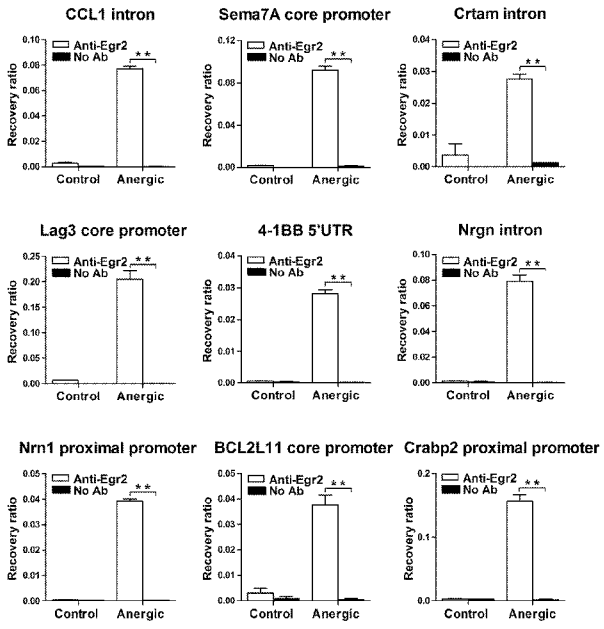

FIG. 2

(57) Abstract: Embodiments concern methods and composition related to anergic T-cells in patients, such as cancer patients. T cell anergy is a hyporesponsive state induced by TCR engagement in the absence of costimulation (Schwartz, 2003). Anergy induction was initially observed in vitro using chemically-fixed antigen presenting cells (APCs). Subsequently, it was found that anergy could be induced by immobilized anti-CD3 mAb or calcium ionophores (such as ionomycin) in vitro, and by superantigen and soluble antigenic peptide in vivo. Indirect evidence has suggested that T cell dysfunction in the tumor microenvironment and establishment of transplant tolerance is partially due to T cell anergy (Gajewski et al., 2011).

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 5/0783 (2014.01)
USPC - 435/6.1
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)
IPC(8) - A61K 35/12, 38/19, 39/00; C07K 16/24; C12N 5/078, 5/0783 (2014.01)
USPC - 424/93.21; 435/6.1, 6.11, 372, 372.3, 377; 514/19.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 38/00, 38/195; C12N 5/0634, 5/0636; C12Q 2600/158; G01N 33/56972 (2014.06)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2004/050706 A2 (BETZ et al) 17 June 2004 (17.06.2004) entire document	1, 2, 50-53, 57, 58, 60-63 --- 59, 64, 65
Y	WO 03/074654 A2 (MCSWIGGEN et al) 12 September 2003 (12.09.2003) entire document	59, 64, 65
A	US 2012/0135014 A1 (POSTLETHWAITE et al) 31 May 2012 (31.05.2012) entire document	1, 2, 50-53, 57, 58, 60-65
A	WO 2012/178160 A2 (WASSERFALL et al) 27 December 2012 (27.12.2012) entire document	1, 2, 50-53, 57, 58, 60-65

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2014	02 OCT 2014
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Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/029173

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-25, 30-49, 54-56
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet(s)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
claims 1, 2, 50-53, and 57-65 to the extent that they read on CCL1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-4, 50-53, and 57-65 are drawn to a method for evaluating or treating T-cell anergy in a patient comprising: a) measuring in T-cells from the patient an increase in expression level(s) of one or more T-cell anergic genes in Table 2 compared to a reference or control level of expression in non-anergic T-cells; and, b) identifying the patient as having anergic T-cells.

Group II+: claims 26-29 are drawn to a method for evaluating T-cell anergy in a patient comprising :a) measuring in T-cells from the patient expression level(s) of one or more T-cell anergic genes in Table 1; b) comparing the level to a reference or control level of expression T-cells identified as anergic; and, c) identifying the patient as having anergic T-cells if the T-cells are determined to have an expression level that is decreased or less than about two-fold increased expression compared to a reference or control level of expression in the T-cells identified as anergic.

Group III+: claims 66-71 are drawn to an array, microarray, chip, or a kit comprising one or more nucleic acid probes for each of at least 5 T -cell anergic genes in Table 2 and one or more reagents for detecting expression of the T-cell anergic gene.

Group IV+: claims 72-75 are drawn to a tangible computer-readable medium comprising computer-readable code that, when executed by a computer, causes the computer to perform operations comprising: a) receiving information corresponding to a level of gene expression in a T-cell sample from a patient comprising one or more T-cell anergy genes in Table 2; and b) calculating a risk score for the sample that identifies the sample as containing anergic T-cells.

The first invention of Group I+ is restricted to a method for evaluating or treating T-cell anergy in a patient comprising: a) measuring in T-cells from the patient an increase in expression level of CCL1 (first named gene in Table 2) as compared to a reference or control level of expression in non-anergic T-cells; and, b) identifying the patient as having anergic T-cells. It is believed that claims 1, 2, 50-53, and 57-65 read on this first named invention and thus these claims will be searched without fee to the extent that they read on CCL1.

Applicant is invited to elect additional genes selected from Table 2 to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a method for evaluating or treating T-cell anergy in a patient comprising: a) measuring in T-cells from the patient an increase in expression level of Crtam as compared to a reference or control level of expression in non-anergic T-cells; and, b) identifying the patient as having anergic T-cells. Additional Table 2 genes will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention being searched/examined.

Group II+ is restricted to a method for evaluating T-cell anergy in a patient comprising: a) measuring in T-cells from the patient expression level(s) of a T-cell anergic gene from Table 1 selected to be accession NM_019465; b) comparing the level to a reference or control level of expression T-cells identified as anergic; and, c) identifying the patient as having anergic T-cells if the T -cells are determined to have an expression level that is decreased or less than about two-fold increased expression compared to a reference or control level of expression in the T-cells identified as anergic.

Group III+ is restricted to an array, microarray, chip, or a kit comprising one nucleic acid probe for each of 5 T-cell anergic genes in Table 2 selected to be CCL1, Crtam, Egr2, Rasgef1a, and Car12 and one or more reagents for detecting expression of the T-cell anergic gene.

Applicant is invited to elect additional genes selected from Table 2 to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a an array, microarray, chip, or a kit comprising one nucleic acid probe for each of 5 T-cell anergic genes in Table 2 selected to be Fhl2, Pscd3, Pacsin1, Tnfrs9/4-1BB, and Bcl211 and one or more reagents for detecting expression of the T -cell anergic gene. Additional Table 2 genes will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention being searched/examined.

Group IV+ is restricted to a tangible computer-readable medium comprising computer-readable code that, when executed by a computer causes the computer to perform operations comprising: a) receiving information corresponding to a level of gene expression in a T-cell sample from a patient comprising a T-cell anergy genes in Table 2 selected to be CCL1; and b) calculating a risk score for the sample that identifies the sample as containing anergic T-cells.

Applicant is invited to elect additional genes selected from Table 2 to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a tangible computer-readable medium comprising computer-readable code that, when executed by a computer, causes the computer to perform operations comprising: a) receiving information corresponding to a level of gene expression in a T-cell sample from a patient comprising a T-cell anergy genes in Table 2 selected to be Crtam; and b) calculating a risk score for the sample that identifies the sample as containing anergic T-cells. Additional Table 2 genes will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention being searched/examined.

INTERNATIONAL SEARCH REPORT

International application No.
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The inventions listed in Groups I+ -IV+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Groups I+, a method for evaluating or treating T-cell anergy in a patient comprising: a) measuring in T-cells from the patient an increase in expression level(s) of one or more T-cell anergic genes in Table 2 compared to a reference or control level of expression in non-anergic T-cells; and, b) identifying the patient as having anergic T-cells, are not found in Group II+, III+, and IV+; the special technical features of Groups II+, a method for evaluating T-cell anergy in a patient comprising: a) measuring in T-cells from the patient expression level(s) of one or more T-cell anergic genes in Table 1; b) comparing the level to a reference or control level of expression T-cells identified as anergic; and, c) identifying the patient as having anergic T-cells if the T-cells are determined to have an expression level that is decreased or less than about two-fold increased expression compared to a reference or control level of expression in the T-cells identified as anergic, are not found in Groups I+, III+, and IV+. The special technical features of Groups III+, an array, microarray, chip, or a kit comprising one or more nucleic acid probes for each of at least 5 T-cell anergic genes in Table 2 and one or more reagents for detecting expression of the T-cell anergic gene, are not found in Groups I+, II+, and IV+; The special technical features of Groups IV+, a tangible computer-readable medium comprising computer-readable code that, when executed by a computer, causes the computer to perform operations comprising: a) receiving information corresponding to a level of gene expression in a T-cell sample from a patient comprising one or more T-cell anergy genes in Table 2; and b) calculating a risk score for the sample that identifies the sample as containing anergic T-cells, are not found in Groups I+, II+, and III+.

The Groups I+ -IV+ share the technical features of a method for evaluating T-cell anergy in a patient comprising: measuring in T-cells from the patient an increase in expression level(s) of one or more T-cell anergic genes compared to a reference or control level of expression in non-anergic T-cells; and a method for treating a patient with immunotherapy comprising administering immunotherapy to the patient after the patient is identified as having non-anergic T-cells. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2004/050706 A2 to Betz et al. discloses a method for evaluating T-cell anergy in a patient (the term 'suppressing an immune response' in a vertebrate means suppressing a vertebrates response to foreign or self-antigens as compared with a suitable control. The suppressive affect of regulatory T-cells of the invention can be measured using methods familiar to those skilled in the art and described herein. Advantageously, the regulatory T -cells of the present invention 'suppress' an immune response by 10% as compared with a suitable control, Pg. 14, Lns. 19-25; To ensure that the effects on the target cell proliferation were purely a result of active suppression by the regulatory population we labelled the target cells with CFSE, Pg. 64, Lns. 13-15; including without limitation immunotherapy, the selected antibodies, receptors or binding proteins thereof of the invention can be administered to any patient, Pg. 50, Lns. 18-21; anergic nature of the regulatory population, Pg. 64, Lns. 7-10) comprising: measuring in T-cells from the patient an increase in expression level(s) of one or more T-cell anergic genes compared to a reference or control level of expression in non-anergic T-cells (Increasing or decreasing the expression may occur as a result of increasing or decreasing mRNA expression respectively, or by increasing or decreasing gene transcription respectively, Pg. 40, Lns.1-3; the term 'suppressing an immune response' in a vertebrate means suppressing a vertebrates response to foreign or self-antigens as compared with a suitable control. The suppressive affect of regulatory Tcells of the invention can be measured using methods familiar to those skilled in the art and described herein. Advantageously, the regulatory T-cells of the present invention 'suppress' an immune response by 10% as compared with a suitable control, Pg. 14, Lns. 19-25); and a method for treating a patient with immunotherapy comprising administering immunotherapy to the patient after the patient is identified as having non-anergic T-cells (Invention may be used as separately administered compositions or in conjunction with other agents. These can include various immunotherapeutic drugs, Pg. 50, Lns. 9-11; wells containing targets CD19+ cell and CD4+CD25- negative cells would show higher incorporation due to the growth of the CD4 +CD25- cells added, while wells containing targets and CD4+CD25+would show lower incorporation due to the anergic nature of the regulatory population, Pg. 64, Lns. 7-10).

The Groups I+ genes do not share a significant structural element responsible for increasing the expression of T cell anergic genes in a patient, requiring "the selection of alternatives genes from Table 2."

The Groups I+ share the technical features of a method for evaluating or treating T-cell anergy in a patient comprising: measuring in T-cells from the patient an increase in expression level(s) of one or more T-cell anergic genes compared to a reference or control level of expression in non-anergic T-cells; and identifying the patient as having anergic T-cells. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2004/050706 A2 to Betz et al. discloses a method for evaluating or treating T-cell anergy in a patient (the term 'suppressing an immune response' in a vertebrate means suppressing a vertebrates response to foreign or self-antigens as compared with a suitable control. The suppressive affect of regulatory T-cells of the invention can be measured using methods familiar to those skilled in the art and described herein. Advantageously, the regulatory T -cells of the present invention 'suppress' an immune response by 10% as compared with a suitable control, Pg. 14, Lns. 19-25; To ensure that the effects on the target cell proliferation were purely a result of active suppression by the regulatory population we labelled the target cells with CFSE, Pg. 64, Lns. 13-15; including without limitation immunotherapy, the selected antibodies, receptors or binding proteins thereof of the invention can be administered to any patient, Pg. 50, Lns. 18-21; anergic nature of the regulatory population, Pg. 64, Lns. 7-10) comprising: measuring in T-cells from the patient an increase in expression level(s) of one or more T-cell anergic genes compared to a reference or control level of expression in non-anergic T-cells (Increasing or decreasing the expression may occur as a result of increasing or decreasing mRNA expression respectively, or by increasing or decreasing gene transcription respectively, Pg. 40, Lns.1-3; the term 'suppressing an immune response' in a vertebrate means suppressing a vertebrates response to foreign or self-antigens as compared with a suitable control. The suppressive affect of regulatory T-cells of the invention can be measured using methods familiar to those skilled in the art and described herein. Advantageously, the regulatory T-cells of the present invention 'suppress' an immune response by 10% as compared with a suitable control, Pg. 14, Lns. 19-25); and identifying the patient as having anergic T-cells (wells containing targets CD19+ cell and CD4+CD25- negative cells would show higher incorporation due to the growth of the CD4+CD25- cells added, while wells containing targets and CD4+CD25+would show lower incorporation due to the anergic nature of the regulatory population, Pg. 64, Lns. 7-10; For therapy, including without limitation immunotherapy, the selected antibodies, receptors or binding proteins thereof of the invention can be administered to any patient, Pg.50, Lns. 19-21).

The Groups II+ genes do not share a significant structural element responsible for measuring the expression of T cell anergic genes in a patient, requiring "the selection of alternatives genes from Table 1."

The Groups II+ share the technical features of a method for evaluating T-cell anergy in a patient comprising: measuring in T-cells from the patient expression level(s) of one or more T-cell anergic genes and comparing the level to a reference or control level of expression T-cells identified as anergic; and, identifying the patient as having anergic T-cells if the T-cells are determined to have an expression level that is decreased. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2004/050706 A2 to Betz et al. discloses a method for evaluating T-cell anergy in a patient (the term 'suppressing an immune response' in a vertebrate means suppressing a vertebrates response to foreign or self-antigens as compared with a suitable control. The suppressive affect of regulatory T-cells of the invention can be measured using methods familiar to those skilled in the art and described herein. Advantageously, the regulatory T -cells of the present invention 'suppress' an immune response by 10% as compared with a suitable control, Pg. 14, Lns. 19-25; To ensure that the effects on the target cell proliferation were purely a result of active suppression by the regulatory population we labelled the target cells with CFSE, Pg. 64, Lns. 13-15; including without limitation immunotherapy, the selected antibodies, receptors or binding proteins thereof of the invention can be administered to any patient, Pg. 50, Lns. 18-21; anergic nature of the regulatory population, Pg. 64, Lns. 7-10) comprising: measuring in T-cells from the patient expression level(s) of one or more T-cell anergic genes and comparing the level to a reference or control level of expression T-cells identified as anergic; and, identifying the patient as having anergic T-cells if the T-cells are determined to have an expression level that is decreased(Increasing or decreasing the expression may occur as a result of increasing or decreasing mRNA expression respectively, or by increasing or decreasing gene transcription respectively, Pg. 40, Lns.1-3; the term 'suppressing an immune response' in a vertebrate means suppressing a vertebrates response to foreign or self-antigens as compared with a suitable control. The suppressive affect of regulatory T-cells of the invention can be measured using methods familiar to those skilled in the art and described herein. Advantageously, the regulatory T -cells of the present invention 'suppress' an immune response by 10% as compared with a suitable control, Pg. 14, Lns. 19-25).

The Groups IIII+ genes do not share a significant structural element responsible for detecting expression of the T-cell anergic gene requiring the "selection of an alternative nucleic acid probe for each of at least 5 T-cell anergic genes in Table 2."

The Groups III+ share the technical features an array, microarray, chip, or a kit comprising one or more nucleic acid probes for each of at least 5 T -cell anergic genes and one or more reagents for detecting expression of the T-cell anergic gene. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2004/050706 A2 to Betz et al. discloses an array, microarray, chip, or a kit (the present inventors developed a custom made DNA array containing probes for 29 chemokine genes as well as two additional putative chemokine genes, Pg. 52, Lns. 16-18) comprising one or more nucleic acid probes for each of at least 5 T-cell anergic genes and one or more reagents for detecting expression of the T-cell anergic gene (The cDNA preparations obtained from these samples were hybridised to the DNA arrays, Pg. 53, Lns. 17-19, To confirm the expression data obtained from our DNA arrays we performed ELISA assays, Pg. 54, Lns. 6-8; to the present invention may be employed in in vivo therapeutic and prophylactic applications, in vitro and in vivo diagnostic applications, in vitro assay and reagent applications, Pg. 47, Lns. 10-14).

The Groups VI+ genes do not share a significant structural element responsible for increasing the expression of T cell anergic genes in a patient, requiring "the selection of alternatives genes from Table 2."

The Groups VI+ share the technical features of a tangible computer-readable medium comprising computer-readable code that, when executed by a computer, causes the computer to perform operations comprising: receiving information corresponding to a level of gene expression in a T-cell sample from a patient comprising one or more T-cell anergy genes; and calculating a risk score for the sample that identifies the sample as containing anergic T-cells. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2012/0135014 A1 to Postlethwaite et al. discloses a tangible computer-readable medium (In one application of this embodiment, the practitioner may provide the computer-based system with information regarding nucleic acids of interests on a computer readable medium, Para. [0125]) comprising computer-readable code that, when executed by a computer, causes the computer to perform operations comprising: receiving information corresponding to a level of gene expression in a T-cell sample from a patient comprising one or more T-cell anergy genes (In another embodiment, the method provides a computer based system with one or more algorithms to determine the presence and/or absence of one or more predetermined nucleic acids of interest and, if present, quantifies the amount of one or more predetermined nucleic acids of interest present in the individual's nucleic acid, Para. [0121]; The present invention provides methods of determining if an individual is likely to develop immune tolerance by detecting the altered expression, either higher or lower expression, or unique expression of nucleic acid sequences, Para. [0048]; Low dose CII (10ug) induces regulatory T cells while high dose (500 ug) induces anergy or clonal deletion, Para. [0184]); and calculating a risk score for the sample that identifies the sample as containing anergic T-cells (The invention includes a method for screening for susceptibility to immune tolerance development, including obtaining a sample from said host comprising nucleic acid, Para. [0013]; The invention includes a method for screening for susceptibility to immune tolerance development, including use of one or more computer programs for use with at least one computer system, where computer program includes a plurality of instructions including at least one instruction for aiding in identification of the presence or absence of said at least one SNP; at least one instruction for associating the presence or absence of said at least one SNP with at least one disease state; and at least one instruction for correlating the presence or absence of said at least one SNP with a score indicating susceptibility of a host to develop immune tolerance, Para. [0015]).

The inventions listed in Groups I+ - IV+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.