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MATURATION & ACCELERATING TRANSLATION **WITH INDUSTRY**

TECHNOLOGY OFFER

SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

THERAPY

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LLT1 ANTIBODIES WITH NEW FUNCTIONAL PROPERTIES

CONTEXT & BACKGROUND

The discovery that Lectin-Like Transcript 1 (LLT1), also known as C-type lectin domain family 2 member D (CLEC2D), is a ligand for the CD161 receptor, also known as NKRP-1A, has led to explore several approaches for modulating the activities of cells of the immune system in the purpose of disease treatment. The inventors propose a new approach based on the use of monoclonal antibodies(Mab). Biological therapeutics are now available for the treatment of some autoimmune and chronic inflammatory diseases and/or cancer. But there is still a need for alternative biological treatments which specifically target pathological tissues without affecting healthy tissue, thus resulting in less severe side effects, the said treatment may be used long-term. The current invention relates to these unmet needs amongst patients with cancer, and in those with autoimmune and chronic inflammatory diseases.

INNOVATIVE COMPONENT & TECHNOLOGY

The present invention relates to the characterization of monoclonal antibodies that are capable of specifically binding to LLT1,
that block the interaction between LLT1 and its receptor CD161 and that have depleting properties in vitro and in vivo. The present invention also relates to polynucleotides encoding such antibodies and cells expressing such antibodies. These Mab have utility in the diagnosis and treatment of cancer and autoimmune/chronic inflammatory diseases, in which LLT1- and CD161- expressing cells play a role in disease pathogenesis.

SCOPE

Cancer, autoimmune diseases, chronic inflammatory diseases

KEYWORDS

Monoclonal antibody, Immune response modifier/ immune check point

OBJECTIVES

To provide a proof of concept that LLT1 constitutes a novel therapeutic target for cancers such as germinal center- derived B cell non-Hodgkin's lymphomas and inflammatory/autoimmune diseases.

DEVELOPMENT & MATURATION STAGE

The inventors have developed murine, chimeric and humanized antibody molecules that specifically bind to LLT1. They currently have 9 humanized antibodies with an affinity similar to the murine anti-LLT1.They have demonstrated using in vitro assays that the antibodies block the interaction between LLT1 and CD161, thereby stimulating the cytotoxicity and cytokine production of NK cells and inhibiting the proliferation and cytokine production of T cells. They have demonstrated using in vitro assays that the antibodies facilitate the removal of LLT1-expressing cells by antibody-dependent cell-mediated cytotoxicity (ADCC).
Preliminary pre-clinical tests in mice xenografted with human B cell lymphomas show in vivo efficacy of the anti-LLT1 antibody alone and in combination with Rituximab (anti-CD20, Mabthera®). Ongoing additional tests assess their activity on solidtumors.

TARGET POPULATION

This invention could be used for the treatment of immune–based diseases, mainly cancer and inflammatory/autoimmune disorders, involving LLT1- and CD161- expressing cells in theirpathogenesis.
This invention could be useful for the diagnosis of cancer and more specifically B cell non-Hodgkin lymphomas.

TARGET PROFILE

Engineered monoclonal antibody (either chimeric mouse.human or humanized) that specifically recognizes LLT1, a transmembrane C-type lectin overexpressed by germinal center non-Hodgkin's B cell lymphomas. LLT1 is not expressed by nonhematopoietic cells and found expressed in vivo by germinal center-derived B cells. LLT1 can be transiently expressed on hematopoietic cells upon activation in vitro. LLT1 is the ligand for the human NKR-P1A (CD161) receptor expressed by Natural Killer cells (NK) and by subsets of T cells, in particular Th17. LLT1 interaction with CD161 inhibits NK cell functions and costimulates T cell proliferation and secretion of cytokines.

INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

PCT **WO201200994**
EP2588498
US2013164299
Patent family entitled : « LLT-1 antibodies with new functional properties » claiming the priority of the European patent application
n° EP2010167668 filed on June 10, 2010 and its extensions :
- granted patent **US 9127052** issued in September 08, 2015 and covering 4F68 antibodies ;
- granted divisional patent **US 2016024215** published in January 28, 2016 covering 2F1 antibodies ;
- European patent application n° **EP11733606** published under the reference EP2588498 (in process of granting)
Owner: CNRS

STRENGHTS & COMPETITIVE ADVANTAGES

Meets current needs in terms of treatment and diagnostic of GC-derived B cell NHLs. No alternative anti-LLT1 mAbs available. Development of the sole highly specific anti-LLT1 antibody with blocking and depleting properties. Humanized anti-LLT1 mAbs have been developed. Companion diagnostic product available. Opportunities: Orphan Drug designation, wider application than simply NHL, in particular if used as Immune Check Pointmodifier (ICP).

INDUSTRIAL APPLICATIONS & OPPORTUNITIES

The antibodies described in this invention have the potential to modulate immune responses by blocking the interaction between LLT1 and CD161. The antibodies may be used to stimulate NK cell-mediated anti-tumoral activity or to decrease T cell activation. The antibodies have depleting properties in vitro and in vivo, facilitating the removal of LLT1-expressing cells by antibody-dependent cell-mediated cytotoxicity (ADCC). The antibodies may also be used for diagnosis.
The invention could be used for the treatment of immune-based diseases, mainly cancer and inflammatory/autoimmune disorders, involving LLT1- and CD161-expressing cells in their pathogenesis. This invention could be useful for the diagnosis of cancer and more specifically B cell non-Hodgkin'slymphomas.

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