

L1 Technology Package for Diagnosis & Therapy of Ovarian and Endometrial Cancer including

P-437 Diagnostic Method on the Detection of the L1 Adhesion Molecule for Ovarian and Endometrial Tumors

P-638 L1 and ADAM10 Promote Adhesion and Migration of Ovarian Carcinoma Cells

P-767 Treatment of Tumors Using Specific Anti-L1 Antibody (clone 9.3)

P-809 Inhibition of Angiogenesis and Tumor Metastasis

Key Facts

- **Promising target for the treatment of highly malignant carcinomas such as ovarian and endometrial cancer**
- **Marker for highly malignant forms of carcinomas (Diagnosis and Prognosis)**
- **Preventing highly malignant carcinomas**

Background

Ovarian and highly aggressive endometrial carcinomas are the most common causes of cancer related deaths among gynaecological cancer diseases. Ovarian cancer is the fifth leading cause of cancer death among women in developed countries. This high death-statistic reflects the nature of ovarian cancer with its extensive metastatic spreading, leading to an advanced stage and poor prognosis for the patient due to therapy resistance. The ability of primary tumor cells to spread and form metastasis is strongly associated with the ability of cells to migrate and become adherent.

The Technology

This technology package is based on the observation that L1 is over expressed in highly malignant carcinomas and human ovarian tumor cell lines.

L1 (CD171) is a neuronal adhesion molecule of 200-220 kDa, belonging to the immunoglobulin superfamily and involved in the migration and fasciculation of neuritis. In adults, L1 is not expressed in normal tissues except for peripheral

nerves. L1 is thus far proved to be a valuable and powerful marker for the diagnosis and prognosis of ovarian and endometrial tumours. ADAM10 is a membrane-bound metalloproteinase which is required for L1 cleavage and the cleavage of autocrine growth factors for the EGF receptor such as HB-EGF, Betacellulin etc.

It could be shown that over expression of L1 or soluble L1 enhanced the haptotactic cell migration on extracellular matrix proteins and promoted enhanced tumor growth. Also mutant forms of L1 or ADAM10 inhibit cell migration and tumor growth. Therefore, the inventors developed a strategy using functional interference with L1 and ADAM10 to hinder tumor cells to migrate and grow and developed an anti-L1 antibody (clone 9.3). This strategy should avoid the formation of highly malignant types of carcinomas due to suppressing of metastatic spreading. Suitable compounds interfering with the biological activity of L1 or ADAM10 for therapeutic use could also be for example: plasmids, RNAi, siRNA, peptides, small molecules, antibodies, etc. or carrier systems containing one of these compounds. To identify further interfering compounds the technology is

also suitable to establish a compound screening system.

Development Stage

In vitro experiments with different cell lines (OVMz, SKOV3ip, OAW 42, CHO, GG, M130, HEK-293 and L1 transfected sublines) and *in situ* experiments were performed. Novel antibodies to L1 were generated. Mab L1-9.3 was selected as developmental candidate and analyzed in various murine isotype forms. A fully humanized form of L1-9.3 that has ADCC function was generated. Tumor growth experiments were carried out using a xenograft model of human ovarian carcinoma in CD1 nude mice (SKOV3ip). MAb-L1-9.3 was found to significantly reduce tumor growth in mice and prolong survival.

Available Tools

- L1- antibodies (murine L1-9.3 Hybridoma and others)
- Chimerized and fully humanized forms of L1-9.3
- ADAM10 antibodies
- Mutant forms of L1 and ADAM10
- Assays (Transmigration, ELISA, Invasion, tumor growth)

Inventors

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Applications

- Therapy of ovarian and endometrial cancer
- Diagnostic tool to detect highly malignant carcinomas
- Screening system to identify further therapeutic compounds

Intellectual Property

Several granted patents and pending applications in Europe and the U.S.

P-437: [WO0204952](#) with equivalents granted in Europe ([EP1172654](#)), USA ([US7618785](#), divisional [US7670601](#)), Canada ([CA2415364](#)) and Japan ([JP5165827](#))

P-638: [WO2006013051](#) pending in Europe ([EP1773879](#)) granted in USA ([US8003599](#))

P-767: [WO2008151819](#) pending in Europe ([EP2170956](#)), Japan ([JP2010529970](#)), Canada ([CA2691075](#)), divisional [TW200918556](#) and granted in USA ([US8138313](#))

P-809: [WO2009127414](#) pending in USA ([US2011171290](#)) and Australia ([AU2008201871](#))

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