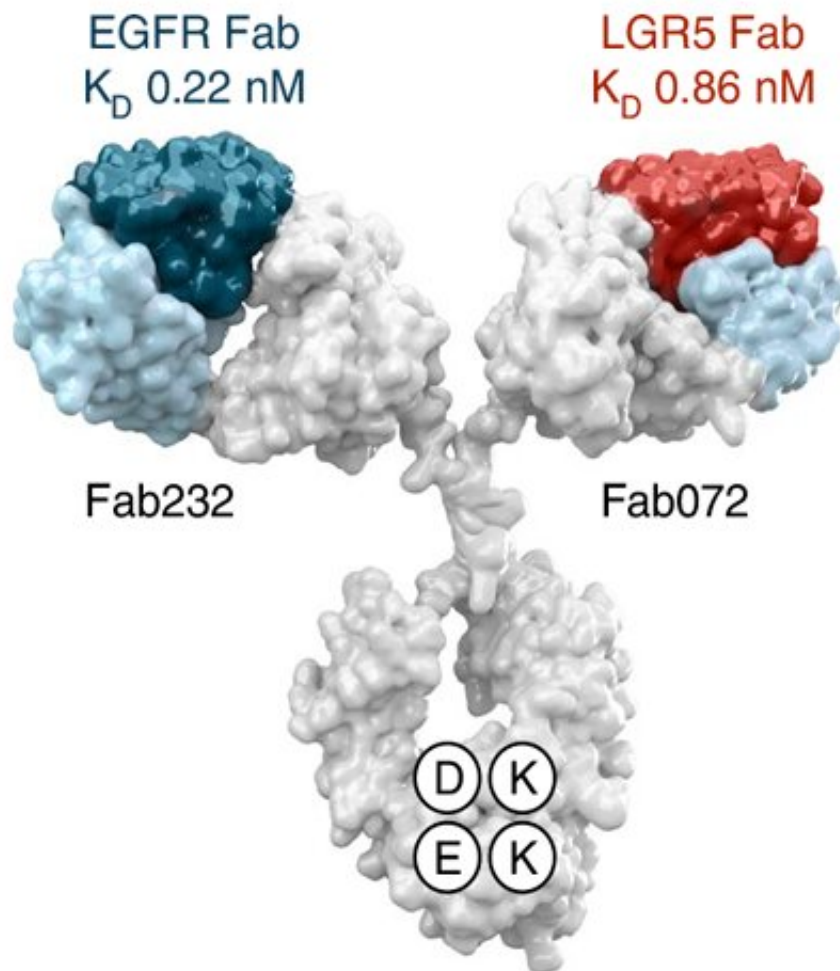


Discovery of MCLA-158, the first clinical candidate screened in organoids targeting cancer stem cells of solid tumors

April 25 2022



Schematic depiction of MCLA-158 showing monovalent affinities of the EGFR (Fab232) and LGR5 (Fab072) Fab arms. Credit: IRB Barcelona and Merus N.V.

Scientists from an international consortium led by Dr. Eduard Batlle, head of the Colorectal Cancer laboratory at IRB Barcelona, ICREA researcher and group leader of CIBER de Càncer (CIBERONC), together with the Dutch company Merus N.V., reveal the preclinical data that has led to the discovery of MCLA-158 and its mechanism of action on cancer stem cells. Named Petosemtamab, the antibody MCLA-158 prevents the onset of metastasis (that is, the spread of cancer to other vital organs) and slows the growth of primary tumors in experimental models of cancer.

Published today in *Nature Cancer*, the study also lays the groundwork for the use of organoids in the drug discovery process undertaken by [pharmaceutical companies](#). Organoids are patient-derived samples that can be grown in the laboratory, and they reproduce certain aspects of the tumor compartment. Until now, their usefulness was being explored in personalized cancer medicine—meaning their value in helping physicians make decisions about the best treatment for each patient. However, for the selection of MCLA-158, a biobank of organoids from [cancer patients](#) was used for the first time to discriminate which new antibody, among hundreds, was most effective and believed to be most suitable for the majority of patients.

In October 2021, Merus N. V. reported preliminary data corresponding to interim efficacy analysis based on investigator review of its sponsored ongoing phase 1 dose expansion clinical trial investigating the safety, tolerability, and anti-tumor activity of MCLA-158 monotherapy in advanced head and neck [squamous cell carcinoma](#) (HNSCC). Three of

seven HNSCC patients achieved partial responses, with one achieving complete response after the data cutoff date of August 2021. Tumor reduction was observed in all seven patients.

"It is highly satisfying to see that our discoveries are helping patients. We started studying [cancer stem cells](#) 15 years ago. The journey to this point has been exciting but also very complex, and it has required a large investment of resources, as well as a great deal of work by many researchers. This study and the collaboration with Merus. N.V. reflects IRB Barcelona's focus: 'The medicine of the future starts here,'" says Dr. Batlle.

MCLA-158: A double-action antibody

Antibodies are proteins that are naturally produced by our bodies to recognize infectious agents or altered cells so that these can be removed by the lymphocytes of the immune system (white blood cells). The antibody described in this work, Petosemtamab ("Peto", MCLA-158: LGR5 x EGFR Biclomics), is a bi-specific antibody that recognizes two proteins, namely EGFR and LGR5, on the surface of cancer stem cells.

EGFR activity promotes uncontrolled cell growth, while LGR5 marks the surface of cancer stem cells, which are responsible for tumor expansion. Dr. Batlle's laboratory is recognized worldwide for its work on the identification and characterization of colorectal cancer stem cells, and it has led work not only on the development of MCLA-158/ Petosemtamab but also on the characterization of its mechanism of action.

In short, MCLA-158/ Petosemtamab degrades the EGFR protein in cancer stem cells that have the LGR5 marker, thereby blocking the growth and survival pathways in the cells that initiate and spread cancer. However, this antibody does not interfere with the functioning of healthy

stem cells, which are essential for the proper functioning of tissues.

The MCLA-158 antibody is a potent inhibitor of colorectal cancer [organoid](#) growth and it blocks the initiation of metastasis, as well as growth in several preclinical models of cancer, including tumors of the head and neck, esophagus, and stomach.

An organoid biobank for drug discovery

For the development and characterization of this antibody, researchers from HUB Organoids built a large biobank comprising organoids derived from patients with colon cancer, organoids from colon cancer metastasis to the liver, and organoids from normal non-cancerous tissue. Scientists from OcellO B.V. (Crown Bioscience) performed high content screening with the organoids.

The use of organoids in the early stages of drug development—in this case, therapeutic antibodies—facilitates the identification of those that are effective for most patients or even against tumors carrying a specific mutation. Using organoids from healthy tissue, an additional advantage is the possibility to identify unwanted side effects of the drugs on organs. This approach has allowed the researchers to assess the harmful effects of the drug on healthy cells and thus withdraw antibodies with greater toxicity in the earliest stages of the study.

More information: Eduard Batlle, Functional patient-derived organoid screenings identify MCLA-158 as a therapeutic EGFR × LGR5 bispecific antibody with efficacy in epithelial tumors, *Nature Cancer* (2022). [DOI: 10.1038/s43018-022-00359-0](https://doi.org/10.1038/s43018-022-00359-0).
www.nature.com/articles/s43018-022-00359-0

Provided by Institute for Research in Biomedicine (IRB Barcelona)

Citation: Discovery of MCLA-158, the first clinical candidate screened in organoids targeting cancer stem cells of solid tumors (2022, April 25) retrieved 8 July 2023 from <https://medicalxpress.com/news/2022-04-discovery-mcla-clinical-candidate-screened.html>

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