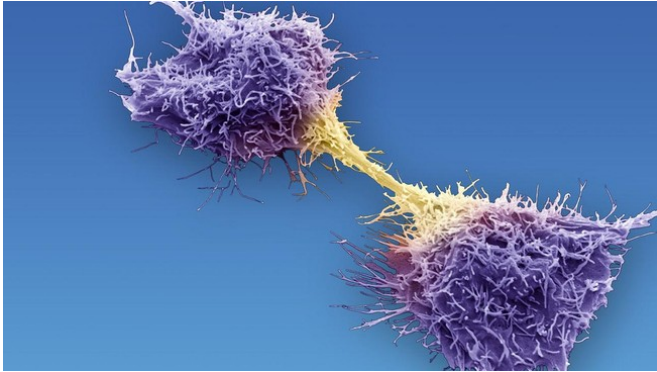


# A cancer therapy that inhibits the Notch signaling pathway

1 September 2017, by Cécilia Carron



Cancer cells. Credit: Cellestia Biotech

EPFL spin-off Cellestia Biotech has just been given the regulatory go-ahead to start clinical testing a molecule it has developed to treat cancers involving mutations of the Notch gene. The molecule is a ray of hope for the 250,000 patients diagnosed every year with this mutation, which sharply reduces their chances of recovery.

The molecule developed by Cellestia Biotech, an EPFL spin-off, is a targeted therapy designed to treat cancers resulting from a mutation of the Notch gene. Clinical trials are scheduled to start soon in Spain. This oral treatment is the first to work by stopping the problem at its roots, i.e., in the cell's nucleus. It inhibits the [protein complex](#) – which allow cancerous cells to multiply – so that they cannot generate signals.

One of the alternatives to chemotherapy currently being investigated by experts is the array of signals generated by proteins in a cell's nucleus. A normal Notch [protein](#) plays an indispensable role in embryonic development and in the formation and maintenance of stem cells. Genetic lesions, however, can result in an abnormal signaling pathway that facilitates the development of

cancerous cells and causes resistance to conventional therapies. This vicious signaling pathway has been the subject of several recent studies that have confirmed its link to breast [cancer](#), leukemia and several types of lymphoma. Around 250,000 patients worldwide are diagnosed each year with a cancer related to this type of genetic lesion.

## Binding with the protein to keep it quiet

The safest way to block the signaling pathway is to cut it off at the source, preventing the protein from activating signals in the nucleus. Molecule CB-103, discovered by Rajwinder Lehal during his doctoral studies in Freddy Radtke's laboratory at EPFL, binds with the protein complex and inhibits its activity inside the nucleus. This cuts off all Notch signals regardless of how they are activated, thereby killing off the [cancerous cells](#). Other therapies that target the Notch [signaling pathway](#) have also been investigated by research groups, but their effects remain peripheral – some block only part of the pathway while others inhibit different mechanisms involved in other cellular processes.

Patents have been filed for the molecule and for the development and marketing of several similar molecules. Both in-vitro and in-vivo tests carried out on the molecule showed excellent efficacy and tolerance. It also demonstrated rapid uptake and distribution in tissues.

The clinical trial will be partly funded by the CHF 8 million in seed financing raised by the startup early this year. The researchers will investigate several factors such as tolerability and the dosages for adult patients with advanced or metastatic solid tumors and hematologic malignancies. Biomarkers have also been developed to ensure that patients taking part in the trial have the right type of cancer for the molecule.

## A highly coveted molecule

"The Notch [pathway](#) has become a key target for cancer therapies because of the critical role it plays in tumorigenesis. That's why it's being researched by so many pharmaceutical companies," says Rajwinder Lehal, Chief Science Officer at Cellestia Biotech. Owing to its potential application for numerous indications, the market for these inhibitors is estimated to be around CHF 10 billion, and sales of CB-103 are expected to amount to CHF 1 billion if several treatments can be developed. The startup has also discovered other [molecules](#) that act in a similar way, and it plans to test them as a therapy for other types of cancer.

Provided by Ecole Polytechnique Federale de Lausanne

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