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PRESS RELEASE

RESEARCHERS MAP ‘FAMILY TREES’ OF ACUTE MYELOID LEUKAEMIA FOR THE FIRST TIME IN PATIENTS TREATED WITH ENASIDENIB

For the first time, a team of international researchers have mapped the family trees of cancer cells in acute myeloid leukaemia (AML) to understand how this blood cancer responds to a new drug, enasidenib. The work also explains what happens when a patient stops responding to the treatment, providing important clues about how to combine enasidenib with other anti-cancer drugs to produce longer-lasting remissions and to prevent relapse.

The study published in *Nature Medicine* today (Monday), is an international collaboration between researchers from the Gustave Roussy Cancer Campus and Inserm in Paris (France), the MRC Molecular Haematology Unit and the MRC Weatherall Institute of Molecular Medicine at the University of Oxford (UK), Memorial Sloan Kettering Cancer Center (USA) and Celgene (USA).

AML is the most common and aggressive blood cancer in adults and is incurable in most patients. About 12-15% of AML patients have a mutation in the IDH2 gene that stops bone marrow cells from differentiating, or maturing, into blood cells that are required for life. Instead these immature cells accumulate in the bone marrow and blood, which is a hallmark of AML. Previous research from the same team [2] showed that enasidenib prompts blood cell differentiation and restores normal blood cell production.

A phase I/II clinical trial showed that the drug was effective in 40% of AML patients with an IDH2 mutation who had failed previous treatments. and this led to the US Food and Drug Administration (FDA) giving approval for enasidenib in 2017. However, after an average of nearly nine months, the cancer returned in these patients.

“Enasidenib is an important new treatment. However, the initial studies did not show which AML cells responded to enasidenib and started to differentiate again. It was also unclear how the cells become resistant to therapy,” said Dr Stéphane de Botton, physician in the haematology department at Gustave Roussy. “We wanted to answer these questions.”

Using samples from 37 patients in the trial who had responded to enasidenib, the team looked at markers on the surface of the bone marrow cells to identify the different populations of bone marrow cells, from the immature, undifferentiated cells, called progenitor cells, through to mature, differentiated cells.

“You can imagine the bone marrow as an assembly line that constantly needs to produce mature blood cells,” said co-author, Dr Lynn Quek, MRC clinician scientist and consultant haematologist at the MRC Weatherall Institute of Molecular Medicine. “In a patient before treatment, this assembly line becomes blocked. Using specialist techniques, we studied bone marrow cells from patients to find out how the bone marrow assembly line becomes blocked and how enasidenib helps to promote differentiation to unblock the assembly line.”

As AML is caused by errors in DNA sequence, or mutations, in blood cells, the team studied the genetic make-up of AML cells. They found that AML cells from the same patient can be grouped into families which share genetic mutations, called clones. Cells belonging to the same clone or family, come from the same ancestor cell. Understanding how clones relate to each other is important as they provide information as to how the AML started in the first place.

“When an AML patient has a bone marrow test, we are taking a snapshot of the family tree of leukaemia cells,” said Dr Quek. “As we treat the AML, there are shifts in the family dynamics as some clones will die and others will grow. In every cancer there are several families or clones of cancer cells. In AML we were able to see how these responded to enasidenib. We used techniques to study genetic mutations on a cell-by-cell basis, and re-constructed the family tree of a patient’s AML. We then tracked changes in the family of AML cells as they responded to enasidenib and as patients lost response to the drug. This is the first time that anyone has done such a detailed study at a single cell level. As enasidenib is a new anti-leukaemic drug, it was vital to understand the effects of the drug on leukaemic cells.”

Co-author, Dr Virginie Penard-Lacronique, research director and team leader at the Inserm unit at Gustave Roussy, said: “We have provided genetic proof that enasidenib was able to differentiate cancer cells so that some of their normal functions were restored, even though they still contained the IDH2 mutation. This is important because unless we can track these clones, we don’t know whether the mature cells in a patient are coming from normal cells after all the cancer cells have been killed or from leukaemic cells that are now able to mature. In this paper we show that in four out of five cases, the mature cells are coming from leukaemic bone marrow cells that can be induced to differentiate by this new drug.”

The cancer returned in almost all the patients in the clinical trial, and the team was able to show for the first time that the leukaemic cells stop responding to enasidenib when some of the clones develop additional mutations. These new sub-clones are resistant to enasidenib, providing clues about the mechanism of drug resistance. This may help in designing future therapy trials to overcome therapy resistance. It may also mean that enasidenib needs to be combined with other anti-cancer drugs to prevent relapse, and clinical trials have already started investigating whether patients respond to these combinations, for how long and whether they are likely to relapse.

Dr de Botton concluded: “Enasidenib a very good example of a modern cancer therapy that specifically targets principally cancer cells, sparing normal cells, and in this regard is very safe and has limited side effects. Now that we have shown that it needs to be combined with other drugs to stop the cancer returning, we think that it’s important that the combination therapy should be given to AML patients early on in their disease. International trials are now taking place comparing combinations of enasidenib and other drugs with the normal standard of care.”

Professor Paresh Vyas, professor of haematology and lead of the Oxford team, pointed out: “The approach we have implemented can be applied to any cancer and to any therapy to understand how any drug attacks each clone in a cancer and how different clones respond to therapy. This makes it a very powerful approach to improve our understanding of how to achieve better outcomes from cancer therapy.”

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Notes to journalists:

[1] “Clonal heterogeneity of acute myeloid leukemia treated with the IDH2 inhibitor enasidenib”, by Lynn Quek et al. Nature Medicine, DOI: 10.1038/s41591-018-0115-6

[2] Previous published studies by some of the same researchers are:

“Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation”, by Fang Wang et al. Science, vol. 340, 3 May 2013; doi: 10.1126/science.1234769;

“Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response,” by Michael D. Amatangelo et al. Blood, 6 June 2017; doi: 10.1182/blood-2017-04-779447;

“Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia”, by Eytan M. Stein et al. Blood, 6 June 2017; doi: 10.1182/blood-2017-04-779447;

“Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML”, by C.D. DiNardo et al. NEJM, 2 June 2018; doi: 10.1056/NEJMoa1716984.

[3] This study received funding from a number of sources, which are listed in full at the end of the paper. They include the UK Medical Research Council (MRC), French National Institute of Health (INSERM), the French National Cancer Institute, the Fondation Association pour la Recherche sur le Cancer, Gustave Roussy, the US NIH and the Memorial Sloan Kettering Cancer Centre, etc.

An embargoed copy of the paper can be obtained by journalists before the paper is published online on Monday from Emma Mason (details below).

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/ About Gustave Roussy

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