Scientists discover how to beat resistance to standard leukaemia drug

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(Medical Xpress) -- Cancer Research UK-funded scientists at The Institute of Cancer Research (ICR) have revealed a technique to kill chronic myeloid leukaemia (CML) cells that have stopped responding to a targeted drug, according to research published in *Cancer Cell* today.

The team carried out the research in CML cells. They showed that drugs currently in early development, called MEK inhibitors, combined with nilotinib (Tasigna) destroyed CML cells after they had stopped responding to imatinib (Glivec), the current standard treatment for CML.

Imatinib and nilotinib kill CML cells by blocking a strong molecular survival signal keeping them alive. The drugs are designed to fit snugly into a protein called BCR-ABL - like a key into a lock - so as to 'lock up' BCR-ABL and prevent it from triggering the survival signal in the first place.

In some cases BCR-ABL changes its shape and imatinib and nilotinib can no longer fit their 'key' into BCR-ABL's 'lock'. The survival signal remains switched on - and these drugs are powerless to turn it off. Survival for these cells means uncontrolled cell growth - the root of cancer.

But the scientists revealed that a second set of molecular 'keys' - drugs called MEK inhibitors - can lock up a protein called MEK, the final checkpoint in the chain of proteins controlling the survival signals.

Nilotinib seems to make resistant cancer cells more responsive to the effects of MEK inhibitors and so the combination of treatments killed these resistant cells.

The research suggested that using MEK inhibitors alongside nilotinib would overcome CML resistance to imatinib and nilotinib.

Lead author, Professor Richard Marais from the ICR, said: "We are learning more about the molecular locks which have 'seized up', keeping survival signals turned on in CML cells. This important research shows that drugs currently in development can free these locks to switch off survival signals and destroy cancer cells.

"It's exciting to discover that the MEK inhibitors can be used alongside nilotinib to kill CML cells that are no longer responding to imatinib or nilotinib alone. Acquired drug resistance is a significant problem in treating chronic myeloid leukaemia, so we're very pleased to have found a potential strategy to overcome this. The next stage is to develop MEK inhibitors further and run clinical trials to see if they can be effective in patients."

There are more than 600 cases of CML diagnosed each year in the UK.

Dr. Julie Sharp, Cancer Research UK's senior science information manager, said: "People diagnosed with leukaemia today are four times more likely to survive their disease beyond 10 years as those diagnosed in the early 1970s. And thanks to the generosity of the public we've been able to invest in research, which has been at the heart of this progress.

"This important discovery increases our understanding of how leukaemia cells respond to drugs and reveals a potential approach to treat the disease after it has become resistant to current treatments."

More information: Nilotinib and MEK inhibitors induce synthetic lethality through paradoxical activation of RAF in drug-resistant chronic myeloid leukaemia. Packer et al, *Cancer Cell*.

Provided by Cancer Research UK