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news

After imatinib: new hopes for chronic myeloid leukaemia

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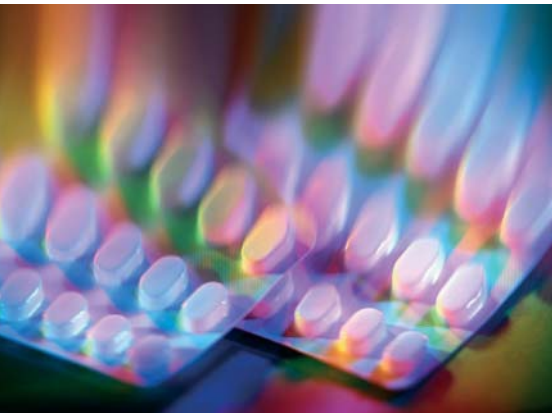
The biological characterization of AMN107, an imatinib-related selective inhibitor of Bcr-Abl, holds out new hopes for patients with chronic myeloid leukaemia (CML) [1]. 'The more inhibitors there are available that target Bcr-Abl, the better the outlook is for these patients,' says researcher James Griffin, Chair of Medical Oncology at the Dana-Farber Cancer Institute, Boston.

Imatinib: revolutionizing treatment

About 15% of all adult leukaemias are CML, in which an initial chronic phase is followed in untreated patients by an accelerated phase and a terminal blast crisis. The underlying cause of CML is the *BCR-ABL* oncogene. This fusion gene encodes the chimeric Bcr-Abl protein, a constitutively active tyrosine kinase that drives the proliferation of immature myeloid cells.



In the 1990s, Brian Druker, Professor of Haematology and Oncology at Oregon Health and Science University, and his colleagues, including scientists at Novartis (Basel, Switzerland), began their search for a molecule that, by selectively inhibiting Bcr-Abl, would provide a targeted anti-cancer drug. Their search culminated in June 2001 with the US approval of imatinib (Gleevec; Novartis). 'Targeted molecular therapy with imatinib has revolutionized the treatment of CML,' says Druker. 'Before imatinib, 5-year survival for patients was about 50%. Now, for the 95% of patients who are diagnosed in the chronic phase of CML, survival is over 95%, and the relapse rate with 42 months follow-up is only 16%'

The resistance problem

In many patients who relapse, mutations in Bcr-Abl reduce the binding affinity of imatinib for the ATP-binding pocket of Bcr-Abl. Consequently, their tumour cells become resistant to imatinib. Similarly, patients diagnosed in the later phases of CML often have a poor response rate to imatinib because of Bcr-Abl mutations. 'Many of the Bcr-Abl mutations underlying resistance only partially reduce the binding of imatinib,' explains Griffin, 'so the Novartis researchers reasoned that if they could make a variant of imatinib that bound more tightly to wild-type Bcr-Abl, it might overcome imatinib resistance.'

Griffin's biological characterization of AMN107, half of which is identical to imatinib, confirms this reasoning. AMN107 binds to wild-type Bcr-Abl with 20 times the affinity of imatinib, is active against many of the imatinib-resistant mutants of Bcr-Abl in vitro, and prolongs the survival of imatinib-resistant CML mouse models [1].

'The development of AMN107 and other Bcr-Abl inhibitors is the next step in the development of better treatments for CML,' comments Andreas Hochhaus, Professor of Haematology and Oncology at the University of Heidelberg, Germany, who identified some of the first imatinib-resistant Bcr-Abl mutations. 'With more powerful inhibitors or combinations of inhibitors, we might be able to suppress the tumour load so that resistant clones never emerge. It's very analogous to HIV treatment where triple therapy is much more successful than monotherapy.'

Other inhibitors on the way

AMN107 is now in early clinical trials: preliminary results of a phase I trial presented at the American Haematological Society (ASH) meeting last December indicate that the drug is well-tolerated and shows some signs of efficacy[2]; phase II trials in Imatinib-resistant patients should start shortly.

BMS-354825 (Bristol-Myers Squibb, Princeton), a Bcr-Abl inhibitor that came out of a drug discovery programme for Src inhibitors, is at a similar stage of development. Like AMN107 and imatinib, BMS-354852 binds to the ATP binding pocket of Bcr-Abl and inhibits many imatinib-resistant Bcr-Abl mutants [3,4]. Finally, researchers at Temple University School of Medicine, Philadelphia, recently described ON012380, a compound that binds to the Bcr-Abl substrate binding site [5] (see also *News*, *Drug*

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With this multitude of inhibitors, say Griffin, Druker and Hochhaus, prospects for CML patients are improving even further. And what is particularly exciting, adds Druker, 'is the speed at which inhibitors are being developed. Imatinib has only been on the market for four years and the first resistance to it was reported the same year. Yet two potentially promising drugs that can overcome resistance are already entering phase II trials.'

References

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Genetic origin of the AIDS epidemic

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TRIM5α, a host cell restriction factor found in human and non-human primates, is a natural cellular defense against retroviral invaders, most notably HIV-1. But whereas Old World monkeys and humans share similar versions of the gene, the simian version blocks HIV-1 infection prior to reverse transcription, halting infection in its tracks. Human TRIM5α cannot, leaving us wide open to HIV-1 infection and eventual progression to AIDS.

A crucial mutation

Now, virologist Jonathan Stoye and colleagues at the National Institute for Medical Research in London, UK have discovered that a single amino acid difference in the human TRIM5α gene, compared with the HIV-resistant rhesus monkey version, is partly to blame for the greatest epidemic to hit humans in the modern age [1]. Constructing chimeras of human and rhesus monkey TRIM5α gene sequences allowed Stoye's group to map and identify the regions involved in HIV-1 restriction. Most astonishingly, however, changing a single amino acid in human TRIM5α to its simian counterpart conferred HIV-1 resistance.

Joseph Sodroski and his team at Harvard University, USA, first described TRIM5α last year [2], showing that TRIM5α influenced HIV-1 susceptibility in a species-specific manner. Although HIV-1 could efficiently enter cells of Old World monkeys, the virus encounters the monkey TRIM5α, resulting in uncoating of the viral capsid prior to reverse transcription occurring. Human TRIM5α was not able to do this sufficiently to block infection.

The rest is history

'If this single change had not occurred, we probably never would have had AIDS in the first place,' says Stoye. 'It shows how susceptible we are to very small changes.'

John Coffin, a virologist at Tufts University, Boston, MA, agrees. 'Had a gene like the rhesus gene been present [in humans], then HIV-1 could not have made it into the human population.'

Still, there are no known humans possessing a TRIM5α containing the protective amino acid, even in the face of selective pressure. 'It's probably unlikely that there are humans that carry this mutation,' says Stoye. 'A small change allows the human protein to block HIV-1,' says virologist Greg Towers, University College London, UK. 'In future, we might imagine a human population that is able to block HIV-1 the way old world monkeys do.'

'Retroviruses have probably forced the evolution of defense mechanisms such as Trim5α,' explains Paul Bieniasz, a virologist at the Aaron Diamond AIDS Research Center in New York, USA. Indeed, the sequence surrounding the amino acid in question appears to have had selective pressures acting it, in what were probably epidemics of retroviruses, distinct from HIV-1, that are long since extinct, he explains. Furthermore, TRIM5α is not the only such host defense mechanism.

But results from other groups suggest that other amino acids may similarly be involved. 'This is clearly an important amino acid but it is not the only one,' says Bieniasz. He and his team have recently identified motifs important for restriction activity.

Similarly, Sodroski and colleagues most recently described three amino acid differences that they believe account for the difference in anti-HIV-1 potency between humans and rhesus monkeys. (ref 3) In a related paper published early online, Harmit Malik and colleagues at the Fred Hutchinson Cancer Research Center in Seattle, WA, examine the genetic differences in TRIM5α among species, suggesting that TRIM5α evolution has been driven by antagonistic interactions with early retroviruses that appeared on the evolutionary scene long before lentiviruses like HIV-1 arose [4].

Novel anti-HIV therapeutics

Understanding how TRIM5α interacts with HIV-1 is an area of particular focus now. Knowledge of this interaction could have important therapeutic implications, explains Coffin, by permitting identification of compounds that mimic Trim5α binding to the viral capsid proteins.

Stoye says a gene-based approach is another potential therapy, once efficient gene delivery methods come to fruition. 'If there is a case where one might contemplate gene therapy for an infectious disease, then this might be one,' he says. Such an approach

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