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From Chinese medicine to anticancer drugs

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Derivatives of indirubin, a compound isolated from a traditional Chinese medicine with antileukemic properties, might provide new anticancer agents that are active against several of the major pathways involved in tumorigenesis, says Gerhard Eisenbrand, Head of the Division of Food Chemistry and Environmental Toxicology at the University of Kaiserslautern, Germany. 'We already knew that indirubin prevents cell proliferation by inhibiting cyclin-dependent kinases [CDKs],' explains Eisenbrand, 'but now we have discovered how some indirubin derivatives drive tumor cells into apoptosis.' In a collaboration with Richard Jove (University of South Florida, Tampa) and his group, Eisenbrand's team report that E804 and some other indirubin derivatives induce apoptosis in human breast and prostate tumor cells by blocking constitutive Stat3 signaling [1].

The Chinese connection

Chinese researchers first noted that the traditional Chinese medicine Danggui Longhui Wan, which contains 11 medicinal herbs [2], was effective against chronic myelogenous leukemia (CML) in 1967. Within 10 years, they had identified Indigofera tinctoria – the source of the dye used in blue jean manufacture – as the medicine's antileukemic constituent. 'They then localized the antileukemic effect to indirubin, a trace isomer of the indigo dye,' explains Eisenbrand, 'and treated >250 CML patients with it in the late1970s.'

Indirubin is no longer used in China to treat CML, says Zhijian Xiao, Consultant Hematologist at the Chinese Academy of Medical Sciences and Peking Union Medical College (Tianjin, China), because it is poorly water soluble and causes gastrointestinal tract problems. Chinese researchers have, instead, developed several indirubin derivatives, one of which – meisoindigo – is widely used in China to treat CML, says Xiao. 'In addition, a Phase II trial is underway to test meisoindigo in combination with all-*trans* retinoic acid in acute promyelocytic leukemia; early results indicate that this combination shortens the time to remission.'

> **'It is not an approach that fits easily into classical drug development schemes'**

Indirubin derivatives: broad specificity antitumor agents

Chinese researchers are continuing to develop indirubin derivatives with anticancer potential, as are western scientists, including Eisenbrand [3]. The first step towards developing such derivatives was to determine the mechanism of indirubin's antitumor activity, explains Eisenbrand. 'By 1999, we had shown that indirubin and some of its analogues were potent CDK inhibitors that bound to the ATP-binding site of these important cell-cycle controllers [4]. We had also shown that indirubin and its analogues were active against a broad spectrum of experimental solid tumours.'

Eisenbrand and his colleagues now report that the indirubin derivative E804 directly inhibits Src kinase activity in human epithelial cancer cells. This prevents the phosphorylation of the transcription factor Stat3, a promising anticancer target [5], and downregulates the expression of the antiapoptotic proteins Mcl-1 and Survivin, two Stat3 target genes. Thus, some of the antitumor activity of indirubin and its derivatives lies in their ability to induce apoptosis.

'With agents like these that are active against small subsets of protein kinases, it is going to be a case of matching the profile of the kinases they inhibit against the profile of aberrant kinases in specific tumor types,' notes Professor Jane Endicott from the Laboratory of Molecular Biophysics at Oxford University, UK. 'It is not an approach that fits easily into classical drug development schemes but agents with selectivity against a small number of targets could be very effective anticancer therapeutics.'

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Eisenbrand agrees that the relatively broad specificity of some indirubin derivatives has great therapeutic potential. 'It is increasingly clear that attacking a single molecular target in cancer cells rarely works because the cells can often circumvent such inhibition.' Eisenbrand now has indirubin derivatives that inhibit CDKs, Stat3 and the VEGF receptor, a component of the pathway that drives tumor angiogenesis, and hopes to take some of these multifunctional derivatives into early clinical trials next year in collaboration with Faustus Forschung Translational Drug Development AG (Vienna, Austria).

Not just anticancer agents

CDK inhibitors based on indirubin could also have therapeutic uses outside the cancer field, for example, in the treatment of parasitic diseases. In this case, derivatives will have to be designed that inhibit the parasite's CDK while leaving the host's CDKs unscathed. Researchers at Keele University and Aberdeen University, for instance, are trying to develop indirubin derivatives specific for CRK3, a CDK from Leishmania mexicana. And Endicott and her collaborators have been examining the crystal structures of indirubin derivatives bound to pfPK5, one of the malaria parasite's CDKs. 'We have no current plans to develop any indirubin derivatives as antimalarial agents,' stresses Endicott, 'but there may be potential in future to take some of the derivatives that have been designed as anticancer agents and investigate their use in this context.'

References

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UK government guidance on Alzheimer's drugs postponed

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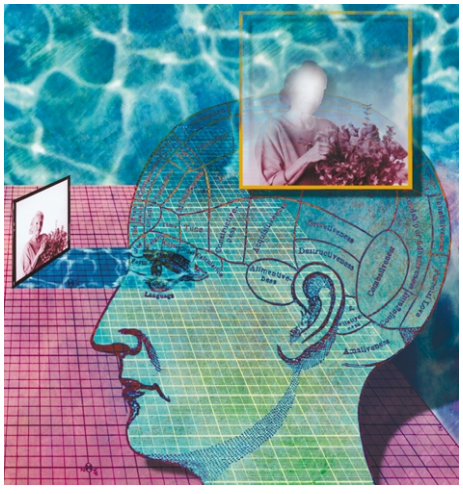
Recently the National Council for Clinical Excellence (NICE) announced that it was delaying publishing its guidance document on the long term benefit of drugs used for the treatment of Alzheimer's disease (AD). Their earlier review of studies assessing short term benefits of these compounds agreed with the manufacturers' conclusions that there was evidence to suggest a benefit to patients. However, last year, NICE issued a call for a review of the long-term benefits of the compounds. They were concerned that the effects in the shorter studies were, at best, quite modest. More data was needed to assess if this benefit was sustained over longer periods. In March 2005 they published their draft report, which concluded that the drugs were of little long-term benefit. The report provoked vigorous protests from patient groups such as the Alzheimer's Society and strong rebuttals from the companies involved.

No justification

Two classes of drugs were involved in this assessment. Aricept®, Exelon®, and Reminyl® all act by raising brain levels of acetylcholine by blocking its breakdown by the enzyme acetylcholinesterase (AChE). Ebixa® (also sold as Axura®) acts by reducing over-activation of the NMDA glutamate receptor, and is the only product with this mechanism licenced for AD.



The NICE report in March 2005 concluded that the longer term use of the compounds only delayed the time for a patient to go to full-time care was only in the order of one month when measured over a five-year period. This, they concluded, did not justify their use either in terms of side effect burden to the patient nor in the cost of the treatment regime. They were due to publish their official guidance early in July but have decided to engage in further consultation with the pharmaceutical companies.

The drug companies that make these medicines including Lundbeck, Pfizer, Novartis, and Shire have argued that the drugs do show beneficial effects in individual patients which will always be lost in the averaging out that occurs in such large studies. Companies and patient groups also argue that the benefits to individual patients in terms of quality of life were not adequately captured in the report.

Concerns

This news will provide a strong incentive to those involved in trying to predict which patients are likely to respond to particular treatments. Genetic or other markers that would identify patients who will respond best to different classes of drugs or even individual drugs would help doctors to identify those patients in advance that will benefit from taking these drugs.

> **'...the drugs were of little long-term benefit'**

The concern for companies is that this report risks raising the bar for much-needed drugs to an unacceptably high level. The cost of a clinical development program that was required to show efficacy over years would simply make the cost of any drug for Alzheimer's prohibitively expensive.

This is the second blow for Alzheimer's disease patients in a year. Earlier this year the FDA put a black box warning on the off-label use of atypical antipsychotics (Abilify, Geodon, Risperdal, Zyprexa) for the control of psychotic symptoms in AD patients. Their review found that the mortality rate was increased in patients receiving these treatments.

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