HIGHLIGHT ADVISORS

AVI ASHKENAZI

GENENTECH, INC., SOUTH
SAN FRANCISCO, CA, USA

JOSE BASELGA

VALL D'HEBRON UNIVERSITY
HOSPITAL, BARCELONA, SPAIN

ANTON BERNIS

NETHERLANDS CANCER
INSTITUTE, AMSTERDAM,
THE NETHERLANDS

MARIA BLASCO

CENTRO NACIONAL
DE INVESTIGACIONES
ONCOLÓGICAS, MADRID, SPAIN

RON DEPINHO

HARVARD MEDICAL SCHOOL,
BOSTON, MA, USA

GLENN DRANOFF

DANA-FARBER CANCER
INSTITUTE, BOSTON, MA, USA

RAKESH JAIN

MASSACHUSETTS GENERAL
HOSPITAL, BOSTON, MA, USA

CHRISTOPH LENGAUER

THE SIDNEY KIMMEL
COMPREHENSIVE CANCER
CENTER, BALTIMORE, MD, USA

LANCE LIOTTA

NATIONAL CANCER INSTITUTE,
BETHESDA, MD, USA

JOHN D. POTTER

FRED HUTCHINSON CANCER
RESEARCH CENTER,
SEATTLE, WA, USA

DAVID SIDRANSKY

JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE,
BALTIMORE, MD, USA

BERT VOGELSTEIN

THE SIDNEY KIMMEL
COMPREHENSIVE CANCER
CENTER, BALTIMORE, MD, USA

ROBERT WEINBERG

WHITEHEAD INSTITUTE FOR
BIOMEDICAL RESEARCH,
CAMBRIDGE, MA, USA

ZENA WERB

UNIVERSITY OF CALIFORNIA AT
SAN FRANCISCO, CA, USA

TARGETED THERAPIES

Inhibiting aurora

Since their discovery in 1997, the mammalian aurora kinases have been implicated in tumorigenesis. They are frequently overexpressed in cancer, which is thought to induce genomic instability and tumour progression. Karen Miller and colleagues now show that an inhibitor of aurora-kinase activity causes arrest and apoptosis of cancer cells, and shows promise as a new anticancer agent.

Although the function of aurora-C is unknown, both aurora-A and aurora-B act at mitosis — aurora-A has a role in spindle formation and centrosome maturation, and aurora-B is a chromosomal passenger protein that is essential for cytokinesis. Fortunately, all three kinases have similar ATP-binding sites, and this is what the authors targeted when designing small-molecule inhibitors. They synthesized VX-680 and showed that it selectively and potently inhibits the aurora kinases. It also inhibits the FLT3 kinase — frequently mutated in acute myeloid leukaemia (AML) and therefore another interesting target for anticancer therapy — which could actually be beneficial.

Consistent with the role of aurora kinases in mitosis, VX-680 caused cell-cycle arrest in a range of cancer cell lines — cells stopped proliferating and arrested, some with a tetraploid DNA content. In synchronized cells, the mitotic cyclin B1 accumulated and subsequently decreased, indicating that mitosis occurred in the absence of cytokinesis. DNA replication then

followed to generate cells with > 4N DNA content.

But how did this cell-cycle arrest affect viability? The cells died by apoptosis after the arrest, and leukaemia, lymphoma and colon cancer cells were most susceptible. VX-680 might therefore cause tumour regression. The authors next examined the effects on primary-tumour samples from patients with AML who were refractory to standard treatment. Importantly, VX-680 abolished colony formation of these cells, including those in which *FLT3* was mutated, potentially broadening the remit of the inhibitor. VX-680 had no effect on non-cycling cells — which would be expected given that its target acts in mitosis — and was able to prevent phosphorylation of a putative downstream target, histone H3. These results support the specificity of VX-680.

So, can VX-680 suppress tumour growth *in vivo*? When the inhibitor was administered intraperitoneally to a human AML xenograft in nude mice, the tumour volume decreased by 98%; this reduction was dose-dependent. VX-680 was also effective in pancreatic and colon cancer xenograft models at well-tolerated doses, and caused regression of colon tumours when administered intravenously.

So, aurora-kinase inhibitors show great potential as anticancer therapy. They are progressing into clinical development, where we hope they will continue to prove useful.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Harrington, E. A. *et al.* VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth *in vivo*. *Nature Med.* **10**, 262–267 (2004)