of unique features compared with other fragment-based approaches. In particular, screening compounds against other members of the same family in addition to the target protein reduces the number of false positives in scaffold identification, and the scaffold-validation step ensures that the scaffold-binding mode is tolerant of substitution of groups around the scaffold, enhancing the efficiency of chemical optimization into lead compounds. In this case, the identified compounds have potential to be further developed into drug candidates that lack the limitations of PDE4 inhibitors that are in clinical development, which have a narrow therapeutic window potentially due to their lack of specificity.

Peter Kirkpatrick

References and links

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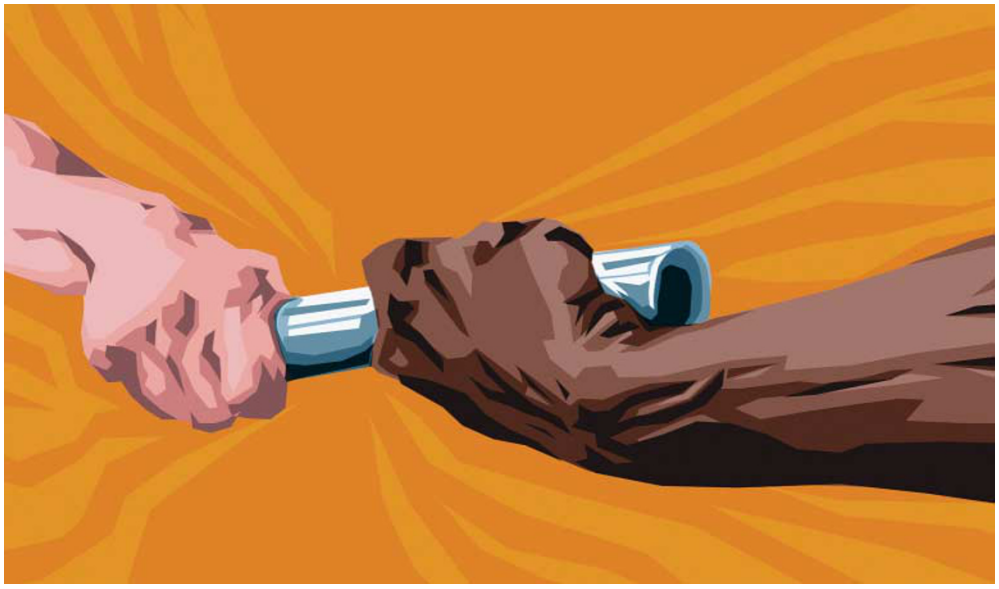

DRUG RESISTANCE

Passing on protection

The overexpression of P-glycoprotein (P-gp) is well established as a cause of multidrug resistance in cancer cells. However, it now seems that drug-resistant cells can physically pass this protein on to drug-sensitive cells *in vitro* and *in vivo*, enabling the recipient cells to survive potentially toxic drug concentrations and, ultimately, to develop intrinsic resistance to chemotherapy. Although cell-to-cell transfer of proteins has been reported before, Andre Levchenko, Steven Larson and colleagues believe that their report in the *Proceedings of the National Academy of Sciences* is the first evidence that a protein transferred between cells can retain its function.

The transfer of P-gp *in vitro* was investigated by co-culturing cells that were resistant to colchicine (a P-gp substrate) with cells that were colchicine-sensitive. Using an anti-P-gp antibody and quantitative fluorescent cytometry, Levchenko *et al.* measured the expression of P-gp over time and found that within several hours the level of P-gp in the sensitive-cell population was increased. Flow cytometry experiments using the fluorescent P-gp substrate rhodamine confirmed that the transferred P-gp was functional, and that its activity could be abolished by the P-gp inhibitor verapamil.

The exact mechanism of transfer is uncertain; however, the authors were able to rule out paracrine signalling and the development of gap junctions. Instead, they suggest that P-gp might be transferred using large membrane microparticles or a process involving cell–cell contact. Transfer was observed between several cell types, including those that make up the tumour cell stroma, and also between cells from different species, which confirms that expression in recipient cells arises from protein transfer rather than gene expression.

Having established transfer *in vitro*, Larson and colleagues studied whether P-gp transfer occurs in tumours grown from mixed (resistant and sensitive) cell populations, using pure populations as controls. They found that not only did transfer occur, but that the expression of transferred P-gp within the tumours was much higher than that observed *in vitro*, suggesting that P-gp transfer *in vivo* is more efficient.

The clinical significance of this is further emphasized by the authors' observation that although P-gp transfer is initially transient, persistent exposure to a selective pressure favouring P-gp , such as colchicine, resulted in a relatively sudden upregulation of *mdr-1* mRNA and a related increase in P-gp expression, after several months of exposure to the selective pressure. The presence of transferred P-gp therefore seems to provide otherwise sensitive cancer cells with protection from toxic chemotherapy that then buys them time to endogenously express their own P-gp, and develop a permanent resistant phenotype.

Joanna Owens

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Steven Larson's Lab:
http://www.mskcc.org/mskcc/html/11337.cfm

Andre Levchenko's Lab:
http://www.bme.jhu.edu/labs/levchenko