compounds to try to identify additional p53 inhibitors, and will also examine the inhibitory properties of synthesized derivatives of pifithrin. David Patterson, President of the Eleanor Roosevelt Institute for Cancer Research (Denver, CO, USA), who was not involved in the study, said, 'This is a novel concept – to be able to suppress the damage of chemotherapy and X-rays with a drug – and it looks like it works extremely well.'

## REFERENCES


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# Selective arginine receptors as antiviral compounds and molecular probes

It might soon be possible to design novel antiviral compounds and molecular probes using a new type of receptor molecule that selectively binds to the amino acid, arginine. Arginine-rich sequences are a feature of several pathogen proteins, including HIV proteins. Blocking the activity of RNA sequences that bind to these arginine-rich sequences might therefore be a novel way to inhibit viral and bacterial replication.

Thomas Bell and Alisher Khasanov (University of Nevada, Reno, NV, USA), together with Thomas James and Anton Filikov (University of California, San Francisco, CA, USA) and Mike Drew (University of Reading, Reading, UK) have synthesized a highly preorganized artificial receptor for guanidinium cations that they say can bind with high affinity and selectivity to arginine in polar solvents such as methanol and even water. The molecular device could then be used either as an antiviral agent or as a nuclear magnetic resonance (NMR) spectroscopic probe for studying arginine-containing protein structure and folding.

### Crucial involvement of arginine

Arginine is crucial to the functioning of nucleotide-binding proteins that mediate several biochemical processes. The replication of the HIV-1 virus involves short, arginine-rich sequences in two important regulating proteins that invoke RNA binding, these being the transcriptional activator TAT and the REV protein. According to Bell and his colleagues[1], small molecules that are tailored to bind selectively to arginine could be used to inhibit these processes.

There have been various efforts to create an arginine receptor for this purpose but one of the problems encountered has been a lack of activity in water, which would then hinder antiviral activity. Such a receptor must also be highly specific for arginine alone and not bind to lysine side-chains. However, both arginine and lysine are found in human and viral RNA-binding proteins and so some sequence-specificity is likely to be necessary to discriminate between the two amino acids.

Thomas Schrader (Dusseldorf University, Dusseldorf, Germany) devised molecular 'tweezers' for binding arginine[2]. However, Bell highlighted that while the molecule resembles the natural arginine receptor, only modest binding was observed. This low activity might be explained by incomplete preorganization of the receptor molecule. In an attempt to avoid this problem, Bell and his colleagues have designed a recognition unit in which a relatively rigid array of hydrogen-bonding groups are fused together in a series of six-membered carbon rings. This design should create perfect 'host–guest' complementarity between the arginine residue and the receptor molecule. The incorporation of various polar groups could then be used to make the host molecule water-soluble.

### Close examination

Bell's team examined the ability of their receptor to bind arginine using NMR spectroscopy. The signals for the receptor protons alone are shifted downfield when a guest arginine molecule binds to the receptor. By contrast, for lysine as the guest molecule, there is very weak binding and so a much smaller shift in the signals is observed. Indeed, a detailed analysis of the spectra revealed that their receptor binds to arginine approximately two hundred-fold more strongly than Schrader's molecular tweezers.

The primary mode of interaction between arginine and the receptor molecule is electrostatic bonding, rather than conventional covalent bonding. Hydrogen bonds form between complimentary charged oxygen atoms on the receptor and the hydrogens attached to the amino nitrogens on the arginine and between amino hydrogens and the nitrogens on the receptor pyridyl groups. By contrast, lysine lacks the


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second amino group and so cannot form this hydrogen bond pair.

The receptor can also be used to bind to a short dipeptide formed by two arginine molecules and does so with high affinity in water. Again, the binding of two lysine molecules is modest in comparison. The detailed network of hydrogen bonds between the host and guest molecules in the solid state with arginine were confirmed using X-ray crystallographic studies, which can, within limits, be used to infer detail concerning the active form in solution.

Activity in water and the ability to specifically bind to arginine residues make the receptor a potentially useful chemotherapeutic agent in treating diseases involving the binding of arginine-rich proteins. 'This molecule might be useful as a drug, but it will most likely require modification, including additional binding sites to produce sequence specificity. This would be a novel approach to antiviral, antibiotic and antifungal drugs', said Bell.

Additionally, the specific binding means the receptor molecule could be used in NMR to perform detailed examinations of proteins for arginine side-chains. It could also have application in helping crystallize proteins in basic regions so that their structure can be more readily studied through X-ray diffraction and related techniques. This, Bell says, would be useful in the characterization of numerous biologically important peptides and proteins including HIV-1 TAT, REV and nucleocapsid proteins. 'By enhancing the fluorescent properties of the receptor or by attaching other fluorophores, a molecular probe for arginine-rich proteins could be produced', adds Bell.

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