# Elsewhere in Biology

## Chosen and summarized by the staff of *Chemistry & Biology*

**A selection of interesting papers published last month in *Chemistry & Biology*'s sister journals, *Current Biology*, *Folding & Design* and *Structure*.**

**Chemistry & Biology** September 1996, **3**:775–777

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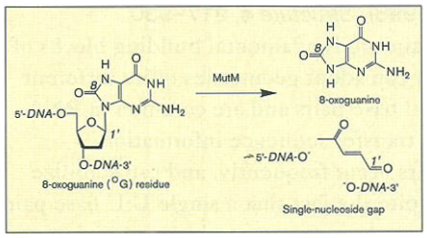
☐ **Cloning of a yeast 8-oxoguanine DNA glycosylase reveals the existence of a base-excision DNA-repair protein superfamily.** Huw M. Nash, Steven D. Bruner, Orlando D. Schärer, Tomohiko Kawate, Theresa A. Addona, Eric Spooner, William S. Lane and Gregory L. Verdine (1996). *Curr. Biol.* **6**, 968–980.

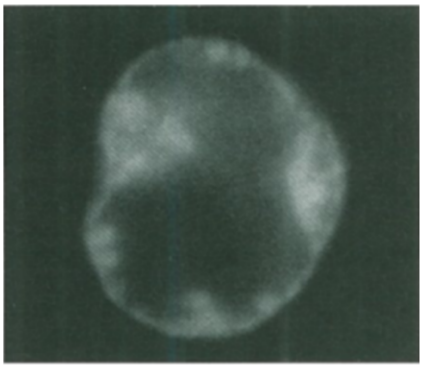
Free radical generators such as reactive oxygen species and ionizing radiation initiate the conversion of guanine (G) residues in DNA to 8-oxoguanine ($^{O}$G), which is highly mutagenic as it preferentially pairs with adenine instead of cytosine during replication. Bacteria are known to have a multicomponent DNA repair system that excises and corrects G:A pairs. Here, the authors identify the first such repair protein from eukaryotes, Ogg1, a yeast base-excision DNA repair protein that processes $^{O}$G paired with C, but acts only weakly on $^{O}$G:A pairs. The protein also has intrinsic β-lyase activity, which proceeds through a Schiff's base intermediate. Targeted disruption of the gene for Ogg1 in yeast revealed a second $^{O}$G glycosylase/lyase protein, which preferentially acts on $^{O}$G:G pairs. The authors suggest that Ogg1 is closely related in three-dimensional structure to endonuclease III from *Escherichia coli*, and have used this comparison to identify an active-site motif shared by many base-excision DNA repair proteins.




1 August 1996, Research Paper, *Current Biology*

☐ **Bcl-2 regulates activation of apoptotic proteases in a cell-free system.** Sabina C. Cosulich, Stephen Green and Paul R. Clarke (1996). *Curr. Biol.* **6**, 997–1005.

Apoptosis is important in the normal development of many multicellular organisms. Aberrations in this process have been suggested to be involved in several major human diseases, but the molecular mechanism that triggers apoptosis remains poorly understood. It is known that the Bcl-2 oncoprotein prevents or delays apoptosis in a wide range of organisms, and that proteases of the interleukin-β-converting enzyme (ICE) family are required, suggesting that these are components of a conserved mechanism controlling the onset of apoptosis.

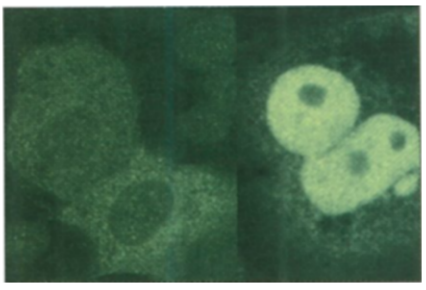


The authors have used a cell-free system generated from *Xenopus laevis* eggs that reproduces the nuclear events characteristic of apoptosis to define the temporal sequence of biochemical events in this process. Bcl-2 prevents apoptosis-like nuclear events only if added before the activation of a protease that appears to be part of the Ced-3 subfamily of ICE-like proteases. This protease cleaves poly(ADP-ribose) polymerase, and its activation is attenuated by Bcl-2. A second Ced-3-related protease, CPP-32, is cleaved later during the apoptotic process in this system. It thus appears that Bcl-2 protects against apoptosis, at least in part, by regulating the activation of a series of ICE-like proteases.

1 August 1996, Research Paper, *Current Biology*

☐ **Comparative mutagenesis of nuclear localization signals reveals the importance of neutral and acidic amino acids.** Joe P.S. Makkerh, Colin Dingwall and Ronald A. Laskey (1996). *Curr. Biol.* **6**, 1025–1027.

Nuclear proteins contain a signal within their amino-acid sequences that directs their selective accumulation within the nucleus. This nuclear localization signal (NLS) binds to the α subunit of the cytosolic receptor importin, the β subunit of which docks at the nuclear pore complex. Previous studies of NLSs from yeast, plants, animals and viruses have suggested that the most important elements of the signal are two clusters of basic amino acids, which are separated by a mutation-tolerant spacer. Over 50% of nuclear proteins contain a motif of this kind. The oncoprotein c-Myc, however, has a different NLS in which only three of the nine residues are basic, and one residue is even acidic. The authors show that, unexpectedly, the identity and position of the neutral and basic amino acids that surround the basic residues in this motif are crucial for its function. All regions of the signal are important for nuclear localization. Thus, the current knowledge of the rules that govern nuclear localization is inadequate.



1 August 1996, Brief Communication, *Current Biology*

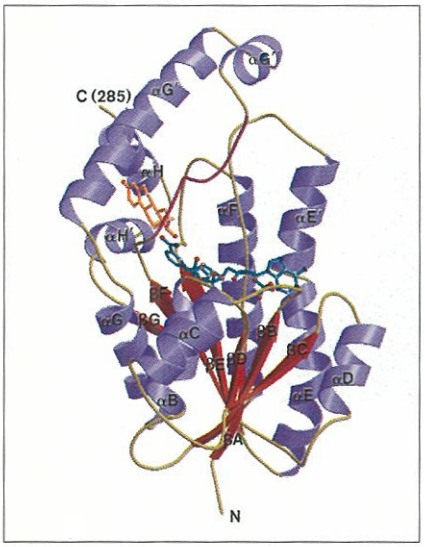
☐ **Conserved features in the active site of nonhomologous serine proteases.** Steven C Bagley and Russ B Altman (1996). *Folding & Design* **1**, 371–379.

Serine protease activity is critical for many biological processes and has arisen independently in a few different protein families. It is not clear, though, to what degree these protease families share common biochemical and biophysical properties. The authors used a computer program to study the properties that are shared by four serine protease active sites with no overall structural or sequence homology. The program systematically compares the region around the catalytic histidines from the four proteins with a set of noncatalytic histidines, used as controls. Some of the reported properties correspond to previously known features of the serine protease active site, including the catalytic triad and the oxyanion hole. Novel similarities between the proteins are also found, including an increased mobility of side-chains near the entrance to the active site, and similarities in the spatial distribution of charged, polar, and hydrophobic groups that stabilize the catalytic residues. Many of these novel properties appear to be preferred, but not required, and can therefore only be reliably observed by aligning the sites and comparing them with carefully selected statistical controls.

27 August 1996*, Research Paper, *Folding & Design*

☐ **The structure of a complex of human 17β-hydroxysteroid dehydrogenase with estradiol and NADP+ identifies two principal targets for the design of inhibitors.** Rock Breton, Dominique Housset, Catherine Mazza and Juan Carlos Fontecilla-Camps (1996). *Structure* **4**, 905–915.

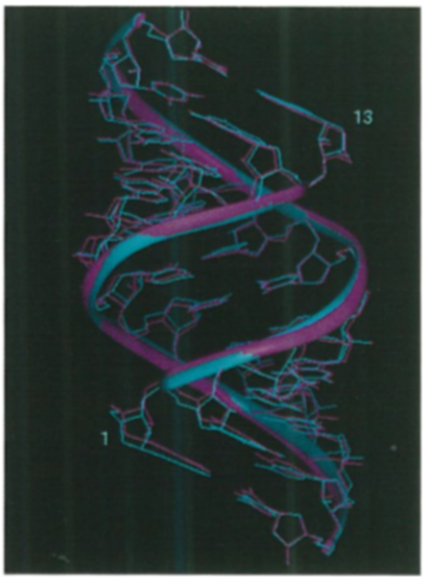
The steroid hormone 17β-estradiol is important in the genesis and development of human breast cancer. Its intracellular concentration is regulated by 17β-hydroxysteroid dehydrogenase, which catalyses the reversible reduction of estrone to 17β-estradiol. This enzyme is thus an important target for inhibitor design. The structure of recombinant human 17β-hydroxysteroid dehydrogenase, type I in complex with estradiol at room temperature has been determined at 1.7 Å resolution, and a ternary complex with NADP+ complex has also been solved. The structures show that estradiol interacts with the enzyme through three hydrogen bonds (involving side chains of Ser142, Tyr155 and His221), and hydrophobic interactions between the core of the steroid and nine other residues. The NADP+ molecule binds in an extended conformation, with the nicotinamide ring close to the estradiol molecule. A triangular hydrogen-bond network between Tyr155, Ser142 and O17 from estradiol probably facilitates the deprotonation of the reactive tyrosine, while the conserved Lys159 appears not to be directly involved in catalysis. Both the steroid-binding site and the NAPDH-binding site can be proposed as targets for the design of inhibitors.




15 August 1996, Research Paper, *Structure*

☐ **The structure of an RNA dodecamer shows how tandem U–U base pairs increase the range of stable RNA structures and the diversity of recognition sites.** Susan E Lietzke, Cindy L Barnes, J Andrew Berglund and Craig E Kundrot (1996). *Structure* **4**, 917–930.

Non-canonical base pairs are fundamental building blocks of RNA structures. They can adopt geometries quite different from those of canonical base pairs and are common in RNA molecules that do not transfer sequence information. Tandem U:U base pairs occur frequently, and can stabilize duplex formation, despite the fact that a single U:U base pair is destabilizing. The authors determined the crystal structure of an RNA dodecamer that forms a duplex containing tandem U:U base pairs at 2.4 Å resolution. The duplex contains an overall bend of 11–12° because of conformational changes at each interface between the tandem U:U base pairs and a flanking duplex sequence. The formation of the U:U base pairs causes small changes in several backbone torsion angles; base stacking is preserved and two hydrogen bonds are formed per base pair, explaining the stability of the structure. The unusual pattern of hydrogen-bond donors and acceptors in the major and minor grooves of this structure could also act as a recognition site.




15 August 1996, Research Paper, *Structure*

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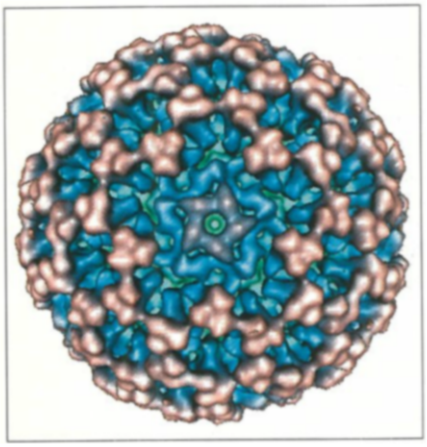
☐ **The structure of aquareovirus shows how the different geometries of the two layers of the capsid are reconciled to provide symmetrical interactions and stabilization.** Andrea L Shaw, Siba K Samal, K Subramanian and BV Venkataram Prasad (1996). *Structure* **4**, 957–967.

Aquareoviruses are important pathogens of aquatic animals and have severe consequences in aquaculture. These viruses belong to the family Reoviridae, whose members generally have a multilayered capsid, formed by several concentric icosahedral shells with different protein compositions. How these proteins, which often are present in unequal stoichiometries, interact between icosahedral layers to stabilize the capsid is not well understood. The authors have determined the three-dimensional structure of aquareovirus to 23 Å resolution using electron cryomicroscopy and computer image analysis. The protein capsid is composed of two structurally distinct icosahedral layers, outer and inner. There are 120 subunits, arranged in dimers, in the inner layer, each of which interacts with two of the 600 subunits in the outer layer. A separate set of closely-interacting proteins forms the five-fold axes of the icosahedra, giving continuous density throughout both layers of the capsid. Comparison of full and empty (lacking RNA) virus structures reveals an RNA shell that lies directly beneath the inner layer. Interactions between the inner and outer layers of the capsid occur chiefly at the icosahedral three-fold axes of symmetry of the outer layer. The channels through the inner layer of the capsid may permit entry of metabolites and exit of newly transcribed RNA.



15 August 1996, Research Paper, *Structure*

☐ **Synchrotron X-ray studies suggest that the core of the transerythrin amyloid fibril is a continuous β-sheet helix.** Colin Blake and Louise Serpell (1996). *Structure* **4**, 989–998.

Amyloid diseases, including Alzheimer's disease and the transmissible spongiform encephalopathies, are characterized by the extracellular deposition of abnormal protein fibrils. The structure of amyloid fibrils from patients with familial amyloidotic polyneuropathy (FAP), which are composed largely or entirely of the soluble precursor protein transthyretin, was investigated by fibre diffraction using synchrotron radiation. The diffraction pattern observed is the first from an amyloid fibril. The pattern is consistent with the cross-β structure previously proposed for the fibril, and reveals a large-scale fibre repeat of 115 Å. The model built from these results suggests that amyloid fibrils have a novel molecular structure consisting of β sheets extended in regular helical twists along the length of the fiber. This implies that the polypeptide chains are hydrogen-bonded along the entire length of the fibre, accounting for the great stability of the structure.

15 August 1996, Research Paper, *Structure*