EDITORIAL

DNA Replication: the Fellowships and the Rings

For a couple of billion years, DNA replication just happened without questions of how, when or why. It happened that I was just a few weeks old when Watson and Crick, in their second paper in *Nature* in 1953, discussed how polynucleotides might assemble spontaneously or even by an enzyme-catalysed process, from unidentified precursors using single-stranded DNA as a template.

What followed was an age of apparent simplicity. Arthur Kornberg and co-workers discovered DNA polymerase (Pol I) in 1956, dissected its function, and used it to uncover basic mechanisms. He and his colleagues at Stanford isolated other DNA modifying enzymes including ligase and nucleases, and discovered how to use them as reagents. With the armoury of DNA modifying enzymes available in refrigerators at Stanford, it is no surprise that recombinant DNA techniques were born nearby in the early 1970s.

But it was not just these new techniques that ushered in the next age, during which the complexity of the problem became apparent. In 1969, John Cairns used brute force to isolate an *Escherichia coli* mutant that grew normally despite its lack of Pol I, and soon after Tom Kornberg isolated Pols II and III from the Cairns' mutant. Pol III turned out to be the true replicative polymerase, now known to have 10 different subunits! Several groups realised the possibility of replicating defined plasmid and phage templates *in vitro*. This was done at first with crude extracts, yielding assays that were used to fractionate them into pure protein factors. Charles Richardson and Bruce Alberts worked on large phages (T7 and T4) that encode their own replication proteins, while Kornberg and also Jerry Hurwitz chose to reconstitute the replication of the DNA of small phages that used only host proteins. By the mid 1980s, this process had yielded over 30 different gene products with roles in host bacterial replication!

We are now in a third age, one of enlightenment. It is an exciting time during which the high-resolution structures and mechanisms of components of the bacterial replication complex are becoming well defined, and this knowledge has been extrapolated to eukaryotic systems. The four Showcase articles in this issue illustrate some of the beauty and complexity of DNA replication, as it is currently understood, in both prokaryotic and eukaryotic systems.

Australian science has played an important role in this journey, from the first steps, and many of our leading molecular biologists cut their teeth on DNA replication. Foremost among our small replication community is Gerry Wake, recently retired from the University of Sydney. Our first Showcase article by Iain Duggin pays tribute to Gerry's distinguished career of focussed research on the mechanism of termination of bacterial DNA replication.

The two articles that follow highlight current knowledge of the bacterial replisome. Patrick Schaeffer and comrades describe its protein complement and their interactions, while Gene Wijffels and friends look at relationships among the many replicative and repair polymerases, noting how many of them interact with the ring-shaped β sliding clamp. This theme of fellowships and rings continues in the article by Bernie Kunz and his colleagues, who describe some of the functions of eukaryotic DNA polymerases in DNA repair, including their interactions with PCNA, the equivalent sliding clamp in higher organisms (see cover graphic).

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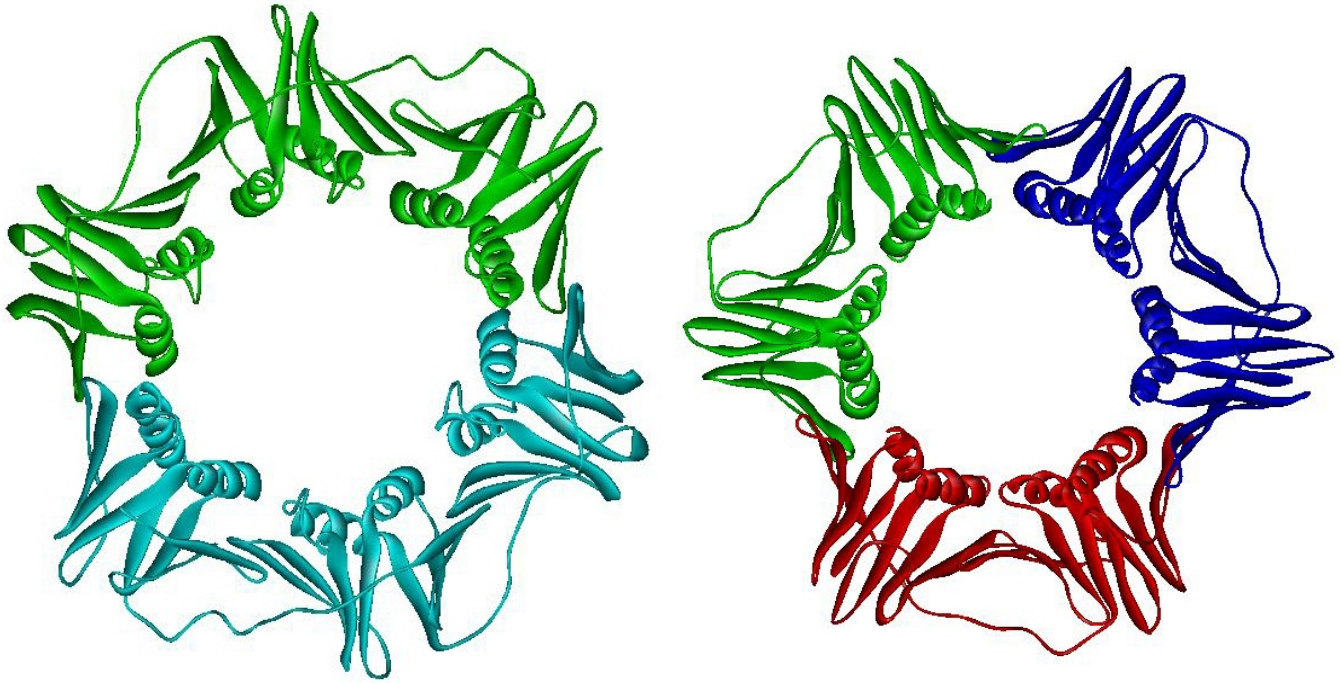
Cover Illustration

Sliding Clamps. *In all organisms, the replicative DNA polymerases never fall off their DNA templates unless they meet some barrier they cannot overcome. This near-infinite processivity is achieved by tethering them to closed ring-shaped sliding clamps that encircle the nascent double-stranded DNA behind them. The dimeric prokaryotic clamp (at left, the β subunit of Pol III; PDB code 1MMI) and its trimeric eukaryotic equivalent (at right, PCNA, proliferating cell nuclear antigen; PDB code 1PLQ) have remarkably similar structures, even though their sequence similarity is minimal. Recent work has shown that both β and PCNA transact among many protein complexes in DNA replication and repair. Figures courtesy of Aaron Oakley.*

DNA Replication and Repair
Guest Editor: Nick Dixon

In the next issue...

In August, Showcase on Research will be on **Cell Adhesion** – *Guest Editor: Michael Berndt*



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