50TH ANNIVERSARY

More Cinderella than ugly sister

Watson and Crick changed biology forever when they described the right-handed double helical structure of DNA in 1953. Below, Shuguang Zhang gives a personal view on the less well-known story of the equally beautiful and functional left-handed DNA.

When I was an undergraduate in China, in 1979, I asked my biochemistry professor why all biological helices seemed to be right-handed, and whether there might be left-handed ones? My professor did not know. Shortly afterwards, my question was answered when Alexander Rich and colleagues reported the discovery of left-handed DNA.

Left-handed DNA consists of two anti-parallel chains, with bases that still form Watson–Crick base pairs. It was named Z-DNA as a result of its zigzag phosphodiester backbone. Before this unexpected discovery, DNA was viewed as structurally static. This finding made it obvious that the molecule is a dynamic entity: its structure depends on its environment.

The new discovery provoked a worldwide race to study Z-DNA. One key finding was that biologically negative supercoiling stabilized Z-DNA. This clearly indicated that Z-DNA could have a functional role.

To investigate this potential role, Rich's lab used antibodies to Z-DNA to probe nuclear activities. They found that the anti-Z-DNA antibodies localized in transcriptionally-active macronuclei in ciliates, and in transcriptionally-active polytene chromosomes in *Drosophila*.

Further studies by Rich's group, and others, were consistent with this finding, confirming that Z-DNA was involved in regulating some genes as well as chromatin remodelling. Studying unstable Z-DNA in cells is a technically daunting and unfashionable pursuit that has discouraged many. Undeterred, Rich and co-workers have pressed on alone, accumulating an impressive body of evidence that shows that Z-DNA is not only biologically relevant but is also important.

The latest exciting findings might indicate a link between the structure of Z-DNA and viral pathogenesis. In a series of experiments, Rich and colleagues show that the Z-DNA binding domain found in vaccinia viruses is required for them to be pathogenic. These results raise the intriguing possibility that smallpox could be treated by blocking Z-DNA binding in variola — the virus that causes it — which has a nearly identical binding domain to vaccinia.

Alexander Rich has a passion for Z-DNA and relentlessly pursues its biological function. His early passions led him to numerous discoveries, including the molecular structure of collagen with Francis Crick in 1955, DNA–RNA hybridization and the mechanism of protein synthesis on polyribosomes. I anticipate that Rich and colleagues will not only elucidate the biological function of Z-DNA, but will also inspire many more discoveries in the coming years.

Shuguang Zhang,
Massachusetts Institute of Technology
Laboratory of Molecular Self Assembly

References and links

FURTHER READING

Wang, A. H.-J. *et al.* Molecular structure of a left-handed double helical DNA fragment at atomic resolution. *Nature* **282**, 680–686 (1979) | Kim, Y.-G. *et al.* Role for Z-DNA binding in vaccinia virus pathogenesis. *Proc. Natl Acad. Sci. USA* (in the press)

WEB SITE

Shuguang Zhang's laboratory:
http://web.mit.edu/lms/www/index.shtml

50TH ANNIVERSARY

Whatever happened to...

Winners of the 1962 Nobel Prizes display their diplomas. Maurice Wilkins is on the far left, Francis Crick is third from the left and James Watson is second from the right. © Bettmann/CORBIS.

Watson and Crick are among the most recognizable names in biology, Wilkins and Franklin perhaps less so, but what happened to these inspirational people after their ideas and dedication made 1953 a watershed year in science?

Francis Harry Compton Crick, the man who, at the age of 30, in his own words "essentially knew nothing", has continued to address 'big' questions since he and James Watson answered one of the biggest. Collaborations with the 2002 Nobel laureate Sydney Brenner produced ideas on protein synthesis and the genetic code. Crick joined the Salk Institute in California in 1976, and this has remained his affiliation up to the present, where he has focused on the problem of consciousness. Most recently, he has been considering the neural correlates of consciousness: the minimal set of neuronal events that give rise to a specific aspect of a conscious precept.

Rosalind Elsie Franklin, often characterized as the wronged heroine of the double helix story, died four years before Watson, Crick and Wilkins received their Nobel Prize in 1962. The Nobel rules preclude posthumous awards, but they also preclude prizes being shared by more than three people, so would she have been honoured even had she been alive? Regardless, Franklin did become something of a feminist icon after Watson was rather dismissive of her in his bestseller of the late 1960s, *The Double Helix*. Her last working years produced what Watson describes as "very beautiful work" on the structure of tobacco mosaic virus.

James Dewey Watson has retained the high profile that he gained after widespread recognition followed on the heels of the 1953 breakthrough. After brief stints working with Alexander Rich, and Crick again, Watson went on to Harvard where he collaborated with Walter Gilbert. In 1968, he took over as Director of Cold Spring Harbor Laboratory, which he revitalized by focusing on tumour biology, eventually becoming its President in 1994. In this role, as well as during a stint at the National Institutes of Health as Associate Director for Human Genome Research and subsequently as Director of the

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Twisting the night away

DNA's big anniversary has not been allowed to slip away with only a few geneticists raising a cheer: the public are also being involved.

Celebrations got off to a serious start in the UK with a public forum on 'Genetics and the Search for Safer Drugs' (6 February, Royal College of Physicians, London). Science festivals in March (24–30, Wrexham) and April (17–22, Edinburgh, Scotland) promise to be more light-hearted, with DNA-based public lectures, discussion forums and interactive workshops. Interaction is also a big part of Kew Garden's celebratory event 'DNA in the Garden' (29 March–11 May, London).

Double helix fever is also gripping the US, particularly in New York, where numerous organizations are taking part in a host of activities under the DNA festival banner. One exhibition promises to tell the story of New York and DNA, placing the discovery in a historical and social context (New York Public Library, 25 February–29 August).

Some events are considerably less public: the DNA gala dinner at the Waldorf Astoria (28 February, New York) was an invite-only affair. Similarly, the flagship celebratory dinner in the UK (23 April, Guildhall, London) will have a restricted guest list, probably featuring the prime minister, members of the royal family, Nobel laureates and, if guest of honour James Watson has his way, Michael Caine, Sean Connery and soccer-star David Beckham!

Watson, surely the busiest man in the world this year, has also been invited to unveil a plaque at the Eagle public house where Francis Crick famously declared to puzzled drinkers on 28 February 1953 'We have uncovered the secret of life' (25 April, Cambridge, UK). Of course, Crick's exclamation came after he and Watson had put together a model of the double helix. Consequently, DNA models feature in several celebratory events including the Watson-adorned DNA50 events at the International Centre for Life (14–17 April, Newcastle, UK).

Maurice Wilkins is also a man in demand in this anniversary year, with appearances at public events in Cambridge ('Who Twists the Helix?', The University Centre, 17–19 March) and London ('DNA Past, Present and Future', King's College, 22 April).

Anyone not able to attend these events will still be able to get into the spirit of the celebration: 'National DNA Day' (25 April) will be celebrated by high schools throughout the USA, and in the UK a special DNA £2 coin will be a nice souvenir for any double helix buff.

So, there is no excuse for the public not to be involved in the party this year, and let us hope that they do get involved because, as Watson says, "DNA is for the world, not just science".

Nick Campbell

References and links

WEB SITE

Cold Spring Harbor Laboratory DNA anniversary site:
http://www.dna50.org/main.htm

National Center for Human Genome Research, he has remained at the forefront of research and policy-making in genetics and molecular biology.

Maurice Hugh Frederick Wilkins has been less publicly prominent than Watson since 1953. In a way this is surprising, given that as well as his work on the structure of DNA he was also involved with the development of the nuclear bomb — an innovation that might even dwarf the profile of the double helix in the public's perception of science in the twentieth century. Wilkins continues to teach and pursue his interest in social responsibility in science, and, at the age of 86, remains an active staff member at King's College, London.

Nick Campbell

References and links

FURTHER READING Watson, J. *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (Atheneum, New York, 1968) | Maddox, B. *Rosalind Franklin: The Dark Lady of DNA* (Harper Collins, London, 2002) | Crick, F. & Koch, C. A framework for consciousness. *Nature Neurosci.* **6**, 119–126 (2003)

50TH ANNIVERSARY

The art of the helix

The beauty of the DNA double helix, together with the social and ethical issues that developments in genetics have raised, are the source of inspiration for many artists. The celebration of the 50th anniversary of the discovery of the DNA structure has catalysed the organization of several art exhibitions with the theme of genetics.

Art can help scientists to communicate the advances that have been made in genetics, and to engage the public in debate about topics such as cloning, genetic modification and gene patenting. For example, an exhibition on the impact of the Human Genome Project — 'How Human: Life in the Post-Genome Era' (International Center of Photography, New York, 28 February–25 May) — that includes works by more than 30 artists and photographers, will reach more people than would ever visit the labs that are responsible for sequencing the human genome.

New York hosts a number of other exhibitions, including 'Genetic Expressions: Art after DNA' (Hecksher Museum of Art, Huntington, 28 June–7 September) and 'From Code to Commodity: Genetics and Visual Art' (The New York Academy of Sciences; until 11 April). The Graduate Center Art Gallery in New York also marks the anniversary of Watson and Crick's discovery with an exhibition in April entitled 'Genomic Issue(s): Art and Science'.

In February and March, the Universal Concepts Unlimited Gallery, New York, presented the work of five female artists in 'Women in Science: Genomically Yours' — an exhibition that was dedicated to Rosalind Franklin, who is also the subject of a play that was shown at the City University of New York in March. Artwork from The Santa Barbara Museum of Art's exhibition 'PhotoGENEsis: Opus 2', which aims to provide an artist's response to the genetic information age, was also exhibited in New York in February, coinciding with the Watson and Crick celebrations.

Outside New York, the 'Paradise Now' exhibition, which is the product of collaborations between artists and scientists, can be seen at the Tulane Museum, New Orleans (until May) and the McKinney Avenue Contemporary, Dallas (June to July). The works presented in this exhibition, including an interesting example of how genetics can be used to develop technologies that are useful to the artist, can also be seen at the Paradise Now web site. Among the exhibitors are Ackroyd and Harvey, who use grass to produce wonderful, but short-lived, images. Photographic negatives are laid on grass and, over time, an image develops as the level of green photosynthetic pigments in the grass alters in response to the amount of light penetrating the negative. Geneticists at the Institute of Grassland and Environmental Research, Wales (UK) have produced a genetically modified 'stay-green' rye-grass that enables the artists to dry their grass pictures, so that they last for longer.

Image by Luisa Estanislao 2002

At the University of Cambridge (UK) — a short distance from where Watson and Crick solved the structure of DNA — the Whipple Museum of the History of Science will host the 'Representations of the Double Helix' exhibition throughout the year.

As well as being a source of enjoyment and discussion for scientists, artists and members of the public, these exhibitions might promote links between scientists and artists. Such links can only improve the ability of scientists to communicate their research and explore the ethical implications of their work.

Catherine Baxter

References and links

FURTHER READING Kemp, M. The *Mona Lisa* of modern science. *Nature* **421**, 416–420 (2003) | Nelkin, D. & Anker, S. The influence of genetics on contemporary art. *Nature Rev. Genet.* **3**, 967–971 (2002)

WEB SITES

Genomic Art:
http://www.geneart.org/genehome.htm

Paradise Now:
http://www.geneart.org/pn-home.htm

WEB WATCH

Celebrating UK geneticists

- http://www.dna50.org.uk

In celebration of the 50th anniversary of the publication of the structure of DNA, the Medical Research Council, *Nature* and the Royal Society have worked together to produce this highly informative web site. It describes past achievements and future prospects for genetic research in the UK. It also advertises the scientific events that are taking place this year as part of the 50 year celebrations. Ethical and social issues that are associated with genetic research are addressed in the Science in Society section.

The key events, from Mendel's studies in the 1850s establishing the particulate nature of inheritance to the elucidation of the structure of DNA in 1953, are included in a useful timeline. This timeline focuses on the principal contributions that UK researchers have made to genetics since 1953, including the invention of Fred Sanger's sequencing technology in 1977 and the development of DNA fingerprinting methods by Alex Jeffreys in the 1980s. Looking to the future, the web site reviews the potential applications that could be developed from our existing knowledge of genetics and molecular biology. The source of much of this information is the UK Foreign and Commonwealth Office publication entitled 'DNA and after, 50 years of excellence'.

The site is easy to navigate, contains useful scientific information and provides a calendar of the events that will be happening throughout the year in the UK — including hands-on workshops for students, and public debates on topical issues. There is also a handy Science in the News section that is contributed by the Royal Society.

Catherine Baxter

50TH ANNIVERSARY

Another brick in the wall

The host of celebratory scientific events that are scheduled for 2003 illustrates just how many bricks have been added to Watson and Crick's 1953 foundation stone over the years.

James Watson was on hand to be honoured at the first of these events "50 Years On: From the Double Helix to Molecular Medicine" (1–5 February, Miami, USA). In the same month, Watson also attended the premier celebratory US meeting

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After the double helix

The 50th anniversary celebrations marking the discovery of the three-dimensional structure of DNA provide an opportunity to reflect on the key developments in the field of genetics over the past 50 years, and to consider the future of genetic research.

Before Watson and Crick's 1953 paper, Avery, MacLeod and McCarty in 1944, and Hershey and Chase in 1952, had provided the experimental data that established DNA as the heritable genetic material. With the knowledge of the structure of DNA, research then focused on its replication and information-encoding properties. In 1958, Meselson and Stahl showed that DNA replication is semi-conservative: new molecules consist of one original strand from the parental molecule and one new strand. Contributions by Crick, Brenner, Nirenberg, Khorana, Matthaei and Holley, among others, enabled the genetic code to be cracked by 1966. However, a remaining challenge is to understand the information that is encoded in regulatory DNA.

DNA sequencing has revolutionized genetics. The Sanger and Maxam-Gilbert methods were published in 1977. The first genome to be sequenced was the bacteriophage FX174 (~5 kb) in 1980 and the first free-living organism to be sequenced was *Haemophilus influenzae* (~1.8 Mb) in 1995. Recent advances have reduced the cost and enhanced the speed of sequencing, so the sequences of several whole genomes, from a wide taxonomic distribution, have now been published — including the much anticipated human genome in 2001.

Another important technical breakthrough occurred in 1983 when Mullis developed the polymerase chain reaction (PCR). Many other tools for molecular biology have been developed over the past 50 years, including restriction enzymes, nucleic acid hybridization techniques, cloning and genetic engineering. The application of these methods has led to some interesting applications. Notably, gene therapy was first used in 1990 to treat a patient suffering with the immune disorder adenosine deaminase (ADA) deficiency; the first transgenic food — the

("The Biology of DNA", 26 February–2 March, Cold Spring Harbor Laboratory).

The European scientific celebrations will be launched with "Nobel Day" at the World Life Sciences Forum (8 April, Lyons, France), which boasts no fewer than 11 Nobel prize winners, including Watson, and covers the entire breadth of the discovery's impact. Watson also finds time to attend a genome-focused symposium ("From Double Helix to Human Sequence — and Beyond" 14–15 April, Bethesda, USA), a Royal Society discussion meeting ("Replicating and Reshaping DNA", 23–24 April, The Royal Society, London, UK) and a conference held on the exact anniversary of the famous publication ("DNA: 50 years of the Double Helix", 25 April, Cambridge, UK).

Following the frenzy of double-helix related activity in April, the programme of scientific events slows down, but continues for the rest of the year. The annual Cold Spring Harbor Symposium this year celebrates both the anniversary of the double helix and the impending completion of the human genome ("The Genome of *Homo sapiens*", 27 May–3 June). The International Congress of Genetics — a flagship event for the community that is only held once every five years — also has a genomic flavour ("Genomes — The Linkage to Life", 6–12 July, Melbourne, Australia).

Meetings in many other disciplines on which genetics has had an impact on in the past 50 years will be hosting symposia or discussions for the anniversary; for example, the symposium on "Exploiting Genomes: Bases to Megabases in 50 years" at the Society of General Microbiology's meeting (8–9 September, Manchester, UK).

Biotechnology is another area that owes a debt to the double helix, and later in the year a symposium at UC Berkeley (10–11 October, San Francisco, USA) will explore its impact over the past 50 years (the ubiquitous Watson will be in attendance!).

So, it will be a busy year for geneticists world-wide, but, as I'm sure most attendees at these meetings will agree, while it must have been great for Watson and Crick to lay the foundation stone, it is also good to be a humble bricklayer on a construction as exciting as this one.

Nick Campbell

FlavrSavr tomato — reached the supermarkets in 1994; and 'Dolly the sheep' — the first cloned mammal — was born in 1996.

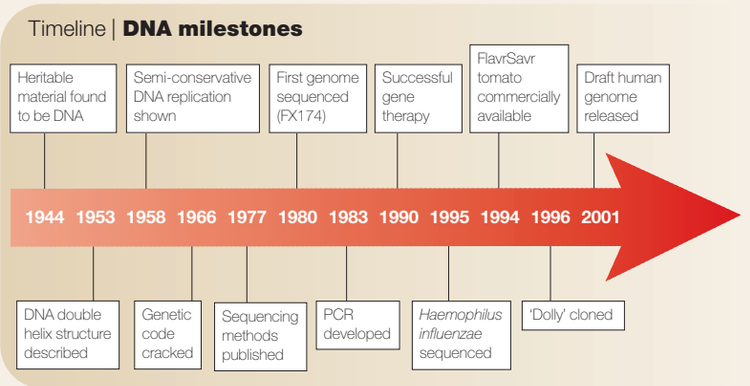
Combining molecular biology techniques with the ever-expanding volume of genomic, proteomic and phenotypic data should enable geneticists to make further exciting developments over the next 50 years. There is little doubt that genetics will continue to benefit society, in particular through improvements in healthcare and agriculture.

Catherine Baxter

References and links

FURTHER READING

The double helix – 50 years. *Nature* **491**, 396–453 (2003)



IN BRIEF

GM ORGANISMS

Impact of genetic manipulation on the fitness of *Anopheles stephensi* mosquitoes.

Catteruccia, F. *et al. Science* **299**, 1225–1227 (2003)

It has been argued that malaria could be controlled by introducing into natural populations transgenic mosquitoes that express genes that impair parasite transmission. For this strategy to be successful, the transgenic mosquitoes must be able to survive and reproduce competitively in the wild . However, this study shows that transgene expression, mutations introduced by transgene insertion, and inbreeding can result in a lower fitness of transgenic mosquitoes relative to wild type.

MOUSE MODELS

Modification of ocular defects in mouse developmental glaucoma models by tyrosinase.

Libby, R. T. *et al. Science* **299**, 1578–1581 (2003)

Human primary congenital glaucoma (PCG) is often caused by mutations in the cytochrome P450 family member *CYP1B1*, and is associated with abnormal ocular drainage structures. This paper shows that *Cyp1b1*-deficient mice provide a good model for this type of glaucoma. Libby *et al.* used these knockout mice to show that tyrosinase gene deficiency increases the severity of the disease phenotype and that this is alleviated by applying dihydoxyphenylalanine (L-dopa). This raises the possibility of new glaucoma therapies.

TECHNOLOGY

RNA interference targeting *Fas* protects mice from fulminant hepatitis.

Song, E. *et al. Nature Med.* **19**, 347–351 (2003)

RNAi can target and silence mammalian genes but can it prevent disease? Song *et al.* show that, in mice, RNAi can silence the gene *Fas* that codes for an important mediator of hepatocyte apoptosis. This indicates that RNAi could be used to prevent the adverse effects of hepatitis that are linked to cell death. The authors test this hypothesis in two models of *Fas*-mediated liver damage, and show for the first time that siRNA can prevent disease *in vivo*.

FUNCTIONAL GENOMICS

Scanning the human genome with combinatorial transcription factor libraries.

Blancafort, P. *et al. Nature Biotech.* **21**, 269–274 (2003)

Blancafort *et al.* report a new technology that could be useful for studying and modulating gene function. They have constructed large libraries of artificial transcription factors that contain between three and six zinc-finger domains (TF_{ZF}s) that can either activate or repress gene expression. TF_{ZF}s can be applied to a cell line that is then screened for a desired phenotype. In this example, TF_{ZF}s were identified that were able to induce expression of the endothelial marker VE-cadherin in non-endothelial cell lines and to repress its expression when combined with a repression domain.

ETHICS WATCH

Bioterrorism and the right to research

A basic tenet of scientific freedom has been the right to research any topic and to publish the results. But that freedom is now under pressure as awareness grows that biological research could be misused to create bioweapons that are directed at human beings, staple crops and livestock[1]. Balancing scientific freedom and public security has become an important challenge for both the scientific community and society.

In reconciling those interests, it is helpful to recall that in most countries there is no clear set of legal rights that protect what scientists may do. In the United States, for example, the rights to free speech protect a scientist's choice of research topic and the publication of results, but they leave room for government restrictions in the methods that are used and the projects that are funded. The right to research and publish does not include the right to use any method to achieve this goal, such as the use of human subjects without their consent, or the use of chemicals or pathogens that pose a high risk of harm. Funding agencies can also set limits on the topics that can be pursued, the methods that can be used and what may be published[2].

Against this backdrop, the attempts of governments to reduce the chance that biological research could be used to produce bioweapons raise issues of policy more than of rights. The main question is whether the burdens on free inquiry and exchange are justified by the threats or dangers that they might pose. The scientific community has made clear its willingness to cooperate in minimizing threats to security[3]. For example, the editors of 20 leading scientific journals have announced that they will weigh the potential harm of publication against the scientific benefits of an article, and make the decision to modify or to publish on that basis[4]. It is essential that the government be also sensitive to the needs of science.

Of special concern in the United States is the maintenance of the longstanding policy that ensures that the results of nonclassified funded research may be published. The scientific community has strongly opposed the creation of a new category of "sensitive, nonclassified research" to restrict publication. Such a category is inherently vague and would probably be administered by nonscientists who are less sensitive to the needs of scientific research[5] .

Also of concern are restrictions on who may work with certain "select agents" that recent security laws now require to be registered and inventoried. Should past drug use, consultation with a psychiatrist, or having been born in certain countries disqualify individuals from working with those materials?

The halcyon days of scientific research that was unfettered by larger concerns about how results might be misused are now over for microbiologists and molecular biologists, as has long been the case for the scientists involved with nuclear energy. Inquiries into the genomic and protein structure of viruses and other microorganisms must continue, but scientists must also act responsibly in publicizing techniques that could yield bioweapons.

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REFERENCES [1]Fraser, C. M. & Dando, M. R. Genomics and future biological weapons: the need for preventive action by the biomedical community *Nature Genet.* **29**, 253–256 (2001) | [2]Robertson, J. A. The scientists right to research: a constitutional inquiry. *Southern California Law Review* **51**, 1203–1281 (1978) | [3]Alberts, B. & May, R. M. Scientist support for biological weapons control. *Science* **298**, 1135 (2002) | [4]Harmon, A. Journal editors to consider US security in publishing. *New York Times* A13 (16 February 2003) | [5]Schemo, D. J. Scientists discuss balance of research and security. *New York Times* A12 (1 January 2003)

Diptych: 'Yin/Yang lilac', by Jacques Deshaies (2002) (detail).

EVOLUTIONARY GENETICS

Chromosomal barriers to sex lifted

Many millions of years ago, two yeast cells became unable to have productive sex with each other. These eventually gave rise to separate species, or what we now know as *Saccharomyces cerevisiae* and *Saccharomyces mikatae* respectively. But how did the original barrier to mating arise in these yeasts, and how has it been maintained for all this time? In studying such speciation events, geneticists have been limited to retrospective studies that infer what might have happened. Now that has changed — in the 6 March issue of *Nature*, Delneri *et al.* actually 'do the experiment' to test the effects of chromosomal translocations on speciation.

The genomes of *S. cerevisiae* and *S. mikatae* are known to vary by at least two reciprocal chromosomal translocations, which disturb the collinearity of the two genomes. If these yeast species attempt to mate, sterile progeny result — presumably from the inability of the two rearranged genomes to complement each other to produce viable spores. We do not know what initiates the speciation process, but it has been speculated that genome rearrangements between protospecies reinforce their reproductive isolation.

Delneri *et al.* effectively backtracked in evolution by engineering laboratory strains of *S. cerevisiae* to the *S. mikatae* state at the translocation breakpoint. The popular Cre/loxP system was used to create large reciprocal translocations, resulting in a new strain with a genome that is more collinear with that of *S. mikatae*. When these engineered strains were mated to *S. mikatae*, viable progeny resulted. Even so, the matings were not 100% fertile, which indicated that the translocation is not the only important genomic difference between the two species. Further important variations might exist at the single-gene scale, which would only be discovered by sequencing both genomes — projects to sequence multiple yeast species are well underway.

Interestingly, the viable hybrid spores that were recovered were often extensively aneuploid, retaining chromosomes from one parent more often than should be the case, and having two copies of many chromosomes. The likely explanation is the duplication of one parental genome followed by some chromosome loss, but future experiments will be needed to discover the details. With this work, Delneri *et al.* have provided a new approach for further exploring these evolutionary mysteries. Although we still do not know what led to the divorce of these two yeasts, we now know what keeps them from reconciling.

Chris Gunter, Associate Editor, Nature

References and links

ORIGINAL RESEARCH PAPER Delneri, D. *et al.* Engineering evolution to study speciation in yeasts. *Nature* **422**, 68–72 (2003)
FURTHER READING Wolfe, K. Speciation reversal. *Nature* **422**, 25–26 (2003)
ENCYCLOPEDIA OF LIFE SCIENCES Speciation: chromosomal mechanisms

RNA WORLD

The expanding universe of tiny RNAs

The finding that RNA can regulate gene expression is among the most exciting discoveries made in recent years. As well as RNAi, PTGS in plants and quelling in *Neurospora*, there are the stRNAs that regulate developmental timing. Discovered in *Caenorhabditis elegans*, the stRNAs *lin-4* and *let-7* have been the defining members of a group of small RNAs that are now referred to as microRNAs (miRNAs). Typical miRNAs are ~22 nt long and are cleaved from larger (~70 nt) precursors that form a characteristic stem-loop structure. Families of miRNA genes are present in both plant and animal genomes. Now, Bartel and colleagues take a computational genomics approach to identify miRNAs that are conserved across vertebrates. Their computational procedure (MiRscan) predicts that vertebrate genomes contain 200–255 miRNA genes, representing nearly 1% of the predicted genes in the human.

MiRscan — the details of which are being published elsewhere — identifies the evolutionarily conserved stem-loop precursors. Within each potential precursor, it scans 21 nt at a time to find the closest match to the original worm miRNAs. The authors compared the human, mouse and *Fugu rubripes* genomes and identified ~15,000 stem-loop segments in the human. All of these fell outside of protein coding regions and were at least partially conserved in mouse and *Fugu*. MiRscan narrowed this number down to 188, but the sensitivity of the scoring indicated that this number might represent 74% of all miRNA genes, setting the maximum number at 255.

Given that some miRNA loci were already known, and that MiRscan identified 107 new candidates, Lim *et al.* point out that no more than ~40 new miRNA loci remain to be discovered in the human. This estimate depends on the accuracy of the MiRscan prediction, so the authors set out to verify their candidates. Although some were closley related to previously cloned miRNAs and others could be detected in a zebrafish cDNA library that had been constructed specifically to contain miRNAs and siRNAs, Lim *et al.* were left with 55 candidates that could not be verified. So, the authors calculated the minimum specificity value and, taking into account the sensitivity of the zebrafish experiment and the incompleteness of the genome, proposed 200 as the lower limit for the total number of human miRNA genes.

Although MiRscan was 'trained' on worm miRNAs, it was able to identify most of the vertebrate counterparts, indicating that although most miRNA sequences have not been conserved, some of the generic features of miRNAs and their precursors have been. The authors also provide a parallel between protein coding and miRNA gene families: miRNA genes represent nearly 1% of the predicted human genes, a proportion that is similar for other families of regulatory genes. Because miRNA genes are absent from yeast, Lim *et al.* speculate that they might have evolved to regulate cell differentiation and developmental patterning. This is certainly true for some of the miRNAs that are already known; undoubtedly, functions will soon be assigned to the newly identified miRNAs.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Lim, L. P. *et al.* Vertebrate microRNA genes. *Science* **299**, 1540 (2003)

FURTHER READING Eddy, S. Non-coding RNA genes and the modern RNA world. *Nature Rev. Genet.* **2**, 919–929 (2001)

WEB SITES

Dave Bartel's lab: http://web.wi.mit.edu/bartel/pub

Chris Burge's lab: http://genes.mit.edu/burgelab

IN BRIEF

EVOLUTION

Drosophila pigmentation evolution: divergent genotypes underlying convergent phenotypes.

Wittkopp, P. J. *et al. Proc. Natl Acad. Sci. USA* **100**, 1808–1813 (2003)

In this quantitative trait analysis, at least four loci were identified by marker association that contribute to the different pigmentation patterns that are observed in *Drosophila novamexicana* and *Drosophila americana*. Although the pigmentation in these species is similar to that seen in other *Drosophila* species that have been studied, the genetic basis of the convergent phenotypes is different. Of the four loci found, only one (*ebony*) had been previously associated with interspecific variation in pigmentation, showing that convergent phenotypes can result from divergent genotypes.

GENE REGULATION

Genome-wide identification of *in vivo Drosophila* Engrailed-binding DNA fragments and related target genes.

Solano, P. J. *et al. Development* **130**, 1243–1254 (2003)

After ultraviolet crosslinking of DNA–protein interactions, the authors used a chromatin immunoprecipitation protocol to find potential targets of Engrailed in the *Drosophila* genome. There were 203 Engrailed-binding fragments situated in intergenic or intronic regions, and the putative target genes that were located near these binding sites were found to be involved in a wide range of developmental processes. Engrailed regulation was confirmed for 12 of the 14 genes, including *frizzled2*, by examining their expression in flies that ectopically expressed *engrailed*.

TECHNOLOGY

A discrete self-assembled metal array in artificial DNA.

Tanaka, F. *et al. Science* **299**, 1212–1213 (2003)

DNA molecule provides a computing machine with both data and fuel.

Benenson, F. *et al. Proc. Natl Acad. Sci. USA* 4 March 2003 (10.1073/pnas.0535624100)

Fifty years after the structure of DNA was determined, its unique chemical properties are increasingly being put to good use. Two new studies take advantage of DNA's highly selective base pairing to use it as a building block for supramolecular ensembles. By replacing hydrogen-bonded base pairs in the double helix with metal-bonded base pairs, Tanaka *et al.* assemble an array of five Cu^{2+} in the middle of the DNA. Uniquely, this method allows metal ions to be arrayed in solution and opens up the possibility of DNA-based nanodevices such as molecular magnets and wires. Benenson *et al.* focus on the potential of DNA for molecular computing. For the first time, they show that the energy generated by hydrolysis of the DNA backbone can drive a molecular computation. The authors suggest that the ability of DNA to act as an energetically efficient information-processing device helps to explain its selection as the mechanism for genetic information transfer.