

has been created by W. Steurer at the web address <http://www.kristal.ethz.ch/QDB>. Up to date information on QC structures, conferences and publications is available at this site. 'Diffuse intensity' and 'streaks' in the diffraction patterns of quasicrystalline materials were presented by N. K. Mukhopadhyay. Various kinds of ordering models for explaining these effects were discussed. A. K. Pramanick showed the presence of different types of ordering in Al-Co-Cu-Ni alloys by analysing their electron diffraction patterns. He discussed the results in terms of the  $e/a$  values of the alloys. Z. Papadopolos (Germany) considered the structural decoration of QC lattices in 3D space by Bergman and Mackay polytopes and showed that steps or traces at the surfaces involving three length scales could be predicted in the Al-Pd-Mn QC system. These distances, mutually scaled by a factor of  $\tau$ , where  $\tau = (1 + \sqrt{5})/2$ , were shown to match with those observed experimentally by P. Theil and coworkers (USA).

K. Saitoh and coworkers (Japan) showed how the high-angle annular dark field scanning transmission electron microscope (HAADF-STEM) and atom location by channeling enhanced microanalysis (ALCHEMI) techniques could be used to obtain the local chemical information in the QC structure. HAADF-STEM method can provide STEM images using electrons scattered at high angles ( $\sim 100$  mrad). Since the scattering amplitude of the electrons is proportional to the square of atomic number ( $Z$ ), the image shows  $Z$ -contrast. Using this technique, they proposed two types of atom clusters of 2 nm size in Al-Co-Ni decagonal phase. Based on

ALCHEMI results, they proposed that Al and TM (transition metal) atoms occupy different sets of sublattice sites. Further, Ni and Co atoms either occupy different sets of sublattice sites or randomly occupy a similar set of sublattice sites. This observation would be helpful for solution of the decagonal QCs. A. Yamamoto and coworkers proposed a modified method of Low Density Elimination (LDE) for solving QC structures. The basic principle of LDE was to eliminate 'negative density' and 'sharpen the peaks in the electron density maps'; multidimensional LDE was used to solve the structure of QCs. Semi-quantitative models were presented for Al-Pd-Mn, Al-Co-Ni and Zn-Mg-Ho QCs, to provide a starting point for constructing a detailed atomic model of these QC systems. E. Rotenberg and co-workers (USA) carried out the photoemission studies on valence band structure of Al-Ni-Co and Al-Pd-Mn QCs, which has generated a lot of interest. This exciting work has also been reported in *Nature* (2000, **406**, 602). An Indian scientist, S. R. Barman (CAT, Indore) was also associated with this investigation. J. Roth (Germany) discussed the effect of shock waves on the stability of quasicrystalline materials. It was noted that weak shock waves reacted with the system elastically. In the intermediate range of shock waves, defect bands were produced, while for strong shock waves QCs and their approximant structures became amorphous.

In the category of IC structures, lectures covered modulated structures with different compositions and their related phase transitions, and electrical and magnetic properties of such materials.

A. Yamamoto (Japan) dealt with procedures for 'automatic analysis of modulated and composite crystals'. H. Boysen (Germany) demonstrated how inclusion compounds affect diffuse scattering and satellite reflections in IC structure. This contribution concentrated on one-dimensional structures consisting of a three-dimensional framework (host), with a chain-like component (guest). The mutual interactions between host (e.g.  $n$ -alkane) and guest (e.g. urea) molecules resulted in modulated structure. J. F. Kelly and coworkers (England) studied the diffraction contrast obtained from the edge of hexagonal crystals of silicon carbide (SiC) with the help of synchrotron radiation source X-ray diffraction edge topography (SRS-XRDET). They proposed a 'sandwich model' for non-degenerate polytype-polytype configuration in SiC structure. It was noted that besides such long-period ordered structures, one-dimensional disorder was also prevalent in SiC.

During the concluding session it was proposed to bring out the conference proceedings which will be dedicated to the memory of P. M. de Wolf for his pioneering contribution to this field. The proceedings will be published as a special issue in *Ferroelectrics*. The next international meeting is scheduled to be held in Brazil in 2003.

**A. K. Pramanick and N. K. Mukhopadhyay**<sup>†</sup>, Center of Advanced Study, Department of Metallurgical Engineering, Institute of Technology, Banaras Hindu University, Varanasi 221 005, India

<sup>†</sup>For correspondence.

(e-mail: mukho@banaras.ernet.in)

## RESEARCH NEWS

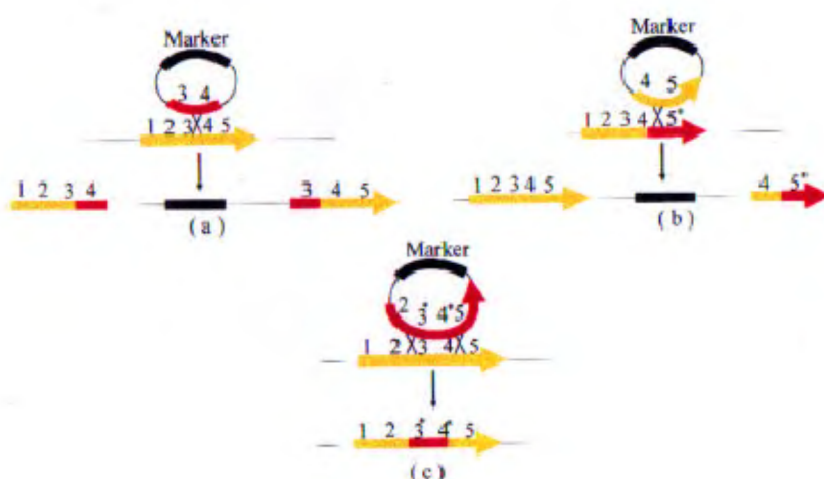
# Gene targeting: Exciting breakthroughs in flies and mammals

*Hina Patel and Pradip Sinha*

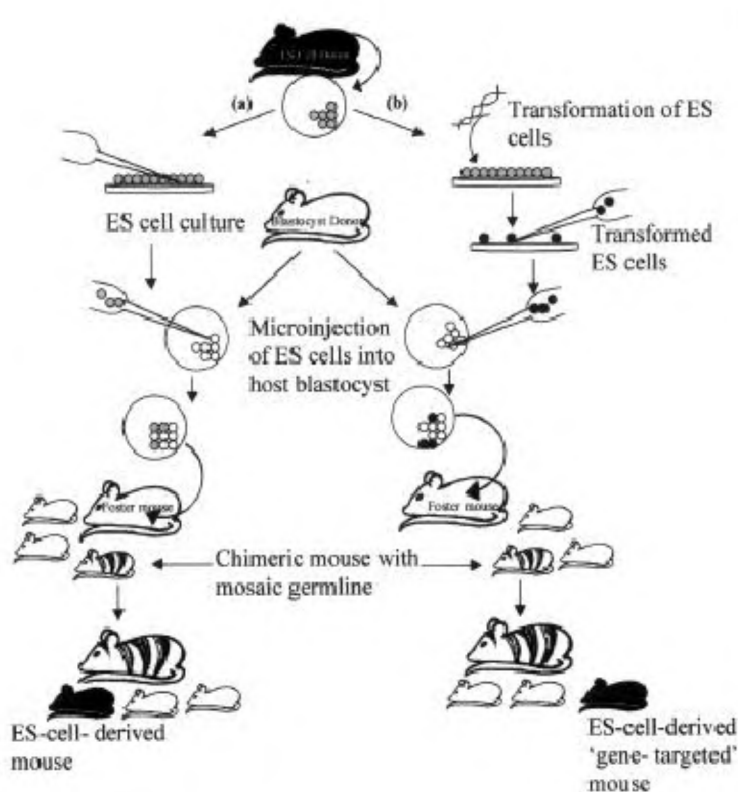
One of the goals of genetic engineering is to transfer cloned genes in the germ-line of desired organisms. This is done by transfer of exogenous DNA, or a

transgene, into a developing embryo or into the nucleus of an egg which then integrates into the host genome. Integration of a transgene in the host genome

in this case is a non-homologous recombination event since the former does not generally carry sequences matching those of the recipient organism. Ran-



**Figure 1.** Strategies for gene targeting. A single crossover event within the region of homology between the recipient genome and the vector DNA results in the integration of the latter into the host genome. Depending on the homology the recombination event can disrupt a gene (**a**) or correct its mutation (Asterisks mark the mutant DNA sequences); **b**, A double crossover event results in the replacement of the sequence on the host genome with that of the transgene; **c**, This strategy can be used for both gene 'knock-in' and 'knock-out'. Gene targeting can be planned by these strategies of recombination.



**Figure 2.** Gene targeting in mice; **a**, Embryonic stem (ES) cells can be isolated from donor mouse (black coat colour) blastocysts, cultured as a cell line and then reintroduced in the recipient mouse (white coat colour) blastocyst (left panel) before its final transplantation into the uterus of a foster mouse. The mosaic embryos develop into chimera which can be identified based on its mosaic coat colours. If the germ cells of a chimera are mosaic, i.e. carry both host and donor cell types, then the progeny mice derived from donor germ cells can be identified on the basis of uniform coat colour (black). Gene targeting in mice involves specific manipulation of the ES cells before their transplantation into host blastocysts; **b**, Cultured ES cells are transformed with the desired DNA and recombinants are selected. Subsequent step of ES cell transfer and development of the chimera is identical to that shown in (**a**).

dom integration of a transgene in the host genome, however, is not a desirable situation, particularly when one wishes its proper developmental expression. The transgene often finds itself in alien chromosomal surrounding in the host genome to which its expression remains highly sensitive. Depending on the site of its integration, the transgene could thus be misexpressed or even silenced completely. Further, random integration of the transgene also means that a desired gene in the host genome cannot be precisely targeted for integration of the transgene, i.e. targeted inactivation of a gene or simply a gene knockout. Targeted gene insertion or briefly, gene targeting, as it is popularly called, demands conditions for homologous recombination. This was achieved in mice over a decade ago<sup>1</sup>. In other model organisms, gene targeting remained largely elusive. Two long awaited breakthroughs in these areas were recently reported in succession – one in the fruit fly, *Drosophila*<sup>2</sup> and the other in sheep<sup>3</sup>. These innovations are expected to usher in a new era in animal transgenesis and break new grounds in gene manipulations. However, first a brief prelude to the historical and technical background to these techniques.

In its simplest outline, gene targeting entails homologous recombination of donor and host DNA that results in an insertion of the former within the host gene of interest (Figure 1 *a, b*) or in a replacement the latter (Figure 1 *c*). Targeting is more efficient with linear than with circular DNAs. A homology of about 5 kb DNA between the transgene and the target host gene is estimated to produce at least one homologous recombination event. However, a homology of as little as 25–50 bp too is reported to be sufficient for homologous recombination in some instances<sup>4</sup>. Minimum homology required for gene targeting varies in different organisms. Further, while gene targeting is direct in unicellular organisms, a meaningful gene targeting in higher animals demands homologous recombination in the cells of the future adult germ cells of the recipient embryos to ensure inheritance. Germ cells, unlike their somatic counterparts, however, are generally inaccessible to direct DNA manipulations in most of the organisms. Thus the challenge that one contends with in gene targeting is that of the im-

providizations necessary for homologous recombination in the germ cells.

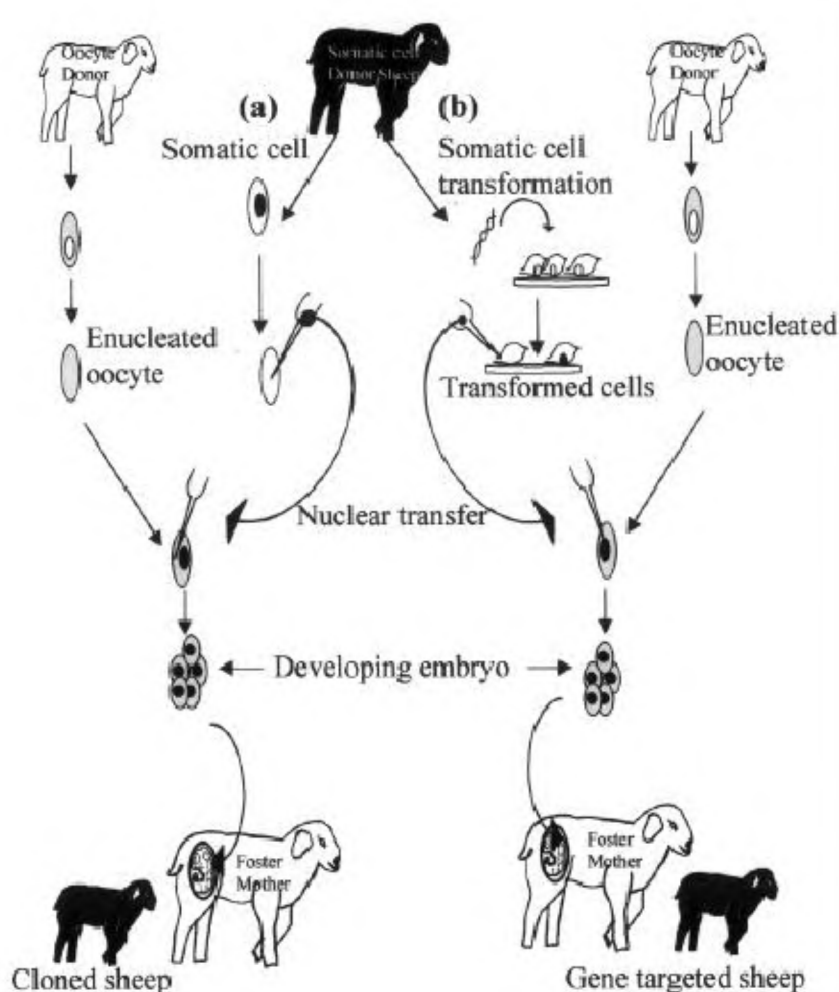
The technique of embryonic stem (ES) cell cultures and their transfer into host blastocyst for development (Figure 2a) is the forerunner for gene targeting technique in mice<sup>6</sup>. Its later improvisation, namely, transfection of ES cell before their transfer into host blastocyst (Figure 2b) finally led to gene targeting in mice<sup>1</sup>. Thanks to gene targeting, the last two decades have seen immense popularity of the mouse model in the study of genetic regulation in embryonic development. Gene targeting has also opened the mouse model to study the genetics of human disorders and gene therapy.

Success with gene targeting in mice stimulated considerable enthusiasm to develop similar strategies in other animal models. Concerted efforts were made to isolate ES cells from various model organisms. Surprisingly, this turned out to be a tough proposition in a number of live stocks including sheep, for instance, where conclusive evidence of isolation of ES cell lines remained elusive. Fortunately, the sheep model turned out to be amenable to normal development following transplantation of a somatic nucleus in an enucleated oocyte (Figure 3a). This technique owes its origin to the classical experiments of Gurdon in *Xenopus*<sup>7</sup> which showed that adult frog could be derived by transplantation of nucleus from somatic cell into enucleated eggs. A comparable breakthrough, described as the cloning of Dolly<sup>8</sup>, served as a forerunner of final gene targeting in sheep. McCreath and co-workers<sup>3</sup> transfected cultured sheep fibroblast cells, in a manner reminiscent of transformation of mouse ES cells, before transferring their nuclei into enucleated host eggs (Figure 3b). The transgene, human *alpha* (1) *antitrypsin* was integrated at the host target gene *alpha* 1 (I) *procollagen*<sup>2</sup> in a manner of the gene replacement strategy explained in Figure 1b. The ES-cells-based gene targeting, as practiced in mice (Figure 2), was thus skillfully sidestepped in sheep using the strategy of transformed fibroblast cell before transferring their nuclei for cloning.

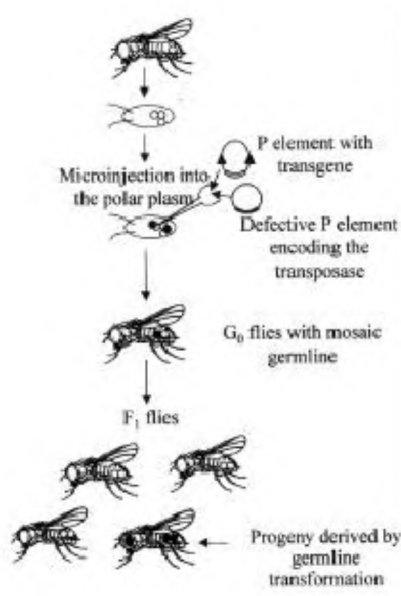
If one were to imagine gene targeting in flies in a manner of that of mice, then transformation of the pole cell in *Drosophila* could have been the closest equivalent to manipulation of ES cells

in mammals. Pole cells, the future progenitors of the adult germ cells, are sorted out early from the rest of the developing embryos and can be transplanted from donor to an irradiated host embryo<sup>9,10</sup>. Fly transformation, however, did not take this route of manipulation of pole cells and, instead, took a fundamentally distinct fashion of gene transfer based on vectors carrying its P transposable element (Figure 4). Germ-line transformation in flies was achieved by the use of Pelement which, aided by its transposase enzyme, mobilizes itself in the fly genome<sup>11</sup>. Transposase apart, the P element has an

absolute requirement of its intact 31 bp terminal repeat sequences. Taking these facts into consideration, two sets of plasmids were designed, one carrying the transposase gene but without intact 31 bp inverted repeats and the other where the gene to be transferred was placed between the 31 bp flanking repeats. Co-injection of both these vectors in the polar plasm ensured that the P vector integrates in the germline of the adult flies derived from the injected embryos<sup>11</sup>. The ease of P element mediated gene transfer revolutionized fly genetics and much of its current success can be traced to the power of this vec-



**Figure 3.** Nuclear transplantation and gene targeting in sheep. **a**, The nuclear transplantation technology includes injection of previously enucleated oocyte derived from the recipient sheep with the nucleus derived from adult somatic cell of a donor sheep. Some embryos derived from the microinjected egg, following implantation into a foster ewe, will develop into lambs which are clones of the donor sheep. **b**, Gene targeting achieved in sheep involved a modification in the sheep cloning technique in that the somatic cells (cultured fibroblasts) of the donor sheep were first transfected with the DNA of interest which was designed for gene targeting (see Figure 1c). Nuclei of the transformed fibroblast cells were then injected into enucleated oocytes. The rest of the technique is identical that shown in (a).



**Figure 4.** Fly transformation. Transformation in the fruitfly is done by microinjection of two P element vectors – one carrying the gene of interest flanked by the 31 bp repeats of the P element and the other carrying the gene coding for transposase, but without intact flanking repeats. The vectors are injected in the polar plasm of the early embryos to target the future adult germ cells for transformation. Gonads of the adults derived from the injected embryos are mosaic of transformed and non-transformed germ cells. Transformed progeny (dark eye colour) from these flies can then be derived by suitable crosses.

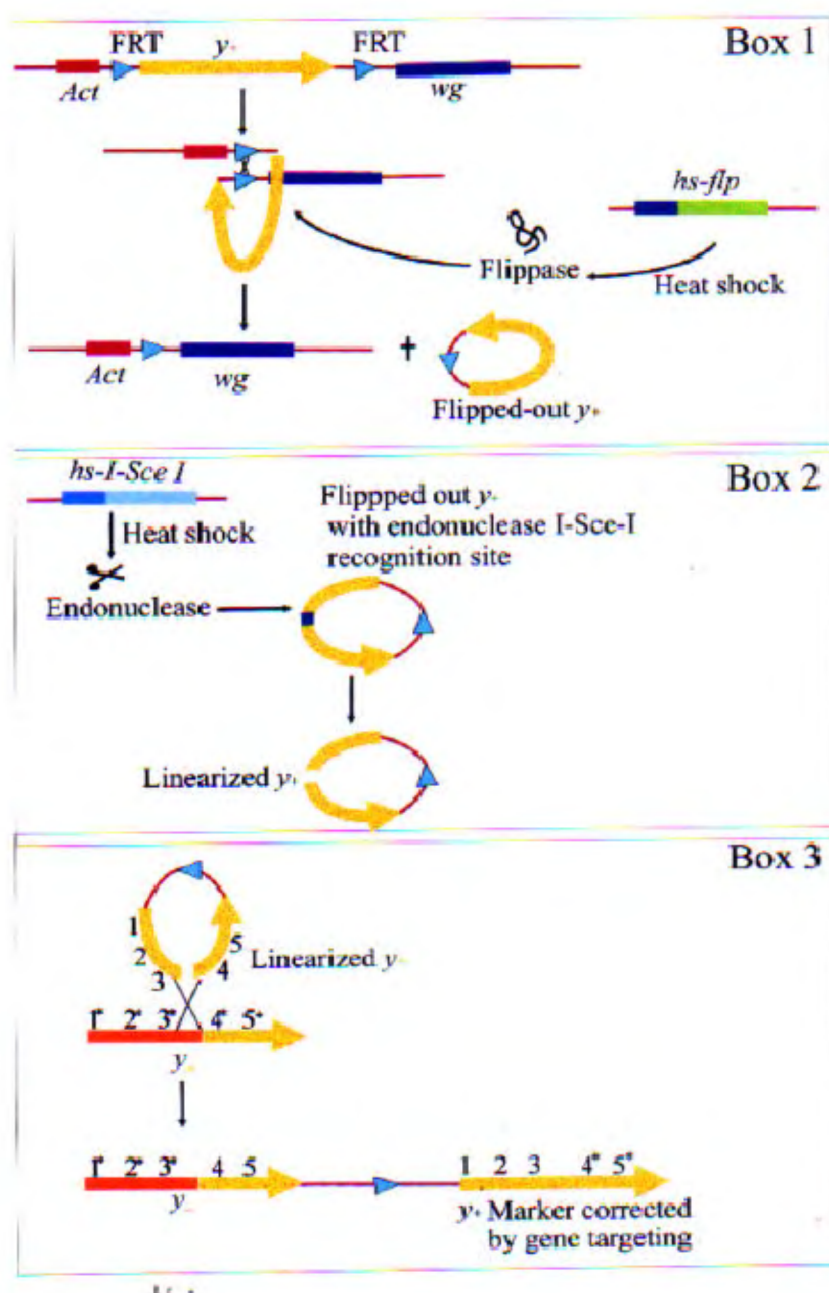
tor. Ironically, P mediated gene transfer stood in the way of gene targeting in flies. The P element usually integrates at preferred 8 bp target sites which are scattered all over the genome<sup>12</sup>. Thus during P mediated fly transformation, the sequence of the gene being carried by the vector is of no consequence so far as its choice of genomic targets is concerned. The integration of the chimeric vector in the fly genome thus remains largely random and, of course, nonhomologous. P mediated fly transformation technique is thus antithesis of homologous recombination and therefore gene targeting. This barrier to gene targeting imposed by the P vector was finally broken by Golic and co-worker<sup>2</sup>. Golic's innovation stands out for the fact that he could achieve gene targeting in the flies not by sidestepping P mediated transformation but by its clever combination with the yeast flippase (FLP) mediated recombination.

To appreciate the nitty gritty of Golic's strategy of gene targeting, a brief account of the use of the yeast FLP in fly genetics would be necessary. Yeast flippase can mediate recombination at its target sequences called the FRT (flippase recombination target) when the latter are placed in suitable orientation and positions for pairing in *cis* or in *trans*. Using this strategy, for instance, a marker placed between two tandem repeats of FRTs could be 'flipped out' (Box 1, Figure 5) by transiently activating expression of the flippase gene from a transgene (*hs-flp*). This strategy was first devised by Struhl and Basler<sup>13</sup> to activate a fly gene, *wingless* (*wg*), in somatic clones such that when the marker ( $y^+$ ) is flipped out, the flanking DNA segments get spliced together to place a constitutive *actin* promoter upstream of the coding region of *wg* (Box 1, Figure 5). Golic saw a clever possibility in this strategy. The  $y^+$  marker (which confers the wildtype body colour), when flipped out, floats as a circular DNA fragment. What if this circular DNA were to be linearized in the germline (Box 2, Figure 5) of the transgenic flies? The linearized  $y^+$  transgene could then target a  $y^-$  marker (mutant allele of *yellow*) of the recipient fly for homologous recombination (Box 3, Figure 5). Golic precisely tried this possibility by introducing a cut site for the endonuclease I-Sce I on the  $y^+$  transgene and providing for transient expression of Scl from another transgene (*hs-I-Sce I*). In a  $y^-$  mutant fly carrying all the three transgenes, namely  $y^+$ , *hs-I-Sce I* and *hs-flp*, the preliminary steps required for gene targeting, i.e. the flip-out of  $y^+$  and its linearization could be induced by a transient heat shock during embryonic and larval development. Final recombination of the  $y^+$  with the endogenous  $y^-$  then follows as matter of probability. Gonads of adults derived from the heat shocked larval cultures are mosaic for two broad categories of gametes – one carrying intact copy of the endogenous  $y^-$  gene and the other where the  $y^-$  marker is targeted for recombination with the  $y^+$  transgene. By suitable crosses, progeny derived from these gametes carrying the 'targeted'  $y^+$  marker can be easily identified. Golic could show extensive evidence of targeted insertion of  $y^+$  transgene (nearly 1 out of 500 progeny examined – a very

high success rate!) by a variety of recombination events. Two important elements are thus at work in Golic's gene targeting technique – one for flipping out and the other linearization of the  $y^+$  transgene. Linearization of the transgene was one of the key factors for enhancing gene targeting in Golic's strategy. Once the transgene is flipped out and linearized, gene targeting is only a matter of course.

Gene targeting can be used as a powerful tool to address a number of questions in fundamental and applied biology. It can be used to introduce mutations in a gene to make it inactive or modify its activity. Conversely, it can also be used to replace an inactive copy of a gene with a functional one, or to express foreign genes in an organism. With the expanding list of organisms whose genomes are sequenced, there is now an explosion of cloned sequences whose functions are yet to be elucidated. Disrupting these sequences and creating their knockouts in model organisms could give clues to their developmental roles. New frontiers are sure to open up for gene therapy of various genetic disorders in humans. The potentials of the fly as a model for study of human diseases like Huntington's disease<sup>14</sup> and Parkinson's disease<sup>15</sup> have already been realized. With the fly genome uncovering a large homology of its genes with that of humans, including cancer genes<sup>16</sup>, the development of the fly model for study of human disease is bound to be swift.

The breakthroughs in gene targeting in flies and sheep carry the seeds for many farfetching applications. These techniques can, in principle, be employed to any species of animals. Transposon-based transformation in mediterranean fruitfly *Ceratitis capitata*<sup>17</sup>, yellow fever mosquito *Aedes aegypti*<sup>18,19</sup>, flour beetle *Tribolium castaneum*<sup>20</sup> and human malaria mosquito *Anopheles stephensi*<sup>21</sup> have been achieved. Gene targeting in these insects, in a manner analogous to that of *Drosophila*, is certainly not a distant possibility. For the animal biotechnologists too it is a time to rejoice. There are more good news in the mammalian models. Following the example of sheep, cloning in livestock animals like goat<sup>22</sup>, cow<sup>23</sup> and pig<sup>24</sup> have been reported. Gene targeting in these livestock would make their selective



**Figure 5.** Gene targeting in flies. The different steps leading to targeted insertion of a  $y^+$  transgene to a mutant  $yellow$  ( $y^-$ ) marker are shown in the Boxes 2 and 3, while Box 1 explains the origin of the 'flip-out' technique. Box 1. Flip-out technique of Struhl and Basler<sup>13</sup>. Flippase mediated excision of a transgene ( $y^+$ ) flanked by two direct FRT repeats. Note that while the  $y^+$  marker is excised as a circular DNA, in the genomic DNA an *actin* promoter is fused to the *wg* gene. Box 2. Gene targeting by linearization of flipped out transgene. In Golic's gene targeting strategy,  $y^-$  flies carried a redesigned  $yellow$  ( $y^-$ ) transgene, i.e. with a *I-SceI* cut site so that the endonuclease provided from another transgene (*hs-I sceI*) cuts the 'flipped out'  $y^+$  for its linearization. Box 3. Recombination of linearized transgene with target gene of host. Recombination between the linearized transgene ( $y^+$ ) with the region of homology with the endogenous  $y^-$  marker produces a corrected version of the  $y^+$  marker (right) and at the same time generates a duplicated mutant  $y^-$  marker (left). This is only one of the several types of recombination events that Golic could observe in his gene targeting experiments. The steps shown in Boxes 2 and 3 are induced in the germline of a  $y^-$  mutant animal which carry all the three transgenes [ $y^-$  (with *I-SceI* cut site), *hs-flp* and *hs-I-SceI*] by brief heat shock during embryonic or larval development.

breeding, for a number of generations, no longer an absolute necessity. Not surprisingly, a mini revolution is now at hand in the pharmaceutical sector – trials are being made to overexpress proteins of therapeutic value in milch animals. To say that a lot of animals can now hope to enjoy the privileges that have been, until recently, solely that of mouse would not be an exaggeration.

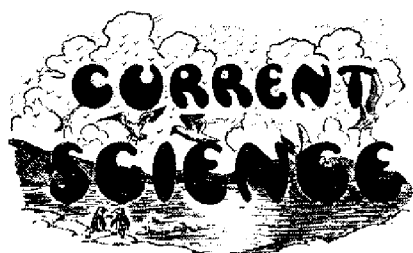
1. Mansour, S. L., Thomas, K. R. and Capecchi, M. R., *Nature*, 1988, **336**, 348–252.
2. Rong, Y. S. and Golic, K. G., *Science*, 2000, **288**, 2013–2018.
3. McCreath, K. J., Howcroft, J., Campbell, K. H. S., Colman, A., Schnieke, A. E. and Kind, A. J., *Nature*, 2000, **405**, 1066–1069.
4. Capecchi, M. R., *Trends Genet.*, 1989, **5**, 70–76.
5. Gordon, J. W., Scangos, G. A., Plotkin, D. J., Barbosa, J. A. and Ruddle, F. H., *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 7380–7384.
6. Bradley, A., Evans, M., Kaufman, M. H. and Robertson, E., *Nature*, 1984, **309**, 255–256.
7. Gurdon, J. B., *J. Embryol. Exp. Morphol.*, 1962, **10**, 622–641.
8. Wilmunt, I., Schnieke, A. E., McWhir, J., Kind, A. J. and Campbell, K. H., *Nature*, 1997, **385**, 810–813.
9. Okada, M., Kleinman, I. A. and Schneiderman, H. A., *Dev. Biol.*, 1974, **37**, 43–54.
10. Illmensee, K. and Mahowald, A. P., *Proc. Natl. Acad. Sci. USA*, 1974, **71**, 1016–1020.
11. Rubin, G. M. and Spradling, A. C., *Science*, 1982, **218**, 348–353.
12. O'Hare, K. and Rubin, G. M., *Cell*, 1983, **34**, 25–35.
13. Struhl, G. and Basler, K., *Cell*, 1993, **72**, 527–540.
14. Jackson, G. R., Salecker, I., Dong, X., Yao, X., Arnheim, N., Faber, P. W., MacDonald, M. E. and Zipursky, S. L., *Neuron*, 1998, **21**, 633–642.
15. Feany, M. B. and Bender, W. W., *Nature*, 2000, **404**, 394–398.
16. Rubin, G. M. *et al.*, *Science*, 2000, **287**, 2204–2215.
17. Loukeris, T. G., Livadaras, I., Arca, B., Zabalou, S. and Savakis, C., *Science*, 1995, **270**, 2002–2005.
18. Coates, C. J., Jasinskiene, N., Miyashiro, L. and James, A. A., *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 3748–3751.
19. Jasinskiene, N., Coates, C. J., Benedict, M. Q., Cornel, A. J., Rafferty, C. S., James, A. A. and Collins, F. H., *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 3743–3747.

20. Berghammer, A. J., Klingler, M. and Wimmer, E. A., *Nature*, 1999, **402**, 370–371.
21. Catteruccia, F., Nolan, T., Loukeris, T. G., Blass, C., Savakis, C., Kafatos, F. C. and Crisanti, A., *Nature*, 2000, **405**, 959–962.
22. Baguisi, A., Behboodi, E., Melican, D. T., Pollock, J. S., Destrepes, M. M., Cammuso, C., Williams, J. L., Nims, S. D., Porter, C. A., Midura, I., Palacios, M. J., Ayres, S. L., Denniston, R. S., Hayes, M. L., Ziomek, C. A., Meade, H. M., Godke, R. A., Gavin, W. G., Overstrom, E. W. and Echelard, Y., *Nature Biotechnol.*, 1999, **17**, 456–461.
23. Wells, D. N., Misica, P. M. and Tervit, H. R., *Biol. Reprod.*, 1999, **60**, 996–1005.
24. Polejaeva, I. A., Chen, S., Vaught, T. D., Page, R. L., Mullins, J., Ball, S., Dai, Y., Boone, J., Walker, S., Ayares, D. L., Colman, A. and Campbell, K. H. S., *Nature*, 2000, **407**, 86–90.

*Hina Patel and Pradip Sinha\* are in the Drosophila Stock Center, School of Life Sciences, Devi Ahilya Vishwavidyalaya, Khandwa Road, Indore 452 017, India*

\*For correspondence.  
(e-mail: psinha@mantraonline.com)

## From the Archives



Vol. III] NOVEMBER 1934 [NO. 5

### Sir James Jeans and the New Physics

The Presidential Address of Sir James Jeans before the British Association is a fascinating piece of work. Most of it is taken up with a presentation of those aspects of modern physics which have influenced modern scientific outlook – as envisaged by Jeans. In the first place, he makes a clear-cut distinction between the methods of the classical physicist and of his modern successor. The former was keen on trying to construct a mental picture whose elements were derived from objects of every-day experience such as ‘billiard balls, jellies and spinning tops’. It is because of this tendency on the part of the ‘old-fashioned’ physicist to visualise a concrete model in his explanation of phenomena, that classical theories or modifications of such theories on classical lines could not be made to embrace the new facts of observation. According to Jeans, the changed outlook of the modern physicist consists in the following: The content of a set of physical measurements is a set of numbers, each number being a ratio. For instance, to take an example given by Jeans, when we say that the wavelength of a certain radiation is so many centimetres we mean that it is a certain multiple of a centimetre, and since we do not

know or rather can never know what a centimetre is in itself, the significant fact in the statement ‘so many centimetres’ is only its numerical part. Once we concede this, it naturally follows that our theoretical picture of the phenomenal world, which consists in synthesising measured data must be mathematical in form.

The solid rock on which the modern physicist builds is ascertained fact and the bricks used in the construction are the ‘observables’. For instance, in the wave theory of light, the solid fact is represented by the word ‘wave’, and the ether with which the classical physicist filled space, space itself and time, are man-made decorations and do not form part of nature. The same is the lot of the space-time continuum of the theory of relativity, for the General Theory shows that it ‘can be crumpled and twisted and warped as much as we please without becoming one whit less true to nature – which of course can only mean that it is not itself part of nature’. The entire knowledge of the outer world comes to our minds through the frame-work of space and time and their product the space-time continuum, as it affects the senses. However important the frame-works may be, they do not form part of nature but are purely mental constructs. The same is the fate of matter. It is as much a pure assumption as ether and is an ‘unobservable’. Classical Physics was based on the hypothesis that matter existed in space and that its history was mechanistically determined for all time, time being independent and objective. The cardinal weakness in this outlook of the classical physicist was that the role given to the mind was that of a passive onlooker without any influence on what it observed. According to Jeans, what the modern physicist has set before himself is the task of studying the impressions that

he gets through ‘the gateways of knowledge’ (i.e. the senses) and not what lies beyond. He is concerned with appearance rather than with reality.

In fact, no satisfactory answer to the fundamental difficulty which one encounters in all forms of extreme subjective idealism, has yet been offered by any philosopher; neither does modern Physics indicate a satisfactory way of meeting it. To Sankara, the famous Indian philosopher, both our perceptions and the things perceived are illusory appearances spread over an unchanging underlying reality. Our perceptions have no higher degree of reality than the things perceived. So in his system the idea that all persons see the same objects is in the mind and therefore is itself illusory.

‘The old physics,’ says Jeans, ‘imagined it was studying an objective nature which had its own existence independently of the mind which perceived it which indeed had existed from all eternity whether it was perceived or not.’ One would infer from this that there is no objective world existing independently of the perceiving mind. How different from this attitude is the view of Max Planck – one of the most prominent among the makers of modern physics! Says Planck: “A science that starts off by predicting the denial of objectivity has already passed sentence on itself.” According to Planck, one of the fundamental theorems of physical science is that there is a real world which exists independently of our act of knowing. So the reader of Jeans’ fascinating address must not forget that there are prominent physicists who differ fundamentally from him on the philosophical implications of the revolutionary changes that have taken place in the domain of Physical Science.