Welcome to the news

Welcome to the new and expanded *Update* section of *Drug Discovery Today*. As part of our committed and continued drive to keep the discovery and development community fully aware of the current global picture of R&D, we have expanded the overall coverage of *Update*.

The new format of *Update* includes expanded *News* and *News in Brief* sections that will provide a supplementary focus on cutting-edge drug targeting and delivery, gene therapy, vaccine development, clinical trial progress and tissue engineering. A *People* section will also be introduced, enabling you to keep abreast of the movements, whereabouts and achievements of the names in the industry. Moreover, we have launched two new core sections, *Features* and *Discussion Forum*.

Features will include interviews with key people either directly involved or associated with the industry; we have kicked off this section by interviewing two men currently in the R&D limelight, Craig Venter (Celera Genomics) and David Bentley (Sanger Centre). This section will be supplemented by our new, regular columnist, Raymond Rowe (AstraZeneca). His 'Private prescription' column will bring a lighter element to the journal and will brighten your day by giving unusual, thought-provoking perspectives on aspects of the industry, occasionally with a humorous touch.

The *Discussion Forum* is where you, the readers, can 'chew the fat' with others about industry-related matters. Here, you can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. The section is designed for rolling discussions and reply letters will be published for as long as the discussion continues. When submitting your letter, please provide your full details; however, if you wish, you may remain anonymous or even assume a pseudonym. Publication of letters in this section is however subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views you provide are intended to be those of your own and are not necessarily intended to represent those of the company you work for. Moreover, the views published here do not reflect the views of Elsevier, *Drug Discovery Today* or its editorial team.

If you have any suggestions or would like to submit topics for the *News* section or letters for the *Discussion Forum*, please get in touch with me at Rebecca.Lawrence@current-trends.com (tel: +44 7611 4143, fax: +44 7611 4485). I look forward to reading your contributions and hope you enjoy reading the revitalized section.

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News & Features Editor

Mouse model for Burkitt's lymphoma will aid understanding and therapy

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Scientists have developed a mouse model for Burkitt's lymphoma (BL), a solid tumour of B lymphocytes. The genetically engineered mouse is the first to develop lymphomas with striking similarities to human BL. The new mouse model is hoped to aid understanding of the molecular and genetic components of this cancer and other lymphomas, as well as permitting the testing of new treatments.

Burkitt's lymphoma

Two variants of BL have been characterized. The African (endemic BL) variant is associated with the Epstein-Barr virus (EBV) in 95% of cases and accounts for over half of all childhood cancers in Africa (approximately 1 in 50,000 children per year). The non-African form (sporadic BL) is rarely associated with EBV and has a tenfold lower frequency

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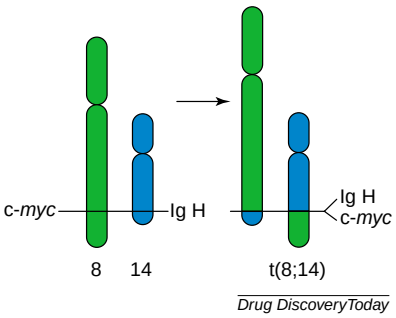

Figure 1. A reciprocal chromosome translocation involving the *myc* oncogene is associated with BL.

worldwide. However, the incidence of the sporadic form is rising, particularly in adults, owing to the spread of AIDS and other immunocompromising diseases.

Regardless of geographical origin, BL is characterized by a reciprocal translocation that transposes the proto-oncogene *MYC* from its normal position on chromosome 8 to one of the immunoglobulin (Ig) loci. The *MYC* gene is juxtaposed with antibody heavy chain (IgH) genes on chromosome 14 (Fig. 1) or, less commonly, with antibody light chain (IgL) genes on chromosome 2 (Igκ) or 22 (Igλ).

The MYC protein normally acts as a signal for cell proliferation and its expression is tightly controlled by its own closely linked regulatory sequences. The translocations obviate this strict regulation, placing the gene instead under the control of sequences that determine expression of Ig genes in normal B cells. As a result, the gene becomes transcriptionally activated and deregulated which, combined with secondary changes in other genes, ultimately results in a clone of cancer cells[1].

Developing a BL mouse model

To develop an appropriate mouse model of the disease, scientists had to elucidate the precise mechanism of *MYC* activation and deregulation, as influenced by the Ig sequences that become linked to it by the translocations. Research efforts thus concentrated on:

- Developing constructs with MYC linked to Ig regulatory sequences and determining which Ig elements were required to induce the pattern of MYC deregulation seen in BL cells[2].
- Producing transgenic mice by introducing these constructs into mice, then
- Assessing the mice for the features of BL-specific MYC activation.

Initial studies involved the development of a construct comprising *MYC* coupled with the IgH intron enhancer (Eμ). However, mice developed tumours bearing a lymphoblastic lymphoma (LL), rather than a BL, morphology[3]. The LLs in these mice were shown to comprise primarily precursor B cells rather than the mature B cells seen in human BL.

Herbert Morse, Chief of the Laboratory of Immunopathology in NIAID (Bethesda, MD, USA), led a collaborative group evaluating the effects of Igλ regulatory sequences on a linked *MYC* transgene. He explains 'The Eμ-*MYC* construct contained only the IgH intronic enhancer, which is often deleted in BL. The λ-*MYC* differs in having a combination of enhancer-like elements that function to establish locus control in B cells *in vitro*[2]. This function now appears to hold in our mice *in vivo*[4].'

The BL mouse model

The group recently showed that mice transgenic for the Igλ-*MYC* construct developed lymphomas similar to human BL (Ref. 4). Diffusely infiltrating lymphomas with the characteristic 'starry sky' appearance (due to macrophage ingestion of dead cancer cells) of BL occurred in multiple founders (i.e. transgene-positive mice that arise from DNA-inoculated fertilized ova) and an established line (i.e. transgenic mice that arise from transgenic females), indicating independence from positional effects, a hallmark of locus control.

Genomic DNA and Southern blot hybridization analyses of IgH organization showed that monoclonal tumors developed from a polyclonal background of cells uniformly expressing *MYC*. Fluorescence-activated cell sorter (FACS®) analyses of cell surface antigen expression demonstrated the lymphomas were of mature (sIg^+) B cells and that they were positive for, for example, IgM and CD19, but were negative for CD5 and T cell markers CD4 and CD8, a phenotype similar to human BL.

The next step

Marshall Licthman, Executive Vice-President for Research and Medical Programs, The American Leukemia and Lymphoma Society (White Plains, NY, USA), comments: 'This model should lead to further insights into the mechanism of lymphomagenesis and also permit correlative studies of specific genic disarray, microenvironmental factors and the type of lymphomatous transformation that result.'

Morse reports that their group is using the mouse model to study the pathogenesis of BL; in particular, they are looking at the role of 3′ enhancers of the Ig loci in the development of the disease. They are developing κ- and IgH-*MYC* constructs, with locus control regions, to assess their effects. A further lymphoma, plasmacytoma (PCT), arises from the same type of chromosomal translocations as BL, but specific environmental effects are thought to induce PCT in preference to BL. The group can now use the mouse model to examine these environmental effects and thus the pathogenesis of PCT.

References

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