100 YEARS AGO

In the New Year's number of *Nature* there appeared an account of a basil, *Ocimum viride*, a plant which is known to the natives of Nigeria as a protection against mosquitoes. Captain Larymore, by whom this information was first obtained, in a recent letter to the *Times* mentions that he has brought home a plant which he has presented to the authorities of the Kew Gardens, and that it may be seen there. He also states that the natives believe in its efficacy when taken as an infusion in cases of malarial fever. Further evidence is offered in another letter to the *Times* by Sir George Birdwood as to the knowledge widely spread among the Hindus of these qualities of the basils, which occur wild, and are generally cultivated in India. Thus, during the formation of the Victoria Gardens in Bombay, the workmen were attacked both by mosquitoes and malaria, when upon the recommendation of the Hindu manager basil plants were placed round the gardens, with the result that the unhealthy nature of the locality was effectually changed.

From *Nature* 14 May 1903.

50 YEARS AGO

At La Rocque, in Jersey, the spring tides go out about two miles leaving many large lagoons with sandy bottoms and depths of from two to four feet of water. Here we often spear flat-fish, plaice, soles, etc., sometimes getting as many as twenty in a tide; here also may be found spider crabs (*Maia squinado*) which are often taken in Jersey for food, but which are considered out of season in the autumn. In September last, the catches of flat-fish were down to about half a dozen, owing to the number of octopuses that continually disturbed the bottom and kept the fish moving. The spider crabs had collected into large heaps, about two feet high and three feet in diameter, with their legs so entangled as to make it difficult to separate a crab from a heap. The octopuses captured some from the outside of the masses, but the greater number survived, and day after day the heaps remained. None of the fishermen to whom I have spoken of this behaviour on the part of spider crabs had ever noticed it previously. The octopuses have now (October) moved to deeper water, and the crabs too have disappeared to their winter quarters.

From *Nature* 16 May 1953.

depletion of the HSC pool, so HSCs generally generate at least one daughter that retains stem-cell properties. This ability to self-renew distinguishes HSCs from all other cell types in the haematopoietic hierarchy, and is likely to be a defining property of stem cells in other organ systems as well.

The phenomenon of self-renewal has attained almost mythical status since the 1960s, when Till and McCulloch first identified and quantified HSCs[5–7]. This early work showed, among other findings, that self-renewal is an intrinsic property of these stem cells. Yet the molecules within HSCs that control self-renewal have remained elusive. Recently, several proteins that are active during embryonic development have been shown to induce self-renewal in adults[1,2]; these include proteins from the Wnt[8,9], bone morphogenetic protein, Sonic hedgehog, and Notch families. But these molecules act on, rather than in, HSCs, begging the question of what lies downstream of them inside the stem cells. One such downstream molecule could be Hoxb4, a gene-transcription factor that, upon overexpression in HSCs, induces significant cell multiplication[10]. However, mice lacking this protein do not show defects in HSC self-renewal.

Lessard and Sauvageau[3] and Park *et al.*[4] have now found that Bmi-1, a transcriptional repressor[11], is essential to HSC self-renewal. Park *et al.* used gene-expression profiling to identify the *Bmi-1* gene as being highly expressed in HSCs in mice and humans. They, and Lessard and Sauvageau, then transplanted HSCs from the fetal liver or adult bone marrow of *Bmi-1*-deficient mice into normal mice. The *Bmi-1*-deficient HSCs generated a normal pattern of blood cells — but the contribution was only temporary, because of an inability to sustain the precursor pool. Moreover, six weeks after bone-marrow HSCs had been taken from these primary recipients and transplanted into secondary recipients, there were no *Bmi-1*-deficient cells in the secondary mice. So the cells had failed a classic test of self-renewal.

These results, together with the fact that *Bmi-1*-deficient mice die of bone marrow failure within two months of birth[12], indicate that *Bmi-1* is essential for the self-renewal of HSCs. After further gene-expression analysis and some functional studies, Park *et al.* suggest that the effects of *Bmi-1* are mediated through its repression of the genes encoding $p16^{Ink4a}$ and $p19^{Arf}$, proteins that respectively inhibit cell proliferation and enhance cell death.

Lessard and Sauvageau[3] also linked *Bmi-1* to the self-renewal of leukaemic stem cells (L-HSCs). There is strong support for the idea that cancer is a stem-cell disease[13]. The best evidence for this comes from studies of acute myeloid leukaemia (AML) in humans, in which most leukaemic cells have limited proliferative capacity and must be constantly replenished by rare, self-renewing L-HSCs[14]. So, like the normal blood system, a clone of leukaemia cells seems to be organized as a hierarchy that originates from a stem-cell pool and retains remnants of the normal developmental programme. It has also been proposed that the initial, cancer-causing ('transforming') mutations in AML occur in HSCs, rather than in lineage-committed precursors (reviewed in refs 15, 16). Self-renewal is a key characteristic of L-HSCs, and so fewer mutations would be required to generate fully leukaemic cells if they were to originate from HSCs (which can already self-renew) as opposed to precursors. This idea predicts similarities in the molecular programmes of normal and AML stem cells.

Lessard and Sauvageau tested this hypothesis by expressing the *Hoxa9* and *Meis1a* genes in mouse fetal liver cells. They had previously shown that, without the need for further genetic changes, these genes reproducibly generate mouse myeloid leukaemia with the same hierarchical organization as the human disease, and that the target for leukaemic 'transformation' in this case does indeed lie in the HSC pool[17]. They have now found[3] that these genes induced leukaemia in *Bmi-1*-deficient mice with the same kinetics and characteristics as in normal mice, implying that *Bmi-1* is not necessary for the leukaemia to begin and progress. But the L-HSCs from *Bmi-1*-deficient mice could not self-renew, resulting in far fewer leukaemic cells in the blood of primary mouse recipients and an inability to produce leukaemic cells in secondary recipients. This result clearly identifies self-renewal as an essential component of the development of leukaemia, distinct from the potent differentiation block and proliferation induced by *Hoxa9* and *Meis1a*.

The authors[3] went on to show that two known targets of *Bmi-1*, the genes encoding $p16^{Ink4a}$ and $p19^{Arf}$, could occasionally become altered in some clones of cultured *Hoxa9–Meis1a*-induced, *Bmi-1*-deficient cells. This could to some extent compensate for the loss of *Bmi-1*, resulting in sustained cell production. But the inability of these highly proliferative subclones to initiate leukaemic growth *in vivo* hints that other targets of *Bmi-1* must also be required for self-renewal.

Together, these exciting findings[3,4] should help researchers to develop methods by which to multiply human HSCs in culture. Moreover, the identification of a gene that is involved in self-renewal in both HSCs and L-HSCs lends strong support to the idea of cancer stem cells, and to the hypothesis that HSCs are the initial target for transformation in some leukaemias. I predict, however, that even lineage-committed cells might occasionally become targets for transformation, if certain cancer-causing mutations restore the self-renewal machinery. Finally,