Saporin Immunotoxins for Treating Human Hematological Malignancies

(continued from page 1)

tissue-binding specificities, and to demonstrate their selective anti-tumor activity both *in vitro* and *in vivo*. Such preclinical investigations are mandatory to justify taking an experimental drug into patients and to ensure, as far as possible, safety of the drug. A poignant reminder here was the disastrous peripheral nerve damage experienced by women with breast cancer treated with a ricin A chain-based immunotoxin which unexpectedly also targeted nervous tissue.[4] The most sensitive *in vitro* method for determining the selective cytotoxic potency of saporin-based immunotoxins is by measuring their ability to selectively inhibit protein synthesis in antigen-expressing cell lines in a dose-dependent manner. This is clearly shown in Figure 2, where increasing concentrations of two immunotoxins: anti-CD19 (BU12-Saporin) and anti-CD38 (OKT10-SAP) show decreasing protein synthesis levels in a target CD19+ CD38+ pediatric acute lymphoblastic leukaemia (ALL) cell line. Note that when the two immunotoxins were used in combination no improvement in performance was seen. When the same two immunotoxins were used individually *in vivo* in SCID mice xenografted with the same ALL cell line, they exerted therapeutic activity in line with the data obtained from the *in vitro* study. However, when the two immunotoxins were used in combination the therapeutic effect was significantly better than either individual drug used alone (Fig 3). This *in vivo* result could not have been predicted from the short-term protein synthesis inhibition assay. We have also made similar findings with *in vivo* models of human B-cell lymphoma[5] and T-cell leukaemia.[6] These observations have provided us with the longer-term goal of conducting clinical trials with combinations of different immunotoxins.

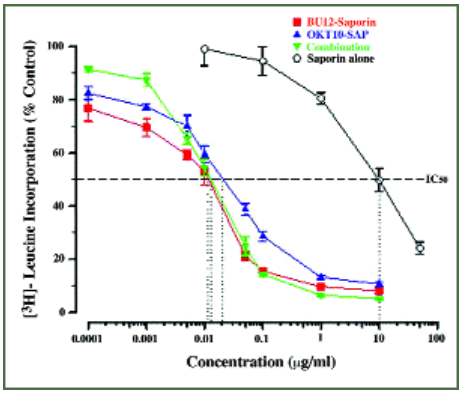

Figure 2 Protein synthesis inhibition in the CD19+/CD38+ acute lymphoblastic cell line, NALM-6, following 48h exposure to increasing concentrations of BU12-Saporin, OKT10-SAP, a combination of both immunotoxins, or saporin alone. The IC_{50} is shown as the point on the x-axis intercept representing the concentration of ITthat inhibits protein synthesis in the target cell line by 50% relative to untreated control cells. Note that the use of a combination of both ITs does not result in any increased cytotoxicity for the target cell line in this particular assay.

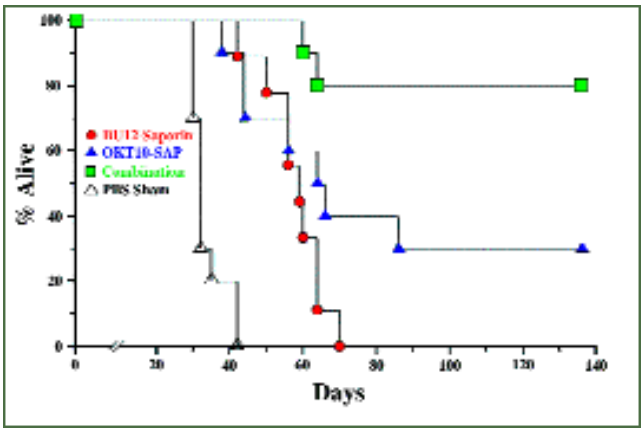

Figure 3. Survival curves of SCID mice xenografted with the human ALLcell line NALM-6 and treated i.v. seven days later with three 10-μg doses of BU12-Saporin, OKT10-SAP, a combination of both ITs (5 μg of each) or sham treated with PBS. Note that greater numbers of SCID-NALM-6 mice survive significantly longer following treatment with the IT combination.

Following preclinical evaluation my laboratory is now directly involved in two separate Phase I clinical trials with BU12-Saporin and OKT10-SAP currently underway in the United Kingdom. Working together with the United Kingdom Children's Cancer Study Group and Cancer Research UK, we are now treating children with relapsed ALL with BU12-Saporin at 11 children's cancer units and adult myeloma patients with OKT10-SAP at two centers. These are early phase dose escalation studies whose primary aims are to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) for both saporin immunoconjugates for use in subsequent Phase II studies. The secondary objective of these studies is to define the pharmacokinetic profile of these drugs in patients and to document any tumor responses.

In conventional Phase I studies, cohorts of three patients receive a fixed dose of drug and are then monitored for toxic side effects, which are carefully graded according to strictly laid down criteria. If toxic side effects occur below grade 3, then the next cohort of patients is permitted to receive the next dose

(continued on page 6)

Upcoming Events

3rd Forum of European Neuroscience (FENS)
Paris France • July 13-17, 2002 • Booth #229

Society for Neuroscience (SFN)
Orlando Florida • November 3-6, 2002