lymphomas[6]) include Bcl-x_L and Bcl-w. The chemotherapeutic agent ABT-737 promotes apoptosis in cancer cells by displacing BH3-only proteins from Bcl-2 family proteins, thereby allowing the BH3-only proteins to facilitate Bak and Bax oligomerization[4,7].

The same machinery that regulates apoptotic cell death in cancer cells is also engaged in neurons after ischemia, and contributes to ischemic neuronal death[8–11]. Thus, the observation by Ofengeim *et al.*[1] that the apoptosis-promoting agent ABT-737 reduced, rather than increased, ischemic brain injury is unexpected. The key to this observation lies in the fact that the cleavage of the C-terminal portion of the Bcl-2 family protein Bcl-x_L produces ΔN-Bcl-x_L fragments with pro-apoptotic effects[12]. The authors found that ΔN-Bcl-x_L was generated in neurons shortly after ischemia reperfusion and that ischemia-induced mitochondrial pore formation was blocked by ABT-737. Moreover, ΔN-Bcl-x_L infused directly into neurons similarly induced the formation of an outer mitochondrial membrane pore and egress of cytochrome *c*, and these effects of ΔN-Bcl-x_L were likewise blocked by co-infusion of ABT-737. In a transgenic mouse strain expressing a modified Bcl-x_L protein lacking the caspase cleavage site, as in wild-type mice treated with ABT-737, there was reduced opening of mitochondrial membrane pores and reduced neuronal death after ischemia reperfusion.

The effect of ABT-737 on neuronal mitochondrial pore formation and ischemic injury is clearly demonstrated in these studies, but the mechanism by which ABT-737 exerts these effects remains less clear. The issue is complicated by the fact that Bcl-x_L is both a regulator of caspase activation and a substrate for caspase cleavage (**Fig. 1**). As Ofengeim *et al.*[1] note, this suggests at least two possible mechanisms by which ABT-737 may affect neuronal survival: by binding to ΔN-Bcl-x_L, thereby blocking its effect on mitochondrial pore formation, and by binding to full-length Bcl-x_L (or other Bcl-2 family members), thereby preventing its cleavage and inactivation. The authors present evidence for both these processes, although how ΔN-Bcl-x_L induces mitochondrial pore formation and how ABT-737 prevents this process remain uncertain.

The question also remains as to why the anti-apoptotic effects of ABT-737 trump the expected pro-apoptotic effects of this drug in post-ischemic neurons, but not in cancer cells. This question is not addressed by Ofengeim *et al.*[1], but the relatively high Bcl-x_L expression in brain[13], and differing levels of signaling for Bak and Bax oligomerization in cancer cells and post-ischemic neurons, may contribute. Alternatively, the reduced formation of large mitochondrial pores in the presence of ABT-737 may favorably affect mitochondrial bio-energetic function after ischemia reperfusion, independent of any other anti-apoptotic effects. Unlike mitochondria in other cell types, most mitochondria in neurons are located in cell processes that are distant from the nucleus and are therefore unable to participate in the cell execution phase of apoptosis. Thus, the pro-survival effect of ABT-737 in neurons may be a uniquely neuronal phenomenon.

Can this approach be used to treat brain ischemia? Perhaps, but a practical hurdle in the treatment of brain ischemia (stroke) is that the vast majority of affected individuals do not present for medical treatment until many hours after the onset of ischemia[14]. Ofengeim *et al.*[1] found that ABT-737 can be effective when given as late as 1 h after ischemia reperfusion, but a much longer treatment window will be necessary for this to be clinically useful. Several therapeutic agents have been shown to be effective in reducing stroke size when given within a few hours of ischemia, but they lacked effect when tested in clinical trials using longer time-to-treat intervals[14,15]. In addition, caspase-mediated cell death may have a larger role in the brief (10-min) brain ischemia used in the authors' model than in the clinically more common setting of cerebral artery occlusion[11]. Future studies using other animal models and with longer post-ischemic time-to-treat intervals could more fully assess the promise of this approach for treating stroke.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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Deep thinking

One of the things that distinguish the picture on the right from a real toy ballerina is the feeling of depth that is evoked by a real object. Motion parallax is one such depth cue, when parts of the moving ballerina that are closer to the observer are more blurred than the parts that are further away. This is more obvious when a landscape is seen from the window of a moving train, when the foreground is more blurred than the background. Combined with other cues, such as binocular disparity (where the image received by each eye is slightly different and this difference depends on the distance of the object casting the image), information from motion parallax helps us to decide which things are near and which are far away.

On page 636 of this issue, Andrew Welchman and his colleagues at the University of Birmingham used functional imaging while testing their observers' perception to determine how these depth cues are combined by the brain. Although it is known that people are very good at combining these cues, there are many ways that these cues might be used by the brain. Information from each cue might be extracted independently, in separate parts of the cortex, or this information might be fused into a single measure.

To test these different possibilities, the authors showed subjects moving or stationary dot patterns that evoked a feeling of depth because of binocular disparity, motion parallax or both. They then looked for brain areas that showed the characteristic signature of extracting information from combining both the cues, rather than extracting information from each independently. They found that the visual cortical area V3B/KO fit this characteristic profile.

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