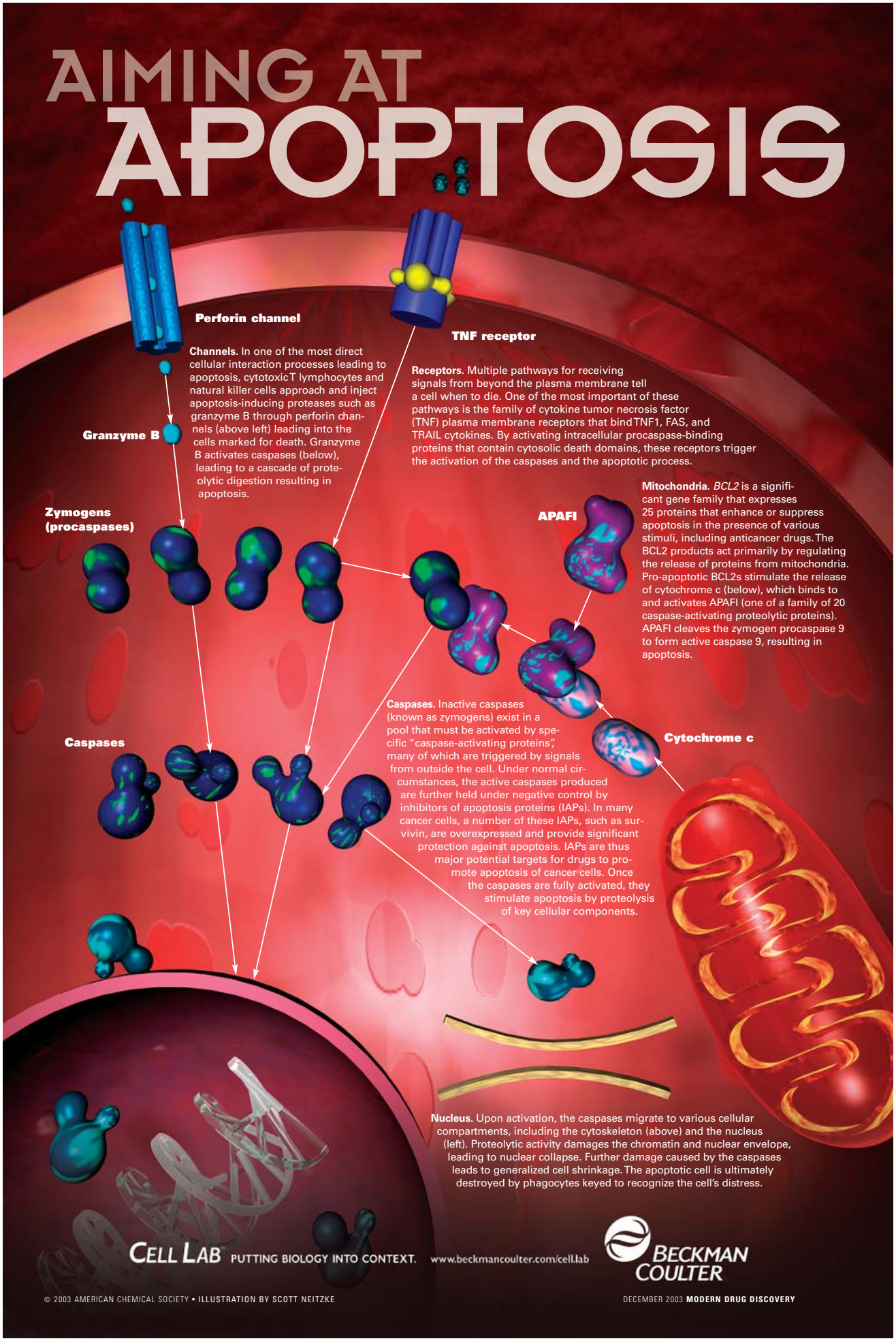
AIMING AT APOPTOSIS



Channels. In one of the most direct cellular interaction processes leading to apoptosis, cytotoxic T lymphocytes and natural killer cells approach and inject apoptosis-inducing proteases such as granzyme B through perforin channels (above left) leading into the cells marked for death. Granzyme B activates caspases (below), leading to a cascade of proteolytic digestion resulting in apoptosis.

Receptors. Multiple pathways for receiving signals from beyond the plasma membrane tell a cell when to die. One of the most important of these pathways is the family of cytokine tumor necrosis factor (TNF) plasma membrane receptors that bind TNF1, FAS, and TRAIL cytokines. By activating intracellular procaspase-binding proteins that contain cytosolic death domains, these receptors trigger the activation of the caspases and the apoptotic process.

Mitochondria. *BCL2* is a significant gene family that expresses 25 proteins that enhance or suppress apoptosis in the presence of various stimuli, including anticancer drugs. The BCL2 products act primarily by regulating the release of proteins from mitochondria. Pro-apoptotic BCL2s stimulate the release of cytochrome c (below), which binds to and activates APAFI (one of a family of 20 caspase-activating proteolytic proteins). APAFI cleaves the zymogen procaspase 9 to form active caspase 9, resulting in apoptosis.

Caspases. Inactive caspases (known as zymogens) exist in a pool that must be activated by specific "caspase-activating proteins", many of which are triggered by signals from outside the cell. Under normal circumstances, the active caspases produced are further held under negative control by inhibitors of apoptosis proteins (IAPs). In many cancer cells, a number of these IAPs, such as survivin, are overexpressed and provide significant protection against apoptosis. IAPs are thus major potential targets for drugs to promote apoptosis of cancer cells. Once the caspases are fully activated, they stimulate apoptosis by proteolysis of key cellular components.

Nucleus. Upon activation, the caspases migrate to various cellular compartments, including the cytoskeleton (above) and the nucleus (left). Proteolytic activity damages the chromatin and nuclear envelope, leading to nuclear collapse. Further damage caused by the caspases leads to generalized cell shrinkage. The apoptotic cell is ultimately destroyed by phagocytes keyed to recognize the cell's distress.