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FROM THE ANALYST'S COUCH

Apoptosis-targeting therapies

Irena Melnikova and James Golden

Abnormalities in the apoptotic cellular machinery can result in either an undesirable increase in cell numbers as exemplified in cancer, or in a damaging loss of cells as seen in neurodegenerative, autoimmune and cardiovascular diseases. Modulation of apoptosis therefore represents an attractive therapeutic approach to the treatment of many disorders¹.

Major therapeutic targets of apoptosis-based compounds include B-cell lymphoma-2 (BCL2) modulators, caspase activators and inhibitors, p53 modulators, inhibitors of apoptosis proteins, protein-kinase-pathway modulators and multiple signal-transduction regulators².

Inducers of apoptosis

The BCL2 protein exerts its oncogenic effects by inhibiting apoptosis and promoting resistance to chemotherapy. The protein is overexpressed in many types of tumours and its overexpression is correlated with poor prognosis. Oblimersen sodium (Genasense; Genta), an antisense drug in development, blocks production of BCL2 by promoting the degradation of BCL2 mRNA. Genta filed a New Drug Application (NDA) for oblimersen in December 2003 based on results of a randomized Phase III trial of oblimersen plus dacarbazine in patients with advanced melanoma. In this study, oblimersen in combination with dacarbazine versus dacarbazine produced a 51% improvement in median progression-free survival and a 72% increase in overall antitumour response rate. However, in May 2004, the FDA rejected the application citing lack of survival-benefit data and increased toxicity associated with oblimersen. Genta withdrew the NDA, reduced its workforce by 45% and terminated an oblimersen collaborative development agreement with Aventis. Some analysts predicted that oblimersen could reach blockbuster potential; clearly that remains to be seen. Genta has restructured the oblimersen programme and Phase III trials are ongoing in chronic lymphocytic leukaemia and multiple myeloma.

Receptors for tumour-necrosis factor-related apoptosis-inducing ligand (TRAIL-R1 and TRAIL-R2) are widely expressed on human tumour cells and seem to regulate the activation of caspases (see below). Tumours expressing TRAIL-R1/R2 undergo apoptosis after binding of TRAIL to these receptors. TRAIL-R

monoclonal antibodies (HGS-ETR1 and HGS-TR2J; Human Genome Sciences) mimic the activity of native TRAIL and cause cancer cells to die. The initial clinical results for advanced solid tumours and non-Hodgkin's lymphoma (NHL) presented at the annual meeting of the American Society of Clinical Oncology in 2004 demonstrate that HGS-ETR1 is well tolerated. Stable disease has been observed in a number of patients enrolled in the trials. Phase I trials of HGS-TR2J were initiated in August 2004. Human Genome Sciences plans to develop TRAIL-R monoclonal antibodies as potential treatments for a broad range of cancers.

Indirect induction of apoptosis

A large number of oncological apoptosis-promoting drugs induce programmed cell death indirectly through targeting proliferative and cell-survival cascades. Some of these drugs have already reached the market, and include imitinib mesylate (Gleevec; Novartis), a small-molecule protein kinase inhibitor; trastuzumab (Herceptin; Genentech), a monoclonal antibody against HER2; gefitinib (Iressa; AstraZeneca), a small-molecule inhibitor of epidermal growth factor receptor (EGFR); cetuximab (Erbix; ImClone Systems/Bristol-Myers Squibb), a monoclonal antibody against EGFR; and bevacizumab (Avastin; Genentech), a monoclonal antibody targeting vascular endothelial growth factor.

An emerging target: the proteasome

The proteasome is the primary component of the protein-degradation system in the cell, and is involved in the regulation of a number of cell processes, including apoptosis³. Bortezomib (Velcade; Millennium Pharmaceuticals) is the first proteasome inhibitor on the market. By blocking the activity of the proteasome, bortezomib causes the build-up of several cell-cycle and apoptosis-related proteins in the cell. One of these proteins is BAX, which promotes apoptosis by blocking the activity of anti-apoptosis protein BCL2.

Bortezomib was approved by the FDA in May 2003 for the treatment of relapsed and refractory multiple myeloma, the second most prevalent blood cancer after NHL. In the US, 45,000 people live with the disease and an estimated 14,600 new cases are diagnosed each year. The effectiveness of bortezomib is based on

response rates (the FDA reviewed bortezomib under the accelerated approval programme). There are no controlled trials demonstrating a clinical benefit, such as improvement in survival. Millennium is committed to expanding the potential use of bortezomib, with ongoing clinical trials in mantle-cell lymphoma, colorectal pancreatic, lung, breast, prostate and ovarian cancers, and NHL.

Inhibitors of apoptosis

Caspases are a family of cysteine proteases that become activated by apoptotic stimuli, and induce apoptosis in injured or diseased tissues in conditions such as myocardial infarction, stroke, sepsis, liver disease, as well as in organ transplantation. IDN-6556 (Idun Pharmaceuticals) is a broad-range caspase inhibitor designed to treat and prevent organ damage. Idun is initially pursuing liver-disease indications for this drug. A Phase II trial in patients with hepatitis C virus (HCV) infections is ongoing. Most HCV infections become chronic, resulting in liver disease and failure. In industrialized countries, HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 70% of liver transplants. Approximately 200 million people worldwide are infected with HCV, with 5 million of those in the US. The current IDN-6556 programme targets patients who have failed HCV treatment (approximately 1 million cases in the US today).

Future perspectives

The global market for therapeutic apoptosis modulators is emerging. In cancer therapy, a number of specific, targeted drugs that selectively induce apoptosis in tumour cells are already available and numerous pro-apoptotic molecules are in the pipeline. The most developmentally advanced apoptosis-inhibiting drugs are for indications such as liver disease, myocardial infarction, stroke and sepsis. However, these therapies are probably many years away from reaching the marketplace. In general, only treatments currently in Phase III clinical trials are expected to contribute significantly to the market value for therapeutic apoptosis modulators during the next 5 years. If successful, drug candidates currently in Phase II clinical trials can be expected to receive approval and reach the market some time in or after 2008. ▶

APOPTOSIS-TARGETING THERAPIES | MARKET INDICATORS

► There are a number of human diseases associated with the apoptotic pathway and cell survival (BOX 1). Many of these diseases, such as Alzheimer’s disease, rheumatoid arthritis, myocardial infarction and cancer, are directly linked with an aging population. Cancer therapeutics promoting apoptosis are already approved and being sold around the world (FIG. 1). The potential for apoptosis-targeting therapies is immense and the market opportunity will be driven by increased incidence of these diseases, demand for innovative treatments and premium pricing of novel drugs. In spite of the difficulties associated with adenoviral-based gene therapies targeting p53 and setbacks for antisense approaches, many of these drugs could achieve blockbuster status. We believe that manipulation of the apoptotic pathway shows long-term promise in treating a host of unmet medical needs (TABLE 1).

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Box 1 | Human diseases associated with apoptosis

Inhibition of apoptosis/increased cell survival

- **Cancer**
- **Autoimmune diseases:** myasthenia gravis; systemic lupus erythematosus
- **Inflammatory diseases:** bronchial asthma; inflammatory intestinal disease; pulmonary inflammation; rheumatoid arthritis
- **Viral infections**

Excess of apoptosis/increase in cell death

- **AIDS**
- **Neurodegenerative diseases:** Alzheimer’s; amyotrophic lateral sclerosis; Huntington’s; multiple sclerosis; Parkinson’s; retinitis pigmentosa; epilepsy
- **Haematological diseases:** aplastic anaemia; myelodysplastic syndrome; lymphocytopenia
- **Tissue damage:** myocardial infarction; stroke; brain and/or spinal cord injury; burns; ischaemic renal damage; polycystic kidney; sepsis
- **Other:** alopecia; muscular dystrophy

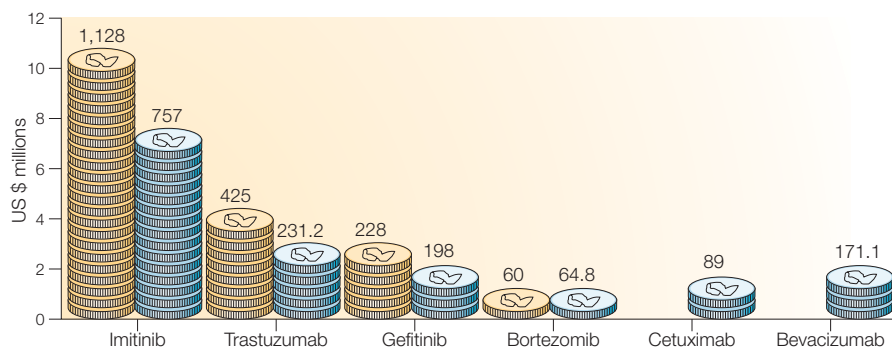


Figure 1 | Sales of apoptosis-promoting oncology drugs. Gold coins represent worldwide sales for 2003 in US \$ millions; blue coins represent worldwide sales for the first half of 2004 in US \$ millions.

Table 1 | Selected apoptosis-based drugs in development

Drug	Company	Technology	Target	Status	Indication
Oblimersen sodium (Genasense)	Genta	Antisense	BCL2	Phase III	Chronic lymphocytic leukaemia; multiple myeloma
Advexin (INGN201)	Introgen Therapeutics	Adenovirus	p53	Phase III Phase II	Head and neck cancer Breast, lung, colorectal and ovarian cancers
SCH58500	Schering-Plough	Adenovirus	p53	Phase III Phase II	Ovarian and peritoneal cancers Head/neck and liver cancers
ONYX-015	Onyx Pharmacaaceuticals	Adenovirus (E1B mutant)	Mutated p53	Phase III Phase II/III	Pancreatic, colorectal, head/neck and liver cancers Non-small-cell lung cancer
IDN-6556	Idun Pharmaceuticals	Small molecule	Caspase inhibitor	Phase II	Hepatitis C infections, acute alcoholic hepatitis, liver transplantation
IDN-6734	Idun Pharmaceuticals	Small molecule	Caspase inhibitor	Phase I	Acute myocardial infarction
HGS-ETR1	Human Genome Sciences	Human mono-clonal antibody	TRAIL-R1	Phase II	Non-Hodgkin’s lymphoma and colorectal cancer
HGS-TR2J	Human Genome Sciences/Kirin	Human mono-clonal antibody	TRAIL-R2	Phase I	Solid tumours
TRAIL/Apo2L	Genentech/Amgen	Protein	TRAIL-R	Phase I	Cancer
CEP-1347	Cephalon/Lundbeck	Small molecule	Mixed lineage kinase inhibitor	Phase II/III	Parkinson’s disease

TRAIL, tumour-necrosis factor-related apoptosis-inducing ligand.