**Apoptosis 2009: Opportunities in Cancer and Other Diseases**

**Description:**

Apoptosis is regarded as the major mode of cell death in cancer and should therefore be considered as a potential target when developing new antineoplastic drugs. An increasing number of companies are doing so, and we anticipate that this approach will pay substantial dividends, both therapeutically and commercially.

This report reviews 370 apoptosis-modulating drug candidates (9% in Phase 3 or later) developed by 233 companies and having 148 molecular targets. The report reveals a transforming market offering growth potential in cancer and other indications. Apoptosis (programmed cell death) is a natural phenomenon and occurs via a tightly regulated complex signaling cascade. Several major classes of drugs on the market - cancer chemotherapeutics, anti-TNF therapies, glucocorticoids - are now known to work, at least partly and/or indirectly, via apoptosis modulation. In cancer and in other diseases, elements of the apoptotic process become dysregulated, offering many direct targets for drug discovery.

This report reveals that many drugs have been reported to induce cancer cell apoptosis in preclinical studies. Traditional chemotherapeutic agents impair cell division and induce apoptosis indirectly. Many of the second generation indirect apoptogens (IAs) in development are biotherapies. They include: monoclonal antibodies, peptides, oligonucleotides, oncolytic viruses, and immunotherapies. The prevalence of indirect apoptotic effects emphasises the importance of screening for apoptotic potential in new anticancer drugs. This is being enabled by the increasing availability of biomarker-based assays of apoptosis.

Cancer is characterized by the (at least) partial suppression of apoptosis, which in turn causes chemotherapy resistance. Of particular interest therefore are direct apoptogens (DAs) designed to overcome treatment resistance due to overexpression of anti-apoptotic genes or downregulation of pro-apoptotic genes. Over one hundred first-in-class DAs directed at one or more of over 40 genes with a direct involvement in apoptosis (identified using the Stanford Research Institute's PANTHER database) are analyzed in this report. The targets include caspases, BCL2 family members, and TP53 (p53). Other targets which are gaining recognition are the proteasome and heat shock proteins (HSPs). Millenium Pharmaceuticals' Velcade is the first proteasome inhibitor (PI) on the US market, and represents the most cancer cell-selective apoptogen approved to date.

We forecast that the market for specific, direct, modulators of apoptosis in oncology will grow from $0.6 billion in 2008 to $12 billion in 2013, an average annual growth rate (AGR) of 64%, when it will represent about 22% of all oncology drug sales. This is well in excess of the AGR for oncology as a whole (which is expected to be almost 14% over the same period). Oncology will itself be the best performing major segment of the overall pharmaceutical market, which will grow at around 6% over the forecast period. Individual forecasts are presented for PIs and other DAs targeting caspases, BCL2 proteins, TP53, and HSPs.

We estimate that indirect modulators of apoptosis (which have varying apoptotic effects, but do not target known apoptotic pathways) comprise around half the oncology market by sales volume and will perform similarly to it, rising from $28 billion in 2008 to $57 billion in 2013, an average AGR of 12%. This corresponds to a fairly constant market share (51% of the oncology market in 2008, falling slightly to 48% by 2013). Forecasts are presented for first generation IAs and for the two main groups of second generation IAs (biologics and small molecules such as kinase inhibitors and hormone antagonists).

Various agents known or suspected to have apoptosis-modulating properties are also in development for indications other than cancer. The two main areas are: CNS disorders (in particular neurodegenerative diseases) and chronic inflammation/autoimmunity (in particular rheumatoid arthritis). Depending on cells being targeted, therapies seek to either promote or interfere with apoptosis. Some of the DAs currently in development for cancer may also find application in the treatment of other diseases.

This report also examines apoptosis-related patents and patent applications filed during the current decade to identify the most prolific filers of patents, technology trends and potential therapeutic applications of apoptosis research.

**Why buy this report?**
Market background

The main application of apoptosis research is presently in cancer treatment. It should be noted that this market is one of the largest and fastest growing sectors of the pharma industry. Of the 370 pipeline agents identified in Apoptosis 2009: Opportunities in Cancer and Other Diseases, 80% are anticancers.

This report segments the apoptosis-related cancer market into:

direct apoptogens (apoptosis-inducing drugs known, during their development, to have apoptosis-related molecular targets)

a. first generation indirect apoptogens (established drugs such as cytotoxics which have turned out to rely on apoptosis for part of their efficacy)

b. second generation indirect apoptogens (recently introduced and pipeline drugs with non-apoptotic targets which nevertheless have apoptotic effects).

c. Opportunities for apoptosis modulators in indications such as CNS disorders and chronic inflammation/autoimmunity are also explored.

Key Features

- Examination of the molecular events in apoptosis which may become dysregulated, providing opportunities for therapeutic intervention.

- Description of morphological criteria for detecting apoptosis, as well as recent methodologies based on detecting specific biological aspects and biomarkers.

- Analysis of 370 apoptosis-modulating drug candidates (9% in Phase 3 or later) from 233 originating companies. These drugs target 148 known gene targets, of which the top 15 are shown in Figure 1.3 from the report, as reproduced below.

- Deployment of Stanford Research Institute's PANTHER Classification System to identify gene targets with a validated role in apoptosis.

- Analysis of 4,872 apoptosis-related patents and patent applications to identify technology trends and potential therapeutic applications.

- Forecasts for the overall oncology-based apoptosis market, and its individual sectors.

Key Benefits

- Utilize biomarker and drug target information in this report to discover and develop drugs with apoptosis-modulating properties.

- Identify emerging areas of opportunity for apoptosis modulators in cancer, CNS diseases, and chronic inflammation/autoimmunity.

- Gain up-to-date competitive intelligence on apoptosis-modulating pipelines and identify the most promising drugs under development.

- Identify the leading originator companies developing apoptosis-modulating drugs.

- Use the patent analysis presented in this report to identify leading assignees, most influential patents and unexploited indications for apoptosis modulation.

- Devise a commercial strategy leveraging apoptosis by utilizing market forecasts for the oncology-based apoptosis market to 2013.

Key Issues raised

- The ideal of cancer therapy is to promote apoptosis of cancer cells. Traditional chemotherapeutic agents (first generation indirect apoptogens) trigger events which result in apoptosis of cancer cells. However, they also kill normal cells. Second generation indirect apoptogens may be less toxic to normal cells.

- Wide prevalence of indirect apoptotic effects suggests that it is always worth screening for apoptotic effects of new anticancer drugs. Wider application of validated biomarkers of apoptosis in preclinical and clinical trials of new drugs is thus highly desirable.

- The utility of current anticancer therapies is limited by drug resistance, either intrinsic or acquired. Direct apoptogens target overexpressed anti-apoptotic proteins or downregulated pro-apoptotic proteins responsible for therapy resistance.

- Neurodegenerative diseases represent an area of unmet clinical need. No therapy for neuroprotection is currently marketed, but new apoptosis-modulating drugs in development show promise.

- Existing treatments for rheumatoid arthritis and other autoimmune conditions (anti-TNF therapies and glucocorticoids) may act partly via apoptosis modulation. However, new apoptosis-modulating therapies with improved specificity are needed.
Key Findings

- In our survey of the apoptosis drug landscape, we identified 370 drugs aimed at 148 known gene targets.
- HSP90 (heat shock protein 90) is numerically the most popular target overall.
- Of particular interest are first-in-class direct apoptogens (over 100 agents identified) which target elements of the apoptotic pathway (over 40 genes).
- The global market for direct apoptogens is forecast to grow from $606 million in 2008 to $12 billion in 2013.
- The leading subgroups of the direct apoptogens market are: proteasome inhibitors; modulators of heat shock proteins; TP53-targeted agents; caspase-targeted agents; BCL2-targeted agents; and multi-target apoptogens.
- Eighteen percent (65) of all apoptosis-modulating drugs in development are anti-inflammatory, and 6% (24) are CNS targeted. Our survey of apoptosis-related patents suggests that future drugs will also target infectious disease.

Key Questions answered

- What types of apoptosis-modulating drugs are on the market?
- Which companies are leading the way in the development of apoptosis-modulating drugs?
- Which assays and biomarkers are increasingly used to define apoptosis during drug development?
- Why should all new anticancer drugs be screened for apoptotic effects?
- How is the apoptosis drug target landscape shaping up?
- What are the most popular targets of direct apoptogens in development for the treatment of cancer?
- How is the global cancer apoptosis market segmented and how are these sectors expected to perform over the period 2008-13?
- What progress is being made in developing apoptosis-modulating drugs for the treatment of CNS diseases and inflammation/autoimmunity?
- What is the nature of the apoptosis-related patent landscape?

Companies, Products/categories and Geographies profiled

Companies profiled/case studies:

The top ten drug originators are:
- Cancer Research Technology
- Theraptosis
- Bioniche Life Sciences
- Introgen Therapeutics
- Pfizer
- Anavex Life Sciences
- TopoTarget
- Bayer
- EpiCept
- BioLineRx

The leading corporate patent assignees (by both the number of applications and the number of granted patents) were:
- Epicicept
- Genentech

Key products/categories profiled:

Apoptosis-related drugs in development for:
- Cancer
- Inflammation
- CNS disorders

Key regions/countries covered:
- North America (USA, Canada)
- Europe (Germany, France, Italy, United Kingdom, Spain, Rest of Europe)
- Japan
- Latin America (Mexico, Brazil, Argentina)
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