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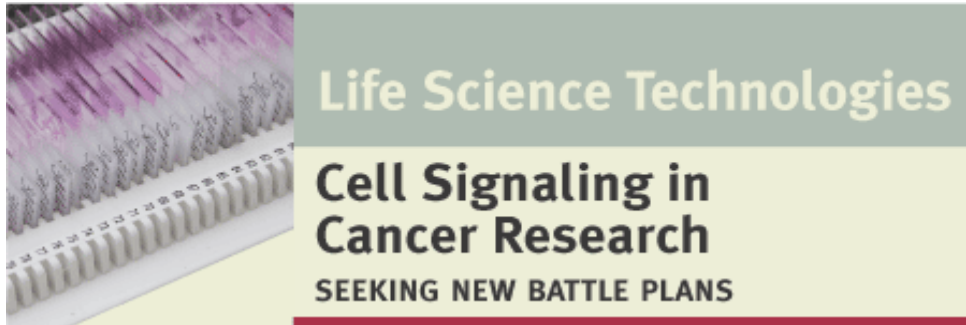
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Life Science Technologies: Cell Signaling in Cancer Research – Seeking New Battle Plans



To fight cancerous cells, scientists continually seek new strategies. Some of the latest treatments target specific cancerous cells for destruction, thereby leaving healthy cells less affected. In other cases, new therapies starve cancerous cells. Many of these approaches depend on understanding how signals control and—hopefully—can be commandeered to contain the division of cancerous cells.

by Mike May and Gary Heebner

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Cancer continues to cause a major public health crisis. According to the **World Health Organization's** statistics: more than 11 million new cases of cancer are diagnosed every year, and it accounts for seven million deaths annually, which makes up 12.5 percent of all deaths worldwide. By 2020, the WHO estimates that 16 million new cases of cancer will appear annually. In spite of the increase in cancer incidence, the National Cancer Institute's late-2005 biannual update indicates decreases in deaths from some forms of cancer: breast, colorectal, lung, and prostate.

In industrialized countries, the increasing age of the population accounts for much of the growth in cancer diagnoses. In addition, Robert A. Weinberg, the Daniel K. Ludwig and American Cancer Society Professor for Cancer Research at the **Massachusetts**

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cancers,” says Weinberg.

Whatever causes the number of people diagnosed with cancer to grow, the cancer therapeutic market grows with it. According to **IMS Health**, drug sales for cancer treatments are expected to more than double in the next five years. That could make oncology therapeutics the fastest-growing drug sector, according to **RBC Capital Markets**.

The key, though, to fighting cancer through better therapeutics depends on a better understanding of the basic biology of this disease. “The major challenge in cancer research is pinpointing causes of cancer on a molecular level,” says Bernhard Zimmermann, head of product management of the advanced imaging microscopy division at **Carl Zeiss**. “One needs a good understanding of signaling pathways, because that is the ultimate basis to designing more specific drugs or vaccines.”

Causes of Cancer

A variety of causes generate cancer, according to Weinberg. Cancer incidence can be affected by lifestyle choices, such as using tobacco products, and obesity, which comes from too many calories and too little exercise. There can also be heritable—or genetic—causes of cancer. “To a very small, extent,” says, Weinberg, “cancer can come from environmental pollution, but that is very minimal.”

No matter what causes cancer, though, it involves cell signaling at some level. Alan Barge, vice president of clinical oncology at **AstraZeneca**, says, “All cancer cells derive an advantage because they either dysregulate, upregulate, or disinhibit pathways that give these cells a proliferate advantage.” He adds, “Signaling is mechanistically involved in any growth advantage.”

Fighting this disease depends on many factors. “The fundamental challenge continues to be the translation of the numerous discoveries of the last two decades about malfunctioning signals into effective anticancer drugs,” says Weinberg. Knowing where to go next, however, can prove difficult. Still, Weinberg believes that drugs that target specific proteins and antibodies that neutralize angiogenic factors are some of the most promising potential therapies ahead.

Selecting Cells

To study cancer, investigators need the right materials—to either watch the normal progression of a tumor or to expose it to potential therapeutics and examine the effects on its growth. This type of work often involves cell culture and specific cancer cell lines. For culture media, researchers can turn to many companies, including **Cambrex**, **HyClone**, **Mediatech**, and **Sigma-Aldrich**. For cell lines, scientists can find many types from **ArtisOptimus**, **ATCC**, **Cambrex**, and **Clontech** (a division of Takara Bio). D.G. Ferneyhough, marketing segment manager of the cell biology business unit at Cambrex, says, “Some cancers are very heterogeneous. The bottom line is that researchers want a model system that represents the disease.”

Cambrex not only offers a wide range of cell culture media and reagents but also markets its Clonetics Skin Cell Systems and Models. “A cell system means a primary cell and a media culture system that is designed to make that cell act, in many ways, like it does in vivo,” says Ferneyhough. “Our cell systems provide cells that perform to a certain set of specifications—month after month, year after year.” Building consistency into a cell system depends on many variables. Mark Powers, senior research and development project group leader at Cambrex, says, “For cells in culture, the environment—chemical and physical—is extremely important. Cancer cells behave differently in different environments, even based on nearby cytokines and oxygen levels. So we try to recreate that in vitro.”

For the Clonetics Skin Cell Systems, Cambrex offers various cell types: keratinocytes, dermal fibroblasts, and melanocytes. Powers says, “These are the basic components of skin that researchers can probe individually.” Ferneyhough adds, “Some researchers use our cells to make more complex skin models. Potentially, those could be used to understand issues like UV [ultraviolet damage], or looking for molecules that would protect against UV damage.”

Observing Carcinomas

To fight cancer, investigators probe continually deeper into the mechanics of this disease. That often

Institute of Technology, says, “The number of cases is also an artifact—the more you look, the more you find.” The good news is that “the age-adjusted death rate from cancer [i.e., per 100,000 population] is declining with the exception of tobacco-related



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involves microscopy. As Zimmermann explains, “Microscopy has a long history in accompanying surgery. A surgeon takes a biopsy, and then a pathologist examines the sample microscopically for disease.” Such examinations play a fundamental role in treating cancer. Likewise, microscopy impacts basic cancer research. Several manufacturers—including Carl Zeiss, **Leica**, **Nikon**, and **Olympus**—have been designing and producing light microscopes for both research and clinical use for many years.

The keys to understanding cancer probably lie in microscopic, and submicroscopic, details. Zimmermann says, “When we talk about cancer or signaling pathways on cellular or organismal levels, it’s critical to understand the underlying protein networks in cells, tissues, or organs.” This, however, poses a tricky challenge. “These networks are very complex,” says Zimmermann, “They are dynamic in space and in time. To understand the cause of a specific cancer, you need to know where and when things are happening and that is what microscopy provides.” He adds that confocal microscopy delivers particularly good spatial resolution and that modern fluorescence labeling techniques add specificity, “letting you take virtually any protein and label it.”

One of the newest confocal products from Zeiss is the LSM 5 LIVE. Zimmermann says, “The LSM 5 LIVE gives the three-dimensional resolution of a confocal microscope, dramatically improves sensitivity, and adds high speed image acquisition.” He adds, “Some processes are so fast that you need millisecond time resolution or better, and the LSM 5 LIVE gives that.” In addition, the LSM 5 LIVE DuoScan includes a second scanner, and this microscope provides sample manipulations. Zimmermann says, “Researchers can perform highly localized photomanipulation with this microscope. For example, you could use a laser to release biologically active substances in a sample and monitor the resulting reaction with extremely high spatiotemporal resolution.”

In thinking of these microscopes related to cancer research, Zimmermann says, “I would argue that confocal microscopy is a basic tool in cancer research, a household technology.” Just before being interviewed, Zimmermann searched Google Scholar for publications mentioning the LSM 510—another Zeiss confocal microscope—and cancer or carcinoma, and he got almost 3,000 hits, many of them from just the past few years.

Following Phosphorylation

To really follow cancer-related networks of interactions, investigators need ways to mark specific molecules. In some cases, scientists even need to mark molecules in ways that reveal the entity’s state, such as being phosphorylated. Such studies depend on a wide range of antibody reagents that come from a variety of companies, including **Alexis Corporation**, **BD Biosciences**, **Biomol**, **Cell Signaling Technology**, **Chemicon**, **EMD Biosciences**, Sigma-Aldrich, and **Upstate**.

In cancer, most of the mutations or defects impact the way that cells communicate with other cells. Roberto Polakiewicz, chief scientific officer at Cell Signaling Technology, says, “To study cell signaling, researchers need a variety of tools, depending on just what a study is doing. For example, genomics tools let you look directly at mutations or chromosomal abnormalities. This has been done forever.” He adds, “Most people working in this field also need antibodies, and we pioneered the use of activation-site-specific antibodies, ones that recognize posttranslational modifications, like phosphorylation.”

Cell Signaling Technology’s antibodies reveal the activity of a molecule. Polakiewicz says, “Localizing enzyme activity tells you that something is happening in the molecule and tells you something about its function at that time.” He adds, “Activation-specific antibodies speed up cancer research

Summarizing the Signals

The **Signal Transduction Knowledge Environment** (STKE) website brings together a wide range of information. Bryan Ray, senior editor at Science, says, “In some ways, it is like an electronic review journal, but it is more than that. It features original reviews, perspectives, and protocols.” This site also provides subscribers with alerts, saved searches, and other features. For example, Ray says, “In ‘This Week in Signal Transduction,’ the editors scan the journals published that week and present short summaries of the highlights.” This site also provides useful sections that are free, including Teaching Resources and Connections Maps, which is a database that gives graphical displays of signaling pathways and links those to information about various components. These maps will continue to grow. As Ray says, “Signaling research is hot and shows no signs of cooling off.”

<http://stke.sciencemag.org/>

significantly.” These antibodies can be applied to immunohistochemistry, for instance, to analyze a tumor biopsy, or flow cytometry to analyze leukemic cells. That could reveal that a pathway is “on” in an aberrant way and could be targeted by a drug. These antibodies could also be used in diagnostics, according to Polakiewicz.

Phosphorylation sites related to cancer can also be mapped through techniques on the verge of high throughput. Polakiewicz says, “In this way, tons of information and data can be applied to cell lines and tumors.” He also mentions that Cell Signaling Technology always looks for new tools and biomarkers or kinases that get activated in cancerous cell lines or tumors.

Tony Ward, director of global and strategic marketing at BD Biosciences, agrees that scientists studying cancer need a collection of tools: the right cells, culture environments that make a cell behave as it would in vivo, and ways to make sure that the cells are performing as expected. He also points out that scientists need ways to look inside cells, such as using antibodies to search for specific proteins or watching the process of phosphorylation.

Ward says, “The biggest thing we have brought to the market in the past year and a half is our PhosFlow, which reveals the phosphorylation status of specific epitopes in an individual cell, whether from a cell line or from whole blood.” He adds, “This lets scientists look at an activation pathway of a protein and measure the ratio of phosphorylation. In other words, you can ask: How turned on is a pathway?” For example, a scientist could apply a potential anticancer compound to a sample and see how it changes protein pathways thought to be related to the progression of that cancer.

Methylation of so-called CpG islands—areas of increased density of guanine-phosphate diester—cytosine dinucleotides—also plays a role in cancer, because these islands are frequent sites of mutation. Scientists can study methylation of these islands with Qiagen’s EpiTect Bisulfite Kit.

A Total Attack

Some companies focus primarily on products related to cancer research. For example, Jay George, chief scientific officer at **Trevigen**, says, “We are a cancer company.” He adds, “We have antibodies, proteins, and tools to quantitatively measure angiogenesis. We also sell products to study and quantify DNA damage and repair, which are both intimately involved with cancer.”

One of the latest products from Trevigen is a basement membrane extract. This is a specialized polymer of extracellular matrix, essentially proteins, that provides a support for cells to adhere to and then differentiate. The main components of the extract include laminin I, collagen IV, and entactin. This product has been used in assays for tumor-cell invasion, angiogenesis, and three-dimensional cell culture. These proteins can also be used to coat plastic ware to make it more amenable as a surface for cell growth. This is an important area because, as George says, “Growing cells on plastic is a very, very artificial system.”

Moreover, Trevigen developed the Directed In Vivo Angiogenesis Assay, called DIVAA, in which scientists can study, for example, the development and support of blood vessel creation by tumors. This assay uses an angioreactor—licensed from the U.S. National Institutes of Health—that is a small silicone tube with basement membrane extract and growth factors in it. George says, “You can put this angioreactor in a mouse and then test a potential antiangiogenesis compound. Then, you can remove the reactor from the mouse and quantify the amount of blood vessel invasion.”

Starving Tumors

As tumors grow, they require increasing vascularization to provide nutrients and eliminate cellular waste. The circulatory system within a tumor is produced and developed by the active recruitment of blood vessels from nearby normal tissue, which can be measured—as just mentioned—with an angioreactor. If compounds can be developed that inhibit this process and are specific to tumor cells, these agents can be used to shrink or eliminate the tumor without damaging normal tissue.

AstraZeneca—among other companies—investigates the potential of agents that prevent the formation of new blood vessels and also attack established tumor blood vessels.

Barge of AstraZeneca explains: “Tumors could not grow beyond about one cubic millimeter in volume without parasitizing the host and acquiring their own blood supply. If you can inhibit neovascularization of tumors you could get an antitumor effect because neovascularization is a pathological process that does not occur in healthy tissue.”

Consequently, many scientists explore ways to stop vascularization of tumors. “We want to understand the molecular biology of neovascularization,” says Barge, “and find processes that might be specific to angiogenesis. This will enable the design of drugs that inhibit the growth of new blood vessels, without affecting the normal ones.” The development of that parasitized blood supply depends on growth factors, such as vascular endothelial growth factor (VEGF). That makes VEGF a prime target.

Barge says, “We have a large number of agents in our pipeline.” For example, scientists at AstraZeneca focus on growth factors and receptors for signal transduction as possible drug targets. Barge says that his company has two antiangiogenesis inhibitors in development—two of which are in Phase III trials. AstraZeneca also has two compounds in clinical trials that target the control of the cell cycle in cancer, and two more cell-cycle compounds that will go into the clinic later this year. Barge and his colleagues also study compounds that could inhibit cancerous invasion or repair DNA damage associated with cancer.

Challenges Ahead

To better understand cancer, George of Trevigen says, “Cancer is a protein disease—mutations of proteins that make them function improperly.” But this complex collection of diseases generates an equally complex mountain of data. Trevigen notes that any meeting of the American Association of Cancer Research involves “miles and miles of posters,” and it’s just too much to consolidate. “For all I know,” says George, “cancer has been cured every year, but there is no way to get all of that data in a searchable, minable form. No one person can comprehend even 0.1 percent of the content at one of these meetings.” So improved informatics will always be desired.

No matter what researchers discover in terms of therapy, though, Weinberg of the Massachusetts Institute of Technology says, “Ultimately, the largest reduction in cancer mortality will come from changes in lifestyle.” The most serious cancer-causing lifestyle remains the use of tobacco, says Weinberg. In addition, eating too much poses a cancer threat. Weinberg says, “An increased body-mass index correlates with increased risk of many types of cancer.” So winning the cancer battle lies in the hands of both scientists and citizens.



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