

TRENDS IN CANCER RESEARCH

First part of a multi-issue series

LET'S WORK TOGETHER

Peeling back the layers of integrated approaches to oncology research

BY DAVID HUTTON

IF THERE IS A HOLY GRAIL in the drug research arena, it may be a cure for cancer.

There are myriad companies working to develop novel therapies to fight this insidious disease, and they are all utilizing innovative methods to come up with potential candidates.

One method that is gaining a lot of traction in research circles is the integrated cancer research team. The integrated cancer research concept moves away from traditional academic models—which are based around collaborative research in similar fields—to a team that covers a wide variety of multidisciplinary research ideas and concepts.

In this first installment of a multi-part series in *ddn*, we focus on the use of integrated approaches for cancer research, with several of the industry's leading cancer authorities offering a look at their own integrated approaches.

A marriage of science and medicine

It seems, though, that an integrated approach can be many things to many people, and whether a process is an integrated approach may be in the eyes of the beholder, according to Beth Hollister, corporate vice president at Charles River Laboratories. She explains that an integrated approach to cancer research marries science and medical aspects of research.

"It is a team approach that can include physicians, scientists, molecular biologists, biologists, chemists and pharmacologists, all

whom are trying get a real picture of what patients need and applying the most advanced scientific techniques to meet those needs," she says. "For integrated approaches that we use at Charles River, we are taking the clinical teams and looking three or four years ahead into cancer drug development and what is currently in clinical trials, where the biology is and looking at what we need to do preclinically to prepare for the next clinical trial. How we do that is to use both benchtop science, such as

in vitro assays, cell-based assays and chemical-based assays, as well as animal models of cancer and apply this current standard of care to the models."

Often, pharma gets a bad rap for not working together. Hollister says the integrated approach goes a long way in dispelling those preconceived notions.

The impression is similar for Robert Shorr, CEO of Cornerstone Pharmaceuticals, who says he views integrated approaches to cancer research as the convergence of a variety of often disparate disciplines and areas of expertise working together to improve cancer treatment.

"Many scientists and oncologists see cancer as many different diseases, since different types of cancer originate from genetically diverse sources and show genotypic and phenotypic differences," he points out. "Moreover, cancers are not foreign cells, they are our own cells and are thus quite difficult to select out and target. Only by combining many disciplines of chemistry, biology (both for cancer and normal cells) and other specialized areas of expertise, can we hope to define and target highly conserved characteristics of cancer cells that are common amongst most, if not all, cancer types."

Shorr notes at Cornerstone—where researchers discover and develop drugs that utilize or target and disrupt a highly conserved feature of cancer cells—the altered manner in which they produce and manage the energy and raw materials necessary for them to live and grow.

"Our aim is to approach cancer as a singular disease in which different types can be treated in a similar fashion," he notes. "Our integrative approach focuses on cutting-edge science and knowledge in cancer metabolism, as well as traditional small-molecule drug discovery, metabolomics, biomarker development and drug delivery, as well as traditional development technologies."

Diverse disciplines converge

According to Dr. Ze'ev Ronai, associate director of the Sanford-Burnham Cancer Center and director of the center's Signal Transduction Program, using multidisciplinary expertise brings together different disciplines.

"Integration of science and engineering is an example," Ronai points out. "Also, integration of molecular, cellular biology, biochemistry, pharmacology, stem cell and structural biology, proteomics, and genomics with nanomedicine offer new means for detection, monitoring and treatment of cancer."

Quite simply, Ronai notes that integrating technological and molecular disciplines "allow one to tackle problems we could not address otherwise. New means for discovery, monitoring and delivery emerge from fusing



Robert Shorr, CEO of Cornerstone Pharmaceuticals, says he views integrated approaches to cancer research as the convergence of a variety of often disparate disciplines and areas of expertise working together to improve cancer treatment. Cornerstone's approach, he says, focuses on cutting-edge science and knowledge in cancer metabolism, traditional small-molecule drug discovery, metabolomics, biomarker development and drug delivery. "Only by combining many disciplines of chemistry, biology (both for cancer and normal cells) and other specialized areas of expertise, can we hope to define and target highly conserved characteristics of cancer cells that are common amongst most, if not all, cancer types," Shorr says.

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The primary advantage of an integrative strategy is that tumors can be classified based on multiple criteria.

"In such cases, cancers like melanoma and breast cancer can be sub-classified into several different groups. We would expect these



Dr. Jeffrey Smith, director of the Center on Proteolytic Pathways

additional groups to reflect differences in the molecular basis of each sub-class; and therefore to better inform the choice of therapy," notes Dr. Jeffrey Smith, director of the Center on Proteolytic Pathways.

Shorr says advantages of an integrative research approach include cross-fertilization of ideas and the integration of different perspectives that "yield new insight and avenues to be pursued that can be extremely exciting and promising."

"With unlimited funding and resources, we would pursue a much more integrative approach than is possible today," he adds. "We need to focus on integrative approaches that offer the greatest potential advantage."

One size does not fit all

Whether there are forms of cancer that can be targeted more effectively through integrative research is a question that generates myriad discussion.

"It is possible that those forms of cancer

that are not as well understood or have had less focus in terms of research may benefit from an integrative approach that utilizes the existing knowledge from other, better understood cancers," Shorr points out.

Ronai adds that an integrated research approach can be expected to be adapted to research on all forms of cancer. It also can help thwart myriad problems, such as resistance.

"Better delivery and monitoring of treatment efficacy will allow us to better refine the pool of tumor cells that require additional or different approaches for treatment and therefore will help address problems of resistance," he says.

Results stemming from an integrated approach to research also can result in innovative, less toxic therapies, he adds.

"It will, as highly refined delivery techniques will result in more efficient and specific targeting, which will result in less toxic therapy," Ronai notes. "Better monitoring will assure selectivity; new approaches in drug design will help alleviate current toxicity problem commonly seen in cancer therapy."

Making resistance futile

Shorr points out that a goal at Cornerstone is to develop therapies that are selectively toxic to cancer cells while having minimal impact on normal cells. "By using our various areas of expertise together, we have developed two platforms that integrate classic drug discovery and development technologies with innovative and diverse technologies and science to make drugs that are more effective and safer," he says. "These two technology platforms use

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two distinct, integrative approaches to cancer research and treatment.”

The platforms include the Altered Energy Metabolism Directed Platform—a platform for the development of drugs that is based on a unique understanding of cancer metabolism, and in particular, mitochondrial processes involved in cancer metabolism; and the Emulsiphan Drug Delivery Platform. Emulsiphan is a novel lipid oil nanoemulsion that integrates traditional chemotherapies with this novel cancer metabolism-based drug delivery technology.

Shorr points out that resistance is a significant issue for all treatment types, be they traditional chemotherapies or molecular targeted therapies.

For a long time, combinations of therapies have been used to maximize the impact on cancers, just as combination therapies are used as standard of care in certain infectious diseases such as in the use of antivirals, (some of the most common examples being combination therapies for HIV and hepatitis C).

“It is not a stretch to imagine that the cancer treatment could resemble antiviral treatments in ongoing maintenance therapies that combine multiple, less toxic treatments designed to keep cancer at bay,” Shorr notes. “Like with antivirals, the integration of drugs that have different mechanisms of action can sometimes create additive and even synergistic effects.”

Down with 'omics

Proteomics, the large-scale study of proteins, particularly their structures and functions, can also offer a tool for the study of relevant

samples in the context of translational cancer research. Ronai suggests that proteomics is certainly part of the toolbox required for integrative medicine, as is personal medicine.

“An example of proteomics studies performed at SBMRI led to discovery of stem cells’ phosphoproteome,” he says. “Such analysis allow us to determine signature of protein activity, in addition to actual expression;

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—Dr. Ze'ev Ronai, associate director of the Sanford-Burnham Cancer Center

the ability to link this information to specific tumor or response to therapy is invaluable as it allows us to reveal actual changes that take place and identify novel targets for therapy.”

However, according to Shorr, the value of proteomics may be more useful in some treatment types than in others.

“Is this relevant to an integrated approach? Yes, but it is only one component,” he explains. “We are focused more on metabolomics and take less from genomics, for example.”

Sound selection

Perhaps the most important current focus in cancer treatment today is selecting the patients who will respond best to a particular therapy or regimen.

“The idea is to not only maximize efficacy, but also to prevent patients from receiving and paying for treatments that will not benefit them



or even negatively affect them,” Shorr notes.

Challenges come from the disease itself. Cancer by its nature poses challenges to researchers because, as Hollister points out, every patient’s cancer is unique.

Hollister points out that there are two ways to look at cancer—the organ type and the actual molecular type of the cancer.

“The old way that cancer was looked at was the organ type,” she explains. “They would treat people based on the organ. For example, if the patient had colon cancer, there would

be a drug treatment for that disease. As we’ve learned more about cancer and broken things down, we’ve learned that within colon cancer there are multiple segments, each with different receptors. The newer approach is to actually treat patient populations based on the receptors.”

Efficiency and efficacy

The integrated research approach also can save time and effort throughout the process, as evidenced by one aspect of Charles Rivers’ efforts.

“The unique thing about Charles River is that we’ve spent millions and millions to create models that are tools for the pharmaceutical industry,” Hollister says. “We take potential therapies and there are hundreds that go through the screening and we have just a few, which have added value when they go to clinic because of the work we’ve done in the modeling.”

The screenings also clean out many compounds that wouldn’t have been effective. As part of our mission to get effective treatment to patients more quickly, you can’t ignore the negatives that are screened out.

In the end, research must yield results for its ultimate measure of success. Ronai notes that there are other benchmarks for success.

“The development of new technologies, which were not available before, clearly bridge disciplines to result in novel means for monitoring, targeting and treatment,” he concludes. “I think the success of an integrated approach can only be measured in the improvement of survival, safety and quality of life for cancer patients. I do believe strongly that success in cancer treatment will depend on an integrated approach and likely an integrated treatment paradigm.” **ddn**

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