BY DENISE MYSHKO

OPPORTUNITIES IN ONCOLOGY DEVELOPMENT

Companies are making steady progress into the research of new therapies to treat cancer, which is the second-leading cause of death in the United States.

> The most radical change in oncology is patient stratification and understanding how to select the right patients for a drug. It's not simply sufficient to treat patients where the target is expressed.
>
> **DR. JENS OLIVER FUNK**
> EMD Serono

Advances in cancer research, knowledge, treatment options, and awareness have increased tremendously in the past 25 years. Rates of new diagnoses and deaths from all cancers have declined significantly for men and women overall and for most racial and ethnic populations in the United States, according to the National Cancer Institute.

These decreases are driven largely by declines in rates of new cases and rates of death for the three most common cancers in men — lung, prostate, and colorectal — and for two of the three leading cancers in women — breast and colorectal. New diagnoses for all types of cancer combined in the United States decreased, on average, almost 1% per year from 1999 to 2006. Cancer deaths decreased 1.6% per year from 2001 to 2006.

But there is still work to be done. The NCI report, released in December 2009, found that in men, incidence rates have declined for cancers of the prostate, lung, oral cavity, stomach, brain, colon, and rectum, but continue to rise for kidney/renal, liver, and esophageal cancer, as well as for leukemia, myeloma, and melanoma. In women, incidence rates decreased for breast, colorectal, uterine, ovarian, cervical, and oral cavity cancers, but increased for lung, thyroid, pancreatic, bladder, and kidney cancers, as well as for non-Hodgkin's lymphoma, melanoma, and leukemia.

The demand for oncology drugs will continue to grow as healthcare systems worldwide emphasize cancer detection and treatment. The global market will expand from around $48 billion in 2008 to more than $85 billion in 2013, according to Cutting Edge Information.

Advances in Oncology Research

The understanding of basic science has improved over the last decade, enabling breakthroughs in oncology therapies. Our experts discuss these advances, as well as those to come.

BITTON. KENDLE. We are on the verge of a significant breakthrough in oncology clinical research and expect these efforts to explode over the next few years. Recent research on the molecular biology of cancer has been quite fruitful in discovering new genes and molecular pathways that explain oncogenesis and the development of the metastatic phenotype. For the first time, a picture of how cancer develops is becoming clear. The main challenge facing the medical and scientific community in this era will be to find strategies to solve the problem of how best to combine mono- and multi-targeted agents with conventional chemo- and hormonal-therapy in order to inhibit the molecular pathways.

PERRONE. BIOCLINICA. One prominent factor contributing to the overwhelming lack of efficacy in oncology products is the growing recognition of redundant pathways. This concept highlights that most therapeutics are developed to block one pathway involved in the pathophysiology of a disease. Over time, alternative pathways compensate and the drug does not retain its efficacy. Several proposed solutions to this challenge include the development of therapies that target two different mechanisms of action, thereby improving overall efficacy and reducing long-term morbidity and mortality. The development of monoclonal antibody-based therapies that target tumor cell surface antigens and biomarkers to predict response to the therapeutic has significantly improved cancer trials.

KELSEY. GERON. There have been a number of very big shifts in oncology. At the beginning of 2000, there were very few targeted cancer

THOUGHT LEADERS

ROBERTO J. BITTON, M.D. Medical Oncologist, Pg. Dip. Health Economics, Senior Project Leader, Operations & Proposal Development, Kendle, a global clinical research organization that provides the full range of early- to late-stage clinical development services for the world's biopharmaceutical industry. For more information, visit kendle.com.

DAVID CHANG, M.D. VP, Global Clinical Development, Hematology/Oncology, Amgen, a human therapeutics company in the biotechnology industry. For more information, visit amgen.com.

JENS OLIVER FUNK, M.D. Senior VP and Global Head of Therapeutic Area Oncology, EMD Serono Inc., an affiliate of Merck KGaA, a biopharmaceutical company focused on growing its product portfolio in cancer, neurodegenerative diseases, and fertility. For more information, visit emdserono.com.

JAMAL GASMI, M.D., PH.D. VP and Global Oncology Therapeutic Area Group Leader, Icon Clinical Research, which specializes in the planning, management, execution, and analysis of Phase II to Phase IV clinical trials. For more information, visit iconplc.com.

RICHARD GAYNOR, M.D. VP of Oncology Product Development and Medical Affairs, Eli Lilly and Co., which is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. For more information, visit lilly.com.

STEPHEN M. KELSEY, M.D. Executive VP, Chief Medical Officer, Oncology, Geron Corp., which is developing first-in-class biopharmaceuticals for the treatment of cancer and chronic degenerative diseases. For more information, visit geron.com.

RICHARD NELSON. VP, Clinical Research, PharmaNet Development Group Inc., a global drug development services company, provides a comprehensive range of services to the pharmaceutical, biotechnology, generic drug, and medical device industries. For more information, visit pharmanet.com.

ALISON O'NEILL, M.D. VP, Medical Affairs, TransMolecular Inc., an oncology-focused biotechnology company committed to developing novel proprietary drugs to diagnose and treat human diseases. For more information, visit transmolecular.com.

ANDREA PERRONE, M.D. VP, Clinical Operations, Medical Director, BioClinica Inc., which supports pharmaceutical innovation with imaging core lab, electronic data capture, interactive voice and Web response, and optimization solutions. For more information, visit bioclinica.com.

MARCO ROMANO. Chief Medical Officer and Head of the Oncology Therapeutic Area Team, Chiltern International Ltd., a global clinical contract research organization with extensive experience conducting and staffing international Phase I to Phase IV clinical trials across a broad range of therapeutic areas. For more information, visit chiltern.com.

RONNY K. SCHNEL. Executive Director, Business Development & Client Services, Criterium Inc., a global, full-service, and technology driven contract research organization that offers clinical research solutions for the biopharmaceutical, pharmaceutical, medical device, and CRO industries. For more information, visit criteriuminc.com.

NANCY SIMONIAN, M.D. Chief Medical Officer, Millennium: The Takeda Oncology Company, a biopharmaceutical company whose development and commercialization activities are focused in oncology. For more information, visit millennium.com.

STEVE TREGAY, PH.D. President and CEO, Forma Therapeutics, which unlocks intractable drug targets to create transformative small molecule cancer therapies. For more information, visit formatherapeutics.com.

JEFF WEISBERG, D.O., FACP. Senior Medical Director, i3 Research, a full-service, global CRO therapeutically focused on: central nervous system, oncology, respiratory and infectious diseases, endocrinology and metabolic diseases, and cardiology. For more information, visit i3global.com.

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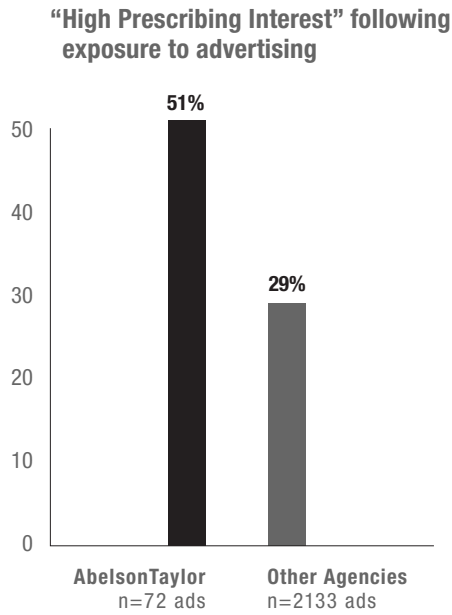

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We are on the verge of a significant breakthrough in oncology clinical research and expect these efforts to explode over the next few years.

DR. ROBERTO BITTON
Kendle

As our understanding of the basic science improves, we know more about the heterogeneity of cancer as not only a disease, but as biologically distinct subtypes.

DR. ALISON O'NEILL
TransMolecular

More is known about cancer now than ever before, and companies are exchanging knowledge with academic groups. Everybody is working to find ways to best use this information to develop drugs.

DR. RICHARD GAYNOR
Eli Lilly

therapies that had any proof of concept. The first small molecule targeted therapy that was demonstrated to have clinical utility was Novartis' Gleevec for the treatment of chronic myeloid leukemia. Since then, there has been a massive explosion in the number of small-molecule inhibitors that are specifically targeted to either genes or specific proteins.

FUNK. EMD SERONO. There certainly has been the advent in new, targeted therapies, but the enhancements of patient survival have been incremental. The most radical change has been in patient stratification and understanding how to select the right patients who will respond to the drug based on predictive biomarkers.

CHANG. AMGEN. There is a move toward addressing nondruggable targets and extending research platforms to affect these pathways. Over the next five to 10 years, there will be more drug candidates in development that go beyond antibodies, tyrosine kinases, or kinase inhibitors.

SIMONIAN. MILLENNIUM. It's important for companies to have an approach that incorporates biomarkers from preclinical studies into clinical studies so as to inform dose selection and go/no go decisions. Those biomarkers help to determine in early clinical development whether the target has been hit and whether downstream pathways are affected.

O'NEILL. TRANSMOLECULAR. Oncology drug development is an evolutionary process. There is the promise of individualized medicine: if we can pinpoint the particular pathways that are disturbed in particular patients then we can spare them the effects of toxicities as well as improve therapeutic outcomes. Increasing cancer-specific efficacy while decreasing systemic toxicity remains the key challenge in developing new drugs to treat cancer. It's an old and seemingly straightforward challenge, but progress in understanding the complexities of cancer cell biology provides us with new tools to go after this goal of improving the therapeutic index.

TREGAY. FORMA. It's well appreciated that going forward there is going to be a systematic understanding of the underlying root causes of cancer. In the past, we've had glimpses of such insights, but there has not been a systematic approach. Cancer genetics will lay out a road map of what the key drivers are in cancer and how targets are interacting.

KELSEY. GERON. There has been a massive explosion of monoclonal antibodies that have been produced as cancer therapies. In the 1990s, there were only two monoclonal antibodies that were being used in the treatment of cancer: Herceptin and Rituxan. Since those drugs have been shown to be clinically useful and commercially valuable, almost every major company has entered into the biologics arena.

ROMANO. CHILTERN. The majority of the current anticancer treatments, including small molecules and monoclonal antibodies, have demonstrated relatively small benefits in comparison with the older chemotherapeutic agents in terms of survival and quality of life. Clinical trials must focus more on the individual response to new treatments based on the use of molecular markers. In this way, expensive target therapies are used more effectively and minimize patient exposure to potential toxic effects.

GASMI. ICON. Oncology drug development poses many challenges, including regulatory requirements, timelines for approval, a lengthy and costly development process, tumor heterogeneity, poor prediction of preclinical models, and differences in international standards of care. Less than 10% of the oncology agents that complete a Phase 1 study achieve approval. In addition, competition for cancer patients to participate in clinical trials has increased dramatically. Currently more than 800 oncology drugs, mainly new targeted agents, are under investigation. As these agents target specific molecules or signaling pathways involved in cellular proliferation, differentiation, invasion, angiogenesis, and migration, the traditional development approach is no longer applicable.

WEISBERG. I3. More than half of all oncology clinical trials are not completed, mainly because they fail to meet enrollment goals; only 3% of cancer patients participate. Additionally, especially with rarer cancers, without access to good tools and information CROs may not be able to locate the right investigators, those who have the right patient population.

NELSON. PHARMANET. The cancer market has become more crowded because of the influx of new therapies in recent years. This has resulted in fewer cancer patients eligible or willing to participate in clinical trials in North America and Western Europe. While Eastern Europe remains a viable alternative, the Asia-Pacific region is a new frontier for the development of oncology drugs. These emerging markets can pose unique operational and regulatory challenges. Adequate review from regulatory agencies and key advisors is essential for the development of safe, meaningful studies, but the risks imposed by long timelines include changes in standard of care, decline in investigator interest, and the emergence of competing trials.

Combination Therapies

Experts say future oncology therapies will combine drugs in a much more rational manner based on the biology and the understanding of pathways.

CHANG. AMGEN. In oncology, combination treatments are important. Because of the level of disease burden and grave illness, there is hope that the activity of two drugs will be more efficacious than a single drug. In the foreseeable future, my guess is that all developments in oncology will be combination treatments. And as we understand more about the pathways and the biology of cancer cells, there will be more attention to combining two novel drugs to optimize and hopefully bring about a synergistic outcome of two drugs used together.

SIMONIAN. MILLENNIUM. Combining novel agents will be complicated, but I believe it's possible. And regulatory agencies are open to discussing these types of development strategies. I am a firm believer that if we want to make big inroads into cancer going forward, we are going to have to move to rationally designed combination therapies. In the last decade, we started to develop more targeted therapies, and a lot of advancements were made in many diseases. Now, regulators, payers, and other stakeholders want to see not just statistically significant results, but a very meaningful difference clinically. It's becoming increasingly more important in preclinical testing to understand the impact of genetic background on drug activity. Next, we need to understand how combining drugs might be relevant to that tumor. Increasingly, companies will begin to collaborate more with one another; they realize that to be successful in the cancer field today a more collaborative approach can set them apart and make a difference for patients.

KELSEY. GERON. As companies become even larger, often they have all of the assets in their own portfolios so they don't need to partner. Bigger companies often acquire smaller companies to gain the assets against a particular target. There are attempts to partner to bring two unapproved drugs together, but that is difficult because of the legal, intellectual property, and downstream royalty implications.

FUNK. EMD SERONO. There will be more precompetitive collaboration because it is important to get the optimum understanding of a drug. For example, any diagnostic would be a value-added component, which then becomes part of the value proposition of the drug. This means it's ultimately beneficial not only for the drug company to be successful but for those companies that develop diagnostic kits.

SCHNEL. CRITERIUM. Researchers try to design trials to answer questions, such as whether a specific type of cancer treatment vaccine works best when it is administered before chemotherapy, after chemotherapy, or at the same time as chemotherapy. Answering these questions can provide researchers with the right direction on how to best use a vaccine. It can also guide future development of combination therapies. Drug delivery methods that were once the realm of science fiction, such as nanoparticles and microcatheterization, are now being tested as practical tools for this use.

New Targets and Technologies

Biomarkers and other targeting methods are expected to come to the forefront in oncology drug development as a way to identify and stratify patients, target therapies, and develop companion diagnostics.

FUNK. EMD SERONO. Predictive biomarkers first need to be defined in preclinical models, and

> Clinical trials must focus more on the individual response to new treatments based on the use of molecular markers, which are able to predict the clinical outcome.
>
> **MARCO ROMANO**
> Chiltern

> Drug delivery methods that were once the realm of science fiction, such as nanoparticles and microcatheterization, are now being tested as practical tools for combination oncology therapies.
>
> **RONNY SCHNEL**
> Criterium

> The development of monoclonal antibody-based therapies that target tumor cell surface antigens and biomarkers to predict response to the therapeutic has significantly improved cancer trials.
>
> **DR. ANDREA PERRONE**
> BioClinica

> Companies are realizing that to be successful in the cancer field today, a more collaborative approach is needed — one that sets them apart and makes a difference for patients.
>
> **DR. NANCY SIMONIAN**
> Millennium

product teams come up with a biomarker strategy during early development. But there is no one easy solution to step into personalized medicine; the journey starts with understanding biomarkers so we can tell whether the drug candidate is working and to what extent.

they need to be further identified and categorized in human patients. Companies need to conduct exploratory studies and analyze multiple markers, not just one. On the translational front, this is also an area of active collaboration between companies and cancer centers.

SIMONIAN. MILLENNIUM. In the future, we'll be able to genotype patients' tumors to give them the appropriate treatments. Even as more cancers are sequenced and more data emerge showing more mutations or genetic abnormalities in a cancer cell, these tend to cluster in a reasonable number of pathways. They are not infinite. This identification then allows us to try to combat a particular tumor, tailored to a particular pathway.

CHANG. AMGEN. Our approach is to have our

BITTON. KENDLE. Cancer clinical trials require a radically different approach to trial methodology to ensure the patient population has fast and equitable access to investigational therapies, improved accuracy in the prediction of clinical benefits, and the selection of only those patients most likely to benefit from a given

Oncology Marketing: Stepping up the Science

Sound Bites From The Field

PHARMAVOICE SPOKE WITH COMMUNICATIONS EXPERTS ABOUT THE CHALLENGES FOR MARKETING ONCOLOGY THERAPIES, AS WELL AS STRATEGIES AND BEST PRACTICES FOR COMMUNICATION ABOUT ONCOLOGY BRANDS.

LEE BLANSETT is Senior VP, Market Access Oncology, at Kantar Health, a healthcare-focused primary research and consulting company. For more information, visit kantarhealth.com.

"Oncology drugs can present a significant marketing challenge as their value propositions are typically very complex. Payer contracting is almost never effective in the U.S. cancer drug market, and value lies almost entirely in the outcome provided to the patient. But articulating an improved outcome can be tough. In many cases, these drugs are very toxic. The side-effect profiles are daunting. At the same time, these are drugs that are frequently used toward the end of a patient's life, and the clinical data will not show that these drugs effect a cure.

Marketers need to develop a proposition that will help payers, patients, and providers understand the value for treating a particular cancer for a particular patient.

In terms of promoting to oncologists, year in and year out, whether it's in Europe or the United States, physicians usually say peer-reviewed journals and conferences have the most value. At the same time, focused interviews with oncologists around the value of sales reps and medical science liaisons (MSLs) reveal that there is a considerable demand for trial information and reprints, and the oncologists appreciate sales reps' ability to arrange for the information to be delivered. Our research also reveals that medical sciences liaisons are very important to oncologists, because MSLs can discuss the scientific and clinical information at a greater level of detail than most reps. Equally importantly, the MSL can reactively respond to questions around pipeline products, ongoing trials, trial design, interim reports, and compendia-approved uses.

In terms of promoting to patients, there is a real need to make sure patients understand how these products can make a difference for them. It's also easy for patients to get confused by conflicting information or start relying on less than optimum sources for their information."

JAY CARTER is Senior VP, Director of Client Services at Abelson-Taylor, a full-service healthcare communications company. For more information, visit abelson-taylor.com.

"The most effective medium for promoting pharmaceuticals in general is a salesforce. Oncology salesforces are well-trained and often are viewed as consultant sales reps; certainly this is a category where credibility and scientific acumen are of great importance.

The oncology community is incredibly sensitive to new clinical information and makes it a practice to pay attention to the output of key clinical meetings such as ASCO, ASH, and the San Antonio Breast Cancer conference. This makes the information that comes in peer-reviewed publications on these topics of great interest to practitioners. This fact actually makes the job more complex for marketers. They need to exercise care in their support of communication vehicles to ensure that there is no appearance of impropriety in sponsoring a vehicle that contains information on off-label use of their brand.

It's important to know the science intimately. Marketers should over-communicate with the customer,

treatment or dose. Adaptive design, particularly a technique known as enrichment, makes this possible. This technique entails including only those patients overexpressing the targeted gene and excluding patients who may have the same tumor type but do not show an overexpression of the gene. This increases the likelihood of observing the clinical benefits to specific cancers along molecular pathways that may be overlooked in traditional, broad-eligibility approaches to randomized trials. Adaptive design also can be used to significantly speed up early development trials to limit the exposure of the patients to sub-optimal drug levels. As trials move to this approach, it will require another shift in trial design as well. Because only subsets of selected patients would be enrolled in these trials, patients may be more difficult to enroll. Therefore, international and multi-institutional trials involving not only North America and Western Europe but

ensure that the salesforce knows the literature surrounding their brands exceptionally well, and always focus upon what is the best thing for the patient.

Companies should partner with academic, professional, and advocacy groups to provide much-needed information to patients on their disease and their therapy. Marketers need to over-communicate on the disease, its prognosis, the therapy, the potential risks and benefits of the therapy, and endeavor to meet the very high information needs of patients and caregivers."

GARNETT DEZEMBER is President of The Navicor Group, an inVentiv Health company and a full-service marketing, advertising, and communications company focused on oncology and immunology products. For more information, visit navicorgroup.com.

"There is a static number of oncologists and hematologists in the marketplace, and it doesn't look like there is going to be growth in that specialty. At the same time, there are many more potential cancer patients who will have to be treated by the same number of oncologists and hematologists. The result of this is there will be access issues not only for the salesforces but also for non-personal promotion. This creates some unique marketing opportunities for marketers.

Education is still going to be critical to physicians but as marketers we have to help our client create new opportunities to provide product information at the physican's or healthcare professional's convenience. There will not be the demise of the salesforce or the typical nonpersonal promotions in the future. But there will be a different type of access.

We are starting to see interactive detailing, where physicians not only go online to access information, but they can actually access a sales representative.

Oncologists access the Internet more than primary care physicians and about 10% more than the general physician population.

One best practice is to be as consistent as possible with branding and messaging across geographic markets, which hasn't always been the case in oncology. Companies would be well served to have one trademark, consistent branding, and analogous global positioning for their products."

DEBBIE FLETCHER is Executive VP, Managing Director at Sudler & Hennessey San Francisco, a global healthcare marketing and communications organization. For more information, visit sudler.com.

"It's challenging to communicate, for example, a complex mechanism of action for a certain product that might be very specialized and translate that into understandable information for different audiences. The science demands in oncology raise the bar, and our staff needs to be able to understand, translate, and filter a tremendous amount of data and create meaningful messaging that is actionable.

As product information needs are higher in an earlier stage of development, our work increasingly moves into the product's lifecycle when clinical data is usually quite limited. Our work to build and evolve the brand over time becomes much more strategic.

Agencies need to have engines that can execute in multiple ways. A given product development's environment is ever-changing and evolving. Medical and strategic functions become so critical in this category for insight generation and planning. We have to be able to see what's coming and be knowledgeable enough to understand the impact of how we're building the brand.

As marketers we need to have access to customers' information in a timely manner and make sure there's a frequent source of data. This should be tied to the overarching goals of the brand and be focused in a certain area or a customer type. Additionally, customer insights need to be incorporated back to fill the gaps between the prescriber and the patient. We need to make sure that as an agency we understand the customers as deeply as we can."

MICHAEL PARISI is President of Altum, a CommonHealth company, a professional healthcare advertising and promotion company focused on high-science and specialty markets. For more information, visit commonhealth.com.

"Oncology marketing is different because of the complexity of what needs to be communicated. In addition, the market moves at lightening speed. Competition is another factor. There are more and more companies moving into the oncology field or declaring they want to be a leader in oncology.

Personalized therapies are changing the market tremendously. Marketers have to look at the impact of the biomarker on the population. If there is a dramatic benefit in a defined patient population, the story gets really strong.

We as an agency are constantly looking at the media mix and making adjustments. The most valuable asset is still the salesforce, but the challenge is that reps don't have the time they used to have with oncologists. Marketers need to look at the mix of rep time in the office, the use of digital promotion, such as e-detailing, and medical science liaisons and other services.

A best practice is to think about the brand story across all audiences, including the oncology nurse, who manages patients. Marketers have to be up front and honest about side effects because the nurses will help set expectations and have better dialogues and communications with the patients."

> Only 3% of cancer patients participate in clinical trials. So there's a large untapped pool of patients who either are not aware that they can be in a trial or may have a negative bias toward trial participation.
>
> **DR. JEFF WEISBERG**
> i3

also emerging markets will become much more common, requiring a global presence for both biopharmaceutical companies and their CROs to effectively develop new compounds.

NELSON. PHARMANET. Improving clinical trials involves improving clinical trial design, including the use of adaptive design and better protocol development. A balanced protocol design can favorably impact the time it takes to enroll patients by not being over exclusionary. Close collaboration with regulatory authorities for the development of a clinical development plan, optimum target product profile, and development of individual clinical trial design are also needed. Strategies that reduce review timelines will also result in the availability of more relevant clinical trials for oncology patients.

Strategies for Success

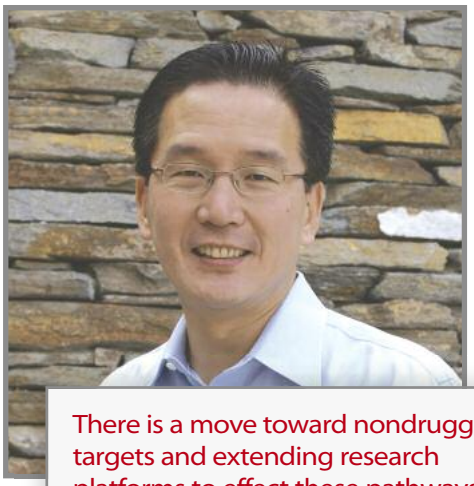
Best practices for oncology drug development provided by our experts include a better understanding of the basic science, a better stratification of patients in trials, and breaking down company silos.

KELSEY. GERON. Understanding the basic science is absolutely critical. It is important never to divorce the drug development process from the basic science. Even after the product has been on the market for years, there are still advantages that can be exploited through an ongoing and iterative understanding of the basic science.

GAYNOR. ELI LILLY. It's important to have information as quickly as possible and use the data to guide future drug development in order to identify the most optimal therapies.

FUNK. EMD SERONO. The key strategy right now can be summarized as smart patient stratification because this has multiple implications. Companies need to understand their drugs and come up with biomarker hypotheses. They need to have multiple technologies at hand to analyze various biomarkers, and they need a clinical trial design that helps to analyze statistically significant differences.

TREGAY. FORMA. Researchers truly need to understand the role of a target in a diseased patient population — the target may not necessarily be lung cancer, but a subset of lung cancer — which is driven through the mechanism of action that can be inhibited through a compound. Finding that link gives a company a chance to define the patient population selectively. Companies can do this today, and as cancer genome research reveals additional information, this ability will improve. In the future, there will be more tools to design even more aggressive therapies.



> There is a move toward nondruggable targets and extending research platforms to effect these pathways; over the next five to 10 years there will be more drug candidates in development that are not simply antibodies or kinase inhibitors.
>
> **DR. DAVID CHANG**
> Amgen

SIMONIAN. MILLENNIUM. Today, our academic collaborators expect there to be a strong preclinical and translational package for a new compound. A big part of the success of early clinical development is working with investigators with translational experience. A strong scientific perspective associated with the development process and having the development team integrated with the research team are big advantages in terms of early phase development and finding the appropriate biomarkers.

O'NEILL. TRANSMOLECULAR. Clearly, applying what we know, or at least hypothesize, about biomarkers early in clinical development improves the odds of identifying patient subpopulations with particular sensitivity to an agent. This knowledge also has the potential to significantly decrease the numbers of patients required to demonstrate efficacy and shorten development time. No discussion of strategies for improving cancer clinical trials would be complete without mentioning the importance of increasing patient participation in clinical trials. This is an old and low-tech answer, but patient participation in well-designed clinical trials is absolutely vital to improving therapeutic outcomes.

GASMI. ICON. The flexible adaptive designs, such as a randomized discontinuation trial, with futility stopping rules to terminate the ineffective treatment arm are of great importance to facilitate the development of effective cancer treatments. Validated specific biomarkers must select potential responders or non-responders, which can effectively subdivide patients into more homogeneous groups. This enables targeting a specific patient population and performing smarter clinical trials.

WEISBERG. I3. There are a couple of strategies to improve oncology trials. First is to improve entrollment by using pharmaco-informatics. By leveraging de-identified databases, the most appropriate sites can be identified. Specific patient populations can be defined by doing strategic searches that locate patients by diagnosis and investigators. Adding statistical feasibility criteria to a formal feasibility study before enrollment is often very helpful to prevent under-enrollment during the course of the study. Second is addressing safety. By studying the drug before enrollment begins, it's possible to understand the class effects of the study drug, as well as possible interactions and known adverse events from pre-clinical studies and earlier phase studies.

GAYNOR. ELI LILLY. At Lilly, we are working to facilitate communication among different groups. We've adopted a business unit model in which different groups have been situated in one organization with one set of objectives. The goal is to get closer to the customer — patient, physician, and payer — so that we can better understand their needs. By having the science, medical, and commercial teams in one organization, we hope to more effectively achieve our goal of delivering value to patients. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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The right solution requires a broader view.

The healthcare environment is filled with complex and often unforeseen challenges. Are your partners helping you see what's next—or are their perspectives too narrow? At inVentiv Health, we are uniquely qualified to see the big picture. With experts in all aspects of product development, launch, and commercialization, we build teams with multiple perspectives to take a broader view, and robust resources to execute seamlessly. Through our five insights-driven divisions—Advance Insights, Clinical, Communications, Selling Solutions, and Patient Outcomes—you get a customized solution for every possible need. To see what you've been missing, contact Dan Twibell at dtwibell@inventivhealth.com.

inVentiv health

accelerate your vision

BY DENISE MYSHKO

A Pipeline Check: COMPANY DEVELOPMENTS

Amgen

DAVID CHANG, M.D. VP, Global Clinical Development, Hematology/Oncology

Amgen approaches cancer research by exploring numerous biologic pathways and multiple scientific modalities. Amgen's cancer therapeutic research targets both tumor cells and the supporting normal cells that the cancer recruits for its own purposes (the "tumor stroma"). Tumor cells and the supporting stromal cells interact to enhance their growth and survival. In particular, tumor cells depend in large part on their environment (the stroma). Amgen's approaches include developing products that target proliferating cells, inhibit cancer cell nutrient supply, and interdict survival signals.

"Over the past several years, we have embarked on the journey of developing drugs using a pathway approach," says David Chang, M.D., VP, global clinical development, hematology/oncology, at Amgen. "We have been focusing on these pathways to see how they affect the growth of cancer cells in human bodies. We are trying to understand the biology of cancer cells and develop drugs that will predict these pathways in a platform-agnostic way."

The company is organized around several different areas: growth regulation, angiogenesis, apoptosis, and hematopoiesis.

With regard to growth regulation, there are multiple mechanisms by which cancer cells escape the normal regulatory processes that serve to control the behavior and fate of normal cells. Restoring control by activating the cellular functions that can inhibit proliferation, promote apoptosis, and regulate cell growth is of significant interest for the development of anticancer therapies.

One product in the company's pipeline that Dr. Chang points to is Vectibix (panitumumab), which is a fully human monoclonal antibody antagonist of the epidermal growth factor receptor (EGFr) pathway. It is on the market for metastatic colorectal cancer with disease progression on or following standard chemotherapy. Vectibix also is in Phase III trials for first- and second-line colorectal cancer and for metastatic and/or recurrent head and neck cancer.

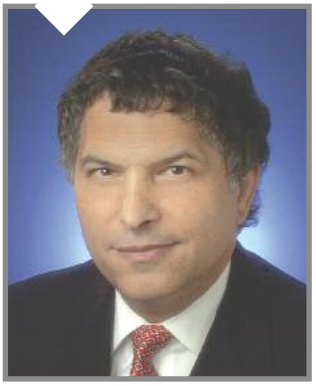
Angiogenesis, the abnormal process of new blood vessel formation, is at the root of many diseases, including cancer. In cancer, tumors induce blood vessel growth by secreting various growth factors (such as VEGF) that can induce capillary growth into the tumor and help the tumor grow and survive.

Apoptosis is a form of cell suicide in which a controlled sequence of biochemical events leads to cell death. In cancer, the dysregulation of apoptosis is critical in the development and survival of tumors.

Hematopoiesis, the formation of blood cells, occurs largely in bone marrow. Many proteins induce formation of the important types of blood cells like red blood cells, white blood cells, platelet-forming cells, and the T and B cells of the immune system.

Eli Lilly and Co.

RICHARD GAYNOR, M.D. VP of Oncology Product Development and Medical Affairs



Eli Lilly aims to be an oncology powerhouse, says Richard Gaynor, M.D., VP of oncology product development and medical affairs.

Within the oncology business unit, Lilly's three key cancer medicines — Alimta, Gemzar, and Erbitux — account for 14% of the company's worldwide revenue. Lilly also has one of the largest clinical-stage oncology pipelines, with 23 products in development.

Supplementing Lilly's oncology pipeline was the acquisition of ImClone, which was completed in November 2008.

"We've established an oncology business unit whose focus is to develop therapies and move them along as quickly as possible," Dr. Gaynor says. "The pipeline is extremely robust and includes small molecules, antibodies, and other chemotherapy agents that are being developed to attack unmet medical needs, such as melanoma, brain cancer, colon cancer, and a variety of other hard-to-treat tumors."

One exciting product in the pipeline is IMC-1121B (ramucirumab). Enrollment in a global Phase III study in first-line breast cancer is ongoing, and a second Phase III study in gastric cancer began enrollment in October 2009. Several additional Phase III ramucirumab studies are projected to begin in 2010. Phase II trials are also expected to be initiated next year, including trials in brain and bladder cancers and additional studies in colorectal and breast cancers.

Dr. Gaynor says this antibody can inhibit a receptor that is involved in angiogenesis.

"We think there are benefits of targeting the receptor directly because there can be several proteins that can bind to this receptor," he says.

Another ImClone molecule is IMC-11F8 (necitumumab), a fully human antibody to the EGFR receptor.

"Compared with Erbitux, 11F8 has similar binding properties to the EGFR receptor, but it's fully human so we think the tolerability will be better than with Erbitux," Dr. Gaynor says. "11F8 is dosed less frequently, a two-week schedule rather than weekly. We've started Phase III clinical trials in both nonsquamous and squamous non-small cell lung cancers in combination with appropriate chemotherapy regimens. In addition, we will be looking at this antibody for the treatment of colorectal cancer and other cancers."

EMD Serono

JENS OLIVER FUNK, M.D. Senior VP and Global Head of Therapeutic Area Oncology

From early to late stage, EMD Serono has 16 trials under way in the United States that target a range of cancers, including breast, prostate, colon, lung, glioblastoma, multiple myeloma, and hematological malignancies.

One product that has the company excited is Stimuvax, which is in Phase III trials as a therapeutic vaccine for non-small cell lung cancer. It is designed to induce an immune response to cancer cells that express MUC1, a protein antigen widely expressed on common cancers, such as lung, breast, prostate, and colorectal.

"Therapeutic vaccines have definitely created a lot of interest, and until recently many attempts have failed in the clinic," says Jens Oliver Funk, M.D., senior VP and global head of therapeutic area oncology at EMD Serono. "We are learning and understanding how to handle vaccines in patients, how to find the right patient setting, how to stratify patients, and how to mechanistically put the data together. In the years to come, therapeutic vaccines will gain importance in the clinic and become part of a new treatment paradigm."

Dr. Funk says beyond the lung and breast studies the company is considering studies of Stimuvax in prostate cancer and colorectal cancer.

"Ultimately, these vaccines work by raising a T-cell response in patients and thereby triggering the T cells to attack the tumor, something that is not working to start with," he says.

Forma Therapeutics

STEVE TREGAY, PH.D. President and CEO

Forma is building a robust pipeline of therapeutics directed at the Achilles' heels of human cancers, such as key targets associated with cancer stem cells, tumor cell metabolism, programmed cell death, or epigenetic disease mechanisms.

Some of the key features of Forma's discovery capabilities include a versatile cell-based screening platform that allows the screening of discrete targets in cells and quantitative genome/proteome-wide profiling and target identification; and a new chemical space through structure-guided drug discovery (SGDD) approaches leveraging proprietary computational and structural biology combined with its integrated chemistry platform, which incorporates diversity orientated synthesis (DOS).

"We believe there is an opportunity to unlock some of the more challenging targets that have historically been intractable to drug discovery, such as protein-protein interactions," says Steve Tregay, Ph.D., president and CEO of Forma Therapeutics. "Forma is set up to assemble those technologies to unlock those targets. The first issue is how to screen these compounds. Forma has a proprietary cell-based platform that allows us to screen direct protein-protein interactions in the context of intact mammalian cells. We also have a computational platform, called CS Mapping, that allows us to intimately understand what portions of protein-protein interactions are essential for binding and the hot spots that are driving the primary binding."

The company has collaborations with Novartis for its cell-based screening platform to discover inhibitors for protein-protein interaction targets in the field of oncology. Forma also has an agreement with The Leukemia & Lymphoma Society (LLS) to accelerate LLS's pipeline of research projects entering late preclinical development. Forma will use its proprietary computational solvent (CS) mapping technology to aid in structure-based drug design with expert computer modeling, screening and medicinal chemistry competence to optimize and prioritize molecules that LLS and its partners may take to the clinic. Forma has collaborations with Cubist and Experimental Therapeutics Centre of Singapore on Diversity Oriented Synthesis.

Geron

STEPHEN M. KELSEY, M.D. Executive VP, Chief Medical Officer, Oncology

Geron is conducting research on a telomerase cancer vaccine, which is in Phase II trials for acute myeloid leukemia. Proof-of-concept Phase I/II clinical trials at Duke University used an ex vivo process in which dendritic cells were isolated from the patient's blood, pulsed with RNA for the telomerase protein component, and then injected into the patient's skin, where they traveled to the lymph nodes and instructed cytotoxic T-cells to kill tumor cells that express telomerase.

In 2006, Geron filed its own IND application to initiate a Phase II clinical trial of the telomerase vaccine using the prime/boost vaccination protocol in patients with acute myelogenous leukemia (AML).

"We don't really know what it is about cancer that makes it immunogenic," says Stephen Kelsey, M.D., executive VP, chief medical offi-

cer, oncology, at Geron. "Cancer should behave like a virus, but it doesn't."

GRNVAC1 is an autologous dendritic cell vaccine targeting telomerase, which is a critical and potentially broadly applicable tumor target. The enzyme is expressed in a wide range of malignant tumors, and its activity is essential for the indefinite replicative capacity of cancer cells that enables their malignant cell growth.

Telomerase expression in AML cells is high, particularly in patients with cytogenetic (chromosomal) abnormalities associated with a high risk of disease progression.

Geron is developing GRNVAC2, an immunotherapeutic DC-based product derived from human embryonic stem cells (hESCs), as a vaccine delivery vehicle. HESC-derived DCs exhibit functional equivalence to DCs from peripheral blood and can be generated using scalable production methods.

In July 2005, Geron entered into a worldwide exclusive research, development, and commercialization license agreement with Merck & Co. for cancer vaccines targeting telomerase by methods other than dendritic cell delivery.

Millennium: The Takeda Oncology Company

NANCY SIMONIAN, M.D. Chief Medical Officer

Millennium's Velcade (bortezomib) was the first drug to specifically target the proteasome in hopes of killing cancer cells. The drug received FDA approval in 2003 for the treatment of patients with relapsed or refractory multiple myeloma. Today, the drug is approved for patients with previously untreated multiple myeloma and relapsed mantle cell lymphoma.

Additional studies are under way to examine its effectiveness in treatment follicular lymphoma and front-line mantle cell lymphoma as well as a subcutaneous formulation.

The proteasome is a protein complex located inside all cells that acts as a "garbage disposal" of excess proteins that are no longer needed.

There are a variety of disease states, including types of cancer, in which a homeostatic balance of cellular proteins can be altered permanently in a way that threatens the viability of the entire organism. It was theorized that some proteins may be signals for cancer cells to multiply, and that blocking this function would cause an overload of protein within the cell and lead to apoptosis.

Protein homeostasis is today what kinases were to the science of drug development in the mid-1980s. It could open a vast frontier for drug development for many disease states with special emphasis in anti-cancer therapeutics.

"This area of research is related to the infrastructure of a cell," says Nancy Simonian, M.D., chief medical officer, at Millennium: The Takeda Oncology Company. "One thing that's become increasingly clear is that cancer cells continue to survive because their infrastructure adapts to stress. In a cancer cell there are a lot of genetic abnormalities, and typically that causes a stress response that would kill the cell, but cancer cells have developed a way to adapt to that stress."

Dr. Simonian says Velcade and other Millennium products in development impact the infrastructure of cancer cells, inhibiting the process that allows cancer cells to adapt to stress.

Millennium's collaboration with Harvard Medical School to conduct joint research in protein homeostasis will build on the already significant expertise of both institutions, accelerating its R&D in this area.

Millennium continues research into this target as well as the pathway it inhabits, the ubiquitin proteasome system (or pathway), also known as the UPS or UPP.

MLN9708, a second-generation proteasome inhibitor developed by Millennium, is currently in Phase I trials for the potential treatment of patients with both solid tumors and hematologic malignancies.

The molecule MLN4924 targets the NEDD8-Activating Enzyme (NAE), a target discovered by Millennium scientists upstream of the proteasome.

This discovery was published in the journal Nature in April 2009. MLN4924 is currently in Phase I clinical trials for the treatment of patients with both solid tumors and hematological malignancies.

TransMolecular Inc.

ALISON O'NEILL, M.D. VP of Medical Affairs

TransMolecular has developed a proprietary compound, TM601 (chlorotoxin), for the treatment of various cancers and ophthalmologic, neo-vascular diseases.

The company is executing a multi-tiered clinical research program to explore the potential of radiolabeled and non radiolabeled TM601 in the treatment of high-grade glioma, malignant melanoma, and other aggressive cancers for which treatment options are limited.

TM601 is a synthetically derived peptide originally isolated from scorpion venom. TM601 specifically binds to and is taken up by tumor cells while not affecting corresponding normal tissues. When administered systemically, TM601 has been shown to cross the blood brain barrier and target tumors.

Local delivery of radiolabeled TM601 (131I-TM601) is being evaluated in recurrent malignant glioma where novel therapies that can directly attack and infiltrate tumor cells while sparing normal cells are desperately needed. A Phase II efficacy study of TM601 administered to the site in patients with recurrent malignant glioma has demonstrated improvement in survival compared with historical controls.

These data are the basis of a special protocol agreement that TransMolecular has attained with the FDA to conduct a Phase III trial in newly diagnosed glioma, where 131I-TM601 will be evaluated in combination with temozolomide and radiotherapy, the current standard of care.

"We are looking for partners to help us continue bringing this project forward," says Alison O'Neill, M.D., VP of medical affairs at TransMolecular. "We have the SPA in place and are now looking forward to initiating the research once a qualified partner is identified." ✦

The Cancer Genome ATLAS

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate the understanding of the genetics of cancer using innovative genome analysis technologies.

The TCGA pilot program developed the infrastructure necessary to systematically characterize the genomic changes in hundreds of tumors. The success of the pilot project, exemplified by the broad use of the publicly accessible data sets, demonstrates the value of this type of investment in cancer research. Having demonstrated the proof of concept the TCGA pilot project set out to accomplish, the National Institutes of Health announced in 2009 the expansion of TCGA.

After a rigorous review process, the scope of the TCGA Research Network has expanded to include more than 20 tumor types and thousands of samples over the next five years. Each cancer will undergo comprehensive genomic characterization that incorporates powerful bioinformatic and data analysis components. The expansion of TCGA is expected to lead to the most comprehensive understanding of cancer genomes and will enable researchers to further mine the data generated by TCGA to improve prevention, diagnosis, and treatment of cancer.

Biospecimen Core Resource

Tissue samples are carefully cataloged, processed, checked for quality, and stored, complete with important medical information about the patient. All information that could be linked to a specific patient is removed before making the data publicly accessible.

Genome Characterization Centers (GCCs)

Several technologies will be used to analyze genetic changes involved in cancer. The genetic changes that are identified will be further studied by the Genome Sequencing Centers.

Genome Sequencing Centers (GSCs)

High-throughput Genome Sequencing Centers will identify the changes in DNA sequences that are associated with specific types of cancer.

Data Coordinating Center (DCC)

The information that is generated by TCGA will be centrally managed at the DCC and entered into public databases as it becomes available. Centralization of data facilities and data transfer between the network and the research community makes data analysis more efficient.

Genome Data Analysis Centers (GDACs)

Immense amounts of data from array and second-generation sequencing platforms must be integrated across thousands of samples. These centers will provide novel informatics tools to the entire research community to facilitate broader use of TCGA data.

Cancers Selected for Study

The cancers selected for study are chosen based on a complex set of criteria including:

- Availability of human tissue collections that meet TCGA standards for patient consent and inclusion of matched normal tissue; and
- Cancers with poor prognoses are prioritized when possible.

The tumor types the TCGA expects to study include: brain, breast, kidney, lung, and ovarian.

For more information, visit cancergenome.nih.gov/wwd/program/. ✦