Genomics and Proteomics May Help Clinicians Individualize Cancer Treatment

M. J. Friedrich

SAN FRANCISCO—Analysis of the genetic mutations behind the transformation and growth of cancer cells provides information that is spurring the development of new and better ways to diagnose and treat cancer. But many researchers are also looking beyond the “blueprint for life” to proteins for insights the genome does not provide.

Proteomics, which includes analysis of protein interactions in a cell (JAMA. 2001;286:2211-2214), is a young field but one that is growing fast. By cataloging the many proteins in the body and discovering how they function in tissues, researchers hope to gain a better understanding of what goes wrong in the protein networks in cancer cells.

The first clinical applications of proteomics are being undertaken at the National Cancer Institute (NCI) in Bethesda, Md, and preliminary results involving patients with breast and ovarian cancer are provocative. But rather than replace genetic analysis, the hope is that information from protein analyses will complement genetic information at many stages of cancer management.

Progress is being made in analyzing and interpreting information generated using both genomic and proteomic technologies, and at the annual meeting of the American Association of Cancer Research presenters reported on some of the molecular approaches being pursued to individualize the treatment of cancer patients.

GENETIC PROFILING OF ALL

For years, researchers at St Jude Children’s Research Hospital, Memphis, Tenn, have used conventional laboratory approaches to individualize drug therapy for children with acute lymphoblastic leukemia (ALL). As a result of their efforts, a disease that 30 years ago was almost always fatal now has a cure rate that approaches 80%.

The key to this success, said James Downing, MD, chair of the department of pathology at St Jude, has been in recognizing that ALL is not one disease but a heterogeneous collection of subtypes of leukemia that respond differently to chemotherapy. By identifying the ALL subtype, clinicians have been able to tailor the intensity of treatment to a patient’s risk of relapse.

But identifying ALL subtypes is a labor-intensive and imprecise endeavor that involves a team of experts to interpret the morphology, immunophenotype, and cytogenetics of tumors, said Downing. To determine whether they could simplify the process, his group used oligonucleotide microarrays to analyze the gene patterns from the leukemic cells of 360 children with ALL whose subtypes were known (Cancer Cell. 2002;1:133-143).

Gene expression profiling was able not only to successfully identify the six prognostically important ALL subtypes but to yield an additional unique profile for a hitherto unknown subtype of ALL. The expression profiles also yielded biologic insights that may eventually prove useful in identifying targets for new therapeutic agents.

The researchers also wanted to determine whether gene expression profiles could predict which patients would fail therapy. Currently, said Downing, there are no good prognostic indicators for relapse. The gene profiles enabled researchers to discriminate between patients with certain ALL subtypes who would remain disease free and those with other subtypes who would relapse. The researchers also identified an expression profile in one subtype that identified the rare children who eventually develop treatment-induced acute myeloid leukemia.

Preliminary conclusions of the study, said William Evans, PharmD, chair of the pharmaceutical department at St Jude and a coauthor of the study, are that it may be possible to predict treatment outcome and gain additional prognostic insight by looking at gene expression patterns in leukemia cells prior to treatment.

PROTEIN RESPONSE TO THERAPY

Rather than using gene expression profiling to infer information about aberrant protein function in cancerous tumors, US government researchers are developing proteomic technologies to directly assess protein activity in patients with cancer. The collaboration between NCI and the US Food and Drug Administration (FDA) in this regard began in 1997 and is led by Lance Liotta,
MD, PhD, of the NCI’s Center for Cancer Research, and Emanuel Petricoin, PhD, of the FDA’s Center for Biologics Evaluation and Research. One of the program’s main goals, said Petricoin, is to use protein profiles to monitor the patient before, during, and after therapy, as well as after recurrence, should that be necessary.

With new technologies, investigators can biopsy the patient’s tumor and examine it to determine the effects of treatment on the proteins and protein interactions in the tumor cells. The researchers anticipate that this information could be put to many uses: to rationally choose the therapy most likely to have an effect on the tumor, to monitor the patient’s response to therapy, to identify the rewiring of protein circuitry that may take place in response to treatment, and to select other therapies.

Two new proteomic technologies—laser capture microdissection, which allows removal of pure tumor cells from the tissue, thus maintaining the original pattern of cells, and a protein microarray to analyze proteins—are being used to examine biopsy samples from patients with breast cancer who are enrolled in a clinical trial at the NIH. The patients are being treated with trastuzumab, a molecularly targeted agent, followed 1 month later by paclitaxel.

The researchers have analyzed protein patterns from about 20 patients and have found that patients who respond to therapy have a reduction in activation of the Akt protein, while no effect on Akt is seen in patients who do not respond to therapy. The Akt protein is normally involved in helping cells avoid apoptosis, or programmed cell death, explained Petricoin. However, when Akt is suppressed, as it is by trastuzumab, the cell’s ability to survive is undermined.

Liotta hypothesized that one of the mechanisms by which trastuzumab works is to make the cancer more sensitive to the apoptosis-inducing properties of paclitaxel. Based on the protein pattern results, the researchers are planning to extend this protein analysis to clinical trials involving the molecularly targeted agents known as ST1571 and ZD1839, studies in which “we’re attempting to look at the changing proteomic information before, during, and after treatment,” said Liotta.

**Predictive Power of Proteins**

Proteomic technologies are also being applied to early detection of cancer of the ovary. Although not a highly prevalent disease, ovarian cancer is a deadly one because most cases are not discovered until they are well advanced. A simple test that detects ovarian tumors early, when the disease has a higher cure rate, is lacking. But devising one could have a dramatic impact on survival, said Elise Kohn, MD, chief of the molecular signaling section in the NCI’s laboratory of pathology and director of clinical protocols in the FDA/NCI proteomics program.

Kohn and her colleagues postulated that pathologic changes in an organ such as the ovary might be reflected in protein patterns in blood serum. According to this theory, a pattern of proteins rather than a single biomarker might provide diagnostic information useful in detecting ovarian cancer even if the identity of the proteins is not known.

Serum samples from 50 unaffected women and 50 women diagnosed with ovarian cancer representing all stages were analyzed using mass spectrometry, which sorts proteins according to their mass and electrical charge to provide a snapshot of thousands of proteins. A computer-based artificial intelligence program then identified patterns of low-molecular-weight proteins that distinguished between unaffected women and women with cancer.

Once the protein patterns were established, they were used to classify another set of 116 masked serum samples, including 50 samples from women with cancer and 66 samples from unaffected women or women with nonmalignant disorders. The algorithm correctly identified 50 of 50 cases of ovarian cancer, including the 18 women with stage I cancer, and 63 of 66 noncancer cases, yielding a sensitivity of 100%, a specificity of 95%, and a positive predictive value of 94% (Lancet. 2002;359:572-577).

Specificity is a major consideration in screening for ovarian cancer because most women who test positive will require exploratory surgery, and Kohn pointed out that a specificity of 95% is unacceptable for this disease. The goal would be to achieve specificity of 99.7% to 99.9%, and the researchers aim to refine the system to improve its specificity. These are preliminary data and further study will be required to confirm the accuracy of this technique as a screening tool in the high-risk and general populations.

These studies represent first steps toward the goal of clinical proteomics, which is to develop individualized therapies predetermined to be effective for patients on an individual basis, to diagnose cancer earlier than is now possible, and to gain better understanding of the protein circuitry of tumors, leading ultimately to better treatments.

Summarizing his vision of the future of cancer treatment, Liotta said, “In the past, the pathologic diagnosis has been based on histology. In the future, it will be based on molecular profiling of tissue both at the genetic and proteomic level. In the past, therapy has been chosen by category of disease. In the future, combination therapy will be aimed and tailored to individual patient profiles or classes of profiles. Select, monitor, and reevaluate—that’s the hope for the future.”
Business Learns Wisdom of Treating Employees With Psychiatric Disability

Mike Mitka

CHICAGO—Many businesses are seeing their health care costs rise as diagnoses of psychiatric disability increase among employees. To stem the flow of red ink, employers are looking for ways to control costs associated with providing mental health care for their workers.

Physicians who read these words know that cost cutting in the corporate world usually places a burden on them—it leads to lower reimbursement, fewer allowed therapy sessions, and an emphasis on pharmacotherapy.

But cost cutting may not be the knee-jerk reaction it once was in the corporate world.

At the American College of Occupational and Environmental Medicine Health Conference this spring, speakers representing some large businesses argued that companies can save overall dollars by increasing resources to treat employees with mental health problems.

Presenters from Bank One Corp of Chicago said their company’s goal when placing employees with a psychiatric problem on short-term disability is to ensure appropriate care, manage a return-to-work plan, and provide follow-up care. This goal is achieved, in part, by requiring that such employees take part in active mental health treatment programs that encourage involvement with a psychiatrist or other mental health professional—usually involving psychotherapy.

This approach comes at a time when the bank, which has more than 73,000 employees, is seeing psychiatric disability costs rising. Daniel J. Conti, PhD, director of Bank One’s Employee Assistance Program, said that in 1989, psychiatric disability was the seventh leading cause of short-term disability at the bank. In 2000, psychiatric disability was the second leading cause (pregnancy was first).

And such disability costs companies. One study estimated that depressed workers have 1.5 to 3.2 more short-term work-disability days in a 30-day period than other workers, with a salary-equivalent productivity loss averaging between $182 and $395 (Health Aff. 1999;18:163-171).

Why is more psychiatric disability being seen in the workplace? Conti suggested that two reasons may be increased physician awareness and diagnosis and public awareness campaigns. Others mentioned increased stress for employees because of leaner staffing and a concomitant requirement for more productivity.

Paul Pendler, PsyD, a psychologist at Bank One, said that the key ingredients of managing psychiatric disability are front-end intervention by the company’s employee assistance program, requiring employees to undergo mental health treatment, having an immediate expectation for a return-to-work plan as part of treatment, and aggressively separating true disability from workplace issues.

THE PHYSICIAN’S ROLE

Pendler expressed frustration that some physicians do not appreciate the way businesses run or the importance of work as therapy. He cited extreme prescriptions an employee might receive, such as “Stress—take 6 to 8 weeks off.”

“We ask providers, ‘What will it take to get the employee back to work?’” Pendler said. “Too often, physicians don’t know.”

Conti added that he has spoken with physicians who have met with a patient three or four times and still do not know what the person does for a living.

Alexander E. Obolsky, MD, a psychiatrist in private practice and not associated with Bank One, said physicians, because of their training and their role as the patient’s advocate, often neglect the employment side of a patient’s life.

“We feel that if we encourage a person to go back to work, we’re helping the corporation and not the patient,” Obolsky said. “Also, a lot of physicians have focused on an individual’s internal state. Now we’re looking at his or her environment, like the family or marriage, but work hasn’t made it into the physician’s focus.”

And work is an important therapy for psychiatric disability, said Wayne N. Burton, MD, Bank One’s corporate medical director.

“In the case of mental health, work is very important to the healing process. Having someone who is depressed staying at home in an unstructured setting will probably make that person more depressed,” Burton said. “Work is also where a lot of people’s friends are, and that support system can help them.”

RETURN TO TALKING

Companies are also finding that psychotherapy plays an important part in improving employee mental health.
New Bioethics Council Offers No Recommendations

Brian Vastag

WASHINGTON—At an April meeting of the President’s Council on Bioethics, the 17-member panel of ethicists, lawyers, physicians, and other scientists fenced over the nuances and implications of embryo cloning, or somatic nuclear cell transfer, for research. As Congress deliberates legislation, the council spent an afternoon trying to balance morality against practicality, philosophy against embryology.

The council’s report on the subject, due this summer, will tackle these broad issues but offer the president no advice, announced chair Leon Kass, MD, PhD. Kass, a bioethicist from the University of Chicago, opened the session by announcing that he did not expect the council to “reach agreement.”

While outside the bioethics council, he said, members may be “interested in victory, we are adopting the pretense we are interested in clarity and wisdom and not in beating the other side down.”

Given the council members’ divergent opinions, one can understand why Kass would want to avoid pounding out cut-and-dried pointers. And in fact, he is not bound to do so. Last December, the council’s charter creating the council does not explicitly request recommendations. It simply states that the council’s purpose is to “advise the President on bioethical issues.”

PREVIOUS ADVISORY BODY SPOKE

The council’s predecessor, the National Bioethics Advisory Commission (NBAC), was formed in 1995 with a similar charge. However, that body chose to give specific counsel. The NBAC’s last report, issued in August 2001, made 30 recommendations aimed at strengthening safety protections for research volunteers.

“We did everything we could to reach consensus,” said Thomas Murray, PhD, president of the Hastings Center and former NBAC member, in a recent telephone interview. Members were never “bludgeoned” to take a position, though, and were free to insert their “dissenting opinions” as Supreme Court justices do. “It was a bracing process,” Murray added. “At some point we had to stop ruminating and say, ‘What does this mean for reality? What does this mean for policy?’”

Another former NBAC member, Patricia Buklar, PhD, a bioethicist at Portland State University in Oregon, told this reporter recently that proffering information over recommendation is “very dubious. You have to make decisions,” she said. “We did make recommendations because we felt it was our job.”

Kass wrote in an e-mail that the council is eschewing pointed guidance because the president wants the “fullest account of the human and moral meaning” of biotechnology. “Liberating” the council from the onus of consensus ensures this, wrote Kass. The White House did not respond to inquiries.

Murray thinks the new council will still lead the president in certain directions. “I think it will be difficult to refrain from making recommendations,” he said, alluding to the well-known anticolonizing views of Kass and council member Charles Krauthammer, MD.

HOW SLIPPERY THE SLOPE?

Kass aired his views on so-called therapeutic cloning in June 2001, 6 months before his appointment as council chair, during testimony before the House Subcommittee on Health. A few years earlier, he said, he had wrestled with finding “a middle way” to ban reproductive cloning while allowing research cloning. But at the hearing he said that he was “now convinced that an effective ban on reproductive cloning requires a ban on all human cloning, including the creation of embryonic clones.” He added that politicians and others “seriously about preventing human reproductive cloning must stop the process from beginning, at the stage where the human somatic cell nucleus is introduced into the egg.”

In fact, an often contentious discussion over the legitimacy of this “slippery slope” argument, a term conceived by ethicists, consumed a sizable chunk of the meeting. Krauthammer, a syndicated newspaper columnist who unfolded his anticolonizing reasoning in a recent article in New Republic, clung most tightly to the slippery slope argument. The approach does not assign any intrinsic worth to an embryo, he said, but asks, “Were we to pursue this research... what will we become?”

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Researchers Promote Truce in Adult vs Embryonic Stem Cell Debate

At the April meeting of the President’s Council on Bioethics, two top stem cell researchers implored the panel to avoid thinking “embryonic cells vs adult cells.” Laboratories with access to a wealth of cells, ranging in developmental age from embryonic through a spectrum of intermediate stages to end-stage adult, will serve as the most fertile grounds for discovery, they said.

“This might surprise you . . . but we are studying stem cells from adult sources, umbilical sources, etc. et cetera. This is the only way . . . that you can have a scientific advance, to compare and contrast the different sources of stem cells,” said John Gearhart, PhD, the developmental biologist at Johns Hopkins University School of Medicine who first cultured embryonic germ cells, which are similar to embryonic stem cells but gleaned from 5- to 8-week-old aborted fetuses.

Catherine Verfaillie, MD, known for her work at the University of Minnesota Stem Cell Institute showing the versatility of blood stem cells, struck a more urgent note. “I think if you were to ban all embryonic stem cell research it would really slow down the insight that could be gained in adult cell research.” Verfaillie told the council that despite her reputation as a pioneer in working with adult stem cells, her laboratory and those of her colleagues at Minnesota study embryonic cells.

Apparently unsatisfied, council member and Princeton University law professor Robert George, DPhil, JD, pushed Verfaillie to predict which cell type will ultimately prove most beneficial. “Currently I can’t answer that question,” said Verfaillie.

Council chair Leon Kass, PhD, a bioethicist at the University of Chicago, seemed resigned to the competitive mood. “And unfortunately, for better and for worse, these [recent stem cell] reports are caught up in the political controversy . . . with people on both sides” promoting either adult or embryonic stem cell research “precisely because they are wed to an either/or choice,” Kass said.—B.V.

Michael Gazzaniga, PhD, director of the Center for Cognitive Neurosciences at Dartmouth College, responded with an analogy. A 16-year-old can obtain a driver’s license, but giving a license to someone who is a day shy of 16 is not “really different.” Subtracting day after day, though, eventually leads to the absurd image of a zygote behind the wheel. “Of course that’s nonsensical,” said Gazzaniga, who proposed to shelve slippery slope positions because “as a species [humans] can form categories.”

William Hurlbut, MD, consulting professor in human biology at Stanford University School of Medicine, proffered a pointed rejoinder. “Some people would say what you’re talking about is not a license to drive, but a license to kill.” Hurlbut continued by outlining his concern. Embryo researchers already recognize that a wealth of data could be obtained by studying cloned embryos in artificial—or real—wombs. He said the temptation to conduct these experiments will be difficult to resist.

And physician/columnist Krauthammer, answering a call to “let science roll” from Daniel Foster, MD, chair of the Department of Internal Medicine at the University of Texas Southwestern Medical School, said, “We let science roll in the 20th century and look what happened. We got eugenics. We got Tuskegee. We got such horrors in mid century that we needed the Nuremberg Code.”

James Wilson, PhD, professor emeritus of management and public policy at the University of California, Los Angeles, countered that the slippery slope argument could have obstructed every conceivable advance: “We must not invent surgery because use of the scalpel to take out an appendix will inevitably . . . lead to the selling of kidneys and livers on the public market. We must not allow neurosurgery, even to cure a terrible tumor, because it will inevitably lead to lobotomy. We must not invent cars because they will lead to fatalities.”

Later, as Kass wrapped up the debate, he said that the slippery slope argument is appropriate. “Development itself is a continuum and the value of embryonic cells increases as they mature, he said. If scientists can make the resulting new tissues medically useful, “it will be hard to resist” practices more ethically questionable than embry research.

A HIGHER PLANE

The session then shifted to a comparison of in vitro fertilization with research cloning. In both endeavors, scientists knowingly create dozens of embryos that will never grow beyond microscopic size. Kass, however, maintained that intention or motive places in vitro fertilization on a higher moral plane than embryo creation—cloned or not—for research, saying “the deliberate exploitative disposition is what bothers me.”

This judging-by-intention amused Oregon’s Backlar. She laughed after a reporter outlined the argument and said, “None of these arguments are new. It’s like, ‘If it’s not to have babies, you’re not supposed to do it.’ They’re borrowing the straight-line Catholic ban on sex” not intended for procreation.

 Doubtless, arguments for a ban on embryo cloning for any purpose will be included in the council’s imminent report, but not as a formal recommendation. During the meeting, Kass himself may have offered the most plausible reason for the bet-hedging. “[N]obody would want to see us as callous to the needs of suffering humanity. Nobody would want to see us [as] cavalier regarding the treatment of nascent life. . . .” □

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