Birthday of a Breakthrough: Fibronectin Research Proves Important, But Not As Originally Expected

In the early 1970s, still a few years before molecular biology and genetics would revolutionize cancer research, scientists assumed that some general change in surface chemistry must occur on tumor cells to distinguish them from normal cells. Find that one difference, they reasoned, and oncologists would gain a foolproof marker to diagnose cancer.

Thirty years ago this past November in the Proceedings of the National Academy of Sciences, a then 28-year-old English postdoc named Richard Hynes, Ph.D., reported that he may have found that foolproof marker. It was a hitherto unknown structural protein positioned on the surface of normal cells, but which was rare or conspicuously absent on tumor cells. Although Hynes would not directly speculate in his paper, it was tempting to imagine that tumor cells might cleave this seemingly growth-promoting surface protein as an essential step in metastasis.

Hynes’ discovery and work in other laboratories set in motion a rush to characterize this mysterious “cancer” protein. Although the cancer breakthrough soon proved to be a false alarm, research on this new structural protein, called fibronectin, would catalyze a string of seminal studies, including the first molecular investigations of cellular adhesion proteins and their receptors, today two hot areas in cancer research.

Despite fibronectin’s hall-of-fame credentials in 20th century cancer research, many scientists note on the 30th anniversary of Hynes’ publication that the protein’s best years may still lie ahead. As many note, the protein remains imperfectly understood, and further clarifying its fundamental role in cell adhesion, cell migration, cell survival, angiogenesis, and other biological processes could shed additional light on the cancer process.

In the Beginning

During a recent interview, Hynes recalled the experiments that led to his single-author PNAS article while he was a fellow at the Imperial Cancer Research Fund in London. “I’d been interested in cell surface proteins from my thesis, and there was a body of literature in the early 1970s suggesting that cell surface changes occur [during oncogenic transformation],” said Hynes, now a scientist at the Massachusetts Institute of Technology in Cambridge.

“The question was: Could one find out which molecules were on the surface of cells and whether they changed?”

Hynes tried unsuccessfully to label and compare surface proteins in a number of ways before he finally had success about a year later using a then-new iodination technique.

“I realized that all of the gels from the normal cells had a big plug of iodine at the top, and the ones from the transformed cells didn’t,” Hynes said, a suggestion that the tumor cells had somehow eliminated the protein. “So, there was something different there. I thought, ‘Oh, my goodness, this is fantastic. This is a big difference.’”

Hynes now laughs, but he and others did not know what to make of this abnormally large protein at the top of the gel. “One of the questions that came up was: Could proteins be that big?” said Hynes. “It seems silly now 30 years later, but a lot of people didn’t believe proteins could be that big. I even had to convince some people that this wasn’t some sort of big aggregate.”

Hynes named his big find with the descriptive, “large external transformation sensitive” protein, or LETS. “The protein was large and external,” he said. “It also was transformation sensitive, so that was the name, not to make any assumptions beyond what we knew.”

Interestingly, Hynes was not alone in discovering the protein. Senitiroh Hakomori, M.D., Ph.D., and colleagues at the University of Washington in Seattle independently published a few weeks later their discovery of the same molecule, calling it “galactoprotein a.”

The following year, Antti Vaheri, M.D., Ph.D., and colleagues at the University of Helsinki weighed in with what they dubbed “surface fibroblast antigen.”

But enthusiasm for the major breakthrough soon waned. At the time, dogma dictated that any cancer-initiating change must be true for all tumor types, and several groups found the change was not universal. But, more problematic, other laboratories could not consistently show that restoring the protein to tumor cells controlled their abnormal growth, as Hynes’ paper suggested. “It turned out not to be the central molecule—the switch,” added Hynes. “Actually, we now know there is no one central molecule. But, back then, we thought there must be a transforming switch. Everybody in the field had such simple-minded views.”

What Is It?

If LETS was not the switch, what was it? The protein clearly influenced tumor cells in culture, altering their shape and behavior. Follow-up work also would determine that it connects normal cells to the supportive, lattice-like extracellular matrix, much like a stitch joins fabric in a seam. It made sense that tumor cells either must snip the protein or possibly downregulate its production to break free of the extracellular matrix and metastasize. Even if fibronectin was not the central molecule, perhaps it still could point scientists in the right direction to find the elusive switch. Or, as turned out to...
be the case, the protein might lead scientists to more regulatory molecules and important cellular pathways often involved in the disease.

“There were lots of unanswered questions and work to do,” said Hynes. “This protein was the first clean molecular difference between normal and tumor cells, and people were trying to do the same sorts of experiments at the same time. So, the field was just ripe for an explosion. Over the next few years, everybody purified and fragmented fibronectin and did a sort of anatomy on the molecule to find out which bits did what.”

All of the slicing and dicing led to a Babel of names for the protein. Adding to the confusion was the Finnish group’s then-stunning discovery that this cell-surface protein was the same as “cold-insoluble globulin,” a protein that had been identified after World War II in plasma. Although researchers later determined that the proteins were slightly different structurally, the surprises continued when it was determined that the proteins were encoded by the same gene, marking one of the first examples of alternative splicing, now an important issue in biology.

By the mid 1970s, Vaheri and colleagues banded together and settled on a common name—fibronectin, joining the Latin fibra, meaning fiber, and nectere, meaning to bind or connect. “There’s a joke about scientists that they’d rather use each other’s toothbrushes than each other’s nomenclature,” Hynes said, laughing. “And so, those of us who had other names were resistant at first, but, by 1978, we just switched to fibronectin.”

**Seminal Studies**

The discovery of fibronectin prompted a reevaluation of the structural glycoproteins and extracellular matrix. Until then, most biologists had written off the extracellular matrix as a boring conglomeration of inert, uninformative molecules. But fibronectin suggested a different story, in which structural glycoproteins linked cells to the extracellular matrix but also participated in orchestrating various aspects of cell behavior.

“Fibronectin is particularly important because it became the paradigm for a molecular understanding of cell adhesion molecules,” noted Kenneth Yamada, M.D., Ph.D., who performed the first fibronectin reconstitution experiments on tumor cells and is now a scientist at the National Institute of Dental and Craniofacial Research at the National Institutes of Health. “Our field has established in a stepwise fashion—using analyses of the effects of cells in culture—that a single protein can regulate key cellular functions such as adhesion, shape, migration, and cell surface architecture.”

A decade after the discovery of fibronectin, Erkki Ruoslahti, M.D., Ph.D., a distinguished professor at the Burnham Institute in La Jolla, Calif., and colleagues identified the three-amino-acid consensus sequence that is necessary for fibronectin to attach to cells. The tripeptide, called RGD, would lead the way to another major biological prize—the integrins, a family of protein receptors that form the transmembrane link between structural glycoproteins and the cytoskeleton. “One thing about RGD is we found it in fibronectin, but we also found it in vitronectin [an adhesive protein in plasma and serum], collagen, and many different proteins,” said Ruoslahti. “So, it’s fundamental to the recognition of proteins by integrins.”

Fibronectin was the divining rod for these and other major discoveries, but the spotlight began to shift away from the protein in the early 1990s. “Well, it’s true that fibronectin now is just one of many matrix proteins, and that the integrins do the signaling,” said Hynes. “It has gone into the background over the last few years, and we’ve all worked on the integrins.”

“But fibronectin has been a cool molecule to work on,” he added. “In fact, the reason that it has kept going for 30 years is matrix and integrins are so important in a lot of different bits of biology. Fibronectin plays a role in thrombosis, development, cancer, inflammation, and other areas. So, you can work on it in a lot of situations and never get bored.”

**Fibronectin and Cancer**

In the mid 1980s, Hynes wrote, “The study of fibronectin, initiated by work with tumor cells, may eventually come full circle to shed new light on the bases of malignant behavior.” Almost 20 years later, is fibronectin starting to come full circle?

“It isn’t there yet, but it is coming full circle,” said Hynes. “I think we need to understand the role it plays in cancer progression better than we do. And, we need a better handle on its role in angiogenesis.”

Some say fibronectin might be more than just a component feeding into a larger cellular system. As Jacqueline Labat-Robert, M.D., a scientist at the University of Paris who has a longstanding interest in structural glycoproteins, summarized in a recent review article, studies suggest our bodies produce more fibronectin as we age, and, as proposed 30 years ago, tumor cells secrete enzymes that snip the protein. According to Labat-Robert, this creates “a vicious circle” of steady...
fibronectin production that ends up scissored into smaller, free-floating fragments that possess altered chemical qualities and which are “a frequent phenomenon” of a number of pathological states, including potentially cancer.

“I am sure that this topic will remain of crucial importance for the next decades,” noted Labat-Robert, adding that the fragment anastellin, which is derived from fibronectin, inhibits angiogenesis, tumor growth, and metastasis formation in laboratory studies. “I do agree that fibronectin fragments may have unique activities,” said Yamada. “However, we feel that fibronectin itself is a novel developmentally regulated protein that is transcriptionally regulated and functions to modulate integrin and cadherin function at specific sites. That is, it is not just a ubiquitous adhesion protein, but can serve as a regulatory protein.”

Ruoslahti said he now views fibronectin more broadly. “While fibronectin is the prototype adhesion protein, there is a lot of redundancy in the adhesion mechanisms,” he said. “So, I don’t think one can look at fibronectin in isolation. However, it is true that, in the anchorage dependence of tumor cells, it’s more important for their survival to be able to attach to fibronectin than to some other protein.” “I think that we all feel that fibronectin has been an incredible conceptual gold mine,” continued Yamada. “The ideas and concepts that it has generated should have considerable relevance for our understanding of the metastatic process even if fibronectin turns out to play only an occasional role. More likely, though, it may well have roles, but often only in concert with the large number of other extracellular matrix proteins and proteoglycans that act through analogous molecular mechanisms.”

—Robert Longtin

‘Mother of Psycho-Oncology’ Discusses Field’s Need for Parity and People Power

Jimmie C. Holland, M.D., is often referred to as the mother of psycho-oncology. After 26 years, she has stepped down as chairman of the Department of Psychiatry & Behavioral Sciences at Memorial Sloan-Kettering Cancer Center, New York, but continues to lead the field in both the United States and throughout the world. Her goal is to make behavioral care more accessible as well as to increase research in the field.

How did you get involved in psycho-oncology?

I went into psychiatry, but I found myself interested in how people who are psychologically healthy face catastrophic events in their lives, like serious illness. I then married and stayed home with children. Meanwhile, my husband Jim [James Holland, M.D.], who was chairman of the Cancer and Leukemia Group B, would bring colleagues home to dinner and they would talk about the new treatments and protocols that were ongoing. I would ask, “But how do these patients feel about this?” and they would say, “We don’t have time to talk about how they feel. We have to look at the toxicities in terms of the blood and kidneys, and so on.” It was then that I vowed that when the children got a little bigger and I had more time, I would look at this.

At that time, there was virtually nothing going on [in mental health for cancer patients] at most places. So when I came to Memorial I was able to set up the first full-time academic service in a cancer center, certainly in the United States and probably in the whole world.

Around 1977, we began in this country to see better cancer treatments, to begin to see people being cured of cancer, and we began to tell people their diagnosis and treatment options. The taboo and stigma had diminished enough that we could talk about it. We began to see books written about cancer. We saw [Margaretta] Happy Rockefeller and Betty Ford as public figures announce that they had breast cancer. These were all just extraordinary changes. We really began to be able to have a subspecialty of psychology at that time because we could finally ask people, “how do you feel about this?”

You have been in the field for more than 25 years, what are the most significant changes you’ve seen?

I think there is an enormous change in the culture of cancer care. There is much more of an acceptance that it is a team that takes care of the patients. Today there is an acknowledgment that every person on the team—the nurse, the social worker, the mental health person, the chaplain—all have different roles to play with the patients and they may all be needed in the care of any particular patient.

We still deal with the stigma of mental illness and the taboos that go with that. There is still the feeling that with an illness you have to be strong, and if you need some psychological help, that is a sign you are a wimp or your will isn’t strong enough to tolerate the stress or the pain. Although that attitude is diminishing, it still prevents some patients from admitting to psychological stress and from asking for help or being willing to come for counseling.

You mentioned that cancer care is a team process. Do most medical oncologists accept the value of psycho-oncology?

I think so. If a patient has significant depressive or anxious symptoms or has problems that are complicating his or her ability to tolerate their treatments or adhere to them, I think most oncologists would see a need to bring in a member of the psychosocial team to consult and to follow the patient and intervene as appropriate.

Not every institution or oncologist’s office has the luxury of having a mental health person, but we are in the process,
through the American Psychosocial Oncology Society, of developing a help line so we can identify counselors in different parts of the country, including in areas where oncologists might not have someone or might not know who was available in their geographic area.

**What would you say have been the biggest hurdles the field has faced during your tenure?**

I think the biggest impediment at the outset was attitudinal, the idea that there was no place for mental health in the care of patients with cancer. We had to show that there was a role for it and that it made it easier for the oncology team to take care of patients.

We had to bring to the field the idea that patients' quality of life—by that we mean how they are functioning in physical, psychological, social, and sexual domains—as related to health is as crucial as any other aspect of care. We began to get it across when we first began to measure quality of life back in the early 1980s in the Cancer and Leukemia Group B. I think we were the first group to try to measure quality of life.

We continue to face this attitudinal hurdle in that reimbursement for mental health counseling is quite low, and we need parity in health insurance reimbursement policies.

We will continue to lobby to get parity for mental health services because when people are physically ill, they have a series of issues to cope with that make it crucial that counseling is available to them, and it needs to be part of their medical health insurance, not as part of a behavioral carve out, which is the way many employers have organized their health insurance.

As it stands now, you can be working in a hospital and taking care of a patient and all of their care is reimbursed—then you hear that there is no reimbursement for the psychological/psychiatric consultation. That has to be done by somebody across town 2 weeks later. And yet here is this person, ill, agitated, in the hospital, and climbing the walls. It is really detrimental for hospitalized patients and it doesn’t make any sense.

**Why are clinical practice guidelines so important?**

Right now there is no institution that audits or monitors for psychological care. There is nothing that says you should have X number of social workers or mental health counselors in a group. The only thing that guides people is their conscience.

We have written guidelines for the management of distress, and this is the beginning of defining the expectation that psychological care is part of total care and that there is a benchmark in this area the same as there is in other aspects of care.

Once we have that benchmark, we can begin to monitor performance in the treatment of distress, as we have in pain, bioethics, and informed consent. Until then, we are not going to get people moving toward giving adequate psychosocial care.

**At a recent symposium on psychosocial oncology, one of the researchers expressed concern about a lack of methodological and statistical rigor in the field. Is that something you see as a problem? Is it getting better?**

I think what has happened is that this is a new field, and we have had to develop new assessment tools for a lot of phenomena that we study. All of the phenomena we study are subjective, from pain to anxiety to depression, so we have had to come up with validated scales to measure them. Meanwhile, the field has been under-funded and we don’t have, as yet, enough well trained researchers to address all of the methodological and research design issues.

We have tended to have too small studies and to use different instruments in different places, and that has made it look like a hodge-podge of outcomes and data that can sometimes be contradictory. We can address this by encouraging the field toward larger multisite trials that will meet statistical power to draw conclusions. We need to use a core set of assessment tools so that we can look across our studies. We will then begin to have the possibility to look at meta-analyses, which has been difficult up to this point.

I think we need more rigor in the field, no question about it. But we’ve come a long way in 25 years.

**What are the major barriers to providing cancer patients with adequate psychosocial services at this point in the United States?**

The biggest barrier is in adequate reimbursement. We have to go to philanthropy. We have to get the institutions to take a loss on it. Oncology practices that want psychologists to work with them in their clinic have to find money to pay for it out of their clinic, whereas their own income comes from reimbursement for services.

There is simply not enough reimbursement for our services so that we can pay for ourselves in most settings. We need to somehow get across the need for having these services as a part of total cancer care and reimbursed in the same way and at the same rate.

**How do you go about doing that?**

Part of my goal at the moment—no longer being chairman and having a little more time—is to have the American Psychosocial Oncology Society...
become a vehicle for giving us a louder voice. My goal is that it will be similar to the American Pain Society. We plan to bring in nurses, social workers, chaplains, psychiatrists, and psychologists all into one organization and work with the wellness communities and the advocacy organizations, which are so powerful and vocal.

I think that unless we can begin to get a louder voice and lobby we are not going to change things. We are having our first national meeting for the multidisciplinary group at the end of January in Orlando.

What is happening at the international level?

We formed the International Psycho-Oncology Society in 1984. We will hold our 6th world congress in Copenhagen in August, and we are petitioning the World Health Organization to consider the society as a nongovernmental organization.

It looks like one of our first projects with WHO will be to try to help them develop guidelines for what the psychosocial aspects of cancer care should be in [countries with different levels of development]: What should they be in the Western world? What should they be in the emerging nations, like eastern Europe, and what should they be in Africa? When there is so little in the way of resources and therefore nothing much to do for their cancer, then treatment aimed at comfort becomes key.

Is there anything else you would like to add?

The comment I would make is that there is an enormous need for support for training in this field, we need to bring people into the field but to do that we need incentives for predoctoral students, for doctoral training, with fellowships and so on. There is an enormous amount of work to be done now that we have overcome some of those initial attitudinal barriers, and there is enormous opportunity for making some leaps forward with better designed studies and with more randomized controlled studies and better evidence-based practice guidelines.

—Rabiya S. Tuma

In Different Cultures, Cancer Screening Presents Challenges

On the whole, rates of breast cancer screening by mammography have increased steadily in women ages 40 and older, Pap smear use for cervical cancer screening is increasing slightly among women ages 18 and older, and colorectal cancer screening rates have recently increased but remain low among people ages 50 and older. But those rates vary among people of different ethnic backgrounds, and understanding how cultural beliefs and other factors play into those disparities can help researchers develop better cancer screening programs.

One of the fundamental issues underlying how cultural beliefs influence behavior is understanding that social norms for discussing various topics differ among groups. “There are whole different ways of communicating and relating to others that go beyond a belief in fatalism or [a sense of] embarrassment about cancer screening—that is the most superficial sort of level looking at culture,” said Rena Pasick, Dr.P.H., associate director for education and outreach at the University of California at San Francisco Comprehensive Cancer Center. “One of the big cultural differences is the difference between collectivist cultures versus individualist cultures.”

Whether people function more fundamentally as autonomous individuals (individualist) or as part of a group (collectivist), this difference has a specific impact on communication. “In collectivist cultures, such as Latino and many Asian cultures, communication is much more indirect,” said Pasick. This is one reason researchers find that approaching people from collectivist cultures with specific, direct information about cancer usually does not work.

“Having control over one’s health may just not be a familiar concept for people from other cultures,” said Helen Meissner, Ph.D., chief of the National Cancer Institute’s Applied Cancer Screening Research Branch. “And it’s important for us to recognize that in how we communicate, because in fact it may be that what we think we are communicating is just alien or unfamiliar to people.”

One such example is research by Hee-Soon Juon, Ph.D., assistant research professor of health policy and management at the Johns Hopkins Bloomberg School of Public Health, who recently examined the adoption of Pap screening by Korean-American women. Juon found three beliefs common in the Korean culture that made Korean-American women less likely to report having had a recent Pap smear: Women who reach menopause do not need Pap tests very often, after women stop having children they do not need Pap tests, and it is embarrassing to have a Pap test.

In the study, Juon found that “about 40% of Korean-American women said that they did not have regular screening because [they had] no gynecological problems. Many elderly women think that a Pap test once in a lifetime will take care of the rest of their life problems.” Korean-American women who have lived in the United States longer tend to become more acculturated and to use gynecological preventive care, said Juon.

Another research issue for gathering information about different cultures is how various questions are interpreted by the audience. “We did survey work in three or four different languages in one study where you want your data to be comparable across cultures and languages and they’re not,” said Pasick, who has worked in African-American, Latino, Chinese, Vietnamese, and Filipino communities. “You can translate your questions and go out and ask them and you will get data back, but it does not mean that you’ve really asked the same question with the same meaning to these different cultures,” she said.

To avoid problems with these and other types of interpretation bias, researchers at Bradley University in Illinois are seeking funding for a proposal that uses a tool most common
in the social sciences, the ethnographic approach. Kerry Ferris, Ph.D., associate professor of sociology at Bradley, said the approach is “not novel in sociology—but in applied health research it is.” The study, being designed to learn more about the subtle social and cultural factors that influence screening rates among poor African Americans within a single community, would avoid the participant bias Ferris’ colleague, Marjorie Getz, instructor in Bradley’s department of psychology, said is inherent in many studies.

“[Participants] know they are being interviewed and there’s always the bias of the individuals wanting to present themselves in a socially desirable framework,” said Getz. “We want to get at the meaning structures—learn how to approach, to appeal, and to understand people’s perspective,” said Ferris.

Another factor inextricably linked to how cultural beliefs play a role in the likelihood that a person will be screened for cancer is socioeconomic status. “If you look at the use of pretty much all cancer screening tests, you see that having health insurance and having a usual source of health care are two of the strongest predictors of whether someone’s going to have a recent screening test or not,” said Meissner. “Most people don’t pay for screening or preventive services out of pocket. It’s something that we pay for with health insurance. So if you don’t have health insurance or a usual source of health care then you’ll be less likely to get screened.”

This applies particularly to immigrants. “Recent immigrants, for instance,” said Meissner, “usually are more socioeconomically disadvantaged when they first come to the U.S., so they may not have jobs that provide health insurance or the resources to have access to preventive services.”

Meissner believes it is difficult to know what effects are from cultural beliefs versus the result of low socioeconomic status. “It’s not to say that culture isn’t important—because it most certainly is—but often many of the disparities that we see in screening are related to socioeconomics. Sometimes it’s hard to disentangle that from culture.”

To address these types of issues that apply across a broad range of populations in the United States, the Centers for Disease Control and Prevention, in partnership with the NCI, sponsor the Cancer Prevention and Control Network through CDC’s Prevention Research Centers. Five of the centers make up the network, which was funded “to create an infrastructure to conduct community-based participatory research and to increase use of cancer screening and use of an informed decision-making process,” said Katherine Wilson, Ph.D., behavioral scientist and public health educator at CDC’s Division of Cancer Prevention and Control.

Now in an infrastructure-building phase, the network’s members are beginning to design protocols around evidence-based strategies. A center in South Carolina is doing a study to increase the use of mammography by rural African-American women and a center in Texas is designing an intervention to increase colorectal cancer screening among Latinos. “One of the benefits of the network is that it’s geographically dispersed and topic-interest dispersed,” said Wilson. “The purpose of funding infrastructure development was to allow time for the centers to strengthen their community networks so they could apply [for funding] wherever they want. We don’t want them tethered to us.”

Pasick has stepped back from researching cancer-screening interventions in favor of learning more about culture in general. “Intervention research led me to realize that there are issues about culture that we didn’t understand,” said Pasick. “Just as you have basic research in the laboratory to look at how different drug components interact with different things...
before you actually go out and create a drug and use it, I want to try to better understand culture and behavior and communication before I will go back again and work on intervention,” said Pasick. In one study, she is now examining the different styles of communication that go on between providers and patients in African American, Latino, and Chinese cultures, with a focus on colorectal cancer screening.

Although cultural barriers are often mentioned as one reason for the disparities in cancer screening among different ethnic and cultural groups, Meissner looks at culture in another way. “I hate to say ‘cultural barriers’ because I don’t like to think of culture as a barrier,” said Meissner. “A culture is what it is and that’s not the barrier. The barrier is that if we don’t understand the culture then we can’t be very effective in communicating what we think may be beneficial for health—like getting cancer screening tests.”

—Christine Theisen

**Related Links**
Checking Out the Neighborhood: Researchers Examine Environment’s Effect on Tumor Growth

Molecular biologists have focused on mutations in tumor cells in an attempt to understand cancer, but as techniques for manipulating genes and cells improve, researchers are finding that it takes more than just a cancer cell to make a tumor. New research presented in October at the American Association for Cancer Research’s International Conference on Frontiers in Cancer Prevention Research indicate that both stromal cells within and near the tumor influence cancer cell growth, as do the senescent cells within the surrounding tissue.

When Robert Weinberg, Ph.D., a lead scientist at the Whitehead Institute in Cambridge, Mass., and colleagues injected three different types of human cancer cells into mice, they found that the different cell types required different amounts of time to form tumors despite the fact that all three cell lines had been transformed with the same genetic changes. After just 15 days, 100% of the human embryonic kidney cells had formed tumors, whereas the fibroblasts required 20 days to form tumors, and by day 60 only 52% of the human mammary epithelial cell (HMEC) injections had given rise to tumors. The differences in the time required to give rise to tumors implied that something outside of the cancer cells themselves was limiting tumor formation, said Weinberg.

The team uncovered a big clue to what this rate-limiting factor might be when one of the researchers looked in the microscope—a technique, Weinberg said, he generally discourages his trainees from using. The investigator found that, although a single cell type had been injected, the tumors that the cells gave rise to were complex.

“He discovered something pathologists have known for at least 100 years,” said Weinberg. “Tumors are histologically complex.” As many as 80% of the cells within the tumor are stromal cells, including fibroblasts, epithelial cells, mast cells, and macrophages. Given these data, the team hypothesized that a rate-limiting step in tumor formation following injection of the transformed cells was the recruitment of supporting cells. To test this hypothesis, the investigators mixed the transformed HMECs with either Matrigel (BD Biosciences), which is a mixture of extracellular matrix proteins and growth factors, or with fibroblasts and then injected the combinations into mice. The tumors formed with the HMEC–Matrigel combination in 50 days, whereas the HMEC–fibroblast combination prompted tumors to form in just 25 days.

Although these results clearly support the idea that part of the delay in tumor formation is the time it takes different tumor cell types to recruit support cells, the team began to consider whether the support cells are innocent participants in the tumorigenic process or if, after they have been in close proximity to cancer cells during the long time it takes most spontaneous cancers to arise, they too take on abnormal characteristics.

To test this idea, they isolated fibroblasts from normal human mammary tissue and from tumor biopsies. When they injected the transformed HMECs into mice with either the normal fibroblasts or the fibroblasts from tumors, they found that the fibroblasts from tumor biopsies accelerated the rate of tumor formation relative to the cells from normal tissue. Additionally, fibroblasts taken from outside the margin of the tumor, where tissue is ostensibly healthy, stimulated growth at an intermediate rate, in between that of the tumor-associated fibroblasts and the normal cells. These data, said Weinberg, imply that perhaps tumor inception has something to do with the receptiveness of the tissue surrounding the cancer cells and that, even if the support cells start off relatively normal, they ultimately become part of the problem in cancer growth.

In a separate set of work, Judith Campisi, Ph.D., a senior scientist at the Lawrence Berkeley National Laboratory in Berkeley, Calif., and a professor at the Buck Institute for Age Research in Novato, Calif., reported that senescent cells may be actively promoting tumor formation as well. When healthy cells receive potentially cancer-inducing insults, they enter a state of senescence, or permanent growth arrest. Until recently, researchers regarded senescence as a relatively harmless fate for cells. However, Campisi’s team found that this might not be the case.

“When cells become senescent, they do not simply turn off their cell cycle,” said Campisi. “It turns out that senescence is a very complex phenotype. Importantly, these cells have altered functional capabilities.” In fact, her team has found that senescent cells secrete proinflammatory cytokines, growth factors, and matrix metalloproteinases that appear to have a direct effect on neoplastic cells.

For example, if the scientists plate different types of epithelial cells on a lawn of either presenescent or senescent fibroblasts, they find that neoplastic epithelial cells show a growth advantage in the presence of the senescent cells. “Premalignant cells are stimulated by senescent cells, but there is no preferential stimulation of normal cells grown on presenescent or senescent lawns,” said Campisi.

To see if senescent cells could alter the growth patterns of cells in an animal model, the team injected preneoplastic SCp2 cells into mice, either alone or mixed with presenescent or senescent fibroblasts. Neither the SCp2 cells
injected alone or with the presenescent cells gave rise to tumors, but the cells mixed with senescent fibroblasts formed very aggressive tumors. Thus, it is clear that senescent cells are actively stimulating tumor cell growth, Campisi concluded.

Campisi argued that, because the number of senescent cells increases as a person ages, this type of signaling could be instrumental in driving mutant cells into full-blown tumors. Therefore, she said, if researchers could find a way to kill senescent cells or reverse their phenotype, they might be able to substantially delay the onset of cancer.

Recently her group found that, if they alter the expression levels of p53 and p16 tumor suppressor proteins using lentivirus gene transfection systems, they could force senescent cells to re-enter the cell cycle. “I was skeptical that this would work,” said Campisi. “Until 2 years ago, we didn’t think it was at all possible; we always considered that the senescence phenotype was irreversible.” Now, with the proof of principle in hand demonstrating that the phenotype can be reversed, Campisi thinks it might be possible to work on a way to use the information to slow tumor induction in whole tissues.

“It is really remarkable that senescent cells are secreting something that enhances proliferation of premalignant cells,” said Nancy Colburn, Ph.D., chief of the Gene Regulation Section at the National Cancer Institute’s Center for Cancer Research.

Both Weinberg’s work and Campisi’s fit into a more modern paradigm in which the context of the tumor’s development is as important as looking at the mutations within a tumor cell. “It is important for us to realize that the place where we are going to have the biggest impact in prevention is by altering or limiting gene regulation at the rate-limiting steps in carcinogenesis,” including tumor initiation and promotion, said Colburn. “Based on these talks it is clear that the critical gene expression might not just be in the tumor cells but in the surrounding stroma. And sometimes that communication is going to bounce back and forth between them.” —Rabiya S. Tuma

Awards, Appointments, Announcements

■ The American Society of Hematology recently announced the winners of several awards. Gary Gilliland, M.D., Ph.D., received the 2003 William Dameshek Prize for his work on the molecular pathogenesis of leukemia. Gilliland is an associate professor of medicine at Brigham and Women’s Hospital and Harvard Medical School, and is a faculty member of the school’s Biological and Biomedical Sciences Program in the Department of Genetics. He is also the Director of the Leukemia Program at the Dana-Farber Harvard Cancer Center, an associate investigator of the Howard Hughes Medical Institute, and a physician at Brigham and Women’s Hospital and the Dana-Farber Cancer Institute.

Janet Rowley, M.D., was awarded the Henry M. Stratton Medal, which honors an individual whose contributions to hematology are well recognized and have taken place over a period of several years. In 1972, Rowley discovered a chromosomal translocation in acute myelogenous leukemia. Discoveries of chromosomal translocations in other types of leukemia followed, cementing the idea that these genetic abnormalities were an important component of the disease. Rowley is the Blum-Riese Distinguished Service Professor in the Departments of Medicine, Molecular Genetics and Cell Biology, and the Human Genetics Section of Hematology/Oncology at the University of Chicago.

Sen. Dianne Feinstein (D-Calif.) received the 2003 Public Service Award from the American Society of Hematology. Feinstein serves as the co-chair of the Senate Cancer Coalition as well as vice-chair of the National Dialogue on Cancer.

Claude Lenfant, M.D., received the society’s first-ever Outstanding Lifetime Service Award. Lenfant, the former director of the National Heart, Lung, and Blood Institute, helped facilitate the formation of the Thalassemia Clinical Network, the Blood and Marrow Transplant Clinical Research Network, and the Transfusion Medicine/Hemostasis Clinical Trials Network.

■ Belinda Seto, Ph.D., has been named deputy director of the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health. Seto was previously the acting deputy director for extramural research at the NIH, where she served as adviser to the NIH director on extramural policy issues and was responsible for developing and implementing policies and procedures for extramural research and training programs funded by the NIH.

■ Larry Norton, M.D., has been named deputy physician-in-chief for breast cancer programs at Memorial Sloan-Kettering Cancer Center, New York. Norton formerly served as the chief of the Division of Solid Tumor Oncology in the Department of Medicine. He will continue to serve as the medical director of the Evelyn H. Lauder Breast Center. He served as president of the American Society of Clinical Oncology from 2001 to 2002.

■ The Susan G. Komen Breast Cancer Foundation announced the winners of its Brinker Awards for Scientific Distinction.

The 2003 Brinker Award winner for advancements in the field of clinical research is Walter Churchill Willett, Ph.D., of Harvard University’s Department of Nutrition in Cambridge, Mass.

Mina J. Bissell, Ph.D., director of the Life Sciences Division at the Lawrence Berkeley National Laboratory in Berkeley, Calif., received the 2003 Brinker Award in the category of research. The awardees received a $10,000 honorarium to be applied to their work.