Why do discoveries take so long to reach the clinic?

When your genes aren’t to blame, what is?

Is tumor sequencing ready to ramp up?
Window on Whitehead

Science for me and YouTube

My daughter is studying biology in high school, and her experience is both amazingly like and amazingly unlike mine at her age.

The amazingly unlike part isn’t hard to figure out. My old biology textbook doesn’t mention recombinant DNA, which had barely been invented. My daughter lives in a world in which the human genome has always been sequenced, sheep have always been cloned, and a certain number of your friends have entered this world via in vitro fertilization.

What’s amazingly like is how she’s learning: teacher, textbook and a little time in the lab. Oh, her biology teacher is fond of educational websites, but those aren’t really important for them.

However dramatically medicine has changed in my lifetime, that’s nothing compared to what she’ll see. As both a medical consumer and citizen, she’ll need to understand the strengths and limitations of the major advances now lurking just over the horizon.

But I don’t think she’ll spend much time reading about them in print.

We still get print newspapers, news magazines and science publications delivered at home. My daughter rarely reads any of them.

What she does, like her friends (and her parents), is spend time on the Web. Lots of time. The Web will be her main channel for tracking the future of biomedicine, as it will be for so many other topics.

And when she can, she’ll be watching videos on the Web.

For years, Whitehead has been filming our principal investigators as they give lectures to our non-scientific staff, and posting those films on our website (www.whitehead.mit.edu/news/video_gallery).

But, as everyone knows, the popularity of Web videos is soaring now with the combination of powerful PCs, fast Internet connections, inexpensive digital video hardware and software, and Web video aggregators.

That’s excellent news for public understanding of biology. Along with the extraordinary power and promise of today’s research comes extraordinary complexity. The popularity of Web videos gives us new ways to dive through all those details to learn about today’s biomedical research.

Enjoy an animation of proteins doing their dances together, and suddenly you understand the basic concept. Watch a researcher explain what her lab studies, and it becomes clear. Show students a postdoc describing how he got excited about his field, and you can inspire them too.

What’s really new is that people don’t have to wander across your website to find this great stuff. Today, for instance, YouTube’s most famous science video shows the startling results of dropping a Mentos mint into a bottle of Diet Coke. But the video aggregation website also is becoming a major resource for high school teachers swapping classroom videos.

So we at Whitehead and our colleagues at other research institutions will be expanding our use of video, along with podcasts and other Web goodies. It’s another way for our scientists to tell their stories—and sometimes, my daughter and her peers will tune in. —Eric Bender

On the cover

Researchers study an enormous range of possible causes and cures for cancers—and the early results of more powerful understandings are just now filtering into clinics. Here, a cultured cell with structure typical of melanoma or breast cancer. Image by Stone

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Cover stories: Questions on cancer

12 A slow saga of success
Ever wondered why the journey from lab discovery to the clinic takes so long?

16 The unusual suspect
Cancer researchers look beyond the genome to the epigenome

21 Out of sequence?
Scientists debate whether it’s time to tackle tumor genomes and epigenomes

Features

5 The RNA connection
Joint projects by David Bartel’s lab highlight the crucial role of collaborations

6 Biofuels and the gene pool
The power of yeast genetics might make ethanol fuel much more cost-effective

8 Mouth to mouth
What can a frog mouth tell us about human birth defects?

10 Network news
Hui Ge sifts through oceans of data to explore how genes collaborate

24 Biology’s big tent
Meet some of the young researchers pouring into life sciences from other fields

26 Targeting the agents of disease
In the war on infectious disease, are we spending smart?

Departments

2 Science digest
Cracking open the black box of autoimmune disease, and a gene that shuts itself off

22 Whiteboard
The link between epigenetics and cancer

28 Fast FAQs
For all the controversies, it’s still early days for stem cell science

29 On the Web
Twenty-five years ago, Jack Whitehead signed the agreement creating the Institute that bears his name
Cracking open the black box of autoimmune disease

Autoimmune diseases such as type 1 diabetes, lupus and rheumatoid arthritis occur when the immune system fails to regulate itself. But researchers have not known precisely where the molecular breakdowns responsible for such failures occur. Now, a team of scientists from Whitehead Institute and Dana-Farber Cancer Institute have identified a key set of genes that lie at the core of autoimmune disease, findings that may help scientists develop new methods for manipulating immune system activity.

“This may shorten the path to new therapies for autoimmune disease,” says Whitehead Member and MIT professor of biology Richard Young, senior author on the paper that appeared online in January in Nature. “With this new list of genes, we can now look for possible therapies with far greater precision.”

The immune system is often described as a kind of military unit, a defense network that guards the body from invaders. Seen in this way, a group of white blood cells called T cells are the frontline soldiers of immune defense, engaging invading pathogens head on.

These T cells are commanded by a second group of cells called regulatory T cells. Regulatory T cells prevent biological “friendly fire” by ensuring that the T cells do not attack the body’s own tissues. Failure of the regulatory T cells to control the frontline fighters leads to autoimmune disease.

Scientists previously discovered that regulatory T cells are themselves controlled by a master gene regulator called Foxp3. Master gene regulators bind to specific genes and control their level of activity, which in turn affects the behavior of cells. In fact, when Foxp3 stops functioning, the body can no longer produce working regulatory T cells. When this happens, the frontline T cells damage multiple organs and cause symptoms of type 1 diabetes and Crohn’s disease.

However, until now, scientists have barely understood how Foxp3 controls regulatory T cells because they knew almost nothing about the actual genes within Foxp3’s purview.

Researchers in Richard Young’s Whitehead lab, working closely with immunologist Harald von Boehmer of the Dana-Farber Cancer Institute, used a DNA microarray technology developed by Young to scan the entire genome of T cells and locate the genes controlled by Foxp3. There were roughly 30 genes found to be directly controlled by Foxp3. One, called Ptpn22, showed a particularly strong affinity.

“This relation was striking because Ptpn22 is strongly associated with type 1 diabetes, rheumatoid arthritis, lupus and Graves’ disease, but the gene had not been previously linked to regulatory-T-cell function,” says Alexander Marson, an MD/PhD student in the Young lab and lead author on the Nature paper. “Discovering this correlation was a big moment for us. It verified that we were on the right track for identifying autoimmune-related genes.”

The researchers still don’t know exactly how Foxp3 enables regulatory T cells to prevent autoimmunity. But the list of the genes that Foxp3 targets provides an initial map of the circuitry of these cells, which is important for understanding how they control a healthy immune response.

“Autoimmune diseases take a tremendous toll on human health, but on a strictly molecular level, autoimmunity is a black box,” says Young. “When we discover the molecular mechanisms that drive these conditions, we can migrate from treating symptoms to developing treatments for the disease itself.”
Dueling RNAs protect cells

Researchers have found that a class of RNA molecules, previously thought to have no function, may protect sex cells from self-destructing. These findings were published in November in Cell.

Central to this discovery is the process of gene expression. When a gene is ready to produce a protein, the two strands of DNA that constitute the gene unravel. The first strand produces a molecule called messenger RNA, which acts as the protein’s template. Biologists call this first strand of DNA the “sense” or “coding” transcript. Even though the other strand doesn’t contain a protein recipe, it may also, on occasion, produce an “antisense” RNA molecule, one whose sequence is complementary to that of the messenger (sense) RNA. Antisense RNA has been detected for a number of genes but is largely considered a genetic oddity.

Using baker’s yeast, Cintia Hongay, a postdoctoral researcher in the lab of Whitehead Member Gerald Fink, discovered that in the case of a gene called IME4, the antisense RNA blocks the sense RNA. Antisense RNA has been detected for a number of genes but is largely considered a genetic oddity.

“The first case where a specific function in a higher cell for antisense RNA has been found,” says Fink, senior author on the paper. “This points to an entirely new process of gene regulation that we’ve never seen before in eukaryotic cells.”

There is a method to this sense/antisense madness. When conditions around yeast cells are good and rich in nutrients, the cells divide by mitosis—that is, the DNA duplicates so that each daughter cell receives exactly the same number of chromosomes as the original cell. But when the yeast cells are starving, IME4 switches on and activates a process called meiosis. Here, the cells divide into germ-cell spores that, like mammalian egg and sperm cells, have half the normal number of chromosomes.

Yeast spores withstand this harsh environment far better than the larger cells from which they spring.

But in some cases, flipping the meiotic switch can be catastrophic. If a cell with only one copy of each chromosome (a haploid cell) is forced into meiosis, its progeny won’t survive. Fortunately, such destructive meiotic division is avoided in haploid cells because they continually produce IME4 antisense RNA, blocking the production of sense RNA. Antisense IME4, then, safeguards against meiosis in cells that can’t handle it.

“This is really the first time we’ve seen a gene regulate itself in this way,” says Hongay. “Considering how widespread these antisense transcripts are,” adds Fink, “I wouldn’t be surprised if these findings eventually lead us to discover an entirely new level of gene regulation.”

New class of RNAs is revealed

An entirely new type of RNA molecules has been discovered by scientists in the lab of Whitehead Member and Howard Hughes Medical Institute Investigator David Bartel.

Reporting in January in Cell, the team describes identifying more than 5,000 of these new molecules, termed 21U-RNAs, in the C. elegans worm. Each molecule contains 21 chemical building blocks (nucleotides), and each begins with the chemical uridine, represented by the letter U. In addition, each of the 5,000 different 21U-RNA molecules comes from one of two chromosomal regions. While the 21Us themselves have diverse sequence patterns, the DNA sequences residing just outside those that give rise to each 21U are identical.

“Using the sequence pattern, we can predict where additional 21U-RNA genes might reside,” says Bartel. “Combining these predictions with the 5,000 that we experimentally identified, we suspect that there are more than 12,000 different 21U-RNA genes in the genome.” Because each gene typically produces a unique 21U-RNA, a very large diversity of molecules is made.

While the genes are “spread out over a wide swathe of the genome, they all share common requirements for expression and common structural features,” says Bartel-lab PhD student J. Graham Ruby, lead author on the paper. “The fact that 21U-RNAs share this common structure and origin suggests an important function,” comments MIT professor and Nobel laureate Phillip Sharp, who was not part of the research team.
Cancer pathway exposed

In the mid-1990s when Whitehead Member David Sabatini, then a graduate student at Johns Hopkins University, discovered a protein called mTOR, he had no idea that within a decade this finding would catch the attention of drug companies worldwide.

Sabatini and others had been investigating the mechanisms behind the success of rapamycin, a drug that helps prevent organ rejection in transplant patients. They found that the drug works by blocking a previously unknown protein, which was eventually dubbed mTOR (for mammalian target of rapamycin).

Scientists soon found that mTOR helps cells detect environmental nutrients and protein growth factors, which in turn influence the size of a cell. When rapamycin blocks mTOR, it tricks the cells responsible for organ rejection into believing that they are starving.

But scientists now realize that mTOR’s significance reaches beyond its relation to rapamycin. mTOR also plays an integral role in many cancers, including prostate and brain cancers.

Reporting in December in Developmental Cell, postdoctoral scientist David Guertin and others in Sabatini’s lab describe using genetic tools to show that mTOR is a critical regulator of a prominent cancer protein called AKT.

In a previous paper, then-postdoctoral researcher Dos Sarbassov, Sabatini, Guertin and colleagues showed that if proteins critical for one aspect of mTOR activity were inhibited, AKT could not activate. This implied that blocking mTOR might prevent AKT from driving tumor growth. “But that paper relied on biochemical techniques, like RNAi, to interfere with mTOR, and so not everyone in the scientific community accepted it,” says Sabatini. “To get the conclusive evidence that mTOR is a major player, you need to knock it out altogether. And that’s what we did here.”

In the recent study, Sabatini’s lab developed mouse models in which genes necessary for this aspect of mTOR activity were deleted. Again, AKT was significantly inhibited in these animal models. “Discovering this new branch of mTOR signaling has changed how we think about mTOR’s role in cancer,” says Guertin. “This work has opened the door to new therapeutic strategies that could have a broad impact in the clinic.”

A new drug target for herpes?

For a family of viruses as widespread as herpes, relatively few drug targets exist. Now, scientists in the labs of Whitehead Member Hidde Ploegh and Harvard’s Rachelle Gaudet have solved the complex structure of a recently discovered protein that is found in a wide range of herpes viruses. This protein may prove to be a potential drug target.

Reporting in the March 9 issue of Molecular Cell, Whitehead postdoc Christian Schlieker described the use of X-ray crystallography to delineate the intricate structure of this protein, called M48 (pictured here in yellow). It turns out that M48 belongs to a class of proteins whose function is to remove ubiquitin (in magenta), a small molecule that flags broken proteins for disposal.

“We don’t know why the virus needs this particular function, but because all herpes viruses contain an activity very much like M48, it must be important,” says Schlieker. “The fact that the enzyme’s architecture is distinct from host proteins makes it an attractive target for therapeutic intervention.”
More than a third of the human genome is partially regulated by microRNAs— tiny snippets of RNA that can disable a gene’s ability to create proteins.

So it’s no surprise that the lab of Whitehead Member David Bartel, the first to report this surprisingly widespread role for microRNAs, has found many colleagues happy to collaborate. At the same time, “as our lab looks at the particular targets of particular microRNAs, then we become interested in what’s going on in other labs that specialize in those targets,” Bartel says.

Here’s a glimpse at some current connections for the 20-person lab—and it is just a glimpse. It shows only the principal investigators, not the postdocs and students who do all the bench work, let alone the ongoing streams of informal discussions. ¶
Now, the benefits of so intimately knowing this microscopic life form are reaching beyond biomedicine into the realm of global warming.

**Farming Fuel**

As politicians finally get serious about the need for the U.S. to decrease dependency on fossil fuels, there is one partial solution that they all like: ethanol.

But ethanol isn’t like crude oil. You can’t just drill down and then catch it as it gushes out. Instead, it takes a lot of energy to produce this colorless grain alcohol. The trick is to use the least energy possible to produce the most ethanol allowable.

So far, that’s been an elusive goal.

In the United States, ethanol is produced chiefly from corn, and working with corn demands a lot of energy. Everything from the growing process to producing fertilizers to harvesting the crop requires oil. Then the corn needs to be made into sugar, which is turned into ethanol—which still needs to be distilled prior to commercial use.

On top of that, you need energy to ship the ethanol to regions of the country where corn isn’t plentiful.

It’s pretty easy for critics to start poking holes in this schematic. Because when it comes to ethanol as an alternative to oil, the energy return on the energy investment is much slimmer than desired.

This is precisely where yeast genetics can help.

Whitehead Member and yeast expert Gerald Fink has teamed up with chemical engineer Gregory Stephanopoulos of Massachusetts Institute of Technology to create a genetically altered strain of yeast that promises to make ethanol production far more efficient—50 percent more efficient.

Ethanol is produced through fermentation. After the corn has been made into sugar, baker’s yeast metabolizes the sugar, producing ethanol.

But there’s an unfortunate irony to this procedure. Yeast doesn’t tolerate ethanol very well. In fact, at certain levels, ethanol is toxic to it. And because yeast is indispensable to

Your kitchen is stocked with one of the mightiest tools of modern biology: yeast.

Common, everyday baker’s yeast, living in little packets in your fridge, and diffused throughout your bread, beer and wine.

This mundane single-cell organism not only allows researchers to beta-test countless genetic tools (many of which are eventually scaled up for human cells) but is employed to screen drugs and even to study certain diseases such as Parkinson’s. For any molecular biologist working today, it’s hard to overstate the contributions of yeast genetics.

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The power of yeast genetics might make ethanol fuel much more cost-effective

By David Cameron

Biofuels and the gene pool

Last year, four billion gallons of ethanol were produced in the United States, while we consumed about 140 billion gallons of gasoline.
the process, there’s no way of getting around using it. The end result is inefficient production.

Many scientists have tried to engineer ethanol-tolerant strains of yeast, usually by tinkering with one or two key genes at a time. Hal Alper, a postdoctoral researcher in both the Fink and Stephanopoulos labs, decided to take a different approach.

Rather than homing in on a single gene, he thought, why not target a regulatory molecule that can affect many genes at once?

**POWER YEAST**

Transcription factors are nature’s equivalent to circuit breakers. Much as one circuit breaker activates the electricity in many rooms in your house, one transcription factor can control the activity of a whole network of genes in a cell. If the one-gene-at-a-time approach couldn’t make yeast more tolerant of ethanol, perhaps transcription factors could.

Alper decided to focus on two transcription factors. One of them, called the TATA-binding protein, yielded startling results in ethanol. When Alper altered this transcription factor, it overexpressed many genes, of which at least a dozen proved sufficient to elicit an improved ethanol tolerance. As a result, this altered strain of yeast could survive high ethanol concentrations. Over a 21-hour period, it produced 50 percent more ethanol than normal strains.

“What we have provided is an enabling technology,” says Stephanopoulos. “A key component of this is that when we think of a cell that makes a biofuel, the production of that biofuel is not a property of a single gene or a single enzyme. The production of ethanol is a property of a whole network of reactions, all of which need to work together so that the cell can make the molecule at efficient rates.”

The greatest significance of this research is that it opens up a new avenue for thinking about engineering other desirable properties in a cell, the researchers say.

“Before this, we had very few tools for improving a process that is controlled by many genes,” says Alper. “Now others can apply this approach for making ethanol production or other phenotypes of interest far more efficient.”

“This is a major contribution,” comments Michael Ladisch, a professor at Purdue University’s Laboratory of Renewable Resources Engineering. “This research demonstrates that ethanol tolerance is not a simple phenomenon. The fact that they’ve identified the genes involved and can efficiently track them is a major step forward.”

“Yeast has been key to advances in basic biology and medicine,” notes Fink. “I am very optimistic that this yeast will also contribute to improving our ability to make alternative fuels.”

**RATHER THAN HOMING IN ON A SINGLE GENE, WHY NOT TARGET A REGULATORY MOLECULE THAT CAN AFFECT MANY GENES AT ONCE?**

Gregory Stephanopoulos, Hal Alper and Gerald Fink celebrate their success in creating yeast that shows higher tolerance for ethanol.

*Here’s how ethanol fuel is created from corn. Yeast does all the heavy lifting in the fermentation process.*

Illustration: Tom Dicke; Photo: Donna Coveney/MIT
Mouth to mouth

What can a frog mouth tell us about human birth defects and evolution?

By Alyssa Kneller

As early embryos, humans bear a striking resemblance to frogs. Both species comprise three basic cell types, arranged in the same general pattern. And that isn’t surprising, considering we evolved from a common ancestor.

But where does the likeness end? The jury is still out on which developmental processes we share.

“Our wild and crazy idea is that animals as different as sea urchins and humans use the same biological mechanisms to organize their heads,” says Whitehead Member Hazel Sive.

Her lab is beginning to test this idea in the frog, *Xenopus*, which is easy to study, and whose mouth is very similar to the human mouth.

Once researchers understand this animal, they will look at other organisms, including more primitive animals whose heads comprise just a hollow cylinder of cells, to compare processes.

Slice a frog embryo approximately 12 hours after it is fertilized and you’ll see three layers—endoderm, mesoderm and ectoderm—which eventually give rise to all of the animal’s tissues.

But the extreme front end (anterior) of the embryo lacks mesoderm, (the middle layer), just comprising the ectoderm and endoderm. Human embryos exhibit the same pattern.

In the most primitive animals, there is no mesoderm anywhere in the animal. Sive thinks that the lack of mesoderm in the extreme front of higher animals is a relic of ancient evolutionary processes, and a persistence of a process that occurred in the most primitive animals.

Sive hopes her research will yield clues about evolution. “This idea isn’t in any developmental biology textbooks yet, but the position of the cells at the front of all animal embryos is remarkably similar,” she says.

The similarity of mouth formation in frogs and humans also will shed light on the mechanisms behind human craniofacial birth defects.

Such defects, which range from cleft palates to underdeveloped jaws, account for three-fourths of all structural birth defects, according to the National Institute of Dental and Craniofacial Research. Cleft palates alone afflict roughly 8,000 newborns in the United States each year.

If frogs and humans use the same genetic circuitry to control formation of the mouth and head, then scientists might be able to apply findings from one species to the other. That’s one reason Sive’s lab is studying mouth development in the frog.

*HOW TO MAKE A MOUTH*

Postdoctoral researcher Amanda Dickinson managed to map the steps required to make the primary mouth, the first opening to form in the embryo, and published her results last July in the journal *Developmental Biology*.

The primary mouth connects the gut to the outside and allows feeding. At a later stage, the secondary mouth—which includes the jaws, teeth and tongue—grows around this hole, allowing organisms to chew.

“We think the primary mouth might play a major role in positioning other parts of the face, which is one of the reasons it’s critical to understand how this initial opening forms,” says Sive.

Although other labs had studied...
particular aspects of primary mouth development in a variety of model organisms, Dickinson was the first to tie this work together in a single critter. Further, she is the first to approach this process using molecular tools, with the ability to identify the genes involved.

Dickinson traced the movement of individual cells as a frog embryo’s gut tube poked through to the outside world (see the image series above). Initially, the endoderm cells at the end of the gut tube are encased by ectoderm. The endoderm and ectoderm are kept separate by a basement membrane between them. This basement membrane begins to disappear where the hole is destined to form, an oddity in biological terms.

“Normally, the endoderm and ectoderm never mix,” says Sive. “As the basement membrane breaks down, these layers have to overcome their hatred of one another.”

The sworn enemies grow flexible as the materials between them disappear. In fact, the endoderm and ectoderm lose so much of their stiffness that they cave toward the center of the embryo, forming a dimple on its surface.

“At around the same time, the two layers begin to mix, which is truly remarkable,” says Dickinson. “It’s as if you shuffled two decks of playing cards.”

As endoderm and ectoderm cells mix, some of them begin to die. The mixed mass grows thinner and thinner until it’s just a single layer of cells. Finally, this layer, which is stretched thin like the membrane of a balloon, pops open in the middle, producing the primary mouth. Dickinson and postdoc Colin DeBakker are now working to pinpoint the networks of genes that control each step of this process.

“The animal would have real problems if holes started appearing all over the body, so we’re interested in the genetic circuitry that coordinates formation of just the right size hole in just the right place,” says Sive.

**CEMENTING EVOLUTION**

New genetic analyses tie into other work in the Sive lab on the extreme anterior region of embryos.

Postdoc Shuhong Li concentrates on the genes and proteins that control a much simpler organ—the cement gland, which sits just below the primary mouth. Sive likens this organ to an underwater Post-it note, which secrets mucus to help frog embryos stick to solid surfaces so they won’t be washed away. The Sive lab has pioneered use of the cement gland as a “marker” for the extreme anterior of the embryo.

Humans lack cement glands, but many aquatic vertebrates depend on them for survival. A cement gland consists of just one layer of cells, so it is easy to study. Li and others have identified many of the proteins that turn on the genes that make the cement gland. Li is building a detailed genetic circuit diagram that describes how this organ is positioned at the extreme anterior.

“My job is to isolate the factors that control which genes are expressed in the region, and more and more evidence shows that some of these regulatory mechanisms play a role in multiple organs and multiple species, perhaps even humans,” he says.

Thus Li’s analysis might help Dickinson and DeBakker unravel the factors that control primary mouth formation in frogs and shed light on the interactions between genes and proteins in humans. And the Sive lab’s studies highlight how basic research on seemingly esoteric organs or systems can yield information that aids human biomedical research.

David Cameron contributed to this story.
Hui Ge sifts through oceans of data to explore how genes collaborate  

By Eric Bender

Consider the worm.

For a multi-cellular organism, *Caenorhabditis elegans* keeps things simple. A typical adult roundworm has 959 cells, no more and no less, and scientists have traced the exact lineage of each cell. The animal goes through life without a brain or much of a sex life (almost all are hermaphrodites).

But *C. elegans* also has about 19,000 genes—almost as many genes as humans. And just as in humans, no gene does its work alone. Instead, tasks are accomplished through highly complex networks of protein interactions.

This is the realm of systems biology, and of Whitehead Fellow Hui Ge, who studies embryonic development in the worm.

“I’ve always been interested in how a fertilized egg develops into a whole organism like us,” says Ge. She gets the big picture on this process by combining data from several high-throughput analysis techniques that cut wide swaths through the worm genome, and using advanced statistical methods to sort through the results.

This systems biology approach starts with the components of a system, and studies how those components work together to achieve a certain function, such as protein synthesis or protein degradation. “It’s important to know not just the individual components of a cell but how they are mapped together,” Ge notes. “It’s like a subway system; if you remove a station, the effect on the system will depend on its position.”

“These are data-driven approaches as opposed to the more traditional hypothesis-driven approaches,” she adds. “We put together all this high-throughput information, and then we can find predictions for uncharacterized genes and connections between them, which we can test. And this can be an iterative process in the lab. You make predictions and validate them, and then that validation can help your prediction techniques.”

**READING THE “INTERACTOME”**

Ge graduated with a bachelor’s degree in biochemistry and molecular biology from the Beijing University in 1999, and won a scholarship to Harvard Medical School.

She arrived just as systems biology began to soar.

“I fell in love with the idea that you can study how the organism works, not just by studying individual genes but understanding what a lot of genes do at a time,” she says.

In a homework assignment for a class taught by Harvard’s George Church, Ge came up with a computational strategy that eventually turned into a paper in *Nature Genetics*.

The strategy was about correlating data from large-scale studies of genes with large-scale studies of protein interactions today’s advances in systems biology began with genome sequencing. Hui Ge is among those creating more powerful next-generation platforms that integrate protein interactions and other kinds of high-volume analyses as well.

*Ge and her co-workers in Marc Vidal’s Harvard lab mapped out interactions between many proteins in the C. elegans worm, in this 2004 Science paper.*
interactions. More specifically, it was to correlate transcriptome data (reflecting which genes a cell expresses under certain conditions) with interactome data (mapping interactions between the proteins). Where the two data sets agreed, clearer pictures of protein roles would emerge.

“She was one of the first researchers to suggest putting data together from very different data sets to get something that was better than the sum of the parts,” says Harvard’s Marc Vidal, in whose lab Ge ended up.

Doing research on yeast, Ge and her co-workers demonstrated “the first global evidence that genes with similar expression profiles are more likely to encode interacting proteins,” as their paper put it. And they showed that the integrated data could help to improve hypotheses generated from either approach alone.

GETTING WORM
Also at the Vidal lab, Ge worked on a big project to map out much of the interactome of C. elegans. Eventually published in Science, this paper had no fewer than eight other co-first-authors. (The worm was the likely target because it was the first multi-cellular organism to be sequenced completely, in 1998.)

Next, Ge and colleagues tackled very early embryogenesis—the process by which the worm divides twice, into four differentiated cells, in the first hour after fertilization.

The scientists combined data from three sources: protein-protein interaction, gene expression, and loss-of-function profiling based on RNA interference. They then made predictions about how the embryonic “molecular machines” work. Testing 10 uncharacterized proteins by seeing where they popped up in live animals, the researchers found that the locations generally were consistent with the proteins’ predicted roles, findings reported in a 2005 Nature paper.

Completing her PhD in genetics, Ge was picked as a Whitehead Fellow. Before starting at the Institute, though, she spent six months at the lab of Harvard’s Craig Hunter, learning the craft of worm wet-lab work.

HEALTHY PAIRS OF GENES
At Whitehead, Ge and colleagues have embarked on two main projects with the worm, the first being further explorations of genetic interactions during embryonic development.

RNA interference studies have highlighted about 2,500 genes whose loss kills the worm embryo. That number seems pretty small compared to the total of around 19,000 genes, she says, and she suggests that it’s because genes can back up each other’s functions.

“We are combining the protein interaction map with the genetic interaction map to predict these pairs that give you a synthetic phenotype,” Ge says. “These genes are not functionally equivalent, but they complement each other’s function. Knowing these kinds of genetically buffering pairs is very important for understanding development but also for understanding disease.” She gives the example of the mammalian p53 tumor suppressor gene: “Even if you knock down p53, a mouse will not get cancer immediately. It increases the chance that when something else is damaged, the mouse will get cancer.”

The second major effort is to take a dynamic view of gene expression that integrates time and space information. “In multi-cellular organisms, at different locations, the molecular networks are actually different, because not all of the genes are expressed at the same time,” Ge says. One student in her lab, for instance, is adding data about location and trying to predict the genes that are expressed in certain tissues such as muscles or skin.

“Quantitative science is providing us with a process that helps us understand biology more quickly and in a systematic way,” says Ge. “Little by little, we are learning how to achieve these projects.”

Today’s attempts at detailed molecular modeling are “still first draft, still relatively fuzzy—just like genome sequencing once was,” acknowledges Ge’s mentor Vidal. “But they are really shaping up.”
“Find something that interests you, and go for it.”

That’s what David Baltimore told postdoctoral researcher Naomi Rosenberg when she entered his MIT lab back in 1973. And one topic that interested Rosenberg was leukemia.

In graduate school Rosenberg had used cell culture techniques to study different diseases, but those techniques didn’t yet exist for this deadly cancer of the blood.

After perusing the scientific literature, she came across the Abelson virus, a pathogen that caused rapid tumor growth when injected in mice. “The speed with which it caused leukemia intrigued me,” recalls Rosenberg, now a professor at Tufts University Medical School.

Rosenberg began trying various methods for infecting healthy blood cells in culture. Then, in 1975, she published her success, using the Abelson virus to induce leukemia in mouse blood cells. “For the first time we had a way to study in a controlled environment how this virus interacts with its target,” she says.

What Rosenberg didn’t know at the time was that this postdoctoral success was one link in a profound—and unsuspected—chain of events that three decades later would culminate in a spectacular cancer drug: Gleevec.

Gleevec treats chronic myelogenous leukemia (CML), which strikes about one-fifth of all leukemia patients—roughly 1.5 cases per 100,000 people. Before Gleevec, the fatality rate of this disease was 100 percent.

Brought to market in 2002, Gleevec represents a revolution in cancer treatment. Rather than carpet-bombing the body with toxins that wipe out the cancer but incite a range of devastating side-effects, and very often fail anyway, Gleevec targets a specific molecular abnormality of CML. Although the drug doesn’t eliminate the cancer, for the majority of patients it knocks it into a kind of permanent remission. As long as patients take Gleevec daily, CML becomes a chronic, and manageable, disease.

Gleevec points to the future of cancer treatment, but it also typifies the serendipitous nature of basic research—and the agonizingly long road that even the most dramatic success stories must follow.

“The journey from the lab bench to the clinic is a slow process,” says Whitehead Member Robert Weinberg. “Most people fail to appreciate the time it takes for a discovery to result in a drug. It would be wonderful if these things turned around quickly. But this process always has—and probably always will—take time.”

## 1960

**Peter Nowell and David Hungerford**

Discover that patients with chronic myelogenous leukemia (CML) have a unique chromosome, soon named the Philadelphia chromosome.

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**A slow saga of success**

If you’ve ever wondered why the journey from lab discovery to the clinic takes so long, follow the decades-long story of Gleevec

*By David Cameron*
**FUSING RESEARCH**

One can argue that the first major Gleevec-related discovery occurred in 1914 when Theodor Boveri, a German cytologist, proposed that cancer results from defects in a cell’s chromosomes. However, most people mark 1960 as the year the story began. That’s when Peter Nowell of the University of Pennsylvania and David Hungerford of Fox Chase Cancer Center noticed that cell samples from CML patients often contained an abnormally small chromosome, soon dubbed the Philadelphia chromosome.

In 1973, Janet Rowley of the University of Chicago found that this chromosome was a kind of hybrid, the result of chromosomes 9 and 21 swapping genetic material.

Between these two findings, another piece of the Gleevec puzzle was discovered—one that then lacked any apparent connection with the Philadelphia chromosome.

Herbert Abelson, then an MD at Children’s Hospital in Boston, discovered in 1969 a virus that caused leukemia in mice. (Named after its discoverer, this was the virus that Rosenberg would use to develop her cell culture platform six years later.)

Since the Abelson virus was one of many able to produce tumors in animals, scientists reasoned that viruses also caused tumors in humans. But this view was gradually overturned in the late 1970s and early 1980s, when Weinberg and many other researchers demonstrated that generally the real culprits were genetic mutations.

Still, years of research with cancer viruses were hardly in vain. In 1976, shortly after Rosenberg’s success in culturing leukemia, a new postdoc in the Baltimore lab, Owen Witte, collaborated with Rosenberg to identify the protein expressed by the Abelson virus. Like many other cancer viruses, the Abelson virus is so tiny that it produces a single major protein. Witte and Rosenberg found that this protein was a hybrid, most likely a result of the viral gene fusing with a normal cellular gene.

“This was a mystery,” recalls Witte. “We had this peculiar protein, but we still didn’t understand what it did.”

At this time, there was no obvious relation between this fusion viral protein in mice and the fused human chromosome that Rowley had found.

**THE HUMAN CONNECTION**

Gleevec is so effective because CML has a clear target. As horrible as the disease is, all of its symptoms completely depends on a single protein, one that the drug disrupts.

In 1984, researchers from both the United States and the Netherlands discovered the strange genetic signature that produced this key protein.

Again, while human cancers generally are not caused by viruses, understanding how the virus worked, and which genes it interacted with in animals, provided scientists with clues for where to look in human cells. A team led by Gerard Grosveld, then at Genetics Erasmus University in the Netherlands, announced that it had located the human version of the Abelson virus gene. While normal human cells contain a healthy version of the Abelson gene, in CML patients, this gene turned out to be located right on the Philadelphia chromosome.

Now that scientists had the gene’s address, Witte immediately started to look for the protein that the human Abelson gene expressed. He discovered that cells from CML patients expressed an over-sized variant of the normal Abelson protein. “It was very strange,” he says.

Like the viral protein, the human CML protein was a kind of hybrid, the byproduct of two unrelated genes (the BCR and Abl genes) fusing together. Called BCR/Abl, this mutant gene on the Philadelphia chromosome created a protein that, like the gene, consisted of two components that in normal cells existed apart from each other. This was the over-sized protein that Witte had discovered in CML cells.

But observing the protein was one thing. Proving it caused cancer was another.

**A SILVER BULLET**

In 1984, David Baltimore, who had become Whitehead Institute’s first Director, moved his lab across the street from MIT...
into the new Whitehead building. Shortly after this, MIT graduate student George Daley joined Baltimore’s group. Daley (who would eventually become a Whitehead Fellow) arrived at the lab already interested in CML in general, and in the newly discovered BCR/Abl gene in particular.

“What wasn’t clear,” says Daley, now a professor at Harvard Medical School, “was whether or not BCR/Abl was the gene that initiated the disease. Weinberg’s research, for example, was suggesting that most cancers needed mutations in a number of key genes to develop, not just one.”

Experiments with cell cultures from both the Baltimore lab and Witte’s UCLA lab suggested that the gene could transform normal human cells into cancer cells that resembled CML.

“But an animal model was still missing,” says Daley. “In order to provide the conclusive evidence that BCR/Abl was indeed the culprit, we needed to demonstrate that it, and it alone, could initiate CML in an animal.”

Many research labs were trying to do this, mostly through incorporating BCR/Abl into the animals’ germ lines. But the BCR/Abl gene was toxic to germ cells, and most of these mice died in utero.

Daley tried a different route.

Using the methods that then-Whitehead Member Richard Mulligan had developed for transferring genes into blood stem cells, Daley transferred the BCR/Abl gene into the bone marrow of mice.

He then took that bone marrow and transplanted it into a second group of mice whose own marrow had been destroyed by radiation.

And the second group of mice developed CML.

“If you think about it,” jokes Daley, “this was really gene anti-therapy.” This experiment proved that the BCR/Abl gene was sufficient to cause CML. “We now knew that for this disease, BCR/Abl was the fundamental drug target,” he says.

1990
George Daley creates animal models of CML, proving that the BCR/Abl gene is sufficient to cause the disease.

1996
Brian Druker and Nicholas Lydon discover a chemical compound that blocks the BCR/Abl protein in human cells.

1998
Clinical trials begin for this compound, which is named Gleevec.

Killing With Kinase

Back in 1980, when Owen Witte first discovered the Abelson virus fusion protein, he also found that it belonged to a family of proteins called kinases. A kinase sends messages through the cell by adding a phosphate to other proteins, which in turn affects those proteins’ activity.

What distinguished the over-sized BCR/Abl protein that Witte had identified from ordinary kinases—and from the normal Abl protein—was that because of its mutant structure, this fusion protein evaded cellular regulation. The BCR/Abl protein was a kinase gone wild.

By the mid-80s a number of researchers were investigating whether kinases could be potential drug targets. One of these was Brian Druker, an oncologist working with Thomas Roberts at Dana-Farber Cancer Institute. Druker had chosen Roberts’s lab over the clinic because he wanted to understand cancer on the molecular level. “Even though we were getting better at using chemotherapy to treat cancers like childhood leukemia, the drugs had terrible side effects,” he says. “What’s more, we didn’t even understand what they did.”

During his nine years at Dana-Farber, Druker began to focus more on CML, collaborating on and off with two Swiss pharma companies, Ciba-Geigy and Sandoz. Although few companies were investing heavily in drugs that blocked kinases, Druker was convinced that CML could respond to such a novel approach. “It was a well-defined disorder that we knew resulted from an activated kinase,” he says. “Block the kinase, and you’d topple the disease. Plain and simple.”

In 1993 Druker left Dana-Farber and took a position at Oregon Health & Science University. “I had one goal at the time: to find a company that had an inhibitor for BCR/Abl and to bring it into the clinic.”

Druker contacted Nick Lydon, a scientist at Ciba-Geigy. Lydon had developed a number of small kinase-blocking compounds that Druker wanted to test. Since kinases pass their phosphate messages by physically interacting with other proteins, almost like two Lego pieces snapping together, the hope was to find a tiny molecule that could wedge itself inside the exact spot where the two proteins fit, thus obstructing the message. The caveat was that such a molecule must be so specific that it could only disrupt BCR/Abl. And while kinases are not as uniform as a box of Legos, they are similar enough to make this a daunting challenge.

While Druker was screening Lydon’s compounds in human bone marrow cells, one named STI571 stood out. By targeting a section of the BCR/Able protein called the “catalytic cleft,” this compound immobilized its ability to transfer phosphates to other proteins. Healthy cells were unaffected.

“At that point I knew we had a potential drug,” says Druker.
In 1996, Druker and Lydon published these findings, the same year that Ciba-Geigy and Sandoz merged and formed the pharmaceutical giant Novartis. While Druker became the academic advocate for STI571, Lydon and Alex Matter, director of the Novartis Oncology Research unit, continued to push STI571 into clinical trials, despite lingering skepticism that simply blocking a kinase could hamper such a deadly disease.

ON TRIAL
The first human trials of the drug occurred in 1998. All 31 patients experienced complete remission.

Over the next four years, 6,000 people entered into clinical trials with STI571, renamed Gleevec (Glivec in Europe and Australia). After the treatment, over 90 percent of people diagnosed with a fairly early stage of the disease were free of symptoms. About 60 percent of patients with advanced CML experienced brief remission, with relapse often occurring after a few months.

“But understand,” says Druker, “for years I’d been treating patients with the disease, telling every one of them that they’d be lucky if they lived five years. And then this! This is one of the best examples I’ve ever seen of science triumphing over disease.”

“It’s unlikely that we’ll find a drug for breast or prostate cancers that works exactly like Gleevec,” cautions Daley. “These more common cancers typically aren’t caused by a single mutated protein. There are usually a few BCR/Abl-like proteins at work. But what we can do is try to develop cocktail drugs, therapies that have two or three compounds that knock out a handful of pathways at once.”

While Gleevec has also proven effective for certain rare forms of gastrointestinal cancer and the blood condition hypereosinophilic syndrome, it isn’t the only such show in town. Iressa and Tarveca, lung cancer drugs, and Herceptin, a breast cancer drug based partly on Weinberg’s research, also successfully target specific molecular signatures. Many similar drugs are in clinical trials.

Many people taking Gleevec today were not even alive when the Philadelphia chromosome was first discovered, nearly 50 years ago. During this period, our understanding of the very nature of cancer dramatically changed, and thanks to the persistence of researchers such as Druker, the genetic revolution that began in the 1970s has finally arrived at the clinic.

Still, the need for fundamental science has never been greater.

“Every once in a while I’ll hear someone suggest that we’ve done enough basic research, and now all our energy should be focused on applying it,” says Weinberg. “Nothing can be farther from the truth. There are still many signaling pathways operating within cancer cells that we just don’t know about yet. Only by meticulously researching how all these other cancers work will we be able to build an arsenal of drugs that disable this disease at the root.”

2002
After stunning success in CML patients, Gleevec is approved by the Food and Drug Administration.

www.whitehead.mit.edu
In 1994, two groups showed that about 57 percent of patients with the most common form of kidney cancer harbor a mutation on the von Hippel-Lindau (VHL) tumor-suppressor gene. This finding led some doctors to wonder about the remaining 43 percent—how do they arise? Stephen Baylin, professor of oncology at the Johns Hopkins University, and his colleague James Herman, now an associate professor at the same institution, decided to delve deeper into this medical mystery by taking a closer look at the VHL gene in patients with the non-hereditary form of this cancer.

His lab uncovered an interesting pattern. In roughly 20 percent of the tumors, the DNA bases forming the VHL promoter (the region where proteins bind to activate the gene) have acquired extra methyl groups. However, the sequence of the DNA bases in the whole VHL gene is usually normal, indicating that the gene has not suffered a mutation. Baylin and his colleagues hypothesized that the extra methyl miscreants were guilty of shutting down the otherwise normal gene. Scientists had already shown that methyl groups block access to DNA, preventing it from being read out, so this was a logical conclusion.
In one breed of mice, intestinal tumors form in two distinct stages, which are partially regulated by epigenetic events, including misplaced methyl groups. First, microscopic tumors, such as the one in the center of the top image, develop. Given the right circumstances, these growths progress into macroscopic tumors (bottom).
Although Baylin was hardly the first scientist to observe odd methylation patterns in the DNA of tumors, he was among the first to produce evidence that this might play a major role in cancer formation. A deluge of papers came out around that time, including a key one by Whitehead Member Rudolf Jaenisch, providing irrefutable proof that misplaced methyl marks can contribute to cancer formation.

“I think the VHL gene was precociously trying to tell us something,” Baylin says. “If you find a gene that has lost its function via a mutation, then you can probably find cases where that gene has lost its function via a modification to the epigenome.”

MARKING UP DNA—AND PASSING IT ON

So what’s the epigenome?

You can think of it as the system that lets each type of cell access parts of the genome for its own particular needs. The epigenome serves as a firewall, hiding certain genes while exposing others. For example, a few methyl groups on the promoter of a gene can keep it concealed and silent in a particular tissue. Though methyl marks are the best understood epigenetic marks, there’s another major group—packaging proteins. For example, some proteins block access to genes by coiling bits of the sequence into neat “spools.”

Epigenetic mechanisms usually help cells express genes at the right time and place. While all of an organism’s cells share the same genes, epigenetics ensures that a brain cell produces dopamine, serotonin and other “brain” chemicals rather than keratin, fats and oils, which are characteristic of a skin cell. At least 200 different types of cells comprise a human being, and each one contains a different epigenome.

Given their essential functions, epigenetic marks hardly serve as DNA accessories. But they can be changed like a pair of earrings or a necklace. For example, an enzyme called Dnmt3a places methyl marks on previously unmethylated DNA. Typically active in developing embryos, this enzyme helps to establish tissue-specific DNA methylation patterns.

Importantly, such marks are replicated during cell division and passed to daughter cells. Thus epigenetic marks are transient in one sense, yet heritable in another.

“This dichotomy is one of the reasons we’re studying epigenetics as it relates to cancer,” says Heinz Linhart, an MD/PhD in Jaenisch’s lab. “Epigenetic marks provide potent therapeutic targets because they can be added or stripped, but we wouldn’t be talking about them if they weren’t heritable. Neither mutations nor misplaced methyl marks would induce tumors if they were diluted out when cells divided.”

Linhart manipulates the epigenomes of mice to explore methylation patterns previously linked to tumor formation. He tinkers with methyl marks and watches the results—an approach that allows him to establish cause and effect.

Jaenisch used a similar approach more than 10 years ago to silence critics of the first studies that provided evidence that epigenetic changes can produce tumors.

THE EPIGENOME LETS EACH TYPE OF CELL ACCESS PARTS OF THE GENOME FOR ITS OWN PARTICULAR NEEDS

Cancer stem cells and epigenetics

A GROWING NUMBER OF scientists accept that not all cells in a tumor are created equal. They believe that a small population of “stem cells” gives rise to the slightly differentiated cells that form the bulk of a tumor. The cancer stem cells divide less frequently than their specialized daughter cells, but live forever.

“It’s still a matter of faith that the stem cell model applies to all cases of cancer, though the evidence is compelling for a small number of solid tumors,” says Whitehead Member Robert Weinberg.

Three recent studies in Nature Genetics, including one by Stephen Baylin, professor of oncology at the Johns Hopkins University, link methylation patterns in cancer cells to patterns of DNA-packaging proteins in embryonic stem cells. The DNA-packaging proteins could leave particular genes, those involved in keeping a cell specialized rather than immature, vulnerable to methylation in adult cells.

“It’s certainly possible that these patterns are fundamentally linked to formation of cancer stem cells, but this needs to be proven,” says Baylin.

In 1994, the same year Baylin completed his kidney cancer study, Jaenisch began to study methylation in tumor-prone mice. Though healthy in most respects, these animals develop large numbers of tumors in their intestines.

Ironically, Jaenisch suspected that missing methyl groups might be to blame. Around 1980, scientists had noticed that the DNA of many tumor cells was missing methyl marks, but they didn’t have the tools to probe the relationship. Furthermore, renowned cancer researcher Bert Vogelstein of Johns Hopkins had observed this “hypomethylation” pattern in the tumor-prone mice and proposed that it was a prerequisite for polyp formation.

In collaboration with Whitehead Member Robert Weinberg, Jaenisch and postdoctoral researcher Peter Laird (now a professor at the University of Southern California) stripped methyl groups from the DNA of their pint-sized subjects and waited for the animals to develop tons of tumors.

The results, published in Cell in 1995, were startling. Rather than mimicking tumor formation, these mice produced fewer tumors. “Though we were puzzled by the outcome, we were pleased to establish a causal relationship between methylation and cancer,” says Jaenisch, who also is
a biology professor at Massachusetts Institute of Technology.

A decade later, Japanese pathologist Yasuhiro Yamada joined the lab. Yamada was particularly knowledgeable about the mice used in the experiment. He knew that their intestinal tumors developed in two distinct stages. First come microscopic tumors that resemble flowers. Given the right conditions, these grow into massive irregular tumors that can be seen with the naked eye (see photos on page 17).

Yamada repeated the 1995 study and discovered that hypomethylation increases the number of tiny tumors but decreases the number of large tumors. The earlier researchers missed the microscopic effect. “Our lab had just shown that global hypomethylation destabilizes DNA big time, so we reasoned that the small tumors result from chromosomal instability rather than epigenetic silencing,” Jaenisch explains.

Linhart and MIT diploma student Eva Moran took the study one step further by setting new methyl marks randomly on the DNA of the tumor-prone mice—a gain-of-function study as opposed to the many loss-of-function studies done previously.

In most tumor cells, DNA is unusually short on methyl groups. Yet the same cells often contain short sequences replete with methyl groups, hot spots that typically fall on the regulatory regions of genes. After Linhart and Moran methylated these hot spots, the mice developed more macroscopic intestinal tumors than usual.

The pair dug deeper and identified a key growth-control gene affected by the misplaced methyl groups. Their findings, which should be published this spring, provide an interesting twist to the intestinal-tumor tale. “In these mice, intestinal tumors arise through a complex interplay between genetic events, global hypomethylation and local hypermethylation,” says Linhart, who is still teasing apart the details of this relationship.

The story of the intestinal tumor demonstrates once again that cancer is rarely simple. The term encompasses a multitude of diseases characterized by the abnormal proliferation of cells. Each of these diseases has its own story filled with its own characters, ranging from genes to viruses to methyl groups. “Epigenetics will not provide a universal cure for cancer because it does not cause every instance of the ‘disease,’” says Linhart. In fact, it might offer more promise as a diagnostic tool. A growing body of evidence suggests that most tumors exhibit epigenetic changes regardless of their origin. So epigenetic patterns could be used to diagnose particular types of cancer, even those caused by genetic mutations. But scientists caution against losing sight of the big picture. “Although methylation changes can be just as important as mutations in particular cases, epigenetics is just one very narrow part of the broad cancer research field,” Weinberg explains.
"THE GOOD NEWS IS THAT EPIGENETIC MARKS ARE REVERSIBLE." —Rudolf Jaenisch

READY FOR DRUGS?
Epigenetic marks have attracted attention from pharmaceutical companies hoping to reverse them. In 2004, the Food and Drug Administration approved Vidaza, a DNA-demethylating drug manufactured by Pharmion Corporation, for use in certain blood diseases such as chronic myelomonocytic leukemia. Vidaza is believed to work indirectly by reducing DNA methylation and directly by killing cells.

This approval was the realization of a dream for Peter Jones, director of the University of Southern California/Norris Comprehensive Cancer Center.

Jones was one of the first researchers to observe methylation patterns in cancer cells during the late 1970s and early 1980s. He was also the first to change those patterns by treating cells with chemicals.

One of the chemicals he used was azacytidine—which became Vidaza, 25 years later. Jones believes other success stories will follow.

“I think these drugs will find much more use in the future because they’re very good at resetting the epigenetic program, which has gone awry in a cancer cell,” he says.

But Jaenisch worries that companies will rush to create drugs before fully understanding the consequences of taking them. He cautions scientists to search for side effects before applying epigenetic therapies. This warning comes from experience. When the Jaenisch lab reduced the number of methyl marks on the DNA of tumor-prone mice, the animals developed fewer macroscopic tumors in their intestines. But in another study, the lab found that loss of methyl marks can cause aggressive lymphomas.

“If you want to use methylation changes as a therapeutic tool, you have to know what you’re doing,” says Jaenisch.

Stephen Baylin is more optimistic. He points out that Jaenisch tinkered with methylation patterns in mouse embryos, when enzymes were still busy setting and stripping methyl marks. He wonders if the lymphomas can be blamed on timing, rather than on the treatment itself. Would mice develop these lymphomas if they were exposed to a demethylating drug as adults?

Despite this debate over side effects, Jaenisch agrees that epigenetic therapies will eventually become a reality. “These therapies should materialize after we develop a robust understanding of the mechanisms involved,” he says. “The good news is epigenetic marks are reversible, which gives us hope to treat thousands of cancer patients someday.”

David Cameron contributed to this story.

Epigenetics and the environment

"THE EPIGENOME ALLOWS the genome to talk to the environment," says Whitehead Member Rudolf Jaenisch. In fact, the epigenome might explain the link between particular diets and increased or reduced risk of cancer.

The long-term Harvard Nurses’ Health Study, for example, showed that women who take a multivitamin pill containing folate (a form of vitamin B9) lower their risk of colon cancer by 20 percent. Folate happens to be a methyl group donor, so perhaps it protects the women by acting on the epigenome.

Or perhaps not. "We don't know if folate modifies the transcriptional state of certain genes, but I do suspect that people have underestimated the plasticity of epigenomes," says Emma Whitelaw, who studies epigenetics in her lab at the Queensland Institute of Medical Research. She points out that some epigenetic marks in plants fluctuate throughout the day as light levels change. It's not unreasonable to hypothesize that epigenetic marks fluctuate in humans over a period of days or years in response to diet.

“I think we're going to discover a lot of layers of epigenetic modification (beyond methylation), and some will be more stable than others,” she says.
On a cold January afternoon, Eric Lander sits in his office at the Broad Institute, explaining a new effort to sequence the DNA of tumors, when his cell phone rings. He answers and listens.

“Do you want me to come over to the hospital tonight?” he asks, then covers the mouthpiece and whispers, “I just want to make arrangements to visit my cousin. Unfortunately, he has a very serious cancer, so this is quite relevant to our conversation.”

Lander’s cousin was diagnosed with a type of bile duct cancer at the end of December. This form of cancer is relatively rare, and with out known therapies.

Getting off the phone, Lander notes that “we could try to use therapies that were developed for other cancers to treat my cousin, but we don’t know which genes are involved, and that’s very frustrating.”

The Broad is participating in a new federally funded venture that could help patients such as Lander’s cousin. The National Cancer Institute recently kicked off a pilot project to sequence the DNA of tumors from patients with particular types of cancer. If the pilot succeeds, the government might fund a massive cancer-sequencing project to determine the genetic components of all types of cancer. Many involve mutations to the same genes, and the resulting information would help researchers map relationships between cancers.

But some scientists feel that NCI should wait to launch the project when federal funding for biomedical research expands. The National Institute of Health’s budget doubled between 1998 and 2003 but is now dropping in real dollars each year. Whitehead Member Robert Weinberg suggests that grant funding should emphasize small, investigator-initiated projects rather than large, collaborative ones.

“I’m not at all convinced that, given the current NIH grant funding climate, we can afford to invest enormous amounts of money in sequencing cancer genomes,” says Weinberg.

“The larger-scale projects generate large databases, which are useful to smaller-scale scientists, but on their own, larger-scale projects hardly yield as much conceptual bang for the buck as smaller-scale projects,” he declares.

“I think there are still some major unsolved conceptual problems that only smaller, more focused research efforts can address.”

Lander, who is both a Whitehead Member and Director of the Broad, counters that the pilot project will cost just 0.5 percent of the NCI budget. “I can’t imagine why you wouldn’t spend 0.5 percent of the budget on cancer genome sequencing, because it would make the other 99.5 percent of the budget twice as efficient,” he says. “And the Human Genome Project taught us that setting a goal often causes costs to drop as the technology grows more efficient. This makes more science possible.”

**SEQUENCING THE EPIGENOMES**

A group of scientists recently proposed another giant project—sequencing several human epigenomes—to advance cancer research. The epigenome lies above the DNA sequence and includes methyl marks as well as proteins that package DNA (for more information see “The Unusual Suspect” on page 16). Aberrant methylation plays a role in many types of cancer.

As president of the American Association for Cancer Research, Peter Jones helped to develop a blueprint for an international project to sequence several human epigenomes. Eventually, he hopes to compare the epigenomes of cancer patients with those of healthy individuals.

“The epigenome is the missing piece between genes and proteins, and we need the sequence to fully understand cancer and make accurate diagnoses,” says Jones, director of the USC/Norris Comprehensive Cancer Center. Like Lander, he believes that larger-scale projects make smaller-scale projects more efficient.

But the proposal faces critics. Some wonder if we know enough about the epigenome to launch such a monumental project. Labs are still uncovering layer upon layer of epigenetic marks that current sequencing technologies miss. And the project requires sequencing numerous epigenomes, because each cell type contains a different set of epigenetic marks.

“My feeling is an epigenome project is a bit premature,” says Emma Whitelaw, of Queensland Institute of Medical Research. “We could save a lot of money by waiting a few years, by which time we should know more about what to look for and where to look for it.”

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THE LINK BETWEEN EPIGENETICS AND CANCER

A. NON-CANCEROUS CELL

One copy of a single chromosome pair is methylated.

MATERNAL CHROMOSOME

Enhancer helps turn on the H19 gene.

Insulator protein binds between two genes, keeping the enhancer away from the first one.

PATERNAL CHROMOSOME

Interaction results in H19 gene product

Methyl groups block access to the DNA between the two genes, preventing the insulator protein and enhancer from binding.

Enhancer helps turn on the lgf2 gene.

Interaction results in lgf2 gene product

H19 gene

lgf2 gene
There are two known types of epigenetic marks—methyl groups and DNA-packaging proteins—which help cells turn on specific genes at the right time and place. Strategically placed methyl groups (shown here in red) can block access to key regions of DNA. Each methyl group consists of a carbon atom surrounded by hydrogen. In the example on the right, misplaced methyl groups on one copy of a single chromosome contribute to cancer by disrupting the balance between two gene products. Ordinarily, only one copy of the chromosome pair is methylated at the location illustrated.

**B. CANCEROUS CELL** Both copies of a single chromosome pair are methylated.

**MATERNAL CHROMOSOME**

1. Enhancer helps turn on the $lgf2$ gene.

2. Interaction results in $lgf2$ gene product

**PATERNAL CHROMOSOME**

1. Enhancer helps turn on the $lgf2$ gene.

2. Interaction results in $lgf2$ gene product

Methyl groups block access to the DNA between the two genes, preventing the insulator protein and enhancer from binding.
Biology’s big tent
Meet some of the young researchers pouring into life sciences from other fields  By Carol Cruzan Morton

Are mathematics and biology separate universes? Oliver King, whose doctoral thesis sorted out a problem in a mind-bending 32 dimensions, says that’s one way to visualize his transition from number theory to protein-folding biology.

When Christopher Love started his postdoctoral fellowship in the immunology research group of Whitehead Member Hidde Ploegh, he had not taken a biology class since high school.

Love knew how to make magnetic nanoparticles organize themselves into microscopic structures and how to create nanometer-thin crystalline coatings of molecules on metals. He wanted to apply such tools from the physical sciences to advance medical knowledge and public health.

Jumping feet-first into a biology lab, he figured, was his best chance to bridge the gap. From the perspective of a surface chemist, immunology seemed the easiest entry point. “I knew there was a lot of contact between cells and that it involved surface interactions—something familiar,” Love says. “It took me a year to understand the terminology. It’s a different language from even other areas of biology.”

He needed even more time to understand how biologists think. “Biology has an extra level of complexity from materials science, physics and chemistry,” Love comments. “I’m amazed at the types of insights biologists can draw from experiments, where it tends to be difficult to control the variables.”

In a recent meeting of the Harvey Lodish lab, discussion turned to the evolution of red blood cells: Why does a red blood cell lack a nucleus?

“The first thing I thought of was the mechanical properties of the cell,” says Shawdee Eshghi, who is just finishing her doctoral work in biological engineering under the joint oversight of Lodish and Linda Griffith in the MIT biological engineering division. “The nucleus is stiff and cannot bend. The hallmark of the red blood cell is its flexibility. That’s not what comes to the minds of most biologists.”

Engineers and biologists think differently. “In engineering, you start with physical laws you know are irrefutable, and if the data don’t support them, you know that the data are wrong,” Eshghi says. “In biology, you don’t have that starting point. It’s very empirical. Classical biology papers use a lot of inductive reasoning: ‘This is our hypothesis. Here are some data to support it. Maybe this is what’s going on. We did another experiment to show this isn’t it.’ They present all the hypotheses and knock them down.”

She adds that engineers have a versatile common language: mathematics. But biological systems need more levels of explanation.
A biologist can be hard to find in the Whitehead lab of Paul Matsudaira. And the lab’s expertise ranges from simulating colliding stars on supercomputers to building joints for robotic arms.

“I wish we could get a biology graduate student to work on Vorticella,” a genus of protozoa, muses Danielle Cook France. “There are tons of open questions.” In the meantime, lab technicians provide the biological expertise and tutoring in protein purification.

France, a biological engineering graduate student, studies the rubber-band-like properties of the stretchy stalk that affixes the tiny pond critter to a rock or crustacean. When she publishes papers, she considers which community she wants to reach, either cell biologists for the subject matter or biophysicists for the underlying imaging. “People either peg you as a biologist or an engineer,” she says.

France, whose mom is a math teacher, set her sights on engineering earlier than most girls. “I see a lot of future in using the biology we know to engineer new things, such as building materials from basic biological components,” she notes. “MIT has given me more confidence about starting my own company. That spirit is in the air.”

Biology at Whitehead and elsewhere is increasingly infiltrated by computational scientists, engineers, mathematicians and others who didn’t train in biology. Whitehead Fellow Paul Wiggins, for example, switched to biology after starting graduate studies in string theory, a cornerstone of modern physics.

Meet the future of biology, represented by King and the scientists below, all part of the next wave of researchers drawn to Whitehead by the challenge of today’s life sciences. »
Targeting the agents of disease

In the war on infectious disease, are we spending enough—in the right places?

By Richard Saltus

Megan Murray, an epidemiologist at the Harvard School of Public Health, is very worried about where her next research dollars will come from. At times, she thinks she may have to fall back on being a practicing physician to make ends meet.

The co-leader of a large study in Peru aimed at identifying risk factors for drug-resistant tuberculosis, Murray has published important papers in the field. But she’s finding that it has become highly challenging to get money from the National Institutes of Health, especially for new projects and for young scientists starting out. Some of her postdocs “are spending more time writing grants than writing papers,” she adds.

At the National Institute of Allergy and Infectious Diseases, where the interim budget for 2007 was $3.8 billion, the proportion of grant proposals that will be funded has fallen over several years to just 10 percent. “We are being crunched,” acknowledges Anthony Fauci, longtime NIAID director. “We’ve had flat funding for the last three years, and with inflation, we’ve had a 10 percent decrease in purchasing power. It’s a bad signal to send for the young people.”

A BIOTERROR MONEY PIT?

Many areas of the world are awash in infectious diseases. Some are longstanding and endemic, such as malaria. Some are of recent origin, such as HIV/AIDS. Others represent new or re-emerging threats such as Ebola or drug-resistant TB, a scourge that’s spreading through South Africa.

Scientists are working on many fronts to unravel the basic biology of dangerous microbes.

But funding for these research efforts is a major bottleneck.

Fauci points out that existing resources are being directed at emerging and re-emerging infections in the context of global health and security. He believes that the intense concern about a possible bird-flu pandemic is an opportunity to reduce the toll of ordinary seasonal influenza with better vaccines and therapies. Spending on influenza has been ratcheted up 10-fold to $222 million, says Fauci. Other NIAID priorities include developing an effective HIV/AIDS vaccine, preventing mother-to-child HIV infections and attacking the worrisome emergence of drug-resistant TB.

Though controversial, the infusion of $1.2 billion in new federal funding for research on potential bioterrorism agents has been a “boon” to NIAID-supported investigations generally, says

“...funds focused on the diseases that people are actually dying from, rather than ones that someone might imagine could be a problem in the event of warfare,” says Harvard epidemiologist Megan Murray.
Fauci. While the money is earmarked for research on a list of “select agents” including anthrax, plague, tularemia and smallpox, it will yield insights and diagnostic tools for fighting civilian infections as well.

But Hidde Ploegh, Whitehead Member and immune-system expert, expresses some leeriness about this funding direction. “To my knowledge, no realistic threat assessment exists for most of the agents on this select list, nor has there been much of a debate over it,” he says. “But because there is more money in biodefense-related projects, you will see investigators move toward these agents.”

“There’s a contrast between what infectious disease people worry about—emerging communicable diseases—and what the bioterrorism people worry about, which is someone appropriating or creating a weapon out of biological material,” remarks Nobel laureate David Baltimore, who recently retired as president of the California Institute of Technology and continues his research on HIV/AIDS.

“Our representatives in government have a grave responsibility to choose whether they advocate a war on terror or a war on microbes or a war on cancer,” says Whitehead Member Hidde Ploegh. “And you can’t spend the same dollar twice.”

PRIVATE PROGRESS

Unexpectedly and dramatically, the funding arena has been transformed in the past several years as wealthy philanthropists have taken up the cause of global public health.

Most notably, the Gates Foundation provided a huge shot in the arm by committing $450 million in 2003 to launch the Grand Challenges in Global Health Initiative. A high priority on the Gates agenda is malaria, which causes an estimated 1.5 to 2.7 million deaths and infects 300 to 500 million people each year, mostly in sub-Saharan Africa.

Patrick Duffy, a prominent malaria expert formerly at Walter Reed Army Institute of Research, was lured to the Seattle Biomedical Research Institute, which receives significant Gates funding. Duffy, whose research focuses on discovering and evaluating antigens for a malaria vaccine, says that the Gates model “is more like corporate funding, in the sense that there are targeted goals and milestones to monitor progress. The NIH model has yielded outstanding basic science, but it’s less well-suited to programmatic approaches to solving problems.”

Enormous gifts from donors such as Gates and his buddy Warren Buffett make a big splash and can make a difference. By contrast, the NIH—principally NIAID—has a record of major sustained funding that adds up over the years. “Over the last 25 years,” Fauci points out, “we’ve spent over $30 billion on HIV/AIDS.” And in that same period, he adds, NIAID has grown, budget-wise, from the eighth- to the second-largest Institute within the NIH.

TIGHTENED BELTS

Still, after Congress doubled the NIH budget to $26.7 billion between 1999 and 2003, the increase in scientists applying for grants combined with the abrupt end of the budget largesse has spread resources thin.

Funders also need to balance basic and applied research. In *Nature Immunology* in 2003, Fauci wrote, “An important challenge for the NIAID is to find a way to preserve a robust commitment to the fundamental, investigator-initiated research that is the bedrock of the research enterprise while meeting expectations for more applied research, including the advanced development of vaccines, therapeutics, and diagnostics.”

Time will tell whether the federal government will eke out enough funding, in the right places, to encourage the next generation of young scientists.

“I personally would largely allocate money on the basis of global disease burden, bearing in mind that epidemic disease can happen without warning,” says Harvard’s Murray. “There is still a need to study potentially epidemic agents. But with malaria, TB and HIV as the main contributors to infectious-disease deaths, those would seem the obvious priorities.”

“We are being crunched,” acknowledges Anthony Fauci, longtime director of the National Institute of Allergy and Infectious Diseases.
Promises and realities in embryonic stem cell research

For all the controversies, it’s still early days for the science

**Whitehead Member Rudolf Jaenisch** weighs in on what we can, can’t and (hopefully) will one day do with human embryonic stem cells.

**What do we know for sure that embryonic stem cells can do?**

Embryonic stem [ES] cells have in principle an enormous potential for research and therapy. We can extrapolate much from our knowledge of mouse ES cells. From these cells, we know we can generate any tissue type in the Petri dish. We also know they’re useful for therapy. We’ve used them to treat a mouse variant of the human disease severe combined immunodeficiency. We showed that one can restore the immune system using customized embryonic stem cells.

But the human system is much more complex. These cells don’t grow rapidly, they’re difficult to grow as single cells, and they suffer chromosomal aberrations quite easily. All these issues we can handle in the mouse.

We need to learn how to make the human ES cells as easy to work with as mouse ES cells. The issues are strictly technical.

**How successful have we been in turning ES cells into specific tissues?**

There are major efforts to derive neurons, heart muscle and blood cells. There have been major successes, but we’re not yet able to produce a tissue for patients.

**What do ES cells offer for basic research?**

These cells have enormous value as research tools. The hope would be to use somatic cell nuclear transfer [SCNT] to generate human models of complex diseases like Parkinson’s, Alzheimer’s and diabetes. [In SCNT, an egg’s DNA would be replaced with DNA from a patient, and the egg would be used to generate patient-specific ES cells.] All the genetic mutations causing the disease would be present in the ES cell.

If we could derive ES cells from a Parkinson’s patient, we would like to coax these cells into forming neurons, and as we study the process, hopefully find the defects that cause the disease. In other words, we can study a very complex disease in the Petri dish with the potential to look for compounds that treat it.

**But does SCNT work in humans?**

It works in mice, cows, sheep and rabbits. It will work in humans. We need to resolve the technical issues.

**Why do we need to keep deriving additional lines of human ES cell?**

The presidentially approved ES lines are useful to an extent. But they were created under conditions that we no longer use.

The Harvard ES lines [not presidentially approved] are also very useful. But what’s become clear in the last few months is that the way you isolate or culture the cells determines how the cells react later. For example, all the human lines that we work with have been isolated under high oxygen concentrations. But if you grow these cells under lower oxygen, they do much better. We need to grow these cells under different conditions and decide what the best conditions are.

**What about alternative means for deriving ES cells?**

These other methods are driven by ethical objections. We did a proof-of-principle experiment in mice to show that one can generate embryonic stem cells without destroying a viable embryo. Generating ES cells from amniotic fluid also has gotten a lot of attention recently, but I think that approach is overblown.

The real goal of the field is to generate ES cells without using eggs. Take a skin cell and treat it in some way that redirects it back to an ES-cell-like cell. Nuclear transfer shows that the egg can do it.
Our silver anniversary

Whitehead celebrates its 25th birthday with a special section of our website that features interviews, videos and slide shows

SCIENTISTS GONE WILD
Watch former Associate Director John Pratt recount a near-death experience in the Himalayas with Whitehead Members Paul Matsudaira and Rudolf Jaenisch. (The hikers narrowly avoided avalanches during their long trek.) This is just one of the videos that highlight the Institute’s tight-knit community. Visit www.whitehead.mit.edu/about/25th/people.

TAPPING YOUR MEMORY
An interactive memory board lets scientists and friends of Whitehead contribute photos and stories about the Institute. Whitehead Members and former postdocs divulge some of their proudest moments in the labs and a few of their colleagues’ most striking character traits. To browse, visit www.whitehead.mit.edu/memories/index.php.

WHO WAS JACK WHITEHEAD?
Meet the extraordinary character who made Whitehead Institute possible. After making millions on medical devices, Edwin C. (Jack) Whitehead dreamed of creating the ideal research environment for smart young scientists. At the end of a decade-long quest, he inked the deal with Massachusetts Institute of Technology that launched Whitehead Institute. “People developed a real respect for Jack,” recalls David Baltimore, Founding Director. “There was sort of a love affair between him and the Institute, which is very rare with founders.” For more about Jack Whitehead, visit www.whitehead.mit.edu/about/25th/jack.

Whitehead 2007
In this seven-minute video overview, Whitehead scientists describe a research environment that inspires creativity and collaboration. Visit www.whitehead.mit.edu/about.
Whitehead Fellow Hui Ge studies how networks of proteins interact in the embryonic *C. elegans* worm. Here is a network backbone with proteins grouped into predicted “molecular machines.” This is from a 2005 *Nature* paper co-authored by Ge, who was then in the lab of Harvard's Marc Vidal. For more information, see page 10. Courtesy *Nature*. 