FALL 2010

Stowers REPORT

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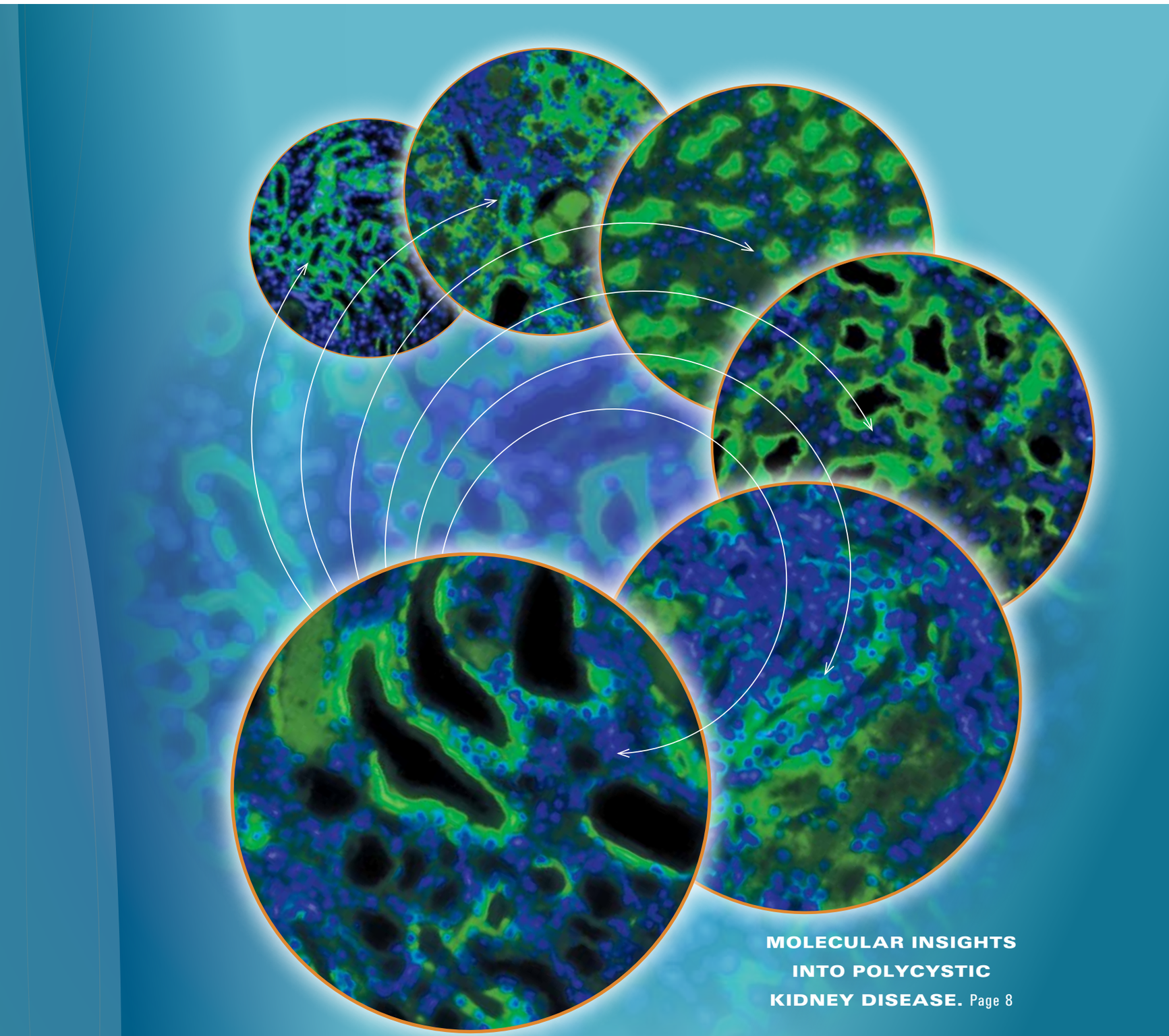

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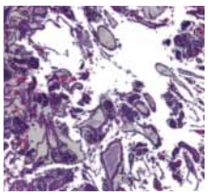

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PRESIDENT'S LETTER

BY DAVID CHAO, PH.D., PRESIDENT AND CEO

This issue of the *Stowers Report* focuses on the link between human disease and transcription, a basic process that helps determine how much protein is made from each gene.

Recent numbers from the Human Genome Project highlight the importance of appropriately regulating transcription and, more generally, gene expression. The 3 billion base pairs of DNA in the human genome are estimated to contain approximately 23,000 genes. Each of these genes encodes different proteins, which together catalyze most of the chemical reactions that form the basis for life. While all cells have roughly the same complement of 23,000 genes, each type of cell differs in how much protein it produces from each gene. Differences in the expression of only a few hundred genes are thought to account for most of the variation among different types of cells.

As an illustration, imagine that genes are analogous to the 88 keys of the piano and that cells are analogous to different songs. No song uses all 88 keys or uses them all at once. Instead, each song takes on its distinctive characteristics based on the combination, timing, and volume of a small number of keys played. Similarly, each cell takes on its distinctive characteristics based on the combination, timing, and level of a small number of genes expressed. Just as 88 keys can give rise to a wide variety of songs, 23,000 genes can give rise to a broad diversity of cell types and behaviors. The control of gene expression is thus centrally important to the generation of diversity in cellular function. When the control of gene expression goes awry, the disruption of normal processes can result in disease, much as the aberrant sound of a stuck piano key can ruin a song.

A crucial point of control for gene expression is transcription. Transcription is the process by which the information encoded in DNA is converted to RNA. Whereas DNA forms the long-lived archival copy of genetic information, RNA forms the relatively short-lived working copies of this information. The working copies of RNA are in turn translated into proteins. Much, and perhaps most, of the variation in protein levels is determined by how many working copies of RNA are produced from each gene at a given time.

Many of the Institute's researchers seek to elucidate the basic molecular mechanisms that regulate transcription. Improving our understanding of this basic process will provide insights into how organisms grow, develop, and respond to their environment. Furthermore, because many diseases are the direct result of transcriptional defects, an improved understanding of transcriptional control will aid the development of new approaches to diagnose or treat disease.

The link between transcriptional regulation and disease is the theme underlying the research highlighted in this issue of the *Stowers Report*. Rong Li and colleagues have found that a specific transcriptional regulator is involved in the normal process by which kidney cells respond to the flow of fluid over their surface, as well as in the abnormal processes that lead to polycystic kidney disease (page 8). Transcriptional regulators often work with other proteins in tightly bound groups or complexes, and Ali Shilatifard and colleagues have discovered that many of the mutations that cause mixed lineage leukemia are linked to one such complex (page 11). Likewise, Jerry Workman and colleagues have discovered a link between one of these transcriptional regulation complexes and a pathway involved in cancer and inflammatory diseases (page 5) and have also revealed how another complex can be disrupted by the actions of an anti-cancer drug (page 2).

Jim and Virginia Stowers founded the Institute because of their conviction that unfettered basic research is a prerequisite for the development of new cures and treatments for disease. The articles in this issue provide an early validation of the Stowers' vision and illustrate how basic research can result in unexpected links between a fundamental biological process and disease.

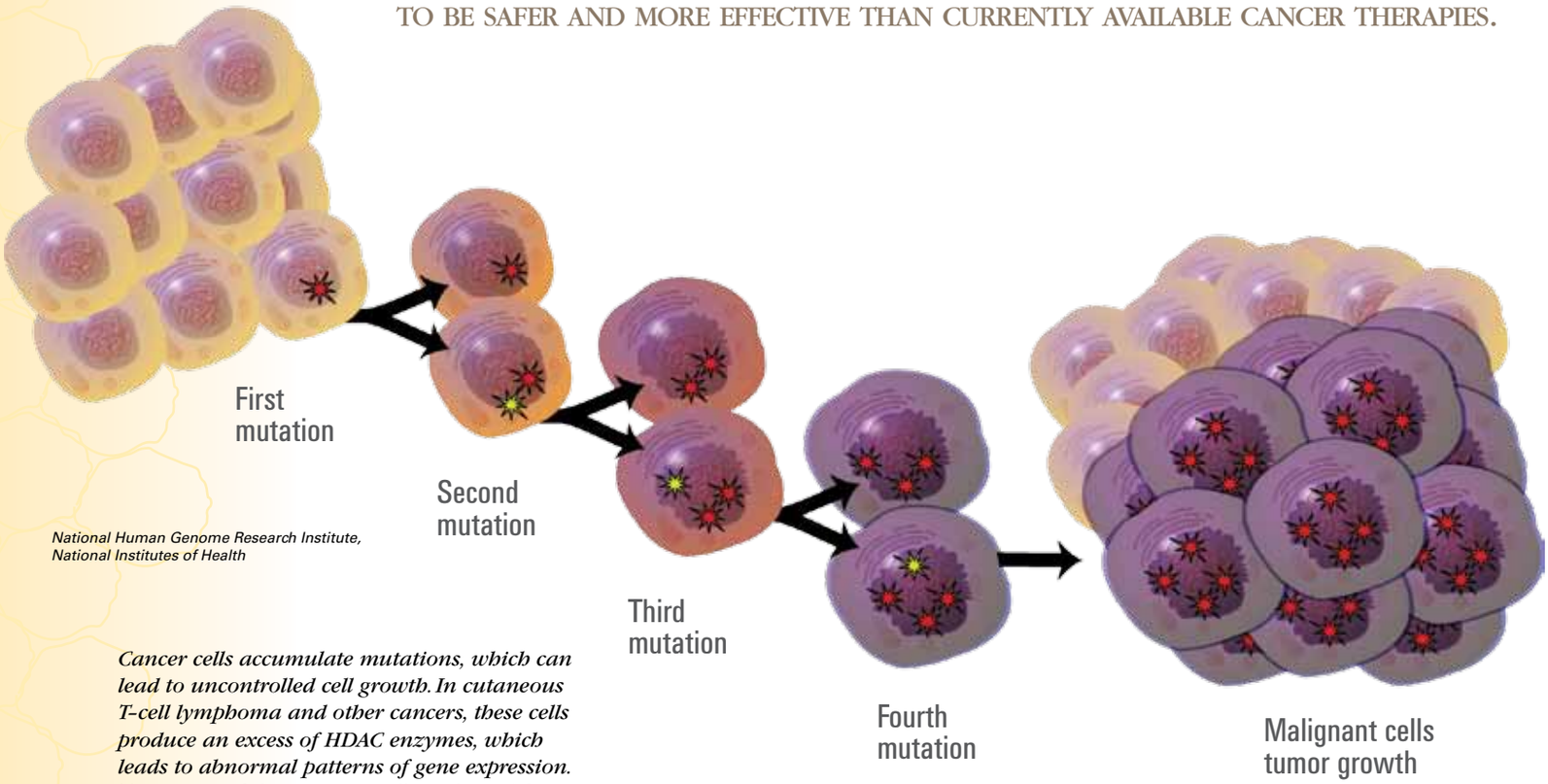
Please join us in sharing Jim and Virginia Stowers' unwavering belief that basic research offers us all "Hope for Life.®"

By Stephanie Huang, Ph.D.

DIGGING DEEPER

Diligent Detective Work Uncovers New Function

In October of 2006, a chemical compound known as suberoylanilide hydroxamic acid (SAHA) was approved by the FDA for treatment of cutaneous T-cell lymphoma, a cancer in which mutated T cells migrate to the skin and cause itchy lesions that eventually form plaques and tumors. The compound is marketed under the name Zolinza® and was the first drug in its class to be approved for cancer treatment. Since its approval, several more drug agents from its class have entered clinical trials — more than 100 clinical trials involving these drugs are currently ongoing. The hope is that this class of drugs will prove to be safer and more effective than currently available cancer therapies.



National Human Genome Research Institute, National Institutes of Health

Cancer cells accumulate mutations, which can lead to uncontrolled cell growth. In cutaneous T-cell lymphoma and other cancers, these cells produce an excess of HDAC enzymes, which leads to abnormal patterns of gene expression. Treatment of these cancer cells with HDAC inhibitors can help to curb cell growth.

# of Cancer Drug

Zolinza belongs to a class of drugs called histone deacetylase (HDAC) inhibitors. Despite the fact that HDAC inhibitors are already in use in the clinic, we are just beginning to understand some of the details of how these drugs exert their effects.

How is it possible that we do not yet fully understand the workings of these drugs, yet Zolinza is already approved by the FDA for cancer treatment? The simple answer is that clinical trials do not explore the molecular mechanisms of a drug — rather, they are solely concerned with the effects of the drug on the disease and patient. Clinical trials assess whether a drug is effective in treating the disease or at reducing symptoms, whether the drug is safe and relatively non-toxic, and whether the positive effects of the drug outweigh the negative effects. Physicians can assess these properties of the drug without knowing all of its molecular details.

In order to improve drug therapies, it is to our benefit to understand as much as we can about the drug's activities within the cell. A study from the Stowers Institute's Workman Lab has revealed surprising results about Zolinza that underline the importance of thorough investigation of drug molecules, even of those already in the clinic.

Known Activities of HDAC Inhibitors

To understand the results from the Workman Lab, we first need to understand how HDAC inhibitors work.

Almost all of the cells in our body (with the exception of red blood cells) carry a copy of our genome in their nuclei. The genome contains the genetic information necessary to build all of our cells and enable those cells to do their work. However, not all of this information is being actively transcribed at all times. Altering the pattern of gene expression, or which genes are turned *on* or *off*, is a process that enables cells to become specialized and perform different functions in different places or at different times.

HDAC enzymes are proteins that help switch genes *on* and *off*. HDAC inhibitors are drugs that block the activity of HDAC enzymes. In cancers such as cutaneous T-cell lymphoma, the mutated cells produce an excess of HDAC enzymes, causing their pattern of gene expression to be abnormal.

Researchers have found that adding HDAC inhibitors to these cancer cells tends to switch *on* tumor suppressor genes and switch *off* genes that promote progress through the cell cycle (the steps preparing a cell for division). Although the underlying details are not yet completely understood, treatment with HDAC inhibitors prevents the growth of these cancer cells. The mechanism of action is more complicated than it may seem, as HDAC inhibitors may affect multiple HDAC enzymes and may also affect other proteins.

Additional Activities of Zolinza

HDAC inhibitors work by directly blocking the action of the HDAC enzymes. HDAC enzymes do not always work alone; instead, many HDAC enzymes function within multiprotein complexes, with each protein individually contributing a different function to the overall complex.

"There was an unanswered question about how these drugs work on bigger multisubunit complexes," explains Karen Smith, Ph.D., Postdoctoral Research Fellow in the Workman Lab and first author on the publication. "I was curious to know what effect these drugs might have on an entire HDAC complex."

In collaboration with the Institute's Proteomics Center, Dr. Smith explored the effects of treating an HDAC complex with Zolinza. She chose to study the Sin3 complex, which in addition to containing the HDAC1 and HDAC2 enzymes, contains several other proteins that help the complex bind to or dock at its target genes. The team found that treatment of the Sin3 complex with Zolinza resulted in the release of a protein called ING2 from the Sin3 complex.

ING2 is responsible for bringing the Sin3 complex to the p21 gene, which encodes a protein that is a key player during the cell cycle. Treatment of cells with Zolinza is known to increase levels of the p21 protein, and increased levels of p21 block the cell cycle. Previous studies showed that HDAC1 and HDAC2 are less present than is normal at the p21 gene after Zolinza treatment. Building on this previous work, the team was able to demonstrate that the decreased presence is because of ING2 — without ING2 in the Sin3 complex, the complex cannot dock at the p21 gene.

Thus, in addition to blocking the actions of HDAC enzymes, Zolinza is also preventing the Sin3 complex from turning *off* the p21 gene, leading to increased levels of the p21 protein and blocking the cell cycle and cell growth.

"I expected [Zolinza] to have either a large effect or none at all on the Sin3 complex," says Dr. Smith. "Instead, I was really surprised that the drug had such a specific effect on one subunit."

Hints for Better Cancer Drugs?

The study from the Workman Lab underlines the importance of thoroughly studying the mechanisms of drug molecules. "The key finding here is that some HDAC inhibitors have effects on HDAC complexes besides inhibition of histone deacetylase activity," explains Jerry Workman, Ph.D., Investigator and senior author on the publication. "Before this study, it was assumed that the inhibitors would inactivate the [HDAC] enzyme but have no other effects. This study shows that dissociation of key subunits targeting the complex to at least one tumor suppressor gene also occurs."

In this case, the additional activity of Zolinza coordinates well with the main or intended effect of the drug, which is to block cancer cell growth. However, it may be possible that other HDAC inhibitors have additional activities that counteract their usefulness. To understand this, further studies will need to be conducted to thoroughly assess all of the effects that Zolinza and other HDAC inhibitors have on different types of cells and various HDAC complexes within the cells.

The study from the Workman Lab also suggests more specific ways of blocking cancer cell division. "HDAC inhibitors used in the clinic affect several enzymes, many of which may not be related to the clinical benefit of these drugs," explains Dr. Workman. "The finding that the inhibitors also dissociate a key subunit specifically from the Sin3 complex opens the possibility of finding more specific inhibitors of this complex — for example, small molecules that target ING2 instead of the deacetylase subunits." Targeting cancer cells in a specific manner remains one of the ultimate goals in cancer drug development. Understanding all of the effects that cancer drugs have on cells may suggest different ways to achieve this specificity and are sure to be appreciated by both researchers and patients.

PAPER: Deacetylase Inhibitors Dissociate the Histone-Targeting ING2 Subunit from the Sin3 Complex

JOURNAL: *Chemistry & Biology*

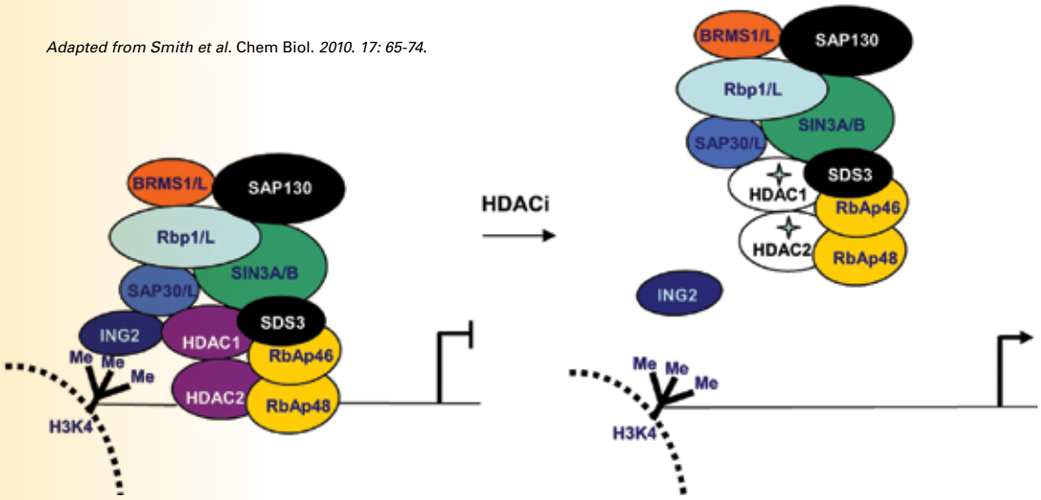
ISSUE: January 29, 2010

AUTHORS*: **Karen Smith, Ph.D.**, Postdoctoral Research Fellow; **Skylar Martin-Brown**, Research Technician III; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Michael Washburn, Ph.D.**, Director of Proteomics; **Jerry Workman, Ph.D.**, Investigator

**Authors' primary appointments are with the Stowers Institute for Medical Research.*

Jerry Workman, Ph.D., Investigator, joined the Stowers Institute in 2003 from The Pennsylvania State University where he was an associate investigator of the Howard Hughes Medical Institute. Learn more about his work at www.stowers.org/labs/WorkmanLab.asp.

Adapted from Smith et al. Chem Biol. *2010. 17: 65-74.*



The ING2 protein (dark blue) is responsible for docking the Sin3 complex at the p21 gene. Zolinza causes ING2 to be released from the Sin3 complex, thereby preventing the complex from docking at the p21 gene and turning it off. *Zolinza treatment leads to increased levels of the p21 protein, which blocks the cell cycle and cell growth.*

By Stephanie Huang, Ph.D.

ACTING DIFFERENTLY UNDER STRESS

The Dual Roles of the ATAC Complex

Rob Sayer, On Stage Lighting, via flickr.com

Gene expression can be adjusted in the same manner that lights can be turned up *or* down *by a dimmer switch. Under osmotic stress, JNK is highly activated and would turn* up *its target genes. ATAC suppresses the stress-induced activation of JNK, keeping JNK target genes expressing at a more normal level.*

WE FEEL STRESSED IF THERE IS A SIGNIFICANT CHANGE IN OUR LIFE — MOVING TO A DIFFERENT CITY OR STARTING A NEW JOB, FOR EXAMPLE. LIKEWISE, CELLS UNDERGO STRESS IF THERE IS A SIGNIFICANT CHANGE IN THEIR EXTERNAL ENVIRONMENT. A RECENT STUDY FROM THE STOWERS INSTITUTE'S WORKMAN LAB PROVIDES INTRIGUING DETAILS ABOUT HOW ONE PROTEIN COMPLEX CAN BEHAVE DIFFERENTLY UNDER CELLULAR STRESS CONDITIONS AND THEREBY HELP TO MAINTAIN THE DELICATE BALANCE OF CELL GROWTH AND DEATH.

Cells constantly monitor and respond to their external environment. If the concentration of key molecules outside of the cell changes, water flows into or out of the cell in a direction that will balance the internal and external concentrations — this is an example of osmosis.

Significant loss or gain of water leads to osmotic stress. How do cells respond to this stress? Many proteins within the cell are dedicated to stress response, and they quickly act to restore a state of normalcy within the cell. Some stress response proteins are mitogen-activated protein kinases, or MAPKs. MAPKs are signaling proteins. By adding chemical tags — in the form of a phosphate molecule — on each other and on other proteins, MAPKs transmit figurative memos throughout the cell. These memos can affect activities of other proteins, and, as we will see below, they can also affect gene expression.

Turning Genes Up and Down to Adjust Internal Conditions

Although our cells contain the genetic information necessary to make all of the cellular components present in our entire body, only a portion of this information is accessible for transcription, or reading, at any one time. When a gene is read, its DNA-encoded information is transcribed into an RNA molecule. The RNA molecule now contains the information necessary to build the gene product, a molecule that is often a protein.

We often talk about genes being turned *on* or *off*, like a light being controlled by an on-off switch. For this story, however, it is important to note that a dimmer switch is a more realistic metaphor than a simple on-off switch. Proteins called transcription factors can bind to DNA and change the levels of expression of the nearby gene — either increasing or decreasing the number of RNA transcripts produced from the gene. In other words, transcription factors can turn *up* or turn *down* the expression of a gene. The

expression level of a gene can exist on a spectrum — from very low levels to intermediate or high levels, and everything in between.

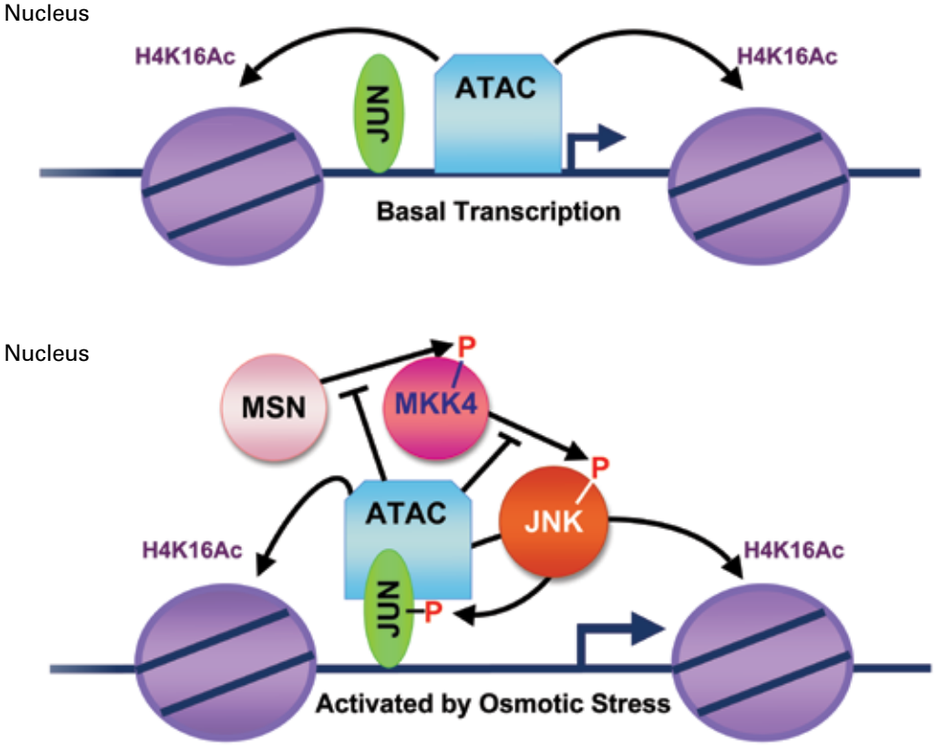
In stress-free conditions, one set of genes might be expressed at intermediate to high levels and provide the information to synthesize proteins that enable the cell to perform its normal functions.

Under conditions of stress, transcription factors may change the pattern of gene expression (i.e., dimmer switches are turned *up* or *down*) in order to synthesize a different set of proteins to enable the cell to respond to the environmental change.

Groups of proteins called histone acetyltransferase (HAT) complexes can work together with transcription factors to help turn genes *up* or *down*. The Workman Lab has discovered several HAT complexes and focused much of their work on understanding how they function and how they regulate gene expression. In 2006, they reported the characterization of a new complex, which they named ATAC. In collaboration with the Institute's Proteomics Center and Arcady Mushegian, Ph.D., Director of Bioinformatics Research, the team found that the ATAC complex interacts with proteins involved in stress response, including MAPKs. The team conducted further experiments to better understand how all of these proteins might work together under osmotic stress conditions.

Revealing the Dual Roles of the ATAC

c-Jun N-terminal Kinase (JNK) is a MAPK that responds to osmotic stress. Under stress, JNK is tagged by other MAPKs. As a result, JNK and its associated transcription factor c-Jun have increased activity. This means that the genes controlled by JNK and c-Jun should be expressed at very high levels (i.e., dimmer switch is turned *up*) when the cell experiences osmotic stress.



The ATAC complex has two different effects on genes regulated by JNK and c-Jun. Under normal conditions (basal transcription), ATAC is necessary to maintain a normal level of expression of these genes. Under stress conditions, ATAC blocks the tagging of JNK and moderates the turning up *of these genes. This prevents an overreaction of the cell in response to osmotic stress, which could otherwise lead to uncontrolled cell growth.*

Suganuma et al. Cell. *2010. 142:726-36.*

However, the team found that the ATAC complex prevents the stress-induced activation of JNK and c-Jun. This means that in the presence of ATAC, JNK is not activated as highly by stress, and the target genes are expressed at a more moderate level. ATAC, in effect, suppresses the stress activation of JNK, c-Jun, and their target genes.

Unexpectedly, the team found that ATAC has the opposite effect on c-Jun in normal conditions. In stress-free conditions, ATAC works with c-Jun to help express its target genes. In fact, the team found that the presence of ATAC is necessary for a normal level of expression of these genes.

"A key finding of the study is that a downstream effector of MAPK signaling also serves to govern the level of the transcriptional response to osmotic stress. This is important so that the cell can deal with the stress conditions without over responding," explains Jerry Workman, Ph.D., Investigator and senior author on the publication.

In other words, under normal conditions, ATAC has a positive effect on the expression of JNK target genes. However, under osmotic stress conditions, ATAC has a negative effect on the expression of these same genes. How does ATAC play these two different roles?

One Complex, Two Proteins with Different Activities

The ATAC complex is composed of 13 different proteins. With some deeper probing into the individual components of the ATAC complex, the Workman Lab found that two different proteins are responsible for the different roles of the complex. One protein, Atac2, is important for the positive effect that the ATAC complex has on the expression of JNK target genes under normal conditions.

Another protein, CG10238, is important for the negative effect that ATAC has on these same genes when the cell is under stress. CG10238, in fact, is directly responsible for preventing the stress-induced activation of JNK and is able to prevent JNK activation whether it is bound to the ATAC complex or as an individual protein. Analysis by Dr. Mushegian revealed that the part of CG10238 that prevents JNK activation evolved from an ancient enzyme that is also present in bacteria.

Bringing Everyone Together in Close Proximity

The Workman Lab also took a closer look at JNK and the MAPKs involved in tagging JNK under stress conditions. They discovered that, in normal conditions, MAPKs are bound to the DNA near the genes controlled by JNK, but the MAPKs are scattered around different parts of the gene.

Under osmotic stress conditions, ATAC moves to the same location where c-Jun is docked and recruits JNK and the other MAPKs. The gathering of ATAC and the other MAPKs in the same location may facilitate the way in which ATAC suppresses the tagging and activation of JNK in stress conditions.

Importance of Duality

To summarize, the ATAC complex has two different effects on genes regulated by JNK and c-Jun. Under normal conditions, ATAC is necessary to maintain a normal level of expression of these genes. Under stress conditions, ATAC prevents what would otherwise be a large increase in the expression of these genes.

Why is this important? ATAC's double role is an example of built-in controls within our cells that keep cells balanced and healthy. Both JNK and c-Jun activate genes that ultimately prevent cell death and aging. Although this may sound like a desirable objective, prevention of cell death and aging can result in the uncontrolled growth of cells. ATAC moderates JNK and c-Jun to prevent an overactivation of their pathways. Without ATAC, cells might overreact in response to stress and activate genes and pathways that would ultimately lead to excessive growth and tumorigenesis.

PAPER: The ATAC Acetyltransferase Complex Coordinates MAP Kinases to Regulate JNK Target Genes

JOURNAL: *Cell*

ISSUE: September 3, 2010

AUTHORS*: **Tamaki Suganuma, Ph.D.**, Senior Research Associate; **Arcady Mushegian, Ph.D.**, Director of Bioinformatics Research; **Selene Swanson**, Senior Research Specialist; **Susan Abmayr, Ph.D.**, Associate Investigator; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Michael Washburn, Ph.D.**, Director of Proteomics; **Jerry Workman, Ph.D.**, Investigator

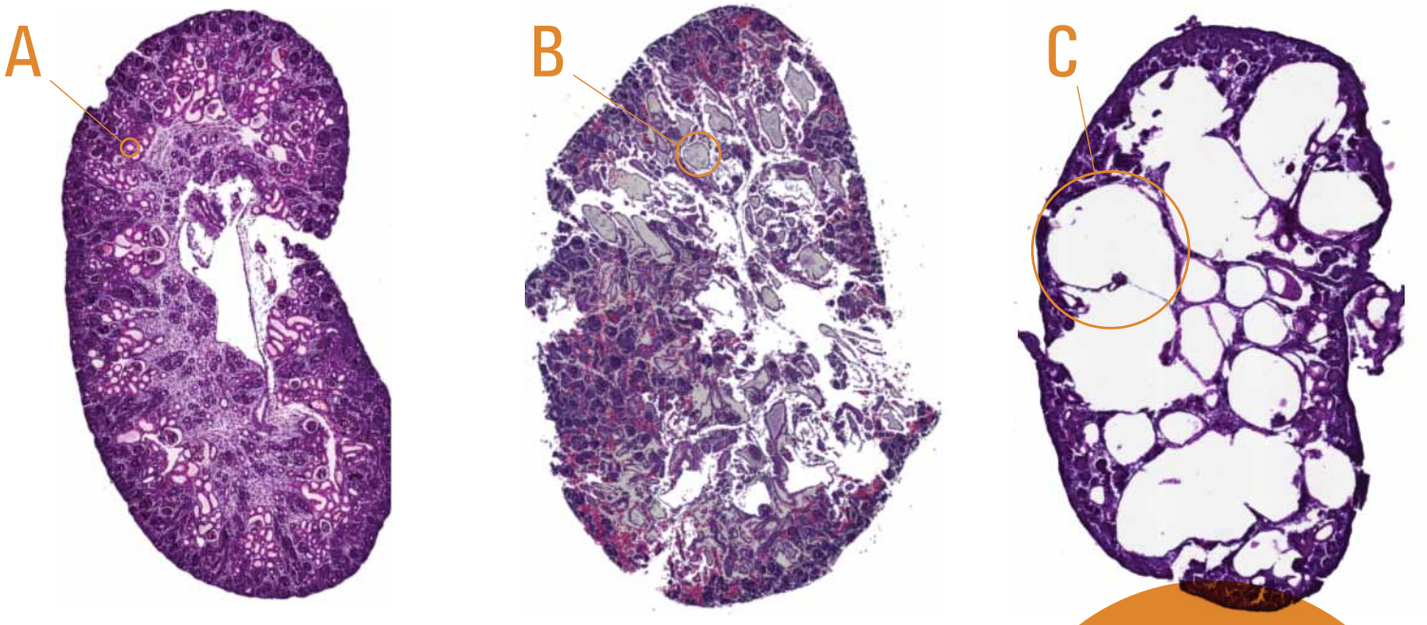
**Authors' primary appointments are with the Stowers Institute for Medical Research.*

Jerry Workman, Ph.D., Investigator, joined the Stowers Institute in 2003 from The Pennsylvania State University where he was an associate investigator of the Howard Hughes Medical Institute. Learn more about his work at www.stowers.org/labs/WorkmanLab.asp.

By Eugenia Park, Ph.D.

CYST PREVENTION Molecular

Adapted from Xia et al. Development. *2010. 137:1075-84.*



Cross-sections from mouse kidneys show decreased cyst formation when HDAC enzyme activity is blocked by a drug. HDAC inhibition enables activation of MEF2C, which prevents cyst formation. The kidney with mutated polycystin and left untreated (C) contains many large cysts, while the kidney with mutated polycystin and treated with the drug (B) contains cysts closer in size to the normal tubules found in the wild-type kidney (A).

ONE OF THE MANY ONGOING PROJECTS IN THE RONG LI LAB SEEKS TO UNDERSTAND HOW KIDNEY CELLS MAINTAIN THEIR IDENTITY. SOME OF THEIR RECENT DISCOVERIES SHED FURTHER LIGHT ON HOW POLYCYSTIC KIDNEY DISEASE MAY DEVELOP AND PRESENT NEW ROUTES TOWARD IDENTIFYING TREATMENTS.

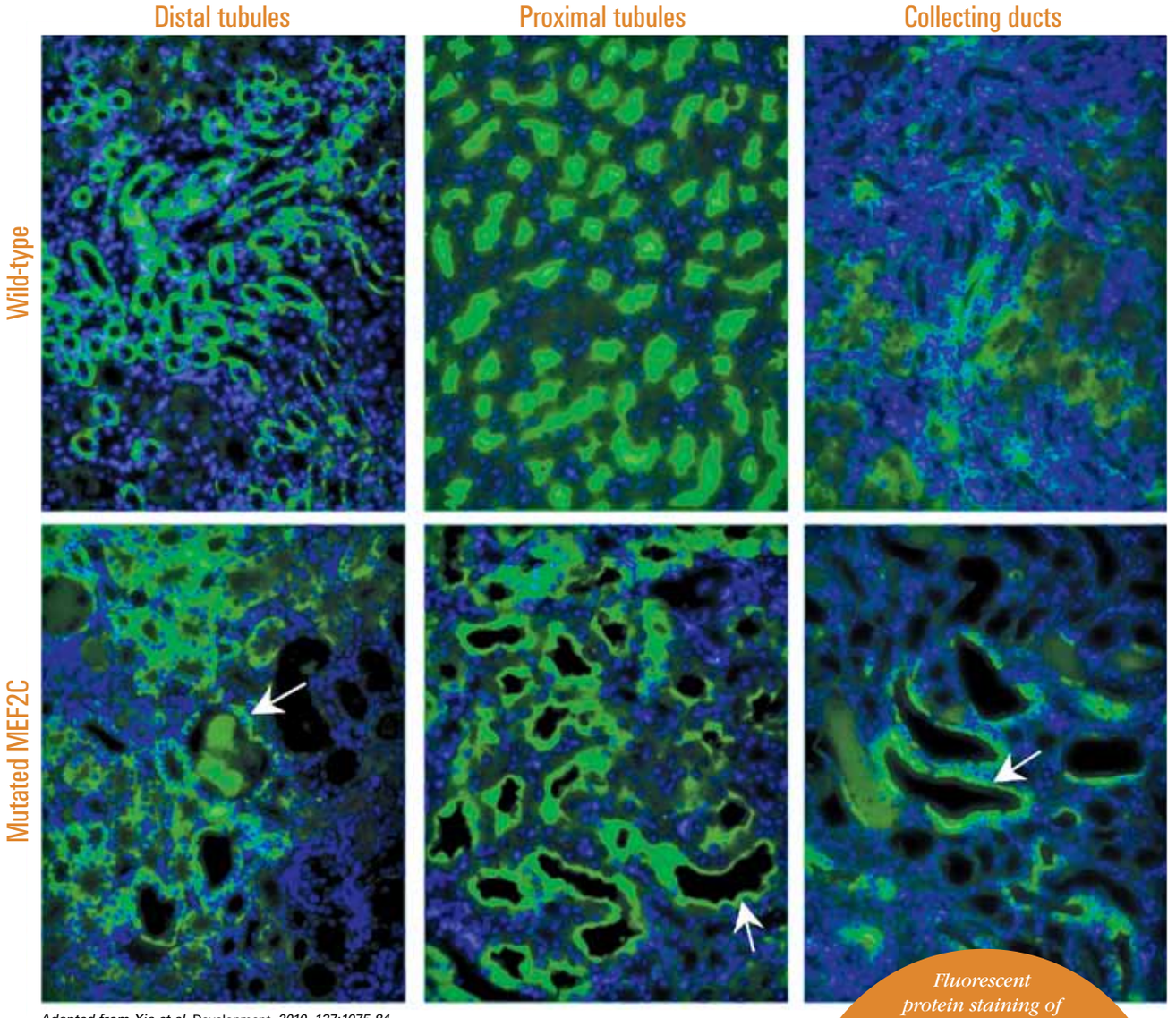
Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening genetic disorder that affects 1 in 500 people in the United States. During the course of the disease, numerous cysts form in the kidneys. With time, these cysts grow and can enlarge kidneys to a point where they weigh anywhere from 20 to 30 pounds each. These kidneys often cause severe pain and display reduced function. Presently, no effective treatments to slow polycystic kidney disease exist. After many years, most sufferers experience renal failure and must undergo transplant or dialysis in order to survive.

Most cases of ADPKD result from mutations in one of two genes, *PKD1* or *PKD2*. These genes encode proteins called polycystins that are important for maintaining the identity of nephrons, the tiny filtering cells from which cysts of polycystic kidney disease arise.

Mutations in polycystins seem to cause kidney cells to revert to an earlier developmental state where they can proliferate to form cysts. As such, scientists are keenly interested in how polycystins function in kidney cells.

Polycystins have long been thought to play a role in triggering cellular processes in response to fluid flow, which bends hair-like protrusions on the surface of nephrons. Although it has long been known that wild-type kidney cells (those with unmutated polycystins) respond to fluid flow with an influx of calcium, the molecular processes initiated by polycystins and the reasons why mutations in polycystins lead to kidney disease remained unclear.

Insights into Polycystic Kidney Disease



Adapted from Xia et al. Development. *2010. 137:1075-84.*

Fluorescent protein staining of cross-sections from mouse kidneys show that mutations in MEF2C lead to cyst formation. The blue stain indicates the nuclei of cells in these cross-sections. The green stain indicates the distal tubules, proximal tubules, or collecting ducts of these kidneys (as indicated in the figure). The white arrows in the mutated MEF2C panels point to enlarged tubules/cysts.

Recent findings from the Rong Li Lab have shed light on how polycystins work. Using gene chips carrying probes for over 39,000 mouse genes, the team identified genes activated in cultured wild-type kidney cells exposed to fluid flow created by a pump. They found that in response to fluid flow, wild-type kidney cells increase levels of mRNA encoding the proteins MEF2C and HDAC5, while cells with mutated polycystin do not. This suggested that polycystins regulate MEF2C and HDAC5 and that these proteins play roles in the formation of cystic kidneys.

The team found that mutations in MEF2C cause mice to develop kidney cysts. MEF2C is a transcription factor, a protein that activates gene expression. One of the genes activated by MEF2C is a gene encoding MIM, a protein that regulates cell structure and maintains proper cell shape. Thus, polycystins increase cellular levels of MEF2C, and MEF2C activity increases levels of MIM, helping to maintain kidney cell identity and prevent cyst formation.

In turn, HDAC5 inhibits MEF2C. The team found that expressing HDAC5 in a cell prevents MEF2C from activating gene expression. As a result, the cell can use HDAC5 to control MEF2C, and it does so by regulating the location of HDAC5. Fluid flow causes wild-type kidney cells to transport HDAC5 out of the nucleus where MEF2C acts. In their experiments, the team saw green fluorescent HDAC5 vacate the nuclei of wild-type cells *(Pkd1$^{+/+}$)* in response to fluid flow while red fluorescent MEF2C stayed within nuclei. Meanwhile, cells with mutated polycystin *(Pkd1$^{-/-}$)* failed to transport green fluorescent HDAC5 out of the nuclei. Thus, in a polycystin mutant cell, HDAC5 remaining in the nucleus prevents MEF2C from expressing genes that prevent cyst formation.

"The identification of MEF2C and HDAC5 as mediators of cyst formation may lead to new drugs for treating polycystic kidney disease and a better understanding of how the structure and function of cells in normal tissues and organs are maintained," says Rong Li, Ph.D., Investigator and senior author on the publication. Tantalizingly, the team has treated polycystin mutant mouse embryos using an inhibitor of HDAC enzymes that acts on HDAC5 and found that such treatment significantly reduced cyst formation.

The findings of the Rong Li Lab carry implications beyond kidney disease. Interestingly, previous work showed that HDAC5 and MEF2C play roles in myocardial hypertrophy, in which heart cells enlarge, leading to a thickening of muscle that decreases the size of heart chambers. In heart cells, HDAC5 prevents MEF2C from expressing genes that affect heart function. The team's discovery that HDAC5 and MEF2C interact in similar ways in kidney cells suggest that very different organs call upon the same proteins to maintain the identity of their cells. "Our findings suggest that MEF2C and HDAC5 are key components of a broadly utilized mechanism to maintain cells' integrity and enhance their function in response to mechanical stress," explains Dr. Li.

PAPER: Polycystin-Dependent Fluid Flow Sensing Targets Histone Deacetylase 5 to Prevent the Development of Renal Cysts

JOURNAL: *Development*

ISSUE: April 1, 2010

AUTHORS*: **Sheng Xia, Ph.D.**, Research Specialist I; **Xiaogang Li, Ph.D.**, formerly Senior Research Associate; **Teri Johnson**, Managing Director of Histology Facility; **Chris Seidel, Ph.D.**, Research Advisor; **Darren P. Wallace, Ph.D.**, University of Kansas Medical Center; **Rong Li, Ph.D.**, Investigator

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Rong Li, Ph.D., Investigator, is also a Professor in the Department of Molecular and Integrative Physiology at the University of Kansas Medical Center. Learn more about her work at www.stowers.org/labs/RongLiLab.asp.

By Eugenia Park, Ph.D.

GOOD PROTEINS GONE BAD

Protein Chimeras in Leukemia

Marie-Lan Nguyen / Wikimedia Commons

The Chimera, according to Greek mythology, was a creature with the body of a lion and head of a goat. Similarly, protein chimeras are composed of disparate parts and can result from chromosome translocation events. One such event produces MLL chimera proteins which are involved in childhood myeloid and lymphoid leukemias.

TRANSLOCATION EVENTS, IN WHICH THE *MLL* GENE FUSES TO ANOTHER GENE, MAY UNDERLIE THE DEVELOPMENT OF CHILDHOOD MYELOID AND LYMPHOID LEUKEMIAS. RECENT WORK FROM THE SHILATIFARD LAB HAS IDENTIFIED A MULTIPROTEIN COMPLEX NAMED DOTCOM THAT MAY EXPLAIN HOW SOME GENE FUSIONS ENDANGER HUMAN HEALTH.

Genes are organized, one after another, onto long pieces of DNA known as chromosomes. Humans have multiple, distinct chromosomes and sometimes one chromosome swaps a portion with another chromosome. Known as translocation, these events sometimes result in the first half of one gene fusing to the second half of another gene. Such a hybrid gene can encode a protein chimera in which a fragment of one protein is fused to a fragment of another protein. Like the mythological Chimera, a creature in which the body of a lion is fused to the head of a goat, a protein chimera brings disparate parts together.

Translocations involving the fusion of *MLL* to any one of several dozen genes occur frequently in childhood myeloid and lymphoid leukemias. These translocations produce MLL chimeras that may contribute to the development of leukemia. MLL chimeras contain a part of the MLL protein, but also contain a part of another protein. Figuratively speaking, MLL chimeras have a body derived from MLL fused to a head derived from one of many seemingly unrelated proteins.

Work from the Shilatifard Lab has revealed that some proteins contributing heads to MLL chimeras are related although they are not structurally similar. Previous work from the team showed that many of the most common heads come from proteins found within a complex called the Super Elongation Complex (SEC). More recently, in collaboration with the Institute's Proteomics Center, the team discovered that some of the less common heads found among MLL chimeras come from proteins that form a complex named DotCom.

The Shilatifard Lab demonstrated that DotCom regulates gene expression triggered by the Wnt signaling pathway. In general, signaling pathways transmit signals from the surface of a cell to the nucleus, causing changes in the expression of target genes. Target genes of the Wnt signaling pathway (Wnt target genes) control processes such as cell proliferation. At the right time and in the right place, Wnt target gene expression can assure that important developmental events such as limb formation proceed smoothly. At the wrong time or in the wrong place, Wnt target gene

expression can wreak havoc on the body. For example, abnormal Wnt target gene expression may drive cell proliferation linked to cancer.

How does DotCom influence Wnt target gene expression? The team found that DotCom modifies nucleosomes, the molecular spools that organize the cell's DNA. Specifically, they found that DotCom adds methyl groups to a particular histone, H3, a component of nucleosomes. In their work, the team used fruit flies, which can be manipulated genetically, to determine that Wnt target gene expression requires a third methyl group on histone H3. Using genetic methods, they blocked the addition of a third methyl group to histone H3 in cells labeled green and saw a corresponding reduction of a red label indicating expression of the gene *senseless*, a Wnt target gene.

This work suggests that MLL chimeras with bodies derived from the MLL protein and heads derived from DotCom drive abnormal Wnt target gene expression. "These MLL chimeras may nucleate DotCom assembly at the wrong place or time, activating powerful genes that control cell proliferation," explains Ali Shilatifard, Ph.D., Investigator and senior author on the publication. In leukemia patients, such abnormal gene expression may cause or exacerbate their cancers.

PAPER: Linking H3K79 Trimethylation to Wnt Signaling Through a Novel Dot1-Containing Complex (DotCom)

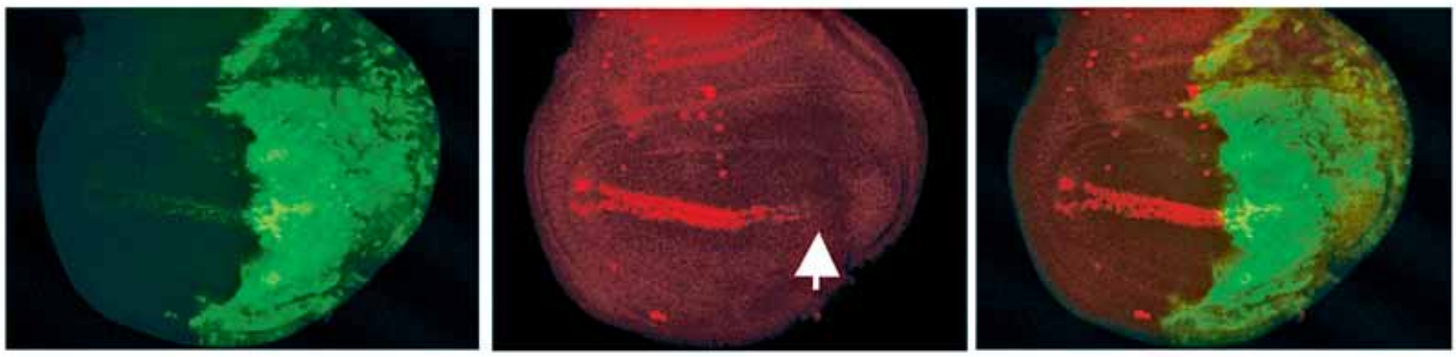
JOURNAL: *Genes & Development*

ISSUE: March 15, 2010

AUTHORS*: **Man Mohan, Ph.D.**, Postdoctoral Research Associate; **Hans-Martin Herz, Ph.D.**, Postdoctoral Research Fellow; **Yoh-Hei Takahashi, Ph.D.**, Postdoctoral Research Associate; **Chengqi Lin**, Research Technician I; **Ka Chun Lai**, formerly Research Technician III; **Ying Zhang, Ph.D.**, Senior Research Specialist; **Michael Washburn, Ph.D.**, Director of Proteomics; **Laurence Florens, Ph.D.**, Managing Director of Proteomics; **Ali Shilatifard, Ph.D.**, Investigator

**Authors' primary appointments are with the Stowers Institute for Medical Research.*

Ali Shilatifard, Ph.D., Investigator, joined the Stowers Institute in 2007 from the Saint Louis University School of Medicine. Learn more about his work at www.stowers.org/labs/ShilatifardLab.asp.



Adapted from Mohan et al. Genes Dev. *2010. 24:574-589.*

Using genetic methods, the team blocked the addition of a third methyl group to histone H3 in cells labeled green and saw a corresponding reduction of a red label indicating decreased expression of the Wnt target gene senseless *(indicated by arrow).*

A DAY OF CELEBRATION
In Honor of Bill Neaves

Bill Neaves, Ph.D., founding President and CEO of the Stowers Institute, became President Emeritus on July 1, 2010. To recognize his numerous academic achievements and crucial role in building the Institute into a world-class biomedical research facility, an all-day symposium and evening reception were held in his honor on June 15, 2010. The Institute's Founders, Jim and Virginia Stowers, joined in the festivities.

Dr. Neaves holds an A.B. *magna cum laude* with highest honors in Biology from Harvard College and a Ph.D. in Anatomy from Harvard University. As a faculty member at The University of Texas Southwestern Medical Center at Dallas, Dr. Neaves conducted research in the field of reproductive endocrinology. He was appointed Dean of Southwestern Graduate School of Biomedical Sciences in 1980.

In June 2000, Dr. Neaves joined the Institute. Since then, he and Robb Krumlauf, Ph.D., Scientific Director, have worked closely with the Institute's Scientific Advisory Board to recruit 25 outstanding laboratory leaders and center directors, some of whom left institutions such as Harvard University and the Howard Hughes Medical Institute to pursue their research at the Institute. Under Dr. Neaves' leadership, the Institute has grown to near capacity of its 600,000 square-foot facility and assembled a staff of more than 500.

"Largely due to Bill Neaves' unparalleled leadership, the Stowers Institute has far exceeded expectations for scientific discoveries and milestones achieved to date, and in a relatively short timeframe, established an international reputation as a medical research organization of excellence," said Richard W. Brown, co-chairman of the Institute.

For a complete biographical sketch of Dr. Neaves, visit www.stowers.org/MediaCenter/NeavesBio.asp.

Symposium in Honor of Bill Neaves

David Chao, Ph.D. – Stowers Institute for Medical Research
Welcome and Overview of the Stowers Institute's First Decade

Robb Krumlauf, Ph.D. – Stowers Institute for Medical Research
Developmental Genetics of Organogenesis

Steve McKnight, Ph.D. – University of Texas Southwestern Medical Center
Discovery of a Pro-neurogenic, Neuroprotective Chemical

Al Gilman, M.D., Ph.D. – Cancer Prevention and Research Institute of Texas
Future of Cancer Research

Bob Alpern, M.D. – Yale University
Memory in Epithelial Function

Hans Deisenhofer, Ph.D. – University of Texas Southwestern Medical Center
Structural Studies on Cholesterol Transport

Peter Baumann, Ph.D. – Stowers Institute for Medical Research
Parthenogenesis as an Alternative to Sexual Reproduction

Bill Danforth, M.D. – Washington University
Placing the Stowers Institute in Regional, National, and International Perspective

Photos by Jay Casillas

Robb Krumlauf and David Chao look on as Bill Neaves speaks to Institute members

From left: Bill Neaves, David Chao, Virginia Stowers, Jim Stowers, Robb Krumlauf, Jim Stowers III

Leanne Wiedemann assists Jim Stowers in signing a champagne bottle for Bill Neaves

Bill Neaves addresses members during the reception in the Gallery

A Decade of Advance

Institute Researchers Organize Functional Stem Cell and Regeneration

Photo by Jay Casillas

Attendees at the Stem Cell and Regeneration Workshop

The Stowers Institute first opened its doors in November 2000. A decade later, the Institute houses 20 independent research programs and three technology development programs, with nearly 350 scientific staff members. To commemorate this anniversary, the Stowers Institute hosted a workshop on functional stem cells and regeneration. The workshop, which took place on October 9-10, 2010, was co-organized by Linheng Li, Ph.D., Investigator; Ting Xie, Ph.D., Investigator; and Janet Rossant, Ph.D., University of Toronto, Hospital for Sick Kids, and member of the Institute's Scientific Advisory Board.

"We organized a workshop to bring together scientists who are working in much diverted areas," explains Dr. Li, speaking on behalf of the three organizers. "The talks, together with the very active and stimulating discussions that followed, were an important brainstorming process to help both speakers and the audience think about the fundamental questions and links underlying stem cell potential, regulation, limitation, tumorigenesis versus regeneration, and longevity of a given organism."

Three concepts were discussed at the workshop:

1. Understanding the molecular underpinnings of reprogramming cells to a stem cell state, which is essentially the opposite of the well-studied process of development, will be essential to the use of reprogramming in regenerative medicine.

Photo by Jay Casillas

Kausik Si

Kausik Si Awarded

In 2003, the M.R. and Evelyn Hudson Foundation created the Hudson Prize to recognize and encourage excellence in basic biomedical research. The award of $75,000 is to be used by the recipient to conduct innovative research and accelerate the pace of laboratory experimentation. The winner is selected each spring based on a combination of factors, including research accomplishments, potential significance of the research and the promise it holds for improving human health, and probable impact of the award on the pace of innovative research.

The winner of the 2010 Hudson Prize is Kausik Si, Ph.D., Assistant Investigator.

Workshop

2. Elucidating the development and regulation of adult stem cells within their microenvironment will provide important insight for precisely directing the development of embryonic stem cells and induced pluripotent stem cells.

3. Some non-mammal species exhibit a remarkable capacity for regeneration. Regenerative potential appears to be associated with many factors, including those affecting longevity, sexual versus asexual reproduction, and the balance between life span and tumorigenesis.

These concepts are likely to guide future advances in stem cell and regenerative biology and bring us closer to the ultimate goal of developing therapies for regenerative medicine.

Speakers at the Workshop

"Embryonic Stem Cell (ESC) and Induced Pluripotent Stem (iPS) Cell" Session
– chaired by Janet Rossant

Janet Rossant – University of Toronto, Hospital for Sick Children
Making Stem Cells and Establishing Cell Fate in the Blastocyst

David Scadden – Massachusetts General Hospital, Harvard University, Harvard Stem Cell Institute
Niche Initiated Oncogenesis

Sheng Ding – Scripps Institute
A Chemical Approach to Controlling Cell Fate

Andras Nagy – Samuel Lunenfeld Research Institute
Mapping the Process of Defined Factor-Based Reprogramming

"Stem Cells in Different Organisms" Session
– chaired by Ting Xie

Su-Chun Zhang – Waisman Center, University of Wisconsin
Stem Cells as a Model of Human Biology

Alejandro Sánchez Alvarado – University of Utah, HHMI
Dissecting Regeneration and Stem Cells in the Planarian Schmidtea mediterranea

Weimin Zhong – Yale University
Mechanisms of Stem Cell Homeostasis

Allan Spradling – Carnegie Institution
Quiescent Diploid and Polyploidy Cells Can Re-enter the Mitotic Cycle and Contribute to Tissue Morphogenesis

"Adult Stem Cell" Session
– chaired by Linheng Li

Ihor Lemischka – Mount Sinai Medical Center
Pursuing Pluripotency

Kateri Moore – Mount Sinai Medical Center
Model Systems to Elucidate Molecular Mechanisms in Stem Cell Niches

Zhigang He – Harvard University, Children's Hospital Boston
Mechanisms of Axon Regeneration in the Adult CNS

2010 Hudson Prize

His research aims to understand how learning and memory formation is enabled through changes in the electrical properties of neurons in the brain. Since biological molecules last only hours or days, one key challenge for the Si Lab is to understand how these molecules are able to store a memory for years or decades. Improving our understanding of the molecular and cellular mechanisms underlying the persistence of memory is significant not only in providing insights into a key neurological process, but also in providing a long-term foundation for developing treatments for memory disorders. Specifically, the Si Lab is characterizing a protein called CPEB, whose prion-like, self-sustaining properties may serve as the basis for maintaining memory.

Dr. Si holds a Ph.D. in molecular biology from the Albert Einstein College of Medicine. He joined the Stowers Institute in 2005 from the laboratory of Dr. Eric Kandel at the Columbia University Center for Neurobiology and Behavior. In addition to his position at the Institute, Dr. Si is also an Assistant Professor in the Department of Molecular and Integrative Physiology at the University of Kansas Medical Center.

Learn more about the M.R. and Evelyn Hudson Foundation at www.thehudsonfoundation.org.

Learn more about the work of Kausik Si at www.stowers.org/labs/SiLab.asp.

Accolades

- **Ali Shilatifard, Ph.D.**, Investigator, received a National Institutes of Health grant, effective in March, and an Innovation Award from Alex's Lemonade Stand Foundation, effective in July.
- **Kausik Si, Ph.D.**, Assistant Investigator, received the Hudson Prize from the M.R. and Evelyn Hudson Foundation, effective in July.
- **Paul Trainor, Ph.D.**, Associate Investigator, was a sub-recipient on a National Institutes of Health grant from the University of Kansas Medical Center, effective in July.
- **Caleb Bailey, Ph.D.**, Postdoctoral Research Fellow in the Kulesa Lab, received a National Institutes of Health Fellowship, effective in September.

Photos by Jay Casillas

Ali Shilatifard

Kausik Si

Paul Trainor

Caleb Bailey

Summer Sc

Undergraduate Students Spend Summer in Lab

For the past four summers, talented undergraduate students have found their way to the Stowers Institute to pursue summer research opportunities. These students have an opportunity to conduct basic biomedical research utilizing cutting-edge technology and advanced research techniques.

This year, 20 students were accepted to the Stowers Scholars Program and spent eight weeks working on a research project under the direction of a mentor in one of the Institute's labs or support facilities. At the end of the summer, the Scholars presented their projects at a poster session. They returned home having gained valuable first-hand laboratory experience and, perhaps, a new perspective on their future career path.

To learn more about the Stowers Scholars Program and view posters from the 2010 Stowers Scholars, visit www.stowers.org/ScientistsSought/TrainingPrograms.asp.

HOLARS

Photo by Jay Casillas

2010 Stowers Scholars (back row from left) Elijah Burton, Megan Fracol, Caitlin Robinson, Swathi Prasad, Christine Janssens, Richard Law, Caitlynn Miller, Laura Blunk, (middle row from left) Ty Crowl, Andrew Satterlee, Roman Becicka, Jessica Samuelson, Dominic Zanaboni, David Casto, (front row from left) Molly Hague, Angela Seat, Kyle Denton, Dennis Chen, Jennifer Logue, Erica Seligson

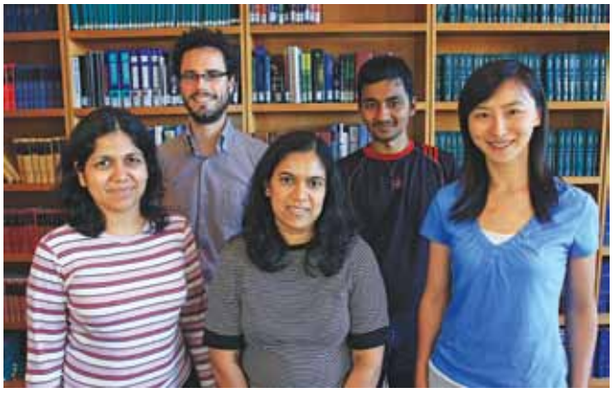
Stowers Scholar	School	Lab	Project
Roman Becicka	Duquesne University	Yu	Identification of Male Mouse Pheromones
Laura Blunk	Truman State University	Cytometry	Analyzing Chromatin Modifications in Hematopoietic Stem Cells: An Evaluation of a Low Cell Number ChIP
Elijah Burton	University of Kansas	Blanchette	Development of an RNA-Affinity Tag for Purification of RNP Particles
David Casto	University of Missouri	Shilatifard	Identification of Transcriptional Regulators of *senseless* in *Drosophila melanogaster*
Dennis Chen	Binghamton University	Kulesa	Development of a Microfluidic Assay to Measure Cell Invasion Behaviors in the Presence of a Chemical Gradient
John 'Ty' Crowl	University of Kansas	Mak	Characterization of RNAi Machinery in *C. elegans*
Kyle Denton	Drake University	Proteomics	Quantitative Proteomic Analysis of Ino80 Chromatin Remodeling Complex in *S. cerevisiae* using MudPIT
Megan Fracol	University of Kansas	Yu	A Biological Response to Predator Signal Detection by the VNO
Molly Hague	Drury University	Trainor	Analysis of Palate Development of Tcof1 Heterozygous Mice
Christine Janssens	Baker University	Mak	A Systematic RNAi Screen for Regulators of Lipid Barrier Formation in *C. elegans* Embryos
Richard Law	Binghamton University	Baumann	Identifying the Cis Acting Elements in the TER1 Intron that Affect Slicing of Telomerase RNA in *S. pombe*
Jennifer Logue	University of Kansas	Krumlauf	Function of Wise/Sostdc1 in Murine Mammary Gland Development
Caitlynn Miller	Indiana University	Shilatifard	Identification of JARID2 Target Genes in *Drosophila melanogaster*
Swathi Prasad	University of Southern California	Si	Experience-Dependent Splicing of *Drosophila* Orb2
Caitlin Robinson	Truman State University	Xie	Understanding the Mechanisms Regulating Spermatogonial Stem Cells in Mouse Testis
Jessica Samuelson	University of Kansas	Si	Characterization of Murashka and xMurashka Antibodies in *Drosophila*
Andrew Satterlee	Kansas State University	Yu	Identification of a Female Mouse-Specific Pheromone
Angela Seat	University of Kansas	Hawley	Deconstructing a Meiotic Mutant in *Drosophila melanogaster*
Erica Seligson	Hamilton College	Cytometry	Flow Cytometric Analysis of the KH2 Embryonic Stem Cell Differentiation State
Dominic Zanaboni	Rockhurst University	Abmayr	Screen for New Players in *Drosophila* Myogenesis

PROMOTING DIALOGUE
2010 Young Investigator Research Days

Every spring, Young Investigator Research Day (YIRD) offers the Stowers Institute's students, postdoctoral researchers, and scientific staff a forum in which to share their research with other members of the Institute. The poster and oral presentation sessions provide valuable opportunities for the scientists to hone their presentation skills and exchange scientific ideas. Unlike previous events, this year YIRD spanned two days (May 3 – 4, 2010) in order to accommodate the growing number of young scientists working at the Institute.

The event was organized by the Crossroads Postdoctoral and Student Association Committee and featured plenary speakers Rocky Tuan, Ph.D., and Cecilia Lo, Ph.D., both from the University of Pittsburgh School of Medicine. Congratulations to the 2010 YIRD award winners and to the event organizers for jobs well done!

Photos by Jay Casillas



Young Investigator Research Day Poster Presentation Winners (back row from left) Norman Pavelka, Ram Kannan, (front row from left) Shruti Haralalka, Geetha Hewawasam, Liang Liang, (not pictured) Katherine Prather, Christine Smoyer

Young Investigator Research Day Oral Presentation Winners (from left) Aissam Ikmi, Arupratan Das, Vikki Weake, Ashleigh Fritz

Best Poster Presentation by Scientific Staff		
Winner: Katherine Prather	Kulesa Lab	Cell Morphometric and Molecular Analyses of Cranial Neural Crest Migratory Behaviors
Runner-up: Christine Smoyer	Jaspersen Lab	Inner Nuclear Membrane Protein Trafficking: Mapping the Route of Mps3
Best Poster Presentation by a Graduate Student		
Winner: Ram Kannan	Baumann Lab	Factors Responsible for Slicing of Telomerase RNA in *S. pombe*
Runner-up: Liang Liang	Gibson Lab	A Genome-Wide Functional Screen for Novel Tissue-Specific Cell Cycle Genes in the *Drosophila* Wing Imaginal Disc
Best Poster Presentation by a Postdoctoral Researcher		
Winner: Geetha Hewawasam	Gerton Lab	Psh1 is an E3 Ubiquitin Ligase that Targets the Centromeric Histone Variant Cse4 in Budding Yeast
Runner-up: Shruti Haralalka	Abmayr Lab	Asymmetry in the Requirement for the RacGEF, MBC: Rethinking Models of Myoblast Fusion
Runner-up: Norman Pavelka	Rong Li Lab	Quantitative Measurement of Yeast Growth in High Throughput
Best Oral Presentation by a Graduate Student		
Winner: Ashleigh Fritz	Gibson Lab	The Molecular Logic of Tentacle Development in the Sea Anemone, *Nematostella vectensis*
Runner-up: Arupratan Das	Rong Li Lab	Role of Lipid Flippases in Cdc42 Recycling and Dynamic Maintenance of Cortical Polarity
Best Oral Presentation by a Postdoctoral Researcher		
Winner: Vikki Weake	Workman Lab	A Novel Histone Fold Domain-Containing Protein that Replaces TAF6 in *Drosophila* SAGA is Required for SAGA-Dependent Gene Expression Independent of the Histone-Modifying Activities of the Complex
Runner-up: Aissam Ikmi	Gibson Lab	Identification and *In Vivo* Characterization of NvFP-7R, a Developmentally Regulated Red Fluorescent Protein of *Nematostella vectensis*

Photo by Don Ipock

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BY JAMES E. STOWERS JR., CO-FOUNDER

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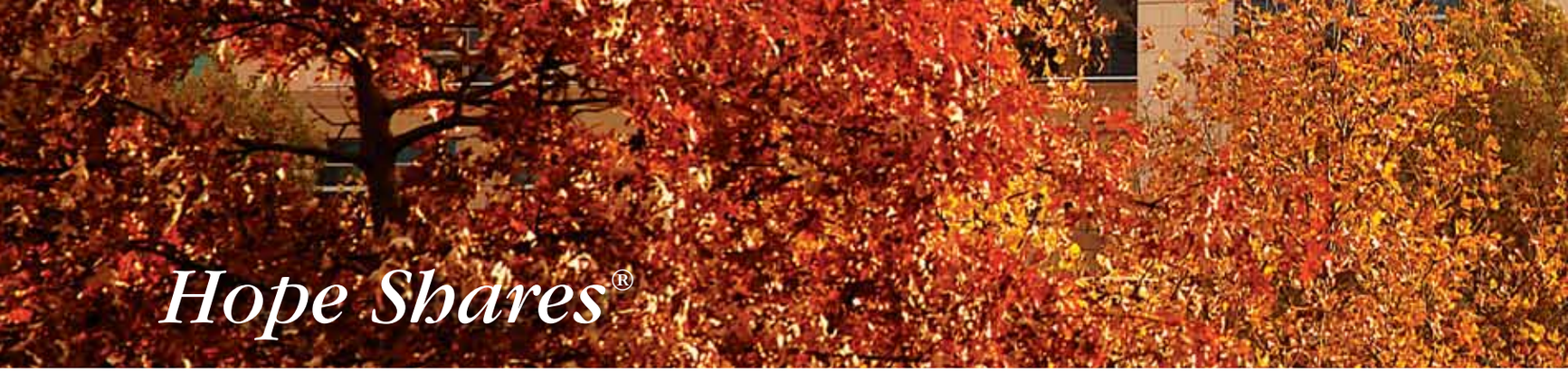

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*Hank Young (*Gameface *book proceeds)*

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Photo by Don Ipock

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