MARY CROWLEY
NEWSLETTER
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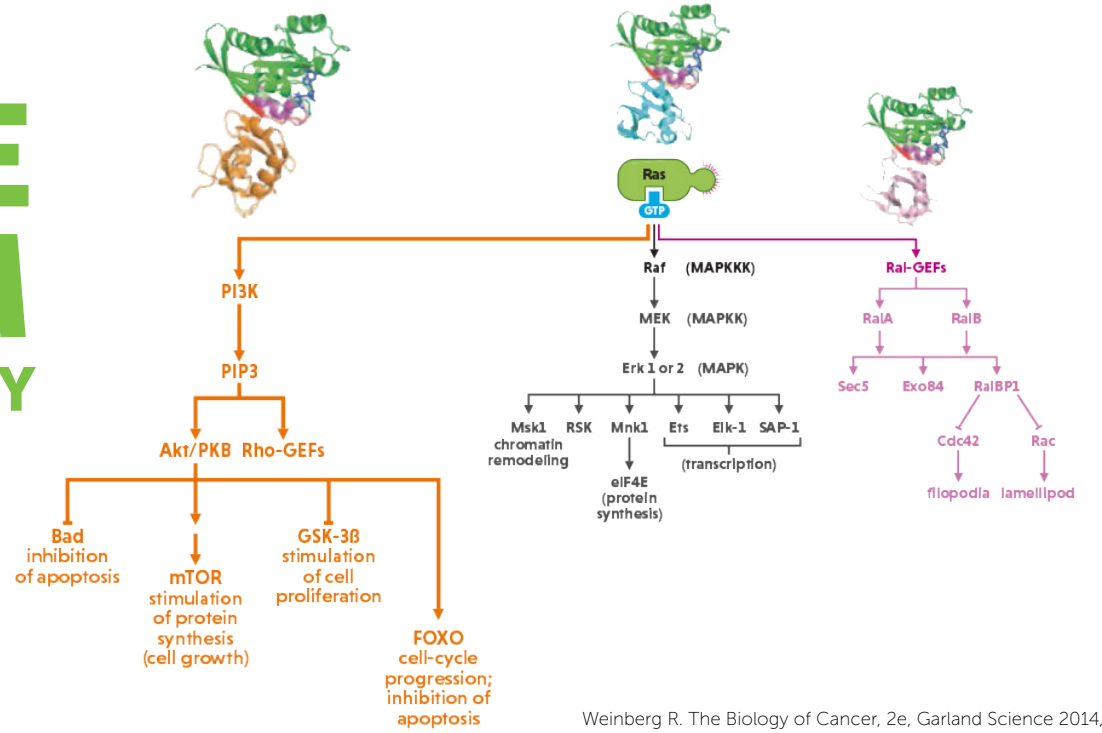
THE PAM PATHWAY



Weinberg R. The Biology of Cancer, 2e, Garland Science 2014, p. 193

Dr. James Strauss, Mary Crowley Physician Investigator, explains that by disrupting a common signaling pathway known as PAM, researchers are finding new ways to halt cancer growth.

PAM refers to a signaling pathway within cells that is involved in the continuous stimulation for cell division that occurs in cancer cells. The enzymes in this pathway interact in sequence. They are **PI3K** (phosphotidyl inositol 3 kinase), **AKT** (because the gene for this enzyme causes thymoma in the AK strain of mice), and **mTOR** (mammalian target of rapamycin).

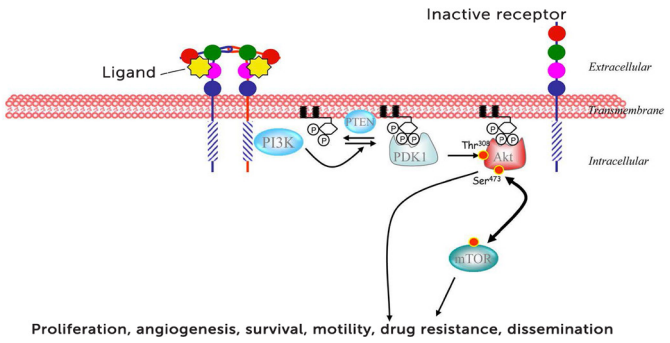
Activation of PI3K is the result of transmembrane receptors that are activated as a result of binding the appropriate signal substance in the extracellular space (the ligand for the receptor) or are activated by a mutation of the receptor. The activation of PI3K is accomplished by the RAS protein that transmits the signal from the transmembrane receptor. Mutations that activate the RAS protein are one of the most frequent in all cancers. The activated PI3K enzyme in turn activates AKT and mTOR. (It is more complicated. Activation of mTOR via another signaling pathway can cause of activation of AKT.)

In addition to the activation by cell membrane receptors or by the RAS protein, the PAM pathway can be activated by mutations in any of the enzymes in the pathway itself. Mutations in PI3K, AKT, or mTOR are found in many tumors especially in breast cancers, ovarian cancers, and non-small cell lung cancers.

Drugs that block activity of this pathway have long been sought because the pathway is frequently involved in many types of cancer. So far there are 2 approved inhibitors of mTOR - everolimus and temsirolimus, used in treatment of kidney cancer, breast cancer, and neuroendocrine cancers. There is one inhibitor of PI3K - idelalisib, an inhibitor of the delta form of PI3K found only in lymphocytes and, therefore, used in the treatment of some kinds of lymphoma.

Mary Crowley currently has 2 open studies that use investigational new drugs that target the PAM pathway (studies: #13-04 and #16-26). Patients are considered for enrollment in one of these studies only if sequencing of the tumor DNA has shown that the tumor has an activating mutation in PI3K or AKT.

By James Strauss, MD, Physician Investigator at MCCR



Ocana, Vera-Badillo, et al. PLOS One 2014; 9:e95219

SPECIAL ANNOUNCEMENT:

MARY CROWLEY WELCOMES MERRICK REESE, M.D., AS CEO

The Board of Mary Crowley Cancer Research is pleased to announce the appointment of Merrick Reese, M.D., to the position of Chief Executive Officer. Doug Adkins, Chairman of the Board, shared the news with Mary Crowley staff on Tuesday, May 9. "With his depth of experience and skill, Mary Crowley is fortunate to have this highly regarded physician serving as our CEO."

Dr. Reese has been a key leader at Mary Crowley since the inception of the organization. In addition to serving as board member, he was an advisor to Mr. Adkins and John T. Mallams, M.D. In the early 1990's. Dr. Reese was also instrumental in recruiting John Nemunaitis, M.D., to succeed Dr. Mallams as Executive Medical Director.

Dr. Reese was born in Dallas, Texas. He completed his medical training and residency at Parkland Memorial Hospital and his Fellowship in Medical Oncology and Hematology at University of Texas Southwestern Medical School.

Dr. Reese was the founder of Texas Oncology, P.A. (TOPA), which is a nationally recognized group of medical oncologists that represents more than 300 physicians across the United States. He later served as the president and chairman of TOPA and Chairman/CEO of Physician Reliance Network, Inc. For much of Dr. Reese's professional career, he has been associated with Baylor Scott & White Health, formerly Baylor University Medical Center, in Dallas, Texas.

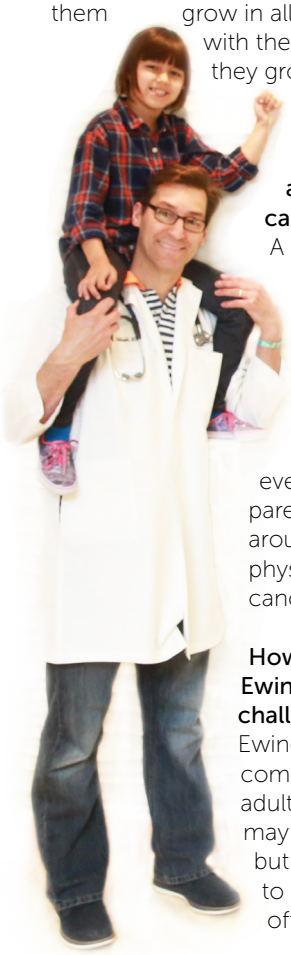
Some of his professional affiliations include: Alpha Omega Alpha Honor Medical Society, American Medical Association, Texas Medical Association, Dallas County Medical Society, American College of Physicians, American Society of Hematology, American Society of Clinical Oncology, American Group Practice Association, American Academy of Medical Directors, and American College of Physician Executives.

Dr. Reese has devoted his career to caring for cancer patients and searching for expanded treatment options.

FIVE QUESTIONS

with **Dr. Maurizio Ghisoli,**
Pediatric Hematology Oncologist at Mary Crowley Cancer Research & Texas Oncology P.A. (TOPA)

Why did you choose pediatric oncology?
I think kids are fun! It's fun to learn about them, to play with them and try to cure them. I love to see them grow in all stages. You get to connect with them, know their life, see how they grow and mature. It's a passion for me.



What has surprised you most about working with pediatric cancer patients?
A surprise is the strong will of children. We tend to think children are fragile, but then they endure so much. Emotionally, they sometimes handle chemotherapy even better than adult patients. I am surprised that some kids even become protective of their parents – instead of the other way around – from the emotional, physical and spiritual suffering of cancer.

How would you describe Ewing sarcoma, and what are its challenges?
Ewing sarcoma is the second most common pediatric and young adult bone cancer. Most patients may respond at the beginning, but it's common for the disease to recur. When it comes back, often, it's incurable.

What makes Mary Crowley different?
I love that Mary Crowley is a patient-focused research center. It's all about bringing therapies to the patients in a rapid way. It's a very friendly environment.

How does Mary Crowley give HOPE to cancer patients?
Mary Crowley looks beyond the traditional approach to cancer. Most of our patients have been through chemotherapy, and it's not working. We are focusing our Ewing's research on the genetics of the cancer. This is the new HOPE — Immunotherapy AND molecular therapy, the "One-Two Punch": first, teaching the immune system to fight the disease; and second, examining the molecular basis of the cancer and personalizing it by blocking the Ewing's mutations with molecular therapy.

Immunotherapy is widely recognized as the new frontier; what's unique about our approach is we use the whole cell, and it's personalized for each patient. Our goal is to control the disease by teaching the immune system to attack the cancer – similar to the way physicians have learned to manage hypertension. That's what we are trying to do with Ewing sarcoma, to transfer rapidly progressing tumors into something more chronic. It's not a cure, but we can hopefully make it more manageable.

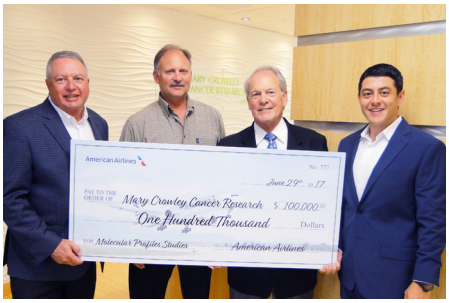
That's how we give HOPE to Ewing's patients.

Dr. Nemunaitis Joins Panel Discussion at Cancer Support Community N. Texas

Cancer Support Community of North Texas (CSCNT) recently invited Mary Crowley's Executive Medical Director John Nemunaitis, M.D., and other cancer experts to speak at a panel discussion titled "The Business, Breakthroughs and Future of Cancer Care" on Tuesday, June 27, at the CSCNT Cancer Center, 8196 Walnut Hill Lane.

Billed as a follow up to Vice President Joe Biden's 2020 Cancer Moonshot progam, the educational event examined the state of cancer care and where it is headed. Dr. Nemunaitis' talk, "Clinical Trials: Promising Therapies that Target Cancer," focused on Mary Crowley's "1-2 Punch," innovative clinical trials that use vaccines, gene therapies and cellular therapies to stop cancer growth AND train the body's immune system to prevent cancer expansion.

CANCER SUPPORT COMMUNITY
NORTH TEXAS



Tim Ahern; John Nemunaitis, M.D.; James Cochran, M.D.; Sean Ahern

American Airlines Gives $100,000 Grant to Mary Crowley

American Airlines has gifted $100,000 to Mary Crowley Cancer Research in honor of Tim Ahern, who is retiring after 39 years with American Airlines. Mr. Ahern has served as Vice-President – Customer Experience since 2015. American Airlines Airlines honors retiring executives by giving a grant to their designated charity organization(s).

"Tim has been a key leader at American Airlines for 39 years and has helped our team succeed through incredible changes and challenges," said American's President Robert Isom. "We are thrilled to make this donation to Mary Crowley Cancer Research in his honor." When Tim's late wife Susie was diagnosed with kidney cancer, he became acquainted with her treating physician, Dr. James Cochran, and discussed his desire to make a donation toward cancer research.

Understanding the value of clinical research, Dr. Cochran suggested Mary Crowley as a site for his donation. The funds will support a project that Dr. Cochran and Dr. John Nemunaitis have developed to further their work in identifying molecular targets that drive cancer growth in certain patient populations. The findings of the project could reveal improved treatment options for cancer patients.

Colon Cancer Alliance Donates $21,000 to Mary Crowley

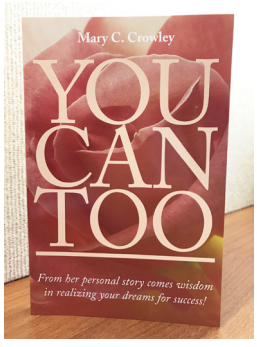
Mary Crowley is pleased to receive a $21,000 grant from Colon Cancer Alliance (CCA) and is grateful for their continued community partnership. The grant will be used to support Mary Crowley's innovative clinical trials for colorectal cancer. Established in 1999, CCA provides assistance to colon cancer patients and aligned with Mary Crowley in 2010 to "knock colon cancer out of the top three cancer killers". In November 2016, Mary Crowley staff members and friends – the Mary Crowley Crawlers – participated in CCA's DFW Undy Run/ Walk for Colon Cancer.

Karina Lupercio Frankie Lupercia, Alicia Myers, Meghan Manley and Alex Preston

MARY CROWLEY CANCER RESEARCH *Gives Back!*

On Saturday, June 24, Mary Crowley staff and friends gathered at North Texas Food Bank (NTFB) for a meaningful service project. After an entertaining orientation, Mary Crowley volunteers sorted frozen meats into 25-lb boxes to be distributed through NTFB's local food pantry partners. Next, the team sorted canned goods. Their hard work paid off for hungry North Texans: Mary Crowley prepared 13.6 pallets of frozen meat and canned goods, which equates to 402 boxes and 10,050lbs of food. According to NTFB, this will feed 8,374 meals to our North Texas neighbors. Mary Crowley employees enjoy "giving back" to the community through DFW-area service activities.

THANK YOU FOR YOUR GIFT TO MARY CROWLEY CANCER RESEARCH!



For gifts of $200 and above, donors will receive a copy of our founder Mary C. Crowley's inspirational autobiography *You Can Too*. Mary tells how she overcame tremendous obstacles to create a better life for herself and her family by starting a business that grew into a multi-million dollar enterprise. She also shares the details of her cancer journey, which ultimately led to the establishment of her namesake cancer research center.

Mary was a woman of deep faith who loved to encourage and inspire people. She often quoted author Carl Bard, "Though no one can start over and make a new beginning, each one of us can start now and make a new ending." Mary's message of HOPE is the foundational vision of Mary Crowley Cancer Research.

Donate today at www.marycrowley.org

Upcoming
EVENTS

Find out more at marycrowely.org

AUG 17, 18, 19	SEPT 14	OCT 5
Pushing Hope Tournament	North Texas	Heart of Gold Luncheon
Ceres Barge Line	Giving Day	**Rutledge Foundation**

MARY CROWLEY CANCER RESEARCH
HOPE LIVES HERE™

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Suite 1500
Dallas, TX 75251

Patient Research Center at Medical City
7777 Forest Lane
Building C | Suite 707
Dallas, TX 75230

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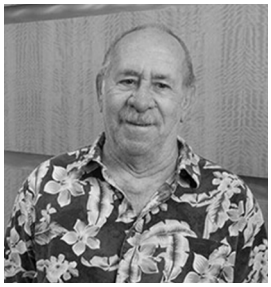
www.marycrowley.org



My Caregiver Story: Chris Zimmer

Jim and I met in Hurst, Texas, in October 1984. We married in September 1986, and our daughter was born in April 1991. Jim and I were very different individuals, but we respected one another. We promised to love each other unconditionally and wholeheartedly forever.

In June 2015, Jim came home from work and asked me if he looked yellow. He wasn't just yellow, he was Homer Simpson yellow! He was diagnosed with State IV pancreatic cancer. I felt like my world was falling apart. Jim, on the other hand, took the diagnosis in stride. I remember sitting and crying. Jim took my hand and said, "Stop crying. I am not dead yet. We still don't know what we are up against, but if things aren't good, how long do you need to be ready to let me go?" I told him two years. So he said, "Our goal is for me to survive this, but if I can't, I'll fight as hard as I can for two years. We'll work together to make sure you are prepared to let me go if the time comes."

So we developed a two-year plan including Jim's treatment, updating our legal documents, planning vacations and discussing what to do if Jim passed. We promised to be honest about how we felt, to remain optimistic and to never wallow in the potential outcome. We had ups and downs, but my task was to encourage Jim to continue to fight. Cancer became our new normal. Jim did chemotherapy for one year, and then his oncologist suggested clinical trials. We decided that Mary Crowley was our best option. In the brief time that Jim was on the clinical trial at Mary Crowley, the doctors, nurses and staff were wonderful. We felt everyone there genuinely cared for Jim.

As Jim's health deteriorated, he became more dependent on me, and I became more stressed. Some days we felt overwhelmed, but there were days of happiness as well. Sadly, our two-year plan came to an end in January 2017, a little short of two years, when Jim passed.

I want to be honest: I am really sad. But each day is a little better than the last. We built an amazing life together, and now I am embarking on a new journey without him. Because of the strong foundation we built together, I will be able to get through the grief. The last two years were not easy, but we never forgot the promise we made over 30 years ago, to love each other unconditionally and wholeheartedly. I have no regrets; I know I did the best I could for him, and that on his deathbed, Jim had no regrets either. Even though the outcome was not what we wanted, we faced it together.

"I am a big supporter of clinical trials and believe that the cure for cancer will be found through this type of research... I wish that the option of participating in the clinical trial had been discussed earlier -- it would have benefitted Jim and also others who suffer from this disease as well."

Chris Zimmer