Director's Overview

It's not about the numbers (unless they are good ones)

By: D. Ross Camidge, MD, PhD

A famous evolutionary biologist, Stephen Jay Gould, was 40 years old when he was first diagnosed with mesothelioma. Looking up the statistics on the disease, as they were in 1982, he read that the median survival was only 8 months from diagnosis. Twenty years later, he died rapidly from a completely different disease, getting, presumably, some small consolation from proving his doctors very wrong in their initial estimates of his survival. Ironically, his second disease was lung cancer, a disease that only a few years ago was almost universally terrible. However, in this year's Lung Cancer Colorado Fund (LCCF) newsletter you will see multiple examples showing that "average" survival rates for lung cancer are not written in stone for anybody. You will read about laboratory work looking to increase our understanding of the biology of cancer and about clinical trials showing benefits from novel approaches. You will see people working in lots of different ways to address lung cancer and other thoracic cancers, including mesothelioma and thymic cancer. You will see people just living their lives to the fullest, making a difference, raising funds for the LCCF, including the donation that has taken our total to over a million dollars since we started.

Andy Bonnett (stage IV Easy Rider). Photo by Jim Schnepf

So remember, life is never just about the numbers, unless they are good ones. Enjoy the ride!

If you are reading this and you or someone you know has a thoracic cancer - please support the LCCF and help change the world for the better. Our LCCF website includes an archive of all the past newsletters and details of where every dollar has gone. What will the future hold?

You get to decide. www.ucdenver.edu/lccf

Broken Windows:

by Garth Sundem

Colorado furthers search for lung conditions that allow growth of cancer

The American Association for Cancer Research (AACR) will fund a major grant led by University of Colorado Cancer Center investigators to pinpoint the lung tissue characteristics that allow cancer cells to grow, potentially leading to new strategies to prevent and treat the disease.

This team project will be led by James DeGregori, PhD, CU Cancer Center Deputy Director and professor in the CU School of Medicine Department of Biochemistry and Molecular Genetics, whose research explores the development of cancer through the lens of evolution, as populations of cells compete for limited resources within the ecosystem of the body. DeGregori's model, called Adaptive Oncogenesis, shows that it is not necessarily mutations alone that cause cancer, but cancer-causing mutations in cooperation with changes in the tissue ecosystem such as inflammation, aging, and immune system imbalance that make cells with these mutations "more fit" than other cells within the same tissue environment.

The group includes additional Colorado researchers from National Jewish Health and the Rocky Mountain Regional Veterans Affairs Medical Center. Co-principal investigator, Dr. Tullia Bruno, who trained in Colorado, will lead a collaborating team at the University of Pittsburgh with co-investigator and pulmonologist, Dr. David Wilson.

Previous work from grant co-investigators including Drs. York Miller, Robert Keith, Moumita Ghosh, and Dan Merrick has shown that interventions modulating lung conditions can reduce the risk of malignant cell growth. Together, with more basic studies from DeGregori's group, findings suggest that altered lung environments (such as due to smoking) can offer an evolutionary advantage to lung cancer cells, and that dampening these lung alterations can reduce this risk.

"Think of the body like a neighborhood. If you walk into a neighborhood with abandoned buildings and broken windows, you can guess the odds that you'll

be mugged without necessarily having to see the mugger. That's what we're doing in the lung – it's the neighborhood that allows these shady characters to be there," DeGregori says.

With AACR support, the team hopes to identify the lung equivalents of "abandoned buildings" and "broken windows" that allow them to predict cancer risk based on conditions of the lung. Eventually, the group hopes their work will lead to interventions to change these conditions for the purpose of preventing or treating lung cancer.

"Current treatments mostly target cancer cells," DeGregori says. "With our approach, instead of targeting cancer cells, we modulate the tissues around these cells that allow cancers to grow."

The current study will use bronchoscopy samples from patients evaluated for possibly cancerous nodules. "They have nodules," DeGregori says. "A little more than half the time it's nothing and a little less than half the time it's cancer. Our goal is to see if we can predict which is which based on other features of the lung."

For example, it may be that bronchoscopy specimens taken from lungs with higher levels of inflammation (as often seen in smokers) are more likely to harbor a cancer. Previous work also hints that the balance of two types of immune cells – cytotoxic T cells that activate the immune system,

and regulatory T cells that turn it off – may influence whether cells with cancer-causing mutations are able to flourish.

"To use another analogy, it's like the classic idea of seed and soil. A malignant cell is the seed. We're looking for features of a fertile soil for cancer. And then we will be able to ask, how do we change that soil to make it less fertile for cancer growth?" DeGregori says.
The work also highlights a shifting paradigm in cancer research that prioritizes collaboration across disciplines and institutions.

"Clinician-scientists on the team will obtain the bronchoscopy specimens; a pathologist will evaluate them; immunologists will explore immune features of these tissues; and bioinformaticians will help us quantify what it all means," DeGregori says.

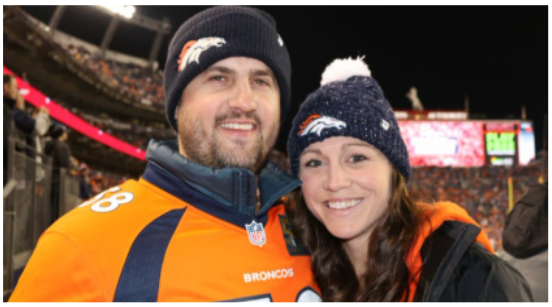
James DeGregori, PhD

"None of this would work without the other components. Without any one of these pieces, the study would never get off the ground."
The three-year, $1.5M grant is expected to accrue approximately 90 patients for evaluation. The group hopes this work will lead to additional exploration by its members and others into the tissue conditions that support and suppress the growth of lung and other cancers.

Lung Cancer Survivor Raises Thousands for Research, Wins Super Bowl Trip

Adapted from the story by Kathy Walsh, Denver CBS4

A young father from Denver with advanced lung cancer was pumped when he found out he was going to SuperBowl 2018. He won the trip after raising nearly $50,000 to fund lung cancer research in Colorado. Matt Arensdorf and his wife, Jen, raised that money in just two months. It will help advance the treatment of lung cancer and it is an investment in Arensdorf's future.



Matt and Jen Arensdorf

In early 2016, life was good for Arensdorf. "32 years old, 3 month old baby, everything was perfect, really," he told CBS4 Health Specialist Kathy Walsh.

Then Arensdorf noticed vision problems. Tests showed tumors in his brain. "Everything kind of comes crashing to a halt," he said. It was cancer that started in the nonsmoker's lungs — stage 4.
"Anybody with lungs can get lung cancer," said Arensdorf. At the University of Colorado Cancer Center, he has had radiation, brain surgery, and two targeted therapies. His cancer isn't curable, but he is a two-year survivor. "It's the research and the new drugs that are keeping me going," Arensdorf said.

He and his wife, Jen, are helping. The two teamed up with former NFL linebacker, Chris Draft. "My wife, Keasha, was 37 years old," said Draft. Keasha was 37 when she died of lung cancer. Now, Draft holds a Super Bowl challenge. Lung cancer survivors raise funds for research. "With more research, we're going to save more lives," said Draft.

The Arensdorfs raised nearly $50,000 for the Lung Cancer Colorado Fund. They scored a trip to the Super Bowl but, most importantly, they tackled the development of future treatments. "We know that money's going to have an impact and we need an impact," said Jen. "His (Matt's) future's dependent on it."

See the full CBS4 video: https://denver.cbslocal.com/2018/01/10/lung-cancer-survivor-super-bowl/

Colorado C-stories: Images of life after a cancer diagnosis

Receiving the news of any cancer diagnosis can be devastating. Patients may feel like their lives are coming to an end, that they will not be able accomplish many goals they had. Yet, time and again, the human spirit (with a little advanced medical care) prevails and people remember to be the people they were before they became patients – not just living with a cancer diagnosis but thriving.

At CU, we see patients from all over the country and the world. Here are a selection of the CU's finest showing that life remains about living, even, or perhaps especially, after a cancer diagnosis.

Send your pictures and a line or two to ross.camidge@ucdenver.edu and each newsletter going forward we'll aim to show others what 'hope' really looks like. Look for more images scattered throughout this newsletter.

Melissa Turner (stage IV snow shoer) heads through the Coeur d' Alene, ID

Lisa Moran (stage IV runner) takes on the Red Rocks 5K

Estate Planning:

Consider including the Lung Cancer Colorado Fund in your estate plans – It makes a huge difference and is not that complicated. Please review the Special Estate Planning LCCF Newsletter Edition available in the clinic rooms or on-line at: www.ucdenver.edu/lccf

Expert panel issues new guidelines for lung cancer molecular testing

by Garth Sundem

Lung cancer treatment often pairs targeted therapies with genetic alterations driving the disease. This makes *detecting* these genetic alterations an essential step in diagnosis. In 2013, an expert panel made up of members of the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published guidelines describing the genetic tests that should be performed to evaluate a patient's lung cancer. Now a similar expert panel updates these guidelines.

"There have been important changes since 2013. We're discovering new genetic alterations driving lung cancer, new drugs to target these alterations, and are refining our use of tests to find these alterations in individual patients," says Dara Aisner, MD, PhD, investigator at the University of Colorado Cancer Center, molecular pathologist at CU School of Medicine Department of Pathology, and one of the panel experts.

One major change is the recommendation to test for alterations to the gene ROS1 in all cases of lung adenocarcinoma, which make up about half of all cases of non-small cell lung cancer. The recommendation is due in large part to a growing body of evidence demonstrating the clinical benefit of treating patients whose tumors harbor this alteration with targeted therapy.

"In clinical practice, many forward-looking centers have already been testing for and treating ROS1 in lung cancer, but putting it into formal guidelines helps to encourage practitioners everywhere to include it in their targets for testing," Aisner says.
Another update to the 2013 guidelines is the use of cell-free DNA in blood, also called *circulating tumor DNA*, to test for genetic alterations when appropriate tissue for testing is unavailable.

"People have been using circulating tumor DNA to try to make a few kinds of decisions – this is one of the first formal guidelines to endorse that use," Aisner says.
On the plus side, Aisner points out, testing via circulating tumor DNA returns very few false-positives – when a test discovers DNA with a cancer-causing genetic change, it is strong evidence that this alteration is, in fact, present in the patient's cancer. However, tests that use circulating tumor DNA also have a high rate of false-negatives, meaning that even if a test of this type fails to discover altered DNA, it may still be present in a patient's cancer.


Dara Aisner, MD, PhD

"For this reason, when there's not enough tissue for other kinds of testing, we recommend tests using circulating tumor DNA to 'rule in' targetable mutations, but not to 'rule out' targetable mutations," Aisner says.

In addition to the use of circulating tumor DNA, the recommendations include another option for molecular testing with very little tissue, namely the expanded use of *cytology* specimens.
"Many lung cancer patients have their diagnosis made by fine needle aspirate – doctors extract cells via a long needle. This allows pathologists to diagnose the existence of cancer, but the sample tends to be very small, and there's been some debate about how useful that small amount of material can be for molecular testing," Aisner says.

One approach with this kind of material is to use what is called a *cytology cell block*, in which the extracted cells are treated similar to a biopsy. Another approach is to place extracted cells directly on a slide, in what is called a *smear preparation*. The previous guidelines specifically recommended

the use of only cytology cell blocks for testing, but the new guidelines endorse using the smear preparation as well.
"This is an important step forward, as it means that for some patients, testing will be possible when it wasn't before," Aisner says.

In fact, the Aisner lab has been instrumental in showing the benefit of using cytology smear preparations for molecular testing in lung cancer.

Aisner also points out an important, intentional omission from these guidelines. Just as many informed clinicians were testing for and targeting ROS1 alterations even before these current guidelines, clinicians are starting to test for and target alterations of the gene BRAF in lung cancer.

"The FDA approved a combination treatment against BRAF alterations in lung cancer and, clinically, many people are starting to include BRAF in the list of tests. This is a case of technology moving faster than our ability to complete systematic reviews of it," Aisner says.

She also points out that while the combination of dabrafenib and trametenib earned FDA approval against lung cancer with BRAF V600 mutation in the United States, the combination hasn't yet earned such approval in other countries, and these guidelines are meant to guide care not just in the United States, but internationally.

Full guidelines are published in the Archives of Pathology and Laboratory Medicine

Cancer rebel leaves terminal diagnosis in his rearview mirror

By: Katie Kerwin McCrimmon

Andy Bonnett is a cancer rebel. Or, maybe he's just a rebel who has told his cancer to take a hike. Cancer, by the way, is a word he rarely utters, even though Bonnett has fought off one of the most killer forms of it, Stage IV lung cancer, for a remarkable 10 years.

Bonnett's too busy living to bother being sick.

Picture Peter Fonda in *Easy Rider*, minus the sideburns and with long, flowing hair. Trade the chopper motorcycle for a green Harley. Ditch New Orleans and the bad drug trips and instead picture Bonnett road-tripping his way to the soaring red rocks of Sedona, Arizona, where he spends his days soaking up organic food, natural spring water and the healing powers of this spiritual place.

Unlike the gents of *Easy Rider*, our hero gets a happy ending. It's the cancer that implodes and lays motionless on a distant highway. Bonnett, on the other hand, gets to ride off into the sunset.

Bonnett's ordeal began in 2008. A Minnesotan, Bonnett loved the satisfaction and sweat of manual labor. "I was part of the blue collar backbone of America. It wasn't glamorous, but I was super proud."

He delayed college until his late 20s when his studies brought him to the University of Denver. He had just graduated and was working his first post-college job as a construction manager for a high-end remodeling firm when the recession hit hard.

At night, Bonnett kept getting reflux. During the days, he sometimes struggled to breathe and had a persistent cough. He was only 33, so he didn't think anything serious could be wrong. Maybe he was just stressed about the possibility of losing his job as the economy tanked. He went to see his doctor, who told him he'd need to go to the ER if the breathing problems persisted. Then he saw other doctors and tried physical therapy for the pain. Bonnett was supposed to get an MRI to help determine what was wrong, but started to feel better, so he put it off for a few months.

Andy Bonnett loves taking road trips and lives in Sedona, AZ., where he embraces beauty and healing. Photo by Jim Schnepf.

Just before Thanksgiving 10 years ago, he went in to see his doctor again. Pain gripped him in the chest, right behind his heart. An MRI showed fluid between his lungs and rib cage. His doctors tested the fluid and called Bonnett back in the next day.

A specialist met him. She told Bonnett he could sit. "I remember the room. I told her I didn't want to sit. She said, 'I'm really sorry to tell you this, but you have lung cancer.'"

It was bad: non-small cell lung cancer that already had spread to Bonnett's lymph nodes and the tissue around his lungs. He was in shock and doesn't remember anything the doctor said after that.

"It was sheer terror," he said. "I kept thinking, 'why me?'"

He had barely smoked in his life. He was young, healthy and slender. All his life, he had been super active: running, hiking, skiing and snowboarding.

Devastated, Bonnett called his mom and his oldest friend. "Hey buddy," Bonnett said. "I'm not feeling well. I need help driving home."

Bonnett went back to Minnesota and received extensive care. Doctors tried all the traditional therapies, but the outlook was bleak. Bonnett asked how long anyone had ever lived with a similar diagnosis.

"Maybe seven years," a doctor told him. Bonnett made a vow to himself: "I'm going to live the longest of anyone."

That was a crazy concept at the time because the cancer was pretty close to killing Bonnett and later made its way to his brain.

But, he's an optimist and a non-conformist, so he focused on living. He ate clean. He never touched alcohol. Chemotherapy had left his body hypersensitive to chemicals, so he avoided bleach and anything else that could cause flare-ups. He even went to Switzerland to try alternative therapies including intensive heat treatments – known as hyperthermia – that essentially give the body a fever to help jumpstart the immune system.

Bonnett was in Switzerland when a pivotal call came from a friend in Denver. She had seen a local TV news story about a woman with lung cancer who was receiving care at UCHealth University of Colorado Hospital. She was participating in a clinical trial for a new lung cancer medication. And, it was working.

Bonnett emailed immediately. Then, he had to hustle. He needed to get tumor samples from Minnesota so the Colorado team could analyze his type of lung cancer. The samples arrived in Colorado in December of 2009.

Then, on New Year's Eve, Bonnett received a call from the lung cancer specialist who would end up saving his life: Dr. Ross Camidge.

"You're in," Camidge said. "Your test results make you a candidate for the drug trial."

Bonnett was stunned and overjoyed. "It was one of the most amazing things that could happen. When you're in that situation and you think you have no hope, then you find out there's a cutting-edge cancer treatment. And it was right in Denver," Bonnett said.

He flew back to the U.S. and had to flush out all the medications from previous treatments. Alone in a dark hospital room, Bonnett felt like he was on a knife-edge of hope and despair. "It was the most excruciating pain I had ever felt in my life," he said. "I thought I was going to die."

When Dr. Camidge saw Bonnett, he wasn't sure that his patient would live long enough to get the treatments, so Camidge expedited the first dose. "He was really unwell," Camidge said. "His cancer had kicked up a notch. There was fluid around his heart."

Researchers and doctors have made great gains in treating lung cancer in recent years and University of Colorado now ranks as one of the best places in the world for lung cancer treatments. Only a year before Bonnett's diagnosis, scientists in Japan had discovered particular molecular changes in some types of lung cancers. And doctors were beginning to use very specific targeted therapies to attack those cancers. Bonnett's cancer had a reactivation of what's known as the ALK gene. It makes abnormal proteins, which, in turn, fuel cancer growth.

Bonnett leathered up and ready to ride.

Exactly when Bonnett needed help, University of Colorado had become one of seven sites in the world to be testing an experimental drug for people with ALK abnormalities. Doctors at the University of Colorado Cancer Center are aggressive in finding experimental therapies for patients. They put as many as 40 percent on clinic trials – 10 times the national average.

Lung cancer patients, like Bonnett, need all the help they can get. Each year, lung cancer kills more people than prostate, pancreatic, breast and colon cancer combined. At an academic medical center, patients benefit from highly specialized experts, who are testing the newest treatments.

"I'm a thoracic medical oncologist. Our surgeons, our pathologists, our radiologists and radiation oncologists also focus very specifically on lung cancer. That specialization is key," Camidge said.

The first drug Camidge tried on Bonnett is called crizotinib. When it works, the drug suffocates the abnormal proteins and prevents them from producing cancer cells. The results were stunning.

"He thought he was going to die. Then, the next day, he texted me and he was out jogging," Camidge recalled with a laugh. "I was thrilled for him."

"It was absolutely crazy. I was feeling so good," Bonnett said. He was able to dive back into life and soon started running again.
Bonnett also joined a group for young cancer survivors called First Descents. The non-profit promotes healing through adventure. Thanks to the First Descents, Bonnett learned to surf in North Carolina, then, took surfing trips to Bali and Mexico. He also learned to kayak in Glacier National Park in Montana and took a second kayaking trip on Oregon's Rogue River.

"Those were some of the most empowering and powerful experiences of my life," Bonnett said. "The trips reignited the fires of hope and not feeling alone. The camaraderie was amazing."

Young cancer survivors often spend a lot of time asking, "Why me?" Bonnett said.

Meeting other young people helped Bonnett move beyond sorrow and anger to embracing life.
"They gave us t-shirts that said 'Out Living It.' There were so many meanings. We were out living and we were outliving cancer."

Mentors taught the young people to appreciate each moment. "We'd look at the water. It's always flowing. It's always moving. It's never the same. Water is life. The river is the teacher, the life giver," Bonnett said.
His adventures sparked joy and a little light-hearted envy in Camidge, who admits to trying surfing himself on one vacation, and promptly spilling into the ocean after about 10 seconds on the board.

"If you're doing your job right as an oncologist, you really should be jealous of your patients' lives, and that's exactly what's going on with Andy," Camidge said. "He shows what's possible with personalized therapy," Camidge said. "It allows us to keep the cancer under control. Andy is pushing past 10 years. He's literally at the cutting edge. There's no rule book to look at. We have to write it each day ourselves, constantly trying to extend how well he's done."

Bonnett ready for a day on the slopes.

While crizotinib was only available through clinical trials at first, the drug worked so well that by 2011, the FDA approved it to treat ALK-positive lung cancer. The drug is not a cure, Camidge said, but it helps doctors keep cancer under control. "My philosophy is that we're turning lung cancer into a long-term condition that we can treat, like asthma or diabetes," Camidge said.

Patients' bodies sometimes adapt to drugs like crizotinib. And, a couple of years after Bonnett's initial treatments, that happened with him. So, Camidge shifted Bonnett to another medication, then another, first brigatimib, then lorlatinib. With each change, Bonnett has helped researchers learn how cancer adapts and how doctors can adapt too. Each innovation has kept Bonnett alive.

"I'm on my third miracle," he said. "I love Dr. Camidge."

The better Bonnett felt, the more he wanted to embrace life by living in a beautiful place. A lifelong fan of road tripping, he calculates that he has logged more than 500,000 miles over the years. Bonnett found his way in 2013 to the red-rock country of Sedona, Arizona. He instantly felt at home. "It's the vibe of the people there. They're not career-driven. They're life-driven," Bonnett said. "It's a very sacred place. There are a lot of healers. It's serene and peaceful. It was a move for a healthy lifestyle."

On an ideal day, he wakes up, drinks a lot of water and meditates. After a healthy breakfast, he heads out to Oak Creek Canyon, about 15 minutes from his home. On the way, he takes in views of Thunder Mountain and Coffee Pot Rock, a formation that looks like an old percolator sitting on a campfire.

In the canyon, Bonnett hops from rock to rock, then finds one where he sits still and uses Reiki, a Japanese healing method, to open himself up to good health.

Bonnett found that when he stopped fighting cancer, and instead opened himself up to healing, he improved.

Andy Bonnett on a hike.

"The harder I fought it, the worse I felt. When I stopped fighting it and submitted to a new path, the healing journey began," Bonnett said.

"It was a monumental turning point and very poignant," Bonnett said. "I became at peace with a very gentle healing process and left the negativity of a battle mindset behind. Many good people around me helped me come to this decision." He's incredibly grateful to all of the supporters who have kept him alive.

"I never could have made it without them," Bonnett said.

He also thinks patients play a big part in their own healing and believes in the yin and yang of alternative and traditional medicine. Bonnett's convinced that natural healing methods keep him as healthy as possible so he can most efficiently absorb cutting-edge medical treatments.
He drinks at least a gallon of high quality water a day, gets regular massages and has an infrared sauna that he uses daily to help break up and sweat out toxins. He also tends to his spiritual life through a non-denominational community in Sedona and gets regular counseling.

"It takes a lot of discipline to be healthy," said Bonnett, who is confident about his prospects.

"The stuff is going to work forever," said Bonnett, now 43. "I feel so good. I feel like a normal person, except when I remind myself that I need to rest."

Along with focusing on healing, Bonnett works part-time in various jobs, including a stint when he learned to build traditional Native-American drums. Over the summer, he took a major road trip, towing his Harley and living out of a 14-foot cargo trailer, which holds the motorcycle on one side and a fold-down bed on the other.

"It's great. It's got a skylight and a fan. I can be on the road for months."

He traveled from Arizona to Montana and Canada then west to Washington, and south through California back home to Arizona, logging more than 13,000 miles over four months.

A friend had told him how beautiful the Canadian Rockies were, so he visited Banff National Park and got to camp at stunning Lake Louise. Later, as Bonnett wound south along the California coast, he often camped on coastal cliffs, where waves crashed loudly ashore all night long, reminding Bonnett of the ocean's power and life-giving force.

During the day, as he rode his motorcycle on curving ribbons of pavement, Bonnett felt completely at peace. "There's nothing else there. It's just you and the bike and the road. It's very calming," Bonnett said. "You're just taking in the elements. You can smell the flowers. You can smell the rain coming off the road and you can feel the different temperatures. It's the ultimate driving experience. There are no distractions – no radio, no GPS."

Now the cancer rebel is back home in Sedona, where's he's counting his blessings.

"I'm the luckiest, unlucky person I know," Bonnett said.

"I'm actually very grateful for my experiences. Otherwise, I would have gone down the path that everyone else takes," he said. "This has caused me to take a different path – one I didn't choose. But it has led to a deeper, more meaningful life. I consider it a gift."

These days, Bonnett's goal is quite simple. "I'm always reaching for more," he said. "I want a cure."

Finally, a potential new approach against KRAS-driven lung cancer

by Garth Sundem

The previous decade has seen dramatic advances in the treatment of non-small cell lung cancer, as genes driving subtypes of the disease including EGFR, ALK, ROS1 and BRAF are paired with drugs that silence their action. However, a major genetic driver of non-small cell lung cancer is still without a targeted treatment. The gene KRAS is known to be mutated in about 25 percent of non-small cell lung cancers (NSCLC) and despite over 10,000 studies related to KRAS listed in the PubMed database and just shy of 500 clinical trials including the search term KRAS at ClinicalTrials.gov, no successful drugs targeting KRAS are in clinical use.

Now a study by researchers at University of Colorado Cancer Center, M.D. Anderson Cancer Center and partner institutions describes a possible new approach against KRAS. The group shows that these KRAS-driven adenocarcinomas, the most prevalent subtype of NSCLC, are also marked by high levels of "gel-forming mucins," as seen in some forms of asthma, chronic obstructive pulmonary disease and cystic fibrosis. The study, published August 9 in the journal JCI Insight, also pinpoints a cause of increased mucin production, namely the gene MUC5AC.

Using independent cohorts of lung cancer tissue samples, the group found that MUC5AC tended to be over-expressed specifically in KRAS-mutated non-small cell lung cancers, and that high expression levels of the Muc5ac mRNA predicted poor patient outcomes. When the group developed mouse models lacking Muc5ac, mice that couldn't produce Muc5ac fared better than mice with Muc5ac. "What's unique about this study is that we were able to use two human cohorts and two animal models. With a lack of the Muc5ac gene in animal models, we saw a decrease in tumor development. In human cohorts, high expression of MUC5AC mRNA was associated with higher mortality. And when we evaluated those patients with KRAS mutations, we showed KRAS-mutant patients with high MUC5AC mRNA expression had higher mortality. This supports that MUC5AC is associated with KRAS," says Alison Bauer, PhD, CU Cancer Center investigator and associate professor in the Department of Environmental and Occupational Health at the Colorado School of Public Health.

Alison Bauer, PhD

“Our collaboration with M.D. Anderson was a great example of team science,” says Christopher Evans, PhD, professor in the CU School of Medicine Division of Pulmonary Sciences and Critical Care. “Frankly, we don’t understand exactly what MUC5AC is doing in lung cancer, and the fact that we were able to replicate our results in two populations and at two places is a big deal.”

MUC5AC is one in a family of genes that produce proteins essential in forming mucus-like gels that line the respiratory tract, digestive tract and other systems. Typically, mucins protect the tissues they coat. But, over-production of these gels in COPD, asthma and cystic fibrosis is associated with obstruction and infection.

“As an aside, these genes always pop up in adenocarcinomas, so much so that the existence of mucins helps to diagnose the condition,” says Evans, whose lab specializes in the study of mucins. “But no one knows what they do in these cancers. It’s not a barrier function and it doesn’t look like mucins are trapping bacteria or anything like that.”

According to Evans, it may be that because mucin proteins are so large (“100 to 1,000 times bigger than other proteins in the cell,” he says), manufacturing these proteins may simply add additional stress to cells that are already feeling the stress brought on by changes in KRAS that initiate the cancer.

“What we’ve done here is identify that whatever role MUC5AC has in KRAS-mutant non-small cell lung cancer, it’s a bad one,” Evans says.

KRAS itself has proved difficult to drug, in part because KRAS is needed for the development of healthy cells and so uniformly muting its action would cause significant side effects. But MUC5AC may be less necessary for healthy cells. And because MUC5AC has been identified as a target outside the field of cancer, drug development efforts are already underway.

“Researchers are targeting MUC5AC transcription factors and working to interfere with the body’s ability to synthesize the Muc5ac protein itself. Also, people naturally express different levels of mucins – up to 40-fold difference – and so there is research aimed at understanding how the body regulates this production,” Bauer says.

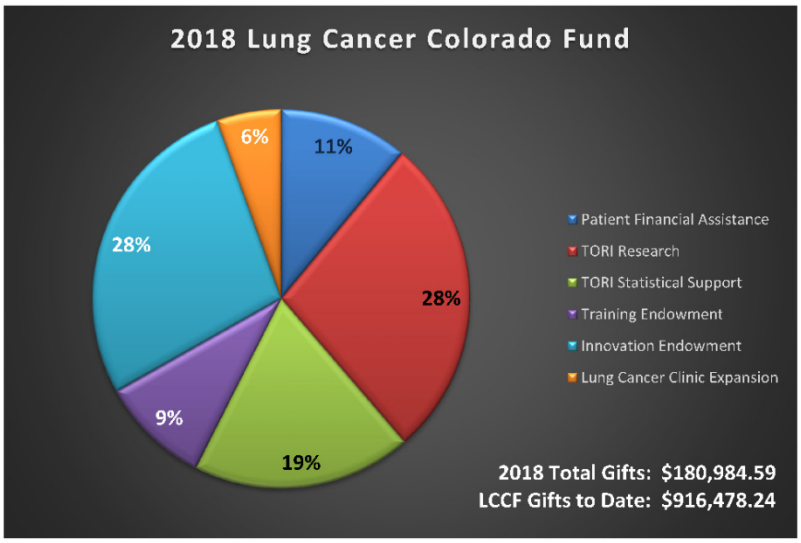
Now with a target in sight, the group hopes this work will invigorate efforts to combat mucins in general and MUC5AC in particular as a strategy against KRAS-mutant lung cancer.

LCCF Expenditures 2018

By D. Ross Camidge, MD, PhD

By December 2018, when the LCCF committee met to review the distribution of the funds raised for the LCCF in the year, the annual amount raised was $180,984.59.

- We gave $20,000 to support patient welfare through our social work department and $50,000 to fund continued research projects within the CU Thoracic Oncology Research Initiative (TORI).
- For infrastructural improvements, we committed to giving $34,000 to increase statistical support for data analysis within TORI and $10,000 for expanding the Lung Cancer Clinical Space.
- We contributed $16,984.59 to our first permanent quasi-endowment (to help support the salary of trainees in any aspect of the program in the future). We hope that a single donor/group will now Complete this permanent Fellowship fund (currently standing at ~250K from LCCF sourcing) and have the Fellowship named by them if they so wish.
- Finally, we began to crowd-source a new quasi-endowment with $50,000, this time for an 'Innovation Fund' with the same goal re a single donor/group taking it over to complete the donation



Quasi-endowments, current monies, endowments and all that jazz:

Beyond the immediate use of funds that the LCCF committee distributes annually as already described, larger donations can sometimes have defined purposes all by themselves. The Development Office at CU (contactable through 303-724-8227 or www.ucdenver.edu/lccf) can help with such plans, and these are especially helpful when you work with your physician and/or the LCCF to craft something that the program and donor are really passionate about together. Sometimes the monies are for immediate use, sometimes they are permanent funds where the principal gift cannot be touched but the interest can be (endowments), or a mix of the two (quasi-endowments, that generate interest but the principal amount can also be used).

The LCCF has had a vision to prime the pump on several quasi-endowments in the hope that each fund, addressing a specific need of the program will then be completed by a larger donor/group who would also be able to name the fund, if they so wish. Please speak to your MD if you are interested in these opportunities.

Colorado C-Stories Continue

Kendall Elliott (stage IV husband) with his wife, Bobbie

Todd Jaycox (Stage IV dad) on family game night with his girls

Cancer survivors' party celebrates hope

By Chris Casey

A decade ago, Ellen Smith went through the “traditional three” therapies for her lung cancer — radiation, surgery and chemotherapy — but still her cancer progressed to Stage IV and the prognosis was bleak. Her physician said he’d done all he could do.

A room full of hope – 5+ Year Survivor’s Inaugural Event September 2018. An annual celebration is being planning.

Her three adult children did some online research and found the website for the CU Cancer Center at the Anschutz Medical Campus. Also, a former co-worker who performed research at CU Anschutz strongly suggested Smith visit the CU Cancer Center. “She probably suggested it five times, and that saved my life,” Smith said. “I say the Lord and CU Anschutz are a good combo, because they saved my life.”

Smith and many other multi-year survivors of lung cancer recently gathered with friends and family for a celebration at the CU Anschutz Health and Wellness Center.

After survivors and their family enjoyed appetizers, dinner and cake — decorated with “And Many More” — along with appearances by the Rockies’ and Avs’ mascots, Dr Camidge, Director of the CU Lung Cancer Program, addressed the gathering. “We are celebrating the proof, demonstrated by all of you here, that long-term survival after a diagnosis of lung cancer is possible,” he said. “We are all here to show people that hope is real. It has a face and friends and family and a plan for next week and next month and next year.”

Survivors at the party had survived at least five years beyond their initial cancer diagnosis, but several had reached 10 years and a few even more. Others congratulating the group included Tom Gronow, chief operating officer at UCHealth; John Mitchell, MD, UCHealth’s chief of thoracic surgery; and Brian Kavanagh, MD, MPH, chair of radiation oncology.

Ann Broo (center) flanked by her sister, Kay and her radiation oncologist, Dr. Brian Kavanagh

The CU Cancer Center is the only National Cancer Institute-designated comprehensive cancer center in the state of Colorado. It is known for its personalized cancer treatments and its robust and diverse clinical research and clinical trials program.

Ben Smith said the treatment options, including clinical trials, made all the difference for his wife. “Early on, our CU doctor said it in the best, clearest and gentlest way: ‘If we proceed and work together on this, we’ll do everything we can do to put it to sleep. And when it wakes up we’ll do everything we can to put it to sleep again.’ He’s done it five different times; five different strategies.”

Gronow called the CU Cancer Center a gem that remains under-utilized in Colorado. “We have people who leave the state to seek care elsewhere, and I know in talking with many of you that you probably couldn’t fathom that, based on the experience you’ve had with the great team here,” he said. “It’s based on the foundation of all the doctors and a lot of other wonderful scientists who support the trials we do, the research we do, so that we can hopefully one day completely defeat cancer.”

Camidge said the lung cancer program’s success at the Cancer Center is attributable to:

Its relatively small size, allowing patients to receive very personalized and responsive care.

An outstanding track record in determining which clinical trials to pursue. Camidge estimates he turns down about five trials a week, waiting to choose the “pick of the litter … We do pretty good at picking those winners.”

A track record of putting about 40 percent of its patients on clinical trials, which is about double the next-best cancer center and about 10 times the national average.A patient catchment area that is much larger than Colorado. Of all the programs at the Cancer Center, the lung cancer program has the highest proportion of

patients, about 20 percent, from out of state. It now offers a remote second-opinion program, allowing patients to call and speak directly to an expert physician in the program from anywhere in the United States or the world.

Camidge said the Cancer Center has helped to either lead or contribute to “pretty much every major discovery in lung cancer disease in the last 10 years.” Given all the success Ellen Smith has had with her treatments — now a 10-year survivor (nine of those at the Cancer Center) — Camidge jokes, “Ellen has almost as many publications as I do.”

Hank Baskett from Clovis, N.M., a seven-year survivor, was the featured speaker and his story and life-affirming message left the room with nary a dry eye. Baskett said he loves everyone at CU Anschutz. “I’m just saying that from day one, the staff, the hospital, the center — from top to bottom — everyone here I’ve met has been beautiful,” he said. “I love the people; I’m blessed.”Baskett said the keys to fighting cancer, besides the incredible health care offered by the CU Anschutz Medical Campus, is to fight and keep living, not bow to the diagnosis. He concluded his remarks by saying: “To the Cancer Center staff, just keep on doing what you’re doing. And to all you survivors, keep living. You’ve got all that life that’s left to be lived!”

Hank Baskett welcomes everyone at the 2018 Lung Cancer 5+ Years Survivor Celebration

Between bites of cake and chats with patients they’ve treated for many years, Camidge, Mitchell and Kavanagh took in the festive scene that, as they said, is “really inspiring and keeps us going.”

Camidge expects that such longtime survivor gatherings of CU Cancer Center patients will become commonplace in future years. He ended his speech with this message:

“To be clear: no one is pretending that we have beaten this disease…. But together — the whole clinical team, the hospital, the university and the patients and their families — we are changing the world, doing things that no one thought possible, making hope possible; one person, one little miracle at a time.”

If you would like to help sponsor the Survivors’ Event at some point in the future – if you have space, ideas or the potential to help with catering – please contact karishma.sack@uchealth.org

Survivor pushes Lung Cancer Colorado Fund over the million dollar mark

by Erika Matich

Emily Daniels was 32 years-old and pregnant with her second child when she was diagnosed with lung cancer. One year later, Emily presented a check for more than $100,000 to the Lung Cancer Colorado Fund (LCCF) bringing the fund over the $1 million mark in 2019.

Emily and Brian Daniels with their children

The past year has been difficult for Emily and her family. It started when she went to the emergency room with tightness in her chest. That's when she was diagnosed. She has since been through seven rounds of chemotherapy and 15 radiation treatments. Emily also has taken two different targeted therapies developed especially for people with a rearrangement in the anaplastic lymphoma kinase fusion gene.

Emily says the summer of 2018 was particularly difficult but her last scan showed improvement and she is hoping that continues.

"I am proof that anyone with lungs can get lung cancer," says Emily. "I did everything right including eating right and exercising. I am feeling good and I want people to know that there is life after this diagnosis."

The Rondis and the Daniels hiking in Steamboat

Now that she's feeling better, Emily has a mission: to raise money for lung cancer research. along with both sides of her family (the Rondis and the Daniels) and friends, Emily held a golf tournament in September 2018. Links for Lungs raised $101,310 for the LCCF which supports the University of Colorado Cancer Center's fight against lung cancer including basic, clinical, and translational research.

With the right care, patients now living a median 6.8 years after stage IV ALK+ lung cancer diagnosis

by Garth Sundem

According to the National Cancer Institute, patients diagnosed with non-small cell lung cancer (NSCLC) between the years 1995 and 2001 had 15 percent chance of being alive 5 years later. For patients with stage IV disease, describing cancer that has spread to distant sites beyond the original tumor, that statistic drops to 2 percent. Now a University of Colorado Cancer Center study published in the

Jose M. Pacheco, MD

Journal of Thoracic Oncology tells a much more optimistic story. For stage IV NSCLC patients whose tumors test positive for rearrangements of the gene ALK (ALK+ NSCLC), treated at UCHealth University of Colorado Hospital between

2009 and 2017, median overall survival was 6.8 years. This means that in this population, instead of only 2 percent of patients being alive 5 years after diagnosis, 50 percent of patients were alive 6.8 years after diagnosis.

“What this shows is that with the development of good targeted therapies for ALK-positive lung cancer, even patients with stage IV disease can do well for many, many years,” says Jose Pacheco, MD, investigator at CU Cancer Center and the study’s first author.

Of the 110 patients on the current study, 83 percent were never-smokers, and had a median age of 53 years. Almost all of these patients were initially treated with the drug crizotinib, which earned FDA approval in August 2011 to treat ALK+ NSCLC, but had previously been available in Colorado and other academic medical centers in the setting of clinical trials. Importantly, after treatment with crizotinib, when patients on the current study showed evidence of worsening disease, 78 percent were transitioned to another ALK-inhibitor, commonly brigatinib, alectinib or ceritinib.

“Many studies have reported shorter overall survival for patients with stage IV ALK+ NSCLC treated with crizotinib. These studies had lower survival outcomes in large part because of a lower percentage of patients receiving next-gen ALK inhibitors after progressing on crizotinib. Patients here were getting next-gen ALK inhibitors in phase 1 and 2 clinical trials before many other centers had access to them,” Pacheco says.

Another factor that influenced survival was the use of pemetrexed-based chemotherapies in ALK+ lung cancer. Often, in addition to targeted therapy with ALK inhibitors, patients will undergo chemotherapy (and sometimes radiation). However, there are many chemotherapies to choose from, and it is often unclear which specific chemotherapies are most successful with specific cancers, stages, and patient characteristics. A 2011 study by CU Cancer Center investigators was the first to suggest that pemetrexed works especially well against the ALK+ form of the disease.

“We try to use mainly pemetrexed-based chemotherapies in ALK+ lung cancer,” Pacheco says, “It is possible shorter survival in other studies may be associated with use of non-pemetrexed based chemotherapies.”

Interestingly, the existence of brain metastases at time of diagnosis did not predict shorter survival.

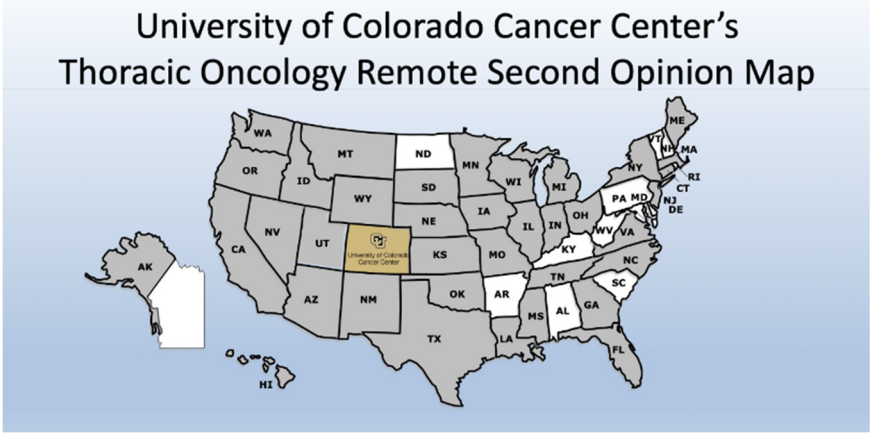
“A lot of the new ALK inhibitors that were developed after crizotinib get into the brain very well, and they work similarly in the brain when compared to outside the brain. And we’re doing more careful surveillance of patients to see when they develop brain mets – instead of waiting for symptoms and then treating, we’re monitoring for the development of metastases with imaging of the brain and if we see something new, we sometimes treat it before it causes symptoms,” Pacheco says.

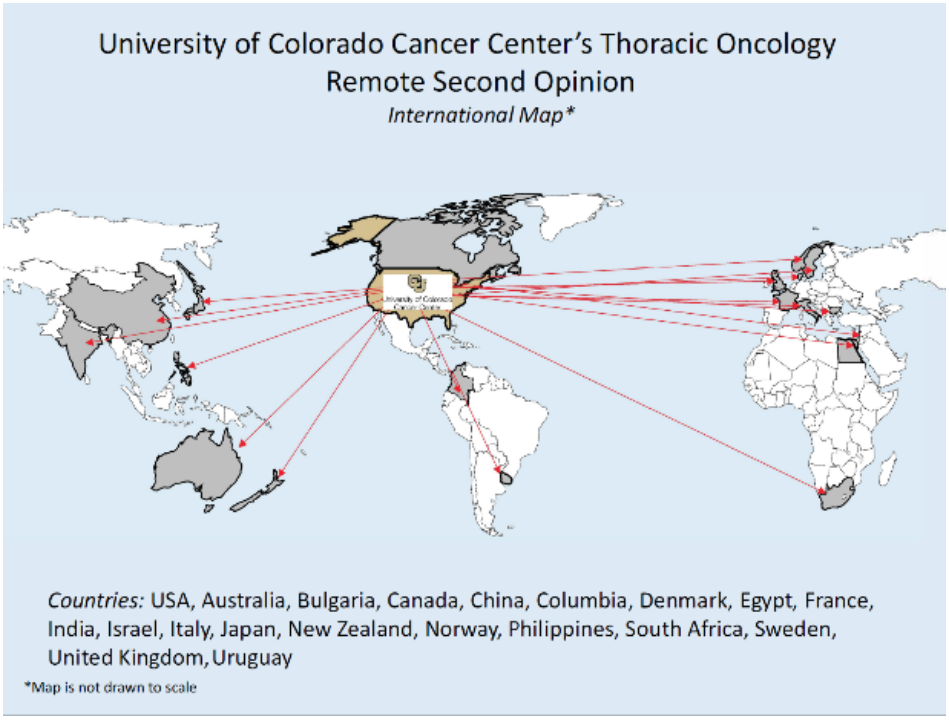
The most predictive factor of shorter survival was the number of organs that were found to carry cancer at the time of diagnosis.

“At this point, 6.8 years is one of longest median survivals ever reported for a NSCLC subpopulation with stage IV disease,” Pacheco says. “It shows the benefit of targeted therapy and how it’s changing survival for a lot of patients. And I think it suggests that for some types of NSCLC, it may become much more of a chronic condition rather than a terminal disease.”

Colorado's National and Global Reach:

Remote Second Opinions given by the Thoracic Oncology Program





Small world: International remote second opinion (RSO) utilizers Lars Soraas (Norway) and Grant Hatch (South Africa) hang out with Dr Camidge in person at the World Conference on Lung Cancer in Toronto, Canada. The RSO program has now benefited patients from 38 states and 20 different countries.

University of Colorado Cancer Center

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