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Mapping Alzheimer's: UCSB's Cristina Venegas follows a genetic puzzle tracing Alzheimer's roots from Colombia

There's a set of childhood memories that UC Santa Barbara film and media studies professor Cristina Venegas returns to once in a while, recollections that stand out because of their peculiar nature.

"I have memories of being a child in Montería, which is an interesting city, and it's on the banks of the Sinú river," she said of a municipality in her native northern Colombia. "I remember the town square facing the church where sometimes you could escape the heat and humidity. And there I can almost still see people who would sit in the park who appeared to be mentally … gone… and people referred to them as 'crazy.' There was also an old man who taught me how to play the guitar. The wife walked around with a cardboard on her forehead all day repeatedly asking what time it was."

This bit of surreality is not hers alone; it's embedded in the cultural memory of South America. Colombian master storyteller Gabriel García Márquez alluded to it in his 1967 tour de force "One Hundred Years of Solitude," calling it "a plague of forgetfulness" that sweeps a fictional remote Colombian town, wiping memory,

identity and meaning from its denizens.

In the 1980s, Colombian neurologist Dr. Francisco Lopera would begin to assemble a real-life medical puzzle,

following reports of young people complaining of memory loss, and finding entire families with the same symptoms going back for generations. He concluded it was an early-onset form of Alzheimer's disease, encoded in the families' genes.

So when Venegas learned about a collaboration in the foothills of the Colombian Andes between Lopera and UCSB neuroscientist Kenneth S. Kosik, something blossomed in her own brain – a story that she and her sister, Emmy award-winning science journalist Marisa Venegas, were uniquely equipped to tell.

"There are so many dimensions to this story that tap into our history and our background," she said, "about how this disease has ravaged the region, and not only the region, but worldwide." With the working title "Mapping Alzheimer's," the Venegas sisters' film aims to tell a story that spans centuries and reaches around the world, to document a fight that has been joined by numerous scientists and advocates, and to highlight the bonds that provide hope for a future without the disease.

"I'm humbled by what they all go through," Cristina Venegas said, "and that's the story we need to tell."

"Serendipity" is probably the word that most aptly describes Kenneth Kosik's career: If he hadn't traveled to the University of Antioquia School of Medicine in Medellín to lecture on the biology of Alzheimer's disease in 1992, he wouldn't have been introduced to Francisco Lopera. If he hadn't met Lopera, he wouldn't have been let into the insular world of the *paisa* — the name the locals of Antioquia have taken for themselves. And if he hadn't been let into their lives, he perhaps wouldn't have embarked on what he calls "an odyssey both geographical and personal" — tracing the path of mutations to the *presenilin1* gene around the world and backward in time.

"I'm enchanted," he said. "That's why I've gone back for 30 years. It exerts some sort of draw over me."

Indeed, the enchantment has drawn him deep into the lush and rugged landscapes of the Colombian *Cordillera Central*, even at the height of violence in the recent history of the country. The clinical and scientific collaboration has navigated its way around tense situations in conflict zones and conducted exploits worthy of any popular thriller. They've visited rough, poor neighborhoods and taken family histories marked by the collateral damage caused by nearly half a century of internecine conflict.

Physician-scientists Kosik and Lopera and their research teams live with one foot in each of two worlds — the highly controlled domain of the lab and the tumultuous field environment. Their goals? To not only investigate the genetic origins of Alzheimer’s, but also to pave the way for a cure.

At the heart of the researchers’ work is an extended family of about 6,000, each of whom bear a heavy burden: They’re either destined to develop Alzheimer’s by the time they’re about 45 years old, or they will bear witness to the inevitable decline of parents, siblings and cousins… often both. This genetic version of Alzheimer’s — as opposed to the “sporadic” type people get much later in life — is autosomal dominant, which means the individual need inherit only one copy of the mutant gene from either parent to develop the dementia themselves. In the presence of the gene the disease is nearly inevitable, coming on like clockwork.

Because of this kindred’s size and homogeneity, they provide an ideal population through which to hone in on the cellular and molecular mechanisms that lead to the development of the sticky plaques and neurofibrillary tangles that are the hallmarks of the disease. Thanks to Lopera’s dedication and relationship-building over the years, the family has time and again volunteered to cooperate with the scientists, welcoming them into their homes, participating in clinical trials,

offering their blood, and at the ends of their lives, their brains.

These conditions set the stage for some difficult dilemmas for the researchers, who have the power to predict who will develop Alzheimer’s, but not to cure or even mitigate the condition. They build family trees and run gene tests — to date, there are a rather astonishing 12 extended families found in Colombia, each with their own distinct mutations to the same gene. In the early days of the collaboration the

researchers had to grapple with whether to deliver the harsh news or remain silent. Kosik writes about this experience in a 1999 account for the journal “The Sciences:”

“I told the grown children that we could now determine which of them would get the disease, and I asked whether they would want to take the test. ‘Before answering,’ I told them, ‘remember that there is no treatment.’ All the children said they would want to take the test. ‘What would they do differently once they knew the result?’ I asked. At that point no one had an answer, except 23-year old González, who later told our nurse that if his test were positive, he would shoot himself.”

Two decades later, and thanks to the modest promise some drugs have shown in slowing down the disease, some of Lopera’s asymptomatic families have been invited to participate in clinical trials with the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), a project of the Washington University School of Medicine. For the trials they will all receive the FDA-approved anti-amyloid drug lecanemab as well as either an experimental anti-tau agent or a placebo, requiring the would-be participants to know their status in order to enroll. Members of Lopera’s Grupo Neurociencias de Antioquia have prepared for this effort by receiving specialized training in genetic counseling.

Into this maze of high stakes and errant genes, clinical trials and incremental progress plunge the filmmakers, who since 2019 have followed the scientists onto the field and into the lab as they trace the origins of and piece together the puzzle that is Alzheimer’s disease. Along the way the documentary team has uncovered clues about Latin America’s colonial past and the role it played in the emergence of such a high concentration of genetic anomalies in a relatively small part of the world. Importantly, they highlight the relationships that don’t show up in clinical trials and in scientific papers, but nevertheless are the reason for and the foundation of the scientists’ progress.

“We wanted to focus on the scientists and this transcultural and collaborative experience of doing research over such a long period of time,” Cristina Venegas explained. “And out of that comes this friendship and incredible bond, and the kinds of discoveries that they’ve been able to make because they’ve been working together, bringing different kinds of methodologies and cultural situations that have led them to ask new questions.”

Teaming up with award-winning documentary filmmaker Marc Shaffer, the storytellers have traveled far and wide within Colombia — as well as Mexico, the United States and Europe — to follow the scientists' efforts to advance the field of Alzheimer's research.

"But the whole point is to concentrate on Latin America, and on the idea that these communities are participants in science and are giving their lives and histories to participate in this long-running research process," Venegas added. Hopes were high that a recently concluded 10-year clinical trial for the drug crenezumab would result in a therapy that would abate or delay the onset of the disease. But the results were disappointing and the researchers, she said, were crushed.

Still, nature always has the final say, and in an act of serendipity has yielded a rare gift: an individual with the *PSEN1* mutation who managed to live well into her 70s without developing the dementia that begins to take down relatives half her age. Thanks to her family's donation of her brain, Kosik and colleagues from Harvard and the University of Hamburg are among the scientists across the globe unraveling this mystery, to which the filmmakers are just as irresistibly drawn.

"Although part of my motivation for embarking on this project stemmed from seeing several members of my significant other's family succumb to the disease, I have been fascinated with Alzheimer's disease since I began my career as a science journalist," Marisa Venegas said. While she and Cristina don't share any concerns about having the *PSEN1* mutation themselves, she added, "seeing so many newly identified families with the mutation in the area so close to where I was born certainly makes me realize how fortunate we are to have been spared its grip."

Anyone who becomes involved in Alzheimer's research quickly learns that it is an exacting, painstaking process to unravel this sticky mystery. But in this story of faith, fortitude, family and fellowship, there's still so much joy to glean from the relatively short but fierce lives of the *paisas* and the other families with the genetic form of the disease, lessons we all can draw from.

"Their attitude toward all of this is incredible," Kosik said. "They just have a wonderful way of mixing tragedy with love for life." This potent mix no doubt buoys patient, researcher and filmmaker alike in the face of overwhelming odds.

“Obviously, we’re not going to get to a point in the story where they solve the mystery,” Cristina Venegas said. Indeed, piecing together the Alzheimer’s puzzle is akin to building a cathedral, brick by molecular brick, in the hope that future generations of the Colombian families — and by extension all those around the world afflicted by the disease — will benefit.

In the meantime, it’s important to squeeze as much life out of every moment as possible, whether it’s the researchers traveling to remote towns on the trail of stories of forgetfulness, or the rural country folk on the front lines of the disease, or filmmakers hoping to complete their film — finances allowing — in the next couple years. By day, Venegas said, the patients are grappling with the worst news of their lives with the researchers. By night, the boundaries soften between physician and patient, researcher and

subject, as they drop their heavy burdens for a few precious hours.

“It’s just incredible to see Ken (Kosik) talking in Spanish and dancing,” said Venegas, dubbing him an “honorary Colombian” for the deep connections he has developed with the families in Antioquia. “He’s in his element.”

To learn more about the film-in-progress, visit Mapping Alzheimer’s.

Epilogue

Dr. Francisco Lopera died on September 10, 2024 at his home in Medellín. He was 73 years old. His death has deeply affected his family, friends, colleagues and the community for which he worked tirelessly for decades to treat and find an Alzheimer's cure.

“Lopera’s approach to clinical medicine was built on his philosophy: ‘They don’t come to us; we go to them,’” Kosik said in an obituary he wrote in the journal Nature . “It produced good science and goodwill, opening the way for new clinical trials and the discovery of rare protective variants.”

Lopera’s dream of finding a cure now falls to his proteges and colleagues around the world who have pledged to carry on the work begun by their legendary mentor.

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