BIOGRAPHICAL MEMOIRS

Wylie W. Vale Jr.

July 3, 1941–January 3, 2012
Elected to the NAS, 1992

A Biographical Memoir by Roger Cone and April Kriebel

In 1992, Wylie Vale Jr. co-founded the company Neurocrine Biosciences with the vision that corticotropin-releasing factor (CRF) could be targeted for the treatment of disease. While the company produced many other successful drug candidates in the intervening decades, it wasn't until 2024 that Neurocrine launched its first CRF antagonist, Crenessity.[1] Although he did not live to see his vision of the first CRF antagonist come to fruition, the thirty-four-year journey would not have deterred him.[2]

Known for his grit, wit, and passion, Wylie had a deep understanding of the sacrifice and determination that science often requires.[3] Mary Stenzel-Poore, who was a postdoctoral scholar in Wylie's lab and is now a professor emeritus at Oregon Health and Science University, recalled the encouragement Wylie gave her when she struggled to obtain her first large, independent grant: "Persistence is the single most important piece in all of this. It is the unsung hero of science."[4]

Wylie leveraged his own iron-clad will to reshape the landscape of neuroendocrinology. During his illustrious career, Wylie discovered CRF, CRF receptors one and two, and three other members of the CRF neuropeptide family. He seamlessly navigated the founding of two companies, Neurocrine and Acceleron Pharma, and championed the advancement of his academic institute, the Salk Institute for Biological Studies, with unapologetic ferocity. Yet, as the mentees and collaborators who worked with Wylie reflect on his career, they recall his humor, his zest for life, and his compassion, underscoring a legacy of both scientific distinction and interpersonal excellence.

Figure 1 Wylie W. Vale Jr. *Photo courtesy of the Salk Institute.*

Early Life and Education

Wylie Vale Jr. was born on July 3, 1941, in Houston, Texas, to Wylie Vale Sr. and Alliene Crittenden Guinn. Wylie Sr. was one of Texas's leading architects, and Alliene, contrary to period norms, had an established career as an interior designer. The couple welcomed their second son, Shannon, in 1955.

Wylie Jr. was more interested in living structures than in the immobile constructions of the family business and pursued a bachelor's degree in biology at Rice University, his father's and mother's alma mater. He graduated in 1964 and immediately pursued a Ph.D. in physiology and biochemistry

at Baylor College of Medicine. There, under the mentorship of Roger Guillemin, he focused on understanding the mechanism of action of thyrotropin-releasing hormone (TRH), which regulates energy homeostasis.[5,6] Wylie's dissertation, which he successfully defended in 1968, was his critical foray into neuropeptide research, a domain he dominated for more than four decades.

Early Career

After completing his Ph.D., Wylie remained in Guillemin's group as a postdoctoral scholar, intent on unraveling the mysteries of TRH. His dogged efforts were instrumental in establishing bioassays for the detection of TRH activity, and his insatiable curiosity led him to self-sacrificing measures.[7] Interested in how TRH affected the body, he injected himself with TRH under physician supervision, reporting back to his fellow lab members, "You wet your pants, your heart raced, you become very light sensitive."[8]

These extreme efforts to understand TRH were not fruitless; in 1970, the Guillemin lab reported the characterization of TRH, publishing the first structure of a hypothalamic peptide.[9] Later that year, Guillemin's group moved from Houston to the Salk Institute.[10] Enticed by the opportunity to continue searching for other hypothalamic neuropeptides, Wylie moved with them.

In 1972, the lab published the amino acid sequence of the gonadotropin-releasing factor hormone (GnRH) and identified somatostatin, a primary inhibitor of growth hormone.[11] Global recognition for the discoveries of TRH and GnRH came in 1977, when Guillemin was awarded the Nobel Prize in Physiology or Medicine. Later, Guillemin acknowledged Wylie's tremendous contributions by admitting that he and Wylie should have shared the podium.[12,13]

Wylie's postdoctoral period in Guillemin's lab also introduced him to Jean and Catherine Rivier. Arriving from Switzerland, they had immigrated to the United States so Catherine could pursue her graduate studies in Guillemin's lab. Jean already had a Ph.D. and also worked in the lab. Wylie, ever hospitable, tried to help the Riviers feel at home in the United States by teaching them the vernacular and taking them to rodeos.[14] His friendship with the Riviers, his deep and enduring hospitality, and his intimate knowledge of neuropeptides laid the foundation not only for his first discovery as an independent researcher but also for the values that came to define his character.

Scientific Giant

In 1978, Wylie left Guillemin's lab to establish his own group at the Salk, which he named the Peptide Biology Laboratory (PBL). Salk president Frederic de Hoffmann gave Wylie a temporary space near the parking lot in which to work. Rather than be deterred by this humble beginning, Wylie focused instead on building an environment of intellectual curiosity and collaboration. The Riviers left the Guillemin lab to work with Wylie, and he began taking on his own trainees. One of his first graduate students, Mark Smith, recalled, "My first impression of Wylie and his PBL was one of youthful exuberance. Surfboards and scuba equipment occupied the makeshift labs alongside the complex sequencers and huge chromatography columns. No one was over forty, and there was great camaraderie. I knew this was going to be a fun place to be a graduate student."[15]

This environment, characterized by optimism and energy, was precisely what was needed to fuel the grueling work of characterizing CRF. Previous work by Guillemin in 1955 had established that hypothalamic cells produced a substance that stimulated adrenocorticotropic hormone (ACTH) release in pituitary cells.[16,17] Yet, the isolation and characterization of the substance, which Guillemin termed CRF, eluded researchers. CRF was technically challenging to isolate because it was present in extremely minimal amounts and was extraordinarily "sticky," making it a difficult molecule to work with.[18] Ronald M. Evans, a hormone specialist and professor at the Salk, noted, "The technological challenge was enormous. This was like trying to climb the Mount Everest of Biology."[19]

Wylie was also limited to working with what was supposedly suboptimal material. Guillemin, who was simultaneously pursuing the characterization of CRF, had access to the aqueous extracts from sheep hypothalami, whereas Wylie had only the hydrophobic fraction.[20] Guillemin assumed that CRF, like many other peptides, would be hydrophilic and would consequently be largely present in the aqueous fraction. In reality, CRF was amphiphilic, possessing both hydrophilic and hydrophobic regions that produced the molecule's "sticky" nature and caused it to be present in both the aqueous extracts and the hydrophobic fractions.[21]

Wylie and his team used 490,000 hypothalamic fragments from sheep to search for CRF.[22] It was a slow and disheartening process. Catherine came to Wylie, frustrated, saying, "I tried, I tried, I tried." Wylie, ever the pragmatist, responded, "Effort only counts through the third grade, Catherine. After that, only results matter."[23] Finally, in 1981, Wylie, Catherine, Jean, and Joachim Spiess published the characterized structure of sheep CRF, hypothesizing that this regulatory peptide may be a key signal in regulating the body's endocrine, visceral, and behavioral response to stress.[24,25] In the frantic race to isolate CRF, Wylie, the mentee underdog, had finished first, solidifying his genius independent of his mentor.

To understand the behavioral effects of CRF and confirm its role in the stress response, Wylie asked George Koob, then

Figure 2 Wylie Vale Jr in the lab. *Photo courtesy of the Salk Institute.*

a staff scientist at the Salk, to inject rats with CRF and observe any behavioral changes. Koob later called Wylie, astounded, saying, "You've got to come see this—the rats are levitating!"[26] The high dose of CRF had caused pre-seizure activity in the rats, causing them to climb the walls of their enclosures, walk on their tippy-toes, and shadow box. Further experiments demonstrated that centrally injected CRF produced dose-dependent locomotor activation in rats, as well as an increase in behavior that indicated increased emotionality.[27]

The 1982 findings substantiated Wylie's claim that CRF played a significant role in stress response. Ronald explained, "The discovery of CRF led to the realization that there was a small family of related neuropeptides that help to control anxiety, depression, anorexia, diabetes, and drug abuse."[28] Wylie continued to substantiate this hypothesis by investigating CRF's role in clinical depression, finding that patients with major clinical depression had elevated concentrations of CRF in their cerebrospinal fluid.[29]

Wylie's pioneering work in peptides was just beginning. In 1983, Vale characterized the growth hormone-releasing factor (GRF) in rats.[30] Previous work in the field had purified a GH-releasing peptide in several different species, but no structure had been reported. Using 80,000 rat hypothalami, Wylie purified and characterized GRF, demonstrating that a synthesized version of GRF stimulated growth hormone secretion in cultured pituitary cells.[31]

Quickly thereafter, his group pivoted to focus on yet another elusive peptide: inhibin. For over half a century, it had been well-established that some substance in testicular fluids helped regulate follicle-stimulating hormone (FSH), a hormone critical to reproduction. In 1985, Wylie's group was one of several to report the isolation of inhibin, a gonadal peptide that suppresses the secretion of FSH by the pituitary.[32] Yet, Wylie's lab had noticed some abnormalities during the inhibin purification experiments when some fractions of the porcine follicular fluid induced the secretion of FSH.[33] Further investigations led Wylie's team to co-discover activin, a stimulator of FSH secretion.[34] Wylie, now intrigued by activin, turned his attention to discovering its receptors.

By 1991, cellular activin-binding sites had already been identified, but the low abundance of the activin receptors made them challenging to characterize. Wylie and his team captured the elusive activin receptor, enabling the characterization of the first receptor of the TGF superfamily.[35,36] Emboldened by his success, Wylie turned his attention back to CRF.

It had been more than a decade since Wylie's seminal publication describing the isolation and characterization of CRF, yet little was known about its receptors. Wylie and his lab characterized two CRF receptors.[37–39] Then, looking at fish and amphibian species, Wylie reasoned that additional peptides that bound these receptors might exist.[40] Over the next six years, Wylie published the discovery of mammalian urocortin I, II, and III, greatly advancing the field's understanding of the CRF signaling system.[41]

Wylie's scientific genius reshaped the landscape of neuroendocrinology. He made massive strides in discovering and characterizing key peptides and receptors, and he was constantly considering the implications of his findings for the bedside. He was a key pioneer at the forefront of a new frontier, a position requiring remarkable bravery and foresight. As Mary reflected, "Wylie himself was absolutely fearless. Almost every scientist would like to be fearless, but in Wiley's lab, not only was it allowed, not only was it encouraged, it was expected."[42] This dauntless attitude shaped not only Wylie's science but his business and leadership ventures as well.

A Businessman and a Leader

Wylie boldly navigated unprecedented spaces. When he arrived at the Salk in 1970, the institute didn't allow its faculty to have interactions with industry. Around 1990, the Salk revised its position, and Ron Evans became the Salk's first faculty member to entertain industry relationships. Wylie, never far from the front lines of innovation, followed suit in 1992 by entertaining a visit from then-venture capitalist Kevin Gorman, a representative of Avalon Ventures who wanted to start a neuroimmunoendocrinology company. Aware that a world-renowned neuroendocrinologist was "right up the street," Kevin arranged a meeting.

Putting on a heavy southern drawl, Wylie spent his first interactions with Kevin asking basic, even naive, questions: "What does this process look like? How would my lab and this company do things?" Over thirty years later, Kevin still chuckled, recalling, "Boy, did he pull the wool over my eyes! He was an incredibly sharp businessman. At a meeting with

other venture capitalists, he raised his desire for a non-dilution clause. I asked him, "Non-dilution? Where the hell did that come from?" Now aware that Wylie had been playing more than a bit coy, Kevin and Wylie began having direct, transparent conversations. It was the beginning of an incredible business partnership, friendship, and company.[43]

Wylie and Kevin co-founded Neurocrine in 1992, and Wylie was tireless in his involvement. Officially, Wylie served on the board of directors and the scientific advisory board and was a contract consultant one day a week. In reality, he was in and out on an almost daily basis, working to define future directions and navigate necessary technology licenses.

Although he was relentless in pursuing Neurocrine's success, Wylie was careful to never advance Neurocrine at the expense of the Salk. Kevin recollected, "Wylie put his heart into Neurocrine and put his soul into the Salk. He walked a tightrope of looking out for the Salk but also advocating for Neurocrine. That was very, very tough, especially in a place that was institutionally grounded in not dealing with commercial entities. He did a magnificent job."

Wylie wasn't shy about demanding the best outcome for the advancement of science, either. Originally, Neurocrine held the licensing rights for the activins as well as CRF. As a fledgling company, Neurocrine had concentrated its efforts on CRF, failing to significantly advance the commercialization of the activin rights. Wylie approached the Neurocrine board and convinced them to return the rights to the Salk. He then formed another company in 2004, Acceleron Pharma, that focused solely on leveraging the activins to develop compounds for anemia, muscle and skeletal disorders, and cancer.[44]

Wylie's leadership at the Salk extended past navigating a new era of industry collaborations. He cared deeply about the Salk as an academic institution and training ground. Mary recalled the atmosphere of the Salk in 1989, when she began her postdoctoral fellowship in Wylie's lab: "The Salk was an extraordinarily competitive place. There were too many Nobel laureates occupying too little square footage, but Wylie had a personality that could minimize that effect and help early-stage or mid-career faculty feel that they had a secure place where they could do their best work."[45] Using an open-door policy and a large dose of integrity, Wylie focused on making the Salk and his own laboratory as nurturing as possible.

A Mentor, A Friend, and a Family Man

Despite the size of Wylie's lab, which frequently exceeded fifty people, he always had time for people, greeting them with compassion and his trademark sense of humor. Wylie was known for being direct but supportive. Mary noted, "He never hesitated to tell you that he thought you were on a long walk for a small drink and encouraged you to think much bigger and bolder."[46]

He was also known for his tremendous amount of emotional intelligence. He was frequently joking and teasing but managed to always be affectionate. He was excellent at adjusting his mentoring style to suit a trainee's needs, and he encouraged his mentees to be creative and independent. And although he was competitive, Wylie had a principled moral code and was selective in choosing his friends and colleagues.

When discerning whether someone should be recruited to a position, Wylie turned to his most trusted advisor—his wife, Mary Elizabeth "Betty" Branard. Having known each other in high school and throughout college, Betty and Wylie reconnected when Wylie was in graduate school. Betty had returned to work at Baylor after a year living in Paris, and the two began dating. They tied the knot on December 20, 1969, and Wylie later described his marriage to Betty as his first and best decision.[47] Wylie valued Betty's perspective immensely. Kevin recalled, "When he was recruiting senior faculty to the Salk, his lab, or to Neurocrine, he put those people in front of Betty, and she told him whether this is a good person or not, whether you should do business with them or not." And Wylie listened.[48]

Wylie's life outside the lab exemplified his joie de vivre outlook. He loved guitar music, hiking, wine, and fly fishing.[49,50] He was dedicated to his family—Betty and their two daughters, Elizabeth and Susannah—and he was continuously attentive to opportunities to include others in their family adventures.[51,52] Mary recalled, "It'd be a Sunday, and he would drag you out of the lab saying, 'We're going to the Anza Borrego desert. Come on.' Four or five of us postdocs or students would pile into cars with him and his family and go."

His inclusive air permeated the holidays as well. He always made sure to send a Christmas card to each of his collaborators, and for Thanksgiving, he invited the whole lab.[53] There were tables in almost every room of his house, and the seats were filled with a great diversity of international representation.[54] According to Kunihiro Tsuchida, once a postdoctoral researcher in the Vale lab, "Wylie always tried to make everyone in the lab feel happy."[55]

By the time of his unexpected passing on January 3, 2012, Wylie had authored more than 1,000 neuroendocrinology publications and had pioneered the Salk into an era of industry collaboration and had founded two biotechnology companies that still exist today. A man of studied priorities, he is remembered not only for his scientific genius but also for his impish grin and wit.

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