Pasko Rakic

Pasko Rakic might be best known in the popular press for arguing that the cortex cannot generate new neurons. But his peers say Rakic combines a scientist's intellect with an artist's grace.

Pasko Rakic is walking briskly across the Yale University campus in Connecticut on an unseasonably mild afternoon in early March. He is explaining how the university's original layout mimics Oxford and Cambridge, but what he really wants to show is a more recent addition to the grounds.

Entering the Beinecke Rare Book and Manuscript Library, a modern cube built in the early 1960s, Rakic has an animated, almost childlike, glee as he describes how the architect brilliantly combined classical materials with modern techniques. Instead of windows, the innovative structure uses reinforced concrete to support ultra-thin panels of marble, allowing an amber glow of sunlight to penetrate while protecting the books from ultraviolet rays. Rakic explains this sophisticated design, enthralled with the interplay of science and art, then turns to the stacks of beautiful rare books in the inner part of the building. "Both [science and art] want to find some meaning or order in the larger picture of chaos," he says.

Rakic, who chairs the neurobiology department at Yale, balances these elements in his own work, often illustrating papers and presentations with original pen-and-ink drawings he creates in a small studio adjacent to his office. Some of these pictures, which show how neurons migrate into position in the developing brain, have become standard textbook illustrations. Produced with classical techniques, the black-and-white figures have a timeless quality, like a microscopist's drawings from a previous century.

Other researchers see a similar timelessness in Rakic's science. "I consider Pasko to be one of the most brilliant neuroscientists not just of this generation but in the history of neuroscience," says Susan Hockfield (*Nat. Med.* **11**, 110; 2005), former provost of Yale and now president of the Massachusetts Institute of Technology. "What he's contributed to neuroscience is really on the order of Cajal or Golgi."

But Rakic himself is almost self-deprecating when discussing his accomplishments. After mentioning that a particular paper of his was widely cited, he quickly apologizes for sounding boastful, saying he is only trying to put the result in context. Though he does not shy away from scientific debates and competition, colleagues say Rakic's generosity is his most notable trait. "He is a delightful collaborator," says Richard Flavell, chair of immunobiology at Yale, who has collaborated with Rakic on several papers. With Rakic, "egos do not get involved at all," Flavell says.

The only challenge in collaborating with Rakic seems to be his perfectionism. "The first paper I did with him, we had 26 drafts. He is compulsive about communication," says Pat Levitt, a former postdoctoral fellow in Rakic's lab who now directs the John F. Kennedy Center at Vanderbilt University in Tennessee.

Rakic often collaborated with his wife, Patricia Goldman-Rakic, considered by many to be one of the most successful female scientists in the world, until her tragic death in 2003. Rakic was attending a meeting in Japan when his wife was struck by a car while crossing a New Haven street. He rushed home to find her in a coma, from which she never awoke.

"He and Pat together were an extraordinary team. They both had enormously productive labs and ... a single-minded pursuit of their research programs," says Hockfield.

Though much of Rakic's work is so fundamental that it is now taken for granted, he is best known in the popular press for his skepticism of the idea that the adult cerebral cortex can grow new neurons. Rakic says he finds that aspect of his reputation unfortunate. "This was a response to one paper several years ago," he says.

The idea of adult cortical neurogenesis has obvious appeal, and remains a focus of intense research in several labs. Manipulating that process, if it exists, could treat a wide range of neurodegenerative diseases. But Rakic remains unconvinced that primates can generate new cortical neurons. Even if they could, he argues, the surrounding neurons would have to form thousands of new connections for the new cells to have any clinical benefit.

Thinking about clinical applications is second nature to Rakic. Born in Yugoslavia, he studied medicine at the University of Belgrade, then embarked on a career as a neurosurgeon. He says surgeons usually repeat the same procedures during their careers, and he wanted more variety. But his training stayed with him. "One of the things I take away from my period of time with [Rakic] was his desire to always challenge me to think about what we were doing ... and how that might relate to disorders," says Levitt. "He's had that [slant] for a long time, but it was not in vogue back in the '70s or '80s."

Rakic's research career began in 1962, with a fellowship at Harvard University. At the time, developmental neuroscience was largely descriptive; scientists knew where the neurons were at various points in development, but not how they got there. Soon after entering the field, Rakic conceived a breathtaking strategy to change that.

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The experiment required a special grant, nearly 200 rhesus monkeys and so much radioactive thymidine that manufacturers had to retool their entire production system to provide it. Describing this historic work, Rakic walks to the hallway outside his office, which is lined on both sides with tall metal cabinets. Opening one at random, he reveals that it is packed from top to bottom, two layers deep, with boxes of histological slides. On each slide is a slice from the brain of a fetal monkey. Rakic injected each monkey with radioactive thymidine at a particular time after conception. Because only replicating cells took up the radioactive label, he could trace the lineages of the brain cells that arose at different times during development.

Though he was primarily interested in the visual system, Rakic realized that nobody would repeat such a costly and complex experiment. For the benefit of future studies, he and his technician sliced the entire brain of each monkey into 7,000 sections.

Combining this *tour de force* with innovative experiments in mice, Rakic worked out the fundamental processes of mammalian neural development. Among other things, he discovered and named the subventricular zone and demonstrated that neurons of the cerebral cortex originate there and then migrate to their final positions, rather than being generated in the cortex.

To date, the monkey slides have yielded more than two dozen papers, and Rakic continues to collaborate with neuroscientists who want to study the collection. Because he used a radiolabel that decays slowly, the slides should be useful for years—much like a well-preserved archive of rare books.

Alan Dove, New Haven