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OBITUARY

Thomas M. Jessell (1951-2019)

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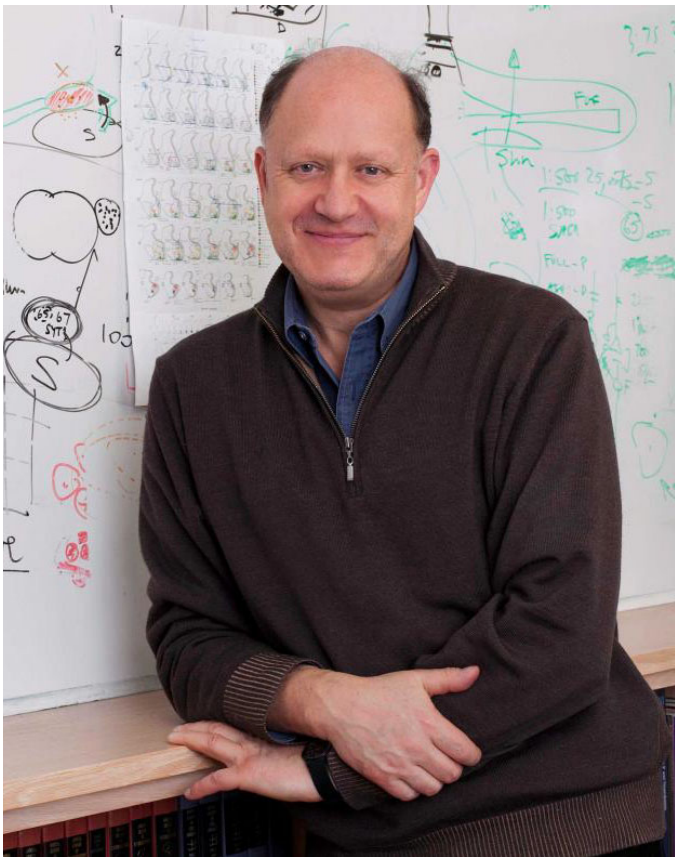
Thomas M. Jessell died on April 28, 2019. Tom revolutionized our understanding of the mechanisms through which neuronal cell type identities are programmed during development to dictate their function in the adult nervous system. Here, we (two former postdocs from his lab) remember some of his most important scientific contributions and how these changed the way we now understand and think about neuronal circuits controlling movement.



Thomas Jessell, Professor of Neuroscience, and Biochemistry and Molecular Biophysics at Columbia University, died on April 28, 2019. Tom redefined what it means to be a developmental neuroscientist. He combined a formidable intellect with an unparalleled breadth of knowledge and a seemingly limitless creativity. His vision and leadership established a field that has revealed the molecular and cellular basis for the assembly of motor and sensory circuits, identifying how spinal cord neurons acquire specific identities and form selective connections that control and coordinate movement. The significance of his contributions is far reaching, offering profound insight into the formation and function of the nervous system, setting the agenda for a generation of developmental biologists and neuroscientists, and leaving a scientific legacy that will continue to influence the field for many years to come. Tom has been a source of inspiration for colleagues, collaborators and competitors; with his death we have lost an irreplaceable scientist.

Tom grew up in the postwar London of the 1950s and ‘60s. His heart was torn between science and art, interests sparked by his grandfather who was an organic chemist and his mother who was a painting conservator. Both passions remained central to his being, so that while his professional life was dedicated to science, he lived it as an artist – creative and inspiring. Drawn in by the realization that to understand the action of drugs on the nervous system, it would be necessary to have knowledge of nervous system organization and function, he studied pharmacology at Chelsea College, part of the University of London. He completed his PhD in 1977 with Leslie Iversen at the MRC Neurochemical Pharmacology Unit, Cambridge, UK, then worked as a post-doctoral fellow in Gerald Fischbach’s laboratory at Harvard Medical School. In 1981, he was appointed Assistant Professor in the Department of Neurobiology at Harvard Medical School. Then in 1985, he moved to Columbia University, where he could fulfil his dream of applying the molecular biology revolution to the nervous system, and was appointed an Investigator of the Howard Hughes Medical Institute (HHMI) the same year. He remained faithful to Columbia University for the rest of his life, where in recent years, his vision as a Director was instrumental in creating the interdisciplinary Zuckerman Mind Brain Behavior Institute (now housed in the newly inaugurated Jerome L. Greene Science Center designed by Renzo Piano), which he pursued with all his energy from conception through construction to operation.

Tom had a unique scientific vision. He saw further and more clearly than others and he possessed the tenacity to pursue long-term goals even when it meant leaving behind what, for others, would be career-defining discoveries that could launch novel and productive fields of research. Already early in his career, his interests in neuropharmacology coalesced into a desire to understand the developmental basis of neuronal circuit assembly and function. To answer this question, it would be necessary to investigate the embryonic development of the nervous system. With his unfailingly scholarly approach, Tom dug deep into almost-forgotten literature from the school of German developmental biologists, to identify the spinal cord as a tractable system in which to make progress. At this time, in the early to mid 1980s, molecular techniques were being introduced and Tom saw their potential: his

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ambition was to transform neural development from a descriptive field into a mechanistic and molecular science. With Jane Dodd, who became his lifelong partner, and with whom he raised three daughters, he initially developed a series of antibodies that recognized distinct neuronal cell types, providing a first molecular view into neuronal formation and connectivity in the spinal cord (Dodd et al., 1984). This strategy, identifying and exploiting cell type-specific molecular and genetic markers, would become the cornerstone of the research program that consumed the next 35 years of his life.

Two major lines of enquiry emerged from these early studies. First, Tom and colleagues focused on mechanisms establishing neuronal projection patterns, showing that the axons of a set of dorsal spinal cord commissural sensory relay neurons are guided ventrally by a chemoattractant factor secreted by floor plate cells residing at the midline (Tessier-Lavigne et al., 1988). This work was a major impetus to the nascent axon guidance field – it was the first study to identify 'guidepost' cells in vertebrates and formed the basis for the subsequent identification of the Netrin family. At the same time, Tom's lab was exploring how the individual fates and positions of neurons in the spinal cord arose. This revealed that bone morphogenetic protein (BMP) signals secreted from the roof plate specify the identity and position of dorsal neurons (Basler et al., 1993; Liem et al., 1995). From the other pole of the neural tube, a remarkable series of studies demonstrated a signal from the floor plate induces motor neurons and interneurons (Placzek et al., 1990; Yamada et al., 1993). The lab went on to identify this signal as the newly discovered molecule sonic hedgehog (Shh), and found that it functions in a graded manner to pattern the ventral neural tube (Roelink et al., 1994). This connected the embryonic spinal cord to key issues – pattern formation and morphogen activity – that were occupying developmental biologists at the time. Indeed, the spinal cord became an important paradigm for these questions and has provided insight into mechanisms operating throughout embryogenesis.

The strategy of identifying and using cell type-specific markers also resulted in the identification of combinatorial codes of transcription factors for distinct progenitor and neuronal subtypes (Ericson et al., 1997; Tsuchida et al., 1994) and sparked efforts to decipher the genetic pathways that link signaling molecules with these transcriptional mechanisms (Briscoe et al., 2000). This led to the striking discovery that the expression of specific transcription factors in neural progenitors is sufficient to induce selected neuronal fates, independently of prior developmental history (Tanabe et al., 1998). The ability to reprogram the fate of cells prompted Tom and colleagues to develop methods to produce functional motor neurons from embryonic stem cells *in vitro* (Wichterle et al., 2002). This pivotal milestone offered proof-of-principle that directed differentiation towards specific cell types, guided by developmental biology knowledge, is a cogent strategy for the use of stem cells in the study and treatment of diseases and acted as spur to the burgeoning stem cell field with analogous approaches rapidly being adopted with great success for different cell types in a host of tissues.

Many of the ideas and concepts developed during this period are now taken for granted. In hindsight, they may look simple and obvious, but to reach these conclusions required penetrating insight and decisive experimentation coupled with an exceptional scholarly knowledge ranging across biology. Each of the breakthroughs involved creative inspiration, a seemingly intuitive sense for which ideas to pursue, and the development and application of new techniques. Tom always stressed that the ultimate reason for a nervous system is to allow movement, and if one would only dig deep enough, understanding the molecular logic of cell types would go a long way to explaining the neuronal circuits at the core of movement control. Tom fulfilled this promise in his own science by using his early groundbreaking insights into how diffusible signals lead to the selection of combinatorial transcription factor expression in spinal cells as a stepping stone for many of his following discoveries.

This later body of work helped to unravel the logic of how postmitotic neuronal cell types emerge, how these newly born neurons assemble into precisely connected neuronal circuits, and how assembled circuits control behavior. To tackle these daunting questions, Tom and colleagues never shied away from grand approaches, usually paired with the selection of clever entry points to simplify a difficult question. Nowhere else in the nervous system has it been possible to gain insight into how a single functional neuronal class – in this case motor neurons innervating skeletal muscle fibers – fractionates into more than 50 subtypes based on connectivity to different targets and an underlying molecular logic, with LIM-HD, bHLH, Hox and ETS transcription factors playing major roles in shaping motor neuron subtype identity and connectivity during development (Dasen et al., 2005; Kania and Jessell, 2003; Lin et al., 1998; Novitch et al., 2001).

Key synaptic inputs controlling the recruitment of motor neurons are derived from sensory neurons, which provide feedback about the periphery to the CNS, and from spinal interneurons, which are essential for the generation of basic movement patterns including left-right and extensor-flexor alternation. By tackling sensory-motor connectivity, Tom and colleagues chose a problem that had been defined physiologically many years before. This work determined the molecular underpinnings of this process by showing that ETS transcription factors and cell surface molecules establish the appropriate functional connections between sensory and motor neurons (Arber et al., 2000; Pecho-Vrieseling et al., 2009). The diversity of spinal interneurons has long been known at the physiological level, but Tom's recent efforts demonstrated that a bewildering molecular diversity of interneuron subtypes emerge during development (Alaynick et al., 2011; Bikoff et al., 2016). To establish causal links between this molecular logic and function, he had begun to explore how the genetic and developmental identity of spinal neurons influences behavior, both for locally projecting and long-range ascending projection neurons in the spinal cord (Azim et al., 2014; Fink et al., 2014). This is a research direction from which many important contributions would have followed, no doubt, had time allowed.

Tom was an exceptional scientist. He was a demanding but truly inspiring mentor and leader. He had the ability to attract and motivate an outstanding cadre of students and postdoctoral fellows who were encouraged and guided to meet his high expectations. The result was an intellectually stimulating, high-achieving environment embedded within the cultural and social excitement of Manhattan; there was always the buzz of new results, the challenge of demanding group meetings, the pressure of writing and refining papers, but anything and everything seemed possible. Tom was extremely broadly read and had the tremendous gift of bringing together apparently disparate facts to form novel explanations. There was no need to go to the library to check papers – Tom recalled all of them (even those written in German) and cited the references by heart. Discussing science with him often felt like solving a puzzle, but one that he made look simple, finding matching partners for pieces in split seconds. Tom was also a perfectionist, which translated into an enormous rigor in

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challenging experimental evidence before believing it; and in weighing and questioning every word written in a paper. We both recall having been sure we were ready to submit a paper after many weeks of writing and rounds of revision only for Tom to say we should 'have another serious go at it'. But the end results were papers to be proud of; for both of us, this rigorous school of challenging facts and not taking the easy road continues to inspire us today.

Tom's array of tools and resources was extremely valuable to the scientific community; he generously distributed reagents to many, to advance their own science. Tom's 'out of the box' thinking was also a treasure for journals who sought his advice on papers and review topics, including in his roles as Reviews Editor at Neuron and as an Editor with Development (1991-2003). Tom was also a tremendous asset when organizing scientific meetings. As co-organizer of the Ascona meetings on neuronal circuits for many years, he challenged the other organizers to invite only the very best, mind-blowing speakers, with an exacting after-the-meeting run down on speaker quality to make the following meeting even better.

Tom received numerous awards. These include the J. Allyn Taylor International Prize for Medicine (with Corey S. Goodman) (1996), the Ameritec Foundation Prize (1998), the Bristol Myers Squibb Distinguished Achievement in Neuroscience Award (2000), the March of Dimes Prize in Developmental Biology (with Corey S. Goodman) (2001), the Kavli Prize in neuroscience (with Sten Grillner and Pasko Rakic) (2008), the Gairdner International Award (2012), the Gruber Foundation Prize (2014), the Vilcek Prize in Biomedical Science (2014) and the Ralph W Gerard Prize (with Ben Barres) (2016). Tom was a Fellow of the Royal Society of London, a Foreign Associate of the US National Academy of Sciences, a member of the Institute of Medicine of the National Academies and a Fellow of the American Academy of Arts and Sciences.

Tom's extraordinary scientific career ended in March 2018, when Columbia and HHMI removed him from all administrative roles as the result of a personal relationship with a student that violated University policies governing the behavior of faculty members in an academic environment. Tragically, by this time Tom was already suffering from increasingly severe neurological symptoms caused by an aggressive neurodegenerative disease that was diagnosed as progressive supranuclear palsy. Although the last years of his life were marred, we prefer to remember him in happier times when he would be the smartest person in a room of smart people, pointing out crucial information in an obscure paper or offering a perceptive opinion about a decisive experiment, all with charm and the driest of wits. His legacy and influence will live on in his numerous former lab members and many generations of neuroscientists who have been educated by his textbook *Principles of Neural Science*, which he co-authored for many years. Tom will be deeply missed.

Acknowledgements

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