Mother of fields

Hazel Sive

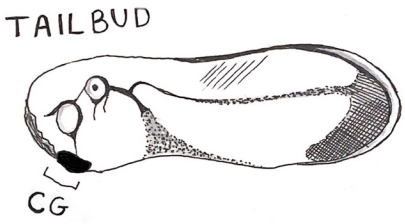
In June 2020 renowned developmental biologist Hazel Sive concluded 28 years as a Whitehead Institute Member and professor of biology at Massachusetts Institute of Technology (MIT). While Sive was a much-lauded teacher and academic leader at MIT — experiences she is now drawing on for her new role as Dean of Northeastern University's College of Science — she is globally recognized for her achievements as a fundamental science researcher. In this piece, she reflects on significant accomplishments in her long, fruitful scientific career at Whitehead Institute.

I have always been drawn to life, to feel part of it in the most spiritual way. And particularly I have spent my career asking, how are vertebrate animals built from cells, so perfectly and intricately? At Whitehead Institute, over the past 28 years, my research group has uncovered profound answers to this question. I am deeply grateful for the opportunity to have been a Whitehead Institute Member, and I am deeply proud of the contributions our research has made. The work of outstanding Sive Lab members has been important and groundbreaking. We have been pioneers in so many areas, I am indeed, the Mother of Fields.

The journey begins

My developmental biology pathway began during an undergraduate project at Wits University in Johannesburg, South Africa. I kept rows of plastic dishes filled with thousands of frog embryos that had all started growing at the same time. As I walked along my rows, I noticed that the embryos were doing exactly the same thing at the same time. When I first noticed, all were composed of eight cells, large enough to see with the naked eye. Hours later they had all become kidney-bean-shaped with a black patch on one end, and at a later point they had all developed eyes and started swimming. It was extraordinary! How, I wondered, did the embryos know what to do and when to do it? There must be a powerful set of instructions connected to some precise timer telling them. Maybe, I thought, I could isolate those instructions and understand this magic. That thought started me on my way.

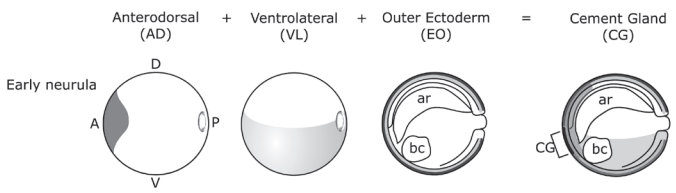
Frogs, and later zebrafish, were what I chose for our studies, because their embryos grow rapidly, and externally in a Petri dish in the lab, and because the embryos are large and easy to observe even at the earliest stages of development. Further, frogs or fish are not so different from people — we all have two eyes, a nose and a mouth, and the same organs. So I figured these animals could teach us something about how people are built.



Frog embryo: The frog Xenopus cement gland (CG) forms at the front of the embryo, and is visible as a dark pigmented patch about a day after development begins (at tailbud stage). We traced its origin back to the early neurula stage, 12 hours earlier. (Drawing by Simone Lassar, adapted from Wardle and Sive, 2003)

The journey unfolds

I started simple, asking 'HOW does the little patch of black pigment get to the front of the frog embryo?' The patch is called the 'cement gland' and secretes a glue that stops the frog embryo from floating away. No-one had asked this question before, and we had to develop new techniques to isolate the genes involved. Over many ground-breaking publications, we started a field, and found that three separate sets of instructions add together to position the cement gland. Some of the genes we isolated have themselves started entire new fields.



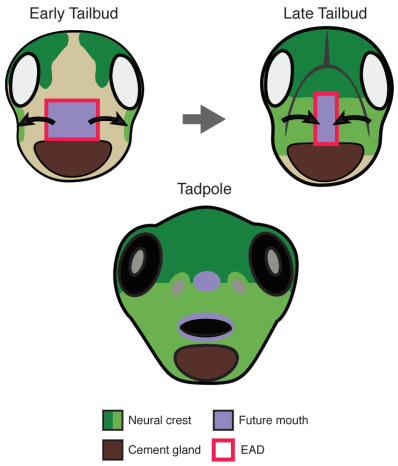
Cement gland patterning: Our work uncovered signals from three regions, Anterodorsal (AD), Ventrolateral (VL) and Outer Ectoderm (EO), that add together to position the future cement gland, many hours before the pigmented region appears. (Wardle and Sive, 2004)

Humans don't have a cement gland, so at the same time we asked: WHEN does the embryo decide to make the brain and spinal cord, organs clearly relevant to people? We identified more than 50 previously unknown genes involved in nervous system formation, including chemical signals and other needed regulators. Amazingly, even when the embryo is just a ball of cells, we showed that it has already decided to make a nervous system and where to place the brain and spinal cord. No one had any idea that these decisions were made so early during development, and our work helped explain how some human birth disorders arise.

Neural patterning: Activities of genes we identified, opl, otx, and fkh5 (black shading) show that regions of the future brain are present at the early gastrula stage, when the embryo is simply a hollow ball of cells. A: anterior or the future head, P: posterior or the future tail. (Drawing by Simone Lassar, adapted from Gamse and Sive, 2000)

Traveling across new frontiers

Another surprising new field came from the cement gland. I realized that a region including the cement gland and lying at the front of the embryo had a special organization of cells, that is present across evolution, including in human embryos. We named this region the Extreme Anterior Domain (EAD). The EAD is important because it becomes the mouth, and we developed a novel facial transplant technique that uncovered the complex, carefully orchestrated mechanisms involved in mouth formation.

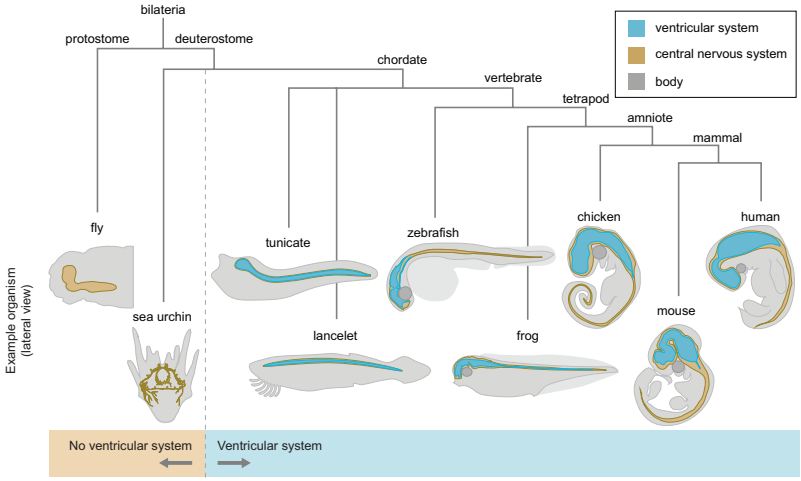


EAD signaling: We defined the Extreme Anterior Domain, and its key role in building the face. During face formation, the EAD (purple) sends signals (arrows) to attract neural crest cells that form cartilage (green), and later, the EAD responds to signals (arrows) leading to mouth formation. (Chen, Jacox et al., 2017)

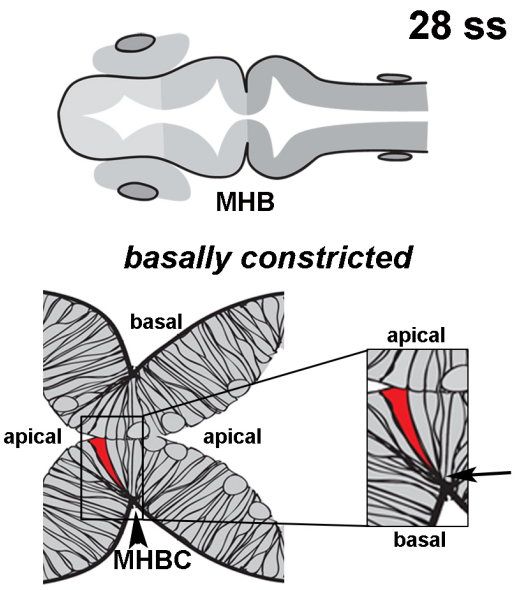
But we discovered something else unexpected — that the EAD produces chemical signals, sending these out to instruct the surrounding cartilages and bones of the face to develop properly. And these signals also instruct the brain to become a certain size, by controlling the number of cells it contains. Wow! From that little patch of black pigment has come an understanding of how the entire head forms, and one way this process may go awry in the devastating birth disorder of microcephaly.

From the very beginnings of the nervous system, our studies moved on to explore later steps. An important direction came from asking 'WHY are the brain and spinal cord tubes?' If the human neural tube (future brain and spinal cord) forms incorrectly, why do catastrophic disorders such as spina bifida and anencephaly arise? We thought it may have to do with the unique cerebrospinal fluid, or CSF that fills the neural tube. In

pioneering studies using the zebrafish, we made the crucial discovery that CSF promotes survival of developing nerve cells and proper brain development. We isolated a CSF factor, RBP4, that increases cell survival. We later uncovered the complex ways that CSF moves through the developing neural tube, carrying a myriad proteins with it. Our contributions included devising several new techniques, and continue to give insight into underlying causes of human neural tube disorders.



CSF: Cerebrospinal fluid within a brain ventricular system is a hallmark of every animal with a complex nervous system. Our work pioneered use of zebrafish to uncover the role of this system in brain development and health. (Fame et al., 2020)



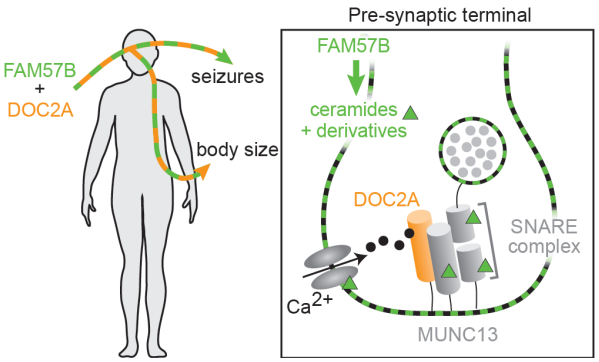
Basal constriction: In the developing zebrafish brain, we discovered a novel change in cell shape, 'basal constriction' (red cell). Basal constriction helps fold the brain for optimal function, and is now known to be widely present during organ formation. (Gutzman, Graeden et al., 2018)

Always thinking hard, we wondered, 'WHY does the brain have its characteristic rounded shape?' since the neural tube starts off long and thin. We thought that a compact brain is less prone to injury than a skinny tube, and set about to understand how the brain acquires its shape. Along the way we made two fundamental discoveries, a cell shape change called 'Basal Constriction' that has started another field, and a 'stretchiness' of cell sheets that we termed 'Epithelial Relaxation', another undescribed process.

Much of our research has been relevant to human disorders; however, some years ago, I decided to actively focus on mental health disorders. These disorders afflict about a quarter of the United States population, but there have been few new treatments for decades. Each disorder involves many genes, whose individual roles are generally not clear.

Our studies pioneered the zebrafish system as a productive tool to analyze genetic contributions, and to uncover possible therapeutic avenues for mental health disorders. We defined gene variants associated with schizophrenia, and gene combinations associated with the severe 16p11.2 deletion

(16pdel) syndrome, a major risk locus for autism and other symptoms. Recently, we showed that the fat (lipid) composition of cells from people affected with 16pdel syndrome is different from that of unaffected people. Likely as a consequence, the synaptic connections between nerve cells, brain activity and behavior are all anomalous in zebrafish models. These novel findings connect metabolism (cellular chemistry) with mental health, and suggest that by correcting lipids, affected people may be significantly helped.



16p11.2 deletion syndrome pathways in mental health: We showed that *FAM57B* and *DOC2A*, genes interrupted in this syndrome, are critical regulators of brain cell connectivity (at the pre-synaptic terminal). *FAM57B* regulates production of certain fats, essential for brain and body health. (McCammon et al., 2017)

What broad travels, since that day I realized that embryos must come with an instruction manual! The important work will continue in my own lab at Northeastern University, and by the scores of talented trainees who were part of my group at Whitehead Institute, and are building their own productive careers.

To make this piece succinct, there was much omitted, and I would like to warmly acknowledge the contributions of all Sive Lab members. Our publications are listed at:

https://www.ncbi.nlm.nih.gov/sites/myncbi/hazel.sive.1/bibliography/41155525/public/?sort=date&direction=descending

I am extremely grateful for the funding that has supported our research.

Finally, to the Whitehead Community (Directors, Faculty, Staff, Trainees, and Donors) who helped build the vibrant, effective Institute landscape in which we worked, my most sincere appreciation.