HUMAN HEALTH
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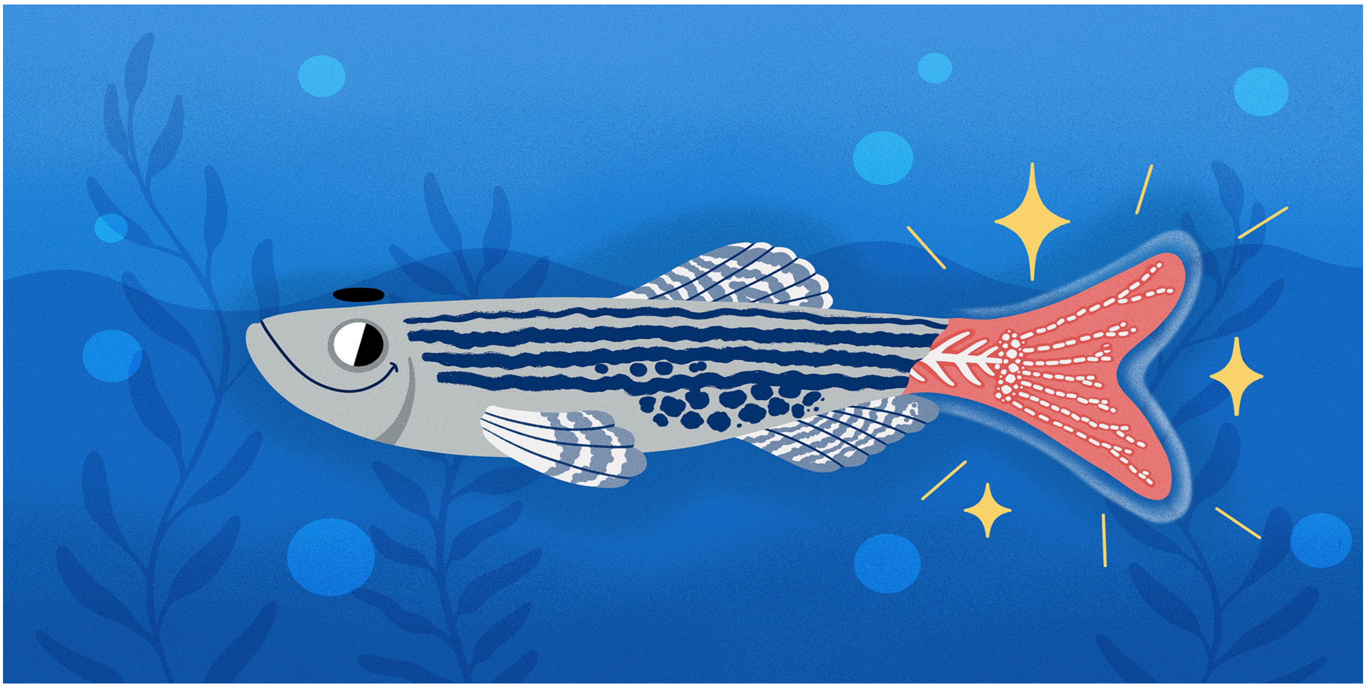

BONE BIOLOGY: FROM A TO ZEBRAFISH

Rachel DuMez[1,2*] *and Isaac Skromne*[2]

[1] *Curriculum in Genetics and Molecular Biology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States*
[2] *Department of Biology, University of Richmond, Richmond, VA, United States*

YOUNG REVIEWERS:

CELIN
AGE: 12

ISHA
AGE: 12

IVAN
AGE: 15

RISHA
AGE: 12

SIRAN
AGE: 15

Even though humans look different from other animals like fish, birds, or snakes, we all have a skeleton that gives our bodies shape, protects our internal organs from harm, and helps us move. Animals with a skeleton and a backbone are called vertebrates. Because all skeletons are built from bones, scientists can learn a lot about human bones by studying them in other vertebrates, including fish. Zebrafish are one vertebrate used by scientists to study how bones are made, age, and are repaired by the body. One cool fact about zebrafish is that they can regrow their tails, including the bones, if they get bitten off by another fish. Scientists can also use zebrafish to learn how new medicines can maintain bone health, or how to fix bones after an accident or disease. In this article, we will discuss how scientists can work with zebrafish to learn about bone biology and health.

SKELETONS ARE MADE OF BONES

The skeleton is the structure that gives shape to your body and allows you to stand and move (Figure 1A). The adult skeleton is made of about

206 interconnected bones, which come in various shapes and sizes (You can read more it in this Young Minds article). For example, some bones are long, like the humerus in your upper arm and the femur in your upper leg, while others are short, like the carpals of the wrists and the tarsals of the ankles. Despite differences in shape, size, and function, bones must be strong and healthy to work properly. A healthy lifestyle that includes nutritious food and regular exercise is the best way to keep your skeleton in good shape.

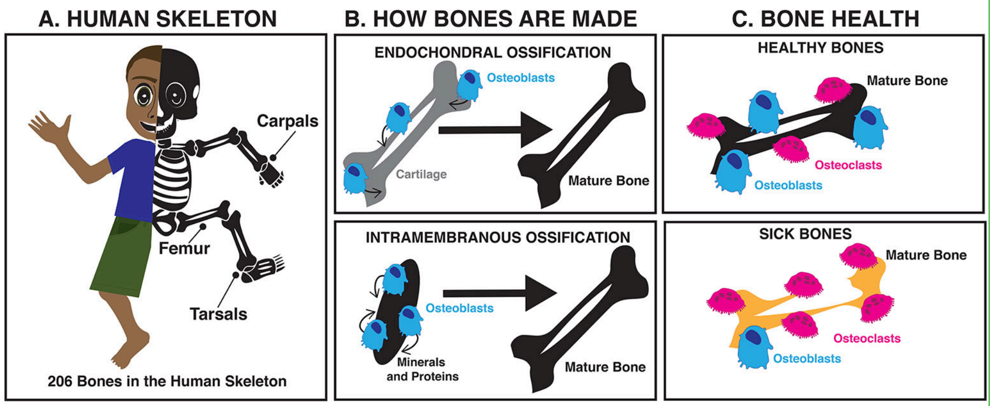

Figure 1

Figure 1

(A) The human skeleton is made of bones, which are built through a process called ossification. **(B)** Building bones from a cartilage mold is called endochondral ossification. Building bones without a cartilage mold is called intramembranous ossification. During ossification, cells called osteoblasts (blue) deposit minerals and proteins, and cells called osteoclasts (magenta) remodel the bone to shape it. **(C)** Osteoblasts and osteoclasts cooperate to maintain bone health. Age or disease can cause osteoclasts to remove bone tissue faster than osteoblast replace it, causing bones to become brittle and sick (Created with BioRender and Adobe Illustrator).

HOW BONES ARE MADE

Through a process called **ossification**, bones start to form before birth and continue to develop throughout childhood, teenage years, and early adult life. Before birth, bones begin forming in one of two ways (Figure 1B). One way is for cells called **osteoblasts** to invade a pre-made **cartilage** mold of the bone and deposit proteins and minerals (specifically calcium) in the jello-like scaffold. Cartilage is a tissue that can give shape to body parts such as your nose or outer ear, but it does not provide a lot of strength. By depositing additional proteins and calcium, osteoblasts transform the soft cartilage into strong bone [1, 2]. Scientists call this type of bone formation **endochondral ossification**. A second way to make bones that does not require a cartilage mold is called **intramembranous ossification**. In intramembranous ossification, the osteoblasts invade a tissue and start making bone by depositing proteins and calcium directly around them. Regardless of how they are made, bones must be further shaped and sculpted (remodeled) to perform their functions in the body [1, 2].

OSSIFICATION

The natural process of hardening a tissue into bone.

OSTEOBLASTS

Cells that deposit proteins and minerals to build bones.

CARTILAGE

A firm but flexible tissue that connects parts of the body together, builds structures like the outer ear, and provides a mold to build bones.

The job of remodeling the bones is the responsibility of cells called **osteoclasts**. When necessary, osteoclasts can remove excess proteins and calcium from bones, for example when bones get damaged [1, 2]. Afterwards, osteoblasts can return, fill in the gaps, and reshape or strengthen the bone [1, 2]. This teamwork between osteoblasts and osteoclasts continues throughout a person's life. During the teenage years, osteoblasts work faster than osteoclasts to increase the length of bones. This is how you and your classmates get taller as you grow up! Later, in adult life, osteoblasts and osteoclasts work equally hard to repair and restore areas of bones that have been weakened by everyday wear and tear (Figure 1C). The cooperation of osteoblasts and osteoclasts keeps a person's bones strong and healthy through their lifetime [1, 2].

BONE BIOLOGY: FROM FISH TO HUMANS

All animals that have a backbone, made up of small vertebrae bones stacked on top of each other, are called **vertebrates**. Vertebrates come in all shapes and sizes—from elephants and whales to mice and fish. Their internal skeletons give vertebrates their unique shapes. Even though vertebrates may look very different from each other on the outside, their bones serve similar functions, such as keeping fragile organs, like the brain, spinal cord, and heart, safe. Zebrafish, a small fish native to India that can now be found in pet stores all over the world, have 74 bones in their skulls. That is many more than the 22 bones in the human skull (Figure 2) [3]. Despite this difference in number, skull bones in both zebrafish and humans fit together to make a case that holds and protects the brain. The skull bones of both zebrafish and humans are built without a cartilage mold, through intramembranous ossification [1–3].

ENDOCHONDRAL OSSIFICATION

Type of bone building method in which a jello-like cartilage mold is transformed into strong bone.

INTRAMEMBRANOUS OSSIFICATION

Type of bone building methods in which cells start depositing proteins and calcium around them to build up bone.

OSTEOCLASTS

Cells that remove proteins and minerals to break down bones.

VERTEBRATES

Animals that have a backbone including mammals, birds, reptiles, amphibians, and fish.

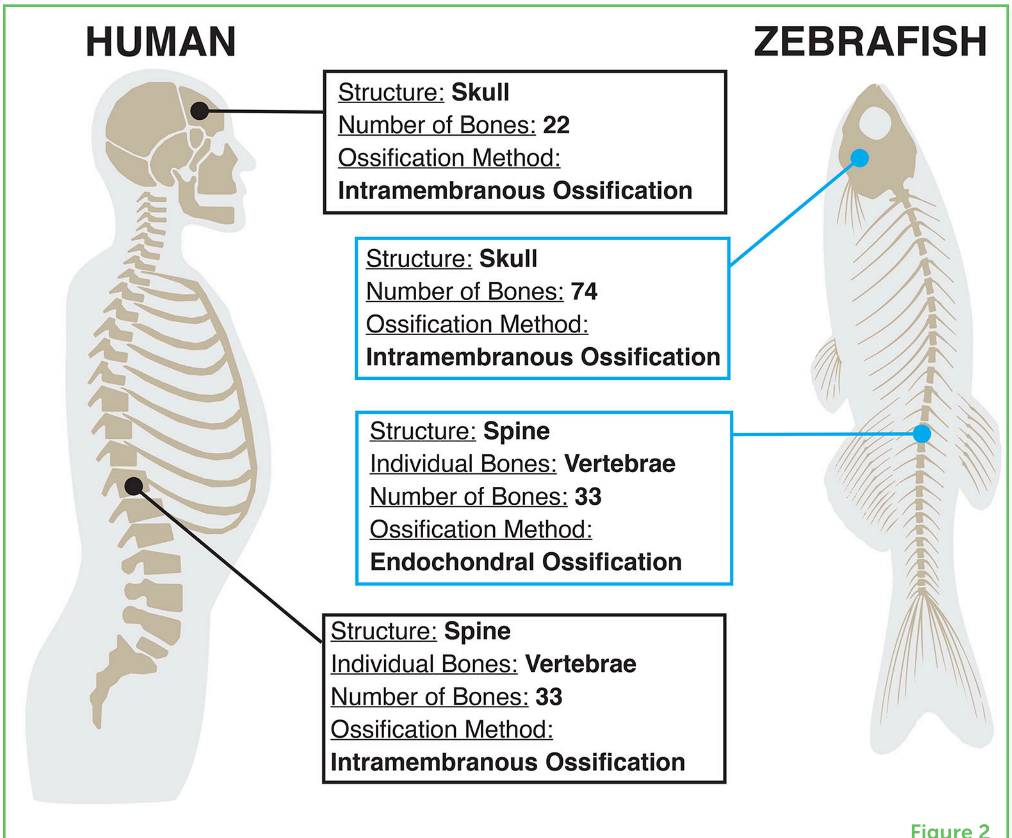

Figure 2

Humans and zebrafish look very different, but their skeletons share many structural and functional similarities. One example is the skull, which protects the brain. The skull is built from a jigsaw puzzle of bones shaped using the same ossification method in both zebrafish and humans, yet the skulls look distinct because the shape and number of pieces differ. Another example is the spinal column, which is made of vertebrae stacked on top of each other. Humans and zebrafish have the same number of vertebrae, but they use different ossification methods to build them (Created with BioRender and Adobe Illustrator).

Interestingly, both zebrafish and humans have a similar number of vertebrae in their spinal columns (about 33), which help maintain body posture and protect the spinal cord (Figure 2) [3]. Despite the similar number, the way that these bones are made in zebrafish and humans is very different: while human vertebrae form from a cartilage mold, zebrafish vertebrae do not [1–3]. Regardless of their form, number, or how they were made, ossified bones are strong to protect internal organs and to give animals their shapes.

BONES IN SICKNESS AND IN HEALTH

Accidents, disease, and age can damage bones. Most of the time, if bones break during an accident, doctors can repair the damage. They do this by putting the bones back in place with the help of an X-ray machine, then stabilizing the area with a cast for 4–8 weeks. Once the bones are set back into place, osteoblasts can come in and repair the damaged area, by depositing proteins and calcium to fuse the broken pieces back together. This results in a healthy, strong bone, with the same shape and function as before the accident.

Sometimes, however, doctors have a difficult time repairing bones because the bones are sick. Sick bones are fragile because they have lost proteins and calcium that normally make them strong. This can happen when osteoclasts remove proteins and calcium faster than osteoblasts can replace them. Doctors do not fully understand why this happens, but they know that this imbalance tends to be associated with age. For example, people over 50 years old are more likely to have weak bones. In fact, two out of 10 adults are diagnosed with weakened bones [4]. While there are some medications that can stop bones from getting weaker, doctors currently have very few medications that help rebuild bones and restore their function. Doctors and scientists are working together to develop new medicines that can be used after accidents or disease, to encourage osteoblasts to restore bones to their original state.

USING ANIMALS TO STUDY BONE BIOLOGY

Before new medicines are given to people, scientists must test them to make sure they are safe. For example, doctors and scientists must know how much of a medication to give to a patient, how long a patient should take a medication for, and whether it should be given as a pill or as a shot. Scientists can answer all these questions by testing new medicines in animals. Non-human animals that can be used to test medicines because they mimic key aspects of human biological processes and diseases are called **animal models**. Before starting an experiment, scientists carefully select the best animal model for the question they are asking.

ANIMAL MODELS

Living, non-human animals that allow scientists to do experiments to improve human health without putting people in danger.

Over the last 20 years, Zebrafish have become a popular animal model to test medications and to learn about bone biology and disease (Figure 3A). Zebrafish are useful for studying bones because the way their bones are made is very similar to the way human bones are made [1–3]. For example, both humans and zebrafish have bones that are built by osteoblasts and osteoclasts using endochondral and intramembranous ossification methods (Figure 3B). The proteins and minerals that osteoblasts use to build and that osteoclasts remove to dismantle bones are also similar. Interestingly, as zebrafish age, their bones can become brittle just like human bones. Humans can live over 100 years, but zebrafish only live about 3 years, making it much easier to study age-related bone breakdown. One additional fun fact that makes zebrafish a useful animal model is that, unlike humans, they can regrow bones. If a zebrafish gets into a fight and one fish bites the tail off the other, the injured fish can regrow its tail fin, including all its bones (Figure 3C) [1–3]. One zebrafish success story involves the discovery of a new class of drugs to treat a human disorder in which muscle is slowly turned into bone. This class of drugs is now being tested in humans [5]. For all these reasons, zebrafish have become a popular animal system to study the effect of medicines on bone formation, healing, and repair.

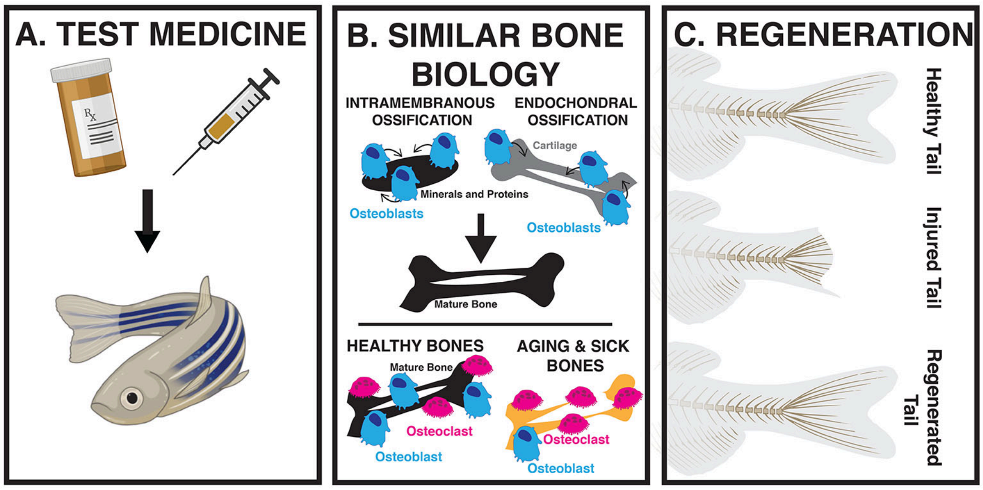

Figure 3

Zebrafish are a powerful animal model to study bone biology. **(A)** Scientists can use zebrafish to test medicines that could one day help repair sick bone tissue. **(B)** Scientists can use zebrafish to study general bone biology because the way humans and zebrafish build, grow, and repair their bones is similar. **(C)** Zebrafish have the remarkable ability to regenerate bones after injury, particularly in their tails. If scientists learn how zebrafish regenerate their bones, they could use this information to help treat people with bone diseases (Created with BioRender and Adobe Illustrator).

CONCLUSION

The skeletons of all vertebrates are made of bones. Bones are strong, they protect the animal's internal organs, and they give the animal its unique body shape. But even the strongest bones can break or become sick. Doctors and scientists are looking for ways to cure people with sick bones and to prevent people from getting sick bones in the first place. Because all animal skeletons are built using the same methods and materials and by the same cells, scientists can learn a lot about how bones are made, how bones get sick, and what medications might cure bone diseases from studying animals, including zebrafish.

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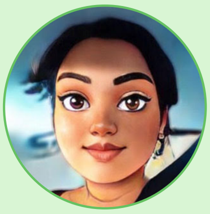
YOUNG REVIEWERS

CELIN, AGE: 12

My hobbies are dancing and making crafts. After starting my junior school life, biology holds so much appeals to me, it is a little complicated but interesting as well! Frontiers is such a good source for me to make further exploration in biology, it was so exciting that I can read a whole scientific article by myself for the first time!



ISHA, AGE: 12

Isha is a 12 year old girl going into 7th grade soon, and any form of reading peaks her interest. She plays multiple instruments, enjoys cooking, loves to read, and 1 day hopes to publish a book of her own.

IVAN, AGE: 15

I am a high school student pursuing a career in computer science. I discovered my interest in biology at the end of middle school, tried for the USA Biology Olympiad, and had since been learning about chemistry as well. I enjoy playing video games and sketching, and I am often involved in volunteering activities like canvassing.

RISHA, AGE: 12

Hi! My name is Risha and I am 12 years old. I play tennis and volleyball. I am a classical dancer and a part of a FTC robotics team. I have also been part of a FLL, and a VEX.IQ robotics team. I like to act and have been a part of multiple musicals. I play the violin and piano. My hobbies include reading and coding.

SIRAN, AGE: 15

From a young age my head has buzzed with questions about the natural world. I wonder how the life operates and the reasons hidden behind those phenomena. At the first time I got in touch with the word "biology," I knew that is exactly the subject right for me. I love dancing and cocking, love different languages and landscapes across different continents.

AUTHORS

RACHEL DUMEZ

I am a graduate student in the genetics and molecular biology Ph.D. training program at the University of North Carolina at Chapel Hill. I grew up in Front Royal, Virginia, and was recruited to swim at the University of Richmond. That is where I had the opportunity to find my passion for scientific research. I have been a part of several research groups including the Skromne Lab. I am involved in several science outreach programs, including Women in Science Promoting Inclusion in

Research Experiences. When I am not in the lab, I enjoy gardening and listening to audio books. *rdumez@live.unc.edu

ISAAC SKROMNE

I am an assistant professor of developmental biology at the University of Richmond, Virginia. I was born and raised in Mexico City. I obtained my undergraduate degree from the National Autonomous University of Mexico and my Ph.D. from Columbia University in New York. Since I was a little kid, I have been interested in biology, how the human body works, and how it changes over time. Now I study how animals develop and change using the zebrafish model system. I am also passionate about teaching and helping students realize their goals. Outside the lab, I enjoy gardening and cooking.