THE DISCOVER INTERVIEW

SEAN CARROLL

A molecular biologist traces the ancient machinery of evolution to a master tool kit of genes—and finds that you and a fruit fly have a lot in common.

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When Sean Carroll was a graduate student at Tufts School of Medicine in Boston, he found himself seduced by spectacular new studies of the humble fruit fly. That work, which eventually won a Nobel Prize for its principals, showed that modifying a single gene during a fly's embryonic development could transform the insect's body plan: Instead of becoming an antenna, a body extension could develop into a leg. Carroll continued to study these genes and, some years later, found that they were not restricted to fruit flies; they turned out to be part of a master tool kit that sculpts the body structures of all animals, ranging from humans to nematode worms.

The discovery of this small set of universal body-building genes gave Carroll and others a fresh way to explore the inner workings of evolution. By observing how the genes changed during the course of embryonic development, scientists could track the emergence of a novel physical trait, the first step toward the creation of a new species. For the first time, researchers had direct access to the machinery of evolution and could actually watch it in the act. A new science, known as evolutionary developmental biology, or evo devo, was born.

One of the great triumphs of modern evolutionary science, evo devo addresses many of the key questions that were unanswerable when Charles Darwin published *On the Origin of Species* in 1859, and Carroll has become a leader in this nascent field. Now a professor of molecular biology and genetics at the University of Wisconsin, he continues to decode the genes that control life's physical forms and to explore how mutations in those genes drive evolutionary change. These days, Carroll also devotes increasing energy to telling the public about his field's remarkable discoveries through a series of books—*Endless Forms Most Beautiful, The Making of the Fittest,* and the brand-new *Remarkable Creatures*. He spoke with DISCOVER senior editor Pamela Weintraub about what his work has taught him about Darwin, the nature of evolution, and how life really works.

It has been 150 years since Charles Darwin proposed his theory of evolution in *On the Origin of Species,* yet in some ways the concept of evolution seems more controversial than ever today. Why do you think that is?

It is a cultural issue, not a scientific one. On the science side our confidence grows yearly because we see independent lines of evidence converge. What we've learned from the fossil record is confirmed by the DNA record and confirmed again by embryology. But people have been raised to disbelieve evolution and to hold other ideas more precious than this knowledge. At the same time, we routinely rely on DNA to convict and exonerate criminals. We rely on DNA science for things like paternity. We rely on DNA science in the clinic to weigh our disease risks or maybe even to look at prognoses for things like cancer. DNA science surrounds us, but in this one realm we seem unwilling to accept its facts. Juries are willing to put people to death based upon the variations in DNA, but they're not willing to understand the mechanism that creates that variation and shapes what makes humans different from other things. It's a blindness. I think this is a phase that we'll eventually get through. Other countries have come to peace with DNA. I don't know how many decades or centuries it's going to take us.

In your new book, *Remarkable Creatures,* you relate how Darwin arrived at his theory of evolution. Can you connect the dots?

As a college student Darwin collected beetles. He was looking for more opportunities to collect when there came this opportunity to

be a naturalist on the British ship the HMS *Beagle.* It was seductive. He could go to faraway places—visit the tropics, places of incredible richness of life relative to cold, damp, gray England. It was difficult to persuade his father to allow him to go—he was just 22—but he got the chance. Two stops in this five-year journey were pivotal. The first came early in the voyage when he arrived on the coast of Argentina and unearthed fossils of many species, including some unknown to science—for instance, fossils of giant, extinct sloths that had been enormous compared with the living sloths he saw in the South American forests. So it planted the seed in his mind that life had changed.

Then Darwin got to the Galápagos Islands. He went from island to island collecting birds—mockingbirds and then finches—and realized that even when the birds appeared to be similar, on each island they were slightly different. After he left the Galápagos, on his way home to England, the lightbulb went on. He realized that if these birds lived on such similar islands but were slightly different from one another, there could be just one explanation: They had started out as a single species, but over time and with separation they had drifted apart and changed.

This insight was widely regarded as heresy, but why?

The prevailing idea was called special creation: that every species was created by a supernatural power and put in place on the earth for a specified role in a specified time by a completely mysterious process. It wasn't open to natural science. Instead, Darwin said no, species are changeable, and the introduction of new species is a completely natural process that follows natural laws just the way physics does. A fundamental aspect of human existence has been to ask how we got here. Evolution is the big answer to that big question. Obviously there are alternative answers that have prevailed for a very long time, but evolution has replaced a supernatural explanation of human origins with a naturalistic one.

Is that why Darwin waited more than 20 years to publish his theory of evolution?

Darwin was a pretty insecure 22-year-old when he boarded the ship. As these thoughts started to occur to him by the time he was about 27, he was just getting his feet under himself back in England. He realized what these thoughts meant, but he was just being accepted into scientific circles, just getting a lot of attaboys. Why risk that? This was not a time to challenge the establishment. You have to look at Darwin the human being to understand why he would not spill the beans.

What piqued your own interest in evolution?

As a kid, I was fascinated by zebras and giraffes and leopards. I kept snakes, and I loved their color patterns. As I got older I asked deeper questions—mainly, how are pattern and form generated? One of the most spectacular pageants on earth involves a complex creature developing from a single fertilized egg. Anyone who's a parent is still amazed that it works. When I was a graduate student, we could watch this happen, but we didn't understand the mechanics. What was going on inside that would put limbs in the right place, put eyes in the right place, carve the circulatory system and the backbone? It was an irresistible mystery, made even more irresistible with the realization that what makes a snake different from a lizard, what makes a zebra different from a giraffe, are changes within that developmental process. Understanding development was a passport to two fundamental questions: How does a complex creature form from an egg, and how have different types of creatures evolved?

These seem like two very disparate ideas: the embryonic development of a single specimen and the evolution of a whole species. How did they get connected?

At first paleontologists were studying evolution on vast timescales through fossils. Then geneticists came on the scene, and they were studying small-scale differences within species based on mutations in genes. What has been called the modern synthesis of the two fields emerged in the 1940s with the idea that the sorts of genetic differences you could observe in populations, right out your window, when compounded and extrapolated over vast periods of time, could account for the large-scale changes we see in the fossil record. So the modern synthesis was a harmonization of those two scales.

But the modern synthesis did not explain evolution in full. It was still just a theory. Where was the empirical evidence? Darwin's theory of descent was a black box. You could not see exactly what kinds of changes were taking place to account for the differences in forms. But the study of embryonic development has allowed us to peer into the machinery of making these creatures. We can study their DNA text and their developing embryos and ask, where do the differences arise? That gave us the empirical data for the theory. You can't necessarily see the change happening in the adult, but you can see that if you change that nucleic acid base right there in that gene, at that particular point in embryonic development, that animal is darker. If you change those three bases over there, that limb is longer. This is the fundamental basis of evolution: changes in DNA. By experimenting with it and visualizing it all the way up the ladder of differences, we now understand that the modern synthesis is correct.

You've said evolution is like compounding interest. How so?

Just like a good money market account, evolution works through incremental change. If variants within a species provide an advantage, no matter how slight, then that form, that capacity, will be favored. If evolving spots on wings makes you more attractive to mates or more evasive to predators, those patterns will dominate. Those varieties will have more offspring. Added up over centuries, millennia, and longer periods of time, natural selection—the competition that takes place in nature between variant forms—is powerful enough to forge all the changes that we've seen on the face of the earth.

It is hard for most people to wrap their brains around such vast stretches of time.

A century ago, Teddy Roosevelt was president and cars were barely in use. That seems like an unimaginable amount of time ago, but biologically and geologically speaking, it was a split second. A million years is just a fraction of the time that upright hominids have had to evolve. It takes time for sea levels to rise, for rivers to cut their course. As temperatures change, as rain forests grow up or deserts emerge, the creatures that live in these regions are adapting and changing too.

You call the combination of evolution and embryonic development evo devo. What is that, exactly?

It is just shorthand for "evolutionary developmental biology," a mini-syllabic description of this field that's concerned with the evolution of development. It's related probably to Devo, the new-wave band of the early 1980s—those were the guys who played with dog dishes on their heads. Before then you could describe evolution as change over time, but we did not have any grip on that process until the 1980s.

Beneath diverse exteriors, all animals share a set of body-building genes. If I had five minutes with Darwin, I would start right there. It would blow his mind.

Right. And that's when you entered the scene?
I was in graduate school doing research in immunology at Tufts University in Boston. I would just hop on the subway and go to seminars at three or four different schools. It's stimulation, right? It's hard to know how all the dots got connected, but I kept hearing that things were not well understood in evolution and things were not well understood in development, and I started thinking: How can I get at the meat? I was looking around for insights when I came across the very thin literature on the genes that sculpt fruit fly bodies, including the study of spectacular mutants. In these mutants, or Frankenflies, a single gene could put legs on the head in place of antennae. Other single-gene mutations gave the flies an extra set of wings or removed its eyes or wings completely. The fact that single-gene mutations could have such dramatic effects raised the question: What were these genes, and what were they meant to do? The quest was to figure out how these genes sculpted the fruit fly body form.

You saw the fruit fly as a window into evolution and development. How did you make the connection?
It was not an obvious call, because the expectation was that fruit flies didn't have anything to do with the development of furry creatures. But in 1983 I found a laboratory where I could do the work, with Matt Scott at the University of Colorado at Boulder. Just as we were getting started, it became clear from our research and others' that these body-building genes were not restricted to fruit flies; they were shared throughout the animal kingdom. It was a real jolt. All of a sudden we could do deep experiments at the most fundamental level to understand how form actually evolved.

So scientists were seeing the same master genes at work in many different species?
Yes. One shocking discovery was the relationship between our eyes and bug eyes. You wouldn't think they had anything in common, right? Bug eyes, with 800 facets, work by different optical principles than human eyes. For almost a century and a half, biologists thought that they had evolved independently, from scratch, and that eyes had been invented many times in the animal kingdom by completely different means—different recipes in different groups of animals. We have now discovered that these eyes are formed by what is recognizable as the same gene, even though those animals have been evolving separately for 500 million years. When we took the mouse version of this gene—the same gene we find in the human—and put it in the fly and tweaked it, we induced fly eye tissue.

Our team showed that the same common gene is critical to building limbs in humans and fruit flies. It turns out that this gene is critical to building virtually everything that sticks out of the body: antennae, legs, horns, whatever. These kinds of experiments shattered our preconceptions and forced people to think differently. Beneath these extremely diverse exteriors was a deeply shared common genetic tool kit. If I had five minutes with Charles Darwin, I'd start right there. It would blow his mind.

Clearly we have entered the age of experimental Darwinism. What are the experiments like, specifically?
We look at lots of species to figure out the ancestral form of a particular molecule. We can reconstruct that ancestral molecule and then retrace the steps that must have taken place to forge the new forms and functions we see today. If you think that the difference between two species involves changes in certain genes, you can swap those genes between the species. We're doing those experiments trait by trait. There's a powerful set of experiments that people have done on vision. Lots of animals differ in the parts of the color spectrum that they see best because of how they are tuned to their environments—whether they live in the deep sea or in caves, whether they mostly go out in the day or at night, or whether they're trying to pick up ultraviolet patterns on flowers or on prey. Sight is really important in helping animals live, and since animals live in lots of different habitats, vision has evolved a lot.

Experiments that look at these changes are very doable in the lab. You can swap genes and change the retinal proteins that detect light. Then you can make very clear predictions about what certain changes mean and verify those things experimentally. For example, mice have been given an extra color vision gene in the lab, and it has been shown that the protein manufactured by that gene expands the scope of their vision by enhancing their ability to see longer-wavelength light without any other changes in the brain.

Can we apply these discoveries to the human realm?
We now know that the human genome and the chimp genome differ by only about 1 percent. Yet our bodies and brains are so different. How can we be so different from other primates if our genes are so much the same? How did we get the dexterity in our hands? How do we walk upright? How are we able to hold this conversation? How did we get big brains? Once you identify the meaningful functional changes that have taken place between us and chimps, you realize that pretty big differences in anatomy and behavior can result from a small degree of genetic divergence. Evo devo has given us the tools to explore this mystery: The same genes are being regulated and then used in a different way. Something is happening a little earlier or in another place or is staying on a little bit longer. These are the time and space dimensions of development. It's like choreography. You've got the same dancers, but the ballet is different based on different cues.

In your book *Endless Forms Most Beautiful,* you refer to the Cambrian explosion, a time when a vast number of new life-forms appeared at nearly the same time. Evolutionary skeptics often point to this kind of abrupt shift—doesn't such rapid change contradict your description of a single master tool kit and slow evolution over long stretches of time?
Prior to about 543 million years ago, you saw things like jellyfish and spongelike creatures, but you didn't see bilateral creatures: worms and trilobites and things like this. Then in the Cambrian explosion, large and complex animal forms erupted. These forms in the Cambrian represent a lot of the major divisions of the animal kingdom we see

blood, one of those genes is completely gone and another is a broken remnant, rotting away. From this we understand that the ancestors of these fish had red blood, but these guys have left that red-blooded lifestyle behind.

The explanation is ecological. The ice fish are living in this extremely cold water, and it may well be that red blood cells are really hard to pump around capillaries in such cold water. Instead, the fish have larger gills and pretty much a scaleless skin. So they're just getting their oxygen passively from the surrounding ocean water. They've abandoned a way of life that has nourished vertebrates for some 500 million years. As for us, humans have junked about 800 genes in the course of our evolution from mammalian and earlier ancestors going back millions of years. Who knows, those lost genes might be useful to us 1,000 years from now, but there's no way to preserve them. I guess we could always try to engineer some things back in.

By contrast, you've said that some genes are immortal.
These genes date back to the early origin of life on the planet, and they're so essential that their text has been preserved for more than 3 billion years. They're involved in very fundamental ways with the decoding of the genetic machinery shared among all organisms. Without these genes you couldn't express your genetic information and produce the proteins you need to live.

When genetic potential met ecological opportunity, you got elephants and bison and giraffes. Ecology is like corking the bottle; take the cork out and things explode.

today. The Cambrian explosion looks abrupt in the fossil record, but the surprising message from evo devo is that all the genes for building big, complex animal bodies long predated the appearance of those bodies. Most of what was needed to create this incredible complexity already existed. The genes were expressed prior to the Cambrian in those more modest, soft-bodied creatures, but they had fewer jobs to do. Complexity evolved by expanding the uses of these genes rather than inventing lots more of them.

It makes you wonder what kind of potential is just waiting to burst out today.
Dinosaurs were the dominant vertebrates right up until the end of the Cretaceous. Mammals existed, but they were smaller, carving lifestyles out of the dinosaurs' way. Take out the dinosaurs and in 10 or 15 million years mammals had evolved into all sorts of large forms and dominated terrestrial ecosystems. When genetic potential met ecological opportunity, you got elephants and bison and giraffes. Think about ecology as corking the bottle; take the cork out and things explode.

You mention in your book *The Making of the Fittest* that every species contains fossil genes.
These are remnants that are no longer used, and the integrity of the genetic text starts to erode. One of my favorite stories concerns the ice fish of Bouvet Island. These creatures live in the cold waters of the Antarctic. They are the only vertebrates without red blood cells to carry oxygen to nourish their tissues. If you look at the genes for hemoglobin, the oxygen-carrying proteins in red

You've presented an avalanche of irrefutable evidence, yet opponents of evolution seem to refute it all. How do you respond?
You can hear me almost chuckling, because it's not reasonable, it's not rational, and as the years click by, it's ever more preposterous, but people still stick to their guns.

Is there anything we can do to help persuade the skeptical public to accept the evolutionary way of looking at life?
Seriously, teach evolution as a core theme in science from the early grades. The universe changes, the earth changes, and life changes with the evolving earth.

Where do you see evolutionary biology going next?
We're in a second golden age. We're not collecting the menagerie of critters that Darwin did or hauling them back to a museum. Instead, we're collecting the genetic recipes of creatures across the planet and trying to figure out how they came to be. We're looking right into the text of evolution, and even into the text of extinct creatures like woolly mammoths and Neanderthals, and asking what made them similar to or different from elephants or from us. A third golden age will come when we understand life beyond earth. How many times has life evolved, and how many origins have there been? Has life moved from planet to planet? Is the chemistry of extraterrestrial life different from that of life on earth? This will be difficult work, but we have to look ahead. Finding life elsewhere in the universe would bring a scientific revolution as big as any we've ever had. ■