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How to respond to CRISPR babies

The claims from He Jiankui that he has used gene editing to produce twin girls demand action. A new registry of research is a good start.

People like to say that science is self-correcting. Events in China last week pose a serious challenge to that reassuring platitude. How do researchers respond to the failure of medical ethics, collective responsibility and professional standards that saw an immature experimental technique used to help produce human babies?

It has not yet been independently confirmed that the Chinese genome-editing researcher He Jiankui altered the DNA of embryos using a gene-editing technique and then implanted them in a woman, as he claims. Such a step would be significant and controversial because it would make a permanent change to the germ line that could be passed on to future generations. (This distinguishes germline editing from the use of gene-editing tools as therapies that correct genetic alterations in somatic cells in blood and other tissues.)

Verification of He's claims could be difficult, given that privacy concerns rightly protect the identity of the parents and their one-month-old twin girls. But many scientists in the field agree on two things: the relative simplicity and widespread availability of the gene-editing tool CRISPR–Cas9 mean that what He claims to have done is eminently possible; and, whether or not he is the first person to have genetically edited a baby, he will not be the last.

So, although testing the accuracy of his claim is a priority, so too is ensuring that any future efforts to genetically edit the germ line of human babies proceed in a much more regulated and responsible way. The scientific community still has the opportunity to take the lead on this — public and political reaction to last week's news has been calmer than many might have expected — and it should do so urgently.

Some argue that the circumstances in which germline gene editing would be beneficial, such as to reverse disease-causing mutations that could not be addressed in any other way, are likely to be extremely rare. Nevertheless, given that research and medicine move fast, a clear regulatory system needs to be devised and put in place in case a credible proposal arises. Such a regulatory system should draw on those that already exist to guide the use of gene-editing tools for research into human development, and more broadly govern medical testing of innovative therapies. But it should not start with the assumption that future germline editing is a foregone conclusion — that is a question for society, not scientists, and one that demands the input of different stakeholders from across the world. Researchers and physicians must ask permission rather than beg for forgiveness.

A solid regulatory system set up by the research community can then be the basis for laws and regulations that individual nations might decide to introduce. Debate was key to framing the law that regulates a mitochondrial-replacement therapy in the United Kingdom, a procedure that also affects unborn babies and means they carry DNA from three people. (Laws are not always the best way to govern emerging medical procedures, but they do offer the deterrence of effective punishment for those who don't follow the rules, unlike self-regulation or guidelines.)

So, how can the gene-editing community set up a better system? A starting point would be a global registry (or national registries) set up by funders or governments to record preclinical research that involves gene editing in human embryos. This would require the objectives, steps and limitations of projects to be spelled out from an early stage. The records should also detail the steps taken for ethical approval and oversight of the research. The 2016 guidelines from the International Society for Stem Cell Research are a good model to follow for regulation of research that involves human embryos and gametes, including research into germline gene editing.

"The scientific community still has the opportunity to take the lead."

Such registries could also provide a mechanism to flag research projects that do not meet high ethical and technical standards, and a route to apply pressure on individuals and their institutions to improve. And they could provide a framework, if the time comes, to define a path to the clinic. They would help to explain the risks and potential benefits to people — such as prospective parents — so they can make more informed choices.

He's claims to have communicated his intentions and actions to the scientific community do not stand up to serious scrutiny. The community — from individual researchers to institutions — can and must do more to encourage more meaningful, transparent engagement and discussion on specific projects. In return, scientists who are trusted to carry out research have the responsibility to welcome and embrace scrutiny. ■

A lonesome life

Genome of legendary Galapagos giant tortoise shares some secrets of longevity.

Lonesome George, the last member of *Chelonoidis abingdonii*, a species of giant tortoise endemic to the tiny island of Pinta in the Galapagos Islands, did not die in vain. Researchers this week present his genome in the journal *Nature Ecology and Evolution* (V. Quesada *et al. Nature Ecol. Evol.* https://doi.org/10.1038/s41559-018-0733-x; 2018), along with the genome of George's distant but still-extant cousin, the Aldabra giant tortoise *Aldabrachelys gigantea*. Comparison of these genomes with those of a diverse range of species unlocks a treasure trove of secrets about how giant tortoises get to be so large, long-lived (typically up to a century) and resistant to infections and cancer.

Once upon a time, islands from Malta to Mauritius could boast their own species of giant tortoise. But nowhere is more synonymous with giant tortoises than are the Galapagos Islands — literally so, because the archipelago gets its name from *galápago*, a Spanish word for turtle.

Marooned in isolated spots and free from predators, Galapagos tortoises became larger than their mainland ancestors, and, having rather relaxed metabolisms, they are able to survive on the meagre rations available on islands. Slow metabolism and large size tends to correlate with long life and infrequent reproduction. It's no surprise, therefore, that the arrival of humans marked out giant tortoises as ripe for extinction. These large creatures moved too slowly to escape slaughter, and bred too infrequently to compensate for the loss. Even when they did manage to breed, their eggs and young were easy prey for other introduced species such as rats, the eradication of which is seen as key to the recovery of giant tortoise populations (see W. T. Aguilera *et al. Nature* **517**, 271; 2015).

Humanity, however, wasn't solely to blame. Comparison of the genome of Lonesome George — who died in 2012 — with that of other tortoises shows that the effective population size of his species had been in slow decline for at least one million years. This is only to be expected for a species of large, slowly reproducing animal confined to a small island, where the choice of mate is limited. The Aldabra giant tortoise experienced more ups and downs; but for isolated island species, downs can all too often prove catastrophic.

Animals that live for a long time take pains to avoid early death, and giant tortoises are among the longest-lived of all land animals. Although the genetics of longevity has been explored in long-lived mammals, extending it to tortoises should illuminate more-general hallmarks of the genetic basis of longevity.

Genes under positive selection in giant tortoises include those whose expression has also been connected with a ripe old age in humans. A detailed study of 891 genes involved in the function of the immune system revealed duplications in tortoise genes not seen in humans, and there are more tumour-suppressor genes in giant tortoises than in vertebrates in general. Duplications of at least one proto-oncogene involved in mitochondrial health might relate to an improved response to oxidative stress, known to be an important factor in ageing.

"One should be cautious in applying the lessons of tortoise longevity directly to humans."

Some details of the giant-tortoise genomes could shed light on aspects of the peculiar evolution and development of tortoises, such as their shell. One should therefore be cautious in applying the lessons of tortoise longevity directly to humans. The longevity of a species is more than a matter of a list of genes — it's connected with all aspects of the species' life history. Although the naked mole-rat (*Heterocephalus glaber*) can live for 30 years, this marks it out as peculiarly long-lived only for rodents, whose lives are generally fast, frenetic and short. It's no great shakes compared with a tortoise, a human or indeed a bowhead whale, whose two-century lifespan makes it the longest lived of all mammals — and which doubtless has many other whale-specific peculiarities. Faced with the specific fate of one's species, life remains very much what you make it. ■

Climate rules

Global leaders have gathered to decide on emissions guidelines — but time is running out.

Delegates to the United Nations climate talks arrived in the old Polish coal-mining town of Katowice at the weekend to learn that the annual meeting faces an uncertain future: incoming Brazilian president Jair Bolsonaro has withdrawn his country's offer to hold the event next year. This unwelcome posturing, from a leader who seems likely to oversee renewed deforestation in the Amazon, shows that global warming is far from the top of the political agenda in some countries. But it also acts as a reminder that political cooperation remains the only effective defence we have against the worst effects of climate change — which would mean a more hostile world for us all.

The annual caravan of government representatives, campaigners and negotiators has rolled into Poland for the 24th Conference of the Parties to the United Nations Framework Convention on Climate Change (COP24) with a clear goal. Delegates from more than 190 countries hope to finalize the rules for how the 2015 Paris climate agreement, which aims to limit global warming to no more than 2 °C above pre-industrial levels, will be put into practice. Negotiating an acceptable plan for curbing emissions and funding climate action will be a tough task. But given the enormity of the environmental and social challenges ahead, there is a need for more than written rules and good intentions.

The Paris agreement is a hybrid of self-imposed national commitments and binding 'top-down' elements, including mandatory emissions reporting and a regular global stock-take of collective progress. Transparent rules and criteria for cooperation among nations, including systems that link countries' individual actions through international carbon markets, are essential for the success of an agreement otherwise plagued by the voluntary nature of national climate targets.

Despite decades of international climate diplomacy, global greenhouse-gas emissions continue to rise. The concentration of carbon dioxide in the atmosphere is now at a level that Earth hasn't experienced for several million years. Since 1900, global temperatures have already increased by 1 °C — with inescapable consequences. Raging forest fires last month in drought-stricken California are a clear warning sign of what a warmer future might hold in store (see Comment, page 27).

A special report released in October by the Intergovernmental Panel on Climate Change found that time is running out to limit global warming to 1.5 °C. Realistically, that horse has already bolted. To keep warming to 2 °C — which would still all but guarantee severe environmental effects — global emissions would need to shrink by at least one-quarter by 2030, and drop to almost zero by 2050. But according to a report released last week by the UN Environment Programme, there is a huge gap between nations' self-imposed targets and the amount of action that is needed to stabilize the climate.

In particular, the world's largest greenhouse-gas emitters, including China, the United States and the European Union, must significantly step up their own efforts to tackle climate change. But will they? US President Donald Trump has already said that the United States will pull out of the Paris agreement, claiming it is bad for the economy. But a report issued by 13 federal agencies in November found that the US economy could shrink by as much as 10% by 2100 if little is done to reduce global warming, and several US states and cities have unveiled their own ambitious emissions-reduction pledges.

Whether China will be able and willing to decarbonize its fossil-fuel-based economy in due time is uncertain, despite encouraging signals from the leadership. China's emissions reporting and verification practices are notoriously non-transparent. The Paris rulebook aims to bolster these mechanisms, and China must show its support for this.

The EU seems best placed to take climate policies to a higher level (of ambition, at least). Ahead of the Katowice conference, the European Commission released a set of scenarios for how the bloc can achieve zero net emissions by 2050 — although member states must still agree on the preferred scenario. Poland and other EU countries that rely heavily on coal might oppose more ambitious targets. In Germany, too, the timing and cost of the planned phase-out of coal-powered plants are causing heated debate. But the EU's initiative is a strong signal that the push for clean energy must involve all sectors of the economy, including industry, transport, building and agriculture.

Katowice, a European coal capital, is an apt place to meditate on the future of fossil fuels. Behind the razzmatazz of these climate-policy talks are simple facts: the world's policymakers must introduce more and stronger measures to boost investment in clean energy and end the use of dirty fuels. Delay is fundamentally contrary to reason. ■