epiblast pluripotent state before implantation, whereas rodents reach it after implantation. For the human embryo, this information is lacking. Given the broad spectrum of biological diversity, it is naive to benchmark expectations about human pluripotency against an umbrella pluripotent state in a different species, even one so beloved as the mouse.

What is the utility of the new ICM-like human pluripotent stem cells? At the level of fundamental biology, they will enable researchers to determine whether the mechanisms responsible for maintenance and exit from pluripotency in mouse embryonic stem cells apply to other mammalian species. From the perspective of biotechnology, the cells should be advantageous with respect to genetic modification, scalability and chimera formation. Gafni *et al.*[1] showed that, compared with conventional human embryonic stem cells, the ICM-like pluripotent cells supported more efficient homologous recombination. It should be noted, however, that previous barriers to genetic modification of human pluripotent stem cells have recently been circumvented through zinc-finger, TALEN and CRISPR technologies. In addition, the ICM-like pluripotent stem cells were more capable of growing as single-cell clones and had a shorter doubling time, which will be beneficial for scaling up production of human pluripotent stem cells. Finally, the authors demonstrated human-mouse chimerism exceeding that previously attained with conventional human embryonic stem cells[9]. Despite extensive cell numbers in anterior regions of the embryos, integration was not confirmed by tissue-specific marker-gene expression and histological analysis.

The most striking potential application of ICM-like human pluripotent stem cells would be to generate 'humanized' whole organs in animals for potential use in regenerative medicine and in modeling whole-organ physiology in human diseases. However, the feasibility of cross-species generation of organs for regenerative medicine is yet to be established, as the vasculature and innervation remain host-derived. Whole-organ generation is but one facet of regenerative medicine, another being *in vitro* derivation of tissue-specific cell types for disease modeling, cellular therapy and drug discovery. Here the advantages of ICM-like pluripotent stem cells are less apparent. Clinically useful cells can be generated directly from epithelial epiblast–like pluripotent stem cells, which are arguably poised for somatic cell differentiation, as in gastrulation. By contrast, ICM-like pluripotent stem cells would first have to be induced to a later developmental state if they follow the natural course of embryogenesis. Regardless of *in vivo* or *in vitro* applications, validation is still required by functional integration of ICM-like human cells into all three germ layers.

In sum, the excitement and intrigue surrounding the report by Gafni *et al.*[1] of the first stable ICM-like human pluripotent stem cells is palpable. With the very recent independent article identifying a distinct human embryonic stem cell state[10], we are likely witnessing the start of a reporting wave defining conditions for the generation of stable ICM-like human pluripotent stem cells. Given the importance of human pluripotency to the stem-cell field, confirmation of ICM-like pluripotency is essential. Like Higgs' Boson to the field of particle physics, human ICM-like pluripotency was predicted from considerations of symmetry and conservation, and we are yet to unlock its potential.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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