repeat that presumably functions in target selection.

In the new work, Stone *et al.*[3] show that ARC1 is an E3 and that ubiquitination is crucial for self-incompatibility. They found that ARC1 can direct ubiquitination *in vitro* and that more proteins are ubiquitinated after a self-pollination than after a compatible pollination. An increase in ubiquitin conjugates was not seen in plants with lower concentrations of ARC1. Adding ubiquitin to a protein targets it for destruction by the cell's garbage-disposal unit, the 26S proteasome. Because the application of a proteasome inhibitor to the pistil also impairs the rejection of self pollen, the targets of ARC1 ubiquitination must be degraded by this multi-enzyme complex.

The substrate(s) of ARC1 ubiquitination, and how SRK affects ARC1 activity, remain unknown. Unfortunately, ARC1 is unlike any other known U-box protein, so guilt by association cannot be used to predict its targets. The large increase in ubiquitinated proteins observed after a self-pollination suggests that a marked shift in target selection occurs in the papilla cell. But how does this shift cause the changes seen during pollen rejection?

Figure 1 shows some possibilities. ARC1 might target proteins in the papilla cell that normally promote pollen germination and direct them to the proteasome for breakdown. Degradation must somehow be restricted to near where the papilla cell and self pollen grain touch, so another possibility is related to ubiquitin's role in vesicle sorting: ubiquitination of specific transport proteins helps to direct the flow of vesicles to appropriate cellular destinations[1]. Consistent with this notion was the finding by Stone *et al.* that when ARC1 is phosphorylated by SRK it is no longer mostly in the nucleus but enters the cytoplasm, where it seems to associate with the endoplasmic reticulum and secretory system. Focused secretory activity at the contact site and localized loosening of the papilla cell wall are events seen soon after a compatible pollination[4]. ARC1 ubiquitination could prevent the delivery of proteins and other molecules that are essential for germination or wall loosening to the contact site of self pollen.

Stone and colleagues' work constitutes a step forward in our understanding of brassica self-incompatibility. But is there a bigger picture as well? Other plant families have evolved self-incompatibility mechanisms that are radically different to that found in brassicas. Self-incompatible species in the Rosaceae family, which includes apple and some other fruit trees, use a different *S*-locus-encoded enzyme — a ribonuclease — to inhibit the growth of self pollen. What isn't clear is the *S*-locus product that identifies self pollen. Two tantalizing reports have shown that a gene encoding another component of the ubiquitination machinery is near the *S*-locus ribonuclease gene in the Rosaceae[9,10]. Possibly, then, ubiquitination helps to control self-incompatibility in both the Rosaceae and Brassicaceae, the family to which brassicas belong. If it does, we shall have to elevate ubiquitin to an even loftier place in the pantheon of plant regulatory molecules. ■

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Cosmology

A just-so story

Lawrence M. Krauss

Physicists are learning to live with Einstein's 'fudge factor', the cosmological constant. New thinking attempts to tie its value to other fundamental constants in elementary particle physics.

The recognition, in the light of observational data, that Einstein's infamous cosmological constant might not be zero[1–3] has changed almost everything about the way we think about the Universe, from reconsidering its origin[4] to re-evaluating its ultimate future[5]. But perhaps the most significant change in cosmological thinking involves a new willingness to discuss what used to be an idea that was not normally mentioned in polite company: the anthropic principle. This idea suggests that the precise values of various fundamental parameters describing our Universe might be understood only as a consequence of the fact that we exist to measure them. To paraphrase the cosmologist Andrei Linde, "If the Universe were populated everywhere by intelligent fish, they might wonder why it was full of water. Well, if it weren't, they wouldn't be around to observe it!".

The reason that physicists have been so reluctant to consider the anthropic principle seriously is that it goes against the grain. Most physicists have hoped that an ultimate physical explanation of reality would explain why the Universe must look precisely the way it does, rather than why it more often than not would not. Into the fray has entered James Bjorken. In a paper[6] published in *Physical Review D*, entitled "Cosmology and the Standard Model", Bjorken proposes a new 'scaling' ansatz, based on well-established notions in particle theory, for exploring how anthropically viable a small cosmological constant might be.

The realization that an extremely small, but non-zero, cosmological constant might exist has changed physicists' interest in anthropic explanations of nature precisely because the value it seems to take is otherwise so inexplicable. In 1996, physicist Steven Weinberg and his colleagues Hugo Martel and Paul Shapiro argued that, if the laws of physics allow different universes to exist with a cosmological constant chosen from an underlying probability distribution, then galaxies, stars and presumably astronomers might not ultimately evolve unless the cosmological constant were not much larger than the one we apparently observe today[7].

Although this suggestion has spurred several authors to reconsider anthropic arguments, the problem in cosmology is that without a fundamental theory underlying such a probability distribution, very few concrete calculations can be performed. Moreover, while the discussion may centre on fundamental parameters, many of the authors of these discussions are cosmologists, so that little explicit use is made of existing notions from the theory of elementary particles.

However, Bjorken — a particle theorist — notes that a cosmological constant provides a fundamental dimensional parameter that asymptotically characterizes any universe: the so-called de Sitter horizon, R_H (what Bjorken calls R_∞). In a universe dominated by a cosmological constant, distant objects recede from an observer at a speed proportional to their distance. Ultimately, beyond a certain, fixed distance, all objects will recede at velocities greater than that of light, and so causal contact will be lost. This distance, the de Sitter horizon, therefore characterizes the effective operational 'size' of an infinite universe undergoing de Sitter-like expansion.

Bjorken suggests that all fundamental dimensional quantities are related to this

de Sitter horizon in a simple way. Taking the Planck scale (where quantum gravitational effects become important, equivalent to an energy of 10^{19} gigaelectronvolts or a length of 10^{-33} cm) as a fundamental scale in nature, Bjorken suggests that other dimensional quantities simply scale in direct proportion to R_H in any universe. In a universe in which R_H is the Planck length, all dimensional quantities, from the grand-unification scale to the mass of the proton, would be identical. As R_H increases, each of these quantities is presumed to have a different scaling factor (in the language of the renormalization group, a different scaling exponent), so that in a universe with R_H equal to that in our currently observable Universe (about 18 billion light years), the different quantities assume the values we measure them to have. With a fixed point at the Planck scale, and a current value, the exponents for each quantity can be inferred.

But it is less clear how very small quantities such as the mass of the electron might scale with R_H. If the small masses are ultimately dependent on small dimensionless coupling constants, they are likely to scale as the logarithm of R_H. But if they are determined by a ratio of some fundamental dimensional scales, they will vary as a power of R_H, according to Bjorken's ansatz. These considerations become important if one wants to use this ansatz to say anything about the likelihood that a universe will assume the values we currently observe it to have. For example, the relative mass of the proton and the neutron and the binding energy of deuterium will depend sensitively on, among other things, the mass of the subatomic particle called the pion.

Bjorken concludes that a surprising number of fundamental constructs in cosmology would be remarkably insensitive to changes in R_H by over 30 orders of magnitude. But he finds that standard nuclear processes associated with stellar evolution — including the famous triple-alpha reaction that allows stars to burn helium to form carbon and is very sensitive to specific beryllium and carbon nuclear configurations — would not be compatible with variations in R_H by more than a factor of about 1.4. This is probably not surprising, because the triple-alpha reaction has long been used in anthropic arguments to constrain variation of the fundamental constants.

In the end, as with so many anthropic arguments, it is hard to know what to make of this result, especially in the absence of any fundamental theory. The suggestion that the small value of the inferred cosmological constant today is tied to the existence of other hierarchies in elementary particle physics through a scaling mechanism is nevertheless quite intriguing as a possible resolution of what is otherwise the most puzzling fine-tuning problem in all of physics. As Bjorken stresses, perhaps attempts to connect concurrent problems in particle physics and cosmology in this way — even though these types of argument are very speculative — might ultimately provide some guidance for researchers as we try to understand what otherwise seems at present to be a remarkably inexplicable Universe. ■

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Stem cells

Self-renewal writ in blood

John E. Dick

The ability to self-renew is a defining property of stem cells, and a protein in blood stem cells that controls their self-renewal has been discovered. That same protein is also crucial for the development of leukaemia.

Between birth and death, people produce of the order of 10^{16} blood cells of different types. These specialized cells are continuously produced from precursor cells, which in turn must be replaced by cells further up the blood hierarchy. Ultimately, the entire blood system is fed by a pool of rare haematopoietic stem cells (HSCs)[1]. But how does this small pool sustain blood production over a lifetime without being depleted? The answer involves a process termed self-renewal: when HSCs divide, one or both 'daughter' cells can retain the properties of the parent, rather than — as is usual after division — becoming more specialized. Despite some interesting findings, we still know little about how the balance is tipped towards self-renewal[2]. This is not just a biological conundrum: it is also important in developing treatments that involve culturing HSCs *in vitro*. On pages 255 and 302 of this issue, Lessard and Sauvageau[3] and Park *et al.*[4] provide new insight into the problem — they describe a gene regulator that governs the self-renewal of both HSCs and leukaemic 'stem cells'.

Cell division is an inherently error-prone process, with mutations arising frequently during the necessary replication of DNA. And the more divisions that occur, the more mutations can accumulate, making the development of cancer more likely. Achieving a lifetime of blood production while avoiding a high rate of malignancy is possible only because the blood system is ingeniously organized as a hierarchy. Most proliferation occurs within pools of progressively differentiating precursors that are committed to particular blood-cell lineages. So the likelihood of acquiring enough cancer-predisposing mutations before the final differentiation into non-proliferating, mature blood cells is low.

At the top of the blood-cell hierarchy are the HSCs, from which lineage-committed precursors are generated. When an HSC divides, in theory both daughter cells could become committed to a specific lineage (Fig. 1). But that would result in the eventual

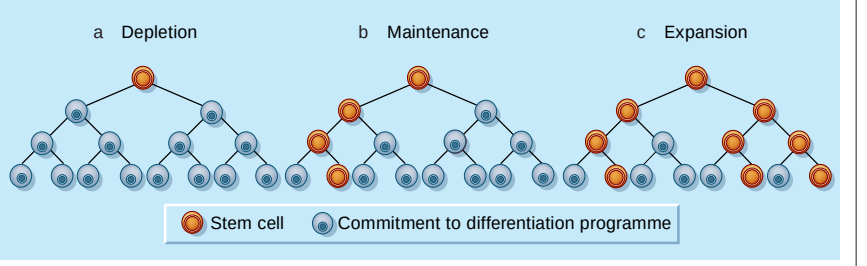

Figure 1 **The choices available to haematopoietic stem cells (HSCs) upon division. Daughter cells can either commit to a programme of differentiation that will eventually result in mature, non-proliferating cells, or retain HSC properties. The choice is probabilistic and governed by intrinsic molecular programmes, including, as now shown[3,4], the transcription factor Bmi-1.** a, **When both daughters are committed, the clone will become depleted of HSCs and will eventually die out.** b, **During steady-state haematopoietic development, the probability that an HSC will generate at least one daughter cell with HSC properties is about 0.5, and the average number of HSCs will be maintained.** c, **Under some circumstances, especially after transplantation[18], both daughters retain HSC properties, and the overall numbers of HSCs increase. A fourth outcome is that both daughters die.**