may indicate positive selection of clones with increased growth potential caused by vector insertion (*2*, *17*, *18*). Is lentiviral vector integration more neutral? Cartier *et al*. report a reassuring picture of highly polyclonal hematopoietic cells transduced with the *ABCD1* gene, which is maintained throughout the follow-up time without evidence for sustained expansion of individual clones or enrichment of common integration sites. But when the authors compared the distribution of integration sites in cells before infusion and after engraftment, they observed an enrichment of integration sites at some gene classes after engraftment. This may suggest that integration was not completely neutral. It may also reflect differences in integration preference between the short-lived progenitors, which constitute most of the cells infused into the patients, and the rare HSCs whose progeny engraft the patients long-term. Longer follow-up and additional testing in this and other diseases will better establish the safety features of lentiviral vectors and how they can be influenced by conditions specific to each study design.

If most lentiviral vector integration is neutral to cell behavior, the tracking of integration site distribution in the different cell lineages reported by Cartier *et al*. may be a first glimpse of live hematopoiesis in humans at the clonal level. The authors used a combination of approaches to maximize the coverage of integration sites in each sample and alleviate the retrieval biases imposed by the DNA restriction and amplification steps of the procedure. This technological rigor will likely become a gold standard for future HSC-based gene therapy trials.

Gene therapy of ALD in the study of Cartier *et al*. provided a benefit similar to that of allogeneic HSC transplantation, despite a relatively low level of gene correction. This unexpected finding indicates that enhanced efficacy in relieving lipid storage may be attained with cells that overexpress the therapeutic gene as compared to normal donor cells. It also suggests that microglia cells might be replaced by infused short-lived progenitors that contain a higher proportion of gene-corrected cells than HSCs. These scenarios might eventually position HSC-based gene therapy as a preferable treatment option for ALD, as it abrogates the morbidity associated with the allogeneic source of HSCs in conventional transplantation. Furthermore, improved HSC transduction protocols may overcome the need for bone marrow conditioning. Although many questions remain to be fully settled, this study clearly supports further testing of HSC-based gene therapy in ALD and other diseases and represents a long-sought rewarding achievement in the field of gene therapy.

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ECOLOGY

Biodiversity and Climate Change

Efforts to elucidate the effect of climate change on biodiversity with detailed data sets and refined models reach novel conclusions.

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Over the past decade, several models have been developed to predict the impact of climate change on biodiversity. Results from these models have suggested some alarming consequences of climate change for biodiversity, predicting, for example, that in the next century many plants and animals will go extinct (*1*) and there could be a large-scale dieback of tropical rainforests (*2*). However, caution may be required in interpreting results from these models, not least because their coarse spatial scales fail to capture topography or "microclimatic buffering" and they often do not consider the full acclimation capacity of plants and animals (*3*). Several recent studies indicate that taking these factors into consideration can seriously alter the model predictions (*4*–*7*).

In one study, Randin *et al*. assessed the influence of spatial scale on the accuracy of bioclimatic model predictions of habitat losses for alpine plant species in the Swiss Alps (*4*). A coarse European-scale model (with 16 km by 16 km grid cells) predicted a loss of all suitable habitats during the 21st century, whereas a model run using local-scale data (25 m by 25 m grid cells) predicted persistence of suitable habitats for up to 100% of plant species. The authors attributed these differences to the failure of the coarser spatial-scale model to capture local topographic diversity, as well as the complexity of spatial patterns in climate driven by topography.

Luoto and Heikkinen reached a similar conclusion in their study of the predictive accuracy of bioclimatic envelope models (which model the relation between current climate variables and present-day species distributions) on the future distribution of 100 European butterfly species (*5*). A model that included climate and topographical heterogeneity (such as elevational range) predicted only half of the species losses in mountainous areas for the period from 2051 to 2080 in comparison to a climate-only model. In contrast, the number of species predicted to disappear from flatlands doubled in the climate-topography model relative to the climate-only model. The two studies suggest that habitat heterogeneity resulting from topographic diversity may be essential for persistence of biota in a future changing climate.

Highly contrasting predictions have also been obtained when bioclimatic models of tropical biomes included the physiological effects of elevated atmospheric CO_2 concentrations and temperature on trees (*6*). Many studies have indicated that increased atmospheric CO_2 affects photosynthesis rates and enhances net primary productivity—more so in tropical than in temperate regions—yet previous climate-vegetation simulations did not take this into account.

To address these issues, Lapola *et al*. (*6*) developed a new potential-vegetation model for tropical South America that includes CO_2 fertilization effects. They then drove this model with different climate scenarios for the end of the 21st century from 14 coupled

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ocean-atmosphere global climate models of the Intergovernmental Panel on Climate Change (IPCC) Fourth Assessment report (*8*). The results indicate that when the CO_2 fertilization effects are considered, they overwhelm the impacts arising from temperature; rather than the large-scale die-back predicted previously (*2*), tropical rainforest biomes remain the same or substituted by wetter and more productive biomes. However, for 2 of the 14 models, this result was dependent on the dry season not extending beyond 4 months; if it does, then the tropical biome becomes savanna (*6*).

These studies highlight the level of complexity that we are faced with in trying to model and predict the possible consequences of future climate change on biodiversity (*9*). They suggest that we should expect to see species turnover, migrations, and novel communities, but not necessarily the levels of extinction previously predicted. For example, Hole *et al*. recently studied model-projected shifts in the distribution of sub-Saharan Africa's breeding bird fauna. They found that in the Important Bird Area protected network, species turnover is likely to be substantial and regionally variable, but persistence of suitable climate space across the network as a whole is remarkably high, with 88 to 92% of species retaining suitable climate space (*7*).

Another complexity, however, is the impact of climate change on already highly altered fragmented landscapes outside of protected areas. Over 75% of the Earth's terrestrial biomes now show evidence of alteration as a result of human residence and land use (*10*). Yet, recent case studies suggest that even in a highly fragmented landscape, all is not lost for biodiversity.

It has long been assumed that in a fragmented landscape, the fragment size and its isolation are important factors in determining species persistence; the smaller and more isolated the fragment, the lower its occupancy. Yet few worldwide studies have attempted to quantify this relation. Prugh *et al*. (*11*) compiled and analyzed raw data from previous research on the occurrence of 785 animal species in >12,000 discrete habitat fragments on six continents. In many cases, fragment size and isolation were poor predictors of occupancy. The quality of the matrix surrounding the fragment had a greater influence on persistence: When the matrix provided conditions suitable to live and reproduce, fragment size and isolation were less important and species were able to persist.

This ability of species to persist in what would appear to be a highly undesirable and fragmented landscape has also been recently demonstrated in West Africa. In a census on the presence of 972 forest butterflies over the past 16 years, Larsen found that despite an 87% reduction in forest cover, 97% of all species ever recorded in the area are still present (*12*). For reasons that are not entirely clear, these butterfly species appear to be able to survive in the remaining primary and secondary forest fragments and disturbed lands in the West African rainforest. However, presence or absence does not take into account lag effects of declining populations; a more worrying interpretation is therefore that the full effects of fragmentation will only be seen in future years.

Predicting the fate of biodiversity in response to climate change combined with habitat fragmentation is a serious undertaking fraught with caveats and complexities. The recent studies discussed here attempt to quantify some of the uncertainty in these predictions. They use larger, more detailed data sets and more-refined models than previously available, thus avoiding the problems often encountered in trying to scale up results from small local-scale studies.

The results also highlight a serious issue for future conservationists: the urgent need to develop a research agenda for regions outside of protected reserves in human-modified landscapes (see the figure) (*13*). Although every measure should be put in place to reduce further fragmentation of reserves, we must determine what represents a "good" intervening matrix in these human-modified landscapes (*11*–*14*). Furthermore, with the combination of climate change and habitat destruction, novel ecosystems are going to become increasingly common. Their conservation will require a whole new definition of what is "natural" (*15*).

Looking beyond reserves. This photo of the boundary between the Mfungabusi Forest, Zimbabwe, and surrounding farmland highlights the contrast between protected and nonprotected landscapes.

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