The Earth and the Sun
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the authors performed this experiment in a mouse model of type 2 diabetes and show that beneficial changes in blood insulin and glucose concentrations arise when the diabetic mice, implanted with these engineered cells, are illuminated.

This study by Ye *et al*. shows that coupling an optogenetic driver to a downstream system can result in biologically meaningful changes. It also extends previous synthetic physiology results to use of such technologies in mammals in vivo with noninvasive stimulation (*8*). Relevant past work includes coupling a light sensor to transcription in bacteria (*9*), driving the heterodimerization of a DNA binding domain and a transcriptional activation domain by light to control gene expression (*10*, *11*), and using the G protein–coupled light-sensitive molecule rhodopsin to actuate potassium currents in neurons in response to light, thereby enabling optical neural silencing (*12*). Ye *et al*. demonstrate that one of the most difficult aspects of designing and implementing synthetic physiology is coupling the optogenetic tool to downstream signaling pathways. For example, using calcium to couple light reception by melanopsin to NFAT-driven transcription may result in unintended side effects of illumination, given the diverse cellular functions that calcium signaling controls. Clearly, synthetic physiology will need to devise more specific coupling strategies for connecting optogenetic tools to downstream synthetic biology processes.

The power of synthetic physiology approaches—leveraging the high speed and dynamic control of optogenetics and the computational power and biological richness of synthetic biology—may open up new applications, ranging from animal models of disease that are modulated by light, to personalized medicine applications in which cells from patients can be probed in vitro using causal tools to assess which pathways are involved in a given disease state. A tantalizing possibility also explored by Ye *et al*. is whether these tools may be useful as components of a new generation of prosthetics, allowing ultraprecise correction of dysfunctional biological processes. Assessing optogenetic methods in nonhuman primates may be of use in exploring such translational possibilities (*13*, *14*).

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PLANETARY SCIENCE

The Earth and the Sun

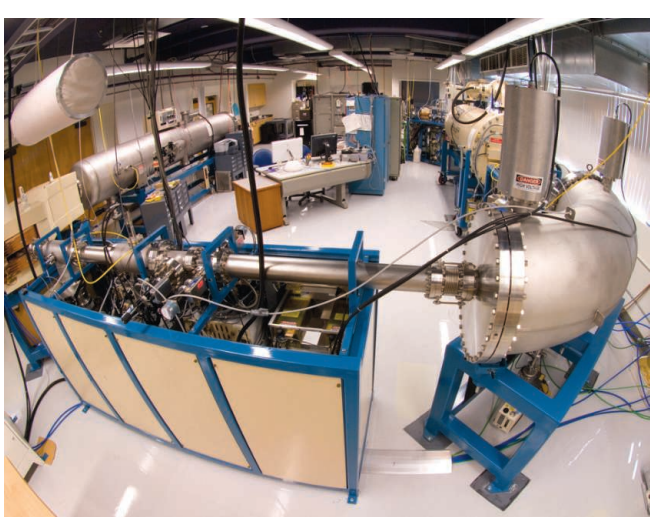
Sample collection by the Genesis spacecraft reveals the isotopic composition of elements in the solar system.

Robert N. Clayton

For more than 2 years, NASA's Genesis mission collected atoms of the solar wind (charged particles ejected from the Sun's atmosphere). Positioned at the Sun-Earth L1 Lagrange point about 1.5 million km from Earth, the spacecraft was well beyond the complicating effects of Earth's atmosphere and magnetic field, which hinder accurate ground-based astronomical measurements. The balance of gravitational forces at the Lagrange point allowed the spacecraft to maintain a fixed relationship to the Earth and the Sun with minimal expenditure of propellant. The highest priority of the mission was to determine the abundances of the stable isotopes of oxygen (^{16}O, ^{17}O, and ^{18}O) and nitrogen (^{14}N and ^{15}N) in the Sun and, by inference, in the whole solar system (*1*). However, on returning to Earth with its payload, the capsule suffered an unplanned hard landing in Utah in 2004, shattering most of the collector materials and thereby greatly complicating the initial sample analysis. After years of developing analytical techniques, McKeegan *et al*. and Marty *et al*., on pages 1528 and 1533 of this issue (*2*, *3*), reveal that these goals have now been accomplished.

Variations in stable isotope abundances have been studied in solar system samples (Earth, Moon, and meteorites), but interpreting this information has been thwarted by the lack of precise knowledge about the isotopic abundances of the initial material from which the elements evolved. It may be surprising that these initial isotopic abundances were not already known for such abundant elements (oxygen ranks third and nitrogen sixth in solar system abundance). Earlier attempts were made to use lunar surface minerals as collectors of the solar wind (metal grains for oxygen, oxide grains for nitrogen), but the results were ambiguous and lacked adequate precision.

The solar wind is very dilute. The small number of atoms implanted in the collector material presents an analytical challenge, as illustrated by mass spectrometer count rates of the key rare isotopes ($^{17}O^{2+}$ and $^{12}C^{15}N^-$) of only 10 to 40 ions per second. In addition, the relatively low velocity of solar wind ions



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From space to lab. The photograph shows the MegaSIMS facility at the University of California–Los Angeles used for oxygen isotope analysis of the Genesis samples (*2*, *3*). The initial sputtering source for oxygen ions is in the far background; the cream-colored cylindrical structure at right is the tandem accelerator; in the right foreground is the electrostatic sector of the double-focusing mass spectrometer; in the left foreground is the magnetic sector; the large silver-colored cylindrical structure at the left contains the ion detectors.

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leads to penetration depths on the order of only 100 nm, so that cleaning of the sample surface must be done with great care. A further hurdle was presented by the large amount of solar wind hydrogen that was implanted in the collector material. For oxygen, this problem was solved by passing the ion beam, accelerated to energies of 1 MeV, through an argon "stripper," to destroy hydride molecules, such as ^{16}OH (see the figure); for nitrogen, the problem was solved by the use of high-mass resolution to avoid interference by isobaric species.

The principal conclusion from the studies of McKeegan *et al*. and Marty *et al*. is that the Earth was not constructed from average solar system materials. Oxygen and nitrogen are major constituents of the Earth and must have been subjected to processes that alter their isotopic abundances. Although mass-dependent isotope fractionation of light elements, such as oxygen and nitrogen, is well known in terrestrial processes, such processes cannot be responsible for the observed variations: For oxygen, the ratios of $^{17}O/^{18}O$ are almost identical for the Earth and the Sun, whereas the abundance of the principal isotope, ^{16}O, is several percent smaller in the Earth than in the Sun; for nitrogen (with only two stable isotopes), the observed difference in $^{15}N/^{14}N$ ratio by a factor of almost 1.7 is far larger than any known mass-dependent isotope effect on Earth. It has been proposed that the large isotope effects in both elements are due to photolysis of their parent molecules (isoelectronic CO and N_2) in which the optical thickness of the abundant species ($^{12}C^{16}O$ and $^{14}N^{14}N$) greatly exceeds that of the rare species ($^{12}C^{17}O$, $^{12}C^{18}O$, and $^{14}N^{15}N$). This "self-shielding" process has been well studied in astronomical settings (*4*) and may have occurred in the early solar system.

Are there other elements that might exhibit similar behavior? Hydrogen, as H_2, might also show self-shielding isotope effects, but this process cannot be observed by an Earth-Sun comparison, because deuterium (^2H) in the Sun has been destroyed by nuclear reactions (*5*). The element carbon is a special case: Although it is a chemical partner with oxygen in the CO molecule, carbon has not shown any dramatically large isotopic variations. The absence of a large isotope effect in carbon can be understood in terms of the "isotopic scrambling" effect that occurs in the reaction $^{12}C^+ + {}^{13}C \rightarrow {}^{13}C^+ + {}^{12}C$, because carbon, unlike nitrogen and oxygen, has an ionization energy less than that of the abundant hydrogen (*6*).

The results of McKeegan *et al*. and Marty *et al*. from the Genesis mission have demonstrated, once again, that return of solar system samples for study in terrestrial laboratories produces vastly better data than remote analysis methods.

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MOLECULAR BIOLOGY

A New Twist for Topoisomerase

Topoisomerase 1 attacks on ribonucleotides in DNA leads to 2– to 5–base pair deletions.

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The worlds of RNA and DNA are not entirely separate. They frequently come together when RNA/DNA hybrids form during replication and transcription, which often induces genome instability (*1*–*3*). An enzyme called topoisomerase (Top) plays an important role in preventing RNA/DNA annealing during transcription (*1*). Another enzyme, ribonuclease H (RNase H), helps maintain genome integrity by removing RNA from hybrids (*2*, *3*). On page 1561 of this issue, Kim *et al*. (*4*) report that Top1, one of the two types of topoisomerase, not only prevents the formation of often deleterious hybrid structures called R-loops, but also participates in the removal of single ribonucleotides (rNMPs), which are incorporated during DNA replication and have escaped the repair system. Using yeast, Kim *et al*. also show that, when there is a rNMP at the site of Top1 cleavage, the enzyme can create irreversible breaks in the DNA strand, assaulting genome stability and perhaps contributing to disease.

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As RNA polymerases traverse DNA during transcription (producing RNA chains), distortions of the DNA can occur in front of and behind the polymerase (see the figure). The distortions cause torsion that compacts the DNA in front of the polymerase (creating a condition called positive supercoiling) and relaxes the DNA behind it (negative supercoiling) (*5*). Topoisomerases must perform molecular gymnastics to restore normal DNA topology (*6*). When Top1 is defective, nascent RNA can anneal to the underwound DNA and thus produce R-loops (see the figure). Similarly, R-loops can form when genes are transcribed at high rates (*1*), or if the proteins that normally interact with the nascent RNA are defective (*2*, *3*). In most cases, the formation of R-loops has deleterious consequences, because the displaced DNA strand is left susceptible to breakage, which leads to transcription-associated mutation (TAM) (*7*, *8*) or transcription-associated recombination (TAR) (*2*, *3*). But when Top1 fails, RNases H can come to the rescue and remove R-loops by cleaving the RNA strand of the R-loop and restoring the original double-stranded DNA (*1*–*3*).

There are two types of RNases H (H1 and H2), and both can process R-loops (see the figure) (*9*). *Escherichia coli* strains in which the genes encoding RNase H1 and Top1 are deleted are not viable. In *Saccharomyces cerevisiae*, *top1*Δ strains are viable when only one RNase H (either H1 or H2) is absent; in contrast, strains are unable to grow when all three enzymes (Top1, RNase H1, and RNase H2) are missing (*10*). RNases H and Top1 are not only linked through transcription and R-loop formation and removal; Kim *et al*. made the intriguing observation that the enzymes are also involved in processing rNMPs embedded in DNA, which are created by a recently described misincorporation error during replication (*11*).

The inclusion of rNMPs into DNA during replication is influenced by a number of factors. For example, DNA polymerase incorporation of ribonucleoside triphosphates (rNTPs) is affected by the high ratio of rNTPs to deoxynucleoside triphosphates (dNTPs) in vivo, the inherent preference of each DNA polymerase for dNTPs, and the system's ability to remove rNMPs once incorporated into DNA (*12*). In vitro experi-