

ticular, it was unclear whether “S₄” existed as a discrete chemical intermediate, or whether it might simply represent a transition state containing S₃ with an oxidized tyrosine (S₃Y_Z^{ox}). The latter would imply an intimate role for Y_Z^{ox} in water oxidation, perhaps through hydrogen-atom transfer (9). In contrast, if S₄ exists as a discrete intermediate, then a range of mechanisms for the terminal reaction preceding oxygen formation are possible. A subtle delay in oxygen release relative to Y_Z^{ox} reduction (10, 11) hinted that S₄ might exist as a discrete intermediate rather than simply being a transition state between S₃ and S₀. This conclusion was strengthened by a recent experiment showing that if one increases the partial pressure of oxygen on photosystem II, water oxidation is blocked at S₃. This suggests that increasing oxygen concentration shifts the equilibrium from S₄ + oxygen to S₃ (12).

Haumann *et al.* (1) used a conceptually straightforward but experimentally challenging “pump-probe” time-resolved x-ray spectroscopy experiment to obtain direct structural evidence for an S₄ state. To appreciate the difficulty of this approach, it is important to remember that even “simple” static x-ray absorption spectroscopy of photosystem II is challenging because of the intrinsically low Mn concentration. The present measurements would have been impossible without the high-brightness third-generation synchrotron sources that provide higher x-ray flux. Kinetic traces (1) show clearly that the S₁→S₂ and S₂→S₃ steps have very similar transient behavior, although the latter is somewhat slower. This finding is important because of the continuing controversy over whether Mn has been oxidized during the S₂→S₃ transition (13). The Haumann *et al.* data provide further support for the growing consensus that Mn is oxidized during both the S₁→S₂ and S₂→S₃ transitions. In contrast, the kinetic transient for the S₃→S₀ transition is distinct, with a 250-μs lag phase followed by a slow 1.1-ms transient phase. The latter phase is of opposite sign, representing Mn reduction to the S₀ state, and corresponds to the observed rate of oxygen release and reduction of Y_Z^{ox}. The former, more rapid phase provides direct evidence for the existence of a discrete S₄ intermediate state.

The lag phase indicates that the S₃ and S₄ states have similar x-ray absorption spectra and rules out several possible mechanisms for oxygen evolution. There has been widespread speculation that water oxidation might use a manganyl (Mn=O) species as the oxidant (9). This possibility was recently ruled out for S₃ (14). The present work by Haumann *et al.* extends this exclu-

sion to S₄ because neither the S₃ nor S₄ state shows an intense transition on the low-energy side of the x-ray absorption “edge” (this is the abrupt increase in x-ray absorption cross section that occurs when the x-ray energy matches the binding energy of the Mn 1s electron). Such “pre-edge” transitions are the spectroscopic signature of manganyl species (14). Alternatively, the high-pressure oxygen studies (12) were interpreted in terms of an S₂ state with an associated H₂O₂ molecule for “S₄.” This too is now excluded, because the Mn would be reduced in this state, relative to the previous S₃ state.

Haumann *et al.* (1) favor a model in which “S₄” contains S₃Y_Z^{ox}. That is, the fourth oxidizing equivalent in the water oxidation cycle resides on the tyrosine cofactor. On the basis of the positive reaction entropy and the equilibrium isotope effect for S₄ formation, they suggest that the 250-μs lag phase represents the lifetime for proton release from an intermediate chemical species bound to the oxygen-evolving complex. Tests of this and more detailed mechanistic studies will await future experiments. For now, the availability of the intense x-ray beams available at third-generation synchrotron sources has permitted the detec-

tion of a new intermediate in the water oxidation reaction. With this demonstration of feasibility, a wide range of other applications of microsecond time-resolved x-ray absorption spectroscopy to chemically and biologically important reactions can now be imagined.

References

1. M. Haumann *et al.*, *Science* **310**, 1019 (2005).
2. J. Barber, K. Ferreira, K. Maghlaoui, S. Iwata, *Phys. Chem. Chem. Phys.* **6**, 4737 (2004).
3. J. Biesiadka, B. Loll, J. Kern, K. D. Irrgang, A. Zouni, *Phys. Chem. Chem. Phys.* **6**, 4733 (2004).
4. N. Kamiya, J. R. Shen, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 98 (2003).
5. D. W. J. Cruickshank, *Acta Crystallogr. D* **55**, 583 (1999).
6. J. Yano *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 12047 (2005).
7. P. Joliot, G. Barbieri, R. Chabaud, *Photochem. Photobiol.* **10**, 309 (1969).
8. B. Kok, B. Forbush, M. McGloin, *Photochem. Photobiol.* **11**, 457 (1970).
9. C. W. Hoganson, G. T. Babcock, *Science* **277**, 1953 (1997).
10. M. R. Razeghifard, R. J. Pace, *Biochemistry* **38**, 1252 (1999).
11. F. Rappaport, M. Blancharddesce, J. Lavergne, *Biochim. Biophys. Acta* **1184**, 178 (1994).
12. J. Clausen, W. Junge, *Nature* **430**, 480 (2004).
13. J. Messinger *et al.*, *J. Am. Chem. Soc.* **123**, 7804 (2001).
14. T. C. Weng *et al.*, *J. Am. Chem. Soc.* **126**, 8070 (2004).

10.1126/science.1120919

PLANETARY SCIENCE

What Do We Need to Know to Land on the Moon Again?

Maria T. Zuber and Ian Garrick-Bethell

In July 1969, the Apollo 11 lunar excursion module *Eagle* descended toward the Sea of Tranquility with Neil Armstrong in command. At 300 m above the lunar surface, short on fuel and looking for a smooth area on which to land, Armstrong “did not like what he saw. A crater as big as a football field was just ahead, surrounded by a field of boulders, some as big as Volkswagens” (1). Despite the obstacles, *Eagle* touched down safely, delivering the first human beings to the surface of the Moon in one of humankind’s greatest technological achievements. As the United States and other nations actively plan to return to the Moon, a renewed discussion of the scientific knowledge of the lunar surface that is needed for future landings is appropriate.

Enhanced online at
www.sciencemag.org/cgi/content/full/310/5750/983

Of the dramatic and successful Apollo 11 landing, one thing can be said with certainty: We won’t do it like that again. Starting with the Ranger 7 spacecraft and continuing with the Lunar Orbiters, images were used to characterize potential lunar landing sites by accumulating statistics of small-scale surface slopes and roughness. Most landings occurred in the maria, relatively smooth volcanic plains marred by small craters surrounded by rougher ejecta blankets and blocks. Two Apollo missions, 14 and 16, landed in non-mare (highland) regions, thanks to the skill of astronauts in manually piloting the lunar modules to locations safe enough for landing. But in today’s risk-averse climate, the Apollo-era knowledge of the lunar surface—and, arguably, even our present knowledge—would not meet expectations with respect to safety. Future landings on the Moon, whether human or robotic, will demand a greater scientific knowledge of the lunar surface. In the selection of a landing site, two factors are relevant: landing safety and

The authors are in the Department of Earth, Atmospheric and Planetary Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. E-mail: zuber@mit.edu; iang@mit.edu

fulfillment of mission objectives. Examples of the latter include in situ scientific hypothesis testing and resource assessment.

In the coming era of lunar exploration, a sensible and readily achievable modus operandi would be that future candidate landing sites undergo a level of scrutiny similar to that of the recent landed missions on Mars. The process to select the Pathfinder and Mars Exploration Rover landing sites (2, 3) represents an extraordinarily successful example of how scientific information was used to make informed engineering decisions that in turn enabled scientific discovery. Whether the goal of a landed mission is driven by exploration or science (leaving aside esoteric debate concerning the difference between the two),

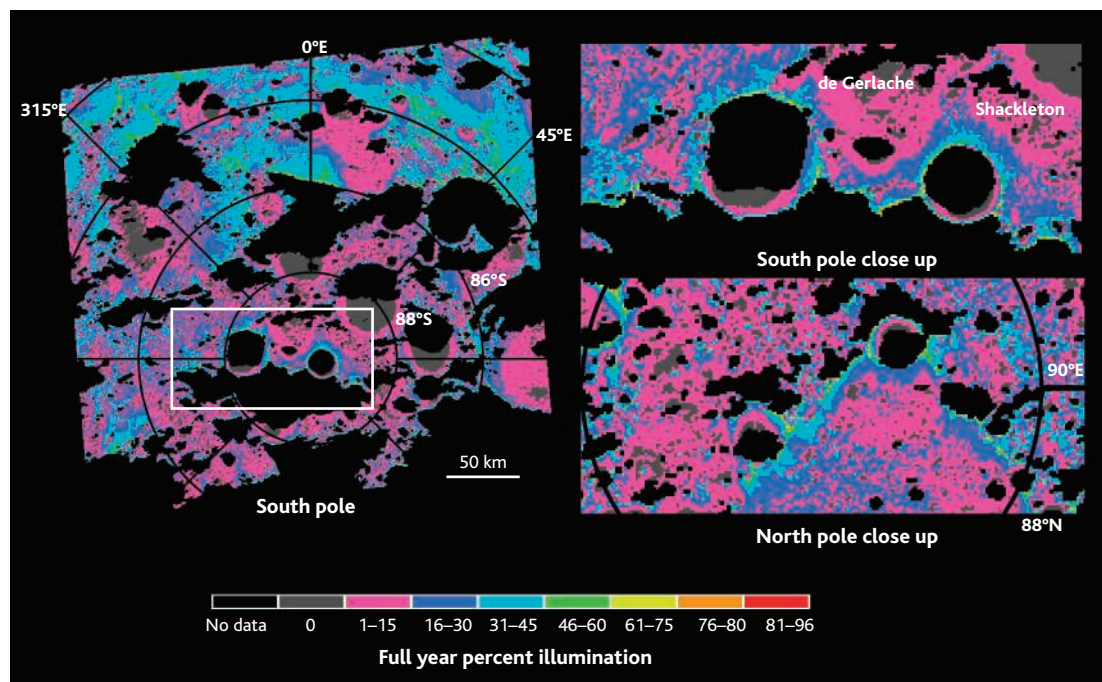
resolution imaging at visible and thermal infrared wavelengths (5). These observations, coregistered with compositional information from orbital spectral sensors, led to the selection of the Meridiani Planum site that provided evidence of a water-rich past on Mars (6).

If we apply criteria used for landing site assessment at Mars to the Moon, our required knowledge is “not there yet” on a global basis. A primary order of business is being able to land precisely where one wants to go, which requires an accurate latitude-longitude grid referenced to the planetary center of mass. On the Moon, positional knowledge varies considerably with location. On the near side, limited locations are known relative to each other to within

quality of the lunar geodetic grid would, for example, challenge our ability to explore the most topographically complex and scientifically important target on the far side: the South Pole–Aitken Basin, 2500 km in diameter and 8 km deep, a potential treasure trove for studying the internal composition of the Moon (12).

A key near-term goal of lunar exploration is resource assessment, in particular the definitive identification of water ice in permanently shadowed craters near the poles (13). Any long-duration mission in the vicinity of permanently shadowed craters would want to avail itself of another valuable resource: near-continuous sunlight that could satisfy power requirements (14). Unfortunately, topography of the quality

needed to unambiguously determine constant darkness or illumination at all near-polar areas does not currently exist. As a case in point, the figure shows a full lunar year illumination cycle at both poles, using topography derived from Earth-based radar observations (15). The majority of south polar terrain is illuminated less than 50% of the time, although near two crater rims at the pole there is 4.7 km² of noncontiguous area illuminated more than 85% of the time, with a subset of this terrain receiving continuous light for more than 200 days per Earth year. In the north, however, there is only 1.1 km² of surface with more than 85% illumination, a discrepancy with illumination estimates obtained from Clementine spacecraft images collected



Potential landing sites. (Left panel) Full lunar year illumination cycle at the south pole, calculated over 12 lunations (each 29.5 days) in 1994, from 10 January to 31 December, sampled every 4 hours. **(Top right)** Close-up of south polar region, with crater rims of de Gerlache and Shackleton dominating the highly illuminated terrain. **(Bottom right)** Same calculation for the north pole. Relative to the south pole, similar amounts of terrain are illuminated in the 1% to 60% range, but less area is found with higher illumination values.

the areas of greatest interest on the Moon will in general be more difficult to access and traverse than were the Apollo sites. In terms of scientific knowledge, a safe landing will require accurate characterization of local slopes on baselines of tens to hundreds of meters, and information about roughness on the scale of meters to decimeters (4). In addition, knowledge of soil properties combined with rock abundance and size distribution data will be required to assess “trafficability” of robotic rovers or human transport vehicles. On Mars, this knowledge has been achieved by careful analysis of candidate landing sites, using a combination of precise altimetry and high-

meters horizontally and to within centimeters radially, thanks to precise positioning provided by laser ranging to retroreflectors at Apollo sites and Soviet landers (7). But globally, absolute positions are known to no better than a few kilometers horizontally and 100 m radially (8). Positional knowledge on the far side is less well known than anywhere else on the Moon, in large part because of the poor quality of our knowledge of the lunar gravity field (9). In contrast, positions on Mars are known on a global basis to 100 m horizontally and 1 m radially (10). Without such knowledge on the Moon, precision landing is more complicated (11) and therefore riskier. The poor

quality of the lunar geodetic grid would, for example, challenge our ability to explore the most topographically complex and scientifically important target on the far side: the South Pole–Aitken Basin, 2500 km in diameter and 8 km deep, a potential treasure trove for studying the internal composition of the Moon (12).

Fortunately, help is on the way. Current and upcoming orbiters, notably ESA’s Small Missions for Advanced Research in Technology (SMART-1, now in orbit), along with Japan’s SELENE (2006), China’s Chang’e 1 (2007), India’s Chandrayaan-1 (2007), and NASA’s Lunar Reconnaissance

Orbiter (2008), carry diverse payloads that will ensure that the fundamental geophysical, geological, and geochemical data needed to make informed decisions about where to land on the Moon will be available within the current decade. In the nearly 40 years since the Apollo 11 landing enthralled and inspired humankind, scientific information gained in the interim can guide and inform future missions, contributing to a rich and sustained program of lunar discovery.

References and Notes

1. A. Chaikin, *A Man on the Moon* (Penguin, New York, 1994), p. 196.
2. M. P. Golombek, R. A. Cook, H. J. Moore, T. J. Parker, *J. Geophys. Res.* **102**, 3967 (1997).
3. M. P. Golombek *et al.*, *J. Geophys. Res.* **108**, 10.1029/2003JE002074 (2003).
4. Of course, knowledge of the lunar surface needs to be coupled with the engineering capability of precision navigation, descent, and landing.
5. The Mars Exploration Program Landing Sites website (<http://marsweb.nas.nasa.gov/landingsites>) is an outstanding resource that allows users to cross-register and analyze data sets relevant to assessing landing sites on Mars.
6. S. W. Squyres *et al.*, *Science* **306**, 1709 (2004).
7. J. O. Dickey *et al.*, *Science* **265**, 482 (1994).
8. D. E. Smith, M. T. Zuber, G. A. Neumann, F. G. Lemoine, *J. Geophys. Res.* **102**, 1591 (1997).
9. A. S. Konopliv, S. W. Asmar, E. Carranza, W. L. Sjogren, D.-N. Yuan, *Icarus* **150**, 1 (2001).
10. D. E. Smith *et al.*, *J. Geophys. Res.* **106**, 23689 (2001).
11. Mission Evaluation Team, *Tech. Rep. NASA TM-X-74200, MSC-01855* (NASA Manned Spacecraft Center, Houston, TX, 1970).
12. C. M. Pieters, S. Tompkins, J. W. Head, P. C. Hess, *Geophys. Res. Lett.* **24**, 1903 (1997).
13. Radar observations of the lunar polar regions yield conflicting interpretations regarding the presence of high-backscatter regions that could be indicative of water ice (17, 18). Neutron spectroscopy from Lunar Prospector (19) shows the presence of hydrogen in both near-polar craters and various other parts of the Moon, and could correspond to either water or hydrogen nuclei implanted by the solar wind (20).
14. Because the Moon's spin axis is tilted only 1.5°, high elevation points at the poles may be illuminated year-round.
15. J. L. Margot, D. B. Campbell, R. F. Jurgens, M. A. Slade, *Science* **284**, 1658 (1999).
16. B. J. Bussey, K. E. Fristad, P. M. Schenk, M. S. Robinson, P. D. Spudis, *Nature* **434**, 842 (2005).
17. S. Nozette *et al.*, *Science* **274**, 1495 (1996).
18. R. Simpson, G. L. Tyler, *J. Geophys. Res.* **104**, 3845 (1999).
19. W. C. Feldman *et al.*, *Science* **281**, 1496 (1998).
20. R. R. Vondrak, D. H. Crider, *Am. Sci.* **91**, 322 (2003).

10.1126/science.1115126

BIOMEDICINE

Separation of Conjoined Hormones Yields Appetite Rivals

Ruben Nogueiras and Matthias Tschöp

When we refer to our “gut feelings,” not many of us actually visualize how the gastrointestinal tract spills myriads of small peptide hormones into our bloodstream to activate defined circuits of the central nervous system. Nevertheless, that picture does reflect a current scientific concept called the “gut-brain axis.” This model consists of a complex network of hormonal and neuronal signaling pathways that is believed to balance numerous homeostatic and behavioral processes (1, 2). In this context, our stomach does not just collect, process, and transport ingested food, but it also represents a multileveled conversational partner of the central nervous system. A key element of this communication process is the hunger-inducing hormone ghrelin, which is believed to convey information about nutrient availability from the stomach to the brain (3, 4).

Zhang and colleagues (5) now report on page 996 of this issue that ghrelin not only has a sibling derived from the same peptide precursor (preproghrelin), but also that this new ghrelin-associated peptide behaves as a physiological opponent of ghrelin. Guided by bioinformatics-based predictions for typical enzymatic cleavage sites, they identified a 23-amino acid region of

preproghrelin that is highly conserved across species, suggesting a relevant biological function. The authors purified a secreted peptide of the predicted size and sequence from rat stomach tissue and also detected it in rat blood. Similar to ghrelin, which requires posttranslational modification close to its amino terminus by acylation (6), the biological activity of the ghrelin-associated peptide also depends on modification, but by much more common amidation at its carboxyl terminus.

The surprising finding is the pharmacological effects of the newly identified peptide in comparison with the known actions of ghrelin. Whereas ghrelin increases food intake and body weight (7), the ghrelin-associated peptide decreases food intake and body weight gain in rodents. Moreover,

Zhang *et al.* observed that the new peptide decelerates gastric emptying and decreases intestinal contractility in mice, both of which counteract the well-defined effects of ghrelin (8). Through a targeted screen of mammalian orphan receptors and subsequent analyses in cultured mammalian cells, Zhang *et al.* show that the ghrelin-associated peptide binds to and activates the orphan receptor GPR39 (9). This G protein-coupled receptor has been mapped to human chromosome 2 and is expressed in multiple tissues, including the stomach, intestine, and hypothalamus. This localization is consistent with a role in energy balance regulation (10). GPR39 is a member of a family that includes the receptors for ghrelin and motilin, another gastrointestinal hormone that stimulates food intake, gastric emptying, and gut motility (9, 11). These facts support a somewhat counterintuitive, but nevertheless intriguing, relationship between ghrelin and the ghrelin-associated peptide.

To denote its anorexigenic actions, Zhang and colleagues named this new gastric hormone obestatin (from the Latin term *obedere*, meaning to “devour”).

THE GHRELIN-MOTILIN RECEPTOR FAMILY MODULATES APPETITE AND GASTROINTESTINAL MOTILITY

Ligands	Receptors	Food intake	Gastric emptying
Motilin	Motilin-R (GPR38)	↑	↑
Neuromedin U	Neuromedin-R1 (GPR66), -R2	↓	↓
Neurotensin	Neurotensin-R1, -R2, -R3	↓	↓
Ghrelin	GHS-R	↑	↑
Obestatin	GPR39	↓	↓

The ghrelin-motilin receptor family and their ligands. Each of these gastrointestinal hormones acts on a specific G protein-coupled receptor from the same family to affect food intake and gastrointestinal motility (9–11). Similar dual effects on satiety and gastrointestinal motility are known for glucagon-like peptide 1, cholecystokinin, or peptide YY. Collectively, these peptides may serve to couple meal termination with inhibition of upper gastrointestinal function to prevent malabsorption and postprandial metabolic disturbances (1, 2, 8).

The authors are in the Department of Psychiatry, University of Cincinnati, Cincinnati, OH 45237, USA, and the Department of Pharmacology, German Institute of Human Nutrition, 14558 Nuthetal, Germany. E-mail: tschoemh@ucmail.uc.edu