SURFACE CHEMISTRY

Direct evidence of acid-base interactions in gecko adhesion

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While it is generally accepted that van der Waals (vdW) forces govern gecko adhesion, several studies indicate contributions from non-vdW forces and highlight the importance of understanding the adhesive contact interface. Previous work hypothesized that the surface of gecko setae is hydrophobic, with nonpolar lipid tails exposed on the surface. However, direct experimental evidence supporting this hypothesis and its implications on the adhesion mechanism is lacking. Here, we investigate the sapphire-setae contact interface using interface-sensitive spectroscopy and provide direct evidence of the involvement of acid-base interactions between polar lipid head groups exposed on the setal surface and sapphire. During detachment, a layer of unbound lipids is left as a footprint due to cohesive failure within the lipid layer, which, in turn, reduces wear to setae during high stress sliding. The absence of this lipid layer enhances adhesion, despite a small setal-substrate contact area. Our results show that gecko adhesion is not exclusively a vdW-based, residue-free system.

INTRODUCTION

The ability of geckos to effortlessly run up and down a vertical wall using their sticky toe pads has garnered considerable attention in the past two decades from biologists interested in the basic understanding of the adhesive system to material scientists interested in developing new synthetic adhesives (1–17). The microstructure of these adhesive toe pads, specifically for one gecko species (Gekko gecko), consists of millions of tiny hair-like structures called setae, which further split at the tip into 200-nm-wide and 5-nm-thick nanostructures referred to as spatulae (1, 8, 13, 18, 19). These nanostructures come into intimate contact with the substrate upon application of a small perpendicular preload and a few micrometers of parallel drag (1). This intimate contact between spatulae and the substrate generates adhesive forces that surpass many times the weight of the gecko (5, 13, 14, 20, 21).

Seminal work by Autumn et al. (1, 2) in the early 2000s suggested that van der Waals (vdW) forces (also known as dispersive forces that arise from instantaneous distortions in the electron cloud) govern gecko adhesion. However, several studies have called into question the relative importance of vdW and non-vdW forces in gecko adhesion (3, 4, 7, 12, 17, 22). First, early studies showed that gecko adhesion to hydroxylated surfaces such as glass and alumina was particularly high, which cannot be explained solely by vdW forces because vdW forces are insensitive to surface chemistry. Lower setal adhesion to a silicon wafer coated with a hydrophobic coating compared to a bare silicon wafer further corroborates these results and suggests that forces other than, or in addition to, vdW interactions may contribute to gecko adhesion (4, 15). Second, gecko adhesion enhances with increasing humidity at the setal and whole-animal level, implying that capillary forces also play a role in gecko adhesion in humid environments (3, 4, 7). Recent studies show that setal material softening and the resulting increase in viscoelastic dampening with increasing humidity may dominate the adhesion response to humidity, but capillary forces could play a role in certain circumstances (10, 23, 24). Third, the adsorption energy of glycine and cysteine molecules [representative amino acids in corneous beta proteins (CBPs) formerly known as β-keratin, the primary constituent of gecko setae (25–30)] calculated using density functional theory (DFT) highlighted that vdW interactions contribute weakly to the overall interaction energy (17). However, glycine and cysteine molecules may not accurately capture the complex setal surface structure and setal-substrate interactions (e.g., the adhesive interface may contain other chemical constituents). Although the abovementioned studies highlight the possibility that geckos may use non-vdW interactions along with universal vdW interactions, direct molecular-level evidence of a non–vdW-based adhesive mechanism remains elusive.

To decipher the type of interactions involved in gecko adhesion, it is important to determine which functionalities are exposed on the setal surface and thereby at the adhesive interface. Previous literature suggests that gecko setae are complex ensembles of cysteine-rich and serine-tyrosine-rich CBPs and a mixture of covalently (bound) and noncovalently (unbound) bonded lipids (25–32). It is clear that unbound lipids make contact with the substrate and are left as a footprint, as revealed by mass spectrometry and surface-sensitive sum frequency generation spectroscopy (SFG) (31). However, the orientation of these lipids (i.e., headgroups or tails) at the setal surface remains unclear. For instance, the superhydrophobicity of the adhesive gecko toe pad and SFG peaks corresponding to lipid molecules at the contact interface led Hsu et al. to conclude that nonpolar tails of unbound lipids were exposed at the setal surface (8, 15, 31, 33). However, the water contact angle of gecko setae does not change even after delipidization (chemical treatment to remove unbound lipids), which raises questions about the orientation of the unbound lipids (15). Orientation of unbound lipids on the setal surface is important because if headgroups are exposed on the setal surface, the setae could interact with substrates using hydrogen bonding, capillary forces, and electrostatic forces, in addition to vdW forces. Thus, identifying whether headgroups or tails are exposed at the setal surface can help resolve the debate on the involvement of non-vdW forces in gecko adhesion.
The primary goal of this study is to investigate the adhesive contact interface of gecko setae with the substrate, and to resolve questions about the exclusivity of vdW forces in governing gecko adhesion. Here, we use interface-sensitive SFG, a second-order nonlinear optical technique, to examine the contact interface between gecko setae and a hydroxylated sapphire (one of the crystal forms of alumina) substrate (31, 34). We specifically take advantage of the presence of hydroxyl (OH) groups on the surface of sapphire and the innate peak shift of sapphire OH groups in response to the nature and strength of intermolecular interactions between sapphire OHs and the material (gecko setae in this case) in contact (35–40). If solely vdW interactions govern gecko adhesion, we would expect the sapphire peak originally at 3710 cm$^{-1}$ (in air) to shift by only 20 to 30 cm$^{-1}$ (36, 38, 39). However, a much higher peak shift would signify the presence of acid-base interactions, a broad term encompassing hydrogen bonding, electron pair donor-acceptor, electrophile-nucleophile, and other polar interactions (41, 42). Acid-base interactions have both electrostatic and covalent bonding characteristics, and the relative ratio of these depends on properties of the two interacting materials (43). By probing the contact with SFG, we plan to determine the nature of interactions (vdW/non-vdW) between gecko setae and hydroxylated surfaces (e.g., glass and alumina). Further, by comparing the shift of sapphire OH groups for gecko setae with model lipid molecules, we will clarify the presence or absence of tails or headgroups at the setal surface and the contact interface.

In addition to investigating the adhesive contact interface of gecko setae and the role of vdW forces in gecko adhesion, our secondary goal is to explore the role of unbound lipids in gecko adhesion. Strong adhesion of geckos to hydroxylated surfaces such as glass and alumina could result in considerable damage to the setae; however, no microscopic images have ever shown signs of wear in gecko setae. The only wear is in the form of a lipid footprint left behind on a surface a gecko clings to or walks on (31). By examining the contact interface before and after detachment using SFG and measuring adhesion forces of pristine and delipidized gecko setae, we explore the role unbound lipids may play in preventing large-scale wear (beyond wear in the form of a lipid footprint) and damage to gecko setae during detachment. This work provides a direct answer to two questions that have not been easy to address in the past two decades: (i) Are there non-vdW interactions at the interface that may contribute to gecko adhesion? and (ii) How does the removal of unbound lipids affect gecko adhesion? The results of this study will expand our understanding of the gecko adhesion mechanism and provide more refined, surface-specific design parameters for designing synthetic gecko-inspired adhesives that adhere more strongly and avoid damage.

RESULTS
We investigated the sapphire-setae contact interface of pristine (with unbound lipids) and delipidized (without unbound lipids) gecko setae using SFG (Fig. 1). First, a blank scan was collected to characterize the sapphire-air interface (i.e., locate the position of the sapphire surface OH peak) and to ensure that the surface was clean (Fig. 1A). Second, gecko setae were preloaded and sheared across the sapphire substrate to engage the adhesive mechanism and induce adhesive contact with the sapphire substrate (Fig. 1B). After the in-contact scan was collected, a final scan was collected after the gecko setae were separated from the sapphire (Fig. 1C).

For pristine gecko setae, the contact interface spectrum in PPP polarization (i.e., P-polarized SFG, P-polarized visible, and P-polarized IR) is dominated by methylene and methyl groups and interacting sapphire OH groups (Fig. 2). Specifically, the signatures observed in the hydrocarbon C-H vibration region (2750 to 3100 cm$^{-1}$, green shaded region) include methylene symmetric (2860 cm$^{-1}$), methyl symmetric (2880 cm$^{-1}$), methyl asymmetric (2925 cm$^{-1}$), and methyl asymmetric (2965 cm$^{-1}$) stretch vibrations, attributed to the tails of phospholipids and other unbound lipids present in gecko setae (31). Similar methyl and methylene signatures are observed in the SSP (i.e., S-polarized SFG, S-polarized visible, and P-polarized IR) spectrum (fig. S1). These hydrocarbon signatures are not observed in the sapphire-air interface SFG spectrum (Fig. 2, red curve), showing that they must be from the gecko setae. The sapphire-air interface SFG spectrum does show a sharp peak at 3710 cm$^{-1}$ in the O-H vibration region (3100 to 3800 cm$^{-1}$, orange shaded region), attributed to the free sapphire OH groups (36, 38, 39). With the gecko setae in contact, the sapphire OH peak becomes broad and shifts to lower wave numbers (∼3600 cm$^{-1}$). This large shift can only be due to acid-base interactions between sapphire OHs and the unbound lipid groups exposed on the surface of gecko setae because vdW interactions shift the sapphire OH peak by only 20 to 30 cm$^{-1}$.

![Fig. 1. Experimental geometry to probe the sapphire-setae contact interface.](http://advances.sciencemag.org/)
pristine gecko setae, the sapphire OH peak shifts by 105 ± 16 cm\(^{-1}\). Delipidized gecko setae demonstrate stronger adhesive forces than pristine setae (Fig. 3B; 64.19 ± 6.70 N/cm\(^2\) vs 34.24 ± 11.42 N/cm\(^2\)) when separating gecko setae from Teflon 12 or 12, as noted by Alibardi et al. (15). However, the observed high-frequency shift (105 ± 16 cm\(^{-1}\)) indicates that the surface of contacting setal tips (i.e., spatulae) must be covered with unbound lipids exposing polar headgroups, instead of the nonpolar tails. This arrangement of unbound lipids on the setal surface inferred from our SFG results is not contradictory to the previously observed high water contact angles on the toe pad, as recent work by Stark et al. (15) demonstrated that superhydrophobicity is a consequence of the hierarchical structure of the toe pad rather than the presence or absence of lipids. Moreover, this lipid arrangement is similar to the arrangement of lipids in mammalian stratum corneum (45, 46).

Exposed headgroups at the setal surface have implications for setal-substrate interactions and thus the adhesive mechanism of geckos. The lipid headgroups, including phosphocholine, phosphophylethanolamine, and carboxyl acid, have the ability to form acid-base interactions with sapphire surface OHs (36, 39, 40) and thus could explain the exceptionally strong adhesion of geckos to clean hydroxylated surfaces (glass and sapphire), contrary to expectations based solely on vdW forces (1, 2, 7, 13, 47, 48). Because strong correlations exist between a material’s acid-base properties and its ability to develop charges (49–51), the observation of acid-base interactions in the SFG spectra could also help explain the charges observed by Izadi et al. (12) when separating gecko setae from Teflon and polydimethylsiloxane substrates. Upon contact electrification, Lewis bases (or electron donors) tend to become positively charged, while Lewis acids (or electron acceptors) tend to become negatively charged, although the exact charging mechanism remains unclear (49–51). In our study, the sapphire surface acts as a Lewis acid; thus, we would expect it to acquire a negative charge that could result in electrostatic interactions with positively charged setae [proposed by Alibardi et al. (28, 29) based on the presence of positively charged CBPs in gecko setae], resulting in appreciably enhanced adhesion, consistent with observed forces. The exposed polar headgroups could also promote the absorption of water molecules on the setal surface, thereby supporting the capillary forces observed in adhesion experiments at setal and whole-animal levels (3, 4, 7, 24). Geckos likely take advantage of multiple forces (vdW, acid-base, and capillary) to successfully adhere to a multitude of substrates in their natural habitats. Weak vdW forces are universal and present at any setal-substrate interface, while strong non-vdWs are more specific to the nature of substrate. vdW forces may be more relevant for gecko adhesion to hydrophobic leaves and trees. In contrast, nondispersion forces may be more relevant for adhesion to natural rocks and mammade hydroxylated surfaces such as glass.

Despite strong adhesion to glass, the interfacial contact of delipidized setae probed by SFG (i.e., sapphire-delipidized setae contact interface) does not detect a signal from functional groups on the surface of delipidized gecko setae and appears similar to the sapphire-air spectrum. This result has two key implications. First, the SFG signal observed from the sapphire-pristine setae interface must be
from unbound lipids. Second, the contact area of delipidized setae must be extremely small. To estimate the contact area of delipidized setae pressed and sheared into contact with the sapphire substrate, we model the contact interface with two regions. In the first region, there is direct contact between the setae and the sapphire surface OH groups, which would result in a frequency shift of sapphire free OH peak to ∼3600 cm⁻¹ (assuming similar frequency shifts of sapphire OH in contact with pristine and delipidized setae). In the second region, air is in contact with the sapphire surface OH groups, which would result in the free OH peak at ∼3710 cm⁻¹. Because the total number of sapphire OHs is fixed, a change in the relative amplitudes of 3600- and 3710-cm⁻¹ peaks can provide information on the percentage of OH groups making contact with the delipidized setae, as shown by Singla et al. (38) with binary liquid mixtures. Using their method, only 2 to 7% of the total sapphire area is in contact with the delipidized setae (see Supplementary Text for details) (38). It is remarkable that such a small area of contact can result in a shear adhesion of over 60 to 70 N/cm². Using the measured shear adhesion force for a single seta reported by Autumn et al. (∼200 μN) and estimated setal density of 19,822 ± 490 per mm² (1, 52), we estimate that ∼15 to 18% of the total sapphire substrate contact area would result in gecko setal shear adhesion of 60 to 70 N/cm², a value similar to the conclusions derived from the SFG experiments (i.e., very small interfacial contact area). Our SFG results are also consistent with nonuniform stress distributions in the gecko toe pad between and within lamellae observed by Eason et al. (44), highlighting the idea that not all setae are actively used for adhesion.

If the true setal area (estimated from the delipidized setal contact spectrum) is so small, it is puzzling why pristine gecko setae display strong methylene and methyl unbound lipid signatures and a frequency shift in the sapphire free OH peak. One reason for this attribute may be related to the process of engaging gecko setae with the sapphire surface (i.e., the load-drag pathway; Fig. 1). Specifically, the cohesive failure within the bulk of the unbound lipid layer allows lipids to spread over a much larger area than the actual contact area. The process is analogous to a paint brush (gecko setae) dipped in paint, leaving paint marks (unbound lipids) behind as it is dragged across the surface. This hypothesis is consistent with the observed similarities in the SFG spectra of pristine gecko setae in contact and after separation (i.e., the paint or footprint left behind).

Using our previous analysis, we can estimate how much surface area is covered by unbound lipids during contact and after separation of pristine setae (38). This analysis suggests that ∼98% of the total contact area is covered by unbound lipids during contact and after surfaces are pulled apart. However, this number does not represent the true area of contact for pristine gecko setae, which is difficult to ascertain in the present work because of the process used for engaging setae. In contrast, negligible residue is left behind after delipidized gecko setae are removed from the substrate, despite their strong adhesion relative to pristine gecko setae. We postulate that having this cohesively weak lipid layer on the gecko setal surface results in cohesive failure within this layer, rather than adhesive failure, and, in turn, reduces the probability of damage to gecko setae as a result of high shear forces. The only wear that occurs is in the form of lipid footprints. The continual maintenance of lipid footprints during multiple adhesive events continues to remain unknown and requires further investigation. One possible explanation could be that the small real contact area (2 to 7%) allows the lipid layer to last longer than that expected for a complete contact. The strategy of using lipids as a sacrificial layer allows geckos to use their setae quickly and repeatedly for a period of a few months before they are replaced with a new set of setae during their natural skin-shedding cycle. This strategy is not limited to geckos; several insects use lipid secretions for quick and easy detachment (53–55).

Using our spectroscopy results, we can build on the previous gecko setal lipid arrangement model proposed by Jain et al. (32) to provide further insights into the organization of lipids on the setal surface. To do so, we use the lipid organization in mammalian stratum corneum to predict the lipid organization in gecko (i.e., reptile) skin, which is not as well known (45, 46). Our proposed lipid arrangement based on the previous model by Jain et al., lipid arrangement in stratum corneum, and our SFG results is shown in Fig. 4 (32, 45, 46). In this model, the CBP-based setae are covered with a...
In this model, the lipids (mixture of bound and unbound lipids; purple) are present as patches in the bulk CBP (formerly known as β-keratin; yellow)-based setae and as a thin coating (unbounding lipids; orange) on the surface of setae. The unbound lipid layer comes in contact with the substrate and is left behind as a footprint (31). The arrangement of unbound lipid layer on the surface of setae is mediated by a monolayer of bound lipids (green). (Right) Sketch of the proposed arrangement of lipids on the pristine and delipidized setal surface derived from our SFG results and lipid arrangement reported in mammalian stratum corneum (45, 46).

monolayer of bound lipids similar to the cornified lipid envelope in mammalian stratum corneum, which is typically formed by transesterification reaction of ω-OH fatty acids, ceramides, and glucosyl-ceramides with glutamate residues of corneocyte proteins (56–58). This monomolecular layer of bound lipids exposes polar headgroups on the periphery and coordinates the multilamellar arrangement of unbound lipids, which again exposes polar headgroups. Both the number of unbound lipid and the lateral packing shown in Fig. 4 are for the purpose of illustration and require further investigation. However, Fig. 4 conveys the general idea that unbound lipids are present at the setal surface with their headgroups exposed, consistent with our spectroscopy results. When the pristine setae are detached, failure occurs within the cohesively weak unbound lipid layer, rather than the strong lipid headgroup-substrate interface, leaving a footprint on the substrate (31, 55). The delipidization process removes this weak unbound lipid layer and likely leaves behind the monomolecular layer of bound lipids. Thus, more force is required to separate the delipidized setae from the substrate than pristine setae, which appear to have a sacrificial lipid layer, consistent with our experimental adhesion results and hypotheses from previous work (28, 31, 53–55).

In summary, the results of our study suggest that the adhesive interactions of geckos with hydroxylated surfaces such as glass and sapphire are dominated by acid-base interactions, rather than solely weak vDW forces. The SFG results also suggest that the unbound lipid layers are oriented on the surface of setae with their headgroups exposed, similar to the lipid arrangement in mammalian stratum corneum (45, 46). Our results using delipidized gecko setae suggest that the actual contact area of setal hairs is small (~2 to 7%) and on par with previous estimates based on single setae and whole-animal adhesion measurements (1, 52). By comparing observations of pristine and delipidized setae, we highlight the important role unbound lipids play in wear and preventing damage to the setae, and suggest that these lipids help in quick and easy peel during detachment.

METHODS

Collection and preparation of gecko sheds
Gecko setal samples were prepared from toe pad sheds (molts) that were collected from Tokay geckos (G. gecko) during their monthly shedding cycle. Details about the precautions taken during the shed collection have been elaborated in our previous studies (32, 33). All procedures using live animals were approved by the University of Akron IACUC 07-4G and are consistent with guidelines published by the Society for the Study of Amphibians and Reptiles (SSAR 2004). Gecko setae were either used in their native state (referred to as pristine gecko setae) or treated with 2:1, 1:1, and 1:2 chloroform:methanol mixtures for 2 hours each and then for 1 hour each to obtain delipidized gecko setae (devoid of unbound lipids). The details of the delipidization protocol can be found elsewhere (32, 56). The pristine and delipidized gecko setae were stored at −20°C before use and allowed to acclimate to room temperature and humidity before all experimental measurements and tests.

Spectroscopic measurements
The contact interface between pristine or delipidized gecko setae and the sapphire substrate was investigated using interface-sensitive SFG, which involves the overlap of a visible beam with a fixed wavelength and an infrared (IR) beam with a tunable wavelength. Overlap of these two beams in both space and time results in the generation of a SFG beam with frequency equal to the sum of the frequencies of two incident beams. The SFG beam is generated exclusively from the interfacial region due to inherent asymmetry present at the interface (34). When the IR beam frequency matches the molecular vibration frequency, the SFG signal is resonantly
enhanced, thereby providing information about the chemical groups present at the interface and their orientation. Details of the laser system used in this study have been elaborated on in previous publications (31, 36, 38, 39, 59).

The sapphire prisms and SFG cells were cleaned using the protocol described by Singla et al. (38). A blank scan was collected for sapphire-air interface at a 42° incident angle using total internal reflection geometry to ensure that the sapphire surface was free of any hydrocarbon contaminants and to locate the position of the sapphire free OH peak. Subsequently, gecko setae, mounted on a plunger (using double-sided tape), were brought in contact with the sapphire prism and sheared in the parallel direction to engage the gecko setae with the sapphire substrate (analogous to adhesion measurements). The contact interface between the gecko setae and the sapphire was investigated at a 42° incident angle to examine the setal chemical groups that make contact with the sapphire surface. The spectral signatures remain unaffected even at a 10° incident angle [previously used by Hsu et al. (31)] with lower overall intensity (fig. S2). Last, setae were taken out of contact and SFG scans were collected to analyze the chemistry of the residue left behind. Measurements were repeated with three different samples (both pristine and delipidized) to ensure reproducible results. SFG spectra were collected in two different polarizations: PPP (P-polarized SFG, P-polarized visible, and P-polarized IR) and SSP (S-polarized SFG, S-polarized visible, and P-polarized IR) at room temperature and ambient humidity. Here, S and P denote the direction of the electric field as perpendicular and parallel, respectively, with respect to the incident plane. Different polarization combinations can provide information on the orientation of molecules at the interface (34).

Adhesion measurements
Sample preparation
Individual setal arrays (i.e., lamellae) were isolated from gecko toe pad sheds (pristine and delipidized) and mounted on 1-cm² glass pieces using commercially available all-purpose super glue. Care was taken to ensure that the glue did not wick into the setal hairs by allowing the glue to slightly cure before mounting. The mounted lamellae were tested in shear adhesion against glass (analogous to sapphire). Glass substrates were cleaned using sequential sonication with acetone, ethanol, and water for 30 min each.

Method of measurement and analysis
Shear adhesion measurements were performed using a custom biaxial friction cell described elsewhere (59), where the shear and normal force sensors were calibrated with known weights. The upper detection limits for the shear and normal force sensors were 1200 and 40 mN, respectively. The glass piece with the lamellar strip and the clean glass substrate were mounted on the friction cell, which was then enclosed inside a box to maintain a controlled humidity environment. The relative humidity (RH) was precisely controlled by adjusting the ratio of dry and wet nitrogen (obtained by bubbling nitrogen through water). The VWR traceable hygrometer positioned inside the enclosure enabled us to track the RH over time. Before beginning adhesion measurements, both the lamella and the glass substrate were equilibrated at 35 to 40% humidity for ~15 min. Then, the lamella (pristine or delipidized) was brought in contact with the glass substrate by applying a ~5-mN preload (normal force). After preloading, the substrate was sheared at a velocity of 5 μm/s using a Newport picomotor in a direction that results in engagement of setae with the substrate (1). Shear adhesion force was recorded as a function of time for only ~500 s to minimize damage to the sample. Sample pictures were collected (Olympus SZX16 microscope) before and after each adhesion test to assess any sample damage. The maximum force recorded during each run was normalized by the lamellar area (calculated using ImageJ) to account for the variation in size of the lamellae (52, 60). We used analysis of variance (ANOVA) to test for a difference in normalized maximum force of pristine and delipidized samples. Gecko identification code was used as a random factor to account for possible differences in adhesive performance among individuals. Toe pad sheds collected from six individuals were randomly assigned to a treatment group (pristine or delipidized). Seven lamellar strips per treatment group were used. Raw data met the assumptions of the statistical model and were not transformed. Means are reported as ± standard error of the mean (SEM).

SUPPLEMENTARY MATERIALS
Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/7/21/eabd9410/DC1

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Singla, A. Y. S., J. A. Stark, P. H. Niewiarowski, A. Dhinojwala, Direct evidence of acid-base interactions in gecko adhesion. Sci. Adv. 7, eabd9410 (2021).

Citation: Singla, A. Y. S., J. A. Stark, C. M. Zoltowski, S. Voleti, A. Y. Stark, P. H. Niewiarowski, A. Dhinojwala, Direct evidence of acid-base interactions in gecko adhesion. Sci. Adv. 7, eabd9410 (2021).
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Sci Adv 7 (21), eabd9410.
DOI: 10.1126/sciadv.abd9410