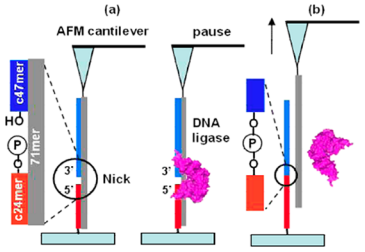
A First Cut on DNA Nicks

Patterning molecules onto substrates can be a necessary part of creating complex nanostructures. To that end, researchers have used enzyme-assisted patterning with atomic force microscopy (AFM) to place molecules with micrometer- or nanometer-scale precision. As interest has turned to progressively smaller features, researchers have sought better control and the ability to transfer a single molecule to a designated place on a substrate. Previous studies have shown that AFM has the potential to pick up just a single molecule, such as DNA, which can be used as in initial building block of a nanostructure.

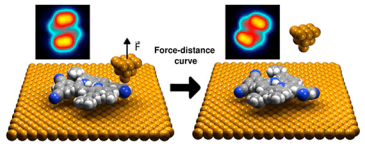
In a new study, Kim *et al.* (DOI: 10.1021/nn301200k) take this research a step further by using AFM to measure the ligation of a nicked double-stranded piece of DNA. The researchers formed the nicked double-stranded DNA by using an AFM tip modified with dendron molecules, creating lateral spacing to lift a single piece of DNA. To this modified AFM tip, they attached a 71mer piece of DNA hybridized to a 47mer DNA strand. They then lowered this molecule onto a 24mer complementary strand tethered onto a substrate in the presence of a DNA ligase. This allowed the smaller strand to hybridize, but left a nick between the 47mer and the 24mer strand. After a pause to let the ligase do its work, the researchers measured the unbinding energy when the AFM tip was retracted. When the nick was sealed, the unbinding force increased significantly. The authors suggest that gaining better understanding of nick sealing using this method could translate into greater ability to build DNA-based nanostructures.



As the Porphyrin Molecule Turns

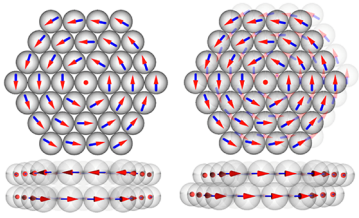
As a critical step toward creating molecular machines, researchers must first find ways to reposition desired molecular components accurately. Previous research has pursued a variety of methods to direct movement or diffusion of molecules, including light, chemical reactions, and electric fields. Scanning tunneling microscopy (STM) is often used to investigate the effects of these methods while also physically repositioning molecules using the probe tip. However, STM cannot determine the elasticity of molecular structures, an important factor in molecular movement. An alternative method is noncontact atomic force microscopy (nc-AFM), which can reposition molecules while also investigating their mechanical properties.

Using this method, Pawlak *et al.* (DOI: 10.1021/nn301774d) employed AFM to investigate the mechanical properties of free-base porphyrin molecules confined to a Cu(111) surface and also used the AFM to move them. The researchers modified these molecules, creating a porphyrin core functionalized with two meso-(3,5-dicyanophenyl) and two meso-(3,5-di-*tert*-butylphenyl) peripheral rings that cause the molecule to take on a saddle shape. The first of these functional groups contains carbonitrile groups (CN), which form strong organometallic complexes. After gently pushing the tip several times into the substrate to make sure it was terminated with Cu adatoms, the researchers used it to investigate the molecule's mechanical properties. Resonance frequency shift data identified the four N atoms in the dicyanophenyl side groups, and retracting the tip lifted the contacted CN group. Using this lift, the researchers were able to rotate the molecules 60° in either direction. The authors note that better understanding of the mechanisms involved might open the way for new mechanically driven manipulation techniques.



Together, We Can Make Great Things

To create large, complex superlattices, researchers often rely on colloidal nanoparticles of various materials, shapes, and ligations. Understanding the mechanisms underlying the self-assembly and packing of these components is crucial to predicting and controlling the structures they form. Many nanoparticle clusters and lattices are stabilized by coupled electric and magnetic dipoles. Previous research suggests that the relative strength and type of these forces combined with the number of particles determines the types of structures formed. For example, colloidal magnetic nanoparticles on substrates at low densities can self-assemble into lines and rings, with increasing density leading to chains and band-like aggregates. Weak dipolar coupling leads to face-centered cubic and hexagonal close-packed lattices. Thus far, it has been unclear what types of stable clusters and lattices can be formed by taking advantage of electric and magnetic dipolar coupling in nanoparticle systems.



In a new study, Baskin *et al.* (DOI: 10.1021/nn301155c) investigate the possibilities of using a series of calculations to determine the energies of assembled particles with dipolar couplings in various clusters and lattices. The researchers first investigated structures with closed fluxes, which tend to be highly stable. In honeycomb plaques composed of one or more rings, their calculations predict either hexagonal close-packed or simple hexagonal lattices based on factors such as orientation of the dipoles, temperature, and nanoparticle size. Further investigation suggested the possibility of creating tubular structures or more exotic orientations, such as closed Möbius strips or hollow icosahedra. The authors suggest that these results might help guide self-assembly of unique structures at different scales.

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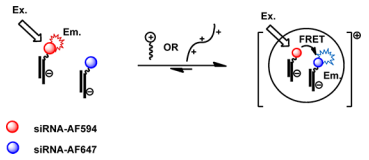
Shining New Light on siRNA

Since the discovery of RNA interference (RNAi) in 1998, researchers have readily harnessed the power of small interfering RNA (siRNA) to regulate and to silence endogenous genes. This research is slowly making its way toward therapies for diseases in humans. To achieve effective delivery, siRNA must be attached to or encapsulated inside a delivery vehicle. Then, once it reaches its target, this nanocomplex must disassemble so that siRNA can be loaded into cells' RNAi machinery. Although these processes are pivotal to the success of siRNA therapeutics, researchers have been unable to track this process without using probes that had the potential to significantly perturb it.

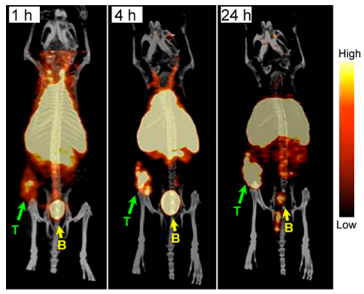
In a new study, Alabi *et al.* (DOI: 10.1021/nn3013838) developed a novel method to follow delivery vehicle siRNA (DV-siRNA) nanocomplex formation, stability, and disassembly by taking advantage of Förster resonance energy transfer (FRET). The researchers labeled two chemically identical siRNA strands with either a FRET donor or a FRET acceptor. Testing these strands in various delivery vehicles, the researchers were able to view assembly as the strands came together and underwent FRET and then later view disassembly as the FRET signal faded after the nanocomplexes were treated with heparin sulfate. They witnessed similar phenomena in transfected HeLa cells, providing evidence that their method also works intracellularly. Dissociation constants measured for the various delivery vehicles showed good correlations with the ability of the siRNAs to silence a luciferase reporter gene. The authors suggest that FRET labels could offer a new way to provide information about siRNA delivery vehicles that might eventually be translated to clinical applications.



Peering Inside the Workings of Au Nanocages

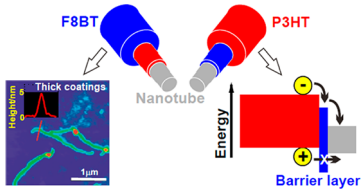
Nanostructures of various types have drawn increasing focus for their potential roles in medicine. In particular, Au nanocages (AuNCs) have recently attracted considerable attention for their possible use in cancer imaging and treatment. Their localized surface plasmon resonance peaks can be customized for use as contrast agents in a range of optical imaging modalities, and their hollow, porous structures are ideal for carrying and releasing therapeutic drugs. Additionally, they readily convert light to heat, making them good candidates for hyperthermia therapy. Yet despite AuNCs' promise, researchers still know little about the pharmacokinetics and *in vivo* tumor targeting capability of these materials due to the difficulties in imaging them in the body.

To resolve these mysteries, Wang *et al.* (DOI: 10.1021/nn300464r) turned to positron emission tomography (PET), a technique used to diagnose and to stage cancer and other diseases. The researchers prepared two different sizes of AuNCs, with 55 and 30 nm edge lengths, and coated these nanostructures with biologically friendly polyethylene glycol. They then functionalized the nanostructures with radioactive $^{64}Cu^{2+}$ ions. When these materials were administered individually to healthy mice at femtomolar doses, PET scans showed that the smaller nanocages were more readily retained in the blood and had lower uptake by the liver and spleen. In a murine breast cancer model, the smaller nanocages were significantly more likely to migrate to the tumor, even infiltrating the tumor's center. The authors suggest that gathering more information about AuNCs through similar imaging techniques could help optimize them for a variety of theranostic applications.



Nanotubes' Polymer Dreamcoats

Single-walled carbon nanotubes (SWNTs) have been a favorite research topic for decades due to their extraordinary electronic and physical properties. In recent years, new studies have shown that these unusual materials can take on different and useful characteristics with the addition of semiconducting polymers bound to the SWNTs. These polymer coatings both prevent SWNT aggregation and modify the nanotubes' native properties. Various polymer coatings thus far have provided enhanced diameter selectivity, improved mechanical properties, and selectively tweaked electronic properties. One particularly promising modification is coating very narrow SWNTs with poly(3-hexylthiophene) (P3HT). This pairing forms a type-II heterojunction energy alignment, allowing excitons from



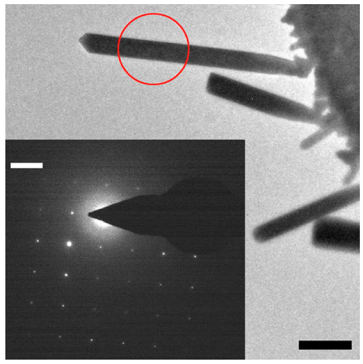
the polymer to dissociate through transferring electrons to the SWNTs. However, even for the smallest SWNTs, the barrier for hole transfer from P3HT is low, reducing charge separation.

Seeking a solution to this conundrum, Stranks *et al.* (DOI: 10.1021/nn301133v) evaluated the addition of a second polymer to the mix. The researchers coated SWNTs first with either P3HT or poly(9,9′-dioctylfluorene-*co*-benzothiadiazole) (F8BT) and then a second coating of the other polymer. Emission spectra showed that when the F8BT-coated SWNTs gained a coat of P3HT, the second polymer engaged in competitive binding and completely replaced the first polymer coat over time. However, when the order of the coatings was reversed, F8BT formed a thick outer layer over P3HT. Time-dependent photoluminescence suggested that the second coat changed the SWNTs' electronic properties, affecting electron and hole transfer. The authors suggest that by tinkering with more than one polymer coating, properties of SWNTs could be customized for specific applications.

Visualizing a Better Battery

Repeatedly cycling through charge and discharge sequences gradually degrades metal electrodes in batteries, producing physical changes that eventually affect power density, lifetime, and, ultimately, utility. For example, lead-acid, zinc-air, lithium, and lithium-ion batteries all have the propensity to develop long, conductive crystals called dendrites from the surfaces of their electrodes, which in time lead to shorted circuits and battery failure. Consequently, gaining a better understanding of the factors that lead to dendrite formation could help researchers engineer better, longer-lasting batteries. Studies to investigate this problem have generally incorporated optical techniques, but high-resolution imaging is necessary to understand the atomic-scale surface kinetics involved in this problem.

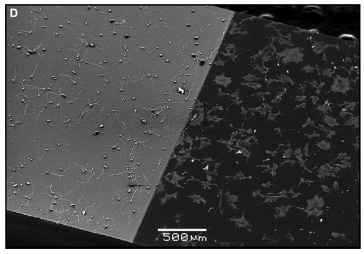
In a step toward that goal, White *et al.* (DOI: 10.1021/nn3017469) used scanning transmission electron microscopy (STEM) *in situ* to watch Pb deposits form on electrodes in an aqueous, saturated solution of lead(II) nitrate. Applying voltage across two electrodes immersed in the solution led to reversible plating on the cathode, with dendrites growing from the surface and eventually shorting the electrodes. The entire process was visible using STEM, as was the concentration of Pb^{2+} ions in the solution increasing and decreasing depending on the applied voltage. Using images from captured videos, the researchers were able to correlate the amount of lead deposited or stripped with the total charge passed through the circuit. The authors speculate that the high-resolution, real-time images of both reactants and products visualized through STEM could help researchers gain better understanding of dendrite formation and, eventually, solve this energy storage conundrum.



Pillars of Knowledge for Stem Cell Differentiation

A basic goal of regenerative medicine is learning how to grow desired cell or tissue types on biomaterials that might then be implanted for therapeutic needs. Previous studies have shown that a variety of methods can steer cell fate on biomaterials, including released growth factors, ligands present on the surface, and physical cues. Notably, the structure of the surface itself can play an important role in driving stem cells to take on particular morphologies and organizations, including determining polarity in polar cells. For example, earlier research using nanopillars (NPs) as substrates demonstrated oriented fibroblast growth and rounding of cells. However, little research has focused on the effects of varying the geometry, spacing, and stiffness of NPs on cell shape and differentiation.

To that end, Bucaro *et al.* (DOI: 10.1021/nn301654e) undertook a systematic analysis of how NP radius, height, and spacing can affect stem cell growth. The researchers grew silicon NPs in square lattice arrays with an aspect ratio of 12:1, varying spacing between 1 and 4 μm. They found that at the critical spacing of 2 μm, stem cells plated on the arrays took on a distinct morphology with rounding of the cell body and pronounced polarization, with axon-like projections aligned with the lattice and extending for hundreds of micrometers. Increasing the aspect ratio to 50:1, which effectively decreased the NP stiffness, exaggerated these effects. The resulting cells, which looked much like neurons, tested positive for a neuron-specific marker. The authors suggest that further testing of various nano scale manipulations to substrates could lead to ways to steer differentiation of stem cells into a variety of useful cell types.



Nanomedicine for Alzheimer's: A Memorable First Step

Alzheimer's disease, the most common form of senile dementia, affects more than 35 million people worldwide. Currently, all therapies reduce symptoms, but none yet exist to attack the roots of this disease. One classic Alzheimer's pathology is the progressive production, accumulation, and aggregation of amyloid-beta peptide (Aβ) in the brain. The Aβ 1-42 (A$\beta_{1\text{-}42}$) monomer is thought to be the most toxic isoform because it aggregates more easily than other types, and the A$\beta_{1\text{-}42}$ oligomer is specifically toxic to neurons. Consequently, considerable efforts have been devoted to learning how to eliminate this peptide and to slow down aggregation.

In a new study, Brambilla *et al.* (DOI: 10.1021/nn300489k) developed a promising solution that involves partnering nanoparticles

with biologically friendly polyethylene glycol (PEG), a material often used to coat therapies used internally to avoid immune system recognition. The researchers coated PEG onto poly(alkyl cyanoacrylate) (PACA) and poly(lactic acid) (PLA) nanoparticles, materials currently in clinical trials to treat hepatocarcinoma and prostate cancer. Through a variety of techniques, including capillary electrophoresis, surface plasmon resonance thioflavin T assay, and confocal microscopy, the researchers found that the PEGylated nanoparticles interacted with and bound to A$\beta_{1\text{-}42}$ in dramatically higher numbers than non-PEGylated nanoparticles, sequestering the peptide both in solution and in serum. Further tests showed that this binding did not affect complement activation, an important part of macrophage clearance, or the adsorption of apolipoprotein-E, another component thought to be important for Alzheimer's pathology. The authors suggest that PEGylation could play a dual role in increasing blood circulation of nanoparticles while attracting and binding A$\beta_{1\text{-}42}$ for clearance.