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Powering Nanodevices with Biomolecular Motors

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Abstract: Biomolecular motors, in particular motor proteins, are ideally suited to introduce chemically powered movement of selected components into devices engineered at the micro- and nanoscale level. The design of such hybrid "bio/nano"-devices requires suitable synthetic environments, and the identification of unique applications. We discuss current approaches to utilize active transport and actuation on a molecular scale, and we give an outlook to the future.

Keywords: molecular devices · motor proteins · nanostructures · nanotechnology · surface chemistry

Introduction

Technological revolutions often involve access to new materials; the mastery of a new material is so fundamental to mankind that historic ages are defined by the state-of-the-art material, hence the "Stone Age" or "Bronze Age". However, some technological revolutions are characterized by the newfound ability to convert energy into mechanical work, based for example, on the invention of the steam engine, which powered the industrial revolution. Will nanotechnology revolutionize the way in which we convert energy, in addition to providing novel materials? Will this revolution be driven by a nanomotor that will power the nanodevices of tomorrow?

Currently, there are no man-made nanomotors that are capable of having an impact on technology in a manner similar to the steam engine, which defined the industrial revolution. However, while the first prototypes of synthetic nanomotors are studied,[1–3] nature already provides us with a wide range of biological nanomotors (Figure 1), which have evolved to perform specific functions at high efficiency.[4,5] Motor proteins like myosins (responsible for muscle contraction) and kinesin serve as actuators and transporters, RNA-based motors facilitate nucleic acid packaging in viruses,[6,7] RNA polymerases move along DNA during transcription,[8] and the flagellar motor propels bacteria.[9] The mechanisms by which biological motors generate force is an exciting field of research in which significant progress has been made.[10,11]

The wide array of biomolecular motors that have evolved in nature may be considered as a gift to the nanotechnolo-

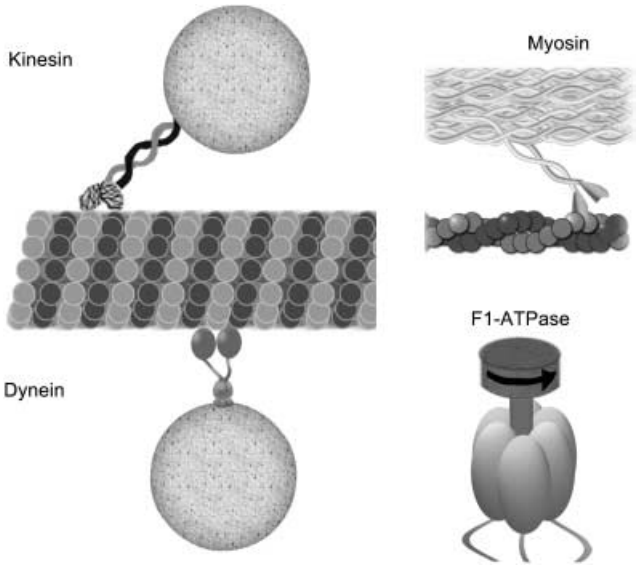

Figure 1. Examples of motor proteins: kinesins, dimeric proteins with a combined weight of 130 kDa, move along microtubules (tubular protein assemblies with an outer diameter of 30 nm), while dragging intracellular cargo towards the periphery of the cell with a velocity of several $\mu m\,s^{-1}$. Dynein moves along microtubules in the opposite direction of kinesin, and then returns cargo to the center of the cell. Myosin motors run along actin filaments. Muscle cells contain large arrays of myosin motors bundled into filaments. The F1-ATPase is a rotary motor, whose central stalk turns when the outer subunits hydrolize ATP. All four motors move in steps which are coupled to the binding and hydrolysis of ATP, and subsequent release of the products.

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gist. To a large degree, we are inspired by biological examples, which prove the principal feasibility and utility to employ molecular motors in different settings. Applying our insights into biology to a synthetic environment will not only enrich our abilities in nanotechnology, but will also test the depth of our understanding of biological systems.

In this article, we will describe the vision of applying molecular motors in miniaturized analytical systems, adaptive and self-healing materials, and directed molecular assembly. Then we will focus on the technical challenge to maximize the compatibility between biological and synthetic components. Finally, we will review a selected number of prototypical nanodevices based on the motor protein kinesin, which include nanoscale transporters,[12] tools for DNA stretching,[13] probes for surface imaging,[14] and a forcemeter for the measurement of piconewton forces.[15]

Application concepts for molecular motors

While developing a vision for the technical applications of molecular motors, we are challenged to connect the inspiration provided by biological examples with technological needs that cannot be met by traditional approaches. We are fortunate, because in the past few years, significant advances have been made in the study of biomolecular motors, and in the understanding of their role in cellular mechanisms; this provides a solid foundation for exploratory thinking. Concurrently, the interest in technological solutions on a molecular- and nanoscale has been rising dramatically, hence creating a market for ideas which exploit the small size of biological motors, and their ability to efficiently convert chemical energy into mechanical work. We will now briefly describe three areas in which the integration of molecular motors can be applied to bring significant advances. They include miniaturized analytical systems, adaptive and self-healing materials, and directed molecular assembly.

Miniaturized analytical systems: The development of miniaturized analytical systems is driven by high-throughput methods and the analysis of biological systems. Nanofluidic systems are desirable; however, fluid transport in nanoscale channels is difficult, since the high surface-to-volume ratio causes a dramatic increase in friction. A potential solution is to selectively bind the analyte to "molecular shuttles" powered by molecular motors, and leave the bulk of the solution at rest.[16]

The close analogy of a "molecular shuttle" to the motor protein-based transport mechanisms employed in neurons (fast anterograde transport) provides a clear vision of the feasibility and utility of such a system.[17] In the axons of neurons, the motor protein kinesin moves along microtubules (cylindrical polymers of tubulin with an outer diameter of 30 nm, and a length of up to 50 μm) at a speed of ~ 1 $\mu m\,s^{-1}$, while carrying vesicles and protein complexes. The average diameter of axons in the human optical nerve is 0.7 μm, which does not inhibit effective transport.[18] This permits us, at least in theory, to scale down the linear dimensions of the average microfluidic device by a factor of 100, which translates into pico- to femtoliter sample volumes. Since the volume of a mammalian cell is in the order of 1 pL, such nanofluidic devices could be used to analyze the content of a single cell, or even defined subcellular compartments, and to interrogate individual molecules.

Adaptive and self-healing materials: Integrated molecular motors can enhance the functionality of such materials, since the motors can potentially rearrange the molecular structure into different nonequilibrium states or actively transport material to an emerging defect site.

A much wider range of internal configurations could be adopted by an active material incorporating molecular motors, compared to current active materials such as poly(*N*-isopropylacrylamide),[19] which change their properties after undergoing a phase transition in response to an environmental cue. While such transitions between different equilibrium states are necessarily limited by the complexity of the phase diagram of the material, molecular motors can dynamically order materials into structures which are not constrained by equilibrium considerations.

Composite materials, which interface molecular motors with nanoscale building blocks, hold particular promise, since positioning of the blocks by thermal motion is relatively slow, and a suitable arrangement of the building blocks offers particular benefits.[20] Several studies have shown that molecular motors can organize polymeric filaments into distinct structures, and the presence of molecular motors can be used to actively control the viscoelastic behavior of a polymeric solution.[21–23]

Exploiting molecular motors holds the promise of creating new classes of materials, which feature controlled adaptation on a molecular- to mesoscopic scale. The intellectual challenge is to design an integrated material, in which the adaptation cannot be mistaken for a simple phase transition between two different states.

Directed molecular assembly: Directed molecular assembly or mechanosynthesis provides a huge opportunity for the application of molecular motors, since the motors can actively control the position of substrates, enzymes, and templates.[24] While directed assembly of molecules by controlled movement of the precursors can be achieved for individual molecules with a scanning probe microscope,[25] the use of such a macroscopic instrument for the assembly of molecules is clearly not efficient. In contrast, imagine a network of nanoscale conveyor belts that selectively transport molecules and control their encounter with their specific reaction partners. In cells, motor proteins have been implicated in controlling the encounter rates between molecules. For example, motor proteins can position mRNA synthesized in the nucleus at defined locations in the cell where they interact with the ribosomes.[26] Localized mRNA then translates into spatially controlled production of proteins. Therefore, to a degree, certain cells thus resemble a nanoscale factory, in which motor proteins distribute the blueprints of parts to different workstations.

The importance of motor-driven transport and assembly processes in nature increases with the size of the molecules

involved, due to the corresponding decrease in diffusive mobility, and the increasing energetic and entropic barriers separating different conformational states. For example, the packaging of viral DNA into empty capsids can be driven by a RNA motor, which forces the DNA strands into the capsid shells.[6] This assembly process results in a supramolecular structure that is not thermodynamically advantageous, since there is a high entropic cost associated with packing the DNA into a tight space.

These, and similar biological examples together with the proof-of-principles experiments, which involve molecular shuttles, inspire a vision of molecular motors integrated into nanoscale drug delivery devices, smart nanomaterials, and active assembly of electronic nanostructures.

Finally, disassembly processes, accelerated by the force exerted by molecular motors, maybe of as much interest as assembly processes. Mechanically disrupting a large molecule, virus, bacterium, or nanodevice may yield valuable insights into the function and stability of these structures under external stresses.

Interfacing Biological Motors with a Synthetic Environment

The interface between biomolecular motors and nonbiological components is a critical element in hybrid nanodevices. Central challenges are to avoid denaturation, concomitant loss of function of motors interacting with synthetic surfaces, and the selective placement of motors into predetermined locations.

Engineering the surface chemistry: Engineering the surface chemistry of synthetic surfaces is one solution to these challenges. A variety of approaches to reduce denaturation has been developed, which include surface precoating with a generic protein (albumin, casein)[27] to restrict the surface–motor contact to small patches in between the pre-adsorbed proteins, and surfaces coated with functionalized polymer brushes,[28] which provide a designated binding site. The adsorption of motors has been selectively prevented by either identifying materials that reduce protein adsorption,[29–31] or by using surface modification strategies originally developed for nonfouling surfaces.[32]

Genetic engineering techniques: Genetic engineering techniques can be applied to define specificic interactions between biomolecular motors and synthetic components, since these techniques allow the sequence and structure of biomolecular motors to be modified.

As a basic proof-of-principle, a simple device was designed and constructed, in which genetically modified F_1-ATPase motors provided a means to actuate nanoscale metallic components.[33] This device consisted of three primary components: 1) a lithographically defined surface of Ni posts, 2) F_1-ATPase motors, and 3) functionalized "nanopropellers" (Figure 2). The interfaces between organic and inorganic components were based on His-tag/Ni-NTA and biotin/streptavidin interactions. In the presence of ATP, F_1-ATPase motors are capable of rotating the nanopropellers (150 nm diameter × 750 nm long) with an angular velocity of 8 Hz, and providing a constant torque of 20 pN nm.

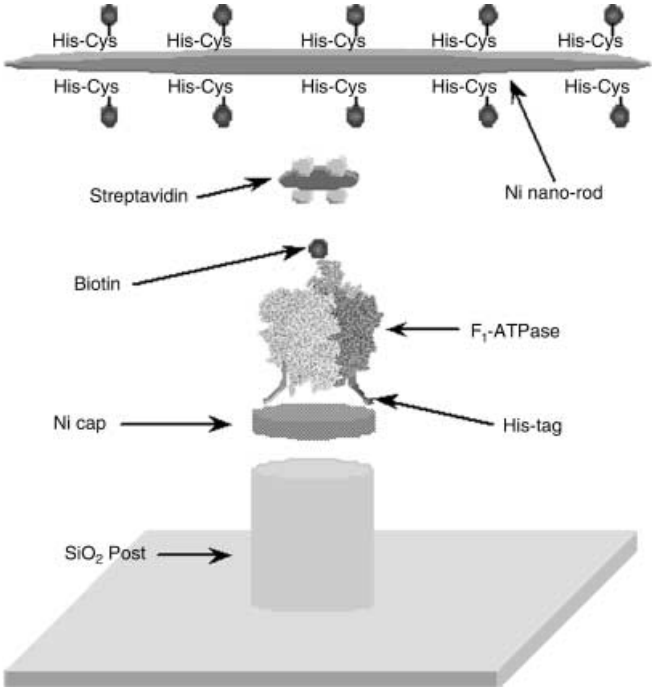

Figure 2. Schematic depiction of the chemical handles used to assemble the F_1-ATPase-powered integrated nanodevice.[21] F_1-ATPase motors were attached to patterned Ni surfaces through 10× His-tags on the β subunit. The rotor (γ subunit) and nano-propeller were functionalized with biotin, and connected by using a streptavidin bridge.

In this example, the F_1-ATPase motor from the thermophilic bacterium *Bacillus* PS3 was genetically engineered to express a 10× histidine (His) tag on the N terminus of the β subunits and a unique cysteine (Cys) in the γ subunit.[34,35] The 10× His-tag is a common fusion sequence introduced to provide an easy and efficient means of purifying recombinant proteins by using Ni–NTA affinity chromatography. This generalized scheme, however, also provides a method for directly attaching recombinant motor proteins to patterned surfaces. By using this method, His-tagged F_1-ATPase motors were attached to Ni–NTA functionalized polystyrene microspheres,[36,37] as well as arrays of nanoscale nickel dots.[38] Since the His-tags were located on the N terminal of the β subunit, the motors were positioned such that the base of the stator (i.e., α/β hexamer) was adjacent to the surface, and the γ subunit (rotor) was positioned perpendicular to the surface. Based on this orientation, the engineered Cys in the γ subunit was fully accessible and provided a thiol "handle" for attaching additional components.

Genetic engineering of chemical "switches": Genetic engineering of chemical "switches" into biomolecular motors, which respond to changes in the local environment, permits active control of motor function. Since the three-dimensional crystal structures for motor proteins have been resolved,

the protein sequence of these motors may be genetically engineered for enhanced functionality. Two primary examples focus on controlling the mechanical functionality of the motors by using the local chemical environment. In the case of kinesin motors, site-directed mutagenesis was used to introduce a cysteine into the neck linker region.[39] Under oxidizing conditions, a disulfide bond formed between the two cysteines of the dimeric kinesin, which in turn inhibited linear translation along microtubules. Subsequent reduction of this bond allowed normal movement of kinesin motors; this cycle could be repeated a number of times.

A more complex approach was used to control the mechanical motion of the F_1-ATPase motor, and involved the introduction of a zinc-binding site into the catalytic region of the enzyme.[37] Control of single F_1-ATPase motors was demonstrated by repeated sequential additions of zinc and a metal chelator. These two examples of protein engineering clearly demonstrate the strategies that may be used to engineer motor proteins with logical control in synthetic environments.

Prototypes of Kinesin-Powered Nanodevices

As one of the applications of molecular motors we discussed the idea of "molecular shuttles"; nanoscale conveyor belts for molecular cargo. In the past few years, we and others have set out to build such molecular shuttles by using motor proteins that move linearly along cytoskeletal filaments.[16]

Conventional kinesin is one of these motor proteins; it is well studied and readily available (Cytoskeleton Inc.).[40] Kinesin motors produce a force of up to 7 pN and take 8 nm steps at a rate of ~100 steps per second at a saturating ATP concentration of 1 mM, while hydrolyzing one ATP molecule per step.[5] The maximum efficiency of the conversion of chemical energy into mechanical work exceeds 50%, which is remarkable, since it is twice as efficient as the average heat engine employed in cars.

The molecular shuttle design chosen by us is based on microtubules that are reconstituted in vitro, (stabilized by adding paclitaxel to the solution), and kinesins that are immobilized on a micro- or nanostructured surface (Figure 3). This setup roughly resembles a conveyor belt, with the stationary motors moving a filament onto which the cargo is loaded.

Conceptually, a transport system requires solutions to the questions of how to direct the movement, how to load and unload cargo, and how to control the speed of the system.[12] A variety of strategies have been employed by us and others to direct the shuttles along predetermined paths; these include chemical modification,[41,42] guiding channels,[12,43–45] and combinations of surface chemistry and topography.[29–31,46–49] In order to permit selective loading with cargo, microtubules can be functionalized with biotin linkers,[50] and fluorescent dyes facilitate observation of these nanoscale filaments.[51] Control over the shuttle velocity can be achieved by controlling the photolytic cleavage of caged ATP in solution;[12] this provides a varying amount of ATP fuel to the motors.[52,53]

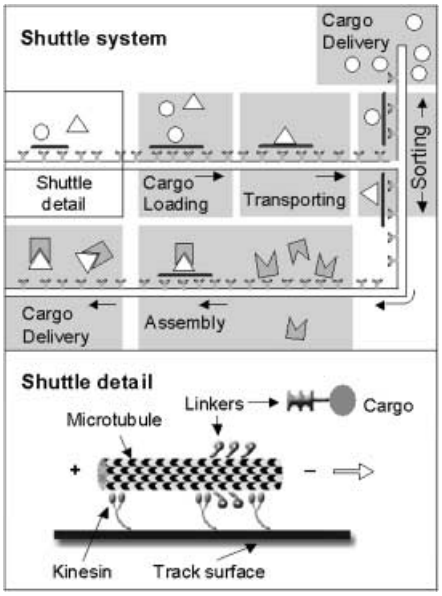

Figure 3. A molecular shuttle system envisioned to load, transport, sort, and assemble nanoscale building blocks. A hybrid design approach, which combines synthetic environments and biomolecular motors, and utilizes surface-bound kinesin motor proteins to transport functionalized microtubules along fabricated tracks. Reproduced with permission from Nano Letters **2003**, *3*, 1651–1655. Copyright 2003 Am. Chem. Soc.

At this point, we have arrived at working solutions for the basic design challenges of guiding, loading, and controlling. Rapid progress has been made in the assembly of devices, which integrate the individual approaches, and molecular shuttles are poised to be a key tool in the technological applications of molecular motors. In the following, we will describe three proof-of-principle experiments, which demonstrate how molecular shuttles can perform a wide range of tasks.

Surface imaging: In surface imaging, active movement of a large number of simultaneously operating probes is very desirable, whether we want to image the surface of the planet Mars by using a swarm of robots, or the surface chemistry of a cell membrane by means of scanning probe microscopy. Molecular motors allow us to design self-propelled nanoscale probes that roam a surface and provide information about surface conditions. A basic implementation of this approach to surface imaging (Figure 4) has been demonstrated by using the molecular shuttles previously described.[14] In this experiment, the movement of hundreds of microtubules on a kinesin-coated surface has been recorded over time. As the microtubules collide with microfabricated posts on the surface, their direction of movement changes, and they weave through this obstacle course. The accumulated information of all microtubule paths can be used to construct a map that reflects the positions of the obstacles. Although this imaging technique is limited by the sensitivity of the proteins and the optical detection of microtubule position, it demonstrates how self-propelled nanoprobes enable a new approach to surface imaging that is very different from classic scanning microscopy.

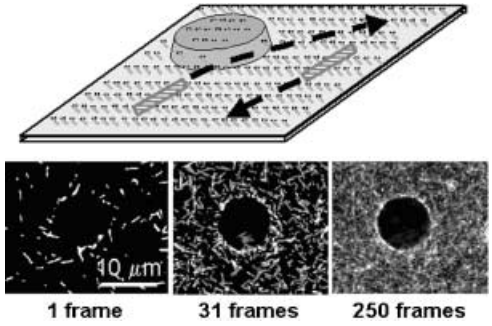

Figure 4. Fluorescently labeled microtubules transported by surface-adsorbed kinesins can serve as nanoscale probes exploring the surface. The sensitivity of the microtubule path to the topography allows an unknown surface to be imaged.[56] For example, a microfabricated pattern of 1 μm high posts divides the surface into an accessible and an inaccessible region, since microtubules that move on the bottom surface are unable to climb a steep incline. Repeated observation of microtubule positions under the fluorescence microscope yields information about the path of several hundred microtubules; these can be superimposed to reveal the surface topography. Bright areas correspond to repeated visits from a microtubule, signifying high accessibility. Reproduced with permission from Nano Letters **2002**, *2*, 113–116. Copyright 2002 Am. Chem. Soc.

Transport and stretching of λ-phage DNA: This has been achieved by molecular shuttles in a recent experiment by Diez et al. (Figure 5).[13] In this experiment, kinesin-driven movement of the microtubule resulted in the linear extension of DNA from its originally globular state. The intended application is in molecular electronics, in which the controlled arrangement of individual molecules and their respective interconnects is required. Properly positioned biological nanostructures, such as DNA[54] or microtubules,[55] can serve as templates for metallization processes that result in nanowires. This hybrid approach to the assembly of nanoscale electronic structures capitalizes on the flexibility of biological assembly processes to transcend the limits of photolithography[56].

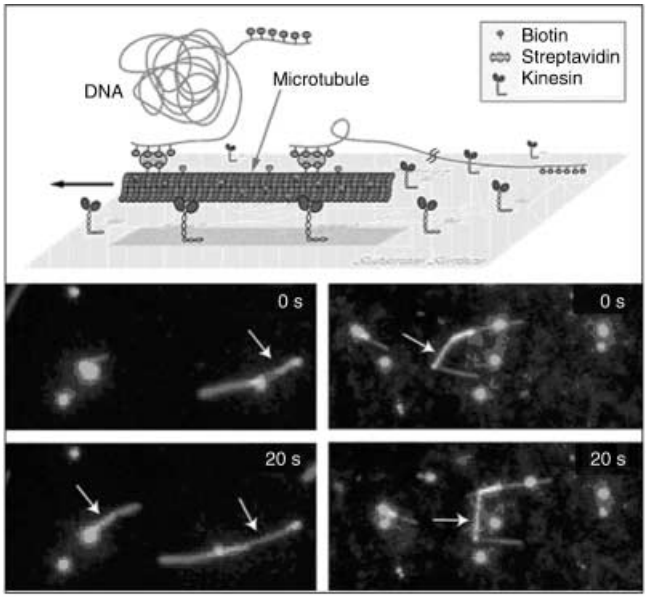

Figure 5. Biotinylated λ-phage DNA can be bound to biotinylated microtubules by streptavidin. ATP-fueled transport of the microtubules on a motor-coated surface results in a stretching of the DNA from its initially globular state into a linear configuration, which potentially can serve as a template for a metallization process. On the left the DNA (marked by arrows) is pinned to the surface on one end and stretched by one microtubule, on the right the DNA is stretched between two microtubules. (Adapted from Diez et al., Nano Letters **2003**, *3*, 1251–1254).

Force measurements: Force measurements on a molecular scale typically require a device capable of exerting piconewton forces, such as optical tweezers or the atomic force microscope. Recently, a miniaturized forcemeter for the measurement of intermolecular bond strengths has been demonstrated.[15] In this case, kinesin motors were used to provide the force to strain and rupture the bond between a receptor–ligand pair. The magnitude of the strain is reflected in the bending of a microtubule attached to the ligand, which serves as a nanoscale cantilevered beam of known stiffness (Figure 6). Inherently, such a device is particularly suited to the study of rupture events between biological receptors and their ligands under physiologically significant loading conditions; these are characterized by the application of piconewton forces on a timescale of seconds.[57] Its small dimensions also permit the assembly of an array of such forcemeters, which would facilitate the observation of a statistically significant number of rupture events.

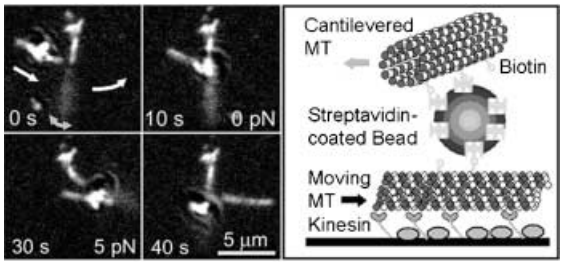

Figure 6. A microscopic forcemeter for the measurement of intermolecular forces in the order of a few piconewton can be assembled from microtubules functionalized with ligands, beads coated with receptors, and kinesins (0 s, 10 s). It consists of a cantilevered microtubule that binds to a streptavidin-coated bead loaded onto a microtubule moved by kinesins. The kinesins push the moving microtubule (30 s) straining the bond between streptavidin and biotin until it ruptures (40 s). Observation of the concurrent bending of the cantilevered microtubule allows the determination of the strain forces based on the known stiffness of microtubules. Reproduced with permission from Nano Letters **2002**, *2*, 1113–1115. Copyright 2001 Am. Chem. Soc.

Conclusion

Since the availability and functionality of man-made nanomotors is still limited, alternative modes of actuation in nanoscale devices and systems must be pursued. Biomolecular motors are fast, efficient, and versatile nanoscale motors that hold significant promise as actuators in integrated nanodevices and systems. A number of prototype devices have been designed and assembled based on the role of motor proteins as intracellular transporters and actuators. These

devices provide proof-of-principle demonstrations regarding the ability to construct simple hybrid nanodevices. Continued technology development in this area, however, will be critical to engineering more complex hybrid devices in the future. Overall, the potential of nature's molecular machines has been recognized, and their applications in synthetic nanoscale systems will be limited only by our creativity and imagination.

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