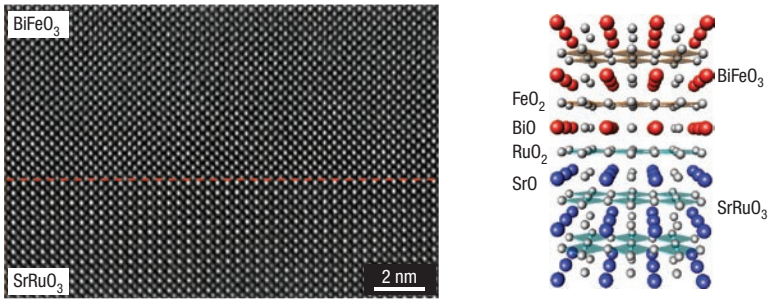

Figure 2 Molecular-beam epitaxy can produce interfaces between dissimilar materials with extremely high quality. The interface shown here is between the ferroelectric $BiFeO_3$ (top) and the ferromagnetic metal $SrRuO_3$. Right-hand side courtesy of J. Mannhart.

group, for example, demonstrated a novel approach to use the strain at an epitaxial interface to couple ferromagnetism in one material to ferroelectricity in another[7]. However, it has become clear that in order to establish deterministic control of ferromagnetism with an electric field, such a mechanism would not be sufficient, and new ones, such as that from Spaldin and colleagues, must be sought.

The calculations developed by the Santa Barbara group have very general applicability and could be invaluable in understanding many systems, such as non-volatile ferroelectric memories or gate oxides in MOSFETs (metal oxide semiconductor field-effect transistors), in which the behaviour often deviates from what is predicted for bulk materials. The group's new paper is also an outstanding example of how *ab initio* theoretical methods are rapidly changing the landscape of cutting-edge materials research. In fact, these techniques have reached such a high level of accuracy that one may ask if the roles of experimentalists and theorists have now been reversed, with the predictions of *ab initio* calculations driving the measurements in the lab. In my opinion, this time has indeed come.

So, what is the next step? Experimentalists are now exploring approaches to create the spin capacitor shown in Fig. 1. For example, my group is looking for the magnetoelectric effect in $SrRuO_3/BiFeO_3$ and $SrRuO_3/Pb(Zr,Ti)O_3$ interfaces. Molecular-beam epitaxy and related techniques can indeed make such heterostructures with the highest quality, as illustrated in the high-resolution electron microscopy image in Fig. 2. Of course, the key issue is finding a way to probe the electronic structure and spin properties of the interface. In this regard, photoemission-based spectroscopy and imaging techniques that are surface sensitive will be essential. Stay tuned for some major breakthroughs in the coming years!

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MOLECULAR SELF-ASSEMBLY

Bioactive nanostructures branch out

A cell-targeting peptide can be assembled into well-defined nanoparticles with different shapes and sizes depending on the number of branches present in the hydrocarbon chain it is attached to.

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Imagine mixing together some simple molecules and, after waiting for a short time, finding that you had made a supercomputer, a molecular robot or a sophisticated nanoelectromechanical device. Harnessing molecular self-assembly[1,2] — the spontaneous organization of molecules into well-ordered ensembles — to make functional synthetic systems such as these is the ultimate dream for many nanotechnologists. These lofty goals sound much more like science fiction than science, so how can we ever hope to reach them? The answer lies in nature, where every biological organism is, at any given moment, living this dream! Even the most primitive bacteria produce pumps, motors, scaffolds and other nanomachines by the hierarchical assembly of discrete building blocks that are made to order.

Inspired by nature, it is perhaps not surprising, therefore, that the self-assembly of nanostructures with biological functions is a particularly attractive area of research, with a large number of applications ranging from drug delivery and imaging agents to molecular scaffolds for tissue engineering[3–5]. In such systems, bioactivity can be achieved by decorating the assemblies with certain peptides — short sequences of amino acids — that are known to have specific cellular functions and molecular recognition properties. However, the precise control of the self-assembly processes and the production of uniform nanoparticles is still far from being a simple task. Nevertheless, the ability to control this phenomenon remains one of the key goals for the transformation of nanotechnology from what is largely a basic research discipline into an applied science.

Now, writing in the international edition of *Angewandte Chemie*, Myongsoo Lee and co-workers[6] from Yonsei University report a general method for the self-assembly of bioactive

nanoparticles with very good control over their shape and size. They looked at a range of molecular building blocks, in which the same bioactive peptide — the so-called Tat cell-penetrating peptide (Tat CPP) — was attached to different hydrophobic chains derived from lipids. Carefully tailoring the structure of the lipid portion of each building block enabled Lee and colleagues to control the self-assembly process and create nanostructures with different geometries.

The Tat CPP is made up of a string of 13 amino acids and comes from a particular strain of the human immunodeficiency virus (HIV). It is a highly charged peptide — containing eight positively charged residues — that can pass through cell membranes, as well as the nuclear membrane. The ability to translocate through these biological boundaries means that Tat CPP is an effective agent for the delivery of other molecules or particles into cells. For the HIV, it is the key that unlocks the host's cells and enables the virus to invade. On the other hand, Tat CPP is a very useful tool for the nanotechnologist who wants to deliver cargo of some type, whether it be a therapeutic or imaging agent, to a cell.

To form self-assembled bioactive nanostructures, Lee's team linked the Tat CPP with various dendritic lipids. Dendrimers — named for the Greek word dendron, meaning tree — are repeatedly branched chemical compounds that have a symmetrical molecular organization[7] (Fig. 1). The structural perfection of the dendritic system allows them to assemble into well-ordered and well-defined formations at the nano-, micro- and even macroscale. In the current work, the dendritic lipids — with either two, four, or eight branches — were based on stearic acid, which contains a long (C_{18}) hydrocarbon chain. These greasy tails were conjugated to the charged Tat CPP through a short flexible linker (Fig. 1). The resulting building blocks were amphiphilic in nature because they contained both hydrophilic (charged peptide) and hydrophobic (lipid chain) groups, the latter of which are key for the hydrophobic interactions that drive the assembly of these molecules in water.

When the molecules were dissolved in pure water, a clear process of self-assembly was evident as the hydrophobic lipid tails clumped together to avoid interacting with the polar solvent. Dynamic light scattering and transmission electron microscopy revealed the formation of nearly monodisperse nanoparticles at relatively low micromolar concentrations. The doubly branched conjugates formed spherical structures 11 and 13 nm in size

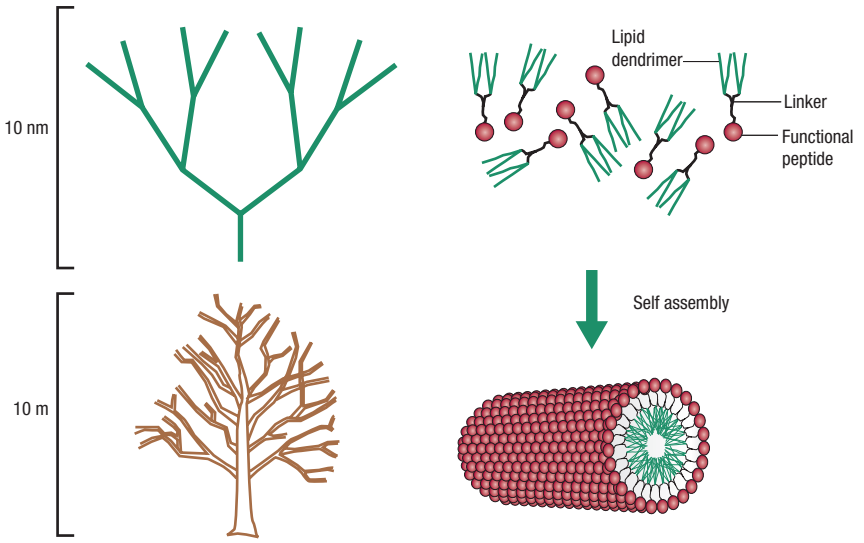

Figure 1 Dendrimers are tree-like molecules that have repeatedly branched structures. The combination of a functional peptide with dendritic lipid groups enables nanoparticles with controlled shapes and sizes to be assembled when the molecules are dissolved in water. The resulting assemblies have a hydrophobic lipid core (green) and a biologically active hydrophilic peptide coating (red).

(in the dried and hydrated conditions, respectively) in which an outer cell of Tat CPP enclosed a core comprising the lipid chains. In contrast, the larger building blocks with either four or eight branches assembled into cylindrical micelles with diameters of about 12 nm and lengths of approximately 100 nm (Fig. 1). The shape of each individual peptide in the assemblies is unchanged, suggesting that the assembly process occurs through the aggregation of the lipid portion of the molecules by hydrophobic interactions. Interestingly, an unbranched lipid–peptide conjugate did not assemble into supramolecular structures, even at much higher concentrations.

What are these well-ordered nanostructures good for? One of the major goals of Lee's team was to demonstrate the functionality of the Tat CPP peptide in the context of the assemblies. In particular, the well-defined nanoscale structure and multivalent presentation of the functional peptide group suggested that this could be an excellent cellular delivery system. This sort of application is indeed envisaged as an important use for nanoscale carriers[8]; however, cytotoxicty is a major issue. In this case, although the assemblies made from the doubly branched building blocks were highly cytotoxic, those made from the four-branch building blocks were much less so and had very similar properties to the individual Tat CPP molecules. To demonstrate the potential of these nanostructures as vehicles for drug delivery, Lee and co-workers loaded the cylindrical micelles with red dye molecules and, using confocal laser scanning microscopy, watched how they were successfully transported into cells. It is not unreasonable to expect that other types of cargo, such as small drugs or even RNA molecules, could also be delivered to the cytoplasm or nucleus by hitching a ride with these well-defined nanostructures.

Our ability to control molecular self-assembly is still in its infancy, and even ingenious scientists are a long way from being able to engineer the sort of functional nanostructures routinely made by the most rudimentary bacterium. However, in small — but steady — steps, we continue to develop increasingly sophisticated and efficient ways to achieve this goal. It may take many more years, but I have no doubt that the day will come when the dream of making functional nanosystems simply by mixing together simple building blocks will become a reality.

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