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*Designing Nanostructures at the Interface
between Biomedical and Physical Systems*
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Design Principles of Living Systems
Focus Group Summary

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Summary:

The task was to determine how to build a “human on a chip.” The problem was that no one really knew what that meant.

Among the 17 experts gathered, amidst backgrounds ranging from materials science to vascular biology, everyone had a slightly different speculation about the intention behind the phrase.

Was it a charge to build a microfluidic system that would give quasi-human responses to drugs—a kind of biomolecular crash-test dummy intended to speed up the expensive early trial phases of drug discovery? Was it some borg-inspired desire to have human processes take place on some injectable piece of plastic—an artificial oxygen filter for asbestos-torn lungs, or emergency islet cells for diabetics? Maybe a trash digester for the colon.

It could be a call to put human sensory systems on a chip. Artificial eyes, ears, nose, tongue, and skin combined together to make the ultimate pseudo human probe. Then again, it's our mind that's *really* what

makes us human, isn't it? Maybe this should be some sort of preliminary mock neural network.

For all I knew, "human on a chip" suggested a recipe for soylent green guacamole.

After a day's discussion, the issue came down to realizing that this was, after all, a nanotechnology conference. The secret of the group's purpose was buried in the implicit fact that, at some point, nanotechnology and the workings of human cellular biology are going to have to merge in a complex and meaningful way. And, scientists today aren't exactly sure how these two technologies are going to interface.

This uncertainty arises because nanotechnology works on a scale where many biological functions at the cellular and sub-cellular level are controlled by weak, non covalent interactions, such as electrostatic, van der Waals forces, hydrogen bonds, and metal coordination chemistry. When you push molecules together, you change their chemical activities. And when you change their activities, you change their physical conformation; it's just occurring on a very, very small scale. While researchers can make pretty good guesses at how fairly simple and uniform nanostructures behave at this level, the complex mosaics of the human body, like the hierarchical assemblies of proteins that make up our cells and tissues, are still outside current understanding.

So, the group devised a way to set up a scheme that would enable a very fundamental meeting between nanotechnology and the human body, while at the same time allowing researchers to find out more about those biological complexities that they don't understand. They reworked their group's title into "Design Principles of Living Systems," at the cell level, and designed a device called a multiplexed dynamic force spectroscopy array.

Inside a human cell, the workings of a single protein—how the long chain of peptides kinks or untangles in order to hide or expose active links—isn't solely dictated by regulatory enzymes or chemical triggers in the environment. The protein is also being tugged, stretched, and scrunched by the surrounding intracellular and extracellular matrix that gives cells their shape. These physical forces radically skew how a protein reacts to chemical and enzymatic cues, and cell function results from this form of interplay between mechanics and chemistry.

The basic schematic of the array looks a bit like an underwater clothesline. The protein to be studied is strung like a tangled cable between two, 20-nm-thick. These can be Carbon, Nickel, Platinum, or Polypyrrole/Gold composite nanowires. Using subtle electric pulses or weak magnetic fields, those two nanowires can be sheared outward, creating a tug-of-war stress on the protein, or pulled inward, bunching the protein up.

Researchers could then use an imaging technique, such as fluorescence resonance energy transfer (FRET) or fluorescence recovery after photobleaching (FRAP), to observe how this protein responds to different enzymatic and chemical cues while under this stress. For more advanced studies, more proteins could be added to the same nanowires or to nearby sets of nanowires to see how the proteins react.

Donald Ingber of Harvard Medical School, who was chosen to act as spokesperson for the group, suggested that a good first object of study would be fibronectin, a relatively well-understood glycoprotein responsible for binding cell membranes to the extracellular matrix that holds multiple cells together. From there, more complex proteins could be observed.

Eventually computer models could be designed around these observations, allowing researchers to more accurately model reactions that cells would have to different stimuli. Being able to individually scrutinize proteins in a mechanically relevant context would also help drug developers pin down what enzymatic and protein pathways are really being affected by potential medical treatments.

The array could also become a finely tuned biosensor. Proteins could be engineered to open different active binding sites under different shear forces, so that modulating the forces would cause the proteins to react if certain molecules targeted to those sights (possibly chemical weapons or illegal drugs) were

present in the surrounding solution.

The plan for the array, however, is far from realistic at this point. The optical methods of observing the individual chemical events and protein structure aren't sensitive enough to observe individual changes in proteins as they happen. Not to mention that there is no method accurate enough to place individual proteins between the wires and reliably attach the ends.

"On top of the technical problems, there is the simple fact that this is also the exact type of research that is not going to get funded through your typical channels," Ingber said. It's too rooted in "maybes" and too far removed from application. But, it might be a good idea to keep in mind for ten years from now...if anyone asks you to design a human on a chip.