# A conversation with Dr. Adam Marblestone and Dr. Eric Drexler, September 1, 2016

## Participants

- Dr. Adam Marblestone – Director of Scientific Architecting, Massachusetts Institute of Technology (MIT) Synthetic Neurobiology Group, and Research Scientist, MIT Media Lab
- Dr. Eric Drexler – Researcher, Future of Humanity Institute, and Oxford Martin Senior Fellow, Oxford Martin School
- Nick Beckstead – Program Officer, Scientific Research, Open Philanthropy Project
- Daniel Martin Alarcon – Scientific Advisor, Open Philanthropy Project

**Note**: These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Dr. Marblestone and Dr. Drexler.

## Summary

The Open Philanthropy Project spoke with Dr. Adam Marblestone of the MIT Synthetic Neurobiology Group and Dr. Eric Drexler of the Future of Humanity Institute (FHI) as part of its investigation into Atomically Precise Manufacturing (APM). Conversation topics included a recent workshop on molecular 3D printing, the prospects of the ideas discussed there contributing to the eventual development of APM, resources needed to create a self-assembling 3D printer, and funding for work in this field.

## Molecular 3D printing workshop

### Plausibility of creating a molecular 3D printer

Drs. Marblestone and Drexler recently organized a workshop on molecular 3D printing (together with Shahar Avin and Seán Ó hÉigeartaigh of Cambridge University, with sponsorship including the US Department of Energy and the Oxford Martin School). They concluded after the workshop that it may be possible for a research program to develop a near-term, proof-of-principle version of a molecular 3D printer by resolving a set of specific research design and implementation questions. This printer would not necessarily be capable of directly producing products that would be broadly economically useful, but would demonstrate key functionality, including:

- **Programmable positioning**: A molecular device that can guide an effector to a specified position relative to a platform by means of series of displacement steps driven by a corresponding series of external operations.
- **Positionally-directed chemical reactions**: The programmable effector above could be used to direct the assembly of molecular building blocks in

any of several ways, either by positioning the building blocks (e.g., by binding them from a dilute solution of blocks) such that they will react with selected sites on a larger structure, or by guiding the functionalization or activation (e.g., by catalytic deprotection) of selected sites on the larger structure such that those sites will react with freely-diffusing molecular building blocks delivered in solution phase. The building blocks would be large molecules (e.g., nanometer scale, containing a few hundred atoms) designed to have mutually compatible surfaces. (Note that, contrary to a widespread misconception, atomically precise manufacturing does not require the manipulation of individual atoms.) In the first approach, the building blocks must have an intrinsic reactivity low enough that they do not react with one another spontaneously in solution, but do react with sites on a product surface when bound and positioned by the printer; in the second approach, they must have selective reactivity with surface sites that have been functionalized/activated by the preceding cycle of printer operations. The structure and function of the final product would be determined by the resulting organization of bonded component blocks. This mode of fabrication would be qualitatively different from self-assembly, as the structure of the product would be provided by external instructions rather than encoded into the components themselves; because the building blocks thus organized would not themselves need to contain the information necessary to direct their organization, they could be smaller, simpler, and reusable in multiple roles.

On the first day of the workshop, participants focused in part on potential specific applications for the first molecular 3D printers. Most participants concluded that applied objectives within reach of an initial focused program could likely be reached by other, more conventional means, such as by direct self-assembly, whereas more ambitious fabrication objectives are by definition more difficult to achieve, and therefore less likely to attract funding or to be accessible to a single initial project. By the second day of the workshop, the group reached a consensus that the demonstration of atomically precise nanoscale printers could in itself generate strong excitement and interest as a technological milestone, independent of the potential direct applications of the products of the first-generation system.

After the workshop, the organizers' impression is that the development of a first-generation molecular 3D printer is more readily achievable and fundable than it had seemed previously.

**Workshop attendees**

- Dr. Mark Johnson, Director of the Advanced Manufacturing Office (AMO) at the US Department of Energy (DOE), helped to fund the workshop, framed

the objective in the context of DOE objectives, and suggested that a prototype system would likely be fundable, independent of its practical application.

- Dr. David Forrest, a Technology Manager at AMO, organized a previous APM workshop funded by the DOE. Dr. Forrest is interested in near-term technical risk reduction, and has asked Drs. Marblestone and Drexler to write a white paper describing research that could be foundational to the development of APM.
- Christian Schafmeister, Professor of Organic Chemistry at Temple University, has developed a set of rigid molecular building blocks called spiroligomers[1], and described their potential value in the development and application of molecular 3D printers. Spiroligomers are cyclic molecules that can be created by peptide synthesis; they are composed of several rings that share spiro atoms, such that no torsional or conformational degrees of freedom are left that would allow one part of the molecule to rotate with respect to the other. Professor Schafmeister has created enough variations on these spiroligomer blocks to make a wide range of shapes that have a preferred 3D structure without folding.
- William Shih, Professor at the Wyss Institute at Harvard University, described some of the relevant state of the art in structural DNA nanotechnology, which enables the construction of frameworks and devices on the scale (~100 nm) required for the implementation of molecular 3D printers. He also described and helped to further the conceptual development of stepper motors to drive the motion of components.
- Other workshop participants included:
    - Adam Marblestone — MIT
    - Andrew Turberfield — Oxford
    - Christian Schafmeister — Temple
    - Roman Jerala — U. of Lubjana, Slovenia
    - Thomas LaBean — Notre Dame
    - Balu Balachandran — DOE
    - Ashwin Gopinath — Caltech
    - Jenny Zhang — Cambridge
    - AJ Venkatakrishnan — Stanford
    - Eric Drexler — Oxford
    - Mark Johnson — DOE

[1] From one of Schafmeister's publications: "Towards this goal, we have developed 'spiroligomers' as shape-persistent and shape-programmable scaffolds, which can project functional groups in defined three-dimensional constellations and are synthesized in a convergent fashion [1,15,16]. Spiroligomers are highly pre-organized macromolecules (600 to 2,000 Daltons), which can be designed to recapitulate the presentation of the relevant side chains of one partner of a protein-protein interaction, bind the other partner and mediate a biological response." Source: Brown, Z. Z. *et al.* A Spiroligomer α-Helix Mimic That Binds HDM2, Penetrates Human Cells and Stabilizes HDM2 in Cell Culture. (2012). doi:10.1371/journal.pone.0045948

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| ● David Forrest | DOE |
| ● (Seán Ó hÉigeartaigh)[2] | Cambridge |
| ● (Shahar Avin) | Cambridge |
| ● (Dmitry Kaminskiy) | Venture capitalist |
| ● (Jim Keravala) | Entrepreneur |

## Progress toward APM

### Molecular 3D printer

Dr. Marblestone and Dr. Drexler think that a research program focusing on developing a molecular 3D printer could make major steps toward the development of APM, first by demonstrating principles, and then by providing capabilities useful to the implementation of next-generation atomically precise fabrication systems. It seems likely that the creation of such a printer could decrease the further time and funding required to achieve APM. However, they are uncertain about whether the primary impact of such a printer would be in its practical applications or in helping the research community to think about APM in a more practical way.

Creating a self-assembled biomolecular device functioning as a 3D printer that can print to roughly one-nanometer resolution would change the community's conception of the limits of positional assembly. The idea of positional assembly is not new, but the demonstrations performed so far (such as dip-pen lithography and moving DNA strands using an atomic force microscopy (AFM) tip) are based on macroscopic control systems that cannot be easily parallelized and that have limited capability to interface with diverse chemical functionalities at the nanometer length scale. A molecular 3D printer made entirely out of self-assembled nanoscale components would be massively parallel by design (e.g., the assembly of milligrams of components would result in on the order of a trillion printer devices that could occupy a small volume and respond to inputs in synchrony). If such printers could work with blocks on a 1 nm scale, they would compete with the best self-assembly methods. Researchers would realize that complex structures at the nanoscale can be created by external instructions, and would direct further attention to better ways of achieving this goal, which is fundamentally different from molecular self-assembly, and ultimately more powerful. Note, however, that printing and self-assembly of components could be used in a synergistic way, expanding the scope of both technologies.

### Scanning probe microscopy

Dr. Drexler is not aware of any promising approaches to APM based on molecular tools in combination with scanning probe microscopy (SPM). Major obstacles to using SPM for this purpose include:

[2] The people in parentheses were primarily at the workshop as observers.

- Individual reactions have been both difficult to make work, and unreliable when they do work.
- A long sequence of individual reactions would be required to make objects of substantial size and complexity.
- The reactions are irreversible, so any mistake in this series of operations would make the object non-functional. Because of geometric constraints, it is unclear how one would make a 3D mechanical device using this process. Dr. Drexler has not seen a credible plan for doing this.
- The potential parallelism of SPM approaches is sharply limited because the control mechanisms are macroscopic and physically connected to individual molecular tools.

## Resources needed to create a self-assembling 3D printer

- **Dr. Marblestone's projection:** Dr. Marblestone thinks that in order to make substantial progress on demonstrating a self-assembled 3D printer, it would be necessary to significantly shift the research priorities of several moderate-to large-sized, successful labs. He estimates that this would cost approximately $10 million over about 5 years for each lab, for a total cost of about $50 million.
- **Dr. Drexler's projection:** Based on his conversations with several research group leaders over the past few years, Dr. Drexler thinks that it would take roughly 3-6 research groups and a total cost of about $10-20 million per year for 3-5 years to develop an effective prototype.

Both Dr. Marblestone and Dr. Drexler believe that, to achieve results reliably on a relatively sort time scale, it is necessary to have several labs working on each technical challenge because, despite advances in DNA origami and other areas, there is a considerable probability of failure in the approach pursued by any given lab, due to the inherent difficulty of biomolecular research. (Part of the promise of molecular 3D printing is to circumvent these difficulties and to speed further developments in molecular engineering.)

The most efficient way to solve an engineering development problem like the molecular 3D printer is to develop a system architecture with functional slots, each of which could be filled in several different ways. There would be substantial technical risk in each proposed solution, but less risk in the project overall.

## Funding for work in this field

### DOE funding for the workshop

This is the second workshop on APM that the DOE has partially or fully supported. Its funding may have increased the community's sense that work in this field is fundable.

**Spiroligomer bricks**

Dr. Marblestone believes that Professor Schafmeister is an accomplished chemist, and that his work on spiroligomer bricks is innovative and has direct paths to important applications. Despite this, Professor Schafmeister has been struggling to find funding for some of his work. He argues that his spiroligomers could serve as a general set of very precise catalysts, superior to the irregular particles that are typically used. With his method it would be possible to perform industrial-scale reactions using precisely-synthesized, enzyme-like molecules in which specific groups are displayed in specific places.

The catalysis community has not yet been highly receptive to this idea. Even when approaching the problem from a chemical synthesis angle, Professor Schafmeister has had trouble finding funding, and it seems even less likely for his work to be funded if it goes in the cross-disciplinary and long-range research direction of positional assembly. Spiroligomers are particularly well-suited for positional assembly, so if a research program were created with the specific goal of building a molecular 3D printer or using positional assembly, that might enable Professor Schafmeister to further develop spiroligomer bricks for catalysis and other applications. Note that there are also other kinds of bricks that would be useful in such a program, e.g., peptoids, designed peptides containing natural and/or unnatural amino acids, or other chemical synthetic bricks.