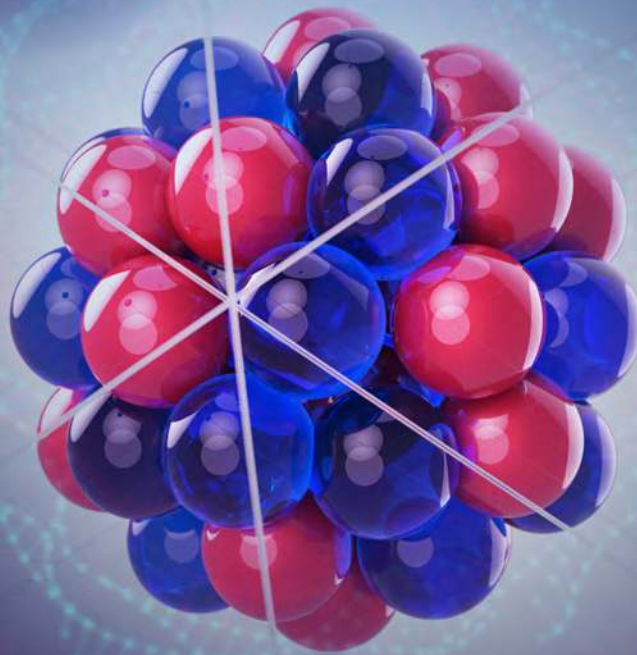




2017 Atomic Precision for Healthspan and Longevity Competition

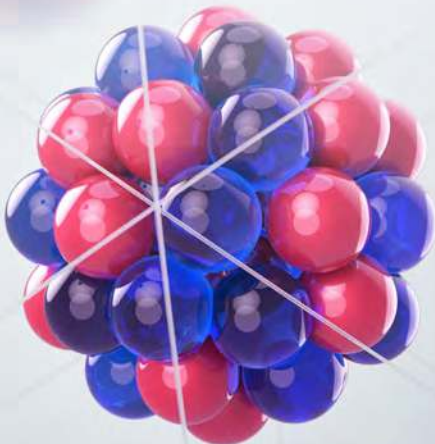
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Sept. 16-17, 2017
Palo Alto, CA

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ABOUT FORESIGHT



The [Foresight Institute](#) steers emerging and world-shaping technologies for beneficial purposes and has done so for more than 30 years. It is our mission to spark innovation across multidisciplinary fields such as synthetic biology, artificial intelligence, and especially nanotechnology. We serve as a nexus for innovation to catalyze research, reward excellence, restrain recklessness, and create community aimed at the long-term flourishing of humanity and the biosphere.

Foresight Team

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EXECUTIVE SUMMARY

Aging populations are a major challenge for the world. Machines small enough to monitor and intervene on individual cells would significantly improve the prospects of treating and preventing age-related diseases. Atomically precise manufacturing has the potential to produce such machines in large quantities and at low cost. We examined this possibility to respond to requests for research generated at the Atomic Precision for Medical Applications workshop [in this workshop series](#).

This Foresight workshop brought together researchers in longevity medicine and nanoengineering to identify near-term opportunities for collaborative projects in this area. These researchers came from academic, government, and commercial labs, and ranged from students to senior researchers.

The participants included a mix of theorists and experimentalists. The theorists provided a long-term vision and designs to aim for. The experimentalists identified feasible steps that can be done relatively soon and can get funded. This combination of viewpoints was especially important for this workshop, which looked for visionary ideas for significant improvements in longevity, and practical steps starting from existing technology and fitting with funding agency priorities (government, commercial, and nonprofit).

The competition aimed to identify productive collaborations among groups in medicine and atomically precise manufacturing. This occurred both through developing near-term project proposals spanning those



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[See the video](#)

fields and enabling researchers in each field to meet those in other fields with whom they might collaborate with in the future.

To achieve these goals, the workshop consisted of overviews of the two fields, exploratory discussions in small groups, and development of collaborative project proposals. The workshop concluded with presentations of these proposals. We summarize the highlights in this report and in the video above. To learn more about our competitions, please reach out.

Toward a long and healthy life for all of us,

Allison Duettmann

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INTRODUCTION

Two introductory talks provided background on the current challenges and prospects in longevity and atomically precise manufacturing.

Longevity

John Furber gave an overview of the mechanisms of aging. For developing interventions, he noted the need to identify the causal pathways of aging, not just incidental biomarkers associated with aging.

Aging is a complex process within and around cells. Numerous problems accumulate during aging, well before significant morbidity becomes evident. In dividing cells, telomeres are degraded at each division, limiting the ability of stem cells to renew tissue. In addition, non-dividing cells accumulate toxic byproducts of metabolism, decreasing their ability to remove those products. In the extracellular matrix, links form between molecules which the body is unable to remove. In the blood, the mix of molecules in the plasma changes during aging, and become less able to support cellular function or become toxic to cells. Stiffening collagen makes it harder for the heart to relax between beats, leading to blood pressure spikes. Within cells, mitochondria turnover, typically every 6 weeks, slows down as we age because the cell removal systems, i.e., lysosomes, become overloaded with chemicals they can't degrade. As we age, poorly functioning immune cells are not removed. Their buildup inhibits the growth of new immune cells, contributing to decreasing immune system performance with age.

This summary of changes during aging shows that multiple pathways lead to senescence. Hence we need to develop tools that can intervene at multiple levels, e.g., the body as a whole, the extracellular matrix, individual cells, and DNA within cells. It is especially important to protect and repair neurons and heart muscle cells.

Interventions include removing senescent cells, genetically engineering cells to repair or avoid effects of aging, and lifestyle changes such as meditation, exercise, and diet.

Current interventions apply biological mechanisms, e.g., genetic engineering. We have a great deal of experience with these approaches, and there is much ongoing effort to improve them. On the other hand, new tools from atomically precise manufacturing, such as nanorobots, remain years away. Even once we manufacture them, it will take a long time to learn how to use them safely and get regulatory approval.

A major challenge for developing interventions is how to evaluate their anti-aging benefits. Specifically, aging is a process that unfolds over decades, but we can't wait that long to evaluate new treatments. Instead, we must determine surrogates we can measure soon after trying a treatment to evaluate its effectiveness. This requires identifying biomarkers that respond quickly.

Some markers indicate aging but do not reflect causal mechanisms of aging. Others are directly involved in the changes seen during aging. Possible markers include telomere length and the accumulation of damaged molecules in cells. While companies are developing panels of biomarkers, it is unclear if or how well they predict remaining lifespan. Thus, we need a better understanding of these or other markers that reliably indicate aging. We learn a bit about possible markers from cross-sectional studies. But due to the large variation among individuals, longitudinal studies, following many people over time, would be much more informative. Unfortunately, such studies are expensive and take a long time.

Thus, developing methods for finding reliable biomarkers is a major opportunity for improving longevity research. This involves both interpreting data we have and collecting more data. For data we have, machine learning could help identify patterns reliably associated with aging. Creating more accurate and smaller sensors (e.g., via atomically precise manufacturing) could collect data over time on a per-cell basis from many cells simultaneously. Such sensors would greatly improve our ability to track changes due to treatments. To be most effective, we need large numbers of small devices (nanorobots), which in turn requires individual devices to be cheap to manufacture, in analogy with the very low cost per transistor made possible by the semiconductor industry.

Beyond finding reliable markers of aging, we also need precise treatment tools. For instance, lipofuscin accumulates in the lysosomes of cells. We need tools that can remove this accumulation, i.e., precise targeting of the tools on a sub-cellular scale and that perform without harming the cell during removal. This is an opportunity for nanorobots.

A summary of pathways discussed at the workshop is in the chart available at <http://legendarypharma.com/chartbg.html>. A review of aging mechanisms is the article "Hallmarks of Aging", DOI: 10.1016/j.cell.2013.05.039

Atomically Precise Manufacturing

David Forrest surveyed the progress toward atomically precise manufacturing and its benefits. We can distinguish two manufacturing paths for atomic precision:

- top-down, analogous to 3D printing by placing and bonding every atom in a specific position, and
- bottom-up, using self-assembly as in conventional chemistry and crystal growth.

Currently, self-assembly produces the widest variety of atomically precise structures. But it is limited in the number

INTRODUCTION

of atoms it can place with useful yields. By contrast, positional assembly guides atoms or molecules to specific locations and applies force to perform desired reactions. This contrasts with self-assembly, which relies on random encounters between molecules. An example of positional assembly in biology is a ribosome making proteins according to instructions provided by mRNA.

Atomically precise manufacturing aims to extend positional assembly to a wider variety of structures than biology provides. Such manufacturing could produce materials with properties much closer to their theoretical limits. For example, the tensile strength of metals is currently limited by atomic-scale defects rather than the bonding strength of the atoms.

Atomically precise manufactured products could have a wide variety of applications. These include food, clothing, shelter, computing, space exploration, environmental remediation, communication, as well as for health and longevity. Thus, the medical applications focused on for this workshop are only one of the many benefits of atomically precise manufacturing.

Atomically precise manufacturing could make nanorobots that are able to individually access, diagnose, and treat cells within the body. This could give molecular control of major diseases associated with aging, such as cancer and dementia.

In spite of these large potential benefits, we are still far from commercial-scale atomically-precise manufacturing. Current demonstrations include additive manufacturing with probe microscopes (e.g., Joe Lyding's lab), molecular lego (e.g., Chris Schafmeister's lab), precise membranes (e.g., Covalent), and molecular motors (e.g., Alex Zettl's lab). Examples in biology include bacteria flagella motors and T4 phage.

The Department of Energy (DOE) has a \$7 million program for atomically precise manufacturing in its Advanced Manufacturing Office. To obtain funding from this or other government programs, researchers must recognize the program manager needs demonstrable outcomes over a few-year funding cycle. This emphasizes funding near term work that reduces technological hurdles preventing progress toward atomically precise manufacturing. While it is fine to have a long-term vision (e.g., nanorobots for medicine), it is important for a proposal to include nearer term projects. For example, a vision to eventually manufacture medical nanorobots could start with improving existing molecular machines (e.g., Fraser Stoddart's lab), or start with modifications to biological machines that existing genetic engineering techniques could perform. Success with nearer term projects will encourage more funding for follow-up steps.

Additional background on atomically precise manufacturing is in David Forrest's presentation at the 2016 Foresight workshop on Atomic Precision for Energy¹.

¹ https://www.foresight.org/Conferences/Atomic_Precision_For_Energy_Report.pdf

NEEDS AND CAPABILITIES

After the overview talks, participants discussed the major challenges longevity treatments need to overcome, and the capabilities atomically precise manufacturing could provide. This part of the workshop aimed to identify overlaps between the needs of longevity treatments and the capabilities of atomically precise manufacturing. These discussions set the stage for the subsequent proposal and development of research projects for applying atomically precise manufacturing to improve health and longevity.

Slowing Aging

We need to learn not only how to use biomarkers as a measure of aging, but also the consequences of changing those markers with treatment. Specifically, will such changes slow or reverse aging (i.e., if markers are causal to aging), or just change the marker but not affect the aging process (if markers are correlated with aging changes, but not causal)?

We need more accurate chemical analysis, e.g., in blood, and with smaller samples, e.g., individual cells, so we can detect significant changes in a small population of cells. This is important because in the early stages of a treatment, changes may only occur in a few cells. Chemicals released by those cells into the blood would be highly diluted. The small change in a diluted sample would be difficult to distinguish from a small, normal variation produced by many cells rather than the target population of the treatment. Thus, we need single-cell measurements over time, instead of a single measurement for the average of population of cells. This is the cell-size version of the difference between cross-sectional and longitudinal epidemiology studies.

An example of this analysis is providing a quantitative measure of all proteins in a sample (blood or tissue), similar to today's ability to measure gene expression. This could help identify biomarkers of aging by comparing young and old samples during longitudinal studies. Extensions to this analysis would measure all molecules in a blood sample. Beyond chemical analysis, it would be useful to quantify microenvironments in blood, in cells, and in a cell's nucleus. This includes molecules, chemical environment (e.g., pH), and physical properties (e.g., stiffness and mechanical support forces). This broad range of measurements, followed over time, could help identify significant age-related

NEEDS AND CAPABILITIES

changes and suggest therapy targets. This level of detail should extend to querying every cell, e.g., identifying its type and whether its is cancerous or senescent.

To improve gene therapy, we need to target the changes to specific cells or target every cell with a single copy of the change. This contrasts with today's gene therapy, where injection delivers more genes to cells near the injection site than those far from the site. This gives a large variation in per-cell exposure, so some get too much and some too little.

In addition to a need to improve the data we can collect, a major practical hurdle is data sharing. We need the data to be easily available to researchers. Currently data is scattered in universities, companies, and government. Access is restricted by privacy, legal, and research competition issues created by funding incentives. We need effective approaches to data sharing in spite of these restrictions.

After discussing needs related to data collection and sharing, the group turned to requirements for improved therapy. This involves both precise tools, such as nanorobots, as well as the knowledge of how to use them effectively.

Tools to operate on cells should include the ability to manipulate apoptosis. This is the best way to remove undesired cells with minimal damage to surrounding cells.

We need tools that can operate within individual cells. These include repairing DNA inside cells, including epigenetics, and removing debris accumulation in cells, such as misfolded proteins, that the cell is unable to remove itself.

We also need to learn how to effectively use such tools when they become available. For example, we need to know how memory is stored in the brain at a molecular level. This is necessary so that tools that replace or repair cells in the brain can be designed to preserve or enhance memory. This is particularly important for treating or preventing dementia. For example, in some cases, restoring brain function of Alzheimer patients appears to restore memory, suggesting disease destroys the ability to retrieve memory but doesn't destroy the memory encoding.

A major aim of developing tools to enhance longevity is to prevent aging damage rather than having to fix damage after it occurs.

Designing Atomically Precise Machines

Atomically precise manufacturing promises to create a wide range of products with superior performance. In addition to developing the manufacturing technology itself, a major challenge is designing these products. Because it is not yet possible to make the molecular machines discussed at the workshop, we must instead rely on computer simulations to determine their behavior and improve their design. Unfortunately, today's computational chemistry is limited in accuracy or number of atoms that are feasible to simulate. As an example, nanorobots with size comparable to bacteria could consist of molecular machines with billions of atoms. Simulating such machines in atomistic detail is far beyond current computational chemistry capabilities. This observation led to discussion of approaches to extend computational chemistry to more complex molecular machines.

One possibility is quantum computing, which could improve computational chemistry by simulating chemistry directly. Such simulations are a potential near-term application of quantum computing. It does not require the large numbers of qubits necessary for practical use of algorithms for other tasks where quantum computers appear to have a substantial advantage, such as factoring.

Machine learning could also improve computational chemistry. This technique could generalize from standard computational chemistry methods, such as density functional theory (DFT) calculations. In this case, machine learning would be applied to data produced by a set of DFT calculations of the behavior of various molecular machines. The learned model could then predict the behavior of new variations of those machines far more rapidly than a new DFT

calculation for each variation. If machine learning is accurate enough, this will enable fast screening of possible molecular devices, allowing designers to focus more intensive computation or synthesis on just the candidates predicted to perform well. Machine learning could not only help identify useful molecular machines, but also suggest reaction sequences to manufacture them. An example is learning reactions to preferentially select among stereoisomers of a molecule.

Molecular Machines for Medicine

Eventual clinical use of molecular machines will face a regulatory challenge. The FDA may be reluctant to permit their use since the mechanisms will be far more complicated than drugs and medical devices evaluated today. Currently, this reluctance is a problem even for approving simple nanoparticles. This suggests regulatory hurdles will be significant problems for complex machines (e.g., nanorobots). Other countries are more receptive to novel approaches, e.g., Germany, China, and India.

Even before their approval for clinical use, molecular machines will be major improvements in detecting proteins and other biomarkers in tissue or blood samples. Since such uses are outside the body, gaining regulatory approval will likely be much easier than for nanorobots operating in the body.

Workshop participants identified a range of capabilities for atomically precise products that would have significant medical benefits.

For instance, we need large numbers of tiny, cell-sized sensors, to address many of the challenges for improving health and longevity identified earlier in the workshop. Ideally, such devices will combine capabilities to sense, compute, and act on individual cells, i.e., nanorobots. These machines need computation to allow sophisticated decision and control. Due to their large numbers and operation deep within the body, they need autonomous control, to handle decisions on a per-cell basis, with only overall guidance via external signals from a doctor.

The machines may need to be re-programmable during operation. As an example scenario, a large number of nanorobots could collect data on many cells. Each robot would observe only one or a few cells so would not have the big picture required to determine any necessary treatment. Instead, the robots could send their observations out of the body. This data, collected from many cells, would be integrated by an external computer and presented to the treating physician. Based on this detailed data, the physician would decide on a treatment strategy, and communicate the plan to the robots. The robots would then act according to these instructions as they apply to each robot's microenvironment.

Sensing is a key requirement for nanorobot diagnosis. For detecting rare molecules, using equilibrium binding could swamp the sensor with high-concentration background molecules unless the sensor is extremely selective. For example, suppose the target molecule concentration is one-millionth that of other molecules and the sensor is fairly selective, e.g., binds the target a thousand times more strongly than the other molecules. In this case, in equilibrium, the other molecules will swamp the binding site. This would make the sensor useless for its intended use if it is not possible to design a much more selective sensor. An alternative approach is kinetic proofreading, which uses an irreversible process, as discussed in the article "Kinetic Proofreading", DOI: 10.1073/pnas.71.10.4135

Atomically precise manufacturing could make selective membranes to improve filtering. Such membranes could improve drinking water and blood filtering. Adding computation to the filtering could analyze constituents and decide which to return to the blood. This could greatly improve dialysis treatments.

PROJECT PROPOSALS

After surveying challenges to improving longevity and the potential of atomically precise manufacturing, participants divided into groups to develop research projects. The aim of these projects was to identify ways to apply atomic precision to health longevity that might be achieved in the relatively near future.

Each group gave a presentation on their project that addressed several questions:

- What medical problem does the project solve?
- What are the innovative claims?
- What are the tangible end goals?
- How could the project benefit other research goals, whether or not the project meets its own goals?

The project discussions included identifying the capabilities of atomically precise machines that would be useful for the project. In particular, identifying:

- What aspects of the project require such machines?
- What are the quantitative specifications of the machines? E.g., size, power, computing, and sensors?

Comparing these requirements from the projects identified the importance of defining terminology to communicate among interdisciplinary researchers.

An overview of the final projects can be found below:

AgeNaut

Create a microscopic device to measure chemicals inside blood vessels. The device would be injected into the blood, attach to a cell, measure its properties, then release and continue flowing through vessels until it gets near skin where it can communicate data to an external receiver. The device is less than 3 microns in size so that it can go through capillaries. It consists of a diamond surface for biocompatibility, surrounding a silicon computer. The device is passive while collecting information from a cell. It receives external power when near the skin to communicate its data.



[See the video](#)

This device is a step toward having a computer at each cell. It obtains measurements without the need for a biopsy, is noninvasive, and provides precise detection of blood contents. Applications include first looking for cancer biomarkers in blood, and later extending to measure aging biomarkers as we learn what those are. The device is not active during its journey through blood, i.e., it is not a continuous sensor. Instead, it acts when it binds to a target cell type.

Open questions: How to remove the devices from the body after use? What is the signal-to-noise ratio of their sensors?

Filtering Cleanup Crew

Use atomically precise membranes made with a selection of pores from a standard library, with sizes and specificity tuned to select and reject specific molecules. The longevity application is filtering the blood to restore blood chemistry to youthful state.



[See the video](#)

Open questions: At a molecular level, what is the difference between young and old blood? Are these molecules distinguishable from other molecules in the blood by size or selectivity of pores that could be fabricated into membranes?

Healthspan Data and AI

Learn to distinguish biological from chronological age with machine learning. This requires significant training data. The learning would attempt to predict, from patient data from a year ago, whether that person died. The project would then look for features predicting death to suggest early interventions.



[See the video](#)

Open questions: How to gain access to longitudinal medical data on a large group of people for training, e.g., obesity as marker for aging? How far in advance can this information identify medical problems?

Nano-Doctor Octopus

Use DNA origami to create structures with multiple binding sites at precisely specified distances. These structures would selectively bind to cells based on recognizing multiple receptors with specific distance relationships among them. The application for longevity is to bind to senescent cells, marking them for removal. This assumes each cell has a unique pattern of binding sites when considering the combination of chemical affinity and the distances between the sites on the cell surface.



[See the video](#)

Open questions: Is there a distinctive pattern of markers for senescent cells, or do they vary among individuals? How useful is including distance as a binding criterion? How much do the biomarkers of senescent cells move around on the cell surface?

Plaque Digger

Create a nanorobot able to recognize and mechanically remove plaques from blood vessel walls. The robot would detect plaque by measuring stiffness of the vessel wall, because plaques are stiffer than normal vessel walls.



[See the video](#)

The protocol for using these robots would start with external imaging to determine the location of plaques. Two-photon near-infrared light would then be targeted to the plaque locations. The robots would only become active when receiving that light. This would allow injecting the robots into the blood while having them active only at plaque locations. The robots have stiffness sensors to distinguish plaque from vessel wall. These sensors allow the robots to remove plaque while not damaging the surrounding vessel wall when they reach it. These robots would be less invasive and more precise than surgical stents, which injure the artery wall.

Open questions: Will removed pieces of plaque trigger clots before they are eliminated from the blood, e.g., by macrophages? Will plaques regenerate after removal? How will robots bind themselves to plaque during operation, i.e., are there receptors on the plaque they could bind to with enough force to allow them to remain in place while digging through the plaque?

AVENUES FOR PROGRESS

A few areas are especially promising for accelerating progress on leveraging atomic precision for increasing healthspan:

Data Limitations

A theme running through the project discussions was the need for quantitative data on aging and the capabilities of atomically precise machines. The current lack of such information and difficulty obtaining it are a major barrier to developing medical applications of microscopic machines. This problem arises from both the technical difficulty of obtaining the data and institutional barriers to sharing the data.

Biomarkers of Aging

A recurring question during the project discussions was exactly what biological measurements the proposed machines should focus on. In particular, what biomarkers of aging could nanorobots reliably use to diagnose and treat aging. This biological data is experimentally difficult to obtain at small scales in the diverse microenvironments that nanorobots would encounter in medical applications.

In addition, researchers face significant cultural and institutional barriers to sharing biological data. For instance, negative experimental outcomes are usually not published. So other researchers don't learn from those experiences what to avoid.

Institutional challenges include creating incentives for researchers to share their data. The current research culture

and competition for funding encourage researchers to limit access to their data so they have time to benefit from it themselves. For sharing clinical data, finding ways to share data while handling patient privacy is important. Developing incentives and a culture for sharing data has been recognized for specific disease categories, such as cancer with the Biden Cancer Initiative, and needs to extend to aging-related diseases more generally. A key part of this institutional problem is funding. That is, who pays to make research data available in a format easy for other researchers to understand and use? Such data curation can be time-consuming and is not supported by most research grants.

Another institutional challenge is gaining broad recognition of aging as a disease to address as a whole, rather than just treating consequences, such as cancer and dementia, after they occur.

Longevity researchers need to standardize experimental results, and make data easily accessible to other research groups. Easily comparing and combining data from different groups is a significant software engineering challenge, and particularly important to support machine learning approaches that require large data sets. This requires not only that the data be available, but available in standard machine-readable formats, including details such as units and measurement conditions to aid reproducibility and combination with other data. Examples of steps in this direction are the collection of quantitative biological data at Harvard's Bionumbers.org project and the Chan Zuckerberg Initiative's development of software tools to facilitate sharing of biological data.

Capabilities of Atomically Precise Machines

The workshop projects proposed several atomically precise machines, particularly nanorobots. A limitation in these discussions was the lack of quantitative estimates of the capabilities of these machines. For instance, what chemical targets could they reliably sense at small scales? How long would those measurements take? What forces do the robots need to apply to biological structures, and how much power would be available to them? How would the robots communicate their information outside the body? How would they be removed from the body after use? How safe would the robots be in the body?

Because these machines cannot yet be manufactured, we can only estimate these properties from dimensional analysis or computer simulations. While computational chemistry can evaluate behavior of molecular machines in isolation, these simulations must be combined with accurate information on the biological environments the machines will operate in. Thus, the computational methods are dependent on the available biological data at scales relevant for robot operations. Such data is particularly important for evaluating the biocompatibility of proposed machines.

These scales span several orders of magnitude. For instance, the term "nanorobot" is applied to machines ranging in size from DNA robots (nanometers) to hypothetical cell-sized robots (microns). The required machine capabilities in some of the project discussions ranged over these sizes. The multiple meanings of "nanorobot" can be a point of confusion when developing and evaluating proposals.

An institutional challenge for developing medical applications of atomically precise manufacturing is the lack of clarity on the regulatory approach to nanorobots at the FDA. This uncertainty adds to the already substantial technical risk of such projects. This risk inhibits funding, both from government programs and private funding for startups.

CONCLUSION

Aging involves changes to the body at the molecular scale. Machines that can operate at this scale offer the potential to significantly improve health and longevity. The workshop discussions and the project proposals identified the most promising opportunities for applying atomically precise manufacturing to this challenge. We encourage further work on solving data limitations, specifying biomarkers of aging, and capabilities of molecular machines to accelerate progress further.





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Sept. 16-17, 2017
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