Workshop on
Synthetic Biology for Aging Research

Division on Aging Biology, National Institute on Aging (NIA)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)

September 6-7, 2023

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Executive Summary

The workshop "*Synthetic Biology for Aging Research"* was convened on September 6 and 7, 2023, by the Division of Aging Biology of the National Institute on Aging, in conjunction with the National Institute on Biomedical Imaging and Bioengineering. The aims of the workshop were to promote the application of synthetic biology principles to the field of aging research and to stimulate collaborative research across the two disciplines. Research on the biology of aging focuses on understanding the cellular and molecular processes that underlie aging and aging-related changes in organismal health, while synthetic biology is focused on engineering living systems capable of performing useful functions. During the workshop, participants explored how researchers can utilize tools from synthetic biology (e.g., synthetic regulatory circuits) to address questions regarding the biology of aging and to develop the capability to intervene in aging processes and impact aging-related outcomes.

The workshop opened with introductory presentations in the fields of aging research and synthetic biology that outlined foundational concepts and major research questions in the two disciplines. A series of short talks were presented, in which participants highlighted their research. During the first two breakout sessions, participants were divided into four groups—each including individuals from both synthetic biology and aging research backgrounds—to identify opportunities for cross-disciplinary collaboration. These opportunities were discussed further during the third breakout session.

The first two breakout sessions generated several ideas for collaboration in the areas of discovery and therapeutic concepts.

Regarding discovery,

- key opportunities to apply synthetic biology to aging research include developing
  - amplifiers, reporters, and recorders of molecular signatures (e.g., biomarkers, phenotypes, dynamics, and heterogeneity) to elucidate aging-related dynamic processes, temporal changes, facets of heterogeneity, and noise;
  - cellular sentinels that can trigger amplifiers that initiate the delivery of a therapy; and
  - molecular readouts of functional metrics or performance that could be used to reflect the state of cell health through its maturation, peak, and decline.
- using synthetic biology tools to perturb aging processes and evaluate the reaction of cells or organoids to help distinguish correlation from causation.
- Integrating synthetic biology approaches to develop new model systems for aging.

Regarding therapeutic concepts, collaborative ideas generated included developing:

- screening tools for drug development; drug delivery strategies;
- cell-based therapies for modulating the aging environment; and
- tools for interrogating and perturbing intercellular coordination and communication.

Synthetic biology could enable greater precision in designing safe and effective therapies by determining which targets and tissues underlie greater lifespan. For example, synthetic

parabiosis—the idea that complicated interventions can be recapitulated into interventions that are simple and translational—could potentially be used to shift or reprogram the overall aging "state" of a patient. The tools of synthetic biology could be applied to develop strategies for rejuvenation through targeted delivery (e.g., to specific tissues, cell types, and the extracellular matrix), to use chromatin engineering to rejuvenate cell states, and to engineer the microbiome to affect aging. Approaches that focus on the mitochondrial axis as a pillar of aging include mitochondrial therapies, the use of synthetic mitochondria, and interrogating organelle-scale contributions to aging. Moreover, synthetic biology could be applied to create a diversity of natural products as inputs into the drug discovery platform for use in aging treatment.

In the third breakout session, four working groups developed potential research plans. **Working Group A** focused on the opportunity to bring orthogonal systems and synthetic biology tools into the *C. elegans* worm model. This model has great potential to integrate novel synthetic biology approaches with aging biology to perform complex research for which existing foundational tools are insufficient. Beginning this work will require determining what is needed to build circuits to facilitate external control of aging-related genes or autonomous control to change aging phenotypes. **Working Group B** discussed collaborative research using sentinel cells—which can report on and respond to cellular biomarkers—to study the aging process. Sentinel cells can report a variety of data (e.g., transcriptomics, proteomics, molecular secretions) that may be used to identify biomarkers of aging. The group also discussed how synthetic biology could be used to interrogate the sender-receiver phenomena within the secretome; this approach could help to elucidate the mechanisms by which senescence spreads and by which the spread is regulated. **Working Group C** focused on collaborative opportunities related to precision aging at the cellular level, and specifically on the development of *in vitro* human cell-culture platforms and synthetic reporters to better understand aging at the single-cell level, induce aged cell states, and screen therapeutics for cellular-level effects. Synthetic biology approaches could be applied to determine whether genes implicated in an aging-related process are causing that process or merely correlated with it—e.g., by applying synthetic regulation to genes or artificially controlling other cellular features—and to build promoters responsive to researcher-selected inputs to control the timing and magnitude of interventions. **Working Group D** suggested opportunities for collaborative work on payload delivery and targeting specific cell types. Given that targeting and killing senescent cells can intervene in aging processes, and senescent cells are very heterogenous, it would be useful to apply synthetic biology to identify and specifically target distinct types of senescence. Another area discussed involved the potential for developing a reporter quantifying increasing inflammation that occurs with aging (i.e., inflammaging). This could be achieved with a cell that hones in on sites of inflammation and reports—over the lifetime of an organism—the location and amount of inflammaging. Another opportunity is to use synthetic biology tools to develop markers for early versus late senescence, then quantify those to inform the creation of a reporter for early-senescent cells versus late-senescent cells. Better understanding this temporal aspect of senescent cells, and their dynamic changes, through longitudinal monitoring in a human or model system could yield a host of insights.

1 Appendix 1

NIA and NIBIB

Synthetic Biology for Aging Research

Gateway Conference Rooms, Bethesda, MD
September 6-7, 2023

AGENDA

DAY 1 – Wednesday, September 6

9:20 AM – 9:30 AM Welcome Remarks

9:30 AM – 10:15 AM Introductions and Overview from Co-Chairs
Josh Leonard, Ph.D., Northwestern University
Birgit Schilling, Ph.D., Buck Institute for Research on Aging

10:15 AM – 11:45 AM Participant introductions:

- ***Flash talks (3 slides/5 min)*** *from Invited participants giving broad overview of their research programs, questions being investigated and experimental approaches*
- ***Lightning talks (1 slide/1 minute)*** *from trainees to introduce themselves and their research projects/expertise*

  Nan Hao, Ph.D., University of California San Diego, "Engineering gene networks to promote longevity"
  Hetian Su, Ph.D. (Trainee), University of California San Diego, "Understand cell longevity as a result of system dynamics"
  Patrick Phillips, Ph.D., University of Oregon, "Genetics of Complex Traits"
  Zach Stevenson, Ph.D. (Trainee), University of Oregon, "Increasing The Throughput of Transgenesis In Animals For Synthetic Biology: T.A.R.D.I.S. (Transgenic Arrays Resulting In Diversity of Integrated Sequences)"
  Birgit Schilling, Ph.D. (Co-chair), Buck Institute for Research on Aging, Role of Senescence and ECM during Aging, and Development of Biomarkers and Aging Interventions"
  Joanna Bons, Ph.D. (Trainee), Buck Institute for Research on Aging, "Investigating Dynamic and Spatial Proteome Remodeling during Aging using Proteomics"
  Nathan Basisty, Ph.D., National Institute on Aging, "Translational Geroproteomics Unit, Developing and applying proteomic tools to enable the translation of age-related disease interventions"
  Bradley Olinger, Ph.D. (Trainee), National Institute on Aging, "What Role Do Senescence Markers Play in Age-Related Clinical Traits?"
  Jennifer H Elisseeff, Ph.D., Johns Hopkins University, "Tissue mapping across the lifespan"
  Joscelyn Mejias, Ph.D. (Trainee), Johns Hopkins University, "Age and Sex Differences in the Fibrosis Immune Response"
  Karmella Haynes, Ph.D., Emory Winship Cancer Institute, "Haynes lab for chromatin epigenetic engineering

Seong Hu "Rick" Kim, Ph.D. (Trainee), Emory University, "Investigating Promoters and Enhancers Targeted by a Synthetic Reader-Actuator in H3K27me3-Enriched Chromatin"
Josh Leonard, Ph.D. (co-chair), Northwestern University, "Development of parts & programs for implementing synthetic biosensing, regulation, and control, and application-driven development of next-generation cell and gene therapies"
Amparo Cosio, Ph.D. (Trainee), Northwestern University, "Can we harness natural receptor mechanisms to engineer synthetic biosensors that respond to therapeutically-relevant molecules?"
Tara Deans, Ph.D., University of Utah, "Synthetic biology: engineering synthetic gene circuits to direct cell fate"
Michell Lewis, Ph.D. (Trainee), Huntsman Cancer Institute, University of Utah, "Engineered Platelets for Therapeutic Delivery"
Laura Segatori, Ph.D., Rice University, "Engineering synthetic regulatory systems to program mammalian cells"
Caleb Bashor, Ph.D., Rice University, "Bashor Lab | We engineer synthetic regulatory circuits in human cells"
A.J. Walters, Ph.D. (Trainee), Rice University, "What if barriers in MSC-based cell therapy could be overcome with synthetic biology?

11:45 AM – 1:15 PM	LUNCH (On your own)
1:15 PM – 2:15 PM	Breakout Session 1 (Landscape analysis and blue-sky ideation)
2:25 PM – 3:25 PM	Breakout Session 2 (Potential Connections and Opportunities)
3:35 PM – 4:00 PM	BREAK
4:00 PM – 5:00 PM	Read out from Day 1 Breakout Sessions (plenary)
5:10 PM – 6:10 PM	Trainee Session (with NIA/NIBIB training officers)
7:00pm –	Group dinner

DAY 2 – Thursday, September 7

9:00 AM – 10:00 AM	Report out and discussion of ideas for collaboration by the co-chairs
10:00 AM – 11:00 AM	Breakout session 3 (open discussion)
11:00 AM – 11:30 AM	BREAK
11:30 AM – 12:30 PM	Synthesis and Feedback (plenary)
12:30 PM – 1:00 PM	Wrap up and closing remarks
1:00 PM	Adjourn