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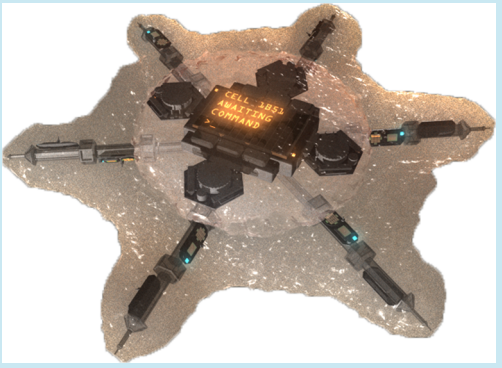
The Rise of Mammals

Joshua N. Leonard*

Department of Chemical and Biological Engineering, Chemistry of Life Processes Institute, Member, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Evanston, Illinois 60208, United States

ABSTRACT: Mammalian synthetic biology represents a vibrant and growing technical discipline. As this nascent field matures, technologies for engineering sophisticated mammalian cell functions are enabling the development of novel therapies that address unmet medical needs. These transformative capabilities are likely to impact clinical practice in ways that have yet to be identified.



"What you see is that the most outstanding feature of life's history is a constant domination by bacteria." —Stephen Jay Gould[1]

While this observation by the preeminent narrator of natural history remains true of the natural world, the field of synthetic biology increasingly includes vigorous activity reaching across all kingdoms of life. In no corner has this transformation been more dramatic than in the emergence of a vibrant mammalian synthetic biology community over the last half-decade. Efforts to implement design-driven engineering of mammalian cell functions initially paired conceptual and experimental tools developed through work in microorganisms with foundational approaches established in cell biology and gene therapy. Today, these efforts are already generating viable therapeutic technologies to address unmet medical needs. However, the greatest impacts of mammalian synthetic biology will almost certainly arise in ways that have yet to be elucidated.

In the burgeoning area of engineered cell-based therapies, leveraging the concept of *cell-cum-device* may help to translate promising preclinical strategies into viable therapies. As engineered mammalian cell technologies move from the lab to the clinic, considerations of safety, efficacy, and manufacturability will increase the importance of evaluating and potentially mitigating performance variability between cells. For autologous cell-based products, variability between patient-donors imposes an additional layer of complexity. Because synthetic biology investigations naturally frame biological functions as engineered systems subject to evaluations of design goals and performance characteristics, this field has already illuminated both sources of cell-to-cell variability and potential strategies for achieving desired behaviors in the face of such biophysical realities. Indeed, developing strategies for achieving the desirably robust performance of engineered mammalian cell functions is an active area of investigation. Ultimately, these approaches could help to address clinical challenges that have already been identified.

No application better illustrates the need for improved control over cell-based therapy performance than immunological therapy for cancer. In the wake of the remarkable success with which Carl June and others have used engineered T cells to treat patients with B cell leukemia[2,3] and several other malignancies, commercial and academic efforts to translate and extend this approach have rapidly proliferated. However, each individual's immune system is unique, as is the manifestation of cancer-associated immune dysfunction in different patients with different cancers. Consequently, identifying generally applicable strategies for striking a balance between effective control of cancer without inducing life-threatening immune excitation has proven challenging. To address this need, synthetic biology approaches may ultimately enable physicians to generate more sophisticated cellular programs and to ensure that such programs are executed consistently to improve both safety and efficacy. Such capabilities could also meet similar needs in other promising areas of research. For example, reprogramming and differentiating stem cells for regenerative medicine could be facilitated by improving on the yields and homogeneity of cell products generated by existing methods. In coming years, striking a balance between complexity, robustness, and manufacturability will be an opportunity and challenge of increasing practical importance as the list of promising preclinical mammalian synthetic biology technologies continues to grow.

Some transformative technologies in the synthetic biology toolkit have yet to be fully harnessed for mammalian cell

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engineering, and the most prominent of these is high throughput synthesis and assembly of DNA. The declining price of DNA synthesis has certainly facilitated research involving mammalian cells. However, no projects in this area yet approach the ambitious scope of synthesizing an entire microbial genome or searching through vast combinatorial genetic space to achieve microbial biosynthesis of novel and/or valuable products. A cogent example of the disruptive impact that such technologies could have in this space is the recent rapid synthesis of a novel influenza vaccine in an epidemiological live-fire exercise.[4] By integrating surveillance, bioinformatics, and rapid DNA synthesis and assembly, this public–private partnership demonstrated that following the detection of a new viral strain, a candidate vaccine was synthesized on the other side of the world in under a week's time. Given that automated DNA synthesis and assembly facilities will soon be in place in core facilities across the globe, how these capabilities will be harnessed for mammalian synthetic biology applications remains largely an open question.

A final opportunity for impact is the development of novel capabilities to drive fundamental research. Similar to GFP, Cre/lox recombination, and optogenetics, mammalian synthetic biology technologies could provide new platforms for interrogating and manipulating physiology at the organismal scale. Such tools could enable researchers to custom-program the manner in which cells communicate with one another and respond to their environments, effectively rewiring complex multicellular networks in manners not previously possible. Thus, mammalian synthetic biology promises to impact fields ranging from neuroscience and immunology to developmental biology and regenerative medicine. Returning to an analogy from natural history, Gould once praised the suitably wry motto of the Paleontological Society: Frango ut patefaciam—*I break in order to reveal*. This statement might also describe some of the profoundly powerful approaches that have elucidated so many inner workings of our cells. Perhaps with the emergence of mammalian synthetic biology, we can add the complementary statement—*I build*.

AUTHOR INFORMATION

Corresponding Author

*E-mail: j-leonard@northwestern.edu.

Notes

The authors declare no competing financial interest.

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