Author biographies:

Dr. Rudolf Jaenisch is Professor of Biology at the Whitehead Institute and the Department of Biology, Massachusetts Institute of Technology. He has generated the first transgenic mice carrying exogenous DNA in the germ line and was the first to use insertional mutagenesis for identifying genes crucial for embryonic development. Key contributions have been the study of epigenetic processes in gene expression, imprinting and X-inactivation and in diseases such as cancer and mental retardation. More recently he has focused on mammalian cloning and on reprogramming somatic cells by defined factors. The possibility to generate patient specific induced pluripotent stem cells has great potential for studying complex human diseases such as Alzheimer and Parkinson's and may offer novel strategies for treatment of disease.

Dr. Yosef Buganim is a Postdoctoral Fellow in the Jaenisch laboratory at the Whitehead Institute in MIT. Buganim received his B.Sc. and M.Sc in Biology with Honors from Bar-Ilan University, Israel, and his Ph.D from The Weizmann Institute, Israel in the Rotter's laboratory. His graduate studies discovered a novel tumor suppressor activity for the wild-type p53 protein in regulating the Ras oncogene activity. His post-doctoral work shed light on the molecular mechanism of somatic cell reprogramming to pluripotency employing single-cell techniques, and also demonstrated direct conversion of fibroblasts into functional embryonic Sertoli-like cells by transdifferentiation. His notable awards include "Wolf Foundation Award for B.Sc studies in Israel and the NIH Ruth L. Kirschstein National Research Service Fellowship. His current research interests include cell fate decisions and cell plasticity.

Dina Faddah is a Ph.D. candidate in the Jaenisch laboratory at the Massachusetts Institute of Technology, Cambridge, utilizing single-cell techniques to understand the molecular mechanisms underlying the reprogramming of somatic cells to pluripotency and the gene regulation of embryonic stem cells. Faddah received her B.S. in Biology with Honors from The University of North Carolina at Chapel Hill in 2006, studying yeast genomic polymorphisms in Jason Lieb's laboratory and Todd Vision's laboratory. From 2006-2008, she was a Postbaccalaureate Intramural Research Training Award Fellow at the National Institutes of Health, Bethesda, Maryland, in Francis Collins' laboratory, investigating Hutchinson-Gilford progeria syndrome.

Online Key points

1. Insights gained from population-based and single-cell studies reveal two major phases during reprogramming.
2. OSK act as "pioneer" factors that open chromatin regions and allow the activation of those genes that are essential for establishment and maintenance of the pluripotent state.

This promiscuous binding of OSK is also essential for the initiation of crucial processes for the reprogramming process such as proliferation and MET.

3. We present evidence supporting a model in which the reprogramming process contains an early stochastic phase that leads to the instigation of a second more deterministic phase that starts with the activation of *Sox2*.
4. How similar are iPSCs and ESCs? The available evidence has not settled whether the alterations seen in iPSCs are the result of the reprogramming process or due to pre-existing genetic and epigenetic differences among parental fibroblasts.

Glossary

1. Deterministic: A collection of actions during the reprogramming process, which must occur in a particular order (i.e. activation or silencing of different combinations of genes) prior to eventual iPSC formation.
2. Stochastic: unpredictable and random action that leads at some point to the activation of genes that then will set the cells on a path to iPSCs.
3. Hierarchical: An arrangement of items that are lined directly or indirectly. For reprogramming, a predictable sequence of gene activations.
4. Pioneer factors: A subset of transcription factors that initially access silent chromatin and direct the binding of other transcription factors during embryonic development. Pioneer factors (OSK in the case of during reprogramming) create a hyperdynamic chromatin state.
5. Promiscuous binding: In this context, the multiple distal genomic sites initially occupied by OSK that do not correspond to the distal genomic regions that are bound by these pluripotency factors in ESCs.

6. Super enhancer: An expansive region of DNA that is bound by proteins and large amounts of Mediator to enhance the transcription of genes.
7. Single-molecule-mRNA-FISH: An in situ hybridization method capable of detecting individual mRNA molecules, thus permitting the accurate quantification and localization of mRNA within fixed sample.
8. Rate limiting step: In this context, a step that is responsible for the low efficiency of the reprogramming process. Reprogrammable cells must pass this step to instigate the late hierarchical phase and to become fully reprogramed. This step determines the length of the reprogramming process.
9. Factor stoichiometry: Different levels of and the ratios between reprogramming factors (OKSM) in single cells.
10. Predictive markers: Genes that are activated early in the reprogramming process in rare cells that have a higher probability of activating the *Sox2* locus and to become fully reprogrammed iPSCs.
11. Hyperdynamic chromatin state: A state of dynamic chromatin characterized by hyper mobility of chromatin-associated proteins in pluripotent cells.
12. Developmental potential: The sum of all the fates a cell can undergo under any experimental condition.
13. Cell plasticity: The ability of a cell to acquire a new identity and to adopt an alternative fate when exposed to different conditions.
14. Transcription factor-mediated reprogramming: Conversion of somatic cell to the pluripotency state using defined transcription factors.

15. Epigenome: Heritable changes in chromatin (such as histone posttranslational modification and DNA methylation) that affect gene expression.
16. Chromatin modifier: A protein that can modify chromatin architecture and thereby control gene expression.
17. Transcriptional amplifier: A protein, like c-Myc, that can increase expression from any active promoter.
18. Cell heterogeneity: Variations among cells that occur due to intrinsic or extrinsic noise.
19. Refractory: Unresponsive to a stimulus or unable to bind a transcription factors.
20. Mediator: A complex comprised of multiple protein subunits that function as a transcriptional coactivator to increase gene expression.
21. Pluripotency initiating factors (PIFs): Protein factors that are responsible for triggering the late deterministic phase responsible for transitioning to the pluripotent state.
22. Reprogramming: Conversion of one cell type to another cell type by transcription factors or chemical defined media.
23. iPSCs: induced pluripotent stem cells. This term was coined in 2006 by Takahashi and Yamanaka.

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ToC Blurb: to be added by editor

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