Late July Spotlight: Genetics and Epigenetics of Development Group (Rocha lab)

Understanding how transcription factors induce divergent cell fates rapidly

Joyce J. Thompson, Daniel Lee, Apratim Mitra, Sarah Frail, Ryan Dale, Pedro P. Rocha

All mammalian life begins with a single-celled totipotent zygote. During embryonic development, successive cell-divisions, and cell-fate specification events, result in the temporal emergence of diverse cell-lineages. Cell fates are typified by gene regulatory networks controlled by lineage-determining transcription factors (TFs). To specify divergent cell-fates from progenitors, lineage-determining TFs are required to modulate chromatin, access their specific targets, and activate a transcriptional program that will promote commitment into a specific lineage, while simultaneously inhibiting alternate fates. How lineage-determining TFs accomplish this massive feat within a rapid time-frame has been a long-standing question which is still poorly understood. We use cell-fate decisions made in the mouse blastocyst as a model system to address this question.
In both humans and mice, three cell-types, trophectoderm (TE), epiblast (Epi) and primitive endoderm (PrE), are specified within the first 90 hours of development by complex interactions between lineage-determining TFs. At embryonic day 3.0 (E3.0; three days post-fertilization), the first cell fate decision uses positional cues to specify the outermost cells as TE, which eventually form the placenta, and internal cells as the pluripotent inner cell mass (ICM). At E3.25, a fluid filled cavity called the blastocoel forms, pushing the ICM to one side of the embryo, now named the blastocyst. Up to E3.5, all ICM cells co-express GATA6 and NANOG, but within the next 24 hours (E3.75-4.0), the balance in expression stochastically tips towards either TF, initiating specification into Epi (NANOG) or PrE (GATA6) fates. At E4.5, this second cell fate decision concludes with segregation of PrE and Epi cells, and the blastocyst implants. While NANOG and GATA6 are drivers of the second cell-fate decision, how they coordinate to maintain plasticity in ICM cells, but oppose each other to drive divergent cell-fates is largely unknown. We used in vitro and in vivo approaches to describe the molecular mechanisms by which GATA6 quickly induces the PrE fate while repressing the NANOG-controlled Epi lineage.

We found that rapid PrE differentiation is achieved through the action of three different mechanisms: fast exchange of transcription factor binding, remodeling of histone acetylation and quick reconfiguration of enhancer-promoter contacts. To activate the PrE program, GATA6 functions as a pioneer TF by inducing nucleosome repositioning at regulatory elements controlling PrE genes, making them accessible for deposition of active histone marks and leading to rewiring of chromatin interactions and ultimately transcriptional activation. Simultaneously, GATA6 also binds regulatory elements of Epi genes followed by eviction of the Epi-specific TFs NANOG and SOX2, loss of active histone marks, and reduction in chromatin accessibility that culminates in transcriptional repression. Unexpectedly, we found that the evicted NANOG and SOX2 are transiently redirected to PrE regulatory elements occupied by GATA6. Our study reveals that Epi and PrE TFs can bind and modulate the same regulatory elements. The ability of GATA6 to bind at both Epi and PrE genes was evident also in uncommitted ICM cells in blastocysts. We propose that the ability of PrE and Epi-specific TFs to extensively bind and regulate the same gene networks contributes to ICM plasticity and allows rapid cell lineage specification by coordinating both activation and repression of divergent transcriptional programs.
Taken together, our study points to a model where GATA6-NANOG cobind at Epi and PrE sites in ICM cells, to preserve plasticity and maintain them in a poised state ready to adapt to either the Epi or PrE fate. In PrE-precursors, which express more GATA6 relative to NANOG, GATA6 binds PrE loci and activates them. At Epi sites, GATA6 evicts NANOG and redirects it to PrE sites, to bring about robust and quick activation. Such co-occupancy of opposing lineage-determining TFs, at genes forming fate-determinant transcriptional programs, provides a plausible mechanism by which divergent lineages emerge by bifurcation of a common progenitor.

Reference

## Mandatory Training Deadlines

### NICHD, DIR Mandatory Training Calendar

| Summer |
|-----------------|------------|--------|-----------------|-----------------|
| Training Title | Audience   | Duration | Estimated Deadline | Delivery |
| Information Security and Management Refresher | All Staff | 60 minutes | July 30 | Online |

| Fall |
|-----------------|------------|--------|-----------------|-----------------|
| Training Title | Audience   | Duration | Estimated Deadline | Delivery |
| USERRA (Uniformed Services Employment and Reemployment Rights Act) | Supervisors | 60 minutes | ~September | LMS |
| VET (Veteran Employment Training) | Supervisors | 60 minutes | ~September | LMS |

| Winter |
|-----------------|------------|--------|-----------------|-----------------|
| Training Title | Audience   | Duration | Estimated Deadline | Delivery |
| NIH Anti-Harrassment Training (NO FEAR/POSH) — Online EEO Training | All Staff | 90 minutes | ~December | LMS |
| Ethics Training Refresher | All Staff | 30 minutes | ~December | Online |

### Training Required Every 3 Years

<table>
<thead>
<tr>
<th>Training Title</th>
<th>Audience</th>
<th>Duration</th>
<th>Estimated Deadline</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Bystander Training (Supervisor &amp; Non-Supervisor Specific Training)</td>
<td>All Staff</td>
<td>2 hours</td>
<td>December 31</td>
<td>Webinar</td>
</tr>
<tr>
<td>NIH Supervisor Refresher Training</td>
<td>Supervisor</td>
<td>16 hours</td>
<td>December 31</td>
<td>LMS</td>
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All timelines are estimated and subject to change. This list is meant to be used as a guide and is NOT a comprehensive list of HHS/NIH/NICHD training requirements. For more information, please visit the NIH Mandatory Training Inventory: [https://hr.nih.gov/training-center/mti/mandatory-training-inventory](https://hr.nih.gov/training-center/mti/mandatory-training-inventory)

## Funding Opportunities

Check back next month!
= Award Calls for Nominations =

Check back next month!

= Lectures & Training Sessions =

Check back next month!

= Procurement Due Dates =

End of the Year Procurement Deadline

In an effort to assist with FY2021 budget planning, below are the End of Year procurement submission deadline dates: see chart below.

Please keep the following in mind when preparing your POTS requests:

- All POTS requests must be submitted to your Administrative Officer (AO) by the COB on the deadline date in the chart below.
- All POTS requests should include a detailed justification.
- Justifications like “supply,” “chemical” or “for lab use” or “lab supply” or “for research experiment” should not be used.
- Micro-Purchase threshold is under $5,000 (must include all charges such as shipping & handling, dry ice, inside delivery, etc.)
- Requests over the Micro-Purchase threshold, $5,000 and above, require additional documentation:
  - Narrative justifications for sole source will not be accepted and the POTS will be returned for the required JOFOC form.
  - Vendor quote(s) from competitive sources
  - Market research: list of all vendors contacted
  - If Sole Source, please include the required JOFOC form; JOFOC form must be completed and signed (contact Sylvia Robinson at 301-827-4346 or Sylvia.Robinson@nih.gov for the forms).
- Trade-Ins: If the quote references a trade-in credit, the trade-in form is required for all Government owned property; this form must be completed and signed (contact Sylvia Robinson at 301-827-4346 or Sylvia.Robinson@nih.gov for the forms).

For any approved request over $250,000, please contact Sylvia Robinson at 301-827-4346 or Sylvia.Robinson@nih.gov as soon as possible so that we may assist with a strategic plan for processing your order and if you need the Acquisition Strategy and Acquisition Plan form that is required for requests at this dollar level.

<table>
<thead>
<tr>
<th>Dollar Thresholds</th>
<th>Deadline Dates</th>
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<tr>
<td>Equipment, Supplies, and Services</td>
<td>$10,001–$15,000</td>
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<tr>
<td></td>
<td>$10,000 and less</td>
</tr>
<tr>
<td></td>
<td>$5,000 and less, P-Card only</td>
</tr>
</tbody>
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= Pertinent Notes & Dates =

Annual DIPHR & DIR Joint Scientific Retreat
Please mark your calendars for the annual DIPHR & DIR Joint Scientific Retreat which will be held virtually this year on **Wednesday, October 27th**. We strongly encourage all NICHD intramural researchers, PIs and lab members, to attend as we celebrate our research achievements and try to spark new ideas and collaborations.

We also invite PIs, staff scientists, clinical fellows, postdoctoral fellows, and graduate students to submit a title and brief abstract of up to 150 words if you are interested in presenting your work.

Titles and abstracts should be sent to **Amaressa Abiodun** at amaressa.abiodun@nih.gov by COB on Friday, **July 30th** for the committee to consider. Preference will be given for talks tailored to a broad audience, since it will include clinicians, epidemiologists, and basic scientists from a range of fields. We envision the talks being shorter format, so the focus should be on the big picture rather than a deep-diving into the data and methods.

On your abstract please also include:

- Your Name
- Your position: PI, staff scientist, clinical fellow, postdoc, graduate student
- Your PI
- Identify which of the following scientific theme(s) from the 2020 NICHD Strategic Plan that your work best aligns with:
  - Understanding the Molecular, Cellular, and Structural Basis of Development
  - Promoting Gynecologic, Andrologic, and Reproductive Health
  - Setting the Foundation for Healthy Pregnancies and Lifelong Wellness
  - Improving Child and Adolescent Health and the Transition to Adulthood
  - Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities

To provide more background on these themes you can access the 2020 NICHD Strategic Plan using this link ([https://www.nichd.nih.gov/sites/default/files/2019-09/NICHD_Strategic_Plan.pdf](https://www.nichd.nih.gov/sites/default/files/2019-09/NICHD_Strategic_Plan.pdf)). We recommend you work with your PI to identify which theme(s) are most appropriate but please feel free to reach out with questions.

**NICHD STRIVE for Change Workshop Series**

NICHD launched its STrategies to enRich Inclusion and achieVe Equity (STRIVE) Initiative to improve equity, diversity, and inclusion (EDI) in all aspects of its research and workforce. STRIVE, which complements NIH UNITE, focuses on taking action to improve EDI within NICHD and the scientific community, and expand health disparities research to develop solutions.

STRIVE will be conducting virtual workshops that will bring together stakeholders from diverse sectors to discuss health disparities research, identify knowledge gaps, and help chart a bold course for future activities.

The next workshop will be:

- August 4, 2021
- **How Social Identity Can Impact and Promote Health: A Look Across Populations, Lifespans, and Generations**
- 10:00 AM–4:00 PM (EST)

To register for this and future workshops in the series, please visit: [https://web.cvent.com/event/739cb88-5d97-4ff0-b053-7379c94108aa/summary](https://web.cvent.com/event/739cb88-5d97-4ff0-b053-7379c94108aa/summary)

**NIH’s Return to Work Guidance**

The NIH Return to Work Guidance was updated in April 2021. Below is the list of changes from the previous version. Full version of the updated guidance here: [Return-to-Work-Guidance April 2021.pdf](https://www.nih.gov/sites/default/files/2021-05/Return-to-Work-Guidance-April-2021.pdf) (2.2 MB)

- Reduced population limitations from one (1) person per 200–250 net square feet to one (1) person per 125 net square feet (pg. 17). Changes in density do not impact numbers of persons allowed in buildings or campuses, as those numbers are predetermined by a waiver request regarding an Executive Order. Increases in allowed density are based on:
  - Increased vaccination rates among NIH staff and within the community
  - Industry trends from other premier biomedical research institutions (e.g., Johns Hopkins University) regarding higher population allowances.
- Section on conducting Activity Hazard Analyses (AHAs) (pg. 12)
  - NIH operations require AHAs to ensure risks are minimized. This version provides guidance on how to conduct required risk assessments.
- Updated guidance on travel and post-travel requirements (pgs. 7–12)
  - Travel guidance was updated to clarify guidelines for return to work after traveling.
  - Updated guidance expedites return to work for personnel that have been vaccinated.
- Updated guidance for international and domestic RTW expectations
- Improved Fit and Filtration of face coverings. Includes information on the knotting and tucking technique, mask fitters/braces, and double masking (pgs. 15–17).
- Information on site visits from outside organizations (e.g., AAALAC, BSAT, etc.) (pg. 23)
- Updates to Appendix IV to include information on improving mask fit during close proximity work (pg. 31–36)
- Updates to Appendix V to reflect knotting and tucking technique, double masking, and mask fitters. Also update to reflect change in Division of Logistics Services (DLS) website which prevents direct link to products from previously hyperlinked recommended equipment. (pgs. 36–37)
- Addition of Appendix VI which describes the knotting and tucking technique for surgical masks (pgs. 38–39)
- Addition of Appendix VII – Selection, Use, Care, and Storage of Mask Fitters/Braces (pgs. 40–41)
- Vaccine related information and post vaccine safety requirements (pg. 6–7)

**Getting to know: NICHD Office of Communications**
Did you know? You can share your scientific findings with broader, public audiences through NICHD’s social media platforms. If you’d like to feature your scientific image, publication, or other content, contact the NICHD Office of Communications at nichdpress@mail.nih.gov.

= COVID-19 Notices =

✅ NICHD email address for questions about COVID-19

The NICHD Office of the Clinical Director has set up an email address for any questions you may have about CDC guidelines, quarantine recommendations, or NIH policies related to COVID-19. The goal is to help reduce the number of calls to the NIH Occupational Medical Service. If you have broad questions about COVID-19, you can send them to NICHDCOVIDInfo@mail.nih.gov, and NICHD clinical staff will respond.


⚠ Staff is encouraged to take advantage of SARS-CoV2 testing on the 5th floor of the NIH Clinical Center—even if you’ve been vaccinated. Starting Tuesday, July 6, 2021, the Employee Asymptomatic Testing Clinic will only be opened on Tuesdays and Fridays. You can schedule an appointment for your test or just walk-in. Drive-through symptomatic testing (“the carline”) is now available on Tuesdays and Thursdays only.

ℹ COVID Notes

Reminder to staff that they are expected to wear masks while on campus. This practice is a courtesy to your co-workers and is essential to safety of our community.

Those interested in a detail as a contract tracer in the Clinical Center should contact the OSD. Please secure the approval of your supervisor prior to volunteering. Note that this detail will entail a substantial full-time commitment, including a required training that is over a week.

In case you missed it: Persistent COVID-19 Information

= NICHD Director’s Newsletter =
Current Edition of the NICHD Director’s Newsletter (July 2021)

= DDIR Web Board =
Current Edition of the Deputy Director for Intramural Research's Web Board

= Trainee Highlights =
For Trainee Highlights, check out this month’s fellows newsletter, The NICHD Connection, Volume 12, Issue 134.

= Congrats and Kudos! =
2021 recipient of the Craniofacial Biology Group Award (Jr. Category)

Congrats to Jeremie Oliver, a predoctoral fellow from the lab of Dr. Rena D’Souza, Director of the National Institute of Dental and Craniofacial Research, as he was awarded the Craniofacial Biology Group Award (Junior Category) for his abstract entitled, “Intra-Amniotic Wnt Agonist Injection for Cleft Palate Correction.” He presented his work virtually to an international panel of judges from the Craniofacial Biology Group during the 2021 International Association of Dental Research (IADR) Scientific Meeting. His presentation included preliminary data on the safety and efficacy of timed, intra-amniotic delivery of a single-dose of Wnt-signaling agonist therapy in mouse embryos for the treatment of palatal clefts in utero.