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Editorial

Meeting report for Odd Pols 2016: Ann Arbor 2.0

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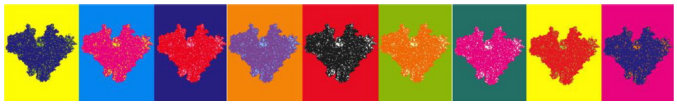
ABSTRACT

The Tenth International Conference on Transcription by RNA Polymerases I, III, IV and V (the 'Odd Pols') was held June 24–28, 2016 at the University of Michigan, Ann Arbor, USA and organized by David Engelke, Deborah Johnson, Richard Maraia, Lawrence Rothblum, David Schneider, Andrzej Wierzbicki and Astrid Engel. The organizers are grateful for the support from the Rackham Graduate School of the University of Michigan for providing the meeting venue. The environment provided a great background with unexpected encounters with fireflies, free live music and a festive fireworks display. The meeting was composed of eleven oral sessions and a poster session. The keynote speaker, Dave Engelke, opened the meeting with his presentation entitled "A personal history of pol III transcription — how we got here from the 'good old days'." The meeting drew attendees from sixteen countries that shared their research discoveries. Here we present some of the highlights from the meeting using summaries provided by the participants.



Artistic image of RNA Polymerase I by Tobias Gubbey, Christoph Engel and Patrick Cramer. Science derived from: Engel et al. (2013) RNA polymerase I structure and transcription regulation. Nature 502: 650-655.

1. Introduction

The 2016 "OddPols" meeting represented the tenth time the participants gathered to share their findings on the "odd" as in "offbeat" RNA polymerases which included Pol I, Pol III, Pol IV and Pol V. Presentations were divided into six general topics. Among the participants, several students presented their work in an oral or poster session. A total of 23 posters were presented.

During the meeting, **Olivier Gadal** conducted a presentation nominating Toulouse, France as the next location for the Eleventh International Conference on RNA Polymerases I, III, IV and V in 2018. The attendees approved the nomination. For more information please contact Dr. Oliver Gadal at the Toulouse University (olivier.gadal@ibcg.biotoul.fr).

2. Plenary sessions

2.1. Keynote address

2.1.1. David Engelke

The meeting opened with the keynote speaker, **Dave Engelke** (University of Colorado Denver, USA), who provided an insight into his scientific journey and anecdotes in a talk entitled "A personal history of pol III transcription — how we got here from the 'good old days".

2.2. Sessions 1–3. Disease and development

In the opening session, **Paul Trainor** (Stowers Institute for Medical Research, MO, USA) discussed ribosomopathies and the conundrum of tissue specific defects that arise from disruptions in the global process of ribosome biogenesis. More specifically he focused on the congenital craniofacial disorders, Acrofacial dysostosis -Cincinnati type, which is cause by mutations in POLR1A, and Treacher Collins syndrome (TCS) which is caused by mutations in TCOF1, POLR1C and POLR1D. Loss-of-function mouse and zebrafish animal models mimic the syndromes observed in humans and each of these genes play a critical role in transcription of rRNAs which is considered one of the rate limiting steps in ribosome biogenesis. Furthermore, **Bruce Knutson** (SUNY Upstate Medical University, NY, USA), presented biochemical and genetic data

Abbreviations: FGFR2, FGF Receptor-2; hESCs, human embryonic stem cells; lncRNAs, long noncoding RNAs; NORs, Nucleolus Organizer Regions; RdDM, RNA-directed DNA Methylation; Pol I, RNA polymerase I; Pol II, RNA polymerase II; Pol III, RNA polymerase III; Pol IV, RNA polymerase IV; Pol V, RNA polymerase V; TBP, TATA-box binding protein; TCS, Treacher Collins syndrome; TMER, tRNA-microRNA encoded RNA; UBF, Upstream Binding Factor.

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from their yeast model system to determine how the Treacher Collins Syndrome mutations in the yeast POLR1D ortholog AC19 affect Pol I/III assembly and function. Based on these observations, a new model for how TCS-mutations disrupt complex integrity was introduced.

Linda van Dyk (University of Colorado, CO, USA) presented data on the Pol III transcribed murid herpesvirus-4 non-coding RNAs from the tRNA-microRNA encoded RNA (TMER) genes. Their data support multifunctional roles for TMERs indicative of viral modulation of cellular RNA-binding proteins underlying the regulation of acute viral pathogenesis.

Work from **Elliot Chen**, a senior Ph.D. student in the Johnson lab (Baylor College of Medicine, TX, USA), demonstrated that Maf1 promotes the induction of mesoderm from embryonic stem cells. His work further revealed that Maf1, and the repression of Pol III-dependent transcription, drives the terminal differentiation of adipocytes. These results uncover a key new biological role for Maf1 and its Pol III target genes in differentiation and development. In addition, **Steven Zheng** (Rutgers University, NJ, USA) presented their studies showing that Maf1 binds to PTEN promoter enhancing its acetylation and activity. Overall the data indicated that Maf1 can act as a transcriptional activator for PTEN which is important for Maf1's tumor suppressor function.

The BMH-21 small molecule shown to have potent anticancer activity specifically inhibits Pol I transcription. Expanding on their previous observations, **Marikki Laiho** (John Hopkins University School of Medicine, MD, USA), presented studies on the effects of BMH-21 on Pol I elongation. In collaboration with **David Schneider** (University of Alabama, AL, USA) they demonstrated that BMH-21 activates a Pol I elongation checkpoint that destabilizes the Pol I complex. The BMH-21 effects on Pol I were also shown to be conserved between the yeast and mammals.

Amy Merrill (University of Southern California, CA USA), presented data from their studies of a rare skeletal disease named Bent bone dysplasia syndrome. Their work demonstrates that the regulation of ribosomal DNA transcription by the Fibroblast Growth Factor FGF signaling pathway in osteoprogenitor cells. Furthermore, the data indicated that the activation of rRNA transcription by FGF Receptor-2 (FGFR2) is sufficient to hold osteoprogenitor cells in a self-renewing state.

Alcohol has been classified as carcinogenic to humans the international agency of cancer research. Target sites for alcohol-related carcinogenesis include the breast, liver and multiple other organs. **Shuping Zhong** (University of Southern California, CA, USA) presented their studies demonstrating that alcohol activates JNKs to upregulate Brf1 expression and Pol III gene transcription, resulting in cell transformation and tumor formation.

The Ross Hannan research group (John Curtin School of Medical Research, ANU Australia) presented their studies on the advances in cancer therapeutic strategies that target ribosome biogenesis. **Kate Hannan** showed data demonstrating that MYC-driven tumors depend on ribosome synthesis and function making it an effective target for new therapeutic approaches. **Elaine Sanij's** presentation focused on their recently published work examining p53-independent cell cycle checkpoints mediated by ATM/ATR in response to acute inhibition of Pol I transcription by CX-5461 (Quin et al., 2016). Their work reveals that CX-5461 induces an unusual chromatin structure in which transcriptionally competent relaxed rDNA repeats are devoid of transcribing Pol I leading to activation of ATM signaling within the nucleoli. They further demonstrate that inhibiting CX-5461-mediated responses improves therapeutic efficacy. Using a mouse model of lymphoma (Eμ-*Myc*) **Ross Hannan** (John Curtin School of Medical Research, ANU Australia) showed that malignancy progression is associated with the epigenetic remodeling that activates silent rDNA repeats. The ChIP-seq and 4C–seq data demonstrated that nucleolar reorganization may drive global genome organizational and transcriptomic changes implicating a role for rDNA in cancer progression beyond ribosome biogenesis.

The role of β-actin on transcription was discussed by **Piergiorgio Percipapalle** (New York University Abu Dhabi, UAE). Through genome-wide analysis of ChIP-seq data from embryonic fibroblasts from β-actin knockout mice, their group found that Pol I-associated β-actin synergizes with NM1 to coordinate permissive chromatin with transcription, impacting the proliferative state of the cell (Almuzzaini et al., 2016).

2.3. Session 4–5. Chromatin

The session was opened with the presentation of **Tom Moss** (Laval University, Quebec, Canada) confirmed requirement for TIF1A/RRN3 in mouse development before the 16 cell stage, regardless of genetic background, and showed that UBF loss caused a general disruption of blastomere heterochromatin. Carrying on from a recent publication (Hamdane et al., 2014), Tom Moss and Jean-Clement Mars, also presented high-resolution ChIP-Seq mapping of the mouse ribosomal RNA genes demonstrating the accumulation of active chromatin markers and an arrested polymerase complex coinciding with CTCF and Cohesin recruitment at the upstream enhancer boundary. Conditional cell lines carrying floxed *ubf* and *tif1a*/*rrn3* genes were used to demonstrate that UBF but not TIF1A was required for the recruitment of the TIF1B/SL1 preinitiation complex to both 47S and Enhancer promoter sites. Further, recent data on the targeting of UBF by cisplatin was briefly discussed (Hamdane et al., 2015).

The effect of ribosomal RNA gene repeats on chromosomal segregation in yeast was the topic of **Austen Ganley**'s (University of Auckland, New Zealand) presentation. Using chromosome loss assays in *Saccharomyces cerevisiae*, their group found that rDNA influences the fidelity of chromosome segregation through Fob1 binding and RENT complex recruitment. Their results suggest a role for rDNA in segregation of both the rDNA-containing chromosome, and global chromosome segregation.

Sui Huang (Northwestern University, IL, USA) discussed her work demonstrating that nucleolar segregation, induced by RPA194 knockdown, significantly impacts the nuclear organization, including other nuclear bodies and gene expressions. Nucleolar segregation, but not ribosome synthesis in general is responsible for the nuclear changes.

Christoph Engel (Max-Planck-Institute, Germany) presented a 4.8 Å cryo-EM reconstruction of Pol I bound to the initiation factor Rrn3 (Engel et al., 2016). While the location of Rrn3 was rather accurately predicted from crosslinking/MS studies earlier (Blattner et al., 2011) the sub-atomic resolution made it possible to describe four interfaces between Rrn3 and the polymerase in detail. Furthermore, a contraction of the active center cleft and a partial retraction of the A12.2C-terminal domain were visible, similar to previous suggestions (Engel et al., 2013).

Pierre Chymkowitch (Oslo University Hospital, Norway) presented the newest results on their ongoing studies in the Sumo proteome control of tRNA synthesis by Pol III. Overall, the data suggest that in addition to TORC1 activity, sumoylation of RNAPIII is key to reaching full translational capacity under optimal growth conditions.

Masayuki Tsuzuki (The University of Tokyo, Japan), showed data from the liverworts, *Marchantia polymorpha* used to identify general characteristics of conserved miRNAs in land plants. Their discoveries suggest that some conserved miRNAs have universal function in land plant development.

Expanding on their studies on their novel mechanism (Iwasaki et al., 2015; Iwasaki et al., 2016), **Ken-ichi Noma** (The Wistar Institute, PA, USA) demonstrated that condensin mutants inhibiting the condensin-TBP interaction also disrupts the ability of condensin to bind to Pol III genes, impairs the proper assembly of mitotic chromosomes and causes a severe defect in gene segregation leading to cellular death.

High-resolution, strand-specific, profiling of the distribution of transcriptionally engaged Pol III was performed in collaboration of the laboratories of **Magdalena Boguta** (Polish Academy of Sciences, Warsaw, Poland), and David Tollervey (The University of Edinburgh, UK). Unexpected findings were: 1). uneven polymerase distribution along all tRNA genes; and 2). the presence of transcription termination read-through on most tRNA genes typically extending 50–200 nt beyond the expected terminator.

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