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## Abstract of the talk

***Ubiquitylation of RNA Polymerase II controls early stages of the transcription cycle***

Control of RNA Polymerase II (Pol II) through ubiquitylation is essential for the DNA-damage response. Here we reveal a distinct ubiquitylation pathway in human cells that targets excessive and defective Pol II molecules at the initial stages of the transcription cycle. This pathway, mediated by ARMC5-CUL3 ubiquitin ligase, drives homeostatic Pol II turnover, and is further enhanced when early stages of transcription - initiation and pausing - are perturbed. Upon ARMC5 loss, Pol II accumulates in the free pool and in the promoter-proximal zone, but is not permitted into elongation. We identify Integrator subunit 8 (INTS8) as a gatekeeper preventing the release of excess Pol II molecules into gene bodies. Combined loss of ARMC5 and INTS8 has detrimental effects on cell growth, with ARMC5 loss exacerbating transcriptional defects seen in INTS8-depleted cells. These findings uncover ARMC5-CUL3 and INTS8 as central to a collaborative checkpoint, monitoring the quantity and quality of transcription complexes before they are licenced into elongation.

## Research positions & Education

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|---|---|---|
| Programme Leader Track | **MRC Laboratory of Molecular Biology**, Cambridge, UK | 2020 – present |
| Postdoctoral Training Fellow | **The Francis Crick Institute**, London, UK | 2015 – 2020 |
| PhD | **CRUK Cambridge Institute**, Cambridge, UK | 2010 - 2015 |
| Diploma | **Molecular Biology, University of Belgrade**, Serbia | 2005 – 2010 |
| Summer Research Internship | **Babraham Institute**, Cambridge, UK | 2009 |
| Summer Research Internship | **École Polytechnique Fédérale de Lausanne**, Lausanne, Switzerland | 2008 |

# Publications

*Under revision:*

**Cacioppo, R.** †, Gills, A. †, **Shlamovitz, I.** †, Crisp, A., Prekovic, S., Berry, S.*, **Tufegdzic Vidakovic, A***. *Ubiquitylation of RNA Polymerase II controls early stages of the transcription cycle.* †shared-first authors; * corresponding authors; **bold** – authors from my lab

*Past publications*

**Tufegdzic Vidakovic, A.**, Mitter, R., Kelly, G. P., Neumann, M., Harreman, M., Rodriguez-Martinez, M., Herlihy, A., Weems, J. C., Boeing, S., Encheva, V., Gaul, L., Milligan, L., Tollervey, D., Conaway, R. C., Conaway, J. W., Snijders, A. P., Stewart, A., & Svejstrup, J. Q. (**2020**). Regulation of the RNAPII Pool Is Integral to the DNA Damage Response.
*Cell*, *180*(6), 1245-1261 e1221. https://doi.org/10.1016/j.cell.2020.02.009

*This work has been featured in a Preview Article: Kook Son and Orlando D. Schärer. Repair, Removal, and Shutdown: It All Hinges on RNA Polymerase II Ubiquitylation. Cell **(2020).***
https://doi.org/10.1016/j.cell.2020.02.053

**Tufegdzic Vidakovic, A.**, Harreman, M., Dirac-Svejstrup, A. B., Boeing, S., Roy, A., Encheva, V., Neumann, M., Wilson, M., Snijders, A. P., & Svejstrup, J. Q. (**2019**). Analysis of RNA polymerase II ubiquitylation and proteasomal degradation.
*Methods*, *159-160*, 146-156. https://doi.org/10.1016/j.ymeth.2019.02.005

**Tufegdzic Vidakovic, A.**, Rueda, O. M., Vervoort, S. J., Sati Batra, A., Goldgraben, M. A., Uribe-Lewis, S., Greenwood, W., Coffer, P. J., Bruna, A., & Caldas, C. (**2015**). Context-Specific Effects of TGF-beta/SMAD3 in Cancer Are Modulated by the Epigenome.
*Cell Rep*, *13*(11), 2480-2490. https://doi.org/10.1016/j.celrep.2015.11.040

Batra, R. N., Lifshitz, A., **Tufegdzic Vidakovic, A.**, Chin, S. F., Sati-Batra, A., Sammut, S. J., Provenzano, E., Ali, H. R., Dariush, A., Bruna, A., Murphy, L., Purushotham, A., Ellis, I., Green, A., Garrett-Bakelman, F. E., Mason, C., Melnick, A., Aparicio, S., Rueda, O. M., . . . Caldas, C. (**2021**). DNA methylation landscapes of 1538 breast cancers reveal a replication-linked clock, epigenomic instability and cis-regulation.
*Nat Commun*, *12*(1), 5406. https://doi.org/10.1038/s41467-021-25661-w

Bruna, A., Greenwood, W., Le Quesne, J., Teschendorff, A., Miranda-Saavedra, D., Rueda, O. M., Sandoval, J. L., **Tufegdzic Vidakovic, A**., Saadi, A., Pharoah, P., Stingl, J., & Caldas, C. (**2012**). TGFbeta induces the formation of tumour-initiating cells in claudinlow breast cancer.
*Nat Commun*, *3*, 1055. https://doi.org/10.1038/ncomms2039

Bruna, A., Rueda, O. M., Greenwood, W., Batra, A. S., Callari, M., Batra, R. N., Pogrebniak, K., Sandoval, J., Cassidy, J. W., **Tufegdzic Vidakovic, A.**, Sammut, S. J., Jones, L., Provenzano, E., Baird, R., Eirew, P., Hadfield, J., Eldridge, M., McLaren-Douglas, A., Barthorpe, A., . . .

Caldas, C. (**2016**). A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds.
*Cell*, *167*(1), 260-274 e222. https://doi.org/10.1016/j.cell.2016.08.041

Fan, Z., Devlin, J. R., Hogg, S. J., Doyle, M. A., Harrison, P. F., Todorovski, I., Cluse, L. A., Knight, D. A., Sandow, J. J., Gregory, G., Fox, A., Beilharz, T. H., Kwiatkowski, N., Scott, N. E., **Tufegdzic Vidakovic, A.**, Kelly, G. P., Svejstrup, J. Q., Geyer, M., Gray, N. S., . . . Johnstone, R. W. (**2020**). CDK13 cooperates with CDK12 to control global RNA polymerase II processivity.
*Sci Adv*, *6*(18). https://doi.org/10.1126/sciadv.aaz5041

Vervoort, S. J., de Jong, O. G., Roukens, M. G., Frederiks, C. L., Vermeulen, J. F., Lourenco, A. R., Bella, L., **Tufegdzic Vidakovic, A.**, Sandoval, J. L., Moelans, C., van Amersfoort, M., Dallman, M. J., Bruna, A., Caldas, C., Nieuwenhuis, E., van der Wall, E., Derksen, P., van Diest, P., Verhaar, M. C., . . . Coffer, P. J. (**2018**). Global transcriptional analysis identifies a novel role for SOX4 in tumor-induced angiogenesis.
*Elife*, *7*. https://doi.org/10.7554/eLife.27706

Vervoort, S. J., Lourenco, A. R., **Tufegdzic Vidakovic, A.**, Mocholi, E., Sandoval, J. L., Rueda, O. M., Frederiks, C., Pals, C., Peeters, J. G. C., Caldas, C., Bruna, A., & Coffer, P. J. (**2018**). SOX4 can redirect TGF-beta-mediated SMAD3-transcriptional output in a context-dependent manner to promote tumorigenesis.
*Nucleic Acids Res*, *46*(18), 9578-9590. https://doi.org/10.1093/nar/gky755