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Abstract

Zinc finger proteins (ZNFs) are the largest family of transcription factors, yet how they activate gene expression and whether they require dedicated coactivators remains unclear. I will discuss the identification of Zincore, a previously uncharacterized protein complex consisting of QRICH1 and SEPHS1, as a novel ZNF-specific coactivator. Both QRICH1 and SEPHS1 are critical for embryonic development in mice and their haploinsufficiency is linked to similar neurodevelopmental defects in humans. We show that among Zincore clients, ZFP91 is a transcription factor that binds to the evolutionary conserved motif CTTTAAR, and the cryo-EM structure of Zincore in complex with ZFP91 bound to this motif. The structure reveals Zincore to recognise the DNA-bound zinc finger domains, explaining the recognition of a wide variety of ZNFs. I will show, also in the light of unpublished data on ZNF652, how this interaction stabilizes the binding of Zinc Fingers to the DNA, thereby locking them on consensus motifs, providing a unique activity for Zincore as a transcriptional coactivator. I will also discuss the use of protein embeddings to classify transcription factors and the potential of such methods to discover new functional annotations.

1. Bianchi D, Borza R, De Zan E, Huelsz-Prince G, Gregoricchio S, Dekker M, Fish A, Mazouzi A, Kroese LJ, Linder S, Hernandez-Quiles M, Vermeulen M, Celie PHN, Krimpenfort P, Song JY, Zwart W, Wessels L, Nijman SMB, Perrakis A, Brummelkamp TR. Zincore, an atypical coregulator, binds zinc finger transcription factors to control gene expression. *Science*. 2025 Jul.3;389(6755)
2. ML Hekkelman, I de Vries, RP Joosten, A Perrakis. AlphaFill: enriching AlphaFold models with ligands and cofactors. *Nature Methods* 20 (2), 205-213

<https://www.nki.nl/research/research-groups/anastassis-tassos-perrakis>
<https://www.oncodeinstitute.nl/research-groups/anastassis-perrakis-group>

Biosketch

I studied biology at the University of Athens and obtained my PhD in chemistry from the University of York for research I conducted at the European Molecular Biology Laboratory (EMBL). After a long-term EMBO fellowship working on DNA mismatch repair, I became a staff scientist and group leader at EMBL-Grenoble. There, I coordinated the development of the first-ever X-ray micro-diffractometer. I also focused on pattern recognition methods for crystallographic electron density map interpretation. For the past twenty-five years, I have worked at the Netherlands Cancer Institute. For the last decade, I have also been affiliated with the Oncode Institute and hold a professorship at Utrecht University. My team manages a diverse portfolio of projects. These range from developing methods to validate and enrich experimental and predicted protein structures to using X-ray crystallography and single-particle cryo-electron microscopy together with biophysical methods. We have used these approaches to understand diverse biological systems (e.g. questions in late mitosis and microtubule modifications) and understand lysolipid signalling to develop new drug leads. Our current focus is on understanding the mechanisms that underlie zinc finger transcription factor-mediated activation of DNA transcription, in relation to the discovery of Zincore.