<u>The EMBO Global Investigator Award was given based on following Research Achievement:</u>

Basal signaling dictates the acute singling response by bookmarking the enhancers:

As during development, enhancers also serve as the mediators of gene expression during signaling events. However, unlike enhancers involved in development, these need to be dynamic in signalling as every signaling event lasts only for a short burst following which a cell gets back to its "native" state but remains poised for the next round of ligand stimulation. Such reversible enhancer dynamics during signalling is not known. *We hypothesised that enhancer bookmarking may establish robust and repetitive signaling response upon every cycle of hormonal signaling.*

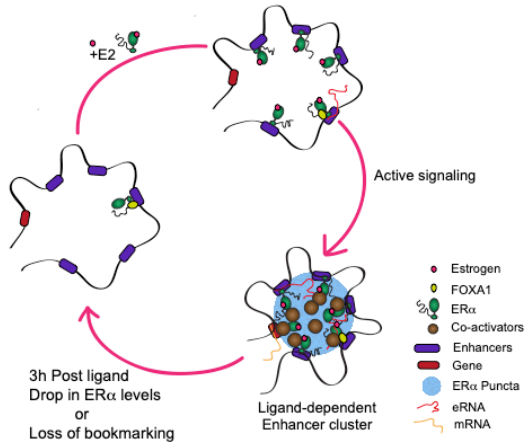

Figure 1: Ligand induced enhancer clusters are pre-seeded by unliganded receptor (Saravanan et al., 2020).

To unravel such unexplored aspects of gene regulation, we use estrogen signalling in breast cancer cells as model system. Upon ligand (estrogen) stimulation, ERα binds to many enhancers and some promoters[7]. We intersected ERα binding profiles, nascent RNA sequencing, HiC contacts (3D-chromtin looping) and live cell imaging before and after ligand stimulation over a period of 24 hours. Using such an integrated strategy, we discovered that even before ligand stimulation, unliganded ERα pre-marked the enhancers that go on to robustly activate the target genes upon ligand stimulation. Further, upon ligand exposure, ERα binds to several EREs relatively proximal to these pre-marked or persistent, ERα-bound enhancers. These persistent sites interact extensively, via chromatin looping, with the proximal new ERα-bound sites, forming ligand-dependent ERα clustered enhancers in 3D (LDEC) (Figure 1).

Interestingly, the LDEC overlap with nuclear ERα condensates that coalesce in a ligand-dependent manner. Furthermore, formation of clustered enhancers, as well as condensates, coincide with the active phase of signaling and their disappearance later, 3h post-signaling, results in the loss of gene expression although persistent sites remain bound by ERα. The deletion of persistent site results in loss of LDEC formation.

Our work shows for the first time that the signaling response is already established *a priori* via bookmarking of the future enhancers. The ligand-induced ERα clustered enhancers around these bookmarked enhancers exist as ERα condensates and provide a novel insight into how these condensates are regulated during the active phase of signaling *in vivo*. Our study provides a simple model of regulation where degradation of transcription factor(s) brings its level below a saturation point for the condensate to remain phase separated marking the end of signaling response. This might be a universal mechanism driving the decline to signaling response.

In summary, we have discovered "mother enhancers" in the genome that play a key role in generating reproducible transcriptional programs upon cyclic/rhythmic signaling like growth hormones. These findings have generated new concepts that such "mother enhancers' are universally present and dictate the transcriptional programs in metazoans.

- Saravanan B, Soota D, Islam Z, Majumdar S, Mann R, Meel S, Farooq U, Walavalkar K, Gayen S, Singh AK, Hannenhalli S, Notani D. Ligand dependent gene regulation by transient ERα clustered enhancers. PLoS Genet. 2020 Jan 6;16(1):e1008516. doi: 10.1371/journal.pgen.1008516.

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EMBO Young Investigator Network: YIP I IG I GIN

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Deputy Director, EMBO
Programme Head

global@embo.org

Heidelberg, 09.12.2019

Results of EMBO Global Investigator Network selections - 2019

Dear Dr. Notani,

We are delighted to inform you that your application has been successful. On behalf of EMBO, we would like to congratulate you and welcome you to the EMBO Global Investigator Network (GIN). Your membership will start **on 1 January 2020** and will last for four years.

The programme offers its current members the following benefits:

The **Annual Young Investigator Programme (YIP) meeting** will take place in Heidelberg, Germany, from 6 - 8 May 2020 and you are invited to attend. **The first GIN meeting** will take place from **3 - 5 March 2021** in New Delhi, India. We will provide you with further details in due course.

Global Investigators have access to the **YIP Sectoral Meetings** (scientific interest groups) that have formed around various topics and are self-organising. Please see the attached document for a list of current sectoral meetings. If you are interested in attending any of them, please feel free to contact the organiser directly.

EMBO Lab Leadership Courses fees are waived for Global Investigators. The selection committee strongly recommends you to take advantage of these courses. You can find course dates for 2020 here: http://lab-management.embo.org

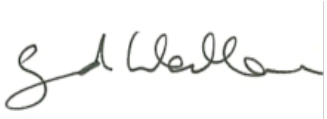
As you already know, a key aspect of the programme is **networking**. EMBO provides funds to support seminars, collaboration visits and joint meetings amongst Global Investigators and with groups outside the EMBO community. We also provide support for you or your group members to attend scientific conferences, or to organise regional or international meetings. Please note that applications for these funds should always be sent to the programme office in advance of the activity.

EMBO also offers to cover **publication charges** (excluding VAT) for papers published by EMBO Global Investigators in **EMBO Press journals**.

For further details of these benefits (including funding limits and application procedures) please see the enclosed programme guide.

Welcome to the Global Investigator Network. We are looking forward to working with you.

Yours sincerely,



Gerlind Wallon, PhD

Deputy Director, EMBO
Programme Head

TERMS & CONDITIONS OF THE EMBO GLOBAL INVESTIGATOR NETWORK

Membership

• Membership in the EMBO Global Investigator Network is for four years.
• Membership may be terminated if the recipient is found culpable of scientific misconduct or for other just cause.
• Global Investigators who, during the normal membership period, move their laboratory to a country that is not an EMBC Associate Member State or co-operation partner forfeit their membership and become former programme members.

Networking

• Networking funds and other benefits of the programme are described in the GIN Programme Guidelines and are subject to change.
• Applications for networking funds should always be sent in advance of the event to the EMBO Global Activities office for approval.

Research integrity training

EMBO expects responsible conduct of research from its awardees. All research activities shall be carried out in compliance with fundamental ethical and research integrity principles. In line with our commitment with these initiatives, we require all Global members of the Global Investigator Network to complete an online course on research integrity from Epigeum. This course was developed by a consortium of 22 research institutions, including EMBO, and is free of charge for our members.

You are expected to take the course (this may be substituted for by any other training available or required by your research institute or funder) within the first year of membership in the programme and submit a certificate of completion to the Global Activities office. All payments related to the programme benefits will be put on hold until you have completed the course. Instructions are attached in a separate document.