Julian Obid

4th year PhD candidate

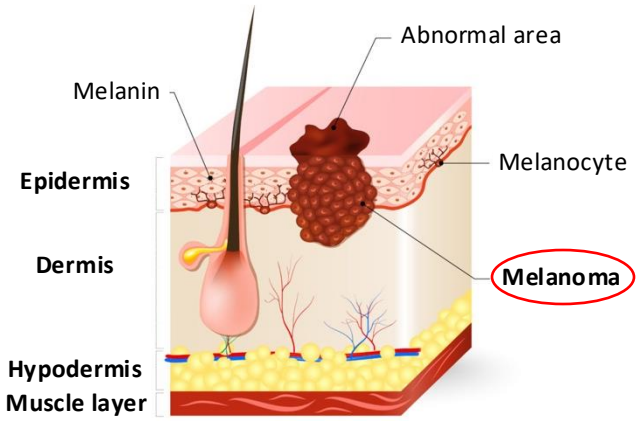
Team of Dr. Frédéric Coin – « Gene expression, repair and pathology »

Shutting down melanoma's super-enhancer–associated oncogenic transcription with novel synthetic ecteinascidins

14e Forum Cancéropôle Est – Besançon
28.11.2025

Malignant melanoma

- Type of **skin cancer** (5% of cases)
- Very **aggressive** (90% of skin cancer deaths)



Long et al., *The Lancet* (2023)

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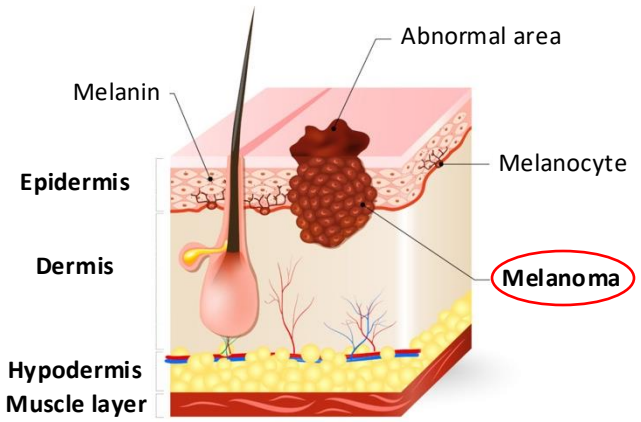
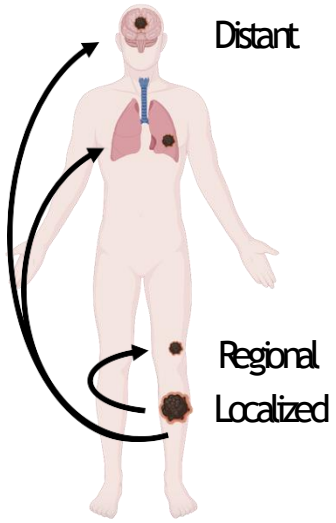
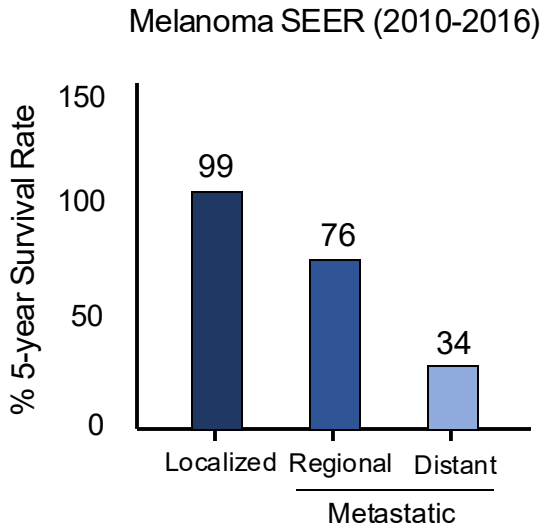
- Strong **invasive** capacity → **Metastasis** (34% 5-year survival)







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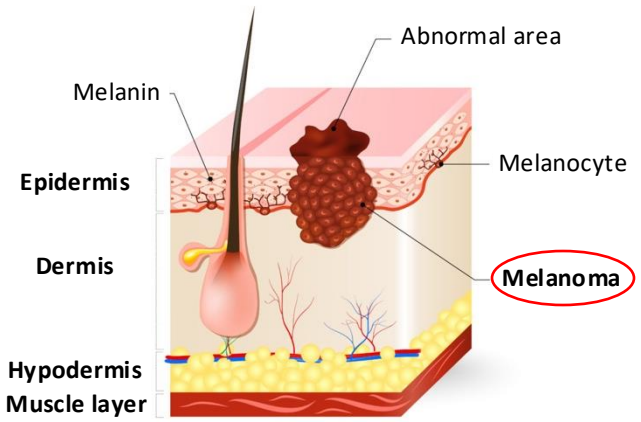
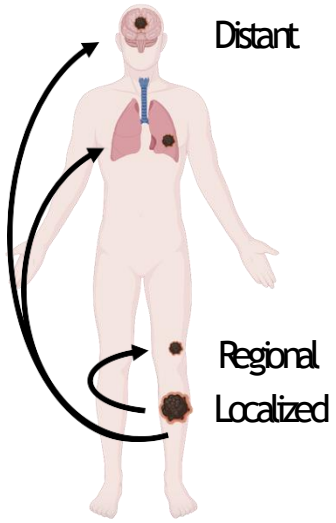
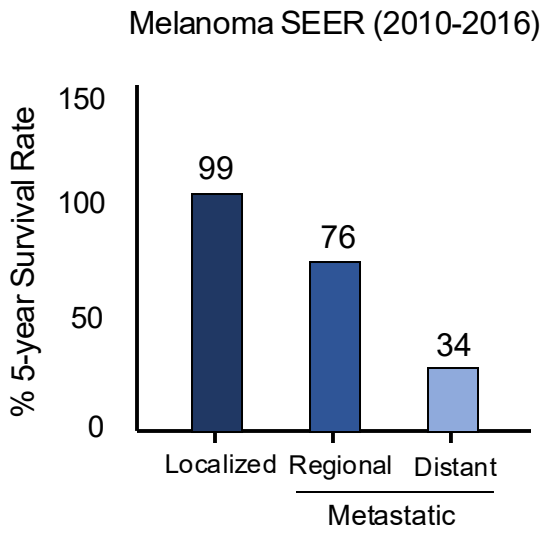
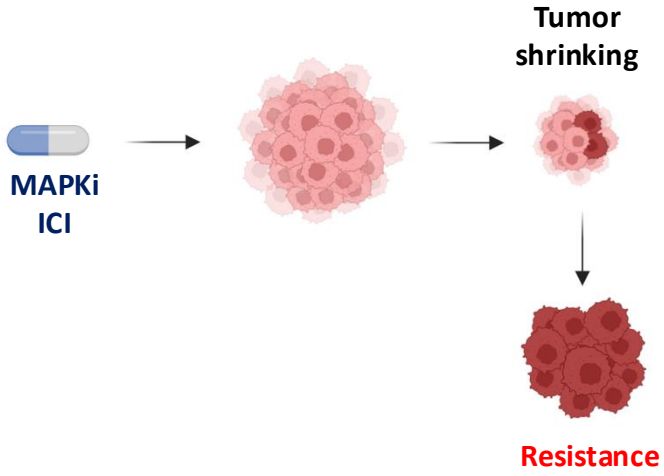
- Very **aggressive** (90% of skin cancer deaths)
- Strong **invasive** capacity → **Metastasis** (34% 5-year survival)
- **Therapeutic options:** MAPK inhibitors (**MAPKi**) and immune checkpoint inhibitors (**ICI**) → **Problem: resistance !**





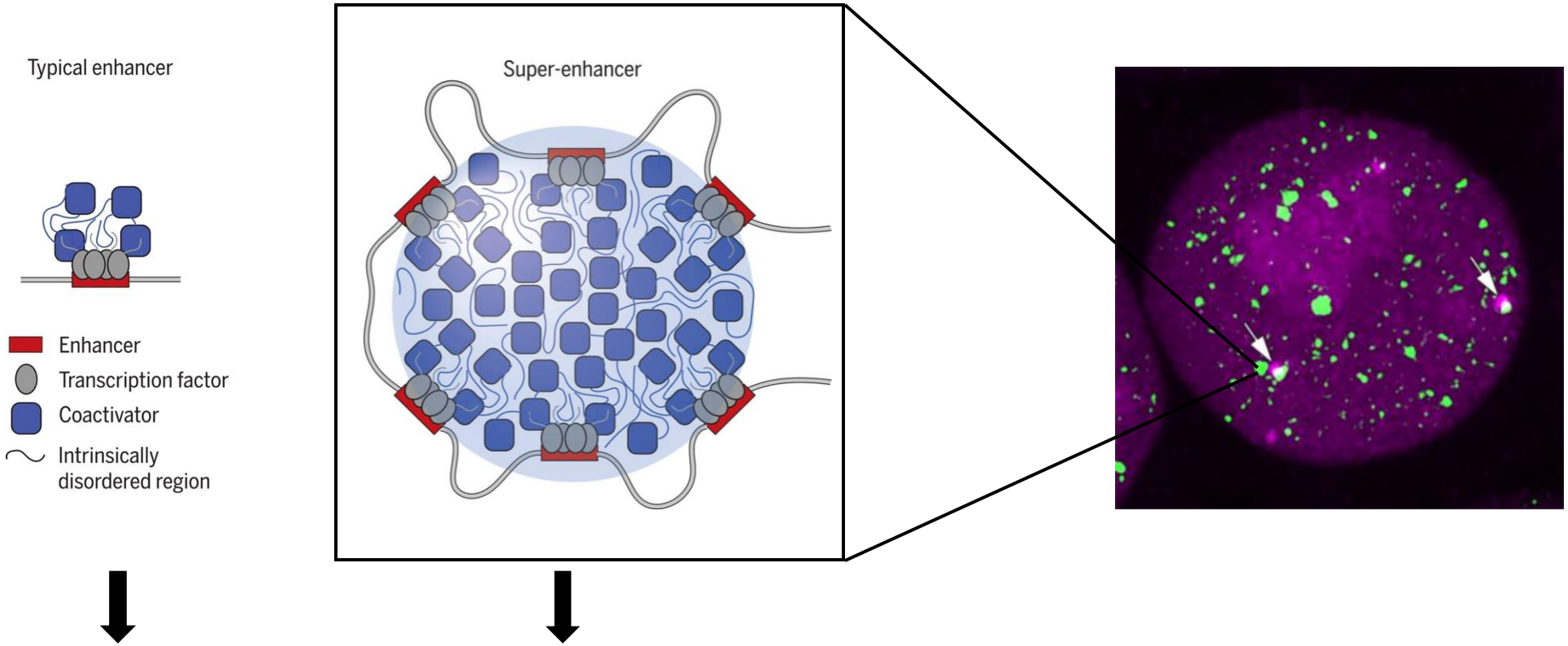




Long et al., *The Lancet* (2023)

Super-enhancers (SEs) as resistance mechanism

- **Clusters** of **long enhancers (<12kb**) abundant in **transcription factors** driving the **overexpression** of **survival oncogenes**
- Form **transcriptional condensates** visible in **microscopy** by specific markers (ex: **BRD4**, **MED1**)



Sabari et al., *Science* (2018)

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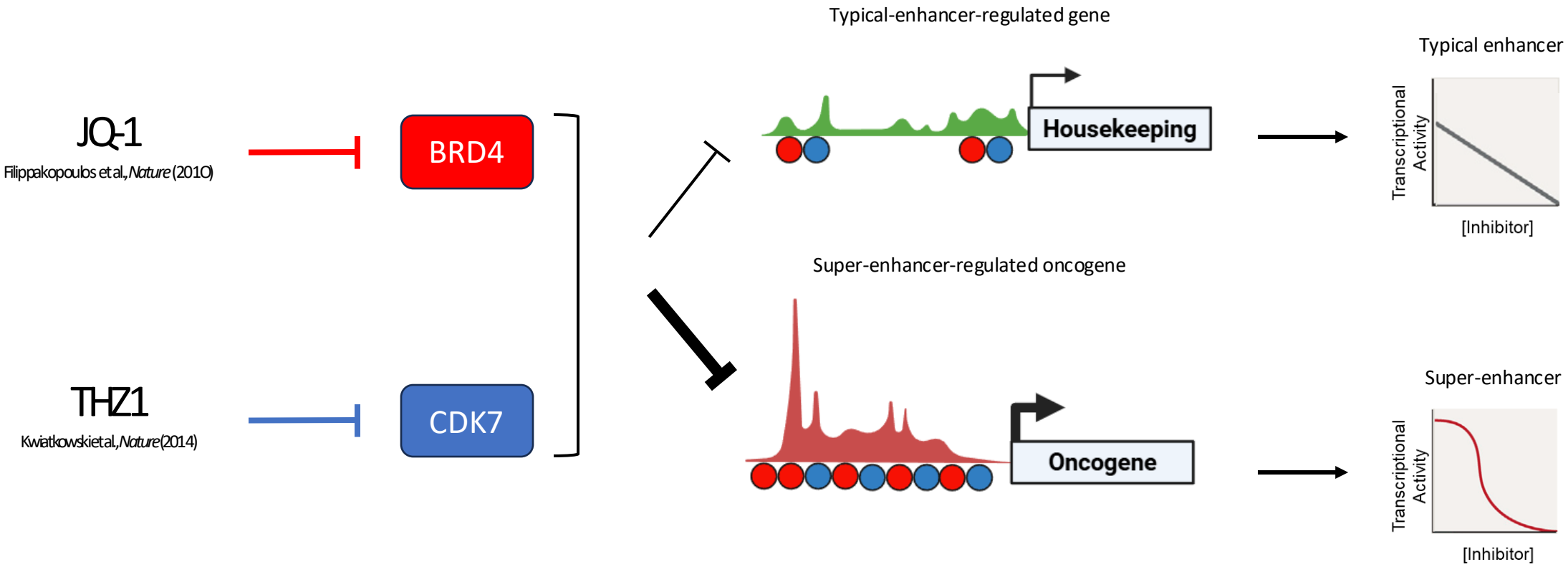


→ **Lack of clinically approved drugs targeting super-enhancers**

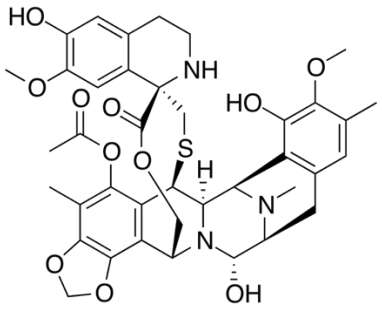
Sabari et al., *Science* (2018); Zanconato et al., *Nat Med* (2018)

Synthetic ecteinascidins

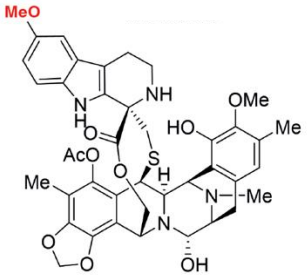
- **Marine-derived** compounds that **bind specific DNA sequences** and **inhibit transcription**

Ecteinascidia turbinata

Trabectedin



Lurbinectedin



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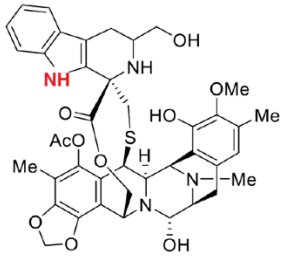
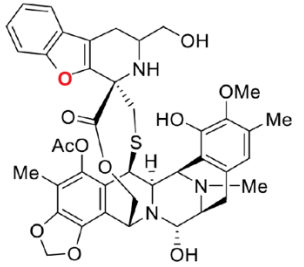


PM54



Santamaria Nuñez et al., *Mol Cancer Ther* (2016); Singh et al., *Clin Cancer Res* (2020)

Synthetic ecteinascidins

- **Marine-derived** compounds that **bind specific DNA sequences** and **inhibit transcription**
- **Lurbinectedin (Lurbi)** recently approved for **small cell lung cancer**

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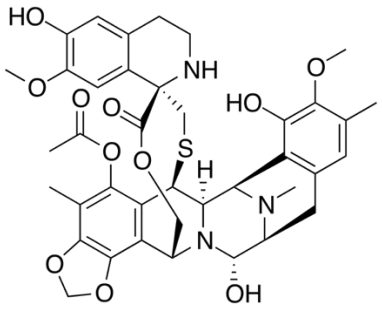

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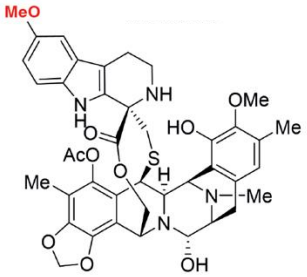

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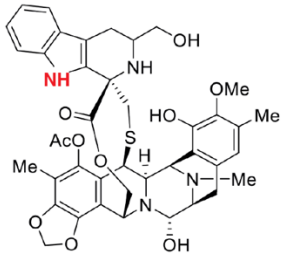

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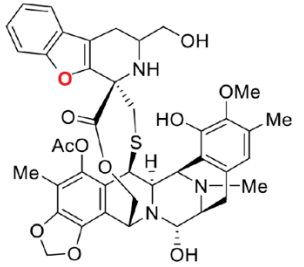

→ Effects on SE-driven programs in melanoma?

Santamaria Nuñez et al., *Mol Cancer Ther* (2016); Singh et al., *Clin Cancer Res* (2020)

Ecteinascidins display potent anti-tumor activities in melanoma models

- Ecteinascidins are **selectively** active ***in vitro*** & ***in vivo*** against **all** melanoma phenotypes, including **MAPKi resistant** cells

Cell line	Phenotype	Driver mutation	IC50 Lurbinectedin	IC50 Ecubectedin	IC50 PM54	IC50 Vemu (MAPKi)
501mel	Melanoma	$BRAF^{V600E}$	**0.4 nM**	**1.2 nM**	**1.7 nM**	**2440 nM**
MM074	Melanoma	$BRAF^{V600E}$	**1.1 nM**	**1.1 nM**	**3.2 nM**	**225 nM**
MM011	Melanoma	$NRAS^{Q61K}$	**0.4 nM**	**1.1 nM**	**1.4 nM**	**Resistant**
IGR39	Melanoma	$BRAF^{V600E}$	**1.1 nM**	**0.7 nM**	**0.8 nM**	**Resistant**
MM029	Melanoma	$BRAF^{V600K}$	**0.4 nM**	**1.3 nM**	**4.2 nM**	**Resistant**
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Cigrang*, Obid* et al., *Nature Communications* (2025)

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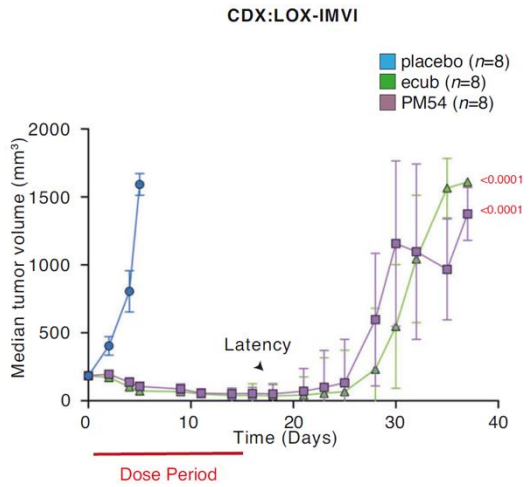
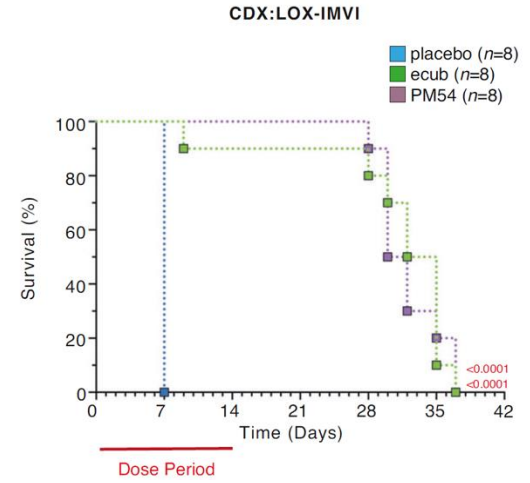
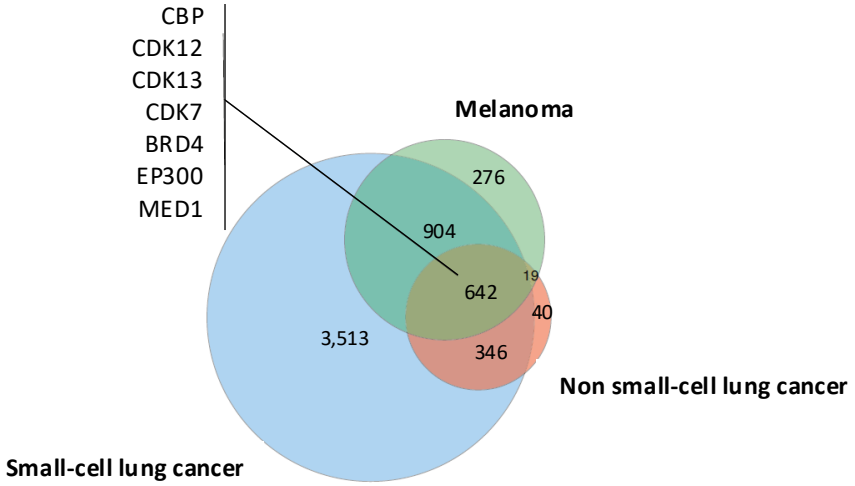


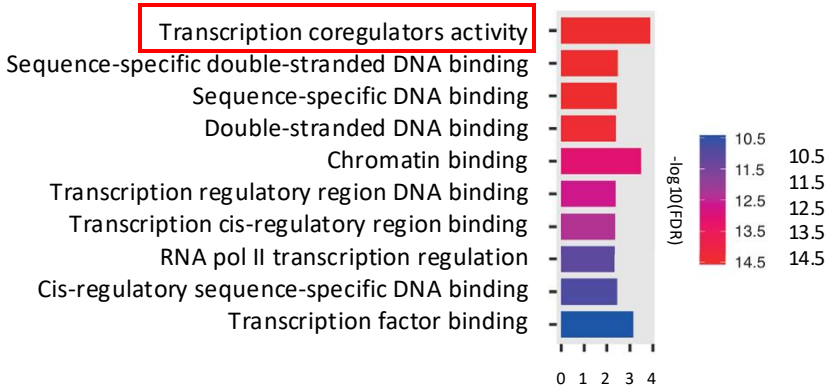


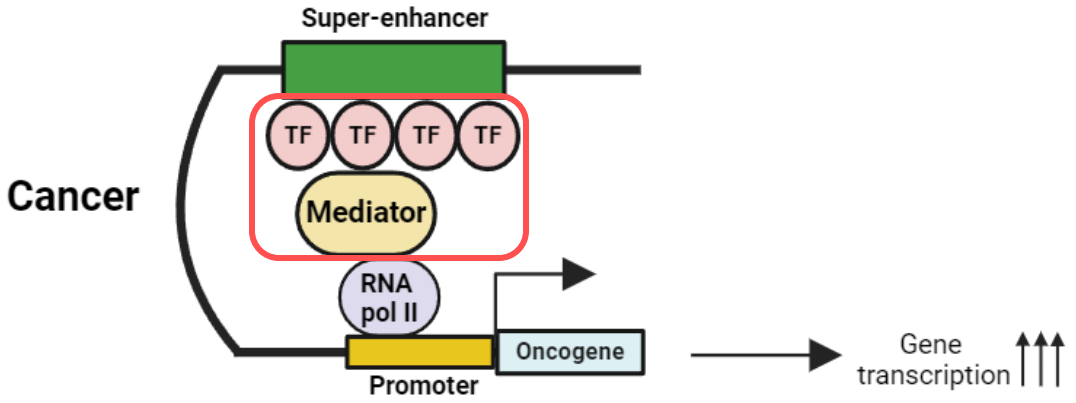
Cigrang*, Obid* et al., *Nature Communications* (2025)

Synthetic ecteinascidins impair SEs-coregulators & disrupt transcriptional condensates

- Ecteinascidins **downregulate** key **transcriptional co-regulators** enriched at **SEs**





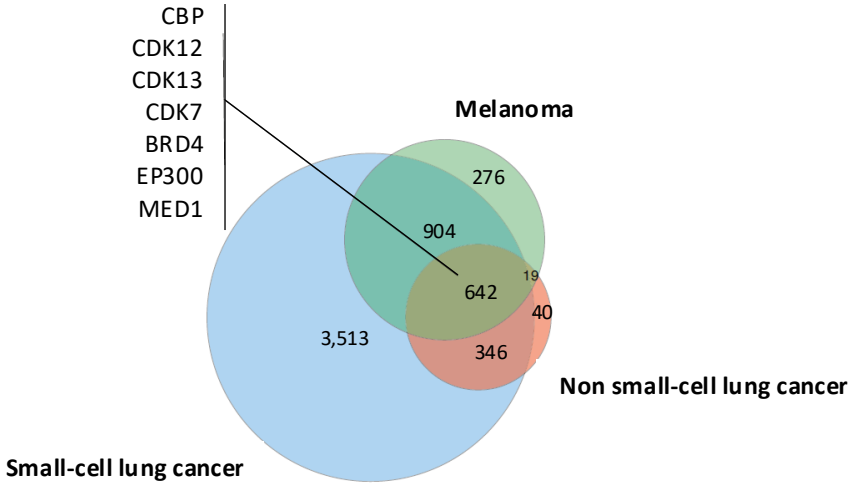


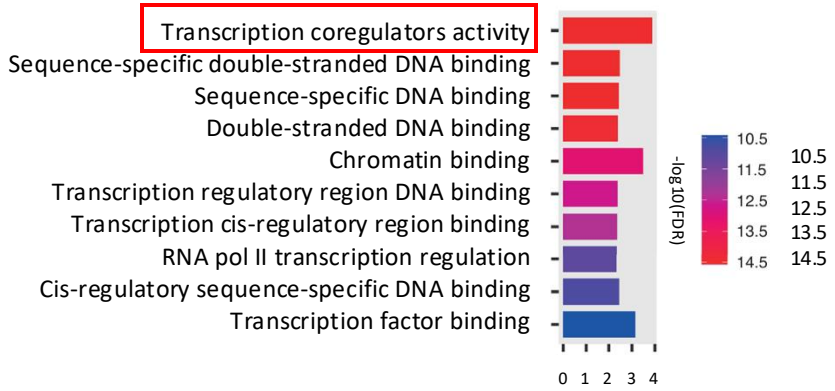
Cigrang*, Obid* et al., *Nature Communications* (2025)

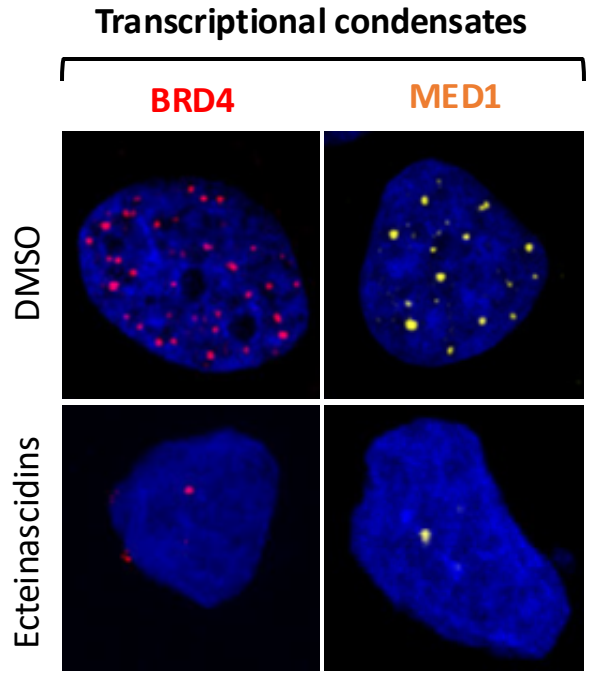
Results

Synthetic ecteinascidins impair SEs-coregulators & disrupt transcriptional condensates

➢ Ecteinascidins **downregulate** key **transcriptional co-regulators** enriched at **SEs** → **Transcriptional condensates disruption**







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Idenitification of synthetic ecteinascidins targets by Chem-map

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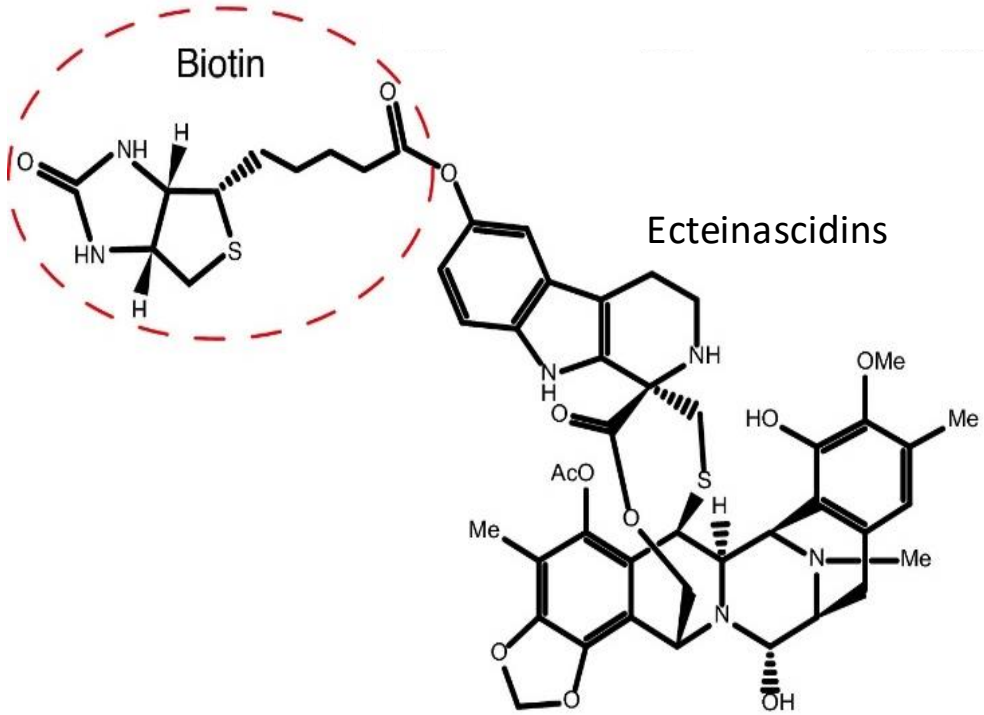

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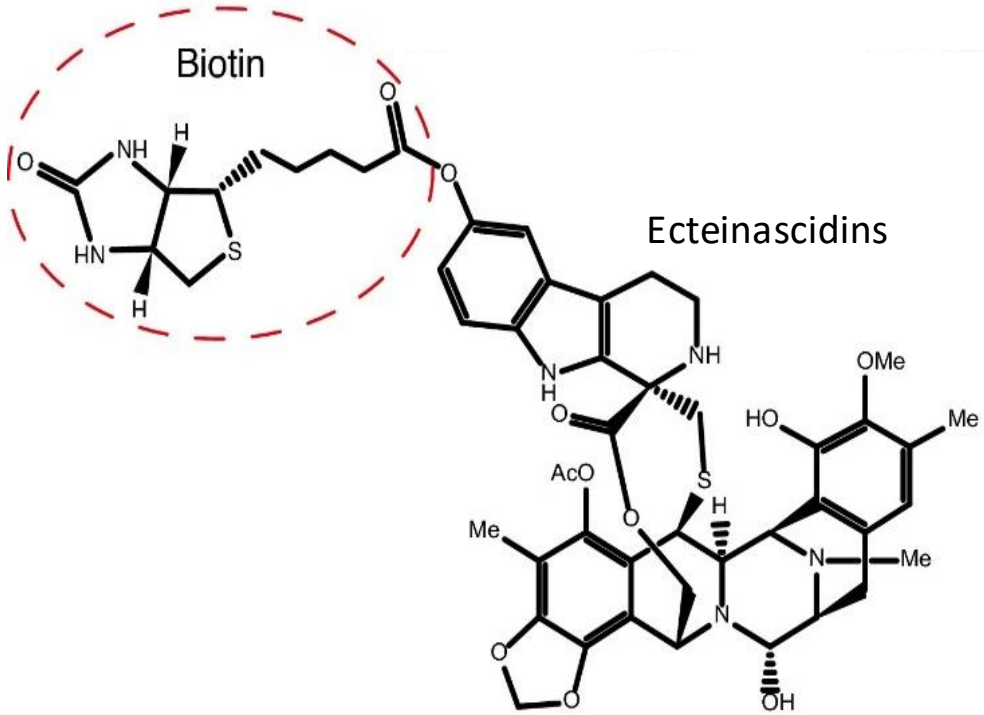

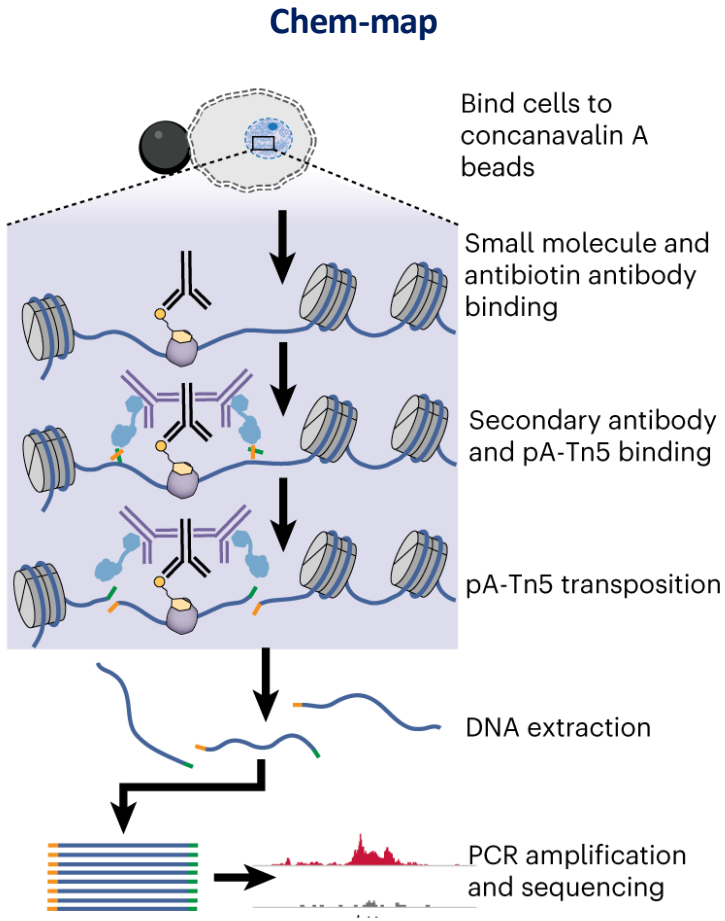

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Synthetic ecteinascidins bind core SE co-regulators promoters

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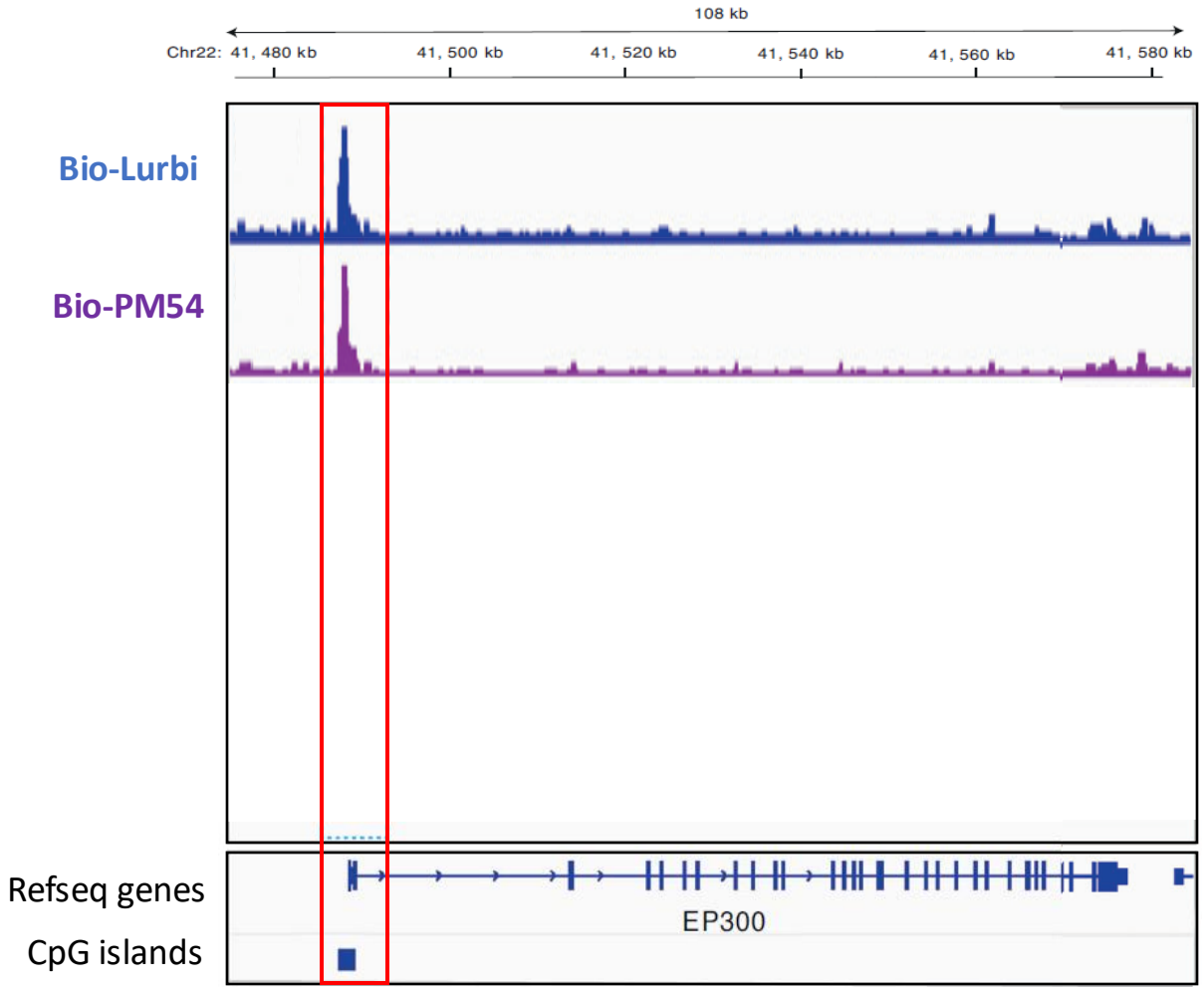

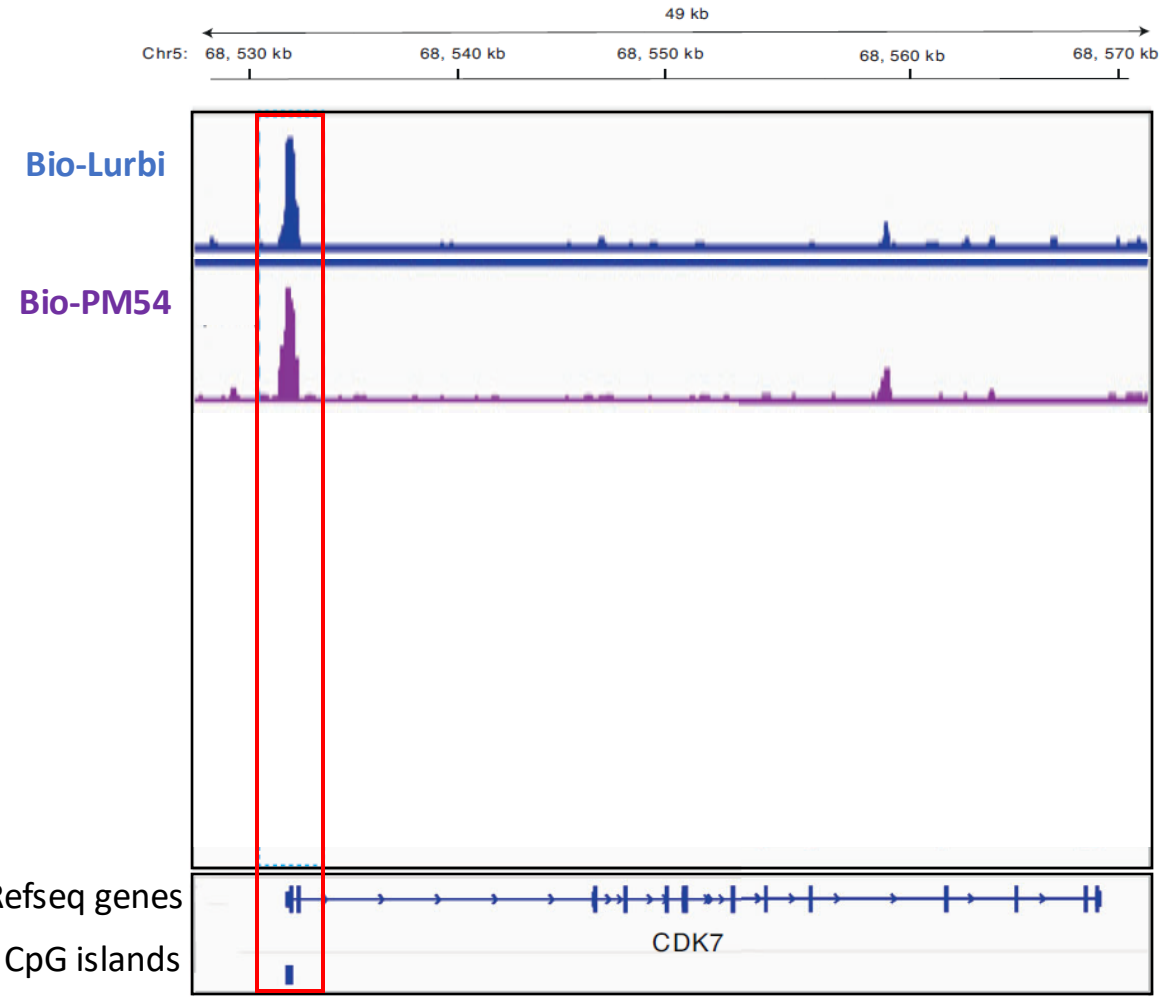

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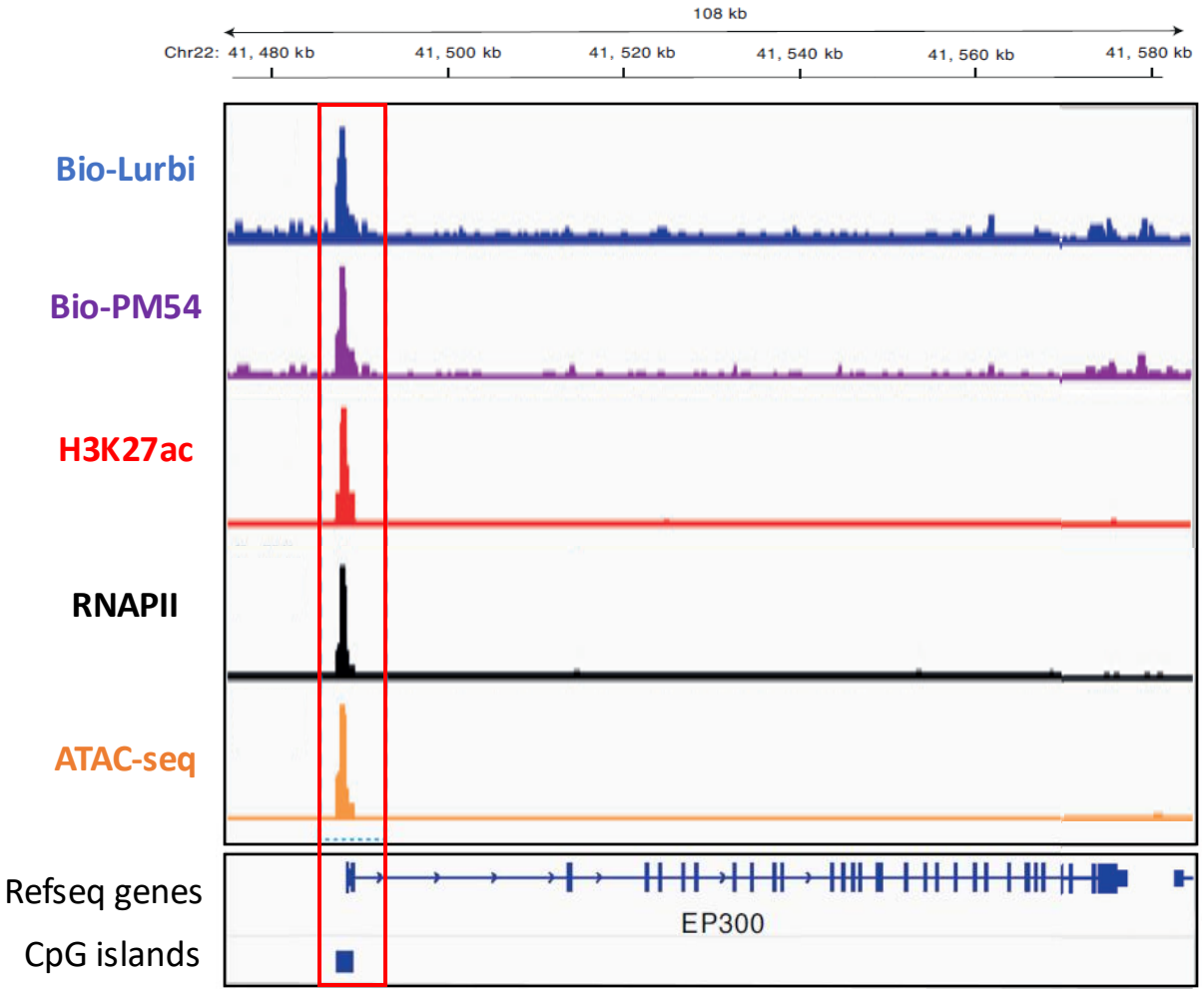

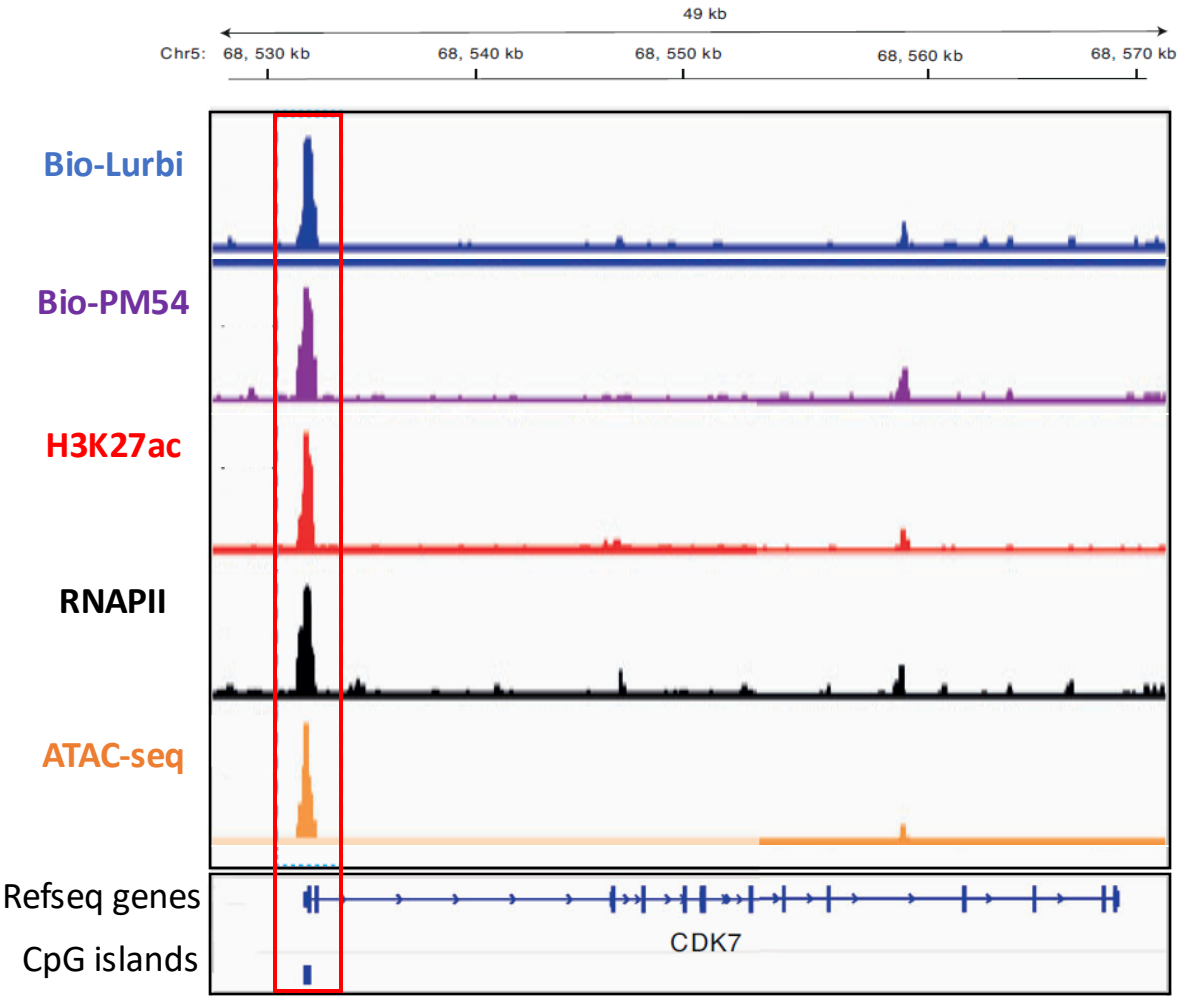

Cigrang*, Obid* et al., *Nature Communications* (2025)

Synthetic ecteinascidins induce two waves of transcriptional inhibition

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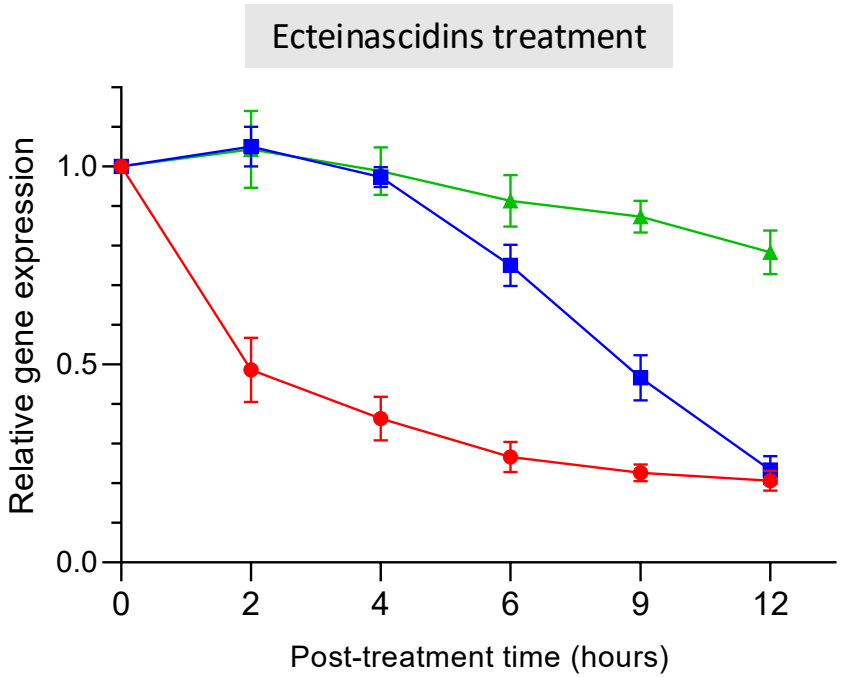

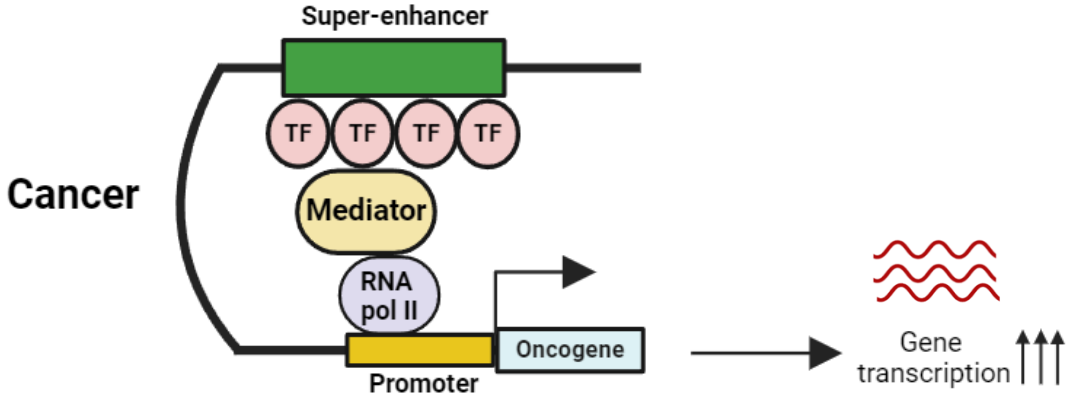

Early-inhibited genes = TFs/regulators enriched at SEs
(Ex: BRD4, CDK7, EP300)

Late-inhibited genes = SEs dependent melanoma oncogenes
(Ex: MITF, SOX10, EGFR, AXL)

Housekeeping genes
(Ex: ACTb, TBP, RPL13A)

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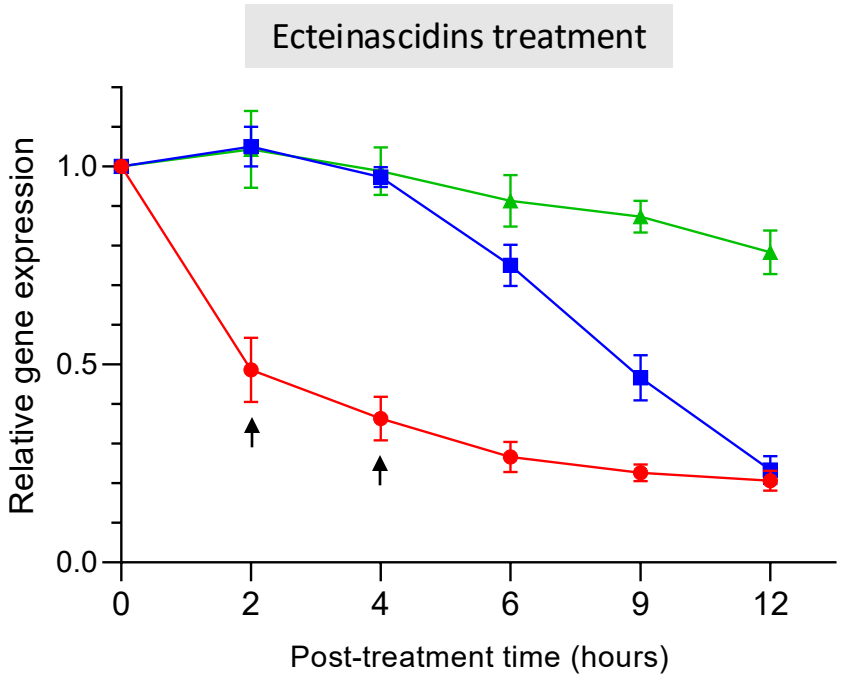

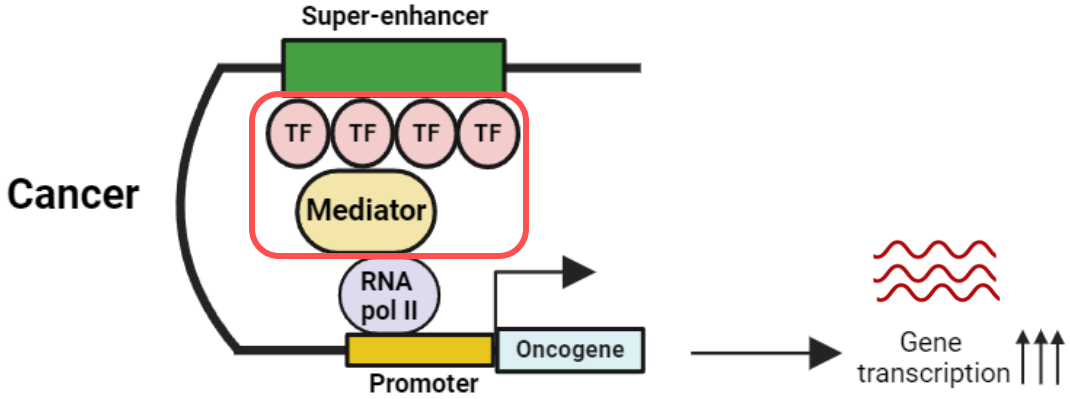

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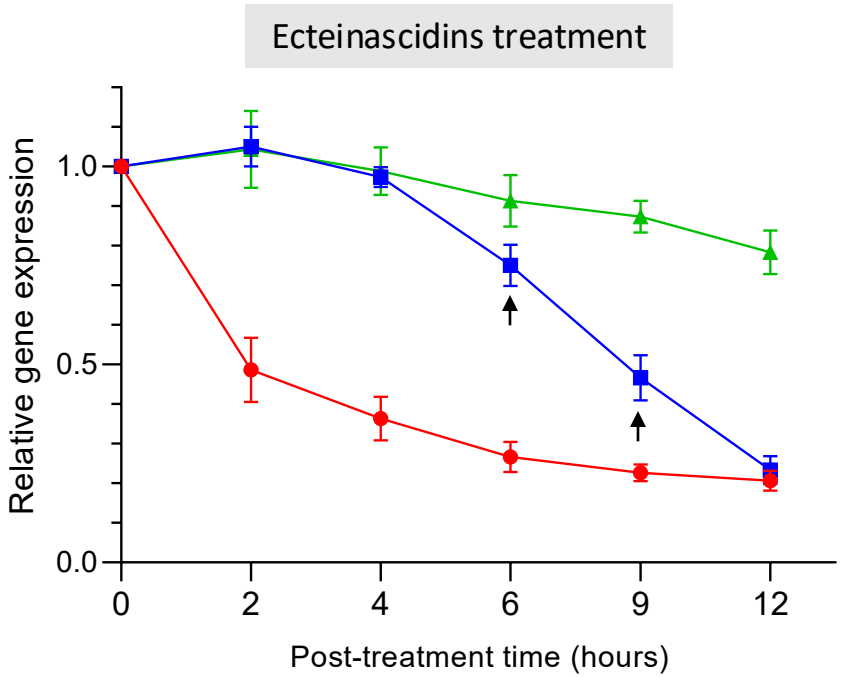

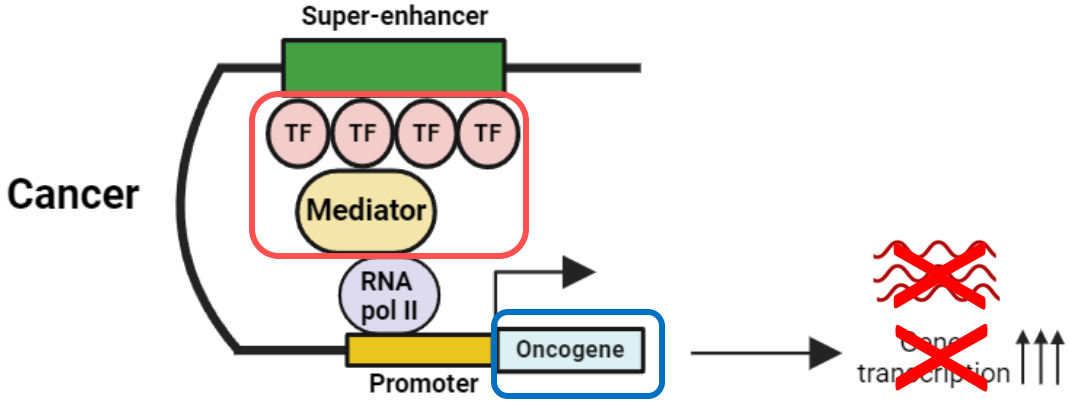

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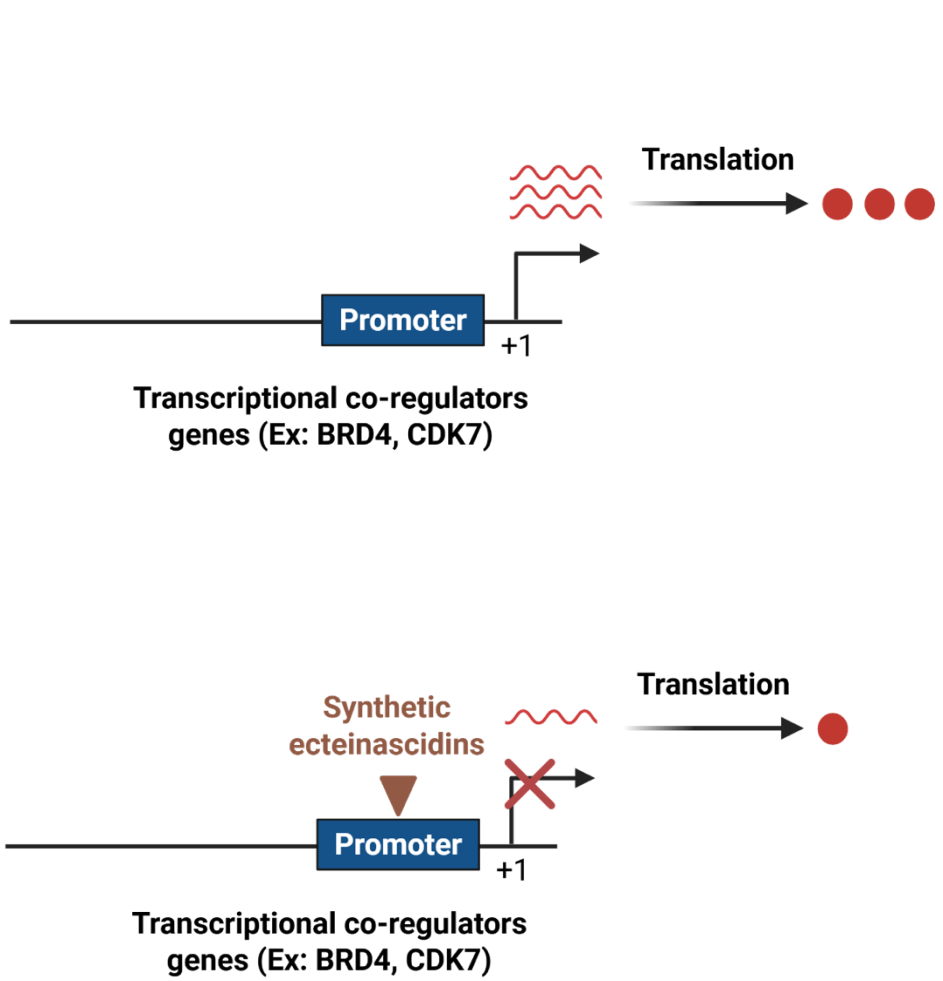
Conclusion

Ecteinascidins disrupt SE transcriptional programs by targeting SE regulators



(1) Inhibition of SE regulators

Cigrang*, Obid* et al., *Nature Communications* (2025)

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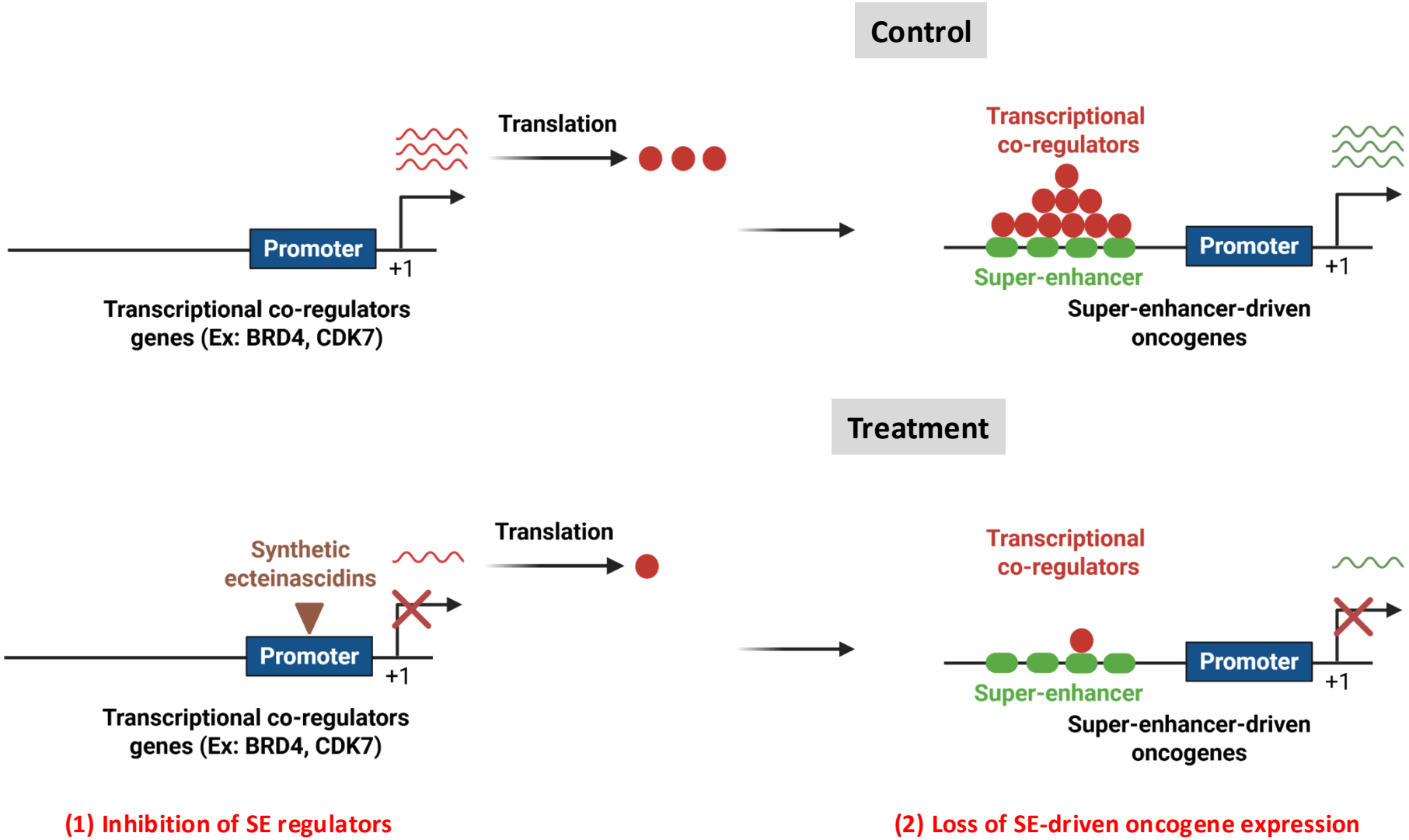

(1) Inhibition of SE regulators

(2) Loss of SE-driven oncogene expression

Cigrang*, Obid* et al., *Nature Communications* (2025)

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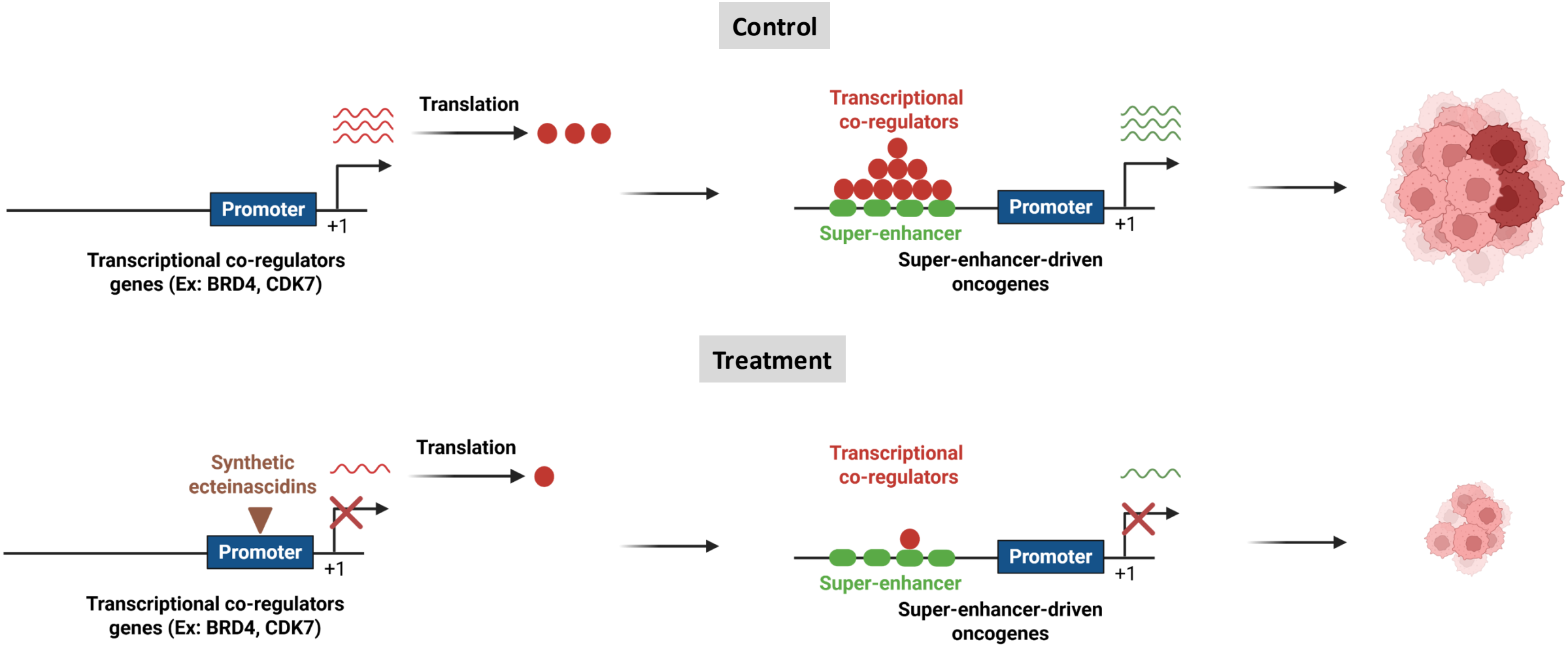

Cigrang*, Obid* et al., *Nature Communications* (2025)

Prospects

Ongoing & future work:

- **Clinical trials** in **advanced** solid tumors patients, including **melanoma:**

RECRUITING

Clinical Trial of PM54 in Advanced Solid Tumors Patients.

ClinicalTrials.gov ID NCT05841563

Sponsor PharmaMar

Information provided by PharmaMar (Responsible Party)

Last Update Posted 2023-06-05

- Genitourinary tract tumors: urothelial carcinoma, clear cell renal carcinoma and prostate adenocarcinoma.
- Cutaneous melanoma.
- Gastrointestinal: esophageal adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, and poorly differentiated (grade 3) gastroenteropancreatic Neuroendocrine Carcinoma (NEC)with Ki67 index >55%.
- Lung: non-small cell lung cancer (NSCLC) and Small Cell Lung Cancer (SCLC).
- Gynecological tumors: epithelial ovarian carcinoma (including primary peritoneal disease and/or fallopian tube carcinomas), endometrial adenocarcinoma and carcinoma of cervix.

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- Efficiency of **co-treatment** with **immune checkpoint-inhibitors:**

Thank you for your attention

Team of Dr. Frédéric Coin:

Dr. Frédéric Coin

Dr. Emmanuel Compe

Dr. Jean-Marc Egly

Amélie Zachayus

Alexis Bedaine

Anthony Hannus

Clara Capelli

Clara Maréchal

Clémence Elly

Jérémy Sandoz

Léane Seno

Maguelone Nogaret

Max Cigrang

Philippe Catez

Past members:

Cathy Braun

Pietro Berico

Team of Dr. Irwin Davidson:

Dr. Irwin Davidson

Alexandre Haller

Antonin Lallement

Youenn Davidson

IGBMC facilities:

Cell culture

Genomeast

Flow cytometry

Imaging facility

igbmc
institut de génétique et de biologie moléculaire et cellulaire

Pharma Mar

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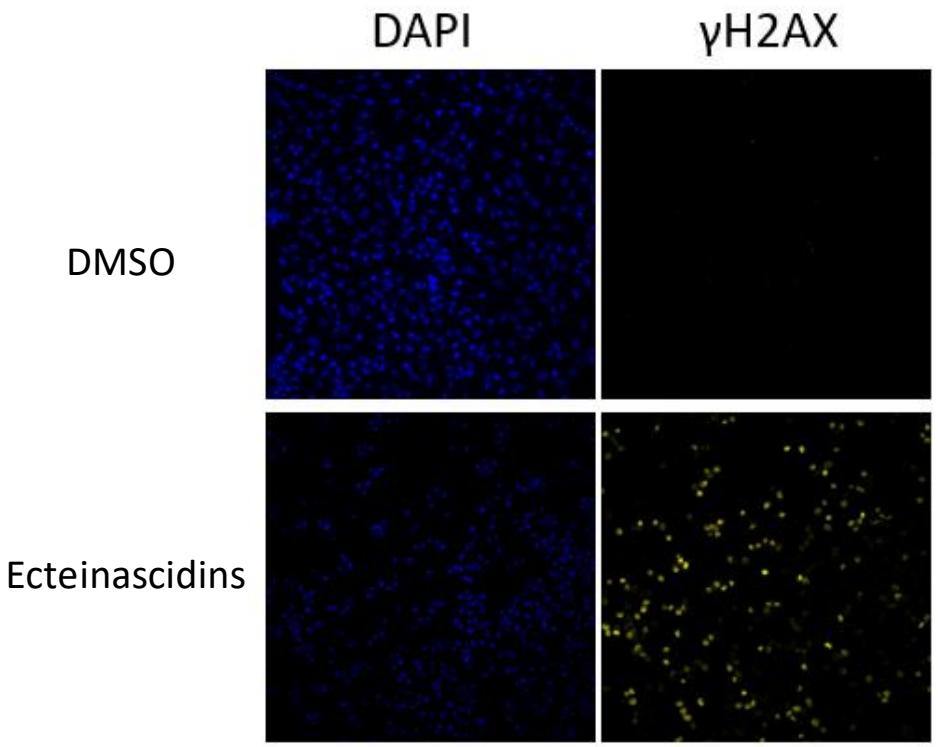
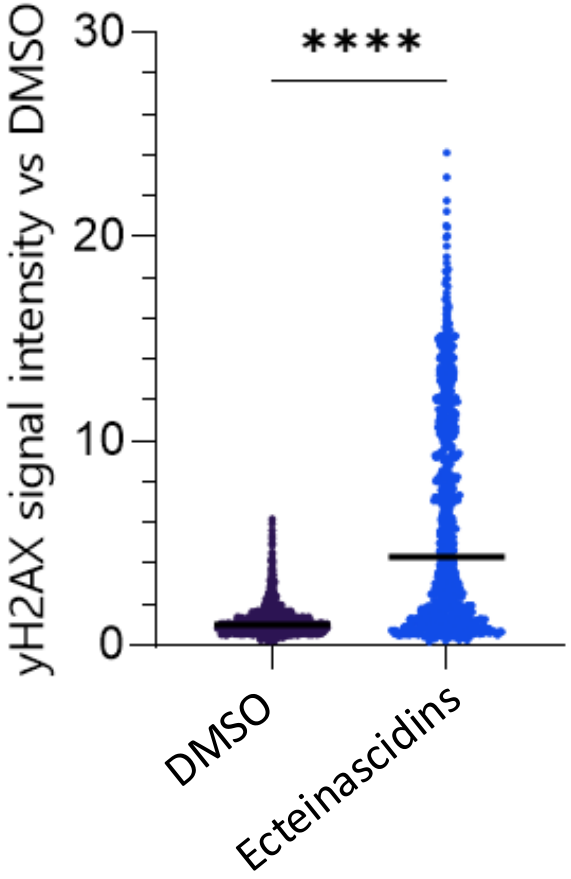
MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR ET DE LA RECHERCHE

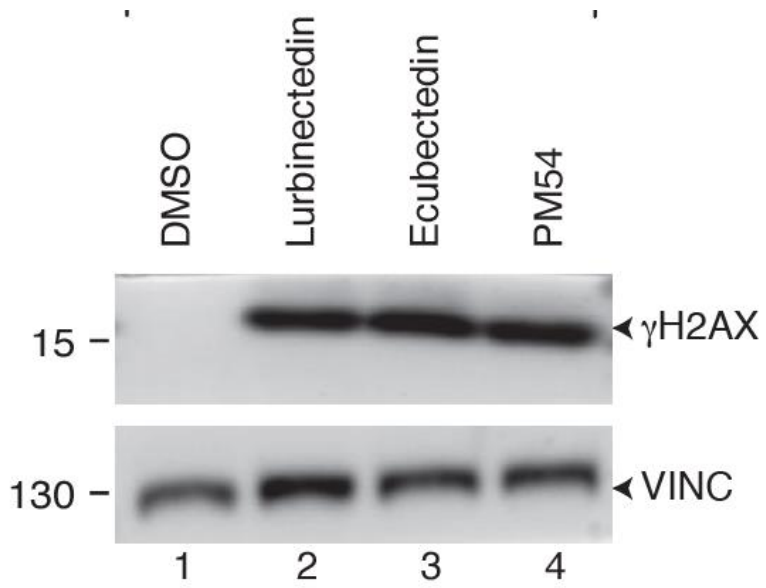
CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

Annexe

Ecteinascidins induce DNA damage in melanoma cells

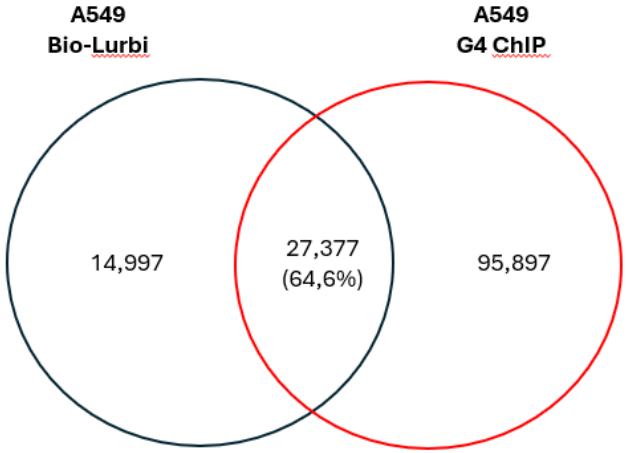


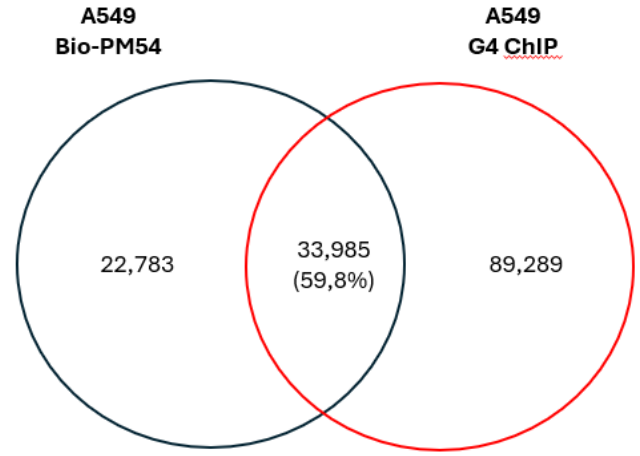


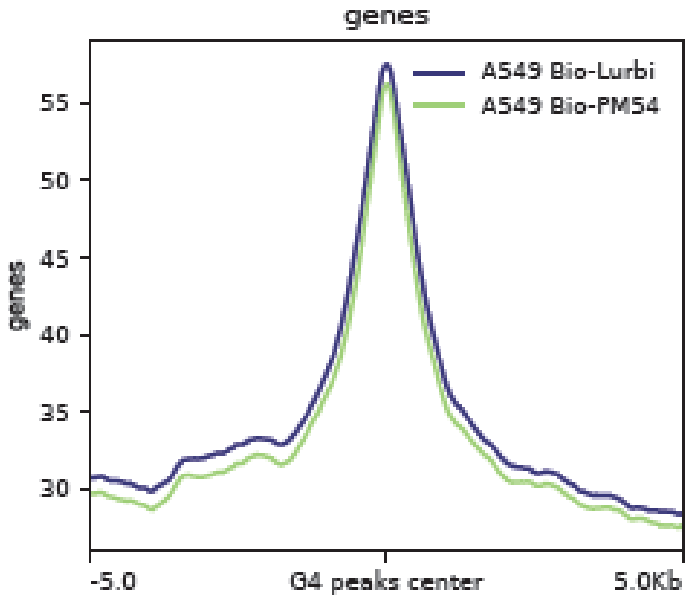


Annexe

Ecteinascidins specifically bind G-quadruplex secondary structures



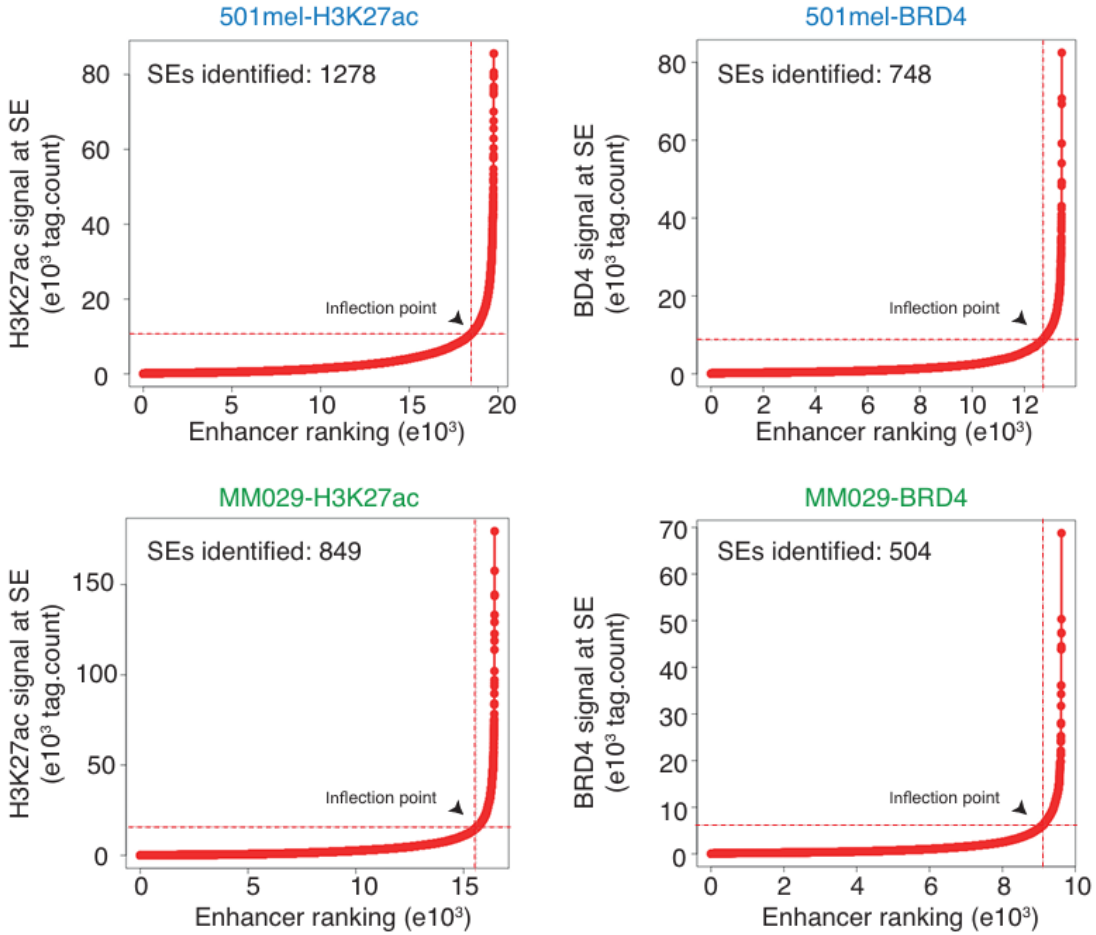


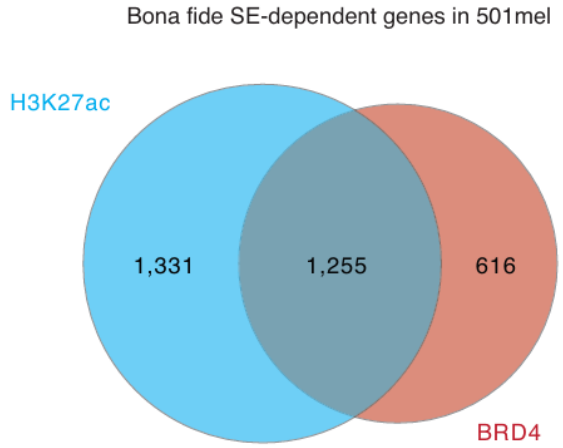


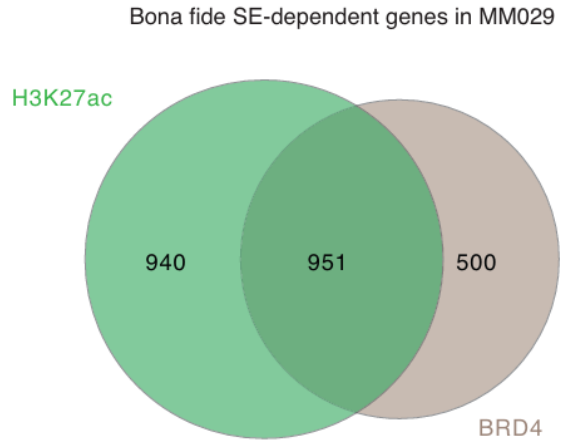
Annexe

Identification of SEs in melanoma cells

➢ **SE-driven genes** in melanoma cells were identified through **ROSE analysis** of **BRD4** and **H3K27ac** Cut&Tag data



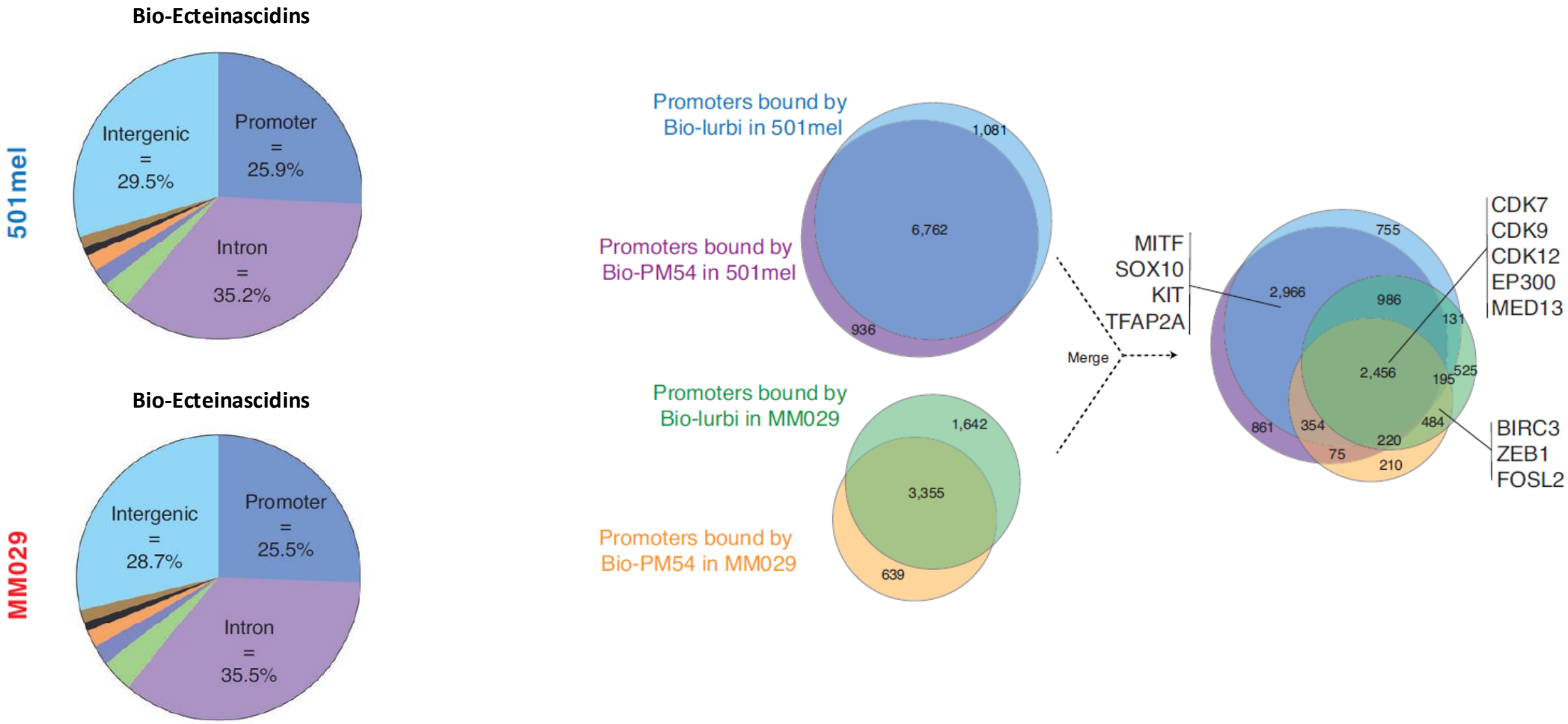




Cigrang*, Obid* et al., *Nature Communications* (2025)

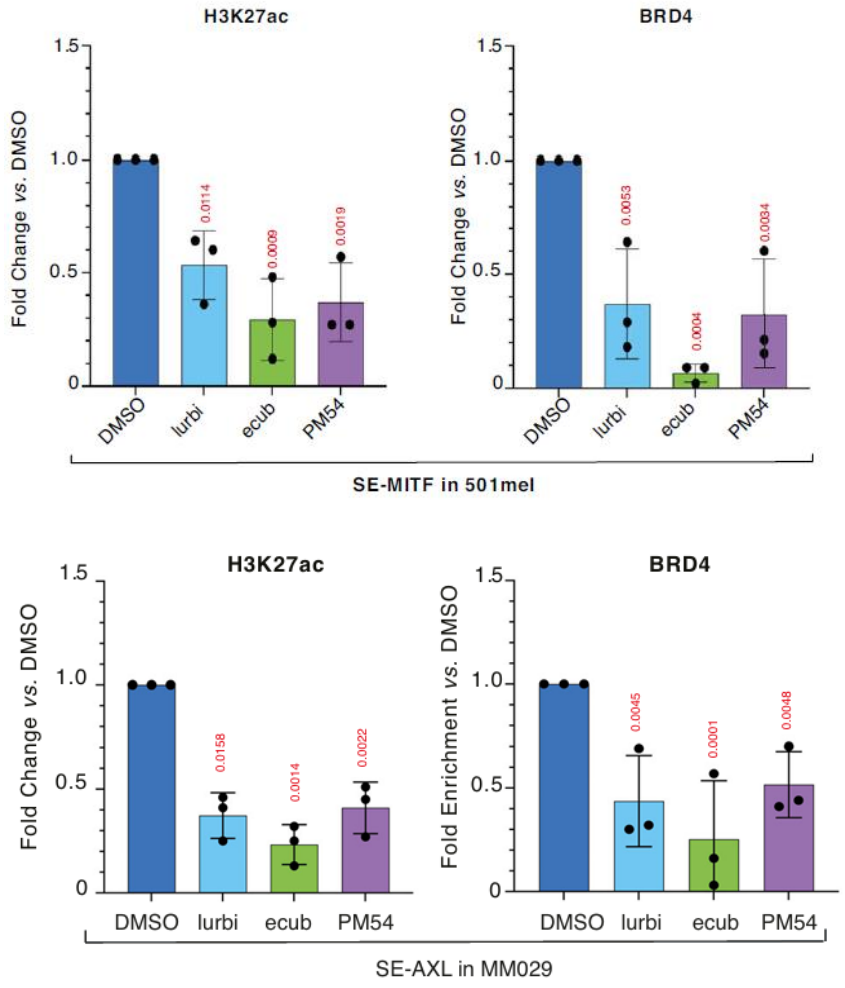
Annexe

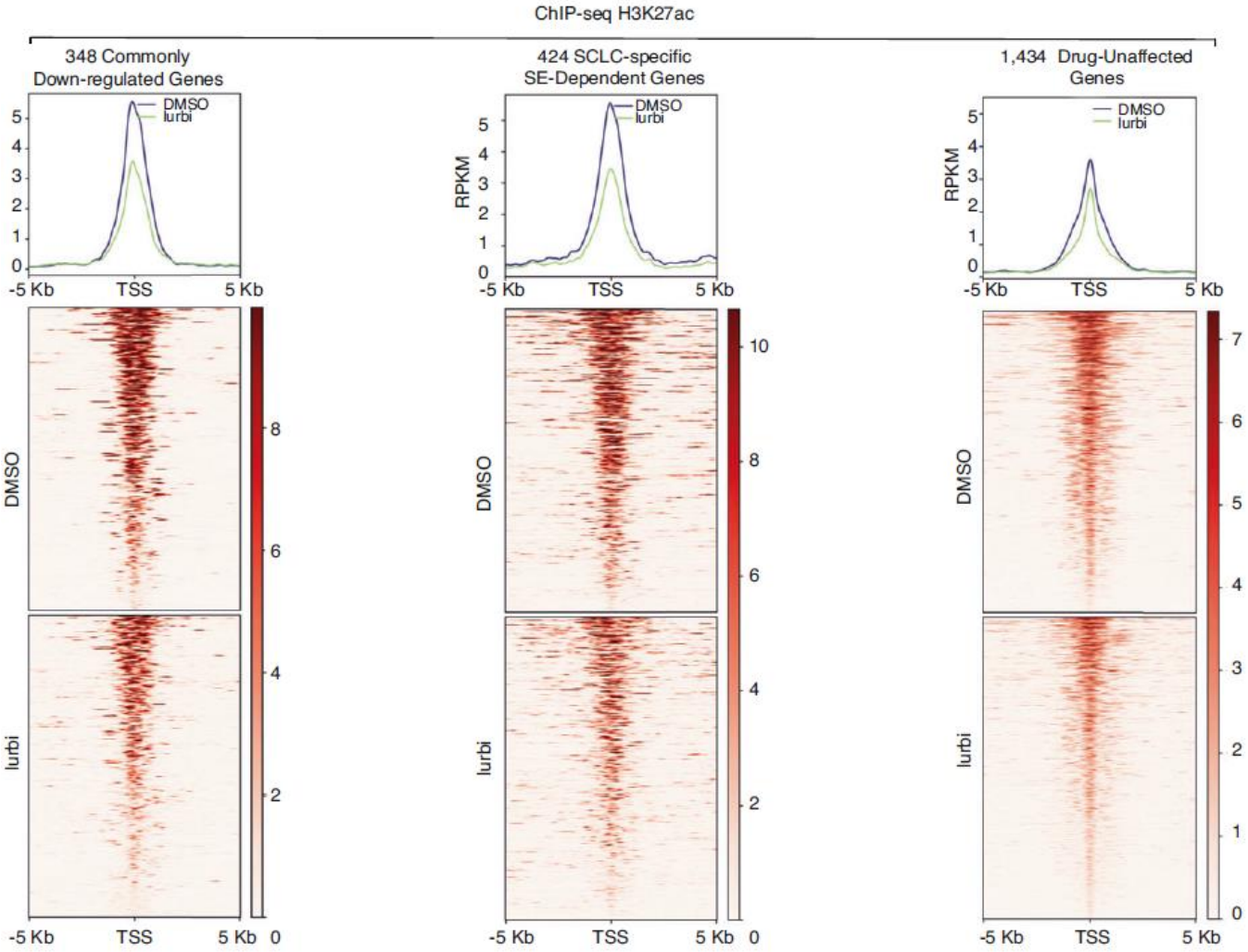
Synthetic ecteinascidins bind promoters of the target genes



Annexe

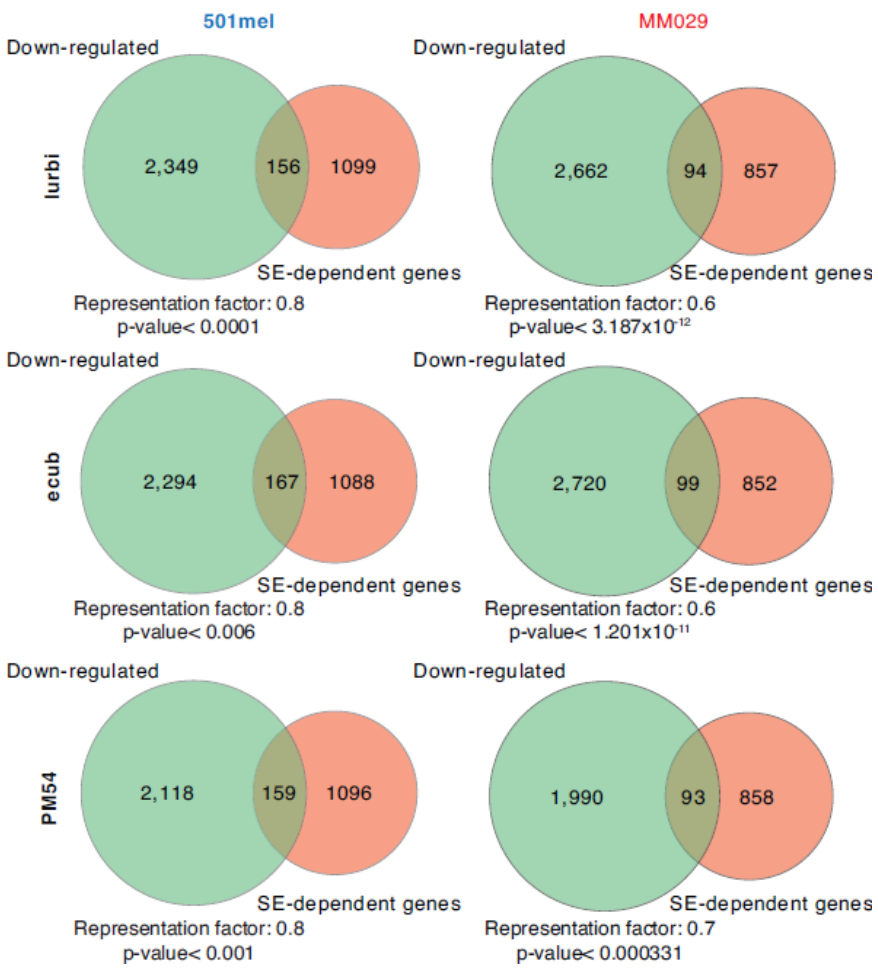
Synthetic ecteinascidins reduce co-regulator enrichment at SEs

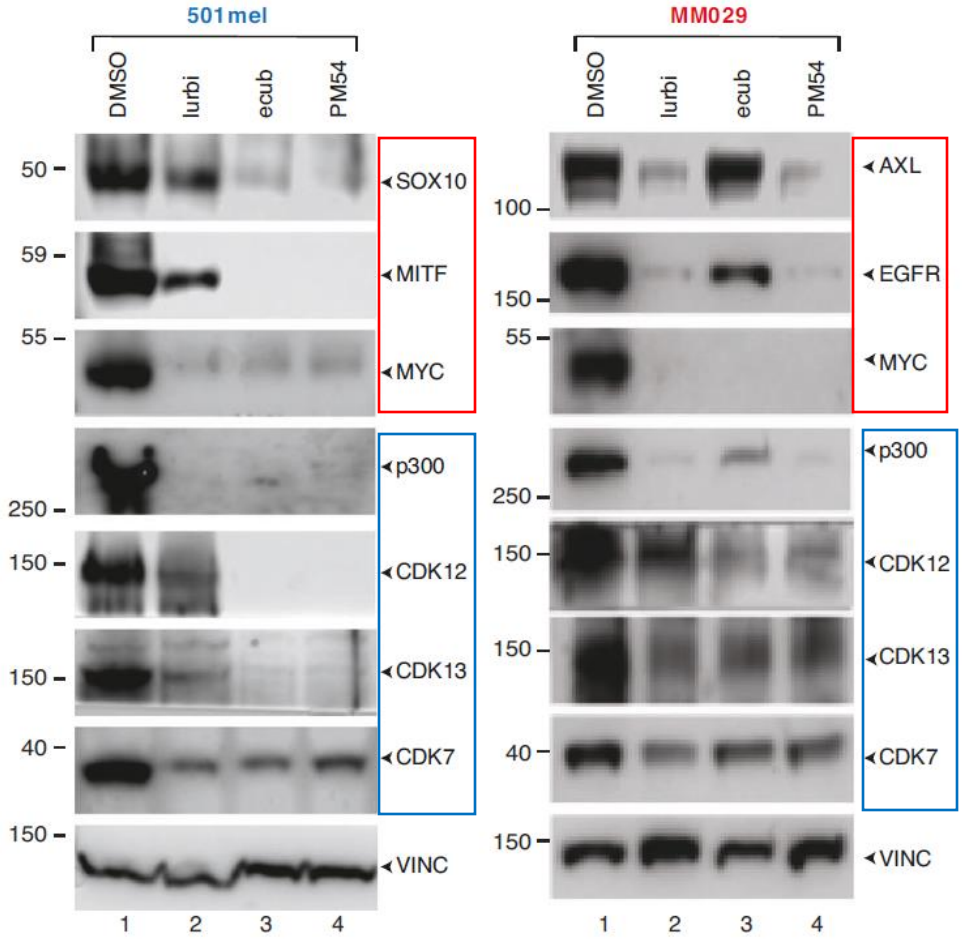




Annexe

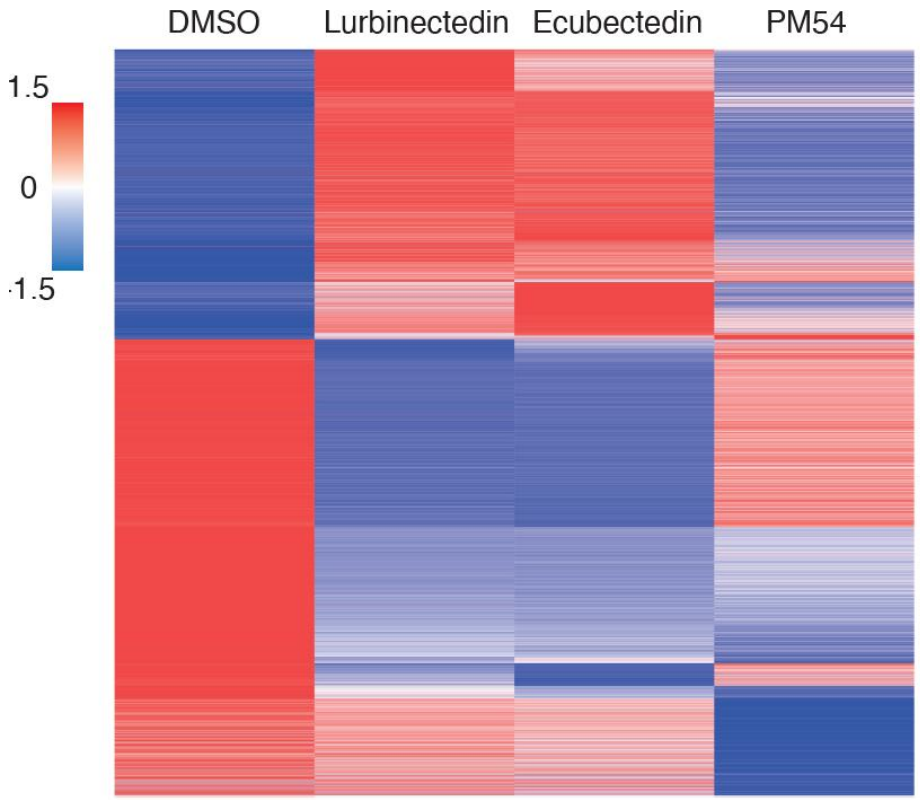
Synthetic ecteinascidins inhibit the expression of SE-dependent genes

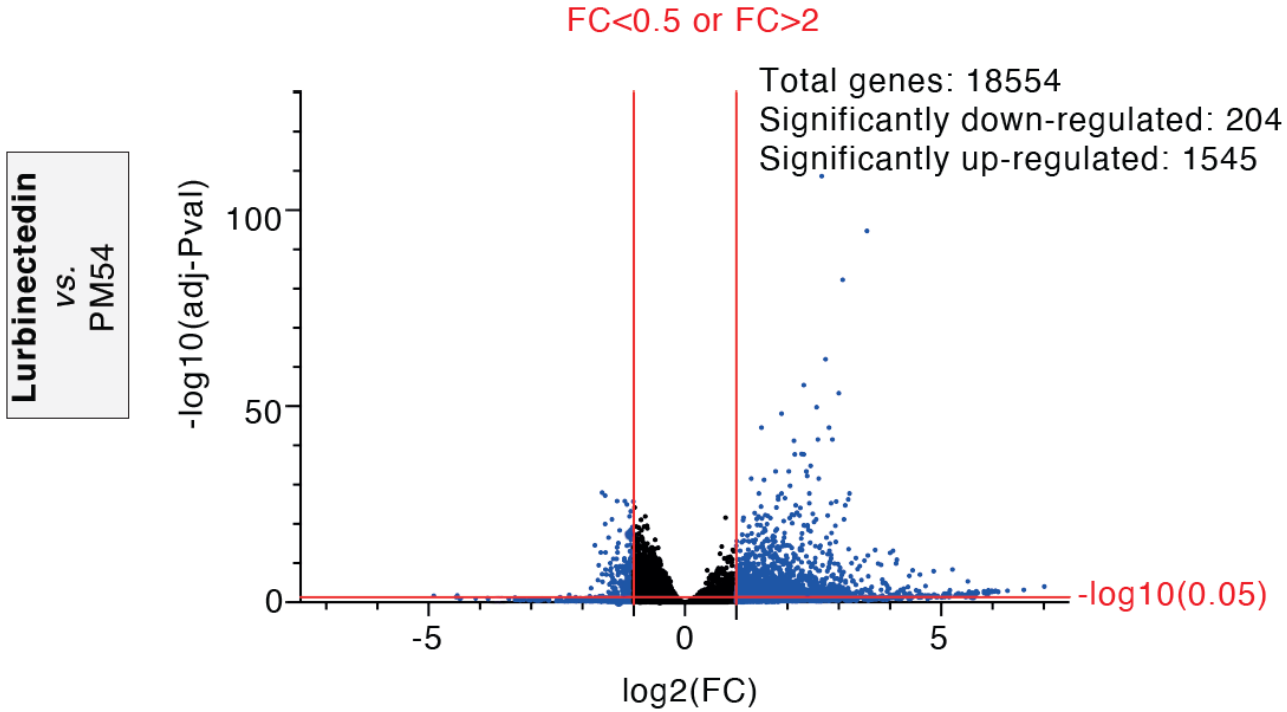




Annexe

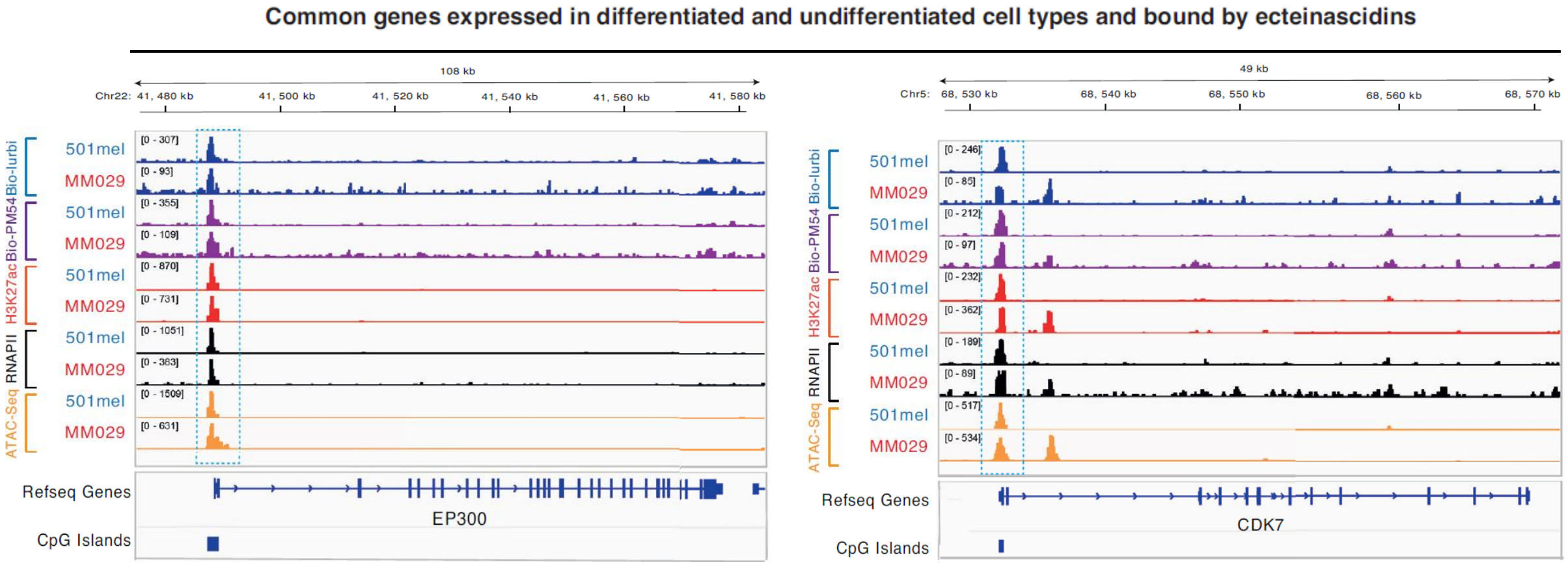
PM54 differentially affects gene expression compared to other Ecteinascidins





Synthetic ecteinascidins commonly bind core SE co-regulators

- Synthetic ecteinascidins **commonly** bind **CpG-dense promoter** regions of core **co-regulators** of **super-enhancers**



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