

Settima edizione di



# AIEOP..

## ...in Lab

**Il targeting della nicchia midollare nella leucemia linfoblastica acuta a cellule B (LLA-B) mediante il blocco di Attivina A rimodella il microambiente e migliora l'efficacia della chemioterapia**

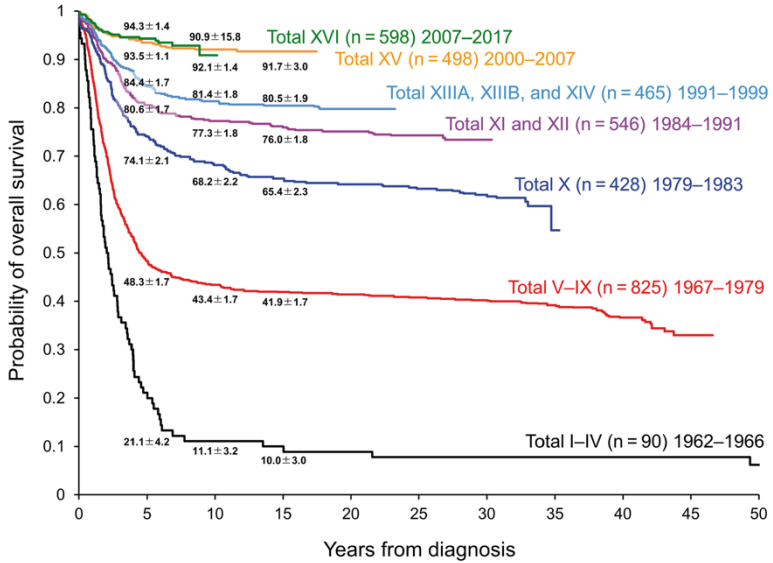
*Erica Dander, PhD*

Milano, 22 e 23 maggio 2026

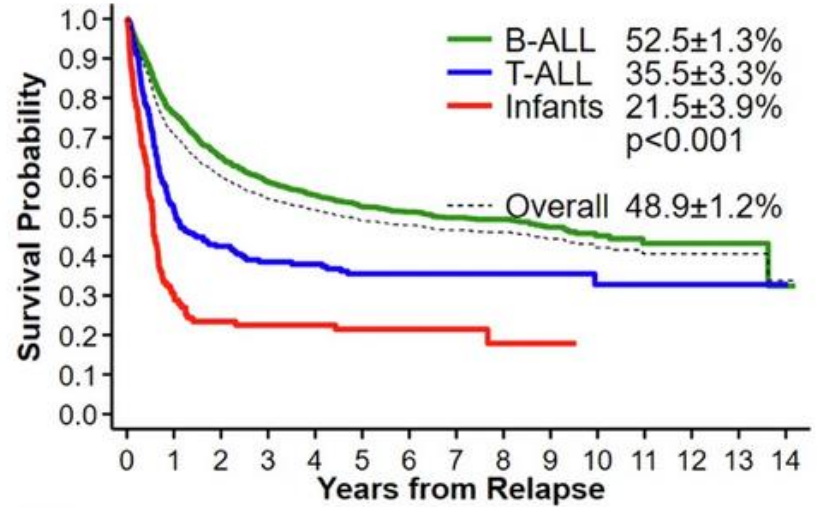
## Disclosures of Erica Dander

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOTHING TO DISCLOSE							

## Pediatric BCP-ALL: A leading cause of cancer-related death in children and young adults

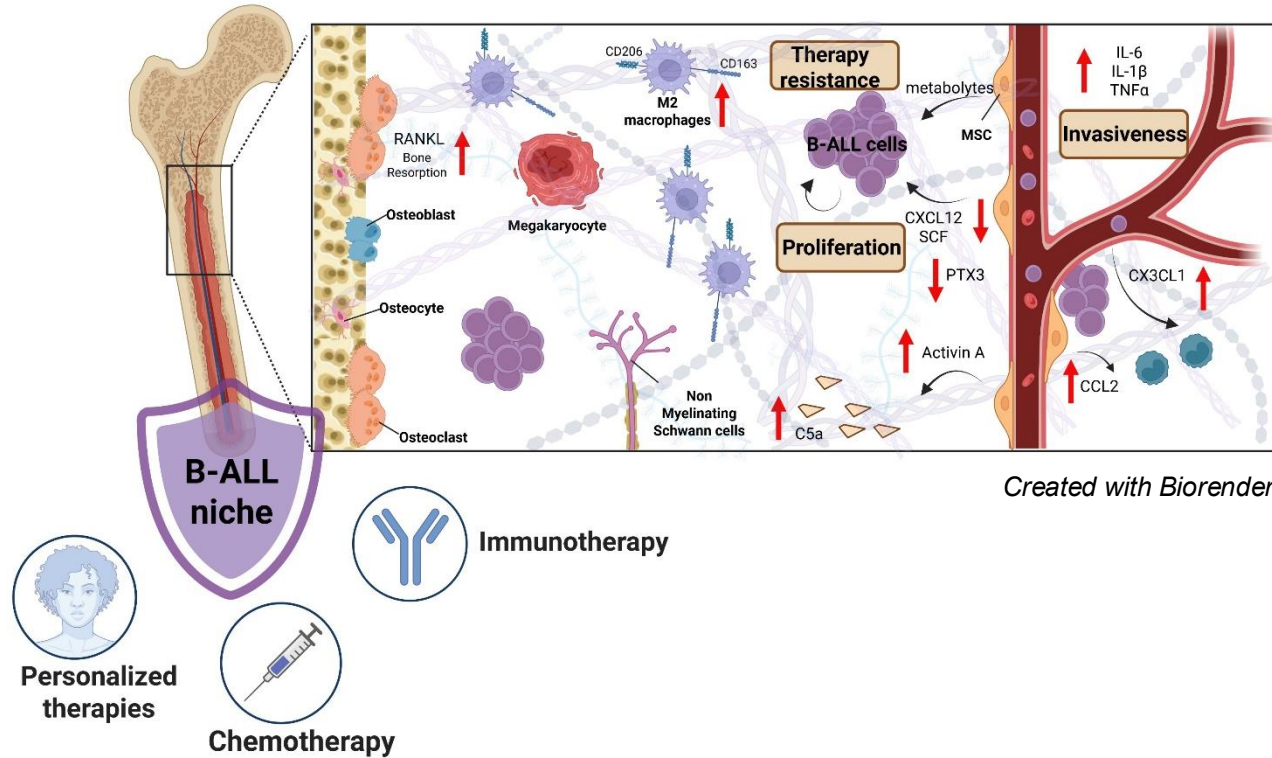


*Haematologica*. 2020 Nov 1;105(11):2524-2539



*Leukemia*. 2024 Nov;38(11):2382-2394

**The altered bone marrow niche shelters leukemic cells and provides essential cues for survival and therapy resistance**



## Activin A a new targetable pro-leukemic factor increased in the leukemic BM niche

Acute Lymphoblastic Leukemia

ARTICLE

### ActivinA: a new leukemia-promoting factor conferring migratory advantage to B-cell precursor-acute lymphoblastic leukemic cells



Federica Portale,<sup>1</sup> Giulia Cricri,<sup>1</sup> Silvia Bresolin,<sup>2</sup> Monica Lupi,<sup>3</sup> Stefania Gaspari,<sup>4,5</sup> Daniela Silvestri,<sup>5,7</sup> Barbara Russo,<sup>1</sup> Noemi Marino,<sup>1</sup> Paolo Ubezio,<sup>3</sup> Fabio Pagni,<sup>8</sup> Patrizia Vergani,<sup>9</sup> Geertruy Te Kronnie,<sup>2</sup> Maria Grazia Valsecchi,<sup>6</sup> Franco Locatelli,<sup>1</sup> Carmelo Rizzari,<sup>7</sup> Andrea Biondi,<sup>1,7</sup> Erica Dander<sup>1\*</sup> and Giovanna D'Amico<sup>1\*</sup>

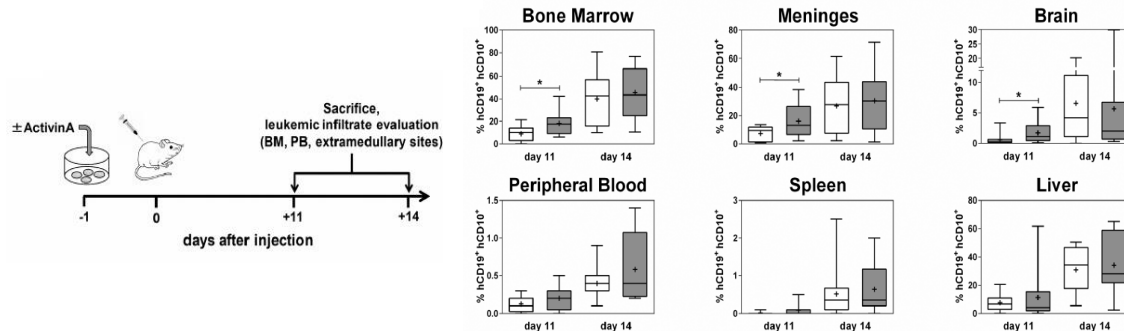
\*ED and GD'A contributed equally to this work

Haematologica 2019  
Volume 104(3):533-545

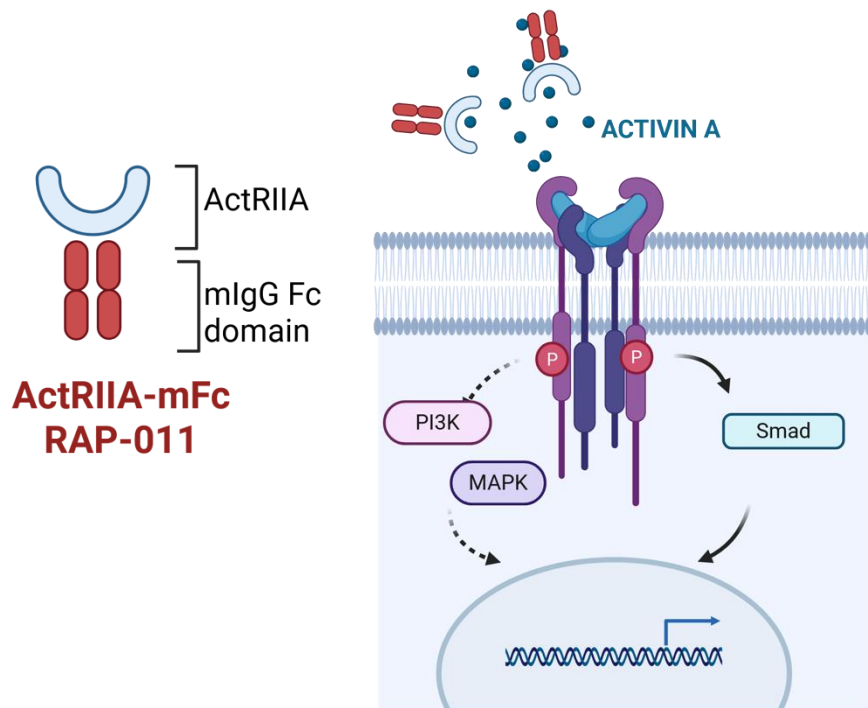
• **Over-expressed** in the BM of BCP-ALL patients and strongly induced in BM-MSc upon leukemic cell stimulation.

• *In vitro*, increased **migratory and invasive properties** of BCP-ALL cells over healthy CD34+ cells.

• In a BCP-ALL xenografts **enhanced BM engraftment and the metastatic potential** of leukemic cells.



## AIM: Targeting the altered B-ALL microenvironment by Activin A trapping



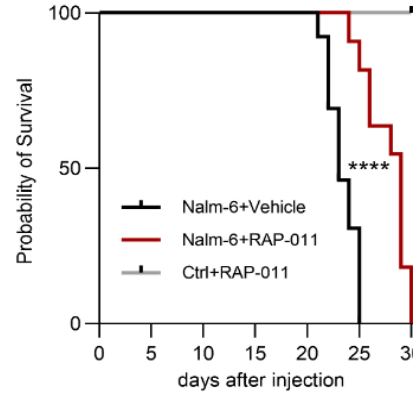
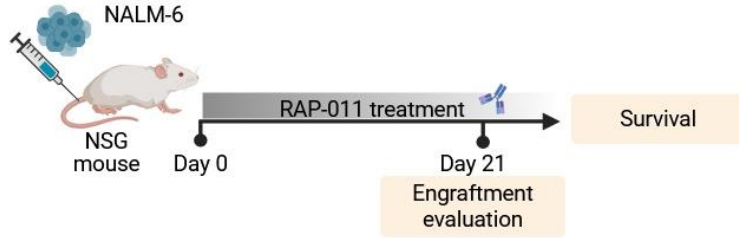
### Sotatercept (ACE-011, human counterpart of RAP-011)

- Malignant **bone disease** and **osteoporosis** to increase mineral density (Phase I/ II studies, discontinued).
- **Anemia** treatment (chemotherapy-induced anemia,  $\beta$ -thalassemia, MDS, CMML, etc.) to promote late-stage erythropoiesis (later superseded by Luspatercept after Phase II studies).
- First-in-class drug for **pulmonary arterial hypertension (PAH)** to improve cardiac and vessel function and oxygen distribution (approved and marketed in USA and Europe) .

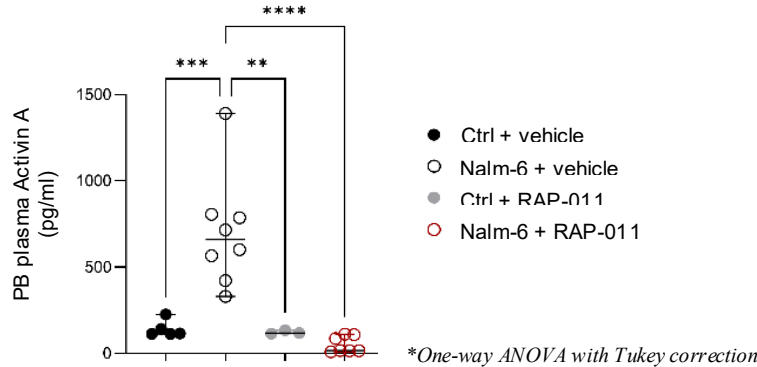
# Activin A trapping delays disease progression and improves the survival of B-ALL xenografts



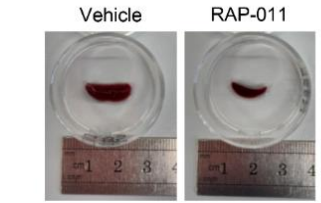
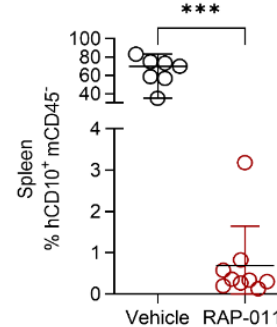
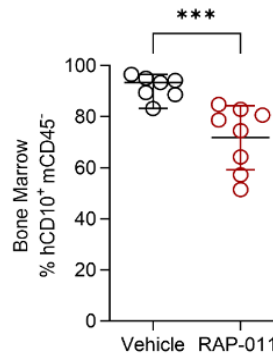
Dr. Alessandra Fallati, PostDoc



\*Log-rank Mantel-Cox test (n=12, 6 mice/group)

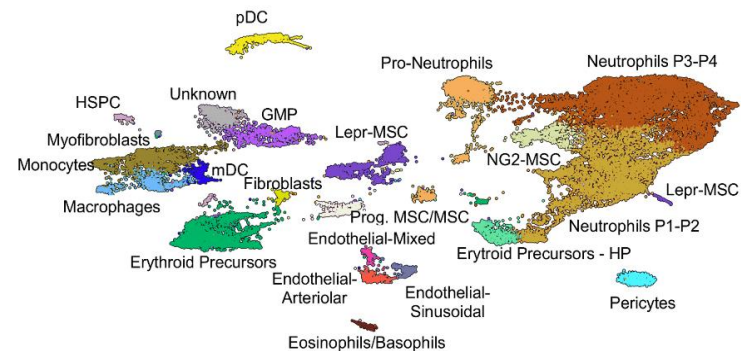
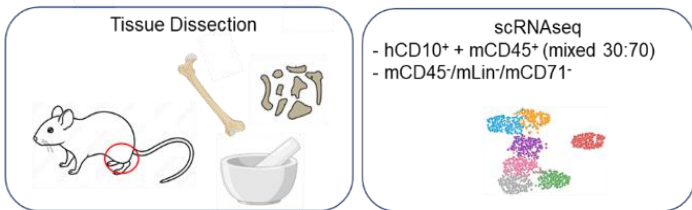


\*One-way ANOVA with Tukey correction

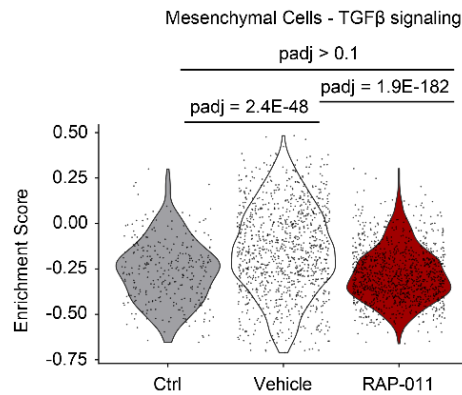


\*Mann-Whitney

# Activin A trapping reshapes the leukemic BM microenvironment: scRNA sequencing

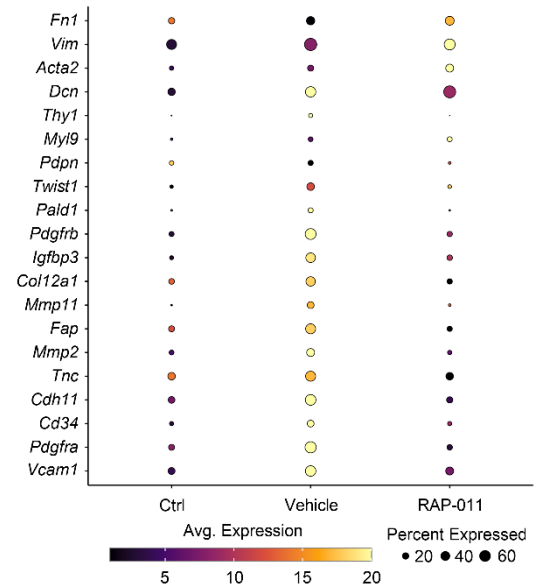


Restoration of normal TGF- $\beta$  signalling



*GSEA, Wilcoxon Rank Sum test with Bonferroni correction.*

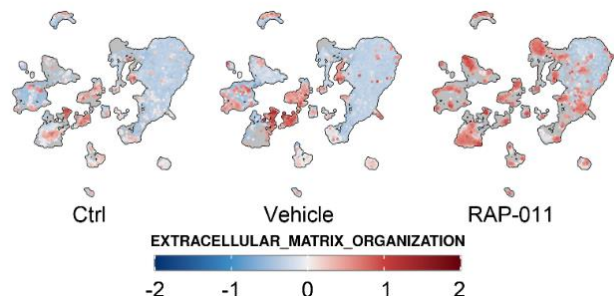
Reversion of leukemia-induced CAF signature in MSCs



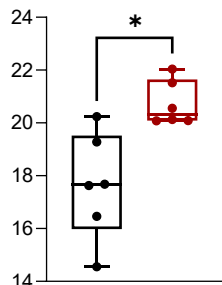
# Activin A trapping reshapes the leukemic BM microenvironment: scRNA sequencing

Extracellular matrix remodeling

Neutrophil function modulation

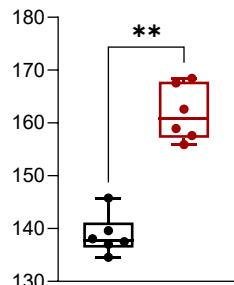


Total bone volume (mm<sup>3</sup>)



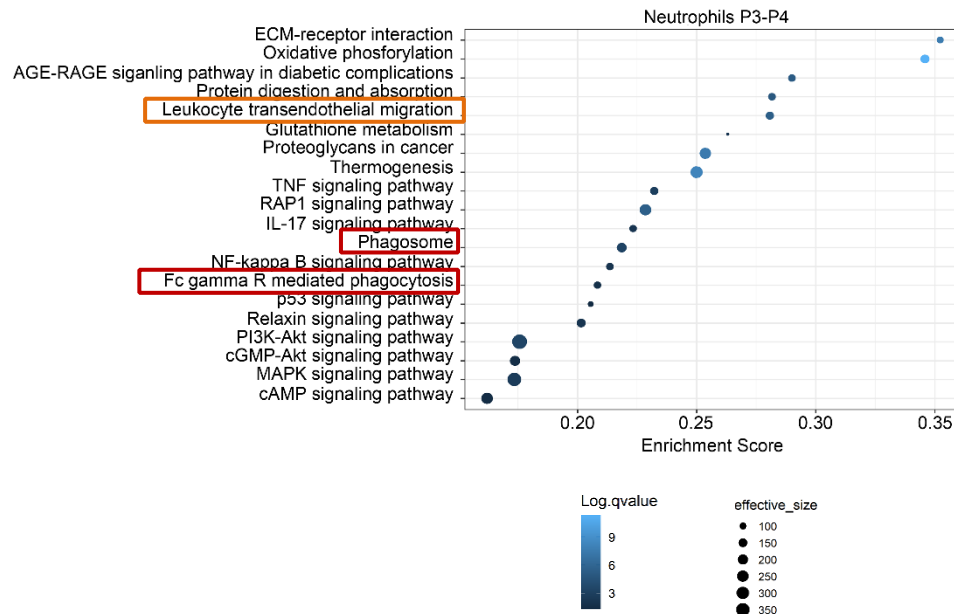
□ Vehicle  
□ RAP-011

Cross-sectional thickness (μm)



\*Mann-Whitney

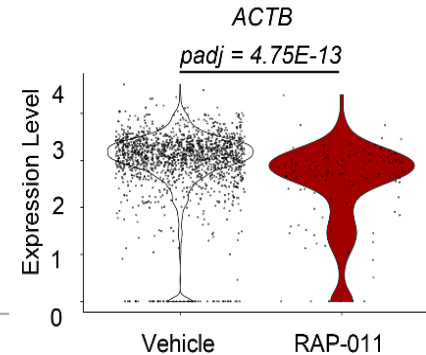
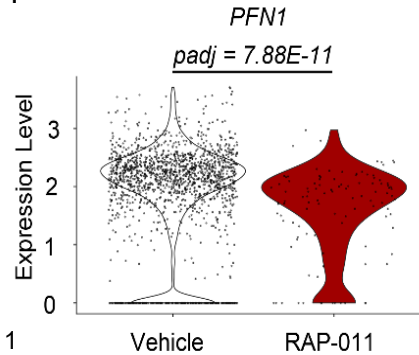
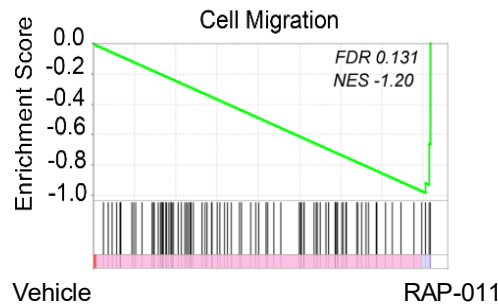
Pathway over-representation analysis treated vs not treated



## Activin A trapping modulates B-ALL cell functions: scRNA sequencing

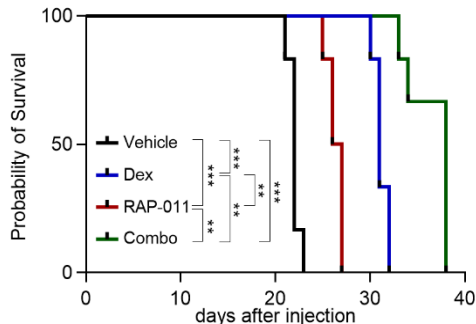
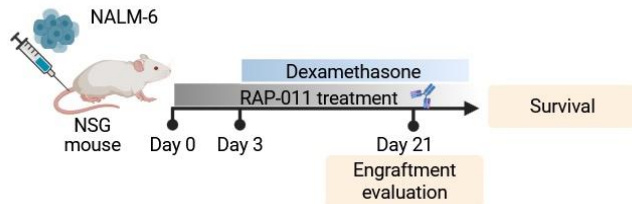
Downmodulation of NALM-6 migratory properties

GSEA on Nalm-6  
treated vs untreated with RAP-011

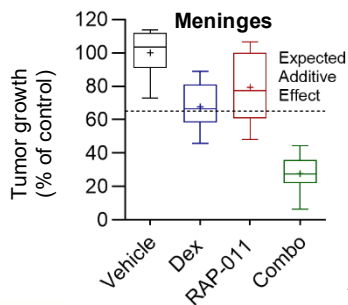
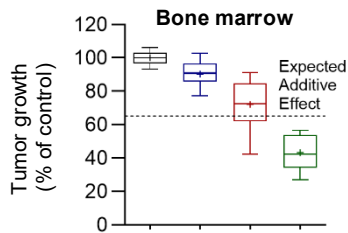


*Padj=Wilcoxon Rank Sum test  
with Bonferroni correction*

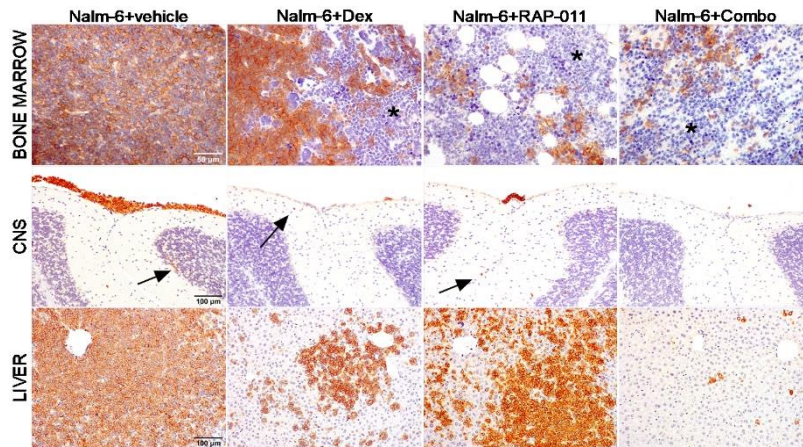
# Activin A trapping enhances dexamethasone-based chemotherapy in Nalm-6 xenografts



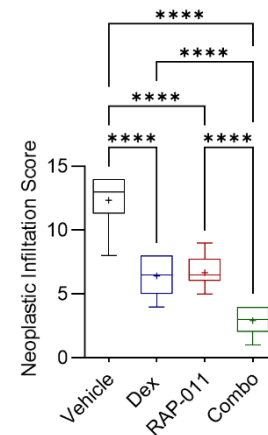
\*Log-rank Mantel-Cox test (n= 6 mice/group)



Combination index Bliss Independence model, n=12 mice/group

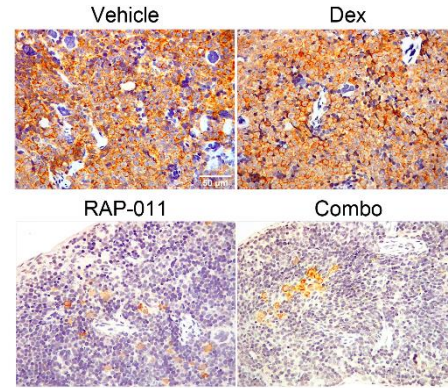
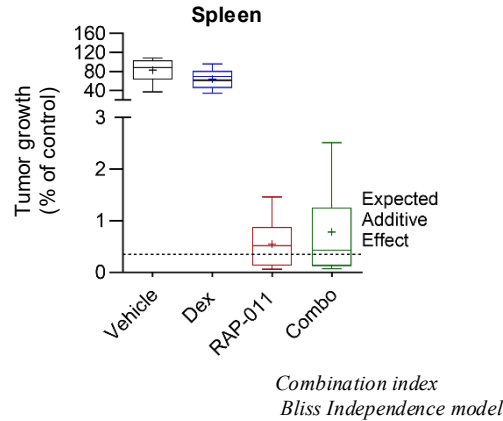
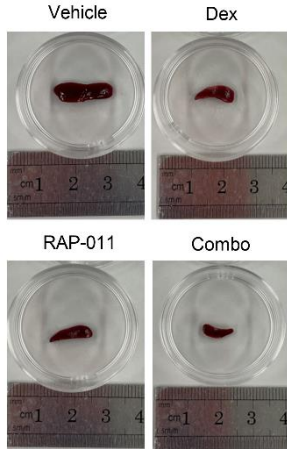


Brown = hHLA-A, \*normal hematopoiesis

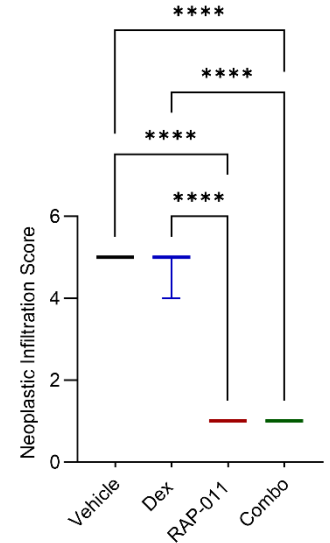


\*One-way ANOVA with Tukey correction

# Activin A trapping enhances dexamethasone-based chemotherapy in Nalm-6 xenografts



Brown = hHLA-A



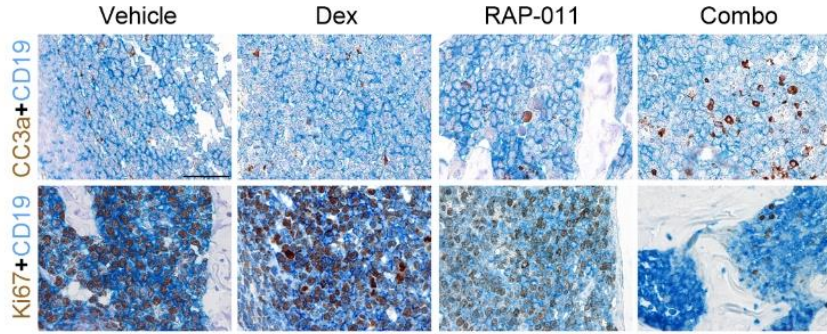
\*One-way ANOVA with Tukey correction

# Activin A trapping increases the pro-apoptotic effect of chemotherapy

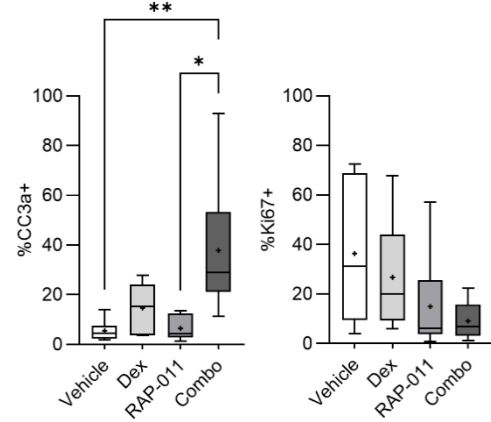
**APOPTOSIS**

**PROLIFERATION**

**Bone marrow**



Scale bar: 50 μm

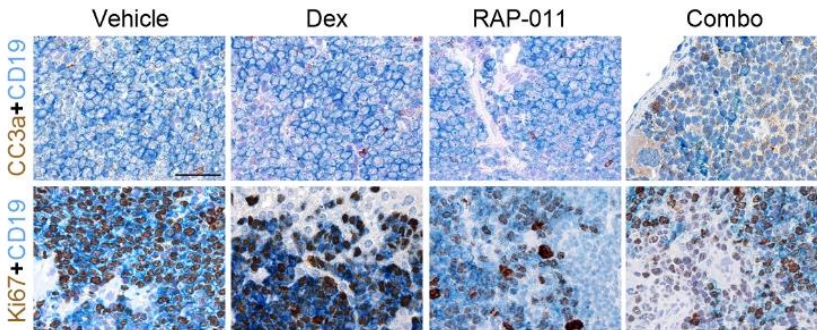


\*One-way ANOVA with Tukey correction

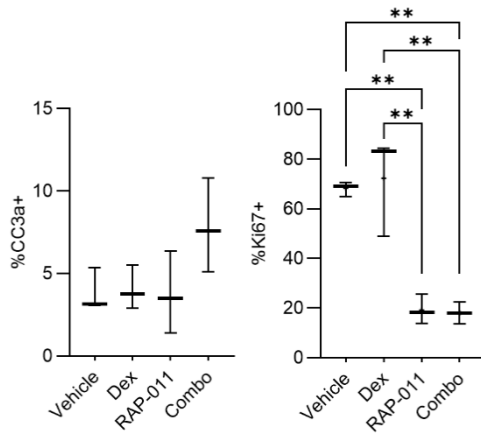
**APOPTOSIS**

**PROLIFERATION**

**Spleen**

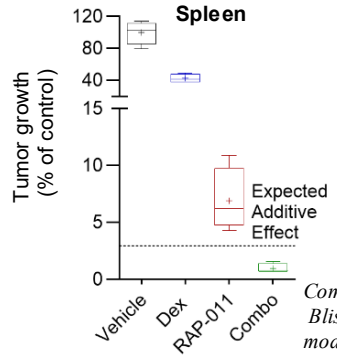
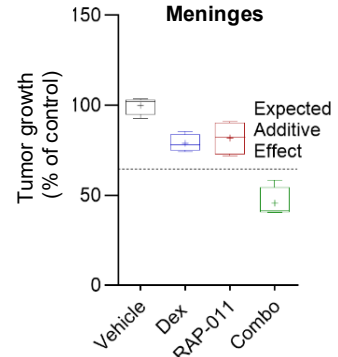
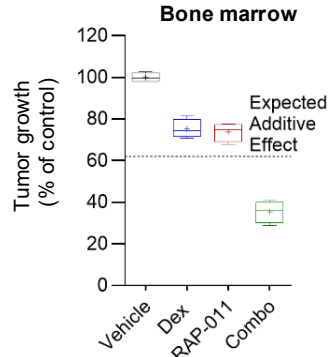
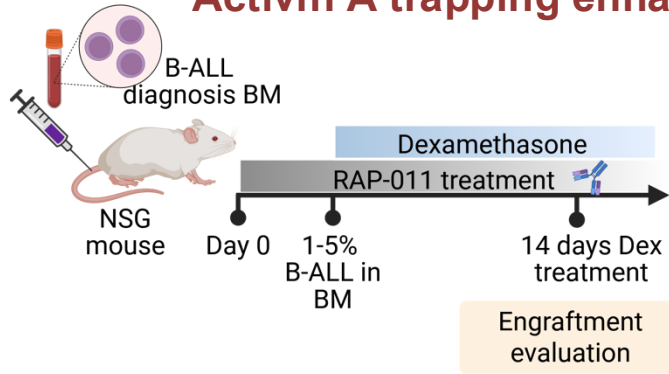


Scale bar: 50 μm

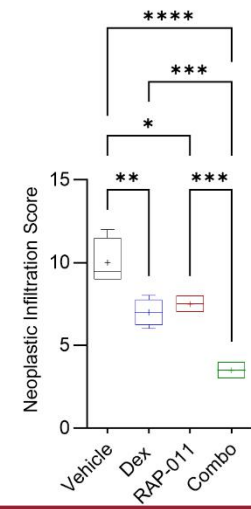
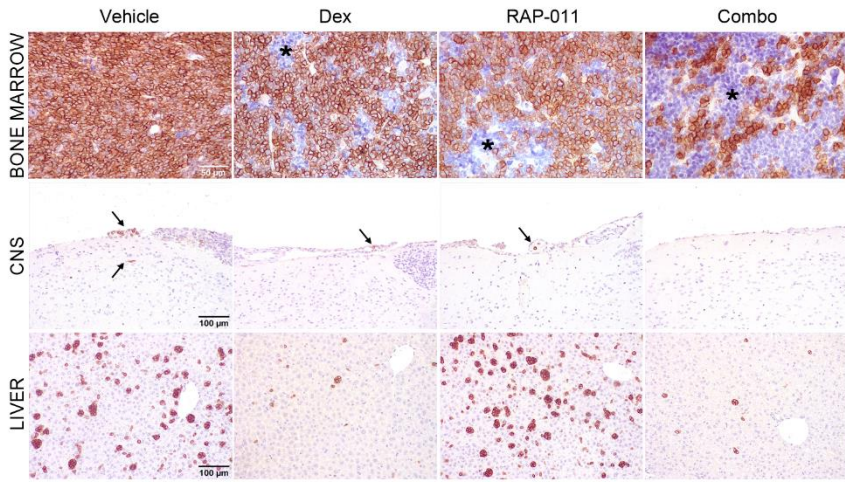


\*One-way ANOVA with Tukey correction

# Activin A trapping enhances dexamethasone-based chemotherapy in PDX

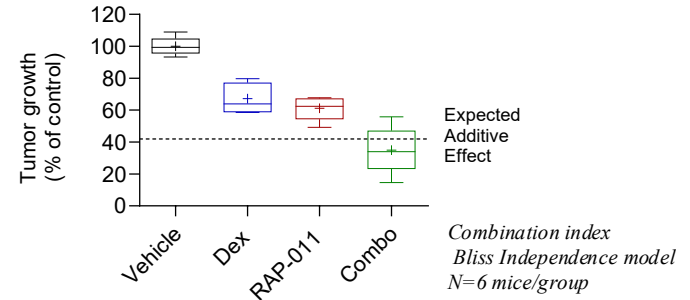
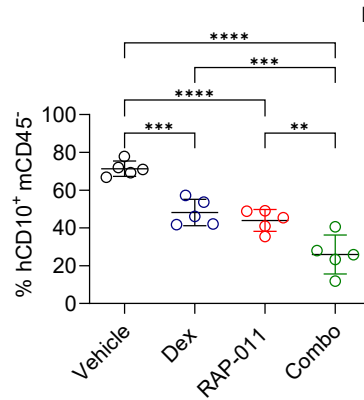
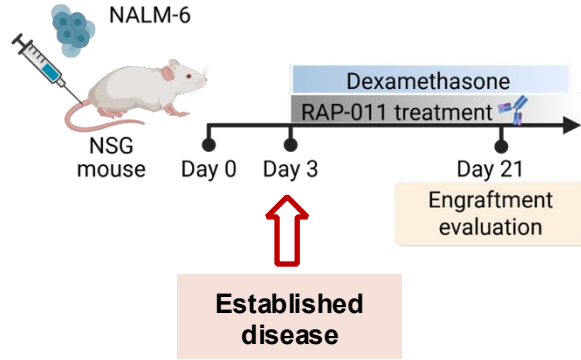


Combination index  
Bliss Independence  
model, n=4 mice/group

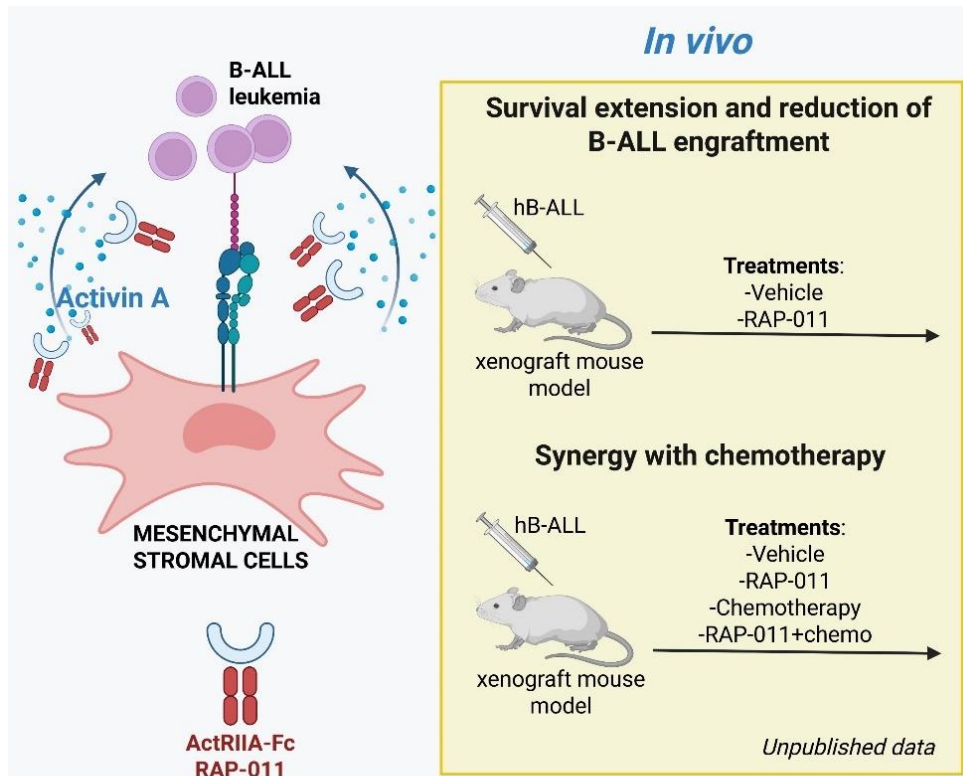


\*One-way ANOVA with  
Tukey correction

## Activin A trapping potentiates dexamethasone-based chemotherapy in Nalm-6 xenografts also when administered on established disease



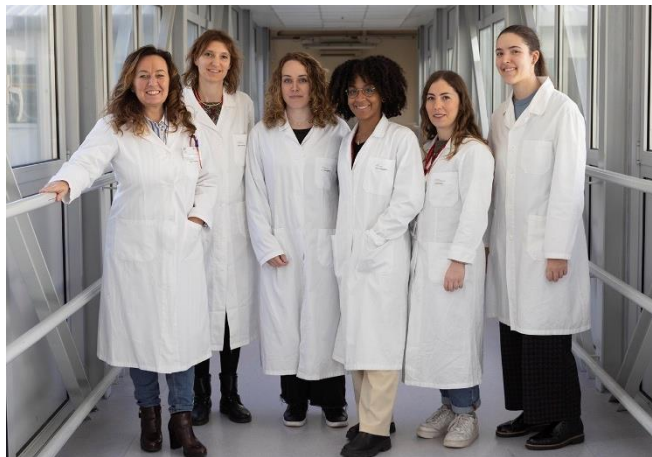
# Conclusions



# Acknowledgements



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