Children's Hospital LOS ANGELES
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4th International Conference
Translational Research in Oncology

Exosomic microRNAs orchestrate Cancer Biology and Resistance to Chemotherapy

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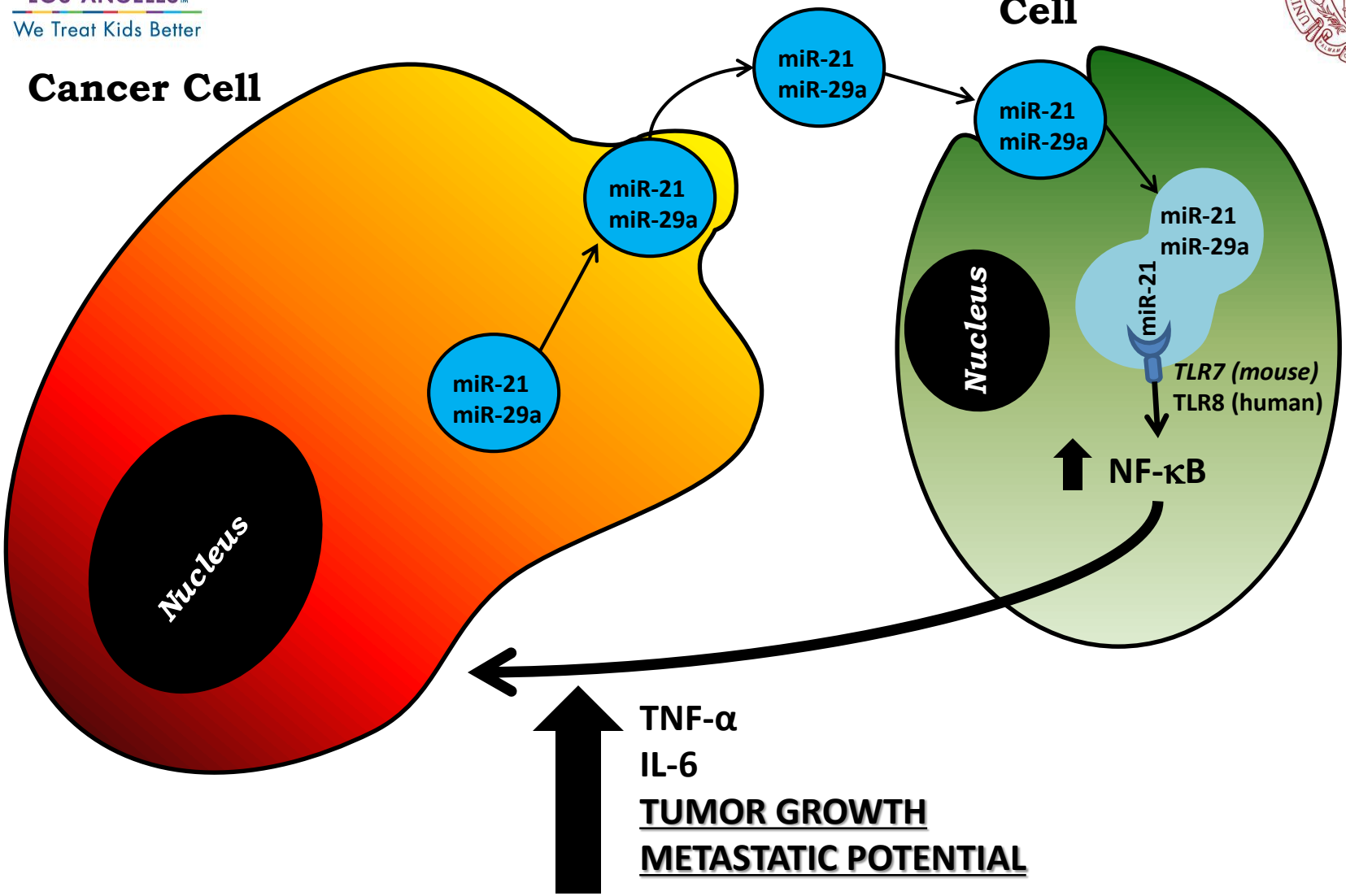
Forli – Friday, November 11, 2016



Fabbri M. et al, PNAS, 2012, 109(31):E2110-6

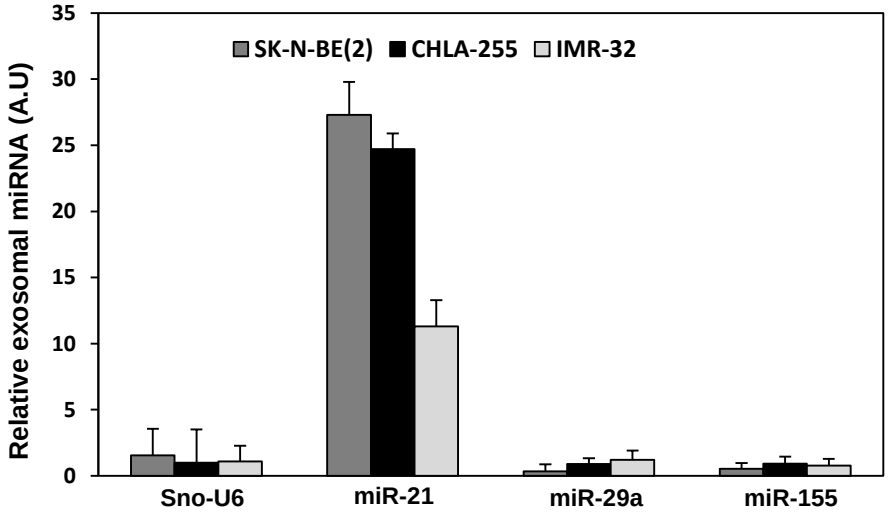
Role of Tumor-Associated Macrophages (TAMs) In Neuroblastoma

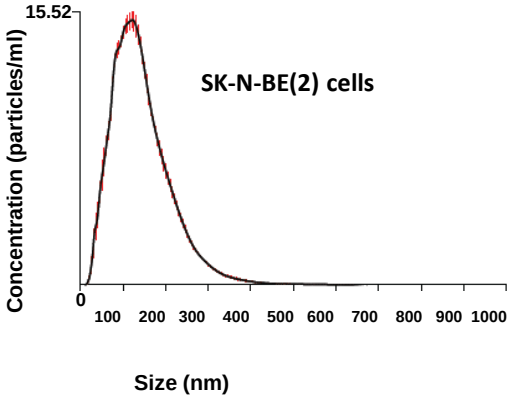
1. Higher TAM infiltration correlates with worse prognosis in NBL.
   (Asgharzadeh S. et al, J Clin Oncol, 2012, 30: 3525-32)

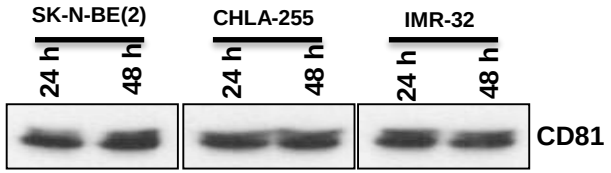
2. High levels of Interleukin-6 in bone marrow TME promote growth and survival of NBL cells.
   (Ara T. et al, Cancer Res, 2009, 69: 329-37)

3. Critical role of STAT3 in IL-6-mediated drug resistance in human NBL.
   (Ara T. et al, Cancer Res, 2013, 73: 3852-64)

Neuroblastoma cells secrete exosomic miR-21, but NOT miR-155

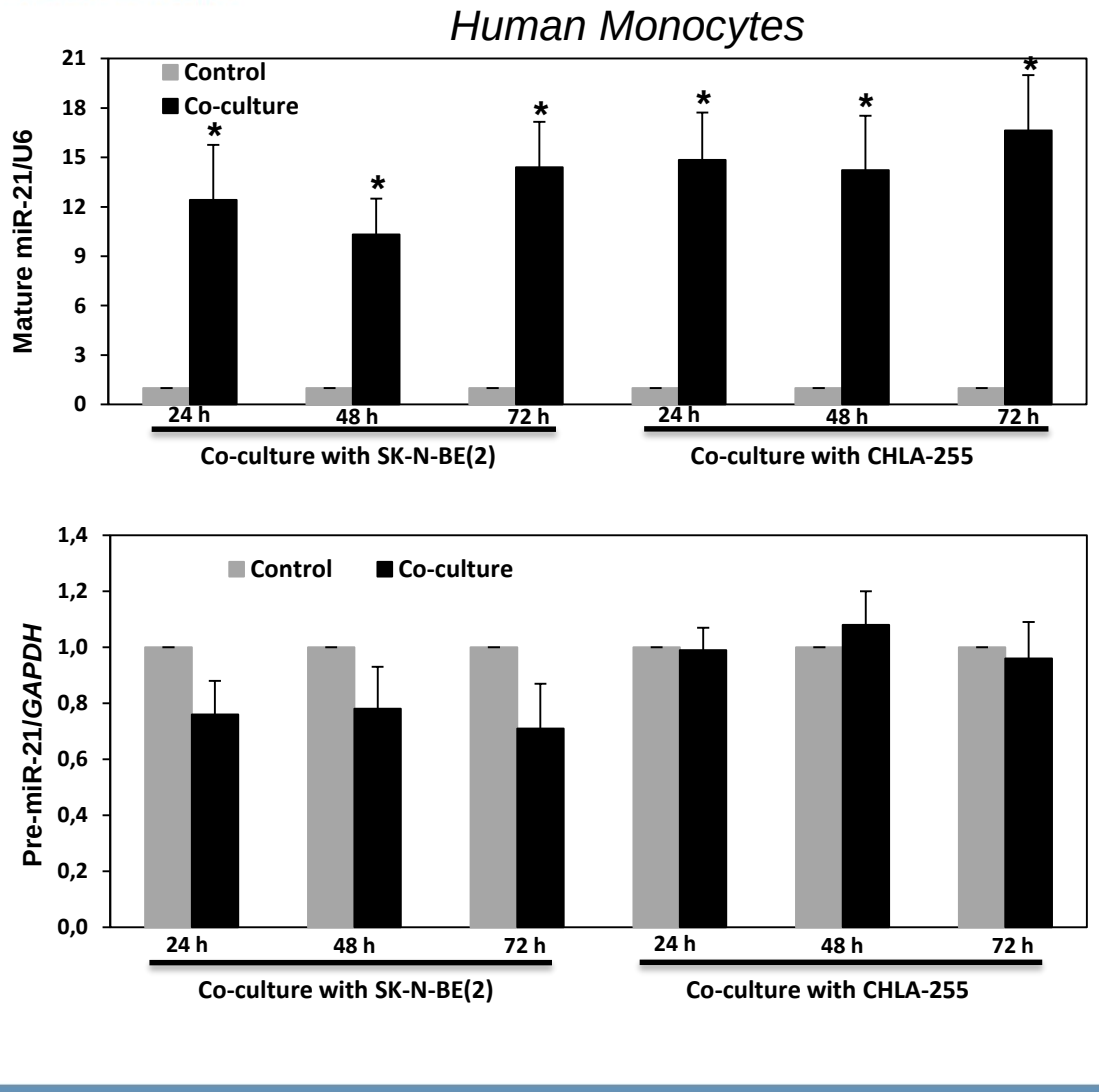


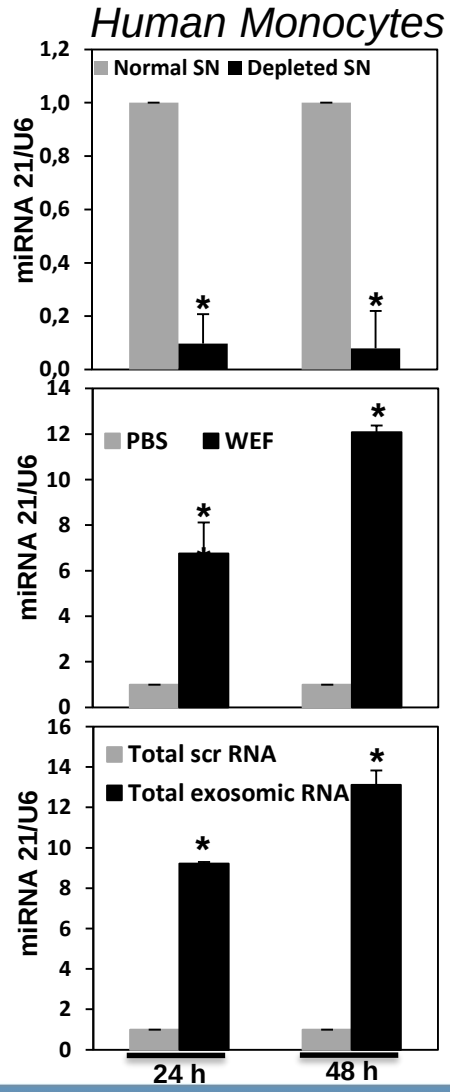




Challagundla K. et al, JNCI, 2015, 107(7)

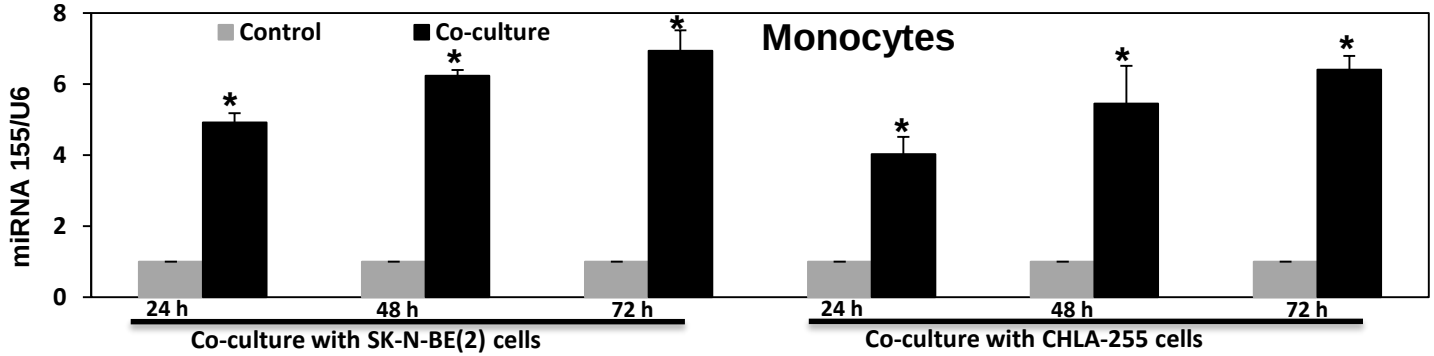
miR-21 is transferred from NBL to Monocytes via exosomes

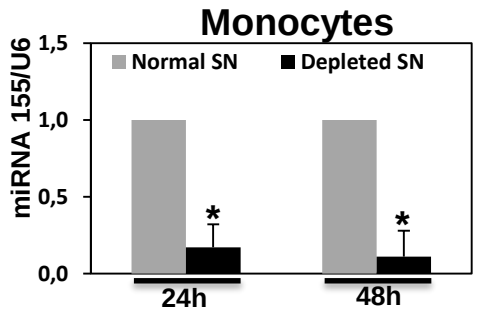


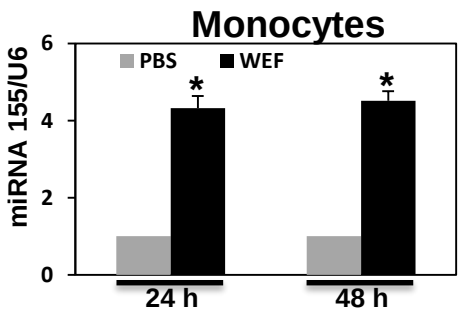


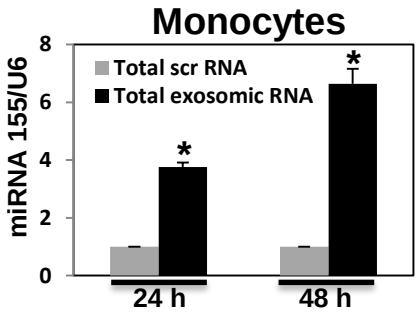
Challagundla K. et al, JNCI, 2015, 107(7)

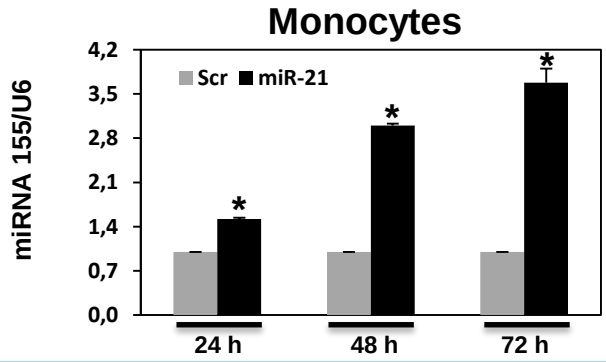
miR-155 is up-regulated in hMonocytes in a miR-21/TLR8-dependent manner

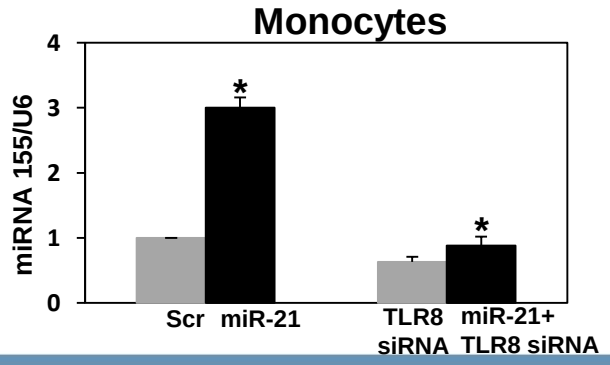




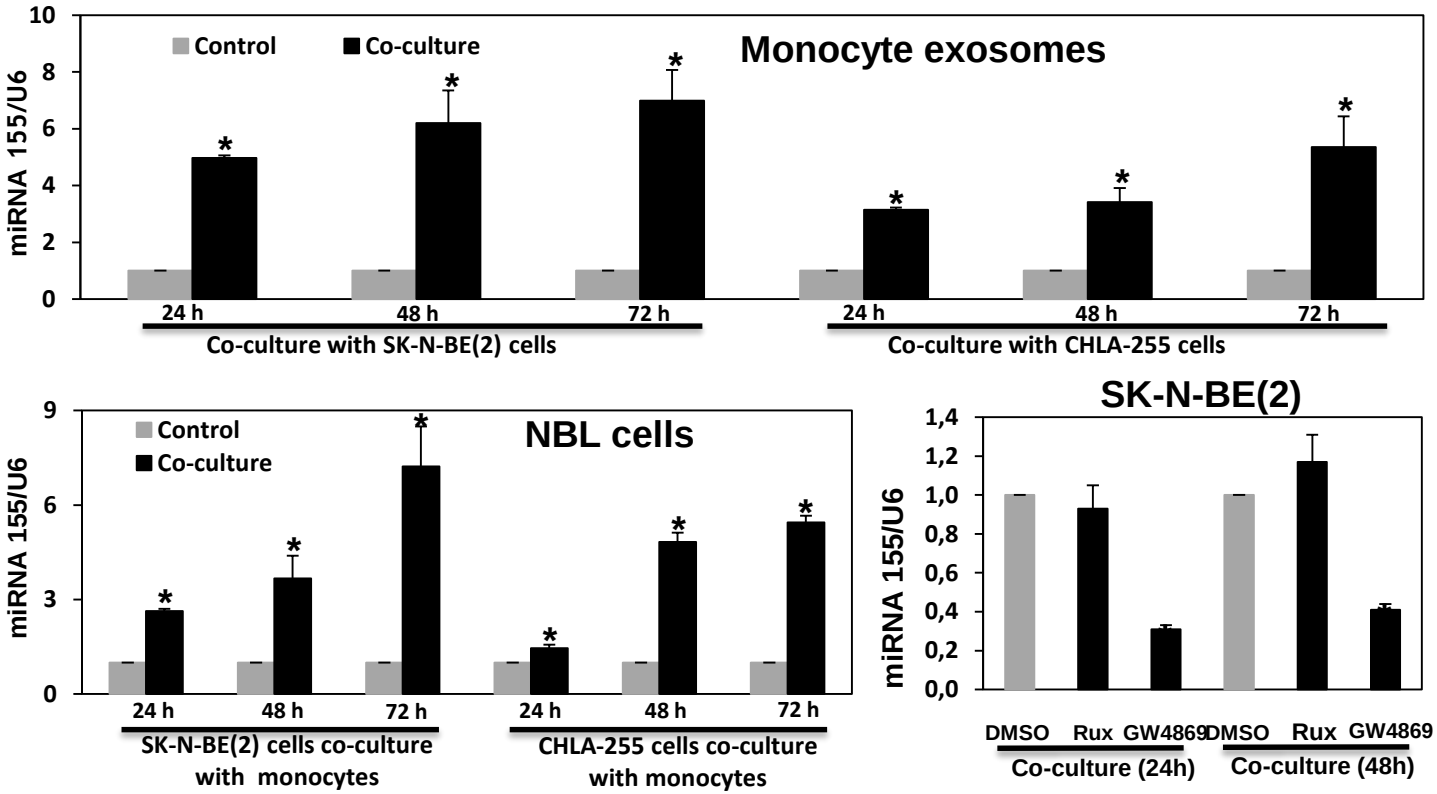




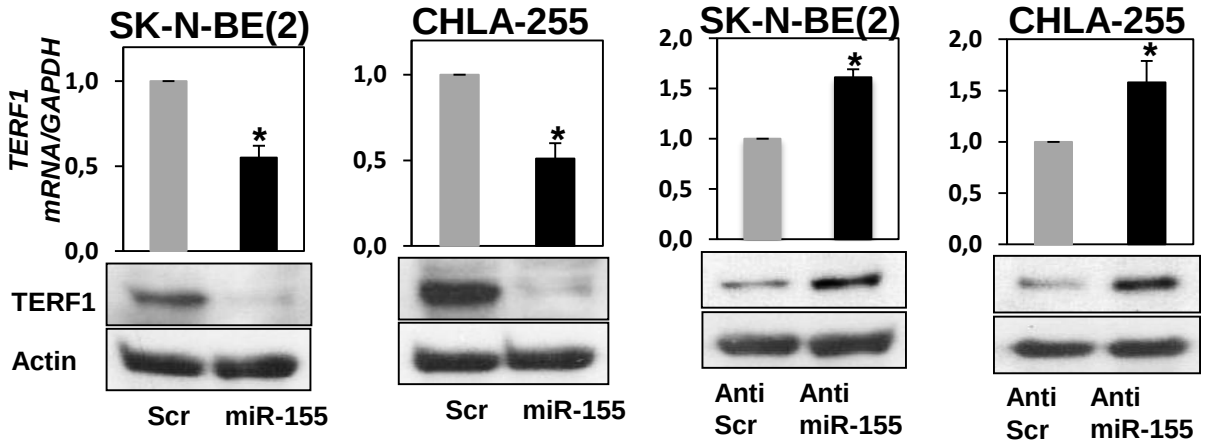


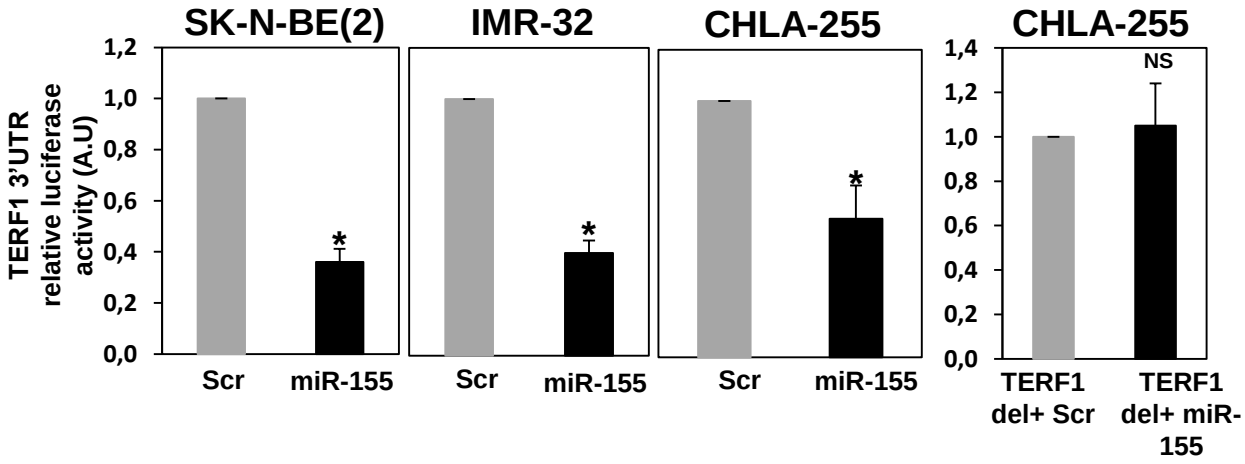


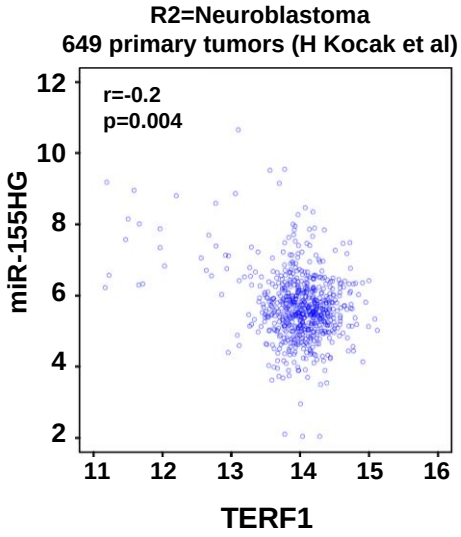
miR-155 is transferred from hMono to NBL cells via exosomes



miR-155 directly targets TERF1

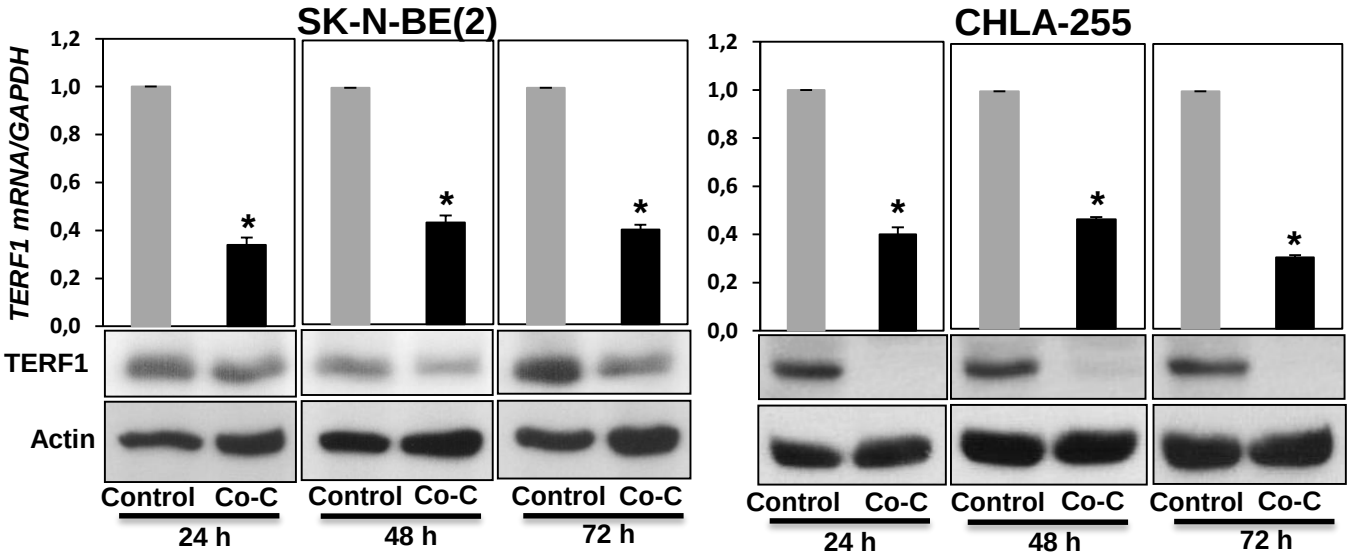


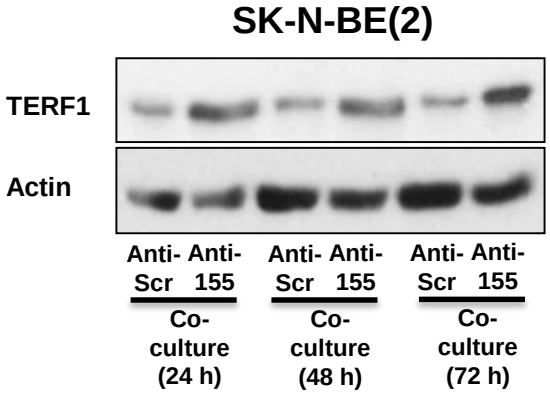




Challagundla K. et al, JNCI, 2015, 107(7)

TERF1 is down-regulated in NBL co-cultured with hMonocytes via miR-155





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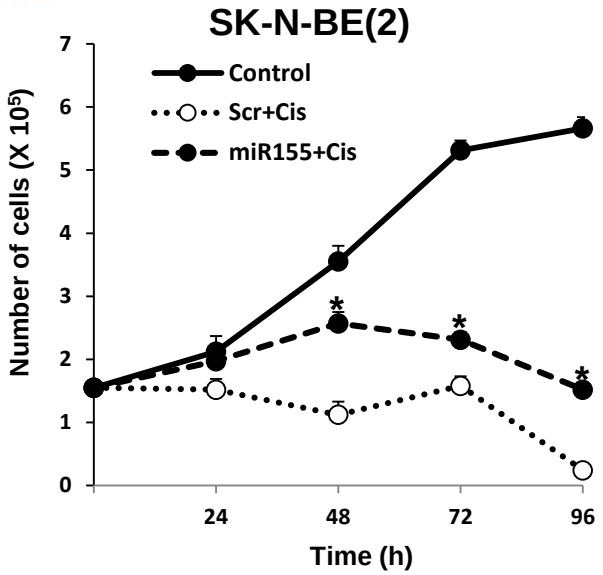
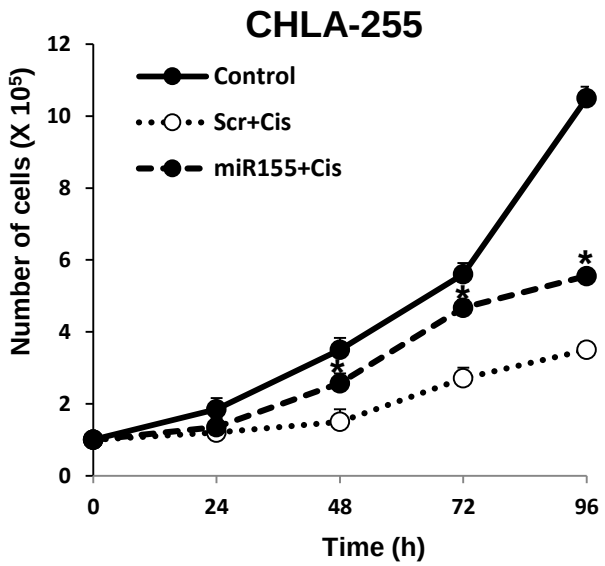
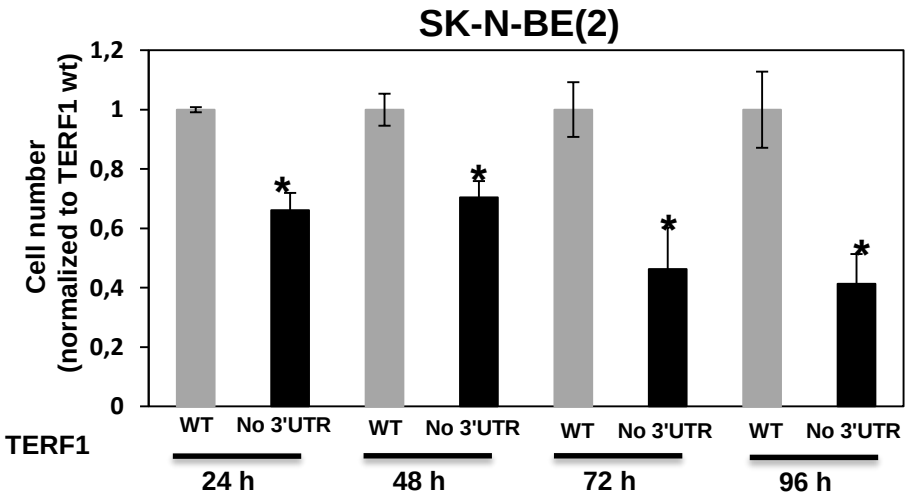
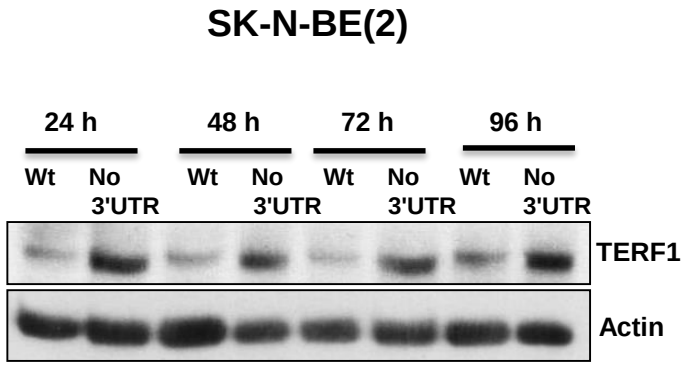
Exosomic miR-155 induces TERF1-dependent resistance to CDDP



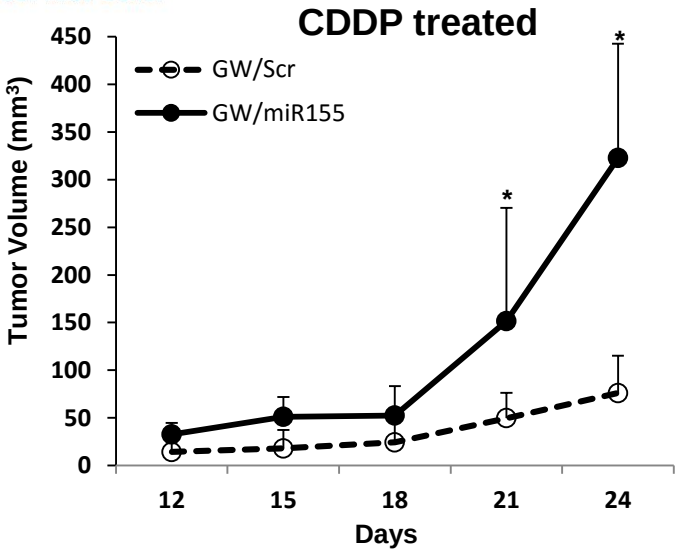


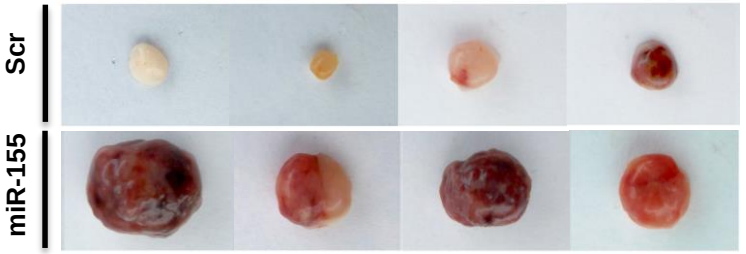


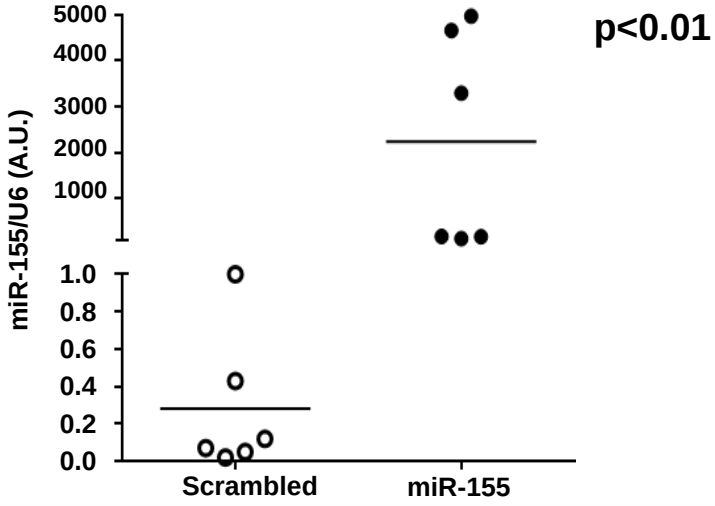


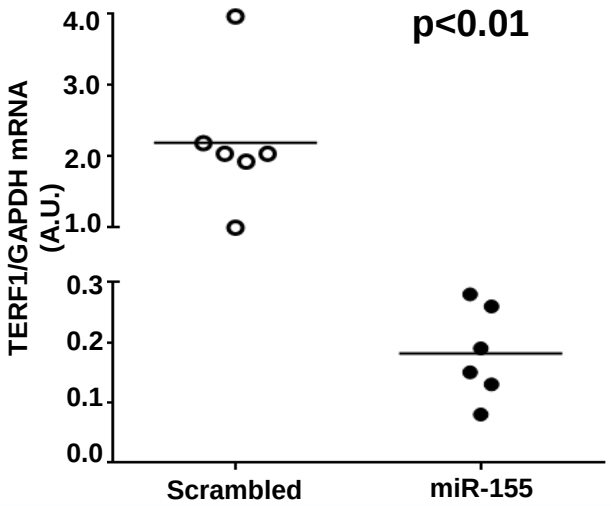
Challagundla K. et al, JNCI, 2015, 107(7)

Exosomic miR-155 increases CDDP resistance *in vivo*









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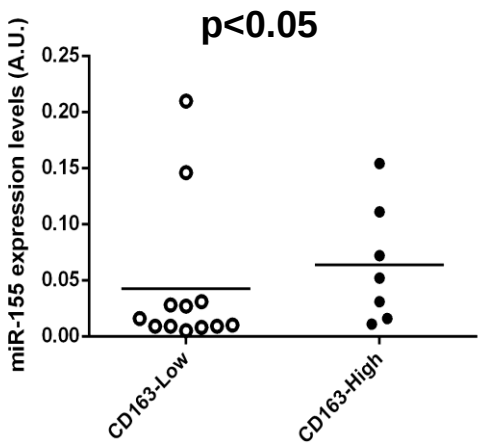
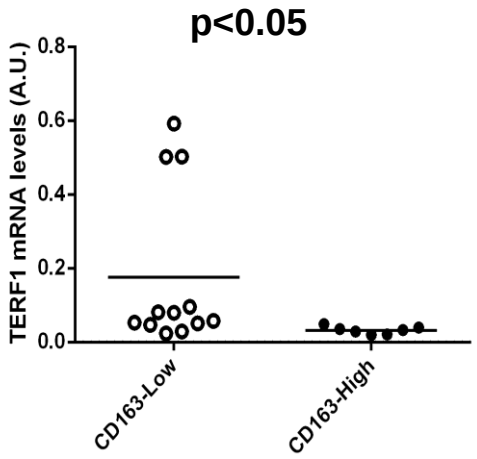
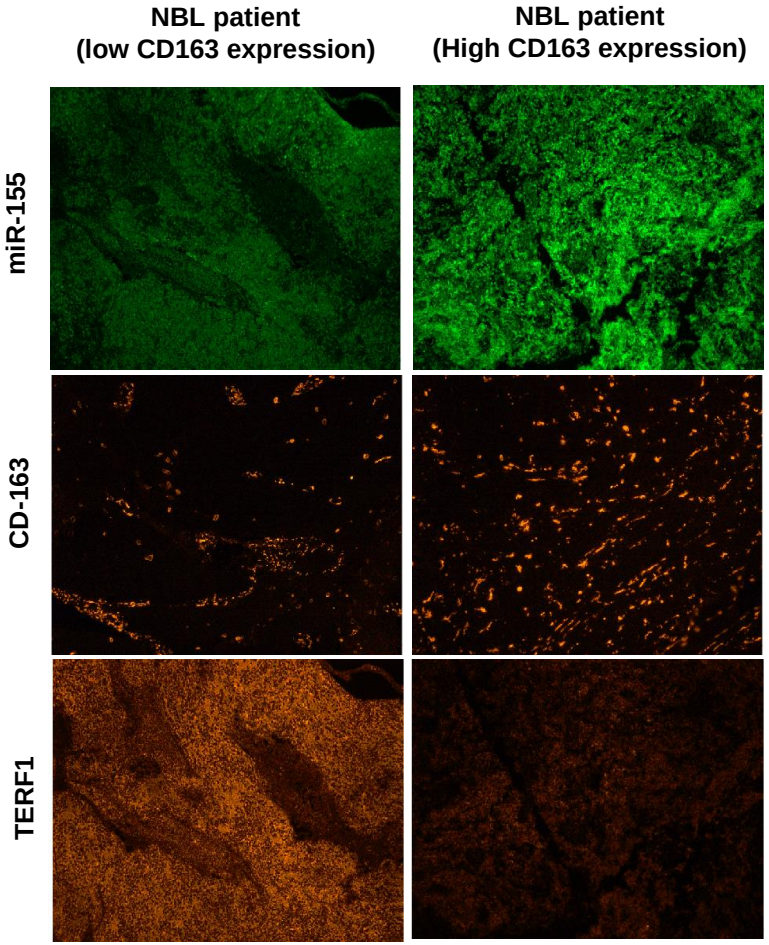
Primary NBLs with higher TAMs have higher miR-155 and lower TERF1







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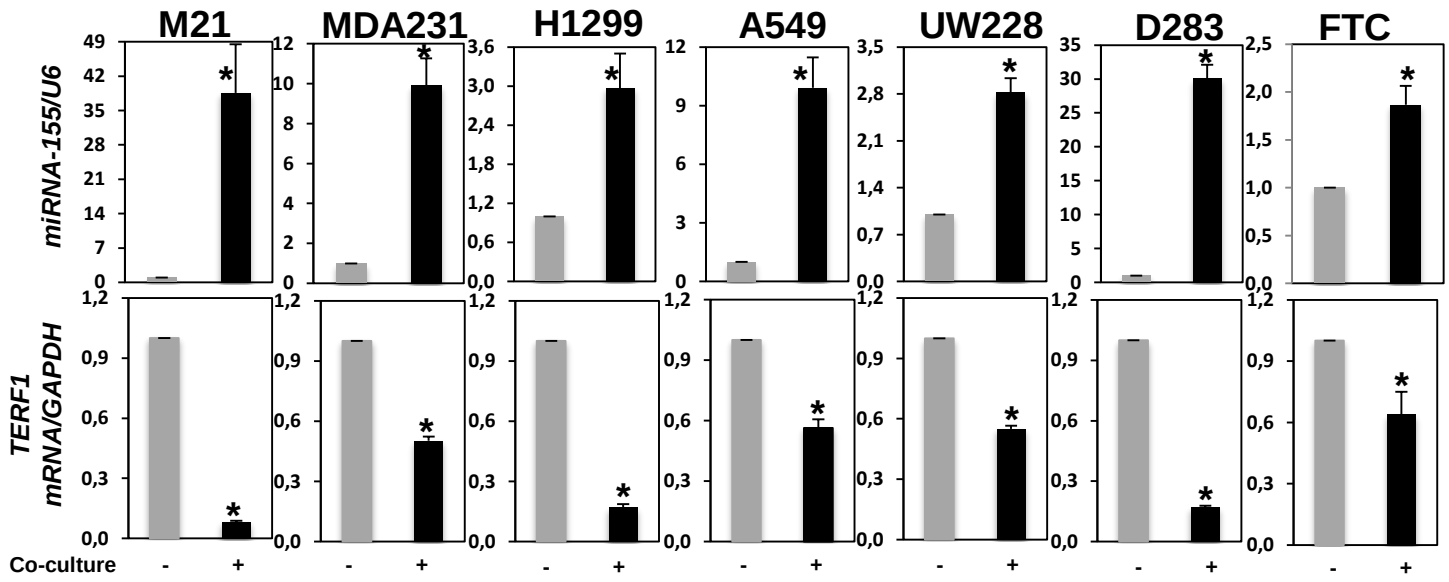
And… beyond Neuroblastoma



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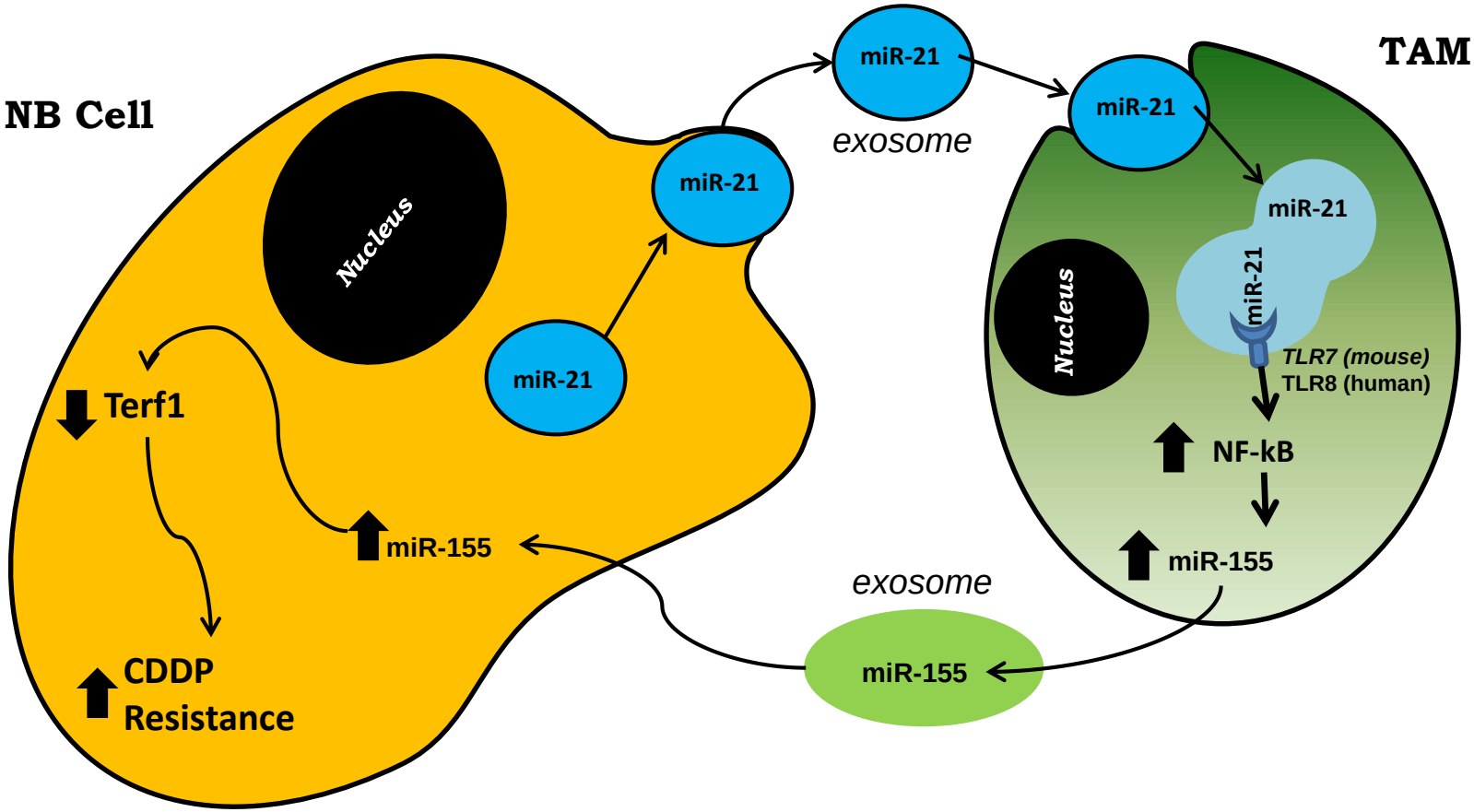
NBL-derived exosomic miRNAs bind to TLR8 in surrounding TAMs and promote NBL resistance to chemotherapy



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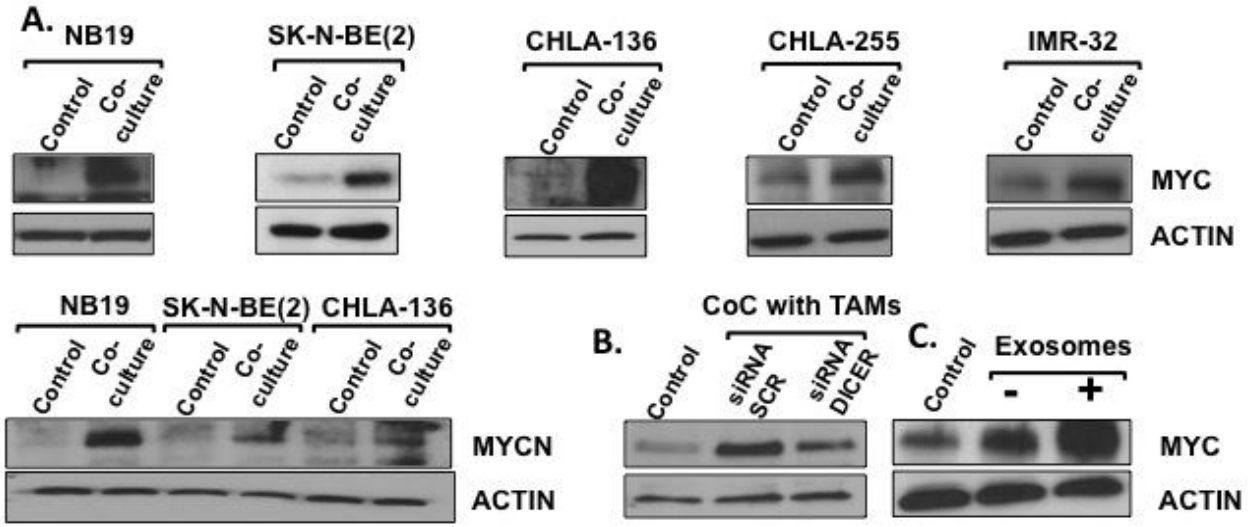
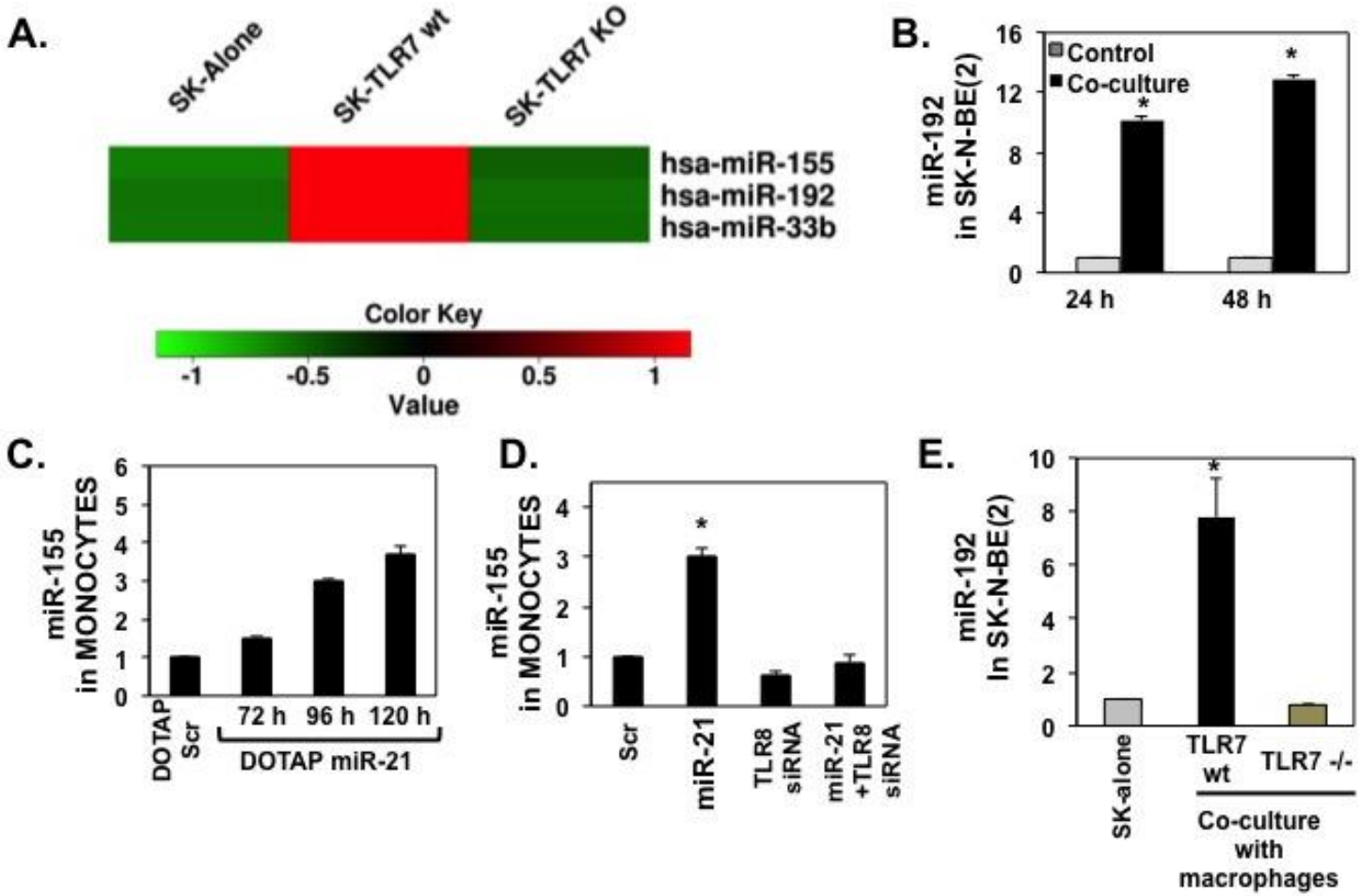
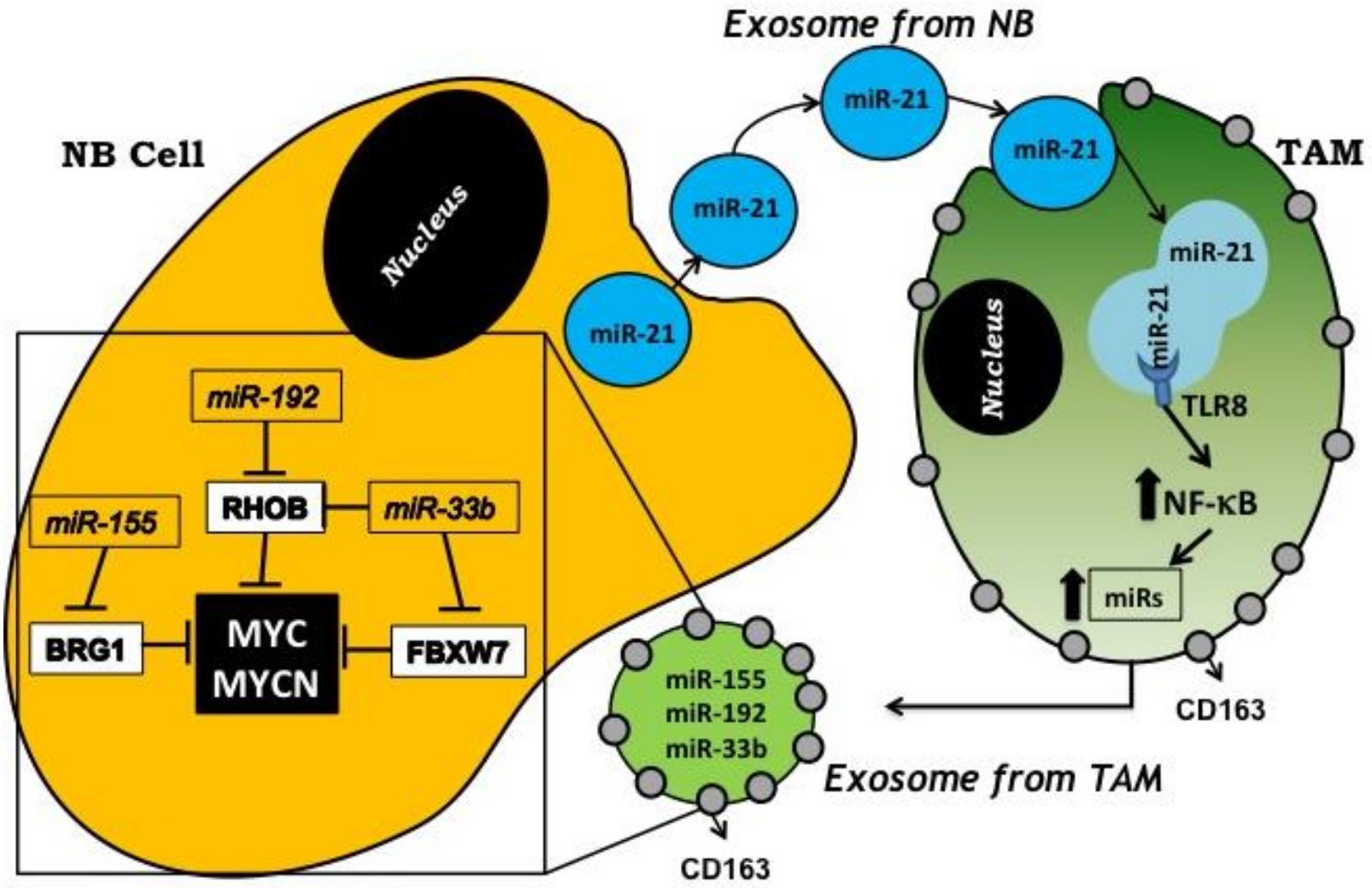
MYC is up-regulated in NB-TAM co-cultures regardless of MYCN status



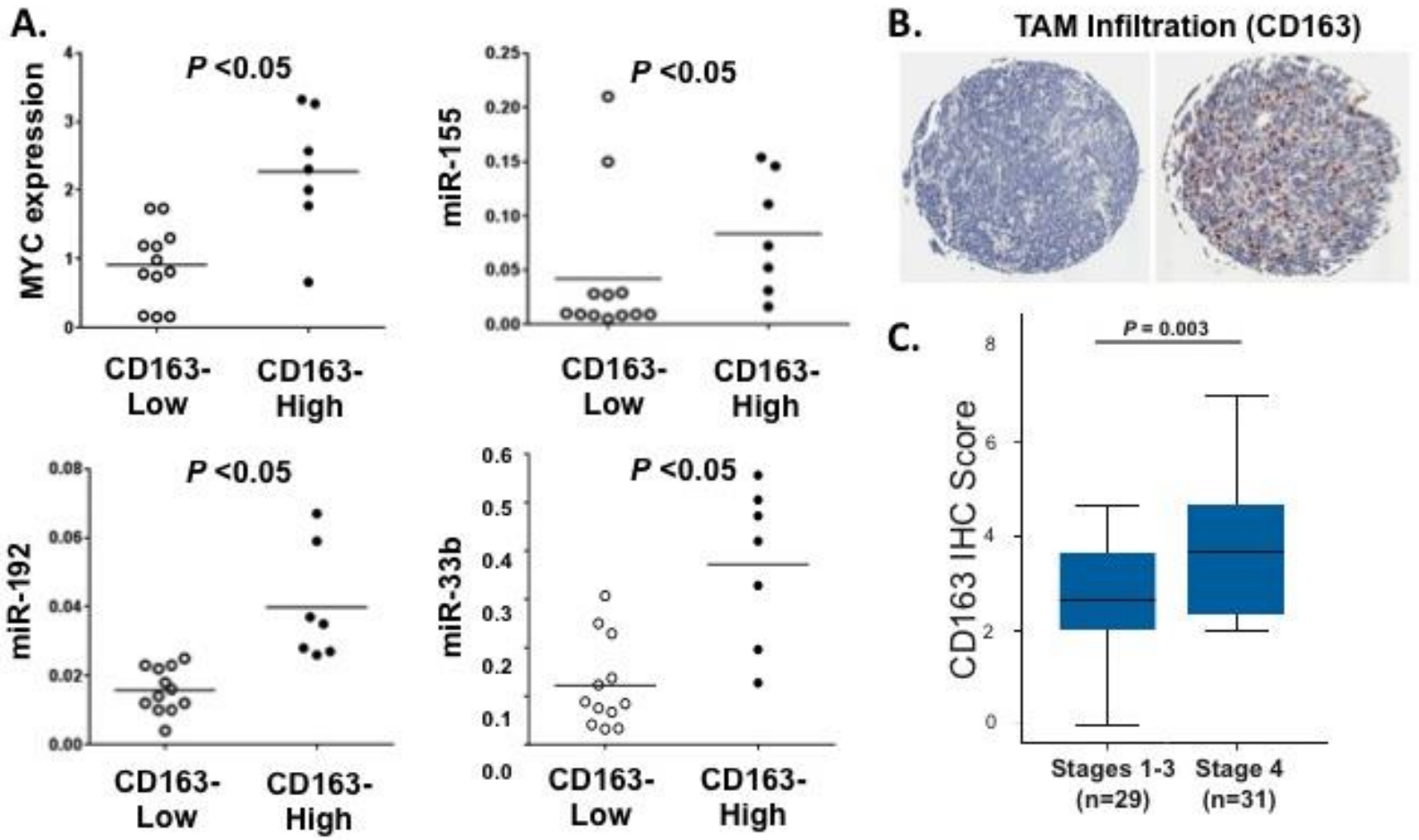
miR-192, -155, -33b are up-regulated in a TLR8-dependent fashion



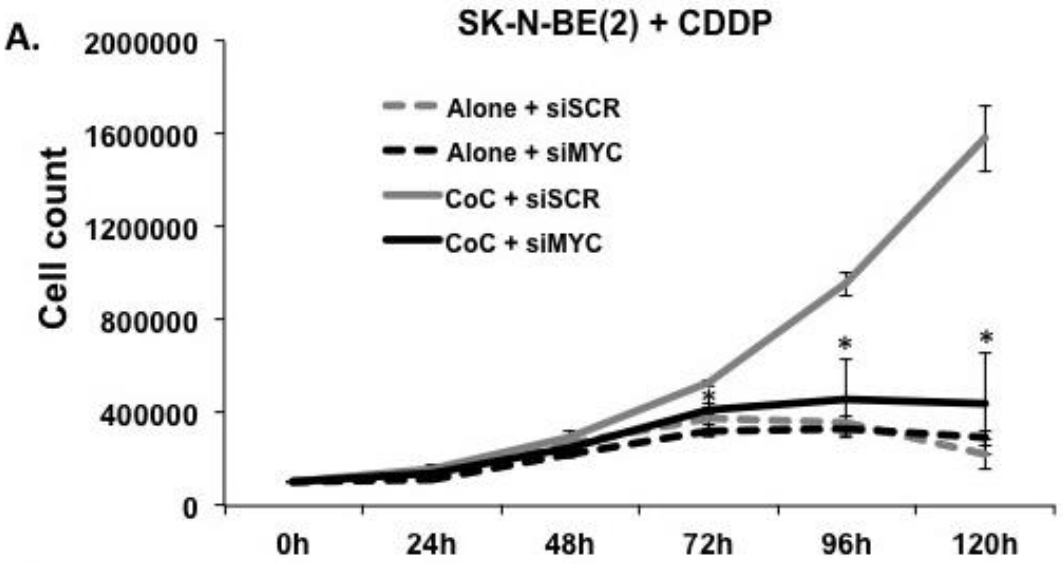
Working Hypothesis

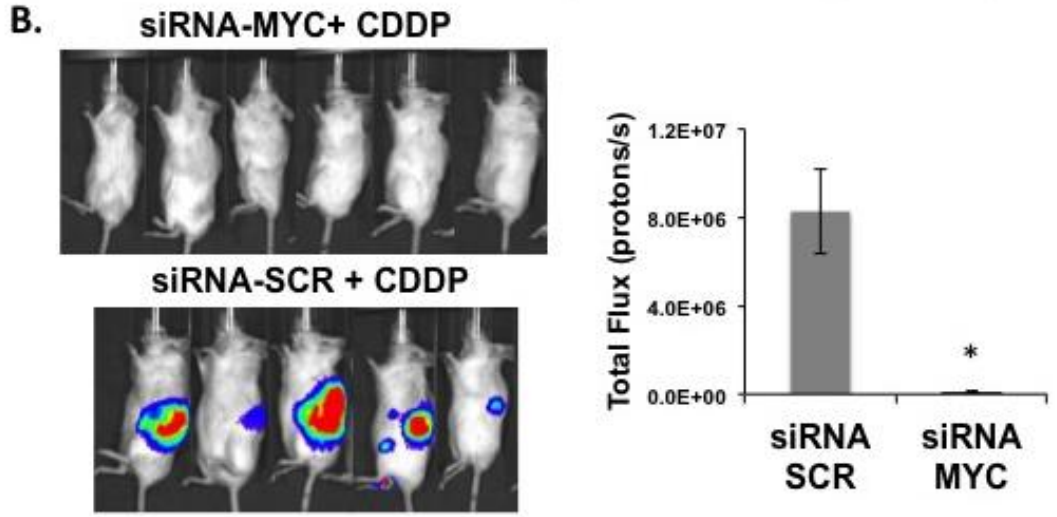


Higher levels of MYC and miR-192, -155, -33b in primary NB with high TAM infiltration

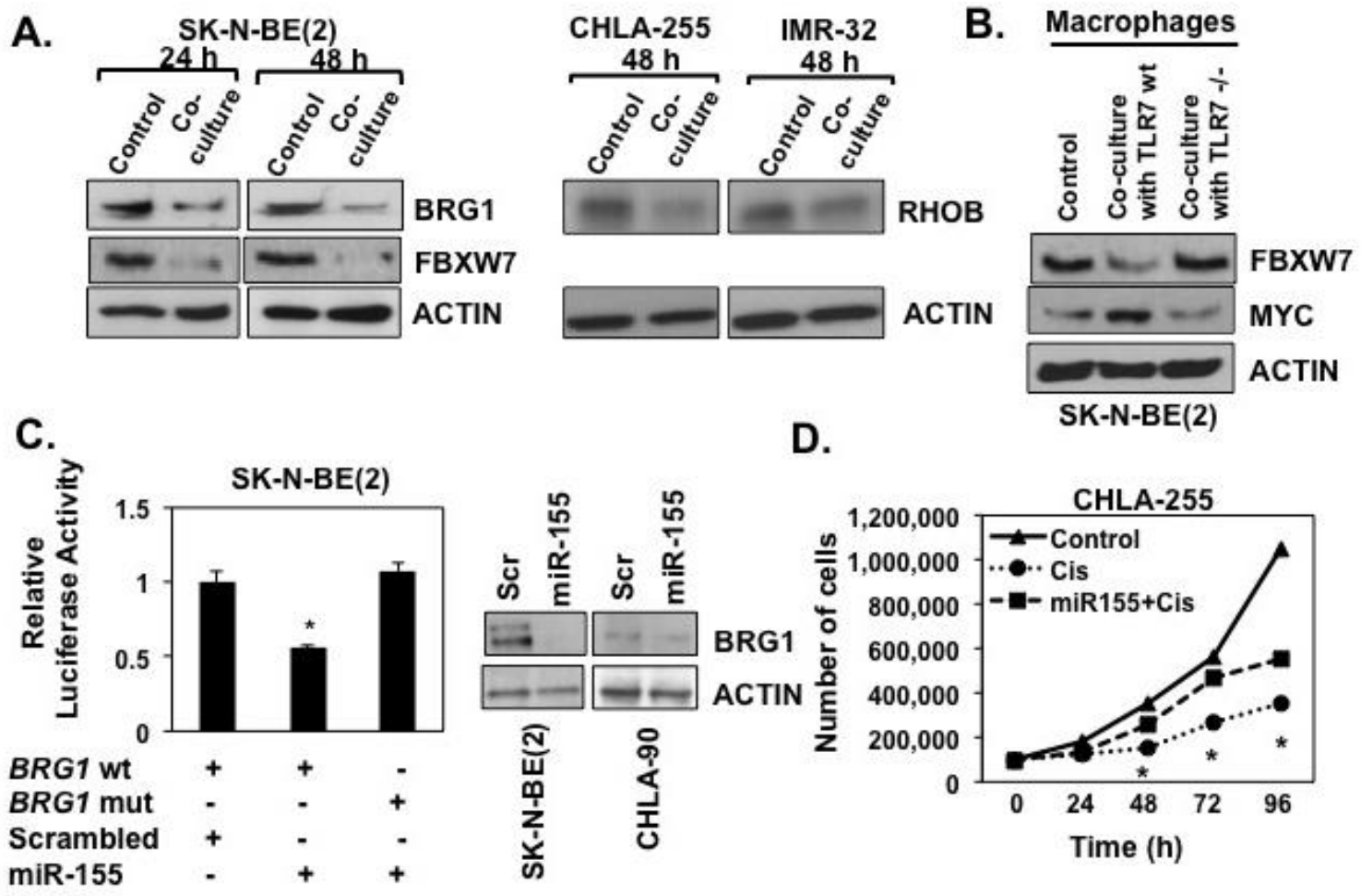


MYC increases chemoresistance in NB

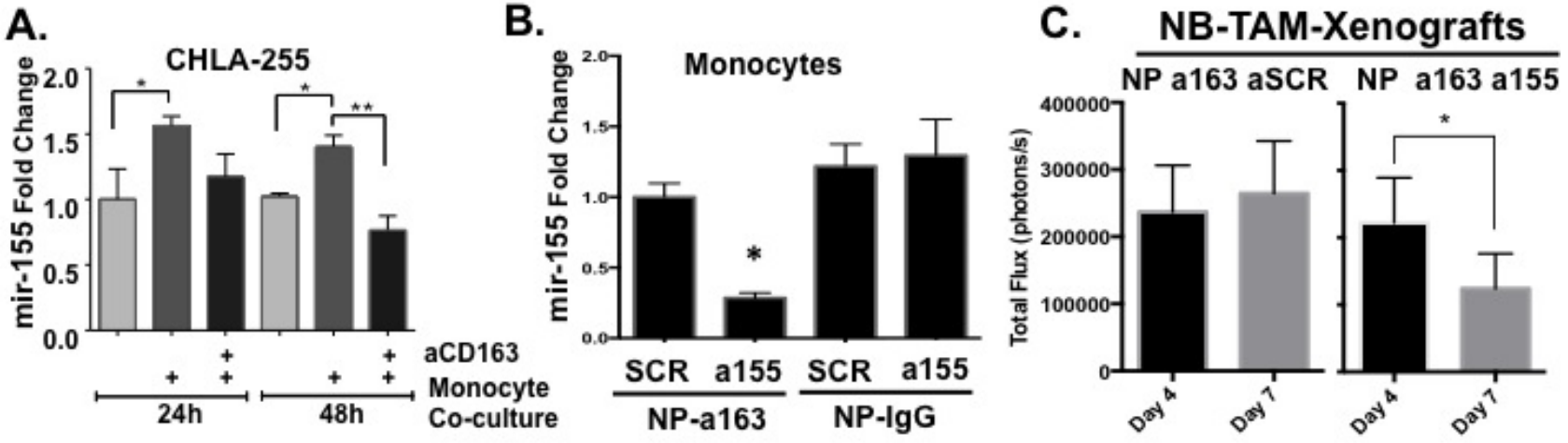




Exosomic miRNAs up-regulate MYC by targeting BRG1, RHOB and FBXW7



A nanoparticle coated with anti-CD163 antibody effectively silences miR-155 and reduces NB growth



Conclusions

- Human TLR8 is the first identified miRceptor
- Exosomal miR-21 released by cancer cells “educates” TAMs to elicit a pro-inflammatory and pro-tumoral response
- TAMs secrete exosomal miR-155 that increases resistance to chemotherapy
- The Tumor microenvironment increases MYC expression in NB and this effect is in part mediated by exosomal miRNAs
- CD163 is a suitable target to direct anti-miRNAs to TAMs

Acknowledgements

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