כללית מעל 100 שנה
הכי טובה למשפחה

מרכז רפואי מאיר
מסונף לפקולטה לרפואה, אוניברסיטת תל אביב

Mesenchymal stem cells conditioning by multiple myeloma cells: translation initiation as the playing field

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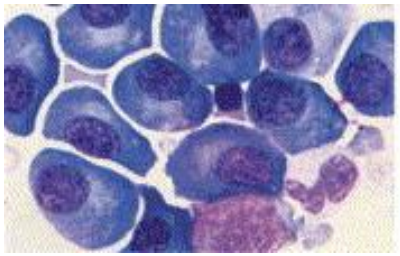
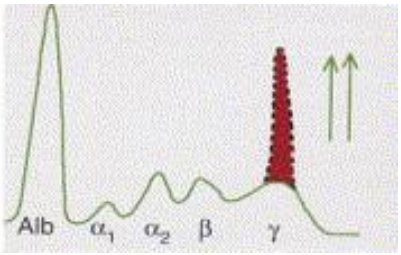
Multiple myeloma characteristics

- A neoplastic disorder of plasma cells (10% of hematological malignancies)

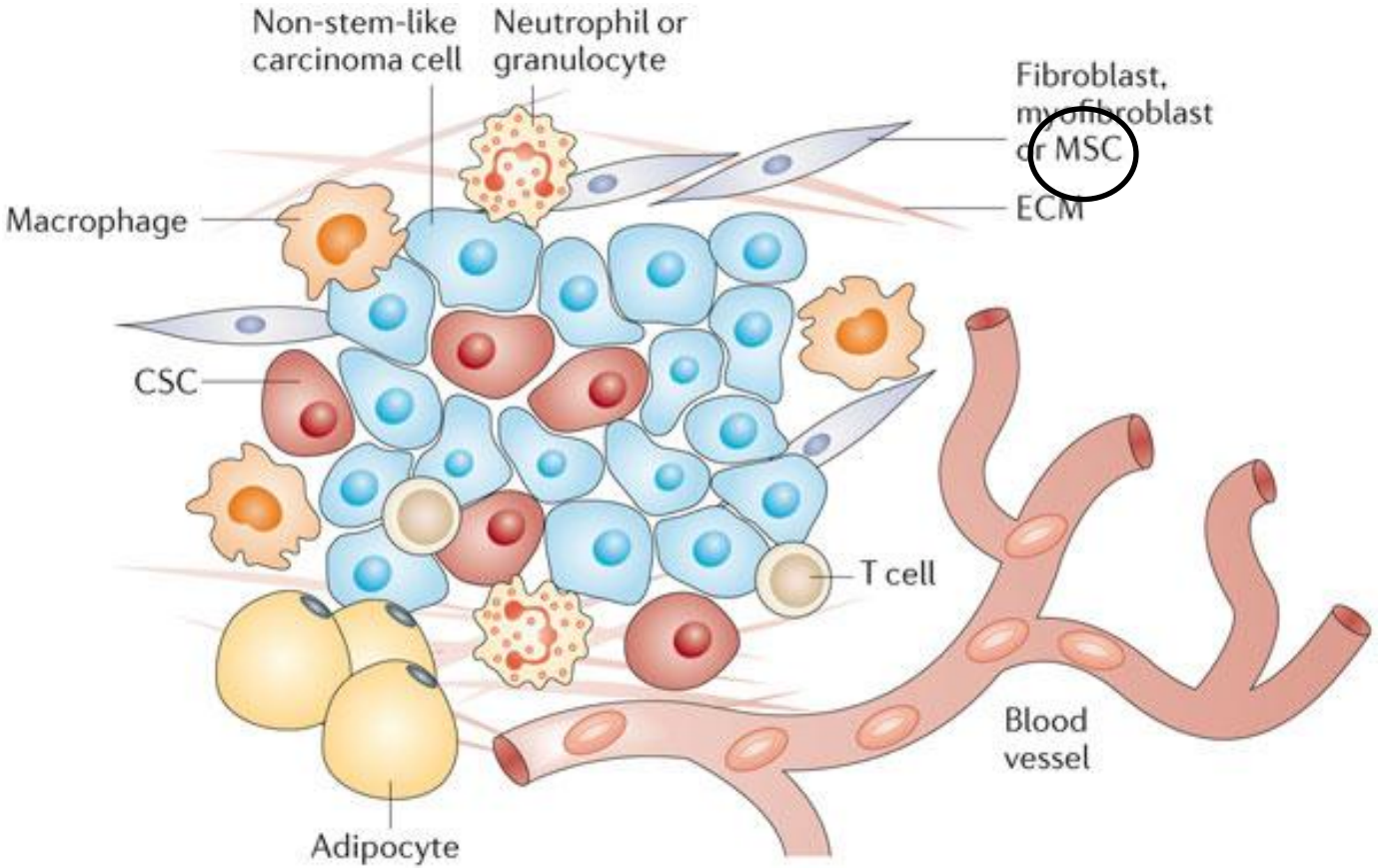
MM remains an incurable disease





MM characterized by extensive protein synthesis.

Cancer Microenvironment



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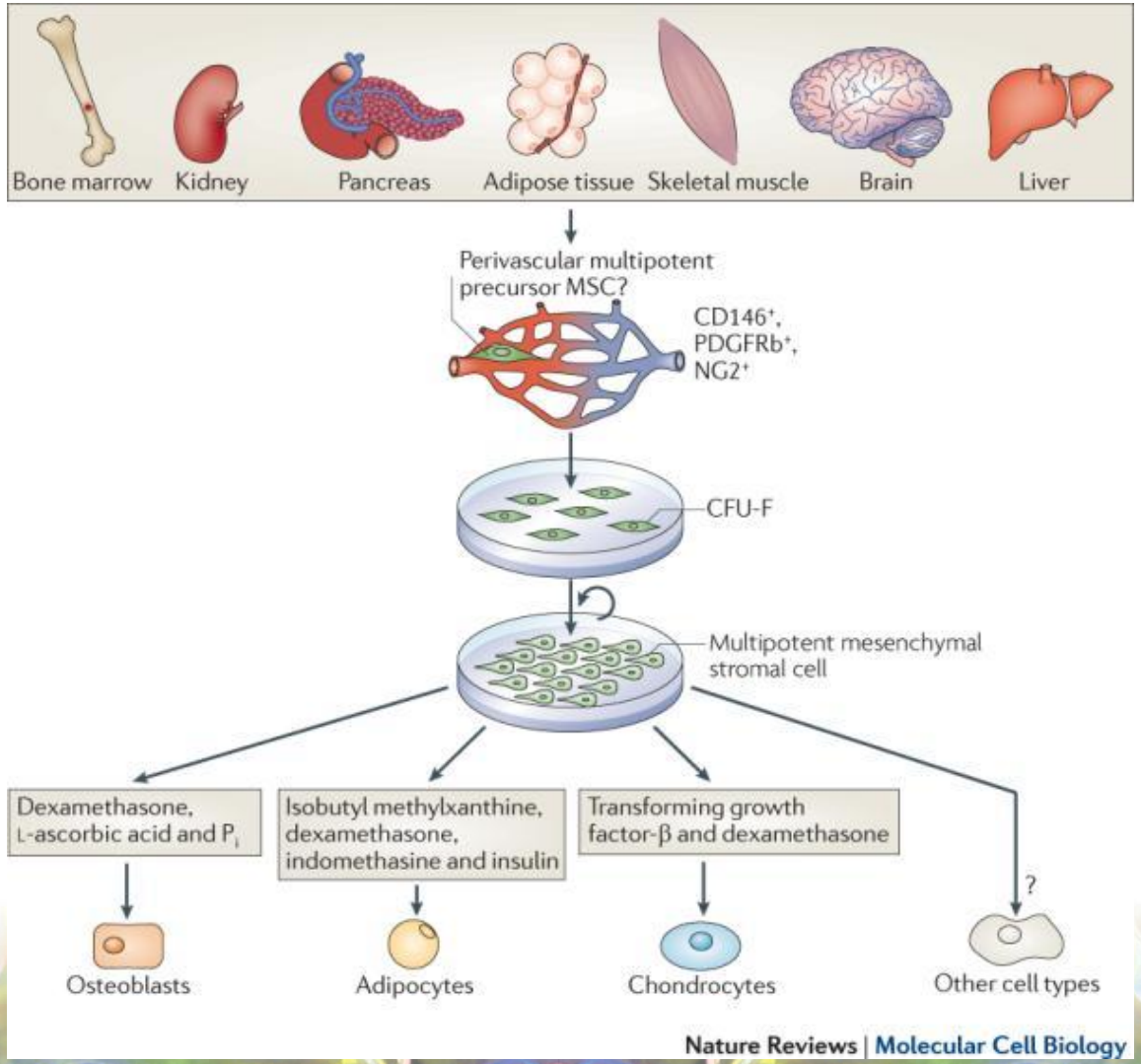
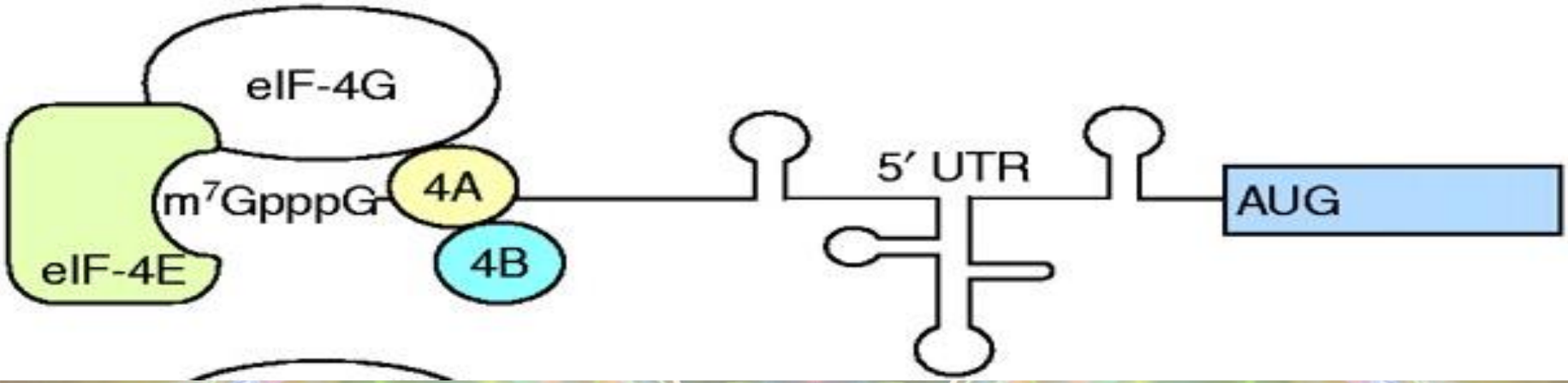
Mesenchymal Stem Cells



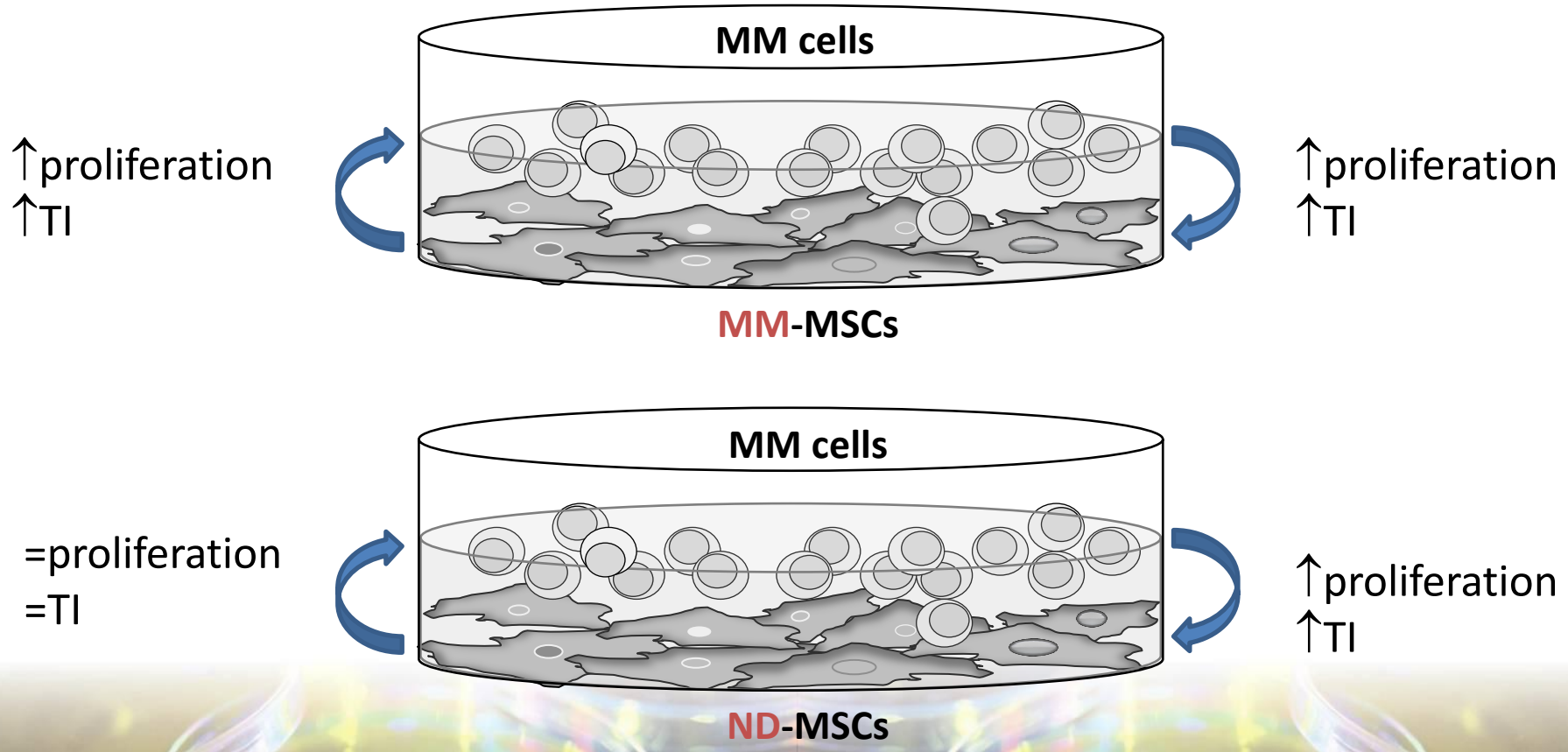
Translation initiation factors (eIF4E, eIF4G): Rate limiting stage of translation process

- Major component of the dynamic dialogue between BM-MSCs and MM cells.
- TI Regulators (MNK, mTOR, 4EBP).
- TI Targets (Smad5, NFKB, HIF1-α, CyclinD, cMyc).



MAJOR FINDINGS

Dynamic dialogue between BM-MSCs and MM cell lines



MSC are isolated from bone marrow aspirates

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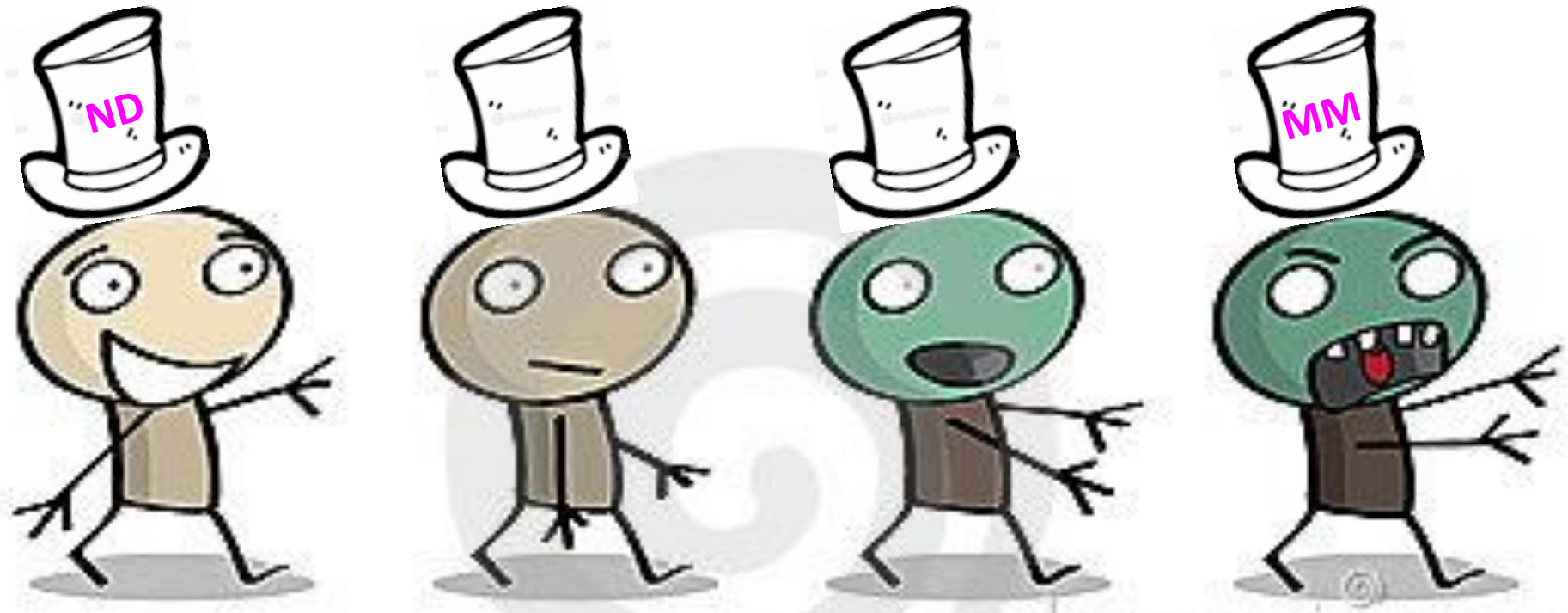
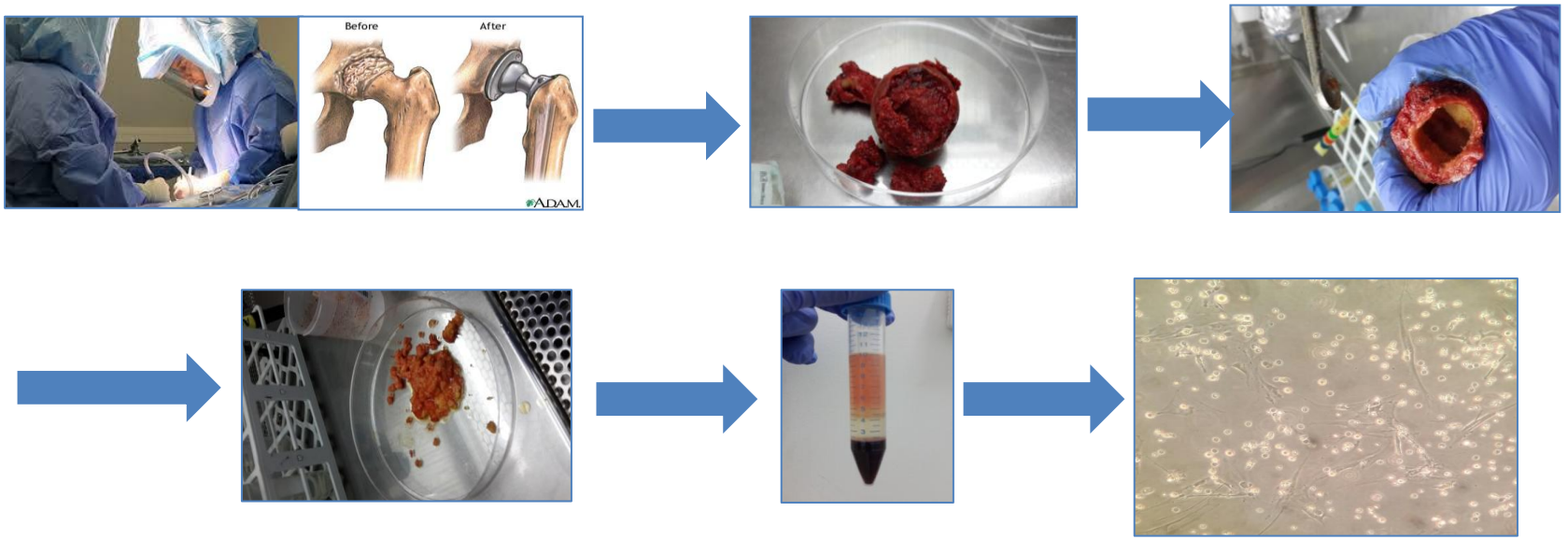
ND-MSCs transformation

- My aim was to explore the changes that ND-MSCs undergo in MM proximity



Results..

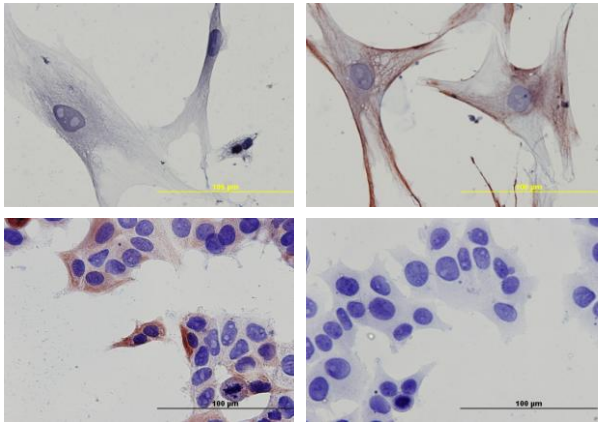
ND-MSCs extraction model



ND-MSCs characterization

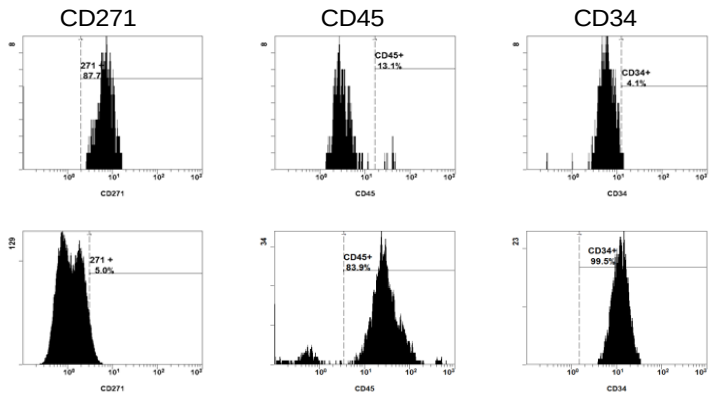
Mesenchymal stem cells

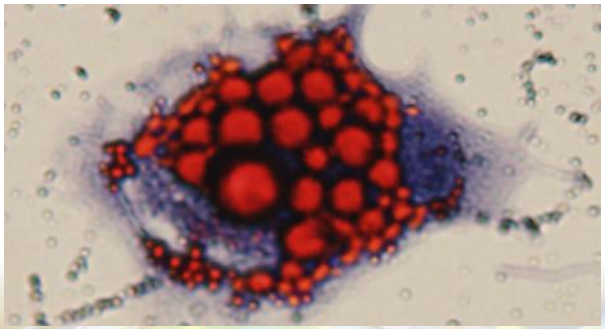
MCF7 cells (Epithelial)



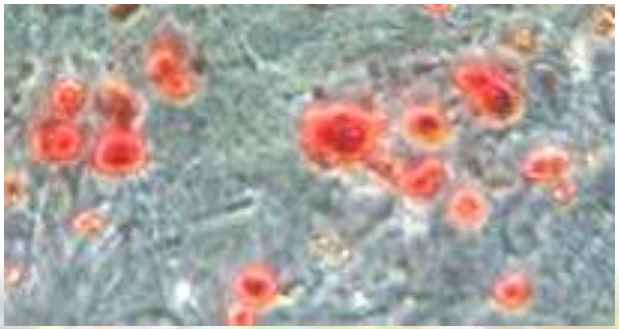
Keratin

Vimentin



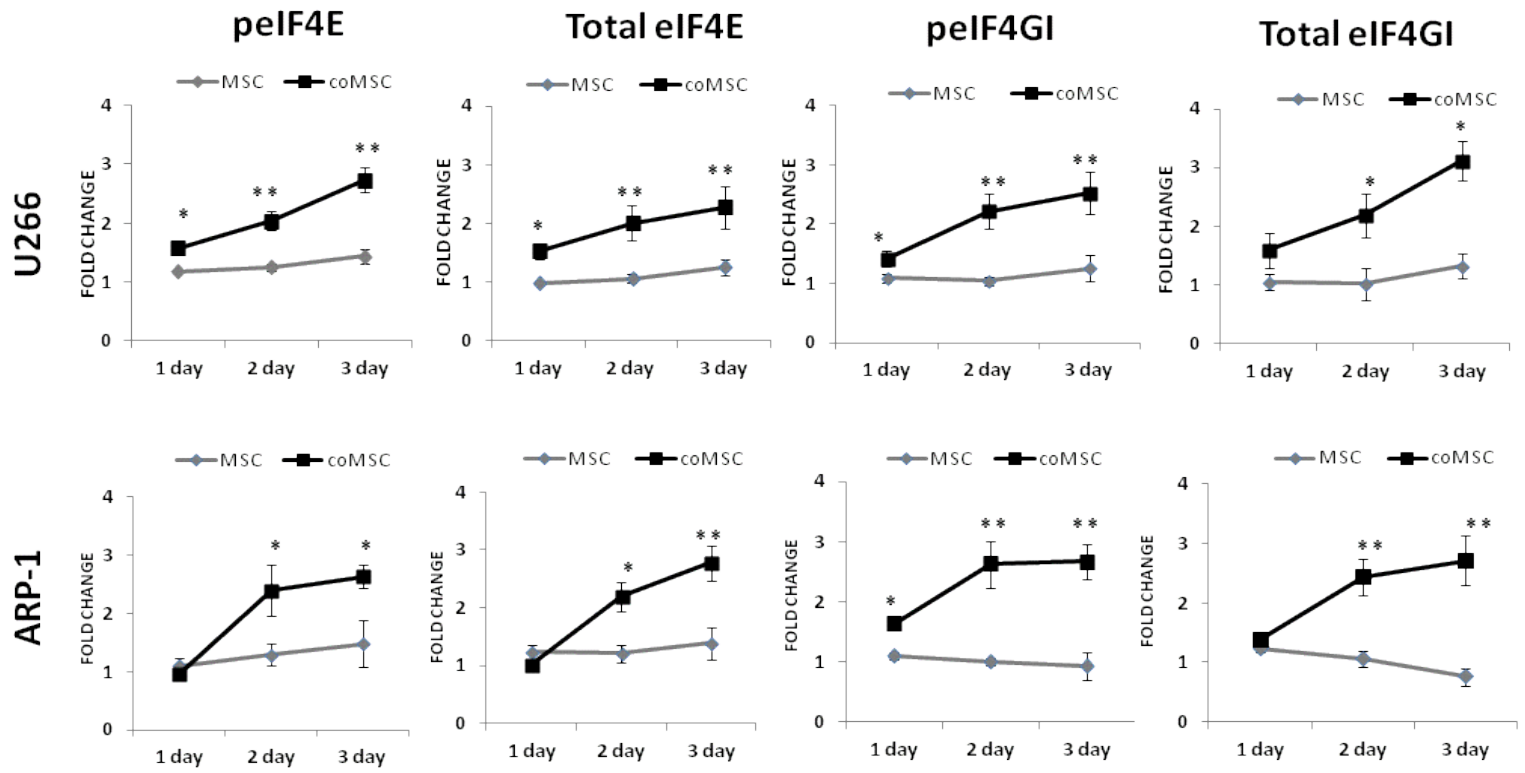


Adipocytes



Osteoblasts

Translation initiation factors are increased in MMcond-MSCs: Timeline

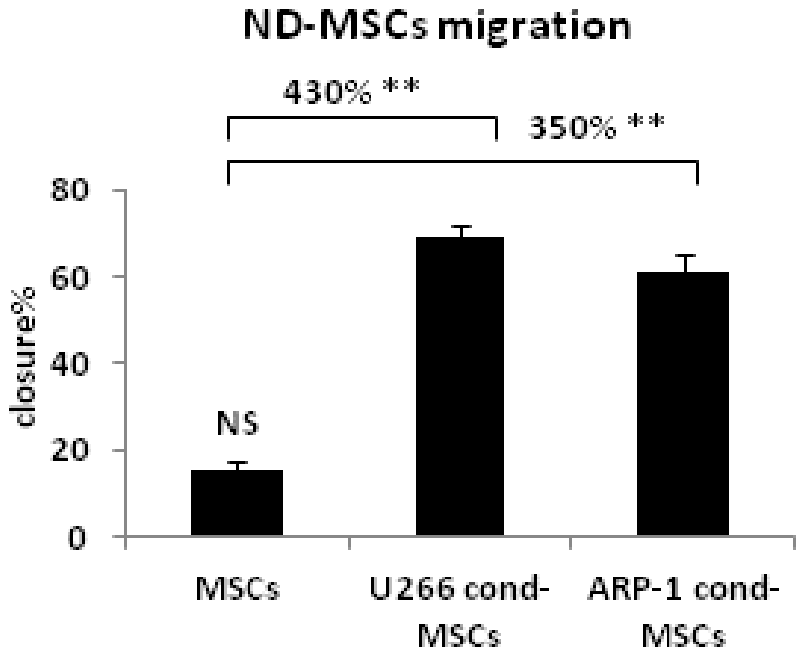


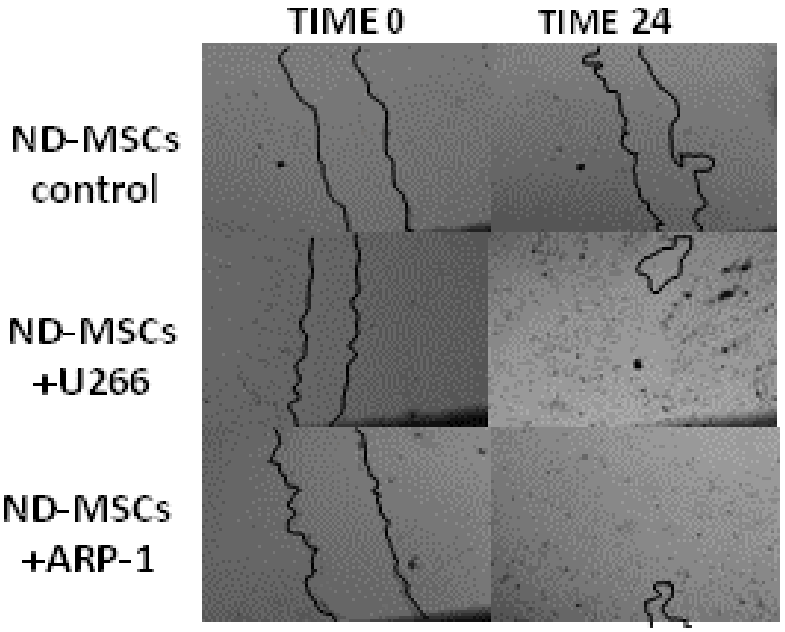
Plato at 4 and 5 days.

eIF4E, eIF4G regulators were elevated at the 1st and the 3rd days.

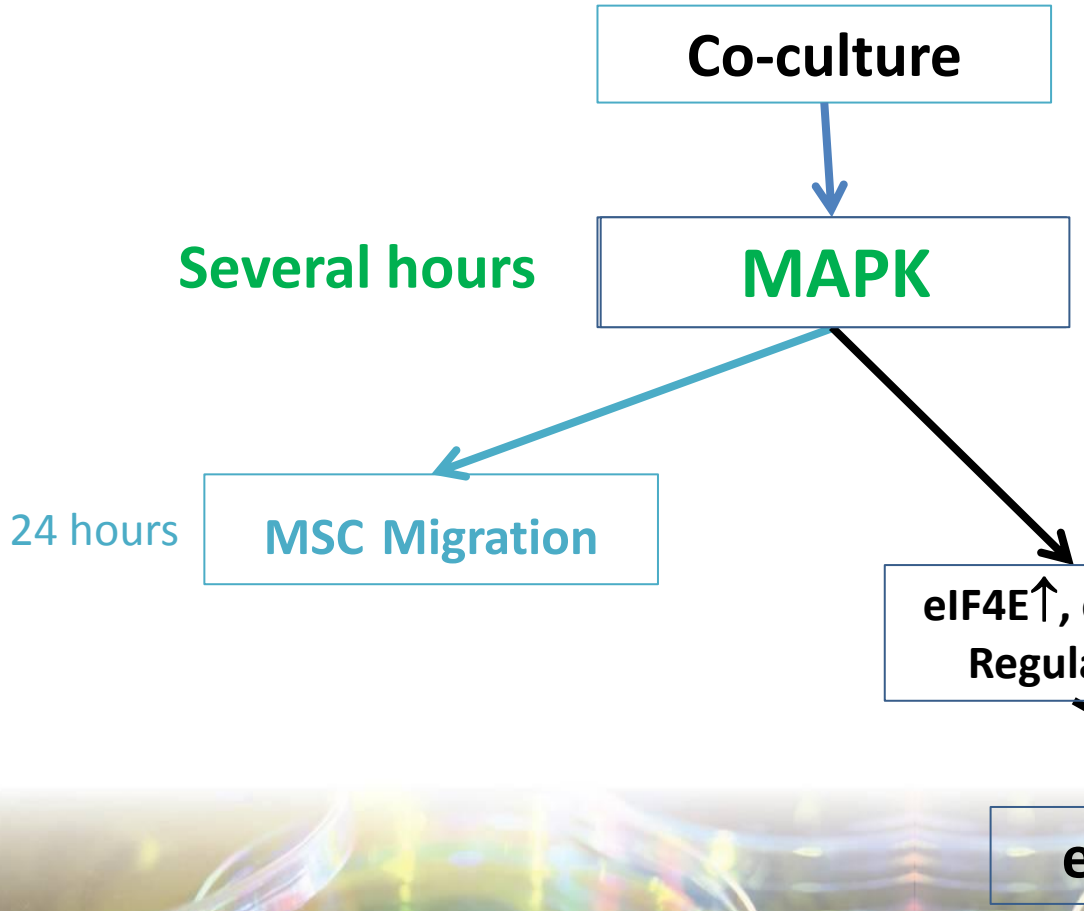
eIF4E, eIF4G targets were elevated at the 3rd day.

MMcond-MSCs display elevated migration (24h)





MMcond-MSCs possible signals



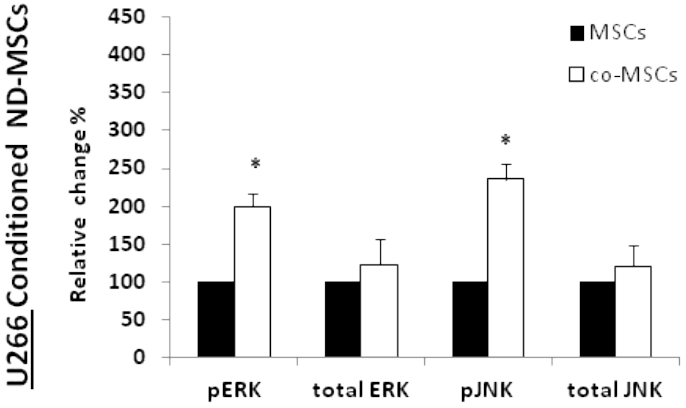
- MAPK phosphorylate mTOR/4EBP and MNK
- MAPK regulate cell migration

MMcond-MSCs show early elevated MAPKs signals and TI factors phosphorylation (1.5h)

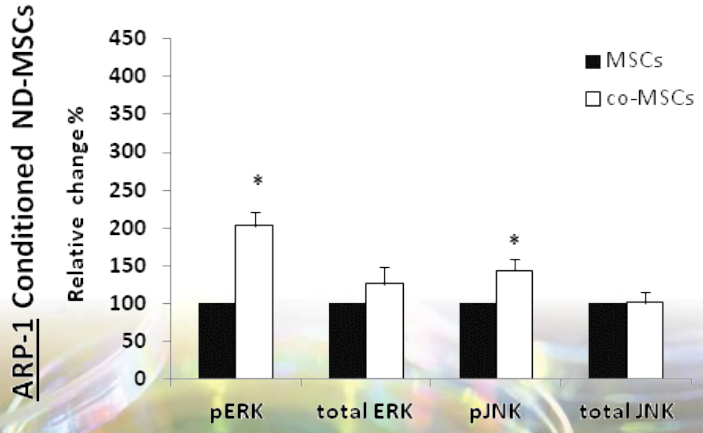
A

MAPKs

U266



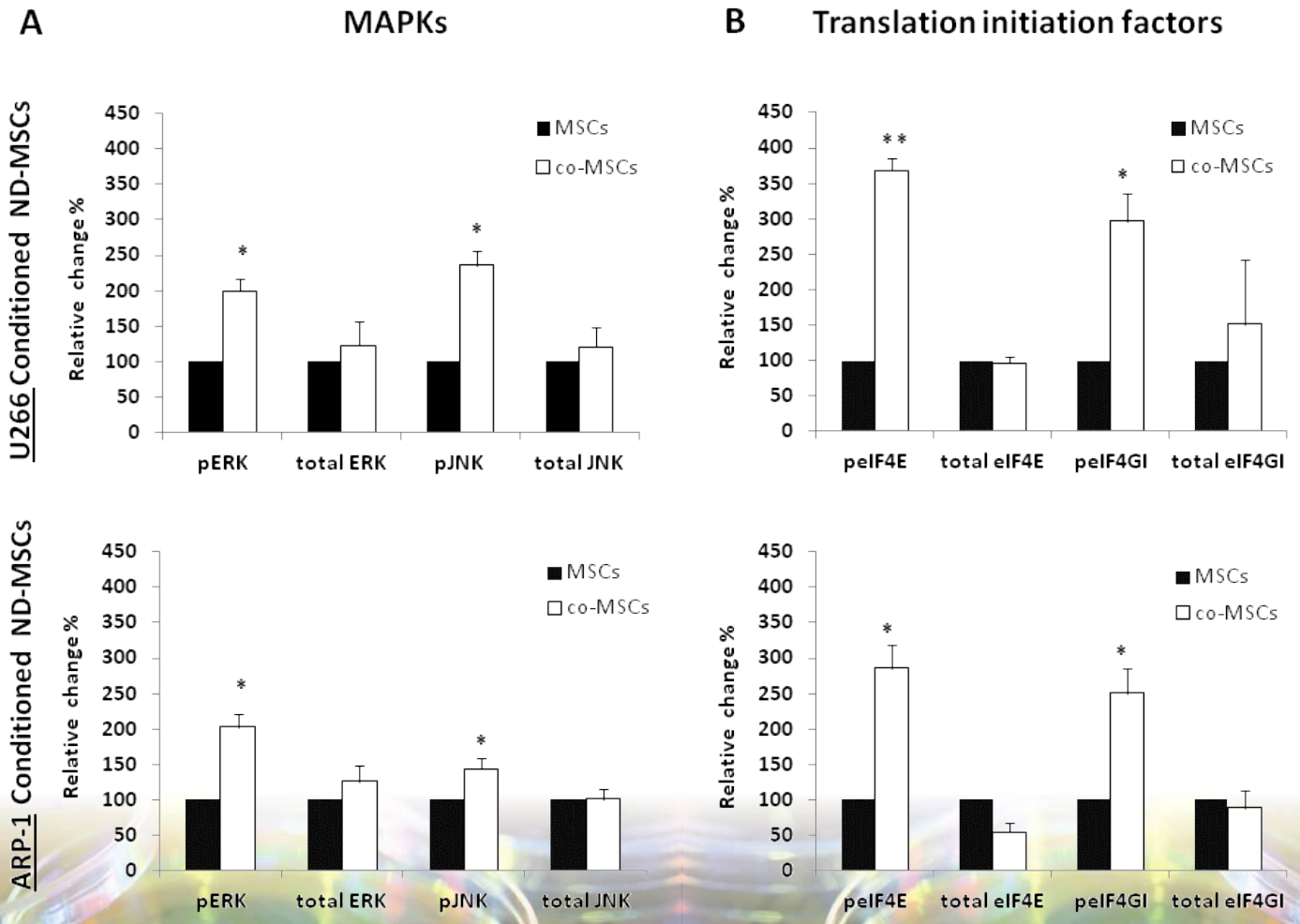
ARP-1



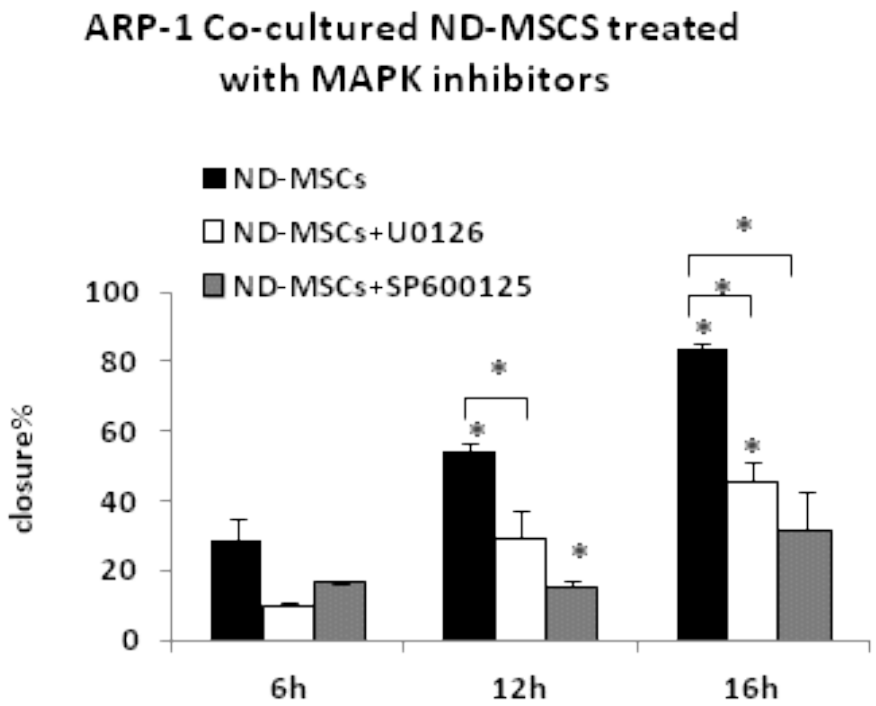
MMcond-MSCs show early elevated MAPKs signals and TI factors phosphorylation (1.5h)

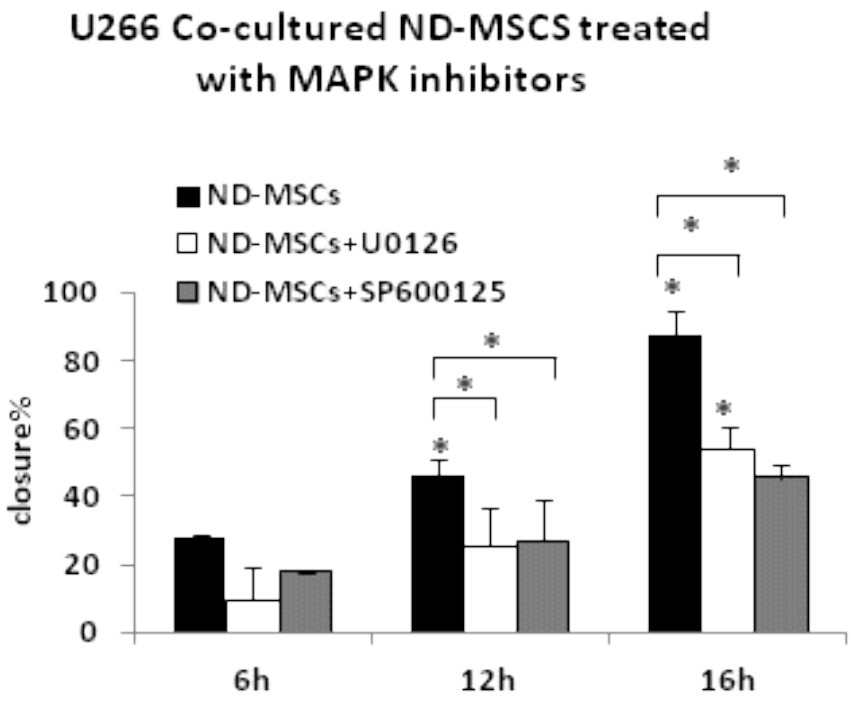
U266

ARP-1

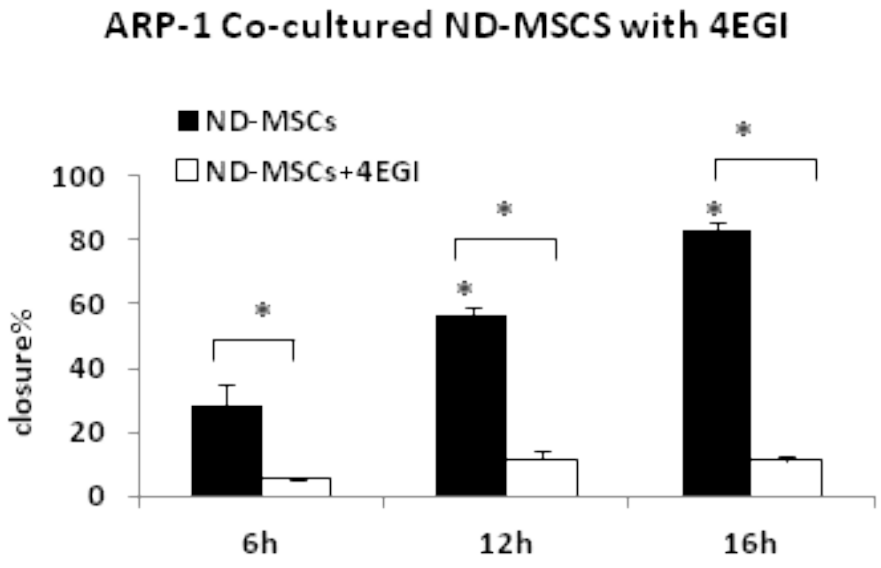


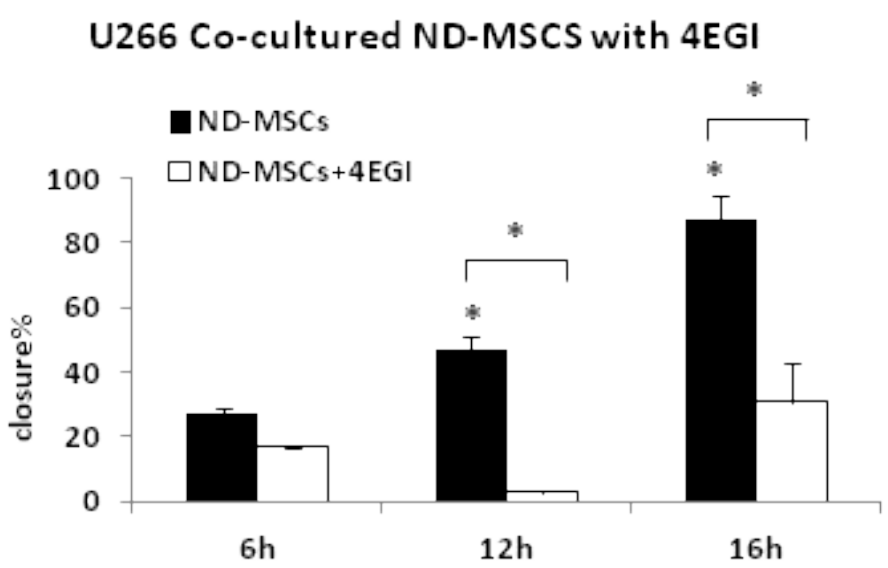
MAPKs inhibitors decrease MMcond-MSCs elevated migration (16h)



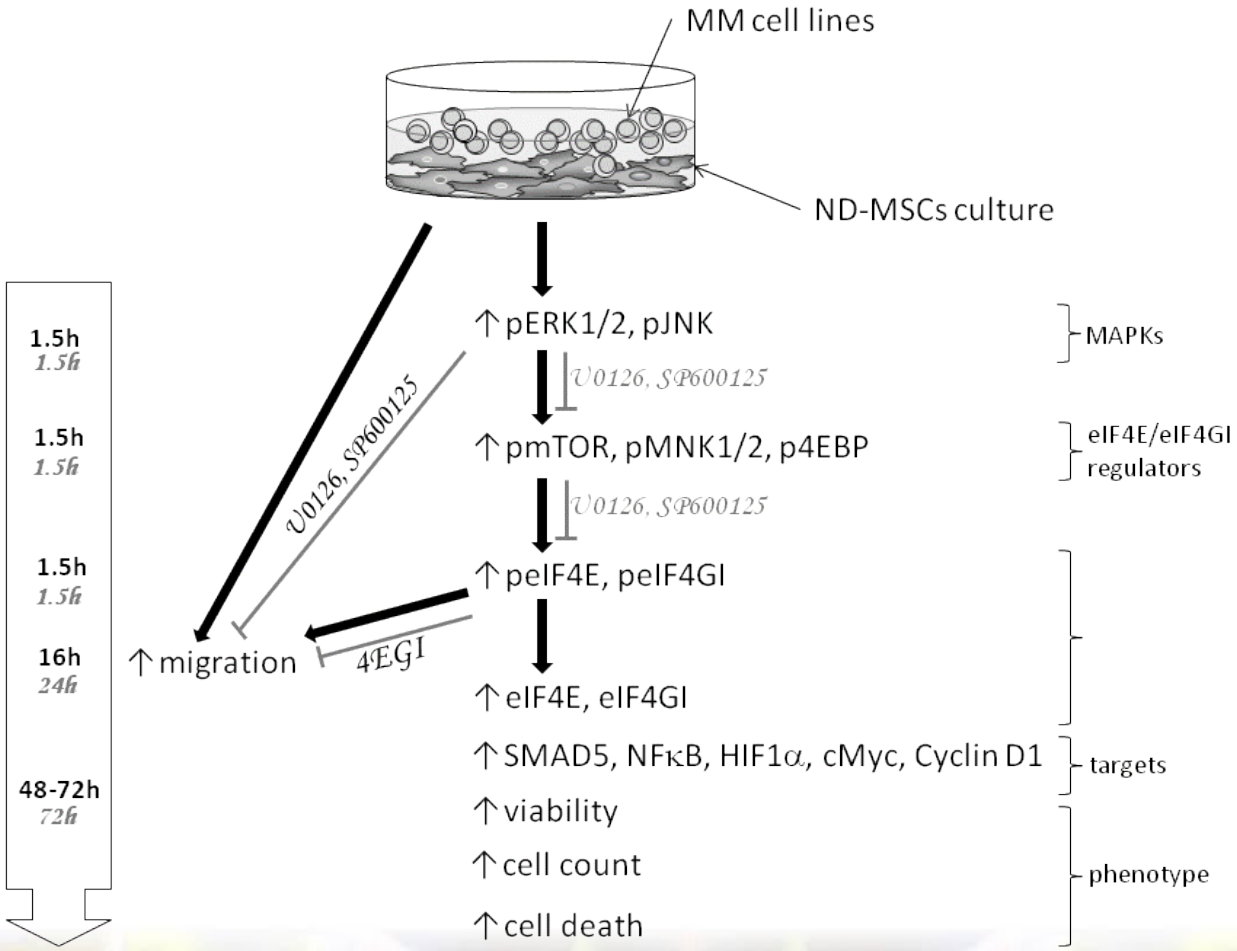


4EGI decreases MMcond-MSCs elevated migration (16h)

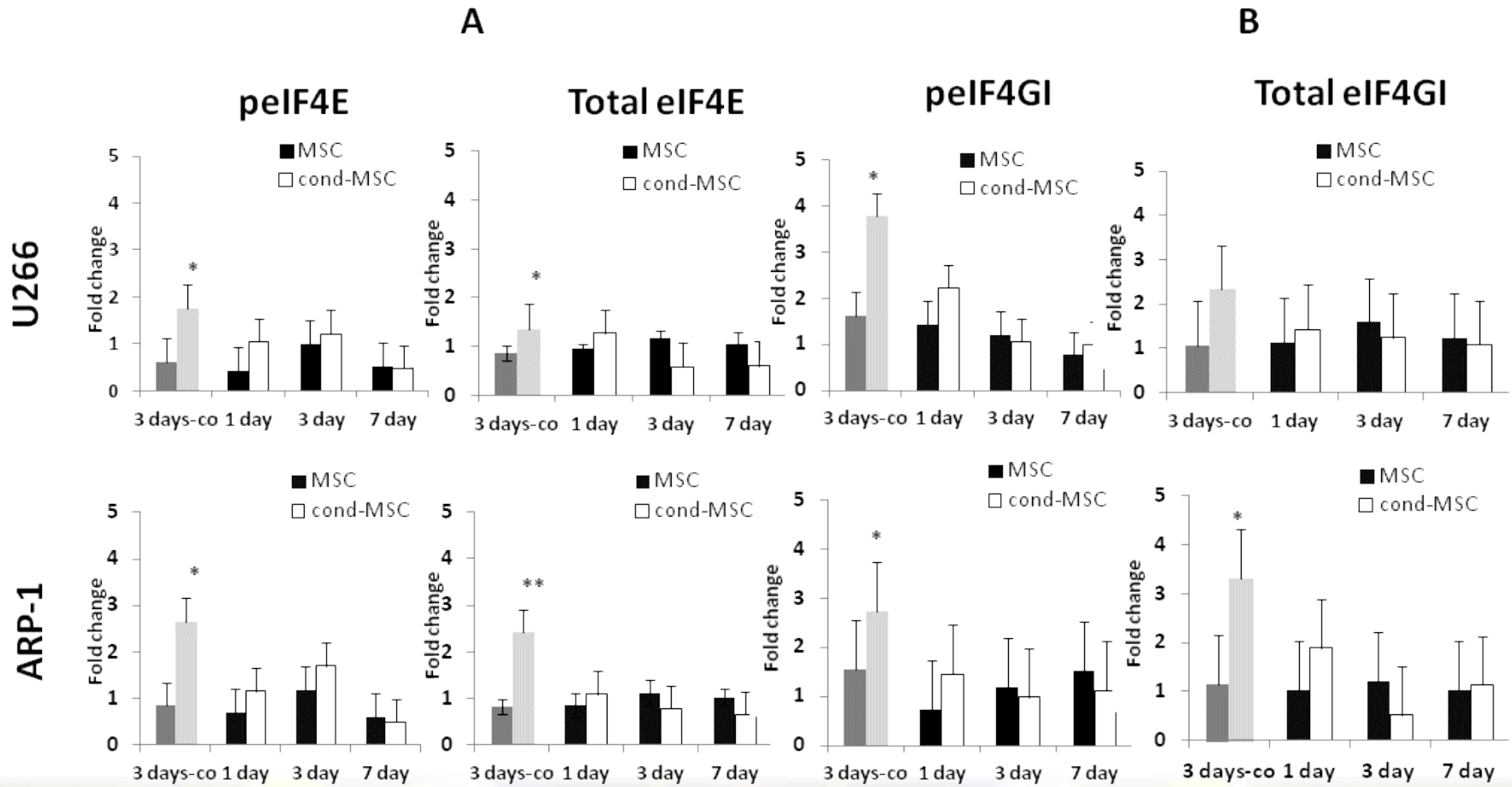




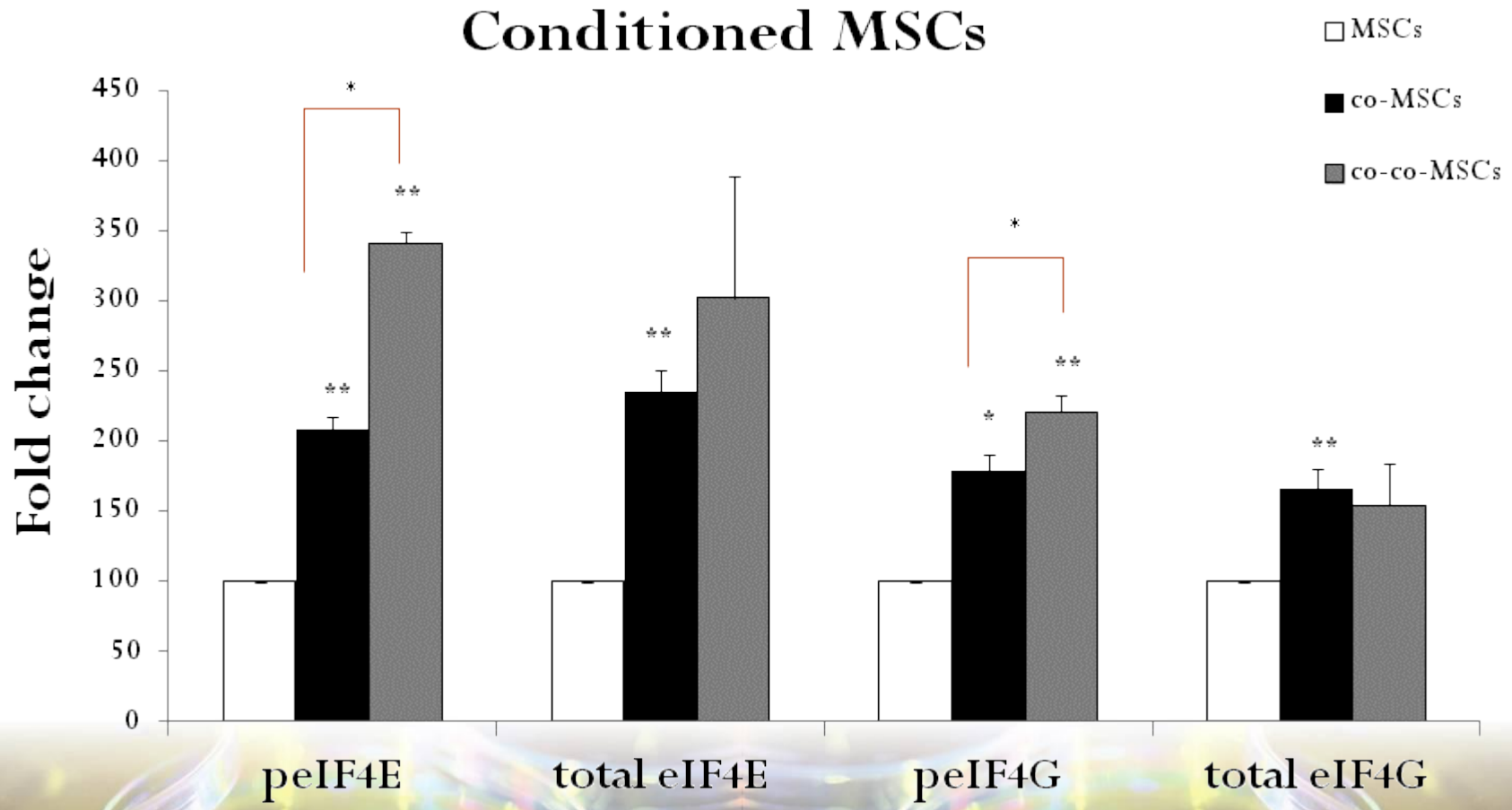
Results summary



The increase in TI in MMcond-MSCs is reversible



Reconditioning of MMcond-MSCs display another elevation of TI factors



Results summary

- ND-MSCs exposed to MM cell lines undergo significant changes in protein synthesis and repertoire as well as migration.
- The changes are time dependent, reversible and can be exacerbated by reintroduction of “fresh MM”.
- Co-culture affected signaling cascade:

  MAPK/eIF4E and eIF4GI/migration and targets.

Significance of my results

- *In vivo*: constant and dynamic refreshment of the niche with new MM cells: in actuality- non reversible and even enhanced ND-MSCs conditioning.
- Increased migration may facilitate the tropism of BM-MSCs to the tumor. Intervention may sabotage the MM niche.
- eIF4E and eIF4GI are important for BM-MSCs protein repertoire and migration, underscoring their potential as therapeutic targets.

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Submitted for publication..

Multiple myeloma cells reprogram bone marrow mesenchymal stem cells' translation initiation thereby promoting their migration

Dabbah M[1,3], Attar-Schneider O[1,3], Zismanov V[1,3], Tartakover Matalon S[1,3], *Lishner M[1,2,3], *Drucker L[1,3]

[1]Oncogenetic Laboratory and [2]Internal Medicine Department, Meir Medical Center, Kfar Saba, and [3]Sackler faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

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Thank you

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Michal Bar

Orthopedic department
Surgery rooms
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