

# Регуляция сигнального пути mTOR факторами плюрипотентности

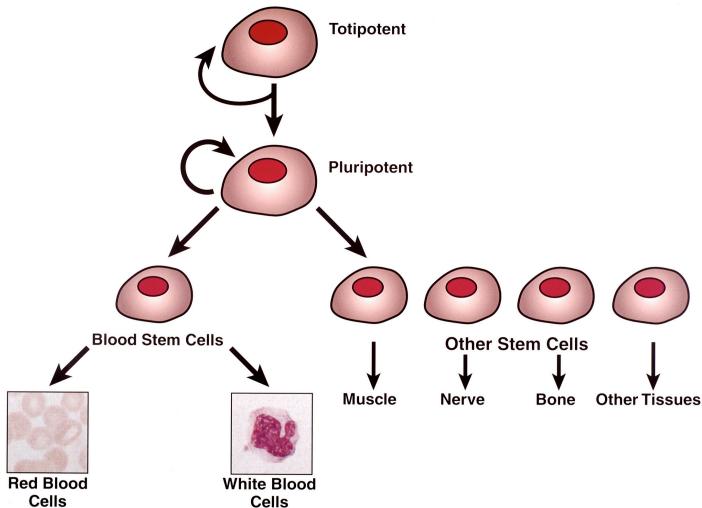
Кураторы:  
Николай Панюшев

Команда m(олот)TORa:  
Пётр Цуриков  
Пётр Болотин  
Наталия Сухих  
Герман Осьмак  
Артём Ильин

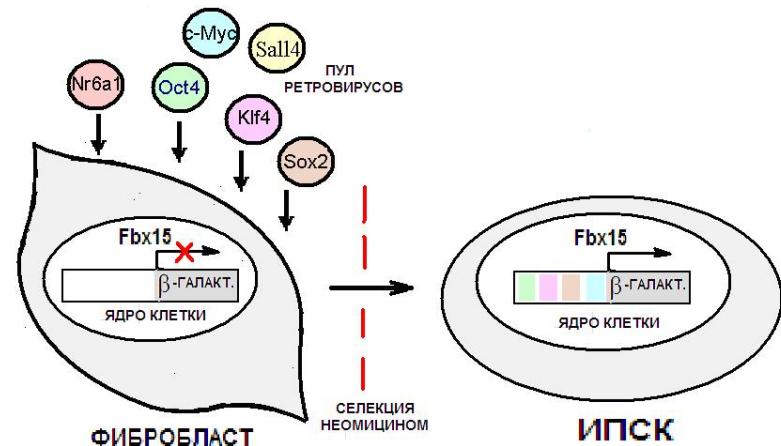
# Постановка задачи

BioHack

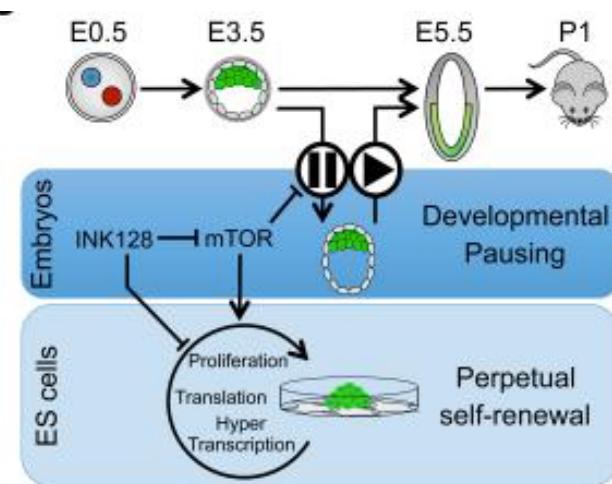
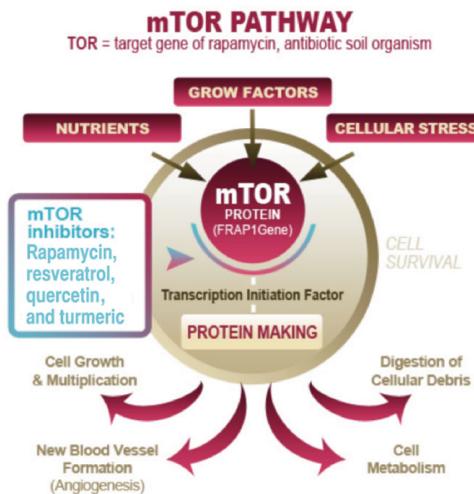
## Hierarchy of Stem Cells



## Факторы плюрипотентности



путь mTOR – участвует в модуляции  
дифференцировки и пролиферации клеток

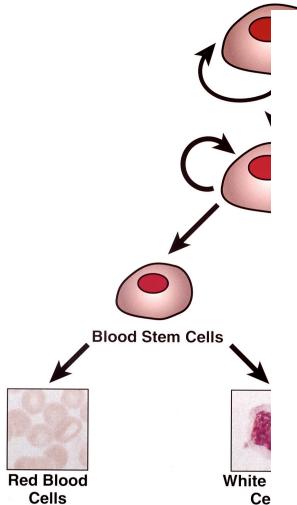


Такахаси и Яманака 2003 г.

# Постановка задачи

BioHack

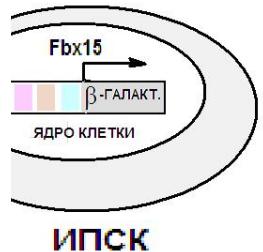
## Hierarchy of Stem Cells



[Nature. Author manuscript; available in PMC 2017 May 23.](#)  
Published in final edited form as:  
[Nature. 2016 Dec 1; 540\(7631\): 119–123.](#)  
Published online 2016 Nov 23. doi: [10.1038/nature20578](https://doi.org/10.1038/nature20578)

## Факторы плюрипотентности

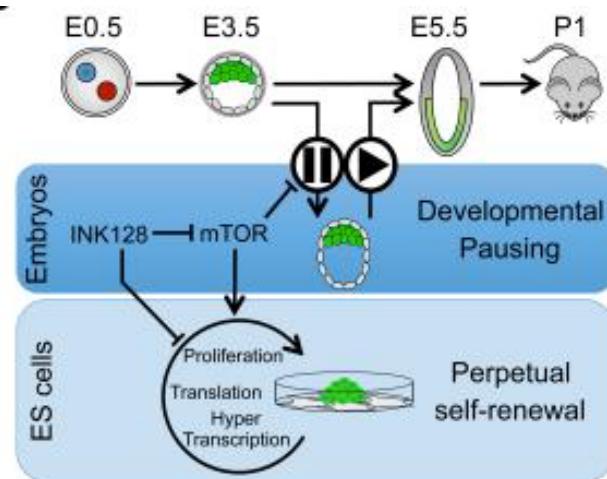
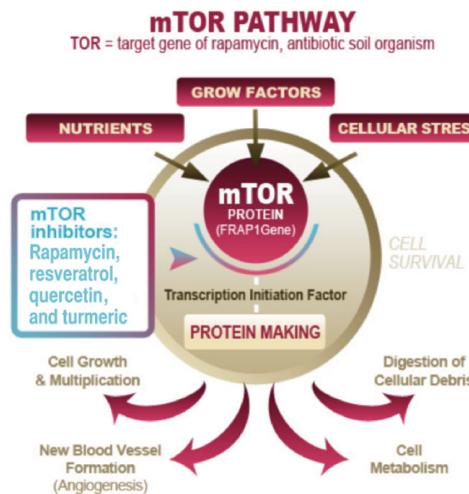
PMCID: PMC5143278  
NIHMSID: NIHMS827222



## Inhibition of mTor induces a paused pluripotent state

Aydan Bulut-Karslioglu,<sup>1</sup> Steffen Biechele,<sup>1</sup> Hu Jin,<sup>2,3</sup> Trisha A. Macrae,<sup>1</sup> Miroslav Hejna,<sup>2,3</sup> Marina Gertsenstein,<sup>4</sup> Jun S. Song,<sup>2,3</sup> and Miguel Ramalho-Santos<sup>1,\*</sup>

[Author information](#) ► [Copyright and License information](#) ►

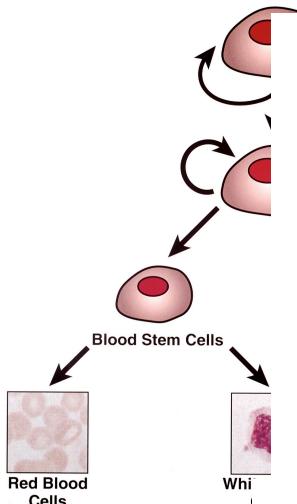


и Яманака 2003 г.

# Постановка задачи

BioHack

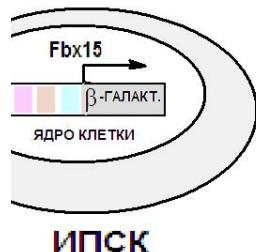
## Hierarchy of Stem Cells



[Nature. Author manuscript; available in PMC 2017 May 23.](#)  
Published in final edited form as:  
[Nature. 2016 Dec 1; 540\(7631\): 119–123.](#)  
Published online 2016 Nov 23. doi: [10.1038/nature20578](https://doi.org/10.1038/nature20578)

## Факторы плюрипотентности

PMCID: PMC5143278  
NIHMSID: NIHMS827222



## Inhibition of mTor induces a paused pluripotent state

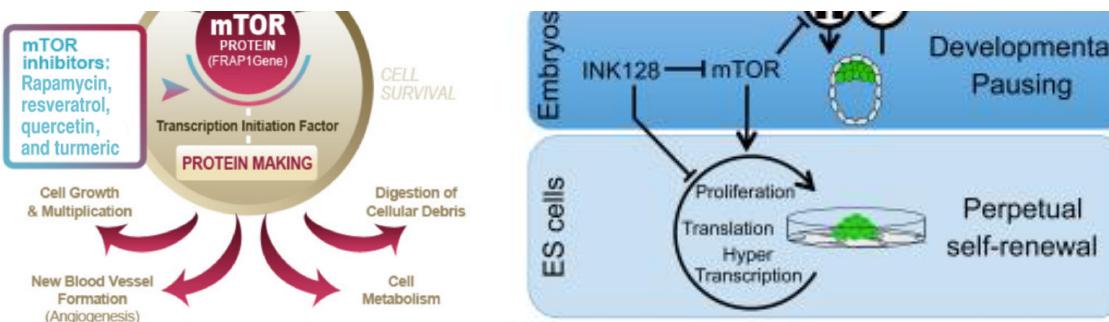
Aydan Bulut-Karslioglu,<sup>1</sup> Steffen Biechele,<sup>1</sup> Hu Jin,<sup>2,3</sup> Trisha A. Macrae,<sup>1</sup> Miroslav Hejna,<sup>2,3</sup> Marina Gertsenstein,<sup>4</sup> Jun S. Song,<sup>2,3</sup> and Miguel Ramalho-Santos<sup>1,\*</sup>

[J Biol Chem. 2014 Nov 14;289\(46\):31818-26. doi: 10.1074/jbc.M114.565838. Epub 2014 Sep 25.](#)

и Яманака 2003 г.

## DEPTOR is a stemness factor that regulates pluripotency of embryonic stem cells.

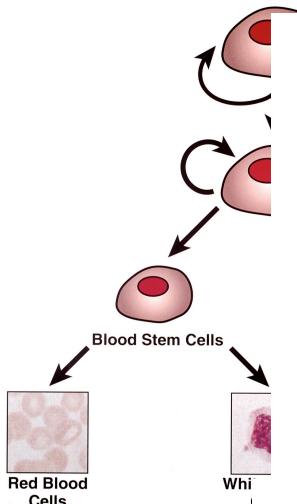
Agrawal P<sup>1</sup>, Reynolds J<sup>1</sup>, Chew S<sup>1</sup>, Lamba DA<sup>2</sup>, Hughes RE<sup>3</sup>.



# Постановка задачи

BioHack

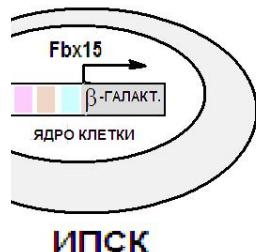
## Hierarchy of Stem Cells



[Nature](#). Author manuscript; available in PMC 2017 May 23.  
Published in final edited form as:  
[Nature](#). 2016 Dec 1; 540(7631): 119–123.  
Published online 2016 Nov 23. doi: [10.1038/nature20578](https://doi.org/10.1038/nature20578)

## Факторы плюрипотентности

PMCID: PMC5143278  
NIHMSID: NIHMS827222



## Inhibition of mTor induces a paused pluripotent state

Aydan Bulut-Karslioglu,<sup>1</sup> Steffen Biechele,<sup>1</sup> Hu Jin,<sup>2,3</sup> Trisha A. Macrae,<sup>1</sup> Miroslav Hejna,<sup>2,3</sup> Marina Gertsenstein,<sup>4</sup> Jun S. Song,<sup>2,3</sup> and Miguel Ramalho-Santos<sup>1,\*</sup>

[J Biol Chem](#). 2014 Nov 14;289(46):31818-26. doi: 10.1074/jbc.M114.565838. Epub 2014 Sep 25.

и Яманака 2003 г.

## DEPTOR is a stemness factor that regulates pluripotency of embryonic stem cells.

Agrawal P<sup>1</sup>, Reynolds J<sup>1</sup>, Chew S<sup>1</sup>, Lamba DA<sup>2</sup>, Hughes RE<sup>3</sup>.

[Mol Cell Biol](#). 2004 Aug;24(15):6710-8.

## mTOR is essential for growth and proliferation in early mouse embryos and embryonic stem cells.

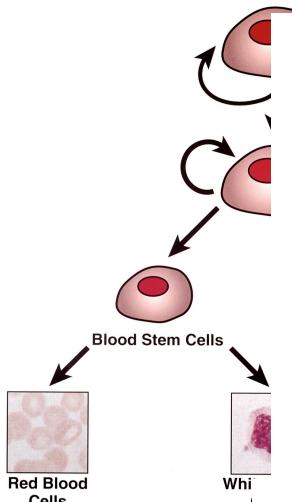
Murakami M<sup>1</sup>, Ichisaka T, Maeda M, Oshiro N, Hara K, Edenhofer F, Kiyama H, Yonezawa K, Yamanaka S.



# Постановка задачи

BioHack

## Hierarchy of Stem Cells



[Nature. Author manuscript; available in PMC 2017 May 23.](#)  
Published in final edited form as:  
[Nature. 2016 Dec 1; 540\(7631\): 119–123.](#)  
Published online 2016 Nov 23. doi: [10.1038/nature20578](https://doi.org/10.1038/nature20578)

## Inhibition of mTor induces a pa

[Aydan Bulut-Karslioglu,<sup>1</sup> Steffen Biechele,<sup>1</sup> Hu Jin,<sup>2</sup> S. Song,<sup>2,3</sup> and Miguel Ramalho-Santos<sup>1,\\*</sup>](#)

[J Biol Chem. 2014 Nov 14;289\(46\):31818-26. doi: 10.1074/jbc.M](#)

## DEPTOR is a stemness factor that re

[Agrawal P<sup>1</sup>, Reynolds J<sup>1</sup>, Chew S<sup>1</sup>, Lamba DA<sup>2</sup>, Hughes R](#)

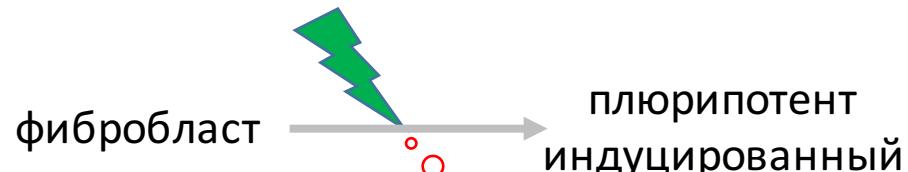
[Mol Cell Biol. 2004 Aug;24\(15\):6710-8.](#)

## mTOR is essential for growth and proliferation in early mouse embryos and embryonic stem cells.

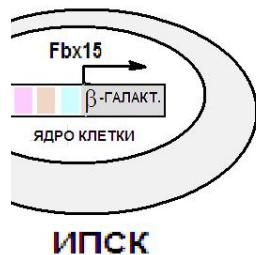
[Murakami M<sup>1</sup>, Ichisaka T, Maeda M, Oshiro N, Hara K, Edenhofer F, Kiyama H, Yonezawa K, Yamanaka S.](#)



## Факторы Яманака (ТФ)



ЮСТИ

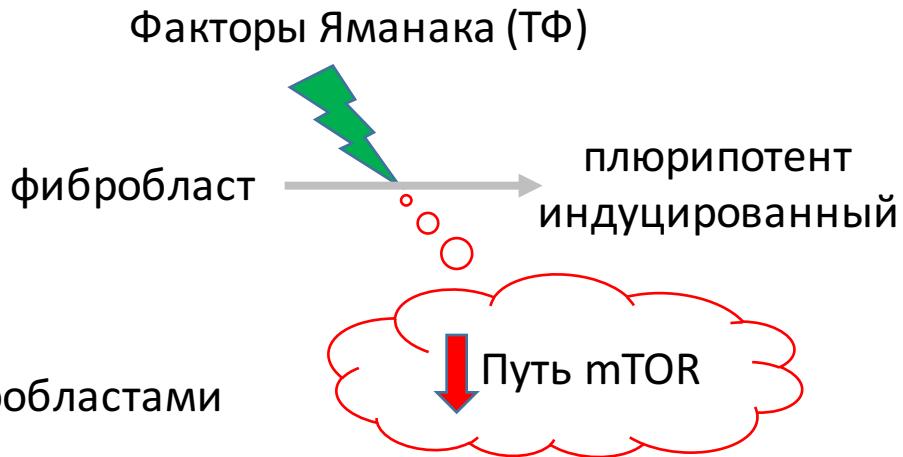


и Яманака 2003 г.

# План работы

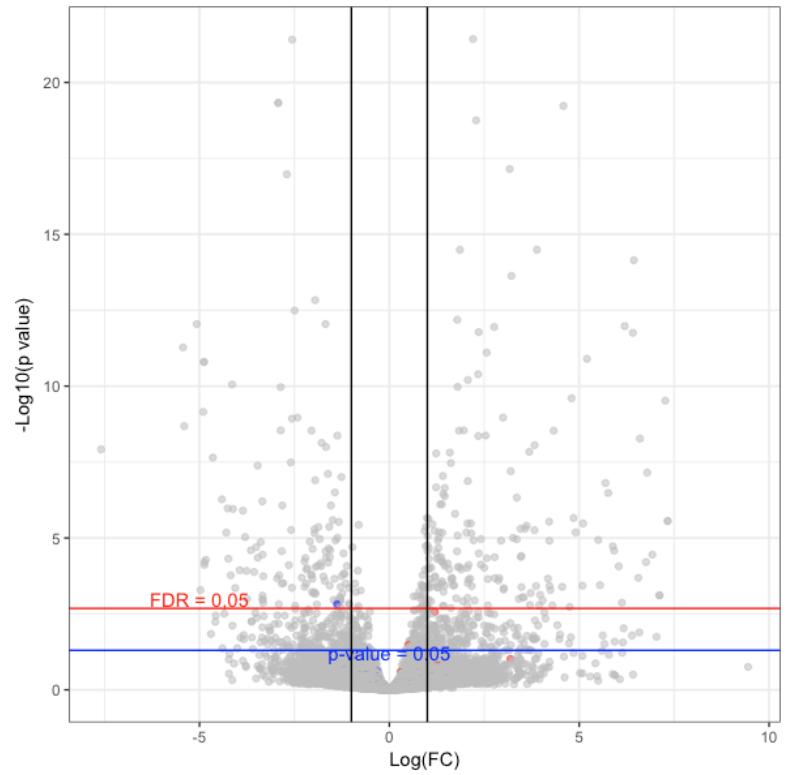
BioHack

- А правда ли путь mTOR меняется?
  - ✓ Сравнить RNA-seq iPSC с фибробластами
- Связывают ли факторы Яманака области генов пути mTOR?
  - ✓ Получить пары ген-ТФ по данным Chip-seq
- Сами по себе факты связывания ген-ТФ или изменения экспрессии пути mTOR ни о чем не говорят, важно их совместное наличие
  - ✓ Прикрутить данные Chip-seq к RNA-seq



# Данные scRNA-seq iPSC vs fibroblasts

BioHack

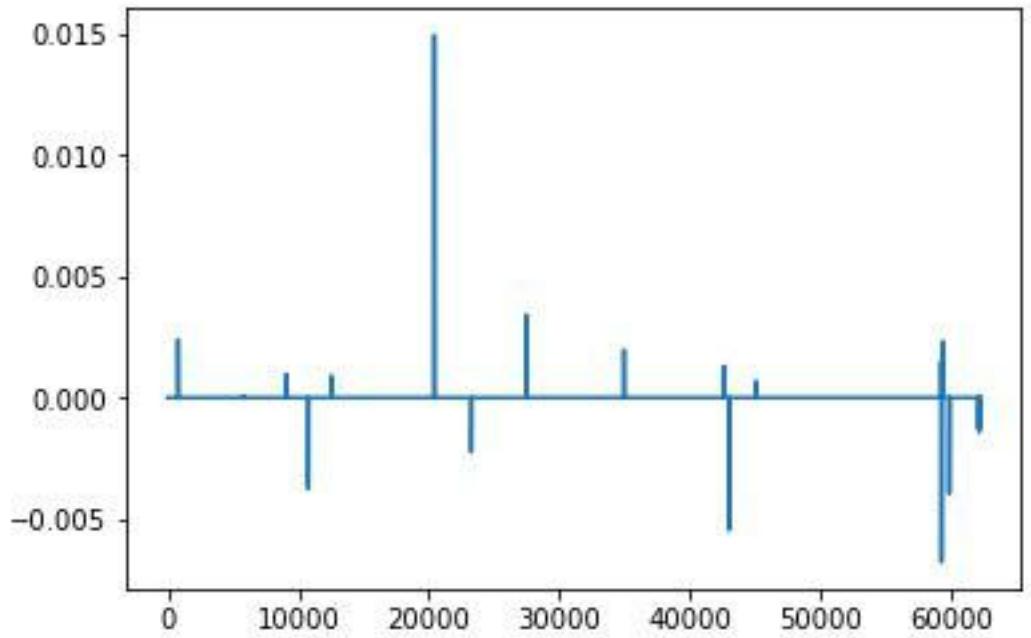


Дифф. экспрессирующиеся гены пути mTOR (edger):

RHOA2, YWHAE3, RAC14, PML5, DEPTOR6,  
MAP2K17, IRS18, HRAS9, EIF4EBP110, SSPO

Логистическая регрессия с L1 регуляризацией для прореживания признакового пространства

$$\sum_{i=1}^m \log \mathbb{P}\{y^{(i)} | x^{(i)}, \theta\} - \lambda \|\theta\|_1 \rightarrow \max.$$

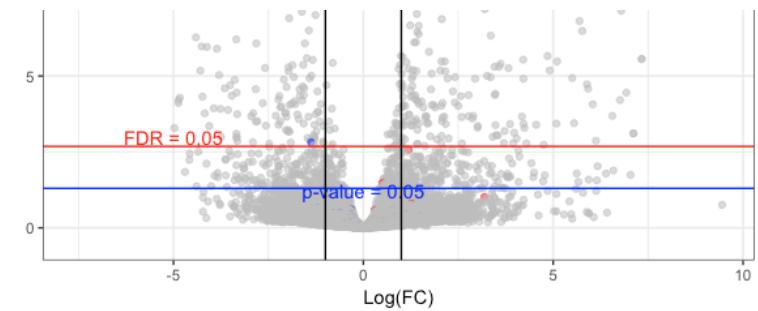




Логистическая регрессия с L1 регуляризацией для прореживания признакового пространства

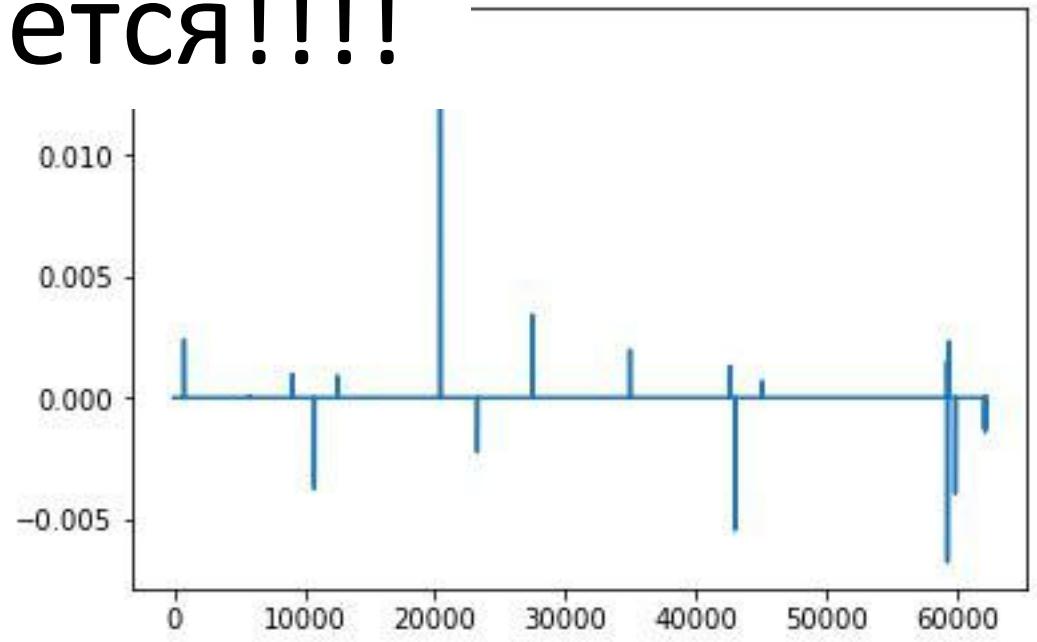
$$\sum_{i=1}^m \log \mathbb{P}\{y^{(i)} | x^{(i)}, \theta\} - \lambda \|\theta\|_1 \rightarrow \max.$$

## И все таки Он меняется!!!!



Дифф. экспрессирующиеся гены пути mTOR (edger):

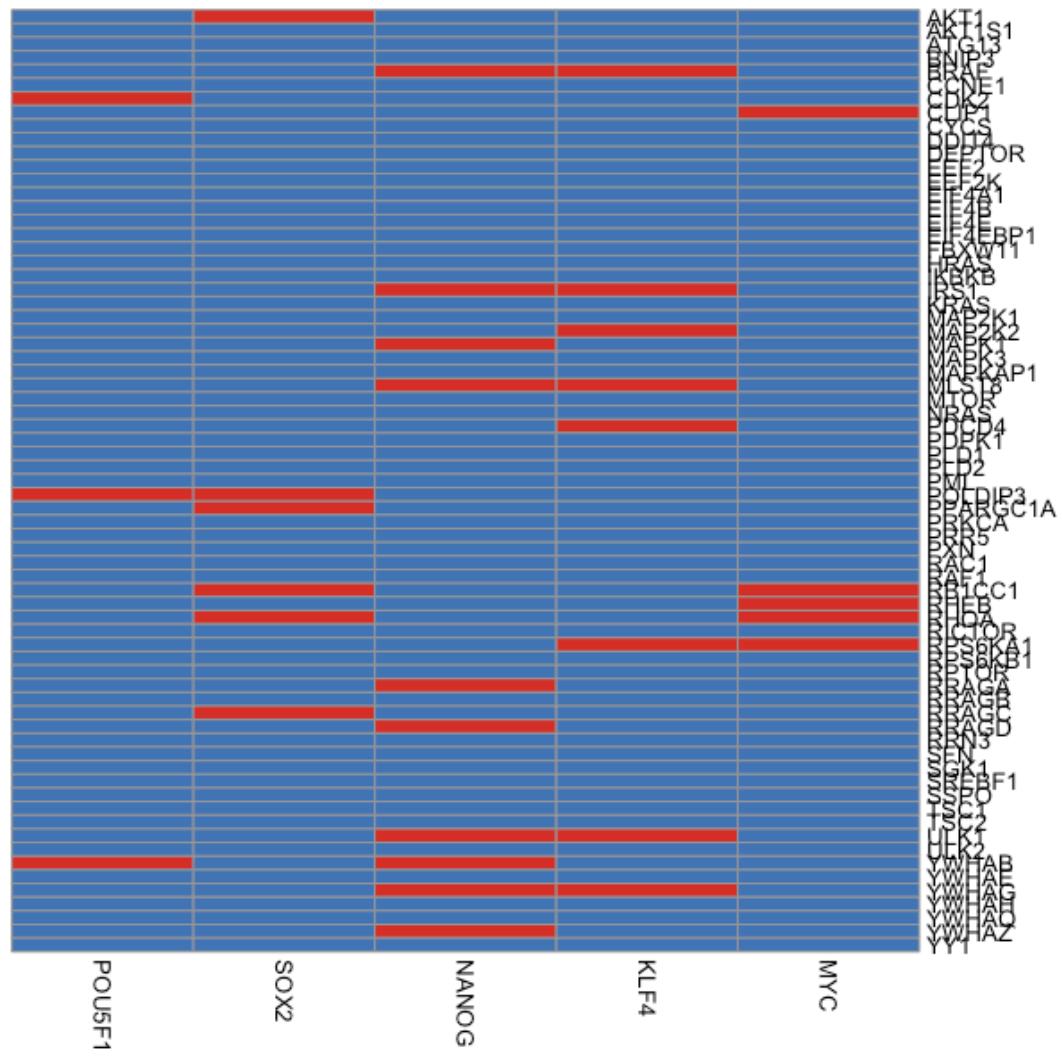
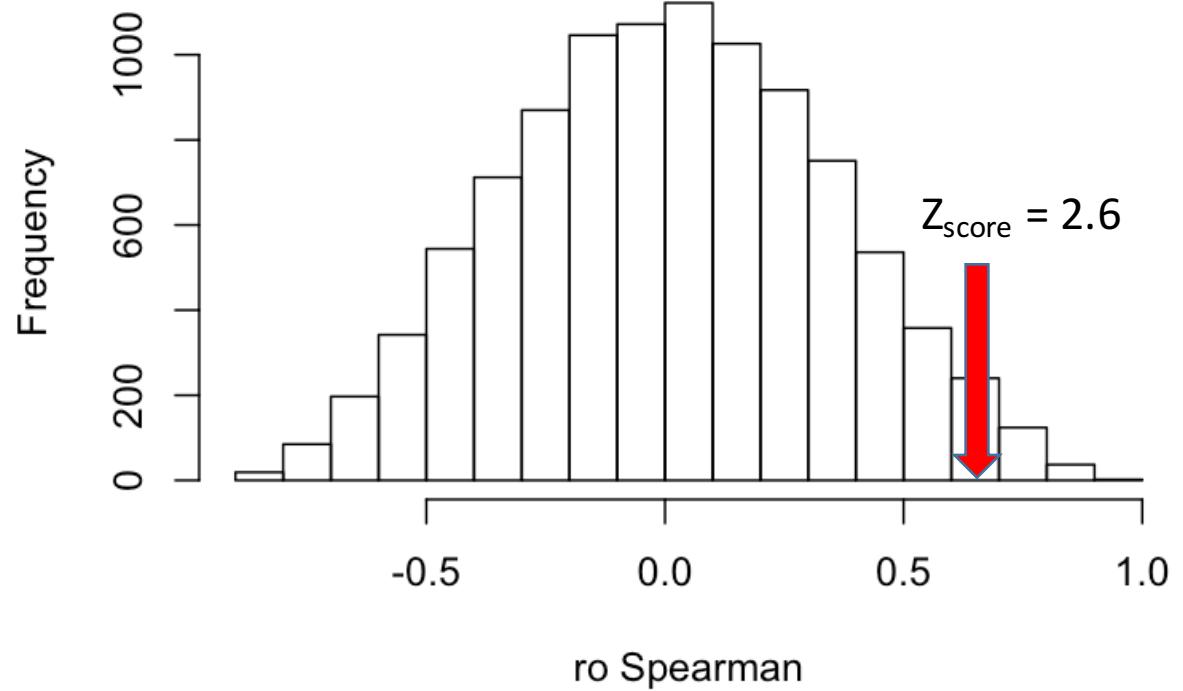
RHOA2, YWHAE3, RAC14, PML5, DEPTOR6,  
MAP2K17, IRS18, HRAS9, EIF4EBP110, SSPO



# От RNA-seq к Chip-seq

# BioHack

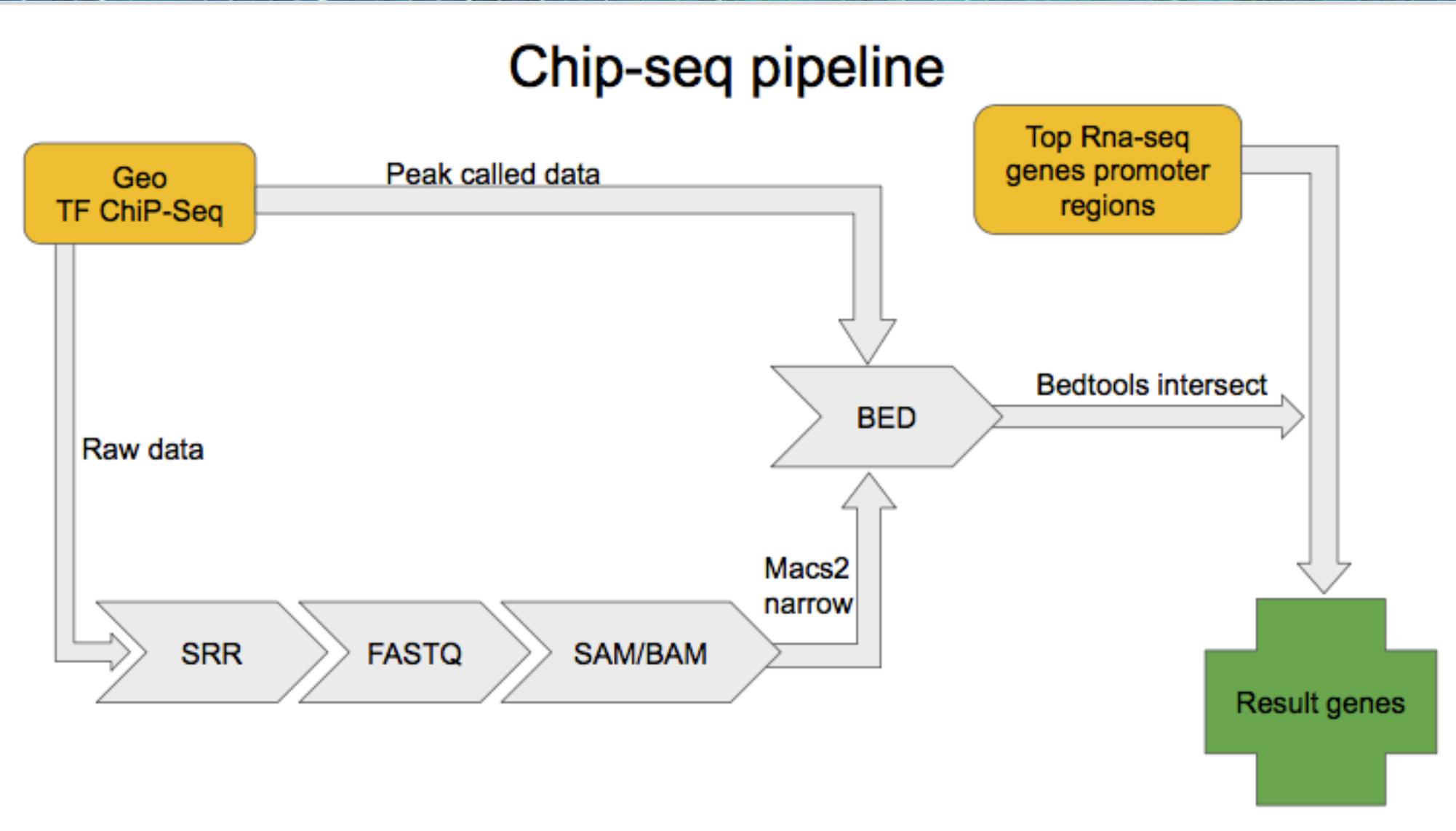
## Probability distribution for random gene pairs from RNA-seq data



# Данные Chip-seq по связыванию TF генами пути mTOR

BioHack

## Chip-seq pipeline



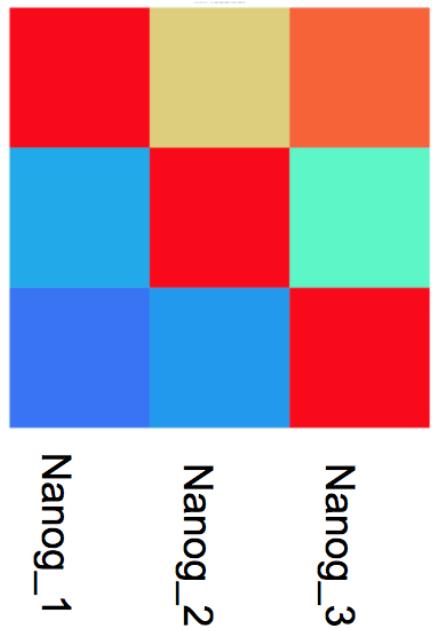
# Данные Chip-seq по связыванию TF генами пути mTOR

BioHack

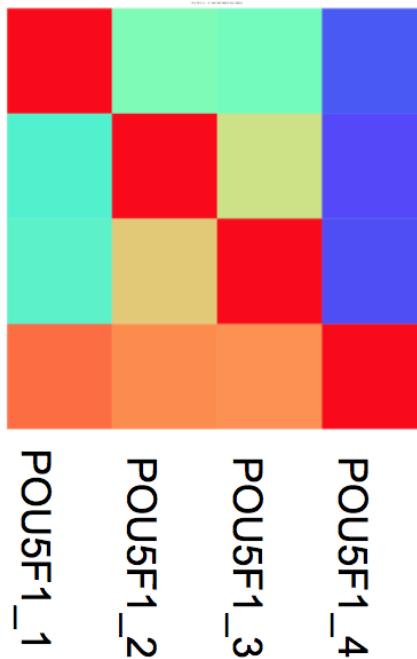
## ChIP-Seq data analysis using Inclusion

- Works with enclosed regions ( $A < B$ )
- Tolerant for shifts
- Non-symmetric
- $\text{number}(A \text{ regions which intersect any } B \text{ regions}) / \text{number}(A)$

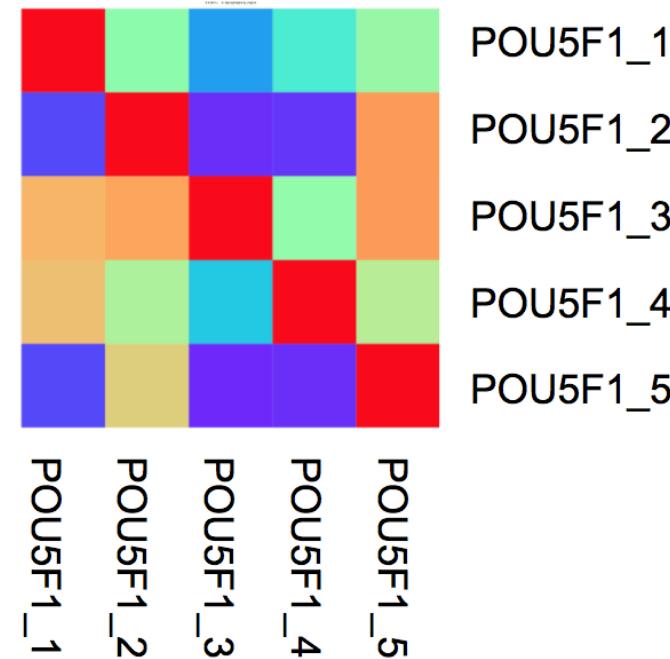
Embryonic NANOG



Pluripotent POU5F1

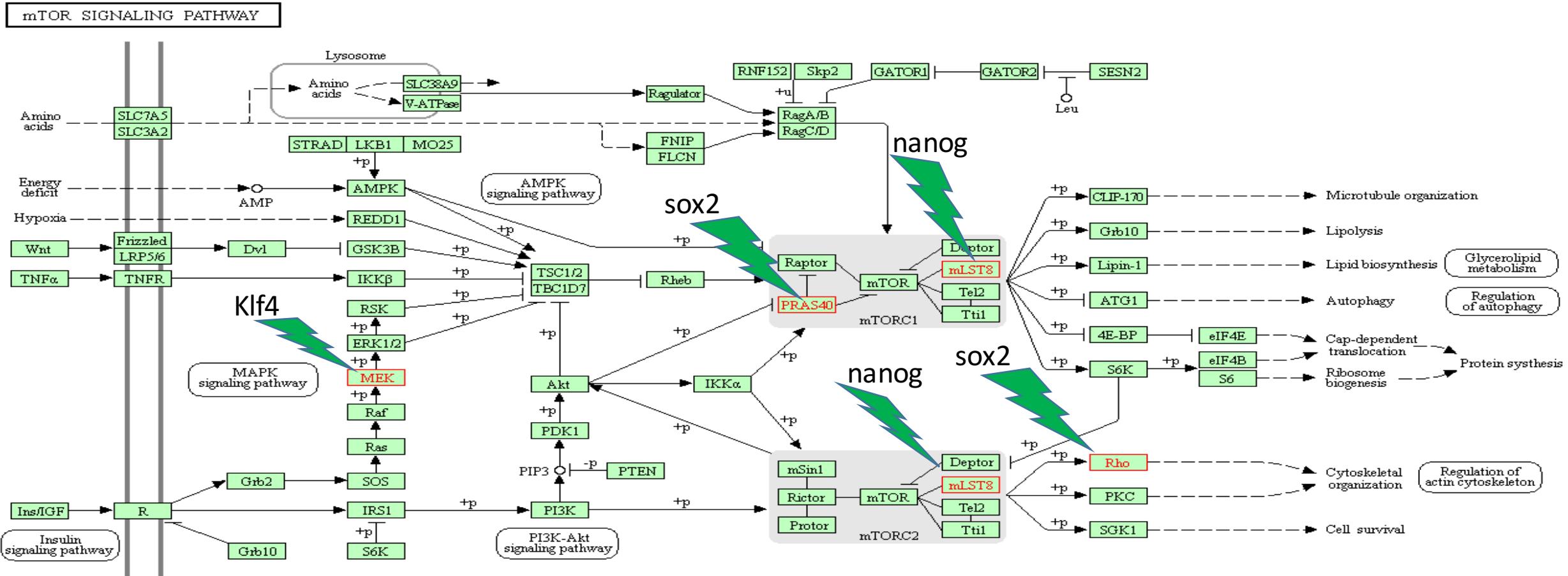


Embryonic POU5F1



# Регуляция пути mTOR отобранными факторами

BioHack



# Регуляция пути mTOR отобранными факторами BioHack

REPO:<https://github.com/PetrTsurinov/mTor>