

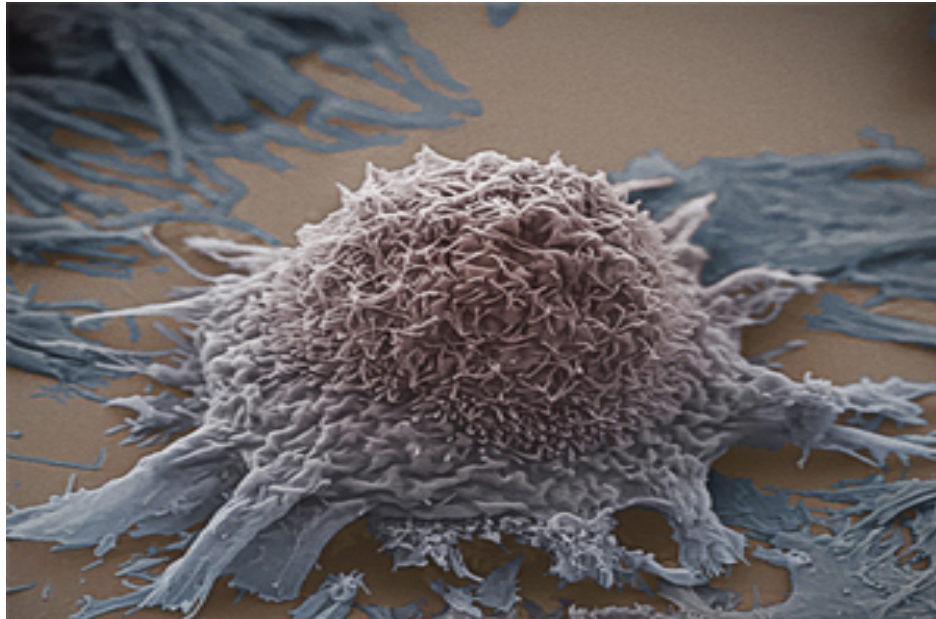
# Pretrkanost tumorskih celic pri iskanju rezervnih poti migracije in invazije

**Janko Kos**

**Fakulteta za farmacijo Univerze v Ljubljani  
Inštitut Jožef Stefan, Odsek za biotehnologijo**

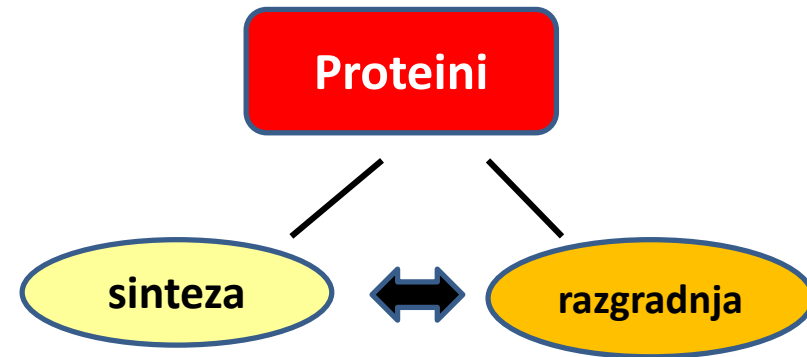
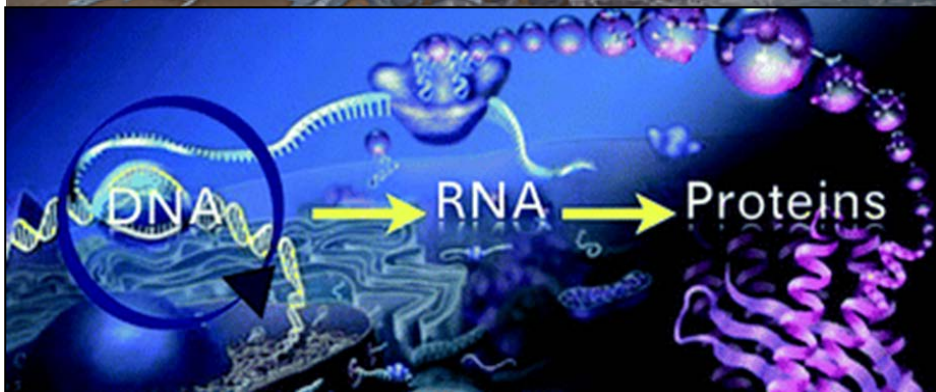


# Celica – osnovna enota življenja

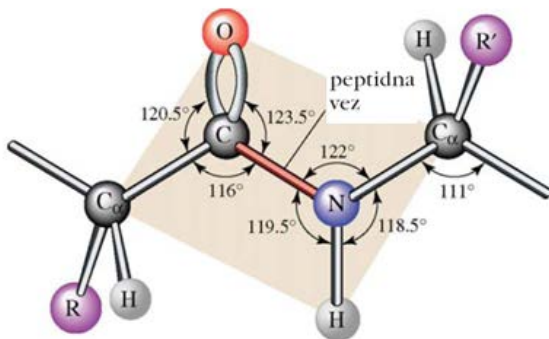
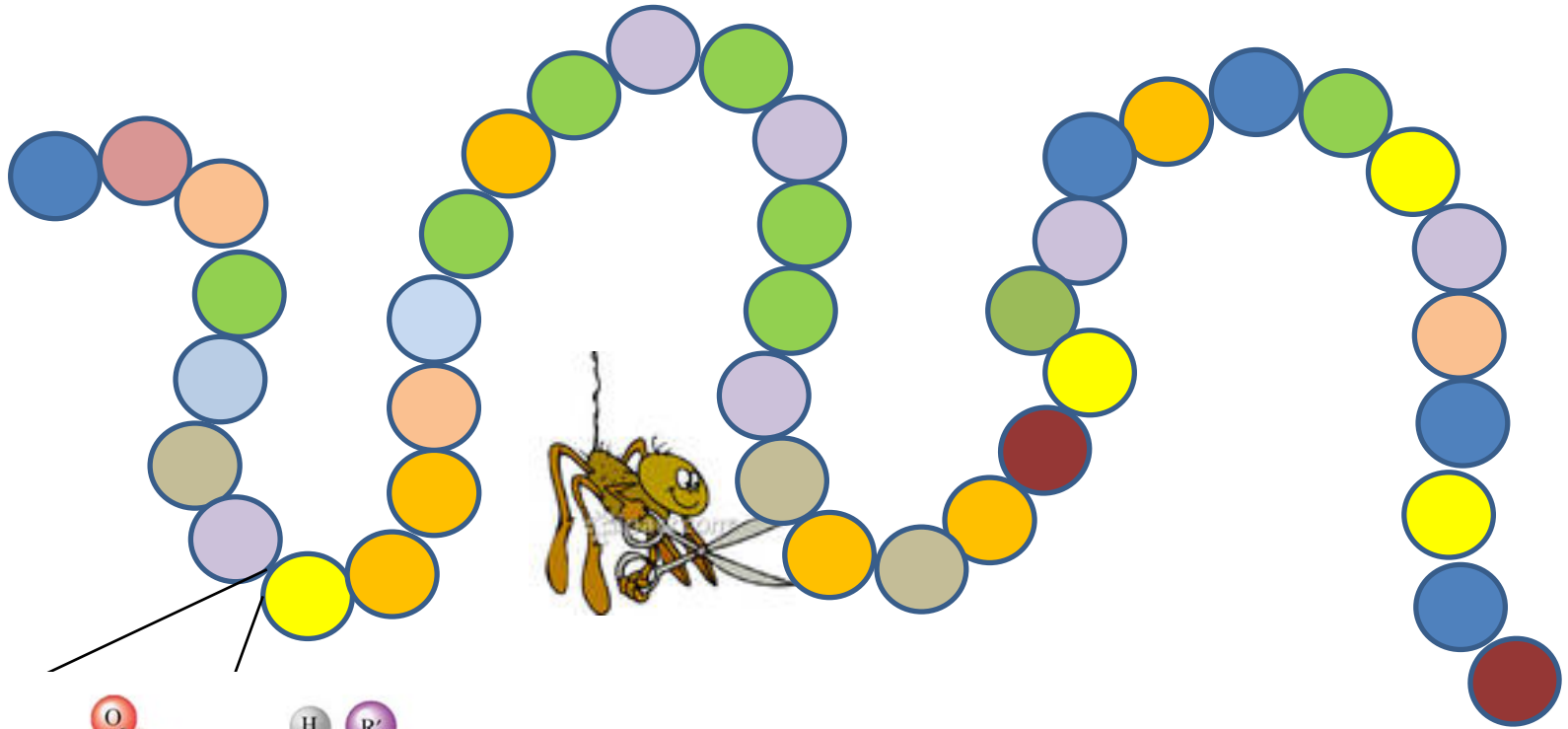


-Nad 20.000 genov,  
ki kodirajo proteine  
(1,5% genoma)

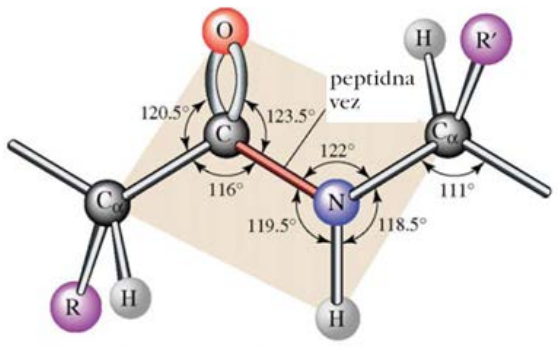
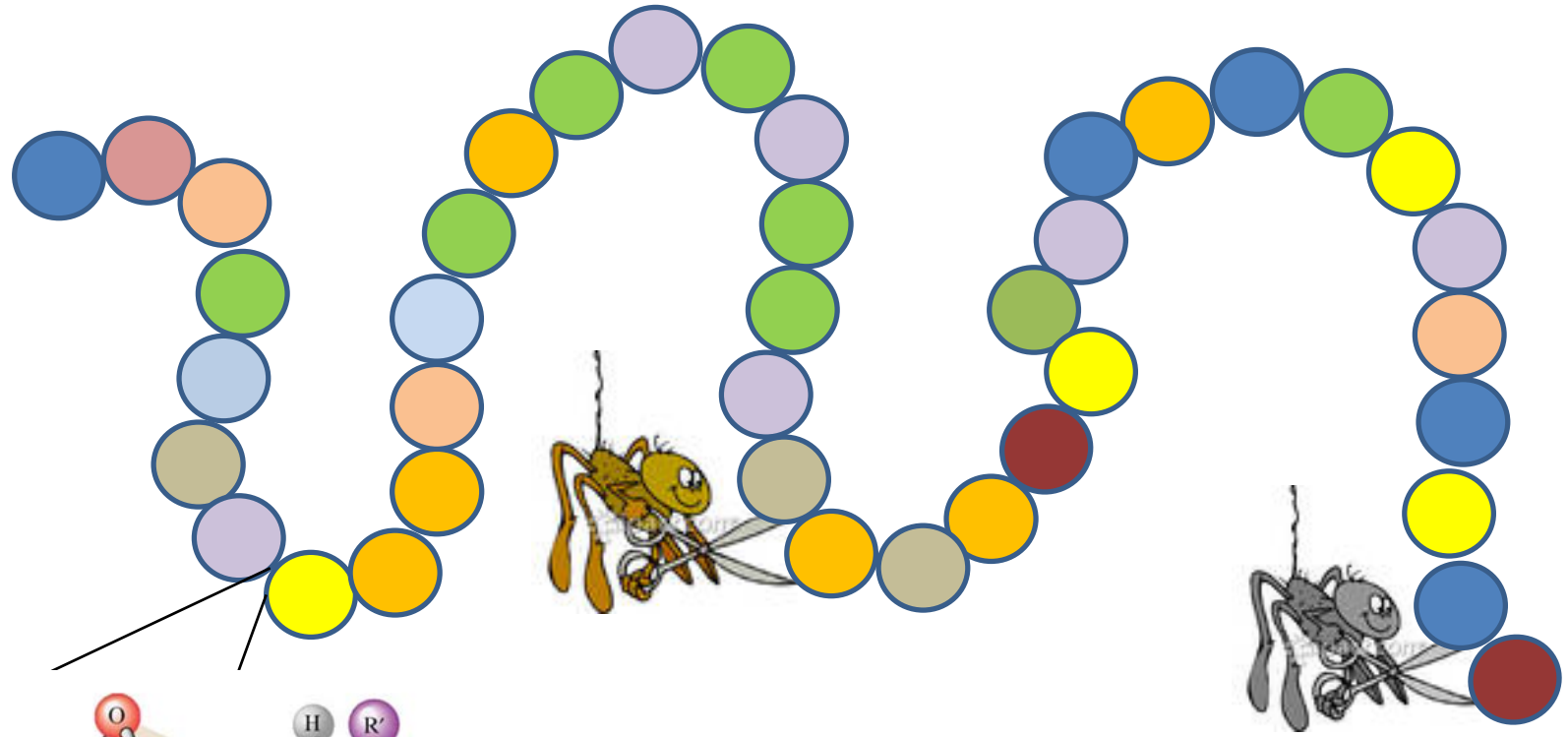
- Proteini izvajajo celične  
dejavnosti (molekule  
življenja)



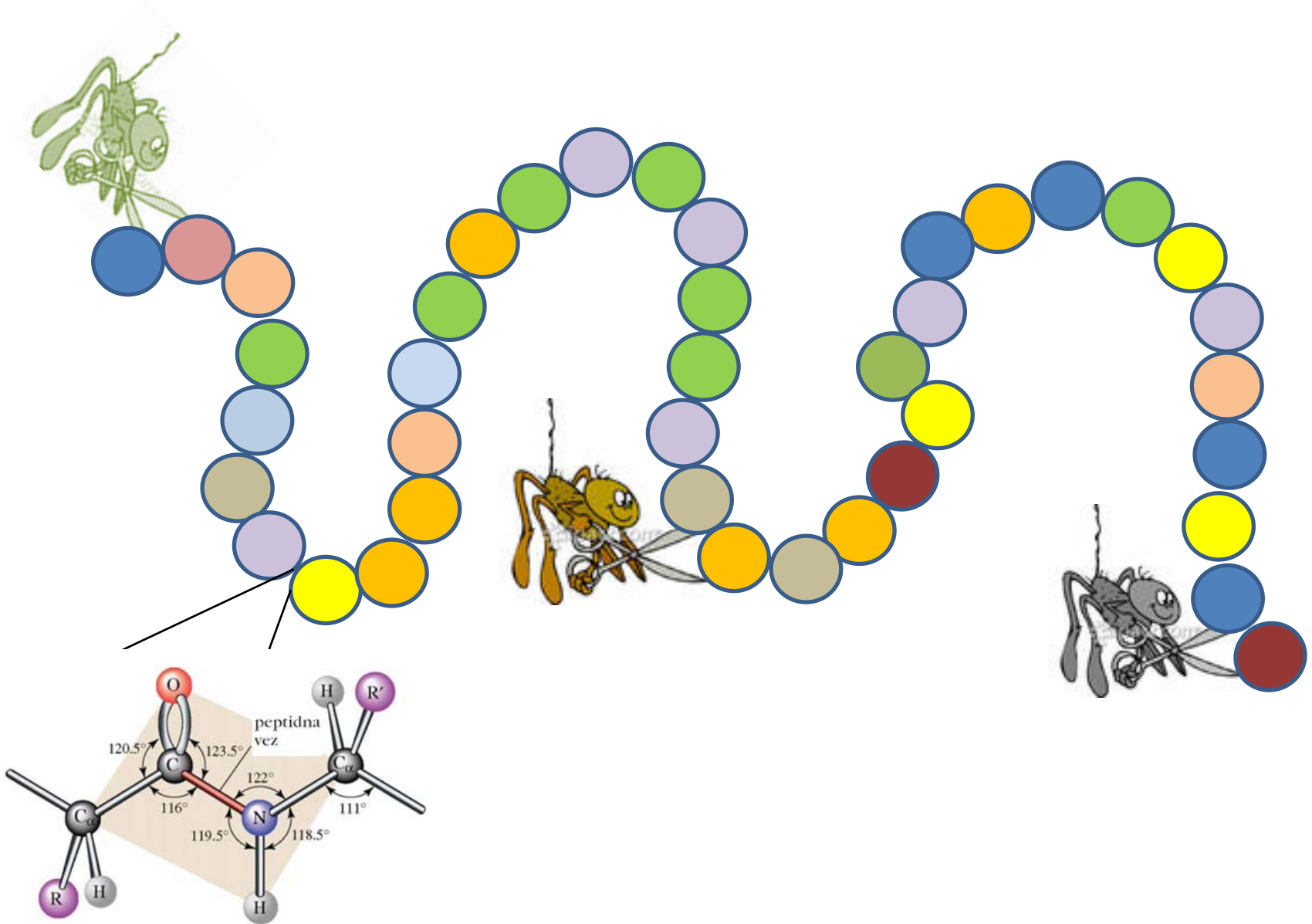
# Proteolizni encimi razgrajujejo peptidno vez



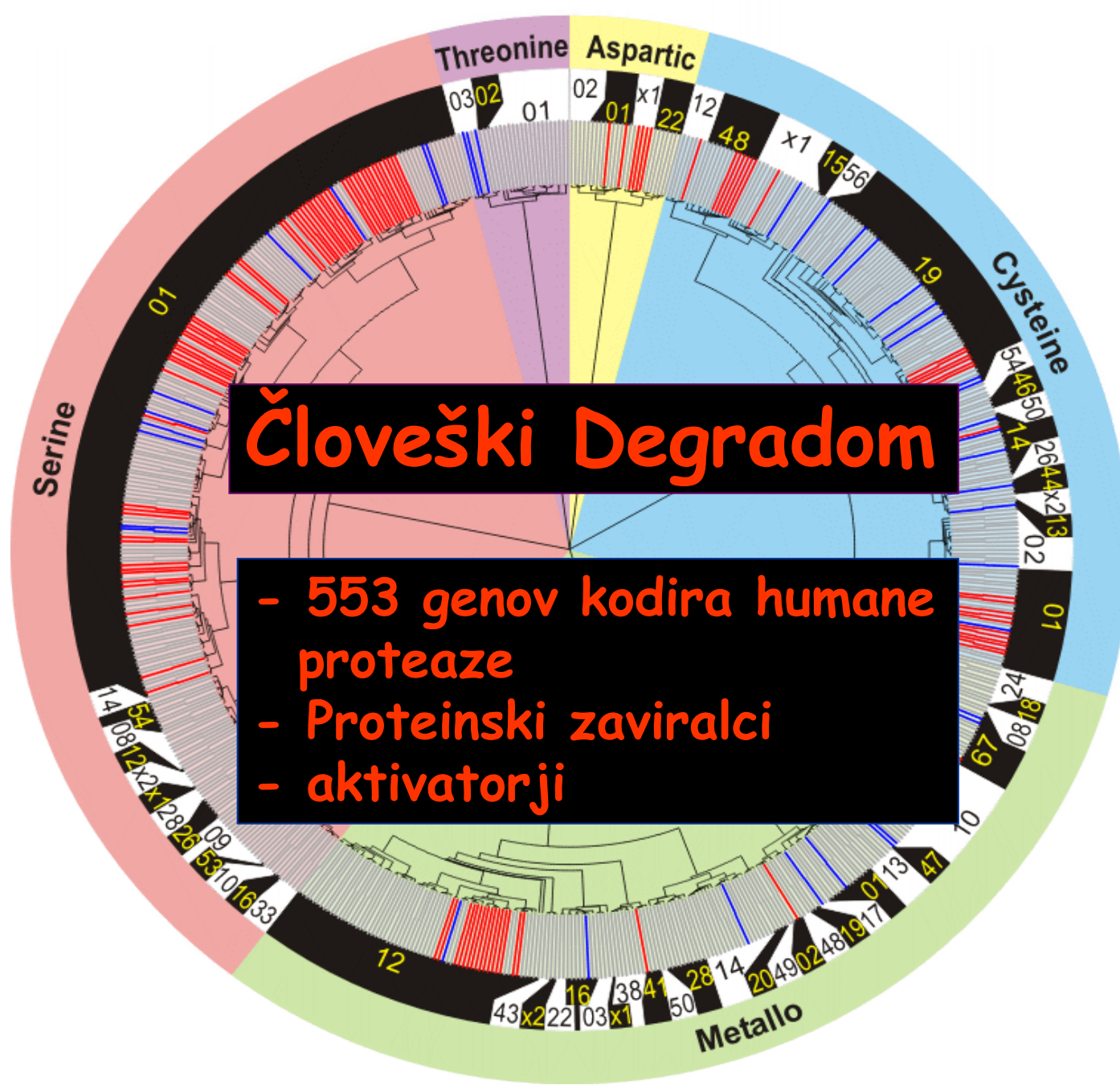
# Proteolizni encimi razgrajujejo peptidno vez



# Proteolizni encimi razgrajujejo peptidno vez

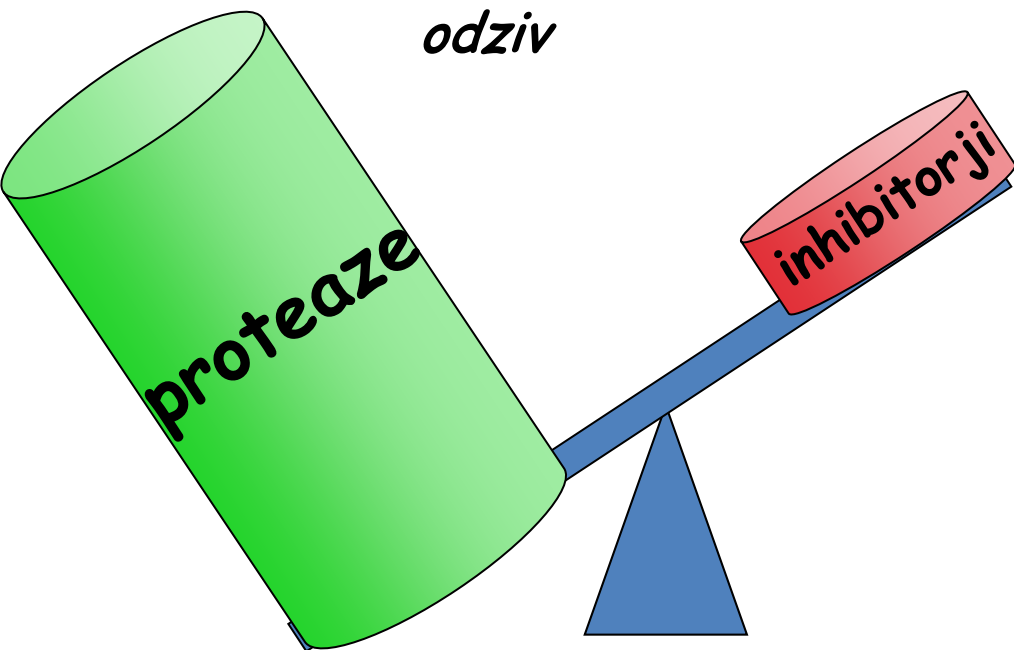




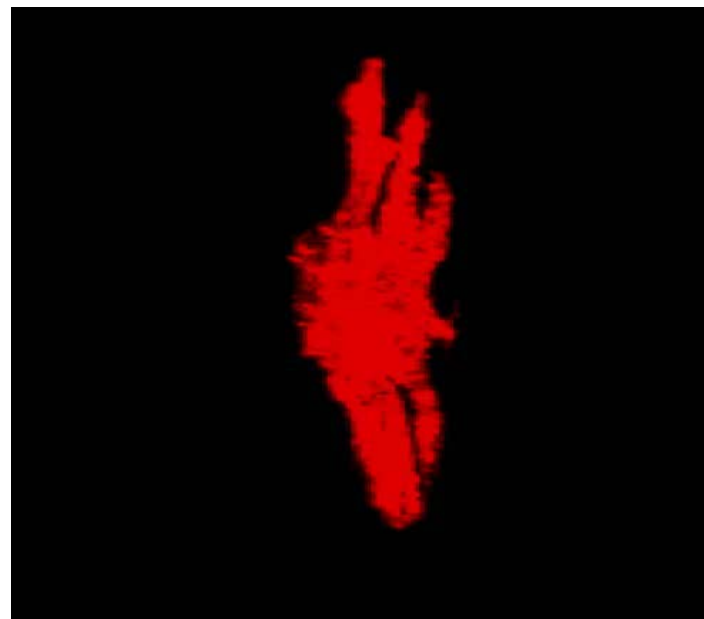


# Porušeno proteolitsko ravnotežje v tumorski celici

*Celični cikel*  
*Proliferacija*  
*Apoptoza*  
*Protitumorski imunski odziv*

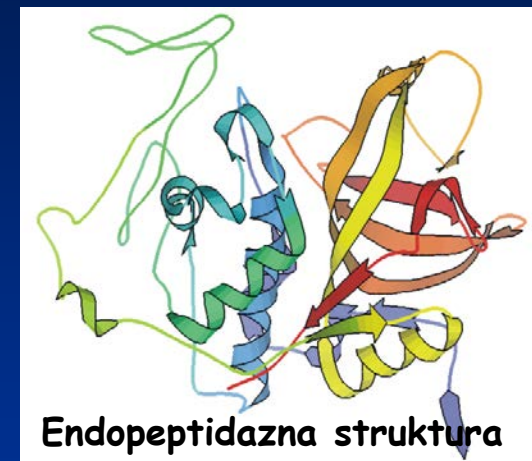
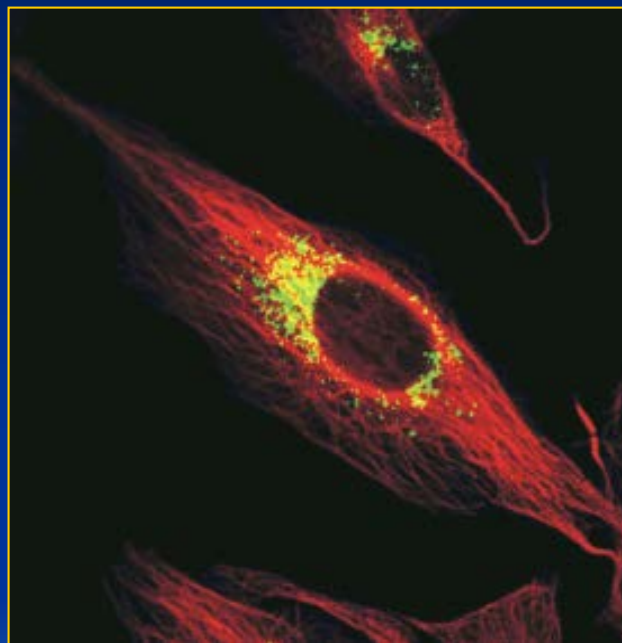
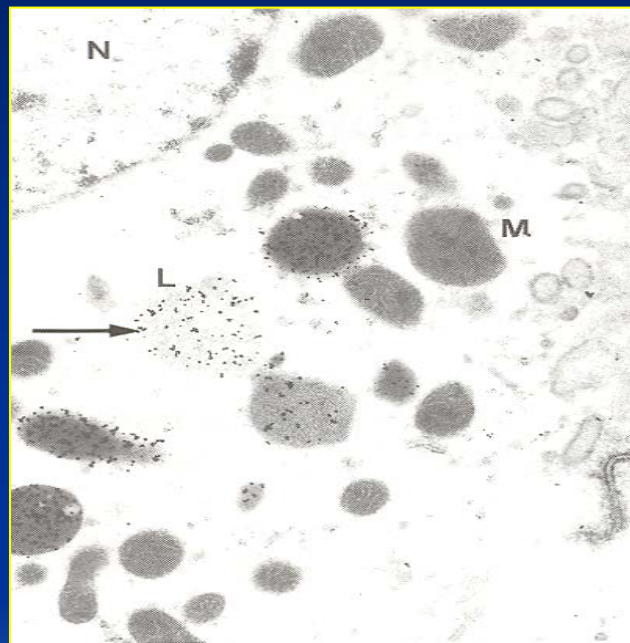


Tumorske celice



Povečana aktivnost katepsina B

# Katepsin B - proteaza, ki pospešuje napredovanje raka

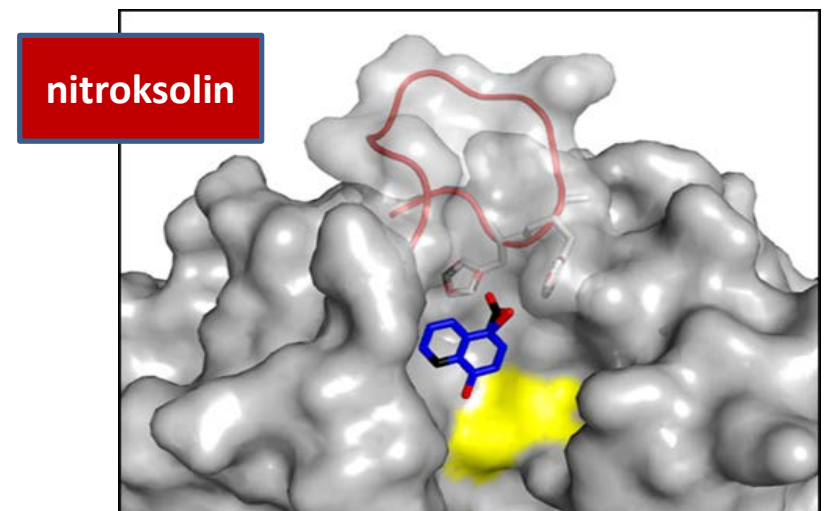
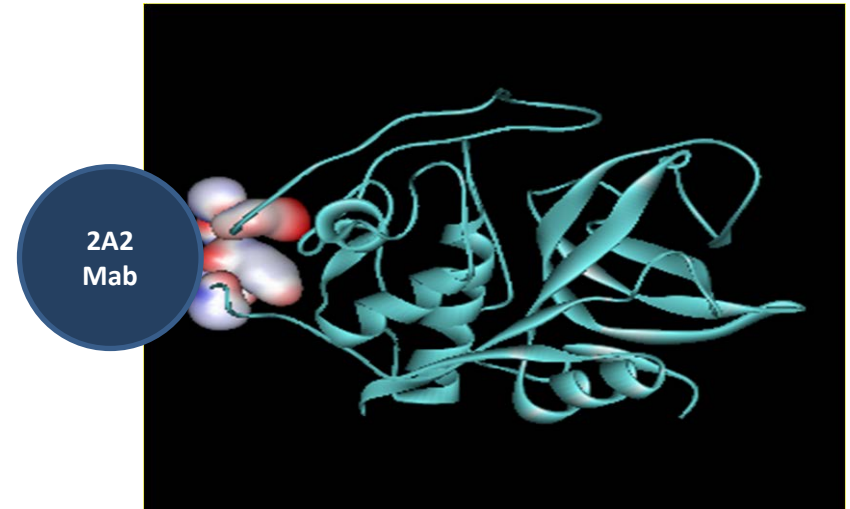
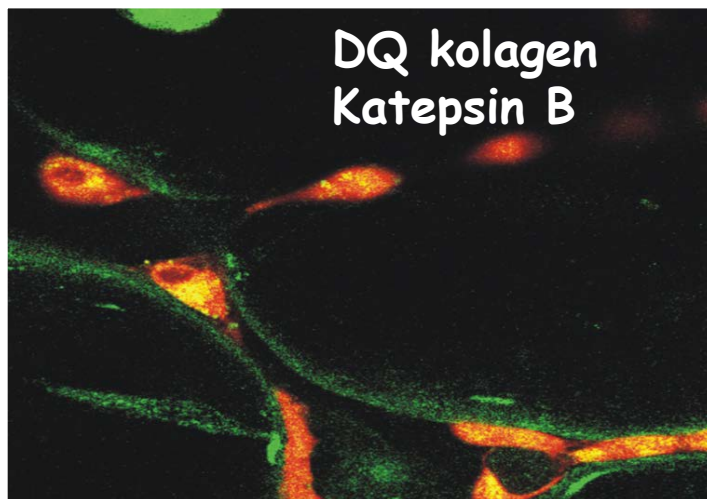
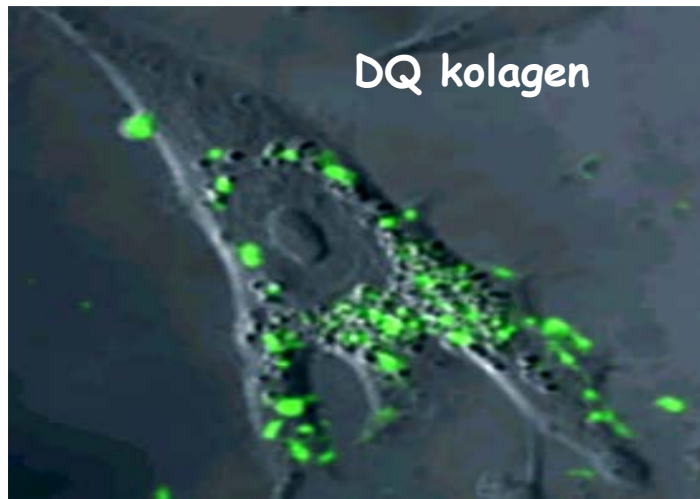


Elektronska mikroskopija katepsina B v normalnih celicah

*Katepsin B v celicah HUVEC*

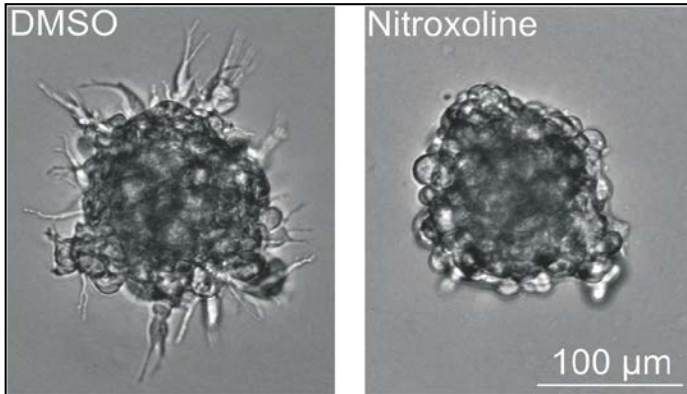
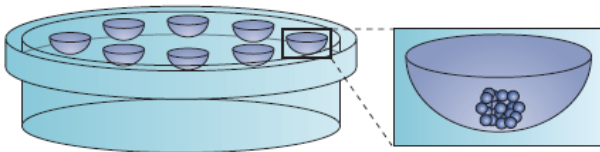


# Katepsin B razgrajuje zunajcelični matriks, kar vodi do migracije, invazije in metastaziranja tumorskih celic

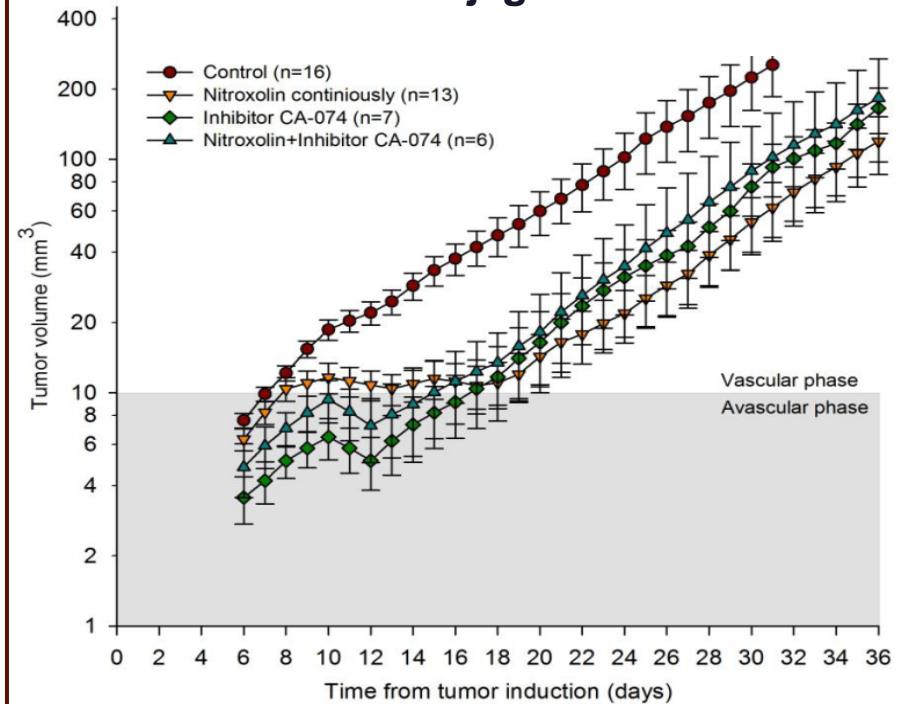


# Nitroksolin zavre rast in metastaziranje tumorjev in vitro in in vivo

## 3D *in vitro* model tumorske invazije

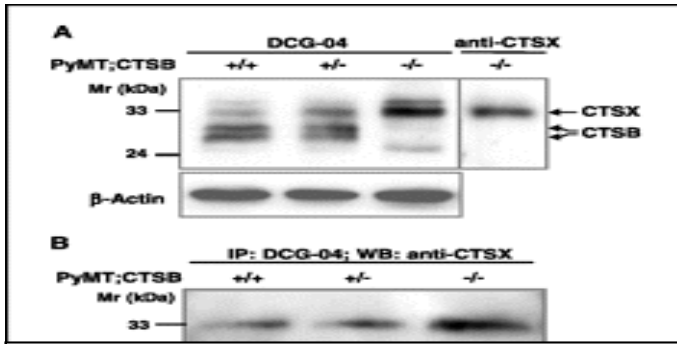


## LPB model mišjega fibrosarkoma

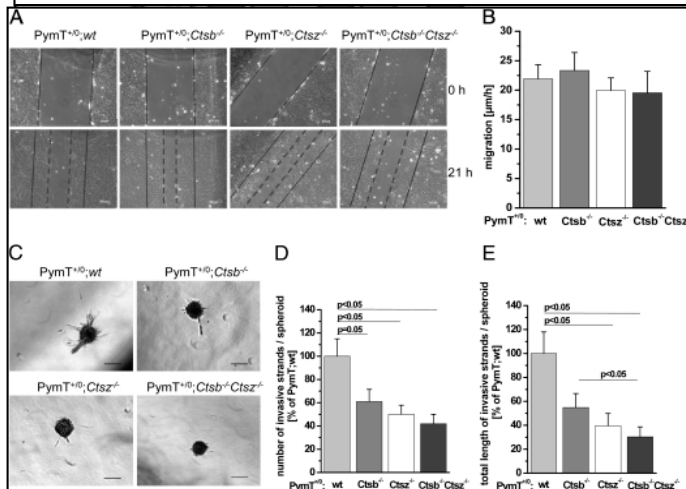
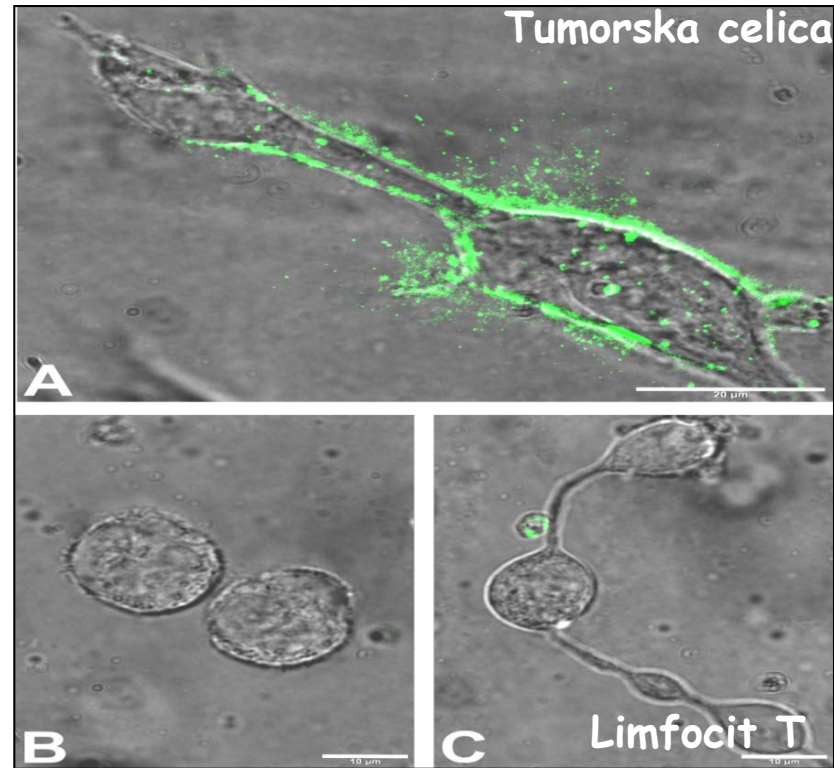


# Resistenca tumorskih celic na zmanjšanje aktivnosti katepsina B

Povečano izražanje katepsina X!

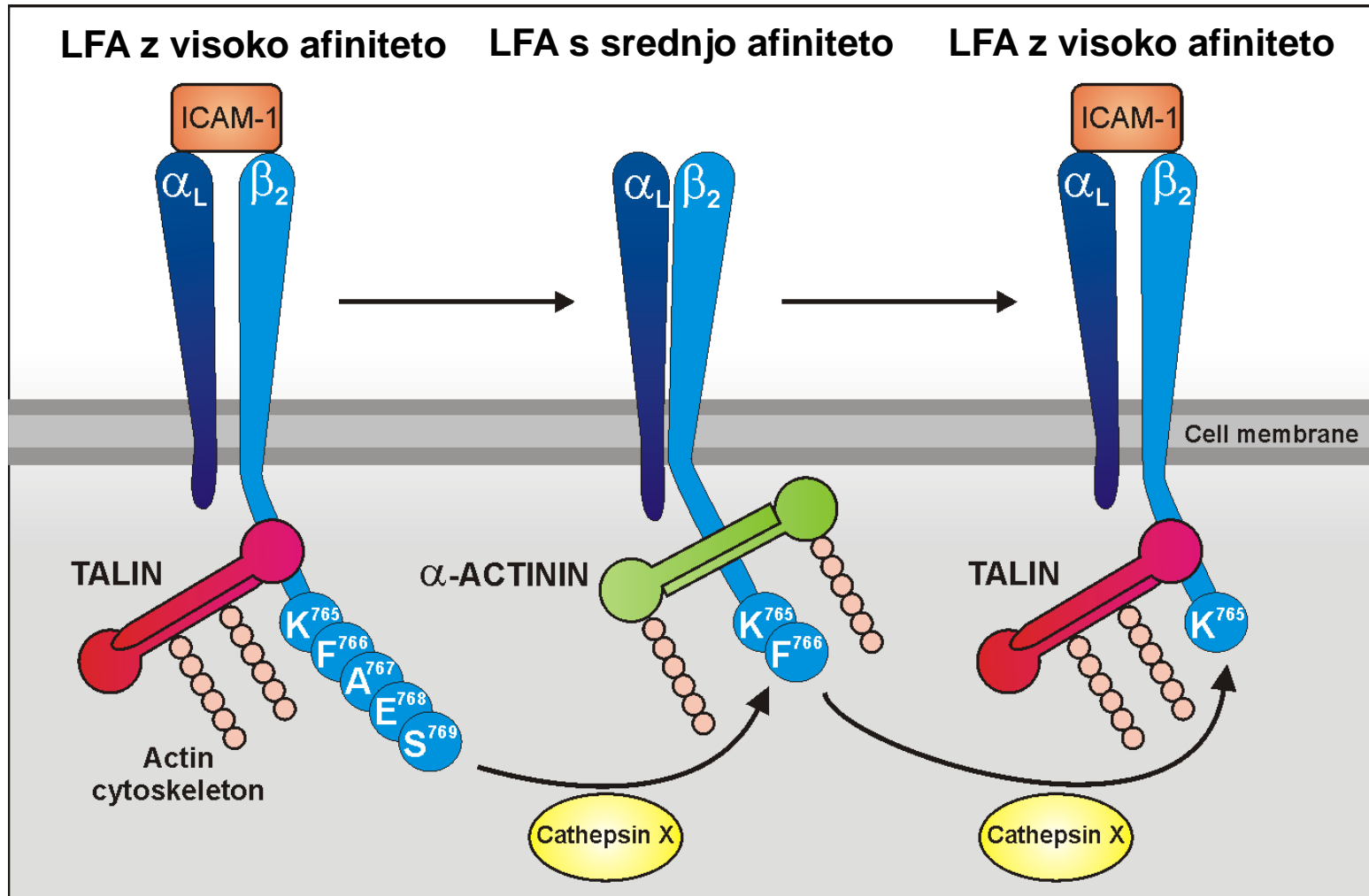


Vasiljeva et al., Cancer Res. 2006



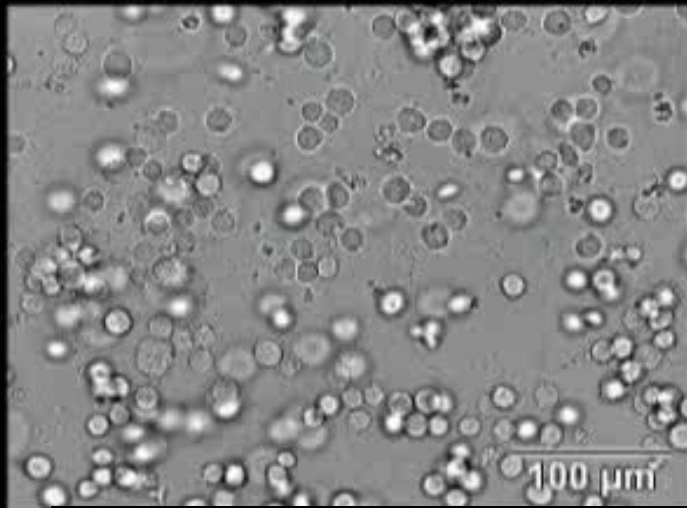
Sevenich et al., PNAS 2010

# Katepsin X razgrajuje beta-2 verigo integrinskih receptorjev

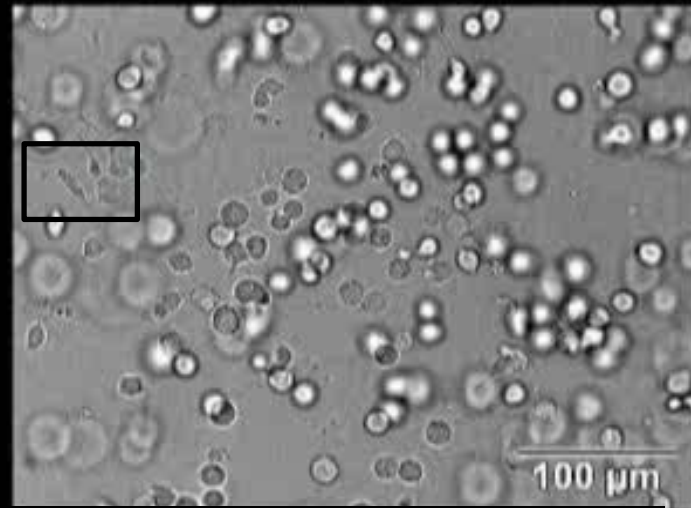


# Katepsin X, nadizražen v limfocitih T

MATRIGEL



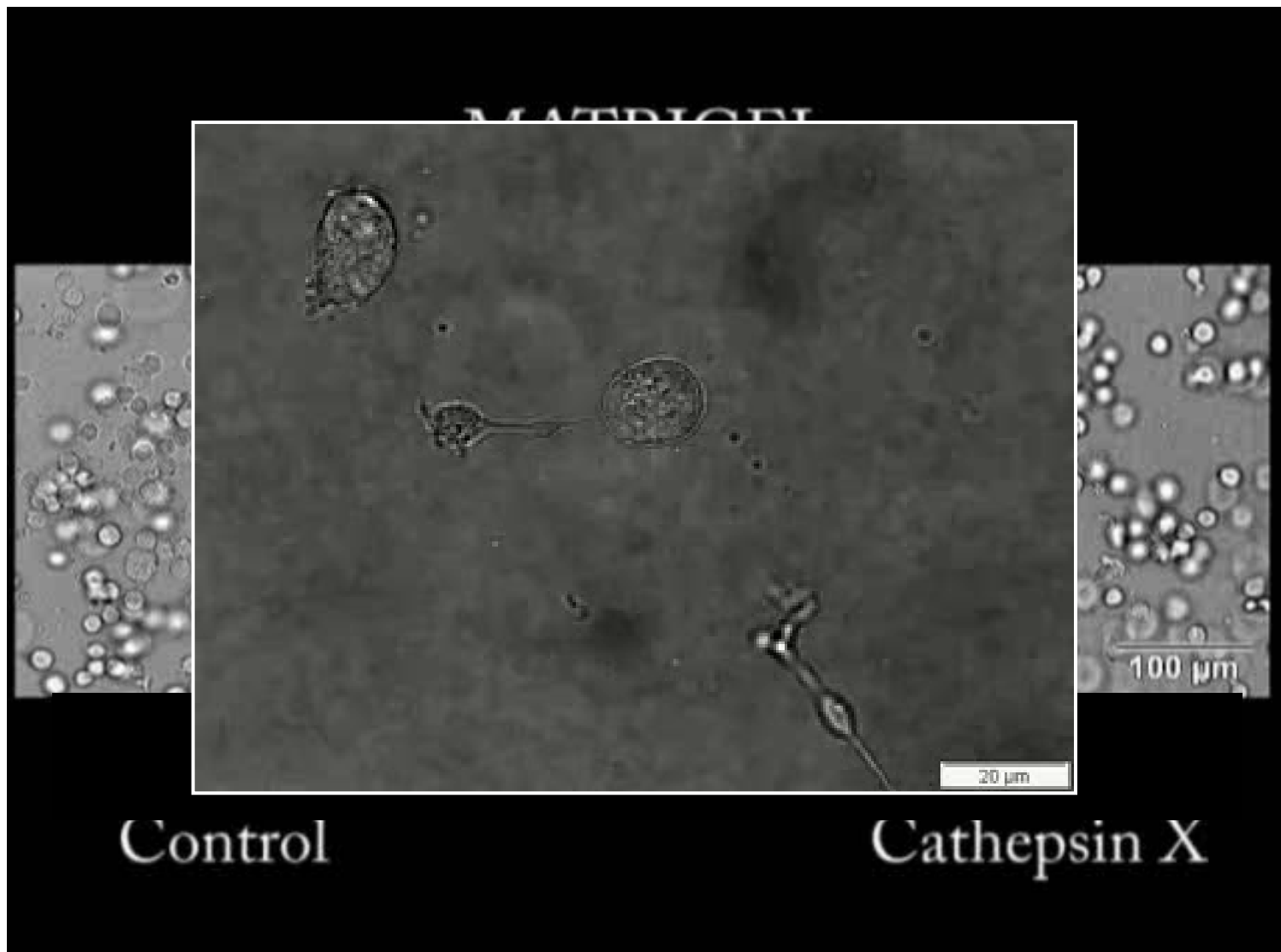
Control



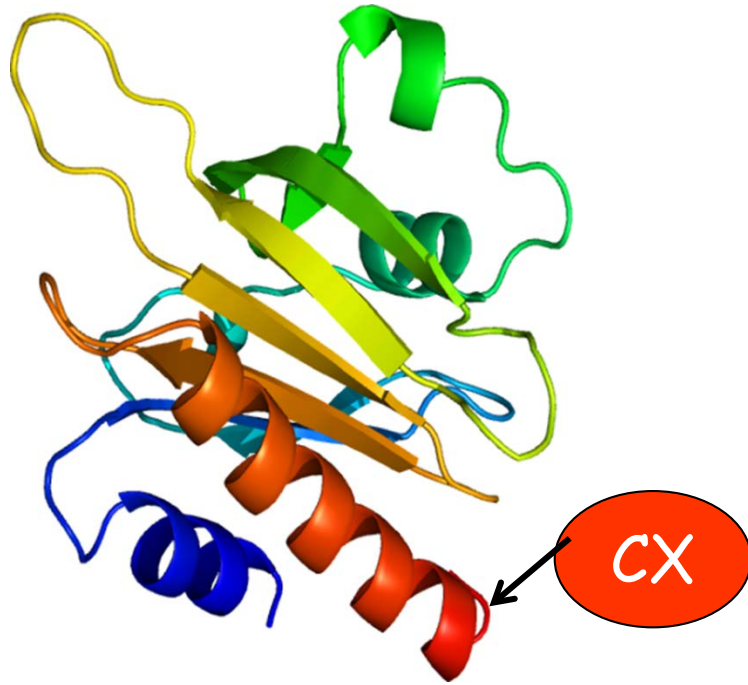
Cathepsin X



# Katepsin X, nadizražen v limfocitih T



# Katepsin X cepi profilin 1



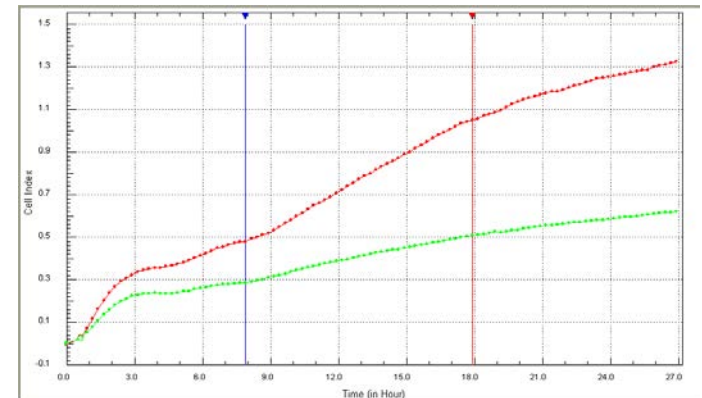
Poly-L-proline vezavno mesto (klatrin, huntingtin, PI - fosfoinozididi)

Vezava ligandov prepreči migracijo tumorskih celic.

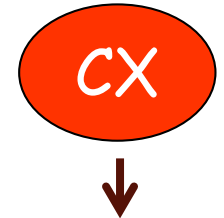
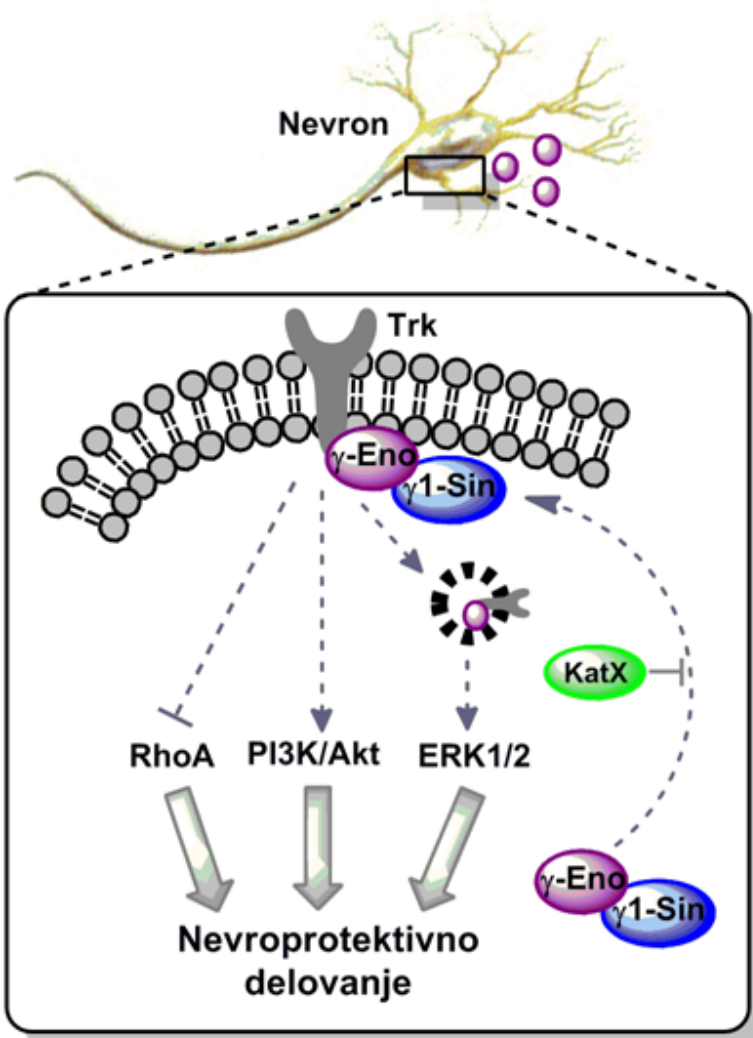
Tumorski supresorski protein  
Uravnava delovanje aktina.

Katepsin X s cepitvijo  
poveča migracijo tumorskih celic

Inhibitor katepsina X AMS36  
zmanjša migracijo PC3 celic

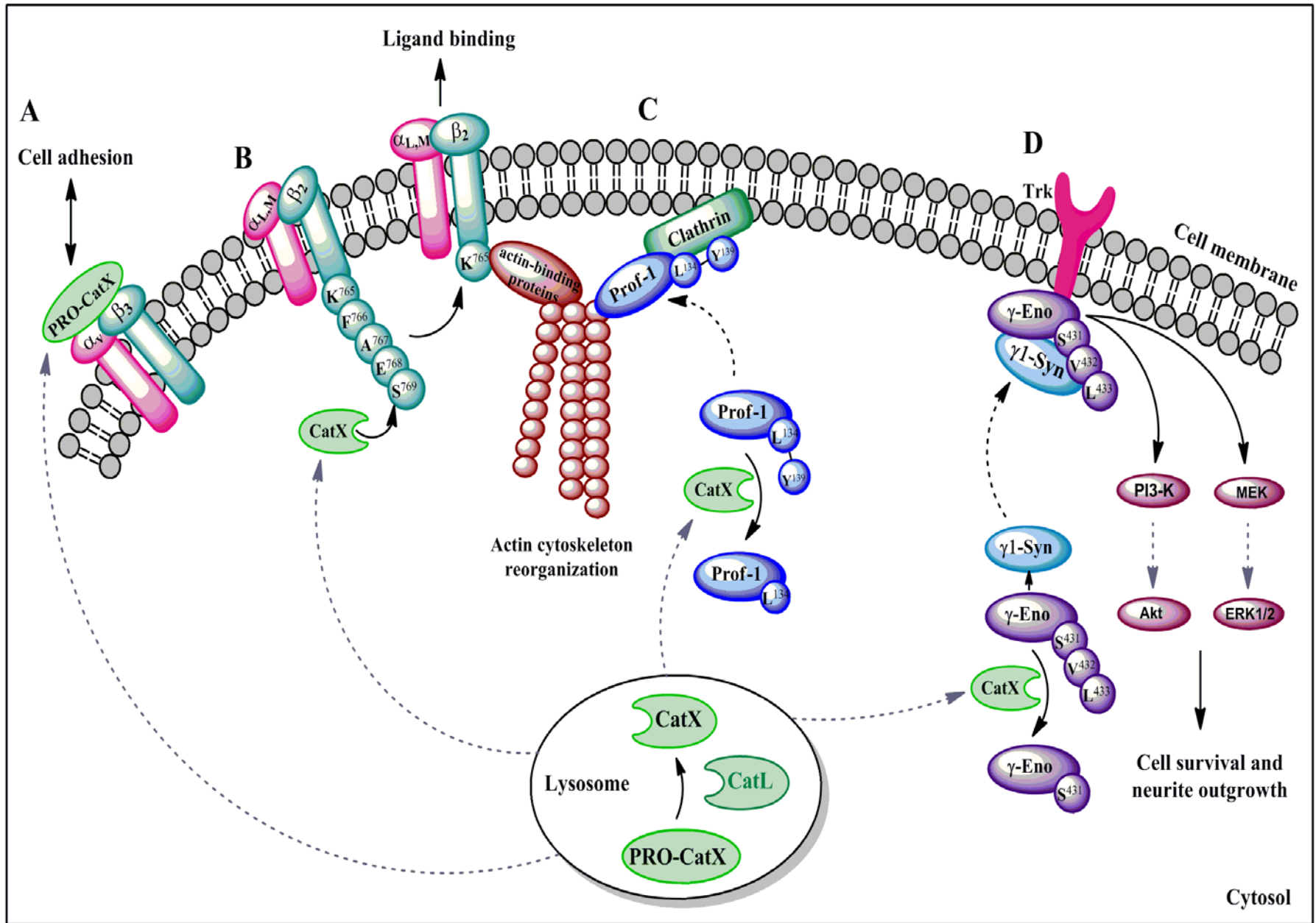


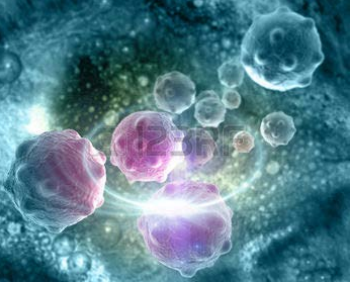
# Katepsin X cepi gama enolazo



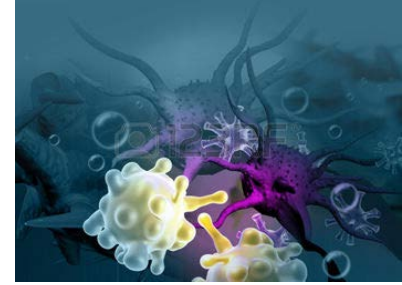
$\gamma$ -enolaza..DEARFAGHNFRNPSVL

- C konec gama enolaze poseduje dodatno aktivno mesto, ki povečuje preživetje nevronskih celic in nevroitogenezo celic
- V tumorskih celicah enolaza pospešuje presnovo glukoze v anaerobni in aerobni glikolizi (predzadnja stopnja - fosfoglicerat v fosfoenolpiruvat) (**Warburgov efekt**)





# Zaključki



- **Vzrok za rezistenco tumorskih celic na zaviralce aktivnosti katepsina B je povečano izražanje in aktivnost sorodne karboksipeptidaze katepsina X.**
- **Mehanizmi promocije raka so pri katepsinu X drugačni kot pri katepsinu B, rezultati pa podobni, to je povečana migracija, invazivnost in metastaziranje tumorskih celic. Katepsin X je dejavnik mezenhimsko –ameboidnega prehoda (MAT) tumorskih celic.**
- **Specifični zaviralci katepsina X lahko zmanjšajo napredovanje raka, zmanjšajo prekomerni imunski odziv in delujejo protektivno na nevronske celice.**



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## ARRS program: P4-0127:

Farmaceutvska biotehnologija: znanost  
za zdravje

ARRS projekti: J4-4123, J4-5529

EU projekti CancerDegradome,  
NanoPhoto