



**CELL GENESYS**

*Changing the Future of Oncology®*

**Metastatic Prostate Cancer Patients Treated with GVAX®  
Vaccine For Prostate Cancer Develop Immunoreactivity to  
Filamin: Role of Filamin in Prostate Cancer Metastasis**

Chinnappa M., Wong L., Aimi J., DeNagel D., Husak P., Sacks N., Borellini F.

# GVAX<sup>®</sup>: PROSTATE CANCER IMMUNOTHERAPY

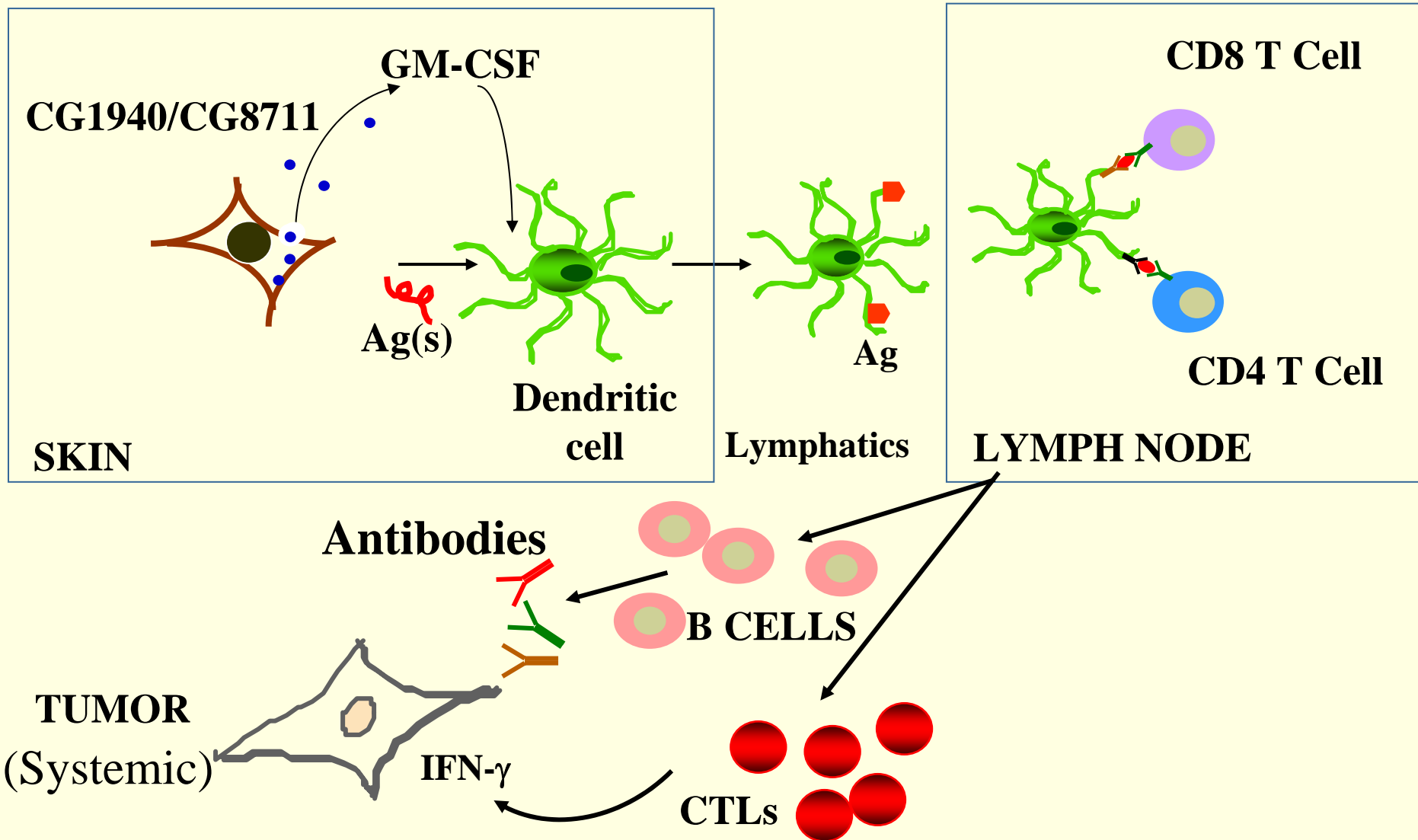


- ✦ Allogeneic whole cell immunotherapy for prostate cancer
- ✦ **CG1940 and CG8711**  
PC3 and LNCaP tumor cells, genetically modified to secrete GM-CSF, irradiated for safety, and injected intradermally into patients
- ✦ Phase 3 clinical trials are ongoing in patients with metastatic hormone refractory prostate cancer



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# GVAX<sup>®</sup> : MECHANISM OF ACTION

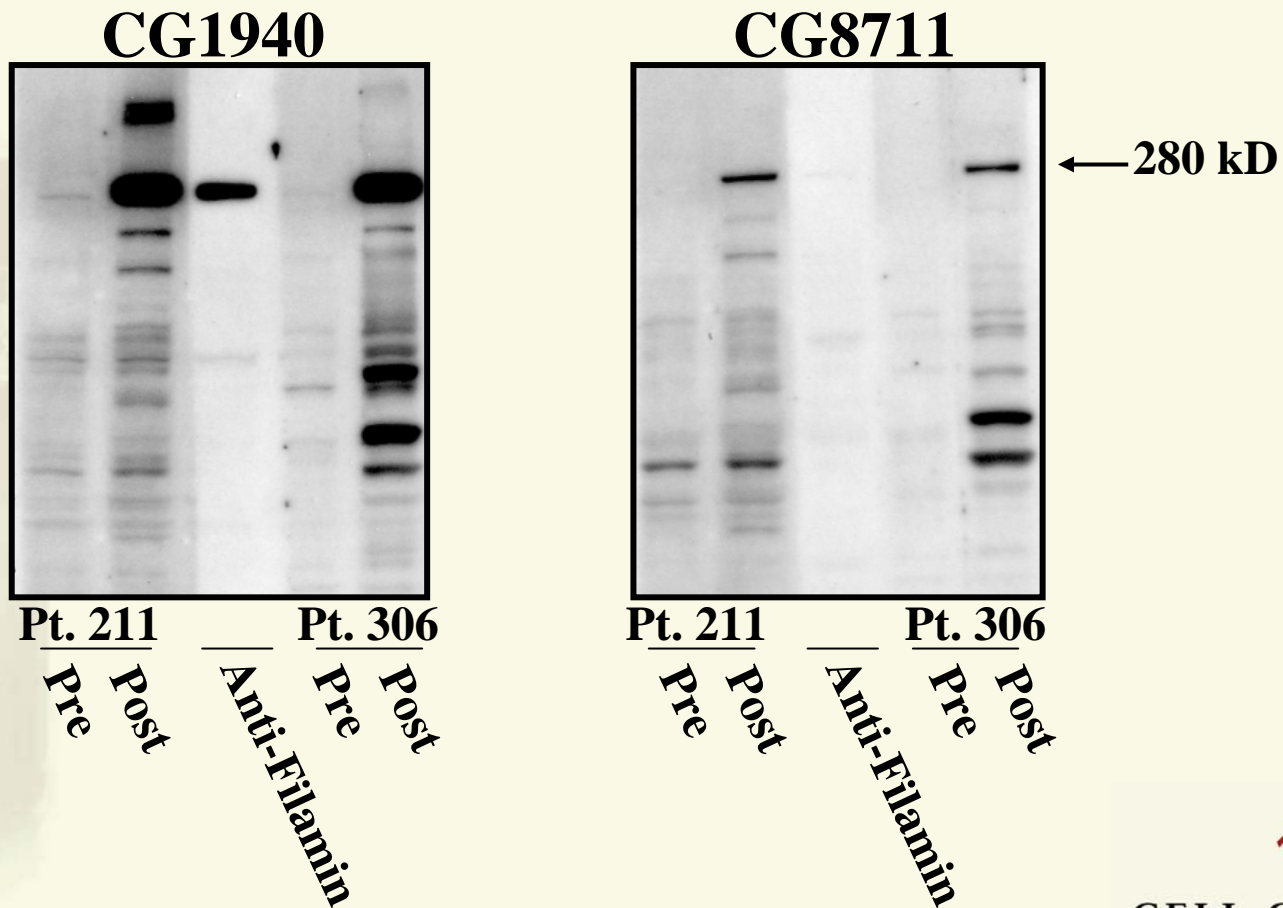


# IDENTIFICATION OF FILAMIN FROM EARLY STUDIES

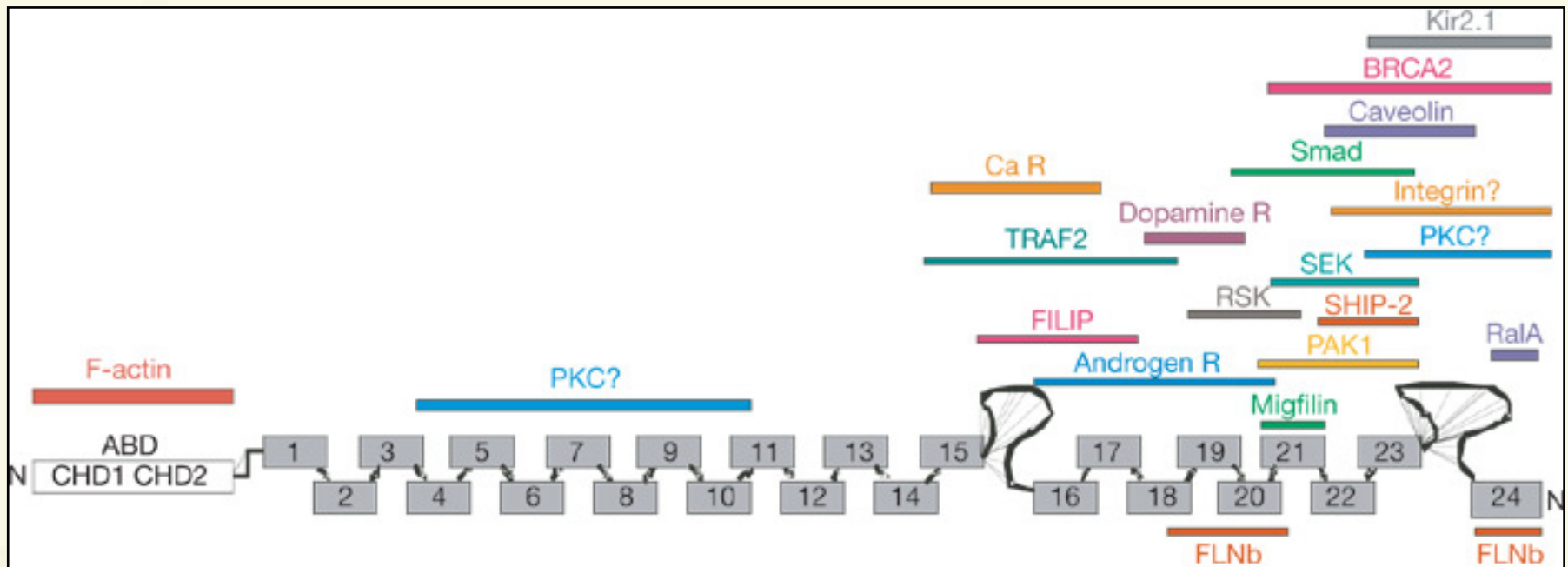
- ★ In a Phase 2 trial, sera from 17/59 patients immunized with GVAX<sup>®</sup> vaccine for prostate cancer, reacted positively in Western Blots to a ~280 kD band in vaccine cell lysates
  - A favorable survival trend was observed in reactive patients compared with non-reactive patients ( $p = 0.09$ )
- ★ Post-immunization serum from one complete responder was reactive to multiple proteins in lysates
  - One major seropositive protein was identified as  $\beta$ -Filamin by mass spectrometry



# PATIENT SERA IMMUNOREACT WITH VACCINE CELL LYSATES



# FILAMIN STRUCTURE

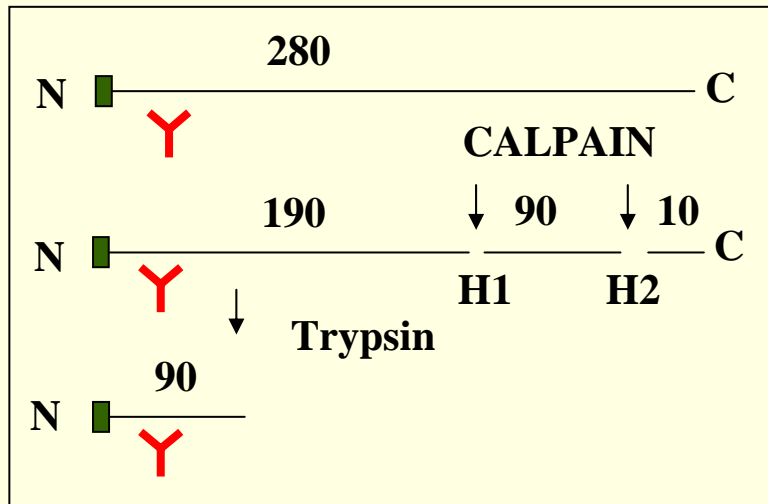


Yuanyu et al., Nature Cell Biology Volume 6, 2004.

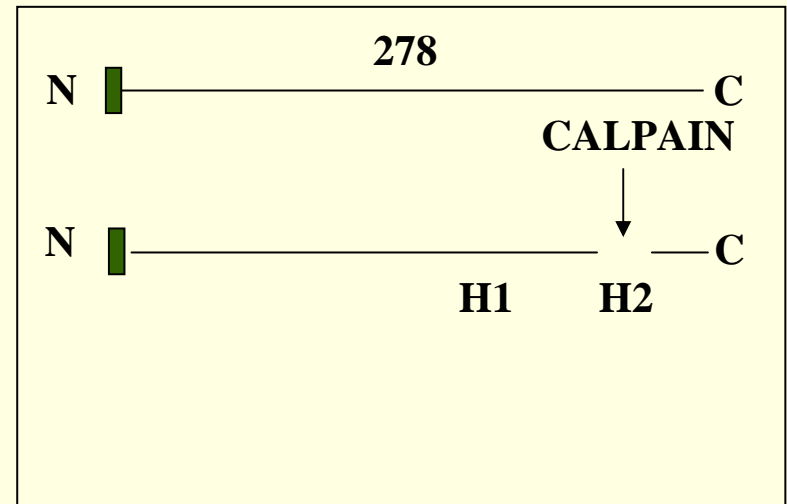


# NON-MUSCLE FILAMIN ISOFORMS

## $\alpha$ -Filamin (ABP-280)

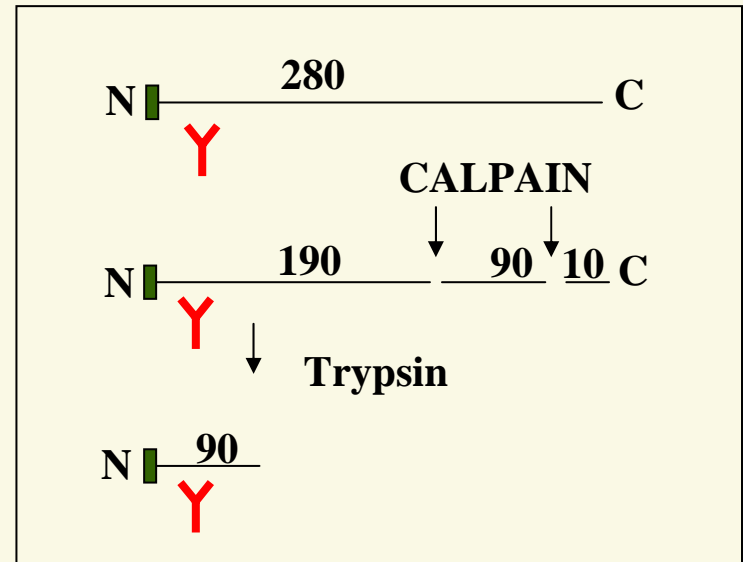
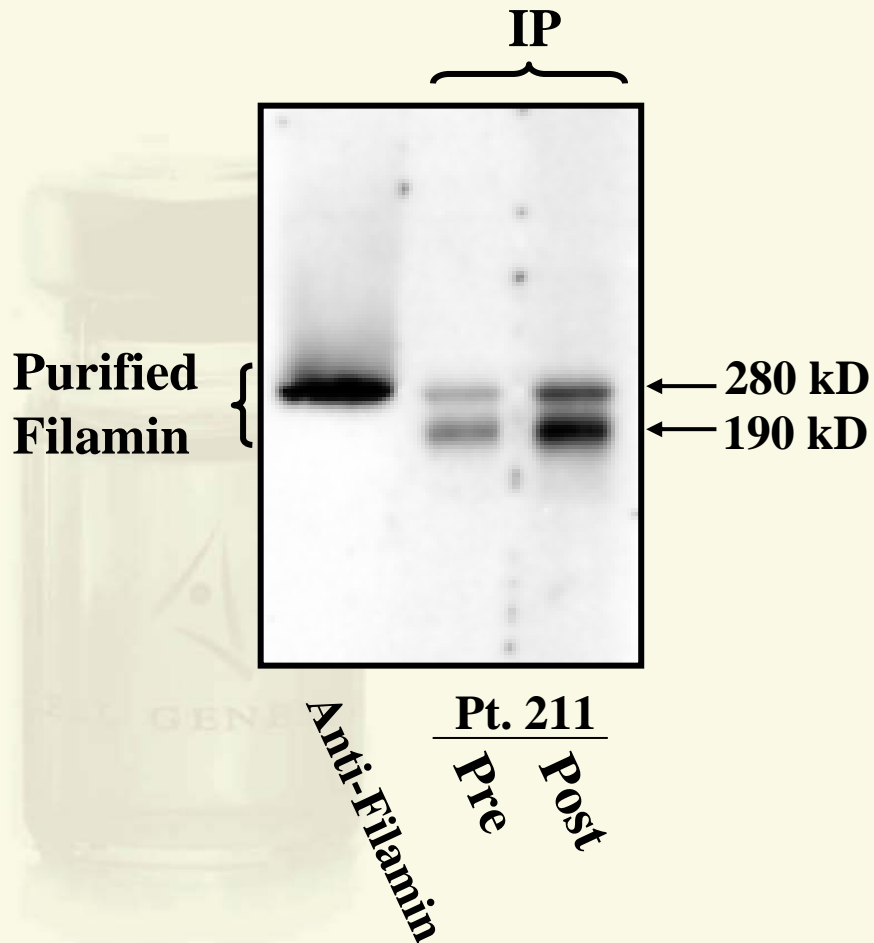


## $\beta$ -Filamin (ABP-278/276)



- ✦ 70% homologous excluding hinge domains
- ✦ H1 is unique and H2 is 44% homologous
- ✦ Both filamin isoforms are proteolytically processed by Calpain

# PATIENT SERUM REACTS TO IMMUNOPRECIPITATED FILAMIN





# FILAMIN EXPRESSION IN PROSTATE CELL LINES CORRELATES WITH METASTATIC POTENTIAL

## LNCaP

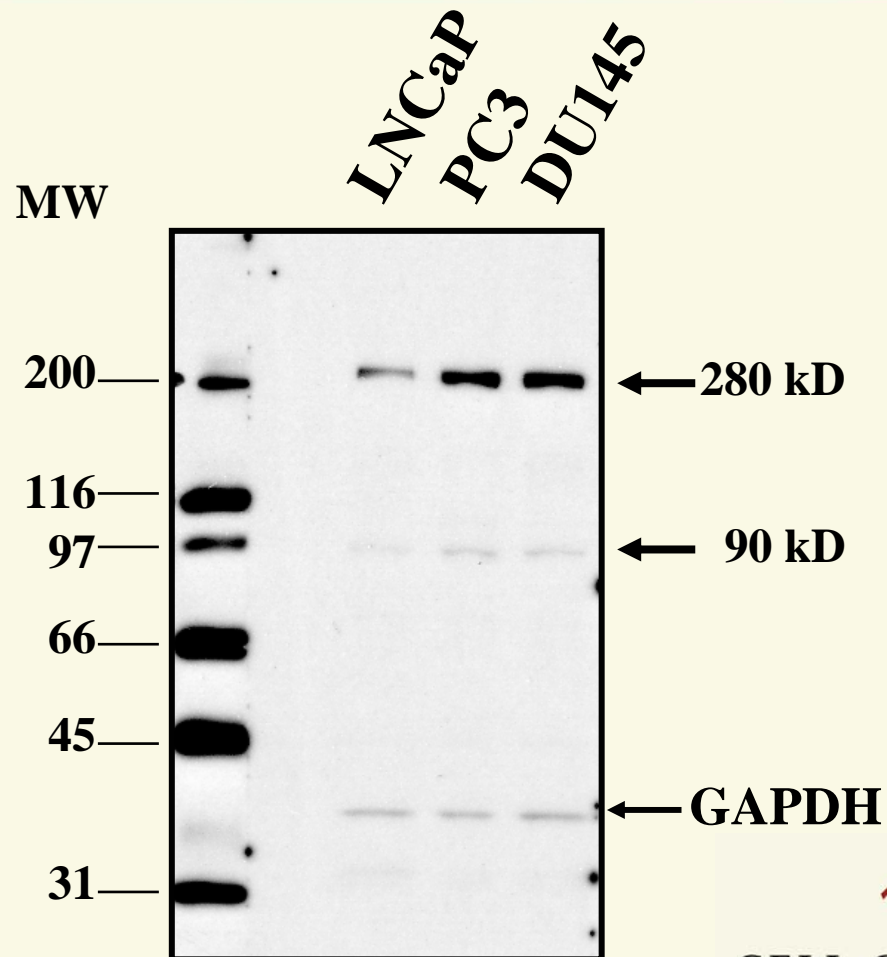
Carcinoma derived from lymph node metastasis

## PC3

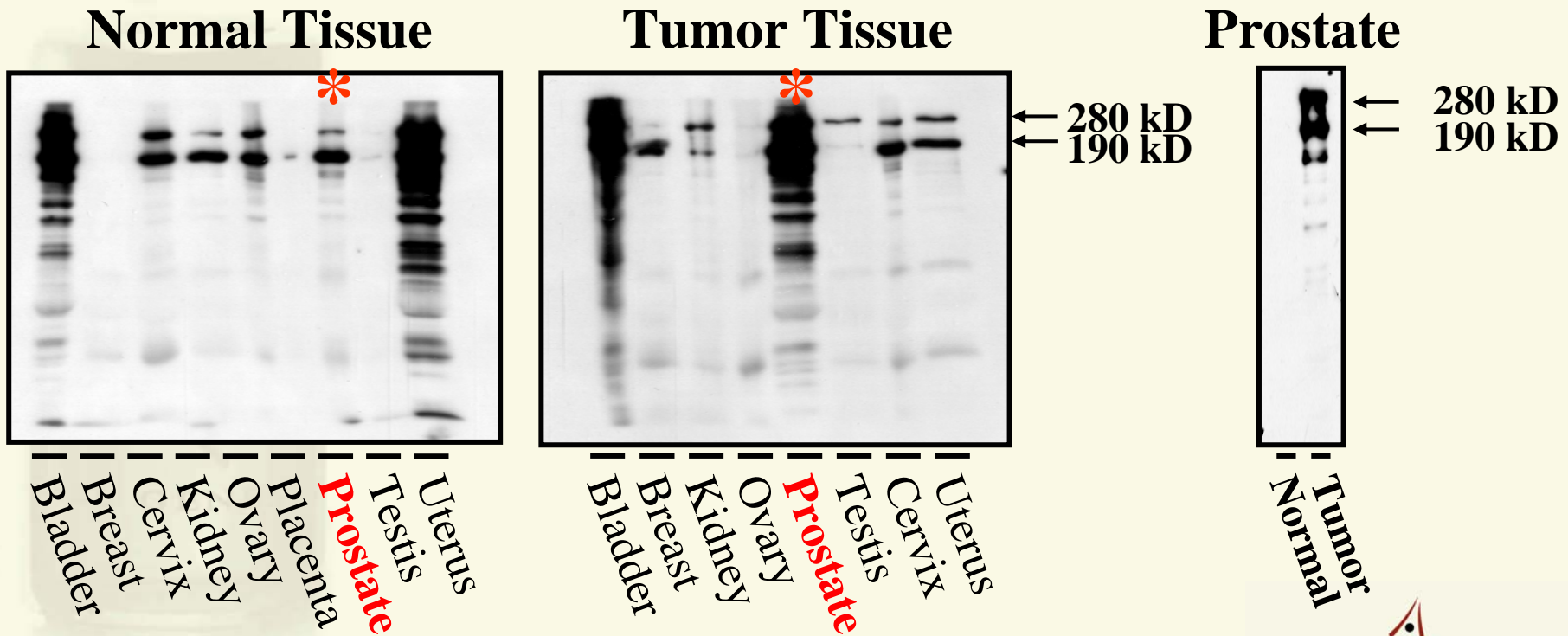
Stage IV prostate adenocarcinoma derived from bone metastasis

## DU145

Prostate carcinoma derived from brain metastasis



# FILAMIN IS OVEREXPRESSED IN PROSTATE TUMOR TISSUE



# SUMMARY

- ✦ Sera from two patients immunized with GVAX<sup>®</sup> reacts with Filamin
  - ✦  $\beta$ -Filamin by mass spectrometry
  - ✦  $\alpha$ - and/or  $\beta$ -Filamin by antibody reactivity
- ✦ Filamin is over-expressed in prostate tumor compared to normal prostate tissue
- ✦ Filamin expression is higher in PC3 and DU145 cells compared to LNCaP correlating with the metastatic potential of these cell lines





# **WHAT IS THE POTENTIAL ROLE OF FILAMIN IN CANCER METASTASIS?**



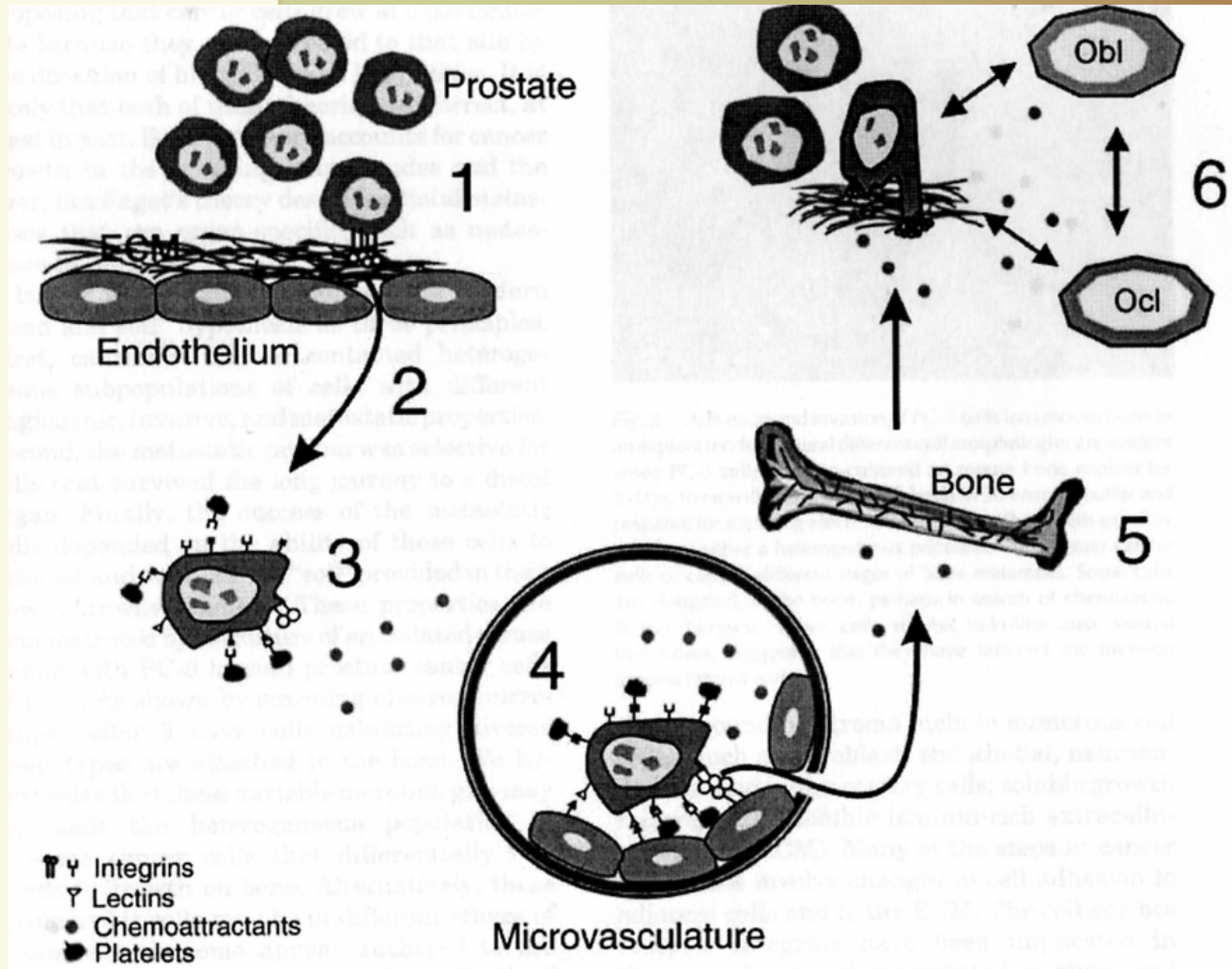
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# FILAMIN AND CALPAIN: ROLE IN CANCER MOTILITY

- $\alpha$ -filamin and tissue factor interact in tumor cell migration  
(Ott et al., The Journal of Cell Biology, 1998)
- Calpain cleavage of adhesion and actin binding proteins are implicated in prostate cancer motility  
(Mamoune et al., Cancer Research, 2003)  
(Rios-Doria et al., JBC 2003 and Cancer Research, 2004)

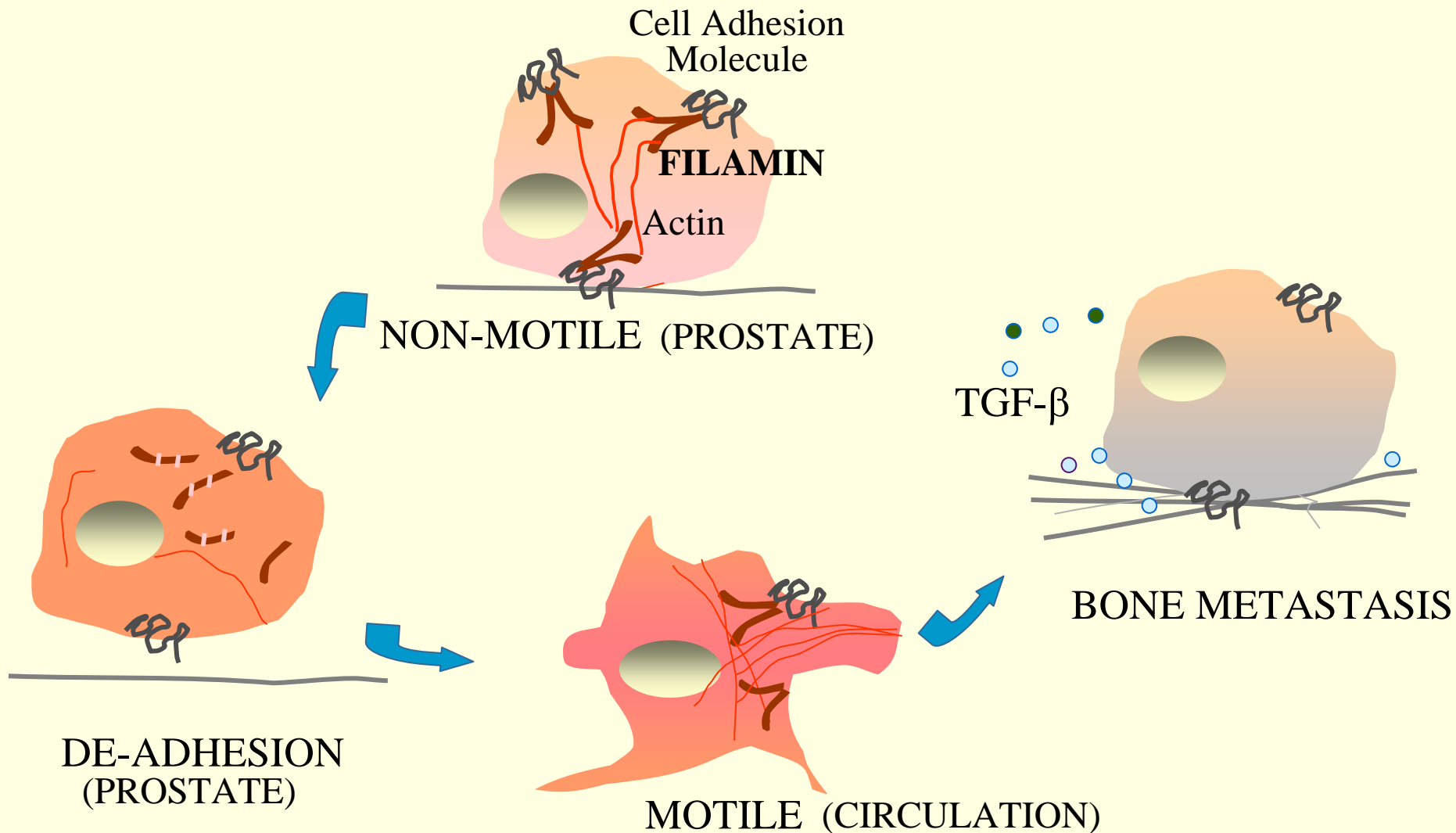


# STEPS IN PROSTATE CANCER METASTASIS TO BONE



Journal of Cellular Biochemistry 91, 2004.

# WORKING MODEL FOR THE ROLE OF FILAMIN IN PROSTATE METASTASIS



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