30th European Congress of Pathology
Pathology: Path to Precision medicine
8 – 12 September 2018, Bilbao, Spain

European Society of Pathology

eIF6 is overexpressed in melanoma of the skin and might be a novel therapeutic target

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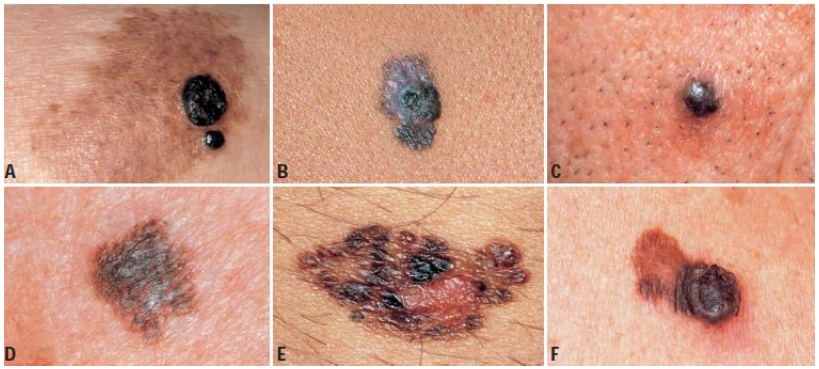
Disclosure:

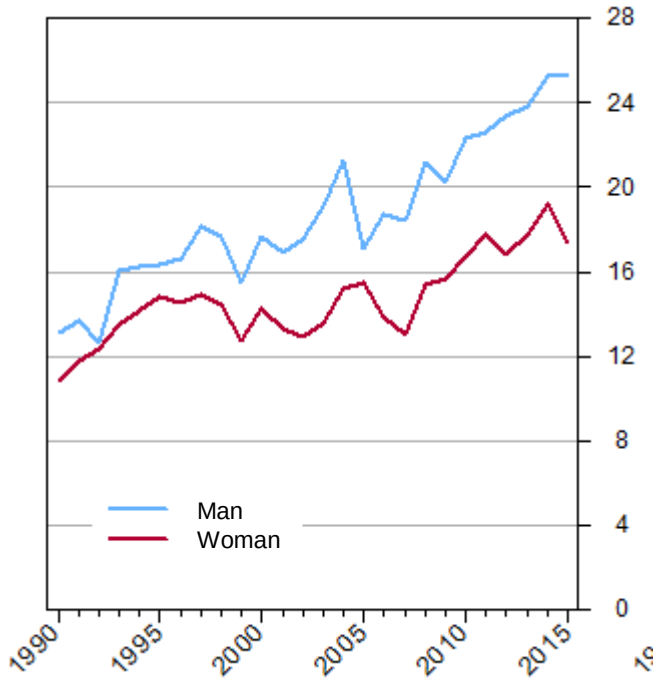
Nothing to declare

No conflict of interest

Melanoma: General

- Incidence rates are still increasing (21/100 000)
- Commonly diagnosed in relatively young people



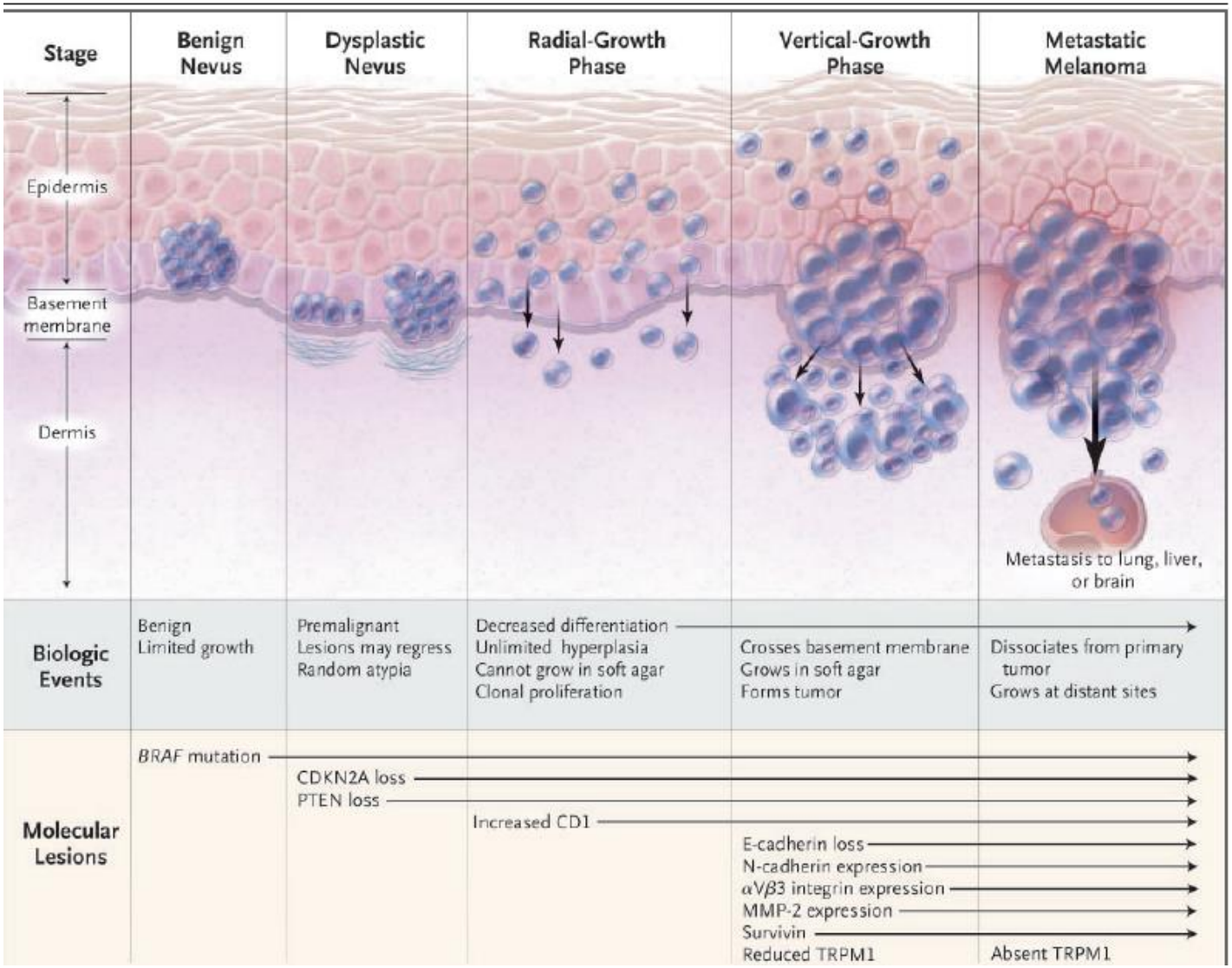


LeBoit et al, *Pathology and Genetics of Skin Tumours (WHO), 2006*

Statistik Austria, 30.08.2018

Skin melanoma: General

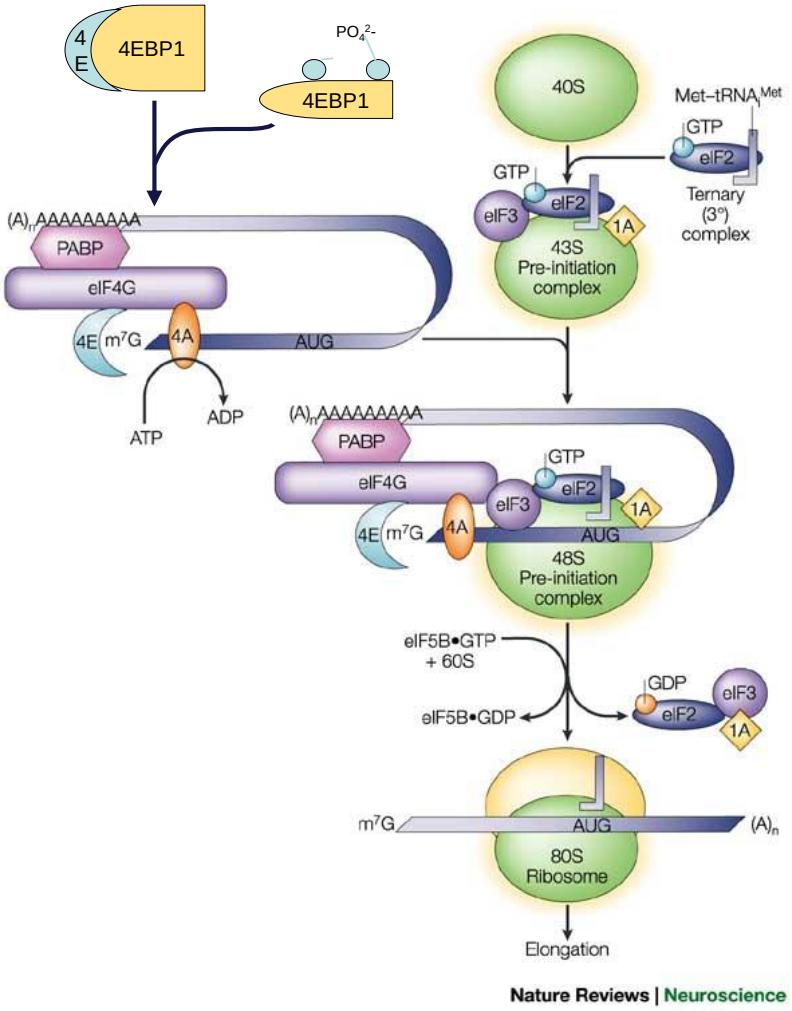
Formation and development of melanoma



Miller et al, N Engl J Med, 2006

eIFs: General

Eukaryotic mRNA translation



Modified after Klann & Dever, Nature Reviews, 2004

- **12 core eIFs involved in translation initation**
- **Formation of 43S pre-initation complex**
  - eIF2, eIF3
- **Recognition of the 5`cap structure of mRNA**
  - eIF4F complex recognises m7G cap
- **5‘UTR scanning**
- **Recognition of the start codon (AUG)**
  - Association of eIF5
- **Recruitment of the 60S ribosome**
  - Hydrolysis of eIF2-bound GTP molecules
- **Formation of the 80S ribosome**
  - Release of eIFs
- **Elongation**

eIFs: Skin melanoma

Research focus in this field mainly focused on eIF2, eIF3 and eIF4 subunits so far

- **eIF4A1** is up-regulated in human melanoma cell lines in vitro

  (Eberle et al, Int. J. Cancer, 1997)

- **eIF4E** is overexpressed in a panel of melanoma cell lines

  (Zhang et al, Journal of Investigative Dermatology, 2015)

- **eIF3F** is decreased**,** overexpression inhibits translation initiation and induces apoptosis in melanoma cells *(Doldan et al, Mol Carcinog, 2008)*

- **eIF2α** expression is increased in melanomas and melanocytic nevi compared to normal tissues *(Rosenwald et al, American Cancer Society, 2003)*

- **eIF4E** is elevated in tumors of melanoma *(Yang et al, Oncology Reports, 2007)*

eIFs: Hypothesis

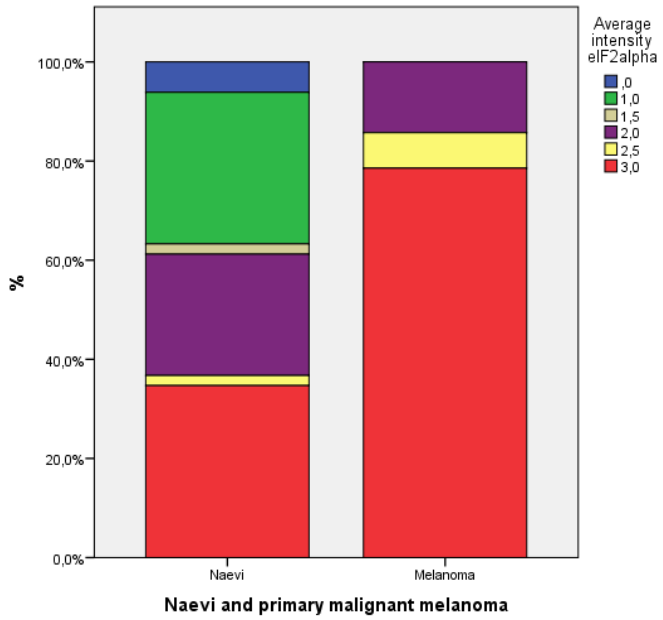
eIF6 is overexpressed in skin melanoma and represents a novel therapeutic target

Experimental Set-up

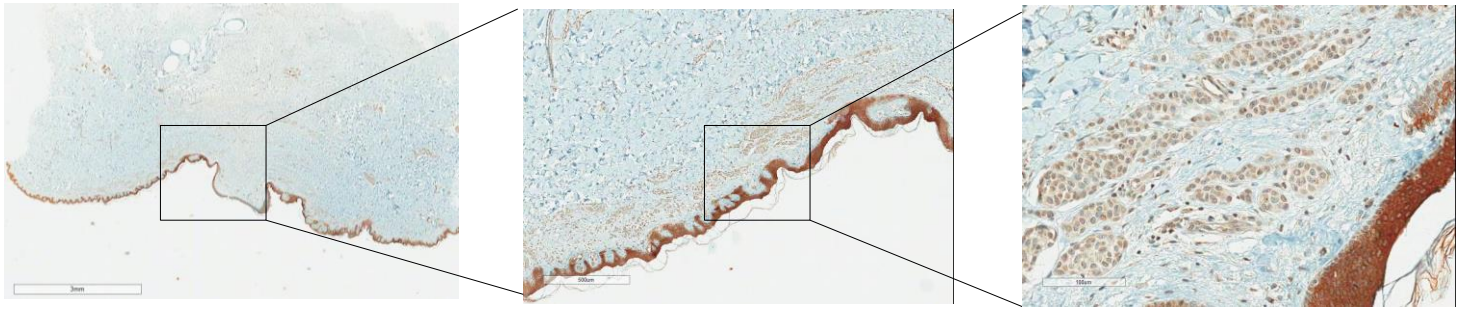
- **Patient-derived tumor samples**
  - eIF2α and eIF6 (Immunohistochemistry)
  - 62 patients - 13 melanoma and 49 benign naevi

- **siRNA knockdown of eIF6 *in vitro***
  - Four melanoma cell lines
    - MCM1 dln and LU1205 (metastatic)
    - MCM1 and WM793b (non-metastatic)
  - eIF6 knockdown verification on mRNA level
  - Migration & Invasion
  - Viability & Apoptosis assay

Results: Patient-derived tumor samples

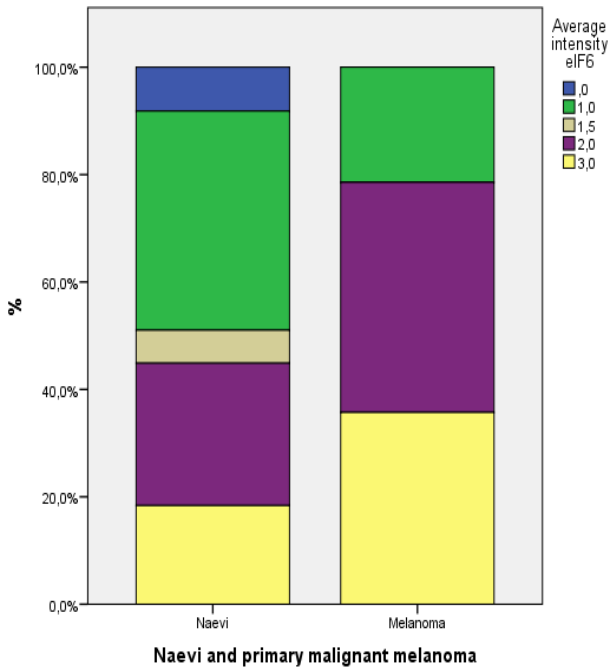


Variable	Sig.
eIF2α Intensity for malignant melanoma (primary and recurrent) vs. Naevi	0.013
eIF2α Intensity for malignant melanoma (primary) vs. Naevi	0.001

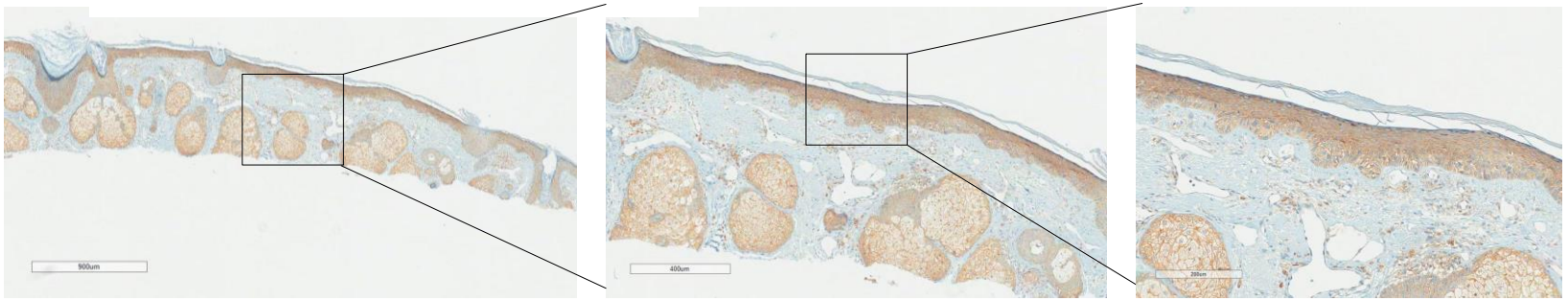


- **eIF2α** is significantly higher expressed in malignant melanoma

Results: Patient-derived tumor samples



Variable	Sig.
eIF6 Intensity for malignant melanoma (primary) vs. Naevi	0.034



- **eIF6** is significantly higher expressed in malignant melanoma

Summary

- Expression of eIF2alpha and eIF6 is significantly increased on protein level in skin melanoma compared to naevi
- siRNA-mediated knockdown of eIF6 reduced cell viability in metastatic and non-metastatic melanoma cell lines

eIF6 might be a novel therapeutic target for malignant melanoma of the skin

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Thank you for your attention!