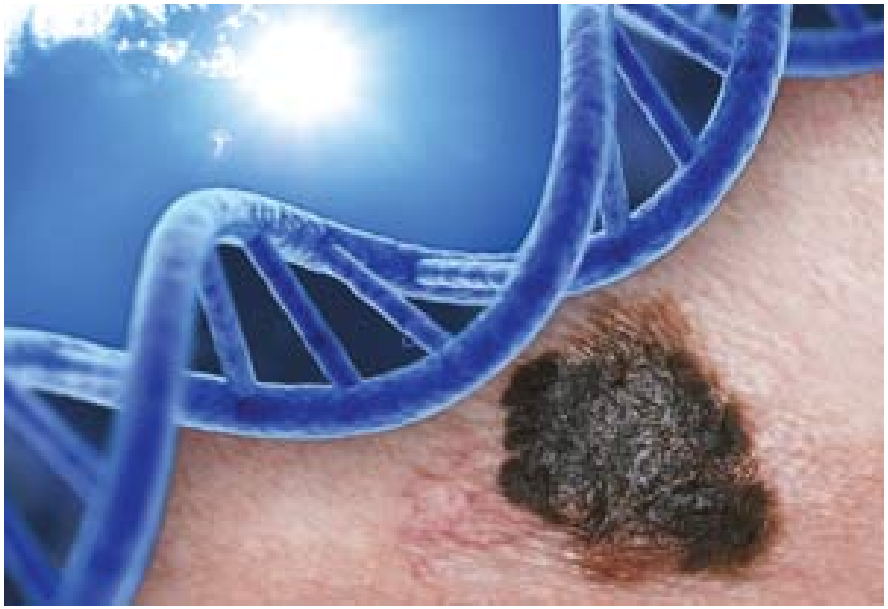
Regulation of melanocyte DNA repair by the melanocortin signaling axis



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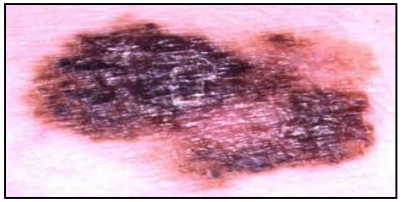
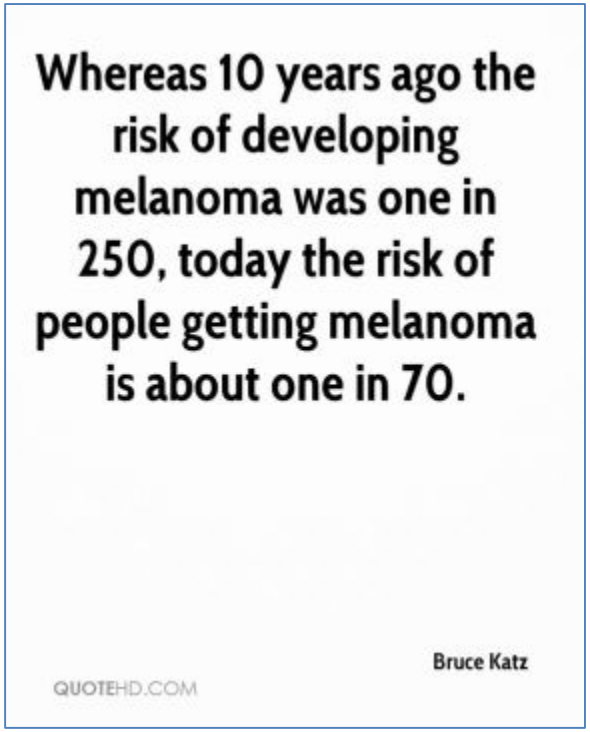
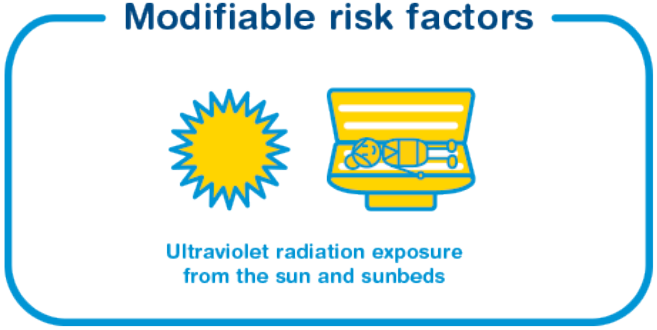
Melanoma

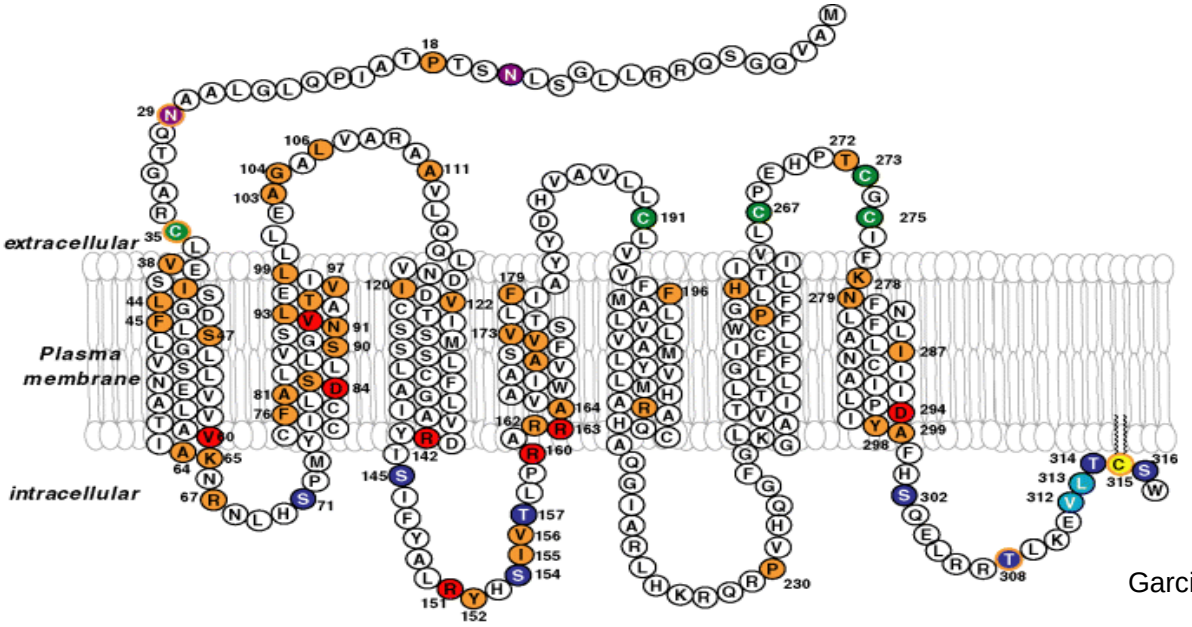


- Melanomas arise from malignant transformation of melanocytes
- Melanoma is the deadliest form of skin cancer
  - ~ 87,110 new cases (SEER, 2017)
  - ~ 9,730 deaths
  - Annually, $3.3 billion of skin cancer treatment costs are attributable to melanoma
- Genetic, phenotypic and environmental risk factors all contribute to melanoma predisposition
- UV exposure is a major risk factor
  - Intermittent UV exposure
  - Childhood sunburn





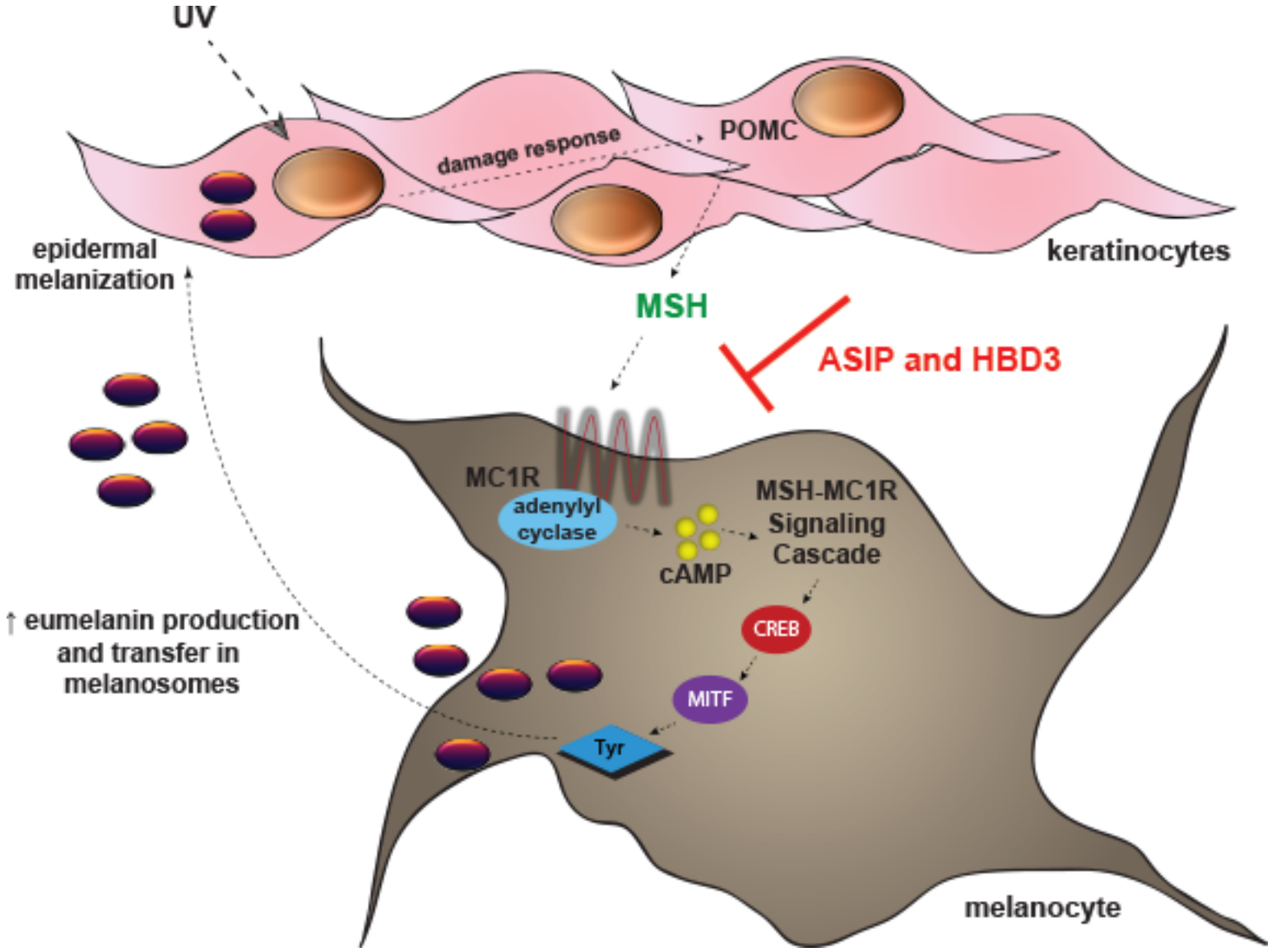
Melanocortin 1 Receptor (MC1R) - A melanoma susceptibility gene



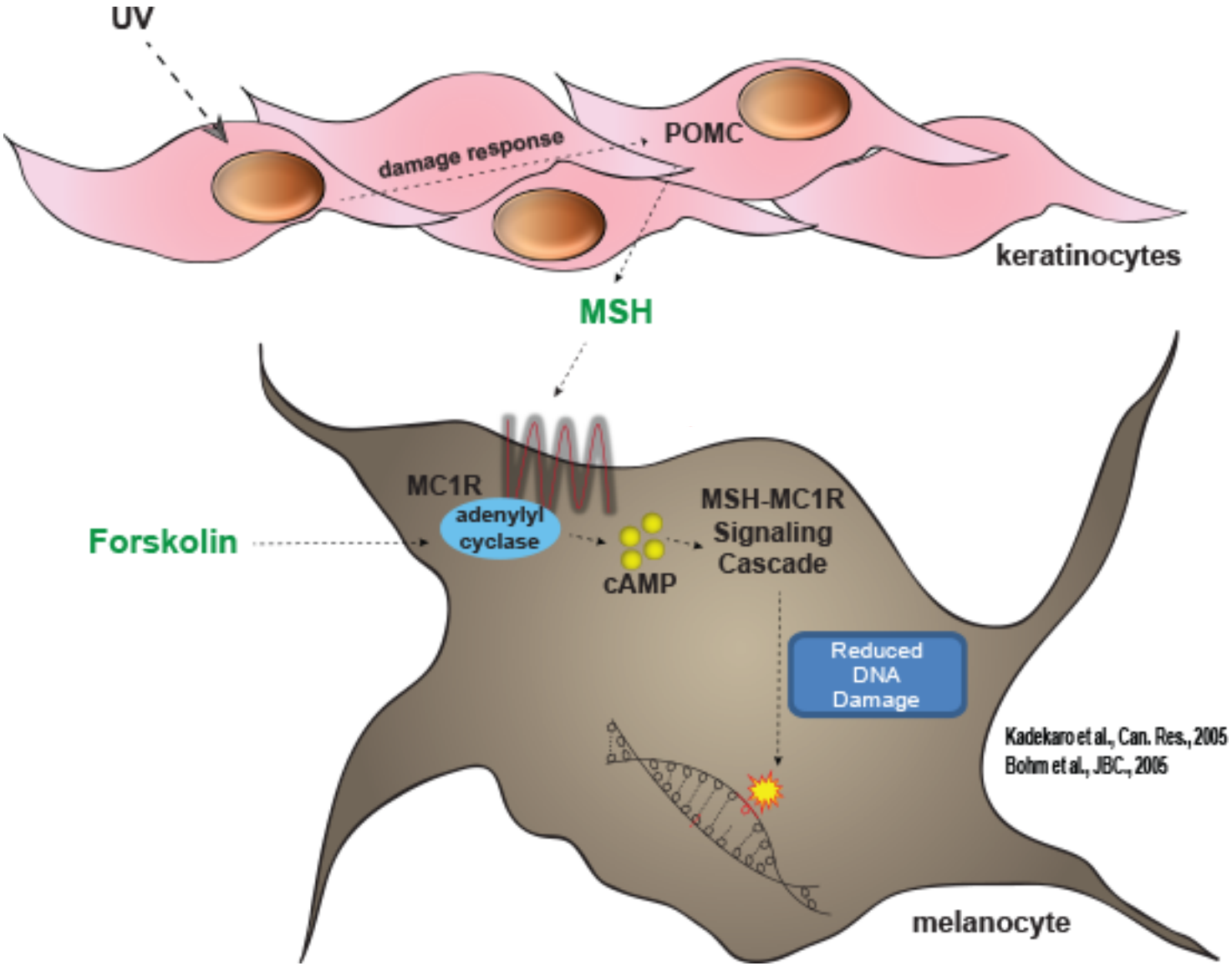
Garcia-Borron et al., *PCM.* 2005

- The melanocortin 1 receptor (MC1R) is a melanocytic transmembrane receptor.
- It regulates pigmentation and adaptive tanning via cAMP generation.
- The MC1R gene is highly polymorphic.
- Loss-of-function MC1R polymorphisms are correlated with melanoma risk .
- Germline MC1R status influences somatic mutation burden in melanoma (Robles-Espinoza et al., *Nature Communications*. 2016).

The Melanocortin Signaling Axis

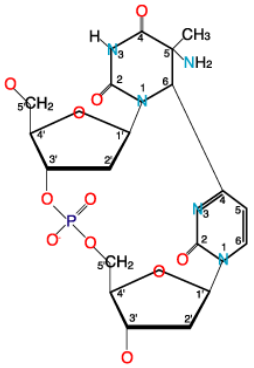


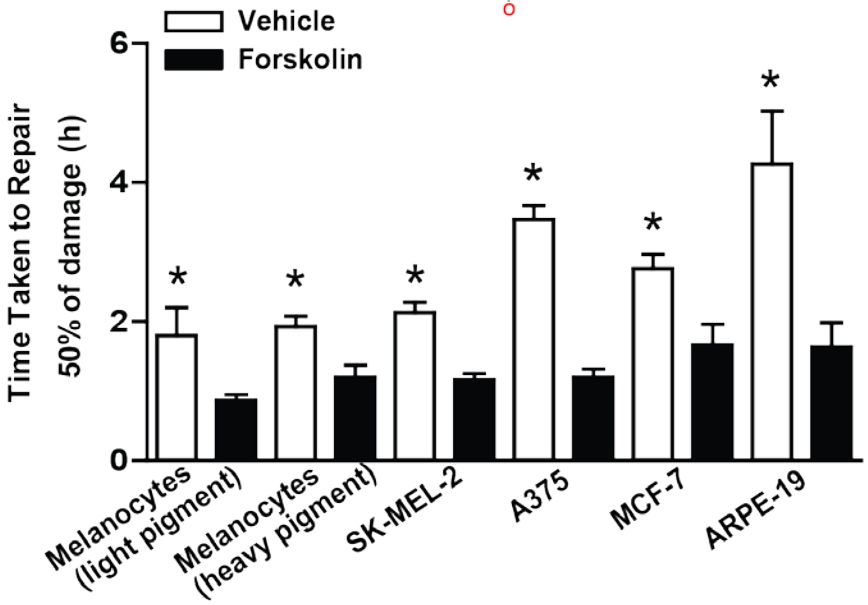
The Melanocortin Signaling Axis



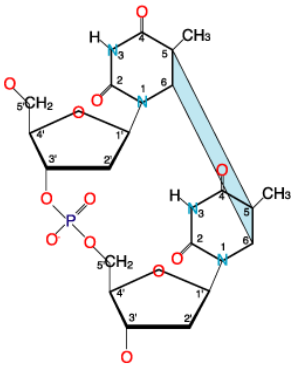
MC1R Signaling Enhances Repair of UV-Induced DNA Damage

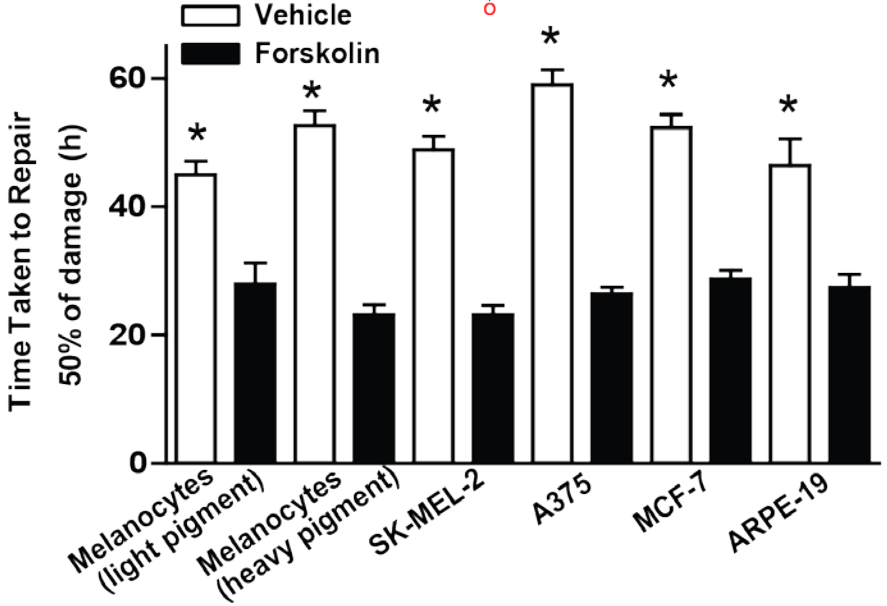
[6,4]-photoproducts





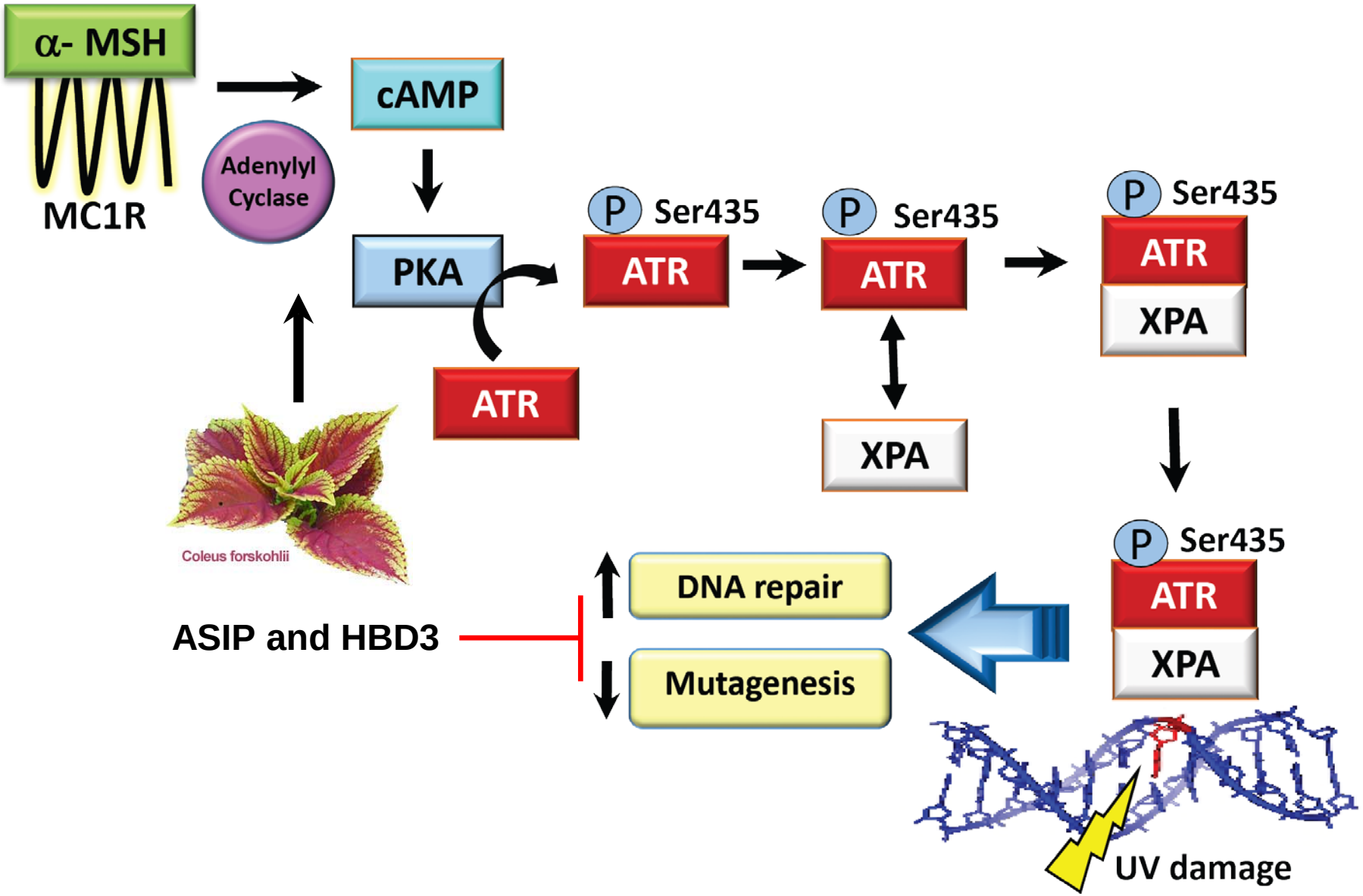
Cyclobutane dimers





Jarrett et al, *Mol. Cell,* 2014

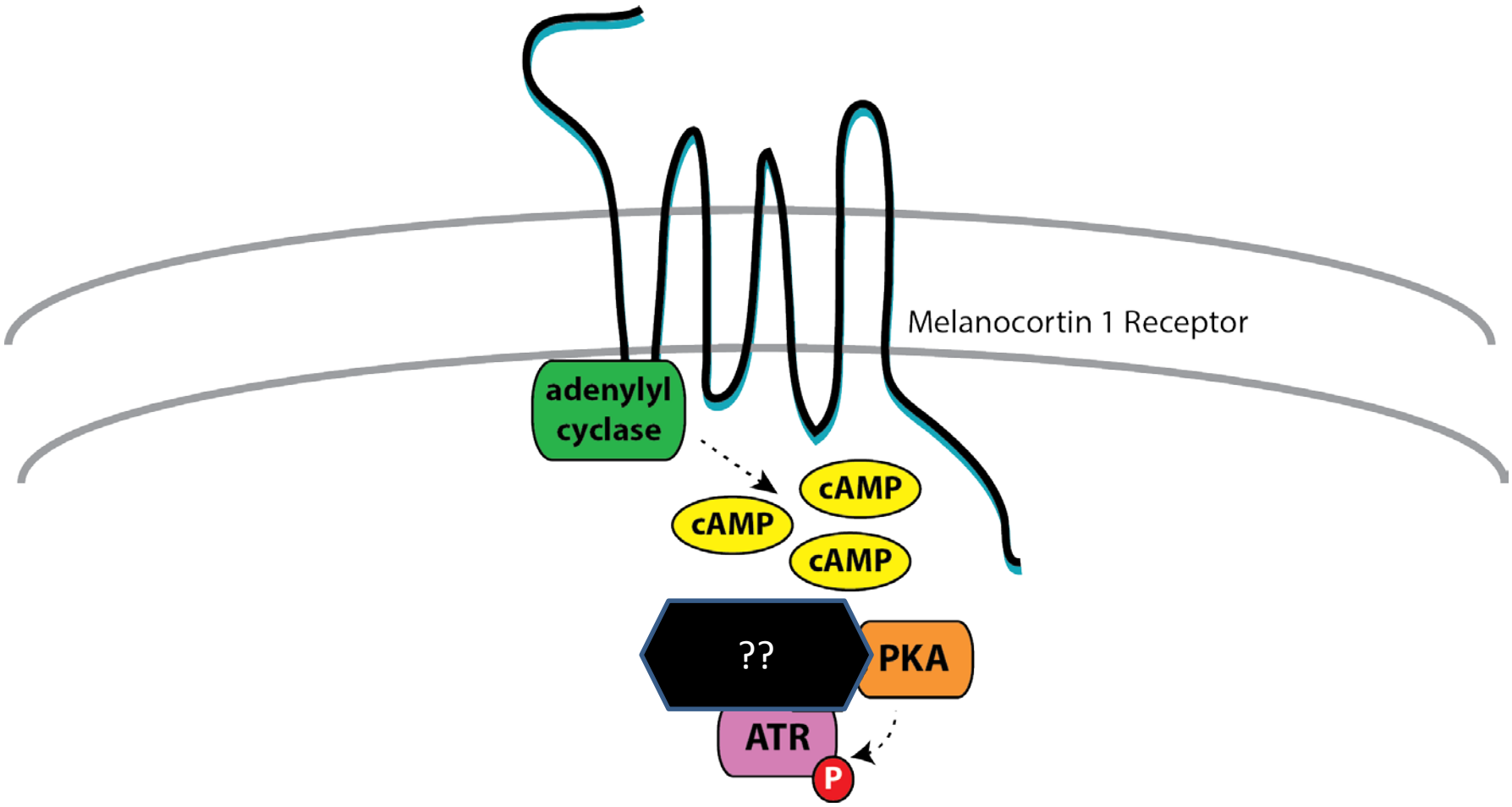
MC1R/cAMP DNA Repair Axis



Jarrett, SG et. al., *Molecular Cell*. 2014

Jarrett, SG., et. al., *J. Investigative Dermatology*. 2015

What are other key proteins involved in the pathway?



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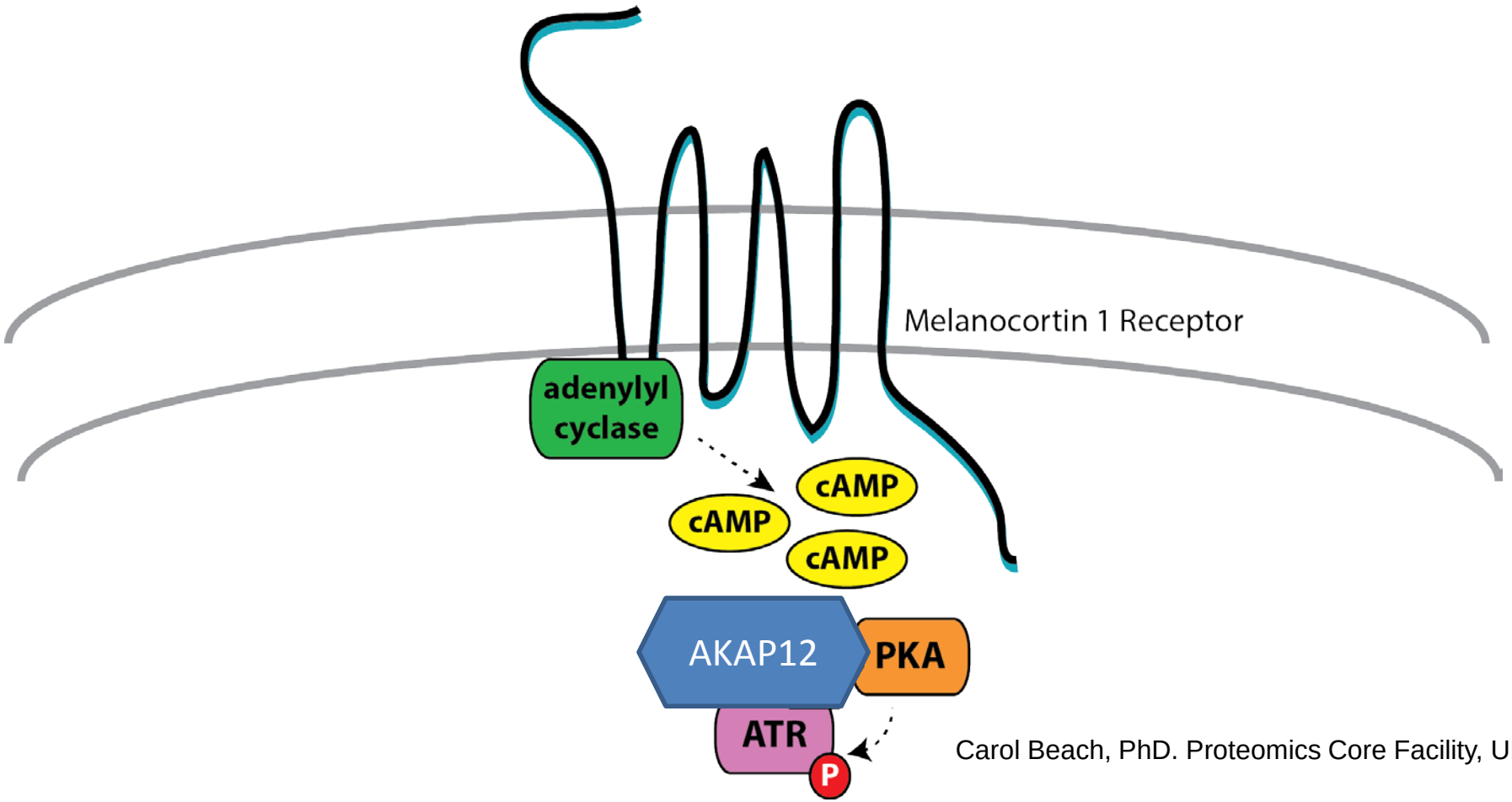


Carol Beach, PhD. Proteomics Core Facility, UK

Kristie Rose, PhD. MSRC Proteomics Laboratory, University of Vanderbilt

A Kinase Anchoring Proteins (AKAPs)

- Family of more > 50 proteins needed for PKA signaling
- Scaffold PKA kinase events
- Regulate PKA localization and activity
  - Brings together PKA with phosphorylation targets and its regulatory proteins

A Kinase Anchoring Protein 12 (AKAP12)

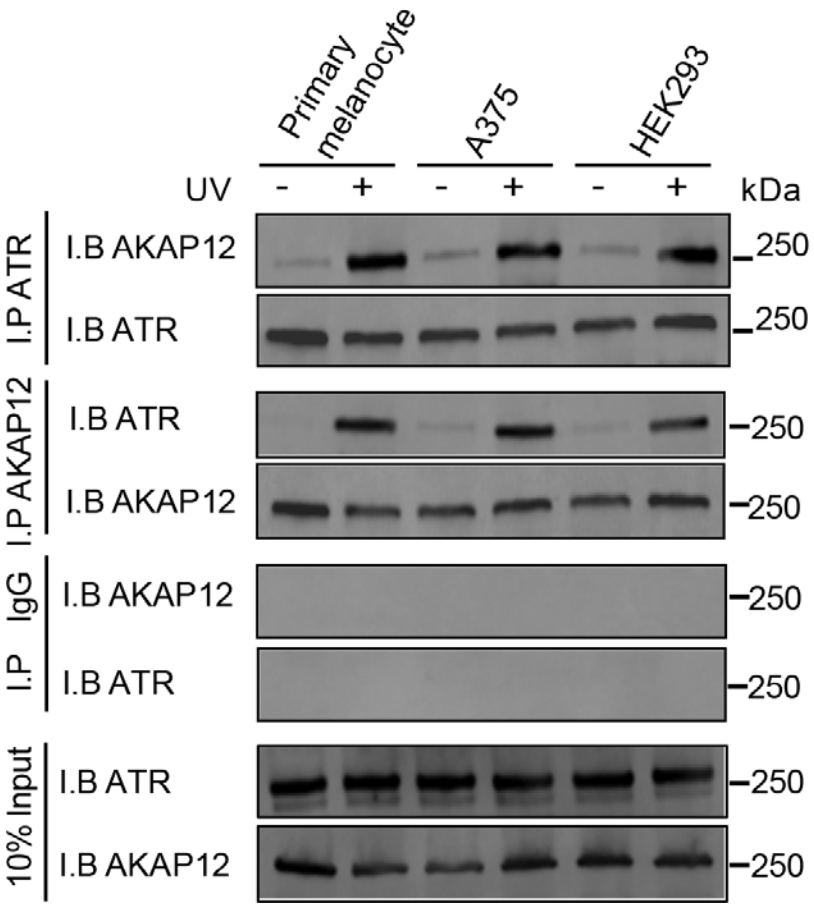
- AKAP12 (also called Gravin and SSeCKS)

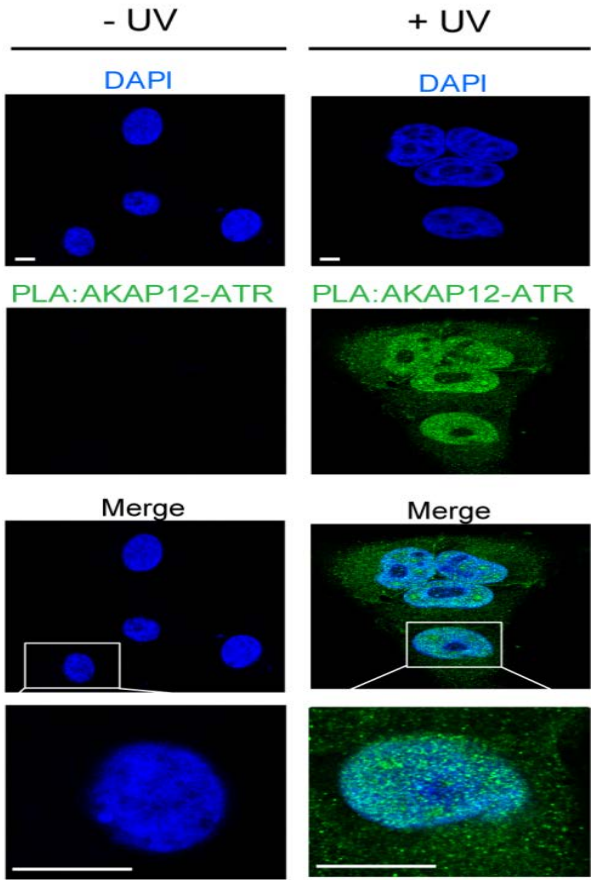
  - tumor suppression, cytoskeletal architecture, β_2-adrenergic receptor desensitization/resensitization, cell cycle regulation

  - AKAP12 found at sites of stalled replication forks following nucleotide depletion, however to date, AKAP12 has not been implicated in DNA repair (Sirbu et al., JBC, 2013).

A-Kinase Anchoring Protein 12 (AKAP12) interacts with ATR

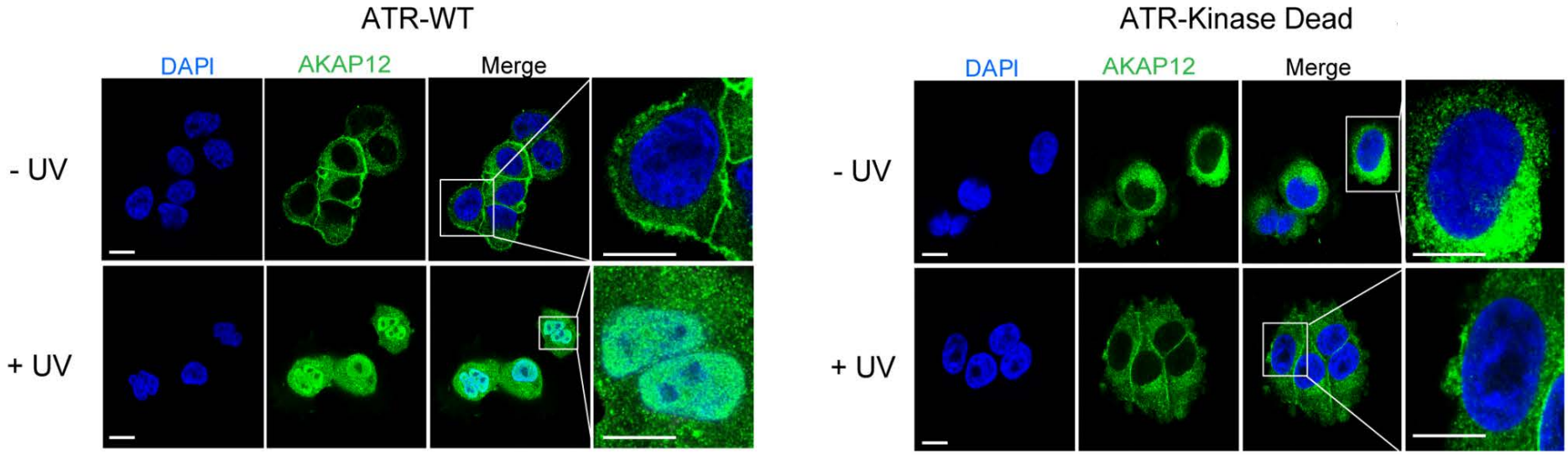
- AKAPs scaffold PKA kinase events and localize PKA with phosphorylation targets





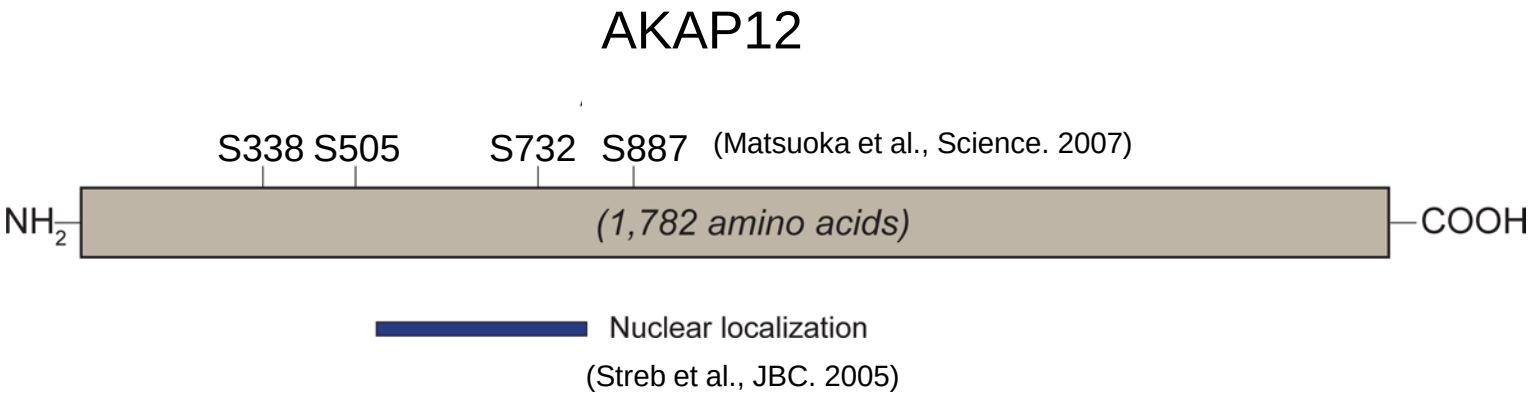
Jarrett, SG., et. al., *Nucleic Acids Research*. 2016

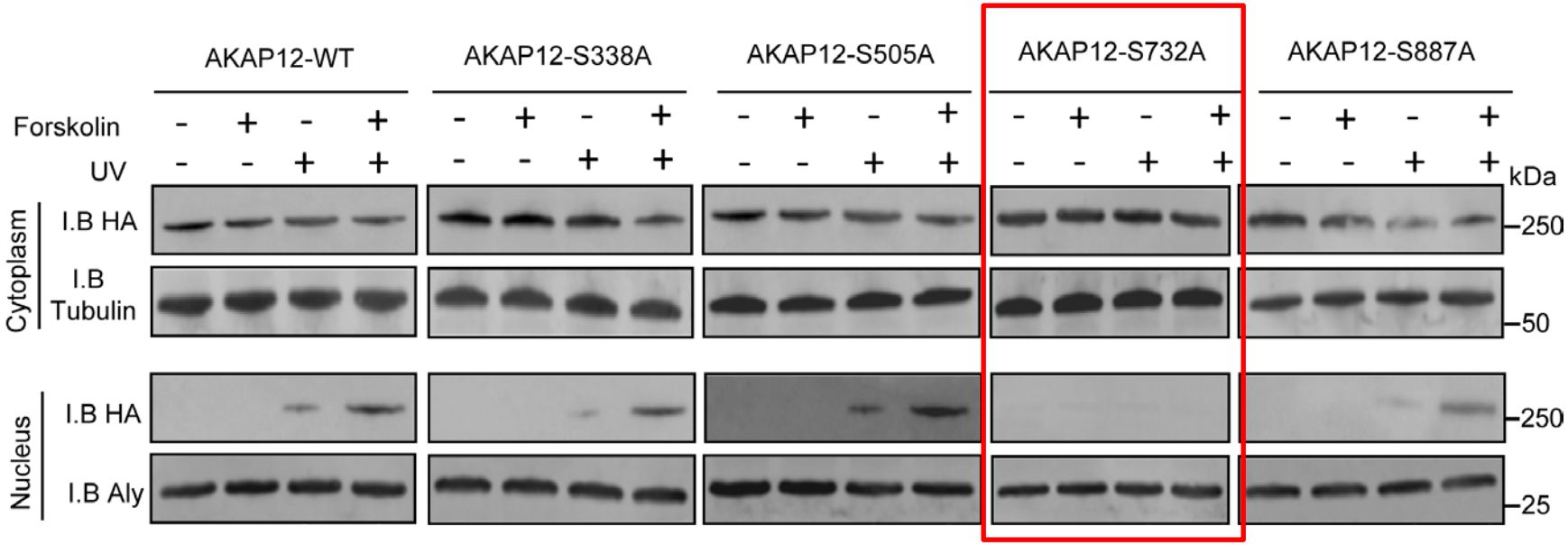
ATR-mediated Phosphorylation of AKAP12 Promotes Nuclear Localization



Jarrett, SG., et. al., *Nucleic Acids Research*. 2016

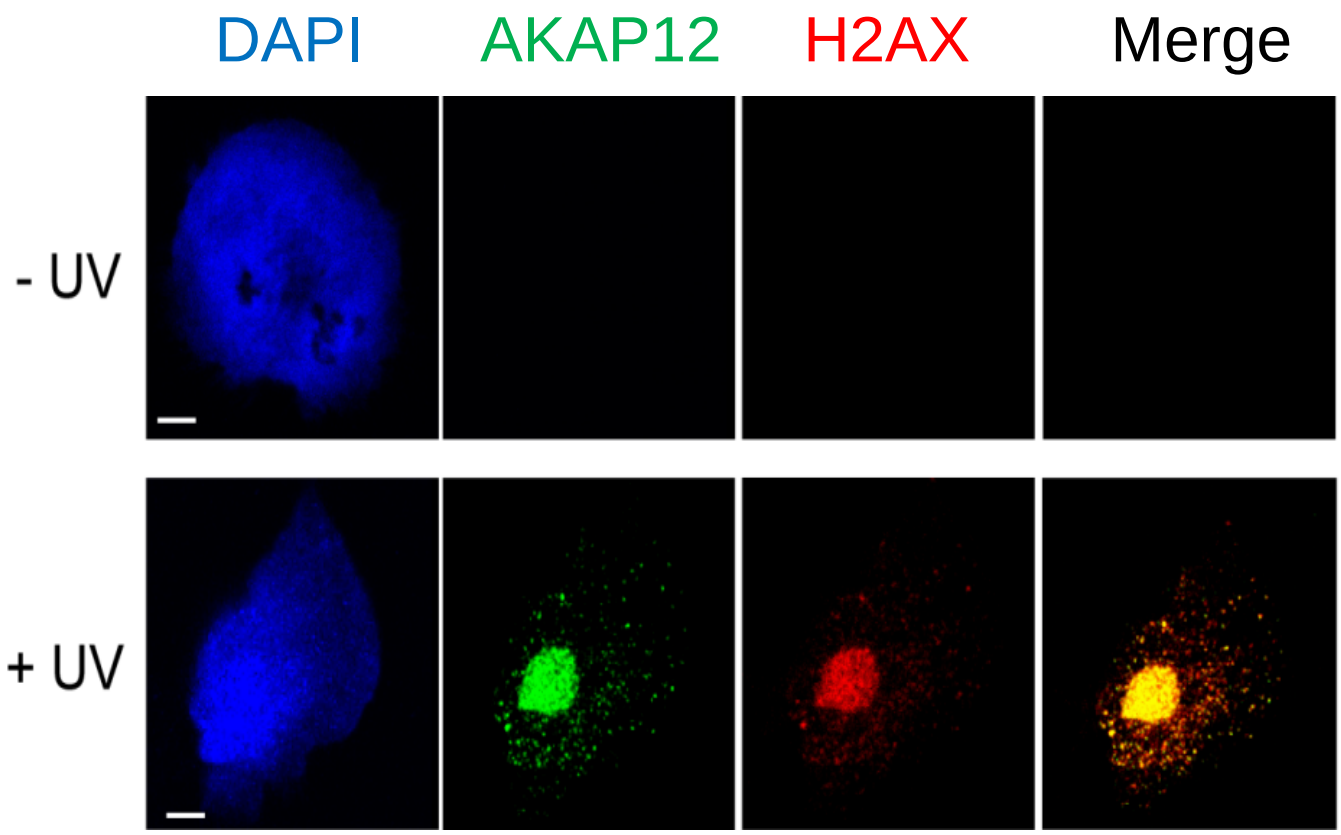
Phosphorylation of AKAP12 at S732 is necessary for nuclear localization



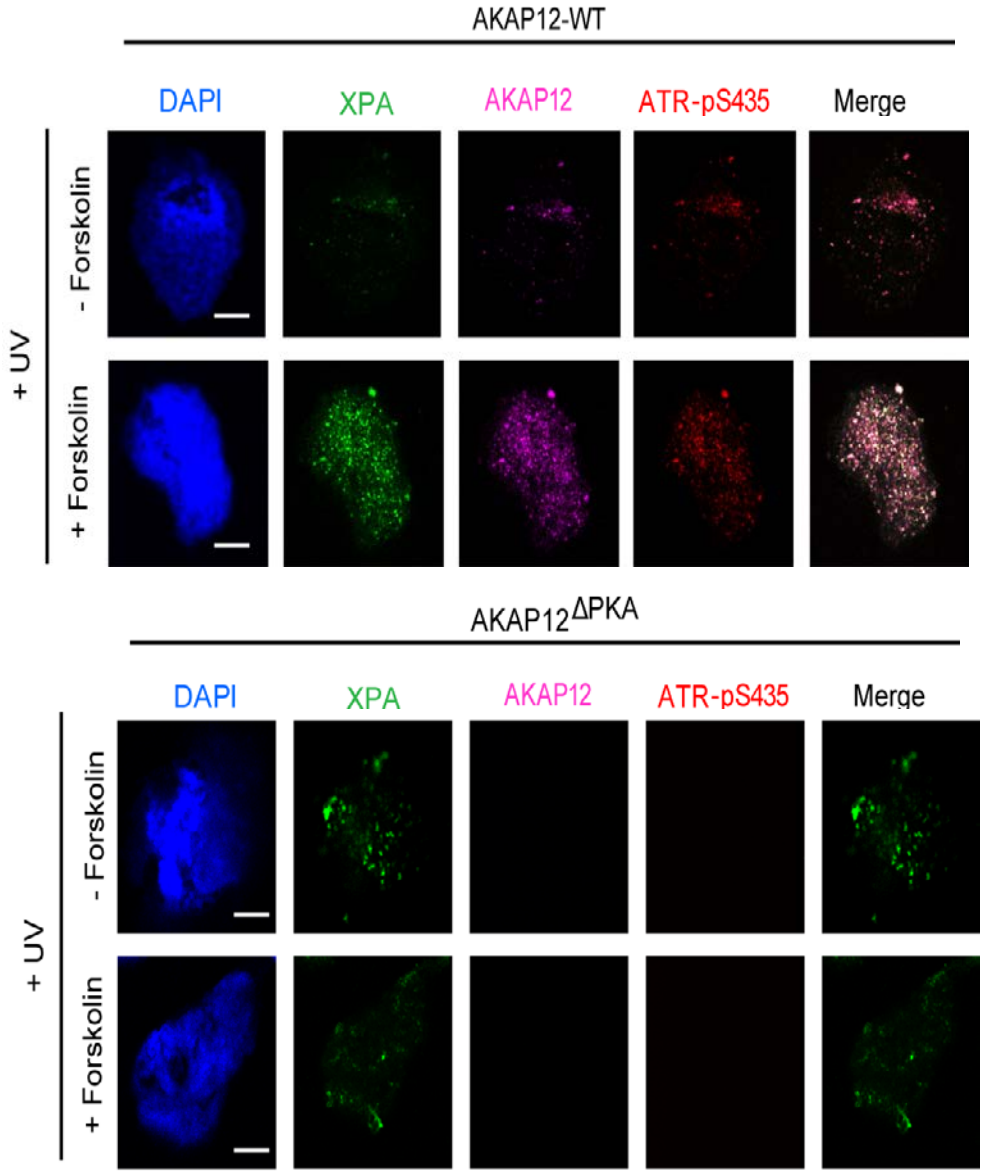


Jarrett, SG., et. al., *Nucleic Acids Research*. 2016

AKAP12 co-localizes with UV-damaged DNA

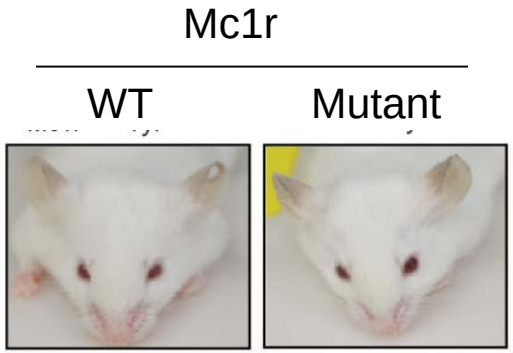


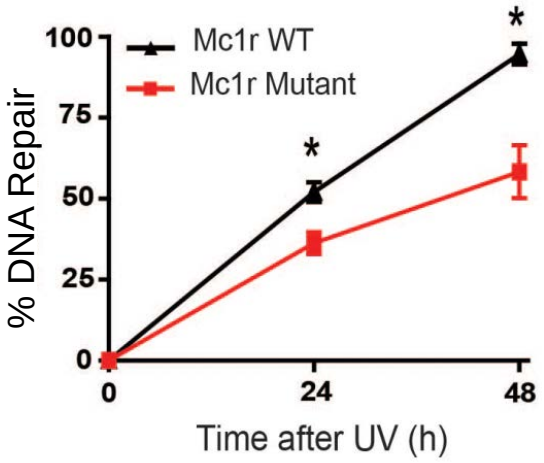
cAMP enhanced co-localization of XPA-ATR-pS435 requires a functional AKAP12

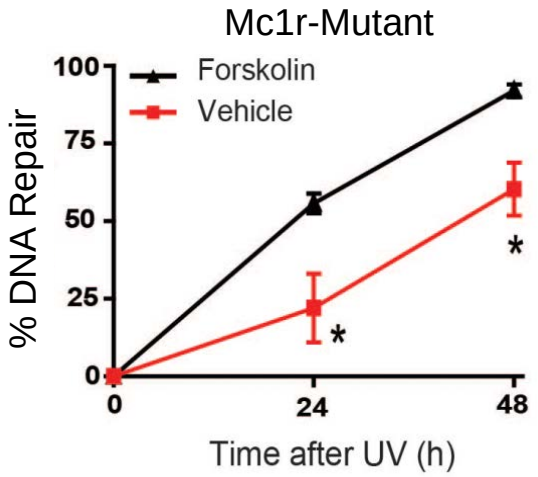


Jarrett, SG., et. al., *Nucleic Acids Research*. 2016

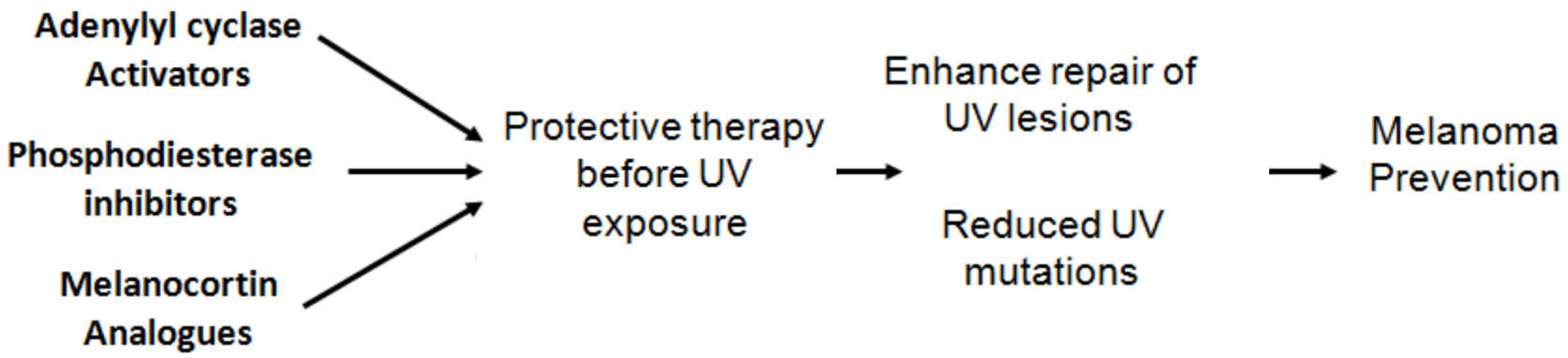
Topical forskolin application enhances DNA repair in Mc1r-mutant mice



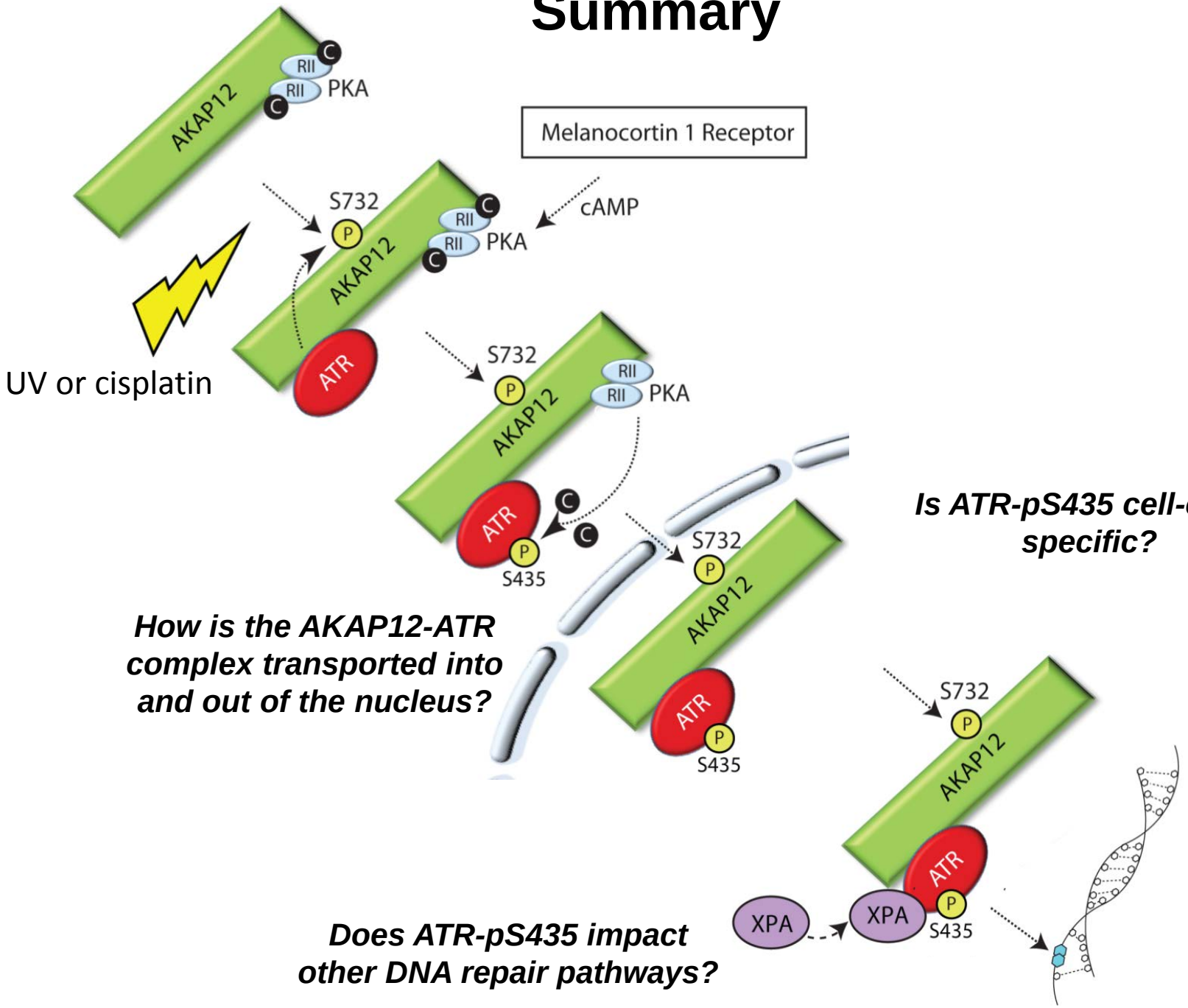




Translational Implications



Summary


AKAP12
RII
RII
C
C
PKA
Melanocortin 1 Receptor
S732
P
cAMP
UV or cisplatin
ATR
S435
How is the AKAP12-ATR complex transported into and out of the nucleus?
Is ATR-pS435 cell-cycle specific?
XPA
Does ATR-pS435 impact other DNA repair pathways?

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