UVI5008, a multiple epigenetic modulator for the treatment of cancer

Universidade Vigo

The Institution and the current pipeline

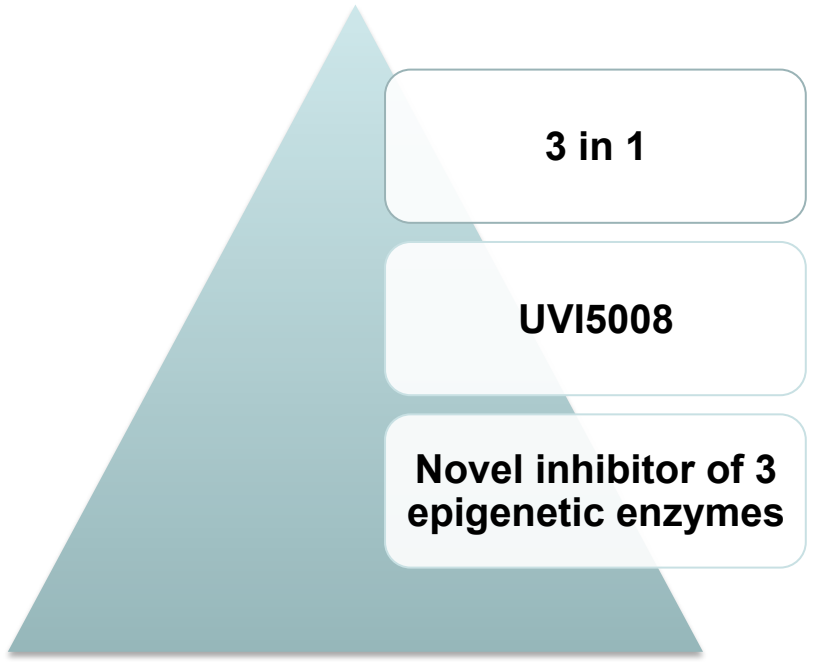
Research group in drug discovery at the Faculty of Chemistry

Current interests:

- Retinoid receptor (RAR and RXR) modulators

- Epigenetic modulators inspired in the structure of natural products
  - HDAC inhibitors
  - DNMT inhibitors
  - KDM inhibitors (KDM4)
  - KMT inhibitors (SETD8, G9a)

The product: UVI5008



HDAC inhibitor

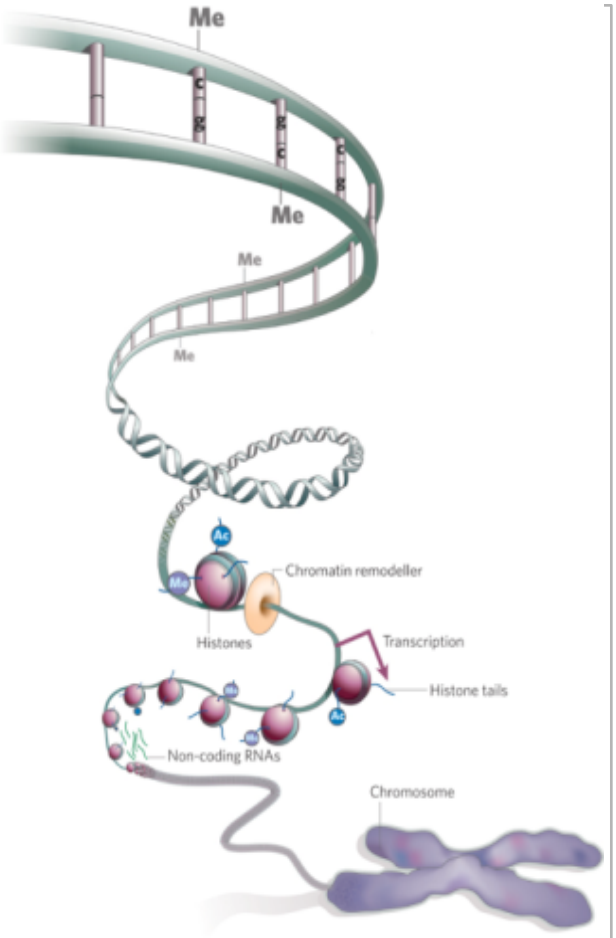
Sirtuin inhibitor

DNMT inhibitor

- First drug for combination therapy and epigenetic therapy
- Strong anti-cancer activity *in vitro* and *in vivo*
- Activities demonstrated in tumors upon treatment *in vivo*
- Drug compatible PK
- Strong IP position

The Promise of Epigenetic Drugs

- Novel therapeutic modality
  - No genotoxicity
  - Reversible action
  - Suited for combination treatment
- Targeting epigenetics is reasonable
  - DNA methylation & histone modification is de-regulated in cancer
  - Gene programs for cell differentiation and growth control are epigenetically silenced
- Epigenetic enzymes constitute a large unexplored reservoir of promising drug targets
  - 3 DNA methyltransferases
  - 11 zinc-dependent Histone Deacetylases (HDACs)
  - 7 NAD-dependent Histone Deacetylases (Sirtuins)
  - Numerous Histone Methyltransferases (HMTs) and Demethylases (HDMs)
  - Other histone modifying enzymes

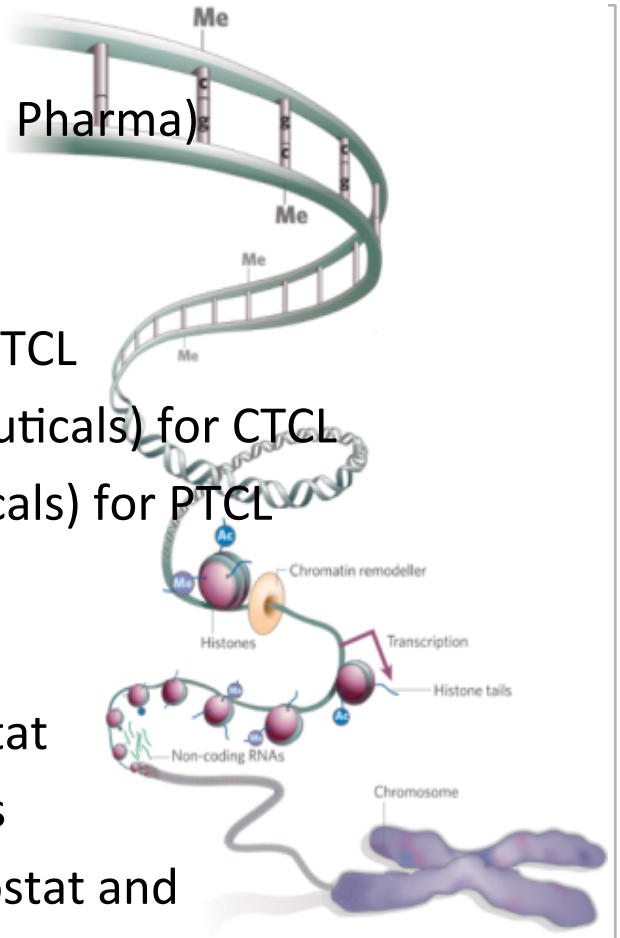


Epidrugs are in Clinical Use

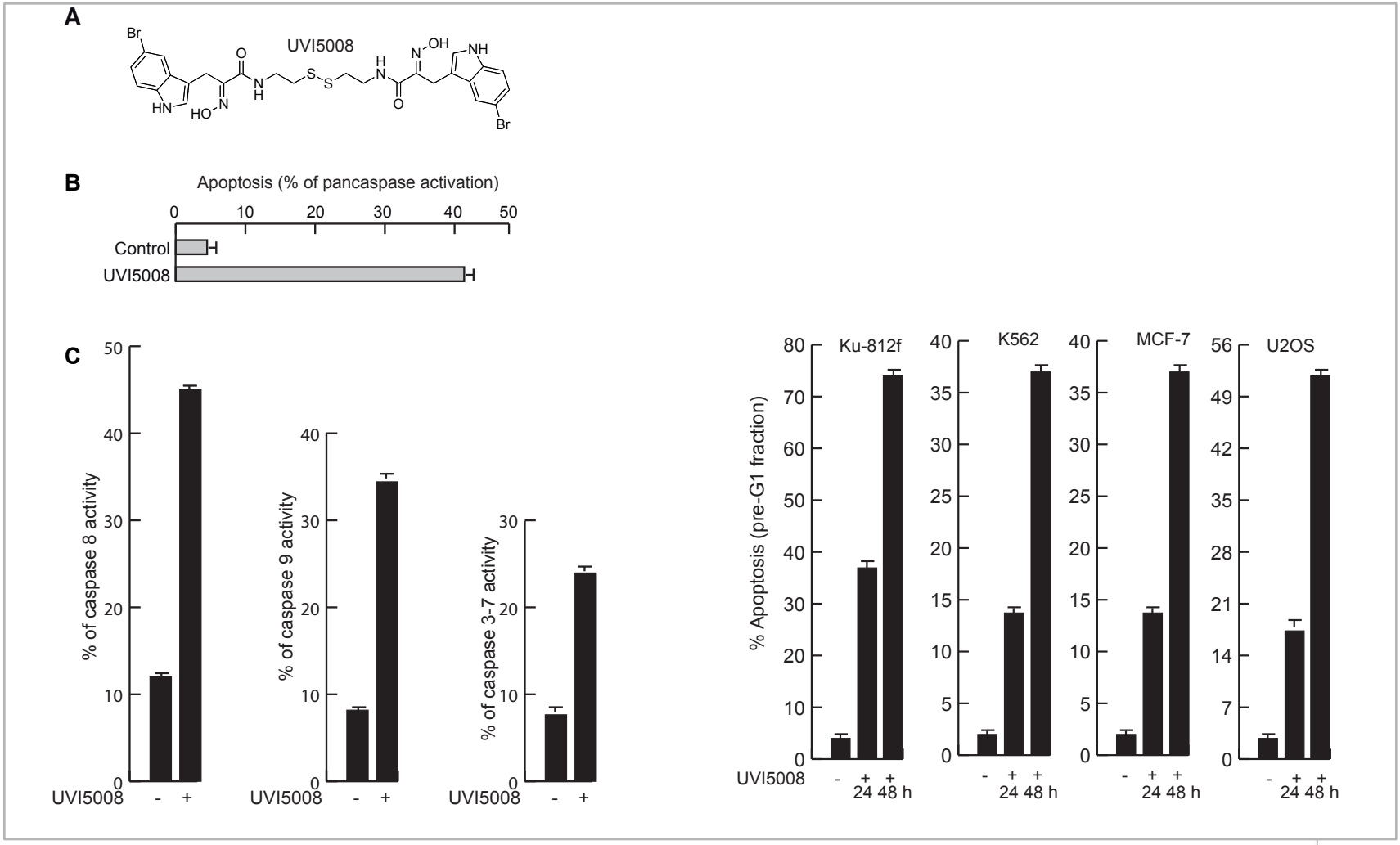
- DNA methylation inhibitors
  - 5-Aza-cytidine and decitabine (2006, MGI Pharma)

  for Myelodysplastic syndrome
- Three HDAC inhibitors approved by FDA
  - Vorinostat (2006; Merck & Co., Inc.) for CTCL
  - Romidepsin (2009; Gloucester Pharmaceuticals) for CTCL
  - Belinostat (2014; Spectrum Pharmaceuticals) for PTCL
- Multiple clinical trials ongoing (2014)
  - Single agent & combo trials with Vorinostat

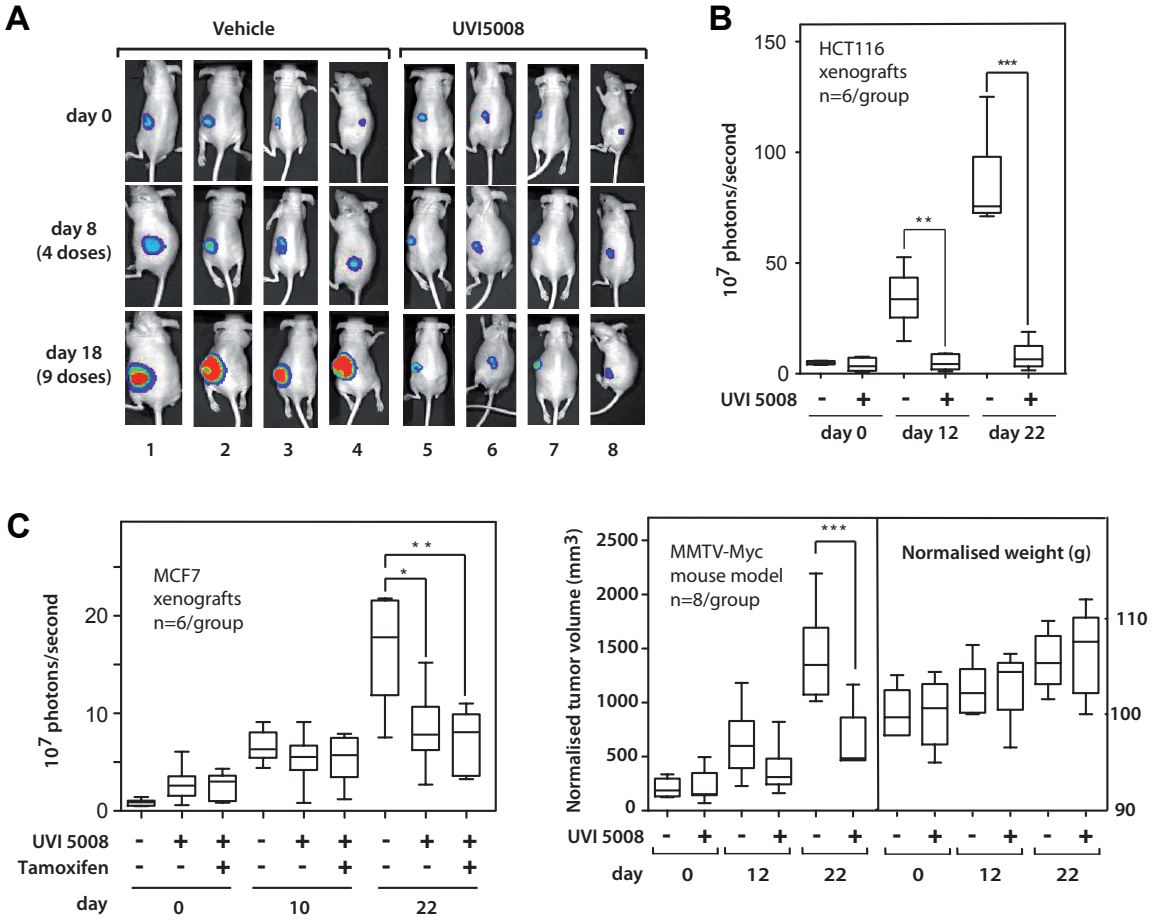
  for a number of solid tumors and leukemias
  - several epi-drug combo trials with Vorinostat and Decitabine (DNA methylation inhibitor)



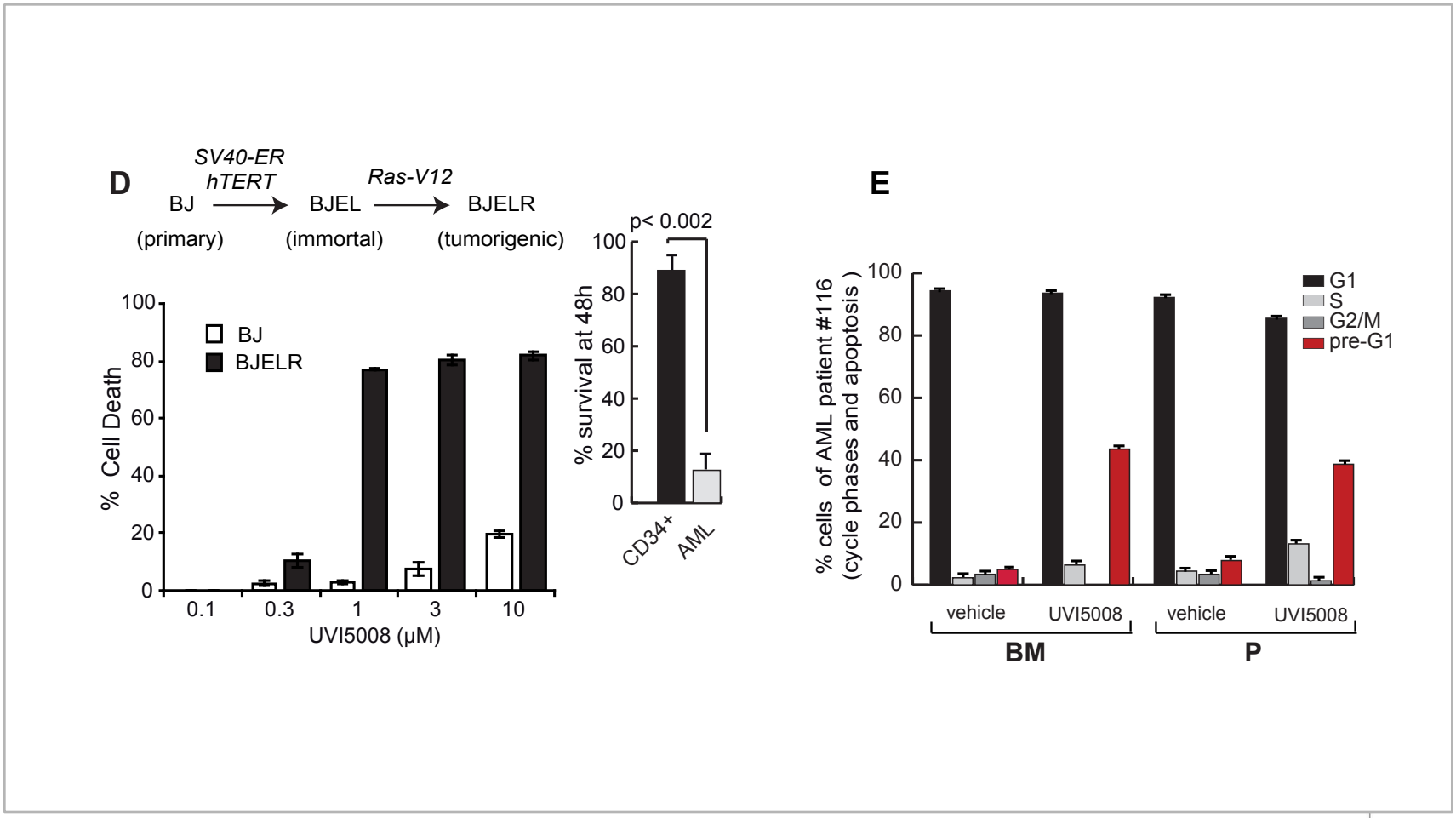
UVI5008 Induces Apoptosis



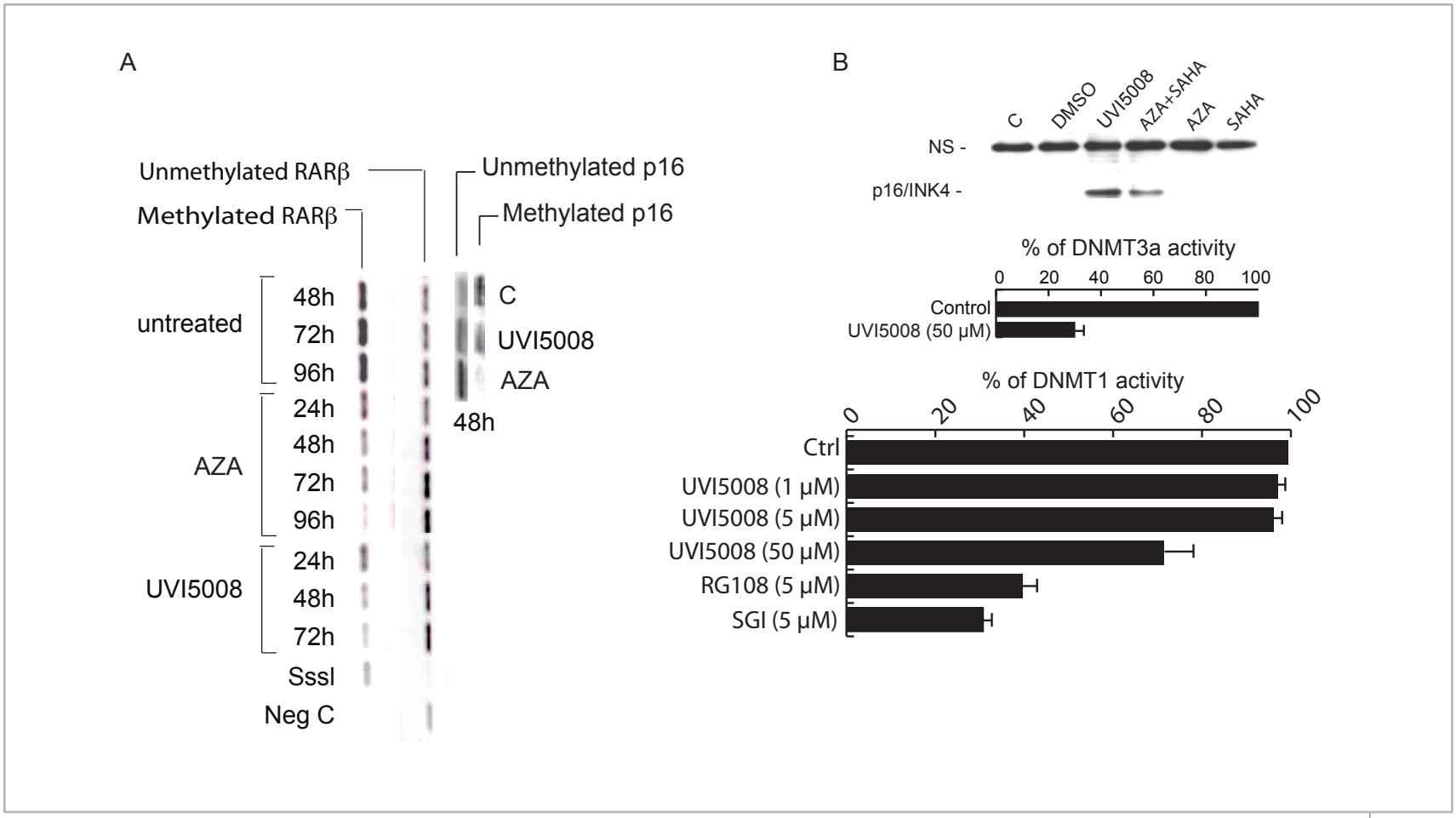
Human Colon Carcinoma Xenografts and Genetic Breast Cancer Models



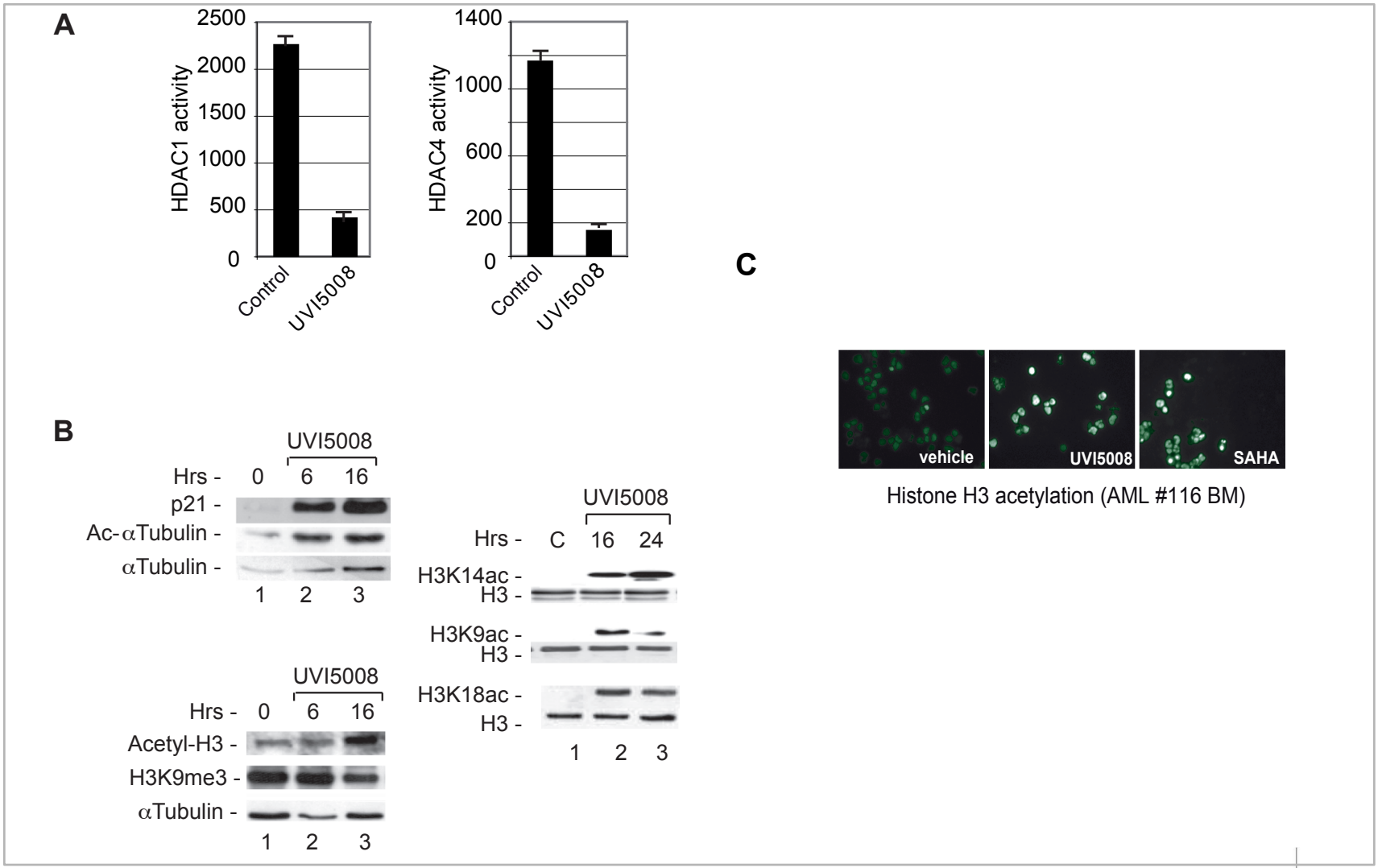
Stepwise Tumorigenesis Model and ex vivo Assays



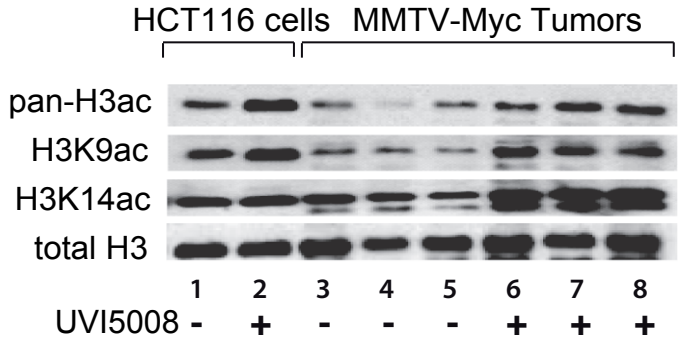
DNMT Inhibition

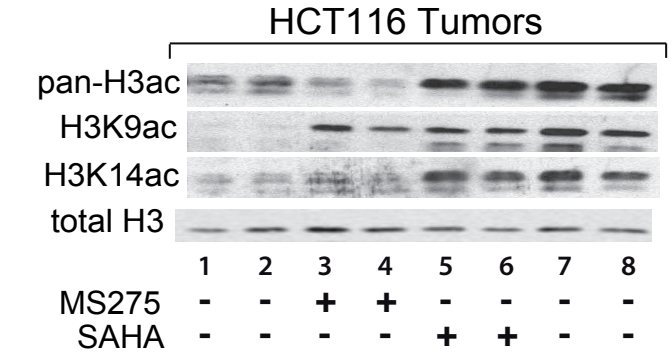


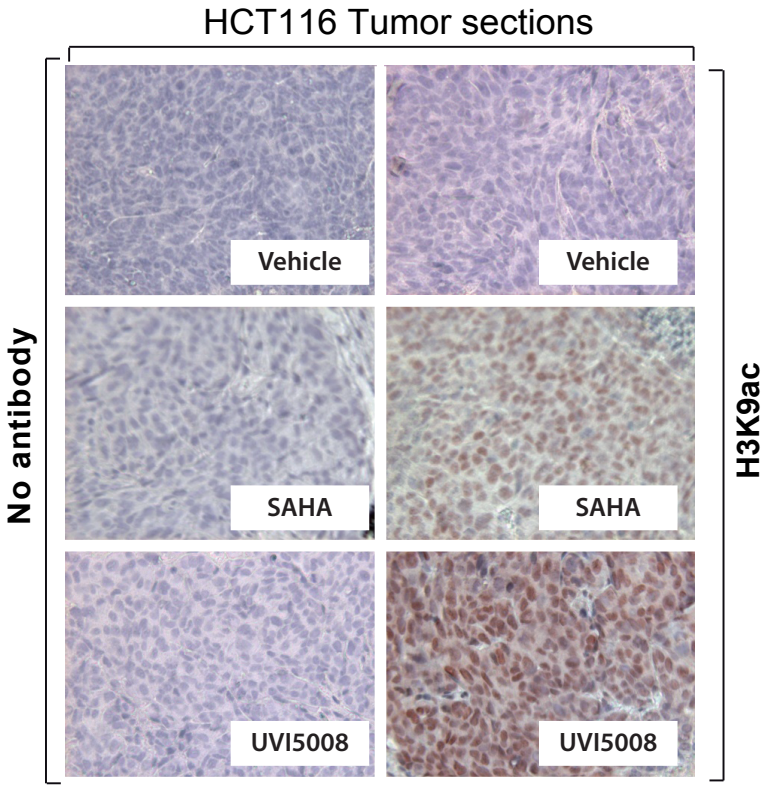
HDAC Inhibition



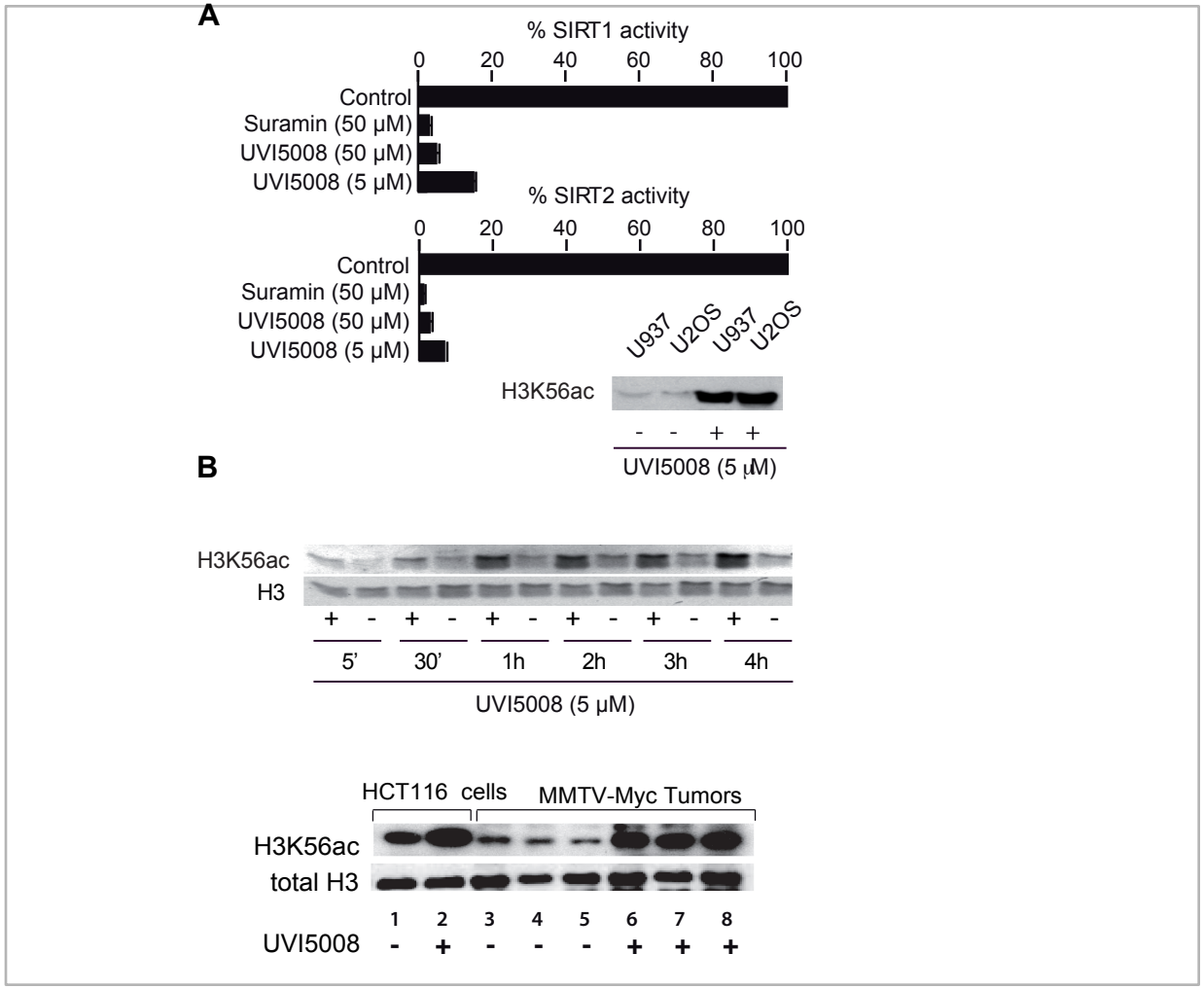
Drug Activity in the Tumor



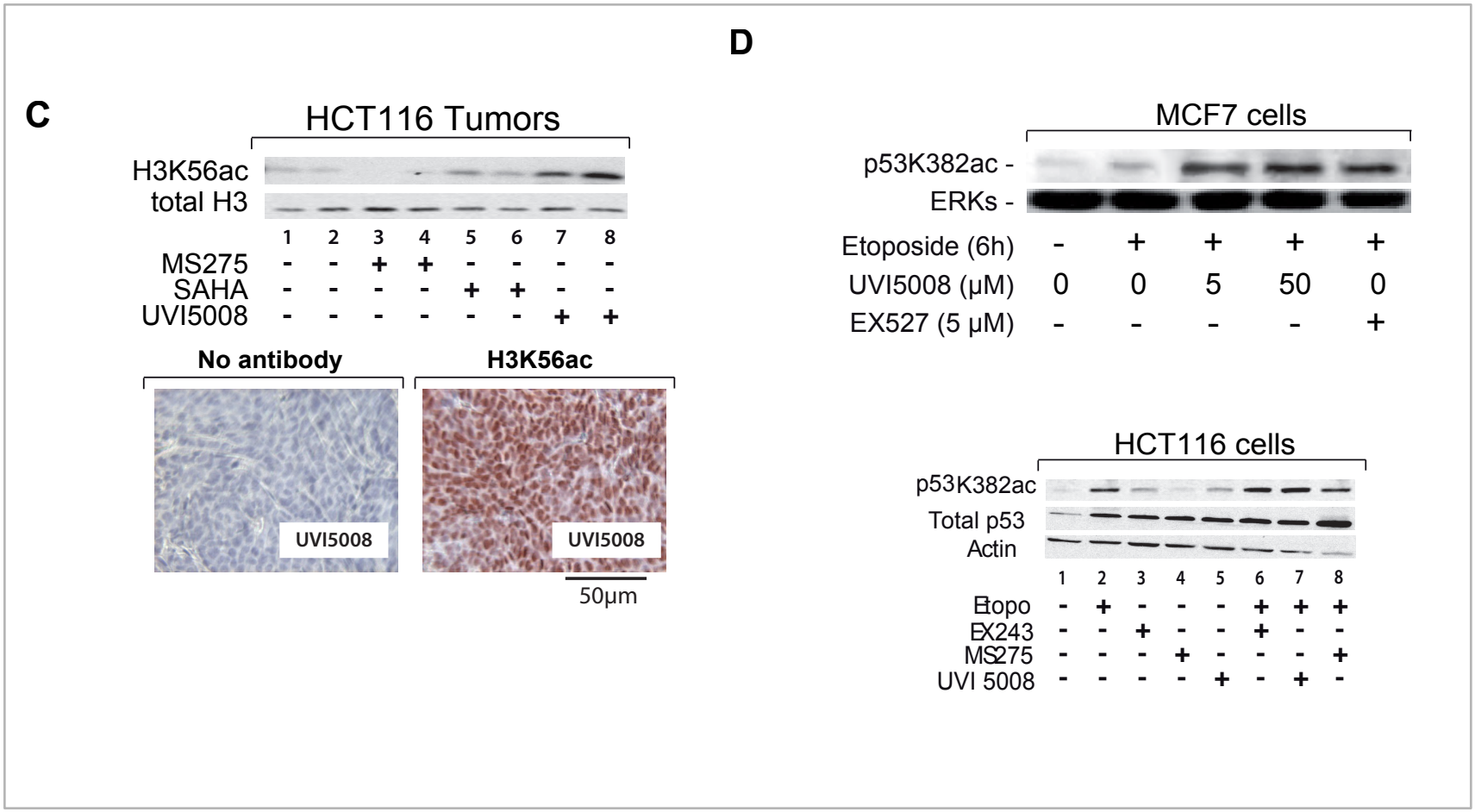




SIRT Inhibition



SIRT Inhibition *in Tumori*



Mechanistic Insights

1) Reactivation of Tumor Supressor Genes (TSGs)

- p21 in HCT116 (p53 +/+ and p53-/-) cells and xenografts
- TNF Superfamily 10: "Frizzled" related (SFRP1, SFRP2) and MLH1 in HCT116 (p53 +/+ and p53-/-) cells and xenografts, and in MCF7, MDA-MB231

2) Induction of apoptosis through several pathways

- Caspase pathway: TRAIL involvement

  (Apoptosis in p53- and BMF-deficient cells)
- ROS-dependent pathway

3) *Ex vivo* treatment of AML cells confirmed the dual implication of TRAIL and ROS

- 39 to 70% apoptosis/20h
- Independent of karyotype and immunophenotype

UVI5008 Potential

- 3 epigenetic enzyme systems targeted by 1 drug
- Tumor-selective action
- Active against human leukemias (AML) and solid cancers (colon, breast cancer, osteosarcoma, prostate and melanoma)
- Active in genetic mouse model for breast cancer
- Broad therapeutic spectrum including p53- or BMF-deficient tumors
- Lower toxicity (mice) than other HDACis

- IP: Patent WO 2008/125988 A1 (Febr 28, 2008): UVIGO (30%), CNRS-INSERM (30%), UNINA2 (30%), UNIJMEGEN (10%)

Stage of Development

- **PK data favourable (CEREP)**
- **In vitro safety profile/binding specificity (CEREP, September 2014, financed by SATT Conectus Alsace)**
- **Pending: ADME and toxicological studies 2nd rodent /dog (GMP material)**