A METHODOLOGICAL MODEL FOR UNCOVERING IMMUNOEPIGENETIC (SIDE?)-EFFECTS OF EPIGENETIC DRUGS (EDs)

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BACKGROUND Epigenetic aberrations of various genes are implicated in the pathogenesis of cancer, autoimmune and neurodegenerative diseases, etc. [1]. EDs indications are rapidly expanding with many phase I/II clinical trials currently in progress for solid and hematological cancers [2], whilst recent studies suggest their possible use as immunosuppressive agents [3]. Our preliminary results indicate that epigenetic drugs affect significantly the function of certain immune cell populations. This effect might represent another mode of EDs action and/or a source of side effects, whilst it presents special interest bearing in mind that various drugs in common use, such as valproic acid, procainamide, hydralazine, etc., dispose an epigenetic function.

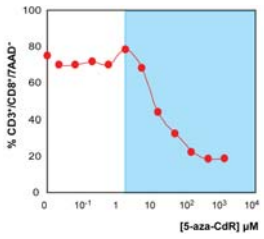
THE MODEL

1. **Isolation/culture of an immune cell line/clone**
2. Determination of the sub-toxic doses of the drug
3. Culture of immune cells in the presence of the drug
4. Functional readouts
5. –omic evaluation
6. Selection of genes
7. **Final readout**: Epigenetic alterations induced on the gene(s) of interest

VALIDATION

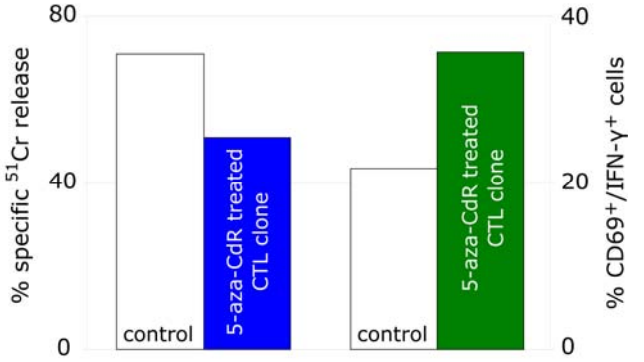
Effect of decitabine (5-aza-CdR) on peptide-specific CD8 cytolytic T cell (CTL) clones

CTL clones specific for MAGE-A3 peptides isolated from cancer patients and healthy individuals



Viability of CTL clones assessed after 5-day culture with varying concentrations of 5-aza-CdR.
Absolute viability conserved in concentrations of the white area.

CTL clones were stimulated by CD3/CD28 antibodies and cultured for 5 days in the presence of 200 nM of 5-aza-CdR



The model continues to be validated…

REFERENCES

1. Germenis AE, Karanikas V. *Immunol Cell Biol* 2007, 85:55-59
2. Esteller M. *N Engl J Med* 2008, 358:1148-1159
3. Johnson J et al. *Transplant Proc* 2008, 40:459-461

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MARIE CURIE ACTIONS