INTRODUCTION

The serotonin 2C receptor (5-HT2cR) mRNA undergoes A-to-I editing by the ADARs enzymes, with effects on pharmacology, cell signaling and brain functions of the encoded proteins (Werry et al., 2008, Pharmacol. Ther.). Such alterations have been evidenced in several studies on neuropsychiatric disorders including major depression and suicide (Simmons et al., 2010, NeuroReport). Interferons (IFN) are used for the treatment of several affections including chronic viral hepatitis, some types of cancers and multiple sclerosis. However IFNs subtype may induce severe forms of depression with possible suicides (Raxion et al., 2005, CNS drugs.). It notably activates the expression of ADAR1a isoform and alters the editing profile of 5-HT2cR mRNA (Yang et al., 2004, Mol. Brain Res.).

Biocortech’s proprietary technique allows to simultaneously and reliably measure all 5-HT2cR mRNA isoforms produced by editing (Poyau et al., 2007, Electrophoresis). An in vitro screening assay has been set up using specific cell line, and IFN treatment as a reference.

OBJECTIVES

- To predict the risk of drug-induced depression/suicidality adverse events on the basis of the modification of 5-HT2cR editing measured for 50 drugs belonging to various therapeutic classes.
- To provide a high confidence rule out test at preclinical stage.

WHAT IS RNA EDITING?

DEFINITION OF AN IFNa EDITING PROFILE

PROCESS WORKFLOW

1. Cell seeding
2. Cell treatment with 50 drugs at 3 concentrations (0.1µM, 1µM, 10µM; n=8)
   - Negative control = vehicle
   - Positive control = IFNα (100 IU/ml)
3. RNA extraction and purification
4. RT-PCR, nested PCR
5. Capillary electrophoresis (CE-SSCP) for editing isoforms detection
6. Data extraction, editing isoforms quantitation and analysis (Biocortech's proprietary software)

DIFFERENT THERAPEUTIC CLASSES MODIFY EDITING PROFILES

DATA ANALYSIS: A POSITIVE PREDICTIVE VALUE OF 90%

For the 50 tested drugs, a Positive Predictive Value (PPV) of 90% was found for occurrence of FDA warning labels and of 83% for depression/suicidality alerts.

CONCLUSION: TEST VALUE AND POSITIONING

- The test displays high positive predictive value (PPV), i.e high probability of occurrence of FDA warning label or depression/suicidality alerts when test is positive :
  - 90% for FDA warning label
  - 83% for depression/suicidality alerts
- Statistical analysis supports positioning of the test as a test to rule out drugs in development at the preclinical stage
- A no-go decision could be taken with high confidence on the basis of positive test results.