TOXICOLOGY SERVICES
• General toxicology:
  - Rodents
  - Non-rodents: dogs, NHPs and minipigs
• Carcinogenicity studies also in rash12 and p53+/− mice
• Genetic toxicology: ICH compliant package
• In vivo toxicology: BCO2, MUSST, OPRA, Photo 3T3, Episilk™
  - Agrochemical / Chemical / REACH
  - QSAR
  - Physical chemistry
  - Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
• Integrated Safety Pharmacology in Toxicology Studies
  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG

• Safety pharmacology core battery
• Early safety pharmacology screening
  - NERG
  - Rodent and non-rodent LVP telemetry
  - Anesthetized models: ECG, ABP, LVP and QA

DMPK AND BIOMARKERS
• Radiolabeled DMPK in all species
• Bioanalysis LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
• Toxicogenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina™)
• Immunology: 10-color flow cytometry, LumineX, Mesoscale

SPECIALIZED EXPERTISE
• Juvenile studies including minipigs
• Fertility studies in rodents and NHPs
• Radiation safety and efficacy studies
• Tissue Cross Reactivity: human and animal tissue banks
• Gene therapy vector biodistribution via qPCR
• ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
• Lead optimization and predictive toxicology services: Leadscreen™

Media Services Ltd
+81 3 3666 9915
atlanbio@mediaservices.jp.com
Fujit 16 Bldg 7F
1-11-2 Nihonbashishi Kayabacho,
Chuo-ku, Tokyo 103-0026, Japan

Croen Research Inc.
+82 31 888 9390
customerservice@croen.co.kr
Advanced Institutes of Convergence Technology - B-6th Fl., 864-1, luido-dong,
Yeongdong-gu, Suwon-si - Gyeonggi-do,
443-270, Korea

CiToxLAB GROUP COMPANIES

CiToxLAB in France
+33 (0)2 32 29 26 26
contact.france@citoxlab.com
B.P. 563 - 27005 Evreux Cedex, France

CiToxLAB in North America
+1 888 353 2240
contact.northamerica@citoxlab.com
445, Armand-Frappier Blvd,
Laval, Quebec, H7V 4B3, Canada

CiToxLAB in Denmark
+45 56 86 15 00
contact.denmark@citoxlab.com
Hestehavevej 36A, Ejby,
DK-4623 Lille Skensved, Denmark

CiToxLAB in Hungary
+ 36 8 645-300
contact.hungary@citoxlab.com
Vezsprémi, Szabadástagpuszta,
8200, Hungary

Atlanbio
+33 (0)2 51 10 01 00
atlanbio@atlanbio.com
www.atlanbio.com
1 Rue Graham Bell - Z.i de Brais
B.P. 40309,
44605 Saint Nazaire Cedex, France

Partner Company
Stemina
+1 608 204 0104
info@stemina.com
www.stemina.com
504 South Rosa Road,
Suite 150 Madison,
Wisconsin 53719, USA

www.citoxlab.com

Skin and eye phototoxicity in the rat: pigment ed versus non-pigmented strains

Cédric Gerbeix, Stephen Turnock, Catherine Thirion-Delalande and Roy Forster
Skin and eye phototoxicity in the rat: pigmented versus non-pigmented strains

Cédric Gerbeix, Stephen Turnock, Catherine Thirion-Delalande and Roy Forster

INTRODUCTION
Pharmaceutical compounds that absorb light in the UV/Vis range and give a positive result in an in vitro assay such as the 3T3-NRU-PT assay must be further evaluated for phototoxicity using an in vivo assay, as specified in the newly published final version of the ICH S10 guidance [1]. For compounds which reach the eye and absorb light above 400 nm, retinal phototoxicity must also be assessed. In addition ICH S10 guidance suggests the use of pigmented strains, depending on the melanin-binding properties of the active principle to be tested.

METHODS
In the present study, pigmented Long-Evans (LE) and albino Sprague-Dawley (SD) rats were used to assess the phototoxic potential of sparfloxacin (SPX) and 8-methoxypsoralen (B-MOP), two known melanin-binding phototoxic compounds, using qualitative and quantitative endpoints. To this end, doses were selected from the UV-LINA protocol which is in routine use in our facility [2]. Groups of 5 rats received the test items by gavage for 6 consecutive days, accompanied by irradiation at 10U UV/A/Vis on days 4 to 6. Local reactions and clinical signs were noted each day. On day 7, animals were sacrificed, ear biopsy and auricular lymph nodes were sampled and weighed, and eyes were also sampled for microscopic examination. Before initiation of the study, a preliminary evaluation was performed to check that a 10 J UVA/Vis dose did not lead to any change in the skin or eye, and to ensure that the selected doses of SPX and B-MOP were well tolerated.

RESULTS
Local reactions and post-mortem parameters:
No local reaction or statistically significant increase in lymph node weight (LNW), lymph node cell count (LNCC) and ear weight (EW) was noted in animals not exposed to UVA/Vis whatever the treatment. In animals receiving sparfloxacin and UVA/Vis exposure, local reactions were noted in both pigmented and non-pigmented strains, but at earlier time points and with higher severity in the albino strain. In addition, increases in lymph node weight, lymph node cell count and ear weight ratios were of higher degree in albino rat than in pigmented rat. The sparfloxacin-related parameters were dose-related in LE rats. In the LE rats treated with B-MOP and UVA/Vis exposure, dose-related local reactions such as erythema/edema were noted. Statistically significant increases in LNW, LNCC and EW were noted from the lowest tested dose-level, and were dose-related.

Eye microscopic examination
We first demonstrated that the amount of UVA/Vis light delivered to the animal did not induce any damage to the retina and cornea structures. Histopathological findings of sparfloxacin-related ocular phototoxicity, consisting in atrophy/degeneration of the retina (loss of outer nuclear layer associated with single cells necrosis/apoptosis), were noted in albino rats only, and demonstrated the photoprotective effect of the melanin pigment in the iris and retinal pigmented epithelium (RPE) of pigmented rats.

Ocular phototoxicity of B-MOP was noted in LE rats in the corneal epithelium namely, with corneal hyperplasia, intercellular edema and single cell necrosis. No phototoxic effect was noted in the retina, highlighting the protective role of melanin contained in the iris and retina at the level of the RPE, since the energy of incoming photons is absorbed and dissipated in these cells.

REFERENCES
[2] Validation of a UV-LINA protocol based on lymph node weight and cell count quantifications to assess phototoxic potential by topical or oral administration to oiled LE, Pearson, S; Stella, R; Lemberg, B; Koralek, J; Drozdov, J; Legrand, R, Powder.

CONCLUSION
The phototoxic potential of both chemicals was demonstrated in pigmented LE and albino SD rats. Findings of systemic phototoxicity were noted in both strains, with greater severity in albino rats. Ocular phototoxicity was never noted at the RPE level in LE rats, but only at the corneal level. These results show that an albino strain is more sensitive than a pigmented strain to the phototoxicity of these two drugs. The UV-LINA protocol in pigmented rats can provide a useful approach to the determination of the phototoxic potential. It may indeed provide a more relevant model for humans than albino models as ocular phototoxicity has not been reported in humans with these two chemicals.