

# Genotoxicity screening for potential carcinogens

*Gentronix has introduced a high throughput screening assay utilising human cells for an *in vitro* mammalian cell assay that is a highly accurate early predictor of genotoxic carcinogenicity. The assay is based on similar technology to that developed for the yeast-based assay systems introduced earlier by the company.*

**L**oss, change or damage to the coded information in DNA is dangerous for all cells. Mis-repair can lead to obvious mutations and cancers. As these are a consequence of damage to genes in the chromosomes, agents that cause such damage are termed genotoxic. Agents that cause more general cellular poisoning by damaging other macromolecular components (ie that do not specifically target DNA) are termed cytotoxic. DNA damage repair systems exist in all living cells and are activated when cells have been exposed to a genotoxic agent. At the heart of the GreenScreen product range from Gentronix are genetically modified cells that produce Green Fluorescent Protein (GFP) when DNA damage occurs.

## Highly accurate early predictor of genotoxic carcinogenicity

GreenScreen HC is the first *in vitro* mammalian cell assay suitable for high throughput screening. It combines exceptionally high sensitivity and specificity, making it a highly accurate early predictor of genotoxic carcinogenicity,

Early validation has already demonstrated that GreenScreen HC can clearly distinguish between true and falsely positive indications of cancer hazard (a common problem with current *in vitro* mammalian assays). This means that genuinely



A computer graphic of a damaged human DNA molecule (courtesy of L'Oreal/Eurelios/Science Photo Library).

## MEET RICHARD WALMSLEY OF GENTRONIX

Dr Richard Walmsley trained as a geneticist at the University of Kent and the University of Chicago.

Following the establishment of a research laboratory in the Faculty of Life Sciences at the University of Manchester, he founded Gentronix Ltd in 1999 on the back of discoveries coming from the yeast genome project. Gentronix was

established to exploit novel technologies, which provide the basis for the GreenScreen products now being commercialised by the company.

It sells its kits for genotoxicity testing both to the pharmaceutical industry and environmental monitoring stakeholders. Dr Walmsley maintains a faculty position at the University of Manchester.



hazardous genotoxic compounds can be identified before proceeding to development, thereby providing the opportunity for significant reductions in wasted time, compound, costs and animal testing. At the same time, harmless compounds falsely identified as genotoxic by current *in vitro* mammalian assays are less likely to be withdrawn unnecessarily from further development, increasing the number of potential leads.

## Microplate assay detects all mechanistic classes of genotoxins

GreenScreen HC detects all direct-acting mechanistic classes of genotoxic chemicals, as well as aneugens and compounds disrupting DNA replication and repair. Results recently reported by Gentronix and a leading pharmaceutical company in the journal *Mutation Research* show GreenScreen HC to have sensitivity comparable to that of mammalian *in vitro* genotoxic tests currently in use, but combined with very high levels of specificity. Developed as a high-throughput 96-well microplate assay, the simple assay format requires only a small amount of compound and is easily integrated with standard automation equipment in order to perform early screening.

## Fulfilling the need for more accurate tests

During a recent workshop organised by ECVAM (European Centre for the Validation of Alternative Methods) there was a consensus that the high occurrence of irrelevant positive results


in genotoxicity tests *in vitro* is unacceptable and that there is an urgent need for more accurate *in vitro* genotoxicity tests, further supporting the belief that the technology will become a valuable new tool in reducing compound attrition due to genotoxicity.

The new human cell assay has already attracted the interest of members of the genotox community in the pharmaceuticals, household goods and cosmetics industries, as well as of regulatory agencies. Four laboratories have already participated in an international, inter-laboratory reliability trial to assess transferability and reproducibility, and grants have been awarded from two UK agencies (NC3Rs and BBSRC) to extend validation and development for alternative assay platforms.

### Opportune timing

The development of the new Gentronix test has come at an opportune moment, given the current widespread discussions about the limitations in existing *in vitro* genotoxicity tests. These discussions will quite likely lead to some adjustments to the protocols and other conservative changes in the current regulatory tests, though the tests themselves remain time-consuming and compound-hungry. The sparing use of

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compound and simple high-throughput format of this new human cell GreenScreen assay, together with its high specificity and sensitivity, make it an attractive addition to the genetic toxicologist's toolbox. At the very least, its early use should contribute to a reduction in the number of genotoxic compounds that reach the regulatory battery. Even used at late stage, it should help internal weight of evidence discussions in assessing what to do with compounds that present conflicting data in regulatory tests. Using it early or later on in the discovery process, it appears that this new GreenScreen assay presents a clear opportunity to save time, compound and money in bringing useful drugs to market. 

### FURTHER INFORMATION

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