ID 10.2
NGS and toxicogenomic signatures of human carcinogens

J. Zavadil[1]*

[1] International Agency for Research on Cancer, Lyon, France
** zavadilj@iarc.who.int*

The International Agency for Research on Cancer (IARC) aims to identify preventable cancer causes; to this end, its existing research programs employ innovative NGS-based approaches to investigate the mutagenic effects of known or suspected human carcinogens. The selection of the tested compounds is primarily informed by the priorities set for carcinogen evaluation and classification by IARC. The effects of the candidate substances are studied in unique collections of human and rodent tumours or in vitro experimental exposure models, by using NGS conducted at the genome-scale. At the core of the NGS analysis is the identification of mutational signatures, the specific mathematical readouts that reveal the external and endogenous mutagenic mechanisms operative in cells, and their impact on cancer driver genes.

Mutational signatures can be ascertained by well-established NGS applications (e.g. WES, WGS), and recent reports indicate that they can also be obtained from error-corrected/ecNGS-generated data. Despite their superior accuracy and sensitivity in true mutation detection, the presently used ecNGS applications typically produce rather low-count mutation spectra and might not be ready for prime-time use in robust signature analysis relying on a large number of somatic/acquired events. Further developments of the ecNGS approaches for reliable mutational signature identification are thus warranted.

One rather unexploited area of applying NGS to studying the mutagenic fingerprints of carcinogens is the genome-scale analysis of mutational signatures and cancer driver events in archived FFPE or EFPE biospecimens. Successful examples of such investigations will be presented, including the discovery of novel mutational signatures in archived tumours associated with exposures to dietary contaminants, iatrogenic agents, and industrial chemicals.

Overall, this presentation will illustrate the power of the NGS approach in improving our understanding of extrinsic cancer causes, and its value in supporting disease prevention efforts aimed at the reduction of modifiable cancer-causing exposures.

Keywords:
Mutational signature; cancer driver; genome-scale NGS; carcinogen; cancer prevention.