

## 【S-4】

**Toxicogenomics of a Multinational Disease:  
Environmental Origin of Endemic Nephropathy**

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Endemic nephropathy (EN) is a devastating disease occurring in rural areas of Croatia, Bulgaria, Romania, Serbia and Bosnia, characterized by its insidious onset, invariable progression to chronic renal failure and a strong association with upper urothelial tract cancer. We hypothesize that chronic dietary exposure to aristolochic acid (AA), an established nephrotoxin and human carcinogen, in the form of home-baked bread, is clearly related to the development of EN and urothelial cancer. This hypothesis is based on reports from Belgium, China, and other countries of patients with aristolochic acid nephropathy and is strongly supported by a pilot epidemiologic study conducted in Croatia (Hranjec et al, *Croat. Med J.* **46**, 116, 2005). Additionally, we have demonstrated the presence of 7-(deoxyadenosin-N6-yl) - and 7-(deoxyguanosin- N2-yl) aristolactam DNA adducts in renal and urothelial tissues from individuals with EN adduct structure was established by mass spectroscopy. We also have shown that A:T to T:A mutations predominate in p53- positive urothelial cancers in patients from the endemic region of Croatia. To explore the possibility that one or more genes involved in biotransformation of AA and/or repair of AA-DNA adducts might account for the varying degree of susceptibility to nephropathy observed among persons exposed to AA, we used high-throughput genotyping to analyze the pattern of single nucleotide polymorphisms in relevant genes of individuals enrolled in the pilot epidemiologic study. This information was then used to establish presumptive haplotypes/genotypes associated with susceptibility to EN and to identify genes associated with the development of this disease. We conclude from our investigations that chronic low-dose dietary exposure to aristolochic acid is responsible, in genetically susceptible individuals, for EN and its associated urothelial cancer.

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