Australian National University

ABC Transporters. A riddle wrapped in a mystery inside an enigma

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Slatyer Seminar Room R N Robertson Building (#46)

ABC transporters are ubiquitous among species. Their ancient origin has been highly conserved, with a deployment of two transmembrane and two cytosolic nucleotide-binding domains. The former allow the substrate translocation pathway, a process that powered by alternating ATP hydrolysis in the nucleotide-binding domains. These proteins are involved in import/export, with prokayotes employing mainly importers of essential nutrients and eukaryotes being exclusively exporters. Both groups have representative members that elaborate multidrug resistance, including human P-glycoprotein (ABCB1) whose over-expression is the commonest cause of cancer chemotherapy failure.

Eleven medium resolution ABC structures are now available yet many unsolved questions remain. In particular, the substrate sites are poorly defined and the mechanistic suite of changes that progress from ATP hydrolysis to substrate import or export in each cycle is ill-defined.

Our work in this field began in 1996 with the functional expression of human P-glycoprotein in *E. coli*. We have made progressive discoveries since, often against the weight of publication power games, including how the ATP cassettes form an allosteric dimer, and completing the geometry of the ATP catalytic sites. This talk will cover our work in ABC transporter research from an historical perspective.

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