

Stellingen behorende bij het proefschrift:

Ontogeny and Pharmacogenetics: Determinants of Age-Associated Differences in Drug Clearance During Human Development

1. Safe and effective drug therapy for infants, children and adolescents can only be achieved when they are included as subjects in clinical trials of drugs that may be of benefit to them (this thesis).
2. Dramatic developmental differences in the expression of a host of drug metabolizing enzymes not only occur but most importantly, are both enzyme and substrate specific. (this thesis)
3. As illustrated by linezolid, the apparent ontogeny of ubiquitously expressed enzymes (e.g., esterases) reflects dramatic acquisition of activity that appears to be responsive to changes associated with adaptation to the extra uterine environment (this thesis).
4. While pharmacokinetic data for midazolam provides a “picture” that reflects the ontogeny of total body CYP3A activity, it suffers from a lack of selectivity for CYP3A4 (this thesis).
5. Cisapride appears to be an ideal pharmacologic probe to assess CYP3A4 activity (this thesis).
6. For CYP2D6 extensive metabolizers, interindividual variability in drug biotransformation may be associated with the number of functional alleles (i.e., one vs. two) inherited (this thesis).
7. There are special ethical and scientific issues that must be considered in order to deliver pharmacogenetics into clinical pediatrics that, if executed poorly, will limit the useful integration of the new biology into clinical therapeutics (this thesis).
8. The apparent drug biotransformation “phenotype is a function of the complex interplay among genes involved in drug transport, cellular receptors, enzymes and signal transduction processes, among others (Leeder JS, *Pediatr Clin North Am* 2001;48:765-781).
9. Society created the “therapeutic orphan” and it is society that must adopt him/her.
10. “Superstition sets the whole world in flames; philosophy quenches them” (Voltaire, *Dictionnaire philosophique*, 1764).
11. “In research, the horizon recedes as we advance, and is no nearer at sixty than it was at twenty. As the power of endurance weakens with age, the urgency of the pursuit grows more intense....And research is always incomplete” (Mark Pattison, *Isaac Casaubon*, ch. 10, 1875).