

The DNA replication initiation machinery as a target for cancer diagnosis and therapy

1. The initiation of DNA replication acts as a convergence point for complex and redundant upstream growth signalling pathways (this thesis).
2. The replicative helicase protein Mcm5 is a sensitive and specific biomarker for bladder cancer detection and is of potential clinical value for the detection of prostate and pancreaticobiliary tract cancers (this thesis).
3. DNA replication initiation factors can provide prognostic information on disease progression and when combined with mitotic markers predict the response to cell cycle specific therapeutic agents in breast cancer and possibly other cancers (this thesis).
4. Perturbation of DNA replication initiation in normal cells by Cdc7 downregulation induces an origin activation checkpoint response coordinated by the cell stress response factor FoxO3a and effected by tumour suppressor and proto-oncogene proteins that arrests untransformed cells in the G1 phase of the cell cycle (this thesis).
5. p53-mutant breast cancer cells have lost the origin activation checkpoint and therefore enter an abortive S phase followed by apoptotic cell death in response to Cdc7 knock down whereas normal mammary epithelial cells undergo reversible cell cycle arrest, thereby identifying Cdc7 as a potent and specific anti-cancer target (this thesis).
6. “The superior protection of the ‘normal’ cells suggests the possibility that pre-treatment with a compound such as SVA or caffeine might protect normal cells preferentially in vivo, and thereby allow a greater differential action of toxic chemotherapeutic drugs on tumor cells in the intact animal.” Pardee A, James L. 1975 Proc. Nat. Acad. Sci. USA, 72:12 4994-8.
7. “We continue to foresee cancer research as an increasingly logical science, in which myriad phenotypic complexities are manifestations of a small set of underlying organizing principles.” Hanahan D, Weinberg RA. 2011 Cell, 144:5 646-74.
8. “Will medical treatments provide cures for most common cancers over the next 60 years? They will probably do so for subsets of the main tumour types, and will undoubtedly extend survival and improve quality of life for many others.” Chabner BA, Roberts TG. 2005 Nat Rev Cancer. 5:1 65-72.
9. “Organisms are not billiard balls, propelled by simple and measurable external forces to predictable new positions on life’s pool table. Sufficiently complex systems have greater richness. Organisms have a history that constrains their future in myriad, subtle ways.”, Stephen Jay Gould.
10. “We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances.”, Isaac Newton.
11. $e^{i\pi} + 1 = 0$, Leonard Euler.