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Rational and random approaches to adenoviral vector engineering

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Citation

Uil, T. G. (2011, January 28). *Rational and random approaches to adenoviral vector engineering*. Retrieved from <https://hdl.handle.net/1887/17743>

Version: Corrected Publisher's Version

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STELLINGEN

Behorende bij het proefschrift

Rational and random approaches to adenoviral vector engineering

1. Lentiviral vector-mediated expression of pIX or fiber variants can facilitate phenotypical pIX- or fiber-pseudotyping of adenovirus. – *this thesis*
2. Adenovirus capsid incorporation of a pIX-single-chain T-cell receptor (scTCR) fusion construct is efficient and correlates with increased transduction of target cells expressing the cognate peptide-MHC complex. – *this thesis*
3. Unless optimized for proper folding in the cytosol, single-chain variable fragment (scFv) antibodies are not suitable as adenovirus targeting ligands genetically fused to adenovirus capsid components. – *this thesis; Magnusson et al. (2002) J. Gene Med.; Hedley et al. (2005) Gene Ther.; Vellinga et al. (2007) Gene Ther.; Poulin et al. (2010) J. Virol.*
4. For adenovirus polymerase (Ad pol), substitution of any one of the five invariant exonuclease domain residues implicated in metal ion binding and exonuclease catalysis leads to an inability to sustain adenovirus replication. – *this thesis*
5. Replacement of Ad pol residues implicated in stabilization of the nascent DNA strand terminus at the exonuclease active site (during proofreading) can considerably increase the 'spontaneous' mutation rate of adenovirus. – *this thesis*
6. 'Mutator' adenovirus polymerases can facilitate the directed evolution of more potently cytolytic adenoviruses. – *this thesis*
7. The minority subpopulation of fiber-encoding major late transcripts that carry 'x' and/or 'y' ancillary leaders likely contributes most to the level of fiber synthesis. – *Uhlen et al. (1982) EMBO J.; Anderson and Klessig (1984) Proc. Natl. Acad. Sci. USA.*
8. While biodistribution properties of an injected viral vector determine which cells are available for transduction, cell transduction capabilities of the vector are not the major determinants of biodistribution. – *Alemanly (2009) Methods Mol. Biol.*
9. "A better understanding of evolutionary principles governing natural viral evolution will drive more advanced methods to successfully engineer novel virus-based gene therapeutics." – *Excoffon et al. (2009) Proc. Natl. Acad. Sci. USA.*
10. "There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved." – *Darwin (1859) On the Origin of Species*
11. "Not many words will be required now to show that Nature has no end set before it, and that all final causes are nothing but human fictions." – *Spinoza (1677) Ethica*
12. "At any street corner the feeling of absurdity can strike any man in the face." – *Camus (1942) Le Mythe de Sisyph*