

## Adenovirus group

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### Overview

Adenoviruses can cause tumours in newborn rodents and can, therefore, be used as a model system for human cancers. By studying the relationship between the virus proteins and the host cell it helps us to understand some of the ways in which human cancers arise.

### Our research group

Adenoviruses serve as an excellent model system for human cancers, in that many of the pathways targeted by the virus, during both infection and transformation, are deregulated in tumour cells. The transforming ability of the virus and the viral DNA resides, primarily, in two early region oncoproteins: E1A and E1B55K. Over the past decades we have engaged in an exhaustive study of the properties of these proteins. At present our interest is focussed mainly on the relationship of adenoviruses to the host cell DNA damage response (DDR). We, and others, have shown that a number of host cell DDR components are targeted for degradation during viral infection. We are now investigating why, and the mechanism by which, a number of novel proteins are also degraded. We have used the study of adenoviruses as a starting point for the characterization of certain cellular proteins which have particular links to the virus and AdE1A and E1B55K components. Thus I (RG) have devoted considerable time and effort to the study of the properties of hnRNPUL-1 (also known as adenovirus E1B associated protein 5[E1B-AP5]), CtIP, and to other DDR components. AST has concentrated on a study of the anaphase promoting complex (APC) and cell cycle regulation.

### Recent publications

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- **Turnell AS, Grand RJ.** (2012) DNA viruses and the cellular DNA-damage response. *J Gen Virol.* 93:2076-97.
- **Polo SE, Blackford AN, Chapman JR, Baskcomb L, Gravel S, Rusch A, Thomas A, Blundred R, Smith P, Kzhyshkowska J, Dobner T, Taylor AM, Turnell AS, Stewart GS, Grand RJ, Jackson SP** (2012) Regulation of DNA-end resection by hnRNPU-like proteins promotes DNA double-strand break signalling and repair. *Mol. Cell;* 45:505-16.
- **Forrester NA, Patel RN, Speiseder T, Groitl P, Sedgwick GG, Shimwell NJ, Seed RI, Catnaigh PÓ, McCabe CJ, Stewart GS, Dobner T, Grand RJ, Martin A, Turnell AS.**(2012) **Adenovirus E4orf3 targets transcriptional intermediary factor 1γ for proteasome-dependent degradation during infection.** (<http://www.ncbi.nlm.nih.gov/pubmed/22205733>) *J Virol.* ; 86:3167-79.
- **Forrester NA, Sedgwick GG, Thomas A, Blackford AN, Speiseder T, Dobner T, Byrd PJ, Stewart GS, Turnell AS, Grand RJ** (2011) Serotype-specific inactivation of the cellular DNA damage response during adenovirus infection. *J. Virol;* 85: 2201-11.
- **Blackford AN, Patel RN, Forrester NA, Theil K, Groitl P, Stewart GS, Taylor AM, Morgan IM, Dobner T, Grand RJ, Turnell AS** (2010) Adenovirus 12 E4orf6 inhibits ATR activation by promoting TOPBP1 degradation. *Proc Natl Acad Sci USA;* 107-12251-6.

### Current projects

#### KSHV and the DNA damage response.

KSHV has been shown to be responsible for Kaposi's Sarcoma as well as a number of rarer conditions. Many viruses are known to activate cellular DNA damage response pathways. This may either be required for viral replication or may be inhibited by the virus, facilitating replication. In this project we are investigating the relationship of KSHV to the damage response in latently infected cells and during lytic infection.

#### Characterization of hnRNPUL1.

hnRNPUL1 (also known as E1B-AP5) was first isolated as a binding partner for adenovirus E1B55K protein. It has since been shown to have roles in RNA metabolism, transcriptional regulation (of, for example, p53) and the cellular DNA damage response. In particular hnRNPUL1 appears to be involved in homologous recombination through interaction with NBS1. We are now investigating whether the proteins have potential kinase activity against nucleotide substrates as well as its interaction with other DNA damage pathway components.

### Staff

#### Principle Investigator(s)

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#### Students

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