## MARK ISALAN

### Biography

**Dr. Mark Isalan** received his Ph.D. in Molecular Biology from the University of Cambridge, UK, in 2000. His PhD thesis was supervised by Prof. Sir Aaron Klug, OM, FRS, and involved engineering zinc fingers to bind new DNA sequences. This work continued postdoctorally at Gendaq Ltd, UK (now owned by Sangamo Biosciences, Richmond CA) and contributed to the CompoZr zinc finger nucleases now available commercially from Sigma Aldrich. In 2002 Dr. Isalan was awarded a Wellcome Trust International Research Fellowship to carry out research on engineering artificial gene networks in Prof. Serrano's group at the EMBL Heidelberg, Germany. Since 2006, he has been a group leader at the EMBL-CRG Systems Biology Unit in Barcelona. The group's work focusses on synthetic gene network engineering, aiming to design biological systems that behave predictably.

### Project

**European Research Council Starting Grant**
Project acronym: ZINC-HUBS
Project full title: Engineering zinc fingers to target cancer hub genes

**Overview**
For the last ten years, protein engineering technologies have been developed to make zinc finger peptides to recognise a wide variety of user-defined DNA sequences. This has enabled the construction of synthetic transcription factors that can upregulate or repress target genes at will. More recently, synthetic zinc fingers have been linked to nucleases to direct double stranded breaks at desired loci within genomes. These breaks increase the efficiency of homologous recombination so that, by providing an exogenous repair sequence, it is possible to repair or mutate endogenous genes. Although zinc finger engineering has reached a state of maturity, there are very few groups in the world who have the technical know-how to adopt this technology, and this has delayed general uptake. We propose to use the expertise we have developed, in both zinc finger engineering and gene repair, to construct zinc finger proteins to recognise some of the most highly-connected (and widely-studied) genes in biology. This will serve as a toolkit for the research community to target these hub genes and either mutate or repair them. As a starting point we propose to target the following genes: TBP (TATA-binding protein), p53, p300, RXR, pRB, RelA, c-jun, c-myc, and c-fos. These genes are the most connected hubs in the human transcription factor network (TRANSFAC 8.2 database) and their mutants are associated with a variety of diseases. We will engineer and characterise zinc finger proteins that recognise these DNA sequences in vitro and induce gene repair in vivo. For example, this will allow cancer cell lines to have particular oncogenes repaired or mutated, within the context of all the other mutations that have been accrued during the process of oncogenesis. This will help to characterise the contribution of network nodes and hubs to the observed phenotypes. Ultimately, some of the gene repair peptides we create will have therapeutic potential, as well as providing tools for systems and networks biology.