Project: Synthetic Antibodies for ChIP-onCHIP

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Introduction

The genetic program of any eukaryotic cell is dependent on dynamic interaction of protein networks with genes on chromosome. Many diseases, with leukemia being one prominent one, are the consequence of deregulation of transcription factors. A modern technique to study the molecular dynamics on chromosomes is chromatin immunoprecipitation (CHIP). However, the technology has its limitations for the applications in humans mainly because of a low sensitivity and the failure to combine it with genetic methods. Here we propose to develop synthetic antibodies that combined with suitable expression strategies extend the potential of the conventional CHIP technology.

Chromatin immunoprecipitation technique (ChIP) has become a major tool for studying protein-DNA-interactions in living cells. It is based on the cross linking of DNA and protein in living cells. DNA bound to a certain protein is precipitated with a specific antibody generated against this protein. Afterwards the enrichment of the precipitated DNA is quantified using the polymerase chain reaction. In theory, this technique allows to monitor the localization of a single protein at any position of the genome. The method is not limited to the analysis of single genes but can be combined with genomic a DNA-microarray analysis. The so-called ChIP-chip analysis allows to monitor protein–DNA interaction throughout the human genome. A bottleneck remains the Chip technique per se, which is dependent on the availability of suitable antibodies that have to track proteins hidden in highly cross-linked protein-DNA networks. The main goal of this new project is the technological advancement of ChIP and CHIP-chip technology through the development of synthetic antibodies with special biophysical properties. This program initially requires to develop suitable expression systems that produce intact proteins fused to synthetic linker regions at physiological levels. The major challenge then will be to develop a strategy that allows to detect these factors with high sensitivity via CHIP. Towards this goal we apply several validated engineered protein-protein interaction pairs. These will be fused one side to cellular factors and used instead of conventional antibodies on the other side. If validated for the use in CHIP these could be further developed into specific synthetic antibodies. We envision that such an alternative CHIP-technology provides access to a broad range application relevant to understanding the cause of human diseases.