Exon/SNP-6 Arrays analyses in monoclonal gammopathy evolution

Elena Dementyeva

Pavel Nemec

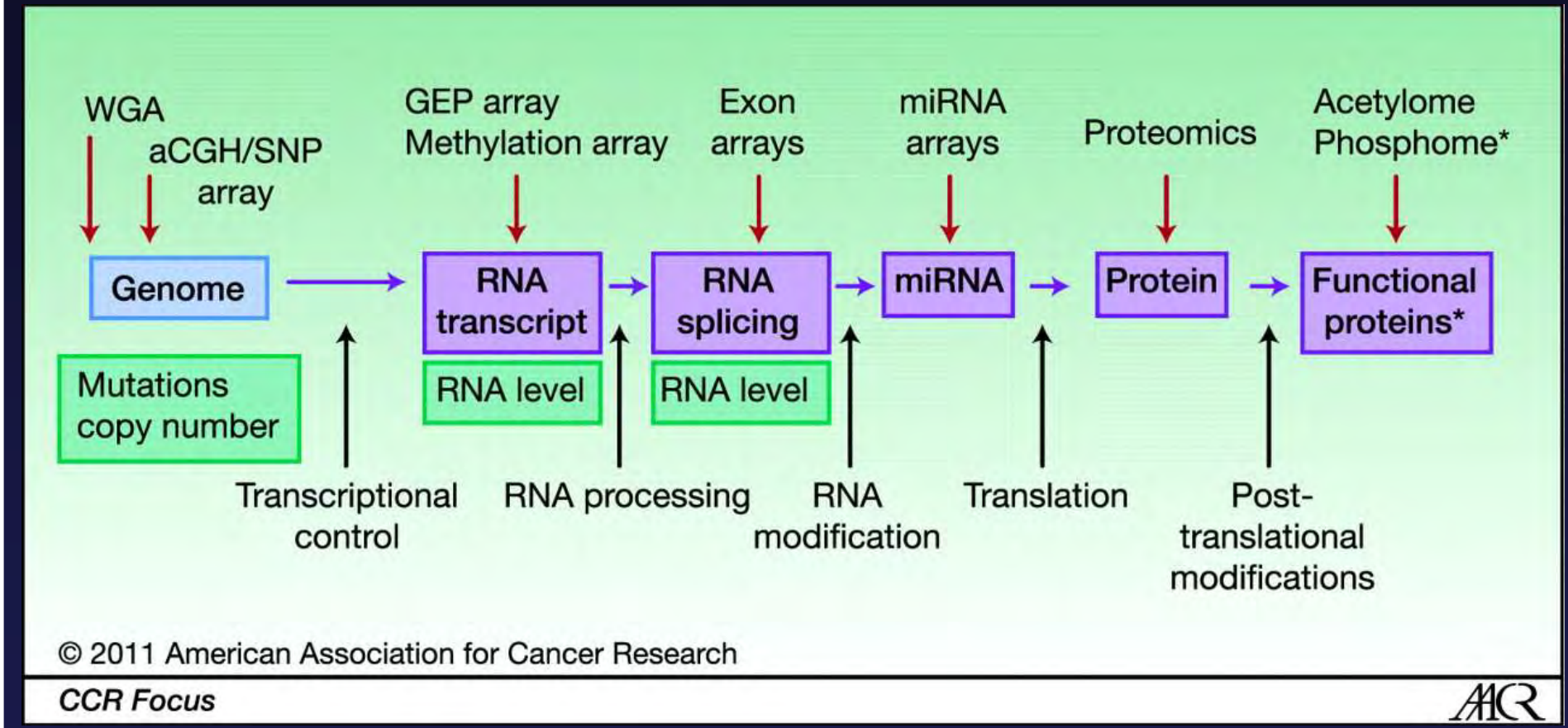
Karen Dybkær Sørens

Hans Erik Johnsen

Roman Hajek

Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University

High-throughput genomic analysis spanning all regulatory checkpoints



Munshi N C, et al. Clin Cancer Res. 2011;17:1234-1242.

Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University

Global View of Myeloma Genome

DNA

- Amplification and Deletion – array CGH

- Single Nucleotide Polymorphism – 500K SNP array

RNA

- Expression changes – expression profile with GeneChip® Human Exon 1.0 ST

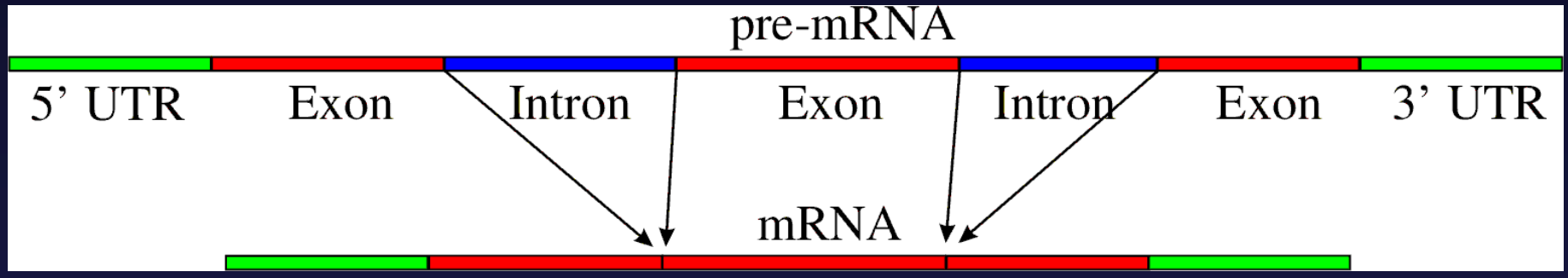
- Alternate splicing – genome-wide Exon analysis with GeneChip® Human Exon 1.0 ST

Exon Arrays

- The GeneChip Human Exon 1.0 ST Arrays gives possibility to analyze alternate splicing in myeloma using high throughput exon array analysis.
- Alternate splicing is an important post translational change that alters specificity of gene function.
- They provides information on expression levels for genes, but as the probe sets are spread evenly over each exon, the array data also provides information on presence of each exon and identify recurrent alternately spliced genes.

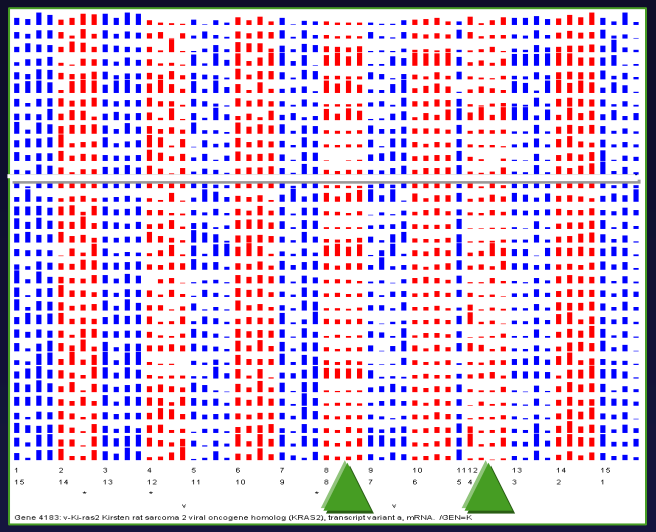
Modifiers of Transcriptome Alternative Splicing

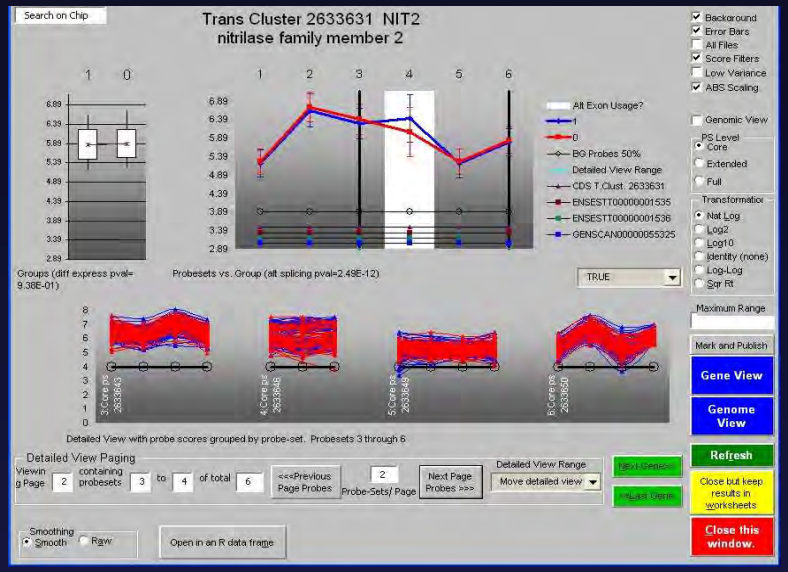
- Allows for multiple proteins from one gene with different function, half life or additive activity



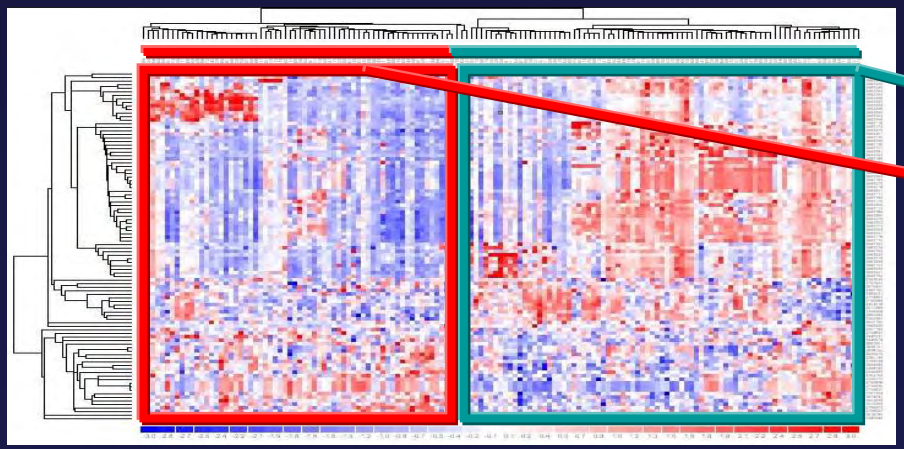
- Alternative splicing produces multiple protein isoforms
- 92–94% of human genes undergo alternative splicing
- 85% have minor isoform frequency of 15% or more
- Isoform frequency varies between tissues
- Protein isoforms may have related, distinct or even opposing functions

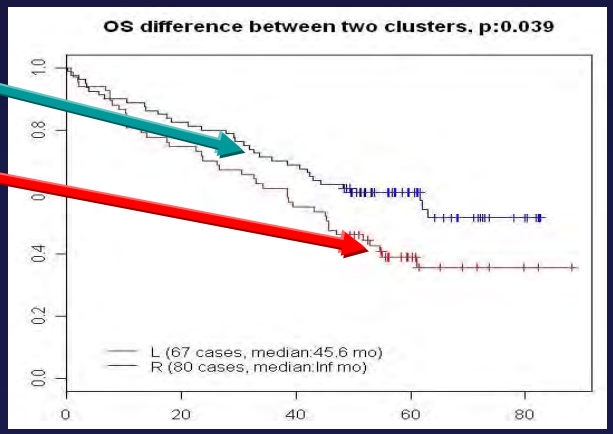
Alternate Splicing is a Frequent Event and Impacts Clinical Outcome In Myeloma





Unsupervised Analysis Identifies Clinically Relevant Subgroups



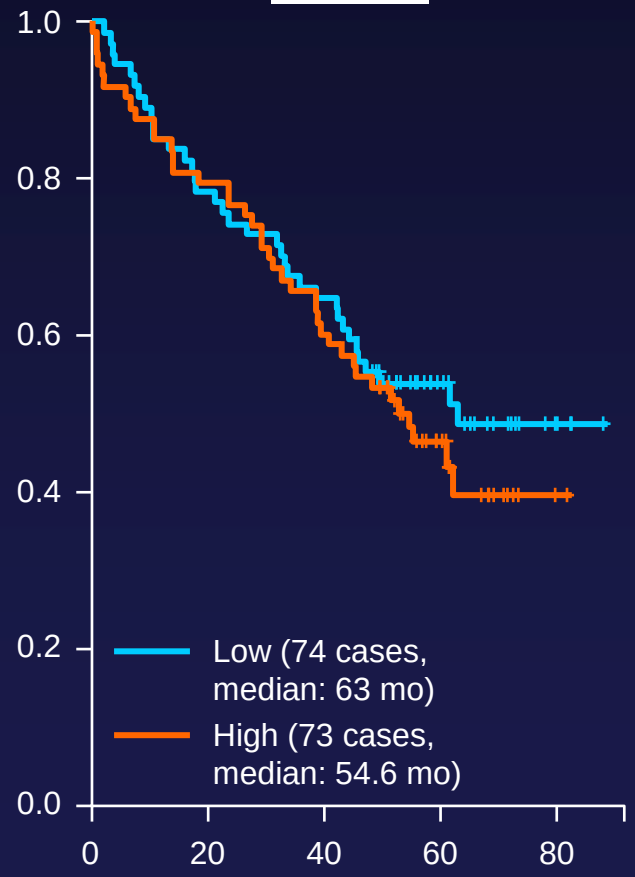


Munshi NC, et al. Blood. 2009;112: [abstract 2846] Updated, presented at ASH 2009.

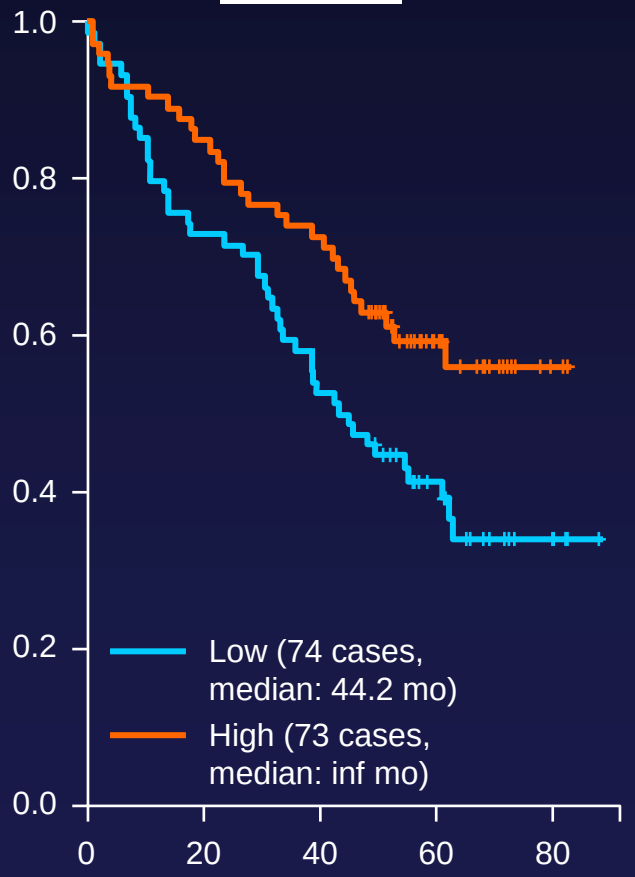
Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University

Spliced Genes Predict Differential Outcome

Gene level xxx, p = 0.46



Exon adjusted level xxx, p = 0.016



Munshi NC, et al. Blood. 2009;112: [abstract 2846] Updated, presented at ASH 2009.

Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University

Exon array is vulnerable to SNPs

- SNPs can affect the hybridization of the probes
  produce misleading exon-level expression values.
- Database for genome-wide search for SNPs within regions that hybridize to probes.
- These affected probes and/or probesets can be filtered in the data processing procedure thus controlling for potential false expression phenotypes when using this exon array.

A comprehensive high-resolution analysis of genomic imbalances from the early to late stages of monoclonal gammopathies

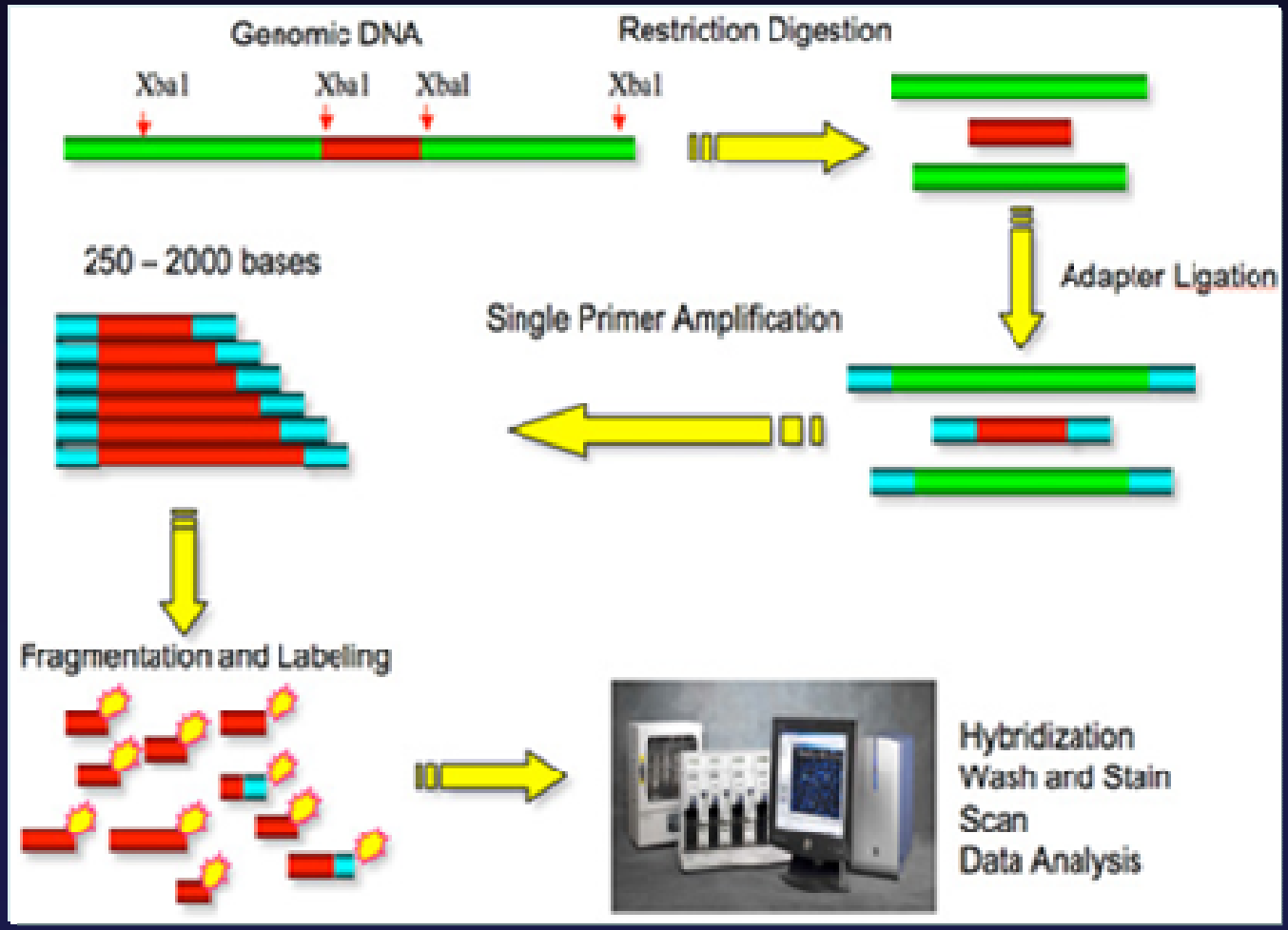
DNA: SNP-arrays

1. Copy number abnormalities (CNA)
2. Copy number neutral LOH (CNN-LOH)
3. Correlation with fragile sites (FRA)

López-Corral L et al. Blood. 2011: [abstract 295] Data presented at ASH 2011.

Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University

Genome-Wide Human SNP-Array 6.0 assay protocol (Affymetrix)



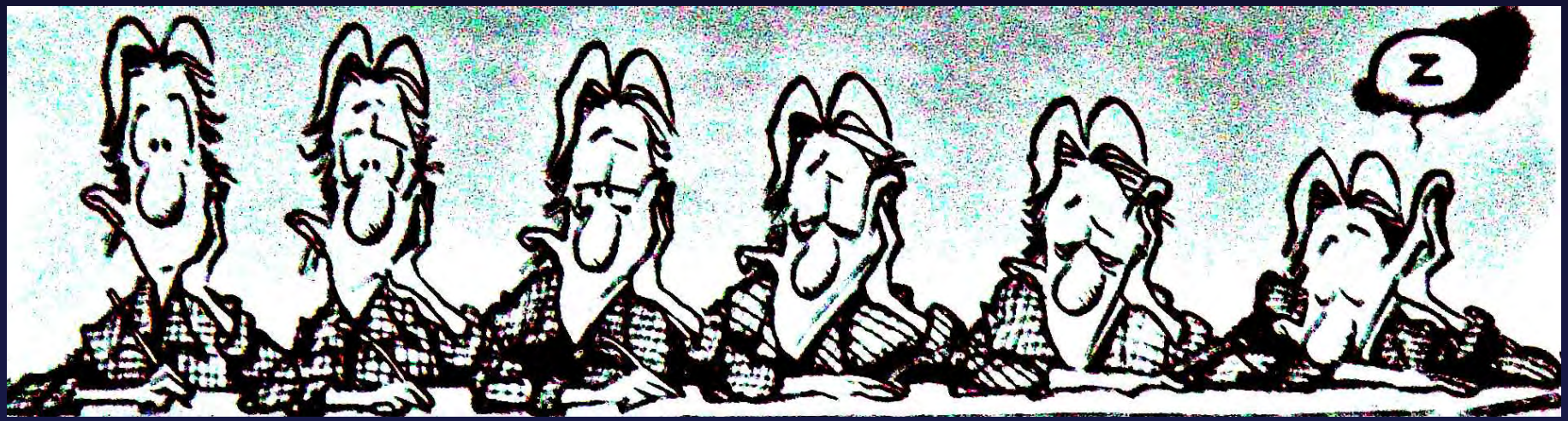
SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies: from MGUS to myeloma status

- The whole genome analysis using SNP-arrays revealed an increasing genomic complexity from MGUS to SMM and to MM.
- The transition from MGUS to MM was not associated with a particular chromosomal imbalance, but rather with an expansion of altered clones that were already present in MGUS.
- More than a half of the genetic lesions were located at fragile sites.

López-Corral L et al. Blood. 2011: [abstract 295] Data presented at ASH 2011.

Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University

Thank you for your attention



Babak Myeloma Group
Dept. of Pathological Physiology
Faculty of Medicine, Masaryk University