HBM4EU project

Genetic variability and the risk of developing asbestos related diseases

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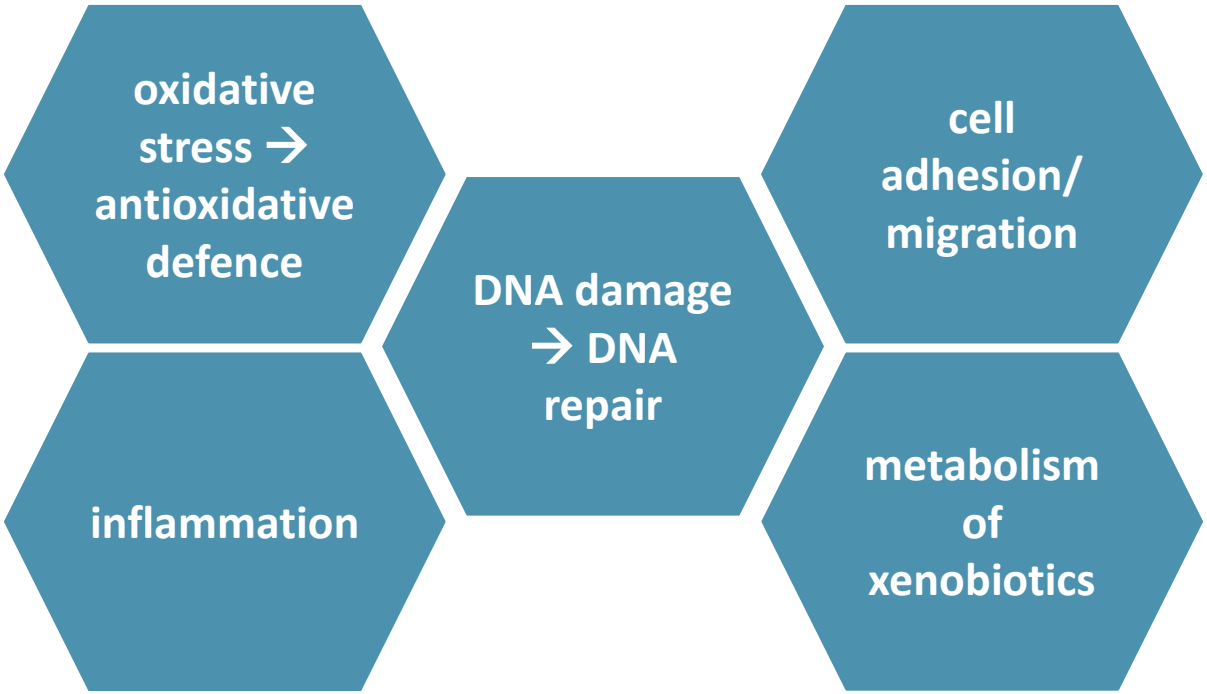
Introduction

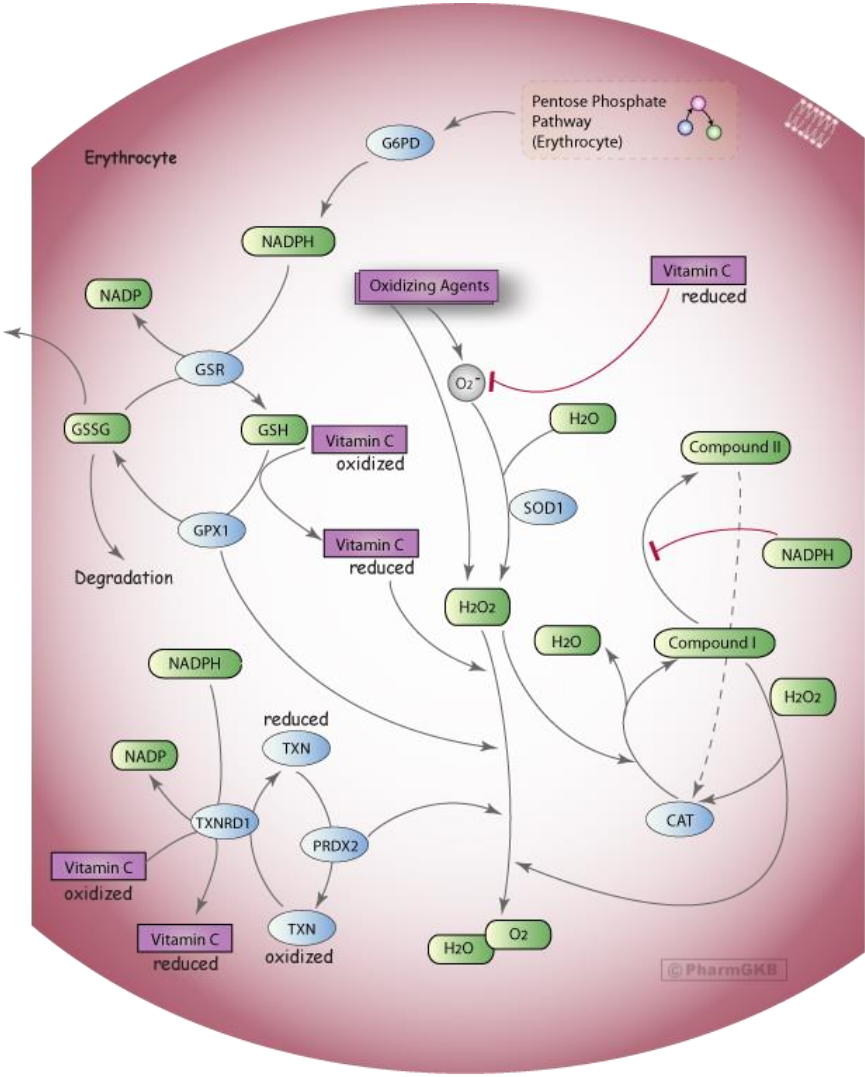
Several metabolic pathways can contribute to development and progression of asbestos related diseases:



Molecular mechanisms involved in development of asbestosis

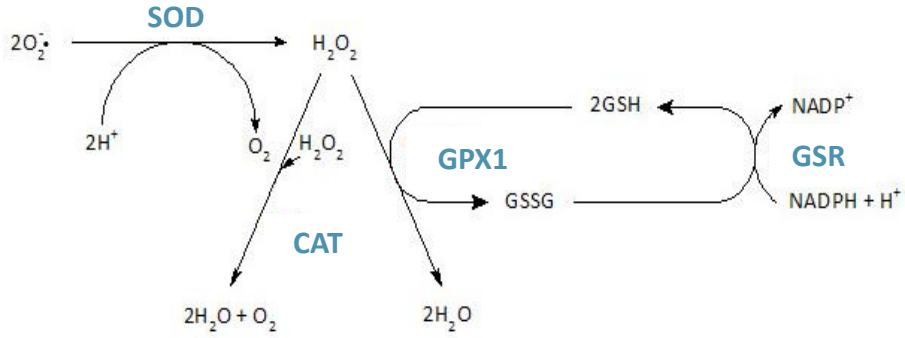
Oxidative stress

- asbestos fibres and interaction of asbestos fibers with macrophages generates harmful reactive oxygen species
- key reactive metabolites in the pathogenesis of asbestos related diseases:
  - superoxide anion (O_2^-)
  - hydrogen peroxide (H_2O_2)
  - hydroxyl radical ($OH^\cdot$)
  - nitric oxide (NO)



McDonagh et al., Pharmacogenet Genomics, 2013

Biomarkers of asbestosis

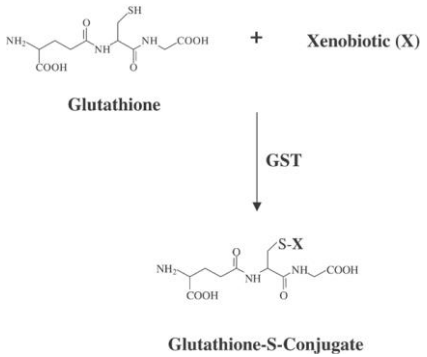


Antioxidative defence

- superoxide dismutase (*SOD*)
  - *SOD* converts O_2^- to H_2O_2
  - mitochondrial *SOD2* rs4880 (p.Ala16Val): decreased risk
  - extracellular *SOD3* rs1799895 (p.Arg213Gly): no influence on risk
- catalase (*CAT*)
  - *CAT* converts H_2O_2 to H_2O and O_2
  - promoter rs1001179 (c.-330C>T): slightly increased risk
- inducible nitric oxide synthase (*iNOS*)
  - iNOS catalyses NO production
  - number of $(CCTTT)_n$ repeats in the promoter region: no definitive results

Franko et al., J Biomed Biotechnol, 2009
Franko et al., J Arh Hig Rada Toksikol, 2008
Franko et al., J Biomed Biotechnol, 2011

Biomarkers of asbestosis



Metabolism of xenobiotics

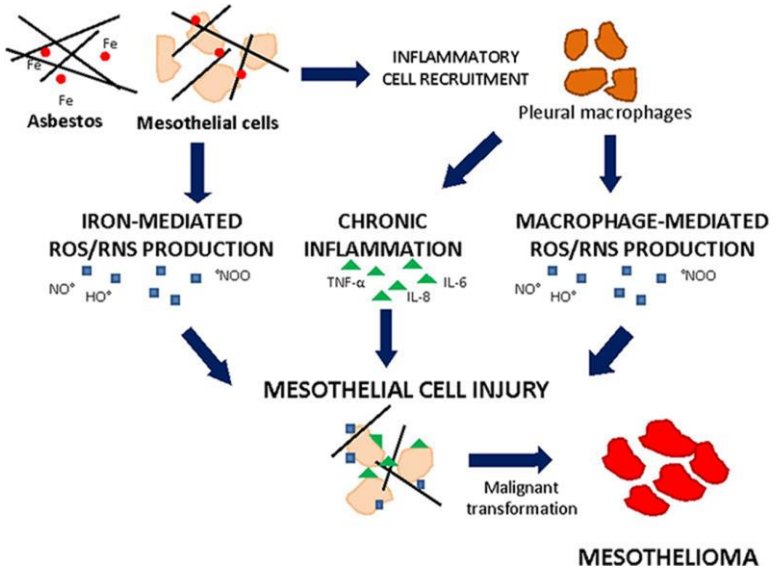
- glutathione S-transferases (*GST*)
  - GSTs catalyse detoxification of xenobiotic substrates
  - *GSTT1* gene deletion: modified risk for severe pulmonary fibrosis; conflicting results
  - *GSTM1* gene deletion: increased risk for development of pleural plaques, not associated with asbestosis
  - *GSTP1*: enzyme with high conjugation capacity significantly increases the risk of developing asbestosis

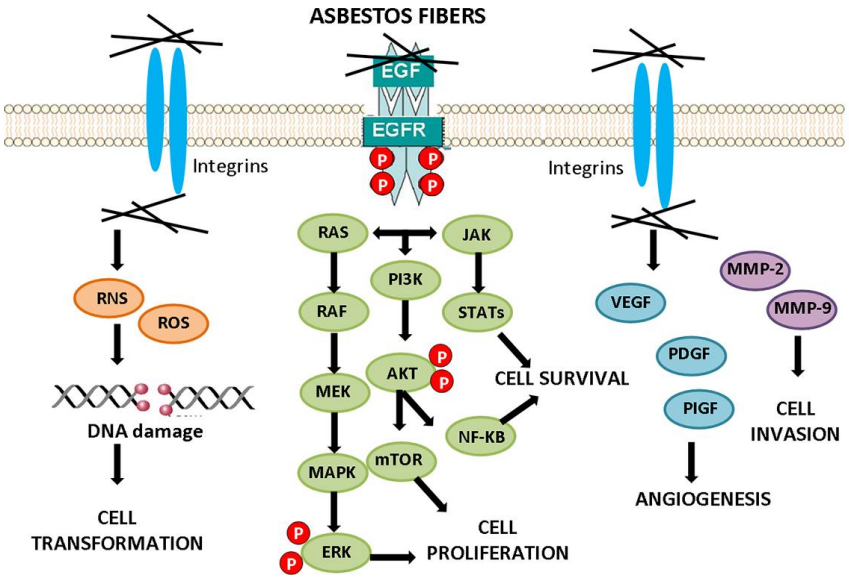
Inflammation

- tumor necrosis factor α (*TNFα*)
  - multifunctional, proinflammatory cytokine
  - promoter rs1800629 (c.-308G>A): increased risk for some fibrotic lung diseases

Kukkonen et al., Eur Respir J, 2011; Franko et al., J Occup Environ Med, 2007; Franko et al., J Occup Environ Med, 2008; Townsend and Tew, Oncogene, 2002; Helmig et al., Biomarkers, 2010

Molecular mechanisms involved in development of MM



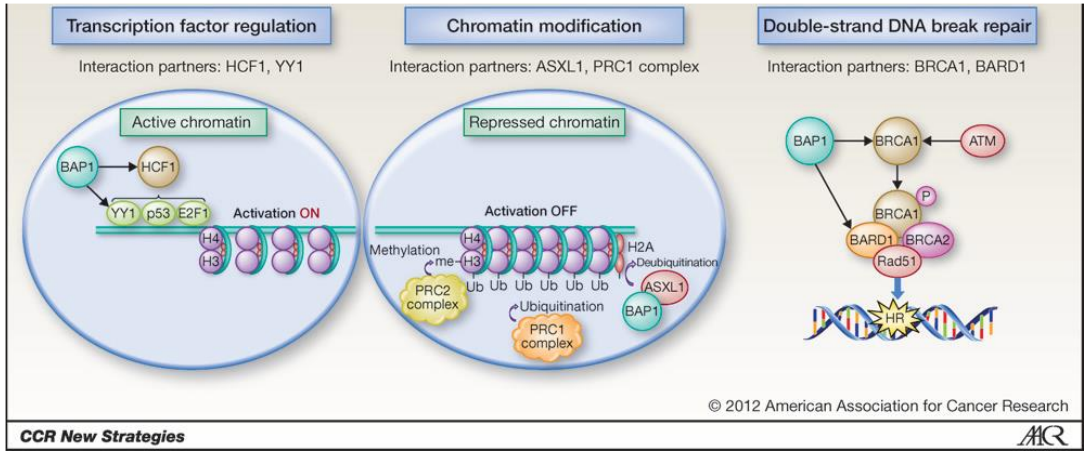


Benedetti et al., Oncotarget, 2015

Biomarkers of MM

Germline mutations

- BRCA1-associated protein 1 (*BAP1*)
  - tumor suppressor: regulation of cell cycle, transcription, chromatin modification, DNA damage response
  - aberrant expression and truncating mutations lead to tumor predisposition syndrome, including increased MM risk
  - less common in sporadic cases

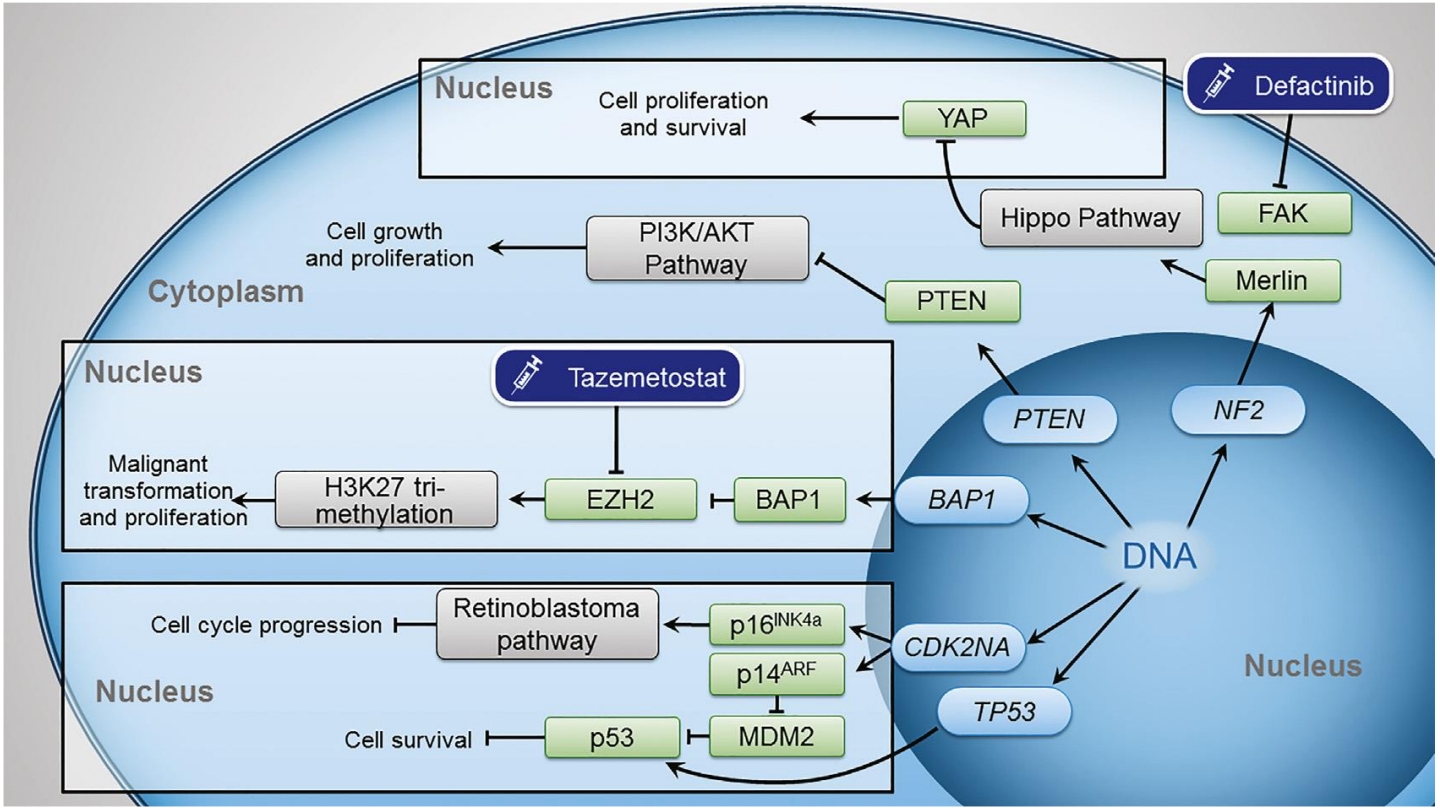


- neurofibromin 2 (*NF2*)
  - tumor suppressor

Melaiu et al., JTD, 2018
Ladanyi et al., CCR, 2012

Biomarkers of MM

mutations involved in malignant transformation are also potential therapeutic targets in MM



McCambridge et al., JTO, 2018

Biomarkers of MM

Polymorphisms

Antioxidative defence

- NAD(P)H quinone dehydrogenase 1 (*NQO1*)
  - NQO1 helps prevent the formation of free radicals
  - rs1800566 (p.Pro187Ser): increased risk
- *SOD2*
  - rs4880 (p.Ala16Val): conflicting results
- heme oxygenase-1 (*HMOX1*)
  - *HMOX1* is involved in heme degradation and plays a protective role against oxidative stress
  - promoter polymorphism: increased risk

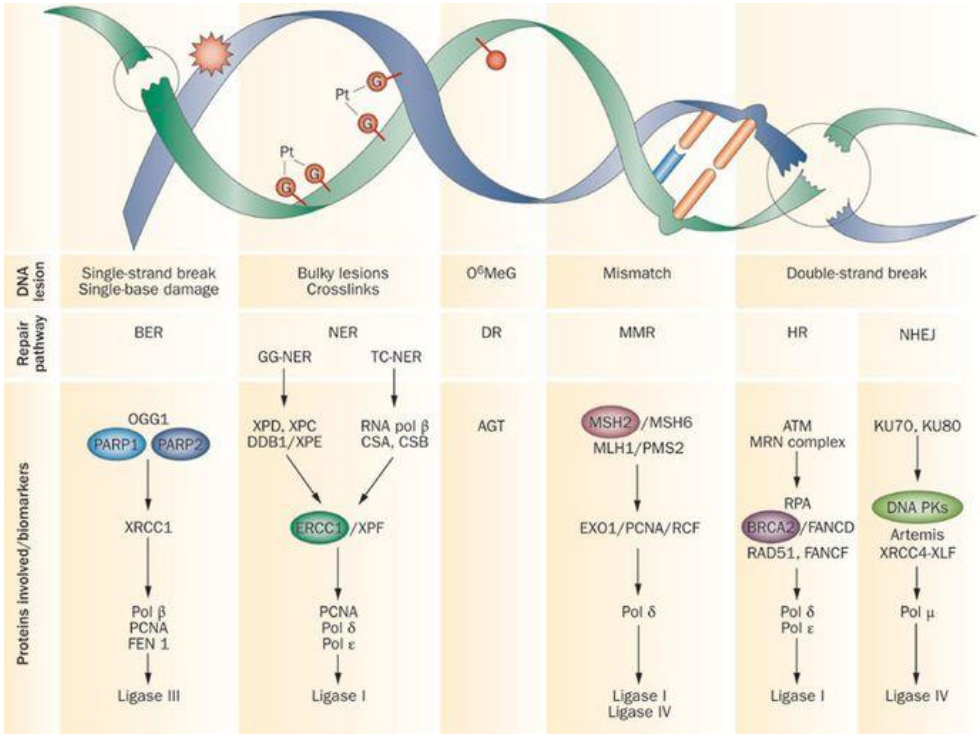
Franko et al., Radiol Oncol, 2018
Melaiu et al., JTD, 2018
Murakami et al., Lung, 2012

Biomarkers of MM

Polymorphisms

DNA repair

- *XRCC1*
  - base excision repair
  - rs25487 (p.Gln399Arg): increased risk
- *ERCC1*
  - nucleotide excision repair
  - rs11615 (p.Asn118Asn): increased risk
- *XRCC3*
  - double-strand break repair through homologous recombination
  - rs861539 (p.Thr241Met): increased risk



Postel-Vinay et al., Nat Rev Clin Oncol, 2012;
Melaiu et al., JTD, 2018; Betti et al., Mut Res, 2011

Biomarkers of MM

Polymorphisms

Metabolism of xenobiotics

- N-acetyl-transferase 2 (*NAT2*)
  - NAT2 is involved in metabolism of carcinogens
  - rate of acetylation asociated with MM risk; conflicting results
- *GSTM1*
  - gene deletion: increased risk

Cell adhesion/migration

- sidekick cell adhesion molecule 1 (*SDK1*)
  - adhesion molecule
  - identified in GWAS studies

Betti et al., Int J Hyg Environ Health, 2009
Melaiu et al., JTD, 2018

Biomarkers of MM treatment response

Factors affecting treatment response:

- **Clinical:** demographic, tumor characteristics
- **Genetic:** drug transport and metabolism, drug targets, DNA repair

MM treatment: gemcitabine & cisplatin doublet or pemetrexed & cisplatin doublet

Response to gemcitabine

- **Target enzyme**
  - *RRM1* rs1042927
- **DNA repair enzymes**
  - *ERCC2* rs13181
  - *XRCC1* rs25487
  - *ERCC1* rs3212986

Response to pemetrexed

- **Folate pathway**
  - *MTHFD1* rs2236225
- **Transporters**
  - *ABCC2* rs2273697

Erculj et al., Pharmacogenet Genomics, 2012; Erculj et al., Ann Oncol, 2012; Erculj et al., J Thorac Oncol, 2012; Goricar et al., Radiol Oncol, 2014

Algorithm for predicting outcome of MM treatment and treatment recommendations

A

MM patient at diagnosis

Clinical characteristics
Pharmacogenetic markers

GEMCITABINE/CISPLATIN | **PEMETREXED/CISPLATIN**

Marker		Score
CRP	<23 mg/	0
	>23 mg/l	0.3
Histological type	other	0
	sarcomatoid	1.1
RRM1 rs1042927	AA	0
	AC+CC	0.6
ERCC2 rs13181	AA	0
	AC+CC	0.2
ERCC1 rs3212986	CC	0
	CA+AA	0.8
XRCC1 rs25487	CC	0
	CT+TT	0.1
ECOG performance status	<2	0
	2	0.3

	1	2	3	4
GEM-score	0	0-0.75	0.75-1.65	>1.65
	favourable PFS		unfavourable PFS	

Marker		Score
CRP	<23 mg/	0
	>23 mg/l	2.4
MTHFD1 rs2236225	GG	0
	GA+AA	0.9
ABCC2 rs2273697	GG	0.6
	GA+AA	0

	1	2	3	4
PMX-score	0	0-2.7	2.7-3.3	3.9
	favourable PFS		unfavourable PFS	

B

Predicted response to gemcitabine		Predicted response to pemetrexed		Treatment recommendation
GEM score>0.75	unfavourable PFS	PMX score>2.7	unfavourable PFS	based on clinical parameters or toxicity markers
GEM score>0.75	unfavourable PFS	PMX score<2.7	favourable PFS	pemetrexed
GEM score<0.75	favourable PFS	PMX score>2.7	unfavourable PFS	gemcitabine
GEM score<0.75	favourable PFS	PMX score<2.7	favourable PFS	based on clinical parameters or toxicity markers

Goricar et al., Sci Rep, 2017

Conclusions

Risk of asbestos related diseases

- germline mutations and SNPs in different pathways contribute to development of asbestos related diseases
- understanding molecular mechanisms enables identification of clinically relevant biomarkers
- next stage: accounting for interactions with environmental factors

Treatment response

- based on clinical-pharmacogenetic models and algorithms, effective chemotherapy could be recommended for each patient leading to improved treatment outcome in MM

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Speaker's information

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