

From MMR to HNPCC

**Understanding hereditary GI cancers
through study of DNA mismatch repair**

Josef Jiricny Institute of Molecular Cancer Research, Zurich

Hein te Riele Netherlands Cancer Institute, Amsterdam

Mutational Load

Endogenous deamination 5-methyl C
Replication slippage -> IDLs
DNA damaging agents

Mechanisms maintaining
genome integrity

(DNA mismatch repair)



Functions of mammalian DNA mismatch repair

Repair of DNA mismatches

Replication errors and slippage

Base:base mispairing (eg hydrolytic deamination)

Coupling DNA damage recognition with cellular response

Methylating agents (Cejka 2003)

Cis-platinum (Aebi 1996) (*not in ES cells - Claij 2004*)

Radiation (Fritzell 1998)

5-FU (Meyers 2001)

Contributory role

Control of illicit recombination

Double stranded break repair

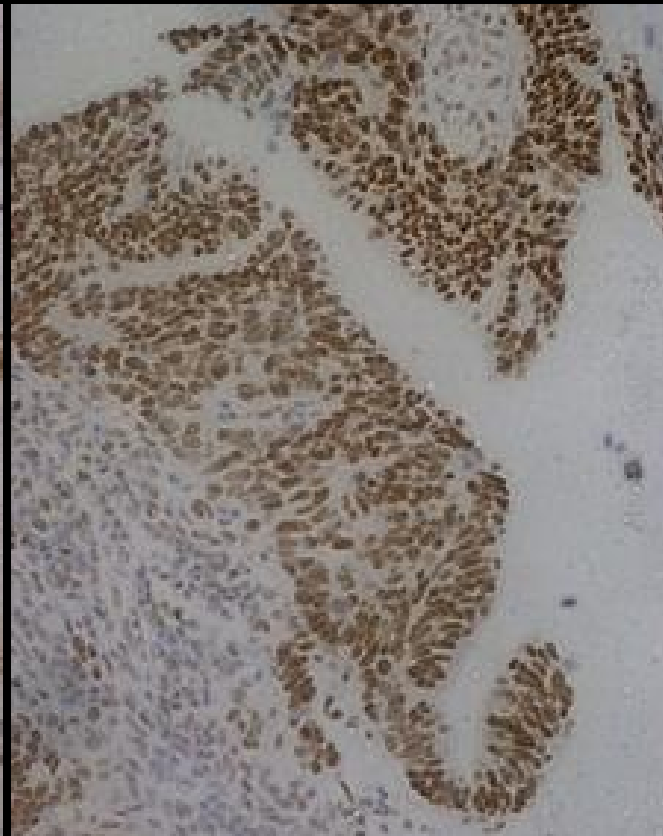
Transcription-coupled nucleotide excision repair

MSH2 immunohistochemistry

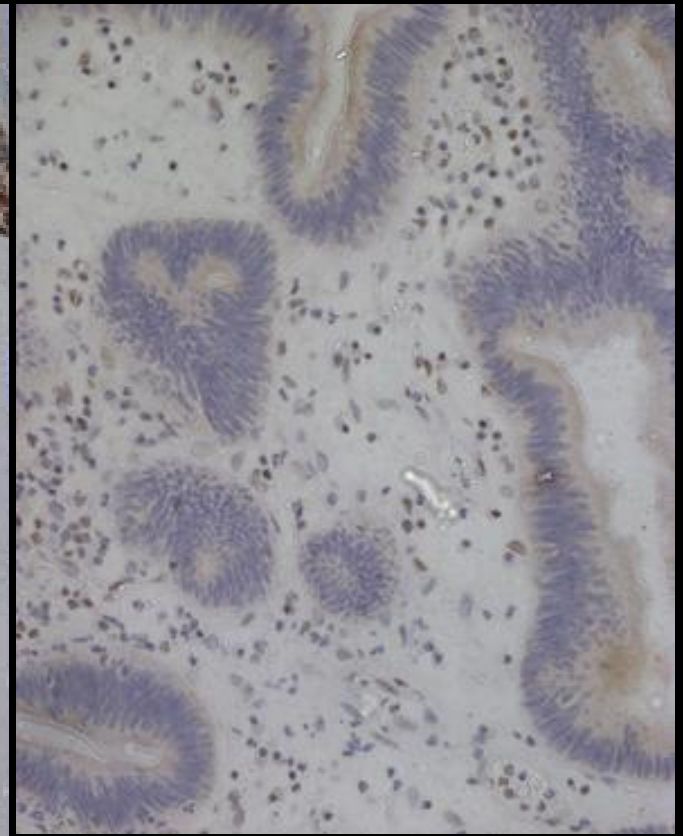
Normal mucosa



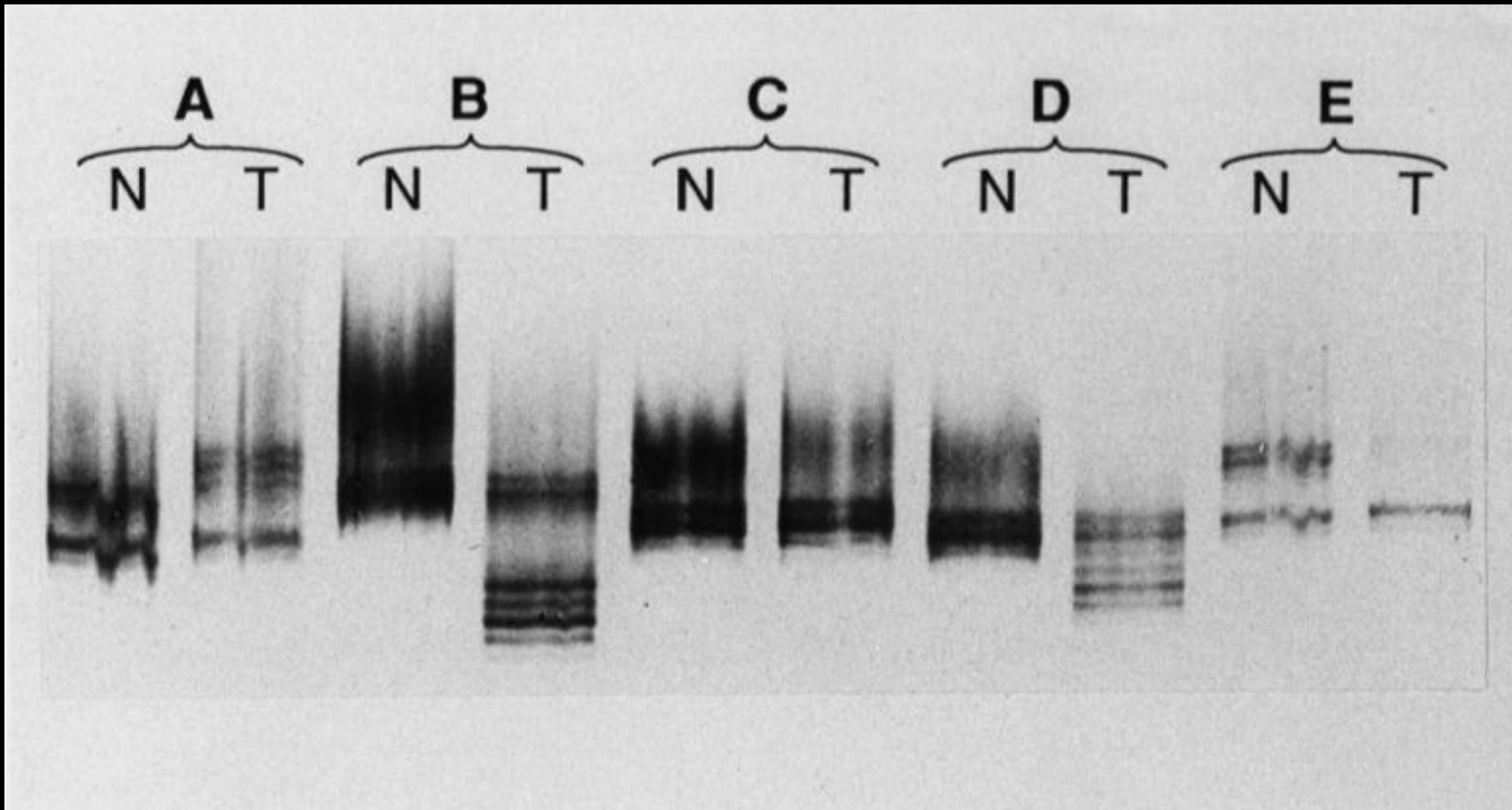
**Cancer
Retained expression**



**Cancer
Loss of expression**

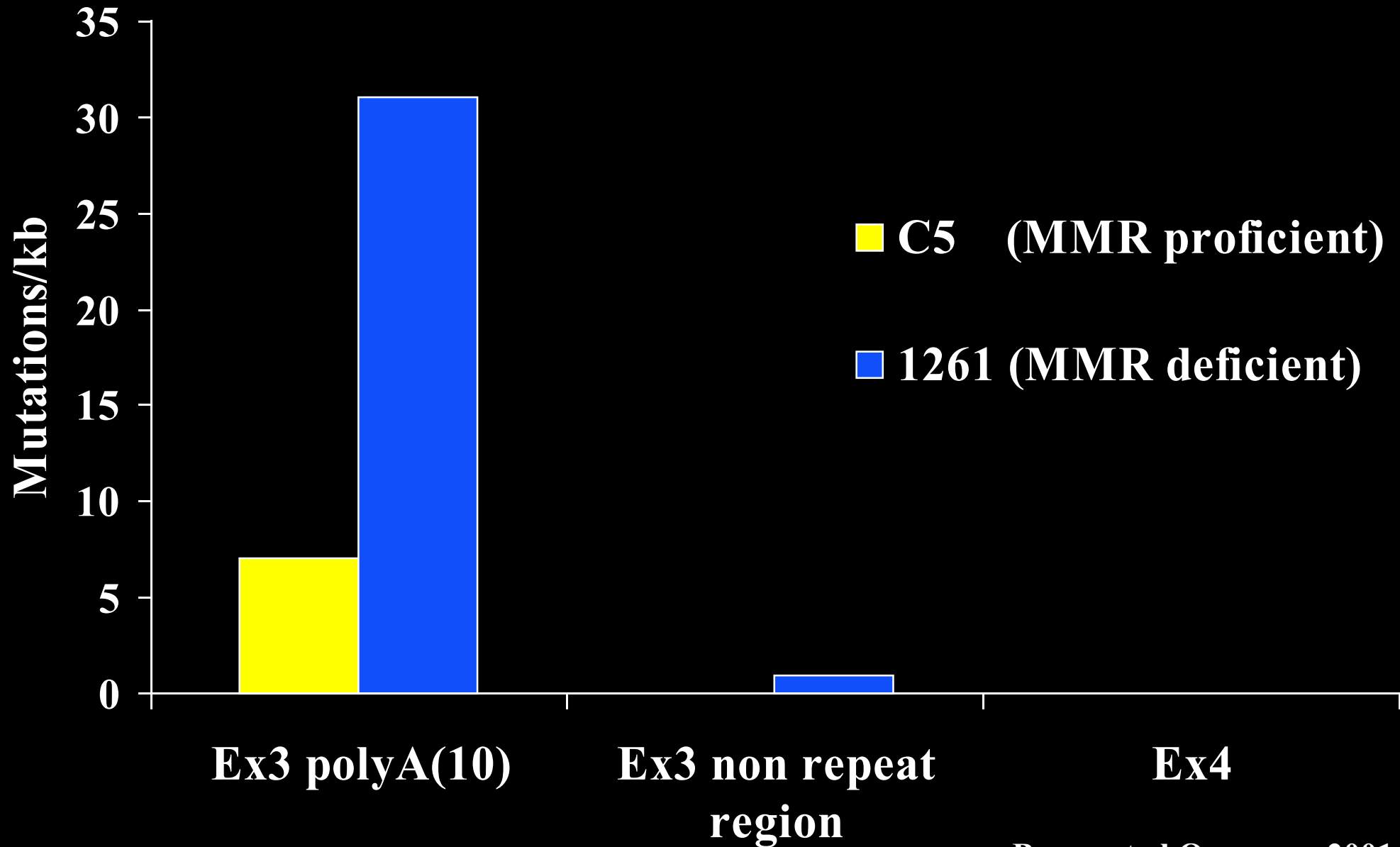


Tumour microsatellite instability

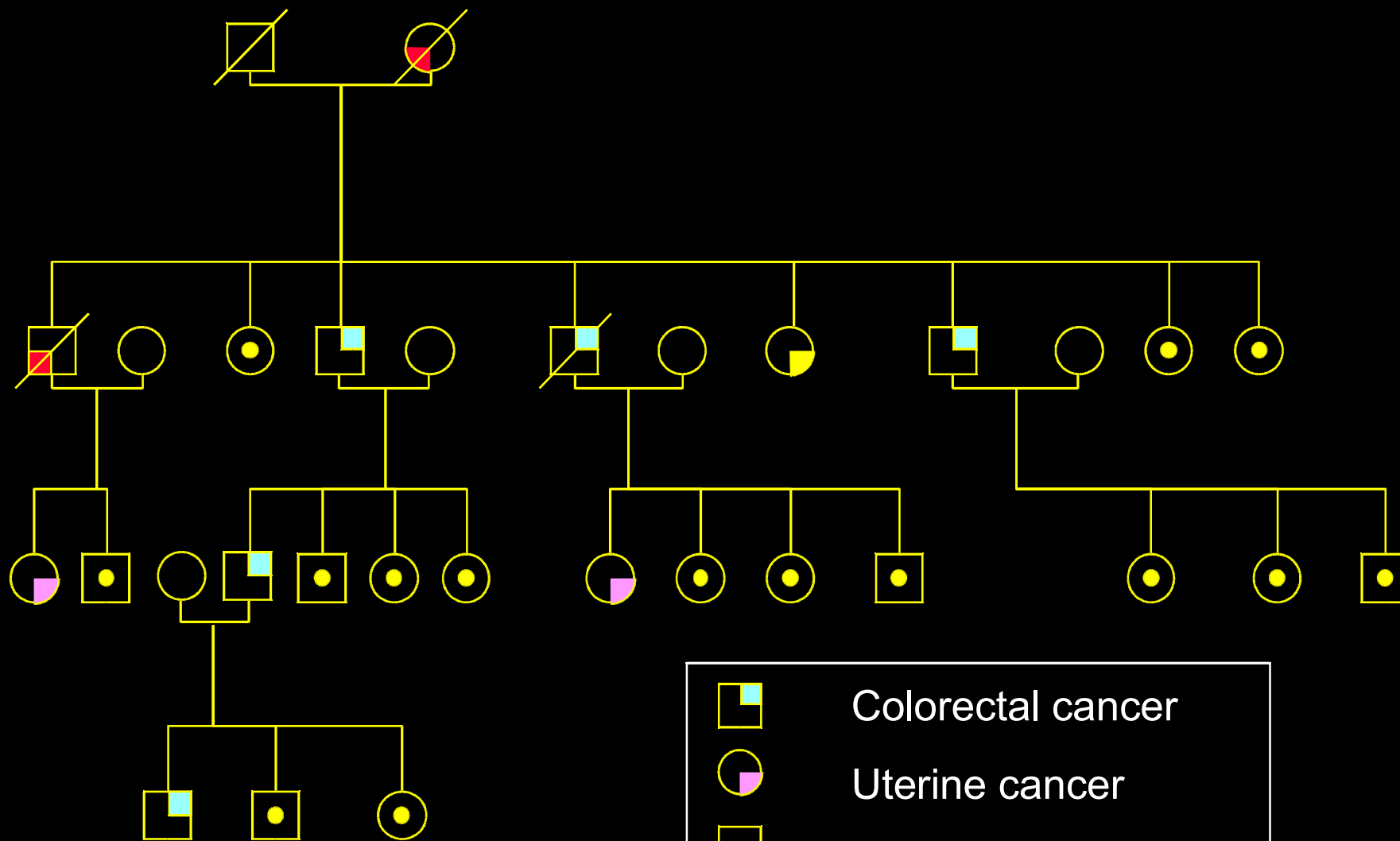


MMR deficient non-tumour cells

Spontaneous mutation frequency in TGF- β RII



Lynch Syndrome kindred



- Colorectal cancer
- Uterine cancer
- Gastric cancer
- 50% risk

Lifetime cancer risk for people with MMR gene mutations

Colon and rectum	Male	80%
	Female	30%
Endometrial		40%
Ovary		9%
Gastric		5-19%
Upper Urinary Tract		10%
Small intestine		<1%
Biliary tract		<1%
Brain		<1%
Breast		<1%)

Is mammalian DNA MMR fully elucidated?

Does current understanding of MMR fully explain the predominance of MLH1, MSH2 (and MSH6) mutations in Lynch Syndrome?

Is there a selective advantage for defective MMR?

What is the role of alkylators/genotoxic stress agents in faecal stream?

Why the clinical tumour spectrum?

Are there implications for therapy of MMR mutation carriers with cancer?

Are there potential therapeutic targets in MMR defective cells?

