# DEPARTMENT OF THE MOLECULAR BIOLOGY OF CANCER

**Head: Pavel Vodička, MD, PhD**
E-mail: pvodicka@biomed.cas.cz
Phone: +420 241 062 694

## LABORATORY OF THE GENETICS OF CANCER

**Pavel Vodička, MD, PhD** | Head of laboratory
E-mail: pvodicka@biomed.cas.cz
Phone: +420 241 062 694

Pavel Vodička, MD, PhD | Research Scientist
Barbara Pardini, PhD | Research Scientist
Veronika Poláková, MSc | PhD Student

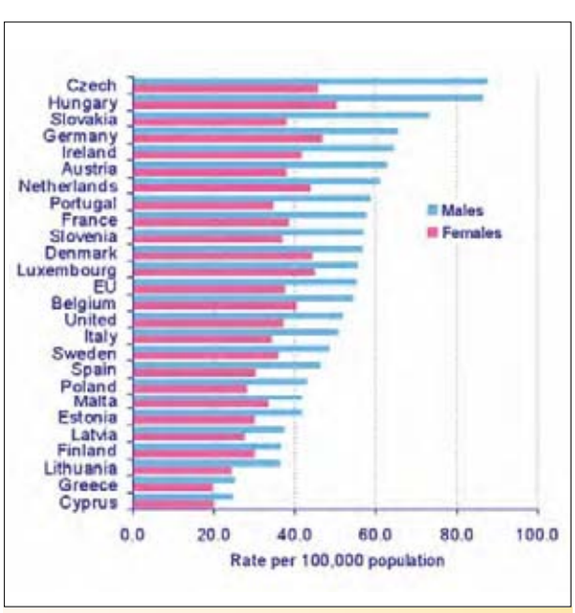
## LABORATORY OF DNA REPAIR

**Alessio Naccarati, PhD** | Head of laboratory
E-mail: Naccarati@biomed.cas.cz
Phone: +420 241 062 694

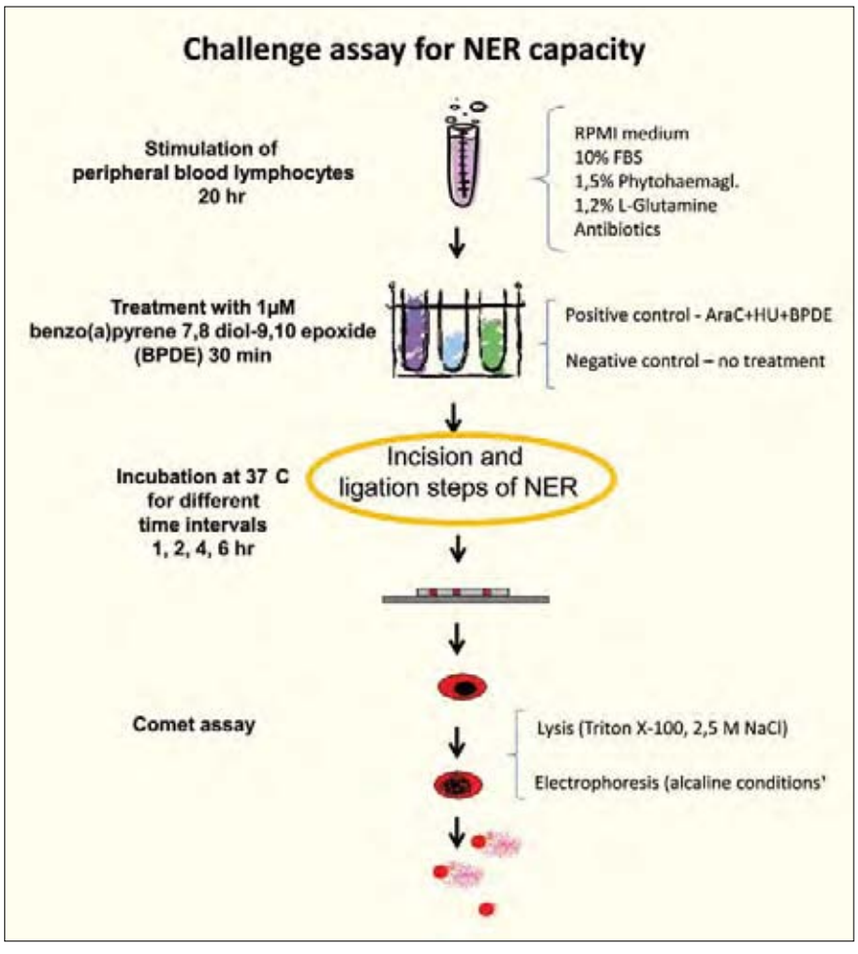
Alessio Naccarati, PhD | Research Scientist
Ľudmila Vodičková, PhD | Research Scientist
Jana Slyšková, MSc | PhD Student
Monika Hánová, MSc | PhD Student

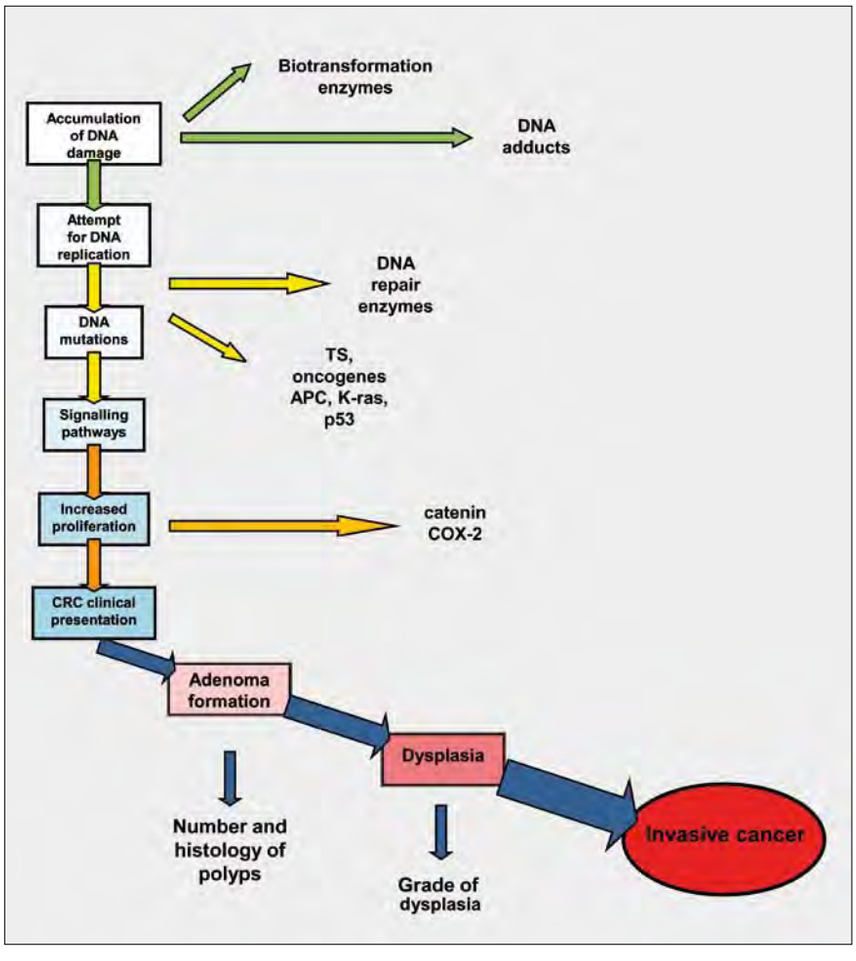

### RESEARCH TOPICS

The department is interested in investigating the molecular events involved in the susceptibility to sporadic forms of cancer. Our particular interest is focused on sporadic colorectal cancer, which poses a serious health problem in the Czech Republic. As part of the identification of common genetic variants that predispose an individual to this cancer, candidate genes within various relevant pathways in colorectal carcinogenesis have been addressed (e. g. DNA repair, cell cycle, biotransformation). The Department has participated in whole genome association studies (GWAS), aimed at the identification of susceptibility loci in sporadic colorectal cancer, and will be involved in detailed investigations of the functional consequences of these loci.




*Age standardized incidence rates, bowel cancer in EU countries (Modified from IARC, GLOBOCAN 2002).*




# Laboratory of the Genetics of Cancer

## RESEARCH TOPICS

– Investigation of the role of transient markers (DNA and chromosomal damage) in carcinogenesis;

– relationship between transient markers of cancer and individual susceptibility (i. e., relevant candidate genes);

– identification of the mechanisms underlying chromosomal and genomic instability;

– investigation of the role of low-penetrance genes (cell cycle, DNA repair) in the risk of sporadic colorectal cancer and other types of cancer;

– the role of genetic variants in pre dicting anticancer therapy outcome and overall prognosis;

– investigation of the links between genotype and gene expression with implications for the proper/improper functioning of the cell;

– investigation of somatic mutations in oncogenes and microsatellite status in adenomatous polyposis coli.

Colorectal cancer (CRC) is a common neoplasia in both men and women (with an estimated risk incidence of 5 % worldwide) and ranks as the fourth most common cancer in the world, with approximately 875,000 new cases diagnosed each year. An increased incidence in Europe has been recorded over the past decade, with a particularly severe situation in the central European region. The incidence of CRC in the Czech Republic ranks third worldwide, while the incidence of rectal cancer, particularly in men, is the highest. Both environmental and genetic factors are involved in the onset of sporadic CRC, which represents the predominant form

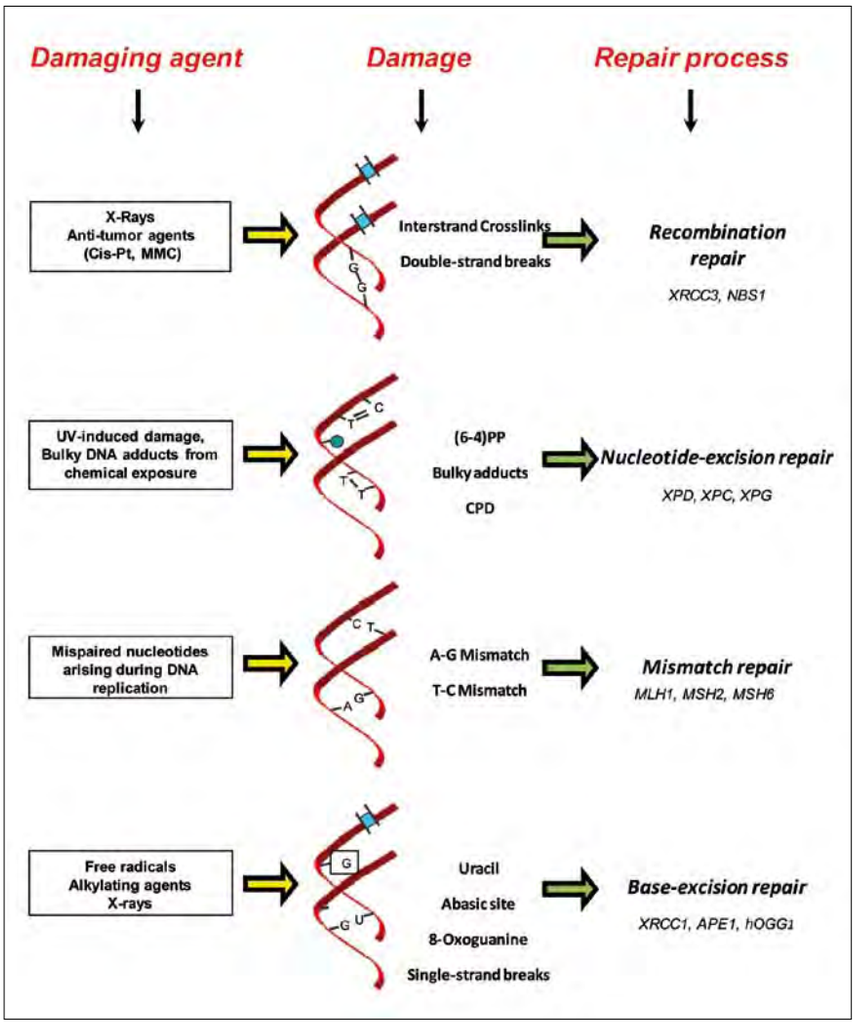
of this cancer (approx. 90% of all cases). It is believed that sporadic CRC involves multiple genes with moderate effects (low penetrance type) and progression occurs due to aggressive gene-environment interactions. The complex etiology of CRC and the observed high incidence in the Czech Republic stress the importance of a systematic approach, combining epidemiological and molecular biological methods, to understand the critical pathways in CRC tumorigenesis. Our recent interest has been oriented towards chemotherapy regimes, usually selected with the help of classical predictive markers such as TNM, which are not equally effective in all patients and which exert significant side effects. An assumption that the genetic profiles of patients could improve the prediction of an individual's response to standard chemotherapy regimes in CRC resulted in a selection of candidate genes, comprising the metabolic, transport, DNA repair and cell-cycle genes. Screening the loci in the above genes may have relevance in pharmacogenomics with the ultimate goal of individualized chemotherapy. Most recently, the participation of the Department in a multicenter study has resulted in the identification of several susceptibility loci of CRC using genome wide association (GWA). A detailed analysis of these loci, regarding their function in tumor cell biology, is ongoing.

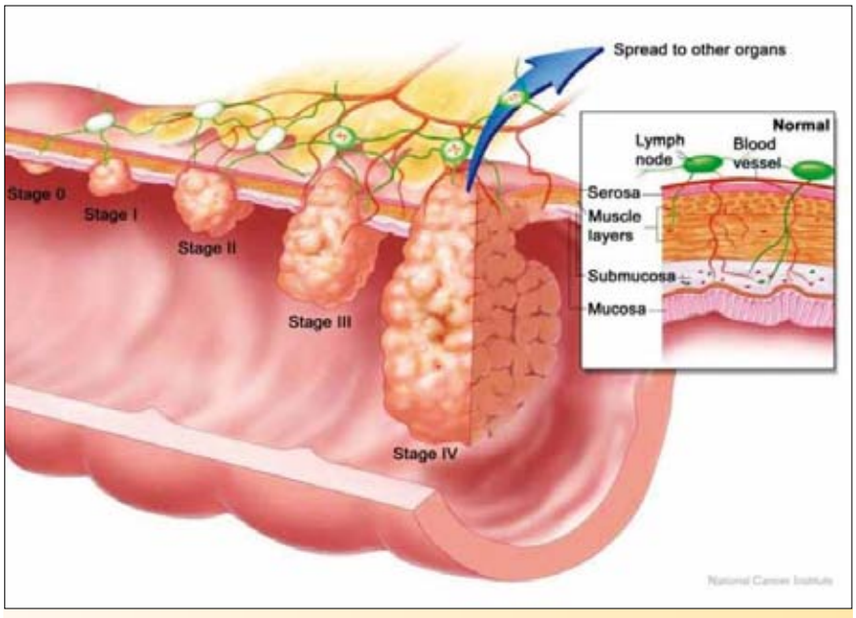
# Laboratory of DNA Repair

**RESEARCH TOPICS**

- Investigation of the mechanisms involved in DNA repair pathways;
- functional tests for DNA repair capacity;
- expression of relevant DNA repair candidate genes;
- interest in genotype-phenotype interactions;
- the role of several DNA repair pathways in carcinogenesis.

Nuclear DNA is constantly exposed to DNA damaging agents from the environment and the diet. Normally, there is a dynamic equilibrium between DNA damage and its removal by effective and accurate cellular repair enzymes. If the steady state is disturbed, the damage measured will increase, but then increased repair activity (through normal enzyme kinetics, with possibly induction or activation in addition) will tend to restore the equilibrium. The steady state level depends on the intrinsic repair rate in the individual's cells, which may be in part genetically determined and in part affected by metabolic or environmental factors. To date, more than 150 human DNA repair genes have been identified, which can be categorized into 5 main pathways: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), double-strand break repair (DSB) and direct repair. The cell cycle and mitotic spindle checkpoints are also critical in this process to ensure that cell proliferation only follows the correct replication and organization of genetic material, respectively. Otherwise, if genetic material is altered, it can be repaired at the DNA level, enabling the cell to replicate. If the genetic damage is too excessive for repair, the cell avoids propagating the damaged DNA by undergoing apoptosis. Thus DNA repair plays an important role in close relationship with cell cycle control in cancer prevention, by removing potentially mutagenic lesions and maintaining chromosomal and genomic stability. DNA repair capacity measurement represents a complex marker inte-






*Stages of colorectal cancer (source: National Cancer Institute).*

grating polymorphisms, gene expression, the stability of the gene product, the effect of inhibitors/stimulators, environmental factors and lifestyle factors. In sporadic cancers, greatly affected by gene-environment interactions, the employment of new and pathway-specific DNA repair assays hallmarks cancer risk identification and the prediction of therapeutical outcome.

## CURRENT GRANT SUPPORT

GA CR, 310/07/1430, Molecular and genetic characteristics of sporadic colorectal cancer in the Czech Republic, 2007–2011.

IGA NR, 8563-5/2005, Genetic profile of xenobiotic metabolising and DNA repair genes in cancer patients and control individuals in the Czech Republic, 2005–2009.

IGA NR, 9423-3/2007, XME, DNA repair and cell cycle regulation genes in head and neck cancer prediction, 2007–2009.

IGA NR, 9422-3/2007, The influence of environmental and genetic factors of pancreatic cancer (genetic profile), 2007–2009.

GA AS CR, IAA 500 200 917, Genetic and immunity in early stages of colorectal adenocarcinoma: inflammatory environment in conventional vs germ-free animal models, and in human samples, 2009–2013.

EEA-researchfund, A/CZ0046/2/0012, Quality and safety of food in relation to colorectal cancer predisposition. A pilot study. 2009–2010.

GA AS CR, IAA 500 390 806, The determination of expression levels of DNA repair and cell cycle genes in peripheral blood lymphocytes in styrene exposed individuals, 2008–2010.

## SELECTED RECENT PUBLICATIONS

**1.** Vodička P, Kumar R, Štětina R, Sanyal S, Souček P, Haufroid V, Dusinska M, Kuricová M, Zámečníková M, Musak L, Buchancová J, Norppa H, Hirvonen A, Vodičková L, Naccarati A, Matoušů Z, Hemminki K. (2004) Genetic polymorphisms in DNA repair genes and possible links with DNA repair rates, chromosomal aberrations and single-strand breaks in DNA. Carcinogenesis 25(5): 757–763.

**2.** Vodička P, Tuimala J, Štětina R, Kumar R, Manini P, Naccarati A, Maestri L, Vodičková L, Kuricová M, Järventaus H, Majvaldová Z, Hirvonen A, Imbriani M, Mutti A, Migliore L, Norppa H, Hemminki K. (2004) Cytogenetic markers, DNA single-strand breaks, urinary metabolites, and DNA repair rates in styrene-exposed lamination workers. Environ Health Perspect 112(8): 867–871.

**3.** Vodička P, Koskinen M, Naccarati A, Oesch-Bartlomowicz B, Vodičková L, Hemminki K, Oesch F. (2006) Styrene metabolism, genotoxicity, and potential carcinogenicity. Drug Metab Rev 38(4): 805–853.

**4.** Vodička P, Štětina R, Poláková V, Tulupová E, Naccarati A, Vodičková L, Kumar R, Hánová M, Pardini B, Slyšková J, Musak L, DePalma G, Souček P, Hemminki K. (2007)Association of DNA repair polymorphisms with DNA repair functional outcomes in healthy human subjects. Carcinogenesis 28(3): 657–664.

**5.** Tomlinson IPM, Webb E, Carvajal-Carmona L, Broderick P, Howarth K, Pittman AM, Spain S, Lubbe S, Walther A, Sullivan K, Jaeger E, Fielding S, Rowan A, Vijayakrishnan J, Domingo E, Chandler I, Kemp Z, Qureshi M, Farrington SM, Tenesa A, Prendergast JGD, Barnetson RA, Penegar S, Barclay E, Wood W, Martin L, Gorman M, Thomas H, Peto J, Bishop DT, Gray R, Maher RE, Lucassen A, Kerr D, Evans DGR, Consortium the CORGI, Schafmayer C, Buch S, Völzke H, Hampe J, Schreiber S, John U, Koessler T, Pharoah P, van Wezel T, Morreau H, Wijnen J T, Hopper JL, Southey MC, Giles GG, Severi G, Castelví-Bel S, Ruiz-Ponte C, Carracedo A, Castells A, Consortium the EPICOLON, Försti A, Hemminki K, Vodička P, Naccarati A, Lipton L, Ho JWC, Cheng KK, Sham PC, Luk J, Agúndez JAG, Ladero JM, de la Hoya M, Caldés T, Niittymäki I, Tuupanene S, Karhu A, Aaltonen L, Cazier JB, Campbell H, Dunlop MG, Houlston RS. (2008) A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23. 3. Nature Genet 40(5): 623–630.

**6.** Pittman AM, Webb E, Carvajal-Carmona L, Howarth K, Di Bernardo MC, Broderick P, Spain S, Walther A, Price A, Sullivan K, Twiss P, Fielding S, Rowan A, Jaeger E, Vijayakrishnan J, Chandler I, Penegar S, Qureshi M, Lubbe S, Domingo E, Kemp Z, Barclay E, Wood W, Martin L, Gorman M, Thomas H, Peto J, Bishop T, Gray R, Maher ER, Lucassen A, Kerr D, Evans GR, CORGI Consortium, van Wezel T, Morreau H, Wijnen JT, Hopper JL, Southey MC, Giles GG, Severi G, Castellví-Bel S, Ruiz-Ponte C, Carracedo A, Castells A, EPICOLON Consortium, Försti A, Hemminki K, Vodička P, Naccarati A, Lipton L, Ho J. W, Cheng KK, Sham PC, Luk J, Agúndez JA, Ladero JM, de la Hoya M, Caldés T, Niittymäki I, Tuupanen S, Karhu A, Aaltonen LA, Cazier JB, Tomlinson IP, Houlston RS. (2008) Refinement of the basis and impact of common 11q23. 1 variation to the risk of developing colorectal cancer. Hum Mol Genet 17(23): 3720–3727.

**7.** Poláková V, Pardini B, Naccarati A, Landi S, Slyšková J, Novotný J, Vodičková L, Bermejo JL, Hánová M, Šmerhovský Z, Tulupová E, Kumar R, Hemminki K, Vodička P. (2009) Genotype and haplotype analysis of cell cycle genes in sporadic colorectal cancer in the Czech Republic. Hum Mutat 30(4): 661–668.