ZETA Corporation

RAbMono™
Rabbit Monoclonal
IVD Antibodies

Target-Validated and Characterized IVD Antibodies for Anatomic Pathology

PRODUCT FOCUS -- DNA mismatch repair (MMR) system

Colorectal cancer (CRC) is one of the most common cancers worldwide and is the third leading cause of cancer-related deaths in the United States. A significant percentage develop CRC due to DNA mismatch repair (MMR) system abnormalities. Zeta Corporation has developed a number of antibodies to the four main MMR genes – **MLH1, MSH2, MSH6 and PMS2**. These antibodies have been rigorously evaluated, and are suitable for ***in vitro*** diagnostics (IVD).

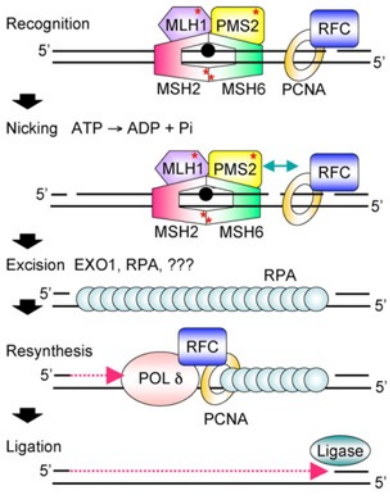
Introduction (Peltomäki, J Clin Oncol)

The DNA mismatch repair (MMR) system is necessary for the maintenance of genomic stability. In a broad sense, all main functions of the MMR system, including the correction of biosynthetic errors, DNA damage surveillance, and prevention of recombination between nonidentical sequences serve this important purpose. Failure to accomplish these functions may lead to cancer.

It is therefore not surprising that inherited defects in the MMR system underlie one of the most prevalent cancer syndromes in humans, hereditary nonpolyposis colon cancer (HNPCC). In addition, acquired defects of the same system may account for 15% to 25%, or even a higher percentage, of sporadic cancers of different organs of the "HNPCC spectrum," including the colon and rectum, uterine endometrium, stomach, and ovaries. Studies indicate that the MMR genes may be involved in the pathogenesis of even a broader spectrum of tumors in one way or another.

Päivi Peltomäki (2003) *J Clin Oncol* **21**:1174-1179.

Schematic for 3′-directed eukaryotic MMR. (Hsieh *et al.*)



Recognition of a mismatch by MutSαα (MSH2-MSH6) or MutSβα(MSH2-MSH3, not shown) and MutLα (MLH1-PMS2) results in the formation of a ternary complex whose protein-protein and protein-DNA interactions are modulated by ATP/ADP cofactors bound by MutSαα and MutLαα (indicated by red *). PCNA may play an important role in the recruitment of MMR proteins to the vicinity of the replication fork via a PIP motif on MSH6 and MSH3. Nicking by the endonuclease function of PMS2 stimulated by ATP, PCNA, and RFC and relevant protein-protein interactions (indicated by green arrow) may establish strand discrimination targeting repair to the newly synthesized strand. MMR is bidirectional and can be 5′-directed as well; this is not shown. HMGB1, a nonhistone chromatin protein that bends DNA also facilitates MMR in vitro at or before the excision step (not shown). Excision by EXO1 and possibly other as yet unidentified exonucleases leads to the formation of an RPA-coated single-strand gap. Resynthesis by replicative polα and ligation restore the integrity of the duplex.

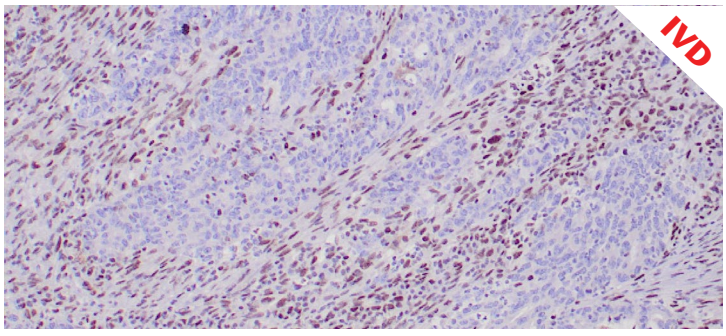
Peggy Hsieh *et al.* (2008) *Mech Ageing Dev* **129**:391-407

MLH1 Rabbit Monoclonal Antibody

Anti-rabbit: Clone ZR347, Cat # Z2656

Immunogen is full-length human MLH1 protein. Recognizes 83kDa MLH1. Suitable for immunohistochemistry (formalin-fixed, paraffin-embedded tissues). Defects in MLH1 are the cause of hereditary non-polyposis colorectal cancer type 2 (HNPCC2). Heterodimerizes with PMS2 to form MutL alpha, a component of the post-replicative DNA mismatch repair system (MMR). DNA repair is initiated by MutS alpha (MSH2-MSH6) or MutS beta (MSH2-MSH6) binding to a dsDNA mismatch, then MutL alpha is recruited to the heteroduplex. Assembly of the MutL-MutS-heteroduplex ternary complex in presence of RFC and PCNA is sufficient to activate endonuclease activity of PMS2.

Related MLH1 ABs	Conality	Cat. #
MLH1 (ZR259)	Rabbit Monoclonal	Z2573
MLH1 (G168-728)	Mouse Monoclonal	Z2076



Human colon adenocarcinoma with Lynch syndrome stained with anti-MLH1, clone ZR347

References:

1. Räschle M *et al.* J Biol Chem 1999; **274**:32368-75.
2. Garg K *et al.* Am J Surg Pathol 2009; **33**(6):925-33.
3. Meijer JW *et al.* Am J Surg Pathol 2008; **32**(8):1246-51.

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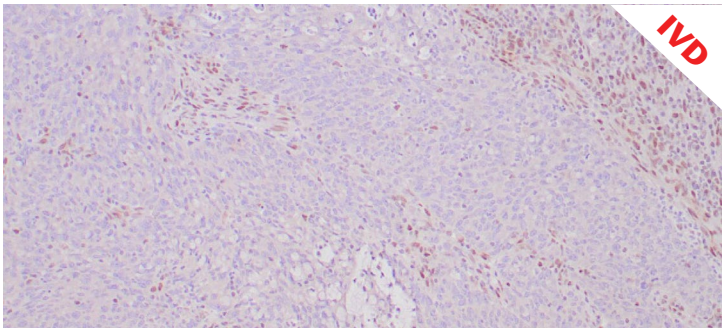
MLH1 Rabbit Monoclonal Antibody
Anti-rabbit: Clone ZR259, Cat # Z2573

Immunogen is full-length human MLH1 protein. Recognizes 83kDa MLH1. Suitable for immunohistochemistry (formalin-fixed, paraffin-embedded tissues). Defects in MLH1 are the cause of hereditary non-polyposis colorectal cancer type 2 (HNPCC2). Heterodimerizes with PMS2 to form MutL alpha, a component of the post-replicative DNA mismatch repair system (MMR). DNA repair is initiated by MutS alpha (MSH2-MSH6) or MutS beta (MSH2-MSH6) binding to a dsDNA mismatch, then MutL alpha is recruited to the heteroduplex. Assembly of the MutL-MutS-heteroduplex ternary complex in presence of RFC and PCNA is sufficient to activate endonuclease activity of PMS2.

Related MLH1 ABs	Conality	Cat. #
MLH1 (ZR347)	Rabbit Monoclonal	Z2656
MLH1 (G168-728)	Mouse Monoclonal	Z2076

References:
1. Räschle M, *et al.* J Biol Chem 1999; **274**:32368-75.
2. Garg K, *et al.* Am J Surg Pathol 2009; **33**(6):925-33.
3. Meijer JW, *et al.* Am J Surg Pathol 2008; **32**(8):1246-51.



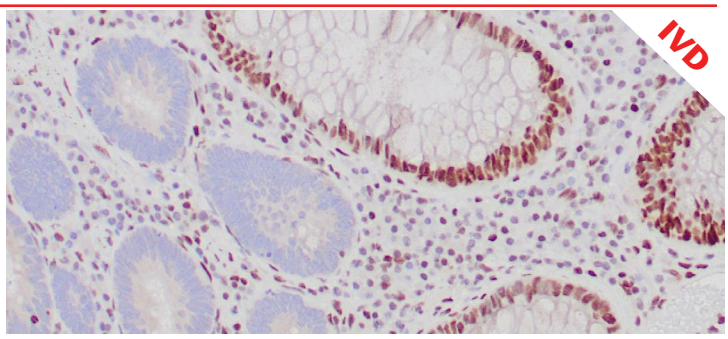
Human colon adenocarcinoma with Lynch Syndrome stained with anti-MLH1, clone ZR259

MSH2 Rabbit Monoclonal Antibody
Anti-rabbit: Clone ZR260, Cat # Z2574

Immunogen is a recombinant fragment (around aa 327-427) of human MSH2 protein. Suitable for immunohistochemistry (formalin-fixed, paraffin-embedded tissues). Mutations in DNA mismatch repair genes are associated with hereditary nonpolyposis colorectal cancer (HNPCC). The demonstration that 10 to 45% of pancreatic, gastric, breast, ovarian and small cell lung cancers also display microsatellite instability has been interpreted to suggest that DNA mismatch repair is not restricted to HNPCC tumors but is a common feature in tumor initiation or progression.

Related MSH2 ABs	Conality	Cat. #
MSH2 (ZM210)	Mouse Monoclonal	Z2456
MSH2 (G219-1129)	Mouse Monoclonal	Z2129

References:
1. Peltomäki P. J Clin Oncol 2003; **21**:1174-9.
2. Lynch H *et al.* Cancer 1996; **78**:1149-67.
3. Leach FS *et al.* Cancer Res 1996; **56**:235-40

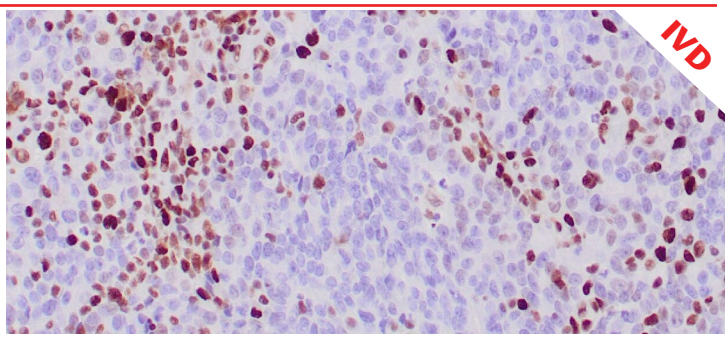


Human colon adenocarcinoma stained with anti-MSH2, clone ZR260

MSH6 Mouse Monoclonal Antibody, monospecific
Anti-mouse: Clone ZM99, Cat # Z2409

Immunogen is a recombinant fragment of human MSH6 protein (around aa 374-540). Monospecific for MSH6. Suitable for immunohistochemistry (formalin-fixed, paraffin-embedded tissues). The finding that mutations in DNA mismatch repair genes are associated with hereditary nonpolyposis colorectal cancer (HNPCC) has resulted in considerable interest in the understanding of the mechanism of DNA mismatch repair. A member of the mismatch repair family, GTBP (also designated MSH6), is an MSH2-related protein that binds to DNA containing G/T mismatches. Findings suggest that the mismatch-binding factor in human cells is composed of a heterodimer of GTBP and MSH2.

References:
1. Peltomäki P. J Clin Oncol 2003; **21**:1174-9.
2. Lynch H *et al.* Cancer 1996; **78**:1149-67.
3. Leach FS *et al.* Cancer Res 1996; **56**:235-40

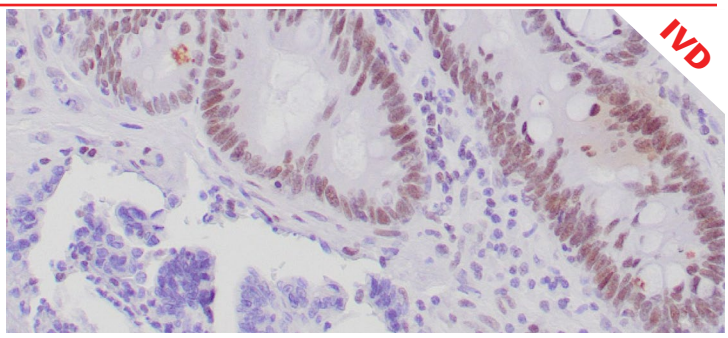


Human colon adenocarcinoma (Lynch Syndrome) stained with anti-MSH6, clone ZM99

PMS2 Rabbit Monoclonal Antibody
Anti-rabbit: Clone ZR317, Cat # Z2621

Immunogen is a synthetic peptide corresponding to residues within aa1-100 of human PMS2 (exact sequence is proprietary). Suitable for immunohistochemistry (formalin-fixed, paraffin-embedded tissues). PMS2 is involved in DNA mismatch repair. It forms a heterodimer with MLH1 and this complex interacts with other complexes bound to mismatched bases. Defects in PMS2 are the cause of hereditary non-polyposis colorectal cancer type 4 (HNPCC4). Mutations in more than one gene locus can be involved alone or in combination in the production of the HNPCC phenotype (also called Lynch syndrome). Most families with clinically recognized HNPCC have mutations in either MLH1 or MSH2 genes. HNPCC is an autosomal, dominantly inherited disease associated with a marked increase in cancer susceptibility. It is characterized by a familial predisposition to early-onset colorectal carcinoma (CRC) and extra-colonic cancers of the gastrointestinal, urological, and female reproductive tracts.

References:
1. Peltomäki P. J Clin Oncol. 2003; **21**:1174-9.
2. Modica I *et al.* Am J Surg Pathol 2007; **31**:744-51.
3. Balogh GA *et al.* Int J Mol Med 2006;**18**:853-7.



Human colon adenocarcinoma (Lynch Syndrome) stained with anti-PMS2, clone ZR317

All antibodies are offered in different format and size with the Suffix after the Catalog #s; "L", "S" & "T" for Concentrated antibodies in 1.0 ml, 0.5 ml & 0.1 ml sizes and Suffix "P" for Ready To Use (RTU) in 7 ml.