Glossary:

α-PIX: alpha-PIX is a Rho GTPase guanine nucleotide exchange factor (Rho-GEF) domain-containing signaling protein that associates with other proteins involved in cytoskeletal-membrane complexes.

Abl: Abelson (Abl) non-receptor tyrosine kinases are central regulators of multiple cellular processes controlling actin dynamics, proliferation and differentiation, but also pathogenesis including cancer. The oncogenic fusion of Abl with the breakpoint-cluster region (Bcr) is known as Bcr–Abl.

ADAM17: ADAM metallopeptidase domain 17(ADAM17) is an enzyme that belongs to the ADAM (A disintegrin and metalloproteases) protein family of proteases.

AID: Activation-induced cytidine deaminase (AID) contributes to immune system diversity by inducing somatic hypermutations and recombinations of human immunoglobulin genes. AID, however, can also induce genetic changes in various genes and may lead to the development of cancer.

AJ: Adherens junctions (AJs) or zonula adherens are protein complexes that occur at cell-cell junctions in epithelial tissues, usually more basal than the tight junctions. AJs are defined as cell junctions whose cytoplasmic domains are linked to the host actin cytoskeleton.

Akt: Akt is a serine/threonine protein kinase (also called protein kinase B, PKB) that plays a crucial role in multiple cellular processes such as transcription, glucose metabolism, cell apoptosis, proliferation and migration.

AlpA/B: Adherence-associated lipoproteins A and B (AlpA/B) are outer-membrane proteins (OMPs) in *H. pylori* with a role in binding to host target cells.

AP-1: Activator protein 1 (AP-1) is an important pro-inflammatory transcription factor. AP-1 controls a number of cellular processes including proliferation, differentiation, inflammation and apoptosis.

Arg: Abl-related gene (Arg) is another non-receptor tyrosine kinase in the Abl family, sometimes also called Abl-2. Arg is expressed in both normal and tumor cells.

Aurora: Aurora kinases are serine/threonine kinases with essential roles in cell proliferation.

BabA/B: Adherence of *H. pylori* to the human gastric epithelial cells is mediated by the fucosylated Lewis b histo-blood group antigen. Two blood group antigen-binding (Bab) proteins were indentified in *H. pylori*, called BabA and BabB.

β-catenin: Beta-catenin is a protein of the cadherin junctional protein complex and can also act as transcription factor that has been implicated as crucial component of various signaling pathways.

***cag*:** cytotoxin-associated genes (*cag*) are encoded by the pathogenicity island (*cag*PAI) of *H. pylori*. *cag*PAI-positive strains are described to be more virulent than those which are *cag*PAI-negative.

CagA: Translocated virulence factor of the *H. pylori* T4SS which is encoded by the cytotoxin-associated gene A.

CagY: CagY (also called HP0527 or Cag7) is a VirB10-homologous protein. It has been proposed that CagY is a major T4SS pilus-associated protein in *H. pylori*.

Cdc42: Cell division cycle 42 (Cdc42) is a well-known member of the small GTPase family, also including Rac1 and Ras (see below). GTPases are a family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP). Small GTPases can regulate a wide variety of processes in the cell including growth, differentiation, movement, lipid vesicle transport and microbial infections. A specific function of Cdc42 is the formation of actin-rich filopodia structures at cell surfaces.

Crk: CT10 regulator of kinase (Crk) adapter proteins are SH2/SH3 domain containing adapter proteins. Crk adapter protein members include the members CrkI, CrkII and CrkL.

c-Met: c-Met is a proto-oncogene that encodes a protein also known as hepatocyte growth factor receptor (HGFR). c-Met is a receptor protein possessing tyrosine kinase activity that is essential for embryonic development and wound healing. c-Met is activated by the "scatter factor" HGF.

Csk: Carboxy-terminal Src kinase (Csk) is a cytoplasmic tyrosine kinase that has been shown to downregulate the kinase activity of c-Src through phosphorylation of its negative regulatory site at tyrosine residue 527.

DupA: Duodenal ulcer promoting protein A (DupA) of *H. pylori* has been suggested as a virulence marker associated with the development of duodenal ulcer disease.

E-cadherin: Cadherins are a class of large transmembrane adhesive proteins and depend on calcium (thus named for "calcium-dependent adhesion"). E-cadherin is a major member in this class and plays important roles in cell adhesion, ensuring that neighboring cells within tissues are tightly connected with each other.

ECM: The extracellular matrix (ECM) is the defining structure of connective tissues in animals. ECM is the extracellular part of animal tissue that commonly provides structural support to the cells in addition to performing various other important functions.

EGFR: The epidermal growth factor receptor (EGFR; also called ErbB-1 or HER1 in humans) is the cell surface receptor for members of the EGF family of growth factors. EGFR family members are tyrosine kinases and play important roles in cell migration, adhesion and proliferation.

EPIYA-motifs: The amino acid motif Glu-Pro-Ile-Tyr-Ala (EPIYA) has been identified in the C-terminus of the *H. pylori* CagA protein. This sequence motif serves as the site of phosphorylation by tyrosine kinases c-Src and Abl.

Erk1/2: Extracellular signal-regulated kinases 1 and 2 (Erk1/2) are members of the Map kinase (MAPK) family. Erk1/2 are widely expressed intracellular signaling molecules which are involved in multiple functions including the regulation of meiosis, mitosis and postmitotic roles in differentiated cells.

FAK: Focal adhesion kinase (FAK) is another classical non-receptor tyrosine kinase. FAK is recruited as a participant in focal adhesion dynamics between cells, and has specific roles in motility and cell survival. FAK is highly conserved in sequence and was originally identified as a substrate for the oncogene protein tyrosine kinase v-Src.

F- and G-actin: Actin is a globular protein found in almost all eukaryotic cells. Monomeric actin (G-actin) can be converted into filamentous actin (F-actin) by a major actin polymerization machinery, the Arp2/3 (actin-related proteins 2 and 3), and plays important roles in many cellular processes such as signalling, motility, muscle contraction or infections.

Fibronectin: Fibronectin, a 250 kDa eukaryotic extracellular matrix protein containing an RGD-motif (see below) plays crucial roles in cell-cell communication, development, tissue homeostasis, and disease development. Fibronectin can classically bind to several integrins, on of which is the integrin member $\alpha 5\beta 1$. The highly complex fibrillar fibronectin meshwork then orchestrates the functions of other extracellular matrix proteins (collagen, fibrin, heparin sulphate and others), promoting cell adhesion, migration, and intracellular signaling.

GGT: γ-glutamyl transpeptidase (GGT) is an enzyme that transfers gamma-glutamyl groups. In *H. pylori*, GGT has been reported to be a virulence factor associated with bacterial colonization, suppression of immune responses and induction of cell apoptosis.

Grb: Growth factor receptor-bound proteins (Grb2 and Grb7 reported here) are SH2/SH3 domain containing adapter proteins with multiple intracellular functions.

HB-GF: Heparin-binding epidermal growth factor (HB-EGF) is a member of the EGF family of proteins. HB-EGF has been shown to play a role in wound healing and has many other functions in health and disease.

Her2/Neu: Member of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases, see above.

HopZ: The *H.pylori* outer membrane protein (Hop) family consists of multiple members. One of these members, HopZ, is associated with binding of the bacteria to host target cells.

HP0421: HP0421 is a gene encoding the enzyme cholesterol-alpha-glucosyltransferase responsible for cholesterol glucosylation by *H. pylori*. Generation of knockout mutants lacking HP0421 corroborates the importance of cholesteryl glucosides for escaping phagocytosis, T cell activation and bacterial clearance *in vivo*.

HtrA: High-temperature requirement A (HtrA) proteins are conserved from mammals to prokaryotes. They act as chaperones and serine proteases with important roles in protein quality control, but can also be secreted from *H. pylori* to function as a novel virulence factor, which cleaves the ectodomain of the cell-adhesion protein E-cadherin.

IceA: Induced by contact with epithelium gene A (*iceA*) in *H. pylori* is a marker for peptic ulceration and increased mucosal concentrations of IL-8.

IL-1β: Interleukin-1 beta (IL-1β) is a member of the interleukin 1 cytokine family. This cytokine is produced by activated macrophages as a pro-protein, which is proteolytically cleaved to its active form by caspase 1. IL-1β is an important mediator of the pro-

inflammatory responses, and is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis. Genetic polymorphisms in the IL-1β gene cluster are suspected of enhancing the production of IL-1β. The latter is associated with an increased risk of both hypochlorhydria induced by *H. pylori* and gastric cancer.

IL-3: Interleukin-3 (IL-3) is a cytokine that can improve the body's natural response to disease as part of our immune system. IL-3 acts by binding to the interleukin-3 receptor. Its function is quite similar to that of GM-CSF (Granulocyte-macrophage colony-stimulating factor).

IL-8: Interleukin 8 (IL-8) is a chemokine produced by epithelial cells and other cell types such as macrophages. IL-8 is a member of the CXC chemokine family and one of the major mediators of pro-inflammatory responses.

Integrins: Integrins are basolateral receptors that mediate attachment between cells and tissues surrounding it including the extracellular matrix. They also play a role in cell signal transduction and thereby define cellular shape, motility and regulate the cell cycle. Integrins are heterodimers composed of α and β chains. A major member of this family is the α5β1 integrin, which is necessary for injection of CagA by *H. pylori*.

IRF7: Interferon regulatory factor 7 (IRF7) is a member of the interferon regulatory factor family of transcription factors. IRF7 has been shown to play a role in the induction of type I interferon and other genes.

JAM: Junctional adhesion molecules (JAMs) are multifunctional cell surface proteins that have multiple evolutionarily conserved structural features in vertebrates. They are known to modulate many cellular functions including migration, polarity, paracellular permeability and proliferation.

JNK: Jun N-terminal kinases (JNKs) were originally identified as enzymes that bind to and phosphorylate c-Jun within its transcriptional activation domain. They are mitogen-activated protein kinases which are responsive to stress stimuli, such as cytokines, irradiation, heat shock and osmotic shock, and are involved in T cell differentiation, apoptosis and pathogenesis.

Lamina propria: The lamina propria is a thin layer of loose connective tissue which lies beneath the gastric epithelium and together with the epithelium constitutes the mucosa.

MALT lymphoma: MALT lymphoma is a form of lymphoma involving the mucosa-associated lymphoid tissue (MALT). It can be frequently found in the stomach, but virtually any mucosal site can be afflicted, too. It is a cancer originating from B cells which is frequently associated with chronic inflammation as induced by *H. pylori* infections.

MAP kinase: Mitogen-activated protein (MAP) kinases are serine/threonine kinases which respond to extracellular stimuli including mitogens, osmotic stress or cytokines. They regulate various cellular activities including gene expression, mitosis, differentiation, proliferation and cell survival/apoptosis.

MEK: Mitogen-activated protein kinase/extracellular signal-regulated kinases (MEKs) are important kinases upstream of Erk1/2 (see above).

MCL1: Myeloid cell leukaemia 1 (MCL1) protein is associated with megalencephalic leukoencephalopathy with subcortical cysts. The function of this gene product is not fully clear, but it seems to play a role in inhibiting apoptosis during infection with *H. pylori*.

MMP: Matrix metalloproteinases (MMPs) are zinc-dependent endopetidases which are capable of degrading all kinds of extracellular matrix proteins, but also can process a number of other bioactive molecules. In this way, MMPs are thought to play a major role on cell behaviors such as cell proliferation, migration, differentiation and host defense.

NapA: Neutrophil-activating protein A (NapA) is a protein in *H. pylori* that was named for its ability to promote neutrophil adhesion to endothelial cells and has been shown to be a major antigen in the human immune response to *H. pylori*.

NF-κB: Nuclear factor kappa B (NF-κB) is a major transcription factor inducing pro-inflammatory responses.

Nod1: Nucleotide oligomerization domain protein 1 (Nod1) is an intracellular host cell receptor which can sense bacterial peptidoglycan, and can activate NF-κB and IRF7.

OipA: Outer inflammatory protein A (OipA) of *H. pylori* is exposed on the surface of the bacteria and has been proposed to induce multiple signaling pathways.

P: phosphate group.

PAI: Pathogenicity islands (also called PAIs) are a distinct class of genomic DNA sequences which are acquired by horizontal transfer events. PAIs are about 10-200 kb in size and can be incorporated in the genome of pathogenic microbes, but are usually absent from non-pathogenic variants. A prime example is the *cag*PAI in *H. pylori*.

Par1: The kinase Par1b (partitioning-defective 1b, also called MARK2 for microtubule affinity-regulating kinase 2) is a central regulator of cell polarity, which was found to play a role in *H. pylori*-induced signalling. Non-phosphorylated form of CagA directly binds Par1b and inhibits its kinase activity to promote the loss of cell polarity.

PI3K: Phosphatidylinositol 3-kinases (PI3Ks) are a family of enzymes capable of phosphorylating a hydoxyl group of the inositol ring of phosphatidylinositol. PI3Ks are involved in many cellular functions such as cell growth, proliferation, differentiation, motility, survival, intracellular trafficking and pathogenesis.

PKCδ: Protein kinase C (PKC) is a family of enzymes that are involved in controlling the function of other proteins through the phosphorylation of serine and threonine residues in these proteins. One of the major members is PKCδ that plays important roles in several signal transduction cascades.

PLCγ: Phospholipase C-gamma (PLCγ) catalyzes the formation of inositol 1,4,5-triphosphate and diaglycerol from phosphatidylinositol 4,5-bisphosphate. This reaction uses calcium as a co-factor and plays an important role in the intracellular signal transduction downstream of RTKs.

PMNs: Polymorphonuclear leukocytes (PMNs) are specific white blood cells and have been named because of their varying shapes of the nucleus, which is usually lobed into three

segments. In common parlance, the term *polymorphonuclear leukocyte* often refers specifically to neutrophil granulocytes, the most abundant type of granulocytes.

Rac: Ras substrate of C3 toxin (Rac) is a prominent member of the small Rho GTPases family, see above. A specific function of Rac1 is the formation of lamellipodia in migrating host cells.

Raf: Serine/threonine kinase involved in transduction of mitogenic signals to the nucleus. Raf is a member of MAP kinase kinase kinases (MAP3Ks) which function downstream of the Ras subfamily of membrane-associated GTPases to which it binds directly. Once activated Raf-1 can phosphorylate to activate the dual specificity protein kinases MEK1/2 which in turn phosphorylate and activate the serine/threonine specific protein kinases Erk1/2 (see above).

Rap1: Ras-proximate-1 or Ras-related protein 1 (Rap1) is a small GTPase (see above) having crucial roles in host cell signalling.

Ras: Proto-oncogene and founding member of the Ras superfamily of GTPases (see above).

RasGAP: Ras GTPase activating protein (RasGAP) is a cytosolic protein that provides two major activities: (i) inactivation of Ras from its active GTP-bound form to its inactive GDP-bound form and (ii) trigger mitogenic signal transmission towards downstream interacting partners through its N-terminal SH2-SH3-SH2 domains.

RGD-motif: The tripeptide Arg-Gly-Asp (RGD) was originally identified as the sequence within the ECM protein fibronectin which mediates cell attachment (see above). The RGD-motif has now also been found in numerous other proteins and supports cell adhesion in many, but not all of these factors. The integrins, a family of cell-surface proteins, act as receptors for cell adhesion molecules. A subset of the integrins recognize the RGD-motif within their ligands, the binding of which mediates both cell-substratum and cell-cell interactions. RGD-derived peptides and corresponding mimetics, in addition to providing insights into the fundamental mechanisms of cell adhesion, are potential therapeutic agents for the treatment of diseases such as thrombosis and cancer.

RocF: Arginase enzyme of *H. pylori* which can significantly reduce the availability of extracellular L-Arg to the host cells to a point where macrophage NO production and killing of bacteria are markedly attenuated.

RTKs: Receptor tyrosine kinases (RTKs) are the high-affinity host cell surface receptors for many polypeptides such as growth factors, cytokines or hormones. Humans encode 58 RTKs, one of which is the profound member EGFR (see above).

RUNX3: Runt-related transcription factor 3 (RUNX3) is a transcription factor that regulates lineage-specific gene expression in developmental processes and is involved in the formation of a variety of cancers. RUNX3 is inactivated by expression of *H. pylori* CagA.

SabA: Sialic acid-binding adhesin (SabA) of *H. pylori*. The ability of many strains to adhere to sialylated glycoconjugates expressed during chronic inflammation might thus contribute to virulence and the extraordinary chronicity of *H. pylori* infections.

Shp1 and Shp2: The SH2 domain-containing protein-tyrosine phosphatase 1 and 2 (Shp1 and Shp2) are tyrosine phosphatases containing two SH2 domains. These tyrosine phosphatases

have emerged as major regulators of receptor tyrosine kinases (RTKs) and cytokine receptor signaling.

Src and SFKs: Src family kinases (SFKs) are a family of non-receptor protein tyrosine kinases, originally identified as an oncogene of the Rous sarcoma virus. SFKs interact with a variety of cellular cytosolic, nuclear and membrane proteins, modifying these proteins by phosphorylation at tyrosine residues. SFKs are therefore involved in a multitude of signaling pathways in health and disease.

Signal peptide: A signal peptide is a short sequence at the N-terminus of a given protein that directs its transport within bacteria. Signal peptides are recognized and cleaved by specific signal peptidases in order to support the transport.

SH2 domain: Src homology region 2 (SH2) is a structurally conserved domain in the Src oncoprotein and in many other intracellular signal transducing host proteins. SH2 domains play a vital role in cellular communication by interacting with phosphorylated tyrosine residues in the same or other proteins. The length of SH2 domains is approximately 100 amino acids and has been found in about 115 human proteins.

SOS: Son of sevenless, a guanine exchange factor and activator for the Ras GTPase (see above).

T4SS: Type IV secretion systems (T4SSs) are found in many Gram-negative bacteria and translocate DNA and protein substrates across prokaryotic cell envelopes generally by a mechanism requiring direct contact with a given target cell. Three types of T4SSs have been described: (i) conjugation systems, operationally defined as machines that translocate DNA substrates to other bacteria by a contact-dependent process; (ii) effector translocator systems, functioning to deliver proteins or other macromolecules to eukaryotic target cells; and (iii) DNA release/uptake systems, which transfer DNA to or from the extracellular milieu. The prototypic and best characterised T4SS is the VirB system of *Agrobacterium tumefaciens* which delivers effector proteins (VirD5, VirE2, VirE5 and VirF) and effector proteins (VirD2) bound to single-stranded (ss) DNA (the so-called T-DNA complex).

TAK1: Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) is a key regulator of signal transduction cascades that lead to stimulus-coupled phosphorylation and activation of the IκB kinase (IKK) complex and transcription factor NF-κB.

TJ: Tight junctions (TJs), also called zonula occludens, are the closely associated areas of two neighboring cells whose membranes join together forming a virtually impermeable barrier to fluid. Although more proteins are present in TJs, the major types are claudins and occludins. These associate with different other proteins located on the intracellular side of the plasma membrane, which anchor them to the host actin cytoskeleton. Therefore, TJs join together the cytoskeletons of adjacent cells.

TM: A Transmembrane domain (TM) usually denotes a single transmembrane α-helix of a given transmembrane protein that anchors it in a given membrane.

TNF-α: Tumour necrosis factor alpha (TNF-α) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction.

TP53: Tumour protein 53 (TP53, also known as protein 53 or p53), is a tumour suppressor protein encoded by the *TP53* gene in humans. TP53 has crucial roles in higher eukaryotes, where it regulates the cell cycle and, thus, functions as a tumour suppressor which is involved in preventing cancer development. The name TP53 was given in reference to its apparent molecular mass of 53 kDa.

TRAF6: The TNF receptor associated factor 6 (TRAF6) belongs to the TRAF protein family. TRAF proteins are associated with, and mediate signal transduction from members of the TNF receptor superfamily.

VacA: The vacuolating cytotoxin A (VacA) of *H. pylori* is paradigm of pore-forming toxins which contributes to the pathogenesis of peptic ulceration. It constitutes a classical autotransporter protein and is secreted into the bacterial culture supernatant. Upon delivery VacA can interact with many components on and within epithelial and immune cells, thus having multiple functions in the infection process.

VRK1: Vaccinia-related kinase 1 (VRK1) belongs to a family of serine/threonine protein kinases. VRK1 localizes to the nucleus and has been shown to promote the stability and nuclear accumulation of a transcriptionally active tumour suppressor protein TP53. VRK1, therefore, may regulate cell proliferation.

ZO-1: The tight junction protein zonula occludens 1 (ZO-1) is located on a cytoplasmic membrane surface of intercellular tight junctions. ZO-1 may be involved in signal transduction at these cell-cell junctions (see above).