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by *Helicobacter pylori*

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# Foreword: New Directions for Investigating Detrimental and Enabling Interactions Between *Helicobacter pylori* and Its Host

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*Helicobacter pylori* infects the stomachs of approximately 4.4 billion persons, over half of the global population, justifying its stature as the most common bacterial infection worldwide. Virtually, all persons infected by this organism develop co-existing gastritis, a signature feature of which is the capacity to persist for decades. Microbial persistence implies a relationship in which the signals of the colonizing organism affect the signals of the host, allowing host and bacteria to participate in a dynamic equilibrium, the intensity of which is dependent upon environmental influences. Unfortunately, there are biological costs for these long-term relationships. For example, chronic infection with *H. pylori* incurs the highest known risk for gastric cancer, and *H. pylori* is the only bacterial species designated by the World Health Organization as a class I carcinogen. With an estimated 1 million new cases per year, gastric adenocarcinoma claims >780,000 lives annually and approximately 80% of the gastric cancer burden and 5.5% of all malignancies worldwide are attributable to *H. pylori*-induced inflammation and injury. Eradication of *H. pylori* significantly decreases the risk of developing cancer in infected individuals; however, universal test and treat strategies for *H. pylori* are

not feasible due to the high prevalence of infection, the fact that only a subset of colonized persons ever develop neoplasia, and the expense and side effects of antibiotic therapy. These observations, in conjunction with evidence that carriage of certain strains is inversely related to esophageal adenocarcinoma, atopic diseases, and inflammatory bowel disease, underscore the importance of identifying mechanisms that regulate pathologic interactions of *H. pylori* with its host which promote the disease. All of the chapters contained in this unique book broadly and comprehensively describe the latest insights about such mechanisms.

The *cag* pathogenicity island is a fascinating *H. pylori* strain-specific gene locus that encodes a type IV secretion system (T4SS), and *cag*<sup>+</sup> strains markedly augment the risk for disease compared to *cag*<sup>-</sup> strains. The protein product of the *cagA* gene (CagA) is translocated by the T4SS into epithelial cells, undergoes tyrosine phosphorylation, and activates a eukaryotic phosphatase (SHP-2) and various other signaling factors, leading to pathogenic cellular responses. Non-phosphorylated CagA also exerts pathologic effects via induction of pro-inflammatory signaling, activation of  $\beta$ -catenin, and disruption of apical-junctional complexes. Recently, elegant studies have demonstrated that gastric stem and progenitor cells can be specifically targeted and activated by *cag*<sup>+</sup> *H. pylori*, which likely contributes to the enhanced carcinogenic risk incurred by these strains.

In addition to the *cag* T4SS, the *H. pylori* genome contains an unusually high proportion of open reading frames that encode outer membrane proteins (OMPs). Consistent with sequence data, *H. pylori* strains express multiple paralogous OMPs, several of which bind to the defined receptors on gastric epithelial cells. The first defined *H. pylori* host receptor partnership involved BabA, a highly conserved OMP encoded by the strain-specific gene *babA2*, which binds the Lewis histo-blood-group antigen Le<sup>b</sup>. A second ligand-receptor coupling involved SabA, an *H. pylori* adhesin that binds the sialyl-Lewis<sup>x</sup> (Le<sup>x</sup>) antigen, an established tumor antigen and marker of gastric dysplasia that is upregulated by chronic gastric inflammation. Host integrin receptors also represent an entry point for CagA injection, and an important role is played by CagL, a T4SS-pilus-localized protein. CagL bridges the T4SS to  $\alpha_5\beta_1$ -integrins on target cells and activates host cell focal adhesion kinase (FAK) and Src to ensure that CagA is phosphorylated directly at its site of injection. Additional Cag proteins (CagA, CagI, CagY) also bind  $\beta_1$  integrin and induce conformational changes of integrin heterodimers, which permits CagA translocation. Recently, a fourth cognate *H. pylori* adhesin-host receptor partnership was identified as an *H. pylori* outer membrane protein, HopQ, which was shown to bind to members of the host carcinoembryonic antigen-related cell adhesion molecule (CEACAM) family of receptors, required for CagA translocation and subsequent signaling within epithelial cells. This remarkable finding has identified an additional target for novel antimicrobial therapeutic strategies as well as providing a framework for new studies of *H. pylori* pathogenesis.

*H. pylori* has not only evolved mechanisms to aberrantly activate inflammatory signaling but to also evade host recognition and clearance. Toll-like receptors (TLRs) orchestrate immune responses targeting pathogens and bridge innate and adaptive immunity via selective recognition of pathogen-associated molecular

patterns (PAMPs). However, *H. pylori* harbors multiple PAMPs that interact differently with TLRs than the respective counterparts in other mucosal pathogens. *H. pylori* FlaA is a non-inflammatory molecule in terms of its ability to activate TLR5. *H. pylori* LPS contains an anergic lipid A core that induces an attenuated TLR4-mediated response. We and others have shown that deacetylation of peptidoglycan allows *H. pylori* to evade host clearance and that pre-activation of Nod1 suppresses *H. pylori*-induced signaling via activation of a Nod1-dependent negative feedback loop. Thus, *H. pylori* has evolved to express an array of diverse phenotypes to subvert obstacles presented by the host, which promotes long-term colonization and, inherently, the development of the disease.

Environmental conditions such as high salt diets or iron deficiency can also augment the risk for disease by enhancing the virulence of *H. pylori*. Exposure of *H. pylori* *cag*<sup>+</sup> strains to increasing concentrations of salt markedly enhances the expression of CagA, and the levels of induction are dependent upon a salt-sensitive motif within the CagA promoter. Iron deficiency also accelerates the progression to carcinogenesis within the context of *H. pylori* infection and iron depletion augments assembly of the *cag* T4SS and translocation of CagA into host epithelial cells. Are there other elements that contribute to *H. pylori*-induced diseases? Studies in mice have determined that the gastric microbiota collaborates with *H. pylori* to augment the progression to gastric cancer, and persons with pre-malignant and malignant gastric lesions have distinct microbial populations in the stomach, which is termed dysbiosis. Restoration of gastric dysbiosis is an exciting area for future research when viewed within the context of data demonstrating that manipulation of the intestinal microbiome improves tumor responses to checkpoint inhibitor therapies. Specifically for *H. pylori*, computational modeling has shown that non-*H. pylori* bacterial lateral gene transfer occurs frequently in gastric cancers and, of interest, 2 of the 5 most targeted host genetic loci for bacterial DNA integration are *CEACAM5* and *CEACAM6*, which encode proteins known to be up-regulated in gastric cancer. Over-expression of CEACAMs in three-dimensional tissue culture systems aberrantly affects tissue organization and architecture and leads to the formation of cancer in mice. Heightened expression of CEACAMs induced by a dysbiotic gastric microbial community may also facilitate *H. pylori* binding, thereby conferring detrimental consequences for the host over prolonged periods of time.

Together, I feel very much delighted to be asked by Steffen Backert to provide this Foreword for the volume on “Molecular Mechanisms of Inflammation: Induction, Resolution and Escape by *Helicobacter pylori*” that he has edited. I was fascinated by the topic list and impressed by the fantastic group of international experts contributing to this book. Ultimately, the book covers crucial investigations that focus on *H. pylori*-induced diseases that will help to construct a paradigm for other cancers that arise from inflammatory foci such as hepatocellular carcinoma and cholangiocarcinoma. Similarly, chronic esophagitis, pancreatitis, and ulcerative colitis each confer a significantly increased risk for the development of cancer within their respective anatomic sites. Thus, a comprehensive understanding of how *H. pylori* initiates gastric cancer will impact our knowledge of how chronic

inflammation leads to malignant degeneration in other organ systems. The insight contained in each of these chapters provides such an understanding and is, therefore, a welcome addition to this field.

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# Abbreviations

~P	Phosphate group
ABCG2	ATP-binding cassette subfamily member G2
Abl	Abelson kinase
ACE	Angiotensin-converting enzyme
ACRG	Asian cancer research group
ADP	Adenosine diphosphate
ADP-Hep	ADP- $\beta$ -D-manno-heptose
AID	Activation-induced cytidine deaminase
AIEC	Adherent-invasive <i>Escherichia coli</i>
AJ	Adherens junction
Aka	Also known as
AKAP	A-kinase-anchoring protein
AKT/PKB	Protein kinase B
ALDH1	Aldehyde dehydrogenase 1
AlpA	Adherence-associated lipoprotein A
AlpB	Adherence-associated lipoprotein B
ALPK1	Alpha protein kinase1
AmiE	Amidase
AmiF	Formidase
AMP	Antimicrobial peptide
AP-1	Activator protein-1
APC	Antigen-presenting cell
APE1	Apurinic/apryrimidinic endonuclease 1
APOBEC	Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like
Arg2	Arginase II
ARHGAP6	Gene name for: Rho GTPase-activating protein 6
ARHGAP26	Gene name for: Rho GTPase-activating protein 26
ARID1A	AT-rich interactive domain-containing protein 1A
ASC	Adult stem cell, adaptor protein

ASPP2	Apoptosis-stimulating protein of p53 2
ATF-2	Activating transcription factor 2
ATM	Ataxia telangiectasia mutated kinase
ATP	Adenosine triphosphate
ATR	ATM and Rad3-related kinase
ATRIP	ATR-interacting protein
B2M	Beta-2-microglobulin
BabA	Blood group antigen-binding adhesin A
BabB	Blood group antigen-binding adhesin B
BAC	Bacterial artificial chromosome
BAFF	B-cell-activating factor
Barx1	BarH-like homeobox 1
BCL2	B-cell lymphoma 2 gene
BCL3	B-cell lymphoma 3-encoded protein
BCL10	B-cell lymphoma 10 gene
BCR	B-cell receptor
BE	Barrett's esophagus
BER	Base excision repair
BIR	Baculovirus inhibitor of apoptosis repeat protein domain
BIRC3	Baculoviral IAP repeat containing 3
BMDC	Bone marrow-derived cell
BMM	Bone marrow-derived macrophage
BMP	Bone morphogenic protein
BrdU	Bromodeoxyuridine
C/EBP	CCAAT/enhancer-binding protein
<i>cag</i>	Cytotoxin-associated gene
<i>cag3</i>	Cytotoxin-associated gene 3
<i>cagA</i>	Cytotoxin-associated gene A
CagA	Protein encoded by <i>cagA</i>
<i>cagC</i>	Cytotoxin-associated gene C
<i>cagI</i>	Cytotoxin-associated gene I
<i>cagL</i>	Cytotoxin-associated gene L
<i>cagM</i>	Cytotoxin-associated gene M
<i>cagPAI</i>	<i>cag</i> pathogenicity island
<i>cagT</i>	Cytotoxin-associated gene T
<i>cagX</i>	Cytotoxin-associated gene X
<i>cagY</i>	Cytotoxin-associated gene Y
cAMP	Cyclic adenosine monophosphate
CARD	Caspase recruitment protein domain
CARMA	CARD-containing protein
Cas9	CRISPR-associated protein 9
CASK	Ca/Calmodulin-dependent serine protein kinase
CASP 1	Caspase 1
Cav1	Caveolin 1
CBM	CARD11-BCL10-MALT1 protein complex

CCKBR	Cholecystokinin B receptor (also called CCK <sub>2</sub> )
CCL/CXCL	Chemokine ligand
CCND1	Gene name for: Cyclin D1
CCNE1	Gene name for: Cyclin E1
CCR	CC-chemokine receptor
CcrM	<i>Caulobacter crescentus</i> DNA methyltransferase
CD	Cluster of differentiation
Cdc6	Cell division control protein 6
CDH1	Gene name for: E-cadherin
CDKN	Cyclin-dependent kinase inhibitor gene
Cdx2	Caudal-type homeobox 2
CEA	Carcinoembryonic antigen
CEACAM	Carcinoembryonic antigen-related cell adhesion molecule
CEA-TCB	Carcinoembryonic antigen-T-cell-specific antibody
CFU	Colony-forming unit
CG	Cholesteryl glucoside
CGD	Chronic granulomatous disease
CGRP	Calcitonin gene-related peptide
CGT	Cholesterol glycosyl-transferase
Chk1	Checkpoint kinase 1
Chk2	Checkpoint kinase 2
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CK1	Casein kinase 1
CLD18	Gene name for Claudin 18
CLP	Common lymphoid progenitor
CLR	C-type lectin receptor
CLS	CBF1 suppressor of hairless Lag-1
CM	CagA multimerization sequence
c-Met	Tyrosine kinase (also called hepatocyte growth factor receptor)
<i>comB</i>	<i>H. pylori</i> competence gene B
<i>comH</i>	<i>H. pylori</i> competence gene H
Cox1	Cyclooxygenase 1
Cox2	Cyclooxygenase 2
CpG	Cytosine-guanine repeats
CRE	cAMP response element
CREB	cAMP responsive element-binding protein
CRISPR	Clustered regularly interspaced short palindromic repeats
CRPIA	Conserved repeat responsible for phosphorylation independent activity
CSC	Cancer stem cells
CSF/MCSF	Colony-stimulating factor
CSFR	Colony-stimulating factor receptor
Csk	Carboxy-terminal Src kinase
CSMD	CUB and sushi multiple domains

c-Src	Cellular sarcoma kinase
CT	Cholera toxin
CTLA4	Cytotoxic T lymphocyte-associated antigen 4
CTNNA1	Gene name for: $\alpha$ -1-Catenin
CTNNB1	Gene name for: $\beta$ -1-Catenin
CTNND1	Gene name for: $\delta$ -1-Catenin
CXCL1	C-X-C motif chemokine ligand 1 (also called keratinocyte chemokine, KC)
CXCL10	C-X-C motif chemokine ligand 10 (also called IL-10)
CXCL8	C-X-C motif chemokine ligand 8 (also called IL-8)
DC	Dendritic cell
DC-SIGN	Dendritic cell-specific HIV-1 receptor (also called CD209)
DDR	DNA damage response
DFMO	Difluoromethylornithine
DGC	Diffuse gastric cancer
DIMT1	DIM 1 dimethyladenosine transferase 1 homolog
DKK	Dickkopf 1
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
DP	Double-positive
DSB	Double-strand DNA breaks
dsDNA	Double-stranded DNA
DU	Duodenal ulcer
DupA	Duodenal ulcer promoting gene A
EAC	Esophageal adenocarcinoma
EBER	EBV encoded small RNA
EBNA	EBV nuclear antigen
EBNA-LP	EBNA-leader protein
EBV	Epstein-Barr virus
ECD	Extracellular domain
ECL	Enterochromaffin-like
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EHEC	Enterohemorrhagic <i>Escherichia coli</i>
EMT	Epithelial mesenchymal transition
Epi-CAM	Epithelial cell adhesion molecule
EPIYA	Glu-Pro-Ile-Tyr-Ala sequence motif
ER	Endoplasmic reticulum
ERBB2(HER2)	Erb-b2 receptor tyrosine kinase 2
ERCC	Excision repair cross-complementing gene
ERK1/2	Extracellular signal-regulated kinase 1/2
ESC	Embryonic stem cell
FADD	Fas-associated protein with death domain
FAK	Focal adhesion kinase

FAP	Familial adenomatous polyposis
FasL	Fas ligand
FBXO24	F-box protein 24
FDA	Food and Drug Administration
Fe	Ferrum (iron)
FGC	Familial gastric cancer
FGF-10	Fibroblast growth factor-10
FGFR2	Fibroblast growth factor receptor 2
FHIT	Fragile histidine triad
Fic	Filamentation-induced by cAMP
FIGC	Familial intestinal gastric cancer
FISH	Fluorescence in situ hybridization
FlaA	Flagellin A
FlaB	Flagellin B
FliC	Flagellin FliC
Foxal	Forkhead box A1
FoxP1	Forkhead box P1
FoxP3	Forkhead box P3
FtsK	Filamentous temperature-sensitive cell division protein K
FZD7	Frizzled 7
GalNAc	$\alpha$ -N-acetylgalactosamine
GAP	GTPase-activating protein
GAPPS	Gastric adenocarcinoma and proximal polyposis of the stomach
GATA6	GATA-binding protein 6
gB	EBV glycoprotein B
GC	Gastric cancer
GCB	Germinal centre B cell
G-DIF	Diffuse subtype of GC
GEC	Gastric epithelial cell
GEJC	Gastroesophageal junction carcinomas
GERD	Gastro-esophageal reflux disease
GGT	Gamma-glutamyl transpeptidase
gH	EBV glycoprotein H
G-INT	Intestinal subtype of GC
GITR	Glucocorticoid-induced TNFR-related protein
gL	EBV glycoprotein L
GlcNAc	N-acetylglucosamine
GMDS	GDP-mannose 4,6-dehydratase
gp42	EBV glycoprotein 42
gp130	Glycoprotein 130
gp350	EBV glycoprotein 350
Grb2	Growth factor receptor-bound protein 2
GSH	Glutathione (reduced form)
GSK-3 $\beta$	Glycogen synthase kinase 3 beta
GSTP1	Glutathione S-transferase P

GWAS	Genome-wide-associated study
GyrA	Subunit A of DNA gyrase
GyrB	Subunit B of DNA gyrase
H2AX	Histone H2A variant X
H <sub>2</sub> RA	H <sub>2</sub> -receptor antagonist
hBD	Human beta-defensin
HBP	Heptose-1,7-bisphosphate
HBV	Hepatitis B virus
HDGC	Hereditary diffuse gastric cancer
HER2/neu	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
HHI	<i>H. pylori</i> HtrA inhibitor
HIF-1	Hypoxia-inducible factor-1
HIV	Human immunodeficiency virus
HK $\alpha$	H,K-ATPase $\alpha$ subunit
HLA	Human leukocyte antigen class II
HLA-B	Histocompatibility complex class I
HNF4 $\alpha$	Hepatocyte nuclear factor alpha
HNPCC	Hereditary non-polyposis colorectal cancer
Hof	Helicobacter OMP family protein
Hop	Helicobacter Outer membrane protein
HopB	Helicobacter Outer membrane protein B
HopC	Helicobacter Outer membrane protein C
HopD	Helicobacter Outer membrane protein D
HopH	Helicobacter Outer membrane protein H
HopP	Helicobacter Outer membrane protein P
HopQ	Helicobacter Outer membrane protein Q
HopS	Helicobacter Outer membrane protein S
HopT	Helicobacter Outer membrane protein T
HopU	Helicobacter Outer membrane protein U
HopZ	Helicobacter Outer membrane protein Z
Hor	Helicobacter Outer-related protein
HPA	Heparanase
HpaA	Neuraminylactose-binding hemagglutinin
HSC	Hematopoietic stem cells
Hsp60	Heat shock protein 60
HspB	Heat shock protein B
HtrA	High temperature requirement A
HU	Histone-like protein
Hupki	Human TP53 knock-in
IARC	International agency for research on cancer
IBD	Inflammatory bowel disease
ICOS	Inducible co-stimulator
ICOS-L	Inducible co-stimulator ligand



ICPi	Immune checkpoint inhibitors
IEL	Intra-epithelial lymphocytes
IFN	Interferon
IFNGR	Interferon gamma receptor
Ig	Immunoglobulin
IgA/B	Immunoglobulin A/B
IGFIIR	Insulin-like growth factor II receptor
IGH	Immunoglobulin heavy chain
IGHV	Immunoglobulin heavy chain variable region
IHF	Integration host factor
IKK	I $\kappa$ B kinase
IL	Interleukin
IL-1	Interleukin-1
IL-12	Interleukin-12
IL-17	Interleukin-17
IL-1R	Interleukin-1 receptor
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-21	Interleukin-21
IL-23	Interleukin-23
IM	Intestinal metaplasia
IMC	Inner membrane complex
iNKT	Invariant NK T-cells
iNOS	Inducible nitric oxide synthase
INS-GAS	Insulin-gastrin
INSR	Insulin receptor
IP <sub>3</sub>	Inositol triphosphate
IPD	Interpulse duration
IPEX	Immunodysregulation polyendocrinopathy enteropathy X-linked
iPSC	Induced pluripotent stem cell
IPSID	Immunoproliferative small intestinal disease
IRAK	IL-1 receptor-associated kinase
IRF	Interferon-regulatory factor
IRG	Interferon-response gene
ISGF3	Interferon-stimulated gene factor 3
ITAM	Immunoreceptor tyrosine-based activation motif
ITIM	Immunoreceptor tyrosine-based inhibition motif
JAK	Janus kinase
JAM	Junctional adhesion molecule
JNK	c-Jun kinase
JUP	Junction plakoglobin
KCNQ1	Potassium voltage-gated channel subfamily Q member 1
KLF	Krüppel-like factor
KO	Knockout

Kras	Kirsten rat sarcoma oncogene
LabA	LacdiNAc-specific adhesin
LacdiNAc	GalNAc $\beta$ 1-4GlcNAc
LAT	Linker for activation of T cells
LBP	Lipopolysaccharide-binding protein
LCK	Lymphocyte-specific protein tyrosine kinase
LDL-C	Low-density lipoprotein-cholesterol
Le <sup>a</sup>	Lewis A antigen
Le <sup>b</sup>	Lewis B antigen
LES	Lower esophageal sphincter
Le <sup>x</sup>	Lewis X antigen
Le <sup>y</sup>	Lewis Y antigen
LFA-1	Lymphocyte function-associated antigen 1
LFS	Li-Fraumeni syndrome
Lgr5	Leucin-rich-repeat-containing G-protein coupled receptor 5
LIMA1	LIM domain and actin-binding protein-1
LL37	37-residue amphipathic $\alpha$ -helical cathelicidin
LMO	LIM domain-only protein fragment
LMP	Latent membrane protein
LOH	Loss of heterozygosity
LPS	Lipopolysaccharide
Lrp	Global regulatory protein
LRR	Leucin-rich repeat
LSP1	Lymphocyte-specific protein 1
LT	Labile toxin
LT $\beta$	Lymphotoxin- $\beta$
M1	Type 1 macrophage
M2	Type 2 macrophage
m4C	N4-methylcytosine
m5C	5-methylcytosine
m6A	N6-methyladenine
MAdCAM-1	Mucosal addressin cell adhesion molecule 1
MAGI-1	Membrane-associated guanylate kinase with inverted orientation 1
MAGUK	Membrane-associated guanylate kinase-like protein domain
MALT	Mucosa-associated lymphoid tissue
MALT1	MALT lymphoma translocation protein 1
MAMP	Microorganism-associated molecular pattern
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase
MARK	Microtubule affinity-regulating kinase
MCL-1	Myeloid cell leukemia 1
MD2	Lymphocyte antigen 96
MDC1	Mediator of DNA damage checkpoint protein 1
MDCK	Madin-Darby canine kidney
MDM2	Mouse double minute 2 homolog

MDSC	Myeloid-derived suppressor cell
MGMT	6- <i>O</i> -methylguanine-DNA transferase
MHC	Major histocompatibility complex
Mincle	Macrophage inducible C-type lectin
miR	Non-coding micro-RNA (also called micro-RNA)
miRNA	Non-coding micro-RNA
Mist1	Basic helix-loop-helix family member a15
MKI	MARK kinase inhibitor
MLC	Myosin light chain
MLCK	Myosin light chain kinase
MLH	Human homolog of MMR from <i>Escherichia coli</i>
MLN	Mesenteric lymph nodes
MLST	Multilocus sequence typing
MMP	Matrix metalloprotease
MMR	DNA mismatch repair
MOI	Multiplicity of infection
MPF	Mating pair formation
Mre11	Meiotic recombination 11 homolog
MRN	MRE11-RAD50-NBS1 complex
mRNA	Messenger ribonucleic acid
MRR	Middle repeat region (CagY)
MS	Multiple sclerosis
MSI	Microsatellite instability
Msi-1	Musashi RNA-binding protein-1
MSI-H	High microsatellite instability
MSI-L	Low microsatellite instability
MSS	Microsatellite stable
Mtase	Methyltransferase
mtDNA	Mitochondrial DNA
MTHFR	Methylenetetrahydrofolate reductase
mTOR	Mechanistic target of rapamycin
MUC5AC	Mucin 5AC
MUC6	Mucin-6
MukB	SMC homolog
MUPP	Multi-PDZ domain protein
MYC	MYC proto-oncogene
MyD88	Myeloid differentiation primary response gene 88
MZB	Marginal zone B
m $\beta$ CD	Methyl- $\beta$ -cyclodextrin
NADPH	Nicotinamide adenine dinucleotide phosphate
NALP1	Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing 1 (also called NLRP1)
NapA	Neutrophil-activating protein A (also called HP-NAP or Dps)
Nbs1	Nijmegen breakage syndrome 1
NCI	National Cancer Institute of the United States

NEIL	Nei-like protein
NEMO	NF- $\kappa$ B essential modifier
NER	Nucleotide excision repair
NF- $\kappa$ B	Nuclear factor-kappa B
NFAT	Nuclear factor of activated T cells
NGS	Next-generation sequencing
NHEJ	Non-homologous end joining
NICD	Notch intracellular domain
NIK	NF- $\kappa$ B-inducing kinase
NK	Natural killer
NLR	Nucleotide-binding domain and leucine-rich-repeat-containing-proteins
NLRP	Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing
NO	Nitric oxide
NOD	Nucleotide-binding oligomerization domain
NOG	Noggin
NOS2	Nitric oxide synthase 2
NOX	NAPDH oxidase
NOXA1	NADPH oxidase activator 1
NRR	Negative regulatory region
NSAIDs	Non-steroidal anti-inflammatory drugs
NTH1	Endonuclease III homolog 1
nTreg	Natural T regulatory
OCT1	Octamer transcription factor1
ODC	Ornithine decarboxylase
ODN	Oligodeoxynucleotide
OGG	Oxoguanine DNA glycosylase
OGG1	8-oxo-guanine-DNA glycosylase 1
OipA	Outer inflammatory protein A
OMP	Outer membrane protein
OMV	Outer membrane vesicle
ONOO <sup>-</sup>	Peroxonitrite
ORC1	Origin recognition complex subunit 1
ORF	Open reading frame
OSCC	Oesophageal squamous cell carcinoma
p38	Mitogen-activated protein kinase p38
p53	Tumor suppressor protein
p53BP1	p53-binding protein 1
PAI	Pathogenicity island
PAMP	Pathogen-associated molecular pattern
PAR1	Protease-activated receptor 1
Par1b	Partitioning-defective kinase 1b
ParA	Chromosome partitioning protein ParA
ParB	Chromosome partitioning protein ParB

PARK	Parkin gene
PARP1	Poly [ADP-ribose] polymerase 1
parS	Centromere-like sequence
PCR	Polymerase chain reaction
PD-1	Programmed death protein 1
pDC	Plasmacytoid dendritic cell
PDCA-1	Plasmacytoid dendritic cell antigen-1
PDCD1LG2	Programmed cell death 1 ligand 2
PDL1/B7H1	Programmed cell death ligand 1
Pdx1	Pancreatic and duodenal homeobox 1
PG	Peptidoglycan
PGC	Pepsinogen C
PGE2	Prostaglandin E2
PGE-M	Prostaglandin E2 metabolite
PHLPP1	PH domain leucine rich phosphatase 1
PI3K	Phosphatidylinositol 3-kinase
PJS	Peutz-Jeghers syndrome
PKC	Protein kinase C
PKLR	Pyruvate kinase isozymes R/L
PLC	Phosphoinositide phospholipase C
PLCE1 1	Phosphatidylinositol-4,5-bisphosphate phosphodiesterase epsilon-1
PLD1	Phospholipase D1
PMN	Polymorphonuclear neutrophil
PPAR $\gamma$	Peroxisome proliferator-activated receptor $\gamma$
PPI	Proton pump inhibitor
Pre-B	Pre-B cell receptor in precursor B cells
PRK2	Protein kinase C-related kinase 2
PRKAA1	Protein Kinase AMP-Activated Catalytic Subunit Alpha 1
PRR	Pattern recognition receptor
PS	Phosphatidylserine
PSC	Pluripotent stem cells
PSCA	Prostate stem cell antigen
PTEN	Phosphatase and tensin homolog
PTGS2	Prostaglandin endoperoxide synthase 2
PUD	Peptic ulcer disease
Rac1	Ras-related C3 botulinum toxin substrate 1
RAG	Recombination-activating Genes
RegIII	Regenerating islet-derived III
REL	Rel homology domain (RHD) in NF- $\kappa$ B transcription factors
RGD	Arg-Gly-Asp sequence motif
RGDLXXL	Arg-Gly-Asp-Leu/Met-X-X-Leu/Ile sequence motif
RhoA	Ras homolog gene family A
RHS	RGD helper sequence
RIDA	Regulatory inactivation of DnaA activity

RIG1	Retinoic acid inducible gene 1
RIPK2	Receptor-interacting serine/threonine kinase 2
R-M systems	Restriction-modification systems
RNA	Ribonucleic acid
RNF43	Ring finger protein 43
RNS	Reactive nitrogen species
RocF	Urea-producing arginase
ROCK	Rho-Kinase
ROS	Reactive oxygen species
RPTP	Receptor protein tyrosine phosphatase
RSPO	R-spondin1
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcriptase-polymerase chain reaction
RUNX3	Runt-related transcription factor 3
SabA	Sialic acid-binding adhesin
SCF	Stem cell factor
SCID	Severe combined immune deficiency
SeqA	Sequestration protein A
SFK	Src family kinase
SH2	Src homology 2
SH3	Src homology 3
SHH	Sonic hedgehog
SHP-1/2	Src homology region 2 domain-containing phosphatase-1/2
siRNA	Small interfering RNA
SLB	Single layer antiparallel $\beta$ -sheet
SLC1A2	Solute carrier family 1 member 2
SLT	Soluble lytic transglycosylase
SMAD2	Mothers against decapentaplegic homolog 2
SMC	Structure maintenance of chromosomes
SMOX	Spermine oxidase
SNP	Single-nucleotide polymorphism
Soj	Sporulation initiation inhibitor Soj
Sox4	Sex-determining region Y (SRY)-box 4
Sox9	Sex-determining region Y (SRY)-box 2
SP1	Specificity protein 1
SP-D	Surfactant-binding protein D
SPEM	Spasmolytic polypeptide-expressing metaplasia
Spo0J	Chromosome partitioning protein
SPR	Surface plasmon resonance
Src	Sarcoma kinase
SSB	Single-strand binding
ssDNA	Single-stranded DNA
STAT	Signal transducer and activator of transcription
STAT1/3/4/6	Signal transducer and activator of transcription factor-1/3/4/6
STMN1	Stathmin

T3SS	Type III secretion system
T4SS	Type IV secretion system
TAK1	Transforming growth factor beta-activated kinase 1
TAKK	Transforming growth factor $\beta$ -activating kinase
TAM	Tumor-associated macrophage
TBK-1	Serine/threonine protein kinase-1
TCF/LEF	T-cell-specific transcription factor/lymphoid enhancer-binding factor
TCGA	The Cancer Genome Atlas
TCR	T-cell receptor
TdT	Terminal deoxynucleotidyl transferase
TER	Transepithelial electrical resistance
TFF	Trefoil factor family
TFH	T follicular helper
TGCT	Tenosynovial giant cell tumor
TGFR	Transforming growth factor receptor
TGF- $\beta$	Transforming growth factor beta
TGF- $\beta$ RII	Transforming growth factor $\beta$ receptor II
Th	T helper cell
Th1	T helper 1 cell
Th17	T helper 17 cell
TIFA	TRAF-interacting protein with forkhead-associated domain
TIMP3	Metalloproteinase inhibitor 3
Tip $\alpha$	TNF-inducing factor $\alpha$
TIR	Toll/IL-1 receptor domain
TIRAP	TIR domain containing receptor protein
TJ	Tight junction
TLR	Toll-like receptor
TME	Tumor microenvironment
TNF	Tumor necrosis factor
TNFR1	TNF receptor 1
Tnfrsf19	Tumor necrosis factor receptor super family 19
TP53	Tumor protein p53
TRAF	TNF receptor-associated factor
TRD	Target recognition domain
TRD1	Target recognition domain 1
TRD2	Target recognition domain 2
Treg	T regulatory cell
TRIF	TIR-domain-containing adapter-inducing interferon- $\beta$
TT	Tetanus toxoid
TWIST1	Twist family BHLH transcription factor 1
UC	Ulcerative colitis
Ure	Urease
UTR	Untranslated region
UV	Ultraviolet

<i>vacA</i> i	Intermediate segment of <i>vacA</i> gene
<i>vacA</i> m	Middle segment of <i>vacA</i> gene
<i>vacA</i> s	Signal segment of <i>vacA</i> gene
VacA	Vacuolating cytotoxin A
Vav	Rac-specific nucleotide exchange factor
VEGFA	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor Receptor
Vill1	Villin-1
VirB10	Inner core protein of the <i>Agrobacterium tumefaciens</i> T4SS
VirB4	Cytoplasmic ATPase of the <i>Agrobacterium tumefaciens</i> T4SS
VirD4	Channel ATPase of the <i>Agrobacterium tumefaciens</i> T4SS
v-Src	Viral sarcoma kinase
WHO	World Health Organization
WWOX	WW domain containing oxidoreductase
XRCC 1/3	X-ray repair cross-complementing group 1/3
$\alpha$ CAG	Cholesteryl-6'-O-tetradecanoyl- $\alpha$ -D-glucopyranoside
$\alpha$ CG	Cholesteryl- $\alpha$ -D-glucopyranoside
$\alpha$ CPG	Cholesteryl-6'-O-phosphatidyl- $\alpha$ -D-glucopyranoside