

Supplementary Materials for:

Clinical Trials, Progression-speed Differentiating Features, and Swiftness Rule of the Innovative Targets of First-in-class Drugs

Ying Hong Li^{1,2,§}, Xiao Xu Li^{1,2,§}, Jia Jun Hong^{1,§}, Yun Xia Wang^{1,§}, Jian Bo Fu¹, Hong Yang², Chun Yan Yu², Feng Cheng Li¹, Jie Hu³, Wei Wei Xue², Yu Yang Jiang⁴, Yu Zong Chen^{5,*} & Feng Zhu^{1,2,*}

¹ Lab of Innovative Drug Research and Bioinformatics, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China

² Innovative Drug Research and Bioinformatics Group, School of Pharmaceutical Sciences and Collaborative Innovation Center for Brain Science, Chongqing University, Chongqing 401331, China

³ School of International Studies, Zhejiang University, Hangzhou 310058, China

⁴ State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Biology, The Graduate School at Shenzhen, Tsinghua University, Shenzhen, Guangdong 518055, China

⁵ Bioinformatics and Drug Design Group, Department of Pharmacy, National University of Singapore, Singapore 117543, Singapore

*Corresponding Author: Prof. Feng ZHU, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China. Tel.: +86-571-88208444; Email: zhufeng@zju.edu.cn; prof.zhufeng@gmail.com. Prof. Yu Zong CHEN, Department of Pharmacy, National University of Singapore, Singapore 117543, Singapore. Tel.: +65-6516-6877; Email: phacyz@nus.edu.sg

§ These authors contributed equally to this work.

Ying Hong LI, Xiao Xu LI, Jia Jun HONG and Yun Xia WANG are Ph.D. or master candidates of the College of Pharmaceutical Sciences, Zhejiang University, China. They are interested in bioinformatics and target discovery.

Yu Zong CHEN is a professor of Bioinformatic and Drug Design Group (BIDD), Department of Pharmacy, National University of Singapore. He is interested in bioinformatics, computation biology, and computer-aided drug design.

Feng ZHU is a professor of the College of Pharmaceutical Sciences, Zhejiang University, China. His research group (<https://idrblab.org/>) has been working in the fields of bioinformatics, OMIC-based drug discovery, system biology & medicinal chemistry. Welcome to visit his personal website at: <https://idrblab.org/Peoples.php>

Running Title: Clinical Trial Swiftness Rule of First-in-class Drug Targets

Supplementary Table S1: The established criterion of efficacy targets.

Target	A protein, DNA, RNA, cell wall/membrane component, or intra-cellular component unambiguously involved in the initiation or progression of a disease, and directly modulated by a drug with adequate potency. Potency criteria vary with assay, technology and target-type. Typically, drugs are expected to exhibit potencies of <500nM (ideally <100nM) in biochemical assays, but drugs of μ M potencies may show adequate potencies in cell-based, in-vivo and clinical studies.
Efficacy target	A target through which a drug mediates its claimed primary therapeutic effect, which is confirmed by biochemical assay and strong cell-based and/or in-vivo evidence linking the target to drug. Drug discovery against the same target is expected to lead to additional drugs of the same claimed therapeutic effect. Drugs typically exhibit potencies of <1 μ M in cell-based assays, but in some cases potencies of 10 μ M range may be acceptable. Criteria for in-vivo tests are less stringent.
Secondary efficacy target of multi-target drugs	A target unambiguously involved in compensatory action or resistance against a drug (e.g. promoting alternative signaling or reducing drug bioavailability), and simultaneous action of a multi-target drug against this target and the main efficacy target exhibits statistically significant improvement of efficacy over that of the drugs against efficacy target only.

Supplementary Table S2: The sources of the collected clinical trial drugs in this study.

PhRMA medicines in development reports

More Than 800 Medicines and Vaccines in Testing Offer Hope in the Fight Against Cancer (2009)

Pharmaceutical Research Companies Are Developing More Than 300 Medicines to Treat Mental Illnesses (2010)

Biopharmaceutical Research Companies Are Developing Nearly 300 Medicines for Cardiovascular Disease (2011)

Biopharmaceutical Research Companies Are Developing Nearly 300 Medicines to Treat Diseases of the Skin (2011)

Biopharmaceutical Research Companies Are Developing More Than 220 Medicines to Treat Diabetes (2012)

Biopharmaceutical Research Companies are Developing Nearly 100 Medicines for Alzheimer's Disease (2012)

More Than 900 Medicines and Vaccines in Clinical Testing Offer New Hope in the Fight Against Cancer (2012)

Pharmaceutical Companies are Developing Nearly 200 Medicines for Mental and Addictive Disorders (2012)

Biologics Research Pushing Frontiers of Science with more than 900 Medicines in Development (2013)

More Than 450 Medicines in Development for Rare Diseases (2013)

Biopharmaceutical Research Companies Are Developing More Than 430 Medicines for Top Chronic Diseases (2014)

Nearly 800 Medicines and Vaccines in Clinical Testing for Cancer Offer New Hope to Patients (2014)

Medicines in Development for Cancer 2015 Report (2015)

Medicines in Development for Neurological Disorders 2015 Report (2015)

Medicines in Development for Diabetes 2016 Report (2016)

Medicines in Development for Osteoporosis 2016 Report (2016)

Medicines in Development for Rare Diseases 2016 Report (2016)

Medicines in Development for Autoimmune Diseases 2016 Report (2016)

Medicines in Development for HIV 2017 Report (2017)

Medicines in Development for Immuno-Oncology 2017 Report (2017)

List of 2017 Medicines in Development for Mental Illness (2017)

Medicines in Development for Alzheimer's Disease 2017 Report (2017)

Medicines in Development for Heart Disease and Stroke 2018 Drug List (2018)

Pharmaceutical databases

Springer AdisInsight database (2015)

Thomson Reuters Pharma™ (2010 and 2012)

CenterWatch Drugs in Clinical Trials Database (2007)

MDL® Drug Data Report (2004)

U.S. National Institutes of Health ClinicalTrials.gov

IUPHAR/BPS Guide to Pharmacology

18 research institutes or organizations of which the drug pipeline reports, the annual reports and the announcements were collected

AERAS Global TB Vaccine Foundation (AERAS)

CSIR-Central Drug Research Institute

Dana-Farber Cancer Institute

Dartmouth-Hitchcock Medical Center

Finlay Institute

Infectious Disease Research Institute

Institut Pasteur

Karolinska Institute

Naval Medical Research Center

QIMR Berghofer

Rogosin Institute

Rutgers University

Sabin Vaccine Institute

St Georges University of London

Texas Heart Institute

University College London

University of Wisconsin School of Medicine

Weizmann Institute of Science

371 companies of which the drug pipeline reports, the annual reports and the announcements were collected

22nd Century Group

4SC AG

7TM Pharma

Abbott

Acadia Pharmaceuticals

Accelaron Pharma

Achillion Pharmaceuticals

Acorda Therapeutics Biotechnology

Actelion Pharmaceuticals

Actinium Pharmaceuticals

ACTIVARTIS Biotech GmbH

Acuity Pharmaceuticals

Adamis Pharmaceuticals

Aduro Biotech

Advantagene

Aeson Therapeutics

AFFiRiS AG

Affitech A/S

Agenus Inc

Alexza Pharmaceuticals

ALK Abello

Alkermes plc

Allegro Ophthalmics

Allergy Therapeutics

Alnylam Pharmaceuticals

AlphaVax

Altimmune

Amarantus BioScience Holdings

Amarillo Biosciences

Amgen

Amicus Therapeutics

Anacor

Anadys Pharmaceuticals

Anavex

Anergis SA

AnGes MG

Angion Biomedica

Aradigm

Archivel Farma SL

Ardana Bioscience

Ardelyx

ARIAD Pharmaceuticals

Arisaph Pharmaceuticals	Arno Therapeutics	Asklepios BioPharmaceutical
Astellas Pharma	Asterias Biotherapeutics	Astex Pharmaceuticals
AstraZeneca	ATLAB Pharma	Avanir Pharmaceuticals
AVARX LLC	Avax Tech	Avicena Group
Baxter	Bayer	Bellicum Pharmaceuticals
Bellus Health	Benitec	BERG
BHV Pharma	Bio Products Laboratory	Biocardia
Biodel Inc	Biogen	Bioheart
Biological E. Limited	Biomarin	Biopton Light Therapy
Biotest Pharmaceuticals	Biotie	BioTime
Birds Pharma AG	Bluebird Bio	Boehringer Ingelheim
Bristol-Myers Squibb	Bukwang Pharmaceutical	CalciMedica
Cancer Advances	Can-Fite BioPharma	Capricor Therapeutics
CardioPharma	CDG Therapeutics	Cebix
Celimmune	Cell Point	CEL-SCI Corporation
CerRx Inc	Cerus	ChemoCentryx
Chugai Pharmaceutical	Circassia	Cleveland BioLabs
CoDa Therapeutics	Cornerstone pharmaceuticals	Covx Pharmaceuticals
CreaGene	Crucell	CTI BioPharma
Curis	Cytori Therapeutics	Cytos Biotechnology AG
CZ Biomed Corp	D&A Pharma	Daiichi Sankyo
DBV Technologies	Debiopharm	Denka Seiken
Dia-B Tech	Diamedica	Diamyd Medical AB
Diasome Pharmaceuticals	Diffusion Pharmaceuticals	Digestive Care
Duska Therapeutics	Dynavax	DynPort Vaccine Company
Eagle Pharmaceuticals	Edimer pharmaceuticals	EigerBio
Eisai Co Ltd	Elcelyx	Eli Lilly
Emergent BioSolutions	Emisphere Technologies	Endocyte
Etubics	Eurovacc	Evoke Pharma
Evotec	Exelixis	Exsulin

Fabre-Kramer Pharmaceuticals	Faron Pharmaceuticals	Fate therapeutics
Ferring Pharmaceuticals	Fina Biotech	FirstString Research
FIT Biotech Oy	Five Prime Therapeutics	FluoroPharma Medical
Forest Laboratories	Forsight vision5	Forum pharmaceuticals
Fresenius	Galapagos	Galena Biopharma
Gemac Pharma	Genentech	Generex Biotechnology
Genetic Immunity	Genmab	Genovax Srl
Genta	Genus Oncology	Genzyme
GeoVax	Geron	Gilead Sciences
GITR Inc	GlaxoSmithKline	GlobelImmune
Gramineer	Green Peptide	GREER
GW Pharmaceuticals	HanAll BioPharma	Hatchtech
Helix BioPharma	Hemodynamic Therapeutics	HepC, Inc
Humanetics	iBio, Inc.	Iconic therapeutics
Idenix Pharmaceuticals	Idera Pharmaceuticals	Ikaria
ImmunoFrontier	Immunomedics	Immunotope
Immunovaccine	Immunservice GmbH	ImmusanT
Incyte	Innate Pharma	Inovio Pharmaceuticals
Inpharma SA	INSYS Therapeutics	IntecPharma
Intellikine	InterMune	Intra-Cellular Therapies
Ion Channel Innovations	Iroko Pharmaceuticals	Isa Pharmaceuticals
ISIS Pharmaceuticals	ISTO Technologies	Izun Pharmaceuticals
JN-International Medical	Johnson & Johnson	Juvaris Biotherapeutics
Juvenon	KaloBios Pharmaceuticals	Karo Bio
Kibow Biotech	Kinex Pharmaceuticals	Kowa Pharmaceuticals
Kringle Pharma	Kyowa Hakko Kirin Pharma	LG Life Science
Lion Biotechnologies	Lundbeck	Lupin Limited
Luye pharmaceutical	MabVax Therapeutics	Macrocare
Macrogenics	MannKind	Marina Biotech
Mati Therapeutics	MaxCyte	Mazence

Medesis Pharma	Medicago	MedImmune
Medinox	Medivir	Mentrik Biotech
MerciaPharma	Merck	Meridian Bioscience
Merrimack Pharmaceuticals	Mesoblast	Metabasis Therapeutics
Meta-IQ	MetronomX	MicRx Pharmaceuticals
MIKA Pharma GmbH	Mistral Pharma	Molecular Targeting Technologies
MolMed S.p.A.	Momenta Pharmaceuticals	MorphoSys AG
multimmune GmbH	Mymetics	Myriad Genetics
NanoBio	Nanotherapeutics	Nektar Therapeutics
NEONC Technologies	Neos Therapeutics	Neurolix
Neurotrope BioScience	NewLink Genetics	NicOx
Nile Therapeutics	NIPPON SHINYAKU	NOLabs AB
Northwest Biotherapeutics	Novartis	Novavax
Novo Nordisk	NRVision L.P.	Nucryst Pharmaceuticals
Ocular Therapeutix	Okairos	Oligovax SAS
Omeros	OncoMed Pharmaceuticals	OncoSec Medical
Onyvax	OPKO Health	Oragenics
Osmotica Pharmaceutical	Otsuka Pharmaceutical	Panagin Pharmaceuticals
Pantec Biosolutions	Peregrine Pharmaceuticals	Pfizer
Pharmalink	Pharmasset	PharmAthene
PhaseBio	Pherin Pharmaceuticals	Piramal Healthcare
Planet Biotechnology	Pluristem Therapeutics	Portola Pharmaceuticals
Prescient Therapeutics	Presidio Pharmaceuticals	Prima BioMed
Profectus BioSciences	Progen Pharmaceuticals	Progenics Pharmaceuticals
Proneuron Biotechnologies	Protein Sciences	Proximagen
Psyadon Pharmaceuticals	Quark Pharmaceuticals	Quest Pharmatech
REGENXBIO	Regulus Therapeutics	Relmada therapeutics
Repligen	Revance Therapeutics	Rigel Pharmaceuticals
Roche	Rockwell Medical Technologies	Sandoz
Sanofi	Santaris Pharma	Savara Pharmaceuticals

SciClone Pharmaceuticals	SCYNEXIS	Seattle Genetics
SEIKAGAKU	Selexys Pharmaceuticals	Shionogi
Sinovac Biotech	Sirna Therapeutics	SkyePharma
Solvay	Spectrum Pharmaceuticals	Stallergenes
Stematix	Stemmedica Cell Technologies	Summit Therapeutics
Suven Life Sciences	Syndax	Taiho Pharmaceutical
Taisho Pharmaceutical	Takara Bio	Takeda Pharmaceutical
Tella Inc	Tetralogic Pharmaceuticals	TG Therapeutics
Theravance Biopharma	Tocagen	Tolerion Inc
Topica Pharmaceuticals	Transition Therapeutics	TransTech Pharma
Triphase Accelerator	TVAX Biomedical	Tyrogenex
Union Chimique Belge (UCB)	United Therapeutics	UroGene
Valneva	VaxInnate	Vectura
Velcura Therapeutics	Veloxis Pharmaceuticals	Vericel
Vertex	Vesta Therapeutics	ViaCyte
Vical	Virax Holdings Limited	ViroBay
Vital Therapies	Xbiotech	XEME Biopharma
Xencor	XOMA Corporation	Zafgen
Zensun	ZIOPHARM Oncology	Zogenix
Zydus Cadila	ZymoGenetics	

Supplementary Table S3: The target name, the corresponding first-in-class drug and the clinical trial progression timeline of the 89 innovative targets (without an approved drug before 2004) with a first-in-class drug approved in the period of 2004-2017.

Target Full Name	Target Name	Time Spend on Clinical Trial Progression (by month)	Start Date of the Clinical Trial (Drug Name; Trial Status)	Date of the First FDA Approval (Approved First-in-class Drug; Disease; Drug Type)
Human Targets of Small Molecular Drugs (40 targets in total, ordered by the time spend from clinical trial phase I to FDA approval)				
Carbamoyl phosphate synthetase 1	CPS1	37	Aug 2008 (N-carbamylglutamate; P2/3) ¹	Mar 2010 (Carglumic Acid; Hyperammonaemia; Small molecular drug) ²
Isocitrate dehydrogenase 2	IDH2	48	Aug 2013 (AG-221; P1) ^{3,4}	Aug 2017 (Enasidenib; Acute myeloid leukemia; Small molecular drug) ⁵
Phenylalanine hydroxylase	PAH	54	Dec 2004 (Sapropterin Dihydrochloride; P2) ⁶	Dec 2007 (Sapropterin Dihydrochloride; Hyperphenylalaninaemia; Small molecular drug) ⁷
Melatonin MT1/2 receptor	MT1/2 receptor	56	May 2002 (Ramelteon; P2) ⁸	Jul 2005 (Ramelteon; Insomnia; Small molecular drug) ⁹
Proto-oncogene B-Raf	BRaf	57	Nov 2006 (PLX4032; P1) ^{10,11}	Aug 2011 (Vemurafenib; Melanoma; Small molecular drug) ¹²
Btk tyrosine kinase	Btk	57	Feb 2009 (PCI-32765; P1) ^{13,14}	Nov 2013 (Ibrutinib; Mantle cell lymphoma; Small molecular drug) ¹⁵
Smoothened	Smoothened	57	Apr 2007 (GDC-0449; P1) ^{16,17}	Jan 2012 (Vismodegib; Basal cell carcinoma; Small molecular drug) ¹⁸

ALK tyrosine kinase receptor	Alk	64	Apr 2006 (PF-02341066; P1) ^{19,20}	Aug 2011 (Crizotinib; Non-small-cell lung carcinoma; Small molecular drug) ¹²
Cystic fibrosis transmembrane conductance regulator	CFTR	74	May 2007 (VX-770; P2) ^{21,22}	Jan 2012 (Ivacaftor; Cystic fibrosis; Small molecular drug) ¹⁸
Renin	Renin	74	Jan 2001 (SPP100; P1) ²³	Mar 2007 (Aliskiren Hemifumarate; Hypertension; Small molecular drug) ⁷
Lymphocyte function-associated antigen-1	LFA-1	83	Aug 2009 (SAR 1118; P1) ²⁴	Jul 2016 (Lifitegrast; Dry eye disease; Small molecular drug) ²⁵
Dipeptidyl peptidase IV	DPP4	90	Oct 2000 (P32/98; P1 Completed) ^{26,27}	Oct 2006 (Sitagliptin; Type 2 diabetes; Small molecular drug) ²⁸
CC-chemokine receptor 5	CCR5	91	Jan 2001 (UK-427,857; P1) ²⁹	Aug 2007 (Maraviroc; HIV infection; Small molecular drug) ⁷
Chloride channel protein 2	CLCN2	93	Apr 2002 (RU-0211; P2 Completed) ^{30,31}	Jan 2006 (Lubiprostone; Chronic idiopathic constipation; Small molecular drug) ²⁸
OX1/2 orexin receptor	Orexin receptor	99	May 2006 (ACT-078573; P1) ³²	Aug 2014 (Suvorexant; Insomnia; Small molecular drug) ³³
Soluble guanylyl cyclase	sGC	99	Jan 2007 (BAY63-2521; P2) ³⁴	Oct 2013 (Riociguat; Chronic thromboembolic pulmonary hypertension; Small molecular drug) ¹⁵
VEGF-2 receptor	VEGFR2	99	Sep 1997 (SU5416; P1) ³⁵	Dec 2005 (Sorafenib; Renal cell carcinoma; Small molecular drug) ⁹

Ret tyrosine kinase receptor	Ret	>104	Earlier than Aug 2002 (ZD6474; P1) ³⁶	Apr 2011 (Vandetanib; Medullary thyroid cancer; Small molecular drug) ¹²
MEK protein kinase	MEK	107	Jun 2004 (ARRY-142886; P1) ³⁷	May 2013 (Trametinib; Melanoma; Small molecular drug) ¹⁵
Extracellular calcium sensing receptor	CaSR	109	Aug 1996 (NPS R-568; P1 Completed) ³⁸	Mar 2004 (Cinacalcet Hydrochloride; Secondary hyperparathyroidism; Small molecular drug) ³⁹
Histone deacetylase	HDAC	110	Aug 1997 (FK228; P1) ⁴⁰	Oct 2006 (Vorinostat; Cutaneous T cell lymphoma; Small molecular drug) ²⁸
Sodium glucose transporter-2	SC5A2	113	Apr 2005 (BMS-512148; P2) ⁴¹	Mar 2013 (Canagliflozin; Type 2 diabetes; Small molecular drug) ¹⁵
Tryptophan hydroxylase	TPH	113	Mar 2009 (LX1606; P2) ⁴²	Feb 2017 (Telotristat Ethyl; Carcinoid syndrome diarrhea; Small molecular drug) ⁵
Apoptosis regulator Bcl-2	BCL-2	114	Oct 2006 (ABT-263; P1/2) ^{43,44}	Apr 2016 (Venetoclax; Chronic lymphocytic leukemia; Small molecular drug) ²⁵
Phosphoinositide-3 kinase delta	PI3K delta	114	Jan 2005 (TG100-115; P1/2) ⁴⁵	Jul 2014 (Idelalisib; Chronic lymphocytic leukemia and follicular lymphoma; Small molecular drug) ³³
Beta 3 adrenoceptor	ADRB3	117	Sep 2002 (YM178; P1) ⁴⁶	Jun 2012 (Mirabegron; Overactive bladder; Small molecular drug) ¹⁸
C-X-C chemokine receptor type 4	CXCR4	120	Jun 2000 (AMD-3100; P1 Completed) ⁴⁷	Dec 2008 (Plerixafor; Autologous hematopoietic stem-cell transplantation in patients with non-Hodgkin lymphoma and multiple myeloma; Small molecular drug) ⁴⁸

Jak3 tyrosine kinase	Jak3	120	Nov 2002 (Tofacitinib; P1) ⁴⁹	Nov 2012 (Tofacitinib; Rheumatoid arthritis; Small molecular drug) ¹⁸
Cyclin-dependent kinase-4/6	CDK4/6	122	Dec 2004 (AG-024322; P1) ⁵⁰	Feb 2015 (Palbociclib; Breast cancer; Small molecular drug) ⁵¹
Protease-activated receptor-1	PAR-1	123	Aug 2005 (SCH 530348; P2) ⁵²	May 2014 (Vorapaxar; Myocardial infarction; Small molecular drug) ³³
Farnesoid X receptor	FXR	124	Jul 2007 (INT-747; P2) ⁵³	May 2016 (Obeticholic Acid; Primary biliary cholangitis; Small molecular drug) ²⁵
Sphingosine 1-phosphate receptor 1	S1PR1	>127	Earlier than Feb 2000 (FTY720; P1) ⁵⁴	Sep 2010 (Fingolimod; Multiple sclerosis; Small molecular drug) ²
Poly ADP ribose polymerase	PARP	131	Jan 2004 (INO-1001; P2) ⁵⁵	Dec 2014 (Olaparib; Ovarian cancer; Small molecular drug) ³³
Phosphodiesterase 4	PDE-4	138	Aug 1999 (CC-1088; P1/2) ⁵⁶	Feb 2011 (Roflumilast; Chronic obstructive pulmonary disease; Small molecular drug) ¹²
Hyperpolarization activated cyclic nucleotide-gated channel	HCN channel	146	Feb 2003 (Cilobradine; P1) ⁵⁷	Apr 2015 (Ivabradine; Heart failure; Small molecular drug) ⁵¹
Jak2 tyrosine kinase	Jak2	>147	Earlier than Aug 1999 (CEP-701; P1) ⁵⁸	Nov 2011 (Ruxolitinib; Myelofibrosis; Small molecular drug) ¹²
Microsomal triglyceride transfer protein	Transfer protein MTP	175	Nov 1999 (BAY 13-9952; P1 Completed) ^{59,60}	Dec 2012 (Lomitapide; Familial hypercholesterolaemia; Small molecular drug) ¹⁸

Rho kinase	ROCK	186	Jun 2002 (Fasudil; P2) ⁶¹	Dec 2017 (Netarsudil; Glaucoma; Small molecular drug) ⁵
AMPA receptor	AMPA receptor	190	Dec 1996 (ZK200775; P1) ⁶²	Oct 2012 (Perampanel; Epilepsy; Small molecular drug) ¹⁸
Cytochrome P450 17A1	CYP17A1	343	Mar 1984 (Ketoconazole; P1 Completed) ^{63,64}	Apr 2011 (Abiraterone Acetate; Prostate cancer; Small molecular drug) ¹²
Human Targets of Biologics (41 targets in total, ordered by the time spend from clinical trial phase I to FDA approval)				
Tripeptidyl-peptidase 1	TPP1	43	Sep 2013 (BMN-190; P1/2) ⁶⁵	Apr 2017 (Cerliponase Alfa; Batten disease; Enzyme replacement therapy) ⁵
Beta-glucuronidase	Beta-G1	49	Oct 2013 (UX003; P1/2) ⁶⁶	Nov 2017 (Vestronidase Alfa-vjvk; Sly syndrome; Enzyme replacement therapy) ⁵
Lysosomal acid lipase	Lysosomal lipase	55	May 2011 (SBC-102; P1) ⁶⁷	Dec 2015 (Sebelipase Alfa; Lysosomal acid lipase deficiency; Enzyme replacement therapy) ⁵¹
Arylsulfatase B	Arylsulfatase B	56	Sep 2000 (rhASB; P1) ^{68,69}	May 2005 (Galsulfase; Mucopolysaccharidosis VI; Enzyme replacement therapy) ⁹
N-acetylgalactosamine 6 sulfatase	GALNS	58	Apr 2009 (BMN 110; P1) ^{70,71}	Feb 2014 (Elosulfase Alfa; Mucopolysaccharidosis IVA; Enzyme replacement therapy) ³³
Proprotein convertase PC9	PCSK9	68	Nov 2009 (REGN727; P1) ⁷²⁻⁷⁴	Jul 2015 (Alirocumab; Familial hypercholesterolaemia; Antibody) ⁵¹
GLP-1 receptor	GLP-1 receptor	73	Mar 1999 (Exenatide; P1) ^{75,76}	Apr 2005 (Exenatide; Type 2 diabetes; Protein analog) ⁹

Receptor activity modifying protein	RAMP	76	Nov 2002 (Pramlintide; P3) ⁷⁷	Mar 2005 (Pramlintide Acetate; Type 1/2 diabetes; Protein analog) ⁹
VEGF-A ligand	VEGF-A	81	Nov 1998 (Bevacizumab; P2) ^{78,79}	Feb 2004 (Bevacizumab; Colorectal cancer; Antibody) ³⁹
Tissue non-specific alkaline phosphatase	Phosphatase AP-TNAP	85	Sep 2008 (Asfotase Alfa; P1/2) ⁸⁰	Oct 2015 (Asfotase Alfa; Hypophosphatasia; Enzyme replacement therapy) ⁵¹
Integrin alpha-4	VLA-4 alpha	86	Mar 1999 (Natalizumab; P1 Completed) ^{81,82}	Nov 2004 (Natalizumab; Multiple sclerosis; Antibody) ³⁹
Complement C5	Complement C5	87	Dec 1999 (Pexelizumab; P1) ⁸³⁻⁸⁵	Mar 2007 (Eculizumab; Paroxysmal nocturnal hemoglobinuria; Antibody) ⁷
Interleukin-12/23 subunit p40	IL-12/23 p40	88	Nov 2003 (CNTO 1275; P2) ⁸⁶	Sep 2009 (Ustekinumab; Plaque psoriasis; Antibody) ⁸⁷
Interleukin-1 beta ligand	IL-1B	95	Sep 2001 (IL-1 Trap; P1 Completed) ^{88,89}	Feb 2008 (Riloncept; Muckle-Wells syndrome; Fusion protein) ⁴⁸
Guanylyl cyclase C	GC-C	97	Jan 2006 (MD-1100; P2) ⁹⁰	Aug 2012 (Linaclotide; Irritable bowel syndrome with constipation; Protein analog) ¹⁸
Programmed cell death protein 1	PD-1	97	Aug 2006 (MDX-1106; P1) ^{91,92}	Sep 2014 (Pembrolizumab; Melanoma; Antibody) ³³
Plasma kallikrein	Plasma kallikrein	102	Dec 2002 (DX-88; P1 Completed) ^{93,94}	Dec 2009 (Ecallantide; Hereditary angioedema; Protein analog) ⁸⁷

Cytotoxic T-lymphocyte protein-4	CTLA-4	102	Sep 2002 (Ipilimumab; P1) ^{95,96}	Mar 2011 (Ipilimumab; Melanoma; Antibody) ¹²
mRNA of APOB	APOB mRNA	107	Aug 2005 (ISIS 301012; P2) ⁹⁷	Jan 2013 (Mipomersen; Familial hypercholesterolaemia; Antisense drug) ¹⁵
SLAM family member 7	SLAMF7	107	Dec 2006 (HuLuc63; P1) ^{98,99}	Nov 2015 (Elotuzumab; Multiple myeloma; Antibody) ⁵¹
B-lymphocyte stimulator ligand	BLYS ligand	109	Feb 2002 (Belimumab; P1) ¹⁰⁰	Mar 2011 (Belimumab; Systemic lupus erythematosus; Antibody) ¹²
Interleukin-17A ligand	IL-17A	109	Dec 2005 (Secukinumab; P1/2) ¹⁰¹	Jan 2015 (Secukinumab; Plaque psoriasis; Antibody) ⁵¹
cADPr hydrolase 1	CD38	110	Mar 2008 (Daratumumab; P2) ¹⁰²	Nov 2015 (Daratumumab; Multiple myeloma; Antibody) ⁵¹
Calcium activated chloride channel	Channel ANO1	114	Dec 2004 (Crofelemer; P2) ¹⁰³	Dec 2012 (Crofelemer; HIV-associated diarrhea; Proanthocyanidin oligomer) ¹⁸
Insulin-like growth factor 1 receptor	IGF1 receptor	115	Jul 1997 (CEP-151; P2) ¹⁰⁴	Aug 2005 (Mecasermin; Failure to thrive in children; Protein analog) ⁹
Receptor activator of nuclear factor kappa-B ligand	RANKL	115	May 2002 (AMG 162; P2) ¹⁰⁵	Jun 2010 (Denosumab; Osteoporosis; Antibody) ²
Ganglioside GD2	Ganglioside GD2	116	Jul 2005 (Dinutuximab; P1) ¹⁰⁶	Mar 2015 (Dinutuximab; Neuroblastoma; Antibody) ⁵¹

Iduronate 2-sulfatase	Iduronate 2-sulfatase	117	Oct 1996 (IDS Gene Therapy; P1/2) ¹⁰⁷	Jul 2006 (Idursulfase; Mucopolysaccharidosis II; Enzyme replacement therapy) ²⁸
Interleukin-6 receptor	IL-6R	119	Aug 2001 (Tocilizumab; P2) ¹⁰⁸	Jan 2010 (Tocilizumab; Rheumatoid arthritis; Antibody) ²
CD80/CD86	CD80/CD86	121	Nov 1995 (BMS-188667; P1) ¹⁰⁹	Dec 2005 (Abatacept; Rheumatoid arthritis; Fusion protein) ⁹
Exon 51 of dystrophin pre-mRNA	Dystrophin pre-mRNA	124	May 2006 (PRO051; P1) ^{110,111}	Sep 2016 (Eteplirsen; Duchenne muscular dystrophy; Antisense drug) ²⁵
B-lymphocyte antigen CD19	CD19	126	Jun 2004 (AMG 103; P1) ¹¹²	Dec 2014 (Blinatumomab; B-cell precursor acute lymphoblastic leukemia; Antibody) ³³
Glucagon-like peptide 2	GLP-2	128	Oct 2003 (ALX-0600; P2) ¹¹³	Dec 2012 (Teduglutide Recombinant; Short bowel syndrome; Protein analog) ¹⁸
Interleukin-6 ligand	IL-6	128	Aug 2003 (CNTO 328; P1/2) ¹¹⁴	Apr 2014 (Siltuximab; Multicentric Castleman disease; Antibody) ³³
Bradykinin B2 receptor	BDKRB2	132	Aug 2004 (Icatibant; P3) ¹¹⁵	Aug 2011 (Icatibant Acetate; Hereditary angioedema; Protein analog) ¹²
SMN2 pre-mRNA	SMN2 pre-mRNA	132	Jun 2007 (HU; P2/3) ¹¹⁶⁻¹¹⁸	Dec 2016 (Nusinersen; Spinal muscular atrophy; Antisense drug) ²⁵
Thrombopoietin receptor	TPO-R	152~163	??? 1995 (PEG-rhMGDF; P1) ^{119,120}	Aug 2008 (Romiplostim; Idiopathic thrombocytopenic purpura; Protein analog) ⁴⁸

Leptin receptor	Leptin receptor	156	Feb 2001 (r-metHuLeptin; P1) ¹²¹	Feb 2014 (Metreleptin; Congenital and acquired generalized lipodystrophy; Protein analog) ³³
Glucarpidase	Glucarpidase	162	Jan 2000 (Glucarpidase; P2) ¹²²	Jan 2012 (Glucarpidase; Delayed methotrexate clearance; Protein analog) ¹⁸
IL-4 receptor alpha	IL-4R alpha	164	Jan 2005 (AER-001; P2) ¹²³	Mar 2017 (Dupilumab; Eczema; Antibody) ⁵
Interleukin-5 ligand	IL-5	167	Dec 2001 (Mepolizumab; P1/2) ¹²⁴	Nov 2015 (Mepolizumab; Asthma; Antibody) ⁵¹
Infectious Disease Species Targets (8 targets in total, ordered by the time spend from clinical trial phase I to FDA approval)				
HIV integrase	HIV integrase	82	Jun 2002 (S-1360; P2) ^{125,126}	Oct 2007 (Raltegravir; HIV infection; Small molecular drug) ⁷
Hepatitis C virus NS5B polymerase	HCV NS5B	86	Oct 2006 (GSK625433; P1) ¹²⁷	Dec 2013 (Sofosbuvir; Hepatitis C viral infection; Small molecular drug) ¹⁵
Anthrax protective antigen	Anthrax PA	89	Jul 2005 (PAmAb; P1) ¹²⁸	Dec 2012 (Raxibacumab; Anthrax; Antibody) ¹⁸
Mycobacterial ATP synthase	TB ATP synthase	109	May 2005 (TMC207; P2) ¹²⁹	Dec 2012 (Bedaquiline Fumarate; Multidrug-resistant tuberculosis; Small molecular drug) ¹⁸
Hepatitis C virus NS3/4A protease	HCV NS3/4A	119	Jun 2001 (BILN 2061; P1) ¹³⁰⁻¹³²	May 2011 (Boceprevir; Hepatitis C viral infection; Small molecular drug) ¹²
Fungal aureus leucyl-tRNA synthetase	Fungal LeuRS	122	Nov 2005 (AN2690; P2) ¹³³	Jul 2014 (Tavaborole; Onychomycosis; Small molecular drug) ³³

Clostridium difficile toxin B	C. difficile toxin B	127	Mar 2006 (MDX-1388; P1) ¹³⁴	Oct 2016 (Bezlotoxumab; Clostridium difficile infection recurrence; Antibody) ²⁵
Cytomegalovirus DNA terminase complex	CMV terminase	146	Mar 2007 (AIC-001; P2) ¹³⁵ ¹³⁶	Nov 2017 (Letermovir; Cytomegalovirus infection; Small molecular drug) ⁵

References for Supplementary Table S3

- 1 NIH ClinicalTrials.gov: NCT00843921. N-Carbamylglutamate (Carbaglu) In The Treatment Of Hyperammonemia. U.S. National Institutes of Health. 2018, NCT00843921
- 2 A. Mullard. 2010 FDA drug approvals. Nat Rev Drug Discov. 2011, 10(2): 82-5
- 3 T. Fujii; M. R. Khawaja; C. D. DiNardo; J. T. Atkins; F. Janku. Targeting isocitrate dehydrogenase (IDH) in cancer. Discov Med. 2016, 21(117): 373-80
- 4 NIH ClinicalTrials.gov: NCT01915498. Phase 1/2 Study of AG-221 in Subjects With Advanced Hematologic Malignancies With an IDH2 Mutation. U.S. National Institutes of Health. 2018, NCT01915498
- 5 A. Mullard. 2017 FDA drug approvals. Nat Rev Drug Discov. 2018, 17(2): 150
- 6 NIH ClinicalTrials.gov: NCT00104260. Study to Evaluate the Response to and Safety of an 8-Day Course of Phenoptin Treatment in Subjects With Phenylketonuria. U.S. National Institutes of Health. 2018, NCT00104260
- 7 B. Hughes. 2007 FDA drug approvals: a year of flux. Nat Rev Drug Discov. 2008, 7(2): 107-9
- 8 NIH ClinicalTrials.gov: NCT00915135. Efficacy and Safety of Ramelteon on Chronic Insomnia. U.S. National Institutes of Health. 2018, NCT00915135
- 9 S. Frantz; M. Belsey; D. Evans; A. Grosvenor; A. Jones; L. Gershell; C. Jones; T. Papp. 2005 approvals: Safety first. Nature Reviews Drug Discovery. 2006, 5(2): 92-93
- 10 A. A. Samatar; P. I. Poulikakos. Targeting RAS-ERK signalling in cancer: promises and challenges. Nat Rev Drug Discov. 2014, 13(12): 928-42
- 11 NIH ClinicalTrials.gov: NCT00405587. Safety Study of PLX4032 in Patients With Solid Tumors. U.S. National Institutes of Health. 2018, NCT00405587
- 12 A. Mullard. 2011 FDA drug approvals. Nat Rev Drug Discov. 2012, 11(2): 91-4
- 13 J. R. Brown. Ibrutinib (PCI-32765), the first BTK (Bruton's tyrosine kinase) inhibitor in clinical trials. Curr Hematol Malig Rep. 2013, 8(1): 1-6
- 14 NIH ClinicalTrials.gov: NCT00849654. Study of the Safety and Tolerability of PCI-32765 in Patients With Recurrent B Cell Lymphoma (PCYC-04753). U.S.

- National Institutes of Health. 2018, NCT00849654
- 15 A. Mullard. 2013 FDA drug approvals. *Nat Rev Drug Discov.* 2014, 13(2): 85-9
 - 16 C. M. Rudin; C. L. Hann; J. Laterra; R. L. Yauch; C. A. Callahan; L. Fu; T. Holcomb; J. Stinson; S. E. Gould; B. Coleman; P. M. LoRusso; D. D. Von Hoff; F. J. de Sauvage; J. A. Low. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. *N Engl J Med.* 2009, 361(12): 1173-8
 - 17 NIH ClinicalTrials.gov: NCT00607724. GDC-0449 in Treating Patients With Locally Advanced or Metastatic Solid Tumors. U.S. National Institutes of Health. 2018, NCT00607724
 - 18 A. Mullard. 2012 FDA drug approvals. *Nat Rev Drug Discov.* 2013, 12(2): 87-90
 - 19 P. Minoo; H. Y. Wang. ALK-immunoreactive neoplasms. *Int J Clin Exp Pathol.* 2012, 5(5): 397-410
 - 20 NIH ClinicalTrials.gov: NCT00585195. A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001). U.S. National Institutes of Health. 2018, NCT00585195
 - 21 J. C. Davies. The future of CFTR modulating therapies for cystic fibrosis. *Curr Opin Pulm Med.* 2015, 21(6): 579-84
 - 22 NIH ClinicalTrials.gov: NCT00457821. Safety Study of Ivacaftor in Subjects With Cystic Fibrosis. U.S. National Institutes of Health. 2018, NCT00457821
 - 23 NIH ClinicalTrials.gov: NCT00223717. Treatment of Supine Hypertension in Autonomic Failure. U.S. National Institutes of Health. 2018, NCT00223717
 - 24 NIH ClinicalTrials.gov: NCT00936520. SAR 1118 in Human Subjects Undergoing Pars Plana Vitrectomy. U.S. National Institutes of Health. 2018, NCT00936520
 - 25 A. Mullard. 2016 FDA drug approvals. *Nat Rev Drug Discov.* 2017, 16(2): 73-76
 - 26 N. A. Motlekar; K. S. Srivenugopal; M. S. Wachtel; B. B. Youan. Evaluation of the Oral Bioavailability of Low Molecular Weight Heparin Formulated With Glycyrrhetic Acid as Permeation Enhancer. *Drug Dev Res.* 2006, 67(2): 166-74
 - 27 H.-U. Demuth; K. Glund; J. Banke-Bochita; K.-L. Rost; S. Fischer; M. Hanefeld; C. H. S. McIntosh; R. A. Pederson. Dipeptidyl peptidase IV (DP IV)-modulation as treatment of impaired glucose tolerance and niddm. *Regul Pept.* 2000, 94(1): 16-16
 - 28 J. Owens. 2006 drug approvals: finding the niche. *Nat Rev Drug Discov.* 2007, 6(2): 99-101
 - 29 E. Van Der Ryst. Maraviroc - A CCR5 Antagonist for the Treatment of HIV-1 Infection. *Front Immunol.* 2015, 6277
 - 30 E. M. Ambizas; R. Ginzburg. Lubiprostone: a chloride channel activator for treatment of chronic constipation. *Ann Pharmacother.* 2007, 41(6): 957-64
 - 31 F. J. John; A. G. Michele; L. P. Myra; U. Ryuji. Efficacy and Safety of a Novel Compound, RU-0211, for the Treatment of Constipation. *Gastroenterology.*

- 2002, 122(Suppl 1): A-315
- 32 NIH ClinicalTrials.gov: NCT00640848. Almorexant in Primary Insomnia (Insomnia). U.S. National Institutes of Health. 2018, NCT00640848
- 33 A. Mullard. 2014 FDA drug approvals. *Nat Rev Drug Discov.* 2015, 14(2): 77-81
- 34 NIH ClinicalTrials.gov: NCT00454558. An Open Multiple Dose Titration Study In Patients With Pulmonary Hypertension. U.S. National Institutes of Health. 2018, NCT00454558
- 35 F. Lavelle. American Association for Cancer Research 1998: promises and prospects for the next century. *Expert Opin Investig Drugs.* 1998, 7(6): 1015-21
- 36 S. R. Wedge; D. J. Ogilvie; M. Dukes; J. Kendrew; R. Chester; J. A. Jackson; S. J. Boffey; P. J. Valentine; J. O. Curwen; H. L. Musgrove; G. A. Graham; G. D. Hughes; A. P. Thomas; E. S. Stokes; B. Curry; G. H. Richmond; P. F. Wadsworth; A. L. Bigley; L. F. Hennequin. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res.* 2002, 62(16): 4645-55
- 37 NIH ClinicalTrials.gov: NCT00085787. A Study of ARRY-142886 in Patients With Advanced Cancer. U.S. National Institutes of Health. 2018, NCT00085787
- 38 S. I. Silverberg; S. Thys-Jacobs; F. G. Locker; E. L. Sanguinetti; T. B. Marriott; J. P. Bilezikian. The effect of the calcimimetic drug NPS R-568 on parathyroid hormone secretion in primary hyperparathyroidism. *J Bone Miner Res.* 1996, 11 Suppl 1S116
- 39 S. Frantz. 2004 approvals: the demise of the blockbuster? *Nat Rev Drug Discov.* 2005, 4(2): 93-4
- 40 NIH ClinicalTrials.gov: NCT00019318. Depsipeptide in Treating Patients With Solid Tumors. U.S. National Institutes of Health. 2018, NCT00019318
- 41 NIH ClinicalTrials.gov: NCT00162305. A Phase IIA Study of BMS-512148 to Assess Safety, Exposure, and Biological Effects in Stable Type 2 Diabetic Subjects. U.S. National Institutes of Health. 2018, NCT00162305
- 42 NIH ClinicalTrials.gov: NCT00853047. Study of LX1606 in Subjects With Symptomatic Carcinoid Syndrome Not Managed by Stable-Dose Octreotide Therapy. U.S. National Institutes of Health. 2018, NCT00853047
- 43 A. Mullard. Pioneering apoptosis-targeted cancer drug poised for FDA approval. *Nat Rev Drug Discov.* 2016, 15(3): 147-9
- 44 NIH ClinicalTrials.gov: NCT00406809. A Study of ABT-263 in Subjects With Relapsed or Refractory Lymphoid Malignancies. U.S. National Institutes of Health. 2018, NCT00406809
- 45 NIH ClinicalTrials.gov: NCT00103350. Safety of TG100-115 for Heart Attack Treated With Angioplasty. U.S. National Institutes of Health. 2018, NCT00103350
- 46 NIH ClinicalTrials.gov: NCT01478490. To Compare Blood and Urine Concentrations of Mirabegron (YM178) in Healthy Poor or Extensive Metabolizers for CYP2D6 and to Assess the Effect of Mirabegron on the Metabolism of Metoprolol. U.S. National Institutes of Health. 2018, NCT01478490

- 47 C. W. Hendrix; C. Flexner; R. T. MacFarland; C. Giandomenico; E. J. Fuchs; E. Redpath; G. Bridger; G. W. Henson. Pharmacokinetics and safety of AMD-3100, a novel antagonist of the CXCR-4 chemokine receptor, in human volunteers. *Antimicrob Agents Chemother.* 2000, 44(6): 1667-73
- 48 B. Hughes. 2008 FDA drug approvals. *Nat Rev Drug Discov.* 2009, 8(2): 93-6
- 49 NIH ClinicalTrials.gov: NCT01736696. Multiple Dose Escalation Study In Medically Stable Subjects With Psoriasis. U.S. National Institutes of Health. 2018, NCT01736696
- 50 NIH ClinicalTrials.gov: NCT00147485. A Phase 1 Study Of An Intravenously Administered Cyclin-Dependent Kinase Inhibitor In Patients With Advanced Cancer. U.S. National Institutes of Health. 2018, NCT00147485
- 51 A. Mullard. 2015 FDA drug approvals. *Nat Rev Drug Discov.* 2016, 15(2): 73-6
- 52 NIH ClinicalTrials.gov: NCT00684515. Trial to Assess the Safety of Vorapaxar in Japanese Subjects With Cerebral Infarction (P05005 MK-5348-017). U.S. National Institutes of Health. 2018, NCT00684515
- 53 NIH ClinicalTrials.gov: NCT00501592. Study of INT-747 in Patients With Diabetes and Presumed NAFLD. U.S. National Institutes of Health. 2018, NCT00501592
- 54 K. L. Napoli. The FTY720 story. *Ther Drug Monit.* 2000, 22(1): 47-51
- 55 NIH ClinicalTrials.gov: NCT00271765. A Study of INO-1001, an Intravenous PARP (Poly [ADP Ribose] Polymerase) Inhibitor in Acute Heart Attack Patients Undergoing Primary Percutaneous Coronary Intervention. U.S. National Institutes of Health. 2018, NCT00271765
- 56 NIH ClinicalTrials.gov: NCT00006097. Chemotherapy in Treating Patients With Chronic Lymphocytic Leukemia. U.S. National Institutes of Health. 2018, NCT00006097
- 57 NIH ClinicalTrials.gov: NCT02264002. Pharmacodynamic Effects, Safety and Tolerability of Cilobradine, Compared to Metoprolol Succinate and Placebo in Healthy Volunteers. U.S. National Institutes of Health. 2018, NCT02264002
- 58 S. J. Miknyoczki; H. Chang; A. Klein-Szanto; C. A. Dionne; B. A. Ruggeri. The Trk tyrosine kinase inhibitor CEP-701 (KT-5555) exhibits significant antitumor efficacy in preclinical xenograft models of human pancreatic ductal adenocarcinoma. *Clin Cancer Res.* 1999, 5(8): 2205-12
- 59 E. A. Stein. Other therapies for reducing low-density lipoprotein cholesterol: medications in development. *Endocrinol Metab Clin North Am.* 2009, 38(1): 99-119
- 60 E. A. Stein; J. L. Isaacsohn; A. Mazzu. Effect of BAY 13-9952, a microsomal triglyceride transfer protein inhibitor on lipids and lipoproteins in dyslipoproteinemic patients. *Circulation.* 1999, 100(18 Suppl): abstract 1342

- 61 NIH ClinicalTrials.gov: NCT00120718. The Effect of Fasudil on Vascular Function in Humans. U.S. National Institutes of Health. 2018, NCT00120718
- 62 NIH ClinicalTrials.gov: NCT00999284. Ophthalmologic Examinations After Infusion of ZK200775. U.S. National Institutes of Health. 2018, NCT00999284
- 63 R. W. Hartmann; P. B. Ehmer; S. Haidar; M. Hector; J. Jose; C. D. Klein; S. B. Seidel; T. F. Sergejew; B. G. Wachall; G. A. Wachter; Y. Zhuang. Inhibition of CYP 17, a new strategy for the treatment of prostate cancer. *Arch Pharm (Weinheim)*. 2002, 335(4): 119-28
- 64 J. Trachtenberg. Ketoconazole therapy in advanced prostatic cancer. *J Urol*. 1984, 132(1): 61-3
- 65 NIH ClinicalTrials.gov: NCT01907087. A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients With Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease. U.S. National Institutes of Health. 2018, NCT01907087
- 66 NIH ClinicalTrials.gov: NCT01856218. An Open-Label Phase 1/2 Study to Assess the Safety, Efficacy and Dose of Study Drug UX003 Recombinant Human Beta-glucuronidase (rhGUS) Enzyme Replacement Therapy in Patients With Mucopolysaccharidosis Type 7 (MPS 7). U.S. National Institutes of Health. 2018, NCT01856218
- 67 NIH ClinicalTrials.gov: NCT01307098. Safety, Tolerability and Pharmacokinetics of SBC-102 (Sebelipase Alfa) in Adult Patients With Lysosomal Acid Lipase Deficiency. U.S. National Institutes of Health. 2018, NCT01307098
- 68 P. Harmatz; Z. F. Yu; R. Giugliani; I. V. Schwartz; N. Guffon; E. L. Teles; M. C. Miranda; J. E. Wraith; M. Beck; L. Arash; M. Scarpa; D. Ketteridge; J. J. Hopwood; B. Plecko; R. Steiner; C. B. Whitley; P. Kaplan; S. J. Swiedler; K. Hardy; K. I. Berger; C. Decker. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *J Inher Metab Dis*. 2010, 33(1): 51-60
- 69 NIH ClinicalTrials.gov: NCT00048620. Study of Recombinant Human N-Acetylgalactosamine 4-Sulfatase in Patients With MPS VI. U.S. National Institutes of Health. 2018, NCT00048620
- 70 C. J. Hendriksz. Elosulfase alfa (BMN 110) for the treatment of mucopolysaccharidosis IVA (Morquio A Syndrome). *Expert Rev Clin Pharmacol*. 2016, 9(12): 1521-32
- 71 NIH ClinicalTrials.gov: NCT00884949. A Study to Evaluate the Safety, Tolerability and Efficacy of BMN 110 in Subjects With Mucopolysaccharidosis IVA. U.S. National Institutes of Health. 2018, NCT00884949
- 72 N. G. Seidah; A. Prat. The biology and therapeutic targeting of the proprotein convertases. *Nat Rev Drug Discov*. 2012, 11(5): 367-83
- 73 Y. Banerjee; K. Shah; K. Al-Rasadi. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med*. 2012, 366(25): 2425-6; author reply 26

- 74 NIH ClinicalTrials.gov: NCT01026597. Ascending Dose Study of the Safety and Tolerability of REGN727(SAR236553) in Healthy Volunteers. U.S. National Institutes of Health. 2018, NCT01026597
- 75 H. Peng; L. L. Want; V. R. Aroda. Safety and Tolerability of Glucagon-Like Peptide-1 Receptor Agonists Utilizing Data from the Exenatide Clinical Trial Development Program. *Curr Diab Rep.* 2016, 16(5): 44
- 76 NIH ClinicalTrials.gov: NCT01507272. Safety and Tolerability of Liraglutide in Healthy Male Volunteers. U.S. National Institutes of Health. 2018, NCT01507272
- 77 NIH ClinicalTrials.gov: NCT00107107. Study of the Long-Term Safety of Pramlintide in Subjects With Type 1 Diabetes Mellitus. U.S. National Institutes of Health. 2018, NCT00107107
- 78 N. Ferrara; A. P. Adamis. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov.* 2016, 15(6): 385-403
- 79 NIH ClinicalTrials.gov: NCT00019539. Monoclonal Antibody Therapy in Treating Patients With Advanced Kidney Cancer. U.S. National Institutes of Health. 2018, NCT00019539
- 80 NIH ClinicalTrials.gov: NCT00744042. Safety and Efficacy Study of Asfotase Alfa in Severely Affected Infants With Hypophosphatasia (HPP). U.S. National Institutes of Health. 2018, NCT00744042
- 81 O. Stuve; J. L. Bennett. Pharmacological properties, toxicology and scientific rationale for the use of natalizumab (Tysabri) in inflammatory diseases. *CNS Drug Rev.* 2007, 13(1): 79-95
- 82 W. A. Sheremata; T. L. Vollmer; L. A. Stone; A. J. Willmer-Hulme; M. Koller. A safety and pharmacokinetic study of intravenous natalizumab in patients with MS. *Neurology.* 1999, 52(5): 1072-4
- 83 A. M. Risitano. Paroxysmal nocturnal hemoglobinuria and other complement-mediated hematological disorders. *Immunobiology.* 2012, 217(11): 1080-7
- 84 J. C. Fitch; S. Rollins; L. Matis; B. Alford; S. Aranki; C. D. Collard; M. Dewar; J. Eleftheriades; R. Hines; G. Kopf; P. Kraker; L. Li; R. O'Hara; C. Rinder; H. Rinder; R. Shaw; B. Smith; G. Stahl; S. K. Shernan. Pharmacology and biological efficacy of a recombinant, humanized, single-chain antibody C5 complement inhibitor in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass. *Circulation.* 1999, 100(25): 2499-506
- 85 NIH ClinicalTrials.gov: NCT00048308. Effect of Pexelizumab on All-Cause Mortality and Myocardial Infarction in Patients Undergoing Coronary Artery Bypass Graft Surgery With Cardio-Pulmonary Bypass. U.S. National Institutes of Health. 2018, NCT00048308
- 86 NIH ClinicalTrials.gov: NCT00320216. A Safety and Effectiveness Study of CNTO 1275 in Patients With Moderate to Severe Plaque-type Psoriasis. U.S. National Institutes of Health. 2018, NCT00320216

- 87 B. Hughes. 2009 FDA drug approvals. *Nat Rev Drug Discov.* 2010, 9(2): 89-92
- 88 D. Burger; J. M. Dayer; G. Palmer; C. Gabay. Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol.* 2006, 20(5): 879-96
- 89 G. Hans-Peter; C. Jacques; L. I. Thomas; M. Harris; O. Howard; S. T. Neil. A phase 1, single dose escalation study of il-1 trap in patients with rheumatoid arthritis. *Arthritis Rheum.* 2001, 44(9 Suppl): S370
- 90 NIH ClinicalTrials.gov: NCT00258193. Phase 2 Study of MD-1100 Acetate on Gastrointestinal Transit in Patients With C-IBS. U.S. National Institutes of Health. 2018, NCT00258193
- 91 K. M. Mahoney; G. J. Freeman; D. F. McDermott. The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma. *Clin Ther.* 2015, 37(4): 764-82
- 92 NIH ClinicalTrials.gov: NCT00441337. A Study of MDX-1106 in Patients With Selected Refractory or Relapsed Malignancies (MDX1106-01). U.S. National Institutes of Health. 2018, NCT00441337
- 93 J. H. Levy; P. S. O'Donnell. The therapeutic potential of a kallikrein inhibitor for treating hereditary angioedema. *Expert Opin Investig Drugs.* 2006, 15(9): 1077-90
- 94 NIH ClinicalTrials.gov: NCT01826916. EDEMA2: Evaluation of DX-88's Effect in Mitigating Angioedema. U.S. National Institutes of Health. 2018, NCT01826916
- 95 M. K. Callahan; J. D. Wolchok. Clinical Activity, Toxicity, Biomarkers, and Future Development of CTLA-4 Checkpoint Antagonists. *Semin Oncol.* 2015, 42(4): 573-86
- 96 NIH ClinicalTrials.gov: NCT00047164. Monoclonal Antibody Therapy in Treating Patients With Lymphoma or Colon Cancer That Has Not Responded to Vaccine Therapy. U.S. National Institutes of Health. 2018, NCT00047164
- 97 NIH ClinicalTrials.gov: NCT00216463. Safety and Tolerability of Varying Load and Dose of ISIS 301012 in People With Elevated LDL-cholesterol Levels. U.S. National Institutes of Health. 2018, NCT00216463
- 98 Y. Wang; L. Sanchez; D. S. Siegel; M. L. Wang. Elotuzumab for the treatment of multiple myeloma. *J Hematol Oncol.* 2016, 9(1): 55
- 99 NIH ClinicalTrials.gov: NCT00425347. Phase I, Multi-Center, Open-Label, Dose Escalation Study of HuLuc63 in Subjects With Advanced Multiple Myeloma. U.S. National Institutes of Health. 2018, NCT00425347
- 100 NIH ClinicalTrials.gov: NCT00657007. Phase 1 Study of Belimumab in Subjects With Systemic Lupus Erythematosus (SLE). U.S. National Institutes of Health.

2018, NCT00657007

- 101 NIH ClinicalTrials.gov: NCT00669942. Double Blind, Placebo-controlled, Study of the Safety, Tolerability and Pharmacokinetics of AIN457 in Rheumatoid Arthritis Patients. U.S. National Institutes of Health. 2018, NCT00669942
- 102 NIH ClinicalTrials.gov: NCT00574288. Daratumumab (HuMax-CD38) Safety Study in Multiple Myeloma. U.S. National Institutes of Health. 2018, NCT00574288
- 103 NIH ClinicalTrials.gov: NCT00101725. A Study of Crofelemer to Treat Diarrhea Irritable Bowel Syndrome. U.S. National Institutes of Health. 2018, NCT00101725
- 104 NIH ClinicalTrials.gov: NCT00001669. A 48-Week (24-Week Baseline Followed by a 24-Week Treatment) Phase II Pilot Study of the Tolerability and Effect/Efficacy of Subcutaneously Administered Insulin-Like Growth Factor-1 (rhIGF) (CEP-151) in Multiple Sclerosis (MS) Patients. U.S. National Institutes of Health. 2018, NCT00001669
- 105 NIH ClinicalTrials.gov: NCT00043186. Determine the Efficacy, Safety and Tolerability of Denosumab (AMG 162) in the Treatment of Postmenopausal Women With Low Bone Mineral Density. U.S. National Institutes of Health. 2018, NCT00043186
- 106 NIH ClinicalTrials.gov: NCT01704872. Ch14.18/CHO Bridging Study. U.S. National Institutes of Health. 2018, NCT01704872
- 107 NIH ClinicalTrials.gov: NCT00004454. Phase I/II Study of Retroviral-Mediated Transfer of Iduronate-2-Sulfatase Gene Into Lymphocytes of Patients With Mucopolysaccharidosis II (Mild Hunter Syndrome). U.S. National Institutes of Health. 2018, NCT00004454
- 108 NIH ClinicalTrials.gov: NCT00144651. Study of MRA in Patients With Rheumatoid Arthritis (RA). U.S. National Institutes of Health. 2018, NCT00144651
- 109 NIH ClinicalTrials.gov: NCT00277225. A Study to Assess the Pharmacokinetics, Immunogenicity and Safety of Escalating Doses of BMS-188667 Given as a Single Intravenous Infusion to Patients With Psoriasis Vulgaris. U.S. National Institutes of Health. 2018, NCT00277225
- 110 E. H. Niks; A. Aartsma-Rus. Exon skipping: a first in class strategy for Duchenne muscular dystrophy. *Expert Opin Biol Ther.* 2017, 17(2): 225-36
- 111 J. C. van Deutekom; A. A. Janson; I. B. Ginjaar; W. S. Frankhuizen; A. Aartsma-Rus; M. Bremmer-Bout; J. T. den Dunnen; K. Koop; A. J. van der Kooi; N. M. Goemans; S. J. de Kimpe; P. F. Ekhart; E. H. Venneker; G. J. Platenburg; J. J. Verschuuren; G. J. van Ommen. Local dystrophin restoration with antisense oligonucleotide PRO051. *N Engl J Med.* 2007, 357(26): 2677-86
- 112 NIH ClinicalTrials.gov: NCT00274742. Safety Study of the Bispecific T-cell Engager Blinatumomab (MT103) in Patients With Relapsed NHL. U.S. National Institutes of Health. 2018, NCT00274742
- 113 NIH ClinicalTrials.gov: NCT00072839. Safety and Efficacy of ALX-0600 in Subjects With Active Crohn's Disease. U.S. National Institutes of Health. 2018,

NCT00072839

- 114 NIH ClinicalTrials.gov: NCT00265135. A Study of CNTO 328 in Subjects With Metastatic Renal Cell Carcinoma. U.S. National Institutes of Health. 2018, NCT00265135
- 115 NIH ClinicalTrials.gov: NCT00097695. Subcutaneous Treatment With Icatibant for Acute Attacks of Hereditary Angioedema. U.S. National Institutes of Health. 2018, NCT00097695
- 116 W. C. Liang; C. Y. Yuo; J. G. Chang; Y. C. Chen; Y. F. Chang; H. Y. Wang; Y. H. Ju; S. S. Chiou; Y. J. Jong. The effect of hydroxyurea in spinal muscular atrophy cells and patients. *J Neurol Sci.* 2008, 268(1-2): 87-94
- 117 C. Xu; X. Chen; S. M. Grzeschik; M. Ganta; C. H. Wang. Hydroxyurea enhances SMN2 gene expression through nitric oxide release. *Neurogenetics.* 2011, 12(1): 19-24
- 118 NIH ClinicalTrials.gov: NCT00485511. A Trial of Hydroxyurea in Spinal Muscular Atrophy. U.S. National Institutes of Health. 2018, NCT00485511
- 119 D. J. Kuter. Milestones in understanding platelet production: a historical overview. *Br J Haematol.* 2014, 165(2): 248-58
- 120 C. A. Schiffer; K. Miller; R. A. Larson; P. C. Amrein; J. H. Antin; V. J. Zani; R. M. Stone. A double-blind, placebo-controlled trial of pegylated recombinant human megakaryocyte growth and development factor as an adjunct to induction and consolidation therapy for patients with acute myeloid leukemia. *Blood.* 2000, 95(8): 2530-5
- 121 NIH ClinicalTrials.gov: NCT00140205. Pharmacokinetics of Leptin Administration During Fasting. U.S. National Institutes of Health. 2018, NCT00140205
- 122 NIH ClinicalTrials.gov: NCT00219791. Study of Glucarpidase (CPG2) for the Management of Patients With Delayed Methotrexate Clearance. U.S. National Institutes of Health. 2018, NCT00219791
- 123 NIH ClinicalTrials.gov: NCT00535028. A Phase IIa Study of Subcutaneous AER 001 on Antigen Challenge In Atopic Asthmatic Subjects (28 Day Study). U.S. National Institutes of Health. 2018, NCT00535028
- 124 NIH ClinicalTrials.gov: NCT00266565. Anti-Interleukin-5 (IL-5) Study for Hypereosinophilic Syndrome. U.S. National Institutes of Health. 2018, NCT00266565
- 125 M. J. Rosemond; L. St John-Williams; T. Yamaguchi; T. Fujishita; J. S. Walsh. Enzymology of a carbonyl reduction clearance pathway for the HIV integrase inhibitor, S-1360: role of human liver cytosolic aldo-keto reductases. *Chem Biol Interact.* 2004, 147(2): 129-39
- 126 NIH ClinicalTrials.gov: NCT00046332. A Study Comparing 4 Doses Of GW810781 Versus Placebo In HIV-Infected Patients. U.S. National Institutes of Health. 2018, NCT00046332

- 127 NIH ClinicalTrials.gov: NCT00439959. Monotherapy Versus Placebo Over 14 or 17 Days in Healthy and Hepatitis C Infected Adults. U.S. National Institutes of Health. 2018, NCT00439959
- 128 G. M. Subramanian; P. W. Cronin; G. Poley; A. Weinstein; S. M. Stoughton; J. Zhong; Y. Ou; J. F. Zmuda; B. L. Osborn; W. W. Freimuth. A phase 1 study of PAmAb, a fully human monoclonal antibody against Bacillus anthracis protective antigen, in healthy volunteers. *Clin Infect Dis.* 2005, 41(1): 12-20
- 129 NIH ClinicalTrials.gov: NCT00523926. TMC207-C202: Study to Evaluate Bactericidal Activity of Multiple Oral Doses of TMC207 in Subjects With Sputum-Smear Positive Tuberculosis. U.S. National Institutes of Health. 2018, NCT00523926
- 130 J. A. McCauley; M. T. Rudd. Hepatitis C virus NS3/4a protease inhibitors. *Curr Opin Pharmacol.* 2016, 3084-92
- 131 D. Lamarre; P. C. Anderson; M. Bailey; P. Beaulieu; G. Bolger; P. Bonneau; M. Bos; D. R. Cameron; M. Cartier; M. G. Cordingley; A. M. Faucher; N. Goudreau; S. H. Kawai; G. Kukolj; L. Lagace; S. R. LaPlante; H. Narjes; M. A. Poupard; J. Rancourt; R. E. Sentjens; R. St George; B. Simoneau; G. Steinmann; D. Thibeault; Y. S. Tsantrizos; S. M. Weldon; C. L. Yong; M. Llinas-Brunet. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus. *Nature.* 2003, 426(6963): 186-9
- 132 NIH ClinicalTrials.gov: NCT02268760. Safety, Tolerance, and Pharmacokinetics of BILN 2061 ZW in Healthy Male Subjects, Combined With Preliminary Evaluation of Food Effect. U.S. National Institutes of Health. 2018, NCT02268760
- 133 NIH ClinicalTrials.gov: NCT00679523. Safety and Efficacy Study of Subjects With Onychomycosis of the Great Toenail. U.S. National Institutes of Health. 2018, NCT00679523
- 134 A. Markham. Bezlotoxumab: First Global Approval. *Drugs.* 2016, 76(18): 1793-98
- 135 S. Stoelben; W. Arns; L. Renders; J. Hummel; A. Muhlfeld; M. Stangl; M. Fischereeder; W. Gwinner; B. Suwelack; O. Witzke; M. Durr; D. W. Beelen; D. Michel; P. Lischka; H. Zimmermann; H. Rubsamen-Schaeff; K. Budde. Preemptive treatment of Cytomegalovirus infection in kidney transplant recipients with letermovir: results of a Phase 2a study. *Transpl Int.* 2014, 27(1): 77-86
- 136 EudraCT2006-006148-69. Phase 2a Randomized, Controlled, Multi-center, Open-label Dose Ranging Proof of Concept Study to Evaluate the Safety, Tolerability and Antiviral Activity of AIC-001 Over 14 Days of Dosing in Patients With Positive HCMV Viremia Under the Conditions of a Pre-emptive Strategy. EU Clinical Trials Register. 2018, 2006-006148-69

Supplementary Table S4: The disease roles and binding-site features of the innovative targets with a first-in-class drug approved in 2004-2017.

Target Name	Disease Indication (Disease Class; ICD-10 Code)	Literature-described Disease Roles (Functional Profiles) of Target	Literature-described Binding-Site Profiles (Drug-binding-site Structural Features) of Target
Anthrax PA	Anthrax (Infectious diseases; A00-B99)	Crucial for the pathogenesis of anthrax ¹	Selective substrate recognition-sites for peptide/mAb binding ²
C. difficile toxin B	Clostridium difficile infection recurrence (Infectious diseases; A00-B99)	Clostridium difficile triggers disease through the release of two toxins (TcdA and TcdB) ³	Binding-site conformation differs from human proteins enables selective mAb binding ⁴
CCR5	HIV infection (Infectious diseases; A00-B99)	Essential for HIV-1 infection as one of the two HIV entry receptors ⁵	Binding-site distinct from those of other chemokines ⁶
CMV-terminase	Cytomegalovirus infection (Infectious diseases; A00-B99)	Viral enzyme required for translocating viral genomic DNA in empty capsid during DNA packaging ⁷	Binding-site of this viral enzyme differs dramatically from that of any human proteins ⁸
Fungal LeuRS	Onychomycosis (Infectious diseases; A00-B99)	LeuRS plays a key role in fungal essential protein synthesis ⁹	Binding-site of fungal LeuRS is different from mammalian proteins ¹⁰
HCV NS3/4A	Hepatitis C viral infection (Infectious diseases; A00-B99)	NS3/4A is responsible for cleavage of the scissile peptide bonds in the polyprotein important for the HCV life cycle ¹¹	Binding-site of this viral protease differs significantly from that of mammalian proteins ¹¹
HCV NS5B	Hepatitis C viral infection (Infectious diseases; A00-B99)	NS5B plays a central role in HCV replication ¹² and its catalytic site is highly conserved across the different HCV genotypes ¹³	NS5B has no functional equivalent in mammalian cells, and is distinct in its binding-site ¹²
HIV integrase	HIV infection (Infectious diseases; A00-B99)	Viral enzyme required for viral replication and without cellular equivalent ¹⁴	Binding-site of this viral enzyme differs dramatically from that of any human proteins ¹⁵

TB ATP synthase	Multidrug-resistant tuberculosis (Infectious diseases; A00-B99)	ATP synthase plays central role in TB's ATP synthesis ¹⁶	Binding-site of mycobacterial ATP synthase enzyme is highly selective compared to homologous eukaryotic enzyme ^{17,18}
Alk	Non-small-cell lung carcinoma (Neoplasms; C00-D49)	Gene rearrangement is an oncogenic driver of ALK+ NSCLC ¹⁹	Target conformation is distinct from other IRK superfamily members ²⁰
BCL-2	Chronic lymphocytic leukemia (Neoplasms; C00-D49)	Important determinant of chemotherapy-induced apoptosis ²¹ and important in the pathogenesis and progression of CLL ²²	Distinct functional domains in Bcl-2 ²³ and distinct features at the peptide-binding-site ²⁴
BRaf	Melanoma (Neoplasms; C00-D49)	Dysregulated signaling through wildtype target is pivotal for renal and other cancers ²⁵ and activating mutations in the target is a driver of melanoma and other cancer ²⁶	Binding-site with displaced DFG motif in wildtype and with a structurally different interior pocket specific to the mutant ^{26,27}
Btk	Mantle cell lymphoma (Neoplasms; C00-D49)	Crucial for the survival or proliferation of leukaemic B cells ²⁸	Active-site similar to TEC, Src and Abl family members, but allows selective covalent binding ^{29,30}
CD19	B-cell precursor acute lymphoblastic leukemia (Neoplasms; C00-D49)	A B cell-specific antigen expressed on chronic lymphocytic leukemia cells ³¹	Unique among membrane immune protein complexes for selective peptide/mAb binding ³²
CD38	Multiple myeloma (Neoplasms; C00-D49)	CD38 is active in the myeloma niche and lead a discontinuous chain of ectoenzymes whose final products are exploited by the neoplastic plasma cell as part of its local survival strategy ³³ and CD38 directly contributed to the pathogenesis of chronic lymphocytic leukemia (CLL) ³⁴	Specific binding-grooves localized in two beta-strands of CD38 ³⁵ and most malignant plasma cells overexpress CD38 at all stages of multiple myeloma ^{36,37}

CDK4/6	Breast cancer (Neoplasms; C00-D49)	CDK4 is required to maintain breast tumorigenesis ³⁸ and CDK6 is one of the three genes critical for the growth of triple-negative breast cancer ³⁹	CDK4's conformation diverges from other family members of known structures ⁴⁰ and CDK6's binding domain also has structural variation with respect to other known family members ³⁹
CTLA-4	Melanoma (Neoplasms; C00-D49)	CTLA-4 plays a key role in restraining the adaptive immune response of T-cells and enhancing the immune response against melanoma ⁴¹	Distinct motif within the cytoplasmic domain of CTLA-4 ⁴²⁻⁴⁴
CXCR4	Autologous hematopoietic transplantation in patients with non-Hodgkin lymphoma and multiple myeloma (Neoplasms; C00-D49)	A critical regulator of multiple myeloma homing ⁴⁵ and critically involved in the survival and trafficking of normal and malignant B lymphocytes ⁴⁶	Structural plasticity of binding-sites allows selective binding of drugs ⁴⁷
CYP17A1	Prostate cancer (Neoplasms; C00-D49)	Prostate cancer is an androgen-dependent disease ⁴⁸ and CYP17 plays a critical role in the androgen biosynthesis ⁴⁹	Distinct structural conformations of CYP17A1 suggesting protein flexibility ⁵⁰
Ganglioside GD2	Neuroblastoma (Neoplasms; C00-D49)	High level of expression and presented on the surface of most neuroblastoma cells ⁵¹	A disialoganglioside distinct in structure for the selective binding of human/mouse chimeric monoclonal antibody ⁵¹
HDAC	Cutaneous T cell lymphoma (Neoplasms; C00-D49)	HDAC activity is critical in establishing the tumor phenotype ⁵²	Distinct histone binding-sites in HDAC ⁵³

IDH2	Acute myeloid leukemia (Neoplasms; C00-D49)	Mutations in IDH2 genes (mIDH2) occur in approximately 12% of patients with acute myeloid leukemia ⁵⁴	Targeting a divalent cation binding residue can enable selective inhibition of mutant IDH1 and suggest that differences in magnesium binding between wild-type and mutant enzymes may contribute to the inhibitors' selectivity for the mutant enzyme ⁵⁵
IL-6	Multicentric Castleman disease (Neoplasms; C00-D49)	MCD is caused by dysregulated production of IL-6 in the lymph nodes ^{56,57}	Structurally diverse and distinct cytokine ⁵⁷⁻⁵⁹
Jak2	Myelofibrosis (Neoplasms; C00-D49)	JAK2 V617F mutation in 50-60% of patients, dysregulation of JAK signaling is the major contributor to the disease ⁶⁰	Flexible binding-site differs from other kinase sites in size and hydrophobicity ⁶¹
MEK	Melanoma (Neoplasms; C00-D49)	A key player and active in ~30% of cancers with activated MAPK signaling ⁶²	Tumors harboring V600EB-RAF are sensitive to target inhibition ⁶³ and unique binding-site distinct from other ATP binding-sites and with low sequence homology to other kinases ⁶³
PARP	Ovarian cancer (Neoplasms; C00-D49)	Critical for single-strand break repair relied upon by BRCA-deficient cancers ⁶⁴	Binding-site with varied local conformation and residues among family members ⁶⁵
PD-1	Melanoma (Neoplasms; C00-D49)	Unique antigen specific and cell intrinsic immunoregulation properties ⁶⁶	Binding-site with different structural features and flexibility for selective peptide/mAb binding ⁶⁷
PI3K delta	Chronic lymphocytic leukemia and follicular lymphoma (Neoplasms; C00-D49)	CLL depends on enzyme subtype which is localized to hematopoietic cells including CLL ⁶⁸	Binding-site with varied residues and conformation flexibility ⁶⁹
Ret	Medullary thyroid cancer (Neoplasms; C00-D49)	Play a central role in the targeted disease ⁷⁰	Binding-site with slightly different side-chain conformations ⁷¹

SLAMF7	Multiple myeloma (Neoplasms; C00-D49)	SLAMF7 appears to play a critical role in the interaction between multiple myeloma cells and their adhesion to bone marrow stromal cells ⁷²	Binding-site with different structural features ^{73,74} and expressed primarily on myeloma cells but not on normal tissues ^{73,74}
Smoothened	Basal cell carcinoma (Neoplasms; C00-D49)	Aberrant derepression of receptor drives basal cell carcinoma ⁷⁵	Binding-site absent of most GPCR class A motifs ⁷⁶
VEGF-A	Colorectal cancer (Neoplasms; C00-D49)	One of the most important factors in the development of colorectal cancer ⁷⁷	Specific and saturable binding sites of VEGF on human umbilical vein endothelial cells ⁷⁸
VEGFR2	Renal cell carcinoma (Neoplasms; C00-D49)	Fundamental reliance of renal cell carcinoma on VEGF signaling and thus the receptor ⁷⁹	Binding-site structural variation with respect to close and remote kinases ⁸⁰
Complement C5	Paroxysmal nocturnal hemoglobinuria (Hematopathy; D50-D77)	Complement-mediated hemolysis plays a role in the anemia of sickle cell disease (SCD) ⁸¹	Distinct binding sites on C5 preventing its activation ⁸²
TPO-R	Idiopathic thrombocytopenic purpura (Hematopathy; D50-D77)	Thrombopoietin (TPO) regulates megakaryocytopoiesis during states of acute thrombocytopenia ⁸³	Distinct drug binding-site distant from the TPO substrate binding-site ^{84,85}
BDKRB2	Hereditary angioedema (Immunodeficiency; D80-D89)	Bradykinin-mediated B2 receptor plays an important role in the onset of angioedema ⁸⁶	Significant decline of B(2) receptor binding-sites resulted by kindling-induced epilepsy ⁸⁷
Plasma kallikrein	Hereditary angioedema (Immunodeficiency; D80-D89)	Critical role in hereditary angioedema pathogenesis ⁸⁸	Distinct domain structure ⁸⁹
APOB mRNA	Familial hypercholesterolaemia (Metabolic disorders; E00-E89)	Mutations caused hyperlipidemia ⁹⁰	Targeted mRNA sequence not repeated throughout the human genome ⁹⁰
Arylsulfatase B	Mucopolysaccharidosis VI (Metabolic disorders; E00-E89)	MPS VI is caused by a deficiency of the enzyme arylsulfatase B ⁹¹	Protein replacement therapy ⁹²

Beta-G1	Sly syndrome (Metabolic disorders; E00-E89)	MPS VII is caused by deficiency of the beta-glucuronidase enzyme ⁹³	Protein replacement therapy ⁹⁴
CaSR	Secondary hyperparathyroidism (Metabolic disorders; E00-E89)	CaSR plays a central role in the development of secondary hyperparathyroidism ⁹⁵ and demonstrates the predominant role in controlling parathyroid gland function ⁹⁶	Distinct allosteric binding-sites located in the heptahelical domain ⁹⁷
CFTR	Cystic fibrosis (Metabolic disorders; E00-E89)	A cause of cystic fibrosis ⁹⁸	Target with unique regulatory region ⁹⁹
CPS1	Hyperammonaemia (Metabolic disorders; E00-E89)	Deficiency of CPSase I causes life-threatening hyperammonaemia ^{100,101}	A selective and allosterically active CPSase I conformation yielded by covalent AGA incorporation ¹⁰²
DPP4	Type 2 diabetes (Metabolic disorders; E00-E89)	Target prevents the inactivation of a receptor that plays a central role in controlling postprandial blood sugar levels ¹⁰³	Binding-site with residue variations and conformational flexibility to accommodate selective binding of substrates and drugs ¹⁰⁴
GALNS	Mucopolysaccharidosis IVA (Metabolic disorders; E00-E89)	Deficiency in GALNS lead to accumulation of substrates, resulting in the development of morquio A syndrome ¹⁰⁵	Protein replacement therapy ¹⁰⁶
GLP-1 receptor	Type 2 diabetes (Metabolic disorders; E00-E89)	A central role in controlling postprandial blood sugar levels ¹⁰⁷	Certain binding-site residues adopt agonist specific conformation to enable selective drug binding ¹⁰⁸
Iduronate 2-sulfatase	Mucopolysaccharidosis II (Metabolic disorders; E00-E89)	Iduronate 2-sulfatase (IDS) deficiency in humans result in the hunter syndrome ¹⁰⁹	Protein replacement therapy ¹¹⁰

Leptin receptor	Congenital and acquired generalized lipodystrophy (Metabolic disorders; E00-E89)	Crucial for energy homeostasis and regulation of food uptake ¹¹¹	Substrate-selective binding-site with structural flexibility ¹¹²
Lysosomal lipase	Lysosomal acid lipase deficiency (Metabolic disorders; E00-E89)	LAL-D is characterized by the deficiency of lysosomal acid lipase which is caused by a congenital disorder of the lipid metabolism ¹¹³	Protein replacement therapy ¹¹⁴
PAH	Hyperphenylalaninaemia (Metabolic disorders; E00-E89)	Phenylketonuria (PKU) results in severe hyperphenylalaninemia ¹¹⁵ and PAH plays a pivotal role in the severity PKU ¹¹⁶	An architecturally distinct tetramer conformation stabilized by the allosteric activator phenylalanine ¹¹⁷
PCSK9	Familial hypercholesterolaemia (Metabolic disorders; E00-E89)	A crucial protein in LDL cholesterol (LDL-C) metabolism ¹¹⁸	Specific substrate site accommodating selective mAb binding ¹¹⁸
Phosphatase AP-TNAP	Hypophosphatasia (Metabolic disorders; E00-E89)	Hypophosphatasia features selective deficiency of activity of the tissue non-specific alkaline phosphatase (TNSALP) ¹¹⁹	Protein replacement therapy ¹²⁰
RAMP	Type 1/2 diabetes (Metabolic disorders; E00-E89)	RAMP is essential for the full functionality of CGRP which plays key role in the pathogenesis of diabetes ^{121,122}	Distinct binding pockets via an allosteric mechanism ¹²³
SC5A2	Type 2 diabetes (Metabolic disorders; E00-E89)	Major role in glucose homeostasis, counts for 90% of glucose reabsorption in the kidney ¹²⁴	Binding-site conformational flexibility to selectively enable substrate entry and binding ¹²⁵
TPP1	Batten disease (Metabolic disorders; E00-E89)	Mutations of the CLN2 gene encoding a soluble lysosomal enzyme, tripeptidyl peptidase 1 (TPP1), cause late infantile batten disease ¹²⁶	Protein replacement therapy ¹²⁷
Transfer protein MTP	Familial hypercholesterolaemia (Metabolic disorders; E00-E89)	Responsible for LDL disease caused by assembly of excessive LDL cholesterol ¹²⁸	Target substrate-site specific for a particular class of lipids ¹²⁹

AMPA receptor	Epilepsy (Nervous system; G00-G99)	Fast synaptic excitation within and between brain regions relevant to epilepsy is mediated predominantly by AMPA receptors ¹³⁰	Clearly distinct domain architecture of this homotetrameric structure ¹³¹
Dystrophin pre-mRNA	Duchenne muscular dystrophy (Nervous system; G00-G99)	Most DMD patients have a deletion of one or more exons (~68%) ¹³²	mRNA sequence not repeated throughout human genome is selected for targeting ¹³³
MT1/2 receptor	Insomnia (Nervous system; G00-G99)	Melatonin MT1 and MT2 receptors located in hypothalamus play a pivotal role in the sleep-wake regulation ¹³⁴	Pharmacologically distinct profiles and varied binding-sites of MT1 and MT2 receptors ¹³⁵
Orexin receptor	Insomnia (Nervous system; G00-G99)	One of the critical regulators of sleep/wake states ¹³⁶	Binding-site with a slightly different motif ¹³⁷
S1PR1	Multiple sclerosis (Nervous system; G00-G99)	Regulator of and altered in disease ¹³⁸	Binding-site with distinguishing characteristics ¹³⁹
SMN2 pre-mRNA	Spinal muscular atrophy (Nervous system; G00-G99)	Homozygous loss of the gene survival of motor neuron (SMN) causes atrophy of proximal skeletal muscles and subsequently the spinal muscular atrophy (SMA) ¹⁴⁰	Sequence of mRNA is distinct from that of the whole human genome ¹⁴¹
VLA-4 alpha	Multiple sclerosis (Nervous system; G00-G99)	Integrin alpha4 mediates organ-specific migration of immune cells to the inflamed brain, thereby playing the critical role in the pathogenesis of multiple sclerosis ¹⁴²	Distinct antigenic sites on the alpha 4 chain (VLA-4) ¹⁴³
LFA-1	Dry eye disease (Ophthalmopathy; H00-H59)	LFA-1/ICAM-1 interaction plays important roles in the cell-mediated immune response and inflammation associated with dry eye disease (DED) ¹⁴⁴	Structurally distinct ¹⁴⁵⁻¹⁴⁷

ROCK	Glaucoma (Ophthalmopathy; H00-H59)	The Rho/ROCK pathway plays a role in adhesion molecule expression and inflammatory cell infiltration in endotoxin-induced uveitis ¹⁴⁸	Binding-site structural variation with respect to close and remote kinases ¹⁴⁹
HCN channel	Heart failure (Circulatory system; I00-I99)	Important role in the generation of cardiac pacemaker activity ¹⁵⁰	Ligand-site with a nearby loop region structurally different from other homologs ¹⁵¹
PAR-1	Myocardial infarction (Circulatory system; I00-I99)	Solely responsible for rapid platelet-activation response in myocardial infarction ¹⁵²	Selective covalent binding-site at non-exposed surface pocket different from most GPCRs ¹⁵³
Renin	Hypertension (Circulatory system; I00-I99)	An over-active renin-angiotensin system leads to renovascular hypertension ^{154,155}	Distinguished structural features of the active site of renin ¹⁵⁶
sGC	Chronic thromboembolic pulmonary hypertension (Circulatory system; I00-I99)	Aberrant NO-sGC signaling has been linked to hypertension ¹⁵⁷	Conformationally distinct sGC-CO complex ¹⁵⁸
IL-5	Asthma (Respiratory system; J00-J99)	Crucial in the pathogenesis and evolution of eosinophilic asthma ^{159,160}	IL-5's distinct structural motifs ^{159,161,162}
PDE-4	Chronic obstructive pulmonary disease (Respiratory system; J00-J99)	PDE4 play an important role in psoriasis ¹⁶³	Several distinct residues of the C-terminus extend into the ligand binding-site ensures PDE4's selectivity ¹⁶⁴
Channel ANO1	HIV-associated diarrhea (Digestive system; K00-K95)	HIV protease inhibitors and chemotherapy agents induce diarrhea through intracellular Ca ²⁺ -dependent mechanisms that are partially driven by the channel ANO1 ¹⁶⁵	Target family with unique structure with respect to other membrane protein classes ¹⁶⁶ and target has low homology (<25%) to other family members ¹⁶⁷
CLCN2	Chronic idiopathic constipation (Digestive system; K00-K95)	ClC-2 controls cell membrane transport of chloride ion ¹⁶⁸ and therefore modulates gastrointestinal neuromuscular functions ¹⁶⁹	A more flexible noncoplanar conformation confers a larger affinity toward the inhibitory binding-site on ClC-2 ¹⁷⁰

FXR	Primary biliary cholangitis (Digestive system; K00-K95)	PBC is cholestatic disease characterized by hepatic accumulation of bile acids ¹⁷¹ and FXR is the receptor for primary bile acids by regulating its uptake ¹⁷²	Novel and specific binding pocket localized near the loop region between helix 1 and helix 2 ¹⁷³
GC-C	Irritable bowel syndrome with constipation (Digestive system; K00-K95)	Unique mechanism in promoting colonic mucosa integrity ¹⁷⁴	Only expressed at intestinal epithelial cells and CNS neuronal cells, specific ligand-site and flexibility of catalytic site for selective binding ^{175,176}
GLP-2	Short bowel syndrome (Digestive system; K00-K95)	Bone loss experienced by short bowel syndrome (SBS) patients could reflect a reduced level of endogenous postprandial GLP-2 production, resulting in impaired attenuation in bone resorption ¹⁷⁷	Protein replacement therapy ¹⁷⁸
TPH	Carcinoid syndrome diarrhea (Digestive system; K00-K95)	TPH regulates the biosynthesis of serotonin in the gastrointestinal tract, and it is localized predominantly in gastrointestinal enteroendocrine cells. Serotonin activates the peristaltic reflexes, regulates gastrointestinal motility, and has a role in intestinal inflammation. Inhibition of TPH with novel molecules represents a new pharmacological tool in the successful management of carcinoid syndrome in patients with gastrointestinal neuroendocrine related diseases including carcinoid syndrome diarrhea ¹⁷⁹	Selectivity of site/sequence, biochemical, and biophysical characterization of the allosteric site on TPH1 is achieved ¹⁸⁰

IL-12/23 p40	Plaque psoriasis (Skin diseases; L00-L99)	Critical for autoimmune encephalomyelitis ¹⁸¹	Selective mAb binding-site ¹⁸²
IL-17A	Plaque psoriasis (Skin diseases; L00-L99)	Cytokine IL-17A has significant role in the development of palmoplantar and pustular psoriasis ¹⁸³	2 distinct binding pockets (beta-hairpin & alpha-helix) on IL-17A represents direct structural evidence of binding site on IL-17A that functions to disrupt the interaction with its receptor ^{184,185}
IL-1B	Muckle-Wells syndrome (Skin diseases; L00-L99)	Pivotal role in a number of autoinflammatory diseases including FCAS and MWS ¹⁸⁶⁻¹⁸⁸	Structurally diverse and distinct cytokine ⁵⁸
IL-4R alpha	Eczema (Skin diseases; L00-L99)	IL-4 receptor alpha governs the signaling of IL-4 and IL-13, which are key drivers of type 2/Th2-mediated inflammation and atopic dermatitis ¹⁸⁹	Interleukin-4 receptor α (IL-4R α) chain is highly expressed in allergy and is needed to correctly balance immune responses ¹⁹⁰
BlyS ligand	Systemic lupus erythematosus (Bone diseases; M00-M99)	A significant role in the autoimmune process ¹⁹¹	Key BlyS-binding residues in the binding site selective for mAb are presented from a beta-turn ¹⁹²⁻¹⁹⁴
CD80/CD86	Rheumatoid arthritis (Bone diseases; M00-M99)	CD80 and CD86 play a determining role in allograft rejection ¹⁹⁵ and have opposing roles in regulation of xenotransplantation rejection, where CD80 drives CMR and attenuates AVR while CD86 drives AVR ¹⁹⁶	Distinct conformations but complementary roles of CD80 and CD86 IgV and IgC domains ¹⁹⁷
IL-6R	Rheumatoid arthritis (Bone diseases; M00-M99)	Plays a key role in the development of rheumatoid arthritis ¹⁹⁸	Unique binding-site of IL-6 allowing specific binding of mAb ¹⁹⁹
Jak3	Rheumatoid arthritis (Bone diseases; M00-M99)	Expressed only in immune cells and only bound by gamma-chain-bearing cytokine receptors involved in the targeted diseases ²⁰⁰	Binding-site local conformation differs from other family members ²⁰¹

RANKL	Osteoporosis (Bone diseases; M00-M99)	Disease process of osteoporosis depends on RANKL ²⁰²	Binding-site with target specific structural features for selective mAb binding ²⁰³
ADRB3	Overactive bladder (Urologic diseases; N00-N99)	Polymorphism in the beta3-AR gene is weakly but significantly associated with overactive bladder syndrome ²⁰⁴	Atypical binding-site in beta 3 adrenoceptor different from other subtypes ²⁰⁵
IGF1 receptor	Failure to thrive in children (Growth failures; R62)	Essential for normal growth and development ²⁰⁶	ATP site with sequence variant region at the interlobe linker to potentially enable selective drug binding ²⁰⁷ and peptide-substrate site influenced by remote residues enables selective peptide binding ²⁰⁶
Glucarpidase	Delayed methotrexate clearance (Drug adverse effects; Y40-Y59)	Significant toxicities are induced by delayed methotrexate clearance ²⁰⁸	Glucarpidase specifically cleaves MTX into nontoxic metabolites ²⁰⁹

References for Supplementary Table S4

- 1 J. G. Bann. Anthrax toxin protective antigen--insights into molecular switching from prepore to pore. *Protein Sci.* 2012, 21(1): 1-12
- 2 V. A. Karginov; E. M. Nestorovich; M. Moayeri; S. H. Leppla; S. M. Bezrukov. Blocking anthrax lethal toxin at the protective antigen channel by using structure-inspired drug design. *Proc Natl Acad Sci U S A.* 2005, 102(42): 15075-80
- 3 S. A. Hirota; V. Iablokov; S. E. Tulk; L. P. Schenck; H. Becker; J. Nguyen; S. Al Bashir; T. C. Dingle; A. Laing; J. Liu; Y. Li; J. Bolstad; G. L. Mulvey; G. D. Armstrong; W. K. MacNaughton; D. A. Muruve; J. A. MacDonald; P. L. Beck. Intrarectal instillation of *Clostridium difficile* toxin A triggers colonic inflammation and tissue damage: development of a novel and efficient mouse model of *Clostridium difficile* toxin exposure. *Infect Immun.* 2012, 80(12): 4474-84
- 4 N. M. Chumler; M. A. Farrow; L. A. Lapierre; J. L. Franklin; D. B. Haslam; J. R. Goldenring; D. B. Lacy. *Clostridium difficile* Toxin B causes epithelial cell necrosis through an autoproducting-independent mechanism. *PLoS Pathog.* 2012, 8(12): e1003072
- 5 R. Nazari; S. Joshi. CCR5 as target for HIV-1 gene therapy. *Curr Gene Ther.* 2008, 8(4): 264-72
- 6 Q. Tan; Y. Zhu; J. Li; Z. Chen; G. W. Han; I. Kufareva; T. Li; L. Ma; G. Fenalti; J. Li; W. Zhang; X. Xie; H. Yang; H. Jiang; V. Cherezov; H. Liu; R. C. Stevens; Q.

- Zhao; B. Wu. Structure of the CCR5 chemokine receptor-HIV entry inhibitor maraviroc complex. *Science*. 2013, 341(6152): 1387-90
- 7 F. M. Marty; P. Ljungman; R. F. Chemaly; J. Maertens; S. S. Dadwal; R. F. Duarte; S. Haider; A. J. Ullmann; Y. Katayama; J. Brown; K. M. Mullane; M. Boeckh; E. A. Blumberg; H. Einsele; D. R. Snyderman; Y. Kanda; M. J. DiNubile; V. L. Teal; H. Wan; Y. Murata; N. A. Kartsonis; R. Y. Leavitt; C. Badshah. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med*. 2017, 377(25): 2433-44
- 8 G. Ligat; R. Cazal; S. Hantz; S. Alain. The human cytomegalovirus terminase complex as an antiviral target: a close-up view. *FEMS Microbiol Rev*. 2018, 42(2): 137-45
- 9 N. Sharma; D. Sharma. An upcoming drug for onychomycosis: Tavaborole. *J Pharmacol Pharmacother*. 2015, 6(4): 236-9
- 10 R. Benarous; C. M. Chow; U. L. Rajbhandary. Cytoplasmic leucyl-tRNA synthetase of *Neurospora crassa* is not specified by the *leu-5* locus. *Genetics*. 1988, 119(4): 805-14
- 11 A. Meeprasert; S. Hannongbua; T. Rungrotmongkol. Key binding and susceptibility of NS3/4A serine protease inhibitors against hepatitis C virus. *J Chem Inf Model*. 2014, 54(4): 1208-17
- 12 C. Pierra Rouviere; A. Amador; E. Badaroux; T. Convard; D. Da Costa; D. Dukhan; L. Griffe; J. F. Griffon; M. LaColla; F. Leroy; M. Liuzzi; A. G. Loi; J. McCarville; V. Mascia; J. Milhau; L. Onidi; J. L. Paporin; R. Rahali; E. Sais; M. Seifer; D. Surleraux; D. Standring; C. Dousson. Synthesis of potent and broad genotypically active NS5B HCV non-nucleoside inhibitors binding to the thumb domain allosteric site 2 of the viral polymerase. *Bioorg Med Chem Lett*. 2016, 26(18): 4536-41
- 13 C. Stedman. Sofosbuvir, a NS5B polymerase inhibitor in the treatment of hepatitis C: a review of its clinical potential. *Therap Adv Gastroenterol*. 2014, 7(3): 131-40
- 14 Y. Pommier; C. Marchand; N. Neamati. Retroviral integrase inhibitors year 2000: update and perspectives. *Antiviral Res*. 2000, 47(3): 139-48
- 15 A. Engelman; J. J. Kessl; M. Kvaratskhelia. Allosteric inhibition of HIV-1 integrase activity. *Curr Opin Chem Biol*. 2013, 17(3): 339-45
- 16 A. Koul; N. Dendouga; K. Vergauwen; B. Molenberghs; L. Vranckx; R. Willebrords; Z. Ristic; H. Lill; I. Dorange; J. Guillemont; D. Bald; K. Andries. Diarylquinolines target subunit c of mycobacterial ATP synthase. *Nat Chem Biol*. 2007, 3(6): 323-4
- 17 K. Andries; P. Verhasselt; J. Guillemont; H. W. Gohlmann; J. M. Neefs; H. Winkler; J. Van Gestel; P. Timmerman; M. Zhu; E. Lee; P. Williams; D. de Chaffoy; E. Huitric; S. Hoffner; E. Cambau; C. Truffot-Pernot; N. Lounis; V. Jarlier. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science*. 2005, 307(5707): 223-7
- 18 S. Deoghare. Bedaquiline: a new drug approved for treatment of multidrug-resistant tuberculosis. *Indian J Pharmacol*. 2013, 45(5): 536-7

- 19 M. Soda; Y. L. Choi; M. Enomoto; S. Takada; Y. Yamashita; S. Ishikawa; S. Fujiwara; H. Watanabe; K. Kurashina; H. Hatanaka; M. Bando; S. Ohno; Y. Ishikawa; H. Aburatani; T. Niki; Y. Sohara; Y. Sugiyama; H. Mano. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*. 2007, 448(7153): 561-6
- 20 R. Roskoski, Jr. Anaplastic lymphoma kinase (ALK): structure, oncogenic activation, and pharmacological inhibition. *Pharmacol Res*. 2013, 68(1): 68-94
- 21 L. A. Hogarth; A. G. Hall. Increased BAX expression is associated with an increased risk of relapse in childhood acute lymphocytic leukemia. *Blood*. 1999, 93(8): 2671-8
- 22 L. E. Robertson; W. Plunkett; K. McConnell; M. J. Keating; T. J. McDonnell. Bcl-2 expression in chronic lymphocytic leukemia and its correlation with the induction of apoptosis and clinical outcome. *Leukemia*. 1996, 10(3): 456-9
- 23 G. Monaco; T. Vervliet; H. Akl; G. Bultynck. The selective BH4-domain biology of Bcl-2-family members: IP3Rs and beyond. *Cell Mol Life Sci*. 2013, 70(7): 1171-83
- 24 M. D. Herman; T. Nyman; M. Welin; L. Lehtio; S. Flodin; L. Tresaugues; T. Kotenyova; A. Flores; P. Nordlund. Completing the family portrait of the anti-apoptotic Bcl-2 proteins: crystal structure of human Bfl-1 in complex with Bim. *FEBS Lett*. 2008, 582(25-26): 3590-4
- 25 S. Wilhelm; C. Carter; M. Lynch; T. Lowinger; J. Dumas; R. A. Smith; B. Schwartz; R. Simantov; S. Kelley. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov*. 2006, 5(10): 835-44
- 26 G. Bollag; J. Tsai; J. Zhang; C. Zhang; P. Ibrahim; K. Nolop; P. Hirth. Vemurafenib: the first drug approved for BRAF-mutant cancer. *Nat Rev Drug Discov*. 2012, 11(11): 873-86
- 27 P. T. Wan; M. J. Garnett; S. M. Roe; S. Lee; D. Niculescu-Duvaz; V. M. Good; C. M. Jones; C. J. Marshall; C. J. Springer; D. Barford; R. Marais. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell*. 2004, 116(6): 855-67
- 28 R. W. Hendriks; S. Yuvaraj; L. P. Kil. Targeting Bruton's tyrosine kinase in B cell malignancies. *Nat Rev Cancer*. 2014, 14(4): 219-32
- 29 D. J. Marcotte; Y. T. Liu; R. M. Arduini; C. A. Hession; K. Miatkowski; C. P. Wildes; P. F. Cullen; V. Hong; B. T. Hopkins; E. Mertsching; T. J. Jenkins; M. J. Romanowski; D. P. Baker; L. F. Silvian. Structures of human Bruton's tyrosine kinase in active and inactive conformations suggest a mechanism of activation for TEC family kinases. *Protein Sci*. 2010, 19(3): 429-39
- 30 A. Turetsky; E. Kim; R. H. Kohler; M. A. Miller; R. Weissleder. Single cell imaging of Bruton's tyrosine kinase using an irreversible inhibitor. *Sci Rep*. 2014, 44782
- 31 F. T. Awan; R. Lapalombella; R. Trotta; J. P. Butchar; B. Yu; D. M. Benson, Jr.; J. M. Roda; C. Cheney; X. Mo; A. Lehman; J. Jones; J. Flynn; D. Jarjoura; J. R.

- Desjarlais; S. Tridandapani; M. A. Caligiuri; N. Muthusamy; J. C. Byrd. CD19 targeting of chronic lymphocytic leukemia with a novel Fc-domain-engineered monoclonal antibody. *Blood*. 2010, 115(6): 1204-13
- 32 A. K. Matsumoto; D. R. Martin; R. H. Carter; L. B. Klickstein; J. M. Ahearn; D. T. Fearon. Functional dissection of the CD21/CD19/TAPA-1/Leu-13 complex of B lymphocytes. *J Exp Med*. 1993, 178(4): 1407-17
- 33 V. Quarona; V. Ferri; A. Chillemi; M. Bolzoni; C. Mancini; G. Zaccarello; I. Roato; F. Morandi; D. Marimpietri; G. Faccani; E. Martella; V. Pistoia; N. Giuliani; A. L. Horenstein; F. Malavasi. Unraveling the contribution of ectoenzymes to myeloma life and survival in the bone marrow niche. *Ann N Y Acad Sci*. 2015, 133510-22
- 34 S. Burgler. Role of CD38 Expression in Diagnosis and Pathogenesis of Chronic Lymphocytic Leukemia and Its Potential as Therapeutic Target. *Crit Rev Immunol*. 2015, 35(5): 417-32
- 35 M. de Weers; Y. T. Tai; M. S. van der Veer; J. M. Bakker; T. Vink; D. C. Jacobs; L. A. Oomen; M. Peipp; T. Valerius; J. W. Slootstra; T. Mutis; W. K. Bleeker; K. C. Anderson; H. M. Lokhorst; J. G. van de Winkel; P. W. Parren. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol*. 2011, 186(3): 1840-8
- 36 H. C. Lee. Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP) as messengers for calcium mobilization. *J Biol Chem*. 2012, 287(38): 31633-40
- 37 M. Ise; K. Matsubayashi; H. Tsujimura; K. Kumagai. Loss of CD38 Expression in Relapsed Refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leuk*. 2016, 16(5): e59-64
- 38 Q. Yu; E. Sicinska; Y. Geng; M. Ahnstrom; A. Zagozdzon; Y. Kong; H. Gardner; H. Kiyokawa; L. N. Harris; O. Stal; P. Sicinski. Requirement for CDK4 kinase function in breast cancer. *Cancer Cell*. 2006, 9(1): 23-32
- 39 D. H. Brotherton; V. Dhanaraj; S. Wick; L. Brizuela; P. J. Domaille; E. Volyanik; X. Xu; E. Parisini; B. O. Smith; S. J. Archer; M. Serrano; S. L. Brenner; T. L. Blundell; E. D. Laue. Crystal structure of the complex of the cyclin D-dependent kinase Cdk6 bound to the cell-cycle inhibitor p19INK4d. *Nature*. 1998, 395(6699): 244-50
- 40 P. J. Day; A. Cleasby; I. J. Tickle; M. O'Reilly; J. E. Coyle; F. P. Holding; R. L. McMenamin; J. Yon; R. Chopra; C. Lengauer; H. Jhoti. Crystal structure of human CDK4 in complex with a D-type cyclin. *Proc Natl Acad Sci U S A*. 2009, 106(11): 4166-70
- 41 S. Mocellin; D. Nitti. CTLA-4 blockade and the renaissance of cancer immunotherapy. *Biochim Biophys Acta*. 2013, 1836(2): 187-96
- 42 H. T. Leung; J. Bradshaw; J. S. Cleaveland; P. S. Linsley. Cytotoxic T lymphocyte-associated molecule-4, a high-avidity receptor for CD80 and CD86, contains an intracellular localization motif in its cytoplasmic tail. *J Biol Chem*. 1995, 270(42): 25107-14

- 43 B. van der Hiel; C. U. Blank; J. B. Haanen; M. P. Stokkel. Detection of early onset of hypophysitis by (18)F-FDG PET-CT in a patient with advanced stage melanoma treated with ipilimumab. *Clin Nucl Med*. 2013, 38(4): e182-4
- 44 J. F. Grosso; M. N. Jure-Kunkel. CTLA-4 blockade in tumor models: an overview of preclinical and translational research. *Cancer Immun*. 2013, 135
- 45 Y. Alsayed; H. Ngo; J. Runnels; X. Leleu; U. K. Singha; C. M. Pitsillides; J. A. Spencer; T. Kimlinger; J. M. Ghobrial; X. Jia; G. Lu; M. Timm; A. Kumar; D. Cote; I. Veilleux; K. E. Hedin; G. D. Roodman; T. E. Witzig; A. L. Kung; T. Hideshima; K. C. Anderson; C. P. Lin; I. M. Ghobrial. Mechanisms of regulation of CXCR4/SDF-1 (CXCL12)-dependent migration and homing in multiple myeloma. *Blood*. 2007, 109(7): 2708-17
- 46 K. Beider; E. Ribakovsky; M. Abraham; H. Wald; L. Weiss; E. Rosenberg; E. Galun; A. Avigdor; O. Eizenberg; A. Peled; A. Nagler. Targeting the CD20 and CXCR4 pathways in non-hodgkin lymphoma with rituximab and high-affinity CXCR4 antagonist BKT140. *Clin Cancer Res*. 2013, 19(13): 3495-507
- 47 B. Wu; E. Y. Chien; C. D. Mol; G. Fenalti; W. Liu; V. Katritch; R. Abagyan; A. Brooun; P. Wells; F. C. Bi; D. J. Hamel; P. Kuhn; T. M. Handel; V. Cherezov; R. C. Stevens. Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. *Science*. 2010, 330(6007): 1066-71
- 48 L. A. Henriquez-Hernandez; A. Valenciano; P. Foro-Arnalot; M. J. Alvarez-Cubero; J. M. Cozar; J. F. Suarez-Novo; M. Castells-Esteve; P. Fernandez-Gonzalo; B. De-Paula-Carranza; M. Ferrer; F. Guedea; G. Sancho-Pardo; J. Craven-Bartle; M. J. Ortiz-Gordillo; P. Cabrera-Roldan; J. I. Rodriguez-Melcon; E. Herrera-Ramos; C. Rodriguez-Gallego; P. C. Lara. Genetic variations in genes involved in testosterone metabolism are associated with prostate cancer progression: A Spanish multicenter study. *Urol Oncol*. 2015, 33(7): 331.e1-7
- 49 J. Song; Z. H. Tao; X. Y. Liu; S. Gong; L. Gan. Relationship between CYP17 gene polymorphisms and risk of prostate cancer. *Genet Mol Res*. 2016, 15(1): 15017866
- 50 D. F. Estrada; A. L. Skinner; J. S. Laurence; E. E. Scott. Human cytochrome P450 17A1 conformational selection: modulation by ligand and cytochrome b5. *J Biol Chem*. 2014, 289(20): 14310-20
- 51 E. Barker; B. M. Mueller; R. Handgretinger; M. Herter; A. L. Yu; R. A. Reisfeld. Effect of a chimeric anti-ganglioside GD2 antibody on cell-mediated lysis of human neuroblastoma cells. *Cancer Res*. 1991, 51(1): 144-9
- 52 B. Barneda-Zahonero; M. Parra. Histone deacetylases and cancer. *Mol Oncol*. 2012, 6(6): 579-89
- 53 I. Becher; A. Dittmann; M. M. Savitski; C. Hopf; G. Drewes; M. Bantscheff. Chemoproteomics reveals time-dependent binding of histone deacetylase inhibitors to endogenous repressor complexes. *ACS Chem Biol*. 2014, 9(8): 1736-46
- 54 E. M. Stein. Enasidenib, a targeted inhibitor of mutant IDH2 proteins for treatment of relapsed or refractory acute myeloid leukemia. *Future Oncol*. 2018, 14(1): 23-40

- 55 G. Deng; J. Shen; M. Yin; J. McManus; M. Mathieu; P. Gee; T. He; C. Shi; O. Bedel; L. R. McLean; F. Le-Strat; Y. Zhang; J. P. Marquette; Q. Gao; B. Zhang; A. Rak; D. Hoffmann; E. Rooney; A. Vassort; W. Englaro; Y. Li; V. Patel; F. Adrian; S. Gross; D. Wiederschain; H. Cheng; S. Licht. Selective inhibition of mutant isocitrate dehydrogenase 1 (IDH1) via disruption of a metal binding network by an allosteric small molecule. *J Biol Chem*. 2015, 290(2): 762-74
- 56 K. A. Lyseng-Williamson. Siltuximab: A Review in Idiopathic (Human Herpesvirus-8-Negative) Multicentric Castleman Disease. *BioDrugs*. 2015, 29(6): 399-406
- 57 J. F. Rossi; Z. Y. Lu; M. Jourdan; B. Klein. Interleukin-6 as a therapeutic target. *Clin Cancer Res*. 2015, 21(6): 1248-57
- 58 P. W. Addis; C. J. Hall; S. Bruton; V. Veverka; I. C. Wilkinson; F. W. Musket; P. S. Renshaw; C. E. Prosser; B. Carrington; A. D. Lawson; R. Griffin; R. J. Taylor; L. C. Waters; A. J. Henry; M. D. Carr. Conformational heterogeneity in antibody-protein antigen recognition: implications for high affinity protein complex formation. *J Biol Chem*. 2014, 289(10): 7200-10
- 59 Y. C. Liu; K. Stone; F. van Rhee. Siltuximab for multicentric Castleman disease. *Expert Rev Hematol*. 2014, 7(5): 545-57
- 60 C. Keohane; D. H. Radia; C. N. Harrison. Treatment and management of myelofibrosis in the era of JAK inhibitors. *Biologics*. 2013, 7189-98
- 61 T. Zhou; S. Georgeon; R. Moser; D. J. Moore; A. Caflisch; O. Hantschel. Specificity and mechanism-of-action of the JAK2 tyrosine kinase inhibitors ruxolitinib and SAR302503 (TG101348). *Leukemia*. 2014, 28(2): 404-7
- 62 G. S. Inamdar; S. V. Madhunapantula; G. P. Robertson. Targeting the MAPK pathway in melanoma: why some approaches succeed and other fail. *Biochem Pharmacol*. 2010, 80(5): 624-37
- 63 J. F. Ohren; H. Chen; A. Pavlovsky; C. Whitehead; E. Zhang; P. Kuffa; C. Yan; P. McConnell; C. Spessard; C. Banotai; W. T. Mueller; A. Delaney; C. Omer; J. Sebolt-Leopold; D. T. Dudley; I. K. Leung; C. Flamme; J. Warmus; M. Kaufman; S. Barrett; H. Tecle; C. A. Hasemann. Structures of human MAP kinase kinase 1 (MEK1) and MEK2 describe novel noncompetitive kinase inhibition. *Nat Struct Mol Biol*. 2004, 11(12): 1192-7
- 64 M. W. Audeh; J. Carmichael; R. T. Penson; M. Friedlander; B. Powell; K. M. Bell-McGuinn; C. Scott; J. N. Weitzel; A. Oaknin; N. Loman; K. Lu; R. K. Schmutzler; U. Matulonis; M. Wickens; A. Tutt. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*. 2010, 376(9737): 245-51
- 65 A. W. Oliver; J. C. Ame; S. M. Roe; V. Good; G. de Murcia; L. H. Pearl. Crystal structure of the catalytic fragment of murine poly(ADP-ribose) polymerase-2. *Nucleic Acids Res*. 2004, 32(2): 456-64
- 66 T. Okazaki; S. Chikuma; Y. Iwai; S. Fagarasan; T. Honjo. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. *Nat Immunol*. 2013, 14(12): 1212-8

- 67 X. Cheng; V. Veverka; A. Radhakrishnan; L. C. Waters; F. W. Muskett; S. H. Morgan; J. Huo; C. Yu; E. J. Evans; A. J. Leslie; M. Griffiths; C. Stubberfield; R. Griffin; A. J. Henry; A. Jansson; J. E. Ladbury; S. Ikemizu; M. D. Carr; S. J. Davis. Structure and interactions of the human programmed cell death 1 receptor. *J Biol Chem.* 2013, 288(17): 11771-85
- 68 I. M. Macias-Perez; I. W. Flinn. GS-1101: a delta-specific PI3K inhibitor in chronic lymphocytic leukemia. *Curr Hematol Malig Rep.* 2013, 8(1): 22-7
- 69 A. Berndt; S. Miller; O. Williams; D. D. Le; B. T. Houseman; J. I. Pacold; F. Gorrec; W. C. Hon; Y. Liu; C. Rommel; P. Gaillard; T. Ruckle; M. K. Schwarz; K. M. Shokat; J. P. Shaw; R. L. Williams. The p110 delta structure: mechanisms for selectivity and potency of new PI(3)K inhibitors. *Nat Chem Biol.* 2010, 6(2): 117-24
- 70 S. A. Wells, Jr.; M. Santoro. Targeting the RET pathway in thyroid cancer. *Clin Cancer Res.* 2009, 15(23): 7119-23
- 71 P. P. Knowles; J. Murray-Rust; S. Kjaer; R. P. Scott; S. Hanrahan; M. Santoro; C. F. Ibanez; N. Q. McDonald. Structure and chemical inhibition of the RET tyrosine kinase domain. *J Biol Chem.* 2006, 281(44): 33577-87
- 72 H. Magen; E. Muchtar. Elotuzumab: the first approved monoclonal antibody for multiple myeloma treatment. *Ther Adv Hematol.* 2016, 7(4): 187-95
- 73 S. Lonial; M. Dimopoulos; A. Palumbo; D. White; S. Grosicki; I. Spicka; A. Walter-Croneck; P. Moreau; M. V. Mateos; H. Magen; A. Belch; D. Reece; M. Beksac; A. Spencer; H. Oakervee; R. Z. Orlowski; M. Taniwaki; C. Rollig; H. Einsele; K. L. Wu; A. Singhal; J. San-Miguel; M. Matsumoto; J. Katz; E. Bleickardt; V. Poulart; K. C. Anderson; P. Richardson. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med.* 2015, 373(7): 621-31
- 74 Y. Wang; L. Sanchez; D. S. Siegel; M. L. Wang. Elotuzumab for the treatment of multiple myeloma. *J Hematol Oncol.* 2016, 9(1): 55
- 75 M. Athar; C. Li; A. L. Kim; V. S. Spiegelman; D. R. Bickers. Sonic hedgehog signaling in Basal cell nevus syndrome. *Cancer Res.* 2014, 74(18): 4967-75
- 76 C. Wang; H. Wu; V. Katritch; G. W. Han; X. P. Huang; W. Liu; F. Y. Siu; B. L. Roth; V. Cherezov; R. C. Stevens. Structure of the human smoothed receptor bound to an antitumour agent. *Nature.* 2013, 497(7449): 338-43
- 77 V. Hanrahan; M. J. Currie; S. P. Gunningham; H. R. Morrin; P. A. Scott; B. A. Robinson; S. B. Fox. The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C, and VEGF-D in the adenoma-carcinoma sequence during colorectal cancer progression. *J Pathol.* 2003, 200(2): 183-94
- 78 Y. Myoken; Y. Kayada; T. Okamoto; M. Kan; G. H. Sato; J. D. Sato. Vascular endothelial cell growth factor (VEGF) produced by A-431 human epidermoid carcinoma cells and identification of VEGF membrane binding sites. *Proc Natl Acad Sci U S A.* 1991, 88(13): 5819-23
- 79 B. I. Rini. Vascular endothelial growth factor-targeted therapy in metastatic renal cell carcinoma. *Cancer.* 2009, 115(10 Suppl): 2306-12
- 80 M. A. McTigue; J. A. Wickersham; C. Pinko; R. E. Showalter; C. V. Parast; A. Tempczyk-Russell; M. R. Gehring; B. Mroczkowski; C. C. Kan; J. E. Villafranca; K. Appelt. Crystal structure of the kinase domain of human vascular endothelial growth factor receptor 2: a key enzyme in angiogenesis. *Structure.* 1999,

7(3): 319-30

- 81 S. T. Test; V. S. Woolworth. Defective regulation of complement by the sickle erythrocyte: evidence for a defect in control of membrane attack complex formation. *Blood*. 1994, 83(3): 842-52
- 82 M. M. Jore; S. Johnson; D. Sheppard; N. M. Barber; Y. I. Li; M. A. Nunn; H. Elmlund; S. M. Lea. Structural basis for therapeutic inhibition of complement C5. *Nat Struct Mol Biol*. 2016, 23(5): 378-86
- 83 M. Chang; Y. Suen; G. Meng; J. S. Buzby; J. Bussel; V. Shen; C. van de Ven; M. S. Cairo. Differential mechanisms in the regulation of endogenous levels of thrombopoietin and interleukin-11 during thrombocytopenia: insight into the regulation of platelet production. *Blood*. 1996, 88(9): 3354-62
- 84 T. Kuhne; P. Imbach. Eltrombopag: an update on the novel, non-peptide thrombopoietin receptor agonist for the treatment of immune thrombocytopenia. *Ann Hematol*. 2010, 89 Suppl 167-74
- 85 R. Stasi. Eltrombopag: the discovery of a second generation thrombopoietin-receptor agonist. *Expert Opin Drug Discov*. 2009, 4(1): 85-93
- 86 F. Bossi; F. Fischetti; D. Regoli; P. Durigutto; B. Frossi; F. Gobeil, Jr.; B. Ghebrehiwet; E. I. Peerschke; M. Cicardi; F. Tedesco. Novel pathogenic mechanism and therapeutic approaches to angioedema associated with C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2009, 124(6): 1303-10.e4
- 87 B. Ongali; M. M. Campos; G. Bregola; D. Rodi; D. Regoli; G. Thibault; M. Simonato; R. Couture. Autoradiographic analysis of rat brain kinin B1 and B2 receptors: normal distribution and alterations induced by epilepsy. *J Comp Neurol*. 2003, 461(4): 506-19
- 88 L. Schneider; W. Lumry; A. Vegh; A. H. Williams; T. Schmalbach. Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol*. 2007, 120(2): 416-22
- 89 M. Pathak; S. S. Wong; I. Dreveny; J. Emsley. Structure of plasma and tissue kallikreins. *Thromb Haemost*. 2013, 110(3): 423-33
- 90 C. Gelsinger; E. Steinhagen-Thiessen; U. Kassner. Therapeutic potential of mipomersen in the management of familial hypercholesterolaemia. *Drugs*. 2012, 72(11): 1445-55
- 91 M. Evers; P. Saftig; P. Schmidt; A. Hafner; D. B. McLoughlin; W. Schmahl; B. Hess; K. von Figura; C. Peters. Targeted disruption of the arylsulfatase B gene results in mice resembling the phenotype of mucopolysaccharidosis VI. *Proc Natl Acad Sci U S A*. 1996, 93(16): 8214-9
- 92 D. D. Horovitz; T. S. Magalhaes; A. Acosta; E. M. Ribeiro; L. R. Giuliani; D. B. Palhares; C. A. Kim; A. C. de Paula; M. Kerstenestzy; M. A. Pianovski; M. I. Costa; F. C. Santos; A. M. Martins; C. S. Aranda; J. Correa Neto; G. B. Holanda; L. Cardoso, Jr.; C. A. da Silva; R. C. Bonatti; B. F. Ribeiro; C. Rodrigues Mdo; J. C. Llerena, Jr. Enzyme replacement therapy with galsulfase in 34 children younger than five years of age with MPS VI. *Mol Genet Metab*. 2013, 109(1): 62-9
- 93 J. Ce; M. T. Rodrigues; E. T. Kafer; V. da Costa Moraes; J. C. Coelho. Beta-glucuronidase activity in dried blood spots: Reduced technique with biochemical

- parameters determined. *Clin Biochem*. 2017, 50(18): 1243-48
- 94 M. B. Kaufman. Pharmaceutical Approval Update. P t. 2018, 43(2): 83-84
- 95 D. Riccardi; D. Martin. The role of the calcium-sensing receptor in the pathophysiology of secondary hyperparathyroidism. *NDT Plus*. 2008, 1(Suppl 1): i7-i11
- 96 L. D. Quarles. Extracellular calcium-sensing receptors in the parathyroid gland, kidney, and other tissues. *Curr Opin Nephrol Hypertens*. 2003, 12(4): 349-55
- 97 K. Leach; A. D. Conigrave; P. M. Sexton; A. Christopoulos. Towards tissue-specific pharmacology: insights from the calcium-sensing receptor as a paradigm for GPCR (patho)physiological bias. *Trends Pharmacol Sci*. 2015, 36(4): 215-25
- 98 M. H. Akabas. Cystic fibrosis transmembrane conductance regulator. Structure and function of an epithelial chloride channel. *J Biol Chem*. 2000, 275(6): 3729-32
- 99 N. Cant; N. Pollock; R. C. Ford. CFTR structure and cystic fibrosis. *Int J Biochem Cell Biol*. 2014, 5215-25
- 100 I. Yefimenko; V. Fresquet; C. Marco-Marin; V. Rubio; J. Cervera. Understanding carbamoyl phosphate synthetase deficiency: impact of clinical mutations on enzyme functionality. *J Mol Biol*. 2005, 349(1): 127-41
- 101 Y. R. Chen; K. Sekine; K. Nakamura; H. Yanai; M. Tanaka; A. Miyajima. Y-box binding protein-1 down-regulates expression of carbamoyl phosphate synthetase-I by suppressing CCAAT enhancer-binding protein-alpha function in mice. *Gastroenterology*. 2009, 137(1): 330-40
- 102 C. R. McCudden; S. G. Powers-Lee. Required allosteric effector site for N-acetylglutamate on carbamoyl-phosphate synthetase I. *J Biol Chem*. 1996, 271(30): 18285-94
- 103 B. Ahren. Islet G protein-coupled receptors as potential targets for treatment of type 2 diabetes. *Nat Rev Drug Discov*. 2009, 8(5): 369-85
- 104 K. L. Longenecker; K. D. Stewart; D. J. Madar; C. G. Jakob; E. H. Fry; S. Wilk; C. W. Lin; S. J. Ballaron; M. A. Stashko; T. H. Lubben; H. Yong; D. Pireh; Z. Pei; F. Basha; P. E. Wiedeman; T. W. von Geldern; J. M. Trevillyan; V. S. Stoll. Crystal structures of DPP-IV (CD26) from rat kidney exhibit flexible accommodation of peptidase-selective inhibitors. *Biochemistry*. 2006, 45(24): 7474-82
- 105 S. Tomatsu; A. M. Montano; V. C. Dung; A. Ohashi; H. Oikawa; T. Oguma; T. Orii; L. Barrera; W. S. Sly. Enhancement of drug delivery: enzyme-replacement therapy for murine Morquio A syndrome. *Mol Ther*. 2010, 18(6): 1094-102
- 106 B. Donida; D. P. Marchetti; G. B. Biancini; M. Deon; P. R. Manini; H. T. da Rosa; D. J. Moura; J. Saffi; F. Bender; M. G. Burin; A. S. Coitinho; R. Giugliani; C. R. Vargas. Oxidative stress and inflammation in mucopolysaccharidosis type IVA patients treated with enzyme replacement therapy. *Biochim Biophys Acta*. 2015, 1852(5): 1012-9

- 107 D. Donnelly. The structure and function of the glucagon-like peptide-1 receptor and its ligands. *Br J Pharmacol.* 2012, 166(1): 27-41
- 108 C. R. Underwood; P. Garibay; L. B. Knudsen; S. Hastrup; G. H. Peters; R. Rudolph; S. Reedtz-Runge. Crystal structure of glucagon-like peptide-1 in complex with the extracellular domain of the glucagon-like peptide-1 receptor. *J Biol Chem.* 2010, 285(1): 723-30
- 109 P. J. Wilson; C. P. Morris; D. S. Anson; T. Occhiodoro; J. Bielicki; P. R. Clements; J. J. Hopwood. Hunter syndrome: isolation of an iduronate-2-sulfatase cDNA clone and analysis of patient DNA. *Proc Natl Acad Sci U S A.* 1990, 87(21): 8531-5
- 110 E. M. da Silva; M. W. Strufaldi; R. B. Andriolo; L. A. Silva. Enzyme replacement therapy with idursulfase for mucopolysaccharidosis type II (Hunter syndrome). *Cochrane Database Syst Rev.* 2016, 2CD008185
- 111 M. Tutone; A. Lauria; A. M. Almerico. Leptin and the OB-receptor as anti-obesity target: recent in silico advances in the comprehension of the protein-protein interaction and rational drug design of anti-obesity lead compounds. *Curr Pharm Des.* 2014, 20(1): 136-45
- 112 B. Carpenter; G. R. Hemsworth; Z. Wu; M. Maamra; C. J. Strasburger; R. J. Ross; P. J. Artymiuk. Structure of the human obesity receptor leptin-binding domain reveals the mechanism of leptin antagonism by a monoclonal antibody. *Structure.* 2012, 20(3): 487-97
- 113 V. Ivashkin; M. Zharkova. Cholesteryl Ester Crystals in Lysosomal Acid Lipase Deficiency. *N Engl J Med.* 2017, 376(9): e14
- 114 C. E. Hollak; G. K. Hovingh. Dyslipidaemia: Lysosomal acid lipase deficiency-a cautious leap forward. *Nat Rev Endocrinol.* 2015, 11(12): 696-7
- 115 S. Keil; K. Anjema; F. J. van Spronsen; N. Lambruschini; A. Burlina; A. Belanger-Quintana; M. L. Couce; F. Feillet; R. Cerone; A. S. Lotz-Havla; A. C. Muntau; A. M. Bosch; C. A. Meli; T. Billette de Villemeur; I. Kern; E. Riva; M. Giovannini; L. Damaj; V. Leuzzi; N. Blau. Long-term follow-up and outcome of phenylketonuria patients on sapropterin: a retrospective study. *Pediatrics.* 2013, 131(6): e1881-8
- 116 C. N. Sarkissian; T. S. Kang; A. Gamez; C. R. Scriver; R. C. Stevens. Evaluation of orally administered PEGylated phenylalanine ammonia lyase in mice for the treatment of Phenylketonuria. *Mol Genet Metab.* 2011, 104(3): 249-54
- 117 E. C. Arturo; K. Gupta; A. Heroux; L. Stith; P. J. Cross; E. J. Parker; P. J. Loll; E. K. Jaffe. First structure of full-length mammalian phenylalanine hydroxylase reveals the architecture of an autoinhibited tetramer. *Proc Natl Acad Sci U S A.* 2016, 113(9): 2394-9
- 118 G. Lambert; B. Sjouke; B. Choque; J. J. Kastelein; G. K. Hovingh. The PCSK9 decade. *J Lipid Res.* 2012, 53(12): 2515-24
- 119 M. P. Whyte; M. Landt; L. M. Ryan; R. A. Mulivor; P. S. Henthorn; K. N. Fedde; J. D. Mahuren; S. P. Coburn. Alkaline phosphatase: placental and tissue-nonspecific isoenzymes hydrolyze phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5'-phosphate. Substrate accumulation in carriers of hypophosphatasia corrects during pregnancy. *J Clin Invest.* 1995, 95(4): 1440-5
- 120 M. P. Whyte; C. R. Greenberg; N. J. Salman; M. B. Bober; W. H. McAlister; D. Wenkert; B. J. Van Sickle; J. H. Simmons; T. S. Edgar; M. L. Bauer; M. A.

- Hamdan; N. Bishop; R. E. Lutz; M. McGinn; S. Craig; J. N. Moore; J. W. Taylor; R. H. Cleveland; W. R. Cranley; R. Lim; T. D. Thacher; J. E. Mayhew; M. Downs; J. L. Millan; A. M. Skrinar; P. Crine; H. Landy. Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med*. 2012, 366(10): 904-13
- 121 F. A. Russell; R. King; S. J. Smillie; X. Kodji; S. D. Brain. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev*. 2014, 94(4): 1099-142
- 122 L. H. Wang; S. X. Zhou; R. C. Li; L. R. Zheng; J. H. Zhu; S. J. Hu; Y. L. Sun. Serum levels of calcitonin gene-related peptide and substance P are decreased in patients with diabetes mellitus and coronary artery disease. *J Int Med Res*. 2012, 40(1): 134-40
- 123 H. A. Watkins; M. Chakravarthy; R. S. Abhayawardana; J. J. Gingell; M. Garelja; M. Pardamwar; J. M. McElhinney; A. Lathbridge; A. Constantine; P. W. Harris; T. Y. Yuen; M. A. Brimble; J. Barwell; D. R. Poyner; M. J. Woolley; A. C. Conner; A. A. Pioszak; C. A. Reynolds; D. L. Hay. Receptor Activity-modifying Proteins 2 and 3 Generate Adrenomedullin Receptor Subtypes with Distinct Molecular Properties. *J Biol Chem*. 2016, 291(22): 11657-75
- 124 J. J. Neumiller; J. R. White, Jr.; R. K. Campbell. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. *Drugs*. 2010, 70(4): 377-85
- 125 S. Faham; A. Watanabe; G. M. Besserer; D. Cascio; A. Specht; B. A. Hirayama; E. M. Wright; J. Abramson. The crystal structure of a sodium galactose transporter reveals mechanistic insights into Na⁺/sugar symport. *Science*. 2008, 321(5890): 810-4
- 126 R. D. Geraets; L. M. Langin; J. T. Cain; C. M. Parker; R. Beraldi; A. D. Kovacs; J. M. Weimer; D. A. Pearce. A tailored mouse model of CLN2 disease: A nonsense mutant for testing personalized therapies. *PLoS One*. 2017, 12(5): e0176526
- 127 A. Markham. Cerliponase Alfa: First Global Approval. *Drugs*. 2017, 77(11): 1247-49
- 128 M. Cuchel; L. T. Bloedon; P. O. Szapary; D. M. Kolansky; M. L. Wolfe; A. Sarkis; J. S. Millar; K. Ikewaki; E. S. Siegelman; R. E. Gregg; D. J. Rader. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med*. 2007, 356(2): 148-56
- 129 F. X. Contreras; A. M. Ernst; F. Wieland; B. Brugger. Specificity of intramembrane protein-lipid interactions. *Cold Spring Harb Perspect Biol*. 2011, 3(6):
- 130 M. A. Rogawski. AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurol Scand Suppl*. 2013, (197): 9-18
- 131 C. R. Midgett; A. Gill; D. R. Madden. Domain architecture of a calcium-permeable AMPA receptor in a ligand-free conformation. *Front Mol Neurosci*. 2012, 456
- 132 E. H. Niks; A. Aartsma-Rus. Exon skipping: a first in class strategy for Duchenne muscular dystrophy. *Expert Opin Biol Ther*. 2017, 17(2): 225-36
- 133 R. Kole; A. M. Krieg. Exon skipping therapy for Duchenne muscular dystrophy. *Adv Drug Deliv Rev*. 2015, 87104-7
- 134 M. Uchiyama. [Melatonin receptor agonist]. *Nihon Rinsho*. 2015, 73(6): 1017-22
- 135 C. Browning; I. Beresford; N. Fraser; H. Giles. Pharmacological characterization of human recombinant melatonin mt(1) and MT(2) receptors. *Br J*

- Pharmacol. 2000, 129(5): 877-86
- 136 T. Sakurai; M. Mieda; N. Tsujino. The orexin system: roles in sleep/wake regulation. *Ann N Y Acad Sci.* 2010, 1200149-61
- 137 J. Yin; J. C. Mobarec; P. Kolb; D. M. Rosenbaum. Crystal structure of the human OX2 orexin receptor bound to the insomnia drug suvorexant. *Nature.* 2015, 519(7542): 247-50
- 138 A. Groves; Y. Kihara; J. Chun. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. *J Neurol Sci.* 2013, 328(1-2): 9-18
- 139 M. A. Hanson; C. B. Roth; E. Jo; M. T. Griffith; F. L. Scott; G. Reinhart; H. Desale; B. Clemons; S. M. Cahalan; S. C. Schuerer; M. G. Sanna; G. W. Han; P. Kuhn; H. Rosen; R. C. Stevens. Crystal structure of a lipid G protein-coupled receptor. *Science.* 2012, 335(6070): 851-5
- 140 M. Jangi; C. Fleet; P. Cullen; S. V. Gupta; S. Mekhoubad; E. Chiao; N. Allaire; C. F. Bennett; F. Rigo; A. R. Krainer; J. A. Hurt; J. P. Carulli; J. F. Staropoli. SMN deficiency in severe models of spinal muscular atrophy causes widespread intron retention and DNA damage. *Proc Natl Acad Sci U S A.* 2017, 114(12): E2347-E56
- 141 D. R. Corey. Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. *Nat Neurosci.* 2017, 20(4): 497-99
- 142 E. Kawamoto; S. Nakahashi; T. Okamoto; H. Imai; M. Shimaoka. Anti-integrin therapy for multiple sclerosis. *Autoimmune Dis.* 2012, 2012357101
- 143 M. R. Campanero; R. Pulido; M. A. Ursa; M. Rodriguez-Moya; M. O. de Landazuri; F. Sanchez-Madrid. An alternative leukocyte homotypic adhesion mechanism, LFA-1/ICAM-1-independent, triggered through the human VLA-4 integrin. *J Cell Biol.* 1990, 110(6): 2157-65
- 144 S. C. Pflugfelder; M. Stern; S. Zhang; A. Shojaei. LFA-1/ICAM-1 Interaction as a Therapeutic Target in Dry Eye Disease. *J Ocul Pharmacol Ther.* 2017, 33(1): 5-12
- 145 C. R. Beals; A. C. Edwards; R. J. Gottschalk; T. W. Kuijpers; D. E. Staunton. CD18 activation epitopes induced by leukocyte activation. *J Immunol.* 2001, 167(11): 6113-22
- 146 S. Li; H. Wang; B. Peng; M. Zhang; D. Zhang; S. Hou; Y. Guo; J. Ding. Efalizumab binding to the LFA-1 alphaL I domain blocks ICAM-1 binding via steric hindrance. *Proc Natl Acad Sci U S A.* 2009, 106(11): 4349-54
- 147 C. P. Semba; T. R. Gadek. Development of lifitegrast: a novel T-cell inhibitor for the treatment of dry eye disease. *Clin Ophthalmol.* 2016, 101083-94
- 148 T. Uchida; M. Honjo; R. Yamagishi; M. Aihara. The Anti-Inflammatory Effect of Ripasudil (K-115), a Rho Kinase (ROCK) Inhibitor, on Endotoxin-Induced Uveitis in Rats. *Invest Ophthalmol Vis Sci.* 2017, 58(12): 5584-93
- 149 K. Gohda; T. Hakoshima. A molecular mechanism of P-loop pliability of Rho-kinase investigated by molecular dynamic simulation. *J Comput Aided Mol Des.*

2008, 22(11): 789-97

- 150 O. Postea; M. Biel. Exploring HCN channels as novel drug targets. *Nat Rev Drug Discov.* 2011, 10(12): 903-14
- 151 X. Xu; Z. V. Vysotskaya; Q. Liu; L. Zhou. Structural basis for the cAMP-dependent gating in the human HCN4 channel. *J Biol Chem.* 2010, 285(47): 37082-91
- 152 P. Tricoci; Z. Huang; C. Held; D. J. Moliterno; P. W. Armstrong; F. Van de Werf; H. D. White; P. E. Aylward; L. Wallentin; E. Chen; Y. Lokhnygina; J. Pei; S. Leonardi; T. L. Rorick; A. M. Kilian; L. H. Jennings; G. Ambrosio; C. Bode; A. Cequier; J. H. Cornel; R. Diaz; A. Erkan; K. Huber; M. P. Hudson; L. Jiang; J. W. Jukema; B. S. Lewis; A. M. Lincoff; G. Montalescot; J. C. Nicolau; H. Ogawa; M. Pfisterer; J. C. Prieto; W. Ruzyllo; P. R. Sinnaeve; R. F. Storey; M. Valgimigli; D. J. Whellan; P. Widimsky; J. Strony; R. A. Harrington; K. W. Mahaffey; T. Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med.* 2012, 366(1): 20-33
- 153 C. Zhang; Y. Srinivasan; D. H. Arlow; J. J. Fung; D. Palmer; Y. Zheng; H. F. Green; A. Pandey; R. O. Dror; D. E. Shaw; W. I. Weis; S. R. Coughlin; B. K. Kobilka. High-resolution crystal structure of human protease-activated receptor 1. *Nature.* 2012, 492(7429): 387-92
- 154 C. V. Ram. Direct inhibition of renin: a physiological approach to treat hypertension and cardiovascular disease. *Future Cardiol.* 2009, 5(5): 453-65
- 155 T. Rosenthal. Drug therapy of renovascular hypertension. *Drugs.* 1993, 45(6): 895-909
- 156 K. S. Misono; J. J. Chang; T. Inagami. Structure of mouse submaxillary gland renin. *Clin Exp Hypertens A.* 1983, 5(7-8): 941-59
- 157 M. L. Marro; C. Peiro; C. M. Panayiotou; R. S. Baliga; S. Meurer; H. H. Schmidt; A. J. Hobbs. Characterization of the human alpha1 beta1 soluble guanylyl cyclase promoter: key role for NF-kappaB(p50) and CCAAT-binding factors in regulating expression of the nitric oxide receptor. *J Biol Chem.* 2008, 283(29): 20027-36
- 158 M. Ibrahim; E. R. Derbyshire; M. A. Marletta; T. G. Spiro. Probing soluble guanylate cyclase activation by CO and YC-1 using resonance Raman spectroscopy. *Biochemistry.* 2010, 49(18): 3815-23
- 159 V. Fainardi; G. Pisi; A. Chetta. Mepolizumab in the treatment of severe eosinophilic asthma. *Immunotherapy.* 2016, 8(1): 27-34
- 160 M. E. Rothenberg. Humanized Anti-IL-5 Antibody Therapy. *Cell.* 2016, 165(3): 509
- 161 Z. Sun; D. A. Yergeau; I. C. Wong; T. Tuypens; J. Tavernier; C. C. Paul; M. A. Baumann; P. E. Auron; D. G. Tenen; S. J. Ackerman. Interleukin-5 receptor alpha subunit gene regulation in human eosinophil development: identification of a unique cis-element that acts lie an enhancer in regulating activity of the IL-5R alpha promoter. *Curr Top Microbiol Immunol.* 1996, 211:73-87
- 162 I. J. Pouliquen; O. Kornmann; S. V. Barton; J. A. Price; H. G. Ortega. Characterization of the relationship between dose and blood eosinophil response following subcutaneous administration of mepolizumab. *Int J Clin Pharmacol Ther.* 2015, 53(12): 1015-27

- 163 P. H. Schafer; F. Truzzi; A. Parton; L. Wu; J. Kosek; L. H. Zhang; G. Horan; A. Saltari; M. Quadri; R. Lotti; A. Marconi; C. Pincelli. Phosphodiesterase 4 in inflammatory diseases: Effects of apremilast in psoriatic blood and in dermal myofibroblasts through the PDE4/CD271 complex. *Cell Signal*. 2016, 28(7): 753-63
- 164 M. Kranz; M. Wall; B. Evans; A. Miah; S. Ballantine; C. Delves; B. Dombroski; J. Gross; J. Schneck; J. P. Villa; M. Neu; D. O. Somers. Identification of PDE4B Over 4D subtype-selective inhibitors revealing an unprecedented binding mode. *Bioorg Med Chem*. 2009, 17(14): 5336-41
- 165 J. R. Thiagarajah; M. Donowitz; A. S. Verkman. Secretory diarrhoea: mechanisms and emerging therapies. *Nat Rev Gastroenterol Hepatol*. 2015, 12(8): 446-57
- 166 J. D. Brunner; N. K. Lim; S. Schenck; A. Duerst; R. Dutzler. X-ray structure of a calcium-activated TMEM16 lipid scramblase. *Nature*. 2014, 516(7530): 207-12
- 167 A. Picollo; M. Malvezzi; A. Accardi. TMEM16 proteins: unknown structure and confusing functions. *J Mol Biol*. 2015, 427(1): 94-105
- 168 N. a. listed. Lubiprostone: RU 0211, SPI 0211. *Drugs R D*. 2005, 6(4): 245-8
- 169 M. Camilleri; A. E. Bharucha; R. Ueno; D. Burton; G. M. Thomforde; K. Baxter; S. McKinzie; A. R. Zinsmeister. Effect of a selective chloride channel activator, lubiprostone, on gastrointestinal transit, gastric sensory, and motor functions in healthy volunteers. *Am J Physiol Gastrointest Liver Physiol*. 2006, 290(5): G942-7
- 170 A. Liantonio; A. Picollo; G. Carbonara; G. Fracchiolla; P. Tortorella; F. Liodice; A. Laghezza; E. Babini; G. Zifarelli; M. Pusch; D. C. Camerino. Molecular switch for CLC-K Cl⁻ channel block/activation: optimal pharmacophoric requirements towards high-affinity ligands. *Proc Natl Acad Sci U S A*. 2008, 105(4): 1369-73
- 171 J. Trottier; A. Bialek; P. Caron; R. J. Straka; J. Heathcote; P. Milkiewicz; O. Barbier. Metabolomic profiling of 17 bile acids in serum from patients with primary biliary cirrhosis and primary sclerosing cholangitis: a pilot study. *Dig Liver Dis*. 2012, 44(4): 303-10
- 172 V. Sepe; E. Distrutti; S. Fiorucci; A. Zampella. Farnesoid X receptor modulators (2011 - 2014): a patent review. *Expert Opin Ther Pat*. 2015, 25(8): 885-96
- 173 U. Meyer; G. Costantino; A. Macchiarulo; R. Pellicciari. Is antagonism of E/Z-guggulsterone at the farnesoid X receptor mediated by a noncanonical binding site? A molecular modeling study. *J Med Chem*. 2005, 48(22): 6948-55
- 174 G. M. Pitari. Pharmacology and clinical potential of guanylyl cyclase C agonists in the treatment of ulcerative colitis. *Drug Des Devel Ther*. 2013, 7351-60
- 175 A. Rauch; M. Leipelt; M. Russwurm; C. Steegborn. Crystal structure of the guanylyl cyclase Cya2. *Proc Natl Acad Sci U S A*. 2008, 105(41): 15720-5
- 176 J. A. Winger; E. R. Derbyshire; M. H. Lamers; M. A. Marletta; J. Kuriyan. The crystal structure of the catalytic domain of a eukaryotic guanylate cyclase. *BMC Struct Biol*. 2008, 842

- 177 I. B. Gottschalck; P. B. Jeppesen; B. Hartmann; J. J. Holst; D. B. Henriksen. Effects of treatment with glucagon-like peptide-2 on bone resorption in colectomized patients with distal ileostomy or jejunostomy and short-bowel syndrome. *Scand J Gastroenterol.* 2008, 43(11): 1304-10
- 178 E. S. Kim; S. J. Keam. Teduglutide: A Review in Short Bowel Syndrome. *Drugs.* 2017, 77(3): 345-52
- 179 T. Swami; H. C. Weber. Updates on the biology of serotonin and tryptophan hydroxylase. *Curr Opin Endocrinol Diabetes Obes.* 2018, 25(1): 12-21
- 180 M. Petrassi; R. Barber; C. Be; S. Beach; B. Cox; A. M. D'Souza; N. Duggan; M. Hussey; R. Fox; P. Hunt; G. Jarai; T. Kosaka; P. Oakley; V. Patel; N. Press; D. Rowlands; C. Scheufler; O. Schmidt; H. Srinivas; M. Turner; R. Turner; J. Westwick; A. Wolfreys; N. Pathan; S. Watson; M. Thomas. Identification of a Novel Allosteric Inhibitory Site on Tryptophan Hydroxylase 1 Enabling Unprecedented Selectivity Over all Related Hydroxylases. *Front Pharmacol.* 2017, 8240
- 181 D. C. Torti; S. R. Feldman. Interleukin-12, interleukin-23, and psoriasis: current prospects. *J Am Acad Dermatol.* 2007, 57(6): 1059-68
- 182 J. Luo; S. J. Wu; E. R. Lacy; Y. Orlovsky; A. Baker; A. Teplyakov; G. Obmolova; G. A. Heavner; H. T. Richter; J. Benson. Structural basis for the dual recognition of IL-12 and IL-23 by ustekinumab. *J Mol Biol.* 2010, 402(5): 797-812
- 183 E. Lee; M. Zarei; C. LaSenna; G. Villada; P. Romanelli. Psoriasis Targeted Therapy: Characterization of Interleukin 17A Expression in Subtypes of Psoriasis. *J Drugs Dermatol.* 2015, 14(10): 1133-6
- 184 A. Espada; H. Broughton; S. Jones; M. J. Chalmers; J. A. Dodge. A Binding Site on IL-17A for Inhibitory Macrocycles Revealed by Hydrogen/Deuterium Exchange Mass Spectrometry. *J Med Chem.* 2016, 59(5): 2255-60
- 185 M. I. Koenders; W. B. van den Berg. Secukinumab for rheumatology: development and its potential place in therapy. *Drug Des Devel Ther.* 2016, 102069-80
- 186 R. Goldbach-Mansky; D. L. Kastner. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. *J Allergy Clin Immunol.* 2009, 124(6): 1141-9; quiz 50-1
- 187 I. Kone-Paut; C. Galeotti. Anakinra for cryopyrin-associated periodic syndrome. *Expert Rev Clin Immunol.* 2014, 10(1): 7-18
- 188 J. Hu; Y. Zhu; J. Z. Zhang; R. G. Zhang; H. M. Li. A Novel Mutation in the Pyrin Domain of the NOD-like Receptor Family Pyrin Domain Containing Protein 3 in Muckle-Wells Syndrome. *Chin Med J (Engl).* 2017, 130(5): 586-93
- 189 M. de Bruin-Weller; D. Thaci; C. H. Smith; K. Reich; M. Cork; A. Radin; Q. Zhang; B. Akinlade; A. Gadkari; L. Eckert; T. Hultsch; Z. Chen; G. Pirozzi; N. M. H. Graham; B. Shumel. Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFE). *Br J Dermatol.* 2017,
- 190 G. Perona-Wright; K. Mohrs; K. D. Mayer; M. Mohrs. Differential regulation of IL-4R α expression by antigen versus cytokine stimulation characterizes

- Th2 progression in vivo. *J Immunol.* 2010, 184(2): 615-23
- 191 M. P. Cancro; D. P. D'Cruz; M. A. Khamashta. The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. *J Clin Invest.* 2009, 119(5): 1066-73
- 192 P. Vashisht; K. Borghoff; J. R. O'Dell; M. Heath-Holmes. Belimumab for the treatment of recalcitrant cutaneous lupus. *Lupus.* 2017, 26(8): 857-64
- 193 N. C. Gordon; B. Pan; S. G. Hymowitz; J. Yin; R. F. Kelley; A. G. Cochran; M. Yan; V. M. Dixit; W. J. Fairbrother; M. A. Starovasnik. BAFF/BLyS receptor 3 comprises a minimal TNF receptor-like module that encodes a highly focused ligand-binding site. *Biochemistry.* 2003, 42(20): 5977-83
- 194 M. Gayed; C. Gordon. Novel treatments for systemic lupus erythematosus. *Curr Opin Investig Drugs.* 2010, 11(11): 1256-64
- 195 L. Bugeon; K. K. Wong; A. M. Rankin; R. E. Hargreaves; M. J. Dallman. A negative regulatory role in mouse cardiac transplantation for a splice variant of CD80. *Transplantation.* 2006, 82(10): 1334-41
- 196 K. A. Hosiawa; H. Wang; M. E. DeVries; B. Garcia; W. Liu; D. Zhou; A. Akram; J. Jiang; H. Sun; M. J. Cameron; R. Zhong; D. J. Kelvin. CD80/CD86 costimulation regulates acute vascular rejection. *J Immunol.* 2005, 175(9): 6197-204
- 197 T. Girard; D. Gaucher; M. El-Far; G. Breton; R. P. Sekaly. CD80 and CD86 IgC domains are important for quaternary structure, receptor binding and co-signaling function. *Immunol Lett.* 2014, 161(1): 65-75
- 198 Y. Yoshida; T. Tanaka. Interleukin 6 and rheumatoid arthritis. *Biomed Res Int.* 2014, 2014698313
- 199 H. S. Abou-Auda; W. Sakr. Tocilizumab: A new anti-rheumatic drug. *Saudi Pharm J.* 2010, 18(4): 257-9
- 200 K. West. CP-690550, a JAK3 inhibitor as an immunosuppressant for the treatment of rheumatoid arthritis, transplant rejection, psoriasis and other immune-mediated disorders. *Curr Opin Investig Drugs.* 2009, 10(5): 491-504
- 201 T. J. Boggon; Y. Li; P. W. Manley; M. J. Eck. Crystal structure of the Jak3 kinase domain in complex with a staurosporine analog. *Blood.* 2005, 106(3): 996-1002
- 202 D. W. Dempster; C. L. Lambing; P. J. Kostenuik; A. Grauer. Role of RANK ligand and denosumab, a targeted RANK ligand inhibitor, in bone health and osteoporosis: a review of preclinical and clinical data. *Clin Ther.* 2012, 34(3): 521-36
- 203 S. Ito; K. Wakabayashi; O. Ubukata; S. Hayashi; F. Okada; T. Hata. Crystal structure of the extracellular domain of mouse RANK ligand at 2.2-Å resolution. *J Biol Chem.* 2002, 277(8): 6631-6
- 204 K. Honda; O. Yamaguchi; M. Nomiya; K. Shishido; K. Ishibashi; N. Takahashi; K. Aikawa. Association between polymorphism of beta3-adrenoceptor gene and overactive bladder. *Neurourol Urodyn.* 2014, 33(4): 400-2

- 205 S. J. Roberts; P. Molenaar; R. J. Summers. Characterization of propranolol-resistant (-)-[125I]-cyanopindolol binding sites in rat soleus muscle. *Br J Pharmacol.* 1993, 109(2): 344-52
- 206 D. Le Roith; A. A. Butler. Insulin-like growth factors in pediatric health and disease. *J Clin Endocrinol Metab.* 1999, 84(12): 4355-61
- 207 S. Favelyukis; J. H. Till; S. R. Hubbard; W. T. Miller. Structure and autoregulation of the insulin-like growth factor 1 receptor kinase. *Nat Struct Biol.* 2001, 8(12): 1058-63
- 208 S. C. Howard; J. McCormick; C. H. Pui; R. K. Buddington; R. D. Harvey. Preventing and Managing Toxicities of High-Dose Methotrexate. *Oncologist.* 2016, 21(12): 1471-82
- 209 S. Schwartz; K. Borner; K. Muller; P. Martus; L. Fischer; A. Korfel; T. Auton; E. Thiel. Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. *Oncologist.* 2007, 12(11): 1299-308

Supplementary Table S5: Human systems features of the innovative targets of first-in-class drugs approved in 2004-2017. These features include the family affiliation and drug-binding domain sequence similarity to the pre-existing targets (with drug approved before 2004), key network descriptors, human systems feature of the on-target (human protein-network topologies, modulated pathways and distributed tissues) and off-target (similarity proteins) collateral effects.

Target Name	Target Family (Affiliation to Pre-existing Targets)	Sequence Similarity E-value to Pre-existing Targets	Orphan Drug Status Assigned (Assigned Date)	Degree	Neigh Connec	No. of Pathway	No. of Tissues	No. of Similarity Proteins	Biomarker / Drug Covalent Binding
Human Targets of Small Molecular Drugs (40 targets in total, ordered by the time spend from clinical trial phase I to FDA approval)									
CPS1	Carbon-nitrogen ligases (new)	0.001	Carglumic Acid (01/20/1998)	20	11.5	2	2	6	None
IDH2	Oxidoreductase (old)	0.003	Enasidenib (06/12/2014)	7	10.7	2	4	8	IDH2-mutated AML ¹
PAH	Oxidoreductase (old)	6e-156	Sapropterin Dihydrochloride (01/29/2004)	4	4.3	1	1	3	None
MT1/2 receptor	GPCR rhodopsin (old)	1e-24	Tasimelteon (01/19/2010)	2	4.0	1	1	8	None
BRaf	Kinase (old)	1e-32	Dabrafenib (01/12/2011) Sorafenib (12/12/2011) Vemurafenib (12/20/2010)	15	23.7	5	1	14	BRAF V600E/K mutation positive ¹ .
Btk	Kinase (old)	3e-79	Ibrutinib (12/03/2012)	3	7.0	5	5	15	Mutations in this gene cause X-linked agammaglobulinemia ² . Ibrutinib is a covalent inhibitor of Btk ³ .

Smoothened	GPCR frizzled (old)	8e-04	None	7	5.9	1	3	8	None
Alk	Kinase (old)	1e-59	Alectinib (01/27/2015) Ceritinib (09/27/2013) Crizotinib (09/13/2010)	2	1.5	1	4	6	ALK gene rearrangement positive ¹ .
CFTR	Acid anhydrides hydrolase (old)	8e-28	Ivacaftor (12/20/2006)	6	4.7	3	1	12	CFTR G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H mutation ¹ .
Renin	Peptidase (old)	9e-04	None	5	6.0	1	4	8	None
LFA-1	Integrin (old)	0.001	None	6	10.7	2	4	5	None
DPP4	Peptidase (old)	0.006	None	2	4.5	1	3	8	None
CCR5	GPCR rhodopsin (old)	2e-41	None	12	14.8	2	3	8	CCR5-tropic HIV-1 ¹ .
CLCN2	Chloride Carrier/Channel (new)	0.002	None	1	1.0	1	3	9	None
Orexin receptor	GPCR rhodopsin (old)	3e-34	None	3	4.7	1	1	18	None
sGC	Phosphorus-oxygen lyase (old)	0.002	Riociguat (09/19/2013)	3	4.3	8	2	17	None

VEGFR2	Kinase (old)	3e-105	Cabozantinib (11/29/2010) Nintedanib (06/29/2011) Ramucirumab (02/16/2012) Sorafenib (12/12/2011) Vandetanib (10/21/2005)	14	27.7	5	5	15	None
Ret	Kinase (old)	1e-74	Cabozantinib (11/29/2010) Ponatinib (11/20/2009) Sorafenib (12/12/2011) Vandetanib (04/06/2011)	25	25.0	1	2	10	Ret mutation positive ¹ .
MEK	Kinase (old)	2e-23	Trametinib (12/20/2010)	15	31.3	10	4	9	None
CaSR	GPCR frizzled (old)	3e-66	Cinacalcet Hydrochloride (05/12/2003)	3	37.7	1	3	23	CaSR mutation positive ¹ .
HDAC	Amidohydrolase (old)	0.001	Romidepsin (09/30/2004) Vorinostat (03/16/2004)	16	29.3	1	3	5	None
SC5A2	Solute:sodium symporter (new)	0.004	None	1	1.0	1	4	10	None
TPH	Oxidoreductase (old)	9e-156	Telotristat ethyl (03/09/2012)	1	7.0	3	3	8	None
BCL-2	Bcl-2 family (new)	0.032	Venetoclax (09/20/2012)	29	29.6	2	1	26	None
PI3K delta	Kinase (old)	2e-15	Idelalisib (10/15/2013)	27	20.4	14	5	6	None
ADRB3	GPCR rhodopsin (old)	7e-33	None	1	23.0	6	3	20	None

CXCR4	GPCR rhodopsin (old)	4e-52	Plerixafor (07/10/2003)	15	75.5	5	2	7	None
Jak3	Kinase (old)	4e-54	None	36	21.8	3	3	11	None
CDK4/6	Kinase (old)	2e-24	None	15	26.0	3	5	27	None
PAR-1	GPCR rhodopsin (old)	5e-31	None	13	8.5	5	5	7	None
FXR	Nuclear hormone receptor (old)	9e-28	Obeticholic Acid (04/09/2008)	3	26.3	1	3	11	None
S1PR1	GPCR rhodopsin (old)	4e-27	None	7	36.3	2	5	8	None
PARP	Pentosyl transferase (old)	0.001	Olaparib (10/16/2013)	24	55.3	1	3	15	None
PDE-4	Sulfuric ester hydrolase (old)	3e-171	None	11	21.2	2	4	24	None
HCN channel	Voltage-gated ion channel (old)	9e-05	None	2	2.5	1	3	33	None
Jak2	Kinase (old)	1e-53	Ruxolitinib (09/05/2008)	75	27.6	5	4	2	None
Transfer protein MTP	Vitellogenin lipid transport (new)	0.005	Lomitapide (10/23/2007)	2	5.0	1	5	7	None
ROCK	Kinase (old)	5e-32	None	16	31.4	2	2	14	None

AMPA receptor	Glutamate-gated Ion Channel (new)	2e-23	None	8	14.9	6	2	17	None
CYP17A1	Oxidoreductase (old)	2e-58	None	7	12.6	2	1	13	Abiraterone inhibits CYP17A1 by selective and irreversible manner via covalent binding mechanism ⁴ .
Human Targets of Biologics (41 targets in total, ordered by the time spend from clinical trial phase I to FDA approval)									
TPP1	Peptidase (old)	0.001	Cerliponase alfa (04/01/2013)	1	1.0	1	4	10	TPP1 deficiency ¹
Beta-G1	Glycosylase (old)	1e-05	Vestronidase alfa-vjvk (02/16/2012)	1	5.0	2	4	10	None
Lysosomal lipase	Carboxylic ester hydrolases (old)	0.011	Sebelipase Alfa (07/01/2010)	2	1.0	1	2	9	None
Arylsulfatase B	Sulfuric ester hydrolase (old)	6e-04	Galsulfase (02/17/1999)	2	3.0	2	4	8	None
GALNS	Sulfuric ester hydrolase (old)	0.011	Elosulfase Alfa (05/15/2009)	1	5.0	2	3	5	Nacetylgalactosamine-6-sulfatase deficient ¹
PCSK9	Peptidase (old)	0.004	Evolocumab (09/12/2013)	1	5.0	1	6	7	Mutational biomarker ⁵
GLP-1 receptor	GPCR secretin (old)	4e-86	None	5	10.2	2	2	14	None

RAMP	RAMP family (new)	7e-04	None	1	8.0	1	3	11	None
VEGF-A	Growth factor: VEGF (new)	0.008	None	22	17.5	5	3	18	None
Phosphatase AP-TNAP	Phosphoric monoester hydrolase (old)	0.009	Asfotase Alfa (09/12/2008)	1	3.0	1	2	8	None
VLA-4 alpha	Integrin (new)	0.003	None	10	12.0	4	4	3	None
Complement C5	Complement system (old)	0.004	Eculizumab (08/20/2003)	5	5.6	1	3	4	None
IL-12/23 p40	Cytokine: interleukin (old)	0.007	None	5	28.0	1	3	11	Deficient IL-12/IL-23 are vulnerable to disseminated infections ¹
IL-1B	Cytokine: interleukin (old)	2e-05	Riloncept (12/20/2004)	6	35.0	1	1	10	None
GC-C	Phosphorus-oxygen lyase (old)	2e-16	None	1	20.0	1	3	6	None
PD-1	Immunoglobulin (old)	2e-05	Nivolumab (01/23/2013); Pembrolizumab (11/19/2012)	2	20.0	1	1	10	High PD-L1 expression ¹
Plasma kallikrein	Peptidase (old)	0.019	None	2	8.5	1	5	7	None

CTLA-4	Immunoglobulin (old)	5e-04	Ipilimumab (10/21/2010)	12	26.9	1	2	9	None
APOB mRNA	mRNA target (old)	N.A.	Mipomersen (05/23/2006)	5	3.4	2	3	8	None
SLAMF7	Immunoglobulin (old)	0.003	Elotuzumab (09/01/2011)	1	20.0	1	3	4	None
BlyS ligand	Cytokine: tumor necrosis factor (old)	5e-08	None	4	9.0	2	3	2	None
IL-17A	Cytokine: interleukin (old)	0.002	None	8	19.6	1	3	3	None
CD38	Glycosylase (old)	0.006	Daratumumab (05/06/2013)	2	39.5	3	6	2	None
Channel ANO1	Calcium-dependent chloride channel (new)	0.005	None	1	6.0	2	1	8	None
IGF1 receptor	Kinase (old)	4e-66	Mecasermin (12/12/1995)	28	58.9	11	4	9	None
RANKL	Cytokine: tumor necrosis factor (old)	2e-11	None	5	50.4	3	2	10	None
Ganglioside GD2	Small molecular target (old)	N.A.	Dinutuximab (12/20/2010)	1	1.0	1	7	0	None

Iduronate 2-sulfatase	Sulfuric ester hydrolase (old)	0.011	Idursulfase (11/28/2001)	27	1.0	2	4	17	None
IL-6R	Cytokine receptor (old)	3e-07	None	16	23.3	5	3	15	None
CD80/CD86	Immunoglobulin (old)	6e-04	Belatacept (02/20/2008)	6	12.7	1	3	25	None
Dystrophin pre-mRNA	mRNA target (old)	N.A.	Eteplirsen (10/23/2007)	21	6.3	1	3	9	None
CD19	Immunoglobulin (old)	0.001	Blinatumomab (05/16/2008)	14	15.4	2	3	15	None
GLP-2	Hormone: glucagon (old)	0.001	Teduglutide Recombinant (06/29/2000)	30	10.9	0	0	20	None
IL-6	Cytokine: interleukin (old)	0.003	Siltuximab (05/26/2006)	32	21.9	1	3	17	None
BDKRB2	GPCR rhodopsin (old)	6e-44	Icatibant Acetate (11/25/2003)	4	11.5	7	4	10	None
SMN2 pre-mRNA	mRNA target (old)	N.A.	Nusinersen (04/18/2011)	12	32.3	1	4	16	Deficiency biomarker ⁶
TPO-R	Cytokine receptor (old)	0.003	Eltrombopag (05/05/2008); Romiplostim (03/27/2003)	4	42.3	1	3	8	None
Leptin receptor	Cytokine receptor (old)	6e-05	Metreleptin (08/22/2001)	4	34.5	3	5	5	None

Glucarpidase	Peptidase (old)	N.A.	Glucarpidase (08/19/2003)	8	1.0	0	0	14	None
IL-4R alpha	Cytokine receptor (old)	0.007	None	16	23.1	4	4	13	None
IL-5	Cytokine: interleukin (old)	2e-04	None	12	25.3	1	1	3	None
Infectious Disease Species Targets (8 targets in total, ordered by the time spend from clinical trial phase I to FDA approval)									
HIV integrase	Integrase (old)	0.002	None	1	1.0	0	P	6	None
HCV NS5B	Integrase (old)	7e-04	None	1	1.0	0	1	12	None
Anthrax PA	Bacterial binary toxin (new)	5e-04	Raxibacumab (11/12/2003)	2	1.0	0	3	2	None
TB ATP synthase	Acid anhydrides hydrolase (old)	6e-04	Bedaquiline Fumarate (01/10/2005)	1	7.0	0	0	17	None
HCV NS3/4A	Peptidase (old)	0.005	None	2	1.0	0	1	12	None
Fungal LeuRS	Carbon-oxygen ligases (new)	0.026	None	1	1.0	0	0	5	None
C. difficile toxin B	Peptidase (old)	0.006	None	3	1.0	0	0	4	None
CMV-terminase	Sulfuric ester hydrolase (old)	0.003	Letemovir (12/12/2011)	1	1.0	0	P	6	None

References for Supplementary Table S5

- 1 U. S. FDA. Table of Pharmacogenomic Biomarkers in Drug Labeling. U.S. Food & Drug Administration. 2018, UCM572698
- 2 I. Fernandez-Vega; L. M. Quiros; J. Santos-Juanes; M. Pane-Foix; T. Marafioti. Bruton's tyrosine kinase (Btk) is a useful marker for Hodgkin and B cell non-Hodgkin lymphoma. *Virchows Arch.* 2015, 466(2): 229-35
- 3 M. S. Davids; J. R. Brown. Ibrutinib: a first in class covalent inhibitor of Bruton's tyrosine kinase. *Future Oncol.* 2014, 10(6): 957-67
- 4 MedEx. Abiraterone Acetate (<https://medex.com.bd/generics/1294/abiraterone-acetate>). MedEx. 2017, Generics1294
- 5 B. Cariou; C. Le May; P. Costet. Clinical aspects of PCSK9. *Atherosclerosis.* 2011, 216(2): 258-65
- 6 S. J. Kolb; C. S. Coffey; J. W. Yankey; K. Krosschell; W. D. Arnold; S. B. Rutkove; K. J. Swoboda; S. P. Reyna; A. Sakonju; B. T. Darras; R. Shell; N. Kuntz; D. Castro; J. Parsons; A. M. Connolly; C. A. Chiriboga; C. McDonald; W. B. Burnette; K. Werner; M. Thangarajh; P. B. Shieh; E. Finanger; M. E. Cudkowicz; M. M. McGovern; D. E. McNeil; R. Finkel; S. T. Iannaccone; E. Kaye; A. Kingsley; S. R. Rensch; V. L. McGovern; X. Wang; P. G. Zaworski; T. W. Prior; A. H. M. Burghes; A. Bartlett; J. T. Kissel. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 2017, 82(6): 883-91

Supplementary Table S6: The population-based disease characteristics of the innovative infectious species targets of first-in-class drugs approved in 2004-2017. These features include the population size of and threat level to the targeted patient of the 8 infectious disease species targets (ordered by the time spend from clinical trial phase I to FDA approval).

Target Name	Disease	Time Spend on Clinical Trial Progression (by month)	Affected Population of the Targeted Disease	Estimated Number of Death Population per year	Other Life-threatening Disease or Problem Caused
HIV integrase	HIV infection	82	29.23 million ¹	25,579 ²	Collapse of human immune system ³
HCV NS5B	Hepatitis C viral infection	86	147.83 million ¹	505 ²	Oncogenic virus infection inducing liver cancer ⁴
Anthrax PA	Anthrax	89	0.0035 million ⁵	5 ⁶	Terrorist attack and weaponization ⁷
TB ATP synthase	Multidrug-resistant tuberculosis	109	3.67 million ¹	1,528 ²	Life-threatening TB-induced sepsis ⁸
HCV NS3/4A	Hepatitis C viral infection	119	147.83 million ¹	505 ²	Oncogenic virus infection inducing liver cancer ⁴
Fungal LeuRS	Onychomycosis	122	600 million ⁹	N.A.	Not a life-threatening disease ¹⁰
C. difficile toxin B	Clostridium difficile infection recurrence	127	1.5 million ¹¹	<1,332 ^{2,*}	Induced non-life-threatening diseases like enteritis ¹²
CMV-terminase	Cytomegalovirus infection	146	2.5 million ¹³	39 ²	Generally not regarded to be oncogenic virus infection ¹⁴

* 1,332 refers to all death population per year for Clostridium difficile infection, and the number for Clostridium difficile infection recurrence should be <1,332

References for Supplementary Table S6

- 1 C. Global Burden of Disease Study. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015, 386(9995): 743-800
- 2 U. S. CDC. Deaths from each cause, by 5-year age groups, race, and sex: united states, 2001. National Center for Health Statistics. 2001,
- 3 A. Trauneker; W. Luke; K. Karjalainen. Soluble CD4 molecules neutralize human immunodeficiency virus type 1. Nature. 1988, 331(6151): 84-6

- 4 I. Rusyn; S. M. Lemon. Mechanisms of HCV-induced liver cancer: what did we learn from in vitro and animal studies? *Cancer Lett.* 2014, 345(2): 210-5
- 5 Orphanet. The portal for rare diseases and orphan drugs (Anthrax, www.orpha.net). Official Website of Orphanet. 2018, Version 5.10.2
- 6 D. B. Jernigan; P. L. Raghunathan; B. P. Bell; R. Brechner; E. A. Bresnitz; J. C. Butler; M. Cetron; M. Cohen; T. Doyle; M. Fischer; C. Greene; K. S. Griffith; J. Guarner; J. L. Hadler; J. A. Hayslett; R. Meyer; L. R. Petersen; M. Phillips; R. Pinner; T. Popovic; C. P. Quinn; J. Reefhuis; D. Reissman; N. Rosenstein; A. Schuchat; W. J. Shieh; L. Siegal; D. L. Swerdlow; F. C. Tenover; M. Traeger; J. W. Ward; I. Weisfuse; S. Wiersma; K. Yeskey; S. Zaki; D. A. Ashford; B. A. Perkins; S. Ostroff; J. Hughes; D. Fleming; J. P. Koplan; J. L. Gerberding; T. National Anthrax Epidemiologic Investigation. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis.* 2002, 8(10): 1019-28
- 7 D. R. Franz; P. B. Jahrling; A. M. Friedlander; D. J. McClain; D. L. Hoover; W. R. Bryne; J. A. Pavlin; G. W. Christopher; E. M. Eitzen, Jr. Clinical recognition and management of patients exposed to biological warfare agents. *JAMA.* 1997, 278(5): 399-411
- 8 M. Shah; C. Reed. Complications of tuberculosis. *Curr Opin Infect Dis.* 2014, 27(5): 403-10
- 9 A. Shemer; H. Trau; B. Davidovici; B. Amichai; M. H. Grunwald. Onychomycosis: rationalization of topical treatment. *Isr Med Assoc J.* 2008, 10(6): 415-6
- 10 D. Milobratovic; S. Jankovic; J. Vukicevic; J. Marinkovic; J. Jankovic; Z. Railic. Quality of life in patients with toenail onychomycosis. *Mycoses.* 2013, 56(5): 543-51
- 11 A. M. Minino; J. Xu; K. D. Kochanek. Deaths: preliminary data for 2008. *Natl Vital Stat Rep.* 2010, 59(2): 1-52
- 12 S. P. Dineen; S. H. Bailey; T. H. Pham; S. Huerta. Clostridium difficile enteritis: A report of two cases and systematic literature review. *World J Gastrointest Surg.* 2013, 5(3): 37-42
- 13 M. Vanheusden; B. Broux; S. P. Welten; L. M. Peeters; E. Panagioti; B. Van Wijmeersch; V. Somers; P. Stinissen; R. Arens; N. Hellings. Cytomegalovirus infection exacerbates autoimmune mediated neuroinflammation. *Sci Rep.* 2017, 7(1): 663
- 14 M. Michaelis; H. W. Doerr; J. Cinatl. The story of human cytomegalovirus and cancer: increasing evidence and open questions. *Neoplasia.* 2009, 11(1): 1-9

Supplementary Table S7: The population-based disease characteristics of the innovative non-infectious species targets of first-in-class drugs approved in 2004-2017. These features include the population size of and threat level to the targeted patients of 81 non-infectious species targets (ordered by the disease classes and the time spend from clinical trial phase I to FDA approval). CA: Canada; EU: Europe; FR: France; IE: Ireland; IN: India; IR: Iran; JP: Japan; UK: United Kingdom.

Target Name	Time Spend on Clinical Trial Progression (by month)	Disease	Disease Class	Affected Population of Targeted Disease	Estimated No. of Death Population per year	Other Life-threatening Disease or Problem Caused
IDH2	48	Acute myeloid leukemia	Neoplasms	0.44 million ¹	0.01 million ²	If left untreated, death usually ensues within months of diagnosis ³
BRaf	57	Melanoma	Neoplasms	3.10 million ⁴	0.06 million ⁴	Sometimes it results in brain metastases, which is fatal ⁵
Btk	57	Mantle cell lymphoma	Neoplasms	0.10 million ^{1,6,7}	In US, <0.001 million ⁸	Life-threatening, slow-growing cancers which involves accumulation of cancerous B-cell ^{9,10}
Smoothened	57	Basal cell carcinoma	Neoplasms	0.10 million ⁶	0.001 million ⁶	Damaging the tissue around but is unlikely to spread to distant areas or to result in death ¹¹
Alk	64	Non-small-cell lung carcinoma	Neoplasms	In US, 0.20 million ^{12,13}	0.13 million ¹⁴	Life-threatening and accounts for about 85% of all lung cancers ¹³
VEGF-A	81	Colorectal cancer	Neoplasms	100.00 million ¹⁵	33.00 million ¹⁵	Cell metastasis of this type of cancer is the major cause of death ¹⁵
PD-1	97	Melanoma	Neoplasms	3.10 million ⁴	0.06 million ¹	Accounting for 1% of skin cancers but causes a large majority of skin cancer deaths ¹⁶
VEGFR2	99	Renal cell carcinoma	Neoplasms	0.24 million ¹⁷	0.10 million ¹⁷	Metastasis of this type of cancer is the most critical cause of death ¹⁷
CTLA-4	102	Melanoma	Neoplasms	3.10 million ⁴	0.06 million ¹	Accounting for 1% of skin cancers but causes a large majority of skin cancer deaths ¹⁶
Ret	>104	Medullary thyroid cancer	Neoplasms	0.04 million ^{4,18}	0.0008 million ¹⁹	Two-thirds of the patients with the sporadic forms of cancer died with metastases ²⁰
SLAMF7	107	Multiple myeloma	Neoplasms	0.43 million ²¹	0.10 million ¹	One typical type of the invariably deadly plasma cell cancers ²²

MEK	107	Melanoma	Neoplasms	3.10 million ⁴	0.15 million ⁶	Accounting for 1% of skin cancers but causes a large majority of skin cancer deaths ⁵
CD38	110	Multiple myeloma	Neoplasms	0.43 million ²¹	0.10 million ¹	One typical type of the invariably deadly plasma cell cancers ²²
HDAC	110	Cutaneous T cell lymphoma	Neoplasms	In CA, 0.007 million ²³	In CA, 0.00001 million ²³	Increasing the risk of type 2 diabetes, and causing secondary cancers ²⁴
BCL-2	114	Chronic lymphocytic leukemia	Neoplasms	0.46 million ⁶	0.05 million ⁶	Many serious complications including Hodgkin's lymphoma, acute leukemia, <i>etc.</i> ²⁵
PI3K delta	114	Chronic lymphocytic leukemia	Neoplasms	0.46 million ⁶	0.05 million ⁶	Many serious complications including Hodgkin's lymphoma, acute leukemia, <i>etc.</i> ²⁵
Ganglioside GD2	116	Neuroblastoma	Neoplasms	In US, 0.019 million ²⁶	0.005 million ²⁶	Embryonal malignancy of the sympathetic nervous system ²⁶
CXCR4	120	Autologous hematopoietic stem-cell transplantation	Neoplasms	0.25 million ¹	0.11 million ¹	Lymphomas-related rejection can affect any organ in the body ²⁷
CDK4/6	122	Breast cancer	Neoplasms	21.36 million ⁴	0.50 million ²⁸	Cell metastasis of this type of cancer is the major cause of death ²⁹
CD19	126	B-cell precursor acute lymphoblastic leukemia	Neoplasms	0.44 million ¹	0.30 million ¹	One of the most commonly encountered pediatric malignancies ³⁰
IL-6	128	Multicentric Castleman disease	Neoplasms	In US, ~0.006 million ³¹	N.A.	Many serious complications including lymphoma could lead to death ³²
PARP	131	Ovarian cancer	Neoplasms	0.79 million ⁶	0.12 million ⁶	Cell metastasis of this type of cancer is the major cause of death ³³
Jak2	>147	Myelofibrosis	Neoplasms	In US, 0.016 million ³⁴	In US, 0.00001 million ⁸	Increasing the susceptibility to infection, such as pneumonia ³⁵
CYP17A1	343	Prostate cancer	Neoplasms	5.70 million ⁶	0.50 million ⁶	Leading to metastatic prostate cancer and bone pain; Compressing the spinal cord ³⁶
CPS1	37	Hyperammonaemia	Metabolic disorders	In US, 0.16 million ³⁷	N.D.D. ³⁸	Generally not considered as a life-threatening disease ³⁸
TPP1	43	Batten disease	Metabolic disorders	In EU, 0.026 million ³⁹	0.026 million ³⁹	Fatal disease which inevitably results in premature death ³⁹

Beta-G1	49	Sly syndrome	Metabolic disorders	In JP, 0.00001 million ⁴⁰	N.A.	Many serious complications including cardiac failure, post-traumatic organ failure, <i>etc.</i> ⁴¹
PAH	54	Hyperphenylalaninaemia	Metabolic disorders	In IR, 0.015 million ⁴²	N.D.D. ⁴³	Generally not considered as a life-threatening disease ⁴³
Lysosomal lipase	55	Lysosomal acid lipase deficiency	Metabolic disorders	0.10 million ⁴⁴	N.A.	Leading to serious problems such as heart attack, stroke and liver failure ⁴⁵
Arylsulfatase B	56	Mucopolysaccharidosis VI	Metabolic disorders	In JP, 0.00003 million ⁴⁰	N.A.	Many serious complications including cardiac failure, post-traumatic organ failure, <i>etc.</i> ⁴¹
GALNS	58	Mucopolysaccharidosis IVA	Metabolic disorders	In JP, 0.00005 million ⁴⁰	N.A.	Many serious complications including cardiac failure, post-traumatic organ failure, <i>etc.</i> ⁴¹
PCSK9	68	Familial hypercholesterolaemia	Metabolic disorders	10.00 million ⁴⁶	0.20 million ⁴⁶	Common inherited lipid disorder that greatly increases the risk for cardiovascular disease ⁴⁶
GLP-1 receptor	73	Type 2 diabetes	Metabolic disorders	360.00 million ⁴⁷	1.50 million ⁴⁷	Resulting in ischemic heart disease, stroke and kidney failure, which are fatal ⁴⁷
CFTR	74	Cystic fibrosis	Metabolic disorders	In IE, 0.004 million ⁴⁸	In US, 0.0005 million ⁸	Many serious complications including liver disease could lead to death ⁴⁹
RAMP	76	Type 1/2 diabetes	Metabolic disorders	435.33 million ⁶	In US, 0.02 million ⁸	Resulting in ischemic heart disease, stroke and kidney failure, which are fatal ⁵⁰
Phosphatase AP-TNAP	85	Hypophosphatasia	Metabolic disorders	In US, ~0.01 million ⁵¹	N.A.	Ranging from extreme life-threatening forms to premature exfoliation of their teeth ⁵²
DPP4	90	Type 2 diabetes	Metabolic disorders	360.00 million ⁴⁷	1.50 million ⁴⁷	Resulting in ischemic heart disease, stroke and kidney failure, which are fatal ⁴⁷
APOB mRNA	107	Familial hypercholesterolaemia	Metabolic disorders	10.00 million ⁴⁶	0.20 million ⁴⁶	Common inherited lipid disorder that greatly increases the risk for cardiovascular disease ⁴⁶
CaSR	109	Secondary hyperparathyroidism	Metabolic disorders	In US, 15.60 million ⁵³	In JP, 0.008 million ⁵⁴	Increasing the risk for the cardiovascular mortality ⁵⁴
SC5A2	113	Type 2 diabetes	Metabolic disorders	360.00 million ⁴⁷	1.50 million ⁴⁷	Resulting in ischemic heart disease, stroke and kidney failure, which are fatal ⁴⁷
Iduronate 2-sulfatase	117	Mucopolysaccharidosis II	Metabolic disorders	0.002 million ⁵⁵	In US, 0.00002 million ⁸	All patients suffering from this disease have reduced life expectancy ⁵⁶

Leptin receptor	156	Generalized lipodystrophy	Metabolic disorders	0.0001 million ⁵⁷	N.D.D. ⁵⁸	Rare disorder characterized by loss of adipose tissue and low leptin levels ⁵⁸
Transfer protein MTP	175	Familial hypercholesterolaemia	Metabolic disorders	10.00 million ⁴⁶	0.20 million ⁴⁶	Common inherited lipid disorder that greatly increases the risk for cardiovascular disease ⁴⁶
MT1/2 receptor	56	Insomnia	Nervous system diseases	1,480.00 million ⁵⁹	N.D.D. ⁶⁰	Generally not considered as a life-threatening disease ⁶⁰
VLA-4 alpha	86	Multiple sclerosis	Nervous system diseases	2.30 million ⁶¹	In US, 0.003 million ⁸	Neurological symptom with autonomic, visual, motor and sensory problems ⁶²
Orexin receptor	99	Insomnia	Nervous system diseases	1,480.00 million ⁵⁹	N.D.D. ⁶⁰	Generally not considered as a life-threatening disease ⁶⁰
Dystrophin pre-mRNA	124	Duchenne muscular dystrophy	Nervous system diseases	0.19 million ⁶³	In US, <0.0007 million ⁸	Common type of muscular dystrophy with average life expectancy of 26 ⁶³
S1PR1	>127	Multiple sclerosis	Nervous system diseases	2.30 million ⁶¹	In US, 0.003 million ⁸	Neurological symptom with autonomic, visual, motor and sensory problems ⁶²
SMN2 pre-mRNA	132	Spinal muscular atrophy	Nervous system diseases	In US, <0.02 million/year ⁶⁴	In US, 0.0055 million ⁸	The leading genetic cause of the infant mortality ⁶⁵
AMPA receptor	190	Epilepsy	Nervous system diseases	45.93 million ⁶	In US, 0.0008 million ⁸	Mortality is related to status epilepticus and sudden unexpected death in epilepsy ⁶⁶
CLCN2	93	Chronic idiopathic constipation	Digestive system diseases	In US, 45.60 million ⁶⁷	N.D.D. ⁶⁸	Generally not considered as a life-threatening disease ⁶⁸
GC-C	97	Irritable bowel syndrome with constipation	Digestive system diseases	In US, 45.90 million ⁶⁷	N.D.D. ⁶⁸	Generally not considered as a life-threatening disease ⁶⁸
TPH	113	Carcinoid syndrome diarrhea	Digestive system diseases	0.50 million ^{65,69}	In US, 0.00004 million ⁸	The substances secreted by carcinoid cells upon cardiovascular systems can be fatal ⁷⁰
Channel ANO1	114	HIV-associated diarrhea	Digestive system diseases	33.21 million ⁷¹	0.94 million ⁷²	Diarrhea is a side effect of drugs used to treat HIV, or it is accompany HIV infection ⁷³
FXR	124	Primary biliary cholangitis	Digestive system diseases	In CA, 1.11 million ⁷⁴	In US, 0.0005 million ⁸	Increasing the risk of hepatocellular carcinoma compared to general population ⁷⁵
GLP-2	128	Short bowel syndrome	Digestive system diseases	0.03 million ⁷⁶	N.D.D. ⁷⁶	Generally not considered as a life-threatening disease ⁷⁶

BLyS ligand	109	Systemic lupus erythematosus	Bone diseases	In US, 0.32 million ⁷⁷	In US, 0.001 million ⁷⁸	Many complications including organ failure and infection could lead to death ⁷⁹
RANKL	115	Osteoporosis	Bone diseases	In EU, 27.60 million ⁸⁰	In EU, 0.003 ⁸⁰	Resulting in increased risk of the fragility fractures ⁸⁰
IL-6R	119	Rheumatoid arthritis	Bone diseases	24.49 million ⁴	0.049 million ⁸¹	Primarily affecting joints and other organs in more than 15-25% of patients ⁸²
Jak3	120	Rheumatoid arthritis	Bone diseases	24.49 million ⁴	0.049 million ⁸¹	Primarily affecting joints and other organs in more than 15-25% of patients ⁸³⁻⁸⁵
CD80/CD86	121	Rheumatoid arthritis	Bone diseases	24.49 million ⁴	0.049 million ⁸¹	Primarily affecting joints and other organs in more than 15-25% of patients ⁸²
Renin	74	Hypertension	Circulatory system diseases	972.00 million ⁸⁶	9.40 million ⁸⁷	A major risk factor for coronary artery disease, stroke, heart failure ⁸⁸
sGC	99	Chronic thromboembolic pulmonary hypertension	Circulatory system diseases	In FR, 0.001 million ⁸⁹	In US, 0.0002 million ⁹⁰	Resulting in right heart failure and thus leading to death ⁹¹
PAR-1	123	Myocardial infarction	Circulatory system diseases	7.00 million ⁹²	In IN, 1.46 million ⁹³	Resulting in cardiogenic shock and can lead to sudden death ⁹⁴
HCN channel	146	Heart failure	Circulatory system diseases	63.60 million ⁶	7.78 million ⁶	Life-threatening disease that could results in ischemic stroke ⁹⁵
IL-12/23 p40	88	Plaque psoriasis	Skin diseases	65.13 million ⁶	In US, <0.00003 million ⁸	Can be fatal as the extreme inflammation and exfoliation disrupt the body's ability ⁹⁶
IL-1B	95	Muckle-Wells syndrome	Skin diseases	0.037 million ⁹⁷	N.A.	Resulting in proteinuria and leading to renal failure ⁹⁷
IL-17A	109	Plaque psoriasis	Skin diseases	65.13 million ⁶	In US, <0.00003 million ⁸	Generally not considered as a life-threatening disease ⁹⁸
IL-4R alpha	164	Eczema	Skin diseases	85.59 million ⁴	N.D.D. ⁹⁹	Very stressful and frustrating condition, and can make daily life uncomfortable ⁹⁹
Complement C5	87	Paroxysmal nocturnal hemoglobinuria	Hematopathy	In UK, 0.00006 million ¹⁰⁰	In UK, 0.00001 million ¹⁰⁰	Resulting in hemolytic anemia and aplastic anemia, which are fatal ¹⁰¹
TPO-R	152~163	Idiopathic thrombocytopenic purpura	Hematopathy	In US, 0.002 million ¹⁰²	In US, 0.0003 million ⁸	Generally not considered as a life-threatening disease ¹⁰²

Plasma kallikrein	102	Hereditary angioedema	Immunodeficiency	In US, 0.006 million ¹⁰³	In US, 0.00005 million ¹⁰³	Potentially life-threatening which primarily from laryngeal edema and asphyxiation ¹⁰⁴
BDKRB2	132	Hereditary angioedema	Immunodeficiency	In US, 0.006 million ¹⁰³	In US, 0.00005 million ¹⁰³	Potentially life-threatening which primarily from laryngeal edema and asphyxiation ¹⁰⁴
LFA-1	83	Dry eye disease	Ophthalmopathy	In US, <4.00 million ¹⁰⁵	N.D.D. ⁶⁰	Generally not considered as a life-threatening disease ¹⁰⁶
ROCK	186	Glaucoma	Ophthalmopathy	60.50 million ¹⁰⁷	N.D.D. ¹⁰⁸	People with primary open angle glaucoma do not have increased mortality rates ¹⁰⁸
PDE-4	138	Chronic obstructive pulmonary disease	Respiratory system diseases	261.60 million ⁶	In US, 0.1 million ⁸	Resulting in ischemic heart disease, high blood pressure, diabetes mellitus, <i>etc.</i> ¹⁰⁹
IL-5	167	Asthma	Respiratory system diseases	241.69 million ²¹	In US, 0.004 million ⁸	Chronic respiratory disease that causes substantial morbidity and mortality ¹¹⁰
IGF1 receptor	115	Failure to thrive in children	Growth failures	In US, 5~10% children ¹¹¹	N.D.D. ¹¹²	Generally not considered as a life-threatening disease ¹¹²
CCR5	91	HIV infection	Infectious diseases	36.90 million ¹¹³	0.94 million ¹¹³	Interfering with immune system and increasing the risk of infections ¹¹⁴
ADRB3	117	Overactive bladder	Urologic diseases	1221.00 million ¹¹⁵	N.D.D. ¹¹⁶	Generally not considered as a life-threatening disease ¹¹⁶

References for Supplementary Table S7

- 1 F. Bray; J. Ferlay; I. Soerjomataram; R. L. Siegel; L. A. Torre; A. Jemal. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018, 68(6): 394-424
- 2 R. L. Siegel; K. D. Miller; A. Jemal. Cancer statistics, 2015. *CA Cancer J Clin.* 2015, 65(1): 5-29
- 3 I. De Kouchkovsky; M. Abdul-Hay. Acute myeloid leukemia: a comprehensive review and 2016 update. *Blood Cancer J.* 2016, 6(7): e441
- 4 G. B. D. Disease; I. Injury; C. Prevalence. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016, 388(10053): 1545-602
- 5 I. J. Fidler. Melanoma Metastasis. *Cancer Control.* 1995, 2(5): 398-404
- 6 G. B. D. Disease; I. Injury; C. Prevalence. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries

- for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017, 390(10100): 1211-59
- 7 A. P. Skarbnik; A. H. Goy. Mantle cell lymphoma: state of the art. *Clin Adv Hematol Oncol*. 2015, 13(1): 44-55
 - 8 U. S. CDC. Deaths from each cause, by 5-year age groups, race, and sex: united states, 2001. National Center for Health Statistics. 2001, 2001(2001): 1
 - 9 E. Doni; G. Carli; A. Di Rocco; M. Sassone; S. Gandolfi; C. Patti; E. Falisi; C. Salemi; C. Visco. Autoimmune haemolytic anaemia in mantle cell lymphoma : an insidious complication associated with leukemic disease. *Hematol Oncol*. 2017, 35(1): 135-37
 - 10 M. Dreyling; W. Jurczak; M. Jerkeman; R. S. Silva; C. Rusconi; M. Trneny; F. Offner; D. Caballero; C. Joao; M. Witzens-Harig; G. Hess; I. Bence-Bruckler; S. G. Cho; J. Bothos; J. D. Goldberg; C. Enny; S. Traina; S. Balasubramanian; N. Bandyopadhyay; S. Sun; J. Vermeulen; A. Rizo; S. Rule. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet*. 2016, 387(10020): 770-8
 - 11 B. O. Cakir; P. Adamson; C. Cingi. Epidemiology and economic burden of nonmelanoma skin cancer. *Facial Plast Surg Clin North Am*. 2012, 20(4): 419-22
 - 12 C. S. Dela Cruz; L. T. Tanoue; R. A. Matthay. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med*. 2011, 32(4): 605-44
 - 13 J. R. Molina; P. Yang; S. D. Cassivi; S. E. Schild; A. A. Adjei. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008, 83(5): 584-94
 - 14 R. L. Siegel; K. D. Miller; A. Jemal. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017, 67(1): 7-30
 - 15 D. Cunningham; W. Atkin; H. J. Lenz; H. T. Lynch; B. Minsky; B. Nordlinger; N. Starling. Colorectal cancer. *Lancet*. 2010, 375(9719): 1030-47
 - 16 C. Karimkhani; A. C. Green; T. Nijsten; M. A. Weinstock; R. P. Dellavalle; M. Naghavi; C. Fitzmaurice. The global burden of melanoma: results from the Global Burden of Disease Study 2015. *Br J Dermatol*. 2017, 177(1): 134-40
 - 17 B. Ljungberg; S. C. Campbell; H. Y. Choi; D. Jacqmin; J. E. Lee; S. Weikert; L. A. Kiemeny. The epidemiology of renal cell carcinoma. *Eur Urol*. 2011, 60(4): 615-21
 - 18 M. Stamatakis; P. Paraskeva; C. Stefanaki; P. Katsaronis; A. Lazaris; K. Safioleas; K. Kontzoglou. Medullary thyroid carcinoma: The third most common thyroid cancer reviewed. *Oncol Lett*. 2011, 2(1): 49-53
 - 19 P. Choksi; M. Papaleontiou; C. Guo; F. Worden; M. Banerjee; M. Haymart. Skeletal Complications and Mortality in Thyroid Cancer: A Population-Based Study. *J Clin Endocrinol Metab*. 2017, 102(4): 1254-60
 - 20 R. Cohen; B. Buchsenschutz; P. Estrade; P. Gardet; E. Modigliani. Causes of death in patients with medullary cancer of the thyroid. *GETC. Groupe d'Etude des Tumeurs a Calcitonine. Presse Med*. 1996, 25(37): 1819-22
 - 21 C. Global Burden of Disease Study. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases

- and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015, 386(9995): 743-800
- 22 J. Luo; J. J. Gagne; J. Landon; J. Avorn; A. S. Kesselheim. Comparative effectiveness and safety of thalidomide and lenalidomide in patients with multiple myeloma in the United States of America: A population-based cohort study. *Eur J Cancer*. 2017, 70(70): 22-33
- 23 F. M. Ghazawi; E. Netchiporouk; E. Rahme; M. Tsang; L. Moreau; S. Glassman; N. Provost; M. Gilbert; S. E. Jean; K. Pehr; D. Sasseville; I. V. Litvinov. Comprehensive analysis of cutaneous T-cell lymphoma (CTCL) incidence and mortality in Canada reveals changing trends and geographic clustering for this malignancy. *Cancer*. 2017, 123(18): 3550-67
- 24 L. Vakeva; T. Lipsanen; H. Sintonen; A. Ranki. Morbidity and Causes of Death in Patients with Cutaneous T-cell Lymphoma in Finland. *Acta Derm Venereol*. 2017, 97(6): 735-38
- 25 A. M. Tsimberidou; M. J. Keating. Richter syndrome: biology, incidence, and therapeutic strategies. *Cancer*. 2005, 103(2): 216-28
- 26 E. Ward; C. DeSantis; A. Robbins; B. Kohler; A. Jemal. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014, 64(2): 83-103
- 27 J. O. Armitage; R. D. Gascoyne; M. A. Lunning; F. Cavalli. Non-Hodgkin lymphoma. *Lancet*. 2017, 390(10091): 298-310
- 28 C. International Agency for Research on Cancer. World Cancer Report 2014. World Health Organization. 2014, 2014(2014): 1
- 29 M. Lacroix. Significance, detection and markers of disseminated breast cancer cells. *Endocr Relat Cancer*. 2006, 13(4): 1033-67
- 30 M. C. O'Leary; X. Lu; Y. Huang; X. Lin; I. Mahmood; D. Przepiorka; D. Gavin; S. Lee; K. Liu; B. George; W. Bryan; M. R. Theoret; R. Pazdur. FDA Approval Summary: Tisagenlecleucel for Treatment of Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia. *Clin Cancer Res*. 2018, 2018(2018): 1
- 31 N. Munshi; M. Mehra; H. van de Velde; A. Desai; R. Potluri; J. Vermeulen. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. *Leuk Lymphoma*. 2015, 56(5): 1252-60
- 32 C. Casper. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *Br J Haematol*. 2005, 129(1): 3-17
- 33 M. Yin; X. Li; S. Tan; H. J. Zhou; W. Ji; S. Bellone; X. Xu; H. Zhang; A. D. Santin; G. Lou; W. Min. Tumor-associated macrophages drive spheroid formation during early transcoelomic metastasis of ovarian cancer. *J Clin Invest*. 2016, 126(11): 4157-73
- 34 J. Mehta; H. Wang; S. U. Iqbal; R. Mesa. Epidemiology of myeloproliferative neoplasms in the United States. *Leuk Lymphoma*. 2014, 55(3): 595-600
- 35 A. Tefferi. Primary myelofibrosis: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2014, 89(9): 915-25
- 36 I. W. van der Crujisen-Koeter; A. N. Vis; M. J. Roobol; M. F. Wildhagen; H. J. de Koning; T. H. van der Kwast; F. H. Schroder. Comparison of screen detected and clinically diagnosed prostate cancer in the European randomized study of screening for prostate cancer, section rotterdam. *J Urol*. 2005, 174(1): 121-5
- 37 C. Right Diagnosis from Healthgrades. Prevalence and Incidence of Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

- (https://www.rightdiagnosis.com/h/hyperornithinemia_hyperammonemia_homocitrullinuria_syndrome/prevalence.htm). Health Grades Inc. 2015, 2015(2015): 1
- 38 J. Haberle; A. Chakrapani; N. Ah Mew; N. Longo. Hyperammonaemia in classic organic acidaemias: a review of the literature and two case histories. *Orphanet J Rare Dis.* 2018, 13(1): 219
- 39 K. Wager; A. A. Zdebik; S. Fu; J. D. Cooper; R. J. Harvey; C. Russell. Neurodegeneration and Epilepsy in a Zebrafish Model of CLN3 Disease (Batten Disease). *PLoS One.* 2016, 11(6): e0157365
- 40 S. A. Khan; H. Peracha; D. Ballhausen; A. Wiesbauer; M. Rohrbach; M. Gautschi; R. W. Mason; R. Giugliani; Y. Suzuki; K. E. Orii; T. Orii; S. Tomatsu. Epidemiology of mucopolysaccharidoses. *Mol Genet Metab.* 2017, 121(3): 227-40
- 41 C. Lavery; C. Hendriksz. Mortality in patients with morquio syndrome a. *JIMD Rep.* 2015, 15(15): 59-66
- 42 M. Ordooei; M. Jafarizadeh; M. Mirzaei; H. Ashoori; A. Zare; H. Shojaeifar. Prevalence of neonatal hyperphenylalaninemia in yazd province, iran. *Iran J Med Sci.* 2015, 40(3): 292-3
- 43 P. Bravo; E. Raimann; J. F. Cabello; C. Arias; P. Peredo; G. Castro; V. Hamilton; K. Campo; V. Cornejo. What should the paediatrician know about hyperphenylalaninaemia? *Rev Chil Pediatr.* 2015, 86(3): 214-8
- 44 Z. Reiner; O. Guardamagna; D. Nair; H. Soran; K. Hovingh; S. Bertolini; S. Jones; M. Coric; S. Calandra; J. Hamilton; T. Eagleton; E. Ros. Lysosomal acid lipase deficiency--an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis.* 2014, 235(1): 21-30
- 45 J. Thompson; R. Solomon; M. Pellegrino; K. Sakai; M. Lewin; M. Feild; M. Castrovinci; L. Sacramone; D. Gillespie. A noise-free molecular hybridization procedure for measuring RNA in cell lysates. *Anal Biochem.* 1989, 181(2): 371-8
- 46 T. B. Repas; J. R. Tanner. Preventing early cardiovascular death in patients with familial hypercholesterolemia. *J Am Osteopath Assoc.* 2014, 114(2): 99-108
- 47 P. Pletcher. Type 2 Diabetes Statistics and Facts (<https://www.healthline.com/health/type-2-diabetes/statistics#5>). Healthline Media. 2017, 2017(2017): 1
- 48 P. Farrell; S. Joffe; L. Foley; G. J. Canny; P. Mayne; M. Rosenberg. Diagnosis of cystic fibrosis in the Republic of Ireland: epidemiology and costs. *Ir Med J.* 2007, 100(8): 557-60
- 49 S. A. Hoda; E. Cheng. Robbins Basic Pathology. *Am J Clin Pathol.* 2017, 148(6): 557-57
- 50 C. M. Ripsin; H. Kang; R. J. Urban. Management of blood glucose in type 2 diabetes mellitus. *Am Fam Physician.* 2009, 79(1): 29-36
- 51 M. P. Whyte. Hypophosphatasia: An overview For 2017. *Bone.* 2017, 102(102): 15-25
- 52 A. Linglart; M. Biosse-Duplan. Hypophosphatasia. *Curr Osteoporos Rep.* 2016, 14(3): 95-105
- 53 C. BMJ Best Practice. Secondary hyperparathyroidism (<https://bestpractice.bmj.com/topics/en-us/1107/epidemiology>). BMJ Publishing Group. 2018,

2018(2018): 1

- 54 H. Komaba; M. Taniguchi; A. Wada; K. Iseki; Y. Tsubakihara; M. Fukagawa. Parathyroidectomy and survival among Japanese hemodialysis patients with secondary hyperparathyroidism. *Kidney Int.* 2015, 88(2): 350-9
- 55 L. A. Bradley; H. R. M. Haddow; G. E. Palomaki. Treatment of mucopolysaccharidosis type II (Hunter syndrome): results from a systematic evidence review. *Genet Med.* 2017, 19(11): 1187-201
- 56 D. A. Whiteman; A. Kimura. Development of idursulfase therapy for mucopolysaccharidosis type II (Hunter syndrome): the past, the present and the future. *Drug Des Devel Ther.* 2017, 11(11): 2467-80
- 57 A. Garg. Acquired and inherited lipodystrophies. *N Engl J Med.* 2004, 350(12): 1220-34
- 58 B. C. Lupsa; V. Sachdev; A. O. Lungu; D. R. Rosing; P. Gorden. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. *Medicine (Baltimore).* 2010, 89(4): 245-50
- 59 T. Roth. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med.* 2007, 3(5): S7-10
- 60 D. J. Buysse. Insomnia. *JAMA.* 2013, 309(7): 706-16
- 61 M. Bishop; P. D. Rumrill. Multiple sclerosis: Etiology, symptoms, incidence and prevalence, and implications for community living and employment. *Work.* 2015, 52(4): 725-34
- 62 A. Compston; A. Coles. Multiple sclerosis. *Lancet.* 2008, 372(9648): 1502-17
- 63 P. A. Romitti; Y. Zhu; S. Puzhankara; K. A. James; S. K. Nabukera; G. K. Zamba; E. Ciafaloni; C. Cunniff; C. M. Druschel; K. D. Mathews; D. J. Matthews; F. J. Meaney; J. G. Andrews; K. M. Conway; D. J. Fox; N. Street; M. M. Adams; J. Bolen. Prevalence of Duchenne and Becker muscular dystrophies in the United States. *Pediatrics.* 2015, 135(3): 513-21
- 64 A. D'Amico; E. Mercuri; F. D. Tiziano; E. Bertini. Spinal muscular atrophy. *Orphanet J Rare Dis.* 2011, 6(6): 71
- 65 E. W. Ottesen. ISS-N1 makes the First FDA-approved Drug for Spinal Muscular Atrophy. *Transl Neurosci.* 2017, 8(8): 1-6
- 66 N. Hitiris; R. Mohanraj; J. Norrie; M. J. Brodie. Mortality in epilepsy. *Epilepsy Behav.* 2007, 10(3): 363-76
- 67 A. P. Hungin; L. Chang; G. R. Locke; E. H. Dennis; V. Barghout. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharmacol Ther.* 2005, 21(11): 1365-75
- 68 A. D. Nelson; M. Camilleri; S. Chirapongsathorn; P. Vijayvargiya; N. Valentin; A. Shin; P. J. Erwin; Z. Wang; M. H. Murad. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. *Gut.* 2017, 66(9): 1611-22
- 69 K. Oberg; D. Castellano. Current knowledge on diagnosis and staging of neuroendocrine tumors. *Cancer Metastasis Rev.* 2011, 30(S1): 3-7

- 70 S. F. Dierdorf. Carcinoid tumor and carcinoid syndrome. *Curr Opin Anaesthesiol*. 2003, 16(3): 343-7
- 71 F. Bhaijee; C. Subramony; S. J. Tang; D. J. Pepper. Human immunodeficiency virus-associated gastrointestinal disease: common endoscopic biopsy diagnoses. *Patholog Res Int*. 2011, 2011(2011): 247923
- 72 J. Levi; A. Pozniak; K. Heath; A. Hill. The impact of HIV prevalence, conflict, corruption, and GDP/capita on treatment cascades: data from 137 countries. *J Virus Erad*. 2018, 4(2): 80-90
- 73 R. C. Pollok. Viruses causing diarrhoea in AIDS. *Novartis Found Symp*. 2001, 238(238): 276-83
- 74 K. Boonstra; U. Beuers; C. Y. Ponsioen. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol*. 2012, 56(5): 1181-8
- 75 D. E. Jones; J. V. Metcalf; J. D. Collier; M. F. Bassendine; O. F. James. Hepatocellular carcinoma in primary biliary cirrhosis and its impact on outcomes. *Hepatology*. 1997, 26(5): 1138-42
- 76 P. Seetharam; G. Rodrigues. Short bowel syndrome: a review of management options. *Saudi J Gastroenterol*. 2011, 17(4): 229-35
- 77 C. G. Helmick; D. T. Felson; R. C. Lawrence; S. Gabriel; R. Hirsch; C. K. Kwok; M. H. Liang; H. M. Kremers; M. D. Mayes; P. A. Merkel; S. R. Pillemer; J. D. Reveille; J. H. Stone. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008, 58(1): 15-25
- 78 C. A. Umscheid; R. K. Agarwal; P. J. Brennan. Updating the guideline development methodology of the Healthcare Infection Control Practices Advisory Committee (HICPAC). *Am J Infect Control*. 2010, 38(4): 264-73
- 79 N. Author. From the Centers for Disease Control and Prevention. Trends in deaths from systemic lupus erythematosus--United States, 1979-1998. *JAMA*. 2002, 287(20): 2649-50
- 80 E. Hernlund; A. Svedbom; M. Ivergard; J. Compston; C. Cooper; J. Stenmark; E. V. McCloskey; B. Jonsson; J. A. Kanis. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2013, 8(8): 136
- 81 R. Lozano; M. Naghavi; K. Foreman; S. Lim; K. Shibuya; V. Aboyans; J. Abraham; T. Adair; R. Aggarwal; S. Y. Ahn; M. Alvarado; H. R. Anderson; L. M. Anderson; K. G. Andrews; C. Atkinson; L. M. Baddour; S. Barker-Collo; D. H. Bartels; M. L. Bell; E. J. Benjamin; D. Bennett; K. Bhalla; B. Bikbov; A. Bin Abdulhak; G. Birbeck; F. Blyth; I. Bolliger; S. Boufous; C. Bucello; M. Burch; P. Burney; J. Carapetis; H. Chen; D. Chou; S. S. Chugh; L. E. Coffeng; S. D. Colan; S. Colquhoun; K. E. Colson; J. Condon; M. D. Connor; L. T. Cooper; M. Corriere; M. Cortinovis; K. C. de Vaccaro; W. Couser; B. C. Cowie; M. H. Criqui; M. Cross; K. C. Dabhadkar; N. Dahodwala; D. De Leo; L. Degenhardt; A. Delossantos; J. Denenberg; D. C. Des Jarlais; S. D. Dharmaratne; E. R. Dorsey; T. Driscoll; H. Duber; B. Ebel; P. J. Erwin; P. Espindola; M. Ezzati; V. Feigin; A. D. Flaxman; M. H. Forouzanfar; F. G. Fowkes; R. Franklin; M. Fransen; M. K.

- Freeman; S. E. Gabriel; E. Gakidou; F. Gaspari; R. F. Gillum; D. Gonzalez-Medina; Y. A. Halasa; D. Haring; J. E. Harrison; R. Havmoeller; R. J. Hay; B. Hoen; P. J. Hotez; D. Hoy; K. H. Jacobsen; S. L. James; R. Jasrasaria; S. Jayaraman; N. Johns; G. Karthikeyan; N. Kassebaum; A. Keren; J. P. Khoo; L. M. Knowlton; O. Kobusingye; A. Koranteng; R. Krishnamurthi; M. Lipnick; S. E. Lipshultz; S. L. Ohno; J. Mabweijano; M. F. MacIntyre; L. Mallinger; L. March; G. B. Marks; R. Marks; A. Matsumori; R. Matzopoulos; B. M. Mayosi; J. H. McAnulty; M. M. McDermott; J. McGrath; G. A. Mensah; T. R. Merriman; C. Michaud; M. Miller; T. R. Miller; C. Mock; A. O. Mocumbi; A. A. Mokdad; A. Moran; K. Mulholland; M. N. Nair; L. Naldi; K. M. Narayan; K. Nasser; P. Norman; M. O'Donnell; S. B. Omer; K. Ortblad; R. Osborne; D. Ozgediz; B. Pahari; J. D. Pandian; A. P. Rivero; R. P. Padilla; F. Perez-Ruiz; N. Perico; D. Phillips; K. Pierce; C. A. Pope, 3rd; E. Porrini; F. Pourmalek; M. Raju; D. Ranganathan; J. T. Rehm; D. B. Rein; G. Remuzzi; F. P. Rivara; T. Roberts; F. R. De Leon; L. C. Rosenfeld; L. Rushton; R. L. Sacco; J. A. Salomon; U. Sampson; E. Sanman; D. C. Schwebel; M. Segui-Gomez; D. S. Shepard; D. Singh; J. Singleton; K. Sliwa; E. Smith; A. Steer; J. A. Taylor; B. Thomas; I. M. Tleyjeh; J. A. Towbin; T. Truelsen; E. A. Undurraga; N. Venketasubramanian; L. Vijayakumar; T. Vos; G. R. Wagner; M. Wang; W. Wang; K. Watt; M. A. Weinstock; R. Weintraub; J. D. Wilkinson; A. D. Woolf; S. Wulf; P. H. Yeh; P. Yip; A. Zabetian; Z. J. Zheng; A. D. Lopez; C. J. Murray; M. A. AlMazroa; Z. A. Memish. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012, 380(9859): 2095-128
- 82 K. G. Saag; G. G. Teng; N. M. Patkar; J. Anuntiyo; C. Finney; J. R. Curtis; H. E. Paulus; A. Mudano; M. Pisu; M. Elkins-Melton; R. Outman; J. J. Allison; M. Suarez Almazor; S. L. Bridges, Jr.; W. W. Chatham; M. Hochberg; C. MacLean; T. Mikuls; L. W. Moreland; J. O'Dell; A. M. Turkiewicz; D. E. Furst. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008, 59(6): 762-84
- 83 E. Baecklund; A. Iliadou; J. Askling; A. Ekbom; C. Backlin; F. Granath; A. I. Catrina; R. Rosenquist; N. Feltelius; C. Sundstrom; L. Klareskog. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum*. 2006, 54(3): 692-701
- 84 E. J. Kim; H. R. Collard; T. E. King. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. *Chest*. 2009, 136(5): 1397-405
- 85 J. A. Avina-Zubieta; H. K. Choi; M. Sadatsafavi; M. Eteminan; J. M. Esdaile; D. Lacaille. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum*. 2008, 59(12): 1690-7
- 86 P. M. Kearney; M. Whelton; K. Reynolds; P. Muntner; P. K. Whelton; J. He. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005, 365(9455): 217-23
- 87 N. R. Campbell; D. T. Lackland; L. Lisheng; M. L. Niebylski; P. M. Nilsson; X. H. Zhang. Using the Global Burden of Disease study to assist development of nation-specific fact sheets to promote prevention and control of hypertension and reduction in dietary salt: a resource from the World Hypertension League. *J Clin Hypertens (Greenwich)*. 2015, 17(3): 165-7

- 88 D. T. Lackland; M. A. Weber. Global burden of cardiovascular disease and stroke: hypertension at the core. *Can J Cardiol*. 2015, 31(5): 569-71
- 89 X. Jiang; Z. C. Jing. Epidemiology of pulmonary arterial hypertension. *Curr Hypertens Rep*. 2013, 15(6): 638-49
- 90 J. O. Ronald. Idiopathic Pulmonary Arterial Hypertension (<https://emedicine.medscape.com/article/301450-overview#a6>). WebMD LLC. 2018, 2018(2018): 1
- 91 D. B. Taichman; J. Mandel. Epidemiology of pulmonary arterial hypertension. *Clin Chest Med*. 2013, 34(4): 619-37
- 92 H. D. White; D. P. Chew. Acute myocardial infarction. *Lancet*. 2008, 372(9638): 570-84
- 93 R. Gupta; P. Joshi; V. Mohan; K. S. Reddy; S. Yusuf. Epidemiology and causation of coronary heart disease and stroke in India. *Heart*. 2008, 94(1): 16-26
- 94 F. Van de Werf; J. Bax; A. Betriu; C. Blomstrom-Lundqvist; F. Crea; V. Falk; G. Filippatos; K. Fox; K. Huber; A. Kastrati; A. Rosengren; P. G. Steg; M. Tubaro; F. Verheugt; F. Weidinger; M. Weis. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2008, 29(23): 2909-45
- 95 B. J. Witt; A. S. Gami; K. V. Ballman; R. D. Brown; R. A. Meverden; S. J. Jacobsen; V. L. Roger. The incidence of ischemic stroke in chronic heart failure: a meta-analysis. *J Card Fail*. 2007, 13(6): 489-96
- 96 A. Menter; A. Gottlieb; S. R. Feldman; A. S. Van Voorhees; C. L. Leonardi; K. B. Gordon; M. Lebwohl; J. Y. Koo; C. A. Elmets; N. J. Korman; K. R. Beutner; R. Bhushan. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008, 58(5): 826-50
- 97 T. A. Tran. Muckle-Wells syndrome: clinical perspectives. *Open Access Rheumatol*. 2017, 9(9): 123-29
- 98 W. H. Boehncke; M. P. Schon. Psoriasis. *Lancet*. 2015, 386(9997): 983-94
- 99 M. Chong; L. Fonacier. Treatment of Eczema: Corticosteroids and Beyond. *Clin Rev Allergy Immunol*. 2016, 51(3): 249-62
- 100 A. Hill; P. Platts; A. Smith; S. Richards; M. Cullen; Q. Hill; E. Roman; P. Hillmen. The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire. *Haematologica*. 2007, 92(92): 25-25
- 101 C. Parker; M. Omine; S. Richards; J. Nishimura; M. Bessler; R. Ware; P. Hillmen; L. Luzzatto; N. Young; T. Kinoshita; W. Rosse; G. Socie. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005, 106(12): 3699-709
- 102 M. A. Feudjo-Tepie; N. J. Robinson; D. Bennett. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. *J Thromb Haemost*. 2008, 6(4): 711-2
- 103 S. J. Kim; J. C. Brooks; J. Sheikh; M. S. Kaplan; B. J. Goldberg. Angioedema deaths in the United States, 1979-2010. *Ann Allergy Asthma Immunol*. 2014, 113(6): 630-4

- 104 A. Nygren; P. Nordenfelt; A. Lindfors; L. Mallbris; J. Bjorkander; C. F. Wahlgren. Swedish children with hereditary angioedema report good overall health and quality of life despite symptoms. *Acta Paediatr.* 2016, 105(5): 529-34
- 105 A. M. Ervin; A. Law; A. D. Pucker. Punctal occlusion for dry eye syndrome. *Cochrane Database Syst Rev.* 2017, 6(6): CD006775
- 106 L. L. Marshall; J. M. Roach. Treatment of Dry Eye Disease. *Consult Pharm.* 2016, 31(2): 96-106
- 107 H. A. Quigley; A. T. Broman. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol.* 2006, 90(3): 262-7
- 108 M. Akbari; S. Akbari; L. R. Pasquale. The association of primary open-angle glaucoma with mortality: a meta-analysis of observational studies. *Arch Ophthalmol.* 2009, 127(2): 204-10
- 109 M. Decramer; W. Janssens; M. Miravittles. Chronic obstructive pulmonary disease. *Lancet.* 2012, 379(9823): 1341-51
- 110 J. G. Elliot; P. B. Noble; T. Mauad; T. R. Bai; M. J. Abramson; K. O. McKay; F. H. Y. Green; A. L. James. Inflammation-dependent and independent airway remodelling in asthma. *Respirology.* 2018, 23(12): 1138-45
- 111 C. Larson-Nath; V. F. Biank. Clinical Review of Failure to Thrive in Pediatric Patients. *Pediatr Ann.* 2016, 45(2): e46-9
- 112 S. Z. Cole; J. S. Lanham. Failure to thrive: an update. *Am Fam Physician.* 2011, 83(7): 829-34
- 113 C. UNAIDS. Global HIV & AIDS statistics: 2018 fact sheet (<http://www.unaids.org/en/resources/fact-sheet>). UNAIDS. 2018, 2018(2018): 1
- 114 C. WHO. HIV/AIDS (<https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids>). World Health Organization. 2018, 2018(2018): 1
- 115 R. S. Eapen; S. B. Radomski. Review of the epidemiology of overactive bladder. *Res Rep Urol.* 2016, 8(8): 71-6
- 116 E. A. Gormley; D. J. Lightner; M. Faraday; S. P. Vasavada. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. *J Urol.* 2015, 193(5): 1572-80