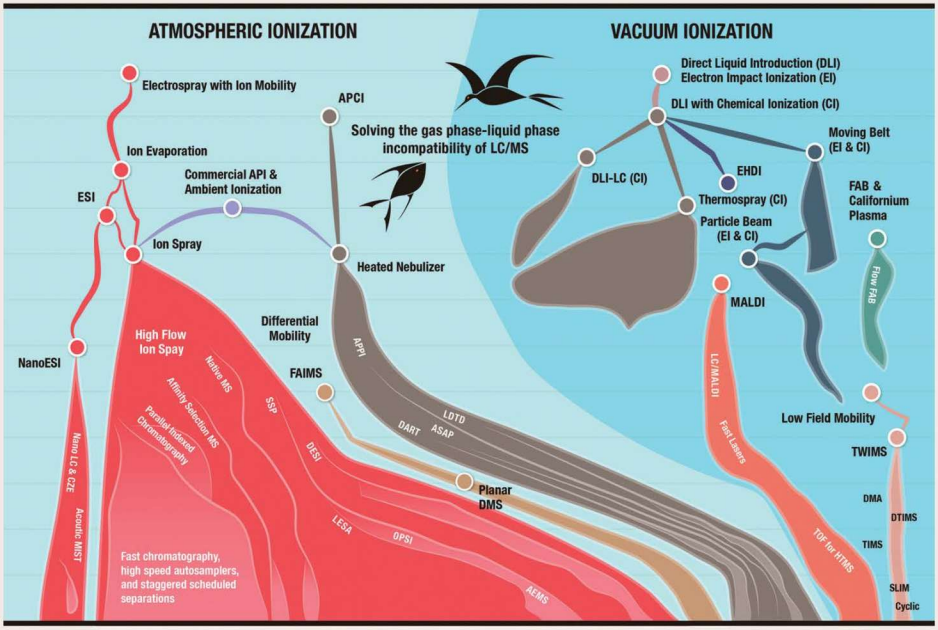
High-Throughput Mass Spectrometry in Drug Discovery

Edited By Chang Liu and Hui Zhang



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Preface

The automated and integrated high-throughput sample analysis is critical to the drug discovery process. Traditional high-throughput bioanalytical technologies such as colorimetric microplate-based readers are often constrained by linear dynamic range. In addition, they need label attachment schemes with the propensity to modify equilibrium and kinetic analysis. On the other hand, mass spectrometry (MS) based methods can achieve label-free, universal mass detection of a wide arrange of analytes with exceptional sensitivity, selectivity, and specificity. However, these techniques are limited by the speed of sample introduction. In recent decades, there have been a lot of efforts to improve the throughput of MS-based analysis for drug discovery. Along with those developments, a dedicated book would be helpful to introduce the fundamentals, experimental details, and applications of a wide variety of technologies that enabled high-throughput mass spectrometry-based screens in supporting broad drug discovery applications. The key research areas include hit discovery by label-free screen, synthetic reaction optimization, lead optimization and SAR support, ADME (absorption, distribution, metabolism, and excretion), toxicology screening, etc.

This book starts with an overview of the 40 years of efforts to improve the analytical throughput of MS-based approaches (Chapter 1). Then, technologies with high-speed sequential and parallel chromatographic sample introduction, high repetition rate lasers, ion mobility, and low-volume MS samplings were summarized.

Due to its high specificity and high sensitivity, the LC-MS technology has been widely used in various steps of the drug discovery workflow. In Part 2 (Chapter 2–3), the efforts to improve the LC-MS analytical throughput are introduced. The development of the high-speed sample introduction for LC-MS and its application on ADME and HTS applications is described in Chapter 2. Another approach for throughput improvement utilizing paralleled multiplexing LC is described in Chapter 3.

Following the conventional LC-MS-based technologies, other electrospray ionization (ESI)MS-based high-throughput platforms without chromatographic

separation are summarized in Part 3 (Chapter 4–7). Direct online solid-phase extraction (SPE) MS and its application in ADME and HTS workflows are described in Chapter 4. The utilization of the acoustic energy for non-contact transfer samples from microplates to MS for high-throughput analysis, including the acoustic mist ionization (AMI) and through the open-port interface (OPI), is summarized in Chapter 5. By skipping the chromatographic separation process, these approaches demonstrated higher analytical throughput than the conventional LC-MS approach. However, there would be the risk of potential isomeric/isobaric interference. Ion mobility spectrometry (IMS) and differential mobility spectrometry (DMS), described in Chapters 6 and 7, respectively, provide the additional dimension of the selectively, potentially solving the specificity issues of these high-throughput technologies for some drug discovery assays.

Part 4 (Chapters 8–10) summarized the MS-based high-throughput hit identification technologies based on the drug-target interaction. Affinity-selection mass spectrometry (ASMS) is a rapidly developing technology for high-throughput hit identification. The off-line and in-line ASMS approaches are introduced in Chapters 8 and 9. In addition, as a direct confirmation tool for the protein-drug binding, native MS has been rapidly developed in the past decade, which is described in Chapter 10.

Part 5 (Chapter 11–13) introduces developments of ambient ionization technologies other than the conventional ESI and their applications in the high-throughput drug discovery workflows, such as Laser Diode Thermal Desorption (LDTD, Chapter 11), Matrix-Assisted Laser Desorption/Ionization (MALDI, Chapter 12), and Desorption Electrospray Ionization (DESI, Chapter 13).

The last chapter (Chapter 14) provides perspectives for future development opportunities after a brief reflection of the realized impacts of high-throughput MS on drug discovery and the pharmaceutical industry.

We believe our goal in this book is accomplished through the extensive coverage of fundamentals, experimental details, and applications of state-of-art technologies that enable high-throughput MS-based screens in supporting drug discovery. We hope it could benefit scientists in pharmaceutical/biopharmaceutical companies and CROs who design and perform the studies and provide analytical support throughout drug discovery processes. We would like to acknowledge the commitment and contributions of all authors of the book chapters and the support and valuable discussions with colleagues and collaborators in the SCIEX research team and Pfizer Discovery Science department. In addition, we sincerely thank the editorial team at John Wiley & Sons, especially Adalfin Jayasingh, Stacey Woods, Jonathan Rose, Andreas Sendtko, and Sabeen Aziz, for their generous support of this book. Finally, we are grateful to our family members for their understanding and support for our editing work in the evening and on weekends.

Chang Liu and Hui Zhang

List of Abbreviations

%-RBA	relative binding affinity percentage
μFLC	microflow liquid chromatography
2d	two-dimensional
2-HG	2-hydroxyglutarate
3CLpro	3-chymotrypsin-like cysteine protease
4EBP1	Eukaryotic translation initiation factor 4E-binding protein 1
A	pre-exponential factor constant
ACE50	affinity competition experiment 50% inhibitory concentration
AChE	acetylcholinesterase
ADC	antibody–drug conjugate
ADE-OPI-MS	acoustic droplet ejection-open port interface-mass spectrometry
ADME	adsorption, distribution, metabolism, and excretion
AEMS	acoustic ejection mass spectrometry
AMI-MS	acoustic mist ionization-mass spectrometry
AMS	affinity mass spectrometry
ANSI	American National Standards Institute
APCI	atmospheric pressure chemical ionization
API	atmospheric pressure ionization
APIs	active pharmaceutical ingredients
APPI	atmospheric pressure photo ionization
ASAP	atmospheric solids analysis probe
ASMS	affinity selection mass spectrometry
ASMS	American society mass spectrometry
Asp	aspartic acid
ATD	arrival time distribution
ATP	adenosine triphosphate

AUC	analytical ultracentrifugation
AUC	area under the curve
BACC	bacterial acetyl coenzyme-A carboxylase
BACE	beta-site APP cleaving enzyme
BAMS	bead assisted mass spectrometry
Bcl-xL	B-cell lymphoma-extra large protein
bdf	batch data file
BE	buffer exchange
Bead-GPS	bead-based global proteomic screening
BFA	bound fraction analysis
BKM120	Buparlisib
BSA	bovine serum albumin
BTE	Boltzmann transport equation
C18	octadecyl stationary phase
C8	octyl stationary phase
CCS	collision cross section
CD	circular dichroism
CDMS	charge detection mass spectrometry
CEM	chain ejection model
cGAMP	cyclic GMP-ATP
cGAS	cyclic GMP-AMP synthase
CHCA	α-cyano-4-hyroxycinnamic acid
CHK1	checkpoint kinase
CID	collision induced dissociation
CIU	collision induced unfolding
CN	cyano stationary phase
CoV	compensation voltage
CPATI	cytosolic proteome and affinity-based target identification
CRIMP	Compression Ratio Ion Mobility Programming
CRM	charged residue model
CV	coefficient of variation
CYP	cytochrome P450
Da	Dalton, measurement unit used in mass spectrometry
DAR	drug-to-antibody ratio
DART	direct analysis in real time
DDI	drug–drug interaction
DEC	desorption enhancing coating
DEL	DNA-encoded library
DESI	desorption electrospray ionization
DHAP	2,5-dihydroxyacetophenone
DHFR	dihydrofolate reductase

diCQA	dicaffeoylquinic acid
DI-GCE/MS/MS	direct injection/on-line guard cartridge extraction/tandem mass spectrometry
DIMS	differential IMS
DIOS	desorption ionization on silicon
DLS	dynamic light scattering
DMA	differential mobility analyzer
DMS	differential mobility spectrometry
DP	declustering potential
DQ	DiscoveryQuant
DSF	differential scanning fluorimetry
DT	drift time
DTIMS	drift tube IMS
DUB	deubiquitilase
E_a	energy of activation
ebox	electronics box
E_d	bound dissociation energy
EDTA	ethylenediaminetetraacetic acid
EHDI	electrohydrodynamic ionization
EI	electron impact
EM	electron microscopy
ERK1/ERK2	extracellular signal-regulated kinase 1 and 2
ESI	electrospray ionization
ESI-MS	electrospray ionization mass spectrometry
E_λ	energy associated with the vibrational wavelength
FAB	fast atom bombardment
FAIMS	high field asymmetric waveform ion mobility spectrometry
FAK	focal adhesion kinase
FASN	fatty acid synthase
FIA	flow injection analysis
FLD	fluorescence detector
FP	fluorescence polarization
FTE	full-time equivalent
FTICR	Fourier-transform ion cyclotron resonance
FWHM	full width at half maximum
GABA	γ-aminobutyric
GC	gas chromatography
GLP	good laboratory practice
GPC	gel permeation chromatography
GST	glutathione S-transferase
GWAS	genome-wide association studies

HBSS	Hank's buffered salt solution
HCV	hepatitis C virus
HDMA	high-density micropatterned array
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HIC	hydrophobic interaction chromatography
HLM	human liver microsomes
HMW	high molecular weight species
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HT-ADME	high-throughput absorption, distribution, metabolism, excretion
HTE	high-throughput experimentation
HT-LC/MS/MS	high-throughput mass spectrometry
HT-MALDI	high-throughput matrix-assisted laser desorption/ionization
HT-MS	high-throughput mass spectrometry
HTRF	homogenous time-resolved fluorescence
HTS	high-throughput screening
IC_{50}	half maximal inhibitory concentration
ID	internal diameter
IDH1	isocitrate dehydrogenase 1
IEX	ion exchange chromatography
IM	ion mobility
IMAC	immobilized metal ion affinity chromatography
iMALDI	immuno-matrix-assisted laser desorption/ionization
IMS	ion mobility spectrometry
IR-MALDESI	infrared matrix-assisted desorption electrospray ionization
IS	internal standards
isoAsp	isoaspartic acid
ITC	isothermal titration calorimetry
ITO	indium tin oxide
IVIVC	in vitro to in vivo correlations
k	rate constant
LC	liquid chromatography
LC/MS/MS	liquid chromatography tandem mass spectrometry
LC-MALDI	liquid chromatography-matrix-assisted laser desorption/ionization
LC-MS	liquid chromatography mass spectrometry
LDLR	low-density lipoprotein receptor
LDTD	laser diode thermal desorption
LESA	liquid extraction surface analysis
LLE	liquid–liquid extraction

LOD	limits of detection
LogD	distribution coefficient
LOQ	limit of quantitation
LPS	lipopolysaccharides
M3	microfabricated monolithic multinozzle
mAbs	monoclonal antibodies
MagMASS	magnetic microbead affinity selection screen
MALDI	matrix-assisted laser desorption ionization
MALDI-2	laser-induced postionization
MALDI-FTICR MS	matrix-assisted laser desorption/ionization Fourier-transform ion cyclotron resonance mass spectrometry
MALDI-TOF MS	matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MetAP2	methionyl aminopeptidase 2
MnESI	microflow-nanospray electrospray ionization
MPS	mesoporous silica
MRM	multiple reaction monitoring
MRO	medical review officer
MS	mass spectrometer
MS/MS	tandem mass spectrometry
MSI	mass spectrometry imaging
MTBE	methyl tert-butyl ether
MTP	microtiter plate
MuRF	muscle RING-finger protein
NADPH	nicotinamide adenine dinucleotide phosphate
NALDI	nanostructure-assisted laser desorption/ionization
Nano-DESI	nanospray desorption electrospray ionization
NAPA-LDI	nanopost array-laser desorption/ionization
NDM-1	New Delhi metallo-lactamase1
NDX	native-denatured exchange
nESI	nano electrospray ionization
NHS	*N*-hydroxysuccinimide
NIMS	nanostructure-initiator mass spectrometry
nL	nanoliter
NMR	nuclear magnetic resonance
nMS	native mass spectrometry
NSAID	nonsteroidal anti-inflammatory drugs
NSP14	nonstructural protein 14
OATP2B1	organic anion transporting polypeptide 2B1
OIMS	overtone IMS
OPSI	open port sampling interface

PAH	polycyclic aromatic hydrocarbon
PBED	polybrominated diphenyl ether
PBS	phosphate-buffered saline, buffer solution about pH 7.4
PCB	polychlorinated biphenyl
PCB	printed circuit board
PC-mass-tags	photocleavable mass-tags
PFAS	per- and polyfluoroalkyl substances
PK	pharmacokinetic
pK_a	acid dissociation constant
PKCα	protein kinase C-α
PMF	peptide mass fingerprinting
PoC	percentage of control
POE	percent of enrichment
PPT	protein precipitation technique
PROTAC	proteolysis targeting chimera
PTP1B	tyrosine phosphatase 1B
PUF-MS	pulsed ultrafiltration-mass spectrometry
PVDF	polyvinylidene difluoride
QA/QC	quality assurance and quality control
qPCR	quantitative polymerase chain reaction
qTOF	quadrupole time-of-flight
QuEChERS	quick easy cheap effective rugged and safe
R	universal gas constant
R^2	coefficient of determination
RAM	restricted access media, usually a type of filtering or extraction media
RAM	restricted access medium
RF-MS	RapidFire – mass spectrometry
ROI	return on investment
RXRa	retinoid X receptor-a
S/N	signal-to-noise ratio
SALLE	salt assisted liquid–liquid extraction
SAM	*S*-adenosyl-L-methionine
SAMDI	self-assembled monolayers and matrix-assisted laser desorption ionization
SAR	structure-activity relationship
SEC	size-exclusion chromatography
SEC-TID	size-exclusion chromatography for target identification
SEM	scanning electron microscope
SESI	secondary electrospray ionization

SEZ	staggered elution zone chromatography
SIK2	salt-inducible kinase 2
SIMS	secondary ion mass spectrometry
Sirt3	Sirtuin 3
SISCAPA	stable isotope standards and capture by anti-peptide antibodies
SLIM	structures for lossless ion manipulations
SLS	static light scattering
SME	small molecular entity
SmyD3	SmyD3 histone methyltransferase
SNP	single-nucleotide polymorphism
SPE	solid phase extraction
SPE-MS	solid-phase extraction mass spectrometry
SPME	solid-phase microextraction
SPR	surface plasmon resonance
SRM	selected reaction monitoring
SSP	surface sampling probe
SUPER	Serpentine Ultralong Path with Extended Routing
SV	separation voltage
SWATH	sequential window acquisition of all theoretical mass spectra
T	absolute temperature in Kelvin
TCP	tumor cell percentage
THC	tetrahydrocannabinol
TIMS	trapped ion mobility
TLC	layer chromatography
TMA-lyase	trimethylamine-lyase
TM-DESI	transmission mode DESI
TM-IMS	transversal modulation IMS
TOF	time-of-flight
TR-FRET	time-resolved fluorescence energy transfer
TRIS	Tris (hydroxymethyl) aminomethane
TWIMS	traveling wave ion mobility
UFA	unbound fraction analysis
UHPLC	ultrahigh-performance (or pressure) liquid chromatography
UHPLC/MS	ultrahigh-performance liquid chromatography-mass spectrometry
uHT-MALDI	ultrahigh-throughput matrix-assisted laser desorption/ionization
uHTS	ultrahigh-throughput screening
UPLC	ultra performance liquid chromatography

UV	ultraviolet, usually meant to describe absorbances between 190 and 400 nm
UVPD	ultraviolet photodissociation
WBA	whole-body autoradiography
XRD	X-ray diffraction
Δ^9-THCC	Carboxylic Δ^9-tetrahydrocannabinol
λ	phonon wavelength