Core tip: This article presents a short review on metabolomics as a tool for biomarker discovery in human gastric cancer, with a primary focus on its use as a predictor of anticancer drug chemosensitivity, diagnosis, prognosis, and metastasis.

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INTRODUCTION

Gastric cancer is the fourth most common cancer and the second most deadly cancer worldwide,[1,2] it is particularly prevalent in Asian countries.[3,4] According to the American Cancer Society, approximately 738000 people died worldwide from stomach cancer in 2008.[5] At present, no effective treatment is available for this disease, and identification of early stage gastric cancer is difficult because it is often asymptomatic or misdiagnosed. Moreover, the prognosis of patients with advanced gastric cancer remains poor due to its high metastatic recurrence[6,7], and the complex molecular mechanisms underlying metastasis are not well characterized[8,9].

Presently, early diagnosis of human gastric cancer or tumor recurrence is primarily based on endoscopy, biopsy and pathological examination. Endoscopy is a widely used method for detecting early stages of gastric cancer[10,12] despite its inconsistent diagnostic efficiency, which stems from variations in the skill and experience of the endoscopist and pathologist. In recent years, several serum biomarkers have been identified as new tools for early screening of gastric cancer in developed countries[11,16]. However, these serum biomarkers are not effective as other screening devices given their low specificity and sensitivity.[3] Recently, epidemiological data have revealed that Helicobacter pylori (H. pylori) infection and dietary factors are...
The main risk factors associated with gastric cancer \cite{1,2}.

An overview of traditional methods involved in gastric cancer detection, diagnosis and prognosis in comparison with metabolomic methods is presented in Table 1. The field of metabolomics may offer practical solutions to the challenges mentioned above. Metabolomics, the study of the unique metabolite signature in a biological system (cell, tissue, or organism) under a given set of conditions \cite{17}, has emerged as a promising technology in the study of human cancers. Metabolites are not merely the end product of gene expression; rather, they are the result of the interaction of the system's genome with its environment. They are an integral part of any cellular regulatory system \cite{18}. Metabolomics is regarded as one of the new high-throughput, "-omics" technologies. Along with genomics, transcriptomics, and proteomics, metabolomics is a scientific field of study that seeks to achieve the aims of systems biology \cite{18,19}. The biological organization of different "-omes" and the flow of information from the genome to the transcriptome, the proteome and finally the metabolome is presented in Figure 1 \cite{20}. Metabolomic studies offer a unique approach for identifying metabolomic pathways that are perturbed under specific conditions \cite{21,22}, thereby providing information different from other "-omic" technologies \cite{8}. In recent years, metabolomic studies have been successfully conducted in various cancer systems, including stomach \cite{21}, lung \cite{23,24}, renal \cite{25,26}, breast \cite{27}, brain \cite{28} and colorectal \cite{29-32} cancer systems. Metabolomic studies have also been conducted in human xenograft models \cite{33-38} (transplantation of living cells, tissues or organs from one species to another). These studies can provide valuable information in terms of novel biomarkers that identify cancerous cells. A biomarker \cite{39} often represents a component found in plasma, whose concentration indicates the presence or the severity of disease states. Biomarkers can therefore serve as an indicator of tumor progression and treatment efficacy. Biomarkers can be chemical, physical or biological in nature. Metabolomic studies typically begin with tissue sampling, followed by sample analysis. Nuclear magnetic resonance spectroscopy (NMR) is the most

| Cancer detection state/stage | Traditional methods | Metabolomics (biomarkers) | Ref. |
|-----------------------------|---------------------|---------------------------|------|
| Diagnosis                    | Endoscopy, biopsy   | Lactic acid, butanedioic acid, malic acid, citric acids, pyruvic acid, 3-hydroxypropionic acid, serine, proline | [91,93,100,101] |
| Prognosis                    | Radiotherapy, chemotherapy surgery | Valine, isoleucine, serine, 3-indoxyl sulfate, hippurate, citrate | [96,99,102] |
| Metastasis                   | Computed tomography (CT) scanning, endoscopic ultrasonography (EUS), positron emission tomography (PET) | Sarcosine, alanine, proline, serine, myo-inositol, glycerol | [90,91,98,103] |
| Chemosensitivity of drugs   | MTT chemosensitivity assay | 1-acyl-lysophosphatidylcholines and polyunsaturated fatty acids | [75,104] |
common method of analysis. The large amount of data generated by this analysis is then statistically processed to identify the metabolites that are differentially expressed between the samples, possibly leading to biomarker selection (Figure 2). The key to identifying potential biomarkers is based on the level of metabolite differences in biological samples taken from cancer patients and normal (control) subjects. Metabolomics also has potential utility in several fields of cancer research, including prognosis,[14,15] diagnosis,[44,45] and drug evaluation and development.[46-48] It can also serve as an alternative strategy for personalized cancer therapy.[49,50]

Several review articles,[12,40,51,52] have been published on metabolomic applications in cancer research,[43,44,45,53-55] biomarker discovery,[49,56,57] and natural product drug discovery.[48] However, none of them have focused on a specific type of cancer, particularly gastric cancer. Hence, the aim of this article is to provide a brief overview of the benefits of metabolomic studies to human gastric cancer research, with a special focus on biomarkers. The remainder of the paper is organized as follows. In next section, we briefly discuss different analytical techniques used in metabolomic studies and methods for data analysis. Then, we review several studies of applying metabolomics to gastric cancer research. Finally, future directions and concluding remarks are presented.

**ANALYTICAL TECHNIQUES**

A number of analytical techniques are currently used for metabolomic studies depending on the particular metabolite of interest. In general, NMR spectroscopy (in most cases 1H-NMR)[58,59] and liquid chromatography (LC)[26,60] are the most commonly used spectroscopic techniques used in metabolomic analysis. Fourier transform spectrometry[61-64] and capillary electrophoresis (CE)-mass spectrometry[65-68] are the major spectrometric techniques used in metabolomic analysis. Generally, a combination of different methods provides more information than a single method when analyzing the complete metabolome. NMR is one of the most common analytical methods for urine and plasma analysis[69] due to its non-destructive nature, quantitative ability, and safe metabolite identification that provides detailed information on molecular structure. However, NMR suffers from poor sensitivity. GC-/MS and LC-/MS are widely accepted techniques for metabolite separation and analysis. Metabolites must be volatile in nature in order to use the GC-/MS technique efficiently. Fatty acids, organic acids and sugars are the best-suited metabolites for GC-/MS. In contrast, LC-/MS can cover a broad range of metabolites, including both volatile and non-volatile compounds. CE-/MS is best suited for studies involving energy metabolism given its ability to simultaneously quantify charged, low-molecular weight compounds. A short overview of the advantages and limitations of the different metabolomic methods is presented in Table 2. GC-MS, LC-MS and NMR are the most commonly used methods in cancer research, especially gastric cancer.

**DATA PROCESSING AND METABOLITE IDENTIFICATION**

Data integration and analysis is an important component of metabolomic studies because a large amount of data is generated, similar to proteomic and transcriptomic studies. Proper management, pre-processing and analysis of these data pose a significant challenge and require sophisticated multivariate statistical software. A sufficient number of statistical algorithms have been developed for the analysis of metabolic data, both in a supervised and unsupervised manner. The important unsupervised methods that have been extensively used in metabolomic analysis include principal component analysis (PCA), hierarchical clustering and self-organizing maps. Supervised methods include ANOVA, partial least squares (PLS), hierarchical PLS, k-nearest neighbors (KNN) and discriminant function analysis. The principle details and applications of these methods can be found elsewhere.[44,50-52] A short comparison of these methods including advantages and limitations is provided in review articles.[41,52,55]
Table 2 Comparison of different analytical techniques employed in metabolomics

| Method                          | Sampling characteristics | Sensitivity | Advantages                                                                 | Disadvantages                                                                 | Ref. |
|--------------------------------|--------------------------|-------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|------|
| Nuclear magnetic resonance (NMR) spectroscopy | Non-destructive; minimum sample required | $10^{-6}$ | Fully automated with a high degree of reproducibility; relatively easy to identify metabolites from simple one-dimensional spectra | Lower sensitivity than mass spectrometry; co-resonant metabolites can be difficult to quantify; drug metabolites can be co-resonant with metabolites of interest | [20,41,105] |
| Gas chromatography-mass spectrometry (GC-MS) | Requires extraction, sample dried and chemical derivation | $10^{-12}$ | A relatively cheap and producible method with a high degree of sensitivity | Sample preparation can be time consuming; not all compounds are suitable for gas chromatography | [20,41,106,107] |
| Liquid chromatography-mass spectrometry (LC-MS) | Requires extraction and concentration (vacuum drying), liquid-liquid extraction | $10^{-15}$ | This method is increasingly being used in place of GC-MS as sample preparation is not a time consuming; has a sensitivity similar to GC-MS | More costly than GC-MS and depends on the reproducibility of liquid chromatography; more difficult to control than GC; can also suffer from ion suppression | [20,41,108,109] |
| Fourier-transform infrared (FT-IR) spectrometry | Uses vibrational frequencies of metabolites to produce a fingerprint of metabolism | $10^{-6}$ | Cheap and good for high-throughput first screening | Very difficult to identify which metabolites are responsible for causing changes; very poor at distinguishing metabolites within a class of compounds | [20,41,110,111] |
| Raman spectroscopy | Non-destructive; minimum sample required, occasionally hydration is needed | $10^{-6}$ | Has the advantage over FT-IR in that water has only a weak Raman spectrum; therefore, many functional groups can be observed | Very poor at distinguishing classes of compounds | [20,41,110,111] |

CHEMOSENSITIVITY PREDICTION AND DEVELOPMENT OF PREDICTIVE MODELS

Chemosensitivity prediction is a challenging task in the treatment of advanced gastric cancer[79]. Chemotherapy with anticancer drugs plays a significant role in the personalized management of gastric cancer[74]. Some patients with gastric cancer do not respond well to these drugs, and in some cases, chemotherapy may cause severe toxicity and functional impairment[75-78]. Hence, it is crucial to select individual patients with high chemosensitivity for the management of cancer by chemotherapy treatment. The two major approaches for predicting the activity of anticancer drugs in gastric cancer are resistance enzyme testing and cell-culture testing (chemosensitivity)[79]. In the past, chemosensitivity predictions have been based on clone formation, cell metabolic activity assays in vitro, proliferation, and tumor growth. Unfortunately, these methods suffer from low specificity, sensitivity, and accuracy[79].

In order to overcome these limitations, high-throughput “-omic” methods have been developed as powerful tools for use in different types of cancer treatments[79-82]. Wang et al[79] described a metabolic approach for chemosensitivity prediction in a human xenograft model of gastric cancer treated with cisplatin and 5-fluorouracil. In this approach, mice were divided randomly into control and treatment groups (i.e., resistant, intermediate, and sensitive groups based on relative tumor growth). Blood plasma was collected, and metabolic profiles were obtained by using high performance liquid chromatography coupled with a quadrupole time-of-flight mass spectrometer (HPLC/Q-TOF-MS). From the metabolic data, a predictive model was developed using a KNN algorithm[83] with 90% accuracy, and 18 chemosensitivity metabolites for gastric cancer were proposed in their study. Key metabolites included 1-acetyl-lysophosphatidylcholine and polyunsaturated fatty acids, which are hydrolysis products of phosphatidylcholine. The 1-acetylphosphatidylcholine biochemical pathway regulates the activity of enzymes like phospholipases A2 and B1 and lysophosphatidylcholine acetyltransferases[84-86]. Thus, these key metabolites could serve as crucial modulators of gastric cancer chemosensitivity.

IDENTIFICATION OF POTENTIAL BIOMARKERS FOR GASTRIC CANCER METASTASIS

Metastasis[22] is the spread of a disease from one organ or part to a non-adjacent organ or part. Most gastric cancer deaths occur as a result of metastasis. It is important to explore the complex mechanisms of gastric cancer metastasis in order to identify the key metabolic markers involved in the process. Several genes involved in gastric cancer metastasis have been reported in the literature[8,9,89]. However, no potential biomarkers were identified as predictors of metastasis and prognosis due to large variations in expression levels. Chen et al[91] have conducted metabolomic studies on human xenograft models to elucidate the underlying mechanisms of gastric cancer metastasis and discover possible biomarkers for diagnosis. Their mice were randomized into control, metastatic, and non-metastatic groups, and tissue samples from each group were collected and analyzed using GC-MS. Their study identified approximately 30 metabolites differentially regulated among the groups. Proline was the most...
BIOMARKERS FOR GASTRIC CANCER
DIAGNOSIS AND PROGNOSIS

Biomarkers play a vital role in early stage diagnosis, disease prognosis, drug target identification, and patient reaction to a particular treatment. Several biomarkers have been proposed for gastric cancer diagnosis and prognosis. For example, serum amyloid A was proposed as a sensitive diagnostic biomarker, and the inhibitor of matrix metalloproteinase-1 was suggested as a potential prognostic biomarker. Kim et al. conducted 1H-NMR-based metabolomic studies on mouse models to identify possible urinary biomarkers for human gastric cancer. A comparison of the NMR spectra for the cancer and control groups is shown in Figure 3, and the metabolite trimethylamine oxide (TMAO) is significantly reduced in cancer cells compared with the control, and it is clearly visible in the spectra. Pattern recognition methods attempting to discriminate the control from the tumor group indicated (Figure 4) a clear separation between the cancer and control groups, thus implying the presence of significant metabolic differences in certain metabolites between these two groups. TMAO, 3-indoxyl sulfate, hippurate, 2-oxoglutarate, and citrate showed significant changes in concentration between cancer and control groups and were proposed as potential urinary biomarkers for gastric cancer detection. Yu et al. established a metabolic model to characterize several different stages of gastric cancer including chronic superficial gastritis (CSG), chronic atrophic gastritis (CAG), intestinal metaplasia (IM), gastric dysplasia (DYS) and GC. CSG showed metabolic patterns distinct from the other groups (i.e., CAG, IM, DYS, and GC, whose plots were closely clustered). IM closely clustered with GC, suggesting that these two stages share similar metabolic patterns. Fifteen metabolites displayed distinct metabolic signatures, facilitating discrimination of CSG and GC and characterization of different stages of GC. These biomarkers can be useful for indicating GC risk. Song et al. developed a similar metabolic model based on metabolomic studies of serum samples from cancer and control groups. In this study, the supervised multivariate statistical method orthogonal partial least squares discriminant analysis was applied to discriminate between cancer and non-cancer groups, but this model failed to distinguish the different tumor node metastasis stages of cancer. In addition, approximately 50
metabolites, many involved in amino acid and fatty acid metabolism, displayed significant metabolic differences between cancer and control groups and were proposed as potential markers for the detection of cancer. In an additional metabolomic study on gastric cancer patients, Wu et al. [99] identified tissue metabolic markers and confirmed that valine metabolism was involved in the metabolic changes associated with gastric cancer. In another study [100], a metabolic diagnostic model was developed to characterize gastrointestinal cancer (esophageal, gastric, and colorectal cancers) based on serum metabolomics.

Thus, biomarkers discovered from metabolomic studies may play a significant role in gastric cancer with regard to early stage detection, diagnosis, prognosis, drug development and chemosensitivity predictions. The complete details of metabolomics studies on human gastric cancer including study population, sample type and analytical method used are presented in Table 3.

CONCLUSION

The use of metabolomics in human gastric cancer to discover novel biomarkers is an emerging field. The metabolomics field is superior to other “-omic” methods, as it provides accurate quantities of metabolites in a particular biological system. Hence, the biomarkers identified by metabolomics are likely to be reliable. NMR, GC-MS and LC-MS metabolic techniques are widely used in gastric cancer research. Furthermore, a large number of multivariate data analysis methods have been developed to analyze metabolomic data; PCA and PLS are the most prominent examples. However, despite the number of statistical tools available in metabolomics, many of these methods have limitations; thus, room for further development exists.

Metabolomics has also demonstrated promise in the development of diagnostic tools for gastric cancers. These studies are based on small cohorts; therefore, larger studies are needed for validation of biomarker utility and thereafter translation to a clinical setting. The ability to obtain a high quality sample along with sample collection, storage and analysis are all factors that have large consequences on metabolic results. This fact underscores the need for standardized protocols. Metabolomic studies are beneficial for cancer identification, diagnosis and prognosis. Moreover, by combining metabolomics with other “-omic” methods, a more comprehensive understanding of the processes involved in cancer development is likely to be generated.

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### Table 3: Overview of metabolomic studies on gastric cancer

| Patients/xenograft model | Sample | Sample size (cancer + control) | Analytical method | Multivariate method | Major findings | Ref. |
|-------------------------|--------|--------------------------------|------------------|---------------------|---------------|------|
| Both                    | Urinary sample | 33 | GC-MS | PCA | Lactic acid, serine, proline, malic acid and fatty acids as potential markers for screening and early diagnosis | [93] |
| Xenograft model Patients | Serum | 60 | GC-MS | OPLS-DA | Sarcosine as a potential biomarker for the progression of gastric cancer metastasis | [98] |
| Patients                | Plasma | 80 | GC-TOF-MS | PLS-DA | Azelaidic acid, glutamate, urate, creatinine, threonate as markers for characterizing the precancerous stages and gastric cancer | [97] |
| Patients                | Serum | 50 | GC-MS | PCA | 3-hydroxypropionic acid and pyruvic acids as potential diagnostic markers for gastric cancer | [100] |
| Patients                | Tissue | 18 | GC-MS with chemical derivatization | HPLC/ Q-TOF-MS | 1-acetyllysophosphatidylcholines and polyunsaturated fatty acids as potential indicators of chemosensitivity for gastric cancer | [75] |
| Xenograft model         | Plasma | 80 | GC-MS | PCA | Lactic acid, butanedioic acid, malic acid and citric acids as potential markers for cancer screening, Alanine, proline, myo-inositol and glyceraldehyde as key markers for identifying cancer metastasis | [91] |
| Xenograft model         | Urinary sample | 24 | GC-MS | PCA | Serine and proline metabolism pathways were enriched in cancer metastasis and may help elucidate the complex molecular mechanisms governing metastasis | [90] |
| Xenograft model         | Tissue | 22 | GC-MS | PCA | | |

PCA: Principal component analysis; PLS: Partial least squares; OPLS-DA: Orthogonal partial least squares discriminant analysis; GC-MS: Gas chromatography-mass spectrometry; PLS-DA: Partial least squares discriminant analysis; GC-TOF-MS: Gas chromatography coupled with time-of-flight mass spectrometry; HPLC/Q-TOF-MS: Ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry.

## REFERENCES

1. **Crew KD**, Neugut AI. Epidemiology of upper gastrointestinal malignancies. *Semin Oncol* 2004; 31: 450-464 [PMID: 15297938]
2. **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; 12: 354-362 [PMID: 16486353]
3. **Brenner H**, Rothenbacher D, Arndt V. Epidemiology of gastric cancer. *Methods Mol Biol* 2009; 472: 467-477 [PMID: 19107449 DOI: 10.1007/978-1-60327-402-3_23]
4. **Leung WK**, Wu MS, Kakugawa Y, Kim J, Yeoh KG, Koh KL, Wu KC, Wu DC, Sollano J, Kachintorn U, Gotoda T, Lin JT, You WC, Ng EK, Sung J. Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol* 2008; 9: 279-287 [PMID: 18308253 DOI: 10.1016/s1470-2045(08)70072-x]
5. **Society AC**. Global Cancer Facts and Figures. 2nd ed. Atlanta: American Cancer Society, 2011
6. **Macdonald JS**. Gastric cancer—new therapeutic options. *N Engl J Med* 2006; 355: 76-77 [PMID: 16822999 DOI: 10.1056/NEJM2006012612]
7. **Cunningham D**, Chua YJ. East meets west in the treatment of gastric cancer. *N Engl J Med* 2007; 357: 1863-1865 [PMID: 17978296 DOI: 10.1056/NEJM2007072512]
8. **Rajdev L**. Treatment options for surgically resectable gastric cancer. *Curr Treat Options Oncol* 2010; 11: 14-23 [PMID: 20358316 DOI: 10.1007/s11864-010-0117-1]
9. **Yilmaz M**, Christofori G. Mechanisms of motility in metastasizing cells. *Mot Mol Cancer Res* 2010; 8: 629-642 [PMID: 20460404 DOI: 10.1158/1541-7786.mcr-10-0139]
10. **Tashiro A**, Sano M, Kinaneru K, Fujita K, Takeuchi Y. Comparing mass screening techniques for gastric cancer in Japan. *World J Gastroenterol* 2006; 12: 4873-4874 [PMID: 16957471]
11. **Sipponen P**, Ranta P, Helske T, Kääriäinen I, Mäki T, Linna A, Suovaniemi O, Alanko A, Härkönen M. Serum levels of amidated gastrin-17 and pepsinogen I in atrophic gastritis: an observational case-control study. *Scand J Gastroenterol* 2002; 37: 785-791 [PMID: 12190091]
12. **Lu X**, Zhao X, Bai C, Zhao C, Lu G, Xu G. LC-MS-based natural products research. *J Chromatogr B Anal Technol Biomed Life Sci* 2008; 866: 64-76 [PMID: 17983864 DOI: 10.1016/j.jchromb.2007.10.022]
13. **Miki K**, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. *Am J Gastroenterol* 2003; 98: 735-739 [PMID: 12738449 DOI: 10.1111/1572-0241.2003.07410.x]
14. **Kita Hara F**, Kobayashi K, Sato T, Kojima Y, Araki T, Fujino MA. Accuracy of screening for gastric cancer using serum pepsinogen concentrations. *Gut* 1999; 44: 693-697 [PMID: 10205207]
15. **Vääränen H**, Vauhkonen M, Helske T, Kääriäinen I, Rasmussen M, Tunturi-Hilnala H, Koskenpato J, Sotka M, Turunen M, Sandström R, Ristikankare M, Jussila A, Sipponen P. Non-endoscopic diagnosis of atrophic gastritis with a blood test. Correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. *Eur J Gastroenterol Hepatol* 2003; 15: 885-891 [PMID: 12867799 DOI: 10.1097/01.meg.0000059169.46867.01]
16. **Kikuchi S**, Kurosawa M, Sakiyama T, Tenjin H, Miki K, Wada O, Inaba Y. Long-term effect of Helicobacter pylori infection on serum pepsinogens. *Int J Cancer Res* 2000; 91: 471-476 [PMID: 10835490]
17. **Goodacre R**, Vaidyanathan S, Dunn WB, Harrigan GG, Kell DB. Metabolomics by numbers: acquiring and understanding global metabolite data. *Trends Biotechnol* 2004; 22: 245-252 [PMID: 15109811 DOI: 10.1016/j.tibtech.2004.03.007]
18. **Rochfort S**. Metabolomics reviewed: a new “omics” platform technology for systems biology and implications for natural products research. *J Nat Prod* 2005; 68: 1813-1820 [PMID: 16378385 DOI: 10.1021/np050255w]
19. **Schmidt C**. Metabolomics takes its place as latest up-and-coming “omic” science. *J Natl Cancer Inst* 2004; 96: 732-734
prostate cancer that recapitulates mixed osteolytic and os-
thesis of a gas chromatography/mass spectrometry method
determination of a gas chromatography/mass spectrometry method
bone cancer. Lung Cancer 2011; 74: 284-292 [PMID: 21411176 DOI: 10.1016/j.jlungen.2011.02.008]

Kim K, Aronov P, Zakharkin SO, Anderson D, Perroud B, Thompson IM, Weiss RH. Urine metabolomics analysis for kidney cancer detection and biomarker discovery. Mol Cell Proteomics 2009; 8: 558-570 [PMID: 19008263 DOI: 10.1074/mcp.M800165-MCP200]

Kind T, Tolstíkov V, Fiehn O, Weiss RH. A comprehensive urinary metabolic approach for identifying kidney cancer. Anal Biochem 2007; 363: 185-195 [PMID: 17316356 DOI: 10.1016/j.ab.2007.01.028]

Gu H, Pan Z, Xi B, Asigau V, Musselman B, Raftery D. Principal component directed partial least squares analysis for combining nuclear magnetic resonance and mass spectrometry data in metabolomics: Application to the detection of breast cancer. Analytica Chimica Acta 2011; 686: 57-63 [DOI: 10.1016/j.aca.2010.11.040]

Monléon D, Morales JM, Gonzalez-Darder J, Talamañtes F, Cortés O, Gil-Benso R, López-Gínes C, Cerdà-Nicolás M, Celda B. Benign and atypical meningioma metabolic signatures by high-resolution magic-angle spinning molecular profiling. J Proteome Res 2008; 7: 2882-2888 [PMID: 18507434 DOI: 10.1021/pr800110a]

Monléon D, Morales JM, Barrasa A, López JA, Vázquez C, Celda B. Metabolite profiling of fecal water extracts from human colorectal cancer. NMR Biomed 2009; 22: 342-348 [PMID: 19006612 DOI: 10.1002/nbm.1345]

Mal M, Koh PK, Cheah PY, Chan EC. Development and validation of a gas chromatography/mass spectrometry method for the metabolic profiling of human colon tissue. Rapid Commun Mass Spectrom 2009; 23: 487-494 [PMID: 19140133 DOI: 10.1002/rcm.3898]

Qiu Y, Cai G, Su M, Chen T, Liu Y, Xu Y, Ni Y, Zhao A, Cai S, Xu LX, Jia W. Urinary metabolic study on colorectal cancer. J Proteome Res 2010; 9: 1627-1634 [PMID: 2021166 DOI: 10.1021/pr900181y]

Qiu Y, Cai G, Su M, Chen T, Zheng X, Xu Y, Ni Y, Zhao A, Xu LX, Cai S, Jia W. Serum metabolite profiling of human colorectal cancer using GC-TOFMS and UPLC-QTOFMS. J Proteome Res 2009; 8: 4844-4850 [PMID: 19678709 DOI: 10.1021/pr0904162]

Meyer LH, Debatin KM. Diversity of human leukemia xenograft mouse models: implications for disease biology. Cancer Res 2011; 71: 7141-7144 [PMID: 22088964 DOI: 10.1158/0008-5472-can-11-1732]

Raheem O, Kulidjian AA, Wu C, Jeong YB, Yamaguchi T, Smith KM, Goff D, Leu H, Morris SR, Calacano NA, Masuda K, Jamieson CH, Kane CJ, Jamieson CA. A novel patient-derived intra-femoral xenograft model of bone metastatic prostate cancer that recapitulates mixed osteolytic and os-
neoblastic lesions. J Transl Med 2011; 9: 185 [PMID: 22053283 DOI: 10.1186/1479-5876-9-185]

Jia Y, Liu M, Huang W, Wang Z, He Y, Wu J, Ren S, Ju Y, Geng R, Li Z. Recombinant human endostatin endostar inhibits tumor growth and metastasis in a mouse xenograft model of colon cancer. Pathol Oncol Res 2012; 18: 315-323 [PMID: 21938482 DOI: 10.1007/s12553-011-9447-y]

Hui X, Chen H, Zhang S, Ma X, Wang X, Huang B. Antitumor activities of recombinant human interferon (IFN)-α1 in vitro and in xenograft models in vivo for colon cancer. Cancer Lett 2011; 311: 141-151 [PMID: 21872598 DOI: 10.1016/j.canlet.2011.07.004]

Huyh H, Choo SP, Tob HC, Tai WM, Chung AY, Chow PK, Ong R, Soo KC. Comparing the efficacy of sunitinib with sorafenib in xenograft models of human hepatocellular carcinoma: mechanistic explanation. Curr Cancer Drug Targets 2011; 11: 944-953 [PMID: 21834756]

Liang F, Wang MY, Huang WB, Li AJ. [Effect of sodium carboxymethylcellulose on the angiogenesis of nude mice with human gastric cancer]. Zhong Yao Cai 2011; 34: 343-346 [PMID: 21823448]

Issaq HJ, Fox SD, Chan KC, Veenstra TD. Global proteomics and metabolomics in cancer biomarker discovery. J Sep Sci 2011; 34: 3484-3492 [PMID: 22102289 DOI: 10.1002/jssc.201100528]

Issaq HJ, Abbott E, Veenstra TD. Utility of separation science in metabolic studies. J Sep Sci 2008; 31: 1936-1947 [PMID: 18348522 DOI: 10.1002/jssc.200700601]

Wang QZ, Wu CY, Chen T, Chen X, Zhao XM. Integrating metabolomics into a systems biology framework to exploit metabolic complexity: strategies and applications in microorganisms. Appl Microbiol Biotechnol 2006; 70: 151-161 [PMID: 16395543 DOI: 10.1007/s00253-005-0277-2]

Dunn WB, Bailey NJ, Johnson HE. Measuring the metabo-
lome: current analytical technologies. Analyst 2005; 130: 606-625 [PMID: 15852128 DOI: 10.1039/b418288k]

Ippolito JE, Xu J, Jain S, Moulder K, Mennerick S, Crowley JR, Townsend RR, Gordon JL. An integrated functional genomics and metabolomics approach for defining poor prognosis in human neuroendocrine cancers. Proc Natl Acad Sci USA 2005; 102: 9901-9906 [PMID: 15998737 DOI: 10.1073/pnas.0507561102]

Ondusi K, Wollman RM, Ambrosone CB, Hutson A, McCann SE, Tammela J, Geisler JP, Miller G, Sellers T, Cliby W, Odunsi K. Metabolomics: a platform for studying drug toxicity and gene function. Curr Drug Targets 2007; 8: 1113-1127 [PMID: 17279667 DOI: 10.2174/138945007781001601]

Nicholson JK, Cornell J, Lindon JC, Holmes E. Metabonomics: a platform for studying drug toxicity and gene function. Nat Rev Drug Discov 2002; 1: 153-161 [PMID: 12120097 DOI: 10.1038/nrd729]

Lindon JC, Holmes E, Bollard ME, Stanley EG, Nicholson JK. Metabonomics technologies and their applications in physiological monitoring, drug safety assessment and disease diagnosis. Biomarkers 2004; 9: 1-31 [PMID: 15204308 DOI: 10.1080/1354730041000168879]

Lindon JC, Holmes E, Nicholson JK. Metabonomics: systems biology in pharmaceutical research and development. Curr Opin Mol Ther 2004; 6: 265-272 [PMID: 15264428]

Clayton TA, Lindon JC, Cloarec O, Antti H, Charuel C, Hanton G, Provost JP, Le Net JL, Baker D, Walley RJ, Everett JR, Nicholson JK. Pharmacometabonomic phenotyping and personalized drug treatment. Nature 2006; 440: 1073-1077 [PMID: 16625200 DOI: 10.1038/nature04648]
