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Clinical Research and more...

Director's note

Dear Reader,

I am pleased to present the third issue of Shimadzu Journal, which features various collaborative research projects and technical reports and applications from our library. Our brand statement "Excellence in Science" reflects our mission to offer state-of-the-art solutions incorporating innovative and cutting-edge technologies to researchers, scientists and engineers in many fields.

Our analytical and measuring Instruments are always required to achieve results faster and more efficiently than ever before while maintaining the accuracy and precision customers need. This requirement extends to all fields of research, including environmental, food safety, pharmaceuticals and diagnostics.

In addition, it's imperative to ensure accuracy, precision, and speed in clinical research, the focus of this issue, which contains information on two collaborations. One is with Dr. Michelle McIntosh of Monash Institute of Pharmaceutical Sciences, Victoria, Australia. She is working on a project to develop a novel aerosol delivery system for oxytocin that can be inhaled by patients from a simple, disposable device immediately after childbirth. The other collaboration is with the National Cancer Center in Japan, which is visualizing drug distribution with microscopic mass spectroscopy to evaluate drug effects and to optimize drug design. The issue also includes information on other applicable topics, as well as the latest news and applications.

We believe that collaborating with researchers is the best and fastest way to develop novel solutions that contribute to society. We are proud to introduce the collaborative research projects mentioned above and show their potential impact.

We will always strive to develop the highest technology and grow together with our customers. We wish to be a reliable innovation provider for customers all over the world, and hope this Journal gives you valuable and beneficial information.

Yours Sincerely,

Teruhisa UEDA, PhD.

General Manager, Analytical & Measurement Instruments Division

CONTENT

The Third Issue Featuring on Clinical Research

Dr. Michelle McIntosh, Monash Institute of Pharmaceutical Science (MIPS), Melbourne, Australia

Dr. Paul Wynne from Shimadzu Australia had the pleasure of speaking with Dr. Michelle McIntosh, Senior Lecturer at Monash Institute of Pharmaceutical Science (MIPS) in Melbourne, Australia; about her work in drug metabolism and disposition. We were particularly interested in her use of a novel delivery system that is enabling life-changing treatment for new mothers in third world countries.

Shimadzu:

Dr. McIntosh, welcome to the Shimadzu Journal.

I was hoping that you would be able to tell us a little about your work at MIPS, your goals for the future and how Shimadzu works as a part of your laboratory?

Dr. McIntosh:

Our most important project at the moment involves the hormone oxytocin.

Every year, over 100,000 women die of postpartum haemorrhage (PPH), a condition of excessive blood loss after childbirth. Although PPH can be effectively prevented or treated with an injection of oxytocin, access to this drug is limited due to the requirements for refrigeration, storage and trained medical personnel for administration. Our team is working on a project to develop a novel aerosol delivery system for oxytocin that can be inhaled by patients from a simple, disposable device immediately after childbirth. This approach will increase access to this life saving commodity in resource-poor settings, where a large number of women give birth outside medical facilities or in understaffed and ill-equipped clinics with limited or no refrigeration facilities.

Developing a product like this from concept through to practice involves many samples collected and many oxytocin analyses to be completed. We have a Shimadzu laboratory equipped with LCMS, LCMSMS and several HPLC systems that support this work.

Shimadzu has also been a generous supporter of our teaching initiatives at MIPS and I feel the whole company understands our passion to have real scientists teaching real science on state of the art equipment. That connection has led to Shimadzu staff teaching in our academic courses and also with the establishment of the Shimadzu Chromatography Laboratory.

Shimadzu:

The oxytocin project is a major part of your work but it also seems to be a project that expresses the wish of all scientists to make a positive contribution to the world. How can it move forward?

Dr. McIntosh:

We are humbled by the recognition that the project has generated and the awards that have been granted to us. It does bode well for the future of science that there is such engagement in the future of preventative medicine. Quite simply, the oxytocin project has the potential to ensure that families grow up with a mother rather than that she be lost in child birth. In the developed world, we do not think about it but for poorer nations, the personal and social impact is enormous. Within a single generation, we can change the outcomes not just for individuals and families but for whole communities. That is a pretty good reason to be working in science.

Shimadzu is still a generous supporter and a vital part of the research and we hope that ultra-sensitive LCMSMS equipment will extend our ability to study the delivery of the oxytocin during clinical trials.

Shimadzu:

The LCMS allows you to measure at lower concentrations but aren't you also interested in metabolic fate?

Dr. McIntosh:

Both. We hope that the exquisite sensitivity of the LCMS-8050 will allow us to measure a variety of biological specimens for oxytocin without the more extensive sample pre-concentration that is needed now. Instrument sensitivity gives us the ability to test smaller samples and that can reduce our costs in logistics, invasiveness of sampling or allow us to increase sample frequency.

Understanding metabolic fate in the concentration range we are working is challenging. To be successful requires the LCMSMS to be fast scanning, fast switching and have sensitivity to generate definitive data.

We are making excellent progress.

Shimadzu:

You mentioned the teaching laboratory that Shimadzu supports at MIPS and it is a project that is very important to us. In the interests of space, we might have to come back in a later edition to hear more about it. Briefly, what has the project meant for teaching chromatography in the modern world?

Dr. McIntosh:

You have really hit the nail on the head by talking about the modern world and the modern student in particular. Education now is a visual process more than in previous generations. The Shimadzu laboratory allows hands-on learning using Problem Based Learning techniques that engage students in not only learning about concepts and equations but also in making practical decisions that can be the difference between an analysis that delivers results and one that does not.

The oxytocin research and many of the other projects running at MIPS now rely on the students having that extra hands-on capability from their undergraduate education. The importance of our up-skilling programmes are reflected in the fantastic research outcomes right across MIPS.

Shimadzu:

Michelle, thank you for spending some time with me and telling our readers about your work. I hope that we can come back in the future and learn some more about the innovative teaching programmes that are been used at MIPS and the impact that the Shimadzu laboratory is having on graduate skills.

Here are her 2013 publications :

Book Chapters

(1)Rajewski, R.A., McIntosh, M.P., 2007, Targeting - Theoretical and Computational Models, in *Prodrugs : Challenges and Rewards*, eds Stella, V.J.; Borchardt, R.T.; Hageman, M.J.; Oliyai, R.; Maag, H.; Tilley, J., Springer, USA, pp. 429-445.

Journal Articles

(2)Sou, T., McIntosh, M.P., Kaminskas, L.M., Prankerd, R.J., Morton, D.A.V., 2013, Designing a multicomponent spray-dried formulation platform for pulmonary delivery of biomacromolecules: The effect of polymers on the formation of an amorphous matrix for glassy state stabilization of biomacromolecules, *Drying Technology [P]*, vol 31, issue 13-14, Taylor & Francis Inc., Philadelphia PA USA, pp. 1451-1458.

(3)Quinn, T.A., Ratnayake, U., Dickinson, H., Nguyen, T., McIntosh, M.P., Zakhem, M.E., Conley, A.J., Walker, D.W., 2013, Ontogeny of the adrenal gland in the spiny mouse, with particular reference to production of the steroids cortisol and dehydroepiandrosterone, *Endocrinology [P]*, vol 154, issue 3, The Endocrine Society, United States, pp. 1190-1201.

(4)Ryan, G., Kaminskas, L.M., Bulitta, J.B., McIntosh, M.P., Owen, D.J., Porter, C.J., 2013, PEGylated polylysine dendrimers increase lymphatic exposure to doxorubicin when compared to PEGylated liposomal and solution formulations of doxorubicin, *Journal of Controlled Release [P]*, vol 172, issue 1, Elsevier BV, Amsterdam Netherlands, pp. 128-136.

(5)Wickramaratne Senarath Yapa, S., Li, J., Porter, C.J., Nation, R.L., Patel, K., McIntosh, M.P., 2013, Population pharmacokinetics of colistin methanesulfonate in rats: Achieving sustained lung concentrations of colistin for targeting respiratory infections, *Antimicrobial Agents And Chemotherapy [P]*, vol 57, issue 10, American Society for Microbiology, Washington DC USA, pp. 5087-5095.

(6)Ryan, G., Kaminskas, L.M., Kelly, B., Owen, D.J., McIntosh, M.P., Porter, C. J., 2013, Pulmonary administration of PEGylated polylysine dendrimers: Absorption from the lung versus retention within the lung is highly size-dependent, *Molecular Pharmaceutics [P]*, vol 10, issue 8, American Chemical Society, Washington DC USA, pp. 2986-2995.

(7)Prankerd, R.J., Tri Hung, N., Ibrahim, J., Bischof, R., Nassta, G., Olerile, L.D., Russell, A.S., Meiser, F., Parkington, H.C., Coleman, H.A., Morton, D.A.V., McIntosh, M.P., 2013, Pulmonary delivery of an ultra-fine oxytocin dry powder formulation: Potential for treatment of postpartum haemorrhage in developing countries, *PLoS ONE [P]*, vol 8, issue 12, Public Library of Science, San Francisco, CA United States, pp. 1-9.

(8)Sou, T., Kaminskas, L.M., Nguyen, T., Carlberg, R., McIntosh, M.P., Morton, D.A.V., 2013, The effect of amino acid excipients on morphology and solid-state properties of multi-component spray-dried formulations for pulmonary delivery of biomacromolecules, *European Journal of Pharmaceutics and Biopharmaceutics [P]*, vol 83, issue 2, Elsevier Science BV, Netherlands, pp. 234-243.

The Oxytocin Revolution

-Saving lives of mothers after childbirths in the third world-

A global innovation that has the potential to prevent women in developing countries from the fatal loss of blood after childbirth has seen Dr Michelle McIntosh of the Monash Institute of Pharmaceutical Sciences win The Australian Innovation Challenge and a $30,000 prize. The work has drawn favorable reviews around the world and captured the social values that underpin Shimadzu's Corporate Philosophy. In this article, Dr Michelle McIntosh and her team describe their efforts to make a significant contribution to Global Health.

Postpartum haemorrhage (PPH) is the loss of blood (>500 mL) following childbirth that, in the absence of preventive measures, may occur in up to 17% of all deliveries[1] . Severe cases of PPH can result in death in as little as two hours if no medical intervention is provided. PPH is the single largest cause of maternal mortality worldwide with the burden occurring overwhelmingly in low income countries (WHO & UNICEF 2012).

Oxytocin is recommended by the World Health Organisation (WHO) as the first-line therapy for prevention and treatment of PPH (WHO 2012). Specifically, administration of an oxytocin injection within 1-2 minutes of birth is a recommended part of the active management of the third stage of labour (AMTSL) for all mothers at every birth. However, access to an oxytocin injection in resource-poor settings is limited because oxytocin in this form requires refrigeration, a needle and syringe, and trained medical personnel to administer the injection. An innovative solution to address these issues involves the development of a shelf-stable, simple to use inhaled oxytocin product. A novel dry powder aerosol oxytocin delivery system can be inhaled by patients immediately after childbirth and removes the need for refrigeration, sterile conditions, trained health workers whilst eliminating the risk of needle-stick injuries and transmission of blood-borne diseases.

Using a technique known as "spray-drying", a team at Monash University Institute of Pharmaceutical Sciences, led by Dr Michelle McIntosh, has engineered a novel dry powder formulation of oxytocin. The powder has been evaluated in a number of simple to use and affordable delivery devices, and has shown to be effectively and consistently delivered with a particle size range necessary for delivery to the lungs. Furthermore, preclinical evaluations have demonstrated that once administered to the lungs the particles containing oxytocin were readily absorbed into the blood stream without any indication of post-administration irritation or inflammation within the respiratory tract.

Crucial to the ongoing development and assessment of the inhaled product for the project has been the requirement for reliable determination of oxytocin content in the prepared powder formulations. To this end, a robust and highly specific assay for oxytocin was developed using a Shimadzu High Performance Liquid Chromatography (HPLC) system employing a Prominence binary pump LC, incorporating LC-20AD gradient pumps, SIL-20A HT autosampler, DGU-20A mobile phase degasser and an ultra violet detection system which was validated with high accuracy and precision. At this stage, several stability studies have been conducted to determine the amount of drug remaining in the developed dry powder formulations when compared to the injectable solution after Using the method developed on the Shimadzu system, Dr. McIntosh's team was able to demonstrate the enhanced stability of the prototype oxytocin dry powder formulations after storage at 50 °C for up to three months. This was in contrast to the injectable solution where greater than 20% of the oxytocin was degraded after only 2 months under the same conditions.

These promising results have been pivotal in advancing the development of an inhaled, low cost and needle-free formulation with a stability profile that significantly improves upon the current injectable solution. Understanding the heat stability of the powder formulation has therefore been a significant milestone for the project where the need to eliminate the requirement for refrigeration is critical to the success of the product. Such an innovation has the potential to address current shortfalls associated with oxytocin use in resource poor settings with the

potential to prevent 41 million cases of PPH and save at least 1.4 million lives over the next decade.

Parallel to the development of a heat stable dry powder formulation of oxytocin the Monash team has also focused on gaining a fundamental understanding on the mechanisms that govern oxytocin degradation. To this end, a Shimadzu 8030 triple-quadrupole mass spectrometer coupled to a LC-30AD/SIL-30AC UHPLC system has been an invaluable tool in allowing the project to investigate oxytocin stability in greater depth.

The sensitivity and ease-of-use of the Shimadzu 8030 system has allowed the Monash team to routinely analyse and identify impurities and degradation products encountered under both standard and accelerated storage conditions. When correlated to

the simultaneous quantitation of the parent oxytocin compound the analysis has provided valuable insight into the mechanisms that govern oxytocin degradation under varying environmental conditions. The team has identified several deamidation products formed from oxytocin degradation, in addition to instability indicating complexes resultant from the formation of dimers and tri-sulfide linkages between oxytocin molecules. All these factors are thought to be the key driving forces that influence the reduced potency and activity of the drug, in particular, for the current injectable solution when stored at elevated temperatures above 4˚C (as commonly experienced in resource poor settings). In turn, although these degradation mechanisms are thought to occur mainly in solution, understanding and identifying the degradation products and mechanisms has nevertheless fed into the main development project allowing the Monash team to optimise formulation strategies that can further enhance stability of the inhaled dry powder product, especially during manufacturing and storage.

In addition to the development of an inhaled oxytocin powder formulation, work undertaken by the team has also provided invaluable insights into the use and stability of the current oxytocin solution formulation when inadvertently frozen during transport and storage to remote areas. In a recent letter to the editor published in the prestigious New England Journal of Medicine[2] the Monash team demonstrated that oxytocin ampoules remained stable when stored for up to seven days on ice, dry ice and from -5˚C to -20˚C. Furthermore, the oxytocin ampoules remained within stability specifications when subjected to five freeze/thaw cycles. Critical to these recent discoveries has been the ability to develop an accurate and high throughput assay on the Shimadzu 8030 system that allowed the samples to be rapidly analysed once subjected to the test conditions in order to minimize any degradation during analysis.

As the work moves on to study drug delivery, metabolism and disposition mechanisms associated with the route of delivery, Dr McIntosh and her team are hoping to use the ultra-high sensitivity of the new Nexera X2-LCMS-8050 to enable sensitive detection and minimally invasive sampling during their studies. This work, although simple in its approach has been invaluable for clinicians and skilled birth attendants in the maternal and global health fields, and has instilled confidence that the potency and efficacy of the oxytocin solution is maintained when inadvertently frozen.

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2. Nassta G.C., Prankerd R.J., and McIntosh M.P. 2013. Effect of Freezing on Oxytocin Ampules. New England Journal of Medicine. 368, 2145-2146.

If you want to know further information about her research, please visit:
http://www.monash.edu.au/pharm/about/news/australian-innovators.html

You can meet her on the video:

If you cannot view the video, please click here.
http://www.shimadzu.com/an/journal/vol2_iss2_video.html

The significance of microscopic mass spectrometry with high resolution in the visualisation of drug distribution

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ABSTRACT

The visualisation and quantitative analysis of the native drug distribution in a pre-clinical or clinical setting are desirable for evaluating drug effects and optimising drug design. Here, using matrix-assisted laser desorption ionisation imaging mass spectrometry (MALDI-IMS) with enhanced resolution and sensitivity, we compared the distribution of a paclitaxel (PTX)-incorporating micelle (NK105) with that of PTX alone after injection into tumour-bearing mice. We demonstrated optically and quantitatively that NK105 delivered more PTX to the tumour, including the centre of the tumour, while delivering less PTX to normal neural tissue, compared with injection with PTX alone. NK105 treatment yielded a greater antitumour effect and less neural toxicity in mice than did PTX treatment. The use of high-resolution MALDI-IMS may be an innovative approach for pharmacological evaluation and drug design support.

Key Words

Drug delivery, Pharmacokinetics, Pharmacodynamics, Biochemical assays

Introduction

Advances in our understanding of cancer at the cellular and molecular levels have promoted the development of new drugs[1,2]. Pharmacokinetic (PK) and pharmacodynamic (PD) studies are very important to evaluate the efficacy and toxicity of new drugs as well as to optimise drug design. For these purposes, tissue homogenate samples are generally analysed by high-performance liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LC-MS)[3]. For the development of anticancer drugs (ACAs), including molecular targeting agents, precise chemical modulation is needed because the small differences between cancer cells and their host cells creates a narrow therapeutic window. In addition, clinical human cancer tissues generally exhibit abundant and versatile stroma, which is the result of the process of tumour cell invasion into tumour vessels, haemorrhage, fibrin clot formation, and replacement with collagen tissues and non-malignant stromal cells. Therefore, it is very important to consider the delivery of ACAs to cancer tissues and their distribution to target cancer cells within this heterogeneous tumour microenvironment. Furthermore, the drug distribution within normal tissues, particularly vital organs, should also be evaluated because ACAs frequently cause adverse effects[4]. A large body of clinical evidence has revealed that neoadjuvant chemotherapy is useful for a variety of solid tumours. The tissue excised during surgery or endoscopic biopsy can be used to investigate drug distribution[5,6]. Thus, a convenient method for evaluating the distribution of clinically used native (non-radiolabeled or non-chemically modified) drugs is urgently required.

Matrix-assisted laser desorption ionisation imaging mass spectrometry (MALDI-IMS) has been developed for the investigation of the distribution of molecules such as small peptides, drugs, and their metabolites[7–12]. Moreover, MALDI-IMS can be used to evaluate numerous molecules in a single measurement without a specialized probe[7–12]. Therefore, this method enables the observation of a drug directly within tissue with the distinction between the original compound and its metabolites.

We have developed a mass microscopy method in which a microscope is coupled with a high-resolution atmospheric pressure-laser desorption/ionisation and quadruple ion trap time-of-flight (TOF) analyser. In this study, we investigated the ability of our mass microscopy technique to visualise the tissue distribution of unlabelled ACA and its micellar formulation and obtain precise regional information about the drug distribution in a specific anatomical area.

Results

The drug imaging system and its application in PTX analysis on the MALDI target.

A schematic representation of our drug imaging system is shown in Fig. 1. Imaging data were acquired using a mass microscope. In the analysis, mass spectrometry (MS) and tandem mass spectrometry (MS/MS) were used for quantification and validation, respectively (Fig. 1).

Paclitaxel (PTX) is a mitotic inhibitor and an ACA that is used to treat various cancers. However, PTX is associated with peripheral neuropathy, a serious adverse affect[13]. NK105, a PTX-incorporating micelle, was developed to address this limitation of PTX[14–17]. On the basis of the enhanced permeability and retention (EPR) effect[17–20], NK105 can be selectively delivered to a tumour, resulting in an enhanced antitumour effect and the minimisation of adverse effects, including peripheral neuropathy. The high efficacy and low toxicity of NK105 have been demonstrated in both preclinical and clinical studies14–17. Although the administered drug content per tissue weight can be determined by conventional HPLC or LC-MS, the detailed drug distribution within the tumour and normal tissue has not been examined. Therefore, we used our drug imaging system to evaluate the difference in the distribution of NK105 and free PTX within tumour and normal peripheral neuronal tissue.

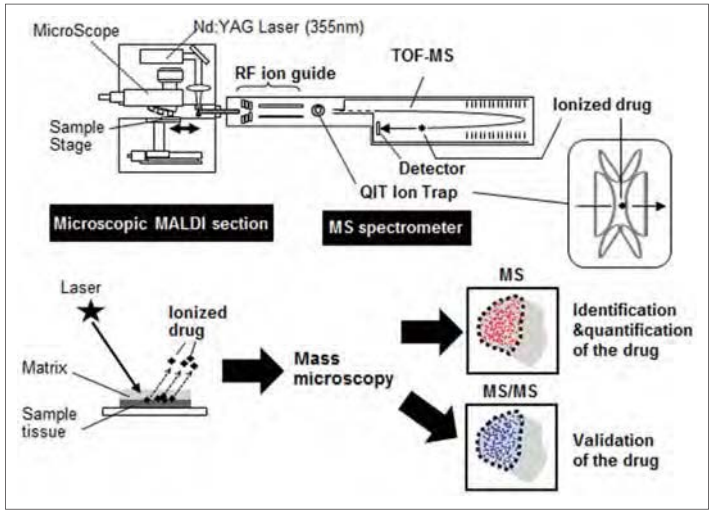

Fig. 1. Drug imaging system.
A schematic illustration of the drug imaging system. The matrix-coated drug sample is ionised and then separated on the basis of its *m/z*. Images from MS or MS/MS analysis are recorded.

Antitumour activity and visualisation of PTX and NK105 distribution within the tumour with MS analysis.

NK105 or PTX was administered at a PTX equivalent dose of 50 mg/kg/day to mice bearing BxPC3 pancreatic cancer xenografts on days 0, 4, and 8. NK105 showed significantly higher antitumour activity than the control (saline) and free PTX (Fig. 2a). To confirm the correlation of the distribution with the antitumour effect, the corresponding tumour sections were subjected to MALDI-IMS. A drug signal originating from PTX was detected in the tumours at 15 min and 1 h after the administration of PTX, but this signal decreased at 6 h and was below the limit of detection by 24 h (Fig. 2b). By contrast, the signal originating from the PTX released from NK105 (rPTX) following the accumulation of NK105 in the tumour was detected at 15 min as well as at 1, 24, 48, and 72 h after the administration of NK105. The signal intensity was greatest at 24 h (Fig. 2c). Tissue sections serial to those for MALDI-MS were also quantified by LCMS (Fig. 2d, e), the results of which correlated with the drug imaging results (Fig. 2b–e). The data did not contradict previous data obtained by HPLC14. The results of the MALDI-MS analysis demonstrate that significant levels of PTX were present in the tumour clusters, including within the centre of the tumour tissue.

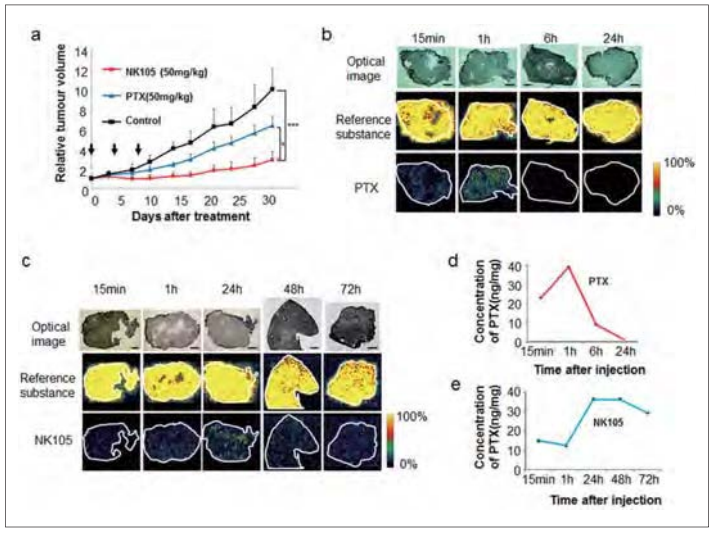

Fig. 2. Antitumour activity and visualisation of PTX and NK105 distribution with MS analysis.
(a) Antitumour activity was examined in an animal model with BXPC3 xenografts. NK105, PTX, or saline (as a control) was administered at a PTX equivalent dose of 50 mg/kg on days 0, 4, and 8. *P< 0.05 (PTX vs. NK105), ***P< 0.001 (saline vs. NK105). Bar = SD. (b)(c) Imaging of PTX within the tumour was performed after PTX (b) or NK105 (c) administration at a dose of 100 mg/kg. The upper, middle, and lower columns display the optical images, reference substance (an arbitrary signal of *m/z* 824.6), and PTX (specific signal of *m/z* 892.3 $[M + K]^+$), respectively. Bar, 1 mm. (d)(e) LC-MS analysis of the PTX concentration in the tumours treated by PTX (d) or NK105 (e). Tissue sections serial to those shown in (b) and (c).

Validation of the PTX and NK105 distribution within tumour tissue by MS/MS analysis.

Validation of the PTX content in each sample was performed in MS/MS mode. A structural diagram and the MS/MS fragmentation pattern (FP) of PTX are shown in Fig. 3a and b, respectively. According to the MS/MS-FP, *m/z* 607.19, which was selected as a PTX-specific fragment peak (Fig. 3c), was observed at a higher level in the tumour tissue sample at 1 h after PTX injection than at 1 h after NK105 injection (Fig. 3d, e).

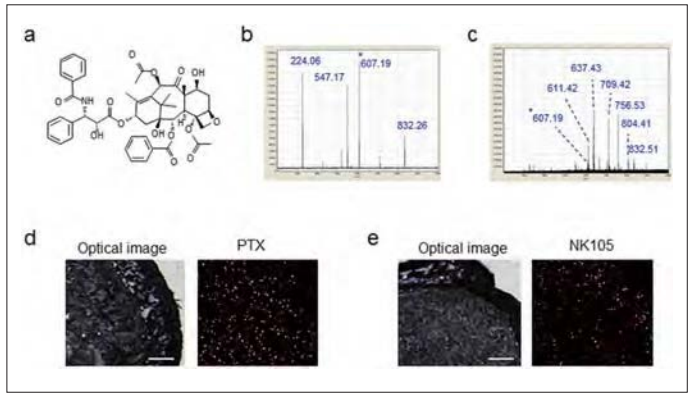

Fig. 3. Validation of the PTX and NK105 distribution within the tumour tissues by MS/MS analysis.
(a) The structure of PTX is shown. (b) (c) The PTX-specific MS/MS fragments at *m/z* 224.06, 547.17, 607.19, and 832.26 are shown in (b). The fragment pattern from MS/MS analysis of the tumour tissue sample is shown in (c). (d) (e) Images obtained by optical microscopy (left) and by MS/MS analysis of PTX (*m/z* 607.19*) (right) in tumours treated with PTX (d) or NK105 (e) at 1 h after injection. Bar, 500 μm.

Peripheral neurotoxicity and visualisation of the PTX and NK105 distribution by MS analysis.

Next, a mechanical stress test that measured the degree of peripheral neurotoxicity demonstrated that the mice in the PTX treatment group exhibited a significantly stronger hypersensitive reaction to the mechanical stress test than those in the control and NK105 treatment groups (Fig. 4a). To confirm the correlation of the distribution with the abnormal neurological reaction, we also applied MALDI-IMS and examined the distribution of PTX in peripheral neural tissue at 30 min, 1 h, and 24 h after administration. The signals surrounding and inside the nerve were lower after NK105 injection than after PTX injection (Fig. 4b, c). LC-MS analysis of the neural samples revealed that the concentration of rPTX after NK105 injection was also lower than that after PTX injection (Fig. 4d).

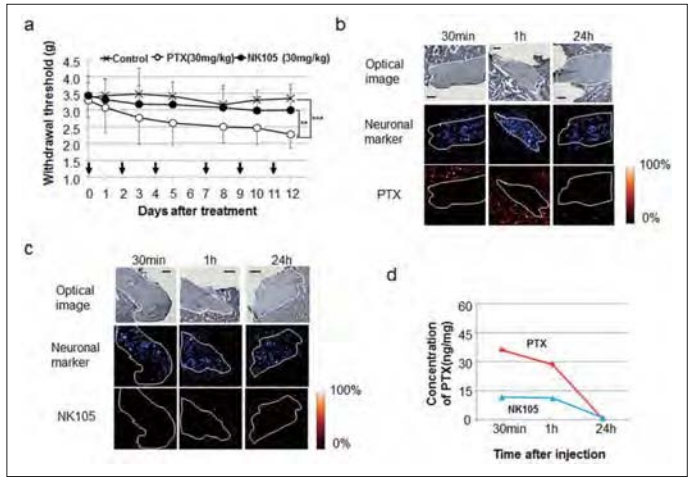

Fig. 4. Peripheral neurotoxicity and visualisation of PTX and NK105 distribution by MS analysis.
(a) Mechanical sensory stress was assayed in an animal model of PTX-induced peripheral neuropathy. NK105, PTX, or saline was administered at 30 mg/kg on days 0, 2, 4, 7, 9, and 11. **P < 0.01 (PTX vs. NK105), ***P < 0.001 (saline vs. PTX). Bar = SD. (b) (c) PTX within neuronal tissue was imaged after PTX (b) or NK105 (c) administration at a dose of 50 mg/kg. The upper, middle, and lower columns show the optical images, a neuronal marker (sphingomyelin-specific signal of 851.6 *m/z*), and PTX (specific signal of *m/z* 892.3 [M + K]+), respectively. The neuronal area is delineated by a white line. Bar, 200 μm. (d) Analysis of the PTX concentration by LC-MS. Tissue sections serial to those shown in (b) and (c).

Discussion

Conventional MALDI-IMS was expected to aid in the analysis of the global distribution of drugs within tissue. However, its application has been limited for a variety of reasons, including its limited resolution[7,8]. Recent progress in MALDI-IMS analysis, including the new features of our instrument, have achieved a MALDI-IMS resolution of 10 µm or less, which is advantageous for evaluating the drug distribution in specific cells or areas of interest within tissues[9–12]. The improved resolution also allows an IMS image to be overlaid on an optical image of the same sample. In fact, we were able to distinguish the nerve component from the surrounding tissue and evaluate the specific distribution of PTX in the region.

Tissue samples should be frozen without liquid solution to avoid the diffusion or loss of the drug from the tissue to the solution. For efficient ionisation in the present study, the sample was coated with a sufficient quantity of matrix by spraying. 2,5-Dihydroxybenzoic acid (DHB) was selected as the matrix to facilitate the efficient ionization of the drug. We are now attempting to use several other matrix materials to enhance the sensitivity of our MALDI-IMS technique. Moreover, we used a combination of MS and MS/MS for the imaging analysis. In the MS analysis, accurate quantification of PTX was demonstrated in vivo. In the MS/MS analysis, the presence of PTX was validated by a fragment-specific signal at 607.19 *m/z*, which does not overlap with any other signals. The combination of MS and MS/MS thus facilitates the accurate evaluation of the drug-originated signal by distinguishing the drug signal from endogenous metabolites with a similar *m/z*.

In this report, MALDI-IMS demonstrated that NK105 successfully delivered a large amount of the PTX payload within the tumour tissue after NK105 injection compared with PTX injection alone. More importantly, the precise localisation and levels of PTX within the tumour tissue were visualised and quantified due to the high resolution of the MALDI-IMS technique. The obtained data did not contradict our MS data or previous data obtained by conventional pharmacological analysis using HPLC[14]. Thus, our data demonstrated that the antitumour activity of NK105 is superior to that of PTX alone. In addition, the peripheral neurotoxicity of NK105 was significantly lower than that of PTX, consistent with the MALDI-IMS data. In fact, in a phase 2 clinical trial of NK105 in patients with previously treated advanced stomach cancer, only one of the 56 patients (1.8%) who entered the trial experienced grade 3 peripheral neuropathy[16]. Phase 2 trials of other PTX formulations, including Abraxane and conventional PTX, have demonstrated that the incidence of grade 3 or 4 peripheral neuropathy is greater than 10%[21,22]. A phase 3 clinical trial of NK105 vs. PTX is now underway, which may elucidate the clinical significance of this micellar drug delivery system (DDS).

Although many studies have indicated that NK105 accumulates selectively in tumour tissue compared to PTX by HPLC or LC-MS analysis, whether NK105 could deliver PTX to cancer-cell clusters within the tumour tissue was unknown. Cancer tissue is heterogeneous and consists not only of cancer cells but also of abundant tumour stroma, the latter of which can act as a barrier against macromolecules, including NK105[23,24]. In the present study, significant levels of PTX, even in the core of the tumour tissue, were observed following NK105 administration, and the NK105 was retained for a long period of time.

Low molecular weight (LMW) ACAs, including molecular targeting agents, can easily extravasate from normal blood vessels and cause various adverse effects. DDS drugs such as NK105, which exhibit low short-term accumulation in normal tissues that lack the EPR effect, can minimise this drug toxicity. Our data clearly demonstrate that the distribution of rPTX from NK105 in the peripheral nerve and surrounding tissues was quite low compared with PTX alone. These observations support the low incidence of peripheral neuropathy when PTX is administered as NK105.

This is the first report describing the precise distribution of a DDS drug by MSI, a new technique developed by our lab and others. Notably, we successfully visualise and quantified the distribution of a non-radiolabeled and non-chemically modified drug in various frozen tissue slices microscopically. In addition to PTX, we have successfully visualised other anticancer agents, including SN-38, epirubicin, and monomethyl auristatin E (MMAE) (data not shown). This success indicates that the MALDI-IMS technique can be applied to clinical biopsy specimens or surgically resected tissues after neoadjuvant chemotherapy. In addition, the data obtained by MALDIIMS can be utilised to facilitate drug design.

Methods

Cells and reagents.

The human pancreatic cancer cell line BxPC3 was purchased from the American Type Culture Collection and maintained in DMEM (Sigma, St. Louis, MO) supplemented with 10% foetal bovine serum (Tissue Culture Biologicals, CA), penicillin, streptomycin, and amphotericin B (Sigma) at 5% CO_2 and 37uC. NK105, a PTX-incorporating 'core-shell-type' polymeric micellar nanoparticle, was supplied by Nippon Kayaku Co. Ltd. (Tokyo, Japan). The weight-average diameter of the nanoparticles was approximately 85 nm, ranging from 20 to 430 nm. PTX was purchased from Tokyo Chemical Industry Co. (Tokyo, Japan).

Drug imaging by mass microscopy.

IMS analysis was performed using an atmospheric pressure (AP) MALDI-IT-TOF mass spectrometer (prototype Mass Microscope; Shimadzu)[25].

To prepare tissue samples, the tumour and sciatic nerve with surrounding tissue were surgically removed from a xenograft model at 15 min, 30 min, 1 h, or 24 h after drug administration (50 or 100 mg/kg). Samples wrapped in gauze were frozen in dry ice powder. The samples were then sectioned at a thickness of 10 µm and transferred to an indium tin oxide-coated glass slide (Sigma). The tissue section was dried (with no washing step) before matrix coating. For the application of the matrix onto the tissue slide, 30 and 50 mg/ml of DHB in 50% methanol and 0.1% trifluoroacetic acid were used. The 30 mg/ml DHB solution (0.4 ml) was sprayed twice, and then the 50 mg/ml (0.4 ml) solution was sprayed once with a 0.2-mm nozzle calibre airbrush (Procon Boy FWAPlatinum;Mr. Hobby, Tokyo, Japan); each spraying step was completed over 5 min. During spraying, the distance between the nozzle and the tissue surface was maintained at 15 cm to keep the surface dry.

IMS analyses were performed in positive-ion mode within a mass range of *m/z* 720–920 for PTX, with a spatial resolution of 30 µm. The laser was irradiated at 40 shots/spectrum at a frequency of 400 Hz, and the power was set to 60–65% using the Mass Microscope operation software. PTX distribution mapping was performed in BioMap (Novartis, Basel, Switzerland) using the *m/z* 892.3 ($[M + K]^+$) signal because the ($[M + K]^+$ signal showed more sensitive mass spectra than did the $[M + H]^+$ and $[M + Na]^+$ signals. The uniformly distributed *m/z* 824.6 ion (corresponding to cerebrosides (42 : 6) + Na) in tumour sections and *m/z* 851.6 ion (sphingomyelin (d18 : 1/24 : 1) + K) in neuronal tissue were used as internal controls to correct the PTX signal intensity.

MS/MS analysis of PTX (*m/z* 892.3) was performed with the CID function of the quadruple ion trap cell on the Mass Microscope. The *m/z* 607.19 fragment ion was generated on the tissue. This ion was also observed for the authentic PTX as the derivative and was used for MS/MS imaging of the drug. The instrument conditions for MS/MS imaging were identical to those used for the MS mapping described above, but the spatial resolution was 15 µm, and the laser power was 50%.

Animal model.

Antitumour activity.

Female BALB/c nude mice (5 weeks old) and DBA/2N mice (8 weeks old) were purchased from SLC Japan (Shizuoka, Japan). The nude mice were inoculated subcutaneously in the flank with 1×10^6 BxPC3 cells. The length (L) and width (W) of the tumour masses were measured every 3 to 4 days, and the tumour volume was calculated using the following formula: $(L \times W^2)/2$. When the mean tumour volume reached approximately 300 mm_3, the mice were randomly assigned to groups of five. Drugs (50 mg/kg) were administered on days 0, 4, and 8 by injection into the mouse tail vein.

Peripheral neuropathy.

To investigate the neurotoxicity induced by PTX and NK105, we designed the following experimental scheme: The development of nocifensive responses to mechanical stimuli was assessed in the mice (ref). Six-week-old female DBA/2N mice were randomly assigned to one of three groups, and their baseline nocifensive responses were measured. We confirmed that the mean latency was statically identical between the groups. The mice were then administered a dose of 30 mg/kg PTX or 30 mg/kg NK105 on days 0, 2, and 4 every week for 2 weeks, for a total of 6 injections (n = 10). Control mice were injected with 5% dextrose solution on the same schedule. After a total of 6 administrations, the mice were tested for transitional changes in their nocifensive responses. Mechanical allodynia was assessed by measuring the latency of paw withdrawal in response to noxious mechanical stimuli using a Dynamic Plantar Aesthesiometer (Ugo Basile, Varese, Italy). The mice were placed on a wire mesh floor in individual Plexiglas cages and were allowed to acclimate for approximately 1 h, during which exploratory and grooming activity was completed. The mechanical stimulus was applied to the plantar aspect of the hind paw using a 2-mm-diameter metal filament. The force was automatically increased at a fixed rate (0–5 g, 0.25 g/sec) until the mouse withdrew its paw. The analysis of paw withdrawal responses was repeated 4 times at 10-sec intervals. The paw withdrawal threshold (g) was determined from the average of the four measurements. None of the mice in this assay were inoculated with tumour cells.

All animal procedures and experiments were approved by Committee for Animal Experimentation of the National Cancer Centre, Tokyo Japan. These guidelines meet the ethical standards required by law and comply with the guidelines for the use of experimental animals in Japan. Statistical analysis was performed using analysis of variance (ANOVA) with Tukey' s multiple comparison tests.

LC-MS.

For LC-MS, several sections immediately adjacent to the sections for IMS imaging were serially collected into a vial, and the drug was extracted into acetonitrile by vortexing. The samples were analysed with a Liquid Chromatograph Mass Spectrometer LCMS-8040 (Shimadzu Corp.). A Kinetex 2.6 µm C18 100A (100 × 2.1 mm) analytical column was used. The injection volumewas 1 µl, and the flow rate was 0.5 ml/min. (A) Acetonitrile and (B) 0.1% (w/v) formic acid solution were used as the mobile phases. The mobile phase was introduced into the spectrometer via electrospray ionisation in positive ion mode under multiple reaction monitoring (MRM) conditions. In terms of the gradient, acetonitrile was conducted at 50% (B) for the first 1.5 min, increased to 100% for 0.25 min, and subsequently decreased back to 50% for 1.25 min. The PTX quantification was performed with the precursor *m/z* 854.45 ion, and the standard curve generated using the product *m/z* 104.95 ion was used. The data were collected in triplicate experiments.

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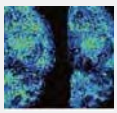
Author contributions

Y.M. developed the method. M.Y., M.F., K.O., Y.K., Y.Y. and M.T. performed the experiments and analysed the data. Y.M. and M.Y. wrote the manuscript.

The prototype Mass Microscope mentioned above is now sold as "iMScope" in all areas, excluding EU Nations and North America. It will be available in EU Nations within 2014.

Shimadzu Selection

These are the articles selected by Shimadzu for this issue. The articles are from application notes, technical reports and Shimadzu Review relating to Clinical Researches with a variety of instruments we produce. The cutting edge technologies are also included. Please obtain the articles of your interest through the links on the titles.



Selection 1 Technical Report

Lipid Analysis of a Mouse Brain by Statistical Analysis Software

The most important element of MS imaging is how efficiently it can analyze the enormous amounts of data acquired by data acquisition. Imaging MS Solution Analysis is dedicated image analysis software for the iMScope that offers easy peak detection, Principal Component Analysis (PCA), Hierarchical Cluster Analysis (HCA), and Region of Interest (ROI) analysis.

Selection 2 Technical Report

Development of a Comprehensive Detection Method of Eicosanoids and Platelet Activating Factor Using Ultra-High Performance Liquid Chromatography/Mass Spectrometry

Using LCMS-8040, simultaneous detection method of eicosanoids and PAF was developed. 54 MRM transitions for 50 eicosanoids and PAF (platelet activation factor) were optimized. Limit of quantitation for several targets was in the subpicogram range.

Selection 3 Shimadzu Review

Simultaneous Analysis of Primary Metabolites by Triple Quadrupole LC/MS/MS

We developed a "Primary metabolites LC/MS/MS method package" that enables the simultaneous measurement of 55 metabolites including those related to glycolysis, the pentose phosphate pathway, and the tricarboxylic acid cycle as well as amino acids and nucleotides when used with a triple quadrupole mass spectrometer.

Selection 4 Shimadzu Review

The Application of Ultra-Fast Triple Quadrupole LC-MS/MS to Forensic Analysis

In recent years, drug abuse and the use of illegal drugs have become a social problem as there are an increasing number of incidents of crime and addiction involving the use of illicit drugs such as psychotropics and hypnotics. The search for and identification of illegal substances has therefore become an issue in the forensic, toxicological, and clinical sectors, and there is a need for fast and highly sensitive simultaneous analysis methods.

Selection 5 Shimadzu Review

Development of Technology for Quality Evaluation of Human Pluripotent Stem Cells by Metabolome Analysis

To establish a technology for quality evaluation of pluripotent stem cells with metabolome analysis, we optimized sample preparation methods and developed an analytical method for gas chromatography/mass spectrometry-based metabolomics. This method enables us to quantify various species of metabolites including those associated with the glycolysis and citric acid cycles with high reproducibility.

Selection 6 Technical Report

Determination of Methylmalonic Acid in Serum, Plasma and Urine by LCMS-8030 using RECIPE ClinMass® Complete Kit MS5000

Measurement of methylmalonic acid (MMA) is used as a specific diagnostic marker for the group of disorders known collectively called as methylmalonic acidemias. The metabolic pathway involves methylmalonyl-coenzyme A (CoA) being converted into succinyl-CoA. Vitamin B12 is also needed for this conversion. Therefore measurement of MMA can be used to diagnose a number of genetic disorders in this pathway and is elevated in 90-98% of patients with B12 deficiency.

Selection 7 Technical Report

Analysis of 25-OH Vitamin D2 / D3 in Plasma and Serum by LCMS-8040 using ClinRep® LC-MS/MS Complete Kit MS7000

Vitamin D measurement has become an important component in clinical assays largely because deficiency is associated with a number of disorders such as rickets, osteomalacia and osteoporosis. When serum concentration falls below 20 ng/mL osteoporosis can result, with normal levels ranging from 20-50 ng/mL. Developments in high pressure fast chromatography LC-MS/MS have now enabled on-line sample preparation methods and analysis times in less than 3 minutes.

Selection 8 Technical Report

Measurement of immunosuppressants, Tacrolimus, Sirolimus, Everollmus and Cyclosporine A from whole blood using on-line SPE and LCMS-8030

Immunosuppressants are an important class of compounds which are commonly used by transplant recipients to avoid organ rejection. In addition, they are used for the treatment of immune-mediated diseases or disorders of the immune system and non-autoimmune inflammatory reactions such as heavy allergic asthma. The therapeutic concentration range of these compounds, typically narrow, requires careful monitoring from whole blood to ensure the correct patient dosage.

Selection 9 Technical Report

Quantitation of 33 benzodiazepines by LCMS-8030 from human serum using RECIPE ClinMass® LC MS/MS Complete Kit MS6000

Benzodiazepines belong to a group of psychotropic drugs that are used for the treatment of anxiety and restlessness as well as for epileptic seizures. Diazepam, one of the most commonly prescribed benzodiazepines, is used to treat a number of conditions by the pharmacological action of enhancing the neurotransmitter GABA by binding to the GABAA receptor, causing CNS depression.

Selection 10 Application Data Sheet

Analysis of metabolites in human serum using GC-MS

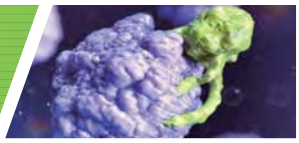
Metabolome analysis, a comprehensive analysis of the various metabolites generated as biological functions are maintained, is widely used in disease biomarker searches and other investigations. To conduct these investigations, it is necessary to identify the metabolites contained in biological samples.

Selection 11 Application Data Sheet

Analysis of Metabolites in Serum Using GCMS/MS

Single quadrupole GC-MS provides excellent chromatographic resolution and enables stable measurements, and is therefore widely utilized for metabolome analyses involving the comprehensive analysis of in vivo metabolites. However, biological samples contain many metabolites and various matrices, so separation with single quadrupole GC-MS can be difficult.

Paradigm Shift in Cancer Diagnosis: Basics and Algorithm



Sen TAKEDA, Kentaro YOSHIMURA Department of Anatomy and Cell Biology, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, JAPAN.

Here is one hypothetical but possible scenario: you decide to visit a hospital because you have been feeling mild bowel discomfort and occasionally experiencing hematochezia. After enduring an endoscopic examination, the doctor tells you that he discovered a small polyp in your colon and, as a result, he took a small piece of tissue for a biopsy. Usually, it takes about one week to receive a final pathohistological diagnosis. During this time, you are likely to be extremely nervous while waiting for the results. However, if your doctor were able to use the machine that we are currently developing, it would take only a few minutes to obtain supportive information for the clinical diagnosis. Therefore, you would be relieved of anxiety as well as the inconvenience of having to visit the hospital repeatedly to receive the final diagnosis.

This machine is not a castle in the air. A couple of years ago, we launched a new project to develop the "rapid cancer diagnostics supportive machine". It is basically constructed on our Single Quadrupole Liquid Chromatograph Mass Spectrometer (Shimadzu LCMS-2020), whose ionization unit is replaced with a new ionization device called PESI. Additionally, we employed a Bayesian inference-based machine learning algorithm, designated dPLRM. Our system requires only a small piece of tissue and minutes to complete the task, as I illustrated using the example above. Now, let's take a brief look at the gadgetry, elementary techniques and resources that come together for this promising approach for the rapid diagnosis of diseases, particularly cancers.

Overview of the System. A small piece of tissue, about the size of grain of rice, is placed on a disposable cartridge, the switch is turned on, and the specific database of interest is selected. The PESI-MS automatically measures the samples by picking up and ionizing them at the optimal conditions. In a couple of minutes, the probability of either cancer or benign tumors is indicated on the display (Fig. 1). In the near future, our system will be able to show us the histotypes, as well as the degree of differentiation, which are indispensable for determining therapeutic protocols. As the gadgetry is constructed on a bench-top basis, it is easily installed in clinical settings or hospitals.

What is the PESI? It stands for Probe ElectroSpray Ionization. Technically, this technique is a derivative of ESI, but is superior in terms of the time required for analyses, as it does not need any sample pretreatment, such as desalting, fractionation and concentration. In PESI, inorganic salts in bodily fluids and tissues that often interfere with measurements do not affect the ionization process per se. Moreover, even sub-picoliters of sample are sufficient for further MS analyses and suppression effects are minimal. Furthermore, the tip of the needle used in the analysis is smaller than the average cell diameter, so it does not damage the samples upon measurement. The non-invasiveness of the system is one of the biggest advantages to medical applications.

Machine Learning and Database. We do not follow conventional multivariate analyses in dealing with the huge amount of data obtained by PESI-MS. All of the spectral peaks observed within certain *m/z* windows are processed for machine learning, designated the dual Penalized Logistic Regression Machine (dPLRM). The datasets containing all spectra are compiled as specific databases for each disease class and these specific databases are referred to by the dPLRM during diagnosis. This enables us to distinguish one group of disease class from others or healthy groups by comparing the data fed into the machine to the databases in a mathematical space with thousands of dimensions. This multidimensional comparison of data draws boundaries that assign a diagnosis to the measured samples. As this algorithm depends on Bayesian inference, this system gains more accurate prediction power by updating the database.

Future Perspectives. This system is a versatile approach that is applicable to various fields, such as pharmaceutical, agricultural and food industries. Needless to say, its application will be extended to the diagnosis of diseases other than cancers. To realize the development and application of this system in multiple fields, we have to construct a database based on measurements of real samples.

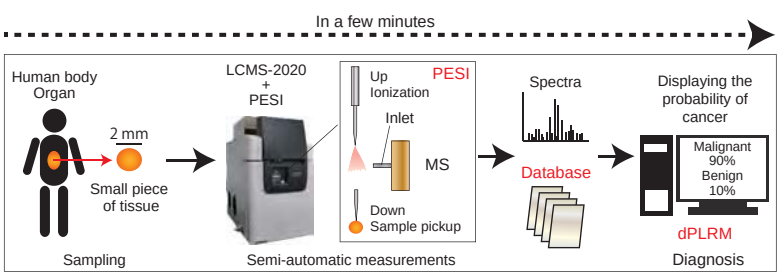


Fig. 1 Overview of rapid cancer diagnostics supportive machine

For Research Use Only. Not for use in diagnostic procedures.

Shimadzu Opens New Quality Center

- A quality assurance base for the Shimadzu Group to promote the provision of high-quality, reliable products and services-

In an effort to improve the quality of products, Shimadzu has opened its new Quality Center at its head office (Sanjo Works) premises (Kyoto, Japan).

It consolidates under one roof the analysis and evaluation equipment and functionality needed for product development and failure analyses. It will work as a center for quality assurance development as well as standard and regulatory compliance.

One of the features of the new facility is a large 10 meter anechoic chamber and two compact ones to perform EMC testing, which had been conducted at external facilities, in-house. It assures compliance with Electro Magnetic Compatibility (EMC)* regulations.

The large one has a 10 meter turntable on the floor, enabling the evaluation of a large instrument from any 360 degree direction. It also has many radio wave absorbers on all of the walls and the ceiling to avoid electromagnetic interferences during measurement. Furthermore, it is covered with more than eight hundred 900 mm×1800 mm-rectangular lead sheets to measure X-rays from X-ray equipment.

In addition to the manufacture of high-quality products, from an early stage of development, three chambers enable faster development. Equipped with large constant temperature and humidity testing chambers for testing large instruments, and various equipment for materials analyses, precise measurements, simulation verification, and reliability evaluation, the center will significantly improve product reliability and safety.

The completed Quality Center is a three-story steel frame building with 5,500 square meters of floor space. The building was constructed incorporating environmental conservation measures, including heat-insulation metal sandwich panels and LED lighting fixtures (a total investment of approximately 1.7 billion yen). The center will begin full operation in summer 2014, after the relocation of equipment from existing buildings and the accreditation of the EMC laboratory.

We expect that the establishment of this new Quality Center will reduce defects, accelerate problem analysis, and provide higher-quality products and more efficient services to customers throughout the world.

* Electro Magnetic Compatibility is the ability of electrical or electronic equipment to operate in proximity to other devices, without suffering or causing malfunctions due to the absorption or emission of electromagnetic noise.

Shimadzu Registers HPLC and LC-MS Instruments as Class I Medical Devices with US Food and Drug Administration

In response to a growing need for analytical measurement in healthcare applications, Shimadzu Corporation, Japan, has registered several of the company's high-performance liquid chromatographs (HPLC) and high-performance liquid chromatograph mass spectrometers (LC-MS) as Class I medical devices with the US Food and Drug Administration (FDA). These are the first Shimadzu analytical instruments registered with the FDA as medical devices.
The use of analytical devices in medical screenings and disease prevention has been on the rise in recent years. Starting in July 2011, the FDA required manufacturers to register analytical instruments as Class I medical devices to ensure their accuracy and reliability when used in healthcare applications.

The following Shimadzu instruments have been registered as Class I medical devices:

- LC-20 CL and LC-30 CL HPLCs
- Single-quad LCMS-2020 CL
- Triple-quad LCMS-8030 CL, LCMS-8040 CL and LCMS-8050 CL

The registered instruments were designed in Shimadzu Corporation's head office (Sanjo Works, Japan) and manufactured at Shimadzu USA Manufacturing (SUM) located in Canby, Ore. Both facilities obtained ISO 13485 certification, the globally recognized international quality management standard for medical equipment, in 2013. SUM is conducting manufacturing of the medical devices mentioned under the FDA regulation 21 CFR 820.

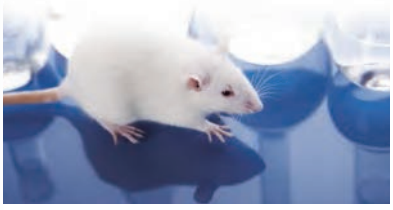
Shimadzu Welcomes and Trains Two Vietnam National University Lecturers

Shimadzu Corporation welcomed two lecturers from the Vietnam National University (VNU) and provided them with training in the use of analytical and measuring instruments. This training was conducted under the Shimadzu-A.Nakamoto Scholarship program as part of activities to assist human resource development that started after Shimadzu's President, Akira Nakamoto, received an honorary doctorate from VNU.
The two selected applicants received training in the Global Application Development Center in the head office from October 7 to November 1.
Dedicated programs were prepared for each lecturer; one focused on food safety issues that influence people's health, while the second one concentrated on R&D and quality control of polymer materials, which have gained attention as advanced materials. They learned about the characteristics of analytical and measuring instruments used for these purposes, analytical methods including pretreatment, and their application in practical cases. They also operated a variety of analytical and measuring instruments, including our ultra fast mass spectrometry (UFMS) series, spectrophotometers, thermal analyzers, and material testing machines, and analyzed the acquired data.
VNU is one of the major centers of advanced education and research in Vietnam. The university and Shimadzu aim to develop and utilize a jointly established cutting-edge research laboratory.
As a global company, Shimadzu will continue to actively exchange human resources and conduct business in cooperation with the international community.

New Products

LC/MS/MS Solution System Packages

Shimadzu LC/MS/MS Method Packages provide fast, simultaneous analytical methods for multiple components in a variety of applications.



LC/MS/MS Method Package for Primary Metabolites

Permits high-throughput analysis of 55 primary metabolites associated with the glycolytic system, TCA cycle, and pentose phosphate pathway as well as amino acids and nucleotides.

LC/MS/MS Method Package for Lipid Mediators

Enables simultaneous analysis of 130 lipid mediators and related compounds derived from arachidonic cascade and its derivatives.

LC/MS/MS Rapid Toxicology Screening System

Features pre-determined analytical conditions, including MRM transitions, LC separation conditions, retention times, spectral libraries, and report files, enabling rapid implementation of a screening method for several classes of substances.

*For Research Use Only. Not for Use in Diagnostic Procedures.

Crude 2 Pure

Purification/powderization after retention and concentration of fractions of target compounds obtained by a preparative LC system

When purifying target compounds from extracts of natural products and synthetic substances via preparative LC, powderization of the target compounds of the fraction is an important process. Ordinarily, it takes time to purify and powderize the target compounds obtained by the preparative LC. It is also difficult to recover high-purity powder.
The Crude2Pure system, which is based on ground-breaking purification methods, provides a new approach that reduces the work of the purification/powderization process after preparation.

Features
- Removing Solvent-derived Components and Recovery of High-Purity Powder
- Fast Powderization of Liquid Fractions
- Setting Samples at Any Time – Open Access –

SPM-8000FM

See the Nano World Come to Life

The new HR-SPM scanning probe microscope uses frequency detection.
This instrument is not only capable of ultra-high resolution observations in air or liquids, but for the first time enables observations of hydration/solvation layers at solid-liquid interfaces.
HR-SPM: High Resolution Scanning Probe Microscope

Features
- Uses the FM-AFM method.
- Noise in air and liquids is reduced to 1/20th that of existing methods.
- Achieves the performance level of a vacuum-type SPM, even in air and liquids.

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