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# Development of a Next-Generation Laser-Scanner System for Life Science Research

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## Abstract

We developed a next-generation laser-scanning system that exhibits sufficient versatility for use in life sciences research. In this report, we describe the configuration of the system and the features of its scanner optics, new functionalities, and user-friendly graphical user interface (GUI). This system has been made commercially available as “Amersham Typhoon” and “Amersham Eraser” by GE Healthcare.

## 1. Introduction

In the fields of biochemistry and molecular biology, an analysis technique in which protein, DNA or RNA is labeled with a radioisotope or a fluorescent dye and separated by electrophoresis and the separation pattern is imaged for analysis is often used. And in the field of drug development, a technique in which a radioisotope-labeled drug is administered to a mouse and the distribution inside the body is imaged for analysis of the pharmacokinetics is often used.

The development of laser scanner system for life science research in FUJIFILM was started for the purpose of imaging radioisotope-labeled samples. In 1987, we developed BA-100 for scanning a radioisotope-exposed imaging plate (phosphor screen) and capturing the image, based on the technology of the medical X-ray image analysis system, the FCR system. BA-100 was originally developed for market search. In 1989, we developed BAS-2000 and its market was established. After that, it was developed into the BAS series. In 1997, we

developed FLA-2000 equipped with the blue laser and the green laser we had developed and put into practice in photo printing systems. The model supported imaging of fluorescent-labeled samples. It was developed into the FLA series.

Since 2009, FUJIFILM has had a global alliance with GE Healthcare Bio-Sciences for the image analyzing systems business in the field of biosciences<sup>1)</sup>. FUJIFILM developed and manufactured the Typhoon FLA7000, 9000 and 9500 laser scanner image analyzing systems and the FLA Image Eraser for erasing latent images of an imaging plate, and they have been sold by GE Healthcare.

As a successor of those models, we have developed a next-generation laser scanner system, the Amersham Typhoon series and Amersham Eraser, based on a new concept in pursuit of improvement of detection sensitivity, versatility and ease of use. In October 2016, GE Healthcare started their sale. This report describes the configuration of the laser scanner system and the features of the scanner optics, new functions and user-friendly GUI.



Fig. 1 External appearance of Amersham Typhoon and Amersham Eraser

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Original paper (Received December 14, 2016)

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Table 1 Specifications of Amersham Typhoon

Item	Amersham Typhoon 5	Amersham Typhoon RGB	Amersham Typhoon IP
Detection modes	Phosphor imaging, Fluorescence (RGB/NIR), Densitometry, Chemiluminescence (Dark scan)	Phosphor imaging, Fluorescence (RGB), Densitometry, Chemiluminescence (Dark scan)	Phosphor imaging
Laser excitation wavelengths	LD488, SHG532, LD635, LD685, LD785	LD488, SHG532, LD635	LD635
Measurable dynamic range	> 5 orders of magnitude		
Bit depth	16-bit		
Scanning area	40 cm × 46 cm	35 cm × 43 cm	
Scanning mode	Auto, Semi-auto, Manual		Manual
Pixel sizes	10, 25, 50, 100 and 200 μm prescan 1000 μm		10, 25, 50, 100 and 200 μm
Standard filters	IP 390BP, Cy2 525BP20, Cy3 570BP20, Cy5 670BP30, IRshort 720BP20, IRLong 825BP30	IP 390BP, Cy2 525BP20, Cy3 570BP20, Cy5 670BP30	IP 390BP
Sample stages	Fluor Stage, Multi Stage, and IP Stage		IP Stage
Data format	16-bit gel, 16-bit img, 16-bit grayscale tif		
Dimensions (W × H × D)	900 mm × 400 mm × 800 mm		
Weight	94 kg	93 kg	92 kg

Table 2 Specifications of Amersham Eraser

	Amersham Eraser
Light Source	LED
IP size	Up to 35 cm × 43 cm
Erasing time	10, 20, 40, and 60 min
Dimensions (W × H × D)	550 mm × 78 mm × 510 mm
Weight	10 kg

Table 3 Sample stage and application

Sample stage	Application
IP stage	Imaging plate (Phosphor screen)
Fluor stage	Gel, Membrane
Multi stage	DIGE gel cassette Tiger plate Glass slide Large glass cassette (33 cm × 42 cm)

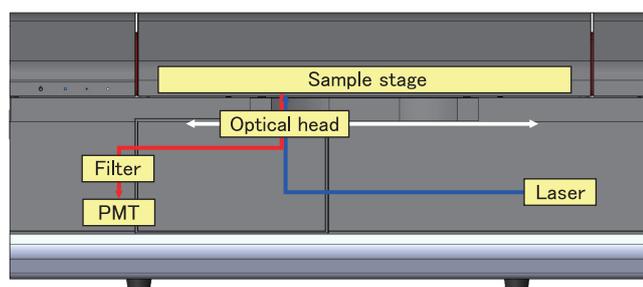


Fig. 2 Overview of the internal structure of Amersham Typhoon

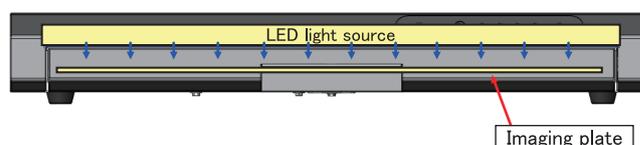


Fig. 3 Overview of the internal structure of Amersham Eraser

## 2. System configuration

Fig. 1 shows the external appearance of Amersham Typhoon and Amersham Eraser. Amersham Eraser can be placed next to Amersham Typhoon on a level by placing on the cabinet for storing sample stages (see below). All the components come in unified designs. Tables 1 and 2 show the specifications of Amersham Typhoon and Amersham Eraser, respectively.

Amersham Typhoon is a laser scanner image analyzing system. While irradiating a laser beam to a sample placed on the sample stage, the system moves the optical head two-dimensionally to scan. The high-sensitive detector (PMT: photomultiplier tube) detects the emission light and an image is captured. Fig. 2 shows the overview of the internal structure of Amersham Typhoon.

Amersham Typhoon comes in several models. Amersham Typhoon IP supports the phosphor imaging mode in which the photostimulated luminescence from an imaging plate is detected. Amersham Typhoon RGB supports, in addition to the phosphor imaging mode, the fluorescence mode for detecting the fluorescence of an RGB-fluorescent-labeled sample, the densitometry mode for visual detection of a dyed sample, and the chemiluminescence (dark scan) mode for detecting the light emitted by a sample labeled with a chemiluminescent substrate without irradiating a laser beam. Amersham Typhoon 5 supports detection of a sample labeled with a near-infrared (NIR) fluorescent dye besides all the modes above. For this purpose, the user can choose Amersham Typhoon with functions suitable for the purpose of analysis. Amersham Typhoon can be equipped with up to five lasers, eight filters and two PMTs. The system is flexibly configured to have the optimal combination of those units for the application. Amersham Typhoon IP or RGB is easily upgradable on-site adding lasers, filters and PMT.

As shown in Table 3, Amersham Typhoon is provided with three types of sample stages to meet various applications.

The IP stage used for scanning an imaging plate is structured to allow scanning without bringing the exposure side of an imaging plate into contact with the stage, to prevent contamination from radioisotope of the imaging plate.

The fluor stage is used for scanning electrophoresed gel or membrane transferred by Western blotting. This stage uses a glass with less autofluorescence to prevent a reduction of the detection sensitivity.

The multi stage meets various applications by adjusting the movable guide plate. The stage is used for scanning DIGE (difference gel electrophoresis) gel cassette, titer plate, glass slide and large glass cassette (33 x 42 cm). The stage is designed to mount up to two DIGE gel cassettes or up to nine titer plates considering the usability.

Amersham Eraser is designed to apply light onto an imaging plate to erase latent images. Fig. 3 shows the overview of the internal structure of Amersham Eraser. While a fluorescent tube is used for the light source in the conventional eraser, LED is employed for Amersham Eraser. This reduces the power consumption drastically (25% compared to the conventional model) and prolongs the service life. A highly uniform surface light source and an extremely thin system body are also achieved (47% compared to the conventional model).

## 3. Scanner optics

The scanner optics of Amersham Typhoon is optimized to enhance the detection sensitivity. That enables scanning of very weak signals. The following sections describe the features.

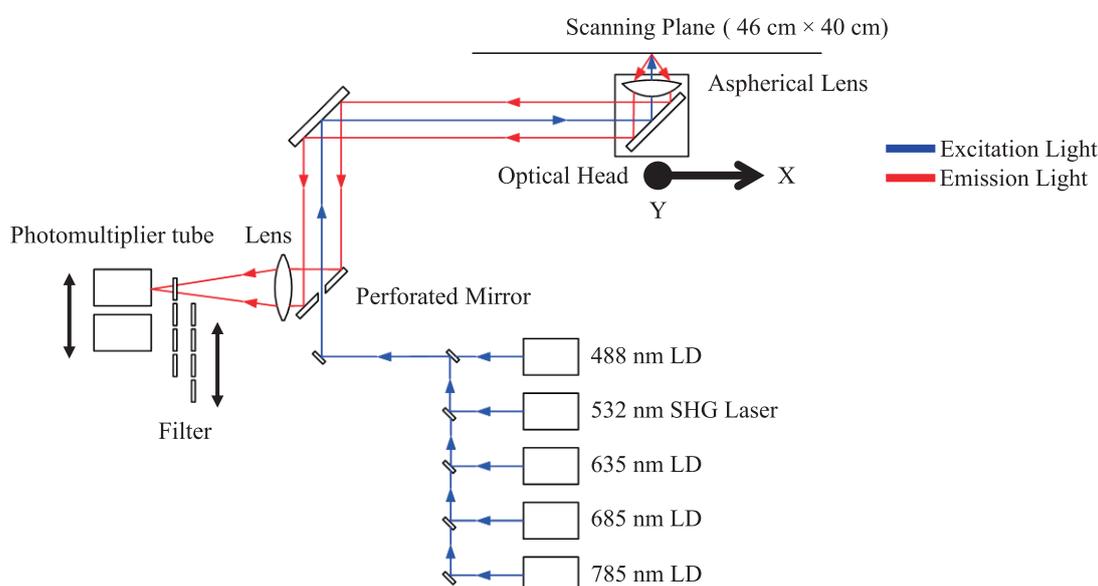


Fig. 4 Overview of the scanner optics

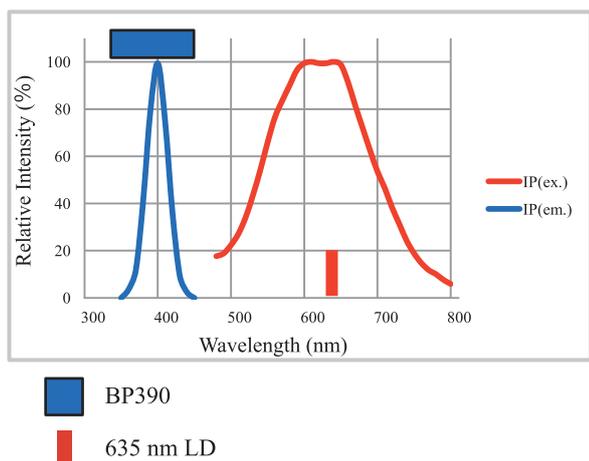


Fig. 5 Spectral characteristics: PSL (photostimulated luminescence) excitation (ex.) and emission spectra (em.) of the imaging plate and the wavelength of the excitation laser and emission filter

### 3.1 Improvement in light collection efficiency

We have developed a new scanner optics consisting of lasers, lenses, mirrors, filters and PMTs (Fig. 4). Using optical simulation, we have optimized the system so that signal light, like fluorescence from a sample, is efficiently collected on the PMT in the whole scanning area (46 x 40 cm) while the optical head is moving in the X-Y direction. The mirrors are applied with a broad-band dielectric multi-layer coat for high efficiency, not an ordinary metal coat. In total, the light collection efficiency is more than doubled the conventional level.

### 3.2 Optimization of laser and filter

Fig. 5 shows the photostimulated luminescence excitation spectrum and the emission spectrum of an imaging plate (photostimulable phosphor: BaF(Br•I): Eu), the excitation laser wavelength and the filter properties used for the phosphor imaging mode. Just as the conventional models, the laser wavelength and the filter properties are optimized.

Fig. 6 shows the spectra of the Cy series fluorescent dyes (Cy2, Cy3 and Cy5), laser wavelength and fluorescent filter properties used for those dyes. As the excitation spectrum of Cy2 has the peak at 489 nm, 473-nm LD is used for the conventional models. For Amersham Typhoon, as it is higher in sensitivity, 488-nm LD is employed.

When Cy2, Cy3 and Cy5 are used in a sample, it is important that crosstalk is small. For instance, when Cy2 is to be detected using 488-nm LD and a fluorescent filter for Cy2 (525BP20), if Cy3 fluorescence is picked up (crosstalk), accurate detection is not performed. To detect fluorescence with high sensitivity and to minimize crosstalk, the laser and the filter are combined the way it optimized the relationship between the laser wavelength and the fluorescent filter properties.

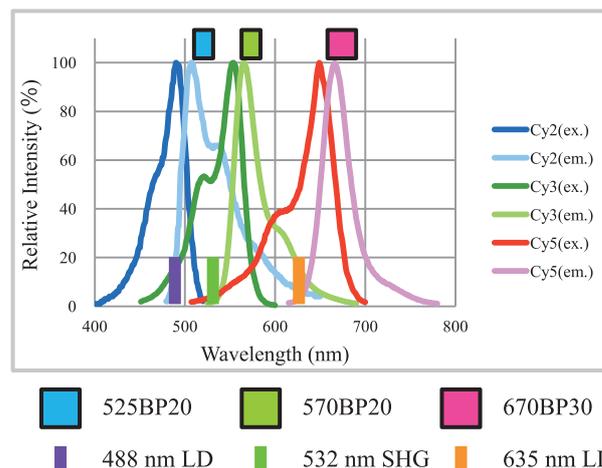


Fig. 6 Spectral characteristics: excitation (ex.) and fluorescence emission spectra (em.) of the Cy dyes and the wavelengths of the excitation lasers and emission filters

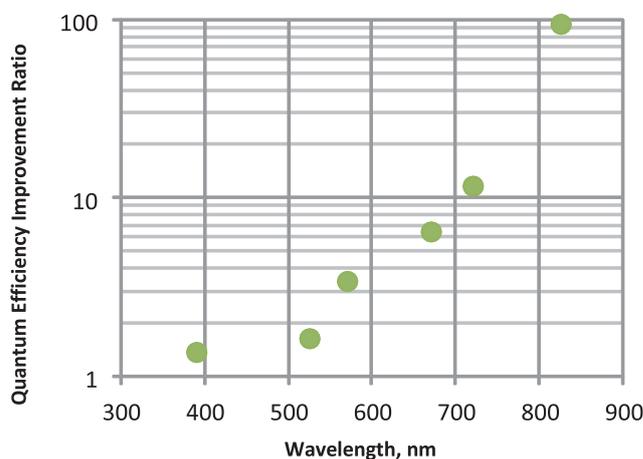


Fig. 7 Ratio of quantum-efficiency improvement

In the near infrared range, the system is designed to detect fluorescence with high sensitivity and to minimize crosstalk, assuming fluorescent dyes with the excitation wavelength (peak) between 670 nm and 700 nm and between 770 nm and 800 nm. Specifically, 685-nm LD and 720BP20 filter are used in combination and 785-nm LD and 825BP30 filter are used in combination.

### 3.3 Optimization of detector

Fig. 7 shows the improved ratio (assuming that of the conventional models as 1.0) of quantum efficiency of PMT for each of main fluorescent wavelengths. Particularly in the near infrared range, exceeding 700 nm, the quantum efficiency is improved 10 to 100 folds. That contributes to great improvement in sensitivity and signal-to-noise ratio.

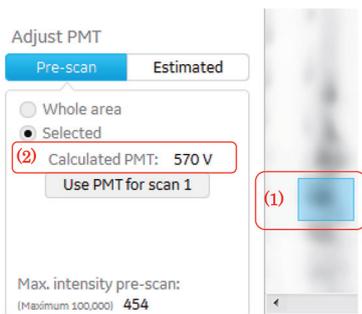


Fig. 8 Semi-auto prescan: (1) area of interest and (2) calculated PMT

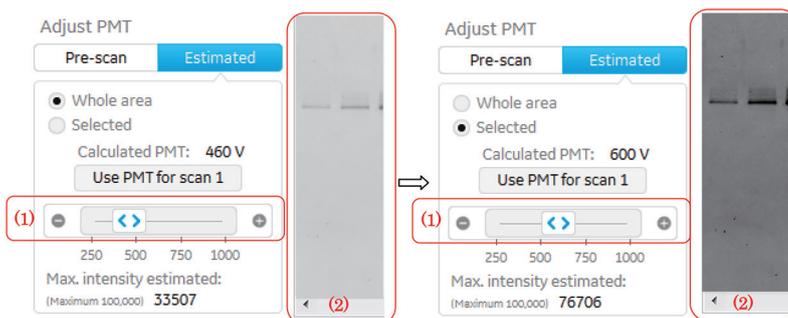


Fig. 9 Semi-auto estimation: (1) ruler and (2) simulated image

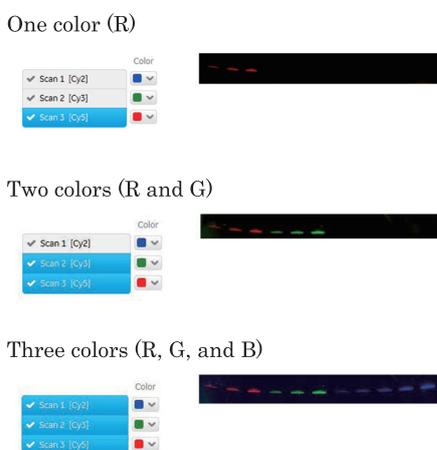


Fig. 10 Overlay view

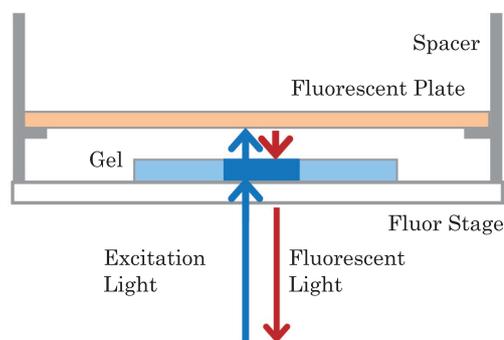


Fig. 11 Overview of the densitometry system

## 4. New functions

### 4.1 Automatic setting of PMT high voltage

If the PMT high voltage setting for scanning is too low, some signals often become invisible. If the setting is too high, some signals often saturate. To solve this, Amersham Typhoon provides new auto and semi-auto functions to perform brief scans with a low resolution (pre-scan) to calculate the PMT high voltage automatically.

In the auto function, PMT high voltage setting is determined from the maximum signal intensity of the whole pre-scanned image and scanning is performed automatically with the setting.

In the semi-auto function, the user determines the PMT high voltage setting while looking at the pre-scanned image. The semi-auto function is divided into two functions. In one of the functions, the user selects an area in the pre-scanned image and the PMT high voltage is calculated from the maximum signal intensity of the selected area (Fig. 8). This

function allows the user to scan by determining automatic setting of a PMT high voltage suitable for the band the user wants to see. In the other function, the PMT high voltage is set by moving a ruler and an image predicted from the setting is displayed (Fig. 9). This function allows the user to scan by determining the PMT high voltage setting while looking at the intensity distribution of the whole image.

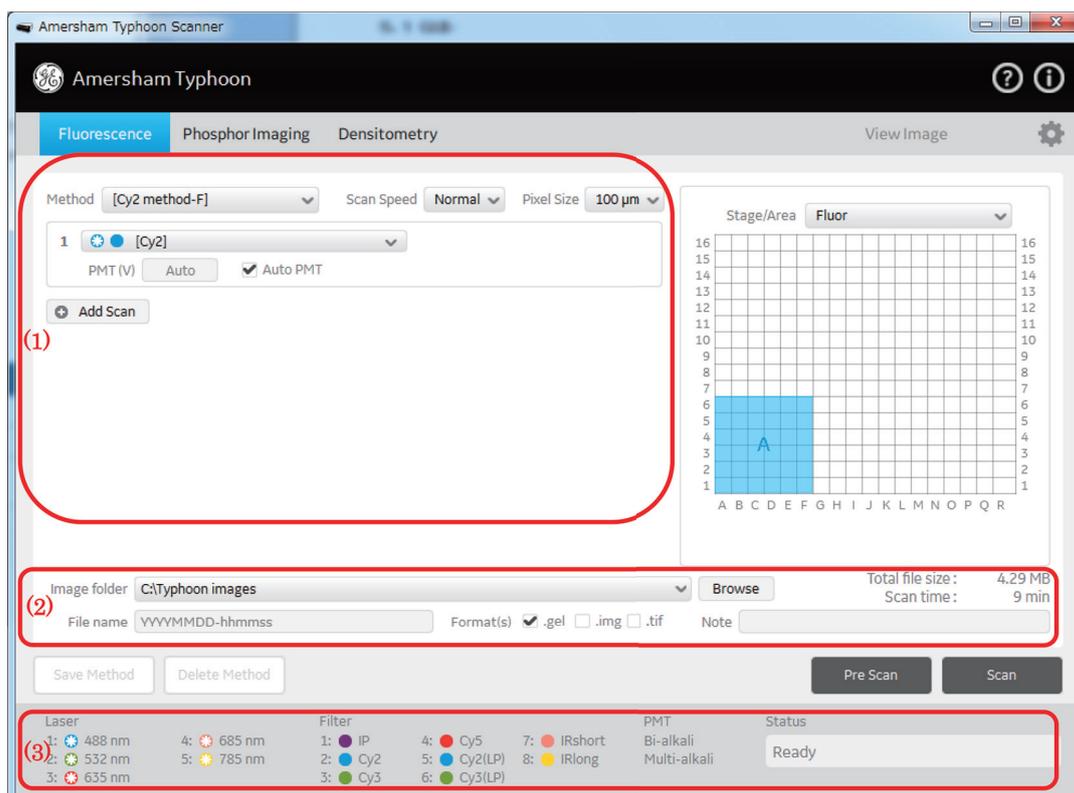
### 4.2 Overlay view

Amersham Typhoon provides an overlay view of up to three colors after scanning a sample using multiple fluorescent labels. As shown in Fig. 10, an image is displayed in one color, overlay in two colors or overlay in three colors.

### 4.3 Densitometry

Amersham Typhoon provides measurement function of relative optical density (OD) of CBB-dyed gel in addition to the conventional digitizing functions.

As shown in Fig. 11, the relative OD is measured using



Part	Function	Description
(1)	Scan settings	Scan settings can be defined.
(2)	Image file settings	Image settings can be defined. Three file formats can be selected.
(3)	Instrument status	The status of the lasers, filters, and PMT are shown in this pane. All units are automatically recognized.

Fig. 12 Fluorescence set up screen

the fluor stage, the spacers and the fluorescent plate for densitometry. The spacer is used to prevent contamination by contact between the fluorescent plate and gel. The excitation light passes through the gel and excites the fluorescent plate. The excited fluorescent light passes through the sample again and is collected on the PMT. As light passes through the sample twice, collected light is attenuated corresponding to about twice the OD of the sample. A new algorithm considering the attenuation enables measurement of the relative OD of a sample.

#### 4.4 Slow scan mode

To further reduce noise, we have developed the slow scan mode, combining oversampling and slow scanning. Oversampling reduces noise by sampling the same pixels several times for shorter time than the sampling time per pixel and averaging. In the slow scan mode, the sampling time per pixel is lengthened and the number of sampling is increased to achieve an image with a high S/N ratio.

## 5. User-friendly GUI

### 5.1 GUI

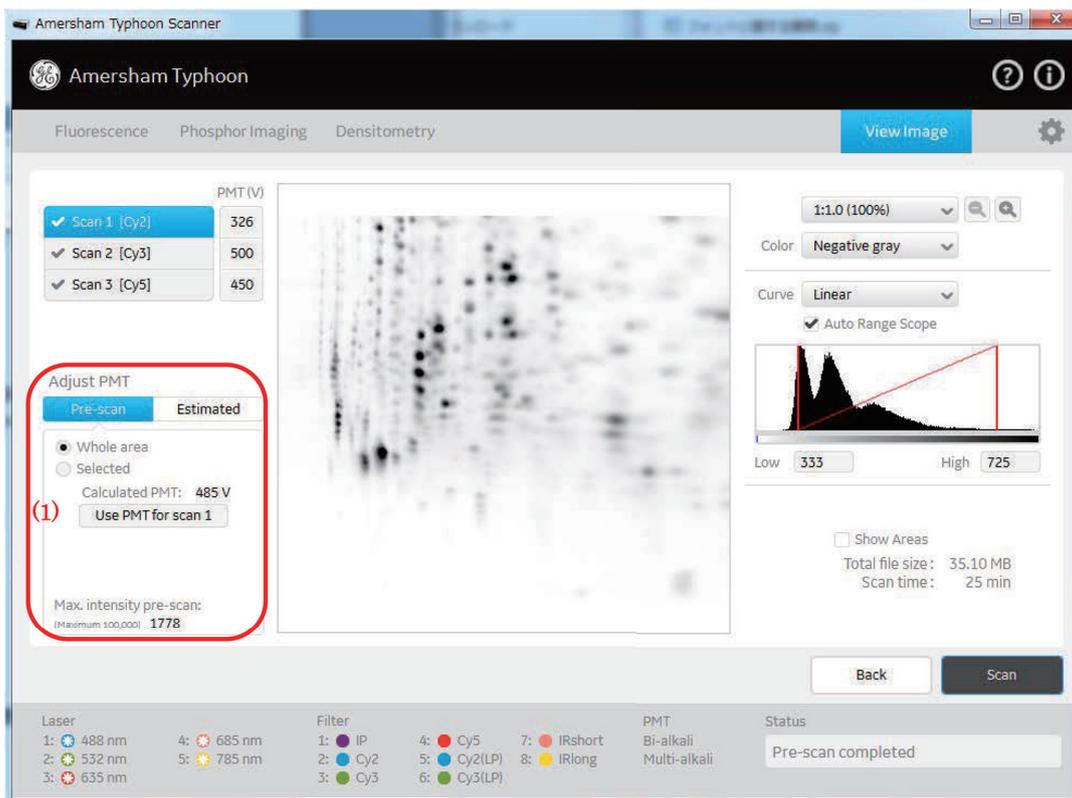
Amersham Typhoon provides user-friendly GUI, equipped with new functions including the aforementioned automatic setting of PMT high voltage, while maintaining the unity with the conventional Typhoon FLA series. Fig. 12 shows an example of the parameter setting screen in the fluorescence mode. Fig. 13 shows an example of a pre-scanned image on screen.

### 5.2 Automatic filter recognition

Amersham Typhoon provides automatic recognition of the filters mounted. If changes are made in the combination of filters, they are reflected automatically on the GUI screen as shown in Part (3) of Fig. 12.

### 5.3 Output file format

As shown in Part (2) of Fig. 12, three file formats (gel, img



Part	Function	Description
(1)	Adjust PMT	The PMT voltage can be adjusted in this pane (Semi-auto). The intensity is displayed in this pane.

Fig. 13 View of the image screen (after the prescan)

Table 4 Imaging mode and file format

Imaging Mode	Fluorescence		Phosphor Imaging	Densitometry
	Normal *1	DIGE		
File Format	gel file img file tif file	gel file	gel file img file tif file	tif file

\*1 Includes chemiluminescence (dark scan)



Fig. 14 Intensity display(after the scan):(1) area of interest and(2) maximum intensity

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and tif) are available in Amersham Typhoon to meet various purposes. In a gel file, the signal intensity is converted to a square root. This format has been supported since the conventional Typhoon FLA series. In an img file, the signal intensity is converted to a logarithm. It is used in the BAS series. A tif file is a general-purpose file format not used for quantitative analysis. Table 4 shows the relationship between imaging modes and output file formats.

#### 5.4 Intensity display

Amersham Typhoon provides display function of the signal intensity of an area selected by the user on screen after scanning or pre-scanning is completed. As shown in Fig. 14, the maximum signal intensity in an area is displayed just by selecting the area on screen.

### 6. Conclusion

We have developed the next-generation laser scanner systems, Amersham Typhoon and Amersham Eraser, based on a new concept in pursuit of improvement of detection sensitivity, versatility and ease of use.

Amersham Typhoon comes in three types to meet various applications. It can be upgraded to a higher-function type by adding lasers and other units. Amersham Eraser is drastically reduced in thickness. Amersham Typhoon, Amersham Eraser and the cabinet for storing stages are unified in design as a system.

To improve the detection sensitivity, the scanner optics is optimized. Improved efficiency in light collection on PMT, optimization of the spectral properties of laser and filter, and improvement in the PMT quantum efficiency have made possible to detect weaker signals.

New functions are added to enhance the versatility. Those functions include the auto and semi-auto PMT high voltage settings to automatically calculate a PMT high voltage from a pre-scanned image, the overlay view to display an overlay image of a sample using multiple fluorescent labels, the densitometry to perform quantitative measurement of a dyed sample, and the slow scan mode to further reduce noise using oversampling technology.

About GUI, new functions are added while maintaining the unity with the conventional Typhoon FLA series to achieve a user interface easy to understand and easy to use. The user-friendliness is also improved by the automatic filter recognition, three output file formats to meet various purposes, and the intensity display for quick check of the signal intensity of a scanned image.

### References

- 1) "FUJIFILM and GE Healthcare form Strategic Alliance in Life Sciences Global alliance in biomolecular imaging". FUJIFILM News. 2009-05-28. <http://www.fujifilm.com/news/n090528.html>.(accessed 2016-12-05)

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