

EN

INSTRUCTIONS FOR USE

HISTO TYPE Rainbow

Test kit for the determination of HLA alleles on a molecular genetic basis

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1. INTENDED USE

The intended use of the HISTO TYPE Rainbow kit is the identification of HLA Class I and II alleles using a validated CFX Real-Time PCR Detection System for PCR amplification. HISTO TYPE Rainbow is an in vitro diagnostic test for tissue typing based on a molecular genetic basis (see Product Description).

The HISTO TYPE Rainbow kit is intended to be used by health care professionals with experience in molecular genetic techniques at:

- transplantation centers
- hospital laboratories
- bone marrow registries

HLA typing for transplanation purposes must follow guidelines issued by professional societies like the European Federation for Immunogenetics (EFI), the American Society for Histocompatibility and Immunogenetics (ASHI) or national societies like the Deutsche Gesellschaft für Immunogenetik (DGI).

2. PRODUCT DESCRIPTION

HISTO TYPE Rainbow kits are used for the molecular genetic determination of HLA Class I and II alleles at 11 loci: HLA-A, B, C, DRB1/3/4/5, DQA1, DQB1, DPA1 & DPB1. Kits are designed to generally detect all alleles at the 11 loci; if any rare alleles are not detected the alleles are listed in Kit Specific Information documents (KSI) which are available from the download section of the BAG website. The primer and probe binding sites are listed there as well. The kit provides low to medium typing results of the common and well documented alleles using CWD list 2.1.0 which is largely based on CWD 2.0.0 list (1). The CWD list 2.1.0 used is available from the document download section of the BAG website. Confirmed diagnostic results of HLA alleles are a prerequisite for a successful organ transplantation.

3. TEST PRINCIPLE

The test is performed with genomic DNA as starting material. The DNA is amplified in a real-time PCR with sequence-specific primers (SSP). The primers were specially developed for the selective amplification of segments of specific HLA alleles or allele groups. The amplicons are detected using sequence-specific fluorescence dye-labelled hydrolysis probes (TaqMan[®]-probes), which increases the sensitivity and specificity of the test compared to the classical SSP.

If amplicons are present, the probes are hydrolysed by the Taq polymerase and a fluorescence signal is generated to enable detection of the amplicon. Five different wavelength ranges of fluorescence signals are measured by the optical detection unit of the real time PCR cycler. The presence of a positive reaction is determined primarily by the Cq point, which is the point where fluorescence signal increases beyond the baseline threshold. For amplification to be valid the amplification must also achieve a certain threshold of fluorescence at the end of the PCR process. This is to prevent false positive reactions.

Each PCR reaction also contains an internal amplification control (Human Growth Hormone gene (HGH)) which is detected in a specific fluorescent channel.

To distinguish positive reactions from negative or irrelevant amplifications the ratio of the Cq of the specific reaction compared to the Cq of the internal amplification is calculated. The thresholds for these Cq ratios (CqR) vary from reaction to reaction and hence the PlexTyper[®] software is required for the analysis of amplification data.

4. MATERIAL

4.1 Contents of the Rainbow kit

- **10x 230 µl Plex Mix**, ready to use, contains dNTPs, Taq Polymerase, reaction buffer. (contains the hazardous substance 2-methylisothiazol-3(2H)-one at a concentration of < 0.05%, see chapter 7 and 13)
- **10x HISTO TYPE Rainbow plates** for HLA-typing. The pre-pipetted and dried reaction mixtures contain HLA-specific primers and probes as well as HGH-specific control primers and probes (oligomixes).
- **10x qPCR Seal**

4.2 Additionally required reagents and devices

- Reagents for DNA isolation (validated extraction kits see 6.2)
- Real time-PCR Cycler (validated cyclers see 4.3)
- Variable pipettes (0.5 – 1000 µl) and pipette tips
- Application spatula for qPCR Seal
- Molecular grade DNase free water.
- Suitable plate centrifuge

4.3 Validated real time-PCR Cyclers

- CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad)
- CFX 96 DX ORM (Bio-Rad, CE certified version of the CFX96 Touch™ Real-Time PCR Detection System)
- CFX Opus 96 Real-Time PCR System (Bio-Rad)
- CFX Opus 96 Dx (Bio-Rad, CE certified version of the CFX Opus 96 Real-Time PCR System)

The following fluorophores are used:

Fluorophore	Select at the cycler	Wave length in nm
F495 FAM	FAM	Excitation: 495 / Emission: 520
O560 (CAL Fluor [®] Orange 560)	HEX	Excitation: 538 / Emission: 559
R610 (CAL Fluor [®] Red 610)	ROX	Excitation: 590 / Emission: 610
Q670 (Quasar [®] 670)	Cy5	Excitation: 647 / Emission: 670
Q705 (Quasar [®] 705)	Quasar 705	Excitation: 690 / Emission: 705

5. STORAGE AND STABILITY

All reagents must be stored at $\leq -20^{\circ}\text{C}$ in temperature-controlled devices. The expiry date is indicated on the label of each reagent. The expiry date indicated on the outer label refers to the reagent with the shortest stability contained in the kit. The freeze-thaw cycle testing has shown that up to 12 cycles for the Plex Mix has no detrimental effects on the quality of the kit.

In use stability: After removal from the freezer the Plex Mix and the HISTO TYPE Rainbow plates have been shown to be stable at ambient temperature for 2 hours before setting up the PCR. The pipetted PCR plates can be stored in the fridge in the dark for up to 16 hours before the PCR run is started.

6. TEST PROCEDURE

6.1 Precautions and special remarks

Molecular genetic techniques are extremely sensitive methods and should only be performed by qualified personnel with experience in molecular genetic techniques.

Special precautions must be met to avoid contamination and thus false reactions:

- Wear suitable gloves (preferably powder-free) during work.
- Use tips with filter insert or integrated stamp.
- Work in two different areas for pre-amplification (DNA-isolation, preparation of the reactions) and post-amplification (detection); use two separate rooms if possible.
- Use devices and other materials only at the respective workplaces and do not exchange them.

6.2 DNA Isolation

The specimen material for the isolation of the genomic DNA must be sent in appropriate collection systems. For genomic material from whole blood use only EDTA or Citrate anticoagulants. The presence of Heparin may potentially inhibit the PCR reaction (2), therefore such collection systems are not suitable and must not be used. It is recommended to use **CE** IvD certified kits for the DNA isolation.

Validated DNA Extraction Kits:

- Qiagen QIAamp DNA Blood Kits (columns)

Both, the manual isolation and automated DNA isolation (QIAcube) are validated.

If the standard method established in the laboratory shall be applied for isolation of gDNA without using one of the specified test kits, it must be validated by the user.

The HISTO TYPE Rainbow test requires 10 – 20 ng DNA per well.

The purity indices must be in the following range:

- $OD_{260} / OD_{280} = > 1,5$ and $< 2,0$
Higher values are an indicator for the presence of RNA, lower values indicate protein contamination.
- $OD_{260} / OD_{230} = > 1,8$
Lower values indicate contamination with carbohydrates, salts or organic solvents.

6.3 Entering sample information into the PlexTyper® Software

It is mandatory to use PlexTyper® Software to analyse HISTO TYPE Rainbow data. It is advisable to enter the sample information into PlexTyper® before setting up the PCR amplification to obtain the unique RUN ID. All import files must be prefixed with a PT number.

When saving a test in PlexTyper®, the software assigns a **Run ID** to the test which is displayed in red in the summary window shown below. This is a consecutive number prefixed with PT (PT1, PT2, PT3....) which is linked to the sample identity and is used as a prefix on the PCR machine export file to correctly link the PCR export to the sample identity.

This Run ID should be used when setting up the file identity in the PCR machine. If the PCR xml export file is not pre-labelled with the RUN ID the file can be manually prefixed with the correct PT Run ID before import into PlexTyper®.



6.4 PCR setup

A pre-mix consisting of Plex Mix, water and DNA is made for the amplification that is subsequently dispensed in the wells 1-95. In well 96 there is the negative control (no template control = NTC) which should only contain water and Plex Mix.

- The reaction volume for each PCR preparation is 10 µl.
- For a single well the following reagents must be pipetted into a reaction tube:

2 µl Plex Mix
1 µl DNA specimen (10-20 ng/µl)
7 µl Molecular grade water

For other DNA concentrations the pre-mix has to be modified accordingly (see below).

A **negative control (NTC)** should be performed. Therefore prepare a PCR reaction with molecular grade water instead of DNA.

2 µl Plex Mix

8 µl Molecular grade water

DNA concentration 10-20 ng/µl

- Add **805 µl** molecular grade water to the vial with 230 µl Plex Mix and mix (vortex briefly 1-3 sec).
- After mixing, pipette **10 µl** of the mix into the NTC well (well 96; position H12 -see also Figure 1 and 2).
- Then pipette **115 µl** DNA into the vial with the remaining Plex Mix-water-mixture and mix (vortex briefly 1 – 3 sec).
- Distribute 10 µl of the DNA/Plex Mix/water solution into each of the wells 1-95 of the HISTO TYPE Rainbow plate (please note figure 1 and 2). The NTC well (well 96; position H12) must not be filled with the DNA mix as this will cause the NTC to be positive and can invalidate the test!

DNA with other concentrations

- Add **8 µl** Molecular grade water and **2 µl** Plex Mix to the NTC (well H12). The NTC well (well 96; position H12) must not be filled with the DNA mix!
- Pipette the DNA and the molecular grade water into the remaining 228 µl Plex Mix according to the following table and mix (vortex briefly 1-3 sec).

Depending on the concentration of DNA, pipette the applicable volumes in the table below to the 228 µl Plex Mix remaining in the vial after setting up the NTC:

Concentration of the DNA [ng/µl]	Molecular grade water [µl]	DNA volume [µl]
2 to 4	350	570
5 to 9	690	230
10 to 19	805	115
20 to 39	860	60
40 to 79	890	30
80 to 150	905	15
151 to 200	912	8

- Distribute **10 µl** of the DNA-Plex Mix-water solution into each of the wells 1-95 of the HISTO TYPE Rainbow plate.

Please note: When pipetting into the PCR wells it is important not to allow the pipette tip to contact the dried mix (dyed blue) in the bottom of the well. It is advisable to pipette to the side of the well to allow the 10 µl to mix by gravity with the dried mix (see Figure 1).

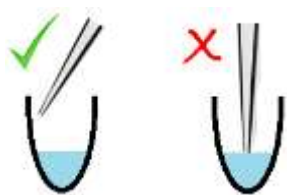


Figure 1

	1	2	3	4	5	6	7	8	9	10	11	12
A	1	9	17	25	33	41	49	57	65	73	81	89
B	2	10	18	26	34	42	50	58	66	74	82	90
C	3	11	19	27	35	43	51	59	67	75	83	91
D	4	12	20	28	36	44	52	60	68	76	84	92
E	5	13	21	29	37	45	53	61	69	77	85	93
F	6	14	22	30	38	46	54	62	70	78	86	94
G	7	15	23	31	39	47	55	63	71	79	87	95
H	8	16	24	32	40	48	56	64	72	80	88	NTC

Figure 2: HISTO TYPE Rainbow plate. In wells A1 to G12 are the dried specific mixes (blue coloured). In well H12 there is the dried NTC (also blue).

Seal the PCR plate with the supplied qPCR seal and briefly spin the liquid down. Make sure that the plate is **completely sealed**, particularly at the edge of the plate. The seal must be free of bubbles to prevent evaporation during PCR. Make sure that the liquid has contacted the dried mix and there are **no bubbles** or air gaps in the reaction wells. If bubbles appear, gently tap the tubes on the laboratory bench to remove them, or preferably briefly spin it down (10 sec). Place the sealed PCR plate in the CFX instrument.

Note: Please make sure that you place the reaction plate into the cycler in the correct orientation as shown in Figure 2 above where the NTC well is in the bottom right corner, position H12.

6.5 Cyclor settings and PCR run

PCR-Program (included in the Rainbow templates)

Step	Time [s]	Temperature [°C]	Ramp rate [°C/s]	Plate read	Cycles
Initial activation	120	96	2.5	-	1
Denaturation	5	98	2.5	-	13
Annealing + Extension	25	68	2.2	-	
Denaturation	5	98	2.5	-	37
Annealing + Extension	25	68	-	Yes	

Note: With the CFX96 Touch™ Real-Time PCR Detection System a **modified heating rate** of the device (ramp rate) must be used. These are listed in the PCR program table above ("Ramp rate" column).

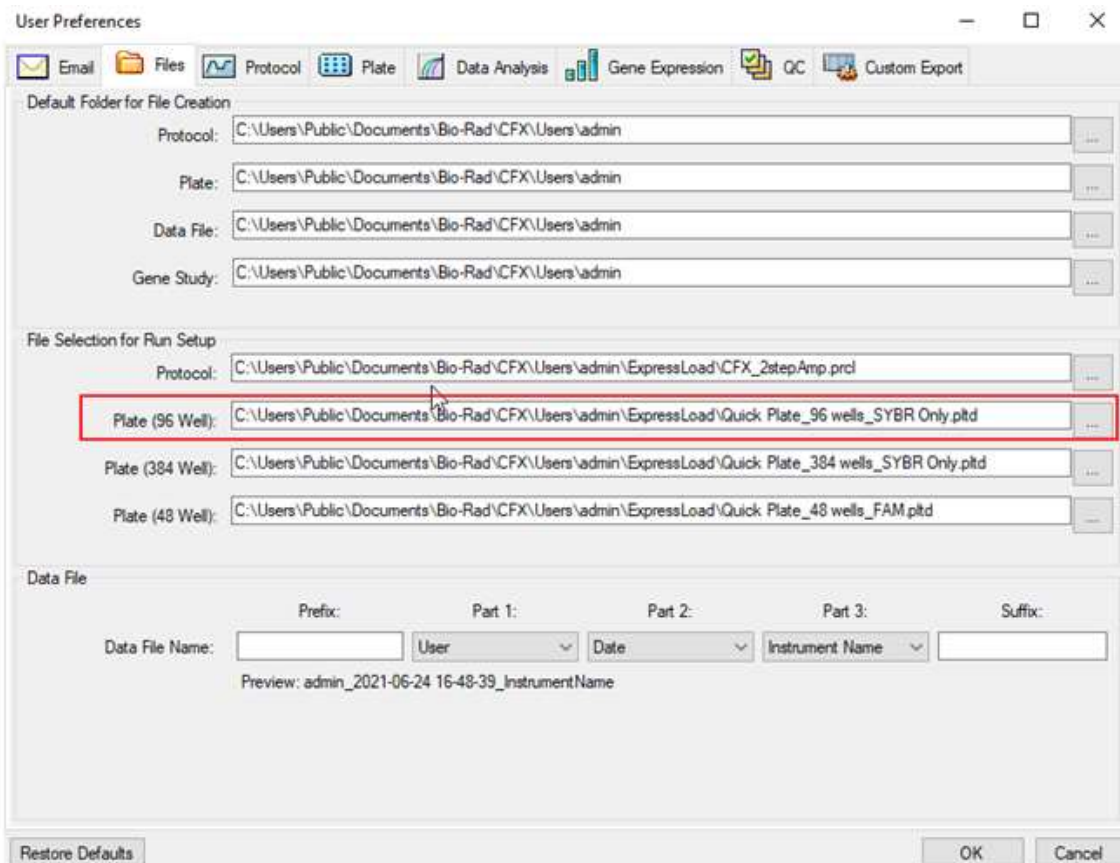
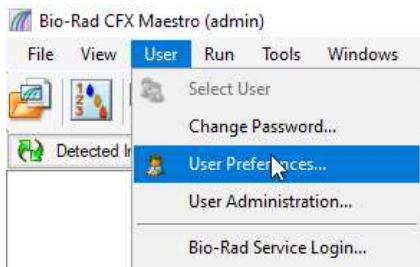
Perform the real-time PCR run from a connected PC.

It is strongly recommended to use the Rainbow templates for the PCR protocol and plate layout which are available from the download section of BAG Diagnostics website. These contain the correct amplification parameters and cyclers settings. They should be saved to the following or a similar path:

Template default path:

C:\Users\Public\Documents\Bio-Rad\CFX\Users\admin\ExpressLoad

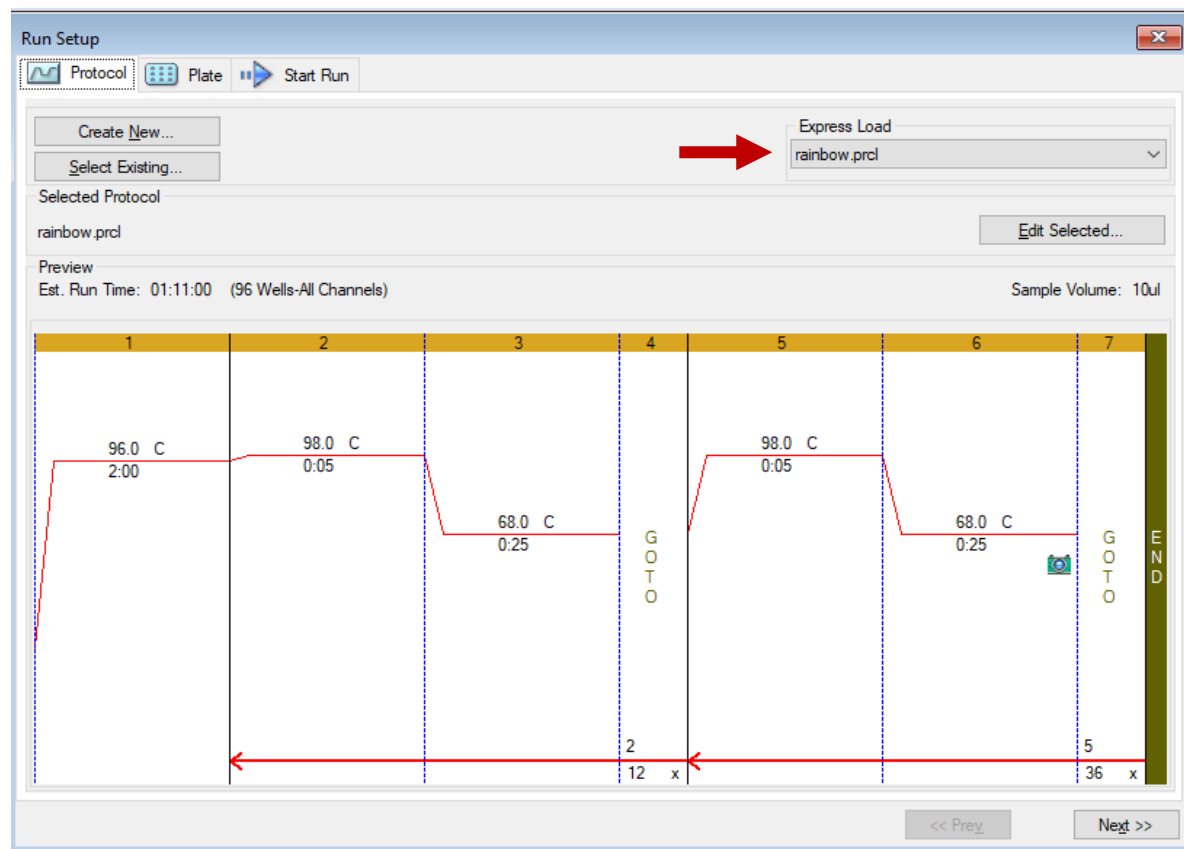
The express load path may differ depending on the Bio-Rad software settings and can be obtained inside the Bio-Rad Maestro software.



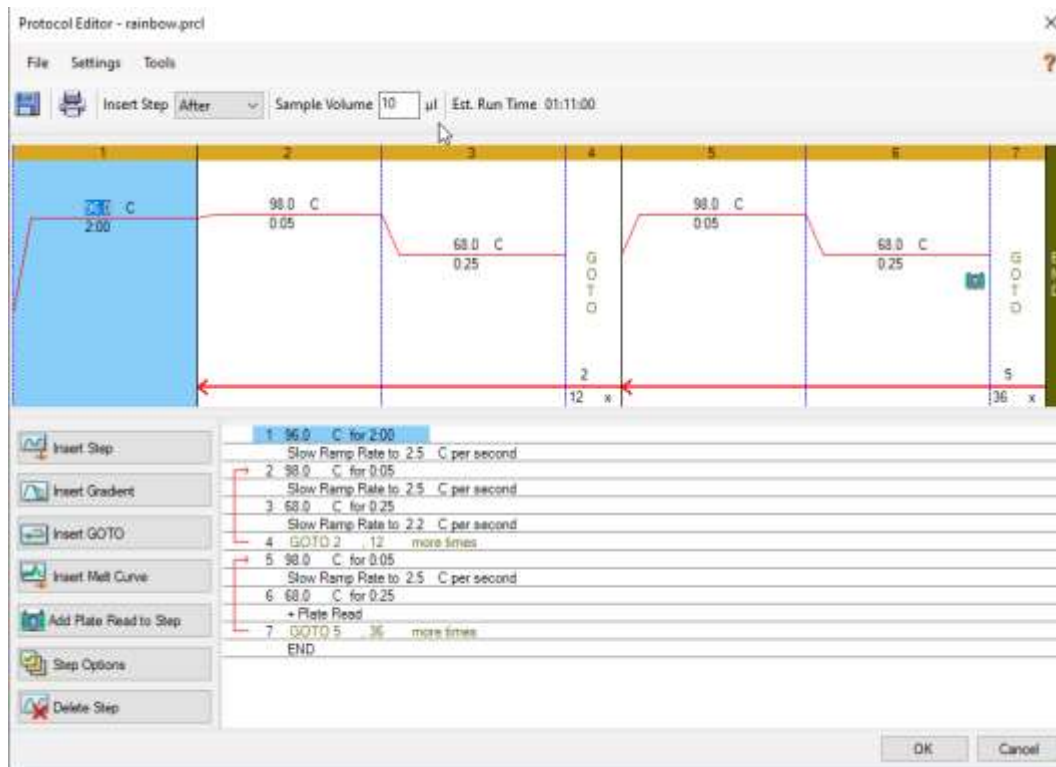
Then the Rainbow templates for the PCR protocol and plate layout can be selected from the express load menu in the run setup of the CFX Maestro software.



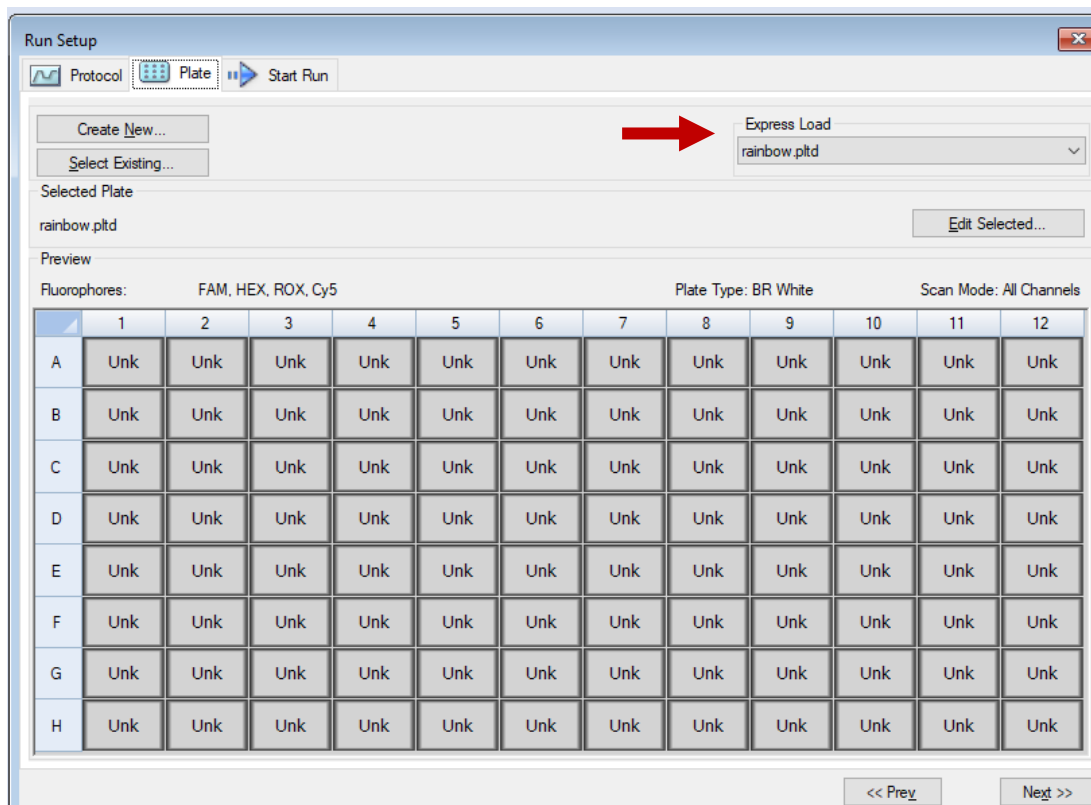
For the protocol choose the "rainbow.pcr1" template from the Express Load dropdown menu:



By clicking on "Edit Selected" the details of the program are shown and the program can be edited (which should not be done if the template is used!):

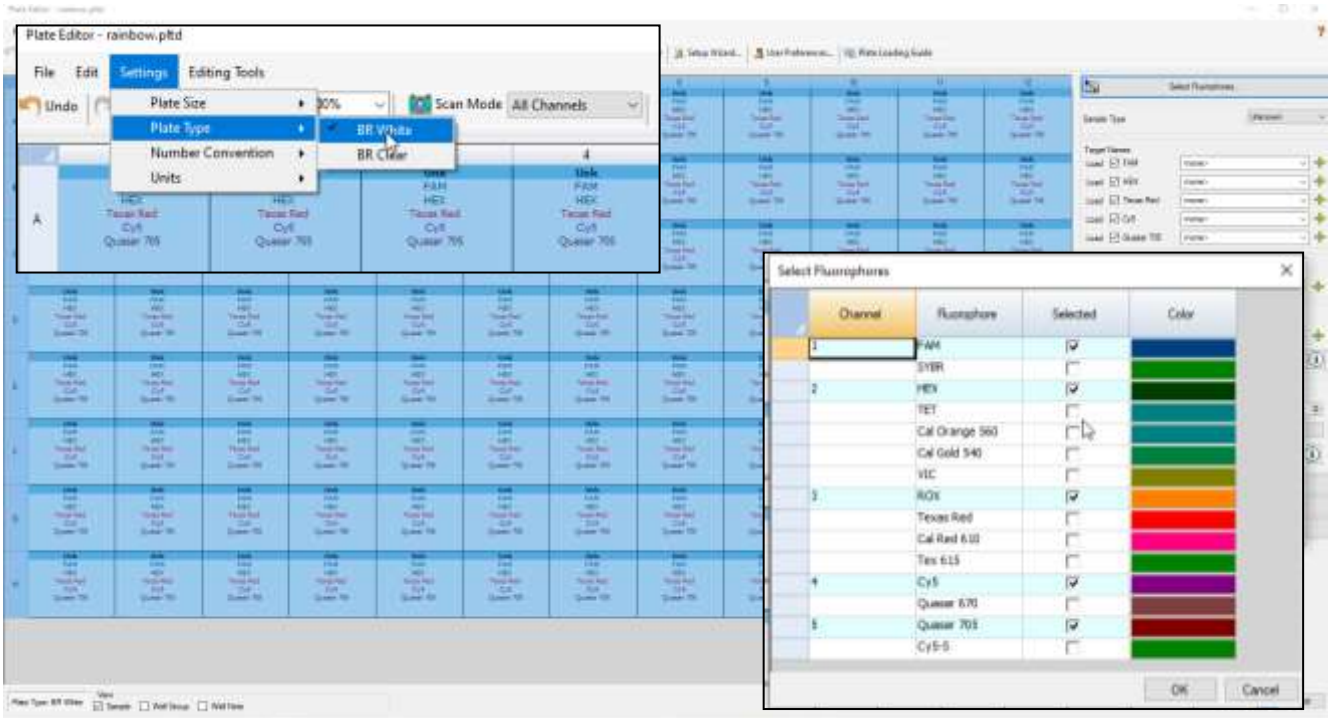


For the plate choose the "rainbow.pltd" template from the Express Load dropdown menu.

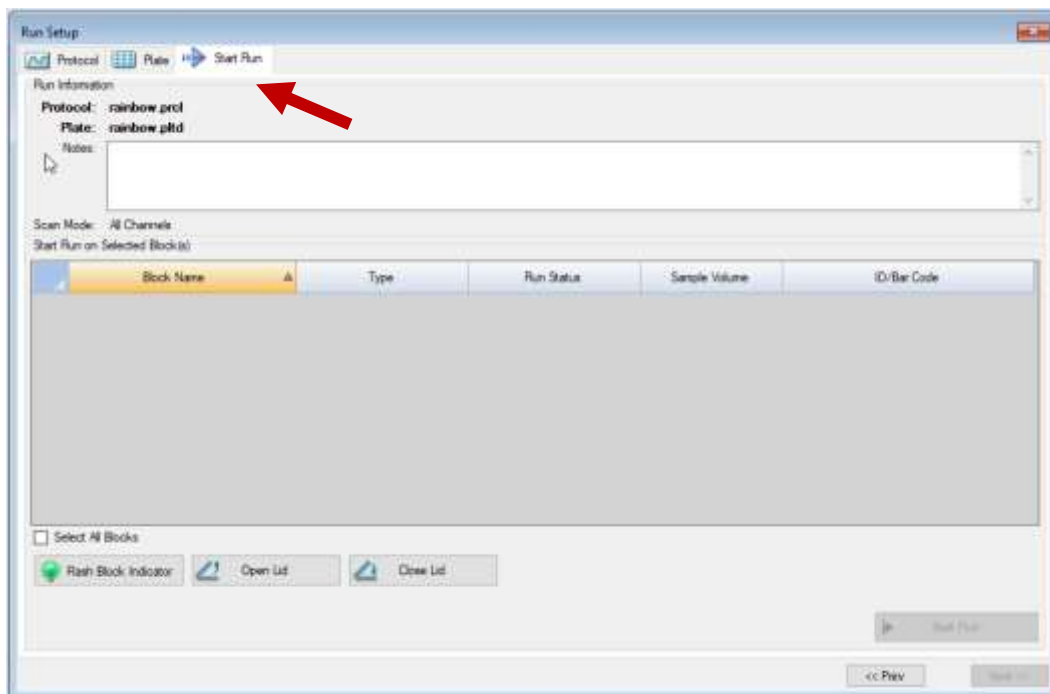


By clicking on "Edit Selected" the details of the plate are shown and the settings must be set as shown in the screenshot below: FAM, HEX, ROX, Cy5, Quasar 705. If the template is used the fluorophores are already set and must not be changed.

It is important that BR White is selected for the Plate Type:



Then start the run and make sure that that the PCR run name contains the **RUN ID** created by the PlexTyper® software as a prefix.



Alternatively: Perform the real-time PCR run with a "stand-alone" Instrument

On the touchscreen of the CFX Instrument select the rainbow protocol and ensure to select scan mode "All Channels" before you start the run.



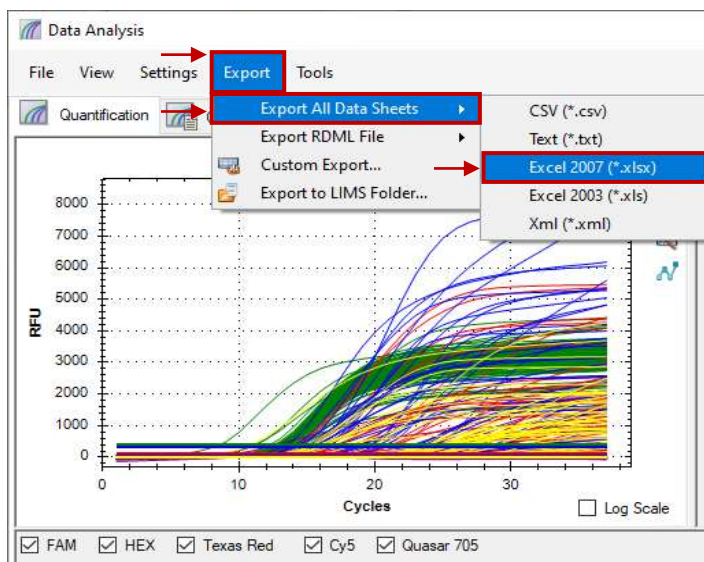
Alternatively: Data Export from a "stand-alone" instrument

After the run, export the data to a USB stick (using the **File Options**). The open and save the data file in the CFX Maestro software.



Data Export from the CFX Maestro Software

From the data analysis screen of the CFX Maestro software export the data using the Excel 2007 format. Transfer the files to a computer with the Plex Typers® software installed.



6.6 Evaluation and interpretation of the results

For evaluation and interpretation of the data it is mandatory to use the PlexTyper® software (available free of charge from BAG Diagnostics) in conjunction with the kit specific data files. The kit files required for the evaluation are available from the BAG Diagnostics download server (www.service.bag-diagnostics.com).

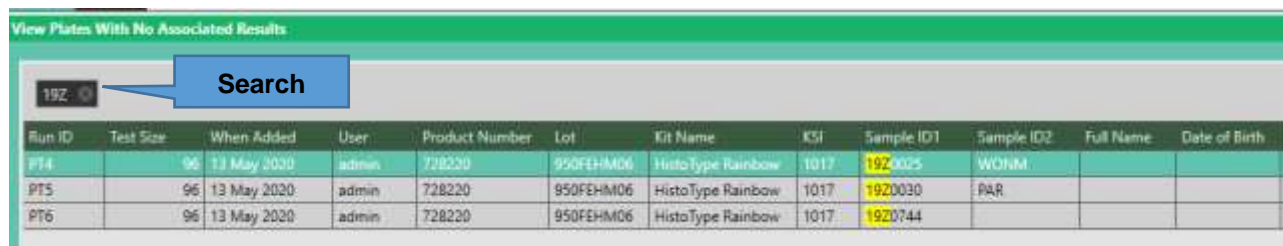
Please make a note of the lot number of the kit. The interpretation kit files are product and lot specific. Use of incorrect kit files could result in incorrect genotyping. For interpretation of the results the raw data must be transferred from the thermocycler to a computer running the PlexTyper® software (e.g. with a suitable USB drive).

HISTO TYPE Rainbow is a 5-channel, 96 well multiplex genotyping test. It is possible to view data on the amplification machine software, but it is not possible to interpret without use of the PlexTyper® software.

6.7 Import of the results file into the PlexTyper® software

Please follow the instructions for use for the PlexTyper® software for interpretation of the data.

Open the PlexTyper® software. From the home screen choose **View plates with no associated results** under **Plates**. A list opens with all tests that are not linked with raw data yet. There is a global **Search** field at the top of the table to search the whole table.



Run ID	Test Size	When Added	User	Product Number	Lot	Kit Name	KSI	Sample ID1	Sample ID2	Full Name	Date of Birth
PT4	96	13 May 2020	admin	728220	950FEHM06	HistoType Rainbow	1017	1920025	WONM		
PT5	96	13 May 2020	admin	728220	950FEHM06	HistoType Rainbow	1017	1920030	PAR		
PT6	96	13 May 2020	admin	728220	950FEHM06	HistoType Rainbow	1017	1920744			

Double click on the required test to be interpreted; this opens the results summary window. Select **Import File** and select the XML file with the correct PT RUN ID prefix (e.g. PT4.xml) exported from the CFX cycler.

Initial loading of the kit file data takes approximately 45 seconds, unless it is already open, the bottom left corner of the screen shows a progress bar. After that the results for user review are presented.

A negative control (NTC) is used as contamination control. If DNA or contaminating amplicon is inadvertently added to the NTC reaction a positive signal will occur. If the Cq is less than 36 it will be detected as possible contamination by the PlexTyper® software and a warning message is generated. Amplification signals above Cq 36 in the NTC are regarded as PCR artefacts and are disregarded. If PCR contamination is suspected, it is advisable to follow local decontamination guidelines and to exchange the reagents.

The raw data collected from the cycler-specific software will be imported into the PlexTyper® software. Based on the Cq values, RFUs (relative fluorescence units), quality scores and the curve progression the PlexTyper® software determines the molecular genetic HLA pattern of the specimens used (see instructions for use for PlexTyper® for details).

7. WARNINGS AND DISPOSAL INSTRUCTIONS

HISTO TYPE Rainbow is **designed for in vitro diagnostic use**. The kit should only be used by specially trained, qualified personnel. All work should be performed in accordance with Good Laboratory Practice.

All materials of biological origin used in the test to obtain DNA (e.g. blood) should be considered as potentially infectious. Therefore, appropriate safety precautions are recommended when handling biological materials as required by Good Laboratory Practice standards. Biological materials must be inactivated before disposal (e.g. by autoclaving). Disposable materials must be autoclaved or incinerated after use.

Spilled potentially infectious material should be removed immediately with an absorbent paper towel and the contaminated area disinfected with an appropriate disinfectant or 70% Ethanol. Material used to remove spills must be inactivated before disposal (e.g. by autoclaving).

Disposal of all specimens, unused reagents and waste should be in accordance with the legislation of the respective country and the local authorities.

Microbial contamination of reagents while taking aliquots should be avoided. The use of sterile disposable pipettes and pipette tips is recommended. Do not use reagents looking cloudy or showing signs of microbial contamination.

The Plex Mix contains the hazardous substance 2-methylisothiazol-3(2H)-one at a concentration of < 0.05%. The following hazardous material labeling is applicable:



Symbol: Warning

See chapter 13 for hazard and precaution statements

A material safety data sheet (MSDS) for the Plex Mix is available for download from www.bag-diagnostics.com. No further MSDS are required according to article 31 of REACH regulation (EC) no. 1907/2006 and the regulation (EC) no. 1272/2008.

8. KIT SPECIFICATIONS

The combination of primers and probes allows the determination of human HLA class I and II alleles according to lot-specific data (low to medium resolution, detection of all alleles with the exception of single rare alleles). The accuracy and reproducibility of the reactivity of the test kit is checked for each lot with control specimens with known HLA-alleles. The kit determines the HLA-Loci A, B, C, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1 and DPB1.

8.1 Specific performance characteristics

8.1.1 Diagnostic sensitivity and specificity

A total of 177 DNA samples pre-typed for all or some of the analysed HLA loci were tested with the HISTO TYPE Rainbow kit to show the correct reactivity. There was a 100% concordance of results with the pre-typings.

Locus	No of samples with previous result for the locus	Concordant	% Concordance
A	177	177	100%
B	177	177	100%
C	177	177	100%
DRB1	174	174	100%
DRB3	165	165	100%
DRB4	165	165	100%
DRB5	165	165	100%
DQA1	161	161	100%
DQB1	171	171	100%
DPA1	117	117	100%
DPB1	141	141	100%

8.1.2 Analytical sensitivity and measuring range

Validation tests have shown that variation of the amount of DNA from 5 ng to 50 ng per reaction has no significant effect on the specific detection of HLA alleles.

8.1.3 Analytical specificity / cross reactive substances

Eight substances that might interfere with the assay were tested and the following concentrations were shown to have no detrimental effect on the results:

Substance	Maximal non-inhibitory concentration
Protein (BSA)	0.2 mg/ml
TE (Tris/EDTA, pH 8.0)	7 mM Tris, 0.7 mM EDTA
NaCl	20 mM
Ethanol	1%
Haemoglobin	0.01 mg/ml
Sodium Citrate	7 mM
DNA extraction buffer 1 (Qiagen QIAamp DNA Blood Kits)	1%
DNA extraction buffer 2 (Qiagen QIAamp DNA Blood Kits)	2%

9. LIMITS OF THE METHOD

During DNA isolation, special attention must be paid to the fact that the RT-PCR method reacts very sensitively to cross-contaminations. Special care should be taken to avoid contamination of kit reagents and other laboratory materials with amplicons or DNA.

The performance of a negative control without DNA in well H12 is strongly recommended. No fluorescence signal below 36 Cq should be detected in the NTC (H12) with molecular grade water. In the case of signal development in the negative control, the PCR laboratory workplace may have to be decontaminated from DNA and the reagents exchanged if necessary. All devices (e.g. pipettes, real-time cyclers) must be calibrated according to the manufacturer's specifications.

10. INTERNAL QUALITY CONTROL

Internal quality controls for new lots can be performed with a combination of DNA specimens with known HLA type. An internal control to verify successful amplification is included in the dried oligomixes. Performance of negative controls (well H12) to detect possible contaminations is recommended. For this purpose, prepare a test without DNA (NTC), see chapter 6.4.

11. TROUBLESHOOTING

For interpretation trouble shooting please see the Instructions for Use for PlexTyper[®] Software.

Symptom	Possible Reason	Potential Solution
FAM signals weak or absent across whole plate	Presence of an inhibitor in the DNA.	Try a different extraction or sample.
	Insufficient DNA in the reaction.	Repeat test with correct amount of DNA.
	Wrong amplification parameters.	Check PCR program.
	Contaminated or degraded DNA.	Check concentration / quality of DNA. Check DNA on a gel. Repeat DNA isolation.
	Degraded Fluorescent probes or primers.	Avoid exposure to light and frequent thawing and freezing. Observe storage conditions.
Poor or no FAM signal in individual wells	Bubbles in the reaction / residual liquid at the inner wall of the tube.	Careful pipetting. Spin down PCR plate.
	User error.	Ensure all wells receive the required volume of reagents.
	Evaporation of the reagents due to incorrect closing of the PCR tubes.	Make sure that the PCR tubes are closed properly. Caution with adhesive foils in the edge area.






Symptom	Possible Reason	Potential Solution
Signal in the Negative Control	Contamination with DNA or amplicon in the negative control.	Repeat the test. Decontaminate the workplace.
	Amplification due to PCR artefact.	Review after import into PlexTyper [®] , if the signal may be below the thresholds and the data may in fact be OK (please note the PlexTyper [®] Instructions for Use).


12. TRADE NAMES USED

TaqMan[®] is a tradename of Roche Molecular Systems Inc.

[®]Cal Fluor & Quasar Dyes are the registered trademark of LGC Biosearch Technologies

13. EXPLANATION OF THE SYMBOLS USED ON THE LABELS

	Sufficient for n tests
	Storage temperature / Upper limit of temperature
	Consult to instruction for use
	Manufacturer
	Use by
CONT	Content, contains
eIFU	Electronic instructions for use
HLA TYPING	Intended use: HLA typing
IVD	For in vitro diagnostic use
LOT	Batch code
PCRFOIL	PCR foil
PCRPLATE	PCR plates
PLEX MIX	Plex Mix: Mastermix, contains dNTPs, Taq polymerase, reaction buffer
REACTIONMIX	Reaction mixes
REF	Catalogue number
RTU	Ready to use

	Warning (see chapter 7)
	<p>H317 May cause an allergic skin reaction.</p> <p>Precautionary statements</p> <p>P101 If medical advice is needed, have product container or label at hand.</p> <p>P102 Keep out of reach of children.</p> <p>P103 Read carefully and follow all instructions.</p> <p>P302+P352 IF ON SKIN: Wash with plenty of water.</p> <p>P280 Wear protective gloves / protective clothing / eye protection / face protection / hearing protection.</p> <p>P333+P313 If skin irritation or rash occurs: Get medical advice/attention.</p> <p>P501 Dispose of contents/container in accordance with local/national regulation.</p>

14. LITERATURE

1. Mack, S.J. et al., 2013. Tissue Antigens 81, 194–203
2. Beutler, E. et al., 1990. BioTechniques 9:166

For further information please refer to our website www.bag-diagnostics.com or contact us directly at info@bag-diagnostics.com