Key FISH probes in the diagnosis and patient management for patients diagnosed with haematological malignancies and solid tumours

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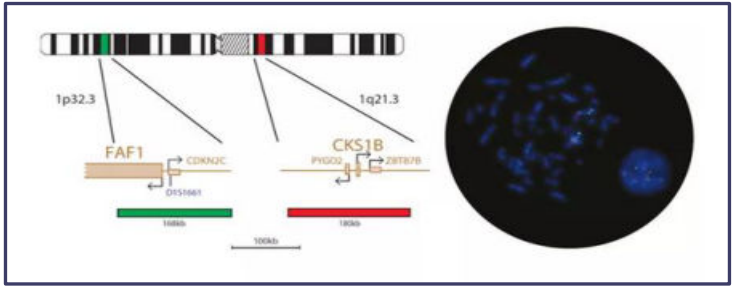
ogt

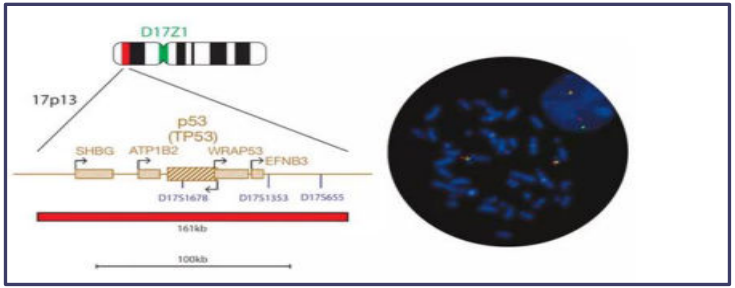
A Sysmex Group Company

What binds us, makes us.

CytoCell FISH Probes

- The CytoCell brand encompasses an extensive range of probes
  - CE-IVD catalogue probes (LP* coded products): OGT CytoCell
  - Ancillaries: Ancillaries
  - RUO myProbes: Custom FISH Probes
- Ranges encompass probes designed for work on wide range of referral types
  - Constitutional
    - LPU, LPE, LPT, LPA and LPF coded catalogue probes
    - MPA coded myProbes
  - Haematology and haematopathology
    - LPE, LPH and LPS coded catalogue probes
    - MPH, and MPD coded myProbes
  - Pathology
    - LPS coded catalogue probes MPD and MPP coded myProbes

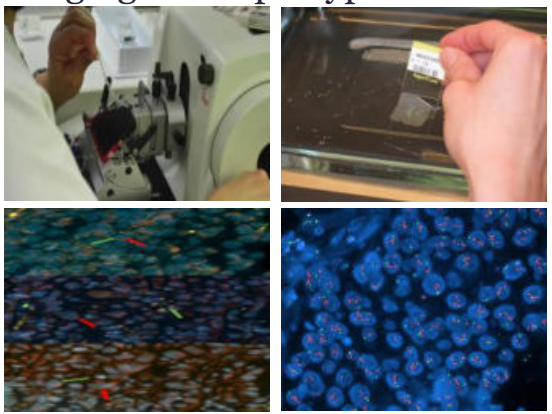




Which probe to use?

- Probe applicability is defined by a range of factors:
  - Referral type
  - Sample and analysis type
  - Regional guidelines
  - Re-imbursement models, access to therapies and other available technologies
  - Microscope set up

- FFPE tissue is the most challenging of sample types to work with
  - Pre-analytical processing
  - Truncation
  - Overlapping nuclei
  - Analytical experience
  - Clonal heterogeneity



Support available

- OGT are unique in that we have HCPC registered clinical scientists and technologists within the company
  - Provide assistance with protocol optimisation, troubleshooting, clinical support and interpretation
  - Over 100 years of combined clinical expertise
  - Worldwide network of contacts in both clinical and research settings

- Support is provided FOC and is part of the after-sales service
  - Partners are trained to a high level, so in-country support also available
  - Site visits, consultation calls, FAS health checks are all available on request

- Development of unique myProbes (RUO) allows for institutions to implement testing for rare abnormalities not available through other commercial providers
  - Research and translational work
  - Changes / additions to guidelines
  - Modifications to existing probes to suit users specific needs
  - Reduction of technical and analytical workloads

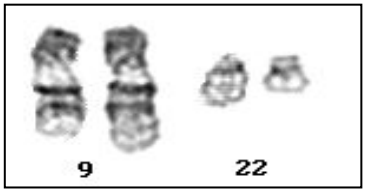
Key Probes by referral type - Haematology

- Extensive portfolio of probes for haematological malignancy work
  - LPH CE-IVD and MPH RUO myProbes
  - LPS/MPD and MPP coded probes work equally well on haematological samples
    - In most cases will give improved signal intensity due to higher fluorophore concentrations

- Selected a number of key probes from catalogue range for discussion across range
  - BCR::ABL1 rearrangement status
  - APL – PML/RARA
  - ALL – RUNX1 abnormalities & 19p13 TCF3 (E2A) rearrangements
  - Myeloma - FISH for IGH fusion partners & t(14;16) IGH::MAF

The t(9;22) BCR::ABL1 Fusion

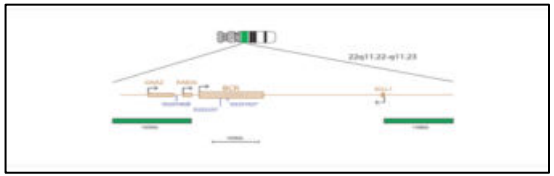
- The Philadelphia chromosome was first recognised in 1973 by geneticist Janet Rowley

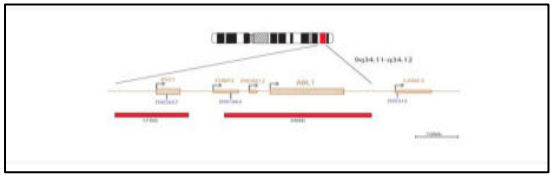


- In 1985, the BCR::ABL1 fusion was confirmed as being the key driver in CML
  - Stam et al, Engl J Med , 1985;313:1429-1433
- The t(9;22) is also observed in ALL, and AML conferring a poor prognosis
  - Treatment with TKI based therapies has revolutionised management of CML, and offered better patient management for Ph+ve acute leukaemia patients
- Rapid BCR:ABL1 confirmation by FISH is widely performed in ALL patients, as allows reporting of results within 24 hours

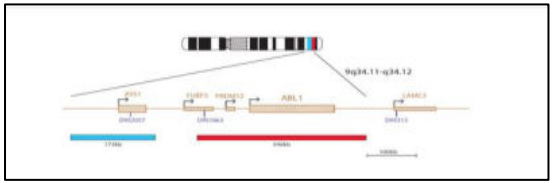
The t(9;22) BCR::ABL1 Fusion

- Cytocell portfolio includes 2 CE-IVD BCR/ABL1 probes
  - LPH007 BCR/ABL Dual Fusion – standard dual colour probe design
  - LPH038 BCR/ABL Plus Translocation, dual fusion – tri-colour design with ASS1 region in aqua





LPH007

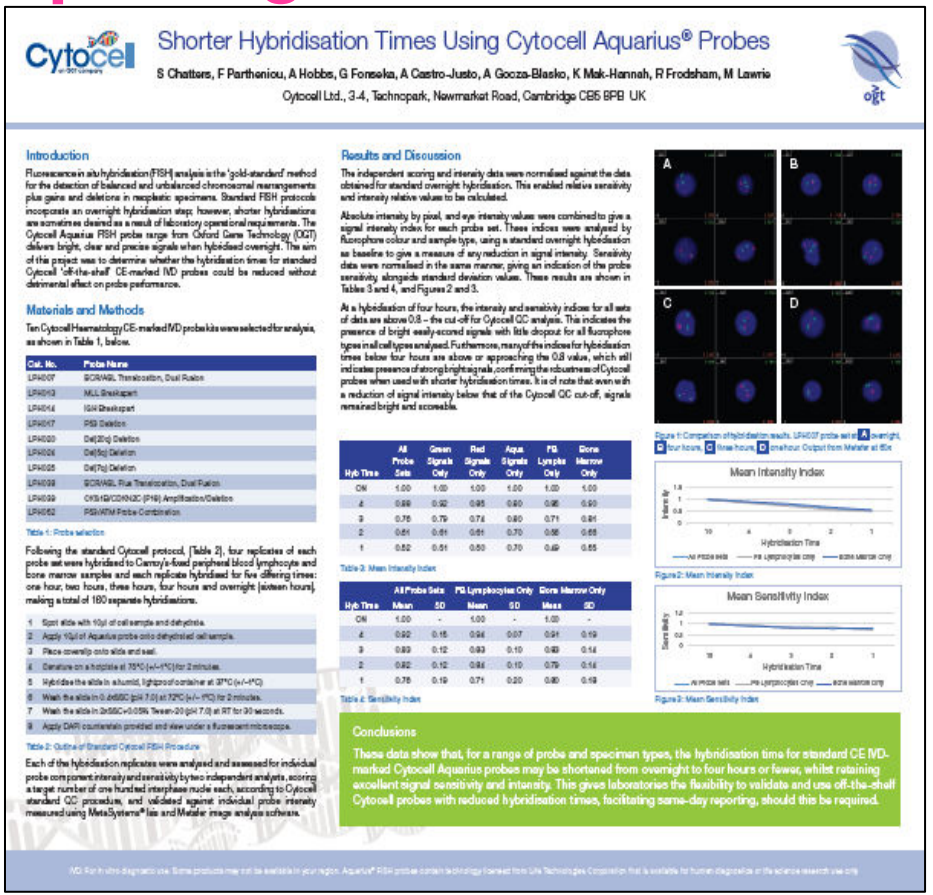


LPH038

- Variant rearrangements with loss of ABL1::BCR; cryptic insertions of ABL1 into BCR etc are widely reported
  - The LPH038 design gives higher sensitivity for low level clones where 1R1G1F signal patterns are observed due to the incorporation of the ASS aqua labelled clone set

FAST FISH – Same Day Reporting

- Same day results using FAST probes widely promoted
- No need for separate buffers, different protocols or increased expenditure
- Dedicated ‘FAST’ probes such as LPH064
- Study by OGT showed CytoCell Aquarius probes deliver reportable results on a 2hr hyb using standard probes and protocols
- FAS support is available to optimise this work, and is FOC



Shorter Hybridisation Times Using Cytocell Aquarius® Probes

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Introduction

Fluorescence in situ hybridisation (FISH) analysis is the ‘gold-standard’ method for the detection of balanced and unbalanced chromosomal rearrangements plus gains and deletions in neoplastic specimens. Standard FISH protocols incorporate an overnight hybridisation step; however, shorter hybridisations are sometimes desired as a result of laboratory operational requirements. The Cytocell Aquarius FISH probe range from Oxford Gene Technology (OGT) delivers bright, clear and precise signals when hybridised overnight. The aim of this project was to determine whether the hybridisation times for standard Cytocell ‘off-the-shelf’ CE-marked IVD probes could be reduced without detrimental effect on probe performance.

Materials and Methods

Ten Cytocell Haematology CE-marked IVD probe kits were selected for analysis, as shown in Table 1, below.

Cat. No.	Probe Name
LPH007	BCR/ABL Translocation, Dual Fusion
LPH013	MLL Breakapart
LPH014	IGH Breakapart
LPH017	P53 Deletion
LPH020	Del(20q) Deletion
LPH026	Del(5q) Deletion
LPH035	Del(7q) Deletion
LPH039	BCR/ABL Rue Translocation, Dual Fusion
LPH059	CKS1B/CDKN2C (P16) Amplification/Deletion
LPH062	P53/ATM Probe Combination

Table 1: Probe selection

Following the standard Cytocell protocol, [Table 2], four replicates of each probe set were hybridised to Carnoy’s-fixed peripheral blood lymphocyte and bone marrow samples and each replicate hybridised for five differing times: one hour, two hours, three hours, four hours and overnight (sixteen hours), making a total of 180 separate hybridisations.

1	Spot slide with 10µl of cell sample and dehydrate.
2	Apply 10µl of Aquarius probe onto dehydrated cell sample.
3	Place coverslip onto slide and seal.
4	Denature on a hotplate at 75°C (+/-1°C) for 2 minutes.
5	Hybridise the slide in a humid, lightproof container at 37°C (+/-1°C)
6	Wash the slide in 0.4xSSC (pH 7.0) at 72°C (+/- 1°C) for 2 minutes.
7	Wash the slide in 2xSSC+0.05% Tween-20 (pH 7.0) at RT for 30 seconds.
8	Apply DAPI counterstain provided and view under a fluorescent microscope.

Table 2: Outline of Standard Cytocell FISH Procedure

Each of the hybridisation replicates were analysed and assessed for individual probe component intensity and sensitivity by two independent analysts, scoring a target number of one hundred interphase nuclei each, according to Cytocell standard QC procedure, and validated against individual probe intensity measured using MetaSystems® Ise and Metafer image analysis software.

Results and Discussion

The independent scoring and intensity data were normalised against the data obtained for standard overnight hybridisation. This enabled relative sensitivity and intensity relative values to be calculated.

Absolute intensity by pixel, and eye intensity values were combined to give a signal intensity index for each probe set. These indices were analysed by fluorophore colour and sample type, using a standard overnight hybridisation as baseline to give a measure of any reduction in signal intensity. Sensitivity data were normalised in the same manner, giving an indication of the probe sensitivity, alongside standard deviation values. These results are shown in Tables 3 and 4, and Figures 2 and 3.

At a hybridisation of four hours, the intensity and sensitivity indices for all sets of data are above 0.8 – the cut-off for Cytocell QC analysis. This indicates the presence of bright easily-scored signals with little dropout for all fluorophore types in all cell types analysed. Furthermore, many of the indices for hybridisation times below four hours are above or approaching the 0.8 value, which still indicates presence of strong bright signals, confirming the robustness of Cytocell probes when used with shorter hybridisation times. It is of note that even with a reduction of signal intensity below that of the Cytocell QC cut-off, signals remained bright and accessible.

Hyb Time	All Probe Sets	Green Signals Only	Red Signals Only	Aqua Signals Only	PB Lympho Only	Bone Marrow Only
ON	1.00	1.00	1.00	1.00	1.00	1.00
4	0.89	0.92	0.95	0.90	0.95	0.93
3	0.76	0.79	0.74	0.80	0.71	0.81
2	0.61	0.61	0.61	0.70	0.56	0.65
1	0.52	0.51	0.50	0.70	0.49	0.55

Table 3: Mean Intensity Index

Hyb Time	All Probe Sets		PB Lymphocytes Only		Bone Marrow Only	
	Mean	SD	Mean	SD	Mean	SD
ON	1.00	-	1.00	-	1.00	-
4	0.92	0.15	0.94	0.07	0.91	0.19
3	0.83	0.12	0.83	0.10	0.83	0.14
2	0.82	0.12	0.84	0.10	0.79	0.14
1	0.76	0.19	0.71	0.20	0.80	0.19

Table 4: Sensitivity Index

Figure 1: Comparison of hybridisation results. LPH007 probe set in A overnight, B four hours, C three hours, D one hour. Output from Metafer at 60x

Figure 2: Mean Intensity Index

Figure 3: Mean Sensitivity Index

Conclusions

These data show that, for a range of probe and specimen types, the hybridisation time for standard CE IVD-marked Cytocell Aquarius probes may be shortened from overnight to four hours or fewer, whilst retaining excellent signal sensitivity and intensity. This gives laboratories the flexibility to validate and use off-the-shelf Cytocell probes with reduced hybridisation times, facilitating same-day reporting, should this be required.

IVD For in vitro diagnostic use. Some products may not be available in your region. Aquarius® FISH probes contain technology licensed from Life Technologies Corporation that is available for human diagnostics or life science research use only

AML - APL and t(15;17) PML-RARA

- Characterised by t(15;17)(q24.1;q21.2) PML-RARA rearrangement. Comprises approximately 5-8% of AML

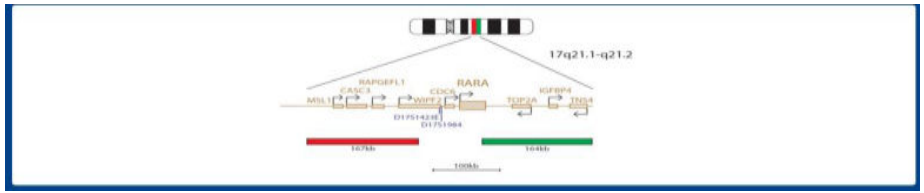
- APL is frequently accompanied by high incidence of disseminated intravascular coagulation (DIC) resulting in intracerebral and pulmonary hemorrhages that may be lethal (10-20% of the cases). In patients with the characteristic morphological picture of an APL and severe coagulation disorders, the onset of therapy with ATRA is justified before genetic analysis

- Confirmation of PML-RARA fusion status required within 24 hours

- Two key probes for APML FISH work

LPH 064 *FAST* PML/RARα(RARA) Translocation, Dual Fusion

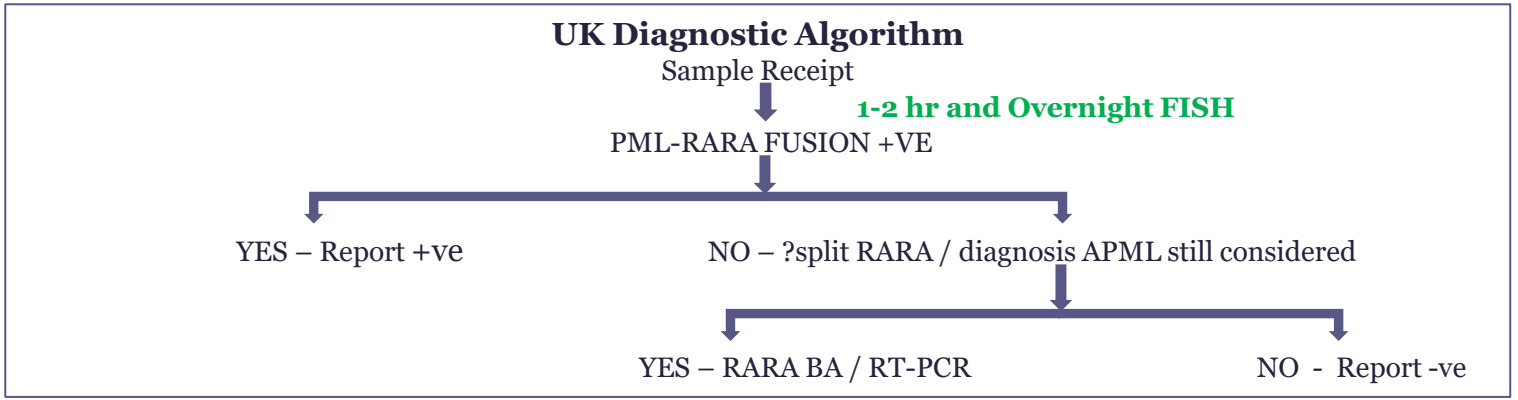
LPH 065 RARα (RARA) Breakapart



AML - APL and t(15;17) PML-RARA

- Variant translocations involving partner genes other than PML are widely reported and can be seen in 2-5% cases
  - Where RARA BA probe becomes critical

- RARA forms fusion gene with other genes in clinically similar APL cases
  - t(5;17)(q35;q21) leading to NPM/RARA
  - t(11;17)(q13;q21) - NOMA/RARA fusions
  - t(11;17)(q23;q1) - PLF/RARA: Does **NOT** respond to ATRA – presence changes management



ALL and RUNX1 abnormalities

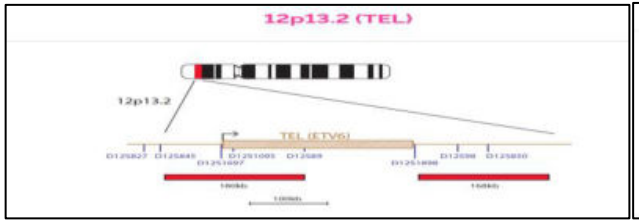
- Acute Lymphoblastic Leukaemia is a neoplasia of the lymphoid lineage
  - Paediatric ALL is the most common haematological neoplasia in children
  - Adult ALL accounts for 20% of all adult haematological malignancies

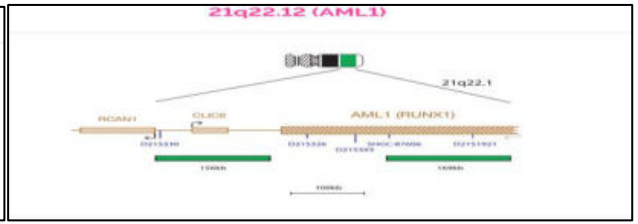
- RUNX1 gene located at 21q22 key gene involved in ALL (primarily children and young adults)
  - The (12;21) ETV6::RUNX1 fusion observed in 25% paediatric B-lineage ALL patients – favourable prognosis
  - Gain of 21 is observed in 100% of high hyperdiploid ALL patients – favourable prognosis
  - RUNX1 amplification is rare, but has a very poor prognostic outcome
  - RUNX1 rearrangements also observed in AML

- The t(12;21) is cytogenetically cryptic by G-banding
  - Upfront FISH with a TEL/AML1 DCDF probe is standard practice
  - UK labs perform FISH on direct preparations for ETV6::RUNX1, BCR::ABL1, KMT2A and TCF3 at sample receipt on all adult and paediatric ALL patients

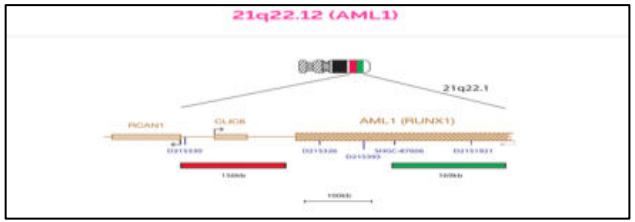
ALL and RUNX1 abnormalities

- CytoCell LPH012 TEL/AML1 (ETV6/RUNX1) DCDF probe confirms presence of t(12;21), and provides information as to RUNX1 copy number status





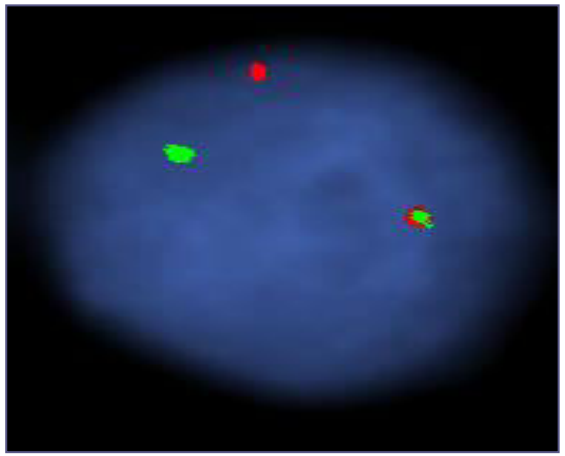
- Where FISH shows 3 x RUNX1 signals – reflex testing with LPH027 AML1 (RUNX1) BA differentiates between gain of 21 and a RUNX1 rearrangement



- Important as RUNX1 fusions other than the t(12;21) would change the management of the patient

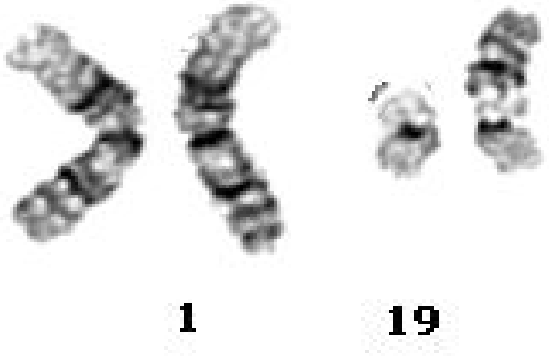
ALL - TCF3 (E2A) Rearrangements

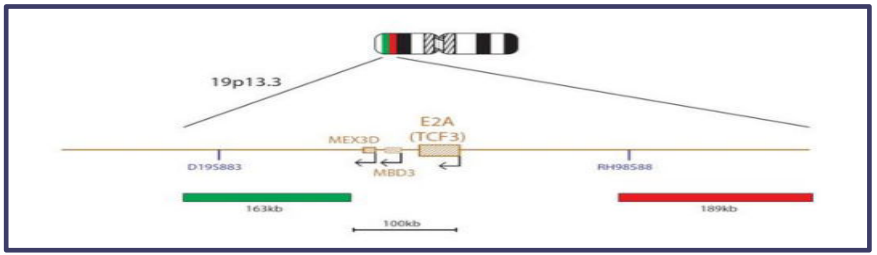
- ~5% adult and paediatric ALL
- TCF3-PBX1 most common
- 80% unbalanced / 20% balanced
- Confirmation of PBX1 involvement critical where a balanced signal pattern seen



LPH 019 E2A (TCF3) Breakapart probe

t(1;19)(q21;p13)/*TCF3-PBX1*
NB: Unbalanced form most common

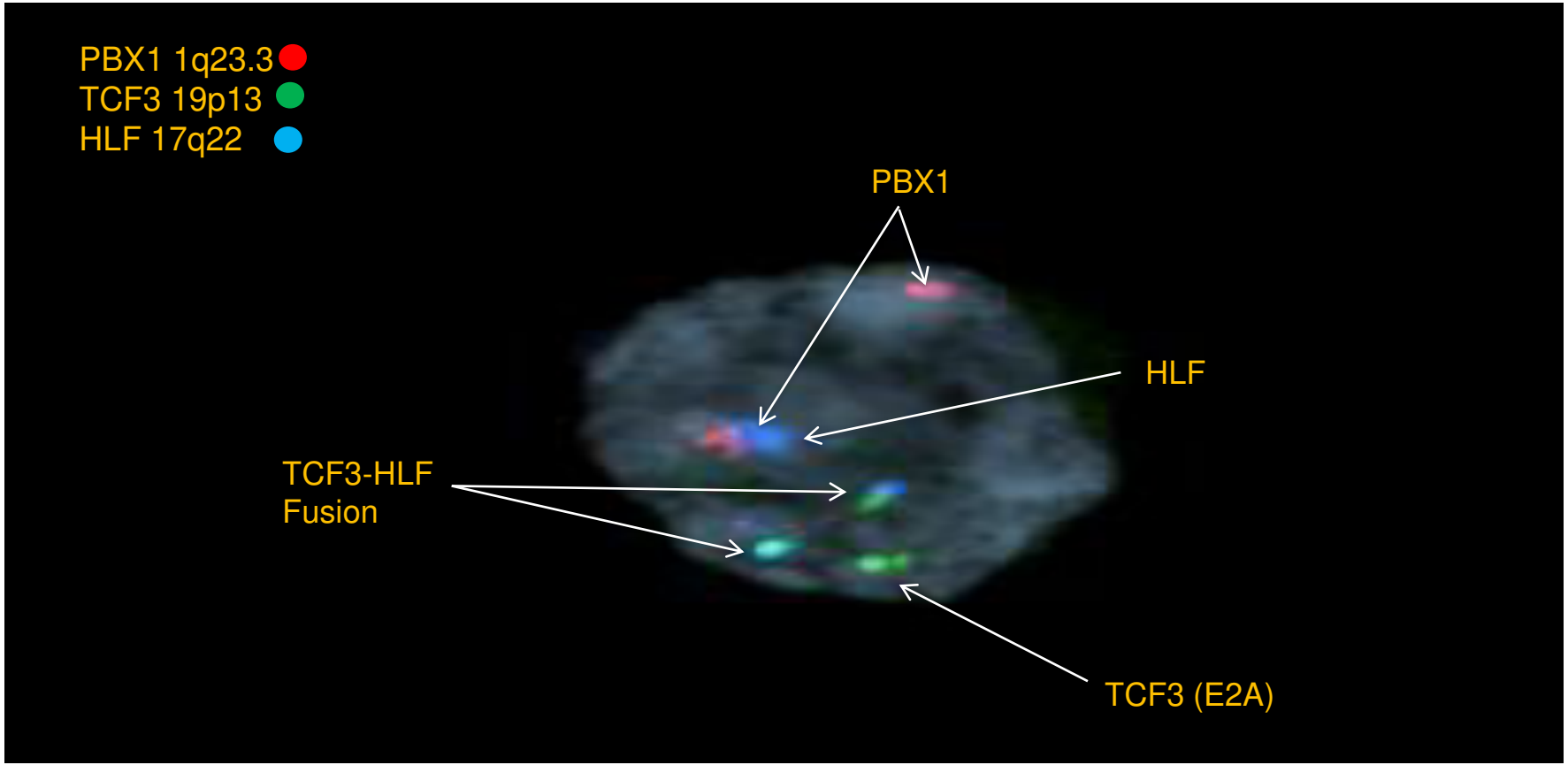




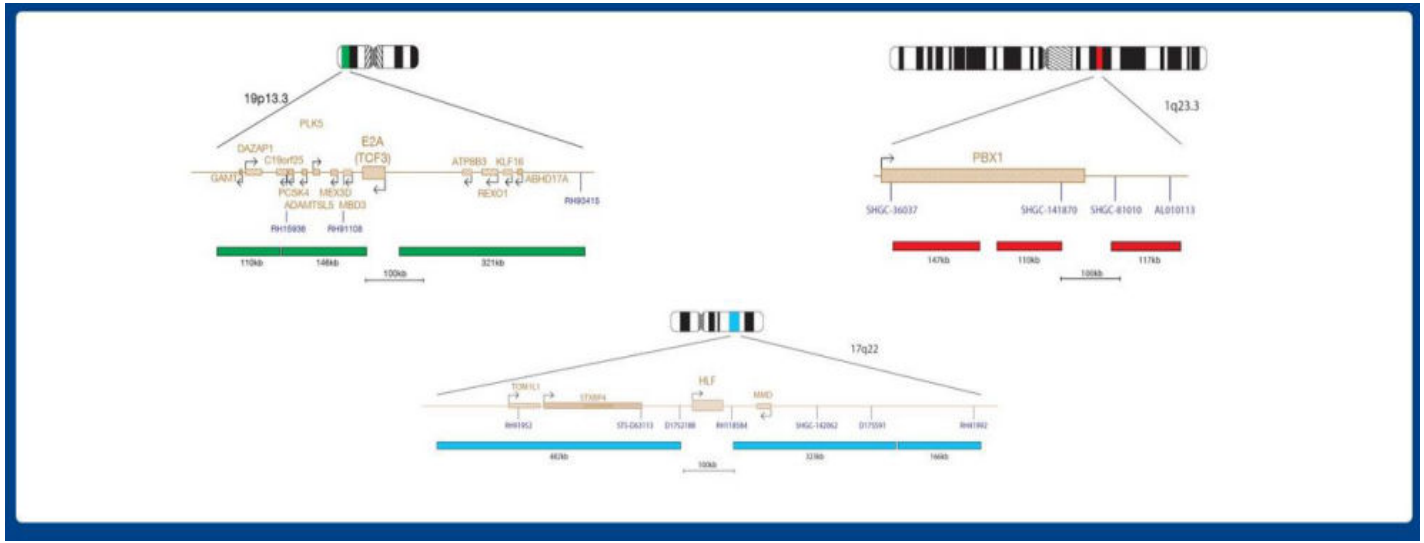
ALL - Case Study: ALL with *TCF3* (19p13) rearrangement

- 5 year old female. Presented with ?AML
- Confirmed as Common/Pre B-ALL by flow cytometry
- FISH:
  - No evidence KMT2A, ETV6-RUNX1 or BCR-ABL1 rearrangements on front-line FISH
  - TCF3 rearrangement positive on second round of FISH testing, with 1R1G1F abnormal signal pattern
- G-band analysis failed
  - Prognosis of *TCF3* rearrangement dependent on fusion partner gene
  - Confirmation of fusion partner critical as BA probe showing balanced rearrangement
    - t(1;19)(q23;p13)/TCF3-PBX1 = intermediate
    - t(17;19)(q22;p13)/TCF3-HLF = poor. Relapse and death within 2 years of diagnosis
- Reflex testing performed with Cytocell LPH 080 E2A/PBX1 *Plus* Translocation Dual Fusion Probe

ALL - Case Study: ALL with *TCF3* (19p13) rearrangement

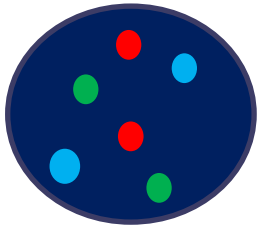


ALL - LPH 080 E2A/PBX1 *Plus* Translocation, Dual Fusion Probe

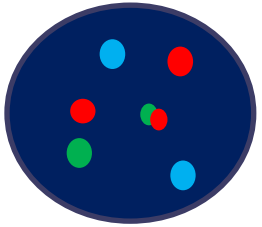


- TCDF probe design
  - Allows for detection of both a TCF3-PBX1 and TCF3-HLF fusion in a single assay
  - Presence of TCF3-HLF changes patient management
  - Requirement of current trial guidance to confirm presence of this rearrangement

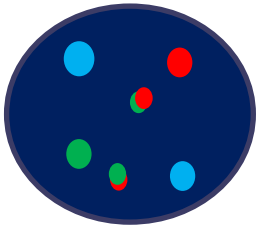
ALL - LPH 080 E2A/PBX1 *Plus*



2G2R2Aq
NORMAL



1G2R2Aq1RGF
TCF3/PBX1 +VE
Unbalanced

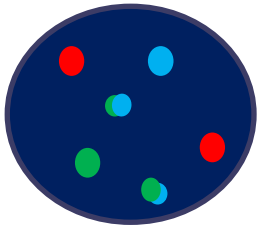


1G1R2Aq2RGF
TCF3/PBX1 +VE
Balanced

PBX1

E2A (TCF3)

HLF



1G2R1Aq2GAqF
TCF3/HLF +ve

Myeloma FISH Testing

- 1ry and 2ry abnormalities in Myeloma with well defined prognostic associations

Primary genetic events			Secondary genetic events		
IgH translocation	Gene(s)	Frequency (%)	Deletion	Gene(s)	Frequency (%)
t(4;14)	*FGFR3/MMSET*	15	1p	*CDKN2C, FAF1, FAM46C*	30
t(6;14)	*CCND3*	4	6q		33
t(11;14)	*CCND1*	20	8p		25
t(14;16)	*MAF*	4	13	*RB1, DIS3*	44
t(14;20)	*MAFB*	1	11q	*BIRC2/BIRC3*	7
			14q	*TRAF3*	38
			16q	*WWOX, CYLD*	35
			17p	*TP53*	7
Hyperdiploidy				Gain	
Trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, 21	NA	50	1q	*CKS1B, ANP32E*	40

SAMPLE RECEIPT

↓

CD138 MACS SEPARATION

FISH RD 1 P53, CKS1B/CDKN2C, IGH BA - ***p53 or CKS1B/CDKN2C abn then report***

↓

IGH Rearranged = Rd 2 (~50% cases)

FISH RD 2 IGH/FGFR3, IGH/MYEOV **- rearr positive report**

↓

-ve for FGFR3 or MYEOV = Rd 3

FISH RD 3 IGH/MAF, IGH/MAFB

Myeloma – IGH testing

- LPH070 IGH Plus BA is probe of choice for initial IGH status testing

  - Use of a DCDF probe for initial screening is not recommended

- For fusion partner confirmation work DCDF probes for below

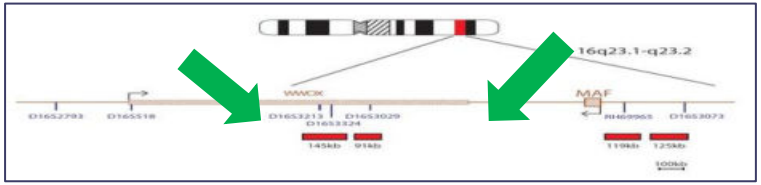
Rearrangement	IGH Partner genes	Clinical significance	Incidence
t(11;14)(q13;q32)	CCND1	Most common IGH rearrangement in PCM. Neutral prognostic effect	20%
t(4;14)(p16;q32)	FGFR3 & MMSET	Poor OS and PFS (25.9M)	15%
t(14;16)(q32;q23)	MAF	Poor OS and PFS (25.9M)	4%
t(6;14)(q21;q32)	CCND3	Standard risk group	4%
t(14;20)(q32;q12)	MAFB	Poor OS and PFS (25.9M)	1%

  - LPH078 IGH/MYEOV Plus (also applicable for t(11;14) in Mantle Cell Lymphoma)
  - LPH074 IGH/FGFR3 Plus
  - LPH108 IGH/MAF Plus V2
  - LPH075 IGH/CCND3 Plus
  - LPH077 IGH/MAFB Plus

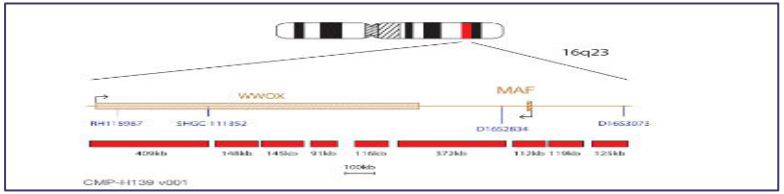
IGH Rearrangements - t(14;16)(q32;q23)

- The t(14;16) IGH-MAF fusion is observed in ~5% patients
  - Adverse prognostic impact / high risk
  - Dysregulation of MAF proto-oncogene
  - Associated with lack of CD56 expression and high proliferative activity

- LPH 108 IGH/MAF Plus v2 Translocation, Dual Fusion probe
  - Probe recently re-designed based on feedback from US laboratories around competitor probes



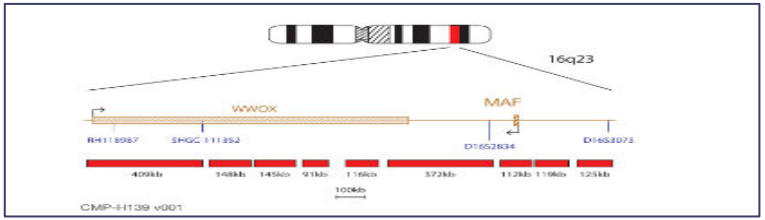
Old MAF Design



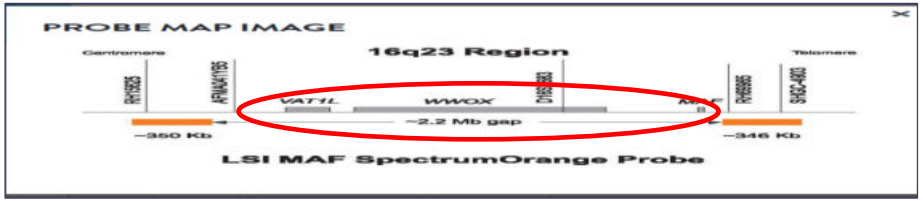
New MAF Design

IGH/MAF v2 Probe

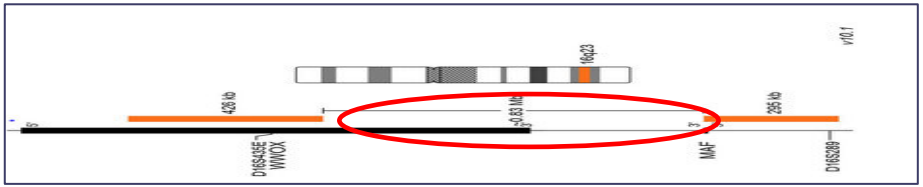
- CytoCell MAF



- C1 – 2.2Mb gap



- C2 – 0.83Mb gap

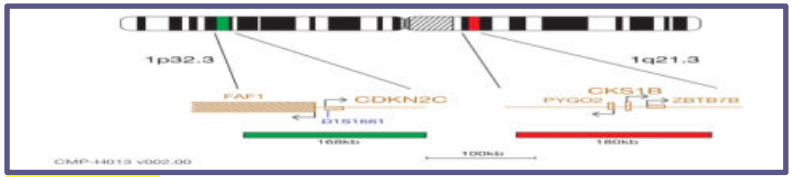


This is important as splitting of MAF with competitor probes can be misinterpreted

Myeloma – 2ry abnormalities

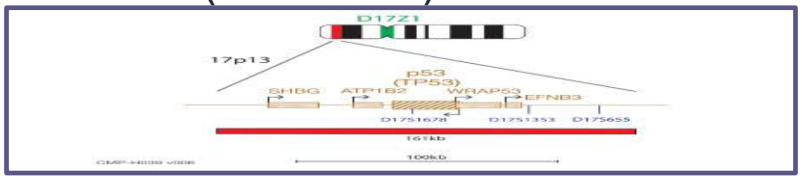
- Key secondary abnormalities in Myeloma include:
  - 1p loss / 1q gain – 35-40% patients. Independent poor prognostic marker

LPH039 CKS1B/CDKN2C(P18) Amplification/Deletion probe



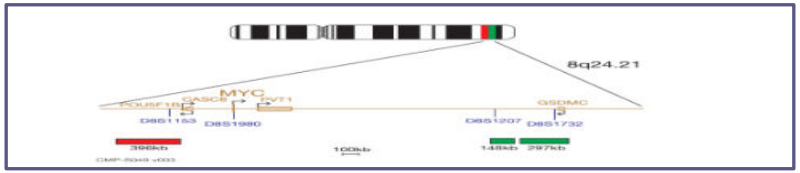
  - TP53 Loss - ~10% patients. Independent poor prognostic marker

LPS 037 P53 (TP53 deletion) Deletion Probe



  - 8q24 MYC rearrangements – up to 47% patients at relapse

LPS 027 MYC Breakapart Probe



Both TP53 and MYC probes are pathology optimised so give better signal intensity

13q status, whilst extremely common has no specific prognostic associations

Key Probes by referral type – Haematopathology and Pathology

- Include Lymphoma and Solid Tumour type referrals
  - Solid tumour referrals are diverse and highly heterogeneous
    - Focus on Neuroblastoma

- CytoCell range includes probes with cross applicability to haematology referrals as well
  - 8q24 MYC gene rearrangements (LPS027)
  - 8p11 FGFR1 amplification events (LPS018)
  - 17p13 TP53 deletions (LPS037)
  - 9p16 CDKN2A deletions (LPS036)

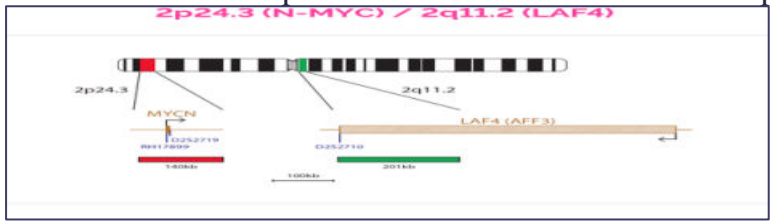
FISH in Neuroblastoma

- Clinically heterogenous paediatric cancer of the sympathetic nervous system that originates from neural crest cells
- Most common extracranial solid tumour in childhood and prognosis ranges from spontaneous tumour regression to aggressive disease resistant to multimodal therapy
  - Over half of patients relapse and 5 year OS is 40-50%
- Prognosis depends on patient characteristics and tumour biology that determine risk classification
  - Genetic testing highly significant. Array + FISH or FISH depending on technology across region

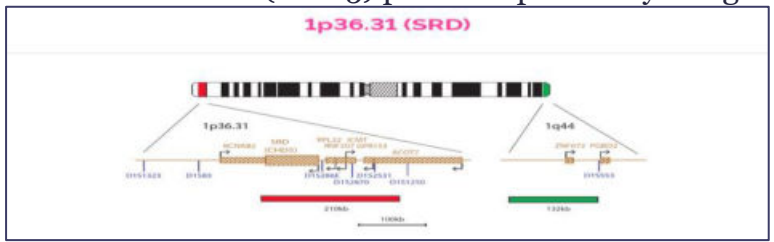
Genetic abnormality	Probes	Comments
N-MYC amplifications	N-MYC amp	Poor prognostic marker. 20% STNB and 50% HR group.
Unbalanced gain 17q	P53/MPO, 17cen / 17qtel	Unbalanced 17q gain can be observed independently of MYC-N amp and poor outcome. See in up to 50% STNB. Telomeric probes not ideal for FFPE work
11q loss	ATM/11cen deletion	See in ~33% STNB, primarily HR group. Custom MPD probe is pathology optimised
1p loss (SRD)	SRD (CHD5) deletion	SRD encompasses smallest common deleted region in neuroblastoma. 1p loss correlates with MYCN-amplification, metastatic disease, and older age. It is present in 23-35% of primary neuroblastoma tumors (Maris et al., 2000)

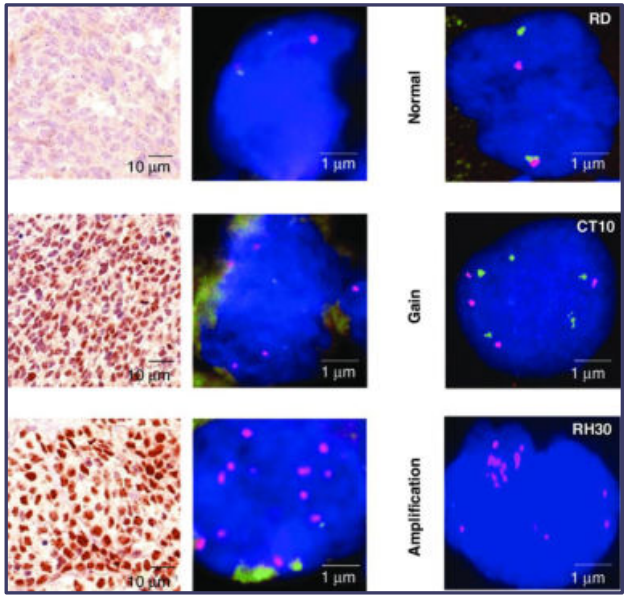
MYCN amplification and 1p loss status

- Amplification of MYCN is the most commonly tested genetic abnormality in STNB
  - Observed as HSR or presence of double minutes
  - LPS019 N-MYC amplification probe designed specifically for this
    - Applicable for work on both FFPE and fresh frozen tissue, touch preps and CSF samples
    - In-built control at 2q11.2 to allow for establishment of ploidy status



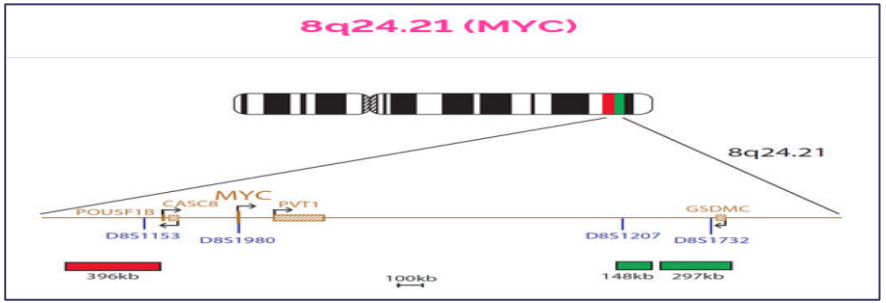
- Deletions of 1p involving SRD region observed in 20-35% cases
  - Older age, and metastatic disease
  - CytoCell LPS010 SRD (CHD5) probe is specifically designed for this





Probes with cross applicability

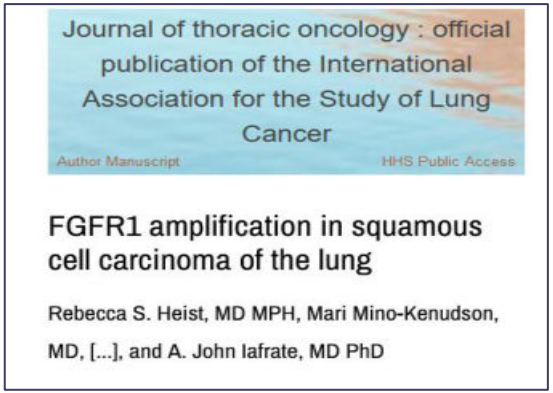
- 8q24 MYC rearrangements and amplification
  - Rearrangements of MYC observed in Lymphoma, Acute leukaemia and Myeloma
  - LPS027 MYC BA probe designed for use on FFPE and BM



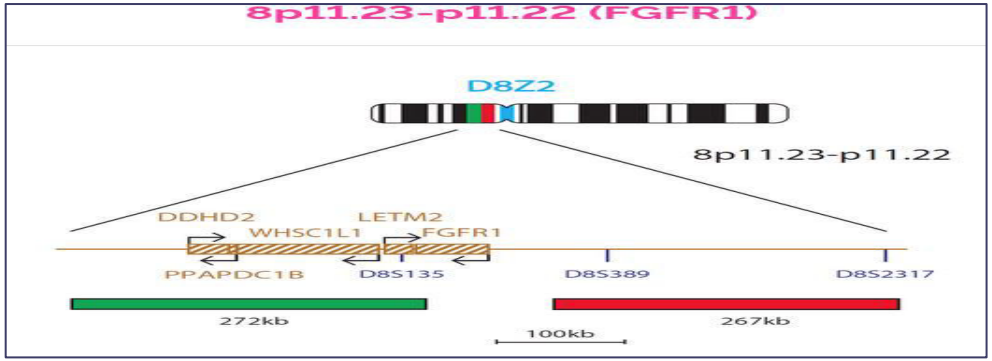
  - BP region encompasses both standard BP region observed in Burkitt Lymphoma and variant position seen in ~20% DLBCL / HG Lymphoma
  - MYC rearrangement testing now added to test requirements for relapsed myeloma patients in UK
  - MYC amplification widely reported in both haematological neoplasia and solid tumours
  - Incorporation of LPE008B to mix allows for amplification / ploidy status testing in single assay
    - Aqua labelled centromerics also include 12 and 17 in catalogue range

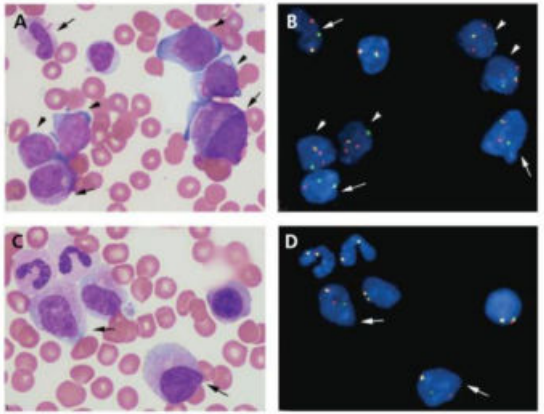
Probes with cross applicability

- 8p11 FGFR1 rearrangements and amplification
  - 8p11 rearrangements recurrent finding in myeloproliferative neoplasia
  - Poor prognosis and associated with rapid transformation to acute leukaemia
  - FGFR1 amplification reported in wide range of solid tumours



- LPS018 FGFR1 Breakapart/Amplification probe is a dual use probe
  - Detects FGFR1 rearrangements and amplification through incorporation of 8cen control in aqua into probe mix





  - Alleviates need to stock 2 different probes in laboratory
    - Reduces internal QC, validation, costs, errors with wrong probe use

myProbes

- myProbes are RUO probes developed to specifications of end user
- Internal QC does not involve clinical validation work up at OGT
  - Labs must perform own validation work prior to implementation

Please note that probes from within the CytoCell myProbe range are RUO products developed by customers to their own specifications, and require review and validation by the end-user to ascertain suitability for intended use

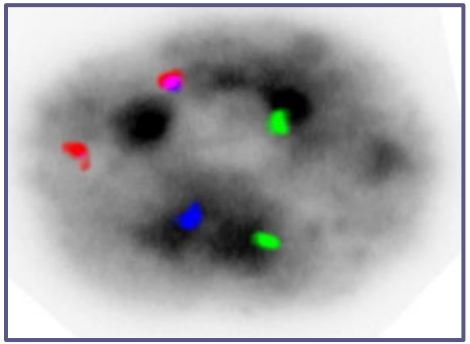
- Extensive range of probes available to order as 10 test kits from existing portfolio
- New projects require minimum initial order of 50 tests, after which can be re-ordered as 10 test kits
  - Include:
    - probes developed by LRF for clinical trials in ALL and paediatric AML
    - unique TC probes for myeloma and acute leukaemia work to reduce technical and analytical workloads
    - probes for rare and ultra rare rearrangements (YAP1, RELA, MAML2, CIC-DUX4, TP63, DUSP22-IRF4 etc etc)
    - specifications and promotional quotations available on request
    - FOC evaluations from short dated probes circulated to labs via partners. Available on a ‘first come first served’ basis
  - For more information please contact Bioproducts team

Filters

- Chroma Filters supplied for all models of microscopes
- Sale or return 30 day trial available
- 69008 Chroma triple R/G/Aq filter reduces analysis time and third opinion rates
  - Implemented in majority of labs across Europe

Testimonial from Polly Talley at HMDS Leeds regarding three x EtAq-R-G triple bandpass filters

We have recently bought three triple band pass filters from OGT and have been hugely impressed by the difference they have made to our FISH analysis workflow. The signals are clear and bright, and allow a full analysis to be completed without the need for reverting to single filters in the majority of cases. Without a doubt they have decreased the time taken to analyse and check cases, but more importantly have increased the analytical accuracy and confidence in the analysis. This is particularly true for the three colour probes where positional information is key, eg the MECOM and PDGFRA breakapart probes. We have also seen a specific benefit with our paraffin sections where simultaneous three colour analysis again has increased confidence and decreased the time taken.



Thank you

Any Questions?

A Sysmex Group Company

What binds us, makes us.