MOLECULAR DIAGNOSTICS UNIT

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OVERVIEW

The Molecular Diagnostics Unit (MDU) is entrusted to provide our National Health System's hospitals with a wide range of sensitive, specific, reliable and updated assays. By using golden standard molecular techniques, we routinely identify alterations in the sequence or expression of key genes that are involved in cancer and that could in turn be used in the diagnosis and/or prognosis of patients, the detection of minimal residual disease in patients showing clinical remission, or for monitoring response to therapy. Our Unit also provides support to CNIO's Clinical Research Units and Research Groups by developing and implementing novel solutions for their research needs. Involved in the global efforts to standardise and improve molecular diagnostics testing in cancer, we work in partnership with international and national consortia dedicated to these objectives. Finally, our Unit remains fully committed to promoting laboratory training and mentoring for students, technicians and medical residents.

"Despite the fact that the COVID-19 pandemic notably disrupted the testing status quo in the area of oncology diagnosis, MDU not only continued to supply our NHS hospitals with assays but also established new ones."

CORE UNIT HIGHLIGHTS

Broadening our genetic testing catalogue

During 2020, we implemented 3 new molecular diagnostic tests based on bi-directional Sanger sequencing. These tests will allow us to provide more comprehensive molecular diagnostics of some haematological malignancies like myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML), for which we were already offering a sizable panel of clinically applicable markers (FIGURE).

The first 2 assays aim to detect mutations in the *ASXL1* (additional sex combs-like 1) gene that plays a role in both embryonic development and chromatin remodelling, and in the *SF3B1* (splicing factor 3b subunit 1) gene, which encodes a catalytic core component of the RNA splicing machinery and is involved in transcription and mRNA processing. Somatic mutations in *ASXL1* and *SF3B1* genes have been observed, among many other cancers, mostly in MDS, CMML and AML. Mutually exclusive, *ASXL1* mutations are prognostic of high-risk MDSs, acute transformation in CMML, and shorter overall survival of patients with AML, while *SF3B1* structural alterations are predictive of a longer overall survival of MDS patients but shorter overall survival in *de novo* AML and chronic lymphocytic leukaemia (CLL) patients.

The third test developed seeks to detect mutations in the *SETBP1* (SET-binding protein 1) oncogene, encoding a binding partner for the multi-function SET oncoprotein involved in apoptosis, transcription and nucleosome assembly. *SETBP1* overexpression is associated with a worse overall survival of elderly AML patients. Furthermore, somatic gain of function mutations of *SETBP1* are associated with myeloid leukemic transformation and convey poor prognosis of MDS and CMML patients.

Tutoring

In 2020 we hosted, in the framework of our training policy, one medical resident.

Diagnostic marker	Targeted exon(s)	MPN	MDS	CMML	AML
ASXL1	13 & 14	v	v	v	v
SETBP1	12		v	v	
SF3B1	14, 15 & 16	v	v	v	v
CALR	9	v			
CEBPA	Whole gene		v		v
WT1	7 & 9				v
TP53	5-8		v	v	v
FLT3	13-15			v	v
IDH1	4			v	v
IDH2	4	v	v	v	v
JAK2	12 & 14	v	v	v	v
KIT	9, 11, 13 & 17				v

Diagnostic marker	Targeted exon(s)	MPN	MDS	CMML	AML
KRAS	2 & 3			v	
MPL	10	v		v	
TET2	3, 6, 7, 9, 10 & 11	v	v	v	v
NPM1	12		v	v	v
NRAS	2 & 3		v	v	v
RUNX1	4, 5, 6 & 8		v	v	v
SRSF2	Whole gene		X	X	X
CBL	7 & 8	X	X	X	
U2AF1	Whole gene		X	X	X
DNMT3A	15-23	X	X	X	X
EZH2	15		X	X	X
PHF6	Whole gene		X		X

FIGURE The addition of 3 new markers (in red) to those already provided (in green) gets us closer to the whole panel of known markers used for the diagnosis/prognosis of myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS), chronic myelomonocytic (CMML) and acute myeloid (AML) leukaemias.