



## SUPPORTING INNOVATION AND TECHNOLOGY TRANSFER IN ONCOLOGY

### ISOSTEM

**p53 isoforms : a major prognostic marker of the metastasis risk**



### CONTEXT & BACKGROUND

The purpose of the use of a biomarker in oncology is to make it possible to adapt the therapeutic choice so that the patients benefit better from their treatment. The biomarker also avoids unnecessary treatment from which the patient would not benefit (over-treatment). Our data indicate that the «p53 isoform» test developed by ISOSTEM would help the clinician in both cases.

The originality of our approach is to target a particular cellular mechanism, alternative splicing. This process generates a tremendous protein diversity, giving rise to modified proteins called isoforms. Splicing defects represent an original pharmacological pathway with a high potential but not yet explored in the context of cellular dysregulation and the formation of metastases. To date, no alternative splicing protein is still used as a prognostic biomarker of metastases and no anti-cancer drug targeting alternative splicing is available. Our published data indicate that alternative splicing of p53 is a more important mechanism than genetic instability to predict the risk of metastasis and patient survival. We developed a robust diagnostic test, usable on paraffin-embedded tumor samples, which detects a particular isoform of p53,  $\Delta 133p53\beta$ . The prognostic value of this biomarker was validated on breast, rectum and colon cancer cohorts.,  
- The increased expression of the  $\Delta 133p53\beta$  isoform of p53 identifies patients at risk for recurrence, thus benefiting from appropriate therapy.

The «p53 isoform» test also allows, and reciprocally, to identify patients who have a low risk of metastasis and who, thanks to this information, can benefit from a reduced treatment to ensure a better quality of life. The ISOSTEM project aims first to compare the test with conventional prognostic criteria. The second objective is to associate a therapy with the biomarker in order to propose a targeted therapeutic option. The third objective is to evaluate the predictive value of current treatments in order to guide decision-making regarding the choice of treatment. The final objective is to try to develop a non-invasive diagnostic test that can be used directly on blood samples (circulating RNA). The use of a p53 isoform as a prognostic marker of recurrence and predictive of the therapeutic response is in breach with the available markers by proposing a biomarker derived from alternative splicing. The project is positioned on the market of the main tumor biomarkers used as prognostic and predictive values and their diagnostic and / or therapeutic applications.

### SCOPE

New approach to identify aggressive metastatic cancers allowing a better therapeutic management of patients

### KEYWORDS

Tumor suppressor p53, alternative splicing, prognostic biomarker



### INNOVATIVE COMPONENT & TECHNOLOGY

Highly sensitive and specific prognostic biomarker which targets an original mechanism not yet exploited in the framework of biomarkers in oncology (First-in-class)



### OBJECTIVES

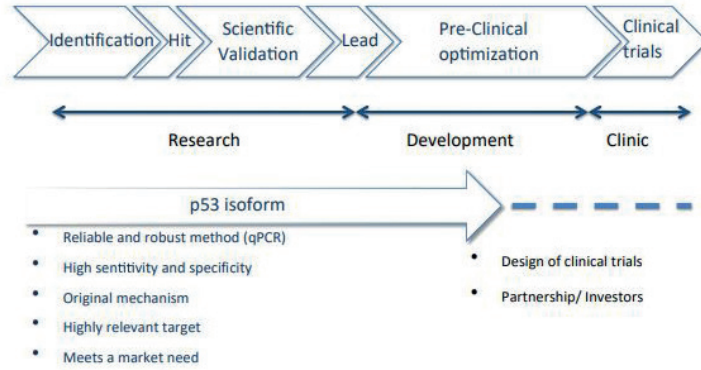
Targeting an unexplored mechanism in cancer development, i.e. alternative splicing, i/ Rapidly provide a new approach to identify aggressive colorectal cancers metastatic cancers allowing a better therapeutic management of patients



## DEVELOPMENT & MATURATION STAGE

To determine the clinical relevance of  $\Delta 133p53\beta$  expression they analysed its expression in a cohort of 273 breast tumours (Gadea et al; 2016, eLife) and a cohort of 60 rectum cancers and demonstrate that  $\Delta 133p53\beta$  expression is a prognostic marker of poor outcome, higher risk of cancer relapse and death, independently of TP53 mutation status. Furthermore they found  $\Delta 133p53\beta$  expression is dominant over TP53 mutation status in predicting cancer recurrence and metastasis. As well as this demonstration of oncogenic capacity of  $\Delta 133p53\beta$ , they investigated its molecular mechanism and show that it promotes cancer stem cell potential in vitro and in vivo (Arsic et al., 2015). A test based on qPCR analysis of mRNA has been developed and validated.

## Positioning in the value chain development



## INTELLECTUAL PROPERTY & PATIENT CO-OWNER(S)

A patent application has been filed claiming the use of a R1R2R3S4LLKGR4R5R6 peptide in either linear or cyclic forms. USA, Canada and Japan national stages are going while the patent has already been granted in Europe (EP2729495B1). Inventors: S. Dedieu, N. Floquet, L. Martiny, C. Schneider, A. Jeanne, E. Sick, M. Dauchez. Co-owners: Reims Champagne-Ardenne University, CNRS.

### INTELLECTUAL PROPERTY & PATENT CO-OWNER(S)

		METHOD FOR TESTING A SUBJECT THOUGHT TO BE PREDISPOSED TO HAVING METASTATIC CANCER USING $\Delta 133P53\beta$		$\Delta 133P53\beta$ AND $\Delta 133P53Y$ ISOFORMS ARE BIOMARKERS OF CANCER STEM CELLS		
<b>Co-Inventors</b>		ROUX Pierre FERNANDES Kenneth BOURDON Jean-Christophe GADEA Gilles ANGUILLE Christelle VINOT Stéphanie		ROUX Pierre ARSIC Nikola GADEA Gilles FORT Philippe RAYNAUD Peggy		
<b>Co-owners</b>		CNRS, UM2, Université de Dundee		CNRS / UM		
<b>Management</b>		CNRS / FIST SA		CNRS / FIST SA		
<b>Family patent</b>	<b>Priority request</b>	US 61/221769 (abd) EP 09305633.1 (abd)	30.06.2009	EP 15305146.1 (abd)	30.01.2015	
	<b>international Extension</b>	PCT/EP2010/059321 WO2011000891	30.06.2010	PCT/EP2016/052095 WO2016120495	01.02.2016	
	<b>National phases</b>	MX/A/2012/000041	IN 10157/DELNP/2011	National phases: Expected: 30.07.2017		
		BR P11011929-9	JP 2012-518089 (abd)			
		CA 2766317	EP 10731498.1			
CN 201080029421.7		(DE,ES,FR,IT,GB, NL)				
US 13/381628 (abd)						



## STRENGTHS & COMPETITIVE ADVANTAGES

- Highly sensitive and robust assay
- First in Class: original mechanism (alternative splicing)
- Highly relevant target (p53)
- Meets market needs

Compared to other prognostic factors, the detection of the p53 isoform  $\Delta 133p53\beta$  benefits of:

- to be monogenic (other markers are multiplex)
- weak error rate (high sensitivity)
- mechanism can be identified
- suitable for associated targeted therapy
- reduced cost
- suitable for any type of cancer samples (frozen or paraffin)



## TARGET POPULATION

Patients with breast and colorectal cancer



## TARGET PROFILE

Early stage newly detected:  
- stage II and III invasive colorectal cancers



## INDUSTRIAL APPLICATIONS & OPPORTUNITIES

This pertinent, robust and original biomarker could be used very early in the primary tumour to classify patients with high risk of metastasis and be helpful to drive therapeutic decisions, in breast and colorectal (CRC) cancers in particular