

# Could glyphosate prime mammary cells for tumorigenesis by reprogramming the epigenome ?



international breast cancer & nutrition  
working together for prevention  
<http://www.pcrn.edu/epigenetics/ibcn.php>



**Presented by Manon DUFORESTEL**

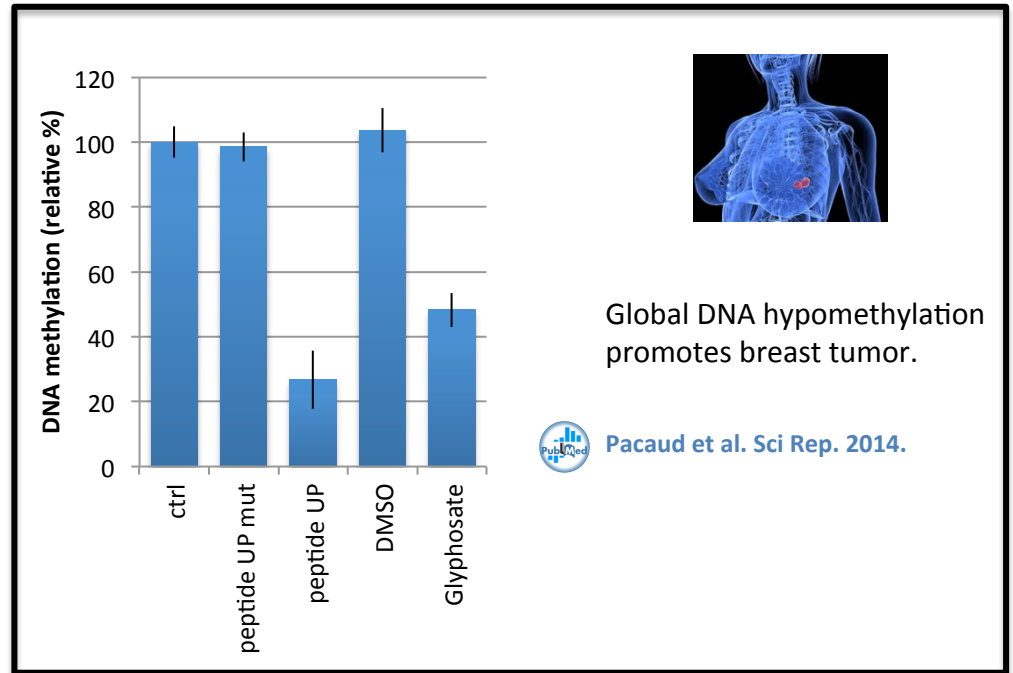
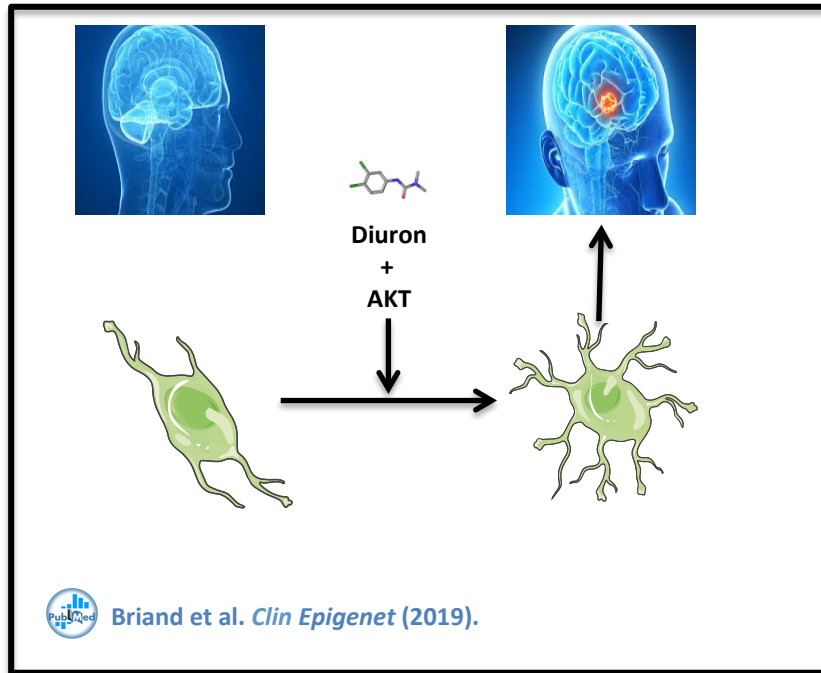
PhD student

Team 9, CRCINA, site ICO Boulevard Professeur Jacques Monod  
44800 Saint-Herblain

**Leader François VALLETTE**

**Supervisor Pierre-François CARTRON**

# CONTEXT



## Is glyphosate carcinogenic by itself ?

## Is glyphosate carcinogenic in combination with a second oncogenic hit ?

Multiple-hit theory in carcinogenesis

Alfred G. Knudson, Jr. *Proc Natl Acad Sci U S A.* 1971 Apr



MCF10A immortal human mammary epithelial cells



qMSRE, ELISA, ChIP, Tumor Xenografts in Nude Mice...

# RESULTS . Figure 1

**A**

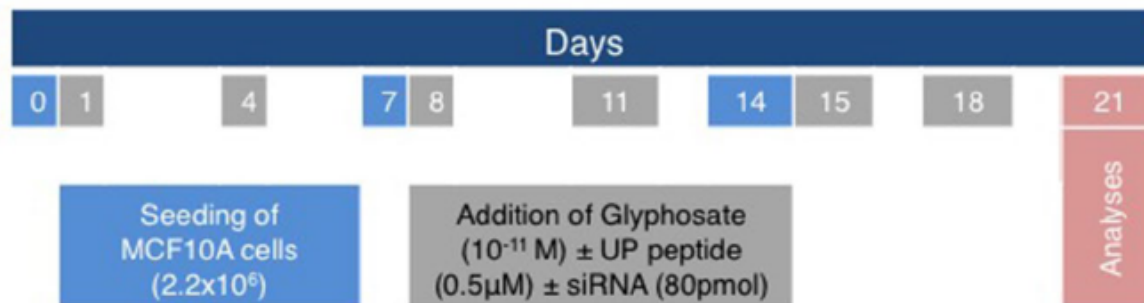
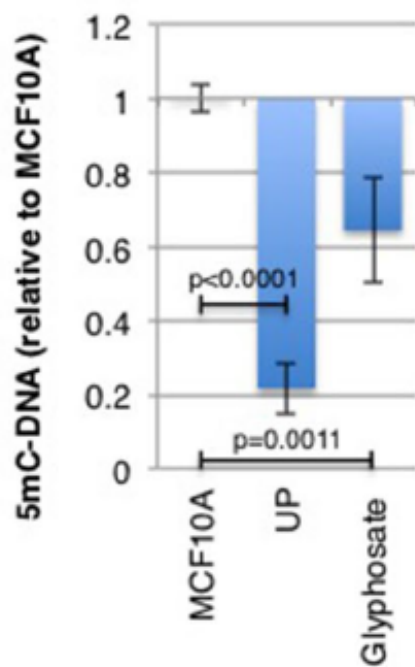


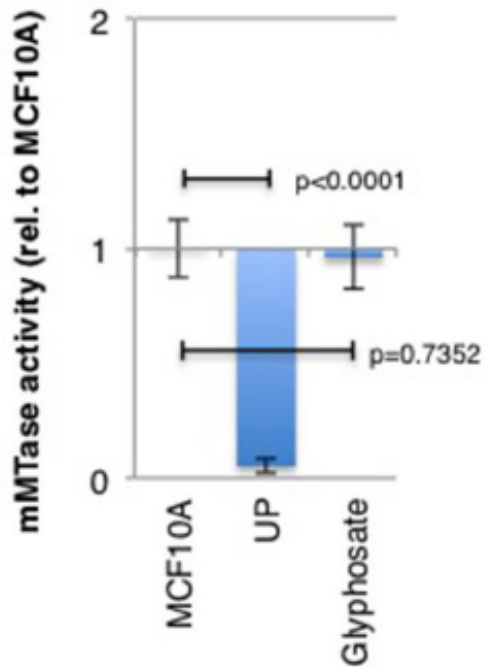
Figure 1.A

- UP peptide = control peptide inducing overall hypomethylation of DNA

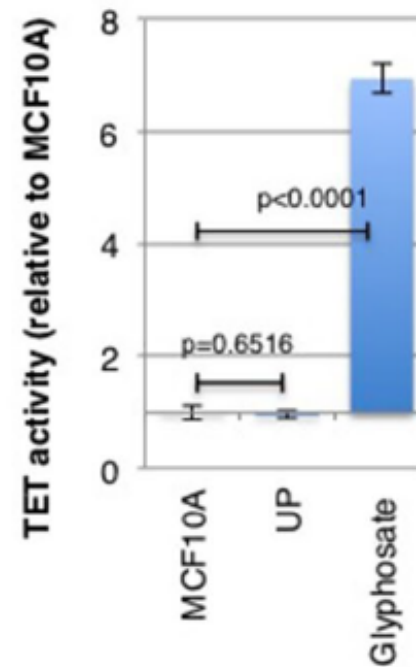
**B**



**C**

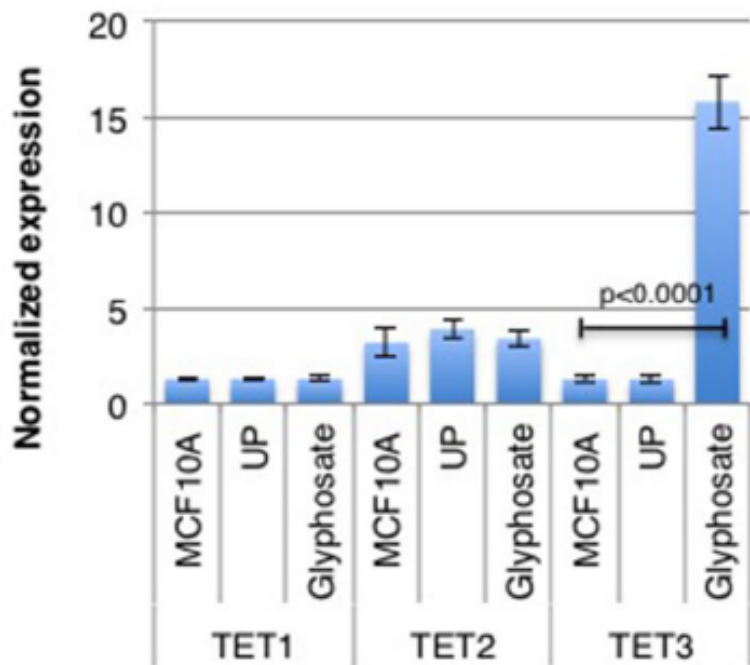


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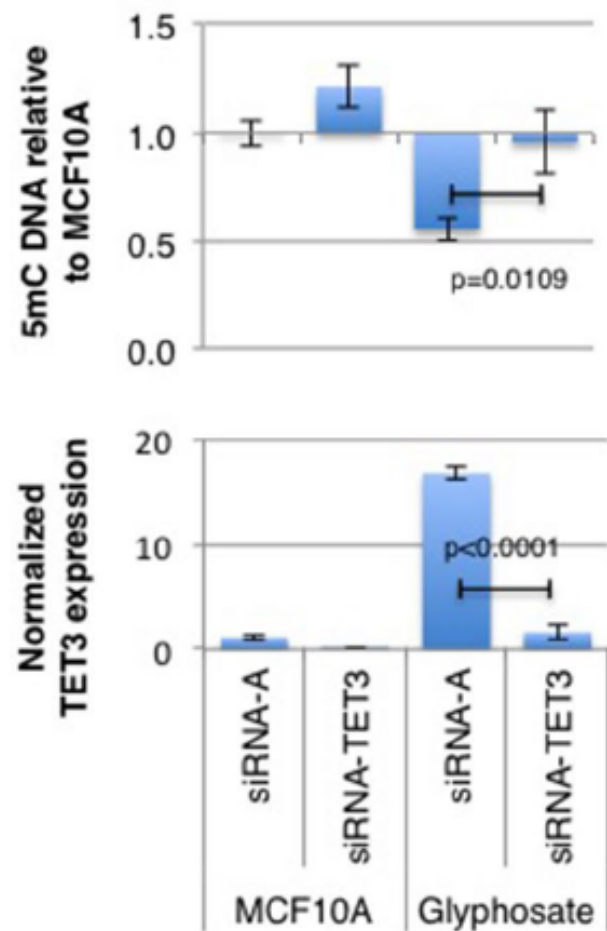


# RESULTS . Figure 1

**E**

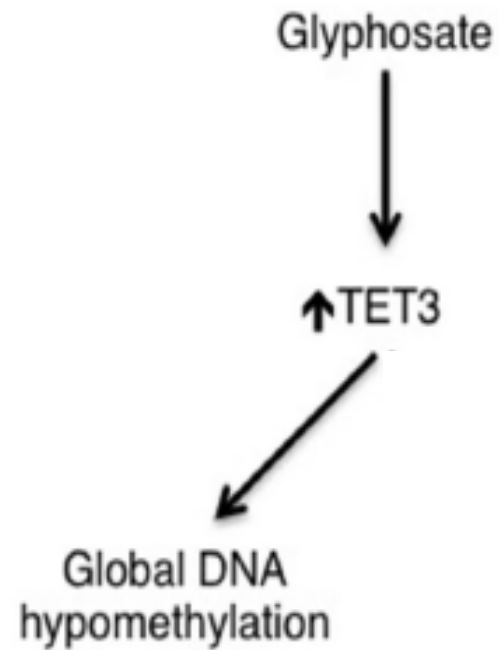


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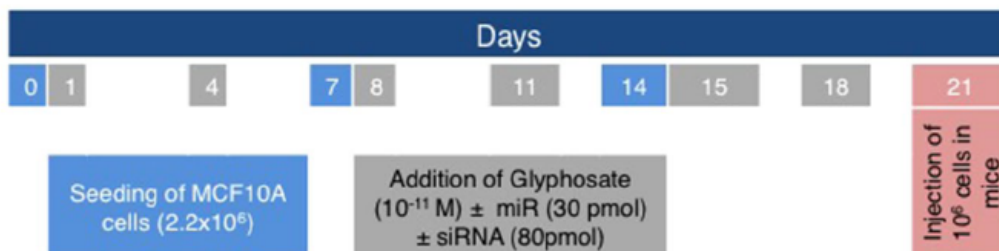


Exposure to glyphosate promotes TET3-mediated global DNA hypomethylation in MCF10A cells.

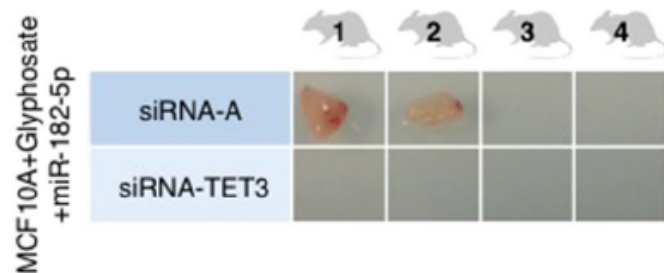


# RESULTS . Figure 2

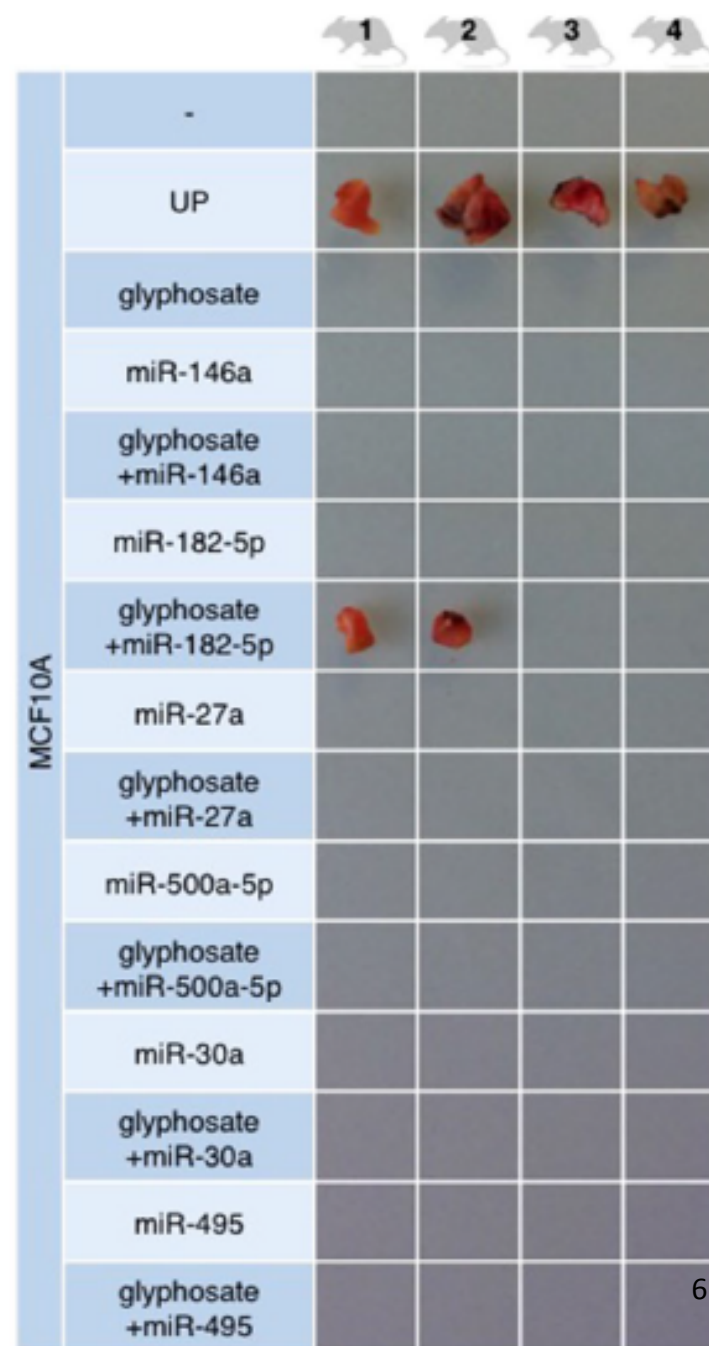
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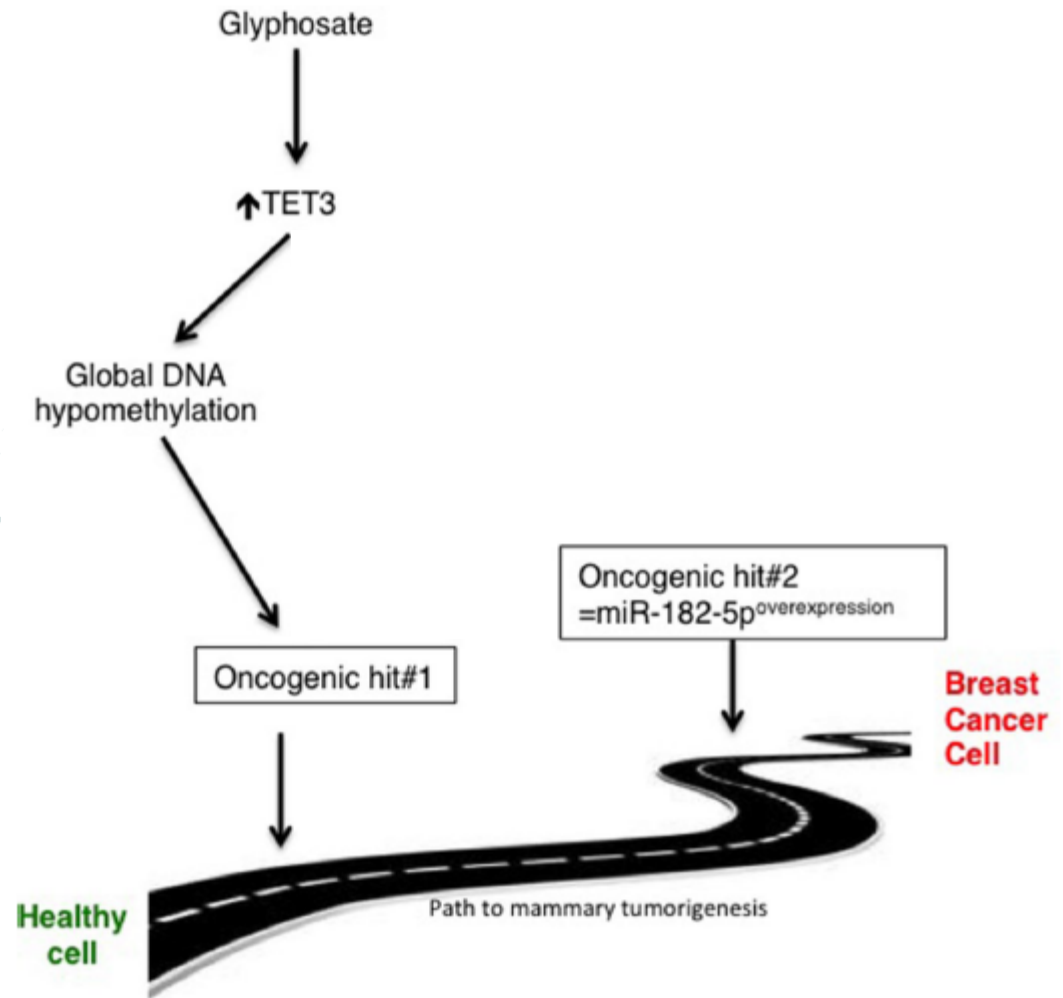
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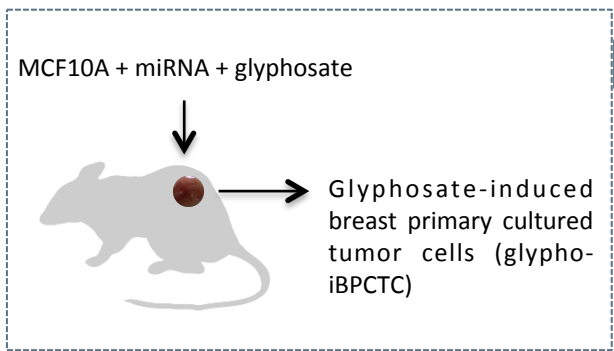
**B**



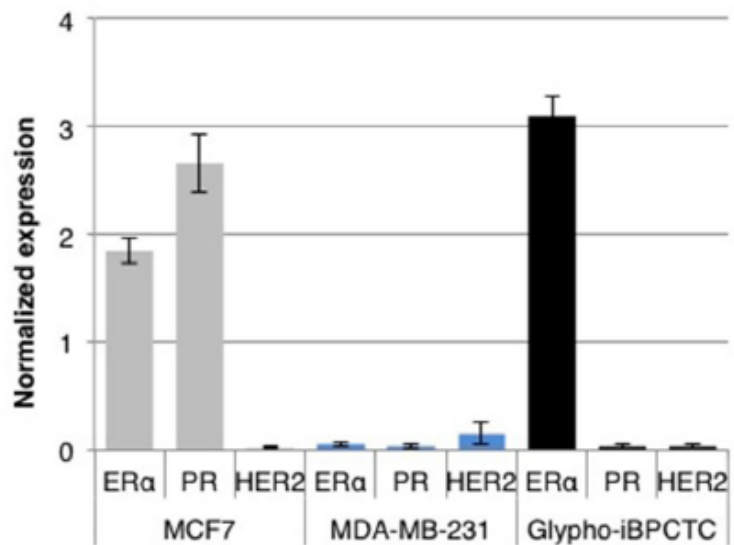
Glyphosate exposure is tumorigenic for MCF10A cells in a “two-factor hit” model.



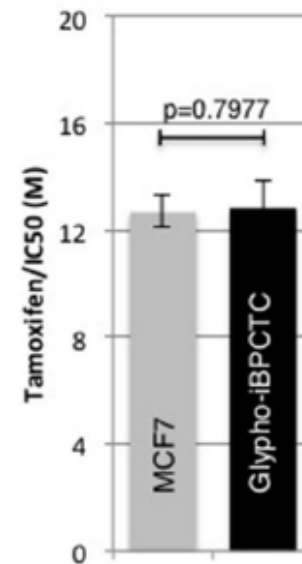
# RESULTS . Figure 3



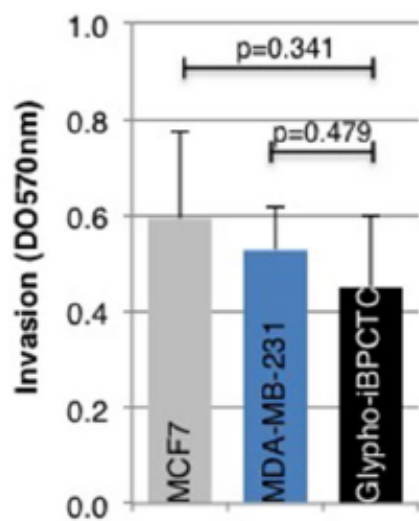
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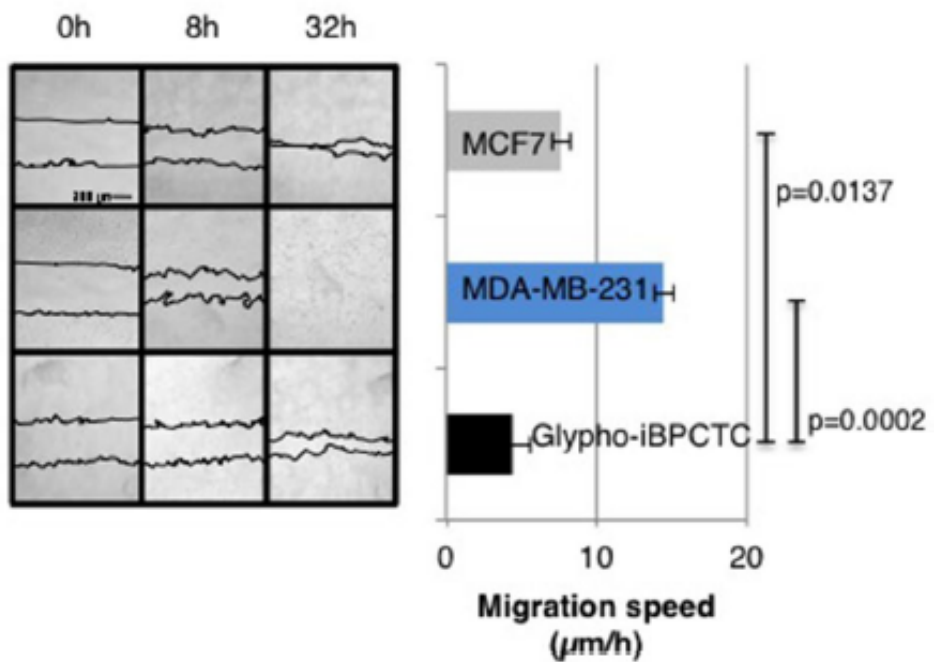
**B**



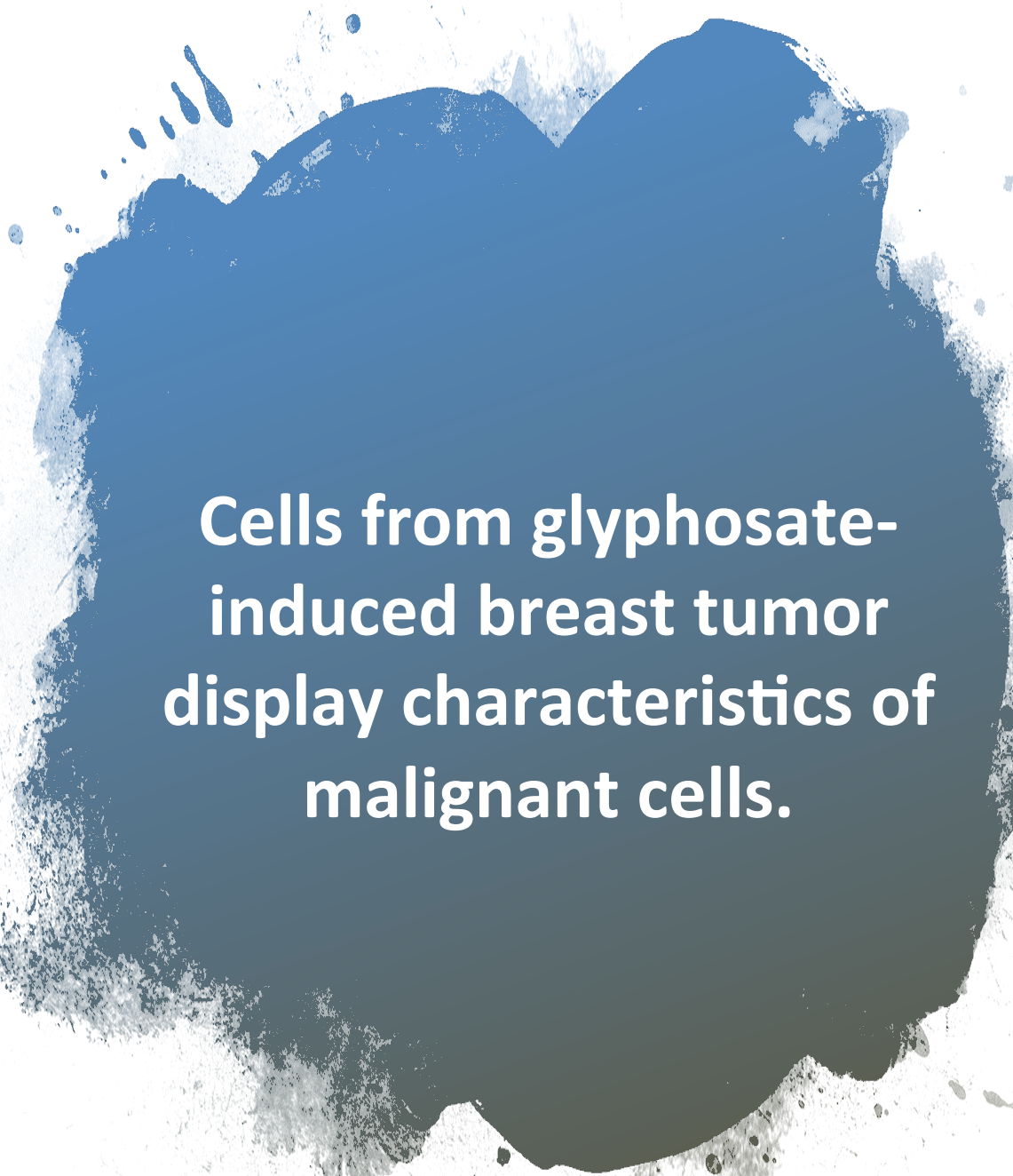
**C**



**D**

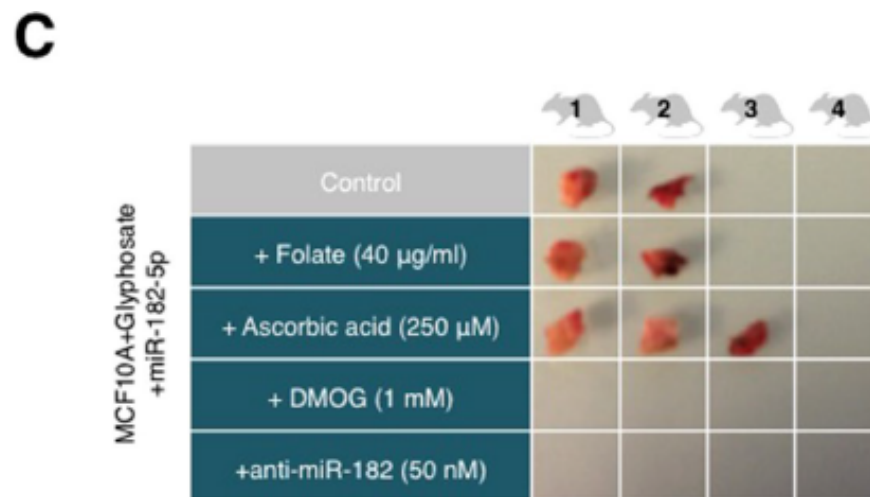
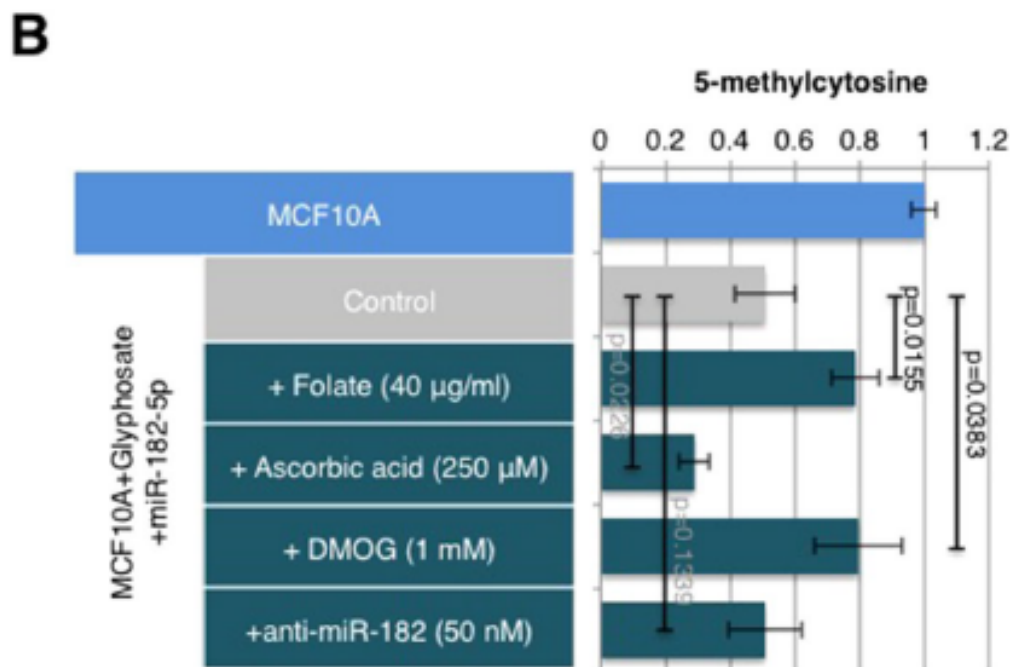
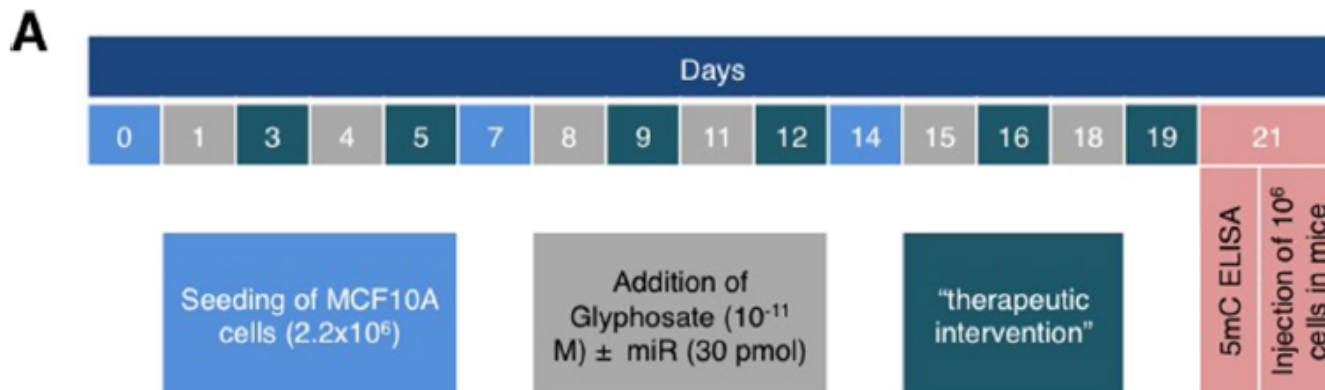


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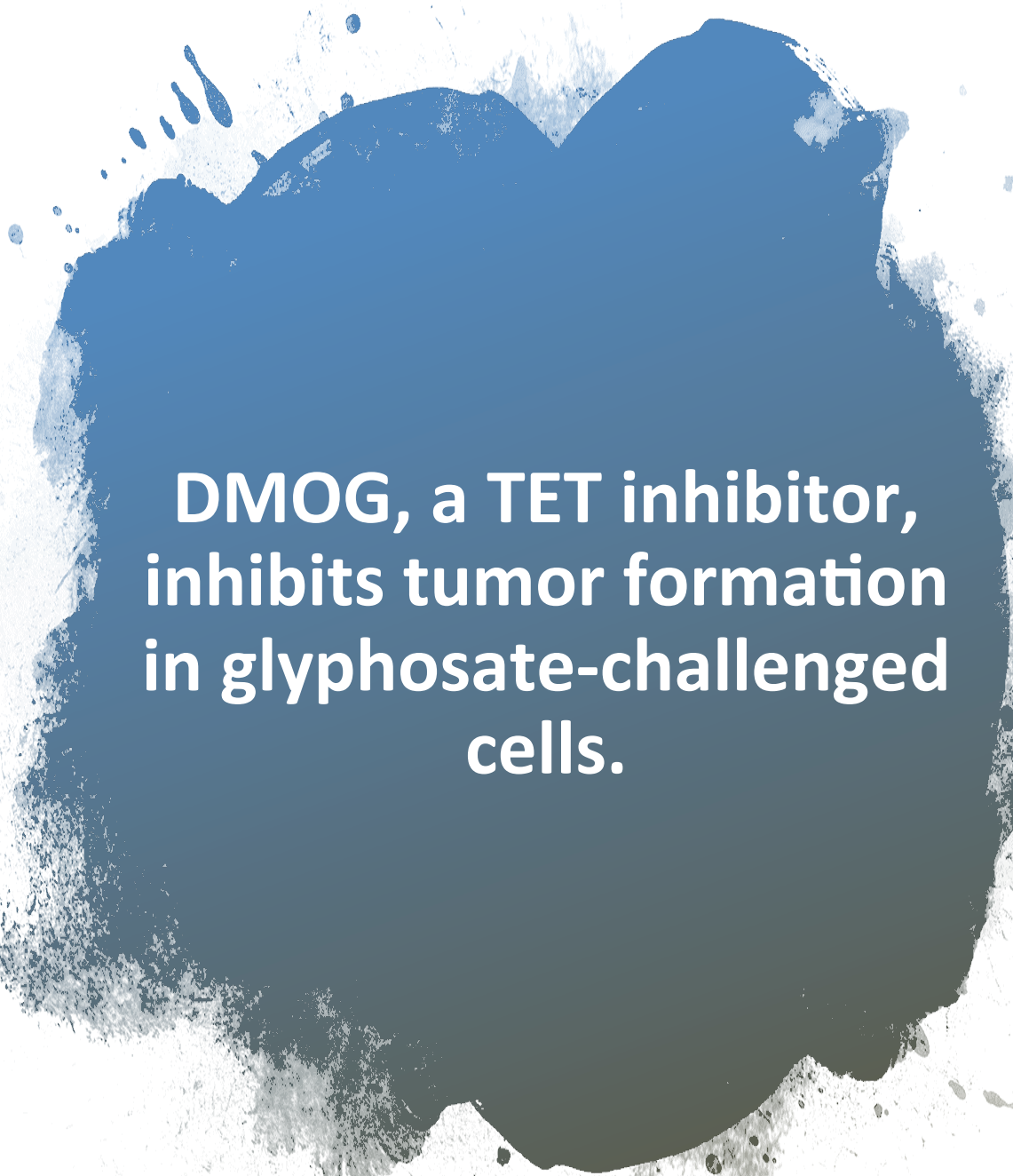


**Cells from glyphosate-  
induced breast tumor  
display characteristics of  
malignant cells.**

# RESULTS . Figure 4



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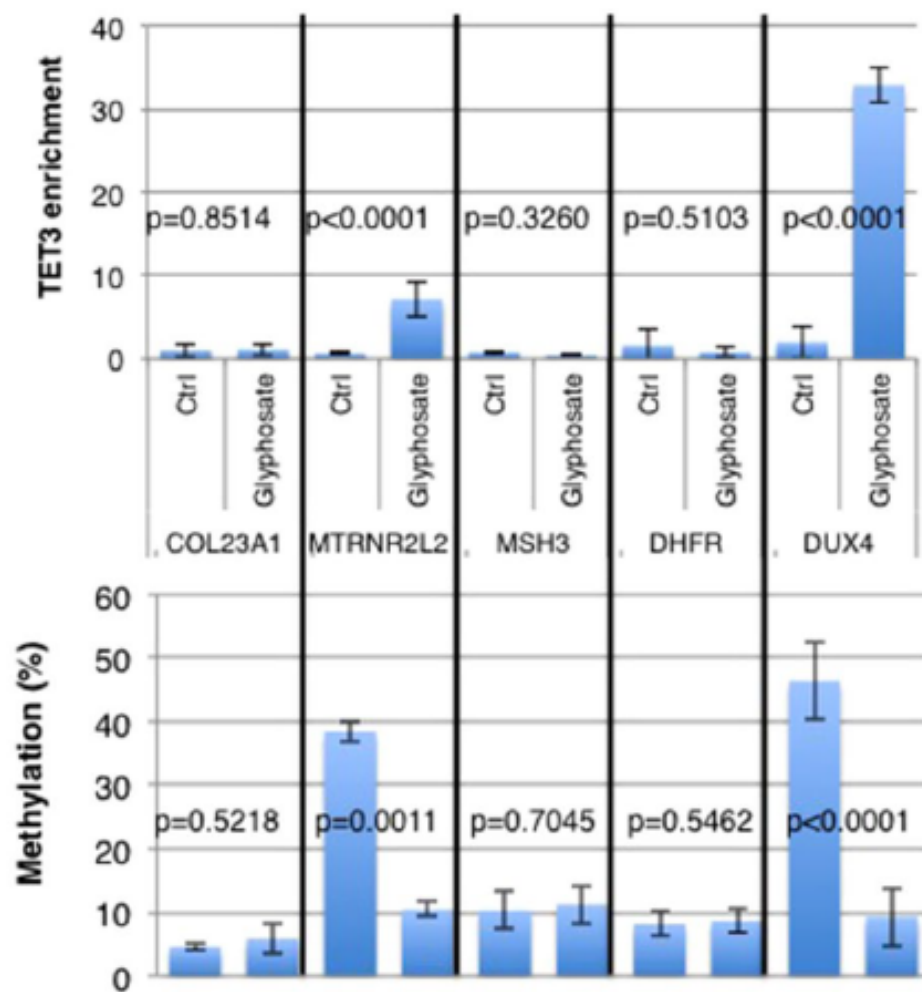


**DMOG, a TET inhibitor,  
inhibits tumor formation  
in glyphosate-challenged  
cells.**



# RESULTS . Figure 5

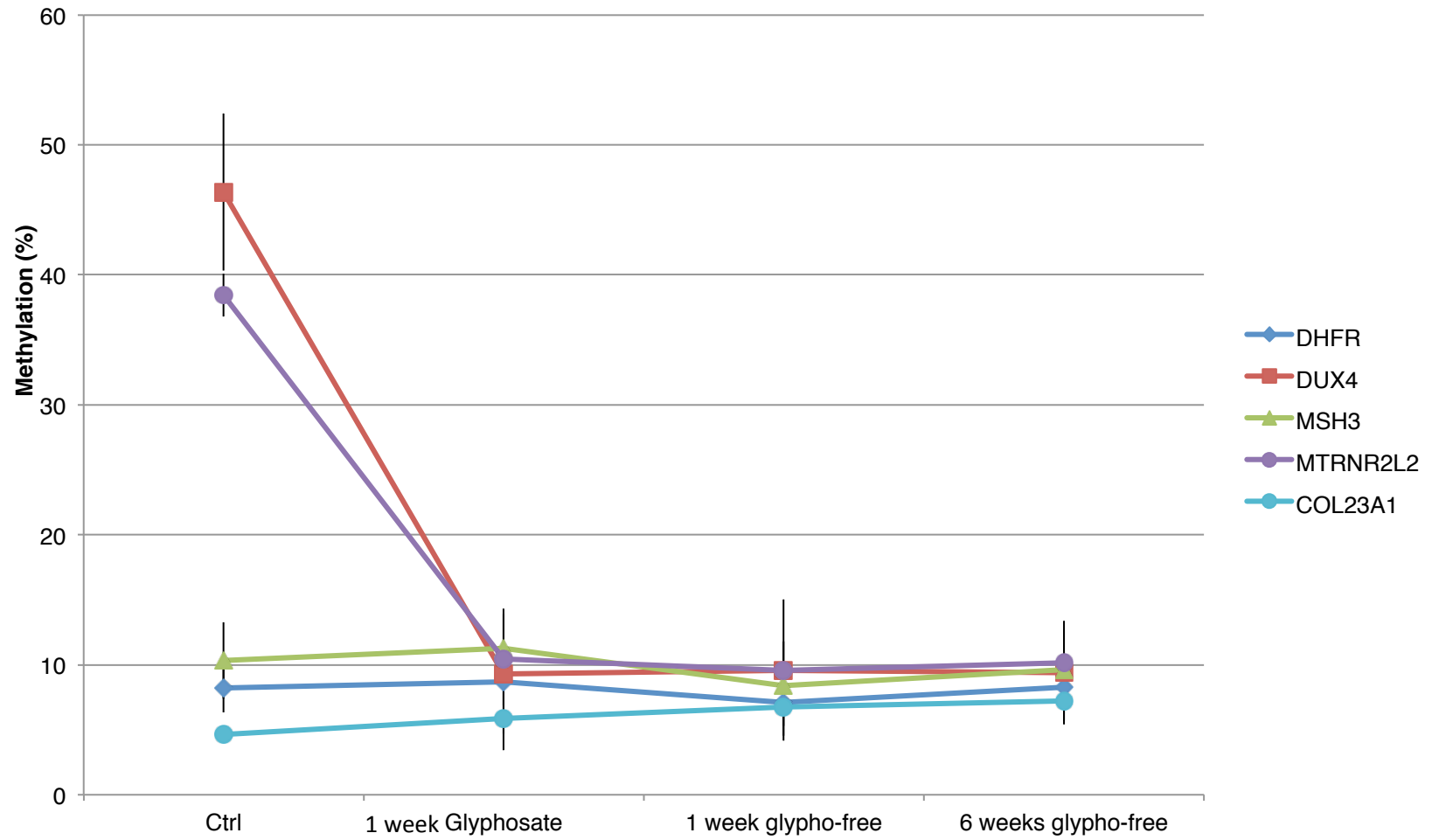
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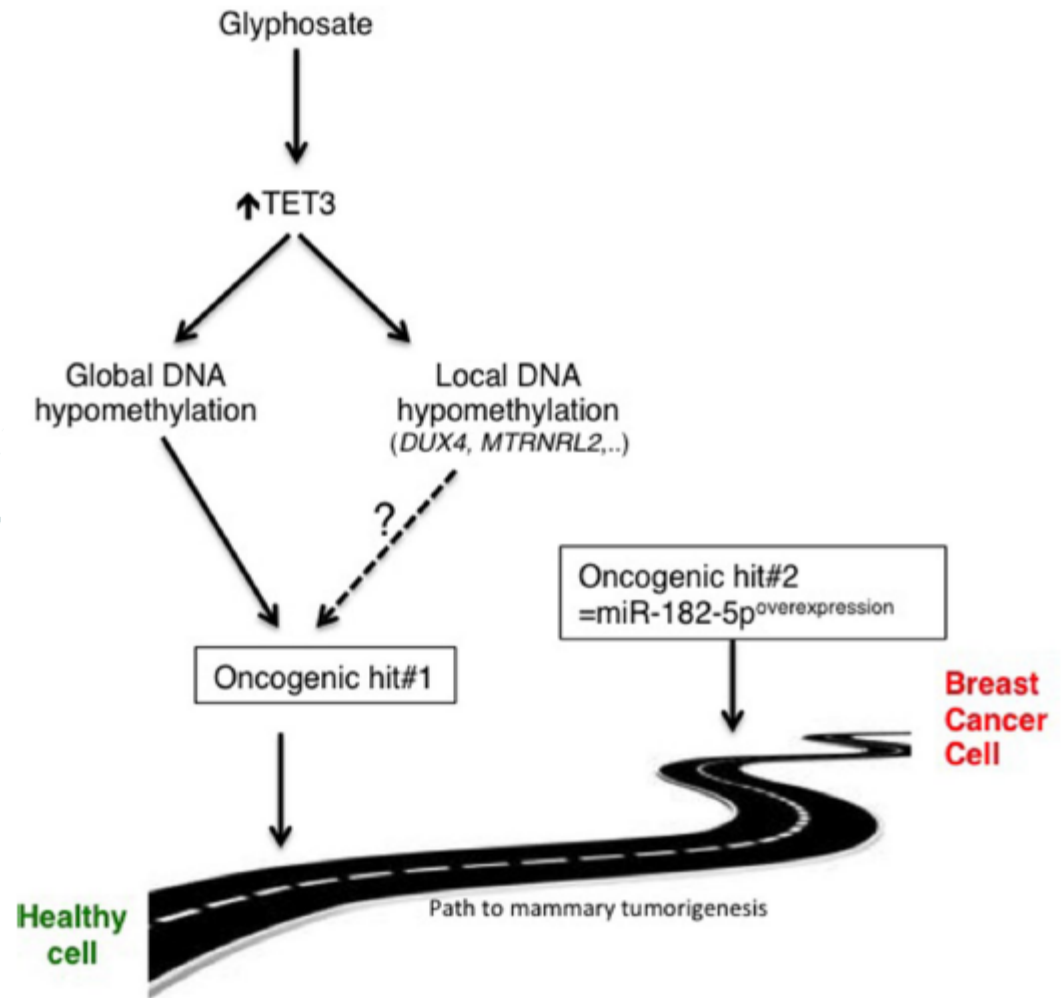


# RESULTS . Figure 5

## C



**Glyphosate exposure induces sustained TET3-mediated gene demethylation.**



In our study  
glyphosate  
exposure is not  
oncogenic by  
itself, but it  
acts as an  
oncogenic hit  
factor.

- Possibly, glyphosate-induced methylome reprogramming might be used for the detection of an increased risk for breast cancer in women living in an environment conducive to this type of pollution.

# Acknowledgments

To co-authors...

Arulraj Nadaradjane  
Gwenola Bougras-Cartron  
Josephine Briand  
Christophe Olivier

Jean-Sebastien Frenel  
Francois M Vallette  
Sophie A. Lelievre  
Pierre-Francois Cartron

...and all the team 9 !























































































































































































international breast cancer & nutrition  
working together for prevention  
<http://www.pcr.univ-lyon1.fr/ibcn/>

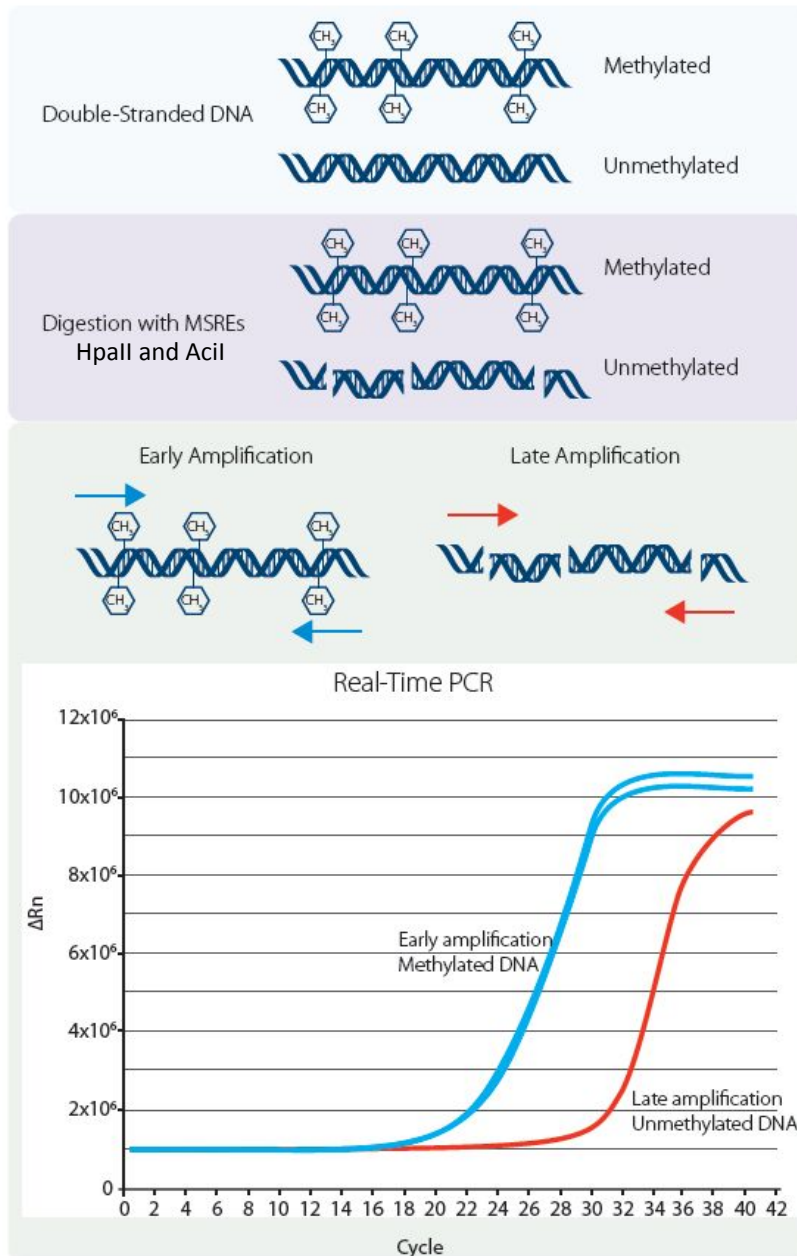


# THANK YOU FOR YOUR ATTENTION

# ADDITIONAL . Supplementary Figure 2B

|                               | MCF-10A (Breast)                                                                    |                                                                                     |                                                                                     |                                                                                     | Astro#40 (Brain)                                                                     |                                                                                       |                                                                                       |                                                                                       | Wi38 (Lung)                                                                           |                                                                                       |                                                                                       |                                                                                       |
|-------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
|                               | 1                                                                                   | 2                                                                                   | 3                                                                                   | 4                                                                                   | 1                                                                                    | 2                                                                                     | 3                                                                                     | 4                                                                                     | 1                                                                                     | 2                                                                                     | 3                                                                                     | 4                                                                                     |
| -                             |    |    |    |    |    |    |    |    |    |    |    |    |
| UP                            |    |    |    |    |    |    |    |    |    |    |    |    |
| glyphosate                    |    |    |    |    |    |    |    |    |    |    |    |    |
| miR-146a<br>PMID: 29915929    |    |    |    |    |    |    |    |    |    |    |    |    |
| glyphosate<br>+miR-146a       |    |    |    |    |    |    |    |    |    |    |    |    |
| miR-182-5p<br>PMID: 28043147  |    |    |    |    |    |    |    |    |    |    |    |    |
| glyphosate<br>+miR-182-5p     |    |    |    |    |    |    |    |    |    |    |    |    |
| miR-27a                       |    |    |    |    |    |    |    |    |    |    |    |    |
| glyphosate<br>+miR-27a        |    |    |    |    |    |    |    |    |    |    |    |    |
| miR-500a-5p<br>PMID: 29162888 |   |   |   |   |   |   |   |   |   |   |   |   |
| glyphosate<br>+miR-500a-5p    |  |  |  |  |  |  |  |  |  |  |  |  |
| miR-30a<br>PMID: 29666469     |  |  |  |  |  |  |  |  |  |  |  |  |
| glyphosate<br>+miR-30a        |  |  |  |  |  |  |  |  |  |  |  |  |
| miR-495<br>PMID: 25070379     |  |  |  |  |  |  |  |  |  |  |  |  |
| glyphosate<br>+miR-495        |  |  |  |  |  |  |  |  |  |  |  |  |

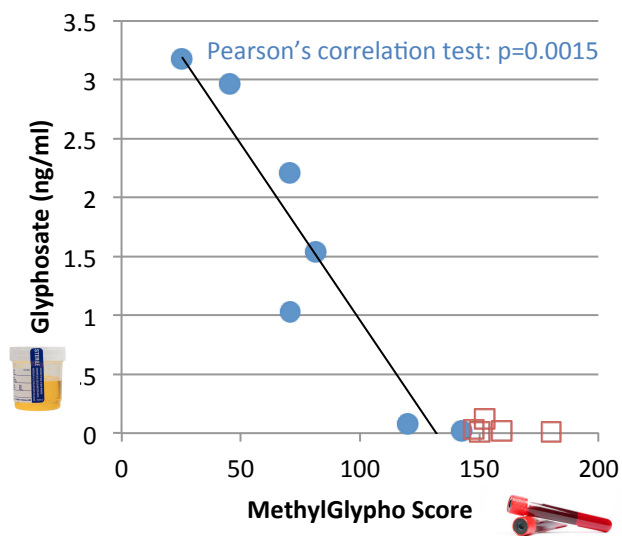
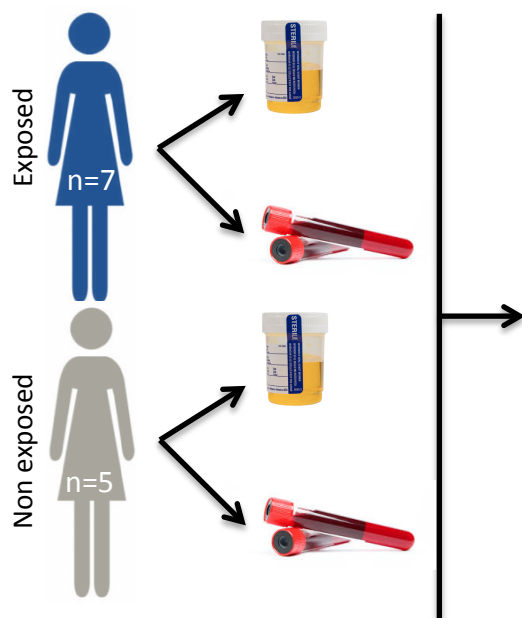
## ADDITIONAL . qMSRE and miR-185-5p



### About miR-182-5p

- miR-182-5p-mediated disruption of the homologous recombination (HR) pathway (Krishnan et al., 2013)
- targets BRCA1 in breast cancer cells (Moskwa et al., 2011)
- CHEK2, another gene involved in the HR, is a direct target of miR-182-5p

## ADDITIONAL . MethylGlypho Score



### About glyphosate

- 0,1 ng/ml maximum value allowed in water
- 1.69 pg/mL in our experiments