PURDUE UNIVERSITY

PURDUE UNIVERSITY
CENTER FOR CANCER RESEARCH

Nutritional effects on breast cell biology: New research tools and risk-on-a-chip models

Sophie A. Lelièvre, DVM, LLM (Public Health), PhD
Department of Basic Medical Sciences

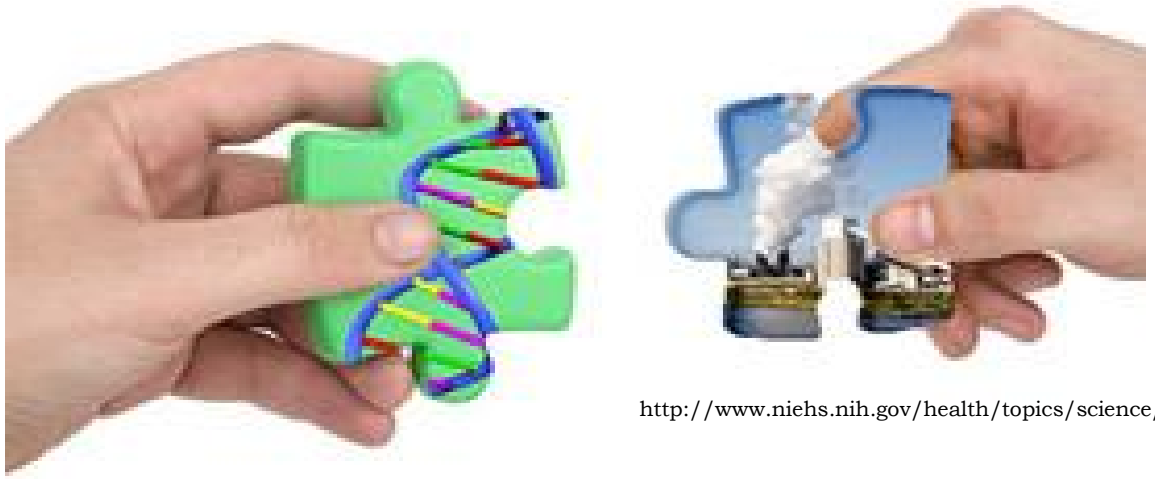
Associate Director, Collaborative Science, Purdue Center for Cancer Research

international breast cancer & nutrition
working together for prevention
http://www.purdue.edu/dp/oncological/ibcn.php

DISCOVERY in IBCN

RESEARCH COMPONENTS OF THE IBCN PROJECT

- Communication
- Economics & Behavior
- Epigenomics/epigenetics and other molecular pathways
- Nutrition
- Public Policy/Law/Anthropology/Sociology
- Engineering (detection, screening, development of preventive intervention)
- Clinical Aspects



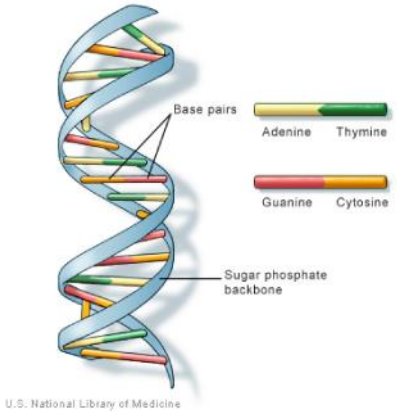
http://www.niehs.nih.gov/health/topics/science/gene-env/index.cfm

Challenges for primary prevention research

- Few studies link epidemiological findings to biological mechanisms of cancer onset
- There is a paucity of models
- The influence of the environment on our genes is a major mechanism for the control of [breast cancer] risk
- Actions to prevent breast cancer onset include the involvement of breast cancer-free individuals and interventions tailored to individuals

PURDUE UNIVERSITY
CENTER FOR CANCER RESEARCH

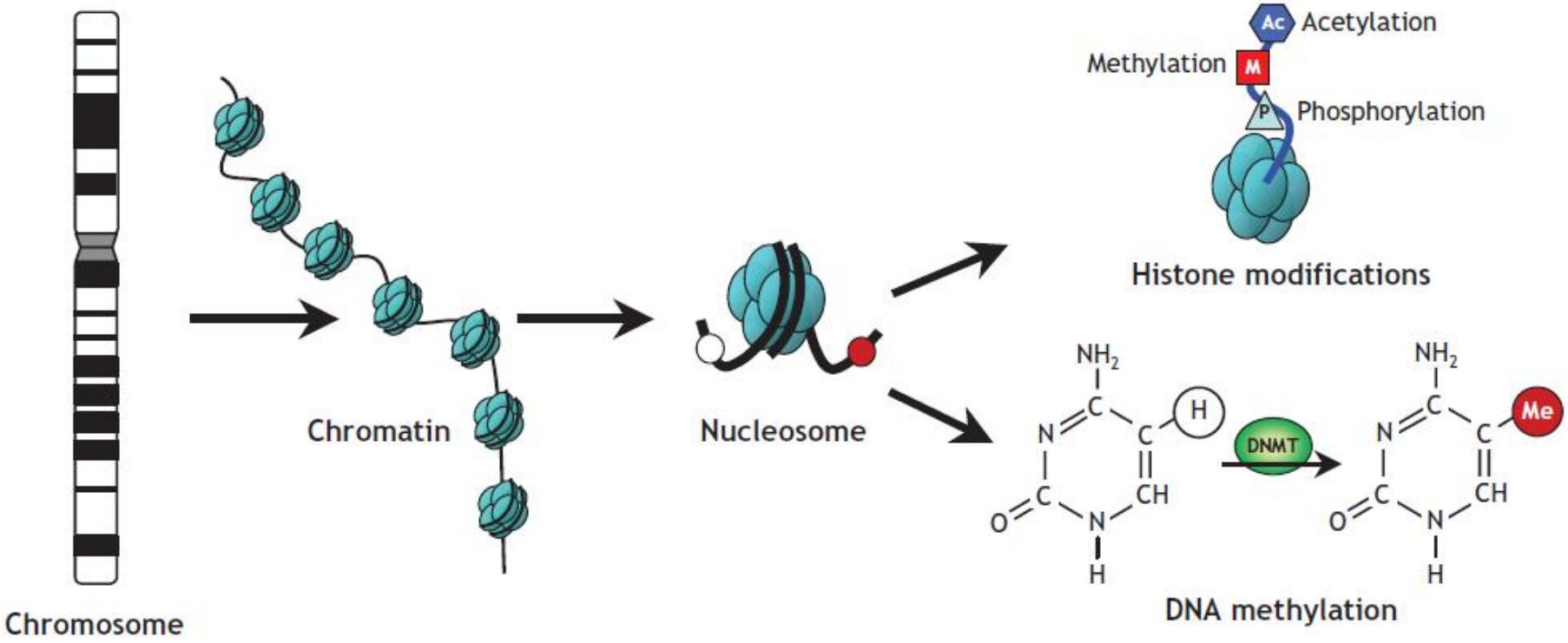
The genetic code tells who we are and about the genetic risk of disease



GCU	CGU	AAU	GAU	UGU	GAG	CAG	GGU	CAU	AUU	CUU	AAG	AUG	UUU	CCU	UCU	ACU	UGG	UAU	GUU
GCC	CGC	AAC	GAC	UGC	GAA	CAA	GGC	CAC	AUC	CUC	AAA		UUC	CCC	UCC	ACC		UAC	GUC
GCG	CGG						GGG		AUA	CUG				CCG	UCG	ACG			GUG
GCA	CAA						GGA			CUA				CCA	UCA	ACA			GUA
	AGG									UUG					AGU				
	AGA									UUA					AGC				

- Differences via mutations and small nucleotide variants
- 23,000 genes
- 3 billion base pairs

The epigenetic code tells what we are and about the influence of the environment on disease risk



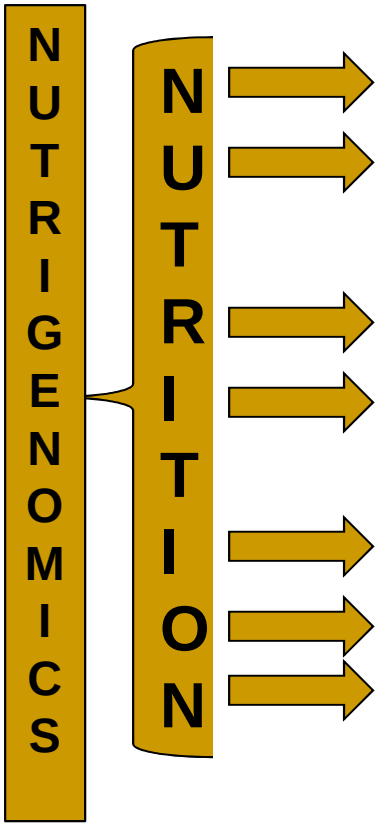
Rodenhiser& Mann CMAJ 2006 174(3):341

The facts:

Some of the breast cancer risk factors identified so far by epidemiologists:

- Nulliparity
- Late age at first birth
- Early menarche
- Late menopause
- Short duration of breast feeding
- Family history of breast cancer
- Alcohol
- Genetic background
- Being overweight
- Height
- Breast density

The thinking:

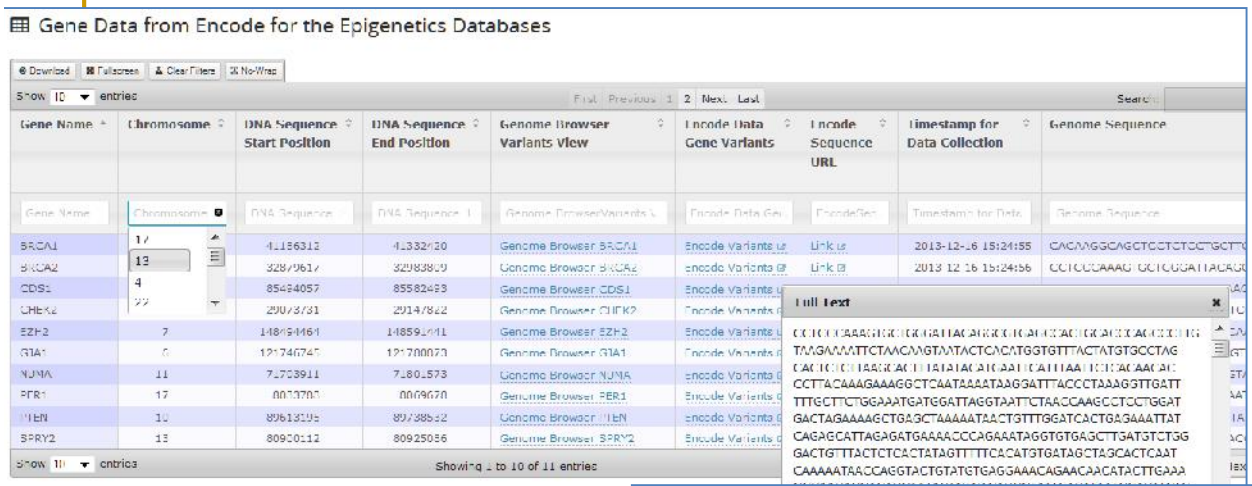


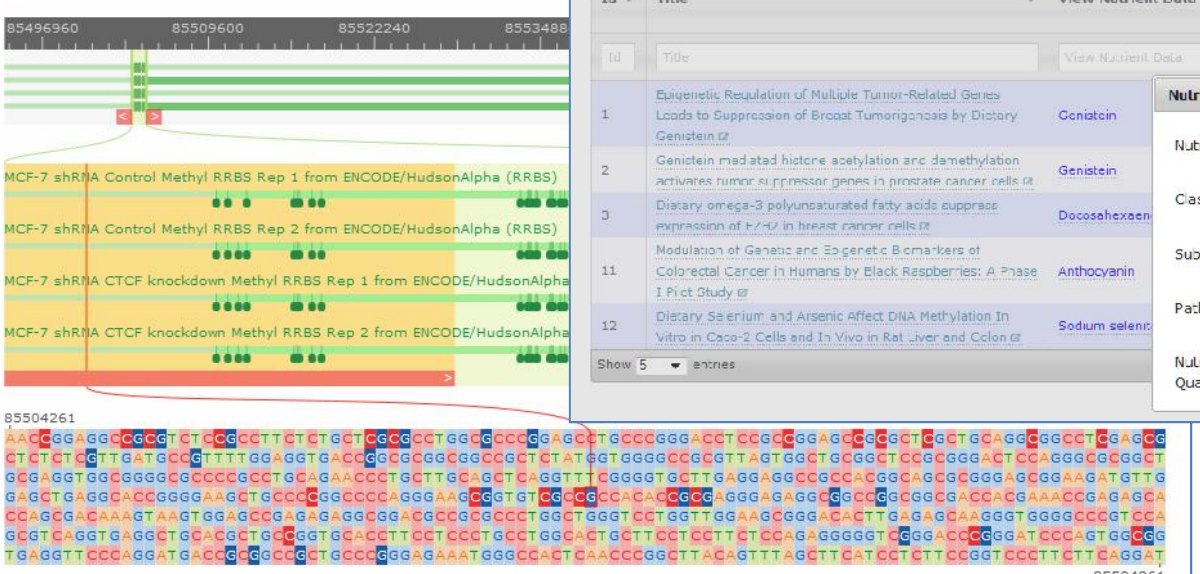
Where Is the information on nutri-epigenomics ?

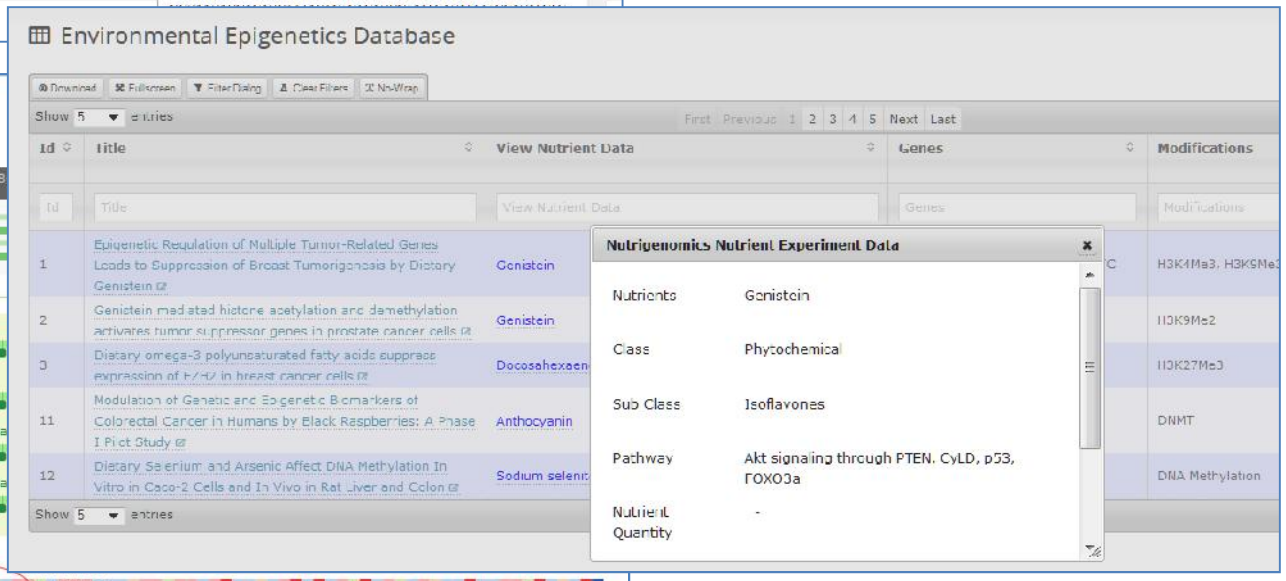
Ruchith Fernando, Jessica Shaw, Teona Cotan, Ann Christine Catlin, Yunfeng Bai,

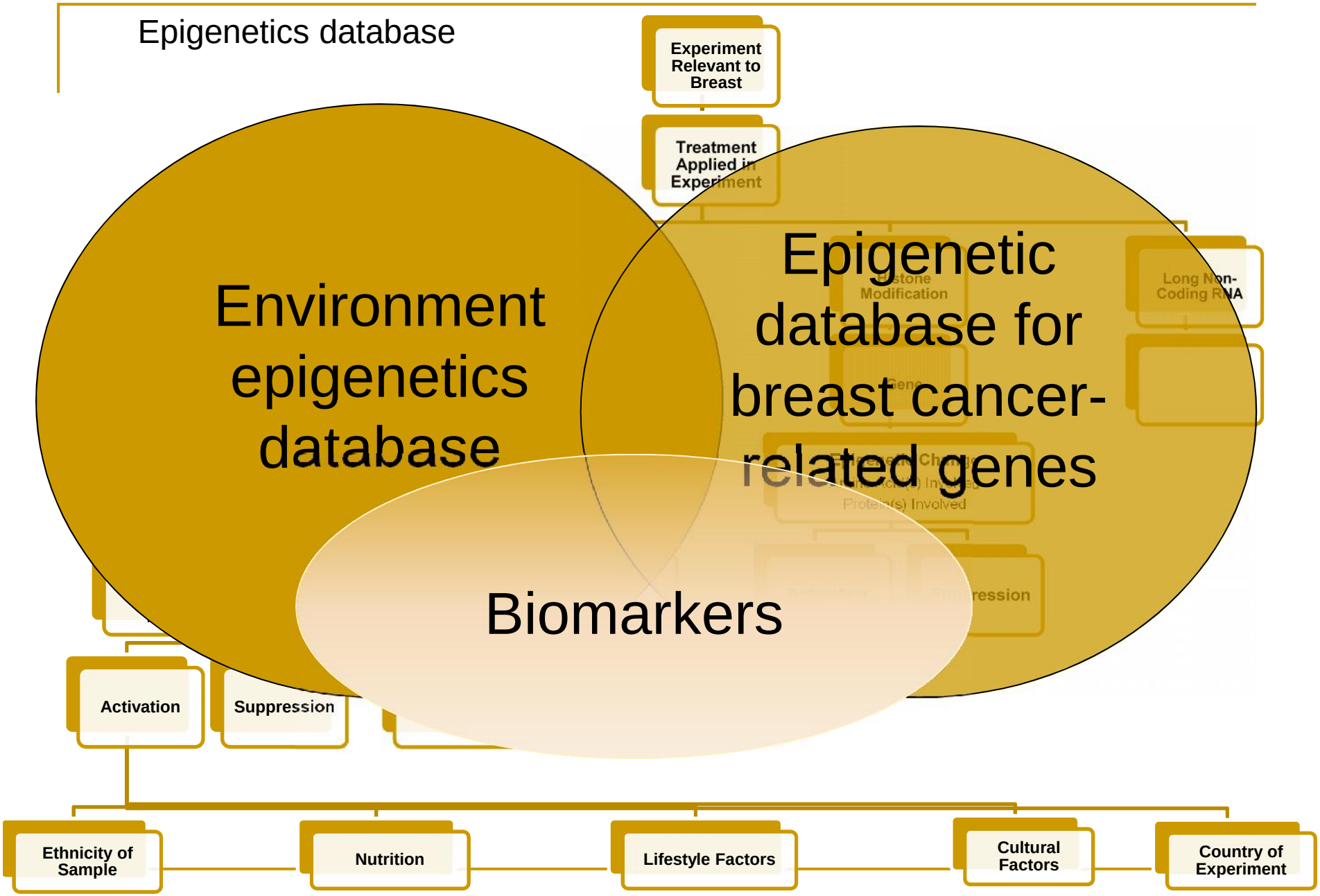
PURDUE UNIVERSITY
CENTER FOR CANCER RESEARCH

Breast and environmental epigenetics databases with USER-TAILORED DATA-VIEWS



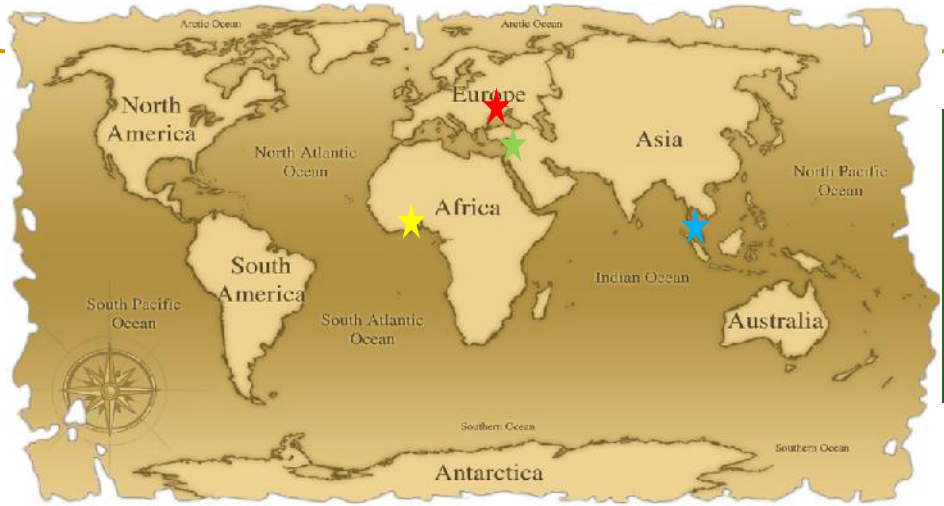






Ann Christine Catlin, Ruchith Fernando, Jessica Shaw, Teona Cotan, Yunfeng Bai, Amy Lossie, Rebecca Doerge

Example of use of the environmental epigenetics database



Romania	Lebanon	Ghana	Malaysia
• **Main**	• **Main**	• **Main**	• **Main**
• Pork	• Beef	• Onion	• Rice
• Beef	• Chicken	• Corn	• Pork
• Egg	• Chickpea	• Fish	• Chicken
• White mushroom	• Tomato	• Plantain	• Tofu
• **Minor**	• **Minor**	• **Minor**	• **Minor**
• Onion	• Onion	• Tomato	• Garlic
• Garlic	• Tomato	• Onion	• Red chilies
• Oil (vegetable)	• Pine nut	• Sugar	• Spring onions
• Carrot	• Rice	• Egg	• Ginger
• **Seasonings**	• **Seasonings**	• **Seasonings**	• **Seasonings**
• Dill	• Garlic	• Sugar	• Light soy sauce
• Parsley	• Vegetable oil	• Palm oil	• Oyster sauce
• Orange peel	• Allspice	• Nutmeg	• Rice wine
• Lemon peel	• Lemon	• Baking powder	• Chicken stock granules

Keys:
Orange- Grains Purple- Proteins Red- Fruits Green- Vegetables Black: Others

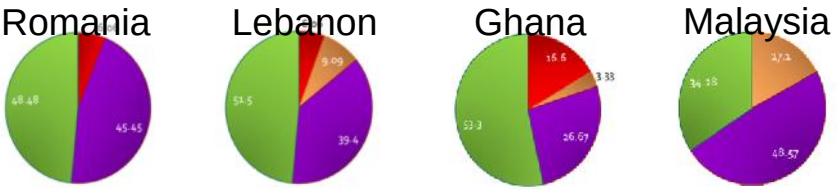
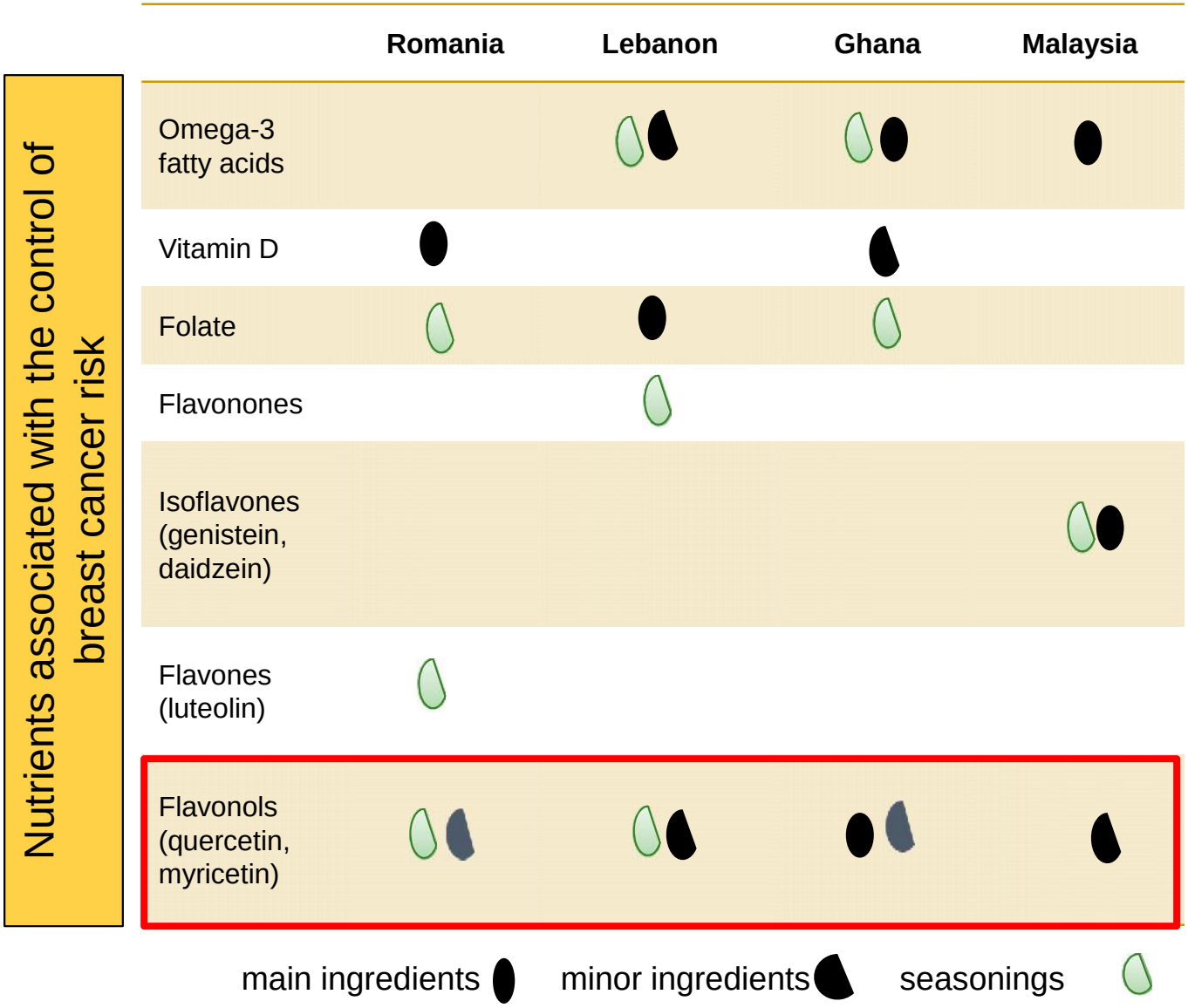


Chart 1: The top four ingredients lists of each country were converted into quantity data. All the data were put into pie chart for comparison.

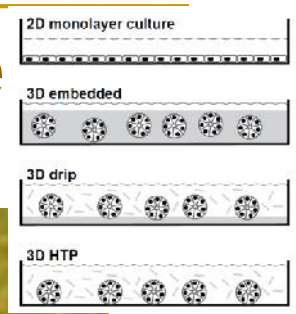
Genevieve Kruzick, Sean Chong

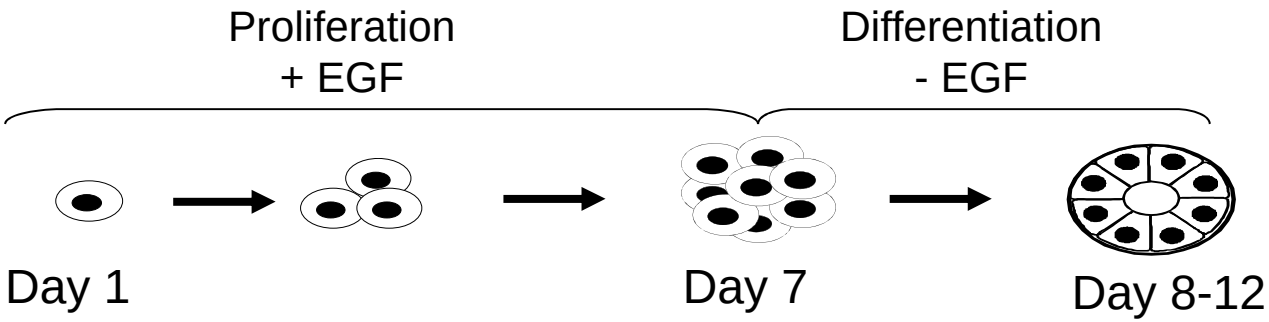
Faculty memtors: Sophie Lelièvre, Barbara Stefanska, Qing Jiang

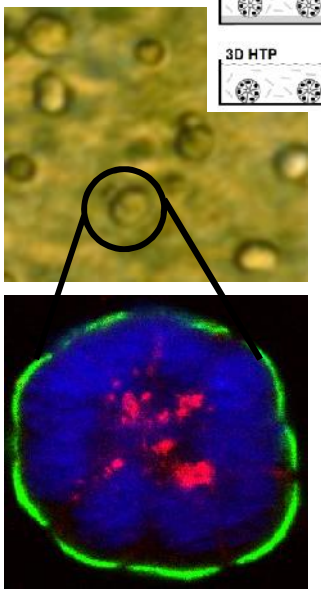


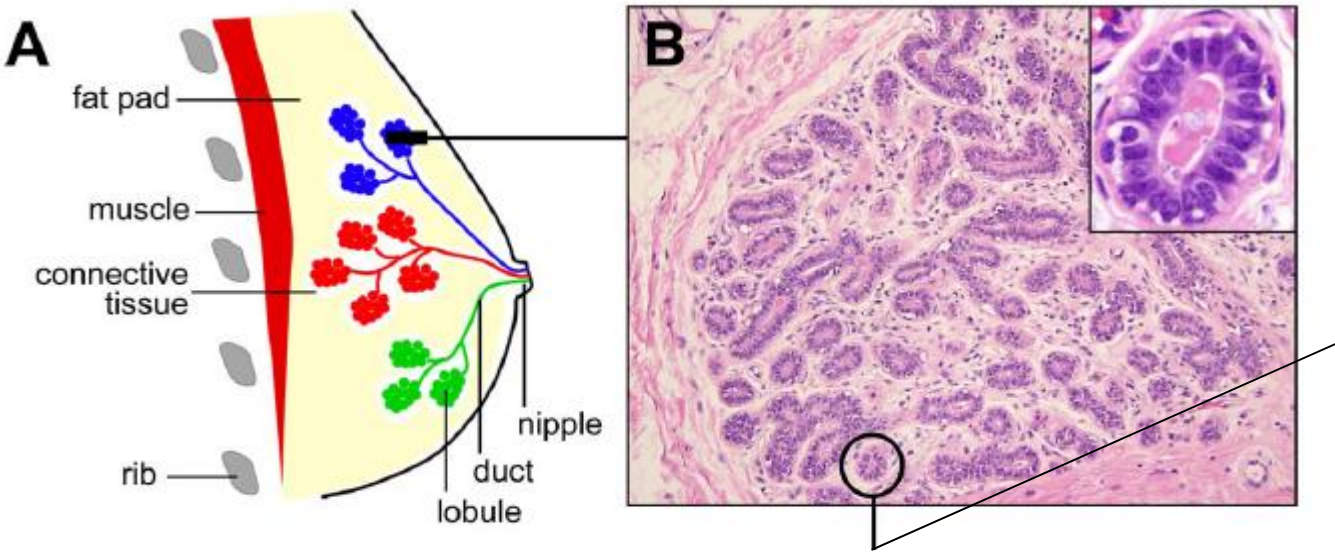
Genevieve Kruzick, Sean Chong

Model: 3D cell culture to mimic tissue architecture

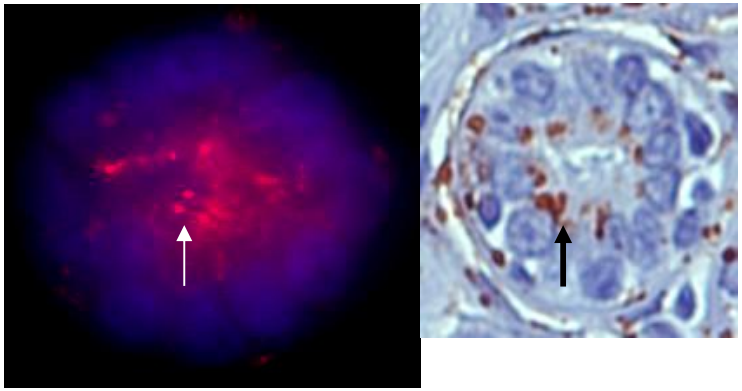




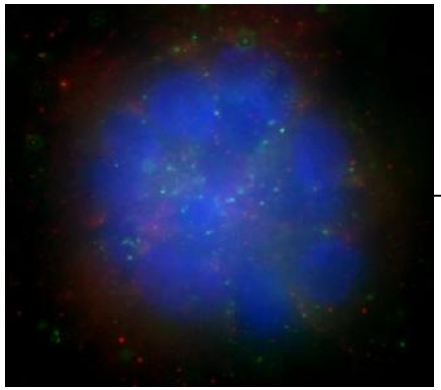




Tissue polarity is an architectural marker of risk



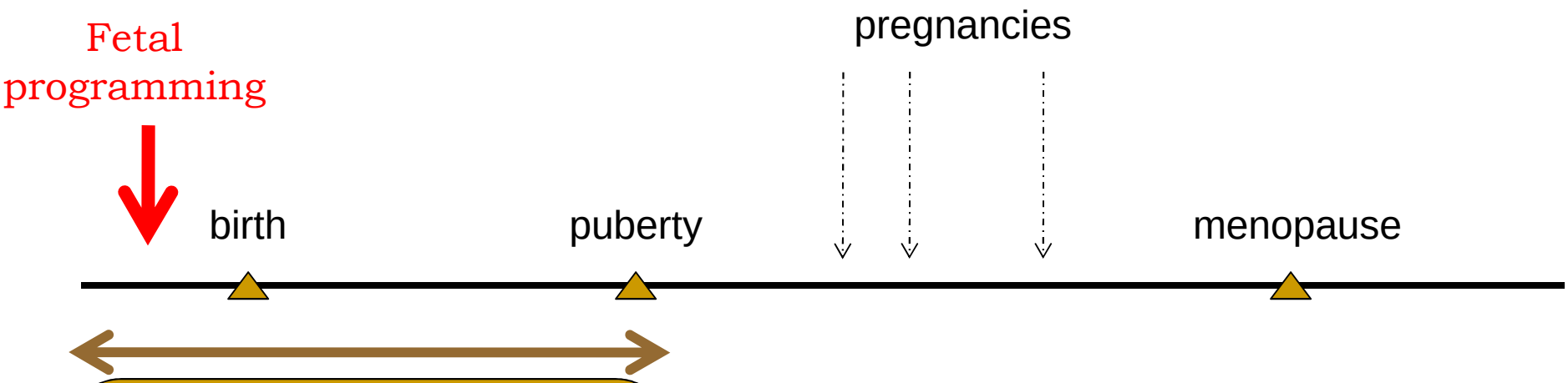
Apical polarity marker



Cells leave quiescence

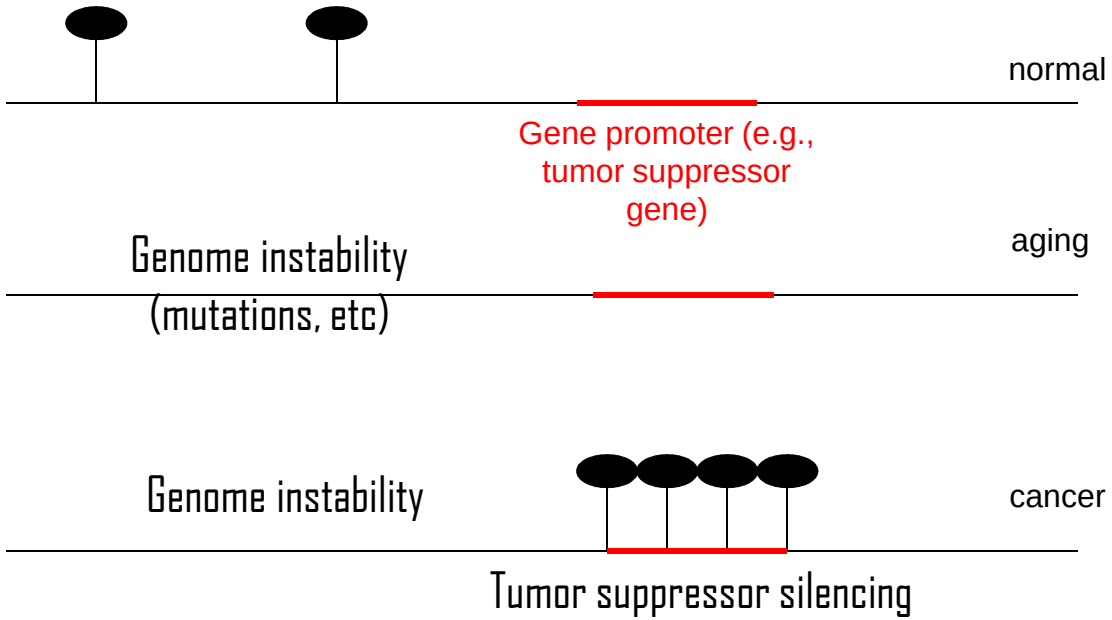
Chandramouly et al JCS 2007–
Lelièvre laboratory

Acting early is paramount



- Huge influence of diet
- Huge influence on breast cancer risk
- Mammary gland under development

DNA methylation is profoundly altered when cancer develops



Methylation site at cytosines

Immature vs. mature epithelium switch is used as a tool to identify epigenetic markers of architectural risk

Pretreatment of breast epithelial cells with CLA before differentiation modifies epigenetic marks

Inappropriate levels of folic acid in immature epithelium prevent proper apical polarity formation and modify the expression of epigenetic marks compared to control

McDole, Atriani et al – Lelièvre laboratory

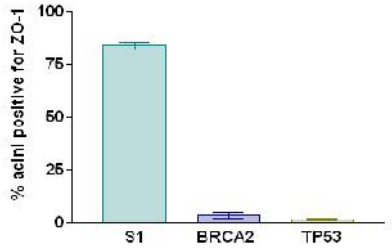
A screening pipeline for foods and nutrients with epigenetic impact on breast cancer risk

- Risk detection system
- Cell culture model of risk
- Transition from breast epigenetic markers to blood-based biomarkers

A reliable risk detection system to link apical polarity and nutriepigenetics

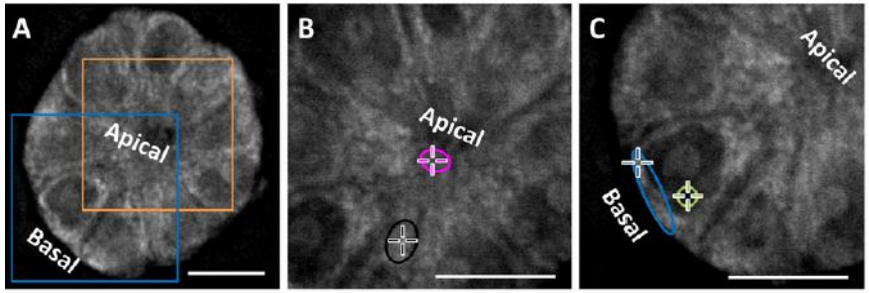
PURDUE-IUPUI

Preclinical models with cell lines derived from patients at different breast cancer risk levels



Epigenetic status? Can modifying epigenetic mark restore apical polarity?

Test of compounds that influence apical polarity and epigenetic mechanisms



protected

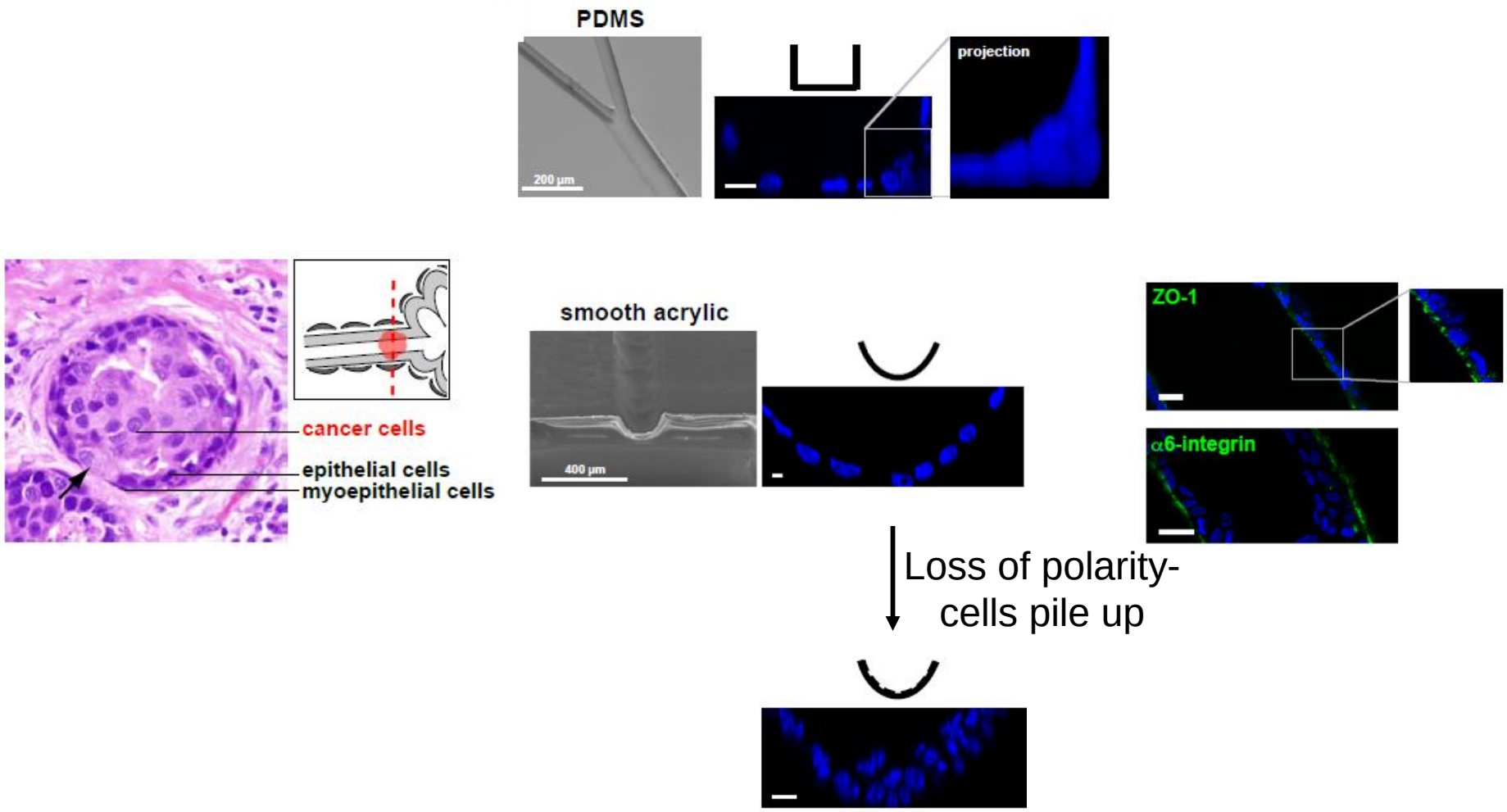
	ApM		BaM
$R = A_{2885}/A_{2850}$	3.32	>	2.31

unprotected

	ApM		BaM
$R = A_{2885}/A_{2850}$	2.48	<	2.80

Yue et al Biophys J 2012---Lelièvre and Cheng laboratories

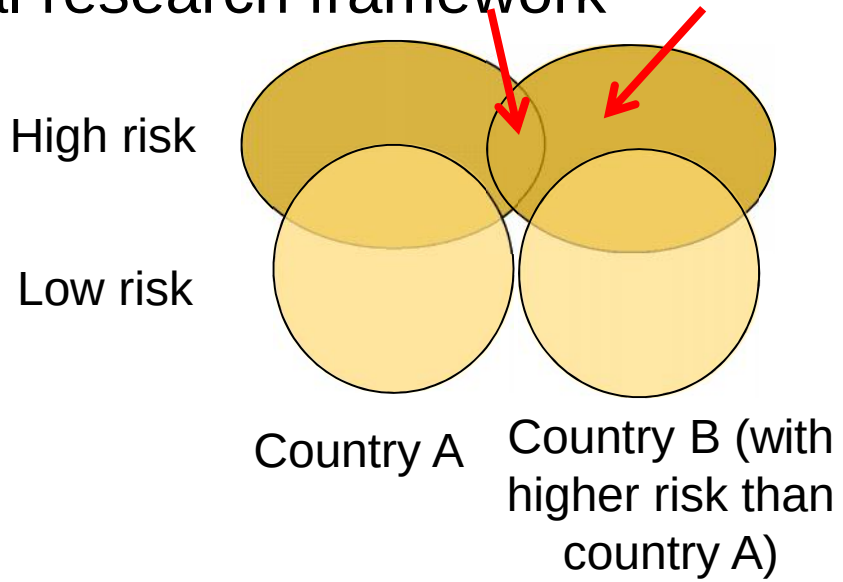
Design of a risk-on-a-chip model



Vidi et al Lab-on-a-chip 2013

Conclusion and perspectives

- **Understanding the nutrient-gene interaction that governs cancer risk requires the use of proper human cell models**
- Nutriepigenomics/nutriepigenetics should serve an international research framework



- The nature of the human subject (i.e., ‘healthy’) requires serious ethics considerations

PUBLIC POLICY AND OUTREACH

Public policy and health care system in Uruguay

- Very well organized health care system and research
  - Cancer registry and cancer surveillance statistics and publication
  - Well developed system of health education.
- Interesting model: Honorary Commission for the Fight against Cancer that links health care providers, public health system and researchers.
- Clear ethics rules for tissue collection

- We need to build the Ethics of Primary Prevention Research: collect healthy tissue; international work with tissues from different countries; protection of individuals when using epigenetic data
- Principles of justice & equity are likely to be the engine for such ethics

EG

Acknowledgements: IBCN trainees

UNDERGRADUATE STUDENTS			
Emma Clohessy	Political Science	Purdue University (USA)	2009-2010
Courtney Sanor*	Health Sciences	Purdue University	2009-2010
Silai Mirzoy*,‡,#	Biological Sciences	Purdue University	2010-2012
Jessica Shaw*	Business	Purdue University	2012-2013
Katya Liotta*	Anthropology	Purdue University	2012-2013
Amanda Haan*	Nutrition Science	Purdue University	2011-2013
Alexandria Hairston	Behavioral Sciences	Purdue University	2013-on
Derek Price	Nursing	Purdue University	2013-on
Alexandra Davies*	Biological Engineering	Purdue University	2013-on
Genevieve Kruzick*	Nutrition, Dietetics	Purdue University	2013-on
Sean Chong*	Nutrition, Dietetics	Purdue University	2013-on
Ashleigh Shields	Communication (public relations)	Purdue University	2013-on
Christopher Duffey	Pharmacy	Purdue University	2014-on
Yann Vicédo#	Volunteer	Pre-undergraduate	2013-on
GRADUATE STUDENTS			
Laurence Gabriel‡,# M.S., LLMPH	Public Law	PhD, Univ. of Rennes 1 (France); Visiting scholar, Purdue University	2010-on
Dana Bazzoun*,‡	Biological Sciences	PhD, American University of Beirut (Lebanon)	2012-on
Charity Woodard	Education	M.S. Purdue University	2013-on
Ruchith Fernando*	Computer Science	PhD , Purdue University	2013-on
Yunfeng Bai*	Basic Medical Sciences	PhD, Purdue University	2013-on
Tharindu Mathew	Computer Science	PhD, Purdue University	2013-on
LaTasha Swanson	Communication	PhD, Purdue University	2013-on
Iliana Tenvooren#	Cell Biology	MS, University of Lyon (France)	2013-on
Charbel BouSaba‡,#	Public Health	MA, School of Public Health (EHESP) (France)	2014-on
POSTGRADUATE TRAINEES			
Sumidinie Fernando*	Computer Science	Purdue University	2013-on
Teona Coten, MD	OBGYN	Visiting scholar, Purdue University	2013-on

Acknowledgments (continued)

FUNDING

- National Institutes of Health
- Congressionally Directed Medical Research/breast cancer program
- Clinical & Translational Science Institute
- Global Policy Research Institute
- Discovery Learning Research Center
- Keck Foundation; UNESCO-L'OREAL Foundation
- Various departments and centers at Purdue University

Colleagues

The many IBCN members

Engineering: Ji-Xin Cheng; James Leary

Nutrition: Kim Buhman

Cell culture work and epigenetics: Rabih Talhouk (AUB), Brittney-Shea Herbert (IUPUI), Rebecca Doerge (Purdue), Amy Lossie (Purdue-NIH))