

Leveraging the Past to Challenge the Present and Define the Future

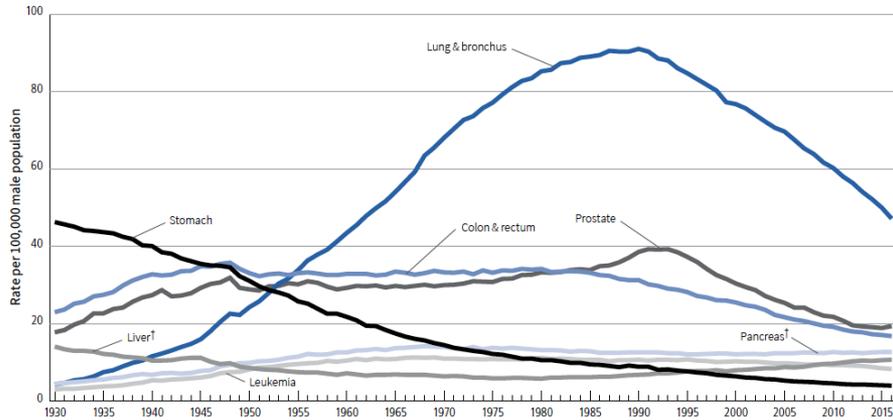
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Associate Director, National Toxicology Program
Scientific Director, DNTP

Converging on Cancer Workshop
April 29, 2019



Good news about cancer

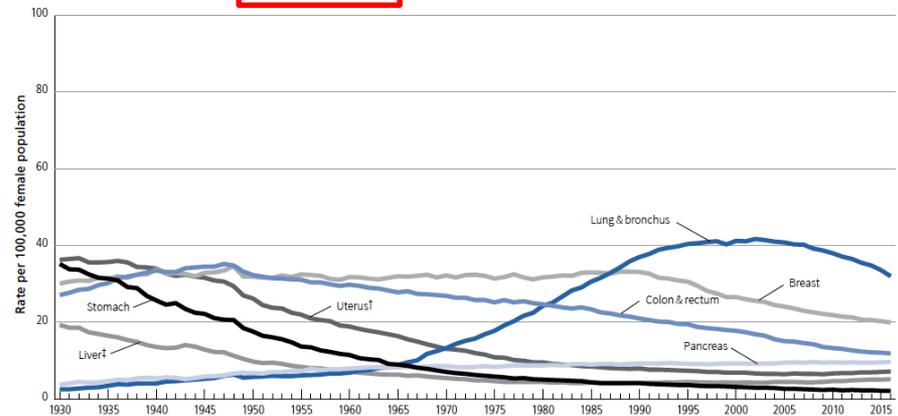
Figure 1. Trends in Age-adjusted Cancer Death Rates by Site, Males, US, 1930-2016



*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.
Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention.
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Death rates for many common cancers are decreasing in both males and females!

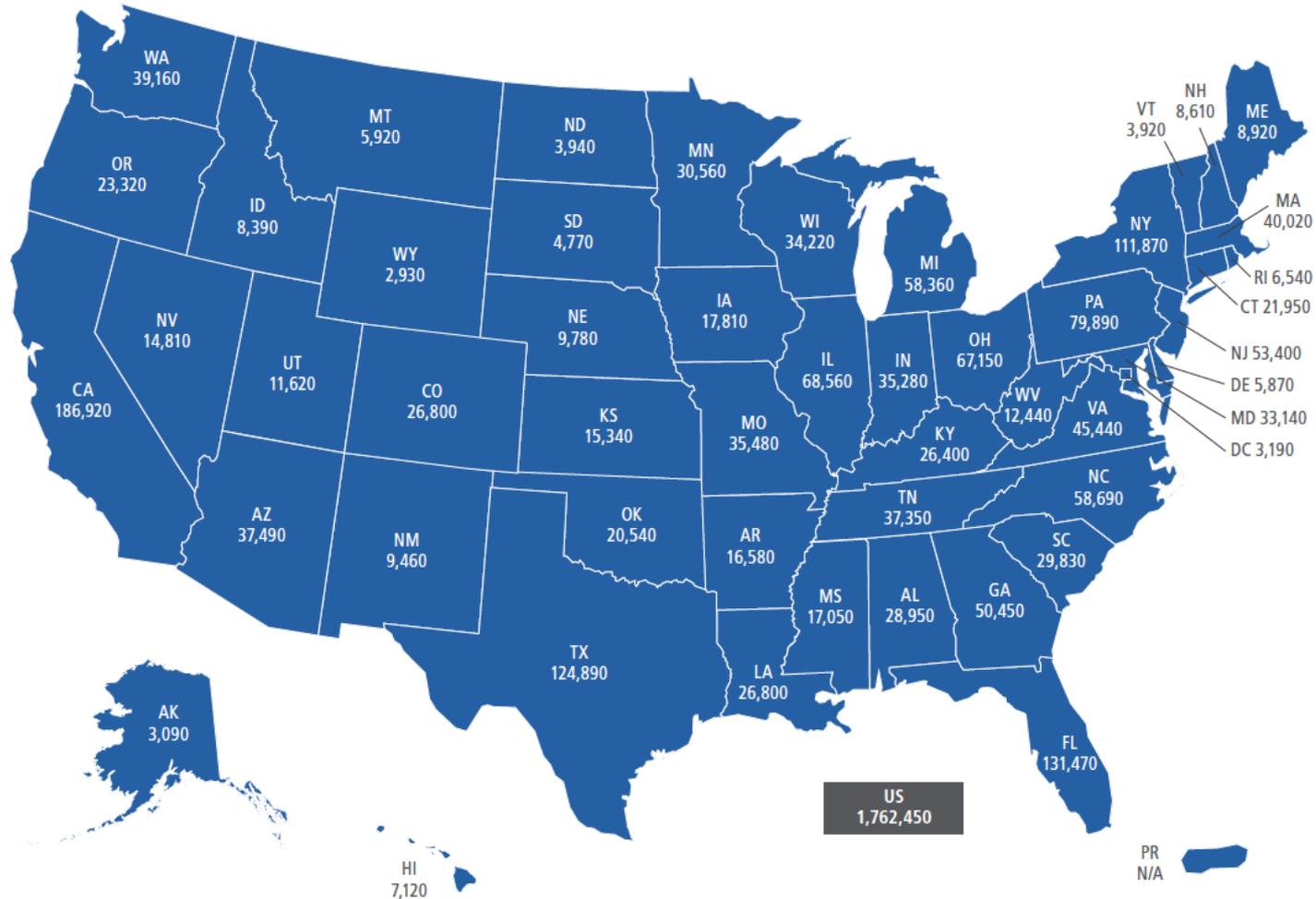
Figure 2. Trends in Age-adjusted Cancer Death Rates by Site, Females, US, 1930-2016



*Per 100,000, age adjusted to the 2000 US standard population. Rates exclude deaths in Puerto Rico and other US territories. †Uterus refers to uterine cervix and uterine corpus combined. ‡The mortality rate for liver cancer is increasing.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, colon and rectum, and uterus are affected by these coding changes.
Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2016, National Center for Health Statistics, Centers for Disease Control and Prevention.
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Cancer remains a significant public health challenge



Estimated numbers of new cancer cases for 2019, excluding basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. Estimates are not available for Puerto Rico.

Note: State estimates are offered as a rough guide and should be interpreted with caution. State estimates may not add to US total due to rounding.





British Journal of Industrial Medicine 1983;**40**:390–401

A brief history of scrotal cancer

H A WALDRON

1775 observation that scrotal squamous cell carcinoma was occupationally linked to chimney sweeps in England.

Pott, P.: *Cancer, Scroti*. Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the modification of the toes and feet. London: Hawes, Clarke, Collins; 1775. p. 63-8.



Fig 1 *Percivall Pott*.



THE RAPID PRODUCTION OF CANCER IN RABBITS BY COAL-TAR

K. ITCHIKAWA (SAPPORO-JAPAN) AND S. M. BAUM (NEW YORK)

From the Pathological Laboratory of the Faculty of Medicine, University of Paris

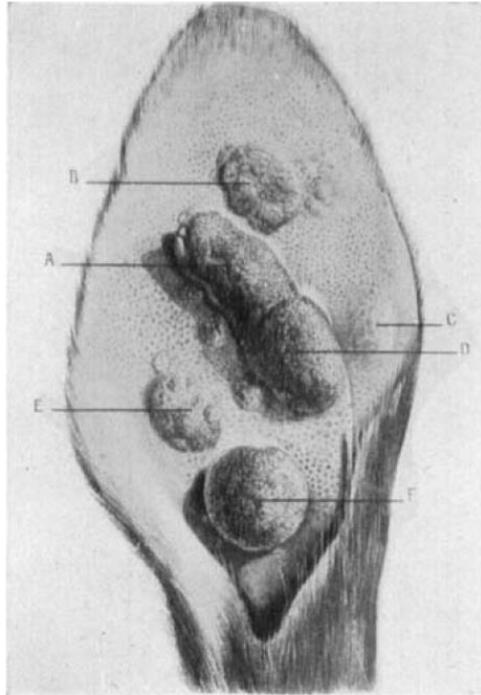


FIG. 2. RABBIT NO. 10 (RIGHT EAR)

Drawing made on 80th day of coal-tar painting. Tumors *A*, *B*, *D*, *E*, and *F*, fully developed carcinoma. Tumor *C*, early stage of carcinoma.

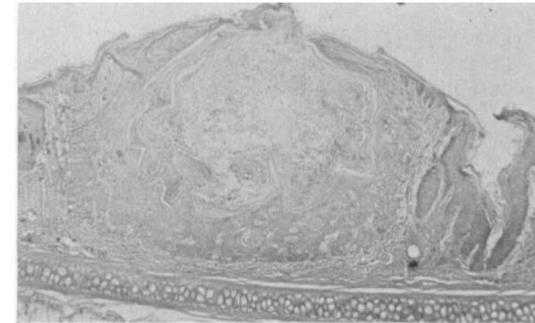


FIG. 5. RABBIT NO. 2 (LEFT EAR)

Tumor *A*. (Biopsy taken on the 35th day.) Earliest stage of carcinoma.

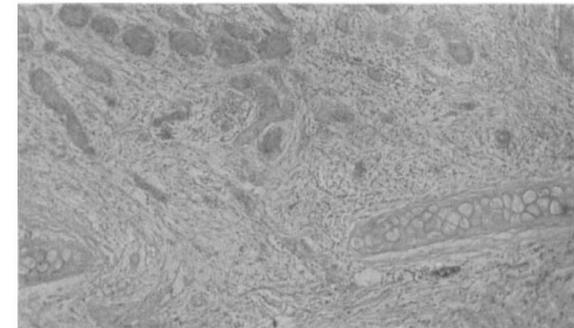


FIG. 6. RABBIT NO. 7 (LEFT EAR)

Tumor *A*. (Biopsy taken on the 47th day.) Fully developed carcinoma. Infiltration of the strands of cancer cells through the intercartilaginous space and passing into the subcutis of the other side.



40+ years of experience

NTP TECHNICAL REPORT
ON THE
TOXICOLOGY AND CARCINOGENESIS
STUDIES IN Hsd:SPRAGUE DAWLEY SD RATS
EXPOSED TO WHOLE-BODY RADIO FREQUENCY
RADIATION AT A FREQUENCY (900 MHz)
AND MODULATIONS (GSM AND CDMA)
USED BY CELL PHONES



NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

November 2018

NTP TR 595

National Institutes of Health
Public Health Service
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NTP TECHNICAL REPORT
ON THE
TOXICOLOGY AND CARCINOGENESIS
STUDIES OF 2,3-BUTANEDIONE
(CAS NO. 431-03-8)
IN WISTAR HAN [CrI:WI (Han)] RATS
AND B6C3F1/N MICE
(INHALATION STUDIES)



NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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August 2018

NTP TR 593

National Institutes of Health
Public Health Service
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



The Curse of Paracelsus



“All things are poison and nothing (is) without poison; only the dose makes that a thing is no poison.”

Paracelsus (1493-1534)

“And by goodness, in toxicology we’re going to make it happen!”

Brian (1962-)

This approach might be better at identifying ‘reagents’ than human risks.



Report on Carcinogens, Fourteenth Edition

For Table of Contents, see home page: <http://ntp.niehs.nih.gov/go/roc>

Substances Listed in the Fourteenth Report on Carcinogens

Bold entries indicate new or changed listings in the Fourteenth Report on Carcinogens.

Known To Be Human Carcinogens

Aflatoxins

Alcoholic Beverage Consumption

4-Aminobiphenyl

Analgesic Mixtures Containing Phenacetin (see Phenacetin and Analgesic Mixtures Containing Phenacetin)

Aristolochic Acids

Arsenic and Inorganic Arsenic Compounds

Asbestos

Azathioprine

Benzene

Benzidine (see Benzidine and Dyes Metabolized to Benzidine)

Beryllium and Beryllium Compounds

Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether

1,3-Butadiene

1,4-Butanediol Dimethanesulfonate

Cadmium and Cadmium Compounds

Who? Where? When?



Some loss in translation?

Table 21.7. Concordance between tumours seen in humans and animals for 60 Group 1 agents by organ and tissue system and tumour site (continued)

Organ and tissue system ^a Tumour site ^a	Number of agents			Overlap ^b (%)
	Humans	Animals	Both	
Lymphoid and haematopoietic tissues	12	10	7	47
<i>Haematopoietic tissues</i>	10	2	2	20
<i>Lymphoid tissue</i>	2	10	1	9
Skin	11	16	7	35
<i>Skin and adnexae</i>	9	16	6	32
<i>Cutaneous melanocytes</i>	3	0	0	N/A
Connective tissues	6	14	6	43
<i>Soft connective tissue</i>	0	9	0	N/A
<i>Blood vasculature (endothelium)</i>	1	0	0	N/A
<i>Hard connective tissue (bone, cartilage)</i>	5	5	4	67
Female breast, female reproductive organs, and female reproductive tract	8	9	4	31
<i>Breast</i>	4	8	2	20
<i>Ovary</i>	3	1	0	0
<i>Uterine cervix</i>	3	2	1	25
<i>Uterus</i>	2	2	1	33
<i>Vulva/vagina</i>	1	0	0	N/A



TOXICITY TESTING IN THE 21ST CENTURY A VISION AND A STRATEGY



NRC Committee on Toxicity Testing and Assessment of Environmental Agents

“Toxicity testing is under increasing pressure to meet several competing demands:

- Test **large numbers** of existing chemicals, many of which lack basic toxicity data.
- Test the large number of new chemicals and **novel materials**, such as nanomaterials, introduced into commerce each year.
- Evaluate potential adverse effects with respect to all critical end points and **life stages**.
- **Minimize animal use**.
- **Reduce the cost and time** required for chemical safety evaluation.
- Acquire detailed **mechanistic and tissue-dosimetry data** needed to assess human risk quantitatively and to aid in regulatory decision-making.



- **Re-envisioning Carcinogenicity Testing at NTP**
- **Developmental Neurotoxicity Modeling**
- **Cardiovascular Hazard Assessment in Environmental Toxicology**

Aims

- Fill a gap in current capabilities
- Build on existing effort
- Align to NIH model
- Leverage our key strengths and value



Cancer in patients

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2019 Estimates

Male				Female			
Estimated New Cases	Prostate	174,650	20%		Breast	268,600	30%
	Lung & bronchus	116,440	13%		Lung & bronchus	111,710	13%
	Colon & rectum	78,500	9%		Colon & rectum	67,100	7%
	Urinary bladder	61,700	7%		Uterine corpus	61,880	7%
	Melanoma of the skin	57,220	7%		Melanoma of the skin	39,260	5%
	Kidney & renal pelvis	44,120	5%		Thyroid	37,810	4%
	Non-Hodgkin lymphoma	41,090	5%		Non-Hodgkin lymphoma	33,110	4%
	Oral cavity & pharynx	38,140	4%		Kidney & renal pelvis	29,700	3%
	Leukemia	35,920	4%		Pancreas	26,830	3%
	Pancreas	29,940	3%		Leukemia	25,860	3%
	All sites	870,970			All sites	891,480	

Male				Female			
Estimated Deaths	Lung & bronchus	76,650	24%		Lung & bronchus	66,020	23%
	Prostate	31,620	10%		Breast	41,760	15%
	Colon & rectum	27,640	9%		Colon & rectum	23,380	8%
	Pancreas	23,800	7%		Pancreas	21,950	8%
	Liver & intrahepatic bile duct	21,600	7%		Ovary	13,980	5%
	Leukemia	13,150	4%		Uterine corpus	12,160	4%
	Esophagus	13,020	4%		Liver & intrahepatic bile duct	10,180	4%
	Urinary bladder	12,870	4%		Leukemia	9,690	3%
	Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,460	3%
	Brain & other nervous system	9,910	3%		Brain & other nervous system	7,850	3%
	All sites	321,670			All sites	285,210	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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Understanding pathobiology

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Cell 144, March 4, 2011 ©2011 Elsevier Inc.

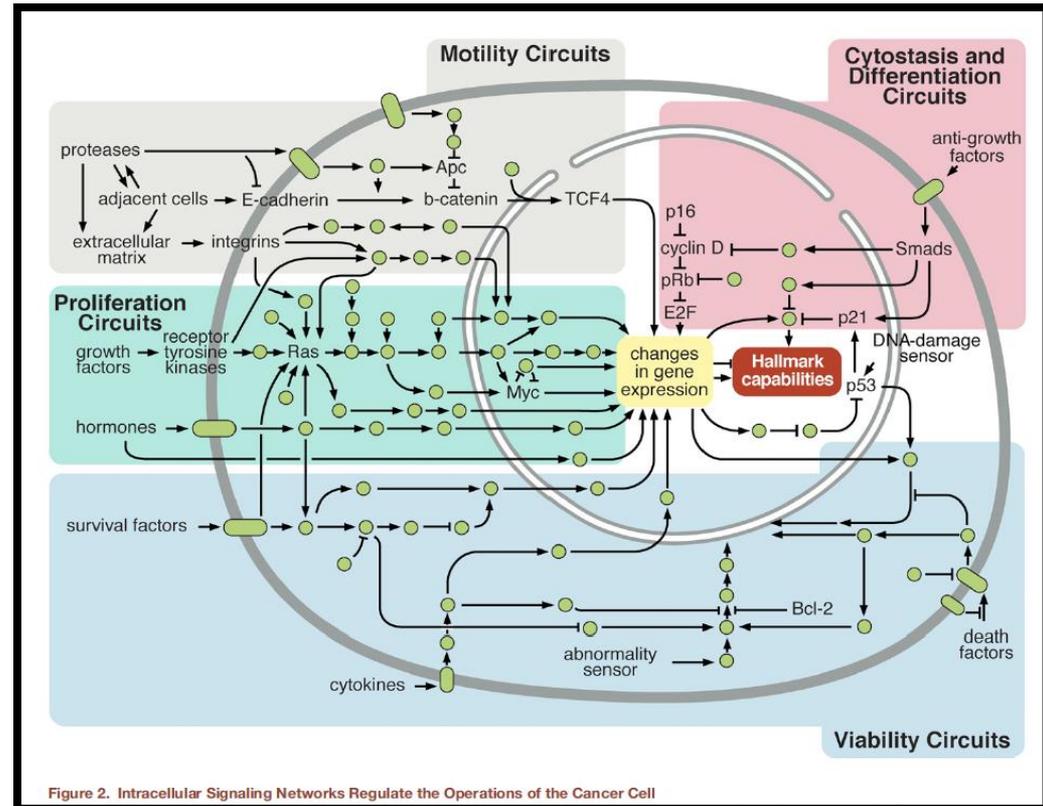
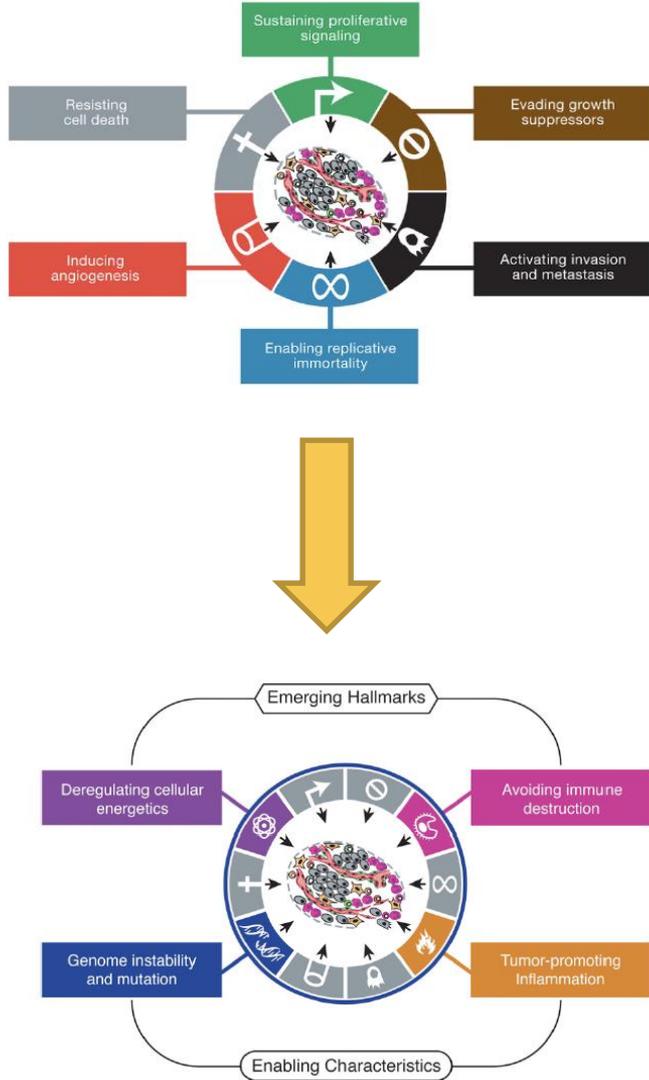
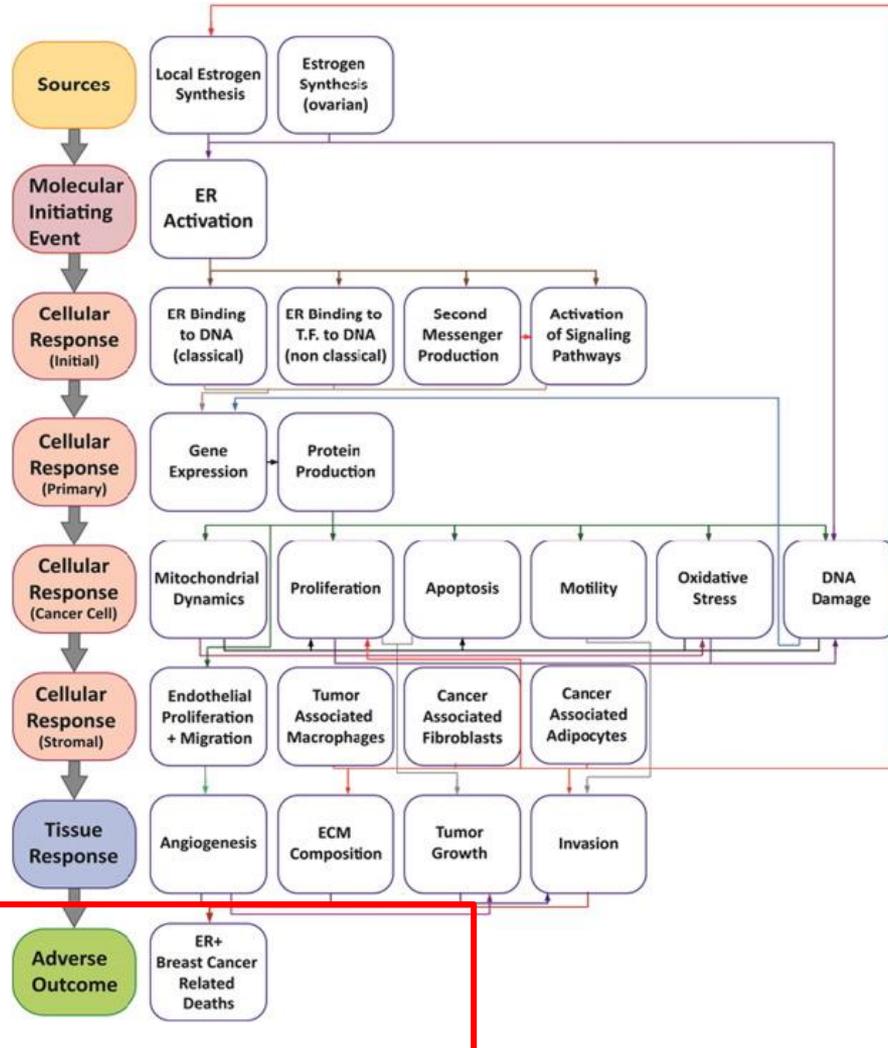


Figure 2. Intracellular Signaling Networks Regulate the Operations of the Cancer Cell



ER pathway to breast cancer



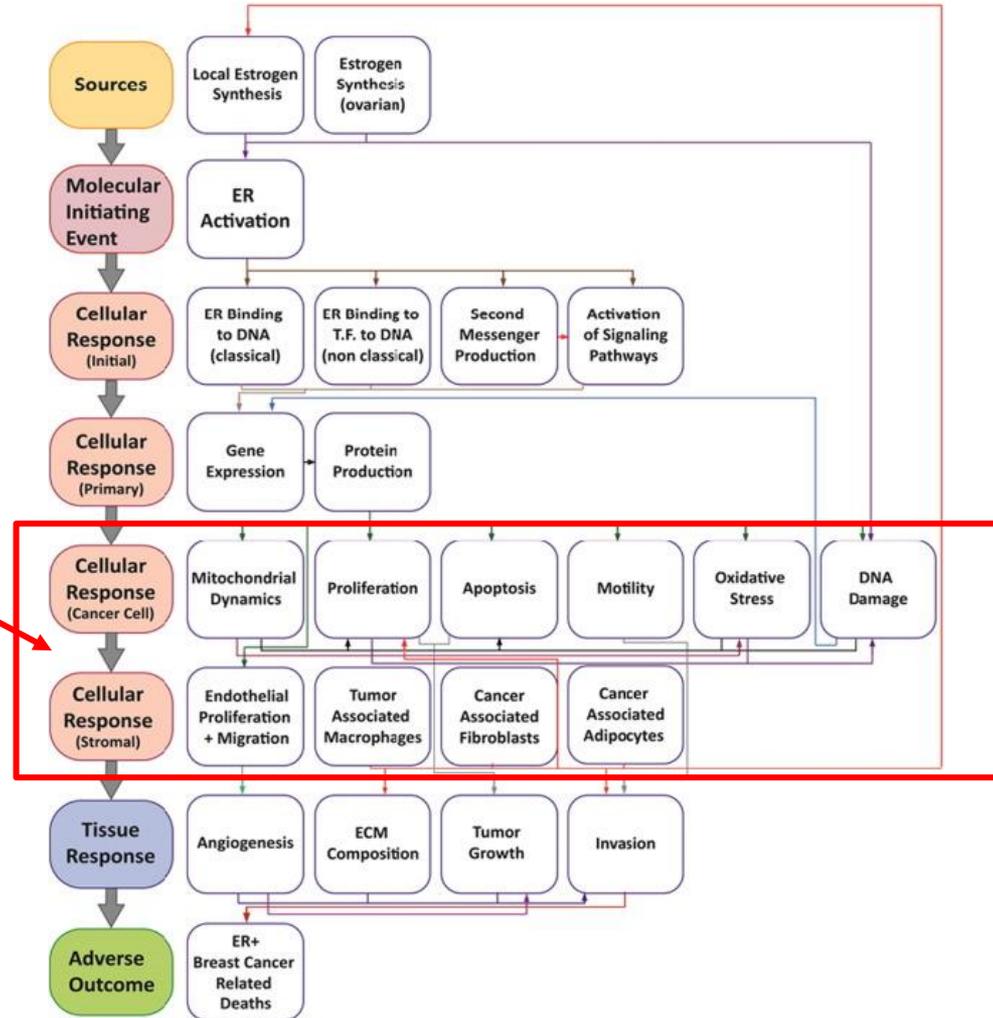
This is what we traditionally model in observational ways.



Key Challenges- Predictive Toxicology Conundrum

ER pathway to breast cancer

This is the inflection point we need to model since it represents the bridge between observation and prediction





Exome Sequencing of Fresh-frozen or Formalin-fixed Paraffin-embedded B6C3F1/N Mouse Hepatocellular Carcinomas Arising Either Spontaneously or due to Chronic Chemical Exposure

Scott S. Auerbach¹, Miaofei Xu¹, B. Alex Merrick¹, Mark J. Hoenerhoff^{1,2}, Dhiral Phadke³, Debra J. Taxman³, Ruchir Shah³, Hue-Hua L. Hong¹, Thai-Vu Ton¹, Ramesh C. Kovi^{1,4}, Robert C. Sills¹, and Arun R. Pandiri¹

Toxicologic Pathology
1-13
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Table 2. Variants from Exome Sequencing of B6C3F1/N Mouse Hepatocellular Carcinomas Which Correspond to Known Mutations in Human Cancer-related Genes from Publicly Available Databases.

Gene	Mutation	Spontaneous			GBE				MEG			Database Match			
		I	2	3	I	2	3	4	I	2	3	COSMIC	IntOGen	NIEHS	SIFT Score
<i>Acss3</i>	G672V								X	X		Yes			0.08
<i>Bcl11a</i>	A189T										X	X	Yes		0.06
<i>Braf</i>	V637E									X	X	Yes	Yes	Yes	0
<i>Ctla</i>	N88S			X	X				X	X		Yes			0.28
<i>Ctnnb1</i>	D32N								X			Yes	Yes	Yes	0
	D32Y									X		Yes			0
	T41A						X					Yes			0
<i>Dnahc5</i>	E3279K							X	X			Yes			0.38
<i>Elmo1</i>	G125A										X	Yes			0
<i>Elk3</i>	P88L										X	Yes			0.06
<i>Gnas</i>	R926C								X	X			Yes		0
<i>Hras</i>	Q61K	X	X	X	X							Yes	Yes	Yes	0.1
	Q61R							X	X			Yes		Yes	0
<i>Kif3c</i>	E76K										X	Yes			0.09
<i>Lrp1b</i>	R1646K										X	X	Yes		0.85
<i>Lyst</i>	Y2952C										X	Yes			0
<i>Rbbp5</i>	L399V										X	Yes			0.08
<i>Slc2a13</i>	R601W								X			Yes			0.01

Note: GBE = ginkgo biloba extract; MEG = methyleugenol; FF = fresh-frozen tissue; PE = formalin-fixed paraffin-embedded tissue; COSMIC = Catalogue of Somatic Mutations in Cancer; IntOGen = Integrative Oncogenomics database.



Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis

Table 1. Key characteristics of carcinogens.

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.



TBD



Building confidence



Analytical
validation

Key Enablers

- replicate human biology
- demonstrate human pharmacology and toxicology
- test for analytical reproducibility
- comparative studies
- evolution of use
- learn to make decisions
- clinical outcomes
- tincture of time/experience

Translational
qualification



Key Challenges- Decision framework

“Possibility means something may happen. Probability means something is likely to happen. Your focus should be on the things that are likely to happen.”

Personal Security Module, U.S. Travel Security Training 2019



TOXICOLOGICAL SCIENCES, 162(1), 2018, 89–98

doi: 10.1093/toxsci/kfx236
Advance Access Publication Date: November 6, 2017
Research Article

Predicting Drug Safety and Communicating Risk: Benefits of a Bayesian Approach

Stanley E. Lazic,^{*,1} Nicholas Edmunds,[†] and Christopher E. Pollard[†]

^{*}Quantitative Biology, Discovery Sciences and [†]Drug Safety and Metabolism, IMED Biotech Unit, AstraZeneca, Cambridge, CB4 0WG, UK

Deterministic



Probabilistic



Key enablers to a different paradigm

- Leveraging a need and willingness to define a different approach
- Aligning on what we know about cancer and carcinogenesis
- Appreciate what it takes to build confidence in a new approach in an area of hazard with this level of sensitivity
- May have to define new questions. Will have to define a novel decision framework
- Partnerships



Thank you!

Questions?