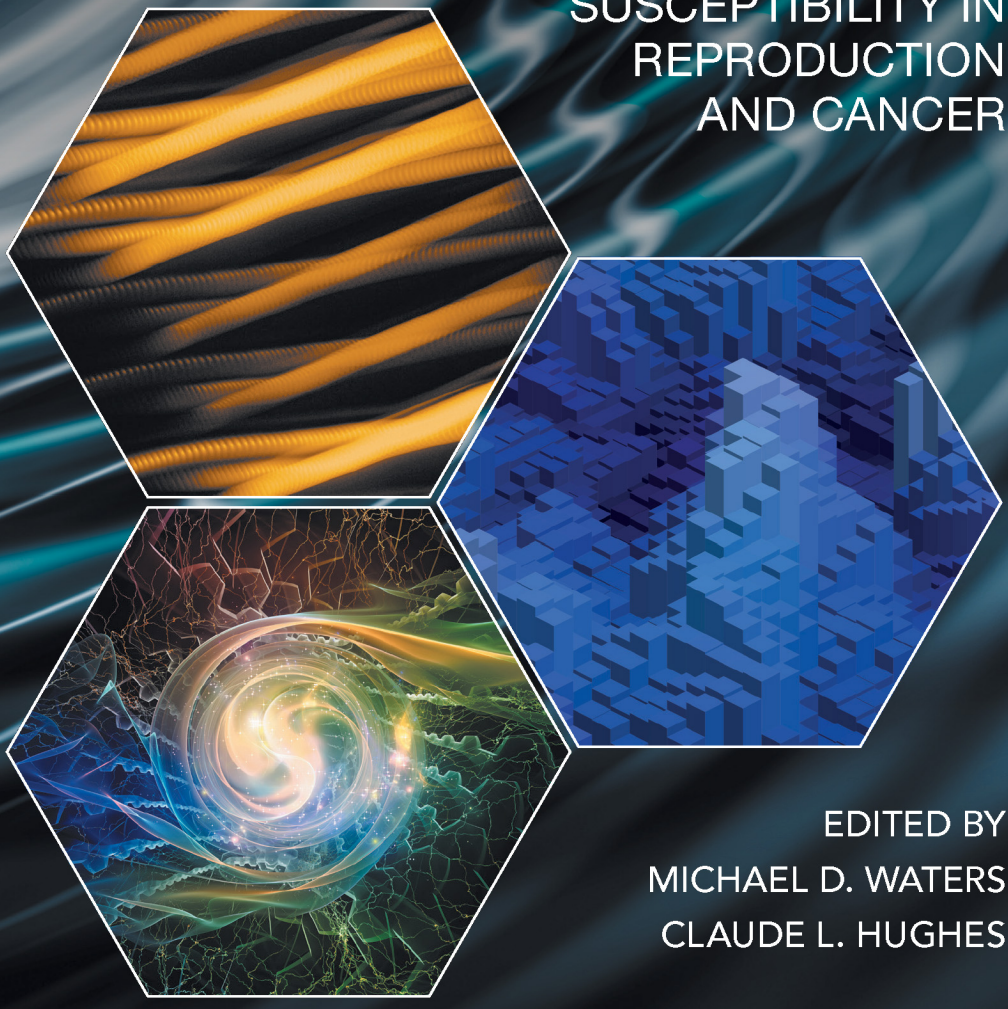
TRANSLATIONAL TOXICOLOGY AND THERAPEUTICS

WINDOWS OF DEVELOPMENTAL SUSCEPTIBILITY IN REPRODUCTION AND CANCER



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Translational Toxicology and Therapeutics

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Windows of Developmental Susceptibility in Reproduction and Cancer

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Part One

Introduction: The Case for Concern about Mutation and Cancer Susceptibility during Critical Windows of Development and the Opportunity to Translate Toxicology into a Therapeutic Discipline

1

What Stressors Cause Cancer and When?

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1.1 Introduction

Translational biomedical research seeks to move laboratory findings based on models *(in silico*, *in vitro,* and *in vivo*) into human clinical trials to more expeditiously develop specific therapeutics, and then back again to the laboratory to inform future discovery [1]. From the background of developmental toxicology, it is well known that toxicant exposures may affect critical events in reproductive development, ranging from early primordial germ cell determination to gonadal differentiation, gametogenesis, external genitalia, or signaling events regulating sexual behavior. Translational genetic toxicology takes advantage of this developmental perspective to assess potential germ line mutagenesis or to study the potential for cancer in the fetus or offspring or the adult as the result of environmental exposures. Translational toxicology must strive to identify applicable therapeutics that can safely and effectively identify and help to mitigate potential harm from natural as well as anthropogenic environmental exposures.

Human exposures to chemicals, physical agents, and social factors are inevitable, thus the human fetus and the adult are subject to exposures and effects that can have lifelong consequences. Particularly, during dynamic developmental intervals described as "critical windows of susceptibility," exposures may have robust and durable effects that drive long-term health outcomes, including metabolism, functional status of organ systems, and cancer risks [2]. These same dynamic developmental intervals should be seen as "critical windows of responsivity" during which favorable/protective interventions should also be highly impactful offering potential durable reduction in

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risks of multiple adverse health outcomes, including cancers. To reduce the lifelong occurrence of preventable cancers, timely protective interventions during "critical windows" should include not only minimization of untoward voluntary exposures and substances of abuse but also active use of protective generally recognized as safe (GRAS) interventions/therapies, including nutritional, dietary supplementation, or well-established/repurposed and/or generally recognized as safe and effective (GRASE) pharmaceutical drugs.

This introductory chapter will promote the elucidation of cell stage, life stage, and lifestyle knowledge of specific cellular and molecular targets of known developmental toxicants, develop a systematic integrated approach to the identification of mutagenic and reproductive toxicants, and discuss sensitive, specific, and predictive animal models, to include minimally invasive surrogate markers, and/or *in vitro* tests to assess reproductive system function during embryonic, postnatal, and adult life. It will argue that integrated testing strategies will be required to account for the many mechanisms associated with development that occur *in vivo*. A key organizing principle used throughout this book is to consider how exposures that incur risk or other exposures/life events that may reduce risk during particular windows of susceptibility/developmental transitions, and thereby impact cancer occurrence.

In consideration of any cause–effect relationship, typically one thinks of the simple questions: Who, what, where, when, and how? Admittedly, "How?" questions are generally the most difficult because that understanding is a synthesis of potentially causal pathways. We aim to consider that the "Who?" and "When?" questions could be seen as people being exposed at different intervals across their respective life spans. Thus, in addition to information regarding what exposures occur that influence cancer occurrence, what is and is not known about exposures to those agents during life span intervals such as childhood, adolescence, across the broader life span, and/or late in life? Assessment of such timing of exposure with cancer outcomes seems to be a critical element if we aim to develop protective interventional strategies. In other words, whether we aim to reduce exposures or advocate protective lifestyle or therapeutic interventions, we must know when those interventions would most effectively impact later cancer outcomes.

Although there are differences between human development and that of laboratory animal models, developmental models have been extremely useful in assessing risks for key human reproductive and developmental processes. Some of these models will be discussed in Chapters 2 and 3. However, such systems have not been fully integrated with models to assess germ line mutagenesis or to study the potential for cancer in the fetus or offspring as the result of environmental exposures. Again, Chapters 2 and 3 will address current proposals for experimental animal test system integration.

To delve into the impact of exposures during "windows of susceptibility/responsivity," we must take into account the unique susceptibilities of the fetus.

Relatively, new information suggests that some widely held notions relevant to fetal exposures are incorrect [3]. Thus, we now know that amniotic fluid can be reabsorbed into the fetal circulation by fetal swallowing as well as via the fetal intramembranous pathway. The latter pathway is thought to be the most important mechanism for the resorption of toxicants, such as ethanol, into the fetal circulation [4]. Together with swallowing, this is a recycling system, through which toxic substances are excreted into the amniotic fluid and reabsorbed into the fetal circulation, thus extending the duration of each exposure [5,6]. This and other information relevant to fetal exposure *in utero* will be discussed in Chapter 8.

1.1.1 General Information about Cancer

Each year the American Cancer Society estimates the number of new cancer cases and deaths that will occur in the United States that year. In 2016, a total of 1,685,210 new cancer cases were expected to be diagnosed and about 595,690 cancer deaths were projected to occur in the United States [7]. Among children up to 14 years of age, an estimated 10,380 new cancer cases were expected to occur in 2016.

Population-based cancer registration began in the United States in 1975. Since then, childhood cancer incidence rates have increased by 0.6% per year. In 2016, 1250 cancer deaths were expected to occur among children. Cancer is the second leading cause of death in children ages 1–14 years, exceeded only by accidents. Childhood cancer death rates declined a total of 66% from 1969 (6.5 per 100,000) to 2012 (2.2 per 100,000). According to the American Society, this was largely due to improvements in treatment and high rates of participation in clinical trials. From 2003 to 2012, the rate of cancer-caused deaths in children declined by 1.3% per year.

Siegel *et al*. [8] reported that during the period 2006–2010, the then most recent 5 years for which there were data, the delay-adjusted cancer incidence rates declined by 0.6% per year in men and were stable in women. At the same time, cancer death rates decreased by 1.8% per year in men and by 1.4% per year in women. The rate of combined cancer deaths per 100,000 populations has declined continuously for two decades, from a peak of 215.1 in 1991 to 171.8 in 2010. The 20% decline during this time period equates to the avoidance of 1,340,400 cancer deaths (952,700 among men and 387,700 among women). Siegel *et al.* reported that the magnitude of the decline in cancer death rates varies substantially by age, race, and sex, with no decline among white women of 80 years of age and older to a 55% decline among black men 40–49 years of age. Remarkably, black men experienced the largest drop within every 10-year age group. The authors noted that progress could be accelerated by applying cancer control knowledge across all segments of the population [8].

While the severity of cancers is often measured in number of deaths, the number of years of life lost (YLL) may be a more appropriate indicator of impact

on society [9]. These authors calculated the YLL of adult cancers in Norway for 2012 and for the prior 15-year period. Their results showed that cancer deaths in Norway in 2012 represented 25.8% of all adult deaths (28.7% in men and 23.1% in women). Cancer deaths represented 35.2% of all YLL, with a 5.0% higher fraction in females than in males (32.8% in men and 37.8% in women) [9].

The etiology of cancer is generally thought to be the product of gene and environmental interactions. Environmental exposures are typically low and to mixtures of constituents that occur indoors and outdoors. Goodson *et al.* hypothesized that low-dose exposures to mixtures of chemicals in the environment may be combining to contribute to environmental carcinogenesis [10]. They reviewed 11 hallmark phenotypes of cancer, with multiple priority target sites for disruption in each area and prototypical chemical disruptors for all targets. Dose–response characterizations and evidence of low-dose effects and cross-hallmark effects for all targets and chemicals were considered. In total, 85 examples of chemicals were reviewed for their actions on key pathways and mechanisms related to carcinogenesis. Although 59% of the chemicals caused low-dose effects, only 15% (13/85) were found to show evidence of a dose–response threshold. No dose–response information was found for the remaining 26% (22/85). The authors speculated that the cumulative effects of individual noncarcinogenic chemicals acting on different pathways in related systems, organs, tissues, and cells could synergize to produce carcinogenic outcomes. They concluded that additional research on carcinogenesis focused on low-dose effects of chemical mixtures needs to be rigorously pursued before the merits of their hypothesis can be further tested [10].

In a published poster abstract, Parkin and Paul [11] estimated the percentage of cancer in the United Kingdom in 2010 resulting from exposure to 14 major life style, dietary, and environmental risk factors. Prevalence and relative risks of exposure to factors, including tobacco smoking, consumption of four different dietary components (fruit and vegetables, meat, fiber, salt) alcohol use, occupation, infections, radiation, hormone use, overweight, physical exercise, and reproductive factors were used to estimate the number of cancers occurring in 2010 attributable to suboptimal exposure levels in the past. These 14 exposures were responsible for 42% of cancer in the United Kingdom in 2010 (males 44%, females 40%). Tobacco smoking was the most important, accounting for about 60,000 new cancers (18.5% of all cancer; 22% in men, 15% in women), with less than 2% being the result of exposure to environmental tobacco smoke. The four dietary components account for 9.4% of cancer (10.7% in men, 7.1% in women). In men, alcohol use (5.1%) and occupational exposures (4.7%) are next in importance and in women, overweight and obesity are next (nearly 7% of cancers). The study is cited because estimates of this kind provide a quantitative assessment of the impact of various exposures. However, they are not synonymous with the fraction of cancers that might reasonably be prevented by modification of exposures. As discussed by the authors, "this requires scenario