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**Review Article**

# Bernard Lerer: Recipient of the 2014 Inaugural Werner Kalow Responsible Innovation Prize in Global Omics and Personalized Medicine (Pacific Rim Association for Clinical Pharmacogenetics)

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**Abstract**

This article announces the recipient of the 2014 inaugural *Werner Kalow Responsible Innovation Prize in Global Omics and Personalized Medicine* by the Pacific Rim Association for Clinical Pharmacogenetics (PRACP): Bernard Lerer, professor of psychiatry and director of the Biological Psychiatry Laboratory, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. The Werner Kalow Responsible Innovation Prize is given to an exceptional interdisciplinary scholar who has made highly innovative and enduring contributions to global omics science and personalized medicine, with both vertical and horizontal (transdisciplinary) impacts. The prize is established in memory of a beloved colleague, mentor, and friend, the late Professor Werner Kalow, who cultivated the idea and practice of pharmacogenetics in modern therapeutics

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commencing in the 1950s. PRACP, the prize's sponsor, is one of the longest standing learned societies in the Asia-Pacific region, and was founded by Kalow and colleagues more than two decades ago in the then-emerging field of pharmacogenetics. In announcing this inaugural prize and its winner, we seek to highlight the works of prize winner, Professor Lerer. Additionally, we contextualize the significance of the prize by recalling the life and works of Professor Kalow and providing a brief socio-technical history of the rise of pharmacogenetics and personalized medicine as a veritable form of 21st century scientific practice. The article also fills a void in previous social science analyses of pharmacogenetics, by bringing to the fore the works of Kalow from 1995 to 2008, when he presciently noted the rise of yet another field of postgenomics inquiry—*pharmacoepigenetics*—that railed against genetic determinism and underscored the temporal and spatial plasticity of genetic components of drug response, with invention of the repeated drug administration (RDA) method that estimates the dynamic heritabilities of drug response. The prize goes a long way to cultivate transgenerational capacity and broader cognizance of the concept and practice of responsible innovation as an important criterion of 21st century omics science and personalized medicine. A new call is presently in place for the 2016 PRACP Werner Kalow prize. Nominations can be made in support of an exceptional *individual* interdisciplinary scholar, or alternatively, an *entire research team*, from any region in the world with a record of highly innovative contributions to global omics science and/or personalized medicine, in the spirit of responsible innovation. The application process is straightforward, requiring a signed, 1500-word nomination letter (by the applicant or sponsor) submitted not later than May 31, 2015.

*Wanderer, your footsteps are*
*the road, and nothing more;*
*wanderer, there is no road,*
*the road is made by walking.*
*By walking one makes the road,*
*and upon glancing behind*
*one sees the path*
*that never will be trod again.*
*Wanderer, there is no road –*
*Only wakes upon the sea.*

Antonio Machado (1875–1939)

''*The real voyage of discovery consists not in seeking new landscapes but in having new eyes.*''

Marcel Proust (1871–1922)

## Introduction

This article announces the recipient of the 2014 inaugural *Werner Kalow Responsible Innovation Prize in Global Omics and Personalized Medicine* by the Pacific Rim Association for Clinical Pharmacogenetics (PRACP): Bernard Lerer, professor of psychiatry and director of the Biological Psychiatry Laboratory, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

The Werner Kalow Responsible Innovation Prize is given to an exceptional scholar who has made highly innovative and enduring contributions to global omics science and personalized medicine, with both vertical and horizontal (transdisciplinary) impacts. The prize is established in memory of a beloved colleague, mentor, and friend, the late Professor Werner Kalow, who cultivated the idea and practice of pharmacogenetics in modern therapeutics commencing in the 1950s. PRACP, the prize's sponsor, is one of the longest standing learned societies in the Asia-Pacific region (http://www.med.niigata-u.ac.jp/psy/PRACP/). It is registered as an Associate Member Society of the International Union of Basic and Clinical Pharmacology (IUPHAR; http://www.iuphar.org), and was founded by Kalow and colleagues more than two decades ago in the then-emerging field of pharmacogenetics (IUPHAR, 2013).

In announcing this inaugural prize and its winner, we seek to highlight the works of prize winner, Professor Lerer. We also contextualize the significance of the prize by recalling the life and works of Professor Kalow and providing a brief socio-technical history of the rise of pharmacogenetics and personalized medicine as a veritable form of 21st century scientific practice.

## Werner Kalow: A Eulogy

### *Recalling a trailblazer who took the study of variable drug responses to heart*

February marked the sixth year anniversary of the passing of Professor Werner Kalow on February 16, 2008 at the age of 91 years. Widely regarded as a founder of the field of

pharmacogenetics, Kalow wrote the seminal book on the role of heredity in person-to-person differences in drug efficacy and safety (Kalow, 1962). The New York Times ran both an article and an editorial on the subject that same year (Schmeck, 1962).

He was an astute observer with a gift of envisioning the grand designs of nature revealed by humble evidence. He catapulted pharmacogenetics to the fore as a legitimate subspecialty of 21st century medicine. But most readers might not know that Kalow became a pharmacologist by happenstance:

> *Kalow had never intended to become a pharmacologist. As a medical student in Germany and Austria in the late 1930s, he had dabbled in research—for instance, he conducted bird surveys on the Baltic coast in the summer of 1937. Drafted into the German Navy in 1938, he was allowed to complete his medical studies. He submitted his thesis, on the effects of adrenal extracts on blood pressure, in 1941. While interning at a naval hospital in South Holland in 1942, he inadvertently insulted a visiting German admiral. The admiral promptly assigned him to be the ship surgeon on a blockade runner, a degrading and dangerous assignment. After several nearly catastrophic attacks by Allied bombers, the ship escaped European waters and delivered its cargo, a hydroelectric generator, to Japan. The return trip did not go as well. The Allied blockade of Europe stranded the crew in the Japanese Empire until 1944. Then a U.S. destroyer sunk the ship off the coast of Brazil and took the crew as prisoners of war. Kalow ended up at a large POW camp, Papago Park, near Phoenix, Arizona. This proved to be a blessing. Since the war had left stateside hospitals short-staffed, the Army recruited Kalow to work as an intern, allowing him to complete his medical training while a POW. When he returned to Germany in 1946, he tried his hand at clinical work, but quickly decided to seek a career in research instead. His choice of specialty was a political one. Most of the University of Berlin, including the Pathology Department, had ended up in the Russian sector. The Pharmacology Department, however, had been bombed during the war and was rebuilt in the American sector. Kalow chose to stick with the Americans and become a pharmacologist. He began his work in January 1947.* (Jones, 2013)

Kalow was not the only one who contributed to the emergence of pharmacogenetics in the 1950s. In a seminal article, Arno G. Motulsky proposed the idea of genetic contribution to adverse drug effects (Motulsky, 1957). Two years later in Heidelberg, Germany, Friedrich Vogel coined the term pharmacogenetics (i.e., long before 'personalized medicine' became a popular term and research topic) (Vogel, 1959).

A towering intellectual, Kalow was driven by genuine and insatiable curiosity to understand beyond what is immediately apparent to the senses. With curiosity and a sense of wonder guided by self-critique, he considered that research could then lead to genuine innovation, or to progressive science that is responsible and attuned to social values (see Table 1 for ''responsible innovation''). Kalow's versatile and long career led to innumerable scientific discoveries and is best appreciated from his own autobiographical account (Kalow, 1995). He received numerous honors, including the prestigious Killam Prize by the Canada Council for the Arts (2001), the Oscar B. Hunter Award from the American Society for Clinical Pharmacology and Therapeutics (1993), the Bernard B. Brodie Lectureship by the Pennsylvania State University College of Medicine (1990), and nomination for the Nobel Prize (1990).

Those of us who had the opportunity to know him as a colleague, mentor, and friend also recall him as a soft-spoken gentleman and an impeccable writer with an immense command of the history of pharmacogenetics, and a fondness for mathematics, crossword puzzles, and sailing on the Great Lakes. The bustling St. Lawrence Sunday Market in Toronto,

Table 1. Responsible Innovation as Concept and Practice

- Robust science and the presence of mechanisms for triangulation (methodological, spatial, and temporal) are at the core of responsible innovation.
- In addition to robust technical aspects, the presence of broad participation and extended peer-review in upstream (scientific design) and downstream science (execution, diffusion, and uptake of science) are essential. For innovation to be responsible, the scientific design and practice space must involve more than traditional technical experts. It must involve a broad array of experienced, engaged and enthusiastic members of the public, such as citizen scholars, patients, policymakers, and other knowledge end-users. This ''opening up'' of the hitherto cloistered scientific design and practice space produces scientific knowledge that is closely embedded with societal values, public interests, and end-user priorities, reflexively attends to broader outcomes emergent from scientific discovery, and thus, becomes socially robust and sustainable.
- Multiple, overlapping, and cross-checking layers of power and collective action that together shape a responsible innovation ecosystem create a knowledge commons that is ''self-corrective'' for socio-technical errors and professional blind spots, ensures against reliance on a single omnipresent scientific, ethics, or moral authority, and thus offers transparent, accountable, cosmopolitan, and self-governing distributed knowledge co-production by innovation actors.
- For a responsible 21st century knowledge society, concentrated power systems inherited from 20th century science, be they centered on technical, philosophical, social science, or bioethics aspects of life sciences and engineering, need to be replaced with distributed, and horizontally structured, knowledge co-production systems that promote epistemic plurality, collective incentives, and nested governance of science and its social and political dimensions.
- Knowledge producers' values and personalities, be they scientists', engineers', bioethicists', social scientists, humanists or artists, are shaped and co-constructed not only by individual agency, but also the social and political systems they are embedded in. Hence, one formidable task to bring these changes about is the introduction of new credit and rewards systems for achievements in science, engineering, social sciences and humanities that offer alternatives to one dimensional individual centric first authorships and attendant incentive systems.

Updated from Özdemir et al., 2013; Dove and Özdemir, 2013b; Dove and Özdemir, 2014; see also the works by de Vries, 2004.

as well as the idyllic northern Ontario and road trips, often were attractions, for they allowed him to contemplate and ponder research questions and events of daily life. He had a sharp eye and natural gift for recognizing truly innovative ideas and persons. He braved quietly a severe form of chronic osteoarthritis and continued to type, with deformed fingers, scholarly articles and analyses until the very end. In all, Kalow's numerous accomplishments remind us why we need to adopt responsible innovation as an indispensable criterion of 21st century science, and also how the PRACP prize contributes to transgenerational capacity in global omics and personalized medicine.

A eulogy should laud a person's life but also be inspirational in its message. It should convey a sense that time is limited and that we need to act *now*, while thinking reflexively about the broadest possible futures and the possible transgenerational consequences of our actions. The introductory quotations from Antonio Machado and Marcel Proust illustrate the two overarching tenets of a trailblazing life and career. These are worthy of reflection in our current restless age while we attempt to have a grasp on the sociotechnical history of pharmacogenetics, and Werner Kalow as a trailblazer of that field.

On the one hand, Kalow sought for and convened scholars and astute observers from around the world. What mattered to him most were new ideas, scholarship, and an ability to examine unchecked assumptions. He appreciated that scholarship was present ubiquitously, no matter locale and scientific discipline, and thus required an open unassuming mind. As Antonio Machado observes, one cannot expect to have a prescribed path to encounter or create genuine scholarship in the pursuit of knowledge-based innovation; one makes the road as s/he travels.

Importantly, the real opportunity costs are not the missed career or financial potentials, but the potentials missed by not having followed one's callings and a reflexively examined life. Kalow often noted to close friends that ''*it is nice to have a hobby. Even better is when your hobby is your occupation, and not merely work.*''

Yet, on the other hand, Kalow's approach to science was also in the tradition of Marcel Proust, who emphasizes that we do not always have to travel far to seek scholarship and an examined life; these are often in our immediate milieu—provided we have the right outlook (''have new eyes''), and courage to examine things transparently, reflexively, and up close, as they really are. Perhaps instinctively, Kalow knew and embodied such essential attributes of a trailblazing scholar early on. A few examples from his career would illustrate this more clearly.

### *Rise of pharmacogenetics was not foreordained*

Pharmacogenetics was a fringe academic interest until the late 1990s. In recalling the rise of pharmacogenetics to its present day popularity, it is instructive to bear in mind that innovations and emergences of new scientific fields are never foreordained (Rajan, 2006; Jasanoff, 2007; Dove and Özdemir, 2013a; 2013b; Jasanoff 2013). They are subject to sociotechnical and political contestation, as we have noted in earlier analyses:

> *Truly original concepts that fundamentally break from the past traditions can remain in obscurity, misrepresented through one-sided critique and professional hyper-jealousy, or rejected outright by existing conceptual frameworks. Innovations tend to be cultivated by crystallization of intellectual entropy in the middle of chaos: that is, at the intersection of new ideas that struggle for survival and future representation on the one hand, and antagonism by existing ideas, institutionalized forms of old knowledge, and human and nonhuman actors in science and society whose power structures may be disrupted by innovations and novel ways of human understanding* (Özdemir et al., 2009a).

While the emergence of some innovations can materialize in less turbulent conditions, this is rarely without contest, nor is it a matter of linear diffusion out of laboratory into broader society. In the early 1950s, the role of heredity in human diseases was not widely acknowledged, nor, surely, were drug-by-gene interactions contributing to variable drug efficacy and safety. A great majority of the discourse in pharmacology and therapeutics at that time was characterized by a focus on environmental determinants, and a discourse that stressed variability in drug pharmacokinetics and pharmacodynamics could not be clearly dissected. It took courage and a focused but farsighted vision to imagine alternative futures of the science and innovation trajectory in the 1950s, with a view to 21st century personalized medicine. The founders of the field of pharmacogenetics and the study of drug-by-gene interactions had to face great professional uncertainty and initial rejection so as to cultivate new ways of thinking in the mid-20th century—particularly, that genes mattered *together with* the environment. This effort to bring about a balance to extant scientific discourse by recognizing the role played (albeit partially) by heredity in drug action was not immediately understood or appreciated (see Özdemir et al., 2009b, for a genealogy of the omics science). On the other hand, individual agency/drive of the pharmacogenetics pioneers such as Kalow was not the only factor that helped to bring together pharmacology and genetics as a new field of inquiry. As Jones aptly observed, ''*with the thalidomide scandals in 1961 and the Kefauver hearings from 1959 to 1962, there was great interest in anything that might improve drug safety*.'' (Jones, 2013). This changing political and regulatory climate in the 1960s in part facilitated (though slowly) pharmacologists to reconsider new explanations, including heredity, that might help predict person-to-person variations in drug pharmacokinetics and pharmacodynamics.

For every first order action such as a scientific discovery, there is a second order consequence (Jasanoff, 2007; Bragazzi, 2013). With the rise of pharmacogenetics, social scientists at times expressed concerns over geneticization and racialization of drug effects (for discussion of the history of genetic determinism/racialization in the master narratives of research funding and pharmacology/personalized medicine, see Özdemir et al., 2009b; Özdemir, 2010). Geneticization describes ''a process whereby there is an increasing tendency to use genetic explanations to describe differences between individuals or groups.'' (Hedgecoe, 2009). While the ''geneticization thesis'' has proved popular among social scientists and bioethicists, empirical data cast doubts on the geneticization thesis of bioethicists as a simple mechanism by which clinical adoption of genetic tests can be explained (Hedgecoe, 2009). Moreover, bioethics and historical analyses of pharmacogenetics have neglected to acknowledge that conducting genetics/genomics research *per se* does not

mean geneticization, nor should genetic research invariably lead to genetic determinism as a consequence (Özdemir et al., 2005; Özdemir, 2010; Jones, 2013). Absent in these social science analyses of pharmacogenetics are the works of Kalow in the late 1990s, wherein he presciently noted the rise of yet another field of postgenomics inquiry—*pharmacoepigenetics*—that firmly opposed geneticization, and underscored the temporal and spatial plasticity of genetic components of drug response. Two of us (V.O. and L.E.) worked with Kalow on his final theme of research that supported the idea of pharmacoepigenetics, and posed the following salient questions (Kalow, 1997, 1999; Özdemir et al., 2000; Özdemir et al., 2005):

- *How do we measure the heritability of drug action?*
- *Do genetic components of drug effects vary over time and space?*
- *Why do we need to recognize genetic components in pharmacology as ever changing constructs subject to temporal and spatial plasticity, rather than as fixed physical constants?*

There has been very little discussion on the ways in which pharmacogenetics, or any genetics/genomics research for that matter, ought to be targeted for phenotypes and clinical contexts where genetic components are abundantly expressed (Özdemir et al., 2005; Micheli et al., 2013). Indeed, pharmacogenetics research resources would be more judiciously spent if they were prioritized for drugs whose effects have the greatest genetic components (Leabman and Giacomini, 2003; Micheli et al., 2013). An estimate of genetic components of drug-related phenotypes also presents the possibility to gauge ''missing heritability'' when the attendant molecular genetic mechanisms are not fully delineated (Özdemir et al. 2000; Micheli et al. 2013). Twin studies that are traditionally employed to measure the heritability of human diseases cannot be readily applied in the case of drug effects, for obvious experimental barriers (i.e., twins have to suffer from the same disease at the same time, and be prescribed the same drugs), the economic costs associated with the twin design, and so forth (Endrenyi et al., 1976; Özdemir et al., 2005).

Kalow set out to address this final challenge in his career by developing a practical statistical method for measuring genetic components of variable drug effects. The classical approach to determine heritability was to use twin studies; that is, by statistically comparing phenotypic differences (e.g., in eye color, clinical manifestations of human diseases, etc.) between the members of identical and fraternal twin pairs. Yet, for most small-molecule drugs with protein targets (e.g., receptors or enzymes), drug effects represent dynamic and reversible biological phenomena that decay over time. Since drug effects are transient (unlike physical characteristics noted above such as eye color), Kalow conceived the idea that it should be feasible to derive heritability estimates in pharmacology by testing the metabolism or effect of a drug administered repeatedly (twice or more often) to a group of people. The repeat pharmacological data in the same person replace those derived from monozygotic twins. Named as the Repeated Drug Administration (RDA) method by Kalow and colleagues, it became possible to estimate, for example, the heritability of CYP3A4 enzyme activity and other pharmacological traits akin to twin studies (Kalow 1997, 1999; Özdemir et al., 2000; Özdemir et al., 2005).

Analyzing the data on CYP3A4 activity with the RDA method made a new important observation. It showed genetic contribution for this major drug metabolizing enzyme was much higher at night than during the day (Özdemir et al., 2000). This made sense as food consumption, liver blood flow, and other environmental factors are clearly less confounding at night than during daytime. Prior to the RDA method, however, it was simply not possible to examine heritability under different spatial and temporal conditions like those that might affect pharmacokinetic phenotypes differentially at day and night.

Kalow's idea for the RDA method demonstrated that heritability of pharmacological responses is not a fixed physical constant. The RDA method in a real sense offered a safeguard against geneticization and genetic determinism in personalized medicine, and elevated pharmacogenetics to a higher level of sophistication and responsible innovation.

This socio-technical history of pharmacogenetics is instructive because it offers ''new eyes,'' in the words of Proust, to understand genetic components and their plasticity in pharmacology. Truly disruptive innovations and new ideas such as pharmacogenetics demand foresight, reflexivity, and self-critique to check one's unchecked assumptions and blind spots as well as those prevalent in a given professional field such as pharmacology and human genetics. Such far ranging, integrative, and versatile vision pioneered by Kalow collectively informed how we presently make sense of, and respond to variable drug effects, and ways in which rational therapeutics and personalized medicine came into being in the 21st century.

Indeed, towering intellects like Kalow are pioneers of a different kind. They are not replicators of themselves with clones of yes-men or yes-women. They provide a compass, but not an itinerary, to guide us on our own journeys of discovery and innovation (Fig. 1).

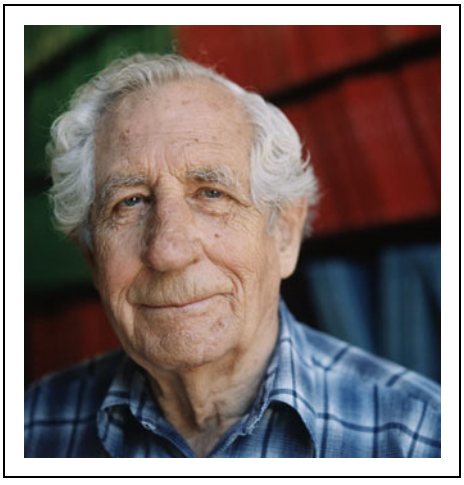

**FIG. 1.** Professor Werner Kalow, MD (1917–2008)

## A Prize for Responsible Innovation in Global Omics and Integrative Biology

PRACP moved to recognize the highly innovative trailblazing scholars in global omics science, personalized medicine, and integrative biology, by establishing the Werner

Kalow Prize. This is timely as omics science and personalized medicine now have global importance and are moving towards applications in both developed and developing countries, including the Asia-Pacific region. The prize goes a long way to cultivate transgenerational capacity and broader cognizance of the concept and practice of responsible innovation for global omics and personalized medicine. The overarching criteria for the prize were comprised of the following:

1. Highly innovative and transdisciplinary contributions to the field of omics science, integrative biology and/or personalized medicine;
2. Tenets of responsible trailblazing work, akin to Professor Kalow, with versatility in intellectual thought across the artificial disciplinary boundaries, and ''daring to imagine'' alternative ways of conceptualizing hypotheses or methodologies that are innovatively distinct from the prevailing dominant norms and conceptual frameworks in a given field (see, for example, Wynne, 2009; Dove, 2012; 2013);
3. Relevance for, and service to, global omics science, with not only experimental contributions but also leadership in knowledge translation and synthesis from cell to society;
4. Fostering collective action in the field of global omics and personalized medicine, thereby cultivating robust linkages between science and global society;
5. While we recognize that not all criteria can be met by a scholar or a research team, *sociological* or *political science* contributions (or at a minimum, awareness of the below issues) are an asset for the following substantive reasons:

   - The entire trajectory of scientific inquiry, from conception of a hypothesis to translational research and application, is subject to internal and external political determinants (Kickbusch, 2005; Dove, 2012). By ''politics,'' we refer to the entire constellation of situations in which ''what is apparent'' differs distinctly from ''what is actually intended or at work'' (Dove and Özdemir, 2013a). Indeed, life itself is political on a day-to-day basis (Rose, 2006)—even a smile can be political if intended to influence others with an oblique agenda. The real risk, however, is not that science is inherently a political enterprise but rather that the political elements remain opaque, thus making science fragile and subject to uncertainties on the innovation trajectory.
   - In response, social and political science scholarship unpacks the politics and human values at play in scientific inquiry, making science transparent, context-sensitive, and responsive, and thus more robust and sustainable in the 21st century (de Vries, 2004). Yet, social science, bioethics, and moral philosophy also have embedded politics, and are not désintéressé in their own practices (Thoreau, 2011; Thoreau and Delvenne, 2012; Özdemir et al., 2014). The idea (assumption) of value-neutral or invariably reflexive social/political science, humanities, and bioethics inquiry is challenged rapidly when one steps into social science, management sciences, bioethics, or philosophy research ''on the ground'' (Thoreau and Delvenne, 2012; Dove and Özdemir, 2013a). When working hands-on in the field, one can observe the more haphazard and messy realities of how politics is ever-present in human practices, be it natural sciences, social/political sciences, or the humanities (de Vries, 2004; Dove, 2013; Dove and Özdemir, 2013a; Kingori et al., 2013; Petersen, 2013; Solbakk, 2013). Hence, scholarship that demonstrates a high degree of reflexivity across one or more of these three knowledge domains, for example, by challenging the all-too-often assumed moral authority of bioethics (i.e., the nascent field of ethics of bioethics), and thus contributing to an emerging strand of ''nested scholarship'' in 21st century (i.e., a sociology of bio-knowledge) will have priority for the Werner Kalow responsible innovation prize. The burgeoning fields of sociology of bio-knowledge and ethics-of-bioethics can usefully ''hold the mirror that allows bioethicists to see how the small and large compromises required to get along in the world have influenced their work.'' (de Vries, 2004). In this vein, de Vries further observes that:

> *Sociology and bioethics have an uneasy relationship. Bioethicists find sociology helpful for describing and analyzing ethical issues, but they are less enthusiastic when bioethics becomes the subject of sociological scrutiny. (…) It was Pitirim Sorokin who suggested that if there are N number of disciplines in the world, the world needs N+1 disciplines; that is, there must be one discipline that studies how the others operate and fit together. That discipline is sociology. It is the ''N+1'' vision of the field that animates sociologists of bioethics*. (de Vries, 2004)

   - Finally, we shall note the present efforts towards building a sociology of bio-knowledge underscore that technical or market innovation in life sciences, alone, is not sufficient, nor are the previous social science and moral philosophy frames that narrowly assigned a passive ''science enabler'' role to bioethics (Petersen, 2013; Özdemir et al., 2014), rather than full epistemic agency and function to independently critique and steer science towards the tenets of responsible innovation, as described in Table 1.

### Bernard Lerer

Professor Lerer's biography is presented in Table 2 and speaks for itself. Throughout a long career dedicated to biological psychiatry, he made highly innovative and transdisciplinary contributions to the field of pharmacogenetics and personalized medicine—contributions that would have been inspired by the works of Antonio Machado (trailblazing disruptive innovation) and Marcel Proust (developing ''new eyes'' for existing conceptual frames). We highlight the selected accomplishments of Lerer below, and the context in which they are significant, with a view to responsible innovation.

First, worldwide, millions of healthy years of life are lost to mental and substance use disorders. These conditions are the fifth-leading cause of overall global disease burden. In many countries, mental health does not receive the research and public health attention it deserves. The global burden of disease attributable to mental and substance use disorders in 2010

Table 2. Biography of Professor Bernard Lerer, MD

Professor Bernard Lerer is Director of the Biological Psychiatry Laboratory at Hadassah-Hebrew University Medical Center, Jerusalem, Israel since 1990. He was recently chosen to lead a National Knowledge Center for Research on Brain Disorders established at Hadassah Medical Center by the Israel Ministry of Science. Professor Lerer was educated at the University of Cape Town, Hadassah and Herzog Hospitals in Jerusalem, and Lafayette Clinic in Detroit. His main research interests are the molecular genetic basis of major psychiatric disorders, particularly schizophrenia, psychopharmacogenetics, and the neurochemical mechanisms of action of antidepressants, mood stabilizers, and electroconvulsive therapy (ECT). He served as Director of the National Institute for Psychobiology in Israel from 1994–2002, Vice President of the CINP (1996–2000), and Founding Editor-in-Chief of the International Journal of Neuropsychopharmacology (1998–2008). Professor Lerer was a founder and past-President of the Israel Society for Biological Psychiatry. He has received the A.E. Bennet Award of the US Society for Biological Psychiatry and the Mentorship Award of the Israel Society for Biological Psychiatry and has been a Fellow of the American College of Neuropsychopharmacology since 1996. He has extensive international research collaborations and has been Visiting Professor at the Universities of Cape Town, Copenhagen, Hiroshima, and Miami. He has received research support from NIH, the European Union, the Israel Science Foundation and the Israel Ministries of Health, Science and Economics. Prof. Lerer has published over 340 papers in peer reviewed journals as well as book chapters and four books. He is married to Ziona Lerer, and has 3 children and 4 grandchildren.

accounted for 183.9 million disability-adjusted life years (DALYs), or 7.4% of all DALYs worldwide (Whiteford et al., 2013). Importantly, Lerer worked on both sides of the disease and therapeutics divide in mental health, developing diagnostics and molecular insights pertaining to both pathophysiology and therapeutics of psychiatric disorders. In the case of substance use disorders, his work on the pharmacogenetics of smoking uncovered genetic mechanisms responsible for increased risk for nicotine addiction, and barriers to smoking cessation in young women who smoke (Rigbi et al., 2011). An important aspect of the latter work was the focus on multifactorial risk factors including personality, life experience, and cognitive profile, in addition to genetic factors with emphasis on gene–environment interactions. This approach was implemented under the programmatic research program entitled ''*Why Do Young Women Smoke?*'' (Greenbaum et al., 2006; Lerer et al., 2006; Segman et al., 2007; Greenbaum et al., 2010).

Second, Lerer's contributions in pharmacogenetics concentrated on both first- and second-generation antipsychotics (Alkelai et al., 2009). Among these, the works on first-generation antipsychotics (FGA) are of particular importance as they accelerated the twin scholarships of ''pharmacogenetics for generic psychotropics'' and the concept of ''drug rescue'' in psychiatry. Most FGAs are available as generic formulations, and are widely accessible at low cost in most global regions. Yet FGAs can cause tardive dyskinesia (TD), an iatrogenic movement disorder observed in approximately 20%–30% of schizophrenia patients on long-term treatment with FGAs. Lerer's work on generic FGAs led to new molecular insights on FGA-induced TD with the promise that the uncovered pharmacogenetics biomarkers might permit safer use of FGAs in subpopulations at low risk for drug-induced TD. Notably, this work was conducted at a time when there was much enthusiasm for the newer and more expensive second-generation antipsychotics in the first decade of the 21st century. Lerer and his team had the foresight to take the road less traveled and invested in research for generic drug pharmacogenetics under the above overarching vision (Lerer et al., 2002). They did so using a robust methodology that involved not only pharmacogenetic association studies of FGA-induced TD, but also meta-analyses of past association data that allowed methodological triangulation across studies (Lerer et al., 2002).

A third strand of work by Lerer and colleagues involved researching the genetic and molecular basis of significant mental illnesses such as schizophrenia and major depression. Employing both candidate gene studies and genome-wide approaches in this pursuit, Lerer and colleagues broadly involved patients and healthy volunteers from diverse regions around the globe. The findings not only contributed to a deeper understanding of mental illnesses, but also cultivated collective action for global omics science (Ng et al., 2009; Alkelai et al., 2011; 2012; Levinson et al., 2012). For example, the discovery by Lerer and colleagues of the association of the *AHI1* gene with susceptibility to schizophrenia, replicated by other groups in different populations, is of considerable significance and noteworthy (Amann-Zalcenstein et al., 2006; Slonimsky et al., 2010). More recently, this line of work to understand the neurobiological role of *AHI1* examined this gene in stress resistance, employing genetically modified mice studied with behavioral techniques and neuroimaging (Lotan et al., 2014). Lerer accelerated community-wide development in biological psychiatry and personalized medicine through his editorial and learned society leadership roles as well (Lerer, 2008). His work was informed strongly by research in basic sciences (Lerer et al., 1980), and dealt not only with drugs, but also other interventions of clinical importance in psychiatry such as ECT (Lerer and Sitaram, 1983) and novel forms of augmentation therapy for major depression using thyroid hormone supplementation (Cooper-Kazaz et al., 2007).

The unifying element in these studies was a focus on the mechanisms of variability questions in psychiatry, on health outcomes related to drugs and other important interventions such as ECT and thyroid hormones, or susceptibility and prognosis of major mental health disorders. These elements were highly consistent with responsible innovation and transdisciplinary scholarship that brought together countless

TABLE 3. "*ON LIVING*" – BY NAZIM HIKMET (1902–1963)

| *Part I* | *Part II* | *Part III* |
|---|---|---|
| Living is no laughing matter:<br>you must live with great seriousness<br>like a squirrel, for example —<br>I mean without looking for something beyond and above living,<br>I mean living must be your whole occupation. | Let's say we're seriously ill, need surgery —<br>which is to say we might not get up<br>from the white table.<br>Even though it's impossible not to feel sad<br>about going a little too soon,<br>we'll still laugh at the jokes being told,<br>we'll look out the window to see if it's raining, | This earth will grow cold,<br>a star among stars<br>and one of the smallest,<br>a gilded mote on blue velvet —<br><br>I mean *this*, our great earth. |
| Living is no laughing matter:<br>you must take it seriously,<br>so much so and to such a degree<br>that, for example, your hands tied behind your back,<br>your back to the wall,<br>or else in a laboratory<br>in your white coat and safety glasses,<br>you can die for people —<br>even for people whose faces you've never seen,<br>even though you know living<br>is the most real, the most beautiful thing. | or still wait anxiously<br>for the latest newscast …<br><br>Let's say we're at the front —<br>for something worth fighting for, say.<br>There, in the first offensive, on that very day,<br>we might fall on our face, dead.<br>We'll know this with a curious anger,<br>but we'll still worry ourselves to death<br>about the outcome of the war, which could last years. | This earth will grow cold one day,<br>not like a block of ice<br>or a dead cloud even<br>but like an empty walnut it will roll along<br>in pitch-black space …<br><br>You must grieve for this right now<br>— you have to feel this sorrow now —<br>for the world must be loved this much<br>if you're going to say "I lived" … |
| I mean, you must take living so seriously<br>that even at seventy, for example, you'll plant olive trees —<br>and not for your children, either,<br>but because although you fear death you don't believe it,<br>because living, I mean, weighs heavier. | Let's say we're in prison<br>and close to fifty,<br>and we have eighteen more years, say,<br>before the iron doors will open.<br>We'll still live with the outside,<br>with its people and animals, struggle and wind —<br>I mean with the outside beyond the walls.<br>I mean, however and wherever we are,<br>we must live as if we will never die. | |

For an English translation in book format, see Hikmet et al. 2002.

patients, citizens and scientists—junior and senior—who contributed to Lerer and his team's work.

We are confident that Kalow, if he were alive today, would agree with the selection of this prize's inaugural winner. Kalow long considered pharmacogenetics as ''a pursuit to unpack the mechanisms of pharmacological variability'' (discussion between W.K. and V.Ö., December, 2005). The works of Lerer are far ranging in both psychiatry and psychopharmacology. Together, they illuminate the mechanisms of pharmacological standard deviations in drug pharmacokinetics and pharmacodynamics, not to mention individual differences in susceptibility to and prognosis of major mental illnesses. This knowledge is a strong foundation for global personalized medicine, considering the works highlighted above that drew extensively from diverse world populations in both developed and developing countries.

## PRACP and the 2014 Werner Kalow Prize

Starting in 2010, the PRACP executives have worked to develop a unique conference under the thematic focus of *global omics in developing world settings*. It was planned initially in Bangkok, Thailand, in cooperation with the World Health Organization and other leading development agencies interested in global science and responsible innovation. This initiative did not come to fruition due to the global economic recession that regrettably continues to pose constraints in organizing large conferences with independent funding. The PRACP will move, instead, however, to serve a ''knowledge federator'' role by catalyzing the planning, design and organization of local and regional workshops by colleagues in the Asia-Pacific region. The outcomes and recommendations of such regional scholarly events will provide a dynamic and real-time map of the needs and priorities for pharmacogenetics and personalized medicine in the region. The society welcomes proposals from interested scholarly groups and persons to organize local or regional symposia on topics of importance for global omics and personalized medicine.

The inaugural Werner Kalow Responsible Innovation Prize in Global Omics and Personalized Medicine constitutes a $5000 award in support of the winning candidate's research. The prize, while not substantial in monetary terms, is nevertheless, we firmly believe, a strong international peer-recognition for Professor Lerer's innovative work by PRACP. May Lerer and countless other transdisciplinary scholars have the ongoing courage to ''make the road one travels'' in the spirit of Antonio Machado, and examine life, science, and society reflexively in the spirit of Marcel Proust. This resonates well with ideas articulated by other scholars' who have written on the art and science of living such as Pablo Neruda, or Nazım Hikmet and his timeless piece entitled ''*On Living*'' (http://www.poets.org/viewmedia.php/prmMID/15804) where he suggests life is the most beautiful thing, and should be lived for humanity and for the future (Table 3).

## Call for the 2016 Werner Kalow Prize

### *Eligibility: Individual scholar or entire research team engaged in responsible innovation*

A new call is presently in place for the 2016 PRACP Werner Kalow prize. Nominations can be made in support of an exceptional *individual* interdisciplinary scholar, or alternatively, an *entire research team* from any region in the world with proven record of highly innovative contributions to omics and/or personalized medicine, but in the spirit of responsible innovation. The application process is straightforward, requiring a signed, 1500-word nomination letter (by the applicant or her/his sponsor) to be forwarded, by surface mail, to *Dr. Vural Özdemir, Independent Scholar in Science Studies, Ataturk Bulvari, No: 23/5, Nazilli, Aydın, Turkey* not later than May 31, 2015. After an initial triage of the top 20 nominations by the search committee co-chairs (V.O. and L.E.), the prize nominations will be ranked by a transdisciplinary committee comprised of the authors of the present article by October 31, 2015, followed by the announcement of the prize in early 2016.

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Other scholars in this mini-review support the concept of responsible innovation as a key criterion of 21st century reflexive science and knowledge ecosystems, and the works for a sociology of bio-knowledge to guide its further conceptual development.

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