DEPARTMENT OF BIOLOGY
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Assessment of the Impact of the Douglaston Tower Construction on the Residents of the Escala Condominium Tower

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Qualifications

I finished my undergraduate studies in Biology at the University of Buenos Aires, Argentina. I got my PhD in Neuroscience and Behavior at the University of Massachusetts, Amherst, where working with Eric Bittman I studied the neuroanatomical interactions between the master circadian clock of mammals and the brain centers that control reproduction. I then continued my research on the neural control of circadian rhythms as a Post-Doctoral Fellow and as an Instructor of Neurology at the University of Massachusetts Medical School. At the laboratory of Dr. William Schwartz, I did research in the neural control of circadian rhythms, both on how neural circuits regulate 24-hour rhythms and on how light synchronizes the circadian clock. I was also an Instructor at Harvard University where I taught a course on Stem Cells, and have been an Invited Professor at several universities including University of Oxford, where I taught and did research under a Leverhulme Fellowship. I joined the University of Washington in 2003, where I am now a Professor of Biology and the Director of the Graduate Program in Neuroscience.

Since my early career as an undergraduate student, my research has been focused on the regulation of circadian rhythms and sleep, a field in which I have authored more than 60 articles (see full curriculum vitae in appendix). Specifically, part of my research is focused on the effect of environmental light on the biological clock of both animals and humans, as well as on the negative outcomes that result from disrupting environmental light signals to the biological clock.

Below I list some of the publications I have authored that are directly related to these topics. Other publications are listed in my curriculum vitae.

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de la Iglesia, H.O., Fernandez-Duque, E., Golombek, D.A., Lanza, N., Duffy, J.F., Czeisler, C.A. & Valeggia, C.R. (2015) Access to Electric Light Is Associated with Shorter Sleep Duration in a Traditionally Hunter-Gatherer Community. *J. Biol. Rhythms*, **30**, 342-350.

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Hsu, Y.A., Gile, J.J., Perez, J.G., Morton, G., Ben-Hamo, M., Turner, E.E. & **de la Iglesia, H.O.** (2017) The dorsal medial habenula minimally impacts circadian regulation of locomotor activity and sleep. *J. Biol. Rhythms*, **32**, 444-455.

Hsu, Y.W., Wang, S.D., Wang, S., Morton, G., Zariwala, H.A., **de la Iglesia, H.O.** & Turner, E.E. (2014) Role of the dorsal medial habenula in the regulation of voluntary activity, motor function, hedonic state, and primary reinforcement. *J. Neurosci.*, **34**, 11366-11384.

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Issue Presented

I have been asked by the residents at The Escala Condominium Tower, a building located at 1920 4th Ave, Seattle, to assess the risk of negative health impacts for residents living in the east-facing units at The Escala resulting from a reduction in natural light if the Douglaston Tower is constructed as currently planned. My opinion is based solely on my expertise in the field of circadian rhythms and sleep.

Summary of my opinions

My conclusion is that the substantial reduction in the natural light exposure that the residents of The Escala will experience will very likely result in negative health outcomes that are the consequence of diminished light input to centers in the brain that regulate circadian rhythms, including the sleep-wake cycle, and mood.

The adverse health outcomes would result from two main factors:

1) The overall reduction in the exposure to bright light during the day reduces the "synchronizer strength" to the circadian system leading to two main adverse consequences:

(a) An increased relative sensitivity to artificial light during the evening, which delays the circadian system and produces a delayed timing of sleep known as delayed sleep phase disorder, and

(b) a general reduction of the amplitude of circadian rhythms.

Both (a) and (b) conditions are associated with adverse physical health outcomes, including increased weight gain, obesity and higher propensity to develop type II diabetes, increased risk of to develop specific types of cancer, and increased risk of cardiovascular disease. They are also associated with higher incidence of mental health disorders including depression.

2) Reduced exposure to light, particularly to morning light, is detrimental for mental health during the winter, when the *photoperiod* — the number of light hours per day — is short. This is particularly true in high latitudes such as Seattle's, where short photoperiods are associated with higher incidence of winter depression. This effect will likely become more prominent with the new proposal — awaiting approval from the United Sates Congress — that Washington State move to permanent daylight-savings time (DST).

Steps taken to develop my opinion

My assessment of the impact of the DougIaston Tower project was based, in part, on two reports that model the reduction of light that would result if the Douglaston Tower is built. The studies model impacts on a unit located on the fifth floor of The Escala. One report was provided by Loveland Building Science and the other by Circa Dies LLC.

I also personally visited a unit on the fourth floor to get a first-hand impression of the impact of the project. I did this visit together with Ed Clark, Director of Circa Dies LLC, which also provided me with an opportunity to ask specific questions about his report. These independent sources of information provided me with an objective and quantitative determination of the reduction in natural light exposure that the construction of the Douglaston Tower would cause on residents of east-facing units at The Escala.

The construction of the Douglaston Tower would cause a very significant reduction in the amount of natural daylight that the residents of east-facing units at The Escala will perceive. Because of their east-facing direction, the decrease in natural daylight will be particularly severe during the morning. This reduction can reach values above 50% depending on the unit and on the direction a resident would face during the morning. Importantly, the reduction in natural daylight would lead to substantial decreases in the number of days per year in which natural daylight would be sufficient to efficiently stimulate the circadian system, as well as in the number of hours per day that this threshold would be met. As I will discuss below, this reduction of light in the morning hours is particularly detrimental for the human circadian system.

I have a thorough knowledge of how light impacts the circadian system as well as centers that regulate mood and sleep. Nevertheless, I did a literature search on these topics at PubMed

(https://www.ncbi.nlm.nih.gov/pubmed/), the gold standard for biomedical bibliography searches, to assure that I had not missed some of the latest publications. My opinion is based on my expertise in the field and the specific information about light exposure reduction that would result from the construction.

Scientific background

Circadian rhythms and the clocks that control them

Virtually all species on earth show daily rhythms in their biology. These rhythms are tightly synchronized to the solar day to optimize the timing of biological processes. For instance, humans are "diurnal" animals, *i.e.,* they are active during the daytime and sleep during the nighttime. This alternation of sleep and wake, known as the sleep-wake cycle, is an example of a daily rhythm. Daily rhythms are typically not a response to the 24-hour environment — light-dark cycle, social interactions, etc. — that we experience but, instead, they are the output of biological clocks that generate these rhythms. These clocks, known as circadian clocks, have the ability to oscillate autonomously, *i.e.,* they do not need any cyclic environmental signals to continue their "ticking." Circadian clocks oscillate with a period that is close, but not exactly, 24 hours; hence, their name *circa* (close) *dian* (day).

The human biological clock has an average period of 24 hours and 20 minutes. Obviously, if we had no way to reset this clock to the correct time it would be rather useless as a clock; imagine how complicated your life would be if each day you wake up 20 minutes later! However, throughout evolution, circadian clocks have adapted to respond to reliable 24-hour environmental cycles or synchronizers, and to be reset by these daily stimuli. The most reliable of these synchronizers is the natural alternation between daylight and darkness*, i.e.,* the natural light-dark (LD) cycle. As a result, virtually all species on earth, and humans are no exception, use the LD cycle to reset the timing of their circadian clocks.

In humans, the clock gets its LD information through specialized cells located in the retina (Figure 1). However, the retinal cells that convey this information to the clock are not the same cells that we use to form images, see colors or read this text. Instead, a subset of cells is highly specialized to relay light information to the clock and other centers that process "non-image-forming" perception of light. This means that in order to reset our clock by light, we do not need to be aware of this perception. A proof of this is that many blind patients can reset their clocks and synchronize their sleep-wake cycles with the LD cycle despite their inability to consciously perceive the light [1, 2].

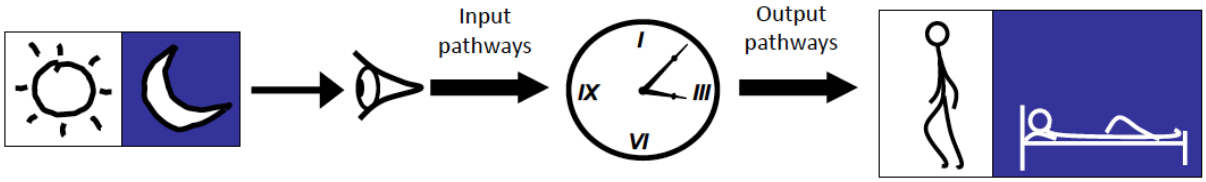

Figure 1. Schematic representation of the simplest circadian system in mammals. A circadian clock oscillates autonomously with a period that is close but not exactly 24 hours. The clock resets its timing to a 24-hour cycle through input pathways that arrive from the retina and convey information about the light-dark cycle. The clock in turn can regulate the timing of physiological and behavioral processes such as the sleep-wake cycle.

Many rhythms, many clocks

The schematic presented in Figure 1 is overly simplistic. In fact, this schematic represented the status of our knowledge of the circadian system until 20 years ago. In the last two decades, however, it has become clear that our body does not have a single circadian clock but instead many of them. How many? Probably as many as we have cells in our body. One may wonder, then, if all these clocks are circa-dian and tick with a period slightly different from 24 hours, how is their timing reset? Do they also

get cues from the LD cycle? In humans, and probably all mammals, the answer is that their timing is reset by internal body signals. These body signals are orchestrated by a “master” clock —like the director of a symphony that sets the timing of each instrument. This master clock is located in the brain and is, in turn, reset by the LD cycle through direct input from the retina (Figure 2).

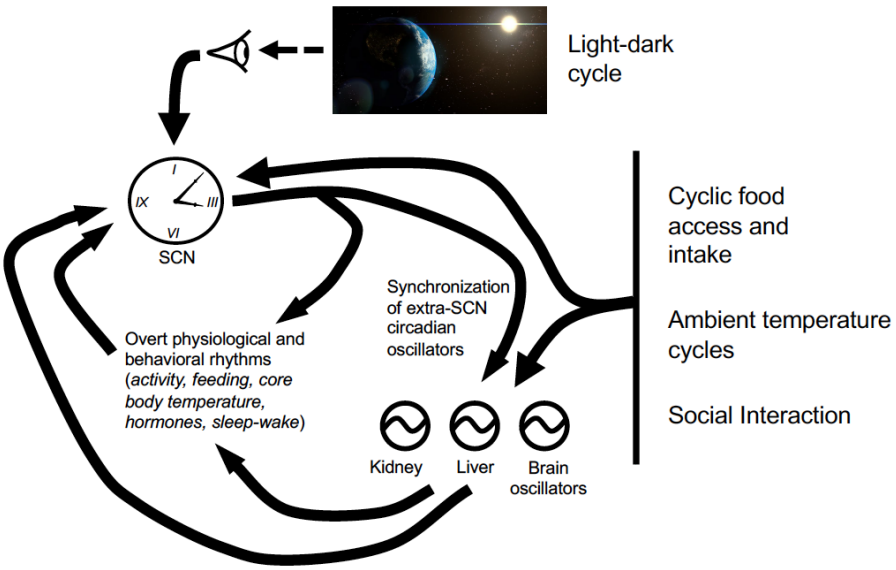

Figure 2. A schematic representation of the current view of the mammalian circadian system. The light-dark cycle resets the master circadian clock (in mammals located in the suprachiasmatic nucleus [SCN]). The master clock in turn resets the timing of clocks throughout the body. The master clock or its subordinate clocks can be also reset by other environmental cues such as cycles in food intake, ambient temperature and social interaction. Circadian rhythms themselves can feed signals back to the master clock.

Thus, our physiology and behavior are temporally organized into 24-hour cycles. This temporal organization is rather pervasive. Practically, all of our hormones are released with a 24-hour rhythmicity; all measurable physiological variables (*e.g.*, blood pressure, temperature, urination, sensitivity to external stimuli) oscillate with a 24-hour period; and — considering our 24-hour sleep-wake cycle — all our behaviors are displayed with a 24-hour periodicity. This rhythmic 24-hour symphony is the result of the carefully orchestrated system of circadian clocks schematized in Figure 2.

Internal synchronization of circadian rhythms

Why do we need a master clock in the brain that coordinates the timing of the remaining clocks in the body? The answer is simple, if we consider that each one of these clocks coordinates a specific function, it is critical that the 24-hour timing of these functions is coordinated in a physiologically meaningful way. For instance, imagine how annoying it would be if your rhythm of urination would be such that you urinated more frequently during the night than during the day, or that your rhythm of alertness would have a peak at 3 am and a trough at 10 am. In this sense, the master clock has a dual job. First, coordinate timing between all its subordinate clocks. Second, to keep that timing in synchrony with the LD cycle (Figure 2). In other words, the exposure to the LD cycle will not only reset the timing of the master clock, but will, in turn, set the tempo of the whole circadian system.

This carefully orchestrated timing can be easily challenged. Most of us have experienced the effects of travelling across time zones. If our 24-hour rhythms were the result of a mere response to the LD cycle, then we should experience no jet-lag; *i.e.,* our body rhythms would immediately adapt to the new time zone. However, because our master clock can only be reset by about one hour per day, it takes us about as many days as hours we want to shift to completely adapt to the new time. This explains why we remain misaligned with the new LD cycle for several days. However, this does not explain why most of us feel pretty miserable while we are experiencing jet-lag. The reason is that on top of the misalignment with the external environment, we also experience an internal misalignment (also known as internal desynchronization or internal desynchrony). In other words, for several days, the clocks within our body will be out of synchrony with each other. The reason for this internal misalignment is that the speed at which different clocks readapt to the new time zone is different, and while after a trip

to Europe our master clock may have reached European time, your liver and gut clocks may still be in Seattle time. This internal misalignment or desynchrony is not only responsible for the malaise we feel during jet-lag but, if experienced repeatedly, it will lead to long-term adverse health effects (see below).

Importantly, other cycles, such as the time at which we eat or socialize can also act as synchronizers that reset both the master and the subordinate clocks (Figure 2). These stimuli, if mistimed, can also cause circadian internal misalignment. Indeed, our modern society challenges our circadian system continuously. On one end of the spectrum, nocturnal work schedules result in severe circadian misalignment. On the other end of the spectrum, even people not working at night typically experience internal misalignment of their circadian rhythms. This is, in part, because we tend to live in indoor environments that both deprive us of exposure to the bright natural daylight, and because these indoor environments are lit during the evening, exposing us to light at a time when it would be dark under natural conditions. Staying up late exposes us not only to out-of-time light, but also to out-of-time stimuli —such as a midnight snack — that further challenges our internal synchronization.

Lack of exposure to natural daylight and its health consequences

The effect of reduced synchronizer strength

Indoor light differs from natural daylight not only in its intensity — being up to 100 times lower intensity than natural light — but also in its quality, having different wavelengths than natural light. As a consequence, reduced exposure to natural daylight has two adverse effects on the regulation of our circadian rhythms that result from reduced strength of the LD cycle as a synchronizer.

First, there is a reduction of the strength of the LD cycle as a synchronizer, which reduces the overall ability of the LD cycle to reset our master circadian clock daily. As pointed out above, our clock has a period that is longer than 24 hours. Consequently, a reduction in the synchronizer strength will make it easier for our clock to drift into later and later times, making it harder to fall asleep at night and wake up in the morning. Importantly, the effect of light in resetting our clock depends on the time at which the light stimulates the clock. Whereas light during the evening delays our clock, light during the morning advances it [3, 4]. Thus, if we miss our morning opportunity to get exposed to light, our clock will default to its natural longer period, which will be further aggravated by exposure to the delaying effects of evening light. The reduced synchronizer strength effect is further complicated by the fact that reduced exposure to bright natural light deprives us of a very arousing stimulus that maintains higher levels of alertness and activity during the daytime, and that improves sleep during the nighttime. This is particularly problematic in older adults, whose master biological clock tends to have a lower ability to drive strong circadian rhythms and whose sensitivity to light is lower [5-8] — most of us are aware of how the elderly doze off during the daytime and wake up frequently during the nighttime. A lack of natural daylight exposure in older adults, who may not have a scheduled daily activity, prevents the stimulatory effects of light, leading to less activity during the day and poorer sleep during the night. A poorly regulated sleep-wake cycle, in turn, aggravates the effects of aging on health. According to data provided by the Escala Concierge, over 60% of east-facing Escala units have a resident over 50 years old; on the fifth floor, 75% are over 50. Furthermore, many of these older adults stay in their residencies for much of the day, relying on their windows to provide their daily exposure to natural daylight.

Second, experiments have shown that a lack of exposure to bright light during the daytime makes our clocks more sensitive to the resetting effects of light [9-11]. Light during the evening, when we typically increase our exposure to artificial light, will cause even bigger delays in our light-hypersensitive clock. Thus, if we expose ourselves to light in the evening, we will not only be self-stimulating and inhibiting sleep-inducing signals in our brain, but we will also set our clock to a later time, making the whole problem worse the next day.

Together, this means that a human circadian system with decreased exposure to bright light during the daytime will lead to circadian rhythms that will be weaker and will have a delayed timing. Because

regardless of the internal timing of our circadian system, we still typically set our alarm clocks to wake up at sunrise, the delayed timing of the circadian system puts many of our physiological rhythms at odds with our sleep-wake cycle. This leads to a common pathology known as delayed sleep disorder, which results from the discrepancy between our biological clock's time and our social time, and represents a chronic state of circadian internal misalignment [12]. This pathology is typically more severe at high latitudes during the winter months when the photoperiod is short; under these conditions we may not get enough exposure to natural daylight during the morning and we rely more on artificial evening light.

Long-term exposure to this misalignment, as it is typical in shift workers, is associated with higher incidence of cancer, cardiovascular disease, metabolic disorders such obesity and type-II diabetes, and mental disease [13, 14]. Importantly, misalignment that does not result from shift work is also associated with similar disease outcomes. Indeed, recent studies suggest that the delayed phase that results from a lack of exposure to morning light, which is particularly prevalent on the west sides of time zones (as it is the case of Seattle) is linked to higher incidence of cancer, metabolic disorders and depression, and these effects are likely stronger for people who have a tendency to later sleep times [13-19]. Importantly, this misalignment is particularly pervasive when we live in time zones that are not aligned with the local solar time and under DST, when our social time is artificially set to a time zone that is located 1 hour east of us. Of note, the Washington State legislature has proposed to move to a permanent DST, which will increase the misalignment between solar and social time during the winter [19, 20]. Although human epidemiological studies do not show causality, several animal studies have demonstrated that the chronic internal misalignment of the circadian system leads to several disease outcomes and even shorter life span [21-28].

The effect of reduced light exposure on mood

Another major consequence of reduced exposure to natural daylight are mood disorders. Until recently, it was believed that the main affective disorder triggered by abnormal exposure to light was winter depression (also known as seasonal affective disorder). This type of depression is highly prevalent at high latitudes like in Seattle, where during the winter the photoperiod is significantly reduced. Indeed, bright light is recommended during the early morning to treat winter depression. The rationale for this timing is that whereas light in the evening delays the timing of the circadian clock, light during the early morning advances it. Thus, a Seattleite during the winter will likely have a delayed circadian system, and light during the early morning will advance her/his clock and improve mood. The effectiveness of light therapy to treat winter depression, as well as the fact that most depressed patients experiencing any type of depression suffer circadian internal misalignment has been considered strong evidence that the internal misalignment of circadian rhythms contributes to the development of depressive symptoms [29, 30].

Importantly, although artificial light therapy is recommended to patients with winter depression, compliance with this treatment is difficult and this type of light therapy is not effective for every patient, a proof of which is that at higher latitudes such as Seattle's up to 10% of residents suffers this mental disorder [31, 32]. The relationship between the reduced photoperiod and depression could be confounded by the fact that other factors other than light change seasonally — social life, weather, physical activity, etc. However, experiments in animal models have established that lack of light, and specifically short photoperiod, can trigger symptoms of depression [33-37].

Whereas the experimental evidence that linked the lack of light exposure to mood disorders until recently pointed to the circadian system as the conduit for the effects of light on mood, recent evidence has demonstrated that light therapy is beneficial for depression in general, not just depression linked to shorter photoperiod in the winter [38]. Furthermore, animal studies have shown that information about the LD cycle can reach mood centers in the brain directly. The non-image-forming photoreceptive cells in the retina that were mentioned above reach not only the master circadian clock but also other centers.

Unusual LD cycles that cause depression, for instance, do this through newly discovered pathways that do not involve the circadian clock [39, 40].

In summary, the beneficial effects of natural daylight on mood and the depressive effects of underexposure to light likely involve not only the circadian system, but also other brain regions that receive light input and directly regulate mood.

It is important to highlight that sleep disruption that may result from decreased exposure to bright natural light — fragmented sleep, increased sleepiness during the day — can itself cause negative mood outcomes such as increased anxiety and depression. Furthermore, chronic poor sleep can lead to a myriad of adverse health outcomes including reduced immune function, impaired cognitive performance, and higher propensity to develop cardiovascular, cerebrovascular and neurodegenerative disease, to name a few [41].

Conclusions regarding the proposal's impacts on Escala residents and what is the basis for those conclusions.

My review of the literature as well as my expertise in the field of the circadian rhythms and sleep leads me to conclude that the substantial reduction in natural daylight exposure that the east-facing apartments at The Escala will experience if the Douglaston Tower is built will likely lead to adverse physical and mental health outcomes in their residents. Adverse physical health outcomes could include cardiovascular disease, metabolic disorders such as increased weight gain and type II diabetes, even a higher propensity to develop specific cancers. Adverse mental health outcomes could include different forms of depression, including winter depression.

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