NTP
National Toxicology Program

Evidence Integration

Ruth Lunn, DrPH
Office of the Report on Carcinogens (RoC)
National Institute of Environmental Health Sciences

Draft RoC Monograph on Night Shift Work and Light at Night
Peer Review Meeting
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Outline

Objective and Approach

Night Shift Work

- Evidence integration
- Definition
- Preliminary listing recommendation

LAN

- Evidence integration
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Objective and Approach

- Night shift work
- LAN

- Integrate the evidence from Sections 1 to 6 and reach a preliminary listing recommendation for night shift work and for exposure to LAN for the RoC
- Adequately define these two exposure scenarios as they relate to cancer.

Approach

Detailed analysis of data for specific evidence stream: examples

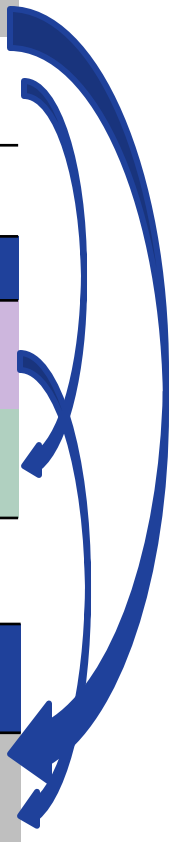
Exposure	Outcome	Type of studies	Strengths & Limitations	Assessment
NSW	Breast cancer	Human epidemiological		
NSW	Melatonin	Human cross-sectional		

Mechanistic related data

Exposure	Outcome	Evidence stream	Confidence	Assessment
Melatonin	Breast cancer	Human & animal Epidemiology & experimental		
Clock gene desynchrony	Cancer	Same as above		

Overall evaluation

Exposure	Outcome	Evidence stream	Confidence of the evidence	Overall evaluation
NSW	Breast cancer	Human & animal Mechanistic & cancer		
LAN	Breast cancer	Same as above		



LAN = light at night, NSW = night shift work

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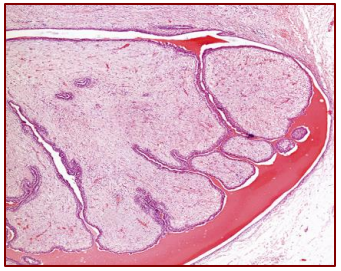
Night shift work increases female breast cancer risk

Exposure → Strong but not sufficient → **Breast Cancer**



Database	Strengths	Limitations
21 studies 1 pooled analysis	Adequate database Consistency across studies Persistent night shift work: frequent and long-term, especially starting in young adulthood Risk unlikely explained by lifestyle confounders	Unable to evaluate circadian disruption per se or specific exposure Evidence: case-control studies and 2 informative cohort studies Most potential biases towards null

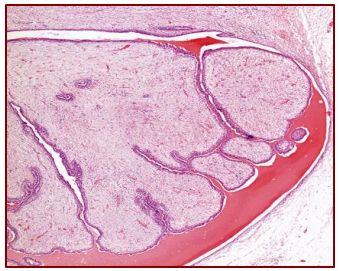
Night Shift Work

Shift work promotes mammary tumor growth in rodents

Exposure

↓ mammary gland tumor latency & ↑ multiplicity

Breast Cancer



Database	Strengths	Limitations
2 studies	Shift work or CJL promotes tumor growth Measured circadian clock genes	Cancer susceptible models or co-exposure models Melatonin deficient mice

CJL = chronic jet lag
SW = shift work

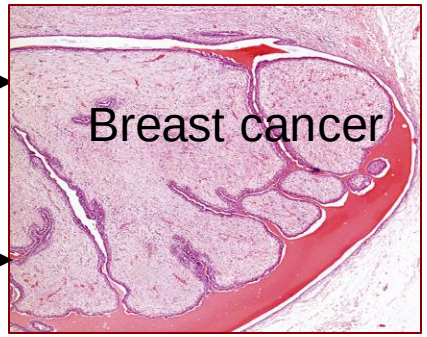
Risk patterns in humans consistent with mechanistic or animal data

Greater risk in humans with recency of exposure and receptor positive cancers

Epidemiology studies

↓ mammary gland tumor latency & ↑ multiplicity

Strong but not sufficient



CJL = chronic jet lag
SW = shift work

Night Shift Work

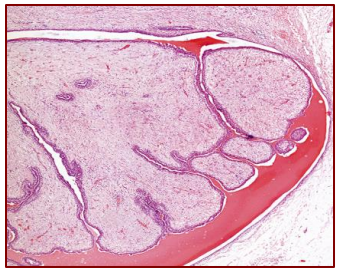
Induces melatonin suppression which promotes cancer growth

Exposure | **Circadian Disruption** | **Biological Effects** | **Breast Cancer**

Epidemiology studies

Low NMT

MT: *In vivo* and *in vitro* studies: Inhibition of oncostatic pathways



↓ tumor growth

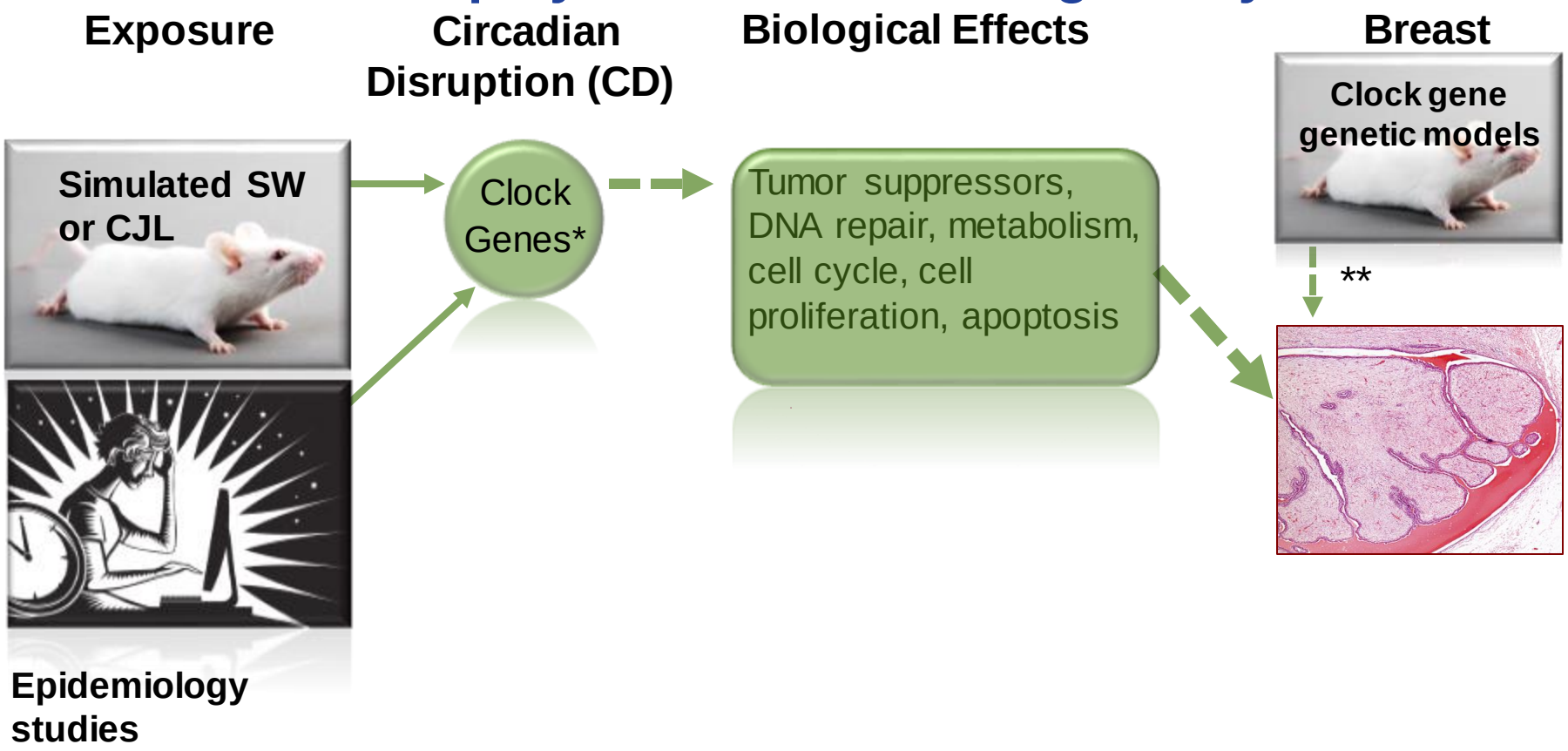
↑ cancer risk

Humans: Low NMT levels

CJL = chronic jet lag; MT = melatonin; NMT = nocturnal melatonin; SW = shift work

Night Shift Work

Induces CD which plays a role in carcinogenicity



CJL = chronic jet lag; SW = shift work

* Altered clock gene expression

* * Cancer not specific for breast cancer

Night Shift Work

Induces biological effects typical of recognized carcinogens

Exposure

Circadian Disruption

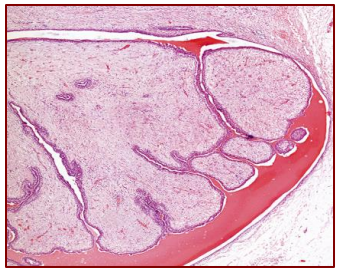
Biological Effects

Breast Cancer

Epidemiology studies

↓DNA repair/↑damage
↑Oxidative stress*
↑Inflammation or altered immune*

Epigenetic changes
↑Estrogen levels**

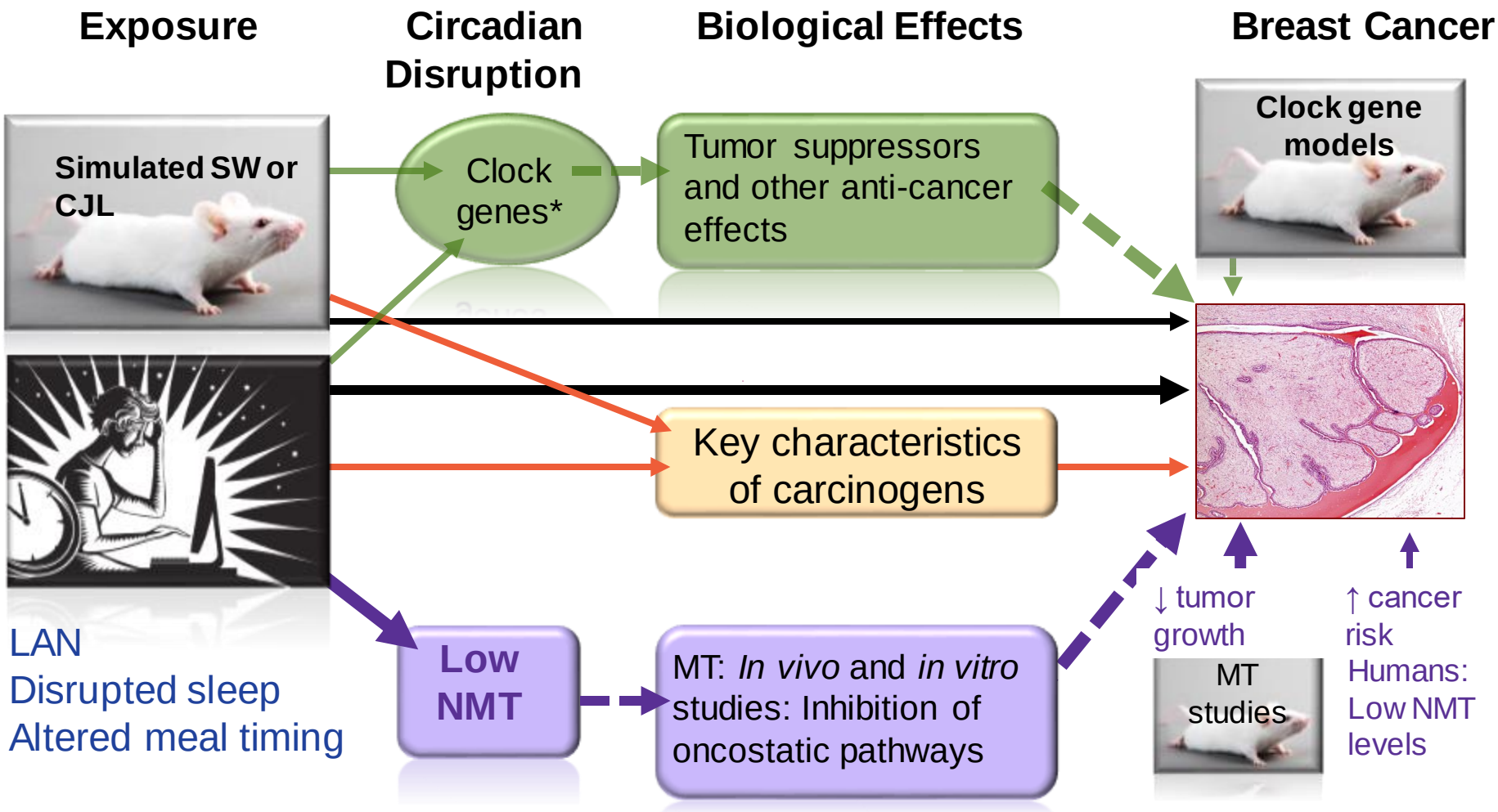


Biological effects observed in cancer animal studies of shift work (*) or LAN (**)

CJL = chronic jet lag
SW = shift work

Night Shift Work

Strong human and mechanistic evidence



CJL = chronic jet lag; NMT = nocturnal melatonin; MT = melatonin; SW = shift work;
* Altered clock gene expression

Night shift work is associated with increased risk of prostate cancer

Evidence stream	Cancer	Findings	Conclusion
Human	Prostate	Consistent findings Less robust than breast cancer	Limited
Human	Colorectal Female hormonal Lung	Inconsistent Few studies or few informative studies	Inadequate
Animal	Multiple	Growth or promotion of implanted tumors or tumors induced by co-exposures to chemical carcinogens	Convincing

Persistent Night Shift Work

Definition of exposure

- *Persistent* defined as frequent and long-term night shift work, especially beginning at an early age
- In general female night shift workers at elevated risk for breast cancer
  - Started working before age 30
  - Worked at least 3 times/week for at least 10 years
  - However, the exact conditions may vary
- Night shift work
  - At least 3 hours between midnight and 5 AM
  - Includes exposure to LAN, disrupted sleep, altered meal timing and other behavioral changes

RoC Listing Criteria: Two Categories

Known to be a human carcinogen

- Sufficient evidence of carcinogenicity from studies in humans

Reasonably anticipated to be a human carcinogen

- Limited evidence from studies in humans
  OR
- Sufficient evidence from studies in experimental animals
  OR
- Belongs to well-defined structurally related class of substances listed in the RoC or demonstrates convincing mechanistic evidence

Conclusions based on scientific judgment considering all relevant information such as chemical structure, metabolism, pharmacokinetics, genetic effects, and mechanisms of action.

Page viii, https://ntp.niehs.nih.gov/go/rocprocess

RoC Listing Criteria

Reach level of evidence conclusion for carcinogenicity from studies in humans*

Sufficient evidence

- Causal relationship between exposure to the agent, substance, or mixture, and human cancer

Limited evidence

- Causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Preliminary Listing Recommendation

Persistent night shift work that causes circadian disruption

Known to be a human carcinogen based on sufficient evidence from studies in humans

- Collective body of evidence from cancer epidemiological studies and mechanistic studies in humans and in experimental animals
- Human epidemiological studies provide evidence that persistent night shift is associated with an increase in female breast cancer risk
- Animal and in vitro mechanistic studies provide evidence that circadian disruption plays a role in the cancer pathway
- Human mechanistic studies provide evidence that night shift work is associated with circadian disruption and similar biological effects as that observed in animal cancer models

Limited evidence that night shift work is associated with an increased risk of prostate cancer

Clarification questions?

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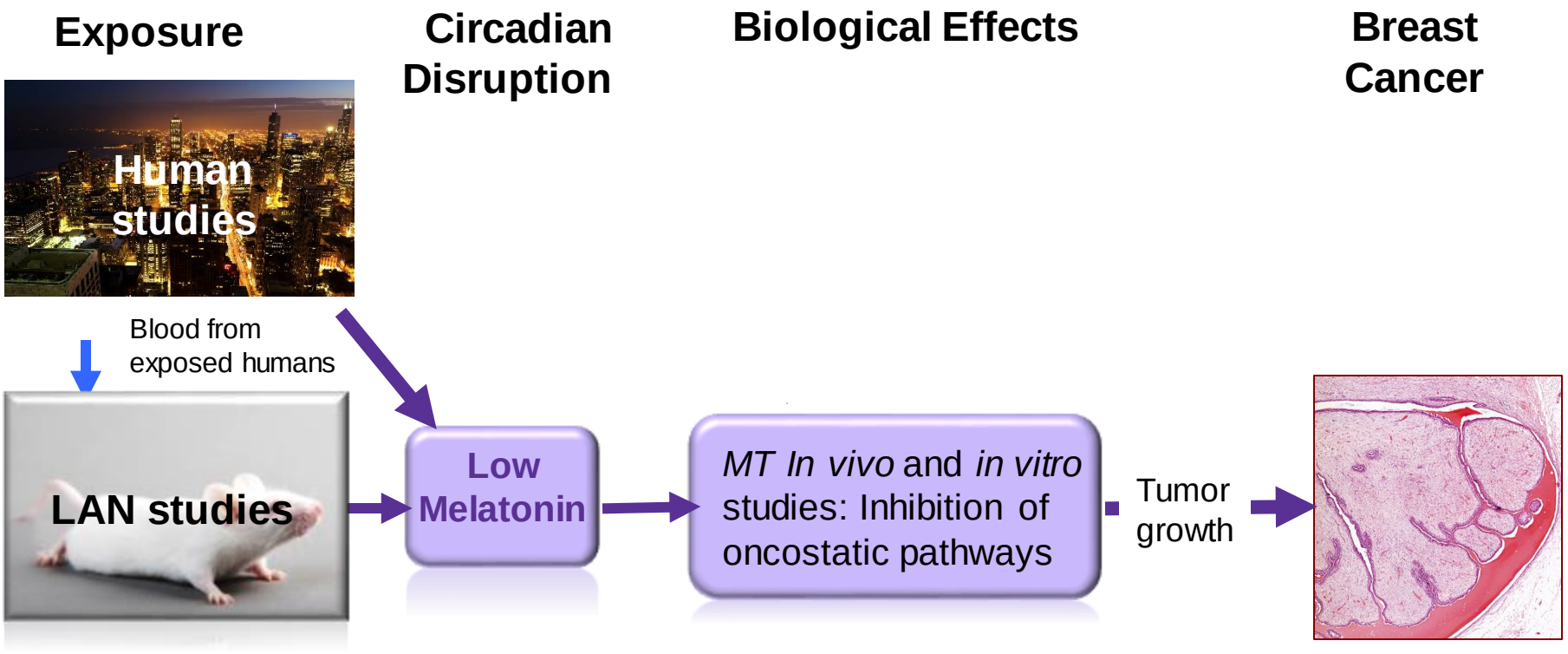
Strong evidence melatonin plays a role in LAN carcinogenicity



Database	Strengths	Limitations
Light proxies Spontaneous tumors, co-exposures, implants	Consistent evidence Human implants	Animals more sensitive than humans Evidence limited to promotion or growth

May increase risk of female breast cancer

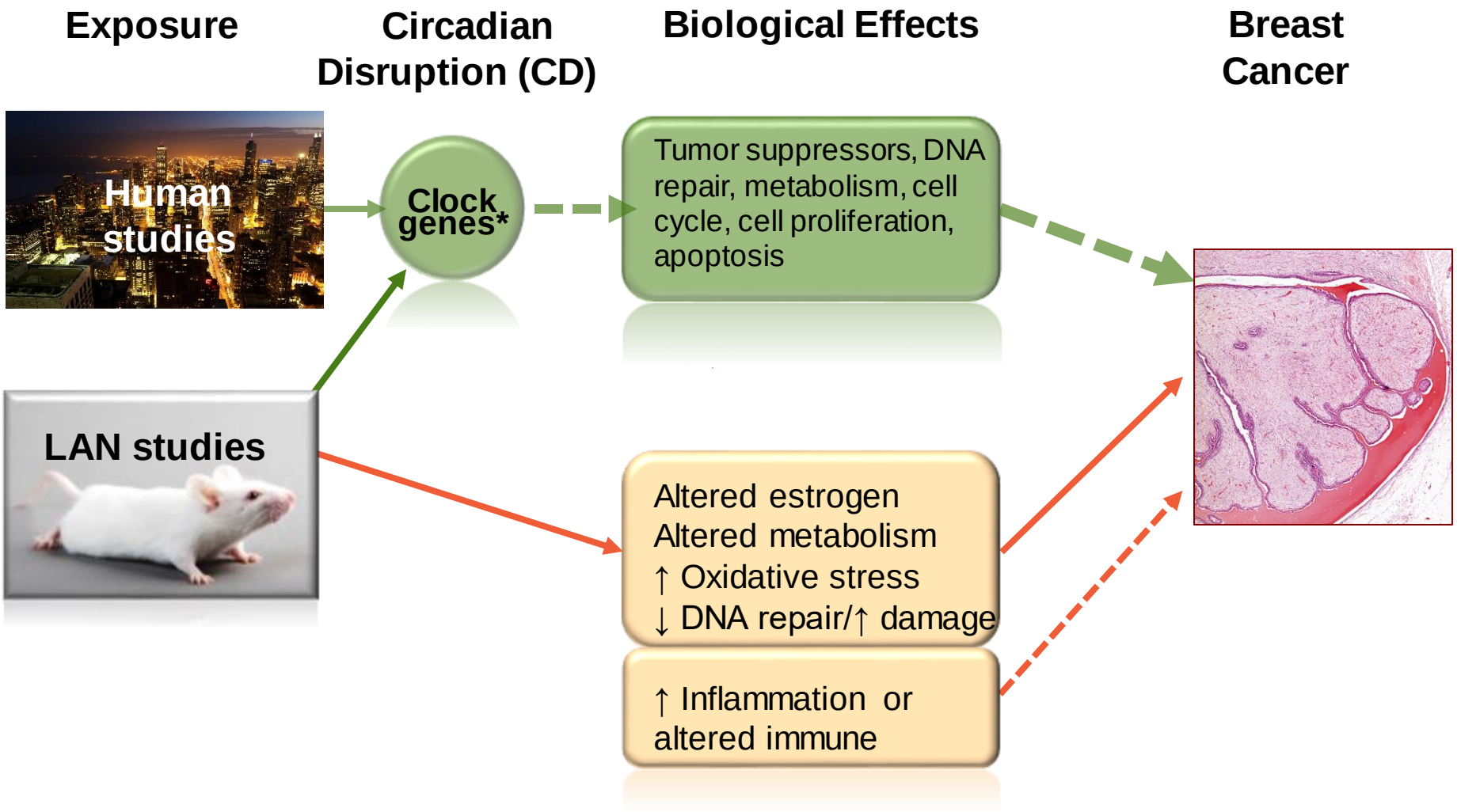
Exposure

Limited evidence
Outdoor

Breast Cancer

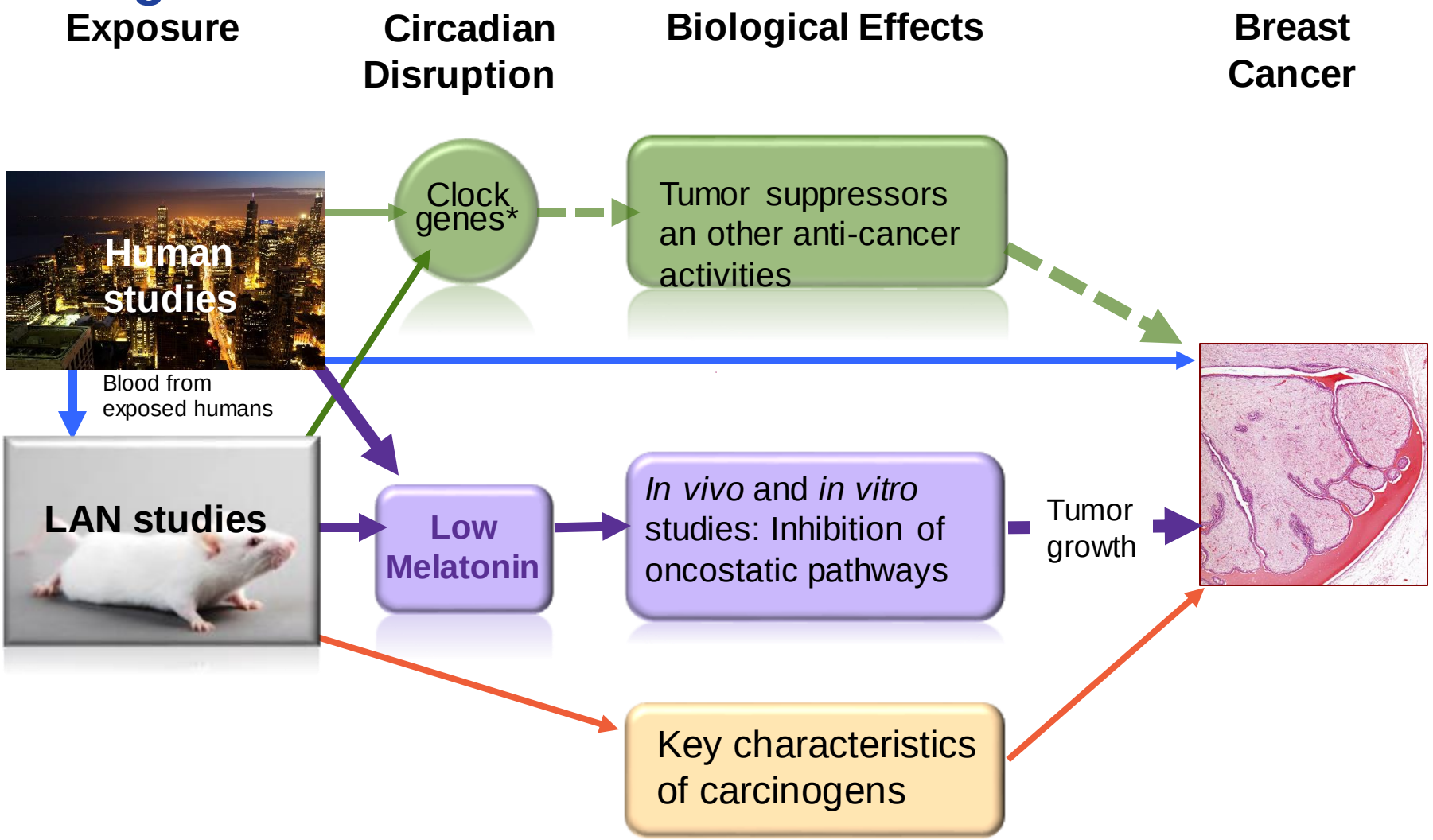
Exposure	Database	Strengths	Limitations
Outdoor LAN	4 studies measured light using satellite 1 study living near strong artificial LAN	Consistent evidence Exposure response 1 case-control study and 1 ecological study specific for blue light	Unclear if satellite is measuring circadian light or is a proxy for other activities
LAN in sleeping area	10 studies	-	Inconsistent findings Exposure metrics varied Self-reported for subjective metrics

Causes CD and effects typical of carcinogens



* Altered clock gene expression

Strong mechanistic evidence



Certain Lighting Conditions

Definition of exposure

- Excessive LAN: Characteristics most likely to cause circadian disruption
  - Shorter wavelength (e.g., blue light)
  - Longer duration
  - Timing: exposure to electric light during the biological night,
  - Higher light intensity or levels
- Insufficient daylight exposure
  - Experimental animal studies
    - Blue light exposure during the day positively affected the circadian regulation and decreased the growth of implanted prostate and liver tumors
  - Humans
    - Night time sensitivity to LAN influence by exposure to light during the day

Preliminary Listing Recommendation

Certain lighting conditions that cause circadian disruption

*Reasonably anticipated to be a human carcin*ogen

- Strong evidence that LAN acts through mechanisms that are likely to cause cancer in humans
  - Toxicological and mechanistic data indicate that exposure to LAN causes melatonin suppression and other types of circadian disruption, which lead to the proliferation and growth of breast or mammary-gland cancer in experimental animals
  - LAN causes biological effects that are characteristics of recognized carcinogens
- LAN causes melatonin suppression and may increase breast cancer risk in humans (i.e., limited evidence of carcinogenicity from epidemiological studies)

Clarification questions?