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Contractor supporting the Office of the Report on Carcinogens (RoC)

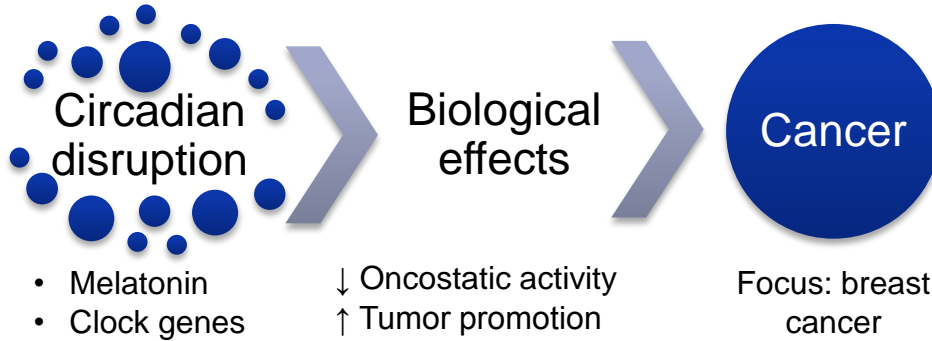
Draft RoC Monograph on Night Shift Work and Light at Night

Peer Review Meeting

5 October 2018



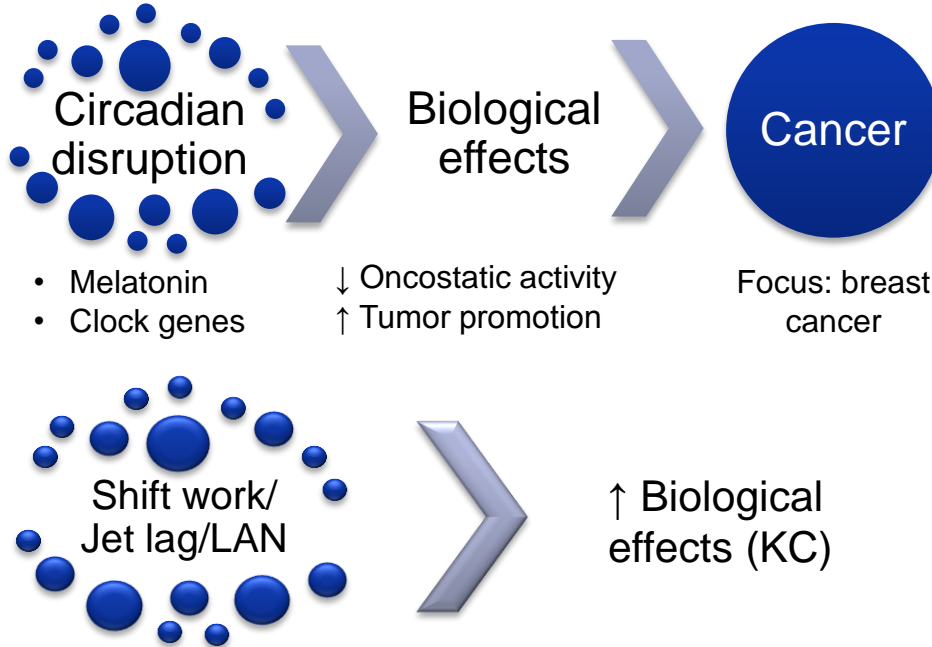
Shift work/LAN, circadian disruption and cancer



6.2: Melatonin & Clock genes



Shift work/LAN, circadian disruption and cancer



6.2: Melatonin & Clock genes

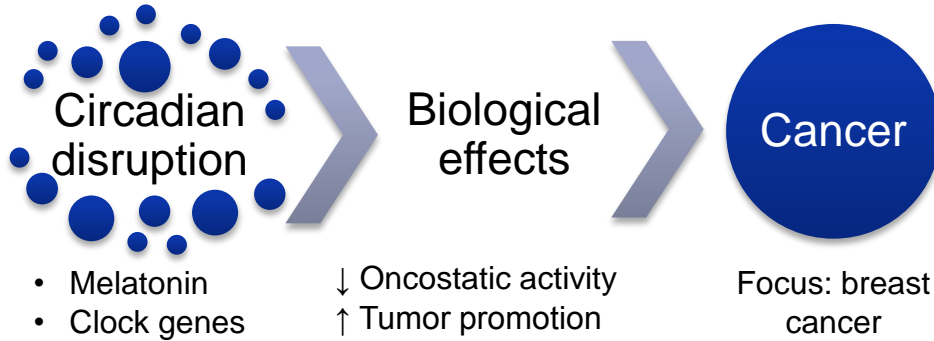
6.3: LAN-related exposures and key events related to cancer

LAN = light at night

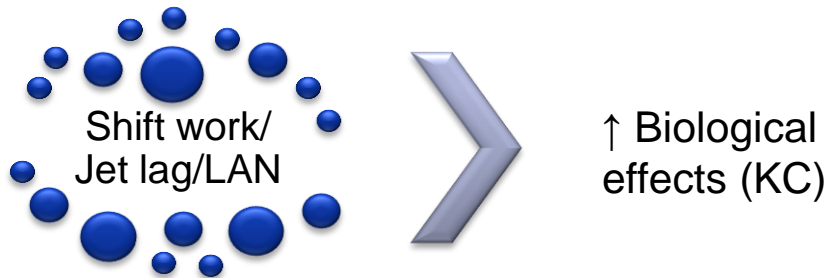
KC = key characteristics of carcinogens



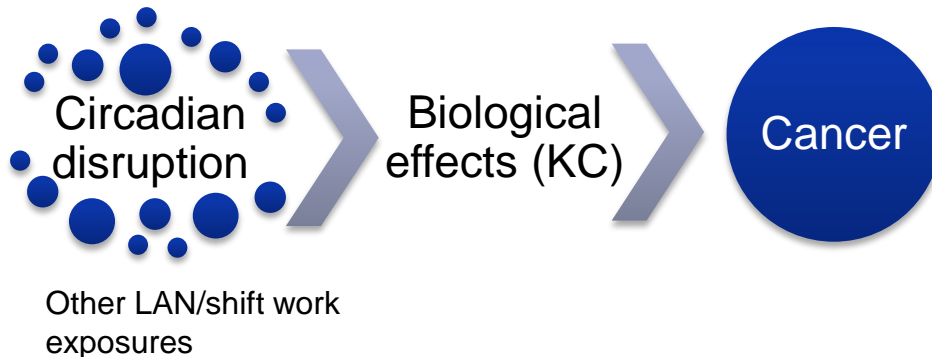
Shift work/LAN, circadian disruption and cancer



6.2: Melatonin & Clock genes



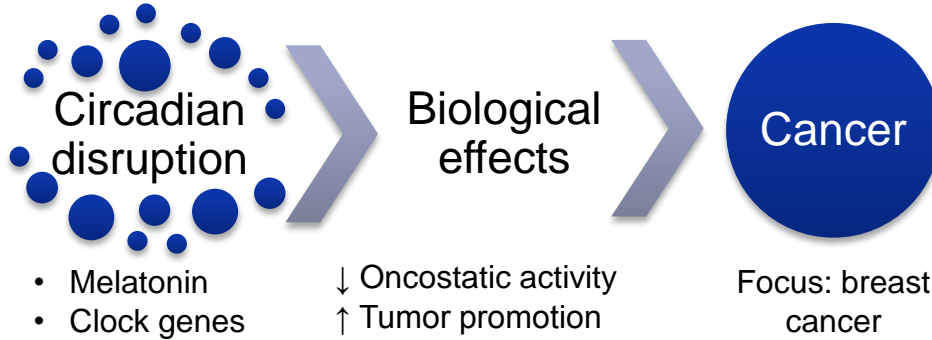
6.3: LAN-related exposures and key events related to cancer



6.4: Other mechanisms (vitamin D, sleep, meal timing)



Shift work/LAN, circadian disruption and cancer



6.2: Melatonin & Clock genes



Is LAN a possible risk factor for breast cancer?

- Breast cancer risk has \uparrow as societies industrialize
- LAN has also \uparrow as societies industrialize
- Known risk factors account for $<50\%$ of cases
- LAN \downarrow nocturnal melatonin production
- Melatonin inhibits breast tumor growth
- Proposed mechanism (melatonin hypothesis)

LAN \rightarrow \downarrow nocturnal melatonin production \rightarrow \uparrow estrogen \rightarrow \uparrow turnover epithelial stem cells \rightarrow \uparrow breast cancer risk



Types of evidence to evaluate the melatonin hypothesis

- Human cancer studies of night shift work (Section 3)
 - Originally thought to be a surrogate for extreme LAN
- Human cancer studies of LAN exposures (Section 3)
- Human studies of melatonin (or proxies) and cancer risk
 - Cohort studies of shift workers
 - Visually impaired/blind populations
- Experimental studies of melatonin and cancer growth
- Mechanistic studies of melatonin



Human studies: melatonin and cancer risk

- Shift workers
 - Some evidence of inverse association with breast cancer
 - Stronger evidence in post-menopausal women (2 independent cohorts)
 - Limited number of studies, inconsistencies



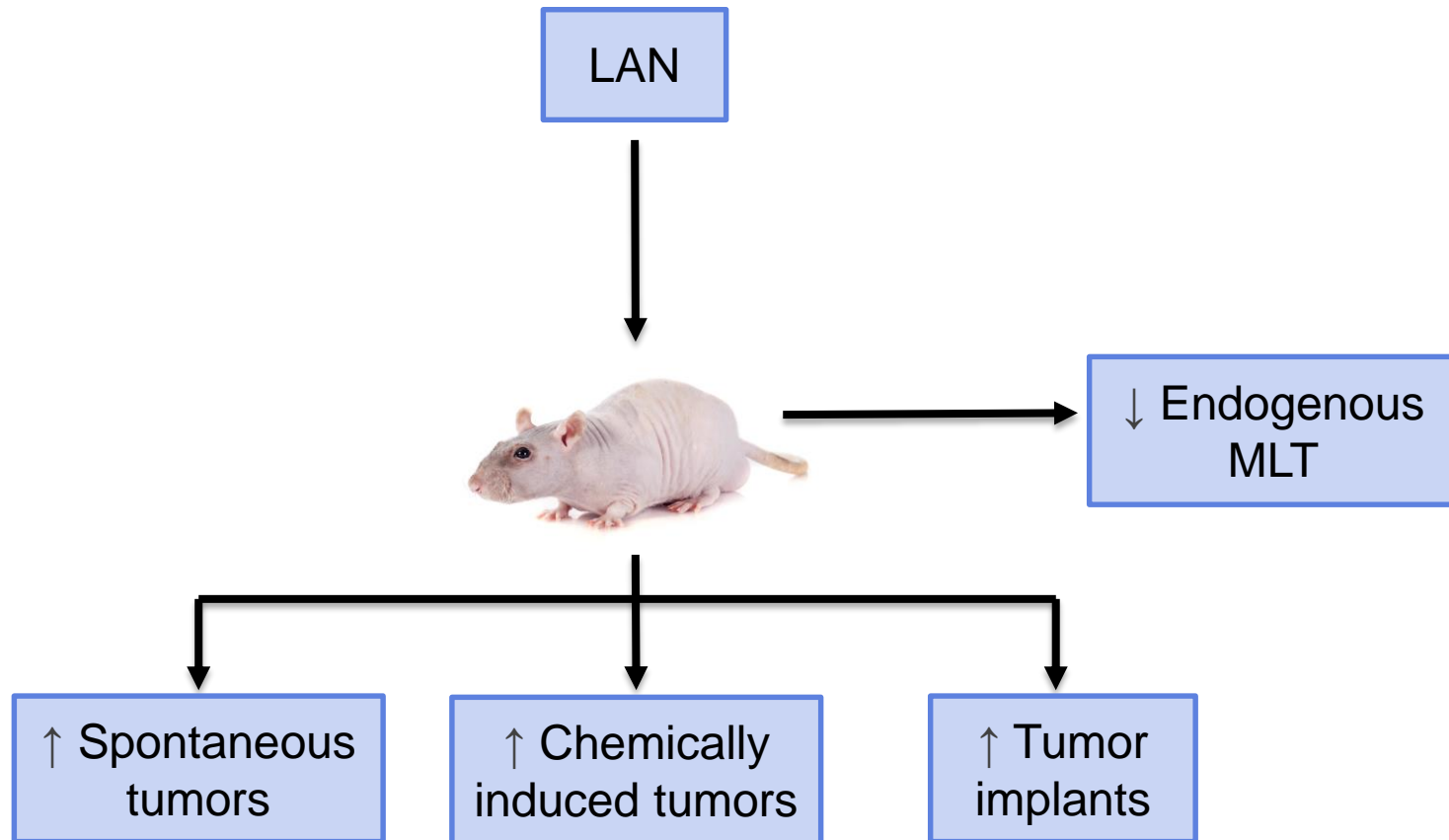
Human studies: melatonin and cancer risk

- Shift workers
 - Some evidence of inverse association with breast cancer
 - Stronger evidence in post-menopausal women (2 independent cohorts)
 - Limited number of studies, inconsistencies
- **Totally blind/visually impaired**
 - Melatonin is not suppressed by LAN in totally blind people
 - Melatonin rhythms: free running/abnormally entrained
 - Breast cancer: Inverse association with blindness and degree of visual impairment (6 studies)
 - Prostate cancer: lower risk (non-significant) (2 studies)



LAN, Melatonin and Cancer in Rodents

LAN suppresses melatonin and promotes tumor growth

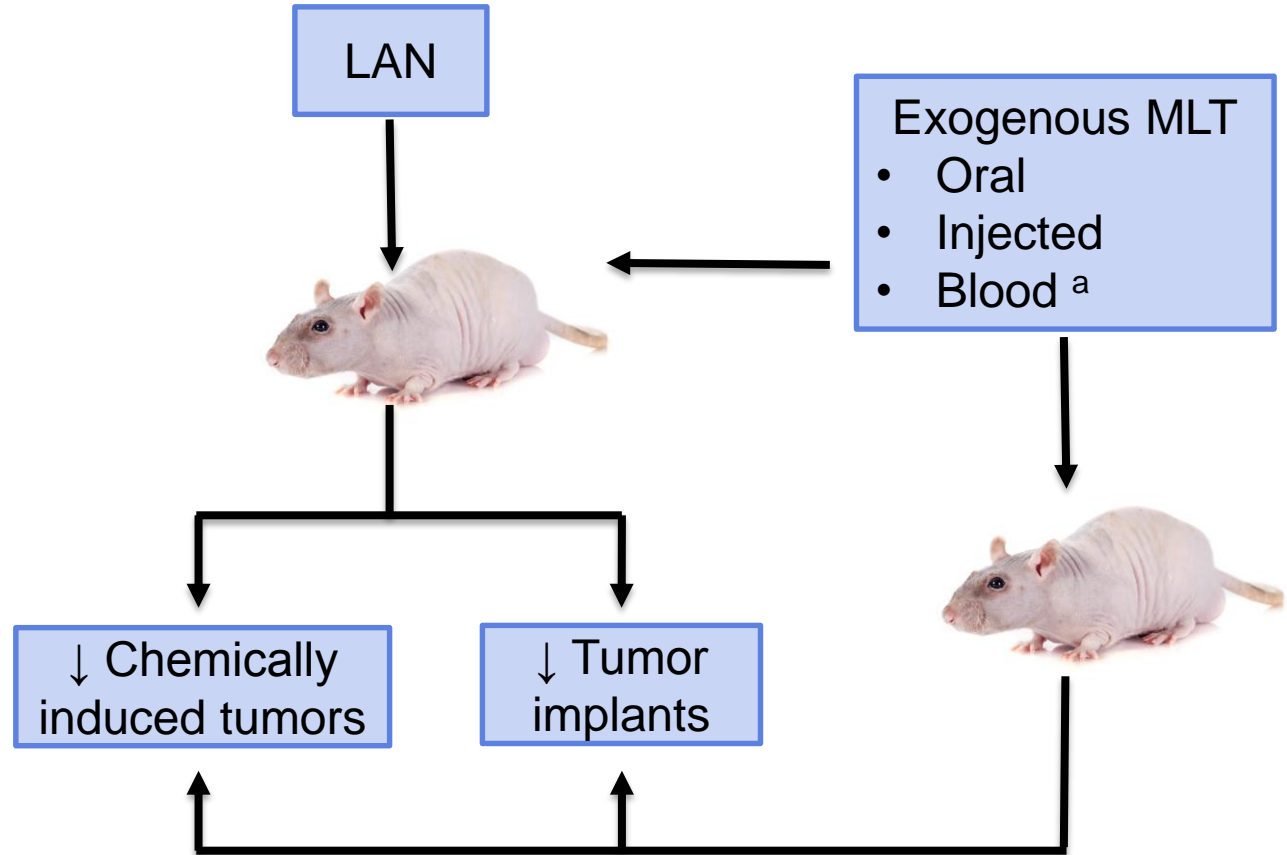


MLT = melatonin



LAN, Melatonin and Cancer in Rodents

Exogenous melatonin suppresses tumor growth



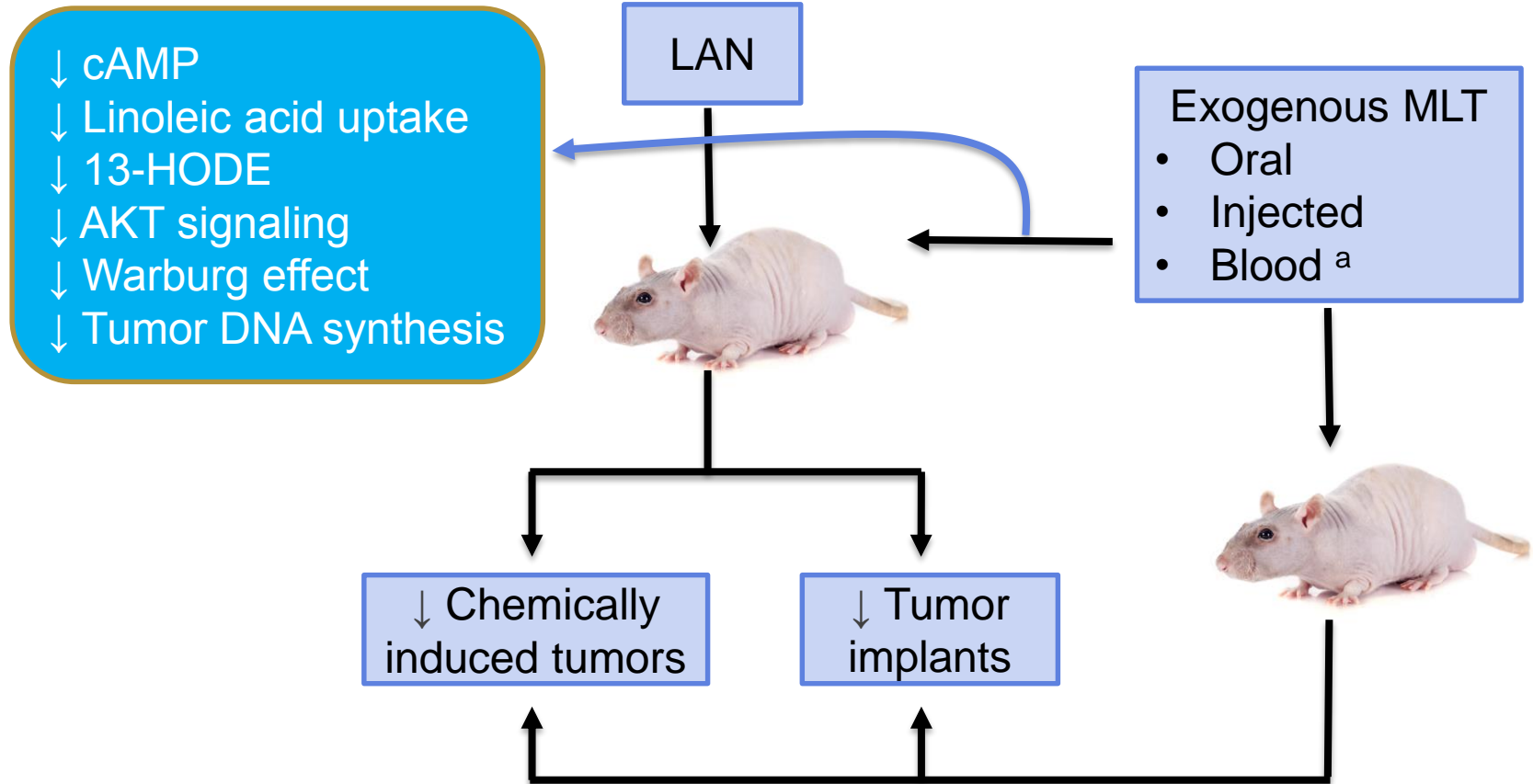
MLT = melatonin

a = Blood collected from humans at night (no LAN) or synthetic MLT added to rat blood



LAN, Melatonin and Cancer in Rodents

Exogenous melatonin suppresses tumor growth



cAMP= cyclic adenosine monophosphate

13-HODE= 13-hydroxyoctadecadienoic acid

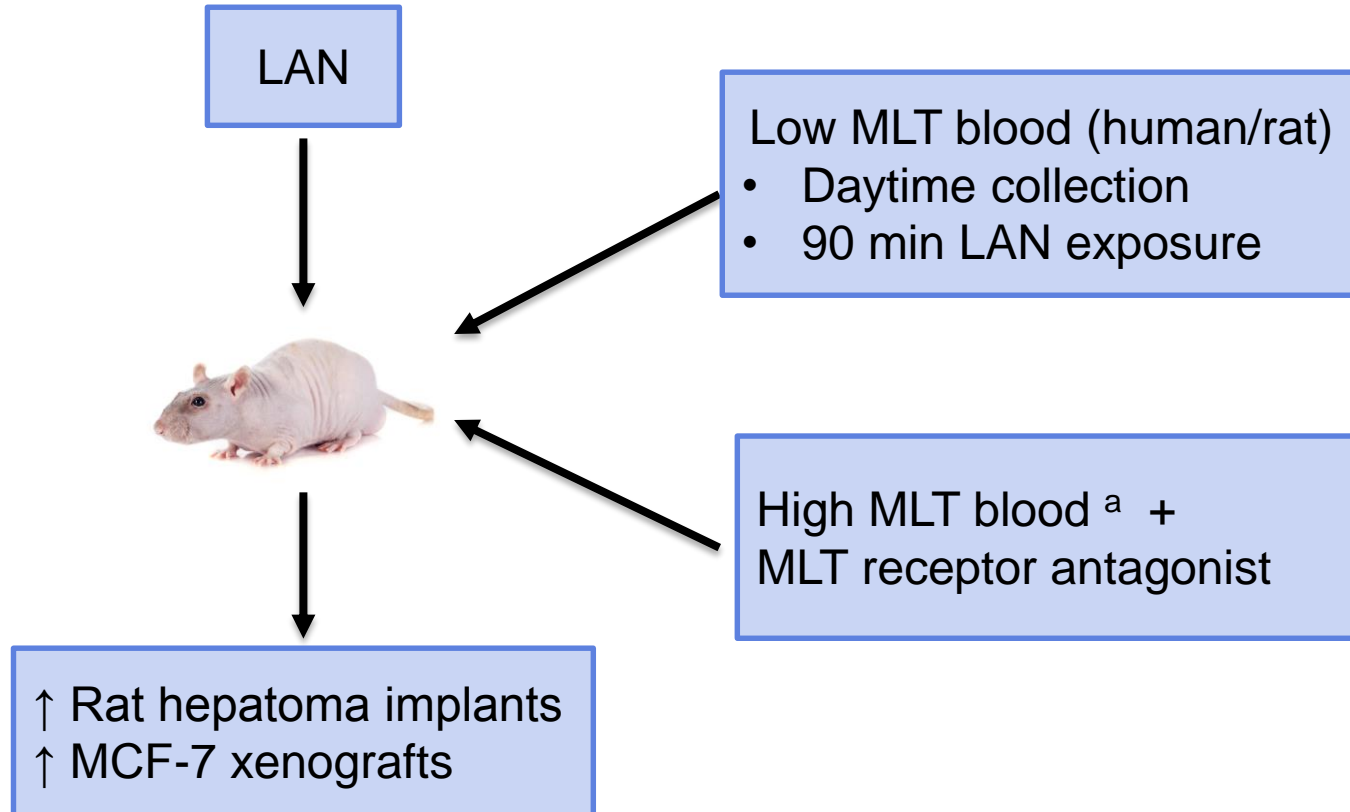
MLT = melatonin

^a = Blood collected from humans at night (no LAN) or synthetic MLT added to rat blood



LAN, Melatonin and Cancer in Rodents

Low MLT blood or high MLT blood + MLT receptor antagonist do not suppress tumor growth



MLT= melatonin

a = Blood collected from humans at night (no LAN) or synthetic MLT added to rat blood



Melatonin is oncostatic via multiple pathways

Mechanism/Pathway	Key events and effects
Estrogen receptor & enzyme modulator	↓ Estrogen receptor (ER α) activation & expression ↓ Estradiol
Antioxidant, oxidative stress response	↓ ROS, NOS ↑ GSH, SOD, catalase
Immune activation	↑ NK cells, leukocytes, monocytes, cytokines, IFN- γ , TNF α ↑ Immunosurveillance
Cell cycle, differentiation & apoptosis	↑ G1, cell cycle length, p53, p21, caspases, differentiation, apoptosis ↓ Cyclin D1, cell proliferation
Telomerase inhibition	↓ hTERT, estradiol-induced telomerase activity ↓ Number of neoplastic cell replication cycles
Angiogenesis inhibition	↓ VEGF, HIF-1 α , ROS, neovascularization
Metastasis inhibition	↓ response to estradiol, cell invasiveness/metastasis ↑ E-cadherin, β_1 -integrin, MT1 receptor
Fatty acid uptake and metabolism	↓ Linoleic acid uptake, 13-HODE ↓ EGFR/MAPK activity



LAN/Shift work effects > melatonin suppression

- Core clock genes
 - Control expression of 2% -10% of the genome
 - Mutations/deregulated expression common in cancers
 - SNPs: increased risk of breast and other cancers

SNPs = single nucleotide polymorphisms



LAN/Shift work effects > melatonin suppression

- Core clock genes
 - Control expression of 2% -10% of the genome
 - Mutations/deregulated expression common in cancers
 - SNPs: increased risk of breast and other cancers
- Desynchronizes central clock/SNS/peripheral clock
 - Disrupted cell signaling pathways and regulatory circuits
 - Loss of cell cycle control and altered metabolism
 - ↑ Cell proliferation and ↓ apoptosis
 - ↓ Tumor suppression and DNA repair

SNS = sympathetic nervous system



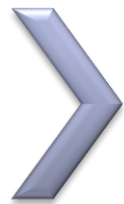
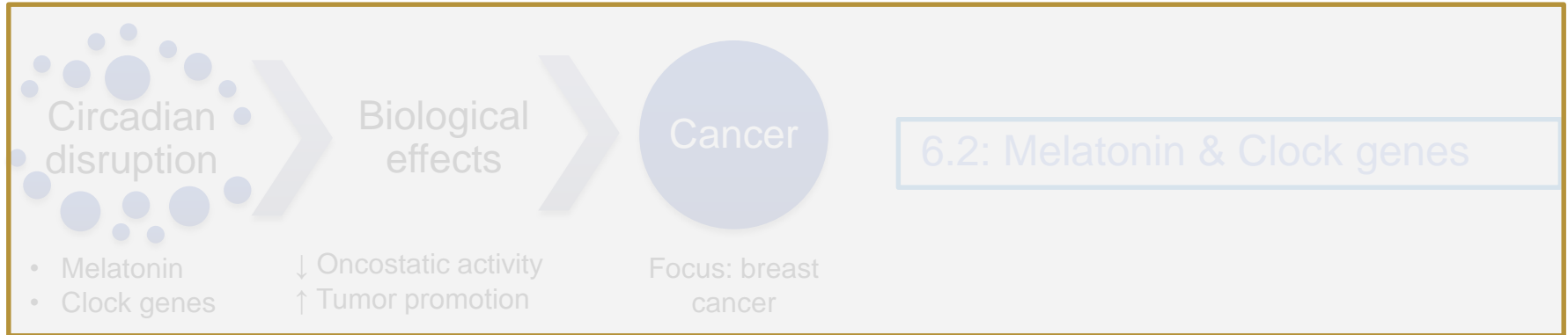
Core Clock Genes: Genetic Models

Mutant mice exhibit a cancer-prone phenotype and accelerated tumor growth

Mutant gene	Tumors	Effect
<i>Bmal1</i> or <i>Per2</i>	Lung	Accelerated tumor growth/progression, ↑ c-Myc, metabolic dysregulation
<i>Bmal1</i> or <i>Per2</i>	Colon	Accelerated tumor growth in vivo/in vitro
<i>Bmal1</i> , <i>Per1</i> , <i>Per2</i> , <i>Cry1</i> , and <i>Cry2</i>	Liver Ovarian Lymphoma	Increased incidence of spontaneous and radiation-induced tumors
<i>Per2</i> , <i>Cry1</i> , and <i>Cry2</i>	Liver Bile duct	Developed 4-8X more tumors than WT mice



Shift work/LAN, circadian disruption and cancer



↑ Biological effects (KC)

6.3: LAN-related exposures and key events related to cancer

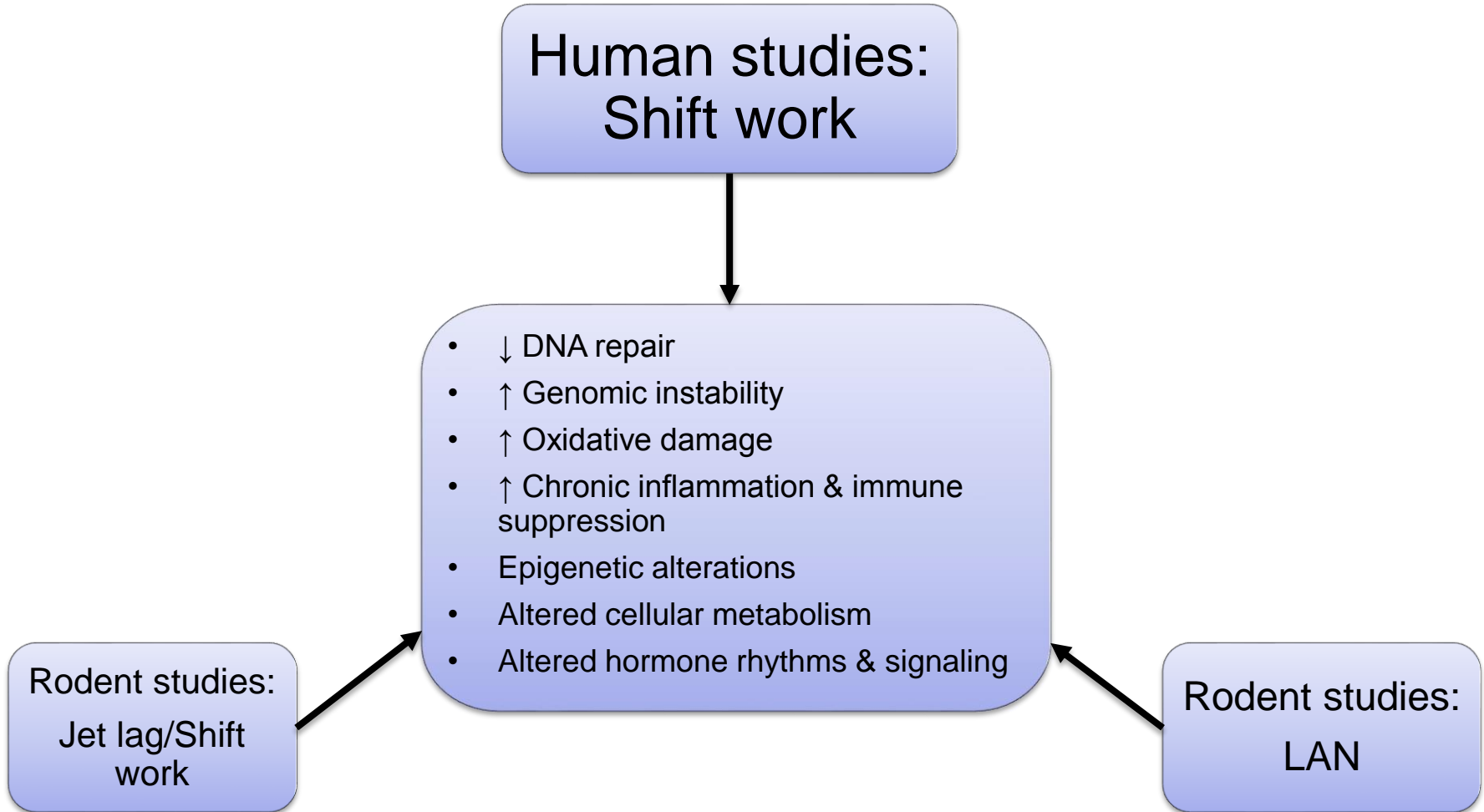
LAN = light at night

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LAN/Shift Work: Biological Effects

LAN/Shift work are associated with KC/other effects

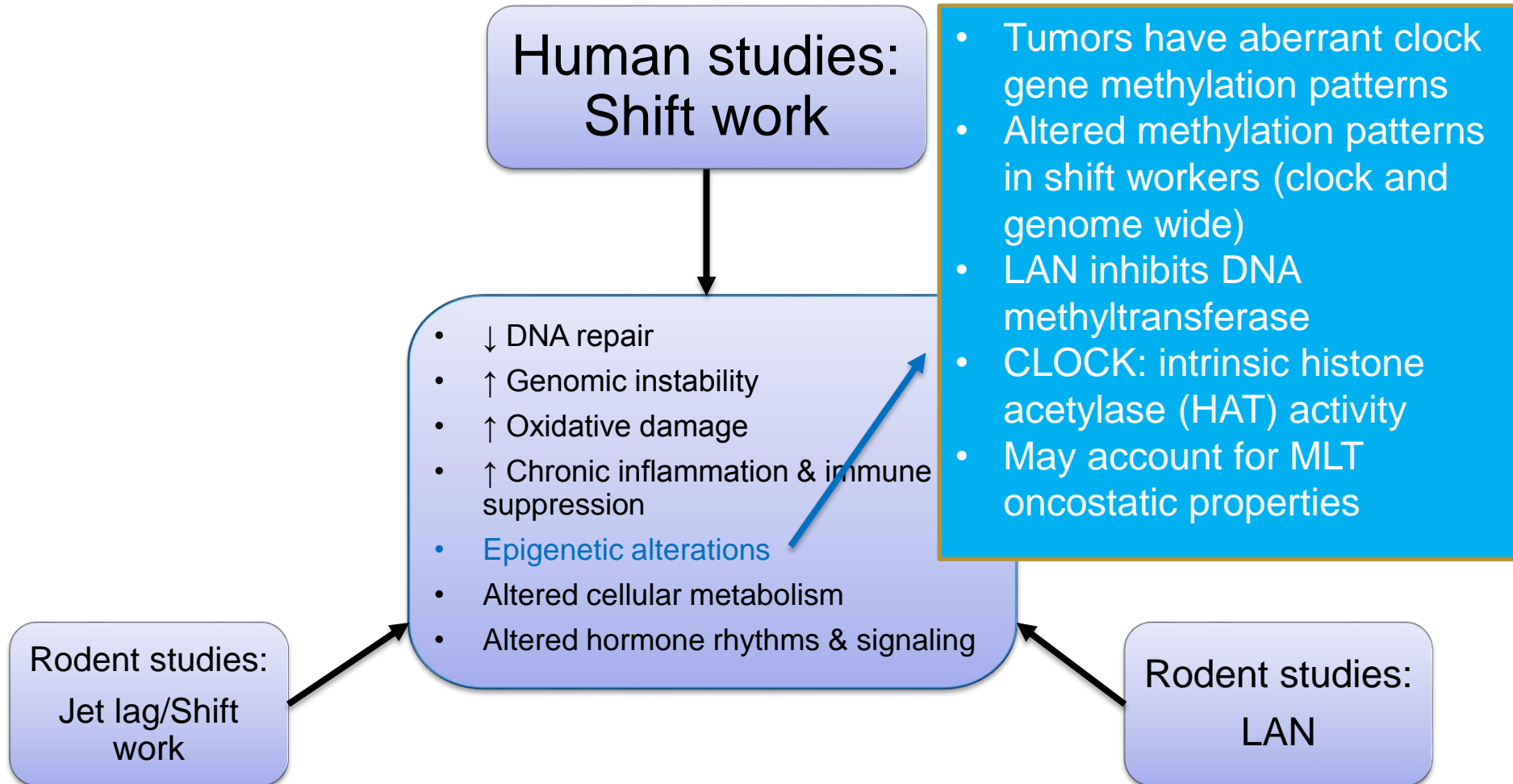


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LAN/Shift Work: Biological Effects

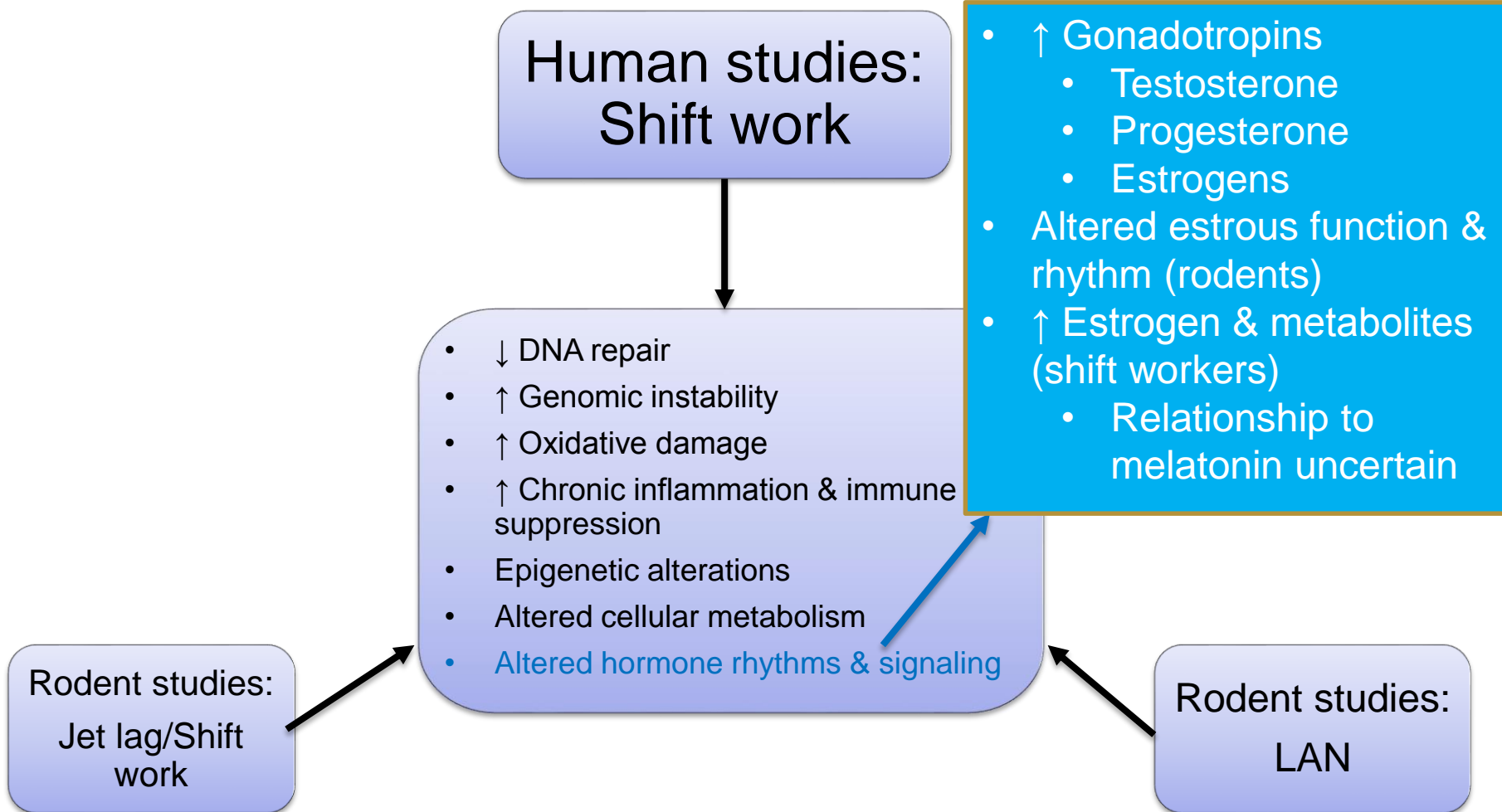
The circadian clock is regulated at the epigenetic level





LAN/Shift Work: Biological Effects

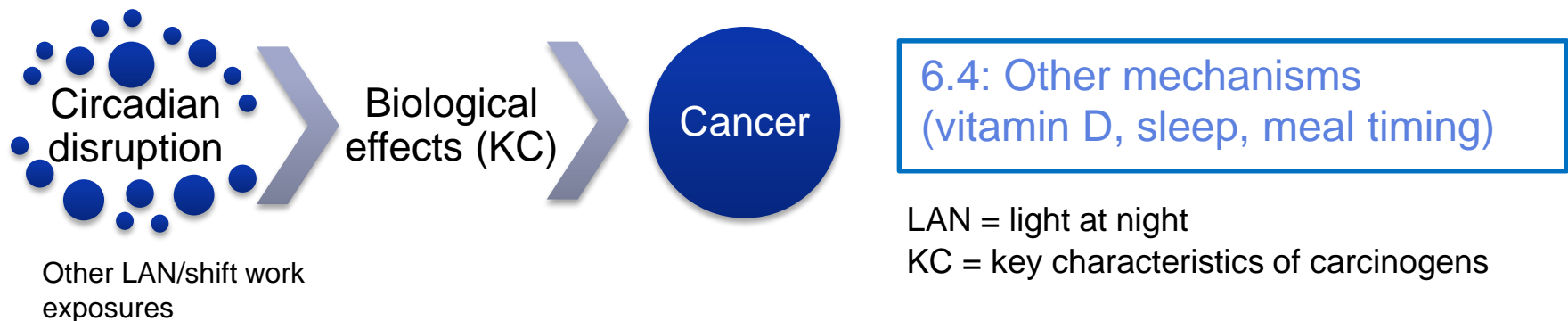
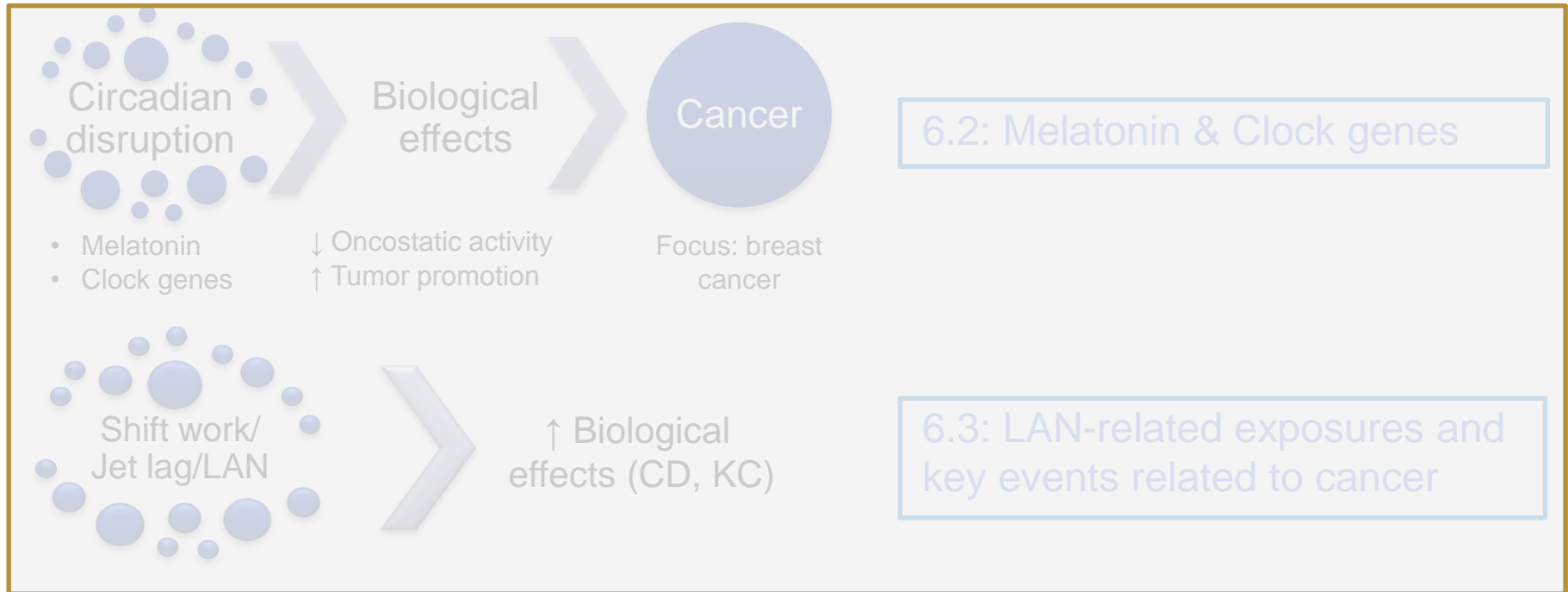
Melatonin regulates sex hormone rhythms





Outline: Mechanistic Data

Shift work/LAN, circadian disruption and cancer





Night Shift Work: Co-exposures

Night shift work is a complex exposure scenario



Light at Night



Sleep
Disruption



Altered Meal
Timing



Vitamin D



Night Shift Work: Co-exposures

Vitamin D regulates many of the same biological processes as melatonin



Vitamin D

- 90% from sunlight exposure
- Regulates > 2000 genes
 - Metabolism
 - DNA repair
 - Antioxidant activity
 - Immune function/inflammation
 - Cell proliferation/differentiation
- Deficiency and cancer
 - Risk factor in human cancers
 - Role in breast cancer uncertain
 - VDR knockouts: ↑ preneoplasia
 - VDR SNPs: ↑ breast cancer risk

VDR = vitamin D receptor

SNPs = single nucleotide polymorphisms



Night Shift Work: Co-exposures

The sleep/wake cycle is bidirectionally associated with the circadian system



Sleep Disruption

- Misalignment with LD cycle
- Disruption affects function of multiple systems:
 - Inflammation and immune response
 - Metabolic (insulin, glucose, leptin, ghrelin)
 - Cellular (DNA damage/oxidative stress, epigenetic)
 - Neuroendocrine
- Role in breast cancer uncertain
 - Mixed results from human studies
 - Plausible mechanisms
 - More studies needed

LD = daily and seasonal light:dark cycle



Night Shift Work: Co-exposures

Meal timing is an important non-photic zeitgeber



Altered Meal Timing

- Peripheral clock entrainment
- Gene expression/biomarkers
 - Glucose homeostasis & energy metabolism
 - Inflammation & immune function
 - Tyrosine kinase signaling
 - DNA damage checkpoints
 - C-reactive protein
 - Oxidative stress
- Role in cancer
 - Restricted feeding ↓ tumor growth
 - After 10:00 PM ↑ breast cancer



Night Shift Work and LAN: Mechanistic Data

Summary

- Melatonin and clock genes
 - Maintain tissue and cellular homeostasis
 - Multiple oncostatic pathways
- LAN, shift work, jet lag induce circadian disruption
 - Melatonin suppression
 - Altered clock gene and clock controlled gene expression
 - Associated with multiple key characteristics of carcinogens
- Complex exposures/interactions
 - Sunlight and vitamin D
 - Sleep disruption
 - Meal timing



Clarification questions?



Night Shift Work and LAN: Mechanistic Data

Reviewer Comments

- Comment on whether the information provided in the Mechanistic and Other Relevant Data section is clear, technically correct, and objectively presented.
- Identify any information that should be added or deleted.
- Provide any scientific criticisms of NTP's synthesis of the mechanistic data for assessing effects of night shift work and light at night.
- Comment on whether the summary captures the key information for each topic.