Leonard Augenlicht, Ph.D.

Positions:
Professor, Medicine and Cell Biology
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Research interests:

Len's lab studies homeostasis and lineage differentiation of the intestinal mucosa, perturbations causing tumors, and novel approaches to chemoprevention and therapy. The lab developed the first array profiling for transcriptome analysis in the early 1980's, predating others by a decade, and holds the earliest broad patents on this approach. They were the first to use banked tissue from cooperative group trials to investigate molecular markers to guide for colon cancer therapy. And their Muc2 knockout mouse is used world-wide to investigate how loss of the mucus barrier alters mucosal physiology, the microbiome and tumor development.

Current focus is on nutritional-genetic interactions establishing risk for tumorigeneis. Nutritional patterns are the primary driver of risk for sporadic colon cancer, the vast majority of the disease. A novel rodent diet, NWD1, models this, with key nutrients recapitulating exposure levels in human high risk populations. NWD1 amplifies tumorigenesis in mouse genetic models, and wild-type mice fed NWD1 are the only model that develops sporadic colon tumors.

In elevating risk, NWD1 elevates mucosal Wnt signaling, alters lineage differentiation, represses Lgr5hi cell stem cell functions, their accumulation of mutations, and efficiency in tumor initiation. This is initiated by NWD1 down regulation of Pprargc1a, repressing Oxphos that represses developmental progression of stem cell progeny in their transit through progenitor cell compartments, triggering mobilization of an alternate stem cell population. The consequent mucosal remodeling adapts the tissue to the nutritional changes, and elevates pathways of antigen processing and presentation causing chronic pro-tumorigenic inflammation, a pathogenic pathway of inflammation in pro-tumorigenic human Inflammatory Bowel Disease.

Current studies focus on: 1) transcriptional mechanisms down-regulating Ppargc1a; 2) the myofibroblast sheath surrounding the NWD1 expanded proliferative compartment that may provide signals triggering alternate stem cell mobilization; 3) interaction of diet with aging in remodeling intestinal stem cells and the mucosa; 4) potential to use these to detect elevated risk and as targets for intervention.

Collaborations; with Winfried Edelmann on NWD1 impact on colon tumorigenesis in his novel humanized mouse model of defective mismatch repair; with Vern Schramm and Edelmann on efficacy and mechanisms of intestinal tumor inhibition by MTDIA, a transition state analogue Schramm developed as an inhibitor of MTAP, a key enzyme in methyl group metabolism; with Libusha Kelly on dietary modulation of a novel gut sulfide pathway she discovered that modifies a broad range of xenobiotics, including carcinogens, and chemopreventive and therapeutic agents.

Len has chaired and served on numerous advisory and review panels for the NIH, and for NASA on the Space Station Utilization Advisory Committee.

Current grant funding:

- R01 CA214625 – Augenlicht, PI (7/17/2018 – 5/31/2023)
  A major nutritional effect on intestinal stem cells and tumors
- R01 CA229216 – Augenlicht, PI (7/05/2018 – 5/31/2023)
  Nutritionally driven sporadic intestinal tumors: impact on stem cells
- R01 CA222358 – Augenlicht and Edelmann, co-PIs (7/05/2018 – 5/31/2023)
  Genetic and dietary Interactions in MMR deficient colon tumorigenesis
- R01 CA248536 (W. Edelmann, PI; Augenlicht, co-investigator) (4/01/2021 – 3/31/2025)
  Analyzing the Hypersensitivity of MMR-deficient Colorectal Cancers to mTOR Inhibition.

Recent publications (selected):

1. Choi, J. et al. Dynamic Metabolic Reprogramming by Dietary Shift Drives Intestinal Stem Cell and Mucosal Plasticity. under review.
2. Firestone RS, et al. Transition state analogue of MTAP extends lifespan of APC(Min/+) mice.Sci Rep 2021;11:8844.
3. Li, W et al. Effects of diet choice on stem cell function necessitate clarity in selection and reporting. Cell Stem Cell 2020;27:11-12.
4. Li, W. et al. The nutritional environment determines which and how intestinal stem cells contribute to homeostasis and tumorigenesis. Carcinogenesis 2019;40:937-946.
5. Li, W. et al. Vitamin D and the nutritional environment in functions of intestinal stem cells: Implications for tumorigenesis and prevention. J Steroid Biochem Mol Biol 2019;198:105556.
6. Augenlicht L. Environmental Impact on Intestinal Stem Cell Functions in Mucosal Homeostasis and Tumorigenesis. Journal of Cellular Biochemistry 2017;118:943-952.
7. Protiva P, et al. Calcium and 1,25-dihydroxyvitamin D3 modulate genes of immune and inflammatory pathways in the human colon: a human crossover trial. Am J Clin Nutr 2016;103:1224-31.
8. Peregrina K, et al. Vitamin D is a determinant of mouse intestinal Lgr5 stem cell function. Carcinogenesis 2015;36:25-31.