Division of Health and Environmental Sciences
Department of Pharmaceutical Health Science & Environmental Toxicology

Faculty members

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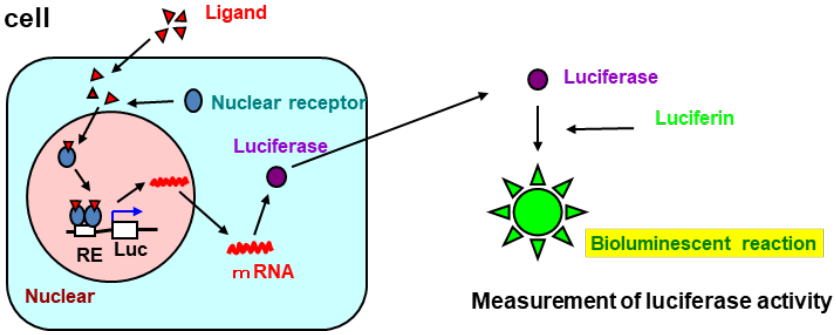
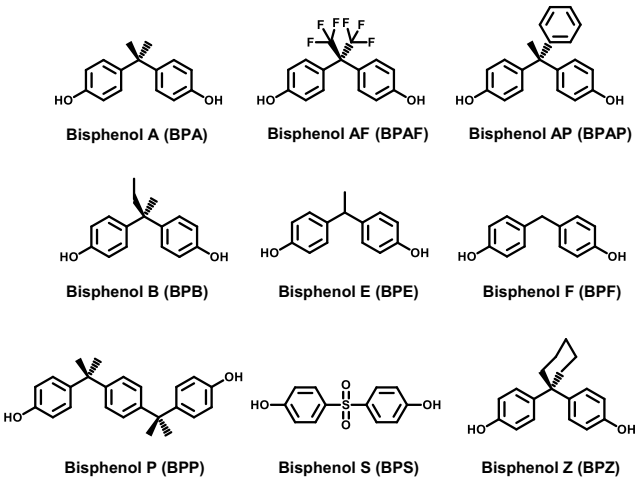
Assistant professor:	Atsuhito Kubota, Ph.D.

Main research in progress

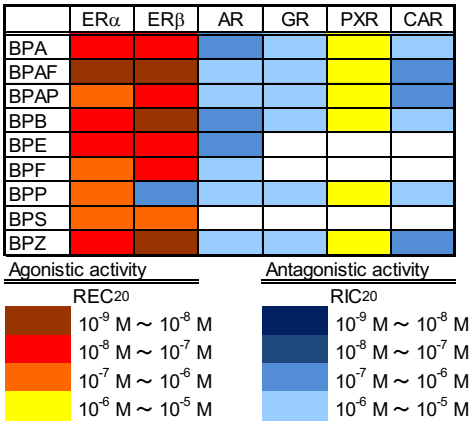
1) Endocrine- and immune-disrupting effects of environmental chemicals via nuclear receptors (NRs).
2) Molecular mechanisms for cancer prevention by foods and the functional components *in vitro* and *in vivo*.
3) Search of key molecules for intestinal immunity in various pathological model mice.



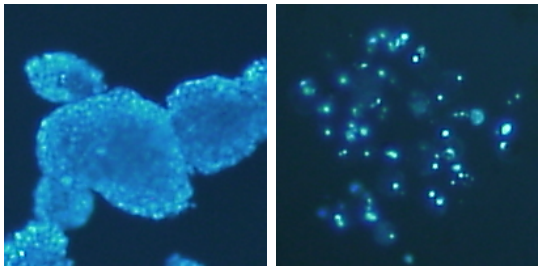
Nuclear receptor (NR)-mediated transactivation assay



Chemical structures of bisphenol A and eight its analogues



Profiling of these compounds on NRs activity



Control **Fucoxanthinol treatment**

A marine bio-functional carotenoid, fucoxanthinol, induced strongly apoptosis in colorectal cancer stem-like colonosphere.

Current publications (Year 2017-2022)

2022

1. **Kubota A**, **Terasaki M**, Sakuragi Y, Muromoto R, Ikeda-Araki A, Takada H, **Kojima H**. Effects of benzotriazole UV stabilizers, UV-PS and UV-P, on the differentiation of splenic regulatory T cells via aryl hydrocarbon receptor. *Ecotoxicology and Environmental Safety* 2022, 238: 113549.
2. **Kubota A**, **Terasaki M**, Takai R, Kobayashi M, Muromoto R, **Kojima H**. 5-Aminosalicylic acid, a weak agonist for aryl hydrocarbon receptor that induces splenic regulatory T cells. *Pharmacology* 2022, 107: 28-34.
3. **Terasaki M**, Murase W, Kamakura Y, Kawakami S, **Kubota A**, **Kojima H**, Ohta T, Tanaka T, Maeda H, Miyashita K, Mutoh M. A biscuit containing fucoxanthin and Colorectal Cancer Prevention. Nutrition and *Cancer* 2022, 13: 1-11.
4. Yokoyama R, Kushibiki A, Yamada S, **Kubota A**, **Kojima H**, Ohta T, Hamada J, Maeda H, Mutoh M, **Terasaki M**. Requirement of CLIC4 expression in human colorectal cancer cells for sensitivity to growth inhibition by fucoxanthinol. *Cancer Genomics & Proteomics* In Press.
5. **Terasaki M**, Ono S, Hashimoto S, **Kubota A**, **Kojima H**, Ohta T, Tanaka T, Maeda H, Miyashita K, Mutoh M. Suppression of C-C chemokine receptor is a key regulation for colon cancer chemoprevention in AOM/DSS mice by fucoxanthin. *The Journal of Nutritional Biochemistry* 2022, 99: 108871.
6. Narita T, Tsunematsu Y, Miyoshi N, Komiya M, Hamoya T, Fujii G, Yoshikawa Y, Sato M, Kawanishi M, Sugimura H, Iwashita Y, Totsuka Y, **Terasaki M**, Watanabe K, Wakabayashi K, Mutoh M. Induction of DNA damage in mouse colorectum by administration of colibactin-producing Escherichia coli, isolated from a colorectal cancer patient. *In Vivo* 2022, 36: 628-634.

2021

1. Sakuragi Y, Takada H, Sato H, **Kubota A**, **Terasaki M**, Takeuchi S, Ikeda-Araki A, Watanabe Y, Kitamura S, **Kojima H**. An analytical survey of benzotriazole UV stabilizers in plastic products and their endocrine-disrupting potential via human estrogen and androgen receptors. *Science of the Total Environmental* 2021, 800: 149374.
2. Murase W, Kamakura Y, Kawakami S, Yasuda A, Wagatsuma M, **Kubota A**, **Kojima H**, Ohta T, Takahashi M, Mutoh M, Tanaka T, Maeda H, Miyashita K, **Terasaki M** Fucoxanthin prevents pancreatic tumorigenesis in C57BL/6J mice that received allogenic and orthotopic transplantations of cancer cells. *International Journal of Molecular Sciences* 2021, 22: 13620.
3. Yokoyama R, **Kubota A**, **Kojima H**, Tanaka T, Mutoh M, **Terasaki M**. Detection of cells displaying high expression of CLIC4 in tumor tissue of patients with colorectal cancer. *In Vivo* 2021, 35: 3165-3173.
4. **Terasaki M**, **Kubota A**, **Kojima H**, Maeda H, Miyashita K, Kawagoe C, Mutoh M, Tanaka T. Fucoxanthin and Colorectal Cancer Prevention. *Cancers* 2021, 13: 2379.
5. **Terasaki M**, Nishizaka Y, Murase W, **Kubota A**, **Kojima H**, Kojoma M, Tanaka T, Maeda H, Miyashita K, Mutoh M, Takahashi M. Effect of Fucoxanthinol on Pancreatic Ductal Adenocarcinoma Cells from an *N*-Nitrosobis(2-oxopropyl)amine-initiated Syrian Golden Hamster Pancreatic Carcinogenesis Model. *Cancer Genomics & Proteomics* 2021, 18: 407-423.
6. **Terasaki M**, Takahashi S, Nishimura R, **Kubota A**, **Kojima H**, Ohta T, Hamada J, Kuramitsu Y, Maeda H, Miyashita K, Takahashi M, Mutoh M. A marine carotenoid of fucoxanthinol accelerates the growth of human pancreatic cancer PANC-1 cells. *Nutrition and Cancer* 2021, 16: 1-16.
7. **Terasaki M**, Inoue T, Murase W, **Kubota A**, **Kojima H**, Kojoma M, Ohta T, Maeda H, Miyashita K, Mutoh M, Takahashi M. A fucoxanthinol induces apoptosis in a pancreatic intraepithelial neoplasia cells. *Cancer Genomics & Proteomics* 2021, 18(2): 133-146.
8. **Terasaki M**, Hamoya T, **Kubota A**, **Kojima H**, Tanaka T, Maeda H, Miyashita K, Mutoh M. Fucoxanthin Prevents Colorectal Cancer Development in Dextran Sodium Sulfate-treated $Apc^{Min/+}$ Mice. *Anticancer Research* 2021, 41(3): 1299-1305.
9. Yokoyama R, **Kojima H**, Takai R, Ohta T, Maeda H, Miyashita K, Mutoh M, **Terasaki M**. Effects of CLIC4 on Fucoxanthinol-induced Apoptosis in Human Colorectal Cancer Cells. *Nutrition and Cancer* 2021, 73(5):

889-898.

10. Endo T, Kimura O, **Terasaki M**, Kobayashi M. Body length, stable carbon, and nitrogen isotope ratios and mercury levels in common minke whales stranded along the coast of Hokkaido, Japan. *Aquatic Mammals* 2021, 47(1): 86-95.
11. Kitagawa T, Kobayashi M, Ohta T, **Terasaki M**, Tsukamoto Y, Takai R, Ishizumi R, Uehara O, Nakagawa K, Akino K, Asaka M, Kuramitsu Y. Nine cases of SARS-CoV-2-PCR-positive samples showed no increase of antibodies against SARS-CoV-2. *IN VIVO* 2021, 35: 2947-2949.
12. Takeda F, Oda M, **Terasaki M**, Ichimura Y, **Kojima H**, Saitoh H. Downregulated expression of intestinal P-glycoprotein in rats with cisplatin-induced acute kidney injury causes amplification of its transport capacity to maintain "gatekeeper" function. *Toxicology and Applied Pharmacology* 2021, 423: 115570.
13. Takeda F, Oda M, **Terasaki M**, **Kubota A**, Asada K, Ichimura Y, **Kojima H**, Saitoh H. Downregulated expression of organic anion transporting polypeptide (Oatp) 2b1 in the small intestine of rats with acute kidney injury. *Drug Metabolism & Pharmacokinetics* 2021, 40: 100411.
14. Yasuda G, Kobayashi M, **Kubota A**, Narumi K, Furugen A, Saito Y, Satoh T, Suzuki N, Iseki K. Analysis of α-Defensin 5 secretion in differentiated Caco-2 cells: Comparison of cell bank origin. *Biological Pharmaceutical Bulletin* 2021, 44: 275-278.

2020

1. Kenda M, Kuželički NK, Iida M, **Kojima H**, Dolenc MS. Triclocarban, Triclosan, Bromochlorophene, Chlorophene and Climbazole on Nuclear Receptors: an in-Silico and in-Vitro Study. *Environmental Health Perspectives* 2020, 128: 107005.
2. Park C, Song H, Choi J, Sim S, **Kojima H**, Park M, Iida M, Lee YJ. The mixture effects of bisphenol derivatives on estrogen receptor and androgen receptor. *Environmental Pollution* 2020, 260: 114036.
3. Tsugoshi Y, Watanabe Y, Tanikawa Y, Inoue C, Sugihara K, **Kojima H**, Kitamura S. Inhibitory effects of organophosphate esters on carboxylesterase activity of rat liver microsomes. *Chemico-Biological Interactions* 2020, 327: 109148.
4. **Terasaki M**, Uehara O, Ogasa S, Sano T, Kubota A, Kojima H, Tanaka T, Maeda H, Miyashita K, Mutoh M. Alteration of fecal microbiota by fucoxanthin results in prevention of colorectal cancer in AOM/DSS-treated mice. *Carcinogenesis* 2020, 42(2): 210-219.
5. **Terasaki M**, Kimura R, Kubota A, Kojima H, Tanaka T, Maeda H, Miyashita K, Mutoh M. Continuity of tumor microenvironmental suppression in AOM/DSS mice by fucoxanthin may be able to track with salivary glycine. *IN VIVO* 2020, 34(6): 3205-3115.
7. **Terasaki M**, Ikuta M, **Kojima H**, Tanaka T, Maeda H, Miyashita K, Mutoh M. Dietary fucoxanthin induces anoikis in colorectal adenocarcinoma by suppressing integrin signaling in a murine colorectal cancer model. *Journal of Clinical Medicine* 2020, 9(1): 90-104.
8. **Terasaki M**, Kuramitsu Y, Kojoma M, Kim SY, Tanaka T, Maeda H, Miyashita K, Kawagoe C, Kohno S, Mutoh M. High fucoxanthin wakame (Undaria pinnatifida) prevents tumor microenvironment formation in an AOM/DSS mouse carcinogenic model. *Journal of Functional Foods* 2020, 64: 103709.
9. **Kubota A**, Imai S, Momo K, Sugawara M, Takekuma Y. Survey Based on Claims Data of New Control-Released Budesonide for Crohn's Disease. *The Journal of Community Pharmacy and Pharmaceutical Sciences* 2021, 13: 54-61.

2019

1. Watanabe Y, Hattori S, Fujino C, Tachibana K, **Kojima H**, Yoshinari K, Kitamura S. Effects of benzotriazole ultraviolet stabilizers on rat PXR, CAR and PPARα transcriptional activities. *Fundamental Toxicological Sciences* 2019, 6(2): 57-63.
2. **Kojima H**, Takeuchi S, Sanoh S, Okuda K, Kitamura S, Uramaru N, Sugihara K, Yoshinari K. Profiling of bisphenol A and eight its analogues on transcriptional activity via human nuclear receptors. *Toxicology* 2019, 413: 48-55.
3. Fujino C, Watanabe Y, Sanoh S, Hattori S, Nakajima H, Uramaru N, **Kojima H**, Yoshinari K, Ohta S,

Kitamura S. Comparative study of the effect of 17 parabens on PXR-, CAR- and PPARα-mediated transcriptional activation. *Food and Chemical Toxicology* 2019, 133: 110792.

4. Fujino C, Watanabe Y, Sanoh S, Nakajima H, Uramaru N, **Kojima H**, Yoshinari K, Ohta S, Kitamura S. Activation of PXR, CAR and PPARa by pyrethroid pesticides and effect of the metabolism by rat liver microsomes. *Heliyon* 2019, 5(9): e02466.
5. Takeuchi S, Tanaka-Kagawa T, Saito I, **Kojima H**, Jinno H. Distribution of 58 semi-volatile organic chemicals in the gas phase and three particle sizes in indoor air and house dust in residential buildings during the hot season in Japan. *BPB Reports* 2019, 2(6): 91-98.
6. Abe T, Itoh T, **Terasaki M**. Total Synthesis of Fontanesine B and its isomer: Their antiproliferative activity against human colorectal cancer cells. *Helvetica Chimica Acta* 2019. [doi: 10.1002/hlca.201900116].
7. **Terasaki M**, Masaka S, Fukada C, Houzaki M, Endo T, Tanaka T, Maeda H, Miyashita K, Mutoh M. Salivary glycine is a significant predictor for the attenuation of polyp and tumor microenvironment formation by fucoxanthin in AOM/DSS mice. *IN VIVO* 2019, 33: 365-374.
8. **Terasaki M**, Iida T, Kikuchi F, Tamura K, Endo T, Kuramitsu Y, Tanaka T, Maeda H, Miyashita K, Mutoh M. Fucoxanthin potentiates anoikis in colon mucosa and prevents carcinogenesis in AOM/DSS model mice. *The Journal of Nutritional Biochemistry* 2019, 64: 198-205.
9. **Terasaki M**, Matsumoto N, Hashimoto R, Endo T, Maeda H, Hamada J, Osada K, Miyashita K, Mutoh M. Fucoxanthin administration delays occurrence of tumors in xenograft mice by colonospheres, withan anti-tumor predictor of glycine. *Journal of Clinical Biochemistry and Nutrition* 2019, 64: 52-58.
10. Tamura S, Narita T, Fujii G, Miyamoto S, Hamoya T, Kurokawa Y, Takahashi M, Miki K, Matsuzawa Y, Komiya M, **Terasaki M**, Yano T, Mutoh M. Inhibition of NF-kappaB transcriptional activity enhances fucoxanthinol-induced apoptosis in colorectal cancer cells. *Genes Environment* 2019. [doi: 10.1186/s41021-018-0116-1].
11. Komatsu T, Katsuyama S, Takano F, Okamura T, Sakurada C, Tsuzuki M, Ogawa K, **Kubota A**, Morinaga O, Tabata K, Sakurada T. Possible Involvement of the μ Opioid Receptor in the Antinociception Induced by Sinomenine on Formalin-Induced Nociceptive Behavior in Mice. *NEUROSCIENCE LETTERS* 2019, 699: 103-108.

2018

1. **Kojima H**, Takeuchi S, Iida M, Nakayama SF, Shiozaki T. A sensitive, rapid and simple DR-EcoScreen bioassay for the determination of PCDD/Fs and dioxin-like PCBs in environmental and food samples. *Environmental Science and Pollution Research* 2018, 25: 1701-1712.
2. Takeuchi S, Tanaka-Kagawa T, Saito I, **Kojima H**, Jin K, Satoh M, Kobayashi S, Jinno H. Differential determination of plasticizers and organophosphorus flame retardants in residential indoor air in Japan. *Environmental Science and Pollution Research* 2018, 25: 1713-1720.
3. Kuhara K, Tokuda K, Kitagawa T, Baron B, Tokunaga M, Harada K, **Terasaki M**, Uehara O, Ohta T, Takai R, Hamada JI, Kobayashi M, Shimo T, Nagayasu H, Kuramitsu Y. CUB domain-containing protein 1 (CDCP1) is down-regulated by active hexose-correlated compound in human pancreatic cancer cells. *Anticancer Research* 2018, 38, 6107-6111.
4. **Terasaki M**, Mima M, Kudoh S, Endo T, Maeda H, Hamada J, Osada K, Miyashita K, Mutoh M. Glycine and succinic acid are effective indicators of the suppression of epithelial-mesenchymal transition by fucoxanthinol in colorectal cancer stem-like cells. *Oncology Reports* 2018, 40: 414-424.
5. **Terasaki M**, Ogawa Y, Endo T, Maeda H, Hamada J, Osada K, Miyashita K, Mutoh M. Glycine is a predictor for a suppressive effect of fucoxanthinol on colonosphere formation under hypoxia. *Anticancer Research* 2018, 38: 2169-2179.
6. Abe T, **Terasaki M**. Synthesis of Phaitanthrin E and tryptanthrin through amination/cyclization cascade. *Helvetica Chimica Acta* 2018, 101, e1700284.
7. **Kubota A**, Kobayashi M, Sarashina S, Takeno R, Okamoto K, Narumi K, Furugen A, Suzuki Y, Takahashi N, Iseki K. Reishi mushroom Ganoderma lucidum Modulates IgA production and alpha-defensin expression in the rat small intestine. Journal of Ethnopharmacology 2018, 214: 240-243.
8. **Kubota A**, Kobayashi M, Sarashina S, Takeno R, Yasuda G, Narumi K, Furugen A, Takahashi-Suzuki N, Iseki K. Gamma-Aminobutyric Acid (GABA) Attenuates Ischemia Reperfusion-Induced Alterations in Intestinal Immunity. *Biological and Pharmaceutical Bulletin* 2018, 41(12): 1874-1878.

2017

1. Zwart N, Andringa D, de Leeuw WJ, **Kojima H**, Iida M, Houtman C, de Boer J, Kool J, Lamoree M, Hamers T. Improved androgen specificity of AR-EcoScreen by CRISPR based glucocorticoid receptor knockout. *Toxicology in Vitro* 2017, 45: 1-9.
2. Takahashi M, Muromoto R, **Kojima H**, Takeuchi S, Kitai Y, Kashiwakura J, Matsuda T. Biochanin A enhances RORγ activity through STAT3-mediated recruitment of NCOA1. *Biochemical and Biophysical Research Communications* 2017, 489: 503-508.
3. Takeuchi S, Anezaki K, **Kojima H**. Effects of unintentional PCBs in pigments and chemical products on transcriptional activity via aryl hydrocarbon and nuclear hormone receptor. *Environmental Pollution* 2017, 227: 306-313.
4. Abe T, Takahashi M, Kano M, Amaike Y, Ishii C, Maeda K, Kudo Y, Morishita T, Hosaka T, Sasaki T, Kodama S, Matsuzawa A, **Kojima H**, Yoshinari K. Activation of nuclear receptor CAR by an environmental pollutant perfluorooctanoic acid. *Archives of Toxicology* 2017, 91: 2365-2374.
5. Masuda A, Masuda M, Kawano T, Kitsunai Y, Nakayama H, Nakajima H, Kojima H, Kitamura S, UramaruN, Hosaka T, Sasaki T, Yoshinari K. Construction of the database of rat repeated-dose toxicity tests of pesticides for the toxicological characterization of hepatocyte hypertrophy. *YAKUGAKU ZASSHI* 2017, 135(5): 611-622. [in Japanese]
6. **Terasaki M**, Kawagoe C, Ito A, Kumon H, Narayan B, Hosokawa M, Miyashita K. Spatial and seasonal variations in the biofunctional lipid substances (fucoxanthin and fucosterol) of the laboratory-grown edible Japanese seaweed (Sargassum horneri Turner) cultured in the open sea. *Saudi Journal of Biological Sciences* 2017, 24(7): 1475-1482.
7. **Terasaki M**, Maeda H, Miyashita K, Mutoh M. Induction of Anoikis in Human Colorectal Cancer Cells by Fucoxanthinol. *Nutrition and Cancer* 2017, 69(7): 1043-1052.
8. Endo T, Kimura O, **Terasaki M**, Fujii Y, Haraguchi K, Ohta C, Koga N, Kato Y. Growth-related changes in non-essential and essential metals in the liver of star-spotted smooth-hounds (dogfish) Mustelus manazo from the northern region of Japan. *Marine Environmental Research* 2017, 131: 156-161.
9. **Terasaki M**, Maeda H, Miyashita K, Tanaka T, Miyamoto S, Mutoh M. A marine bio-functional lipid, fucoxanthinol, attenuates human colorectal cancer stem-like cell tumorigenicity and sphere formation. *Journal of Clinical Biochemistry and Nutrition* 2017, 61(1): 25-32.
10. **Kubota A**, Shindo H, Fukushima Y, Komatsu T, Sakurada T, Yasuda T, Fushiya S, Kondo Y, Sakurada C, Takano F. Effects of Kampo Extract Boiogito and Its Alkaloid Sinomenine on Nociceptive Pain in Mouse Models. *Pharmacometrics* 2017, 92: 83-89.