**Supplementary Table 1. Characteristics and Response to Agents of the Animal Models Employed In this Paper**

1. **MNU-Induced Mammary Cancer in Sprague-Dawley Rats**

**Characteristics:** Cancers (minimally invasive adenocarcinomas) induced in adolescent Sprague-Dawley rats. All tumors are ER+ and by genomic analysis are similar to human well-differentiated ER+ cancers (roughly 50% of tumors have *Ha Ras* mutations not routinely observed in humans) and tumors are virtually diploid.

**Response to Agents**: Tumors respond to hormonal treatments including SERMs, aromatase inhibitors, and ovariectomy. Tumors also respond strongly to RXR agonists and EGFR inhibitors. Tumors fail to respond to statins, NSAIDs, antioxidant response element (ARE) agonists, and metformin. Agents that are highly effective in prevention tend to work in therapy in the model.

1. **MMTV-*Neu* /P53ko Transgenic Mice Develop *Neu* Overexpressing ER+ Mammary Cancers**

**Characteristics**: Cancers (mammary carcinomas) induced in adolescent transgenic mice. All tumors are ER-, overexpress wild type *Neu*, and have altered P53 like human ER- Neu over expressing tumors. Unlike MMTV-Neu mice, the tumors that develop in MMTV-Neu/P53Ko mice do not have mutations in Neu transmembrane domain.

**Response to Agents**: Strong response to RXR agonists and EGFR inhibitors, and more surprisingly, to SERMs. Model fails to respond to statins, NSAIDs, and metformin. A limited number of agents have been tested when early lesions already exist, and yield positive results (RXR Agonists, EGFR Inhibitors).

1. **Min Mice Develop Multiple Intestinal Lesions**

**Characteristics:** Mice have germline mutation in the APC gene induced by the mutagen ENU. Mutations in APC are found in human familial adenomatous polyposis patients and most sporadic colon polyps and cancers. The mice develop tumors primarily in the small intestine; unlike humans, in whom tumors occur in the colon.

Response to Agents: Model responds strongly to various NSAIDs, coxibs, DFMO, and EGFR inhibitors. Model does not respond to RXRs or metformin. Response is seen in mice with clear adenoma burden at the time of agent initiation.

1. **AOM-Induced Colon Cancers in Fischer-344 Rats**

**Characteristics:** Colon tumors are induced by the organ-specific carcinogen, AOM. The tumors are minimally invasive adenocarcinomas in colon. Tumors have mutations in β-catenin, the same pathway found in humans (APC gene) and roughly 40-50% of tumors have Ki Ras mutations like humans.

**Response to Agents**: Tumors strongly respond to various NSAIDs, coxibs, DFMO and EGFR inhibitors, and don’t respond to RXRs or metformin. Agents effective even in rats with aberrant crypt foci.

1. **OH-BBN-induced Invasive Bladder Cancers in Female Fischer-344 Rats**

**Characteristics:** Tumors induced by organ-specific carcinogen hydroxybutyl(butyl)nitrosamine are invasive bladder cancers. These tumors look histopathologically similar to human invasive bladder cancer. RNA analyses have shown substantial overlap between invasive human bladder cancer and the changes observed in the rodent tumors.

**Response to Agents**: Model strongly responds to various NSAIDs, coxibs, and EGFR inhibitors. Model minimally responds to metformin and ARE agonists. PPAR gamma agonists and RXR agonists enhance tumor formation. There is some data in humans that PPAR gamma agonists enhance “luminal” bladder cancers. The strong agents (NSAIDs and EGFR inhibitors) are effective even when rats have developed invasive microcarcinomas.

1. **UV-induced Squamous Cell Skin Cancers in SKH Hairless Mice**

**Characteristics:** Squamous cell skin cancers induced by repeated UVB exposure. This is the same carcinogen as in man. Histologically, tumors look like those in humans. Both mouse and human SCCs driven by P53 mutations at dyrimidine sites.

**Response to Agents:** Model strongly responds to various NSAIDs, coxibs, and DFMO. Model minimally responds to Vitamin E, PPAR gamma agonist. The strong agents (NSAIDs and DFMO) are effective even when mice have developed papillomas and early squamous cell cancers.

Abbreviations: AOM = azoxymethane; APC = Adenomatous polyposis coli; DFMO = difluromethylornithine; EGFR = epidermal growth factor receptor; ENU = *N*-ethyl-*N*-nitroso urea; ER = estrogen receptor; MMTV = mouse mammary tumor virus; MNU = *N-*methyl-*N*-nitrosourea; NSAID = nonsteroidal anti-inflammatory drug; PPAR = peroxisome proliferator-activated receptor; RNA = ribonucleic acid; RXR = retinoic X receptor; SERM = selective estrogen receptor modulator.

**Supplementary Table 2. Materials Relating to Reproducibility of Suboptimal Doses [ppm (mg/kg diet) or mg/Kg BW/day, i.g]**

Mammary Cancers

**Vorozole**

Experiment 1 - Vehicle Control - 4.5 ± 0.6; Vorozole, 0.16 mg/Kg BW 2.4 ± 0.4 (.47%↓);

 Vorozole, 0.32 mg/Kg BW - 1.28 ± 0.46 (72%↓)

Experiment 2 - Vehicle Control - 5.2 ± 0.7; Vorozole, 0.12 mg/Kg - 2.8 ± 0.4 (46%↓)

Experiment 3 - Vehicle Control - 4.6 ± 0.7; Vorozole, 0.16 mg/Kg - 3.0 ± 0.6 (35%↓)

**Tamoxifen**

Experiment 1 - Vehicle Control - 7.3 ± 1.3; Tamoxifen,.0.4 ppm - 4.4 ± 0.7 (40%↓)

Experiment 2 - Vehicle Control - 7.4 ± 1.5; Tamoxifen, 0.66 ppm - 3.6 ± 0.9 (51%↓),

 Tamoxifen, 0.13 ppm – 7.2 ± 1.3 (3%↓)

 Experiment 3 - Vehicle Control - 3.9 ± 0.9; Tamoxifen, 0.0.4 ppm - 2.7. ± 0.6 (.31%↓)

**Gefitinib**

Experiment 1 - Vehicle Control - 4.1 ± 0.6; Gefitinib, 3.0 mg/Kg BW - 1.9 ± 0.4 (54%↓)

Experiment 2 - Vehicle Control - 5.2 ± 0.7; Gefitinib, 2.0 mg/Kg BW - 2.6± 0.3 (50%↓)

Urinary Bladder Cancers

**Naproxen** (30-40 mg Kg BW i.g).

Experiment 1 - Vehicle Control - 19/27 (70% of rats with large tumors (>200 mg) and an average bladder weight of 344 mg. Naproxen (40 mg/Kg BW) - 8/30 (27% of rats with large tumors) and an average weight of 209 mg (40% ↓).

Experiment 2 - Vehicle Control - 24/35 (69% of rats with large tumors (>200 mg) and an average bladder weight of 356 mg. Naproxen Control (30 mg/Kg BW) - 7/30 (23% of rats with large tumors) and an average weight of 185 mg (48% ↓).

Experiment 3 - Vehicle Control - 24/25 (96% of rats with large tumors >200 mg) and an average bladder weight of 408 mg. Naproxen control (30 mg/Kg BW) - 9/25 (36% of rats with large tumors) and an average weight of 210 mg (48%↓).