Potential probe for early ovarian cancer

June 24 2019, by Anivarya Kumar

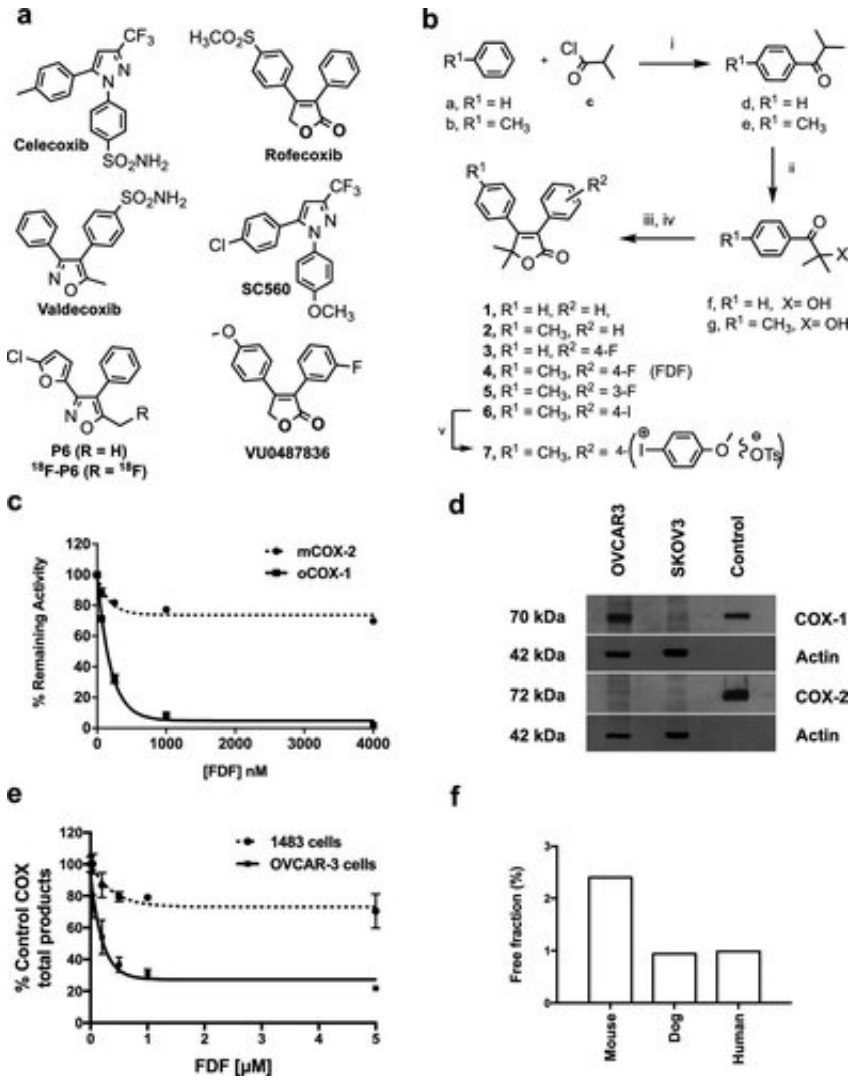

Figure 1. (a) Structure of COX-2-selective inhibitors (celecoxib, rofecoxib, and valdecoxib) and COX-1-selective inhibitors (SC560, P6/18F-P6, and VU0487836). (b) Chemical synthesis of FDF and analogs, (i) AlCl3, CHCl3, 0–25 °C, 1.5 h, (ii) trioctylmethylammonium chloride (Aliquat 336), NaOH, CCl4, toluene, 25 °C, 16 h, (iii) substituted-phenylacetic acid, CMC, 4-(dimethylamino)pyridine, CH2Cl2, 25 °C, 18 h, (iv) DBU, 40–50 °C, 3 h, (v)

anisole, m-CPBA, p-TSrt 16 h. (c) Inhibition of purified ovine COX-1 or mouse COX-2 by compound 4 (FDF). (d) Levels of COX-1 and COX-2 expression in OVCAR3, and SKOV3 cells by western blot analysis (cropped gels are displayed) using ovine COX-1 antibody (Santa Cruz# SC-19998) and human COX-2 antibody (Cayman# 100034), the full-length gels are presented in Supporting Figure S29, (e) inhibition of COX-1 and COX-2 in OVACR3 and 1483 HNSCC cells by FDF. (f) Plasma protein binding of FDF in mouse, dog, and human.

Ovarian cancer is the fifth leading cause of cancer death in women and one of the most difficult malignancies to detect at an early stage.

Emerging clinical evidence suggests that the enzyme cyclooxygenase-1 (COX-1) contributes significantly to tumorigenesis in ovarian cancer. Thus COX-1 could serve as a novel target for molecular imaging probes to improve early detection and response to treatment.

Now in the American Chemical Society journal *ACS Omega*, Md. Jashim Uddin, Ph.D., Lawrence Marnett, Ph.D., and colleagues report the discovery of FDF, a furanone-based novel COX-1 selective inhibitor with adequate properties to enable its use for in vivo imaging.

In two distinct animal models of ovarian cancer, xenografts expressing high levels of COX-1 demonstrated targeted uptake of the compound containing the F-18 radioisotope (18F-FDF) compared to tissues expressing low protein levels.

This indicates that 18F-FDF may be the first feasible radiotracer validated for targeted PET/CT imaging of neoplastic tissues that express elevated levels of the COX-1 enzyme.

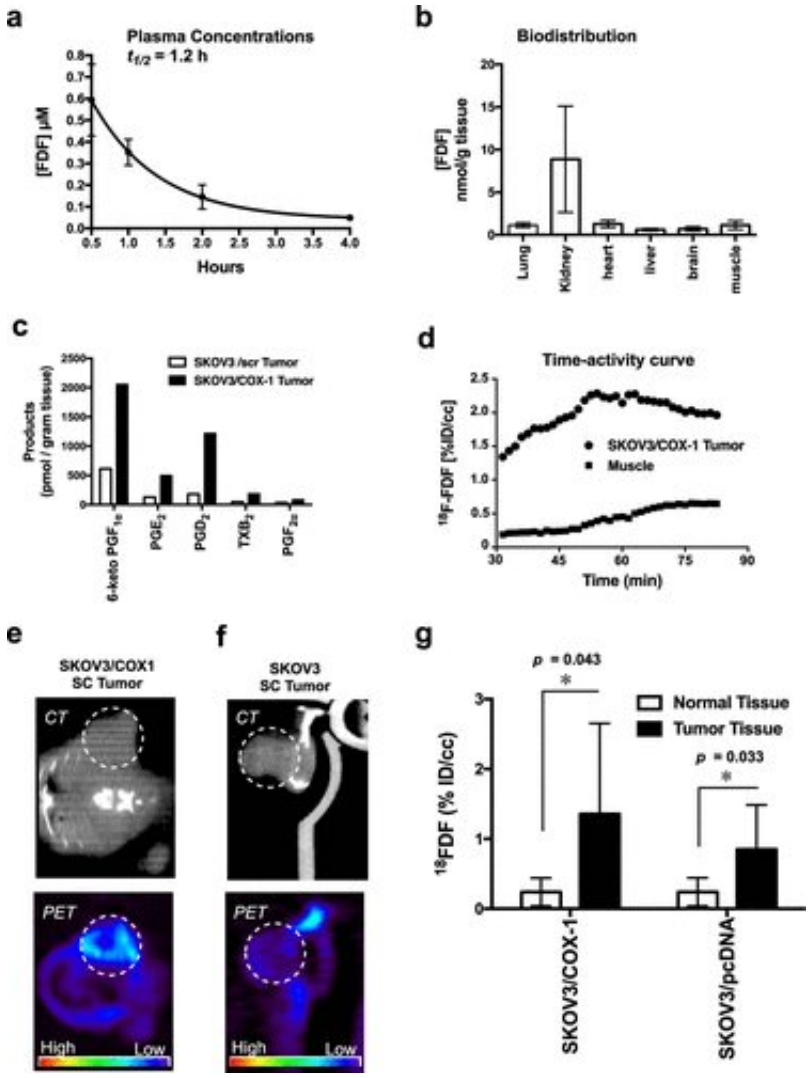

Figure 3. (a) In vivo plasma half-life of FDF in CD-1 mice. (b) In vivo biodistribution in C57BL/6 mice. (c) Level of COX-1 products in SKOV3/pcDNA tumors and SKOV3/COX-1 tumors analyzed by LC–MS/MS (d) time–activity curve of [18F]FDF in subcutaneous tumor vs muscle tissues. (e) In vivo PET/CT imaging of SKOV3/COX-1 (high COX-1-expressing) subcutaneous tumors implanted in mice. (f) In vivo PET/CT imaging of SKOV3/pcDNA (low COX-1-expressing) subcutaneous tumors implanted in mice. (g) Image analysis of [18F]FDF signal intensity in subcutaneous tumors vs muscle by AMIDE software.

More information: Md. Jashim Uddin et al. Discovery of Furanone-Based Radiopharmaceuticals for Diagnostic Targeting of COX-1 in Ovarian Cancer, *ACS Omega* (2019). DOI: 10.1021/acsomega.9b01093