Recent progress in the development of molecular cancer therapies also arise from the inhibition of drug efflux pumps of the ABC family to overcome multidrug resistance as well as the inhibition the proteasome activity. In the manuscript, Feteke and co-workers investigated a common substrate specificity of the P-glycoprotein and proteasome pathway. Their data indicate that indeed the 20S and 26S proteasome and P-glycoprotein have overlapping anthracycline substrate specificities as proven in cell lysates, total cells and drug accumulation by proteasome inhibition in P-glycoprotein over expressing KB8-5 cells. Taken together, their results add a further facet to the plethora of substrates for P-glycoprotein and the proteasome and may represent a novel contributing mechanism in the action of anthracyclines with implications for the use of inhibitors of either pathways in cancer therapy.

Overall the paper is well written using an appropriate methodology. The experiments and data are described in a consistent manner.

Minor Essential Revisions
1. The discussion section is highly focused. To further improve the discussion, additional possible mechanisms like interfering with the topoisomerase II activity to restore chemosensitivity of tumor cells by inhibition of the proteasome by anthracyclines should be discussed in brief (e.g. Ogiso Y, Tomida A, Lei S, et al. Proteasome inhibition circumvents solid tumor resistance to topoisomerase II-directed drugs. Cancer Res 2000; 60: 2429–34.)

Editorial changes
1. Page 6 line 9; change to “German collection of microorganism and cell cultures”
2. Page 6 line 18; change to “were added”
3. Page 7 last paragraph; Drug accumulation assay. Although cited as described elsewhere, a brief description of the method for determining drug concentration in cytoplasm and nucleus as displayed in figure 3 should be included.
4. Page 8 line 11; delete the sentence “ECV304 cells were maintained…….” and insert in the following sentence “Twelve hours…. ECV 304 cells…..”
5. Page 9 line 4-6; better so say “Experimental data are presented as mean +/- standard error of the mean from at least three independent experiments.”
6. Page 11 line 19; “accumulation of daunorubicin”…..
7. Page 13 line 16; please complete the sentence “…can both be activated ???
8. Page 13 line 19; delete “possible”
9. Figure 1 and figure 3A. If possible, significances and p-values should be included in the figures
What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests