GDCh

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UNIVERSITÄT GREIFSWALD

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Das **Institut für Biochemie** lädt gemeinsam mit dem **Institut für Pharmazie** und den Ortsverbänden
der **Deutschen Pharmazeutischen Gesellschaft** und der **Gesellschaft Deutscher Chemiker** zu einem

K o l l o q u i u m der DPhG und der GDCh

Großer Hörsaal des Instituts für Biochemie

Felix-Hausdorff-Str. 4, Greifswald

Montag, 11. Juni 2018, 16 Uhr c.t.

Prof. Viktor Brabec

Institute of Biophysics, Czech Academy of Sciences, Brno, Czech Republic

spricht zum Thema:

The epigenetic effects of antitumor platinum(IV)-conjugates

Abstract:
Substitutionally inert platinum(IV) prodrugs, combining bioactive axial ligands with platinum(IV) derivatives of antitumor platinum(II) compounds, represent a new generation of anticancer drugs. The rationale behind these prodrugs is to release, by reductive elimination inside the cancer cell, an active platinum(II) drug which binds nuclear DNA as well as bioactive ligands that potentiate toxic effects of the platinum(II) drugs by an independent pathway(s).
Epigenetics are stable heritable traits or phenotypes that cannot be explained by changes in DNA sequence. Here, we investigated anticancer effects and mechanisms of action of platinum (IV) derivatives of conventional antitumor platinum(II) complexes containing, as axial ligands, compounds that target *epigenetic* modifications. We chose the axial ligands known to inhibit histone deacetylase activity thereby decondensing chromatin and subsequently increasing the accessibility of DNA within chromatin to DNA-binding platinum agents. Other epigenetic ligands were those triggering global DNA hypermethylation thereby protecting the genome against global hypomethylation, a hallmark of cancer. We found that these platinum(IV) derivatives destroyed cancer cells with markedly greater efficacy and selectivity than conventional platinum(II) drugs. The results also indicate that the enhanced cytotoxicity of the platinum(IV)-conjugates is a consequence of several processes involving enhanced cellular accumulation, affecting activity and expression of epigenetic modification enzymes, reducing mitochondrial membrane potential in cancer cells and yet other biochemical processes which potentiate antitumor effects. Collectively, the remarkable antitumor effects of platinum(IV) prodrugs containing compounds that target *epigenetic* modifications as axial ligands are a consequence of the multifunctional and simultaneous actions of DNA-binding platinum(II) drugs and epigenetic compounds. These agents act by different mechanisms in tumor cells, which may result in a markedly enhanced and unique antitumor effects of this class of platinum(IV) prodrugs.

Einladender
Prof. Dr. Patrick Bednarski

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Vorsitzende des Ortsverbandes der GDCh