NMR-AIDED DESIGN OF CLINICAL STAGE PROTEIN-PROTEIN-INTERACTION INHIBITORS: THE MCL-1 SUCCESS STORY

Markus Schade,[a] David Hargreaves,[b] Rodrigo J. Carbajo,[a] Michael S. Bodnarchuk,[a] Philip B. Rawlins,[b] Martin Packer,[a] Sébastien L. Degorce,[c] Alex Hird,[c] Jeffrey Johannes,[c] Elisabetta Chiarparin[a]

[a] Chemistry, Oncology R&D, AstraZeneca, Cambridge CB4 0WG, UK.
[b] Discovery Sciences, AstraZeneca, Cambridge CB4 0WG, UK.
[c] Chemistry, Oncology R&D, AstraZeneca, Waltham, Massachusetts 02451, USA
Markus.Schade1@astrazeneca.com

The structure-based design of small-molecule inhibitors targeting protein-protein interactions (PPIs) remains a huge challenge as the drug must bind typically wide and shallow protein sites. A PPI target of high interest for hematological cancer therapy is Myeloid cell leukaemia 1 (Mcl-1), a pro-survival guardian protein from the Bcl-2 family. Despite previously considered undruggable, six small molecule Mcl-1 inhibitors have recently entered clinical trials.

Here we report the free in solution NMR conformational analysis of the clinical stage Mcl-1 inhibitors AZD5991, AMG-176 and S64315, and compare the free 3D conformers with the protein-bound conformers determined by crystallography.[1] Our data reveal high plasticity of the Mcl-1 protein and a marked ligand-induced pocket deeping. NMR-based free ligand conformer analysis demonstrates that such unprecedented induced-fit is uniquely achieved by designing highly rigid inhibitors, preorganized in their bioactive conformation. By elucidating key chemistry desgin principles, this work provides a roadmap for targeting the largely untapped PPI class more successfully.

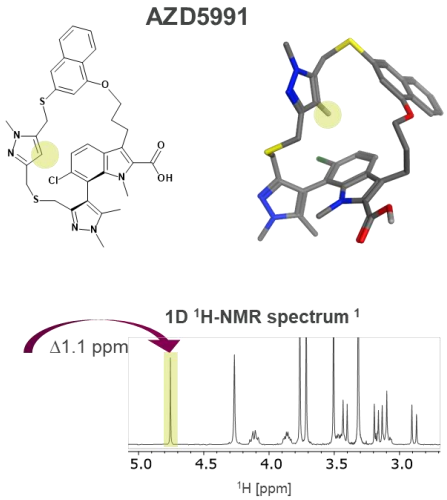

Figure 1. The free in solution conformer of Mcl-1 inhibitor AZD5991 shows a characteristic ^{1}H-NMR fingerprint signal (green background), indicating aromatic ring packing and pre-structuring in the bioactive, protein-bound conformation. The arrow highlights the upfield shifted ^{1}H signal compared with the 2D-HOSE predicted value.

Acknowledgements. This work has been supported by Astrazeneca.

REFERENCES

[1] A. E. Tron, et al., *Nat. Commun.* **2018**, *9*, 5341.