Metallodrugs

Gold Metallodrugs to Target Coronavirus Proteins: Inhibitory Effects on the Spike-ACE2 Interaction and on PLpro Protease Activity by Auranofin and Gold Organometallics**

Maria Gil-Moles, Uttara Basu, Rolf Büssing, Henrik Hoffmeister, Sebastian Türck, Agnieszka Varchmin, and Ingo Ott* [a]

Abstract: Gold complexes have a long tradition in medicine and for many examples antirheumatic, anticancer or anti-infective effects have been confirmed. Herein, we evaluated the lead compound Auranofin and five selected gold organometallics as inhibitors of two relevant drug targets of severe acute respiratory syndrome coronaviruses (SARS-CoV). The gold metallodrugs were effective inhibitors of the interaction of the SARS-CoV-2 spike protein with the angiotensin converting enzyme 2 (ACE2) host receptor and might thus interfere with the viral entry process. The gold metallodrugs were also efficient inhibitors of the papain-like protease (PLpro) of SARS-CoV-1 and SARS-CoV-2, which is a key enzyme in the viral replication. Regarding PLpro from SARS-CoV-2, here reported inhibitors are among the very first experimentally confirmed examples with activity against this target enzyme. Importantly, the activity of the complexes against both PLpro enzymes correlated with the ability of the inhibitors to remove zinc ions from the labile zinc center of the enzyme. Taken together, the results of this pilot study suggest further evaluation of gold complexes as SARS-CoV antiviral drugs.

The current pandemic outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unprecedented global health crisis with to date more than 29 million infected individuals.[1,2] While the world struggles with the control of the fast outspread of this coronavirus and its enormous impact on healthcare, economy and society, efforts to develop vaccines and therapeutics have been undertaken worldwide at a rate, which modern drug discovery has not witnessed ever. The lack of an effective antiviral drug for the treatment of the Coronavirus disease-2019 (COVID-19) has triggered major drug repurposing efforts; however, to this date no approved therapeutic has proven to have sufficient efficacy in the many ongoing clinical trials. The urgent development of new innovative drug candidates against SARS-CoV-2 is the most important mission that medicinal chemists are currently facing.

Regarding drug activity evaluation, several molecular pathways have been in the focus of the search for a possible COVID-19 treatment based on strategies that had already been considered for the SARS-CoV and Middle East respiratory syndrome MERS-CoV outbreaks.[3] Amongst others these include the entry of the coronavirus into the host cell (e.g. the interaction of TMPRSS2[4] or ACE2 with spike proteins of the coronavirus[5]), the viral replication process in the host cell (e.g. the proteases 3CLpro[6] and PLpro[7,8]), transcription, the nucleocapsid protein, or exocytosis of the new virion.[3,7,9]

Gold complexes have a long lasting history in medicine and have been used as disease modifying antirheumatic drugs (DMARDS) for the treatment of rheumatoid arthritis. Intensive research on other possible therapeutic applications of the lead compound Auranofin and other gold species has focused on antancer and anti-infective agents. The application of gold complexes as antiviral drugs has not been studied very intensively, although some promising results suggest a possible future use as human immunodeficiency virus (HIV) therapeutics.[10]

Here we report the results of a pilot study, in which we investigated the effects of Auranofin and selected experimental gold metallodrugs (see Figure 1) on two relevant coronavirus targets (spike protein, papain like protease, PLpro). Whereas Au-1,[11] Au-3[12,13] and Au-5[14] were selected from our previous works on organometallic gold metallodrugs, Au-2 and Au-4 have not been reported before and their synthesis and characterization are described here. Complexes Au-1 to Au-5 are organometallics containing either a N-heterocyclic carbene (NHC) or an alkynyl ligand. Complexes of these types have demonstrated promising activities in a fast increasing number of recent reports.[15]

The entry of SARS-CoV-2 into target cells is facilitated by the spike (S) protein of coronaviruses and mediated by the angiotensin-converting enzyme 2 (ACE2) as the entry receptor.[1-4] The S1 subunit of the SARS-CoV-2 spike protein contains the
receptor binding domain (RBD). Binding of the RBD to the human ACE2 receptor can be measured by ELISA allowing to evaluate inhibitors of the S protein ACE2 interaction. In this assay, the gold complexes Au-1 to Au-5 and Auranofin displayed good IC_{50} values in the range of 16–25 μM and were thus slightly more active than the reference drug Chloroquine (IC_{50} value: 31.9 μM).

An essential step in the replication of coronaviruses is the processing of the replicase polyprotein by proteases, such as the papain-like protease (PLpro), resulting in anumber of non-structural proteins (nsp) that are involved in downstream binding and replication events.[3,7] SARS-CoV-1 PLpro shares 83 % sequence identity with PLpro from SARS-CoV-2, structural components of the active sites of the enzymes do not substantially differ. As a cysteine protease PLpro is a likely target for gold-based drugs, which generally are known to interact with sulfur-containing molecular targets.

The inhibitory activity of the gold compounds towards PLpro from SARS-CoV-1 and SARS-CoV-2 was determined by an enzymatic FRET assay. Against PLpro from SARS-CoV-1, Au-1, Au-2 and Au-5 exhibited IC_{50} values in the range of 5–7 μM matching the potency of the reference inhibitor Disulfiram. Complexes Au-3 and Au-4 were less active with IC_{50} values of 14 μM. Auranofin remained the lowest active gold compound with an IC_{50} value of 25.5 μM (Table 1).

Against PLpro from SARS-CoV-2, the gold compounds Auranofin, Au-1, Au-2 and Au-5 as well as the reference inhibitor Disulfiram displayed strong inhibitory activity with IC_{50} values close to 1.0 μM. Notably, Au-3 and Au-4 were inactive against SARS-CoV-2 PLpro with IC_{50} values above 50 μM.

The missing activity of Au-3 and Au-4 against SARS-CoV-2 PLpro and their lower activity against SARS-CoV-1 PLpro compared to the other gold compounds indicates that the absence of the more easily exchangeable chlorido, and phosphate ligands prevents a stronger interaction of the gold center with the enzyme. It should also be noted that complexes Au-3 and Au-4 with their moderate interaction against SARS-CoV-1 PLpro followed the opposite trend than the other compounds, which were more active against SARS-CoV-2 PLpro than against the enzyme from SARS-CoV-1.

Cysteine residues in both types of studied SARS-CoV PLpro are the likely binding sites for gold metallodrugs and this interaction will be facilitated by ligand replacement reactions at the gold center. Importantly, a preprint report confirms that the catalytic cysteine 111 in the active site of SARS-CoV-2 PLpro can engage in Michael addition reactions with the β-carbon of vinyl groups of inhibitors.[16] Coordination of the gold center to

**Table 1. Inhibition of the spike-ACE2 interaction and PLpro activity (mean values and standard deviations, n = 3–4); n.d. not determined. Benzimidazole was used as a negative reference in both assays.**

|                  | spike-ACE2 (IC_{50} μM) | PLpro SARS-CoV-1 (IC_{50} μM) | PLpro SARS-CoV-2 (IC_{50} μM) |
|------------------|-------------------------|-------------------------------|-------------------------------|
| benzimidazole    | >100                    | >100                          | >100                          |
| Chloroquine      | 31.9 ± 5.4              | n.d.                          | n.d.                          |
| Disulfiram       | n.d.                    | 6.5 ± 0.4                    | 1.05 ± 0.33                  |
| Auranofin        | 22.2 ± 2.8              | 25.5 ± 1.2                   | 0.75 ± 0.13                  |
| Au-1             | 19.4 ± 5.7              | 6.3 ± 1.6                    | 1.04 ± 0.02                  |
| Au-2             | 20.0 ± 2.3              | 5.5 ± 0.5                    | 1.44 ± 0.22                  |
| Au-3             | 21.3 ± 6.8              | 14.2 ± 0.3                   | >100 (53 %)[a]               |
| Au-4             | 25.0 ± 4.2              | 14.1 ± 2.1                   | >50 (94 %)[a]                |
| Au-5             | 16.2 ± 2.4              | 6.7 ± 0.9                    | 0.96 ± 0.07                  |

[a] The percentage indicates the enzyme activity at the highest applied dosage.

Figure 1. left: simplified SARS-CoV-2 life cycle, gold drugs targeting the viral entry and replication are symbolised by golden bars; right: gold metallodrugs used in this study.
this cysteine residue is suggested as a very likely molecular mode of interaction for gold metallodrugs.

Besides the catalytic cysteine PLpro hosts several cysteine residues in a putative labile Zn-binding domain, which is responsible for correct folding of the protein and stabilization of the local geometry. Ejection of Zn\(^{2+}\) from this site represents another likely mechanism for inhibition of PLpro.\(^{[17]}\) Of note, the replacement of zinc from zinc-finger motifs and formation of so-called gold-fingers has been well documented.\(^{[18]}\) Interestingly, a very recent paper reports on the dual activity of thiol-reacting inhibitor Disulfiram as zinc removing agent as well as modifier of the catalytic cysteine of SARS-CoV-2 PLpro.\(^{[19]}\) As Disulfiram displayed similar activity with the Au-1, Au-2 and Au-5 against both types of PLpro, it could be speculated that these compounds share such dual activity against the enzyme. Thus we evaluated the ability of the inhibitors to replace zinc ions from PLpro by measuring the released zinc with a zinc selective fluorescent dye.

In the experiments with SARS-CoV-1 PLpro, the most efficient inhibitors Disulfiram, Au-1, Au-2 and Au-5 were effective zinc ejectors, while Auranofin as the lowest active enzyme inhibitor was not an efficient zinc ejector. The zinc removing activity of the moderate SARS-CoV-1 PLpro inhibitors Au-3 and Au-4 was strongly time-dependent.

In the studies with SARS-CoV-2 PLpro all compounds except Au-3 and Au-4 were efficient zinc ejectors (Figure 2). These results are in excellent agreement with the inactivity of Au-3 and Au-4 against SARS-CoV-2 PLpro as well as the high activity of Auranofin against this enzyme. Taken together, the results of the zinc ejection experiments correlate very well with the activity profile of the gold complexes in the enzymatic FRET assays and explain the differing activities of the complexes against the two types of PLpro.

In conclusion, we have demonstrated that gold complexes can target two relevant pathways in the life cycle of corona viruses. The strongest activity was noted against SARS-CoV-2 PLpro with Auranofin and the organometallic gold complexes Au-1, Au-2 and Au-5. The compounds belong thus to the very first potent inhibitors of the target enzyme. Their activity against the enzyme correlates very well with their zinc ejecting efficacy.

Notably, the inhibition of the replication of SARS-CoV-2 by Auranofin in human cells at low micro molar concentration (below the IC\(_{50}\) value for cytotoxicity) was reported very recently.\(^{[20]}\) For Au-1, Au-3 and Au-5 strong cytotoxic activity and effects on the cellular signaling have been reported previously.\(^{[11,12,14]}\) Such strong effects on host cells at this stage would hamper accurate characterization of possible antiviral effects in cell based models. Hence, a desirable reduction of cytotoxicity against host cells should accompany the ongoing target identification and structure optimization efforts.

The screening of gold and other metal-based drugs towards relevant SARS-CoV-2 molecular targets in combination with a toxicity evaluation is definitely warranted and is ongoing in our laboratories.

### Experimental Section

**General**

Chemicals and reagents were obtained from Sigma–Aldrich, TCI, Alfa Aesar and ACROS unless otherwise noted. NMR spectra were recorded on a Bruker DRX-400 AS or an AV III HD 500 NMR spectrometer; Positive-ion ESI (electrospray ionization) mass spectra were recorded on a Finnigan MAT95 XL or a LTQ-Orbitrap Velos linear iontrap coupled with orbitrap mass analyser (ThermoFisher Scientific). Elemental analyses were conducted in a Flash EA1112 apparatus. A VictorTM X4 Perkin–Elmer 2030 multilabel reader was used for the inhibitor assays. Complexes Au-1, Au-3 and Au-5 were prepared as previously reported.\(^{[11,12,14]}\)

\((1,3\text{-Diethyl-benzimidazol-2-ylidene})\text{trichloridogold(III)}\) (Au-2)

Au-2 was prepared according to a reported procedure with modifications.\(^{[21]}\) Au-1 (98.8 mg, 0.243 mmol, 1.0 equiv) and dichlorobenzene (106.7 mg, 0.389 mmol, 1.6 equiv) were dissolved in dichloromethane (4 mL) and the mixture was stirred for 24 h at room temperature under protection from light. Afterwards the solvent was removed under vacuum, the residue was washed three times with n-hexane and diethyl ether each and two times with cold chloroform. The complex Au-2 was dried under vacuum at 40 °C. Yield: 80.1 mg (0.168 mmol, 69%), yellow-orange powder; \(^1\)H NMR (500 MHz, D\(_2\)O): \(\delta = 8.05\) (dd, \(J_{HH} = 6.2\) Hz, \(J_{OH} = 3.1\) Hz, 2H, ArH), 7.60 (dd, \(J_{HH} = 6.2\) Hz, \(J_{OH} = 3.1\) Hz, 2H, ArH), 4.72 (t, \(J_{HH} = 7.2\) Hz, 4H, CH\(_2\)), 1.52 (t, \(J_{HH} = 7.2\) Hz, 6H, CH\(_3\)); \(^{13}\)C NMR (126 MHz, DOI: 10.1002/chem.202004112
\[ \text{[D2]DMSO}; \delta = 147.2 \ (\text{ArC2}_{\text{quat}}), 132.7 \ (2 \cdot \text{ArC}3_{\text{quat}}), 125.9 \ (2 \cdot \text{ArC}4 - \text{Ar}7), 113.0 \ (2 \cdot \text{ArC5}, \text{ArC6}), 43.3 \ (2 \cdot \text{CH}_3); \text{elemental analysis: calcld} (\%) \text{ for } C_{20}H_{12}N_{12}Cl_2: C 72.67, H 2.95, N 5.87; \text{found: } C 72.55, H 2.89, N 5.61; \text{MS(ESI): } m/z 473.0 \ [\text{M–Cl} + \text{MeOH}]^{+}, 209.1 \ [\text{M–AuCl}_3]^{+}. \text{Notably, upon oxidation of gold(I) to gold(III) a significant upfield shift of the carbon signal can be observed in the } ^{13}C\text{-NMR spectra.}\text{[21]} \text{Here the car-}

The inhibition of PLpro was determined according to reported protocols with minor modifications.\text{[24]} \text{The inhibitor compounds were prepared as stock solutions in DMSO and diluted hundredfold with HEPES buffer (50 mM HEPES, pH 7.5, 0.1 mM bovine serum albumin, 0.1% Triton-X100) to micromolar concentrations. Volumes of 50 \mu M of 350 nm His$_{6}$-SARS-CoV-1 PLpro (SouthBayBio) or of 200 nm SARS-CoV-2 PLpro (Elabscience) in HEPES buffer or blank HEPES buffer (negative control) were added to the wells of a black 96-well microtiter plate (Nunclon, Nunc). Volumes of 50 \mu M of the inhibitor solutions or 1% DMSO in HEPES buffer (positive control) were added. The resulting solutions (175 nm SARS-CoV-1 PLpro or 100 nm SARS-CoV-2 PLpro 0.5% DMSO, 0.1–10 \mu M test compound or blank HEPES buffer) were mixed and incubated at 37 °C for one hour. A volume of 100 \mu M of 1.00 \mu M Z-Arg-Leu-Arg-Gly-Gly-AMC (Bachem Bioscience) was added to all wells. The resulting solutions were mixed and the fluorescence measurement was measured immediately every 30 s for 10 min \((I_{\text{max}} = 355 \text{ nm}; I_{\text{min}} = 460 \text{ nm})\) at 37 °C using a Victor$^{\text{TM}}$ X4 Perkin Elmer 2030 multilabel reader. The increase of emission over time followed a linear trend \((r^2 > 0.97)\) and the enzymatic activities were calculated as the slope thereof. The \%IC$_{50}$ values were calculated as the concentration of the inhibitor that was required to decrease the enzymatic activity to 50% of the positive control. The wells containing the negative control were used to confirm the absence of false positive results by reaction of the inhibitor compound with the fluorogenic substrate.}

\text{Zn-ejection assays with SARS-CoV-1 and SARS-CoV-2 PLpro}

\text{To determine if the inhibitors are Zn-ejecting agents the presence of the Zn$^{2+}$ cation in solution was measured according to a recently published preprint.\text{[25]} The inhibitor compounds were prepared as stock solutions in DMSO and diluted hundredfold with HEPES buffer (50 mM HEPES, pH 7.5) to 100 \mu M concentrations. Volumes of 50 \mu M of 1 \mu M His$_{6}$-SARS-CoV-1 PLpro (SouthBayBio) or SARS-CoV-2 PLpro (Elabscience) in HEPES buffer or blank HEPES buffer (control for false positive results) were added to the wells of a black 96-well microtiter plate (Nunclon, Nunc). Volumes of 50 \mu M of the inhibitor solutions or 1% DMSO in HEPES buffer (control) were added. The resulting solutions (500 \mu M SARS-CoV-1 PLpro or SARS-CoV-2, 0.5% DMSO, 50 \mu M test compound or blank HEPES buffer) were mixed. A volume of 100 \mu M of 2.0 \mu M of zinc-specific fluorophore FluorZin$^{\text{TM}}$-3 (Invitrogen/LifeTechnologies) was added to all wells. The resulting solutions were mixed and the fluorescence emission was measured after 10 min every 10 min for 90 min \((I_{\text{max}} = 485 \text{ nm}; I_{\text{min}} = 535 \text{ nm})\) at 37 °C using a Victor$^{\text{TM}}$ X4 Perkin Elmer 2030 multilabel reader. The relative fluorescence was calculated by dividing the absolute fluorescence emission of the well containing the inhibitor by the absolute fluorescence of the respective well containing the enzyme but no inhibitor (control).}
Wells containing the inhibitor but no enzyme were used to check for false positive results. None of the tested compounds showed false positive results.

Acknowledgements

Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Auranofin • coronavirus • gold complexes • metallodrugs • SARS-CoV-2

[1] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-O. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X.-R. Shen, X. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Yang, G.-F. Xiao, Z.-L. Shi, Nature 2020, 579, 270–273.

[2] C. Wang, P. W. Horby, F. G. Hayden, G. F. Gao, The Lancet 2020, 395, 470–473.

[3] A. K. Ghosh, M. Brindisi, D. Shahabi, M. E. Chapman, A. D. Mesecar, ChemMedChem 2020, 15, 907–932.

[4] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M. A. Müller, C. Drosten, S. Pühlmann, Cell 2020, 181, 271–280.

[5] a) D. Wrapp, N. Wang, K. S. Corbett, J. A. Goldsmith, C.-L. Hsieh, O. Abiona, B. S. Graham, J. S. McLellan, Science 2020, 367, 1260–1263; b) R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, Q. Zhou, Science 2020, 367, 1444–1448; c) X. Ou, Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, Z. Xiang, Z. Mu, X. Chen, J. Chen, K. Hu, Q. Jin, J. Wang, Z. Qia, Nat. Commun. 2020, 11, 1620.

[6] L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauvering, S. Becker, K. Röss, R. Hilgenfeld, Science 2020, 368, 409–412.

[7] A. Zumla, J. F. W. Chan, E. I. Azhar, D. S. C. Hui, K.-Y. Yuen, Nature Rev. Drug Disc. 2016, 15, 327–347.

[8] J. R. Clasman, Y. M. Baez-Santos, R. C. Mettelman, A. O’Brien, S. C. Baker, A. D. Mesecar, Sci. Rep. 2017, 7, 40292.

[9] a) D. L. McKee, A. Sternberg, U. Stange, S. Lauper, C. Naujokat, Pharm. Res. 2020, 157, 104859; b) J. S. Morse, T. Lalonde, J. G. Zhang, R. W. Liu, ChemBiochem 2020, 21, 730–738.

[10] a) K. E. Traher, H. Okamoto, C. Kurono, M. Baba, C. Saliou, T. Soji, L. Packer, T. Okamoto, Int. Immunol. 1999, 11, 143–150; b) R. W. Y. Sun, W. Y. Yu, H. Sun, C.-M. Che, Chembiochem 2004, 5, 1293–1298; c) T. Okada, B. K. Patterson, S.-Q. Ye, M. E. Gurney, Virology 1993, 192, 631–642; d) P. N. Fonteh, F. K. Keter, D. Meyer, Biometals 2010, 23, 185–196.

[11] R. Rubbiani, I. Kitanovic, H. Alborsina, S. Can, A. Kitanovic, L. A. Onambélé, M. Stefanopoulou, Y. Geldmacher, W. S. Sheldrick, G. Wolber, A. Prokop, S. Wolff, Ingo Ott, J. Med. Chem. 2010, 53, 8608.

[12] R. Rubbiani, S. Can, I. Kitanovic, H. Alborsina, M. Stefanopoulou, M. Koskoschka, S. Mönchgesang, W. S. Sheldrick, S. Wolff, I. Ott, J. Med. Chem. 2011, 54, 8646.

[13] X. Cheng, S. Haeberle, I. Luca Shytaj, R. A. Gama-Brambilla, J. Theobald, S. Ghafoory, J. Wolker, U. Basu, C. Schmidt, A. Timm, et al., Commun. Biol. 2020, 3, 519.

[14] V. Andermark, K. Göke, M. Koskoschka, M. A. Abu El Maaty, C. T. Lunn, T. Zou, R. W.-Y. Sun, E. Aquiló, L. Oehniger, L. Rodriguez, H. Bunjes, S. Wolff, C.-M. Che, I. Ott, J. Inorg. Biochem. 2016, 160, 140–148.

[15] a) A. Casini, R. W.-Y. Sun, I. Ott, Metallo-drugs: Development and action of anticancer agents (De Gruyter), pp. 199–217; b) M. Mora, M. C. Gimeno, R. Visbal, Chem. Soc. Rev. 2019, 48, 447–462; c) E. Cerrada, V. Fernández-Moreira, M. C. Gimeno, Advances in Organometallic Chemistry.

[16] W. Rut, Z. Lu, M. Zmudzinski, S. Patchett, D. Nayak, S. J. Snips, F. El Ouailid, T. T. Huang, M. Bokes, M. Drag, S. K. Olsen, bioRxiv 2020, https://doi.org/10.1101/2020.04.29.068890.

[17] B. K. Malti, ACS Pharmacol. Transl. Sci. 2020, 3, 1017–1019.

[18] C. Abbehausen, Metallomics 2019, 11, 15–28.

[19] K. Sargsyan, C.-C. Lin, T. Chen, C. Grauffel, Y.-P. Chen, W.-Z. Yang, H. S. Yuan, C. Lim, Chem. Sci. 2020, 11, 9904–9909.

[20] a) H. A. Rothan, S. Stone, J. Natekar, P. Kumari, K. Arora, M. Kumar, Virology 2020, 547, 7; b) T. Marzo, L. Messari, ACS Med. Chem. Lett. 2020, 11, 1067–1068.

[21] H. Sivaram, J. Tan, H. V. Huynh, Organometallics 2012, 31, 5875–5883.

[22] J. Y. Z. Chiou, S. C. Luo, W. C. You, A. Bhattacharyya, C. S. Vasam, C. H. Huang, I. J. B. Lin, Eur. J. Inorg. Chem. 2009, 1950–1959.

[23] a) A. K. Ghosh, J. Takayama, Y. Aubin, K. Ratia, R. Chaudhuri, Y. Baex, K. Sleeman, M. Couchlin, D. B. Nichols, D. C. Mulhearn, B. S. Prabhakar, S. C. Baker, M. E. Johnson, A. D. Mesecar, J. Med. Chem. 2009, 52, 5228–5240; b) K. Ratia, S. Pegan, J. Takayama, K. Sleeman, M. Couchlin, S. Balijji, R. Chaudhuri, W. Fu, B. S. Prabhakar, M. E. Johnson, S. C. Baker, A. K. Ghosh, A. D. Mesecar, Proc. Natl. Acad. Sci. USA 2008, 105, 16119–16124.

Manuscript received: September 10, 2020
Accepted manuscript online: September 11, 2020
Version of record online: October 19, 2020