

## **Publications (selected)**

### **1. Originalarbeiten**

- 1.1 Ribosome Function and Translation, S. 2-3**
- 1.2 Antibiotic Drug Development, S. 3-6**
- 1.3 Resistance Mechanisms and Antibiotic Genotype-Phenotype Relationships, S. 7-10**
- 1.4 Laboratory Drug Susceptibility Testing, S. 10-12**
- 1.5 Molecular Diagnostics and Clinical Microbiology, S. 12-15**
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### **2. Weitere Publikationen**

- 2.1 Reviews (Englisch), S. 19-20**
- 2.2 Letters und Invited Comments, S. 20-21**
- 2.3 Book Contributions (Englisch), S. 21-22**
- 2.3 Reviews (Deutsch), S. 22-23**
- 2.5 Textbooks, S. 23-24**
- 2.6 Lehrmaterial, S. 24-25**

## 1. Originalarbeiten

### 1.1 Ribosome Function and Translation

pKa of adenine 2451 in the ribosomal peptidyl transferase center remains elusive  
L. Xiong, N. Polacek, P. Sander, E.C. Böttger and A. Mankin  
RNA 7: 1365-1369 (2001)

Essential mechanisms in the catalysis of peptide bond formation on the ribosome  
M. Beringer, C. Bruell, L. Xiong, P. Pfister, V.I. Katunin, A.S. Mankin, E.C. Böttger  
and M.V. Rodnina  
J. Biol. Chem. 280: 36065-36072 (2005)

Mitochondrial deafness alleles confer misreading of the genetic code  
S.N. Hobbie, C. Bruell, S. Akshay, S.K. Kalapala, D. Shcherbakov and E.C. Böttger  
Proc. Natl. Acad. Sci. U.S.A. 105: 3244-3249 (2008)

XBP1 mitigates aminoglycoside-induced endoplasmic reticulum stress and neuronal cell death  
N. Oishi, S. Duscha, H. Boukari, M. Meyer, J. Xie, G. Wei, B. Roschitzki, E.C. Böttger and  
J. Schacht  
Cell Death Dis. 6: e1763 (2015)

Mutant MRPS5 affects mitoribosomal accuracy and confers stress-related behavioral alterations  
R. Akbergenov, S. Duscha, A.-K. Fritz, R. Juskeviciene, N. Oishi, K. Schmitt, D. Shcherbakov,  
Y. Teo, H. Boukari, P. Freihof, P. Isnard-Petit, B. Oettinghaus, S. Frank, K. Thiam, H. Rehrauer,  
E. Westhof, J. Schacht, A. Eckert, D. Wolfer and E.C. Böttger  
EMBO Rep. 19: e46193 (2018)

Ribosomal mistranslation leads to silencing of the unfolded protein response and increased mitochondrial  
biogenesis  
D. Shcherbakov, Y. Teo, H. Boukari, A. Cortés Sanchón, M. Mantovani, I. Osinnii, J. Moore,  
R. Juskeviciene, M. Brilkova, S. Duscha, H. Santhosh Kumar, E. Laczko, H. Rehrauer, E. Westhof,  
R. Akbergenov and E.C. Böttger  
Commun. Biol. 2: 381 (2019)

Mitochondrial misreading in skeletal muscle accelerates metabolic aging and confers lipid accumulation  
and increased inflammation  
D. Shcherbakov, S. Duscha, R. Juskeviciene, L.M. Restelli, S. Frank, E. Laczko and E.C. Böttger  
RNA 27: 265-272 (2021)

Mitochondrial mistranslation in brain provokes a metabolic response which mitigates the age-associated  
decline in mitochondrial gene expression  
D. Shcherbakov, R. Juskeviciene, A. Cortés Sanchón, M. Brilkova, H. Rehrauer, E. Laczko  
and E.C. Böttger  
Int. J. Mol. Sci. 22: 2746 (2021)

Random errors in protein synthesis activate an age-dependent program of muscle atrophy  
in mice  
J. Moore, R. Akbergenov, M. Nigri, P. Isnard-Petit, A. Grimm, P. Seebeck, L. Restelli,  
S. Frank, A. Eckert, K. Thiam, D.P. Wolfer, D. Shcherbakov and E.C. Böttger  
Commun. Biol. 4: 703 (2021)

Silencing of the ER and integrative stress responses in the liver of mice with  
error-prone translation  
J. Moore, I. Osinnii, A. Grimm, B. Oettinghaus, A. Eckert, S. Frank and E.C. Böttger  
Cells 10: 2856 (2021)

ER-misfolded proteins become sequestered with mitochondria and impair mitochondrial function  
A. Cortés Sanchón, H. Santhosh Kumar, M. Mantovani, I. Osinnii, J.M. Mateos, A. Kaech,  
D. Shcherbakov, R. Akbergenov and E.C. Böttger  
Commun. Biol. 4: 1350 (2021)

Phenotype of Mrps5-associated phylogenetic polymorphisms is intimately linked to mitoribosomal misreading

R. Juskeviciene, A.-K. Fritz, M. Brilkova, R. Akbergenov, K. Schmitt, H. Rehrauer, E. Laczko,  
P. Isnard Petit, K. Thiam, A. Eckert, J. Schacht, D.P. Wolfer, E.C. Böttger, D. Shcherbakov  
Int. J. Mol. Sci. 23: 4384 (2022)

Premature aging in mice with error-prone protein synthesis

D. Shcherbakov, M. Nigri, R. Akbergenov, M. Brilkova, M. Mantovani, P. Isnard Petit,  
A. Grimm, A.A. Karol, Y. Teo, A. Cortés Sanchón, Y. Kumar, A. Eckert, K. Thiam, P. Seebeck,  
D.P. Wolfer and E.C. Böttger  
Science Adv. 8: eabl9051 (2022)

Error-prone protein synthesis recapitulates early symptoms of Alzheimer disease in aging mice

M. Brilkova, M. Nigri, H. Santhosh Kumar, M. Mantovani, J. Moore, C. Keller, A. Grimm,  
A. Eckert, D. Shcherbakov, R. Akbergenov, P. Seebeck, S.-D. Krämer, D.P. Wolfer,  
T.C. Gent and E.C. Böttger  
submitted for publication

## 1.2 Antibiotic Drug Development

Structural basis for selectivity and toxicity of ribosomal antibiotics

E.C. Böttger, B. Springer, T. Prammananan, Y. Kidan and P. Sander  
EMBO Rep. 2: 318-323 (2001)

Mutagenesis of 16S rRNA C1409-G1491 base pair differentiates between 6'OH and 6'NH<sub>3</sub><sup>+</sup> aminoglycosides

P. Pfister, S. Hobbie, C. Brüll, N. Corti, A. Vasella, E. Westhof, and E.C. Böttger  
J. Mol. Biol. 346: 467-475 (2005)

Analysis of the contribution of individual substituents in 4,6 aminoglycoside-ribosome interaction

S.N. Hobbie, P. Pfister, C. Bruell, E. Westhof and E.C. Böttger  
Antimicrob. Agents Chemother. 49: 5112-5118 (2005)

Binding of neomycin-class aminoglycoside antibiotics to mutant ribosomes with alterations in the A-site of 16S rRNA

S.N. Hobbie, P. Pfister, C. Bruell, P. Sander, B. François, E. Westhof and E.C. Böttger  
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A genetic model to investigate drug-target interactions at the ribosomal decoding site

S.N. Hobbie, C. Bruell, S. Kalapala, S. Akshay, S. Schmidt, P. Pfister and E.C. Böttger  
Biochimie 88: 1033-1043 (2006)

Engineering the rRNA decoding site of eukaryotic cytosolic ribosomes in bacteria

S.N. Hobbie, S.K. Kalapala, S. Akshay, C. Bruell, S. Schmidt, S. Dabow, A. Vasella,  
P. Sander and E.C. Böttger  
Nucleic Acids Res. 35: 6086-6093 (2007)

Genetic analysis of interactions with eukaryotic rRNA identify the mitoribosome as target in aminoglycoside ototoxicity

S.N. Hobbie, S. Akshay, S.K. Kalapala, C.M. Bruell, D. Shcherbakov and E.C. Böttger  
Proc. Natl. Acad. Sci. U.S.A. 105: 20888-20893 (2008)

Genetic reconstruction of protozoan rRNA decoding sites provides a rationale for paromomycin activity against *Leishmania* and *Trypanosoma*  
S.N. Hobbie, M. Kaiser, S. Schmidt, D. Shcherbakov, T. Janusic, R. Brun and E.C. Böttger  
PLoS Negl. Trop. Dis. 5: e1161 (2011)

Dissociation of antibacterial activity and aminoglycoside ototoxicity in the 4-monosubstituted 2-deoxystreptamine apramycin  
T. Matt, C.L. Ng, K. Lang, S.H. Sha, R. Akbergenov, D. Shcherbakov, M. Meyer, S. Duscha, J. Xie, S.R. Dubbaka, D. Perez-Fernandez, A. Vasella, V. Ramakrishnan, J. Schacht and E.C. Böttger  
Proc. Natl. Acad. Sci. USA 109: 10984-10989 (2012)

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S. Salian, T. Matt, R. Akbergenov, S. Harish, M. Meyer, S. Duscha, D. Shcherbakov, B.B. Bernet, A. Vasella E. Westhof and E.C. Böttger  
Antimicrob. Agents Chemother. 56: 6104-6108 (2012)

4'-O-substitutions determine selectivity of aminoglycoside antibiotics  
D. Perez-Fernandez, D. Shcherbakov, T. Matt, N.C. Leong, I. Kudyba, S. Duscha, H. Boukari, R. Patak, S.R. Dubbaka, K. Lang, M. Meyer, R. Akbergenov, P. Freihofer, S. Vaddi, P. Thommes, V. Ramakrishnan, A. Vasella and E.C. Böttger  
Nature Comm. 5: 3112 (2014)

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R.E. Lee, J.G. Hurdle, J. Liu, D.F. Bruhn, T. Matt, M.S. Scherman, P.K. Vaddady, Z. Zheng, J. Qi, R. Akbergenov, S. Das, D.B. Madhura, C. Rathi, A. Trivedi, C. Villellas, R.B. Lee, Rakesh, S.L. Waidyarachchi, D. Sun, M.R. McNeil, J.A. Ainsa, H.I. Boshoff, M. Gonzalez-Juarrero, B. Meibohm, E.C. Böttger and A.J. Lenaerts  
Nature Med. 20: 152-158 (2014)

Identification and evaluation of improved 4'-O-(alkyl) 4,5-disubstituted 2-deoxystreptamines as next generation aminoglycoside antibiotics  
S. Duscha, H. Boukari, D. Shcherbakov, S. Salian, S. Silva, A. Kendall, T. Kato, R. Akbergenov, D. Perez-Fernandez, B. Bernet, S. Vaddi, P. Thommes, J. Schacht, D. Crich, A. Vasella and E.C. Böttger  
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In-vivo efficacy of apramycin in murine infection models  
M. Meyer, P. Freihofer, M. Scherman, J. Teague, A.J. Lenaerts and E.C. Böttger  
Antimicrob. Agents Chemother. 58: 6938-6941 (2014)

Aminomethyl spectinomycins as novel therapeutics for drug resistant respiratory tract and sexually transmitted bacterial infections  
D.F. Bruhn, S.L. Waidyarachchi, D.B. Madhura, D. Shcherbakov, Z. Zheng, J. Liu, Y.M. Abdelrahmand, A.P. Singh, S. Duscha, C. Rathi, R.B. Lee, R.J. Belland, B. Meibohm, J.W. Rosch, E.C. Böttger and R.E. Lee  
Sci. Transl. Med. 7: 288ra75 (2015)

Influence of 4'-O-glycoside constitution and configuration on ribosomal selectivity of paromomycin  
T. Matsushita, W. Chen, R. Juskeviciene, Y. Teo, D. Shcherbakov, A. Vasella, E.C. Böttger and D. Crich  
J. Am. Chem. Soc. 137: 7706-7717 (2015)

Synthesis and antiribosomal activities of 4'-O-, 6'-O-, 4''-O-, 4',6'-O- and 4'',6''-O-derivatives in the kanamycin series reveal differing target selectivity patterns between the 4,5- and 4,6-series of disubstituted 2-deoxystreptamine classes of aminoglycoside antibiotics  
T. Kato, G. Yang, Y. Teo, R. Juskeviciene, D. Perez-Fernandez, H.M. Shinde, S. Salian, B. Bernet, A. Vasella, E.C. Böttger and D. Crich  
ACS Infect. Dis. 1: 479-486 (2015)

Structure-based design and synthesis of apramycin-paromomycin analogues: importance of the configuration at the 6'-position and differences between the 6'-amino and hydroxy series

A.R. Mandhapaty, G. Yang, T. Kato, D. Shcherbakov, S.N. Hobbie, A. Vasella, E.C. Böttger and D. Crich  
J. Am. Chem. Soc. 139: 14611-14619 (2017)

Development of a novel lead that targets *M. tuberculosis* polyketide synthase 13

A. Aggarwal, M.K. Parai, N. Shetty, D. Wallis, L. Woolhiser, C. Hastings, N.K. Dutta, S. Galaviz, R.C. Dhakal, R. Shrestha, S. Wakabayashi, C. Walpole, D. Matthews, D. Floyd, P. Scullion, J. Riley, O. Epemolu, S. Norval, T. Snavely, G.T. Robertson, E.J. Rubin, T.R. Ioerger, F.A. Sirgel, R. van der Merwe, P.D. van Helden, P. Keller, E.C. Böttger, P.C. Karakousis, A.J. Lenaerts and J.C. Sacchettini  
Cell 170: 249-259 (2017)

Structure-activity relationships of spectinamide antituberculosis agents; a dissection of ribosomal inhibition and native efflux avoidance contributions

J. Liu, D. Bruhn, R. Lee, Z. Zheng, T. Janusic, D. Shcherbakov, M. Scherman, H. Boshoff, S. Das, K. Raskesh, S. Waidyarachchi, T. Brewer, B. Gracia, L. Yang, J. Bollinger, G. Robertson, B. Meibohm, A. Lenaerts, J. Ainsa, E.C. Böttger and R. Lee  
ACS Infect. Dis. 3: 72-88 (2017)

N6', N6''', and O4' modifications to neomycin affect ribosomal selectivity without compromising antibacterial activity

G.C. Sati, D. Shcherbakov, S.N. Hobbie, A. Vasella, E.C. Böttger and D. Crich  
ACS Infect. Dis. 3: 368-377 (2017)

Effects of the 1- N-(4-amino-2 S-hydroxybutyryl) and 6'- N-(2-hydroxyethyl) substituents on ribosomal selectivity, cochleotoxicity, and antibacterial activity in the sisomicin class of aminoglycoside antibiotics

S. Sonousi, V.A. Sarpe, M. Brilkova, J. Schacht, A. Vasella, E.C. Böttger and D. Crich  
ACS Infect. Dis. 4: 1114-1120 (2018)

Design, multigram synthesis, and in vitro and in vivo evaluation of propylamycin: a semisynthetic 4,5-deoxystreptamine class aminoglycoside for the treatment of drug-resistant *Enterobacteriaceae* and other Gram-negative pathogens

T. Matsushita, G. Sati, N. Kondasinghe, M. Pirrone, T. Kato, P. Waduge, H. Santhosh Kumar, A. Cortes Sanchon, M. Dobosz-Bartoszek, D. Shcherbakov, M. Juhas, S.N. Hobbie, T. Schrepfer, C. Chow, Y. Polikanov, J. Schacht, A. Vasella, E.C. Böttger and D. Crich  
J. Am. Chem. Soc. 141: 5051-5061 (2019)

In vitro activity of apramycin against multidrug-, carbapenem- and aminoglycoside-resistant *Enterobacteriaceae* and *Acinetobacter baumannii*

M. Juhas, E. Widlake, J. Teo, D.L. Huseby, J.M. Tyrrell, Y.S. Polikanov, O. Ercan, A. Petersson, S. Cao, A.F. Aboklaish, A. Rominski, D. Crich, E.C. Böttger, T.R. Walsh, D. Hughes and S.N. Hobbie  
J. Antimicrob. Chemother. 74: 944-952 (2019)

Modification at the 2'-position of the 4,5-series of 2-deoxystreptamine aminoglycoside antibiotics to resist aminoglycoside modifying enzymes and increase ribosomal target selectivity

G.C. Sati, V.A. Sarpe, T. Furukawa, S. Mondal, M. Mantovani, S.N. Hobbie, A. Vasella, E.C. Böttger and D. Crich  
ACS Infect. Dis. 5: 1718-1730 (2019)

Apralogs: apramycin 5-O-glycosides and ethers with improved antibacterial activity and ribosomal selectivity and reduced susceptibility to the aminoacyltransferase (3)-IV resistance determinant

J.C.K. Quirke, P. Rajasekaran, V.A. Sarpe, A. Sonousi, I. Osinnii, M. Gysin, K. Haldimann, Q.J. Fang, D. Shcherbakov, S.N. Hobbie, S.H. Sha, J. Schacht, A. Vasella, E.C. Böttger and D. Crich  
J. Am. Chem. Soc. 142: 530-544 (2020)

Aminoglycosides - time for resurrection of a neglected class of antibacterials?

E.C. Böttger and D. Crich  
ACS Infect. Dis. 6: 168-172 (2020)

Synthesis, antibacterial action and ribosome inhibition of deoxyspectinomycins

S. Dharuman, L.A. Wilt, J. Liu, S.M. Reeve, C.W. Thompson, J.M. Elmore, D. Shcherbakov, R.B. Lee, E.C. Böttger and R.E. Lee  
J. Antibiot. 74: 381-396 (2021)

Efficacy of EBL-1003 (apramycin) against *Acinetobacter baumannii* lung infections in mice

K. Becker, V. Aranzana-Climent, S. Cao, A. Nilsson, R. Shariatgorji, K. Haldimann, B. Platzack, D. Hughes, P. Andrén, E.C. Böttger, L. Friberg and S.N. Hobbie  
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Synthesis and antibacterial activity of propylamycin derivatives functionalized at the 5"- and other positions with a view to overcoming resistance due to aminoglycoside modifying enzymes

D. Lubriks, R. Zogota, V. Sarpe, T. Matsushita, G. Sati, K. Haldimann, M. Gysin, E.C. Böttger, A. Vasella, E. Suna, S.N. Hobbie and D. Crich  
ACS Infect. Dis. 7: 2413-2424 (2021)

An advanced apralog with increased in-vitro and in-vivo activity toward Gram-negative pathogens and reduced ex-vivo cochleotoxicity.

A. Sonousi, J. Quirke, P. Waduge, T. Janusic, M. Gysin, K. Haldimann, S.N. Hobbie, S. Sha, J. Schacht, Ch. Chow, A. Vasella, E.C. Böttger, S. Xu and D. Crich  
ChemMedChem 16: 335-339 (2021)

Influence of ring size in conformationally restricted ring I analogs of paromomycin on antiribosomal and antibacterial activity

M. Pirrone, S.N. Hobbie, A. Vasella, E.C. Böttger and D. Crich  
RSC Med Chem. 12: 1585-1591 (2021)

Antibacterial activity of apramycin at acidic pH warrants wide therapeutic window in the treatment of complicated urinary tract infections and acute pyelonephritis

K. Becker, S. Cao, A. Nilsson, M. Erlandsson, S.K. Hotop, J. Kuka, J. Hansen, K. Halidmann, S. Grinberga, T. Berruga-Fernandéz, D.L. Huseby, R. Shariatgorji, E. Lindmark, B. Pltzack, E.C. Böttger, D. Crich, L.E. Friberg, C. Vingsbo Lundberg, D. Hughes, M. Brönstrup, P.E. Andrén, E. Liepinsh and S.N. Hobbie  
EBioMedicine 73: 103652 (2021)

Apramycin overcomes the inherent lack of antimicrobial bactericidal activity in

*Mycobacterium abscessus*

P. Selchow, D. Ordway, D. Verma, N. Whittel, A. Petrig, S.N. Hobbie, E.C. Böttger and P. Sander  
Antimicrob. Agents Chemother. 66: e0151021 (2022)

Structure-activity relationships for 5" modifications of 4,5-aminoglycoside antibiotics

J.C.K. Quirke, G.C. Sati, A. Sounousi, M. Gysin, K. Haldimann, E.C. Böttger, A. Vasella, S.N. Hobbie, D. Crich  
ChemMedChem. 17: e202200120 (2022)

### 1.3 Resistance Mechanisms and Antibiotic Genotype-Phenotype Relationships

Molecular basis of streptomycin resistance in *Mycobacterium tuberculosis*: alteration of the ribosomal protein S12 gene and point mutations within a functional 16S ribosomal RNA pseudoknot

M. Finken, P. Kirschner, A. Meier, A. Wrede and E.C. Böttger  
Mol. Microbiol. 9: 1239-1246 (1993)

Genetic alterations in streptomycin resistant *Mycobacterium tuberculosis*: mapping of mutations conferring resistance

A. Meier, P. Kirschner, B. Springer, U. Vogel, F. Bange and E.C. Böttger  
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Identification of mutations in the 23S rRNA gene of clarithromycin-resistant *Mycobacterium intracellulare*

A. Meier, P. Kirschner, B. Springer, V.A. Steingrube, B.A. Brown, R.J. Wallace and E.C. Böttger  
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Genetic basis for clarithromycin resistance among isolates of *Mycobacterium chelonae* and *Mycobacterium abscessus*

R.J. Wallace, A. Meier, B.A. Brown, Y. Zhang, P. Sander, G.O. Onyi and E.C. Böttger  
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Molecular mechanisms of clarithromycin resistance in *Mycobacterium avium*: observation of multiple 23S rDNA mutations in a clonal population

A. Meier, L. Heifets, R.J. Wallace, Y. Zhang, B.A. Brown, P. Sander and E.C. Böttger  
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Introducing mutations into a chromosomal rRNA gene using a genetically modified eubacterial host with a single rRNA operon

P. Sander, T. Prammananan and E.C. Böttger  
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Correlation of molecular resistance mechanism and phenotypic resistance level in streptomycin resistant *M. tuberculosis*

A. Meier, P. Sander, K.-J. Schaper, M. Scholz and E.C. Böttger  
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The role of ribosomal RNAs in macrolide resistance

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Mol. Microbiol. 26: 469-480 (1997)

A single 16S ribosomal RNA substitution is responsible for resistance to amikacin and other 2-deoxystreptamine aminoglycosides in *Mycobacterium abscessus* and *Mycobacterium chelonae*

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Fitness of antibiotic-resistant microorganisms and compensatory mutations

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P. Pfister, N. Corti, S. Hobbie, C. Bruell, R. Zarivach, A. Yonath and E.C. Böttger  
Proc. Natl. Acad. Sci. U.S.A. 102: 5180-5185 (2005)
- Directed mutagenesis of *Mycobacterium smegmatis* 16S rRNA to reconstruct the in-vivo evolution of aminoglycoside resistance in *Mycobacterium tuberculosis*  
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K.S. Long, C. Munck, T.M.B. Andersen, M.A. Schaub, S.N. Hobbie, E.C. Böttger and B. Vester  
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K. Miksits und E.C. Böttger

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Medizinische Mikrobiologie, Skript Hauptvorlesung

E.C. Böttger

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