BIOGRAPHICAL SKETCH

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NAME: Ebright, Richard H.

eRA COMMONS USER NAME (credential, e.g., agency login): EBRIGHT1

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if aplicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	DATE	FIELD OF STUDY
Harvard University, Cambridge MA	A.B.	05/1981	Biology (*summa cum laude*)
Harvard University, Cambridge MA (with Jon Beckwith)	Ph.D.	01/1987	Microbiology and Molecular Genetics

A. Personal Statement

My research focusses on the structure, mechanism, and regulation of bacterial transcription complexes, and on the development of inhibitors of bacterial transcription as antibacterial therapeutic agents. My research employs tools of structural biology, biophysical chemistry, and drug discovery. My research contributions include defining the structural organization of transcription initiation complexes, defining the "scrunching" mechanism of initial transcription, defining the "recruitment" mechanism of transcription activation, defining the structural basis of bacterial transcription-translation coupling, defining novel antibacterial targets in the bacterial transcription machinery, and identifying novel antibacterial agents that exhibit activity against drug-resistant bacterial pathogens. I direct a laboratory of approximately ten postdoctoral associates, graduate students, and technicians and serves as project leader on two NIH grants.

I will serve as PI on the project.

Ongoing and Recent Support

Prokaryotic transcription termination
NIH-NIGMS, R01-GM041376; 08/15/23-08/14/27

Center to develop therapeutic countermeasures to high-threat bacterial agents
NIH-NIAID, U19-AI142731; 05/01/19-04/30/24

Citations

Yin. Z., Kaelber, J., and Ebright R.H. (2019) Structural basis of Q-dependent antitermination. *Proc Natl Acad Sci USA* **116**, 18384-18390. PMC6744881.

Wang, C., Molodtsov, V., Firlar, E., Kaelber, J., Blaha, G., Su, M., and Ebright RH. (2020) Structural basis of transcription-translation coupling. *Science* **369**, 1359-1365. PMC7566311.

Yin, Z, Bird JG, Kaelber JT, Nickels BE, Ebright RH. (2022) In transcription antitermination by Qλ, NusA induces refolding of Qλ to form a nozzle that extends the RNA polymerase RNA-exit channel. *Proc Natl Acad Sci USA*. **119**, e2205278119. PMC9388147.

Molodtsov, V., Wang, C., Firlar, E., Kaelber, H., and Ebright, R.H. (2023) Structural basis of Rho-dependent transcription termination. *Nature* **614**,367-374. PMC9911385.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2013- Board of Governors Professor, Department of Chemistry, Rutgers University, New Brunswick, NJ
1997-2013 Investigator, Howard Hughes Medical Institute
1995-2013 Professor, Department of Chemistry, Rutgers University, New Brunswick, NJ
1992-1995 Associate Professor, Department of Chemistry, Rutgers University, New Brunswick, NJ
1987-1992 Assistant Professor, Department of Chemistry, Rutgers University, New Brunswick, NJ
1987- Laboratory Director, Waksman Institute of Microbiology, Piscataway NJ
1984-1987 Junior Fellow, Society of Fellows, Harvard University, Cambridge, MA

Honors

2017 Rutgers University Chancellor's Award for Research Excellence
2016 Member, American Academy of Arts and Sciences
2013 National Institutes of Health MERIT Award
2012 Theobold Smith Society Waksman Award
2011 Fellow, Infectious Diseases Society of America
2004 Fellow, American Association for the Advancement of Science
1998 Rutgers University Board of Trustees Research Excellence Award
1996 Fellow, American Academy of Microbiology
1995 American Society for Biochemistry and Molecular Biology Schering-Plough Award
1990 Johnson and Johnson Discovery Research Fellowship
1989 Searle Scholar Award
1980 Phi Beta Kappa

C. Contributions to Science

1. Sequence-Specific Protein-DNA Interaction

Ebright helped define the basis of sequence-specific protein-DNA interaction and developed artificial sequence-specific DNA cleaving agents.

Using genetic approaches and photocrosslinking approaches, Ebright established that sequence-specific DNA binding proteins recognize DNA sequences through direct contacts between amino acids and DNA bases. By conjugating a DNA cleaving agent to a sequence-specific DNA binding protein in a manner that permitted activity in specific complexes but not in nonspecific complexes, Ebright constructed a high-specificity DNA cleaving agent able to cleave megabase DNA substrates at single sites.

Ebright, R.H., Cossart, P., Gicquel-Sanzey, B., and Beckwith, J. (1984) Mutations that alter the DNA sequence specificity of the catabolite gene activator protein of *E. coli*. *Nature* **311**, 232-235.

Ebright, R.H.(1986) Evidence for a contact between glutamine-18 of lac repressor and base pair 7 of *lac* operator. *Proc. Natl. Acad. Sci. USA* **83**, 303-307. PMC322846.

Blatter, E., Ebright, Y., and Ebright, R.H. (1992) Identification of an amino acid-base contact in the GCN4-DNA complex by bromouracil-mediated photocrosslinking. *Nature* **359**, 650-652.

Pendergrast, P.S., Ebright, Y., and Ebright, R.H. (1994) High-specificity DNA cleavage agent: design and application to kilobase and megabase DNA substrates. *Science* **265**, 959-961.

2. Transcription: Transcription Activation

Ebright provided the first mechanistic and structural description of transcription activation.

Ebright analyzed transcription activation by *Escherichia coli* catabolite activator protein (CAP) at the *lac* promoter. He showed that transcription activation requires a small patch of the activator ("activating region") and a small patch of a flexibly tethered module of RNA polymerase ("activation target"), showed that transcription activation involves direct interaction between activating region and activation target, determined a crystal structure of the complex between activating region and activation target, and, most recently, determined an EM structure of the intact transcription-activation complex. His results establish that transcription activation by CAP at *lac* proceeds by a "recruitment" mechanism, in which interactions between CAP and RNA polymerase facilitate binding of RNA polymerase to DNA.

Zhou, Y., Busby, S., and Ebright, R.H. (1993) Identification of the functional subunit of a dimeric transcription activator protein by use of "oriented heterodimers." *Cell* **73**, 375-379.

Chen, Y., Ebright, Y., and Ebright, R.H. (1994) Identification of the target of a transcription activator protein by protein-protein photocrosslinking. *Science* **265**, 90-92.

Blatter, E., Ross, W., Tang, H., Gourse, R., and Ebright, R.H. (1994) Domain organization of RNA polymerase α subunit: C-terminal 85 amino acids constitute a domain capable of dimerization and DNA binding. *Cell* **78**, 889-896.

Benoff, B., Yang, H., Lawson, C., Parkinson, G., Liu, J., Blatter, E., Ebright, Y., Berman, H., and Ebright, R.H. (2002) Structural basis of transcription activation: structure of the CAP-αCTD-DNA complex. *Science* **297**, 1562-1566.

3. Transcription: Structures of Transcription Initiation Complexes

Ebright defined the structural organization of the nucleoprotein complexes that perform transcription initiation.

Using distance restraints from systematic photocrosslinking and systematic fluorescence resonance energy transfer (FRET), Ebright constructed the first structural models of bacterial, archaeal, and eukaryotic transcription-initiation complexes. Using x-ray crystallography, Ebright determined the first atomic structure of a promoter-dependent, initiation-factor-dependent, functional transcription initiation complex. More recently, using x-ray crystallography, Ebright determined atomic structures of transcription initiation complexes engaged in *de novo* initiation and initial transcription, providing comprehensive structural descriptions of the protein-DNA interactions involved in promoter recognition, promoter unwinding, *de novo* initiation, and initial transcription. Most recently, using x-ray crystallography, Ebright determined the first atomic structures of a gene-specific transcription activation complex and of Mycobacterial transcription initiation complexes.

Naryshkin, N., Revyakin, A., Kim, Y., Mekler, V., and Ebright, R.H. (2000) Structural organization of the RNA polymerase-promoter open complex. *Cell* **101**, 601-611.

Mekler, V., Kortkhonjia, E., Mukhopadhyay, J., Knight, J., Revyakin, A., Kapanidis, A., Niu, W., Ebright, Y., Levy, R., and Ebright, R.H. (2002) Structural organization of RNA polymerase holoenzyme and the RNA polymerase-promoter open complex. *Cell* **108**, 599-614.

Zhang, Y., Feng, Y., Chatterjee, S., Tuske, S., Ho, M., Arnold, E., and Ebright, R. (2012) Structural basis of transcription initiation. *Science* **338**, 1076-1080. PMC359305.

Feng, Y., Zhang, Y., and Ebright, R.H. (2016) Structural basis of transcription activation. *Science* **352**, 1330-1333. PMC4905602.

4. Transcription: Mechanisms of Transcription and Transcription-Translation Coupling

Ebright elucidated the mechanisms of initial transcription and promoter escape in transcription initiation and defined the sequence determinants and mechanisms of transcriptional pausing in transcription elongation, and defined the factor requirements and structural basis of transcription-translation coupling.

Using ensemble and single-molecule FRET, Ebright showed that the transcription initiation factor σ is not obligatorily released in promoter escape but, instead, can remain bound to RNA polymerase, translocate with RNA polymerase, and recognize regulatory DNA sequence elements during transcription elongation. Using single-molecule FRET and single-molecule nanomanipulation, Ebright showed that initial transcription involves a "scrunching" mechanism, in which RNA polymerase remains stationary on promoter DNA and reels in downstream DNA, and that promoter escape involves the accumulation of stress through scrunching, followed by the use of accumulated stress to break RNA polymerase-promoter interactions.

Using high-throughput sequencing approaches, Ebright and collaborators showed that transcription start-site selection also involves scrunching, defined, genome-wide, DNA sequence determinants for pausing during transcription elongation, and demonstrated roles of a sequence element recognized by RNA polymerase--the "core recognition element"--in transcription initiation, transcription elongation, and transcriptional pausing.

Most recently, using cryo-EM, Ebright defined structures of transcription termination, transcription antitermination, and transcription-translation-coupling complexes.

Kapanidis, A., Margeat, E., Ho, S.O., Kortkhonjia, E., Weiss, S. & Ebright, R.H. (2006) Initial transcription by RNA polymerase proceeds through a DNA-scrunching mechanism. *Science* **314**, 1144-1147. PMC2754788.

Chakraborty, A., Wang, D., Ebright, Y., Korlann, Y., Kortkhonjia, E., Kim, T., Chowdhury, S., Wigneshweraraj, S., Irschik, H., Jansen, R., Nixon, B.T., Knight, J., Weiss, S., and Ebright, R.H. (2012) Opening and closing of the bacterial RNA polymerase clamp. *Science* **337**, 591-595. PMC3626110.

Wang, C., Molodtsov, V., Firlar, E., Kaelber, J., Blaha, G., Su, M., and Ebright, R.H. (2020) Structural basis of transcription-translation coupling. *Science* **369**, 1359-1365. PMC7566311.

Molodtsov, V., Wang, C., Firlar, E., Kaelber, H., and Ebright, R.H. (2023) Structural basis of Rho-dependent transcription termination. *Nature* **614**,367-374. PMC9911385.

5. Transcription: Transcription Inhibitors, Antibacterial Drug Discovery Targeting Transcription

Ebright is elucidating binding sites and mechanisms of antibacterial agents that function by inhibiting bacterial transcription and is developing small-molecule inhibitors of bacterial transcription as antituberculosis drugs and broad-spectrum antibacterial drugs.

Ebright defined the binding sites and mechanisms of the antibiotics microcin J25, streptolydigin, myxopyronin, corallopyronin, ripostatin, GE23077, salinamide, pseudouridimycin, and fidaxomicin, and of synthetic antibacterial agents of the CBR, phloroglucinol, and aroyl-aryl-phenylalaninamide classes.

Ebright validated myxopyronins, phloroglucinols, and pseudouridimycins as advanced leads for broad-spectrum antibacterial therapy (with activity against priority pathogens in culture and in animals) and validated aroyl-aryl-phenylalaninamides as leads for antituberculosis therapy (with activity against *Mycobacterium tuberculosis* in culture and in animals). Guided by crystal structures of bacterial RNA polymerase in complex with these leads, Ebright and colleagues are designing, synthesizing, and evaluating analogs of these leads, seeking novel compounds with improved antibacterial activities and improved pharmacological properties.

Prompted by crystal structures indicating that rifamycins--a class of RNA polymerase inhibitors currently used as antibacterial drugs--and GE23077 interact with adjacent binding sites on RNA polymerase and can bind simultaneously to RNA polymerase, Ebright and colleagues linked a rifamycin to GE23077 and showed that the resulting "bipartite inhibitor" had exceptional potency and exceptional ability to overcome target-dependent resistance. Guided by crystal structures, Ebright and colleagues are designing, synthesizing, and evaluating additional novel bipartite inhibitors comprising rifamycin-site ligands linked to GE23077-site ligands.

Mukhopadhyay, J., Das, K., Ismail, S., Koppstein, D., Jang, M., Hudson, B., Sarafianos, S., Tuske, S., Patel, J., Jansen, R., Irschik, H., Arnold, E., and Ebright, R.H. (2008) The RNA polymerase "switch region" is a target of inhibitors. *Cell* **135**, 295-307. PMC2580802.

Maffioli, S., Zhang, Y., Degen, D., Carzaniga, T., Del Gatto, G., Serina, S., Monciardini, P., Mazzetti, C., Guglierame, P., Candiani, G., Chiriac, A.I., Facchetti, G., Kaltofen, P., Sahl, H.-G., Dehò, G., Donadio, S., and Ebright, R.H. (2017) Antibacterial nucleoside-analog inhibitor of bacterial RNA polymerase. *Cell* **169**, 1240-1248. PMC5542026.

Lin, W., Mandal, S., Degen, D., Liu, Y.., Ebright, Y., Li, S., Feng, Y., Zhang, Y., Mandal, S., Jiang, Y., Liu, S., Gigliotti, M., Talaue, M., Connell, N., Das, K., Arnold, E., and Ebright, R. (2017) Structural basis of *Mycobacterium tuberculosis* transcription and transcription inhibition. *Mol. Cell* **166**, 169-179. PMC5438085.

Lin, W., Das, K., Degen, D., Mazumder, A., Duchi, D., Wang, D., Ebright, Y., Ebright, R.Y., Sineva, E., Gigliotti, M., Mandal, S., Jiang, Y., Liu, Y., Yin, R., Zhang, Z., Eng, E., Thomas, D., Donadio, S., Zhang, C., Kapanidis, A., and Ebright, R.H. (2018) Structural basis of transcription inhibition by fidaxomicin (lipiarmycin A3). *Mol. Cell* **70**, 60-71. PMC6205224.

6. Complete List of Published Work in MyBibliography

https://www.ncbi.nlm.nih.gov/myncbi/richard.ebright.1/bibliography/public/?sortby=Pubdate&sdirection=descending