BIOGRAPHICAL SKETCH

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NAME: Randall J. Cohrs, PhD

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

POSITION TITLE: Professor of Neurology

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Southern Illinois University, Carbondale, IL	BA	1975	Microbiology
Southern Illinois University, Carbondale, IL	MS	1980	Biological Sciences
Southern Illinois University, Carbondale, IL	PhD	1986	Microbiology

A. Personal Statement

For more than 25 years, my lab has studied the molecular virology of varicella zoster virus (VZV), with a strong focus on virus transcription in latently infected human ganglia. This work has necessitated acquisition of multiple ganglia removed at autopsy from more than ~800 humans and has shown that during latency, virus is in neurons, that VZV DNA is circular, and that VZV gene transcription is restricted. We have pioneered construction of cDNA libraries from latently infected human ganglia enriched for VZV transcripts and confirmed by sequencing, that latent VZV transcripts, unlike latent HSV-1 transcripts, contain a 3'-poly[A] tail. The promoters for VZV open reading frames (ORFs) 21 and 29, two latently expressed virus genes were mapped and their encoded proteins were analyzed. To extend our transcriptional analysis to the entire VZV transcriptome, we were the first to construct arrays to quantify VZV transcripts from all predicted virus ORFs. We characterized the transcriptional pattern of all VZV genes during productive infection in tissue culture. We also determined that VZV gene transcription is dependent on continuing virus DNA replication, and that the rate of VZV mRNA decay is the same for both high and low abundance virus transcripts. While the arrays successfully characterized the VZV transcriptome in cells infected with wild-type virus, attenuated vaccine virus and mutated VZV, we had to devise a more sensitive and specific multiplex PCR assay to identify the complete VZV transcriptome in latently infected human ganglia. Using this novel technology, my lab detected transcripts from 12 VZV ORFs in latently infected human ganglia. This finding confirmed our previous quantitative study which revealed that VZV ORF 63 is the most prevalent and abundant virus gene transcribed during latency. Importantly, we were the first and remain the only one to show that in latently infected human ganglia, histones are bound to specific sites on the latent VZV genome, and that these histones contain posttranslational modifications indicative of active gene transcription. Overall, our studies established that during latency in human ganglia, VZV transcription is limited to ORF 63 and during early stages of virus reactivation virus transcription undergoes generalized deregulation resulting in transcription of multiple immediate-early, early and late VZV genes; a condition recently seen in early stages of HSV-1 reactivation. Thus my lab has finally united the seemingly contradictory findings from two human neurotropic alphaherpesviruses into a general theme explaining reactivation as modification of epigenetic regulation of latent virus genome followed by conditions potentiating virus DNA replication.

Finally, realizing that the alphaherpesvirus field was disjointed, lacked communication and needed a means to communicate, I established the Colorado Alphaherpesvirus Latency Society where each year leading clinical/basic investigators in the field assemble to communicate new ideas as they mentor postdoctoral fellows and early-stage investigators.

As the Project 2 Leader in this proposed Program Project, I will explore the hypothesis that adventitial fibroblasts isolated from GCA-positive TAs undergo epigenetic reprogramming such that they are proinflammatory, raising the possibility of treatment with histone deacetylase inhibitors. To test this hypothesis, I will 1) quantify soluble proinflammatory cytokines from adventitial fibroblasts isolated from GCA-positive/VZV antigen-positive TAs acquired at biopsy from patients with clinical features of GCA and from normal temporal arteries acquired at autopsy, 2) determine the extent of host gene differential transcription associated with establishment of a chronic proinflammatory phenotype in cultured adventitial fibroblasts isolated from GCA-positive/VZV antigen-positive TAs and normal temporal arteries, and 3) identify enhancer/promoter epigenetic modifications responsible for continued activation of proinflammatory pathways in adventitial fibroblasts from GCA-positive/VZV antigen-positive and normal TAs by ChiP-seq.

Ongoing and recently completed projects that I would like to highlight include:

P01-AG 032958 (NIH/NIA)
Nagel (Program Director); Role: Project Leader/Project 2
03/01/2009 – 12/31/2023
A Major Contributor of Serious Multisystem Disease in the Elderly: Varicella Zoster Virus-induced Inflammation
Project 2: Investigating the VZV-Induced Epigenetic Modifications of Vascular Adventitial Fibroblasts that Contribute to Persistent Inflammation and VZV Vasculopathy

R01-AI151290 (NIH/NIAID)
Cohrs (PI)
11/17/20 – 10/31/25
Role of VZV Latency Transcript (VLT) and ORF63 in Latency and Reactivation

R01-NS093716 (NIH/NINDS)
Cohrs (PI)
07/01/15 – 06/30/21
Neurobiology of Varicella Zoster Virus

B. Positions, Scientific Appointments and Honors

Other Experience and Professional Memberships

2015-present	Adjunct Professor, Department of Immunology & Microbiology, UCSOM, Denver. CO
2011-present	President, Colorado Alphaherpesvirus Latency Society
2010-present	Program Director, Rocky Mountain Branch of ASM
2009-present	President, Rocky Mountain Virology Association
2005-present	Professor, Department of Neurology, UCSOM, Denver, CO
2004-present	Ad-Hoc Reviewer, Infectious Diseases and Microbiology Integrated Review Group
2000-present	Consultant, Habitability/Environmental Factors, NASA Johnson Space Center, Houston, TX
1999-2005	Associate Professor, Department of Neurology, UCSOM, Denver, CO
1997-2001	Consultant, SmithKline Beecham Pharmaceuticals, King of Prussia, PA
1990-1999	Assistant Professor, Department of Neurology, UCSOM, Denver, CO
1989-1990	Instructor, Department of Neurology, UCSOM, Denver, CO
1987-1989	Senior Res. Associate, Dept. Molecular Biology, AMC Cancer Research Center, Denver, CO
1985-1987	Research Associate, Dept. Molecular Biology, AMC Cancer Research Center, Denver, CO
1984-1985	Research Assistant, Dept. Molecular Biology, AMC Cancer Research Center, Denver, CO

C. Contributions to Science

For more than 25 years, my lab has studied the molecular virology of varicella zoster virus (VZV), with a strong focus on virus transcription in latently infected human ganglia. This has necessitated acquisition of multiple ganglia removed at autopsy from more than ~800 humans.

1. My lab has shown that during latency, virus is in neurons, that VZV DNA is circular, and that VZV gene transcription is restricted. I pioneered construction of cDNA libraries from latently infected human ganglia enriched for VZV transcripts and confirmed by sequencing, that latent VZV transcripts, unlike latent HSV-1 transcripts, contain a 3'-poly [A] tail. The promoters for VZV open reading frames (ORFs) 21 and 29, two latently expressed virus genes were mapped and their encoded proteins were analyzed.
   a. Laguardia, J. J., **Cohrs, R.J.**, Gilden, D.H. (1999) Prevalence of varicella-zoster virus DNA in dissociated human trigeminal ganglion neurons and nonneuronal cells. J. Virol. 73:8571-8577. PMCID: PMC1112877
   b. Clarke, P., Beer, T., **Cohrs, R.**, Gilden, D.H. (1995) Configuration of latent varicella-zoster virus DNA. J. Virol. 69:8151-8154.
   c. **Cohrs, R. J.**, Barbour, M., Gilden, D.H. (1996) Varicella-zoster virus (VZV) transcription during latency in human ganglia: detection of transcripts mapping to genes 21, 29, 62, and 63 in a cDNA library enriched for VZV RNA. J. Virol. 70:2789-2796. PMCID: PMC190136
   d. **Cohrs, R. J.**, Randall, J., Smith, J., Gilden, D.H., Dabrowski, C., van Der, K.H., Tal-Singer, R. (2000) Analysis of individual human trigeminal ganglia for latent herpes simplex virus type 1 and varicella-zoster virus nucleic acids using real-time PCR. J. Virol. 74:11464-11471. PMCID: PMC112425

2. To extend our transcriptional analysis to the entire VZV transcriptome, my lab was the first to construct arrays to quantify VZV transcripts from all predicted virus ORFs. I characterized the transcriptional pattern of all VZV genes during productive infection in tissue culture. I also determined that VZV gene transcription is dependent on continuing virus DNA replication, and that the rate of VZV mRNA decay is the same for both high and low abundance virus transcripts. While the arrays successfully characterized the VZV transcriptome in cells infected with wild-type virus, attenuated vaccine virus and mutated VZV, I had to devise a more sensitive and specific multiplex PCR assay to identify the complete VZV transcriptome in latently infected human ganglia. Using this novel technology, my lab detected transcripts from 12 VZV ORFs in latently infected human ganglia. This finding confirmed our previous quantitative study which revealed that VZV ORF 63 is the most prevalent and abundant virus gene transcribed during latency. Realizing that VZV ORF 63 is a critical gene in latency, we constructed recombinant mouse IgG1 antibodies to detect the virus protein and its post-translational phosphorylations. Modifying the recombinant Ig-technology, we have identified the most antigenetic protein complex of VZV in humans.
   a. Cohrs**, R. J.**, Hurley, M.P., Gilden, D.H. (2003) Array analysis of viral gene transcription during lytic infection of cells in tissue culture with varicella-zoster virus. J. Virol. 77:11718-11732. PMCID: PMC229365
   b. Nagel, M. A., Choe, A., Traktinskiy, I., Cordery-Cotter, R., Gilden, D., **Cohrs, R.J.** (2011) Varicella-zoster virus transcriptome in latently infected human ganglia. J. Virol. 85:2276-2287. PMCID: PMC3067783
   c. Mueller, N. H., Bos, N.L., Seitz, S., Wellish, M., Mahalingam, R., Gilden, D., **Cohrs, R.J.** (2012) Recombinant monoclonal antibody recognizes a unique epitope on varicella-zoster virus immediate-early 63 protein. J. Virol. 86:6345-6349. PMCID: PMC3372203
   d. Birlea, M., Owens, G.P., Eshleman, E.M., Ritchie, A., Traktinskiy, I., Bos, N., Seitz, S., Azarkh, Y., Mahalingam, R., Gilden, D., **Cohrs, R.J.** (2013) Human anti-varicella-zoster virus (VZV) recombinant monoclonal antibody produced after Zostavax immunization recognizes the gH/gL complex and neutralizes VZV infection. J. Virol. 87:415-421. PMCID: PMC3536365

3. Importantly, my lab was the first and remains the only one to show that in latently infected human ganglia, histones are bound to specific sites on the latent VZV genome, and that these histones contain posttranslational modifications indicative of active gene transcription. Overall, my studies established that during latency in human ganglia, VZV transcription is limited to ORF 63 and during early stages of virus reactivation virus transcription undergoes generalized deregulation resulting in transcription of multiple immediate-early, early and late VZV genes; a condition recently seen in early stages of HSV-1 reactivation.

Thus my lab has finally united the seemingly contradictory findings from two human neurotropic alphaherpesviruses into a general theme explaining reactivation as modification of epigenetic regulation of latent virus genome followed by conditions potentiating virus DNA replication.

a. Gary, L., Gilden, D.H., **Cohrs, R.J.** (2006) Epigenetic regulation of varicella-zoster virus open reading frames 62 and 63 in latently infected human trigeminal ganglia. J. Virol. 80:4921-4926. PMCID: PMC1472082
b. Ouwendijk, W.J., Choe, A., Nagel, M.A., Gilden, D., Osterhaus, A.D., **Cohrs, R.J.**, Verjans, G.M. (2012) Restricted varicella-zoster virus transcription in human trigeminal ganglia obtained soon after death. J. Virol. 86:10203-10206. PMCID: PMC3446590
c. Henderson, H.H., Timberlake, K.B., Austin. Z.A., Badani, H., Sanford, B., Tremblay, K., Baird, N.L., Jones, K., Rovnak, J., Frietze, S., Gilden, D., **Cohrs, R.J.** (2016) Occupancy of RNA polymerase II (S5P) and RNA polymerase II (S2P) on VZV genes 9, 51 and 66 is independent of transcript abundance and polymerase location within the gene. J. Virol. 90:1231-1243. PMCID: PMC4719599

4. Currently we are investigating the molecular pathways to VZV reactivation. In collaboration with NASA, we developed a low gravity-based system to maintain VZV infected human neurons for >3 months where the virus establishes a low-level persistent infection sporadically shedding cell-free virus. While this system may model postherpetic neuralgia, and we are investigating *in vitro* infections of human neurons in culture to simulate latency, we are focusing our efforts to understand virus reactivation from latently infected human trigeminal ganglia. We have optimized culture conditions to maintain neuronal health in multiple random samples and induce VZV DNA replication. We have now developed the platform to prospectively analyze the molecular pathways involved in latently infected human ganglia from induction of virus DNA replication to assembly and release of infectious virus.
   a. Goodwin, T. J., McCarthy, M., Osterrieder, N., **Cohrs, R.J.**, Kaufer, B.B. (2013) Three-dimensional normal human neural progenitor tissue-like assemblies: a model of persistent varicella-zoster virus infection. PLoS. Pathog. 9:e1003512.
   b. Baird, N. L., Bowlin, J.L., Hotz, T.J., **Cohrs, R.J.**, Gilden, D. (2015) Interferon gamma prolongs survival of varicella-zoster virus-infected human neurons *in vitro*. J. Virol. 89:7425-7427. PMCID: PMC4773560
   c. **Cohrs, R. J.,** Badani, H., Bos, N., Scianna, C., Hoskins, I., Baird, N.L., Gilden, D. (2016) Alphaherpesvirus DNA replication in dissociated human trigeminal ganglia. J. Neurovirol. 22:688-694. PMCID: PMC5055419
   d. **Cohrs, R.J.**, Badani, H., Baird, N.L., White, T.M., Sanford, B., Gilden, D (2017) Induction of varicella zoster virus DNA replication in dissociated human trigeminal ganglia. J. Neurovirol. 23:152-157. PMCID: PMC5464606

5. Finally, I found that each area in virology advances faster when individuals studying different viruses exchange information, set collaborative goals and share equipment & reagents. To this end I was selected President/CEO of the Rocky Mountain Virology Association where 80-100 individuals meet annually to expand virology and mentor the next generation of basic/clinical scientist. Along with Dr. Joel Rovnak, the Rocky Mountain Virology Association has grown from a small disjointed meeting to a premier meeting of regional virologist that is enhanced by the attendance of world-class invited lecturers. The meeting focuses on many different viruses (from Dengue to Herpes) and includes significant contributions from researchers studying Prion biology. In addition, the secluded venue was selected because it fosters attendance by all to all talks. More importantly, the dining hall setting for all meetings provides unparalleled opportunities for mentorship through discussions between established and early-stage investigators as well as promising new students. Taken together the Rocky Mountain Virology Association meetings have permitted my growth in mentorship; a fact witnessed by my resent award of the Mentor of the Year by the Metropolitan State University.

a. Rovnak, J., Perera, R., Hopken, M. W., Read, J., Waller, D. M., **Cohrs, R.J.** (2020) The 19th Rocky Mountain Virology Association Meeting. Viruses 12:85. PMCID: PMC7019928

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=cohrs+r