

Hematology

Division Details

RESEARCH AND TRAINING DETAILS

Faculty	12
Joint Appointment Faculty	2
Research Fellows and Post Docs	5
Research Graduate Students	1
Total Annual Grant Award Dollars	\$2,939,144
Total Annual Industry Award Dollars	\$365,245
Total Publications	46
CLINICAL ACTIVITIES AND TRAINING	
Clinical Fellows	4
Inpatient Encounters	1,346
Outpatient Encounters	5,859



Row 1: E Mullins, C Tarango, C Quinn, P McGann

Row 2: T Kalfa, K Ricci, R Ware, O Niss, L Shook

Row 3: P Malik, L Luchtman-Jones, R Gruppo, J Palumbo

Significant Publications

Niss O, Quinn CT, Lane A, Daily J, Khoury PR, Bakeer N, Kimball TR, Towbin JA, Malik P, Taylor MD. Cardiomyopathy with Restrictive Physiology in Sickle Cell Disease. *JACC Cardiovasc Imaging*. 2016 Mar; 9(3):243-52.

Different cardiac morphologic features and mortality risk factors identified in sickle cell disease, have not been a unifying pathophysiology to explain these findings or link the adverse factors to cardiac phenotype. This study identifies a unique cardiomyopathy with features of restrictive physiology and anemia-related hyperdynamic physiology in patients with sickle cell disease. The cardiomyopathy of sickle cell disease is the likely pathophysiology that links cardiac phenotype to the adverse risk factors of sickle cell disease.

Adams GN, Rosenfeldt L, Frederick M, Miller W, Waltz D, Kombrinck K, McElhinney KE, Flick MJ, Monia BP, Revenko AS, **Palumbo JS**. **Colon Cancer Growth and Dissemination Relies upon Thrombin, Stromal PAR-1**, **and Fibrinogen**. *Cancer Res*. 2015 Oct 1;75(19):4235-43.

This paper documented, for the first time, that the central hemostatic protease, thrombin, plays an unexpected and multifaceted role in colon cancer progression, driving not only metastasis, but also tumor proliferation and local invasion. We also showed that at least two downstream thrombin targets, stromal cell-associated protease activated receptor-1 and fibrinogen, are significant determinants of tumor growth, suggests thrombin coupled to tumor growth in this setting through multiple distinct mechanisms. These studies also represented the first cancer context where fibrinogen was unambiguously demonstrated to promote tumor growth. Taken together

with previous studies from our laboratory showing that the thrombin/fibrinogen axis is a major determinant of intestinal tumorigenesis, these studies suggest that hemostatic system components play a broad role in colon cancer progression, driving very early steps important in tumor formation, as well as later steps critical for tumor growth and dissemination. An important implication of these studies is that therapies targeting thrombin generation and/or downstream thrombin functions, including therapies with little or no bleeding risk, could represent a novel and effective way to prevent colon cancer and/or an adjuvant treatment for this important malignancy.

Konstantinidis DG, Giger KM, Risinger M, Pushkaran S, Zhou P, Dexheimer P, Yerneni S, Andreassen P, Klingmüller U, Palis J, Zheng Y, Kalfa TA. Cytokinesis failure in RhoA-deficient mouse erythroblasts involves actomyosin and midbody dysregulation and triggers p53 activation. *Blood*. 2015 Sep 17;126(12):1473-82.

Erythropoiesis is a remarkably industrious process producing two million reticulocytes per second in a healthy adult. To maintain a normal hemoglobin level and avoid anemia, the mechanisms of cell proliferation and cell division have to be fully optimized. To understand this process better, we developed a mouse model with erythroid-specific deletion of RhoA, which is a member of the Rho GTPase family of proteins that act as molecular switches, turning on or off a wide variety of biological processes. This model was embryonic lethal and caused severe dyserythropoietic anemia by mouse mid-gestation. Cytokinesis failure caused by RhoA deficiency resulted in p53 activation and p21-transcriptional upregulation with associated cell-cycle arrest, increased DNA damage, and cell death. Our findings demonstrated the role of RhoA as a critical regulator for efficient erythroblast cytokinesis and proliferation and the p53 pathway as a powerful quality control mechanism in erythropoiesis.

Ndeezi G, Kiyaga C, Hernandez AG, Munube D, Howard TA, Ssewanyana I, Nsungwa J, Kiguli S, Ndugwa CM, **Ware RE**, Aceng JR. **Burden of sickle cell trait and disease in the Uganda Sickle Surveillance Study (US3): a cross-sectional study**. *Lancet Glob Health*. 2016 Mar;4(3):e195-200.

In collaboration with Makerere University and the Uganda Ministry of Health, we created a specialized Sickle Cell Laboratory and trained local personnel to conduct a large prospective surveillance study of sickle cell trait and disease across the Republic of Uganda. Researchers analyzed dried blood spots collected for the Early Infant Diagnosis HIV testing program by hemoglobin electrophoresis at the Uganda Central Public Health Laboratory, mapping results by region and district to provide a geospatial display of the sickle cell burden. The study tested almost 100,000 samples with an overall prevalence of 13.3% sickle cell trait and 0.7% sickle cell disease. Substantial variation note included ~20% trait primarily in the East Central and mid-Northern regions. Sickle cell disease was less common in children older than 12 months, or who were HIV positive, which is consistent with comorbidity and early mortality. Based on these results, targeting hemoglobinopathy screening in the highest burden districts has commenced.

Division Publications

- Adams DM, Hammill AM, Mobberley-Schuman PS, Trenor CC, 3rd. Comment On: Steroid-Resistant Kaposiform
 Hemangioendothelioma: A Retrospective Study of 37 Patients Treated with Vincristine and Long-Term Follow-Up. Pediatr
 Blood Cancer. 2015; 62:2056.
- 2. Adams DM, Trenor CC, 3rd, Hammill AM, Vinks AA, Patel MN, Chaudry G, Wentzel MS, Mobberley-Schuman PS, Campbell LM, Brookbank C, Gupta A, Chute C, Eile J, McKenna J, Merrow AC, Fei L, Hornung L, Seid M, Dasgupta AR, Dickie BH, et al. **Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies.** *Pediatr.* 2016; 137:e20153257.
- 3. Adams GN, Rosenfeldt L, Frederick M, Miller W, Waltz D, Kombrinck K, McElhinney KE, Flick MJ, Monia BP, Revenko AS, Palumbo JS. Colon Cancer Growth and Dissemination Relies Upon Thrombin, Stromal Par-1, and Fibrinogen. Cancer Research. 2015; 75:4235-43.
- 4. Alsaied T, Alsidawi S, Allen CC, Faircloth J, Palumbo JS, Veldtman GR. **Strategies for Thromboprophylaxis in Fontan Circulation: A Meta-Analysis.** *Heart.* 2015; 101:1731-7.

- Anyanwu J, Williams O, Sautter C, Kasirye P, Hume H, Opoka R, Latham T, Ndugwa C, Ware R, John C. Novel Use of
 Hydroxyurea in an African Region with Malaria: Protocol for a Randomized Controlled Clinical Trial. pmc/PMC4937184. JMIR
 Research Protocols. 2016; 5:e110.
- Arumugam PI, Mullins ES, Shanmukhappa SK, Monia BP, Loberg A, Shaw MA, Rizvi T, Wansapura J, Degen JL, Malik P. Genetic Diminution of Circulating Prothrombin Ameliorates Multiorgan Pathologies in Sickle Cell Disease Mice. *Blood*. 2015; 126:1844-55.
- 7. Burkes SA, Adams DM, Hammill AM, Chute C, Eaton KP, Welge JA, Wickett RR, Visscher MO. **Skin Imaging Modalities Quantify Progression and Stage of Infantile Haemangiomas.** *Br J Dermatol*. 2015; 173:838-41.
- 8. Burkes SA, Patel M, Adams DM, Hammill AM, Eaton KP, Randall Wickett R, Visscher MO. Infantile Hemangioma Status by Dynamic Infrared Thermography: A Preliminary Study. Int J Dermatol. 2016; 55:e522-32.
- 9. Chonat S, Chandrakasan S, Kalinyak K, Ingala D, Gruppo R, Kalfa T. **Atypical Haemolytic Uraemic Syndrome in a Patient with Sickle Cell Disease, Successfully Treated with Eculizumab.** *Br J Haematol.* 2016.
- 10. Cohen R, Smith E, Arbabi S, Quinn C, Franco R. **Do Red Blood Cell Indices Explain Racial Differences in the Relationship between Hemoglobin A1c and Blood Glucose?** *J Pediatr.* 2016; 176:7-9.
- 11. Comi AM, Sahin M, Hammill A, Kaplan EH, Juhasz C, North P, Ball KL, Levin AV, Cohen B, Morris J, Lo W, Roach ES, Sturge-Weber Syndrome Research Workshop. Leveraging a Sturge-Weber Gene Discovery: An Agenda for Future Research. *Pediatr Neurol*. 2016; 58:12-24.
- 12. Dong M, McGann PT, Mizuno T, Ware RE, Vinks AA. **Development of a Pharmacokinetic-Guided Dose Individualization Strategy for Hydroxyurea Treatment in Children with Sickle Cell Anaemia**. *Br J Clin Pharmacol*. 2016; 81:742-52.
- 13. Englum BR, Rothman J, Leonard S, Reiter A, Thornburg C, Brindle M, Wright N, Heeney MM, Jason Smithers C, Brown RL, Kalfa T, Langer JC, Cada M, Oldham KT, Scott JP, St Peter SD, Sharma M, Davidoff AM, Nottage K, Bernabe K, et al. **Hematologic**Outcomes after Total Splenectomy and Partial Splenectomy for Congenital Hemolytic Anemia. *J Pediatr Surg.* 2016; 51:122-7.
- 14. Flood VH, Christopherson PA, Gill JC, Friedman KD, Haberichter SL, Bellissimo DB, Udani RA, Dasgupta M, Hoffmann RG, Ragni MV, Shapiro AD, Lusher JM, Lentz SR, Abshire TC, Leissinger C, Hoots WK, Manco-Johnson MJ, Gruppo RA, Boggio LN, Montgomery KT, et al. Clinical and Laboratory Variability in a Cohort of Patients Diagnosed with Type 1 Vwd in the United States. Blood. 2016; 127:2481-8.
- 15. Gaballah M, Shi J, Kukreja K, Raffini L, Tarango C, Keller M, Krishnamurthy G, Racadio J, Patel M, Cahill AM. **Endovascular Thrombolysis in the Management of Iliofemoral Thrombosis in Children: A Multi-Institutional Experience.** *J Vasc Interv Radiol.* 2016; 27:524-30.
- 16. Giger KM, Kalfa TA. Phylogenetic and Ontogenetic View of Erythroblastic Islands. Biomed Res Int. 2015; 2015:873628.
- 17. Goldenberg NA, Abshire T, Blatchford PJ, Fenton LZ, Halperin JL, Hiatt WR, Kessler CM, Kittelson JM, Manco-Johnson MJ, Spyropoulos AC, Steg PG, Stence NV, Turpie AG, Schulman S, Kids Dott Trial Investigators. Multicenter Randomized Controlled Trial on Duration of Therapy for Thrombosis in Children and Young Adults (the Kids-Dott Trial): Pilot/Feasibility Phase Findings. J Thromb Haemost. 2015; 13:1597-605.
- 18. Hankins JS, McCarville MB, Rankine-Mullings A, Reid ME, Lobo CL, Moura PG, Ali S, Soares DP, Aldred K, Jay DW, Aygun B, Bennett J, Kang G, Goldsmith JC, Smeltzer MP, Boyett JM, Ware RE. Prevention of Conversion to Abnormal Transcranial Doppler with Hydroxyurea in Sickle Cell Anemia: A Phase lii International Randomized Clinical Trial. *Am J Hematol*. 2015; 90:1099-105.
- 19. Huang Y, Shaw M, Warmin M, Mullins E, Ayres N. Blood Compatibility of Heparin-Inspired, Lactose Containing, Polyureas Depends on the Chemistry of the Polymer Backbone. *Polym Chem.* 2016; 7:3897-905.

- 20. Konstantinidis DG, Giger KM, Risinger M, Pushkaran S, Zhou P, Dexheimer P, Yerneni S, Andreassen P, Klingmuller U, Palis J, Zheng Y, Kalfa TA. Cytokinesis Failure in Rhoa-Deficient Mouse Erythroblasts Involves Actomyosin and Midbody Dysregulation and Triggers P53 Activation. Blood. 2015; 126:1473-82.
- 21. Ljung R, Kenet G, Mancuso ME, Kaleva V, Rusen L, Tseneklidou-Stoeter D, Michaels LA, Shah A, Hong W, Maas Enriquez M, Investigators of the Leopold Kids Trial. **Bay 81-8973 Safety and Efficacy for Prophylaxis and Treatment of Bleeds in Previously Treated Children with Severe Haemophilia A: Results of the Leopold Kids Trial.** *Haemophilia*. 2016; 22:354-60.
- 22. Luchtman-Jones L, Pressel S, Hilliard L, Brown RC, Smith MG, Thompson AA, Lee MT, Rothman J, Rogers ZR, Owen W, Imran H, Thornburg C, Kwiatkowski JL, Aygun B, Nelson S, Roberts C, Gauger C, Piccone C, Kalfa T, Alvarez O, et al. **Effects of Hydroxyurea Treatment for Patients with Hemoglobin Sc Disease.** *Am J Hematol.* 2016; 91:238-42.
- 23. McGann P. Time to Invest in Sickle Cell Anemia as a Global Health Priority. Pediatr Ann. 2016; 137:e 20160348.
- 24. McGann P. Improving Survival for Children with Sickle Cell Disease: Newborn Screening Is Only the First Step. Paediatr Int Child Health. 2015; 35:285-86.
- 25. McGann P, Ware R. Hydroxyurea Therapy for Sickle Cell Anemia. Expert Opin Drug Saf. 2015; 14:1749-58.
- 26. McGann PT. Hydroxyurea for Abnormal Tcds: Safe to Switch? Blood. 2016; 127:1738-40.
- 27. McGann PT, Grosse SD, Santos B, de Oliveira V, Bernardino L, Kassebaum NJ, Ware RE, Airewele GE. A Cost-Effectiveness

 Analysis of a Pilot Neonatal Screening Program for Sickle Cell Anemia in the Republic of Angola. *J Pediatr.* 2015; 167:1314-9.
- 28. McGann PT, Schaefer BA, Paniagua M, Howard TA, Ware RE. Characteristics of a Rapid, Point-of-Care Lateral Flow Immunoassay for the Diagnosis of Sickle Cell Disease. *Am J Hematol*. 2016; 91:205-10.
- 29. McGann PT, Tshilolo L, Santos B, Tomlinson GA, Stuber S, Latham T, Aygun B, Obaro SK, Olupot-Olupot P, Williams TN, Odame I, Ware RE, Reach Investigators. Hydroxyurea Therapy for Children with Sickle Cell Anemia in Sub-Saharan Africa: Rationale and Design of the Reach Trial. Pediatr Blood Cancer. 2016; 63:98-104.
- 30. McGann PT, Tyburski EA, de Oliveira V, Santos B, Ware RE, Lam WA. **An Accurate and Inexpensive Color-Based Assay for Detecting Severe Anemia in a Limited-Resource Setting.** *Am J Hematol.* 2015; 90:1122-7.
- 31. Mullins TL, Miller RJ, Mullins ES. **Evaluation and Management of Adolescents with Abnormal Uterine Bleeding.** *Pediatr Ann.* 2015; 44:e218-22.
- 32. Nayak RC, Trump LR, Aronow BJ, Myers K, Mehta P, Kalfa T, Wellendorf AM, Valencia CA, Paddison PJ, Horwitz MS, Grimes HL, Lutzko C, Cancelas JA. Pathogenesis of Elane-Mutant Severe Neutropenia Revealed by Induced Pluripotent Stem Cells. J Clin Invest. 2015; 125:3103-16.
- 33. Ndeezi G, Kiyaga C, Hernandez AG, Munube D, Howard TA, Ssewanyana I, Nsungwa J, Kiguli S, Ndugwa CM, Ware RE, Aceng JR. Burden of Sickle Cell Trait and Disease in the Uganda Sickle Surveillance Study (Us3): A Cross-Sectional Study. Lancet Glob Health. 2016; 4:e195-200.
- 34. Niss O, Quinn CT, Lane A, Daily J, Khoury PR, Bakeer N, Kimball TR, Towbin JA, Malik P, Taylor MD. Cardiomyopathy with Restrictive Physiology in Sickle Cell Disease. *JACC Cardiovasc Imaging*. 2016; 9:243-52.
- 35. Prasad J, Gorkun O, Raghu H, Thornton S, Mullins E, Palumbo J, Ko Y-P, Hoeoek M, David T, Coughlin S. **Mice Expressing a Mutant Form of Fibrinogen That Cannot Support Fibrin Formation Exhibit Compromised Antimicrobial Host Defense**. *Blood*. 2015; 126:2047-58.
- 36. Quinn C. Do Not Leave for Tomorrow What You Can Do Today. Pediatr Blood Cancer. 2015; 62:1879-80.
- Quinn CT. Minireview: Clinical Severity in Sickle Cell Disease: The Challenges of Definition and Prognostication. Exp Biol Med (Maywood). 2016; 241:679-88.

- 38. Quinn CT, St Pierre TG. Mri Measurements of Iron Load in Transfusion-Dependent Patients: Implementation, Challenges, and Pitfalls. Pediatr Blood Cancer. 2016; 63:773-80.
- 39. Rivera CP, Veneziani A, Ware RE, Platt MO. Original Research: Sickle Cell Anemia and Pediatric Strokes: Computational Fluid Dynamics Analysis in the Middle Cerebral Artery. Exp Biol Med (Maywood). 2016; 241:755-65.
- 40. Salloum R, Fox CE, Alvarez-Allende CR, Hammill AM, Dasgupta R, Dickie BH, Mobberley-Schuman P, Wentzel MS, Chute C, Kaul A, Patel M, Merrow AC, Gupta A, Whitworth JR, Adams DM. Response of Blue Rubber Bleb Nevus Syndrome to Sirolimus Treatment. *Pediatr Blood Cancer*. 2016; 63:1911-4.
- 41. Serai S, Fleck R, Quinn C, Zhang B, Podberesky D. Retrospective Comparison of Gradient Recalled Echo R2*and Spin-Echo R2

 Magnetic Resonance Analysis Methods for Estimating Liver Iron Content in Children and Adolescents. *Pediatr Radiol*. 2015; 45:1629-34.
- 42. Unruh D, Srinivasan R, Benson T, Haigh S, Coyle D, Batra N, Keil R, Sturm R, Blanco V, Palascak M, Franco RS, Tong W, Chatterjee T, Hui DY, Davidson WS, Aronow BJ, Kalfa T, Manka D, Peairs A, Blomkalns A, et al. **Red Blood Cell Dysfunction Induced by High-Fat Diet: Potential Implications for Obesity-Related Atherosclerosis.** *Circulation*. 2015; 132:1898-908.
- 43. Ware RE. Optimizing Hydroxyurea Therapy for Sickle Cell Anemia. Hematology Am Soc Hematol Educ Program. 2015; 2015;436-43.
- 44. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, Odame I, Fuh B, George A, Owen W, Luchtman-Jones L, Rogers ZR, Hilliard L, Gauger C, Piccone C, Lee MT, Kwiatkowski JL, Jackson S, Miller ST, Roberts C, et al. Hydroxycarbamide Versus Chronic Transfusion for Maintenance of Transcranial Doppler Flow Velocities in Children with Sickle Cell Anaemia-Tcd with Transfusions Changing to Hydroxyurea (Twitch): A Multicentre, Open-Label, Phase 3, Non-Inferiority Trial. Lancet. 2016; 387:661-70.
- 45. Wood JC, Cohen AR, Pressel SL, Aygun B, Imran H, Luchtman-Jones L, Thompson AA, Fuh B, Schultz WH, Davis BR, Ware RE, TWiTCH Investigators. **Organ Iron Accumulation in Chronically Transfused Children with Sickle Cell Anaemia: Baseline Results from the Twitch Trial.** *Br J Haematol.* 2016; 172:122-30.
- 46. Wood JC, Pressel S, Rogers ZR, Odame I, Kwiatkowski JL, Lee MT, Owen WC, Cohen AR, St Pierre T, Heeney MM, Schultz WH, Davis BR, Ware RE, TWiTCH Investigators. Liver Iron Concentration Measurements by Mri in Chronically Transfused Children with Sickle Cell Anemia: Baseline Results from the Twitch Trial. Am J Hematol. 2015; 90:806-10.

Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Ralph A Gruppo, MD	Hemophilia Comprehensive Care	Maternal & Child Health Bureau (Hemophilia Foundation of Michigan)	H30MC00015	10/1/1997 - 5/31/2016	\$22,000
Ralph A Gruppo, MD	Zimmerman Program for the Molecular and Clinical Biology of VWD	National Institutes of Health (Medical College of Wisconsin)	P01 HL081588	2/1/2013 - 1/31/2017	\$200
Ralph A Gruppo, MD	MY Life, Our Future: A Hemophilia Genotyping Initiative	American Thrombosis & Hemostatis Network	ATHN2014MLOF2	2/1/2014 - 9/30/2017	\$1,850
Theodosia A Kalfa, MDPHD	Rho GTPases in Terminal Erythroid Maturation	National Institutes of Health	R01 HL116352	9/26/2012 - 6/30/2017	\$376,762

Karen Ann Kalinyak, MD	The Mid-South Clinical Data Research Network	Patient-Centered Outcome Research Inst. (Vanderbilt University)	CDRN1306048691	7/1/2014 - 6/30/2016	\$525
Patrick McGann, MD-MS	Therapeutic Response Evaluation and Adherence Trial: A Prospective Study of Hydroxyurea for Children with Sickle Cell Anemia	National Institutes of Health	K23 HL128885	9/1/2015 - 5/31/2020	\$345,870
Eric Mullins, MD	Mechanisms Linking Hemostatic Factors to Neuroinflammatory Disease	National Institutes of Health	K08 HL105672	8/22/2011 - 7/31/2016	\$131,085
Joseph S Palumbo, MD	Hemostatic Factors Drive Prostate Cancer Pathogenesis	National Institutes of Health	R01 CA193678	4/15/2016 - 3/31/2021	\$356,850
Joseph S Palumbo, MD	Coagulation Factors as modifiers of the Colon Cancer Microenvironment	National Institutes of Health	R01 CA204058	4/5/2016 - 3/31/2021	\$356,850
Lisa M Shook	Cincinnati Sickle Cell Project	Health Resources & Services Admin (Ohio Department of Health)	03130011SK0512	7/1/1998 - 6/30/2016	\$123,469
Lisa M Shook	Sickle Cell Treatment Demonstration Program	Health Resources & Services Admin	U1EMC27863	9/1/2014 - 8/31/2017	\$850,000
Russell Ware, MD-PHD	Genetic Variants Influencing the Phenotypic Expression of Sickle Cell Anemia	Doris Duke Charitable Foundation	2015132	9/1/2015 - 8/31/2018	\$162,000
Russell Ware, MD-PHD	Prospective Analysis of the Pharmacokinetics and Pharmacodynamics of Hydroxyurea Treatment in Ugandan Children with Sickle Cell Anemia	Doris Duke Charitable Foundation	2015190	11/1/2015 - 10/31/2017	\$56,000
Russell Ware, MD-PHD	Genetic Variants Influencing the Phenotypic Expression of Sickle Cell Anemia	Doris Duke Charitable Foundation	2016074	6/1/2016 - 11/30/2017	\$70,400
Russell Ware, MD-PHD	Endothelialized Microfluidics for Sickle Cell Disease Research & Drug Discovery	National Institutes of Health (Emory University)	R01 HL121264	1/1/2014 - 12/31/2018	\$18,374
Russell Ware, MD-PHD	Accurate and Inexpensive Point-of-Care Diagnosis of Sickle Cell Anemia	Doris Duke Charitable Foundation (Rice University)	R06981	9/1/2013 - 8/31/2016	\$48,930
Russell Ware, MD-PHD	Genetic Modifiers of Transfusional Iron Overload	National Institutes of Health (Baylor College of	R21 HL123641	8/1/2015 - 7/31/2017	\$17,979

Total Annual Grant Award Dollars \$2,939,144

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Eric Mullins, MD	Baxter Healthcare Corp.	\$57,335
Charles T Quinn, MD	Amgen, Inc.	\$291,910
Russell Ware, MD-PHD	Biomedomics, Inc.	\$16,000
Total Annual Industry Award Dollars		\$365,245