OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Robert P. Doyle Ph.D.

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

POSITION TITLE: Meredith Professor of Chemistry/Associate Professor of Medicine

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE(if applicable) | Completion DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| University of Dublin | BA | 05/1998 | Natural Sciences |
| University of Dublin | P. Grad. Dip | 05/2000 | Statistics |
| University of Dublin | PhD | 11/2001 | Chemistry |
| Australian National University | Postdoctoral | 01/2002 | Drug Delivery |
| Yale University | Postdoctoral | 02/2003 | Molecular Biology and Protein biochemistry |

**A. Personal Statement**

I am a medicinal chemist with an interest in nutraceutical and pharmaceutical drug development for the treatment of vitamin and mineral deficiencies as well as obesity and type 2 diabetes. I have a broad background in synthetic inorganic and bioconjugate chemistry, drug delivery and protein biochemistry. In 2005, I was appointed as an Assistant Professor of Chemistry at Syracuse University being subsequently promoted, with tenure, to Associate Professor in 2009 and then full Professor in 2014. In 2016, I was named the Laura J. and L. Douglas Meredith Professor. In 2011, I was appointed adjunct Associate Professor of Medicine at SUNY, Upstate Medical University (UMU), Syracuse, NY- in the Department of Medicine at UMU. As a PI, I have focused on the medicinal chemistry of vitamin B12 and itsdietary pathway, as well as iron and zinc complexation. Most recently, my group (in collaboration with that of Professor Matthew Hayes (University of Pennsylvania)) has developed a unique GLP1-R agonist devoid of hypophagia and nausea/malaise for the treatment of diabetes. I have a documented record of accomplished research in the fields of with several key publications, grants (e.g. NIDDK), invited reviews and talks, special issue invitations *etc*.

Tinoco AD, Lucchese B, Peterson CW, Doyle RP, Valentine AM. On the Evolutionary significance and metal binding characteristics of a monolobal transferrin from *Ciona intestinalis. Proc. Natl. Acad. Sci. U.S.A.* 2008; 105: 3268-3273.

Doyle RP, Henry KE, Burke RM, Elfers CT, Roth CL. Vitamin B12 conjugation of Peptide-YY3-36 decreases food intake compared to native Peptide-YY3-36 upon subcutaneous administration in lean rats. *Endocrinology*.2015; 156: 1739-1749.

Doyle RP, Bonaccorso RL, Chepurny OG, Becker-Pauly C, Holz GG. Enhanced Peptide Stability Against Protease Digestion Induced by Intrinsic Factor Binding of a Vitamin B12 Conjugate of Exendin-4. *Molecular Pharmaceutics*. 2015; 12: 3502-3506.

Doyle RP, Kuda-Wedagedara ANW, Workinger JL, Nexo E, Viola-Villegas N. [89Zr-Cobalamin PET Tracer: Synthesis, Cellular Uptake, and Use for Tumor Imaging.](https://www.ncbi.nlm.nih.gov/pubmed/29104950) *ACS Omega*. 2017; 2:6314-6320.

Doyle RP, Chepurny OG, Bonaccorso RL, Leech CA, Wöllert T, Langford GM, Schwede F, Roth CL, Holz GG. Chimeric peptide EP45 as a dual agonist at GLP-1 and NPY2 receptors. *Scientific reports*. 2018; 8:3749.

Doyle RP, Mietlicki-Baase EG, Liberini CG, Workinger JL, Bonaccorso RL, Borner T, Reiner DJ, Koch-Laskowski K, McGrath LE, Lhamo R, Stein LM, De Jonghe BC, Holz GG, Roth CL, Hayes MR. [A vitamin B12 conjugate of exendin-4 improves glucose tolerance without associated nausea or hypophagia in rodents.](https://www.ncbi.nlm.nih.gov/pubmed/29327400) *Diabetes, obesity & metabolism*. 2018; 20, 1223-1234; PMID: 29327400

**B. Positions and Honors.**

**Position and Employment**

2005-2009 Assistant Professor of Chemistry, Syracuse University, Syracuse, NY

2009-2014 Associate Professor, Department of Chemistry, Syracuse University, NY

2011- Adjunct Associate Professor of Medicine, Upstate Medical University, Syracuse, NY

2013- Adjunct Researcher, Syracuse Veteran’s Affairs Medical Center, Syracuse, NY

2014- Professor of Chemistry

2016- Laura L. and Douglas J. Meredith Professor

**Honors**

Enterprise Ireland Fellowship, University of Dublin, Trinity College, Ireland 1998

RSC Fellowship, Australian National University, Canberra, Australia 2002

Rudolph Anderson Foundation Fellowship, Yale University, Connecticut, USA 2004

ACS New Investigator Award Syracuse University, New York, USA 2009

Associate Member ‘Faculty of 1000’ 2009-

NIH (NIDDK) Peer Review Committee “How Insulin Binds Its Receptor and Effects Signaling” 2009

Plenary Speaker, Gordon Conference Vitamin B12, Oxford University, Oxford, UK August 2009

Wellcome Trust Biomedical Science *ad hoc* reviewer 2010

DTRA Peer Review Committee “Flora, Fauna, and Microorganisms as Screening Indicators 2011

Invited Speaker, Boeringher-Ingelheim (Ridgefield, CT) February 2011

James K. Duah-Agyeman Award for Outstanding Faculty, Syracuse University, New York 2011

Editorial Advisor ‘*Biochemistry Journal*’ 2011-

Invited Speaker**,** American Pharmaceutical Association AGM (Washington DC). October 2011

Invited Speaker,ACS “Medicinal Chemistry in Academia” (MARM, Baltimore, MD)), May 2012

Invited Speaker, Vitamin B12 symposium (Nancy, France), August 2012

Research highlighted in *Scientific American* 306, 20, 2012

Invited Speaker**,** University of Zurich, Switzerland September 2012

Outstanding Faculty Advisor of the Year, College of Arts and Sciences Syracuse University, New York 2012

Central New York College Technology Educator of the Year 2013

Invited Speaker, Pfizer, Cambridge, MA, February 2013

Invited Speaker, International Conference on Porphyrins and Phthalocyanines-8, Istanbul, Turkey, July 2014

Invited Speaker, Polish Academy of Sciences, Institute of Organic Chemistry, Warsaw, Poland, February 2016

Invited Speaker, Institute of Molecular Sciences, University of Valencia, Spain, February 2016

Invited Speaker, Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark February 2016

Awarded Laura L. and Douglas J. Meredith Endowed Professorship, March 2016

Invited Speaker, International Conference on Porphyrins and Phthalocyanines-9, Nanjing, China, July 2016

Invited Speaker, Eli Lilly and Company, Indianapolis, IN, USA August 2016

Invited Speaker, FASEB (Folic Acid, Vitamin B12, and One-Carbon Metabolism), CO, USA, August 2016

Invited Speaker, American Chemical Society (NERM), NY, USA, October 2016

Invited Speaker, University of Pennsylvania, Philadelphia, PA May 2017

Invited Speaker, University of North Carolina, Chapel Hill, November 2017

Invited Speaker, 9th International Conference on Porphyrins and Phthalocyanins, Munich, Germany July 1st-6th 2018

Invited Speaker, University of Pennsylvania, Department of Biochemistry and Biophysics, September 13th 2018

**C. Contribution to Science**

1. 2003-2005: Characterization of monolobal transferrin from *Ciona intestinalis*

As a postdoctoral researcher working in the laboratory of Prof. Ann Valentine in the Department of Chemistry at Yale University, I worked with a collaborative team to recombinantly express and characterize an evolutionary monolobal ancestor of the human bilobal iron transport protein, transferrin (Tf), from the ascidian, *Ciona intestinalis*. Modern bilobal Tfs were believed to arise from a proposed monolobal Tf, of which the Ascidian protein possessed the putative characteristics when preliminary investigations were conducted on small quantities isolated from the native organism. Full solution studies, made possible by recombinant expression in the yeast *Pichia pastoris*, revealed a significant improvement in iron(III) binding driven by cooperativity was lost in the monolobal Tf and suggested a major evolutionary advantage to bilobal transferrins. These findings were reported in the journal *PNAS* (USA).

* Tinoco AD, Lucchese B, Peterson CW, Doyle RP, Valentine AM. On the Evolutionary significance and metal binding characteristics of a monolobal transferrin from *Ciona intestinalis. Proc. Natl. Acad. Sci. U.S.A.* 2008; 105: 3268-3273.
1. 2011-2018: Development of vitamin B12 bioconjugate based approaches to therapy and imaging

As a PI at Syracuse University and SUNY,Upstate Medical University in, I have led a team that seeks to exploit the need for cells to access vitaminB12 to develop probes to target and treat cancer. Three primary contributions in this area are (i) We demonstrated the presence of the Intrinsic Factor-B12 transport protein cubilin in the lung cancer cell line A549. This result has opened up the possibly of targeting cubilin in the diagnosis and treatment of lung cancer through the use of B12-probes (*Chem. Commun*. 2011; 47: 9792-9794), and (ii) conducted the first PET imaging studies using a B12 probe, establishing that tumors ranging from pancreatic to breast could be identified with significant radio-64Cu probe uptake (*ChemMedChem*.2014; 9: 1244-1251). (iii) More recently, we have developed a new vitamin B12 PET probe based on **8**9Zirconium(*ACS Omega* 2017, 2:6314-6320).Results document the feasibility of developing a B12-based tracer suitable for both in vivo and ex vivo studies of B12 trafficking and uptake and with the potential to visualize tumors expressing TC receptors, such as CD320 with reduced background.

* Doyle RP, Vortherms AR, Kahkoska AR, Rabideau AE, Andersen LL, Madsen M. A water soluble vitamin B12-Re(I) fluorescent conjugate for cell uptake screens: Use in the detection of cubilin in the lung cancer line A549. *Chem. Commun*. 2011; 47: 9792-9794.
* Doyle RP, IkotunOF, Marquez BV,Fazen CH, Kahkoska AR, Lapi SE. Investigating a vitamin B12 conjugate as a PET imaging probe. *ChemMedChem*.2014; 9: 1244-1251.
* Doyle RP, Kuda-Wedagedara ANW, Workinger JL, Nexo E, Viola-Villegas N. [89Zr-Cobalamin PET Tracer: Synthesis, Cellular Uptake, and Use for Tumor Imaging.](https://www.ncbi.nlm.nih.gov/pubmed/29104950) *ACS Omega*. 2017; 2:6314-6320.

3. 2012-2018: Demonstration of improved pharmacokinetic and pharmacodynamic properties for vitamin B12 conjugates of endocrine peptides Exendin-4 (Ex-4) and PYY3-36

As a PI at Syracuse University and Upstate Medical University, working in collaboration with Christian Roth (MD), a pediatric endocrinologist at Seattle Children’s Research Institute, we demonstrated that a significant improvement in both the pharmacodynamics and pharmacokinetic parameters of the appetite-suppressing gut hormone PYY3-36 could be achieved by conjugation to B12, a significant step in the possible development of a PYY3-36 based drug for obesity treatment. Our work was highlighted by Dr. Stephen Bloom (Imperial College, London, U.K.), a pioneer in the discovery of several gut hormones, in his Bayliss-Starling Prize lecture in 2014.

* Doyle RP, Henry KE, Burke RM, Elfers CT, Roth CL. Vitamin B12 conjugation of Peptide-YY3-36 decreases food intake compared to native Peptide-YY3-36 upon subcutaneous administration in lean rats. *Endocrinology*.2015; 156: 1739-1749.

In addition, we have demonstrated that considerably improved (up to 5-fold) resistance to gut (trypsin and chymotrypsin) and kidney (meprinβ) proteases can be achieved through conjugation of exendin-4 to B12 and subsequent binding to endogenous B12 binding protein Intrinsic factor (IF). A highlight is the fact that, at physiologically relevant levels of kidney protease meprin β, ~ 100% of GLP-1 receptor agonism was maintained for IF-B12-Ex-4 relative to zero agonism for unconjugated Ex-4 under the same condition.

* Doyle RP, Bonaccorso RL, Chepurny OG, Becker-Pauly C, Holz GG. Enhanced Peptide Stability Against Protease Digestion Induced by Intrinsic Factor Binding of a Vitamin B12 Conjugate of Exendin-4. *Molecular Pharmaceutics*. 2015; 12: 3502-3506.

**Most Recently, working with the team of Prof, Matthew Hayes, Perelman School of Medicine, Department of Psychiatry, University of Pennsylvania, we have demonstrated that we could remove GLP1-receptor agonist associated side-effects of nausea/malaise and hypophagia through conjugation of Exendin-4 to vitamin B12. This is the first instance of a system that allows a GLP1-R agonist to maintain peripheral function while preventing access to the CNS.**

* Doyle RP, Mietlicki-Baase EG, Liberini CG, Workinger JL, Bonaccorso RL, Borner T, Reiner DJ, Koch-Laskowski K, McGrath LE, Lhamo R, Stein LM, De Jonghe BC, Holz GG, Roth CL, Hayes MR. [A vitamin B12 conjugate of exendin-4 improves glucose tolerance without associated nausea or hypophagia in rodents.](https://www.ncbi.nlm.nih.gov/pubmed/29327400) *Diabetes, obesity & metabolism*. 2018; 20, 1223-1234; PMID: 29327400

**4. 2017-2018: Developed the first dual agonist of a GLP1-receptor and appetite suppressing receptor NPY2-R.**

**We recently reported on the development of EP45, a dual agonist of GLP1-R and NPY2-R, a proof-of-concept design that**

suggests a new strategy to treat the co-existing metabolic disorders of type 2 diabetes and obesity.

* Doyle RP, Chepurny OG, Bonaccorso RL, Leech CA, Wöllert T, Langford GM, Schwede F, Roth CL, Holz GG. Chimeric peptide EP45 as a dual agonist at GLP-1 and NPY2 receptors. *Scientific reports*. 2018; 8:3749.

**Complete List of Published Work in My Bibliography:**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/robert.doyle.1/bibliography/45718848/public/?sort=date&direction=ascending>.