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 *(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
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 drug development for the treatment of obesity and type 2 diabetes. I have a broad background in synthetic chemistry, drug delivery and protein biochemistry. Of particular relevance to this proposal I worked, as an RSC postdoctoral fellow at the Australian National University (2002-2003), on vitamin B_{12} (B_{12}) small molecule conjugates for drug delivery. As a Rudolph Anderson Foundation Postdoctoral fellow at Yale University (2003-2005), I worked on recombinant protein expression in bacterial and yeast hosts and associated biochemical characterization. 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 part a consequence of my collaborative research efforts with Prof. George Holz in the Department of Medicine at UMU. As a PI I have focused on the chemistry of B_{12}, exploiting both its properties and dietary pathway for drug delivery, focusing over the past ten years on peptide conjugates of insulin, GLP-1, Exendin-4 and PYY_{3-36}. Most recently, my group has developed the first, single peptide, dual agonist of the anorectic receptor Y2-R and the glucoregulatory receptor GLP1-R. I have a documented record of accomplished research in this field with several key publications, grants (e.g. NIDDK), invited reviews and talks, special issue invitations *etc*.

Over the past three years in particular, through funding from the NIH/NIDDK (PI; Doyle) in the form of a R15 AREA award, and in collaboration with Dr. Christian Roth, Dr. Ernie Blevins, Dr. Damian Allis and Dr. George Holz (collaborators on this proposal), we laid the groundwork for this R-01 application, as evidenced in our recent publications in the journals *Endocrinology* (**2015**, 156, 1739-1749), *Molecular Pharmaceutics* (2015, 12, 3502-3506) and *ChemMedChem* (2016, 11, 1015-1021) and the extensive preliminary data reported within the proposal. For this resubmission, the latter two publications are new, as is the developed of the dual agonist and the collection of strong food intake reduction data out to 10 days in obese male and female rodents. These publications and new data demonstrate the positive impact a B_{12} conjugate of the appetite suppressing gut hormone PYY_{3-36} (B_{12}-PYY_{3-36}) has on food intake and body weight gain reduction, paving the way for a PYY_{3-36} based obesity medication. They also show how improved proteases resistance

occurs through B_{12} conjugation and, most significantly, that improved brain uptake can be achieved. The work also now describes for the first time for B_{12}-peptide conjugates, how to, *a priori*, design conjugates for optimum receptor agonism through the first solution structure studies (NMR) of a B_{12}-peptide conjugates (B_{12}-PYY_{3-36}) with associated constrained molecular dynamics calculations. The R15 award, recent publications and strong new preliminary data collected by this team in consequence to the intiital R-01 submission also clearly document the successful and driven working relationship between the groups in Syracuse (Doyle, Holz, Allis) and Seattle (Roth, Blevins) and the established collaboration in terms of access to meprin β with Dr. Becker-Pauly. I successfully administered the award and coordinated the team efforts across the country, including the training of Doyle group undergraduate and graduate students in the Roth lab at Seattle Children's Research Institute, a core tenet of the R15 AREA award.

I believe I have the documented expertise, and the environment, and experience, to ensure successful completion of this research project. In addition, I believe the strong relationship, necessary logistical structure and complimentary skills needed to ensure a successful project are in place.

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, Fazen CH, Valentin D, Fairchild TJ. Oral Delivery of the Appetite Suppressing Peptide $hPYY_{3-36}$ through the Vitamin B_{12} Uptake Pathway. *Journal of Medicinal Chemistry*. 2011; 54: 8707-8711.

Doyle RP, Henry KE, Burke RM, Elfers CT, Roth CL. Vitamin B_{12} conjugation of Peptide-YY_{3-36} decreases food intake compared to native Peptide-YY_{3-36} 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 B_{12} Conjugate of Exendin-4. *Molecular Pharmaceutics*. 2015; 12: 3502-3506.

Doyle RP, Henry KE, Kerwood DJ, Allis DG, Workinger JL, Bonaccorso RL, Holz GG, Roth CL, Zubieta J. Solution Structure and Constrained Molecular Dynamics Study of Vitamin B12 Conjugates of the Anorectic Peptide PYY(3-36). *ChemMedChem*. 2016; 11:1015-1021.

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 B_{12} 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

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.

2. 2011-2014: Development of B_{12} based approaches to cancer cell imaging and therapy

As a PI at Syracuse University and Upstate Medical University, I have led a team that seeks to exploit the need for rapidly proliferating cells to access B_{12} to develop probes to target and treat cancer. Two primary contributions in this area are (i) We demonstrated the presence of the Intrinsic Factor-B_{12} 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 B_{12}-probes or anti-cancer conjugates (*Chem. Commun*. 2011; 47: 9792-9794), and (ii) conducted the first PET imaging studies using a B_{12} probe, establishing that tumors ranging from pancreatic to breast could be identified with significant radio-^{64}Cu probe uptake (*ChemMedChem*. 2014; 9: 1244-1251). More recently, we have expanded on these results and shown that intravenous administration of Intrinsic factor bound B_{12}-^{99m}Tc SPECT probes significantly reduces background uptake through B_{12}-receptors found across all proliferating, non-cancerous, tissues, thus overcoming a major-road block to the use of B_{12} conjugates in imaging and therapy (unpublished data).

- Doyle RP, Vortherms AR, Kahkoska AR, Rabideau AE, Andersen LL, Madsen M. A water soluble vitamin B_{12}-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, Ikotun OF, Marquez BV, Fazen CH, Kahkoska AR, Lapi SE. Investigating a vitamin B_{12} conjugate as a PET imaging probe. *ChemMedChem*. 2014; 9: 1244-1251.

3. 2012-2015: Demonstration of improved pharmacokinetic and pharmacodynamic properties for vitamin B_{12} conjugates of endocrine peptides Exendin-4 (Ex-4) and PYY_{3-36}

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 PYY_{3-36} could be achieved by conjugation to B_{12}, a significant step in the possible development of a PYY_{3-36} 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. This work was reported in the journal *Endocrinology*.

- Doyle RP, Henry KE, Burke RM, Elfers CT, Roth CL. Vitamin B_{12} conjugation of Peptide-YY_{3-36} decreases food intake compared to native Peptide-YY_{3-36} 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 (meprin β) proteases can be achieved through conjugation of exendin-4 to B_{12} and subsequent binding to endogenous B_{12} 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-B_{12}-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 B_{12} Conjugate of Exendin-4. *Molecular Pharmaceutics*. 2015; 12: 3502-3506.

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.