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.)

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>Completion Date MM/YYYY</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>University of Dublin</td>
<td>BA</td>
<td>05/1998</td>
<td>Natural Sciences</td>
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<td>University of Dublin</td>
<td>P. Grad. Dip</td>
<td>05/2000</td>
<td>Statistics</td>
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<td>Australian National University</td>
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<td>Drug Delivery</td>
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<td>Yale University</td>
<td>Postdoctoral</td>
<td>02/2003</td>
<td>Molecular Biology and Protein biochemistry</td>
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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\textsubscript{12} (B\textsubscript{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\textsubscript{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\textsubscript{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 development 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\textsubscript{12} conjugate of the appetite suppressing gut hormone PYY\textsubscript{3-36} (B\textsubscript{12}-PYY\textsubscript{3-36}) has on food intake and body weight gain reduction, paving the way for a PYY\textsubscript{3-36} based obesity medication. They also show how improved proteases resistance

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occurs through B\textsubscript{12} conjugation and, most significantly, that improved brain uptake can be achieved. The work also now describes for the first time for B\textsubscript{12}-peptide conjugates, how to, \textit{a priori}, design conjugates for optimum receptor agonism through the first solution structure studies (NMR) of a B\textsubscript{12}-peptide conjugates (B\textsubscript{12}-PYY\textsubscript{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 initial 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 \(\beta\) 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.


Doyle RP, Henry KE, Burke RM, Elfers CT, Roth CL. Vitamin B\textsubscript{12} conjugation of Peptide-YY\textsubscript{3-36} decreases food intake compared to native Peptide-YY\textsubscript{3-36} upon subcutaneous administration in lean rats. Endocrinology. 2015; 156: 1739-1749.


B. Positions and Honors.

**Position and Employment**

2005-2009 \hspace{1em} Assistant Professor of Chemistry, Syracuse University, Syracuse, NY
2009-2014 \hspace{1em} Associate Professor, Department of Chemistry, Syracuse University, NY
2011- \hspace{1em} Adjunct Associate Professor of Medicine, Upstate Medical University, Syracuse, NY
2013- \hspace{1em} Adjunct Researcher, Syracuse Veteran’s Affairs Medical Center, Syracuse, NY
2014- \hspace{1em} Professor of Chemistry
2016- \hspace{1em} 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
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).

2. 2011-2014: Development of B\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{12}-probes or anti-cancer conjugates (Chem. Commun. 2011; 47: 9792-9794), and (ii) conducted the first PET imaging studies using a B\textsubscript{12} probe, establishing that tumors ranging from pancreatic to breast could be identified with significant radio\textsuperscript{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\textsubscript{12}\textsuperscript{99mTc} SPECT probes significantly reduces background uptake through B\textsubscript{12}-receptors found across all proliferating, non-cancerous, tissues, thus overcoming a major-road block to the use of B\textsubscript{12} conjugates in imaging and therapy (unpublished data).


3. 2012-2015: Demonstration of improved pharmacokinetic and pharmacodynamic properties for vitamin B\textsubscript{12} conjugates of endocrine peptides Exendin-4 (Ex-4) and PYY\textsubscript{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\textsubscript{3-36} could be achieved by conjugation to B\textsubscript{12}, a significant step in the possible development of a PYY\textsubscript{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\textsubscript{12} Conjugation of Peptide-YY\textsubscript{3-36} decreases food intake compared to native Peptide-YY\textsubscript{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 \(\beta\)) proteases can be achieved through conjugation of exendin-4 to B\textsubscript{12} and subsequent binding to endogenous B\textsubscript{12} binding protein Intrinsic factor (IF). A highlight is the fact that, at physiologically relevant levels of kidney protease meprin \(\beta\), ~ 100% of GLP-1 receptor agonism was maintained for IF-B\textsubscript{12}-Ex-4 relative to zero agonism for unconjugated Ex-4 under the same condition.
