For TCU/RCAF Use Only:
Action _____
Amount _____
Project Code _____

TCU RESEARCH AND CREATIVE ACTIVITIES FUND

GRANT APPLICATION

<table>
<tr><td colspan="3">Principal Investigator: Yulia Sevryugina
Academic Rank: Assistant Professor</td></tr>
<tr><td colspan="3">Department: Chemistry
College or School: Science & Engineering</td></tr>
<tr><td>Date of Appointment to TCU:
August 2013</td><td>Degree: Ph.D., Chemistry</td><td>Date Conferred: May 2007</td></tr>
<tr><td colspan="3">Project Title: Boron-based Anti-addiction Medication</td></tr>
<tr><td colspan="2">Amount Requested: $9,899.69</td><td>Project Period: June 1, 2014-May 31, 2014</td></tr>
<tr><td colspan="3">Authorizing Signatures:
Principal Investigator: _____
Department Chair: _____
Dean of School/College: _____</td></tr>
<tr><td colspan="3">ABSTRACT (200 WORDS OR LESS; NOTE 5 POINTS POSSIBLE ON EVALUATION SHEET)

Recent data provided by the National Institute of Drug Abuse (NIDA) show that 20.6 million Americans (8% of the population) are currently classified as having substance dependence or abuse; amongst them, 1.4 million are current users of cocaine – one of the most abused drugs, and one for which there is no medication available. Recent advances in addiction research are revealing long-lasting changes in the brains of individuals addicted to drugs, which supports the concept of addiction as a disease of the brain. We will prepare and study a series of new medications, which can be efficacious for treating substance use disorder, specifically addiction to cocaine and methamphetamine. The challenges with current anti-addiction medications are their poor water solubility, high ability to dissolve in fats, fast metabolism that leads to their decomposition in the blood stream, and unwanted side effects (movement disorders, mood alterations, depression, etc.). We propose a new type of anti-addiction medications based on boron clusters that have easily adjustable fat and water solubilities, and remarkable bio-stability. This project involves synthesis of anti-addiction medications using a combination of organic, inorganic, and boron chemistry synthetic techniques and thorough characterization of the resulting compounds using available at TCU analytical instrumentation.</td></tr>
<tr><td colspan="3"></td></tr>
</table>

Does this proposed research:

☐ **Yes** ☒ **No** **Involve human subjects? If yes, date of Committee review:**

☐ **Yes** ☒ **No** **Involve live animals? If yes, date of Committee review:**

☐ **Yes** ☒ **No** **Involve radioactive substances?**

☐ **Yes** ☒ **No** **Involve scheduled drugs?**

Type of Application:

☒ **New Project/SEED Project**

☐ **Continuing Project**

Renewal of TCU/RCAF Grant No.:

Supplement to other grant application:

Source:

Amount Requested:

Funding Period Requested:

Proposal Status:

☐ **Awarded** ☐ **Denied** ☐ **Pending**

☐ **Ongoing project for which external funding is not possible.**

The proposal <u>must</u> include explanation for the lack of external funding applications.

Previous TCU/RCAF Grants:

Grant No.: **Year:**

Grant Title: : _____

Grant No.: **Year:**

Grant Title: : _____

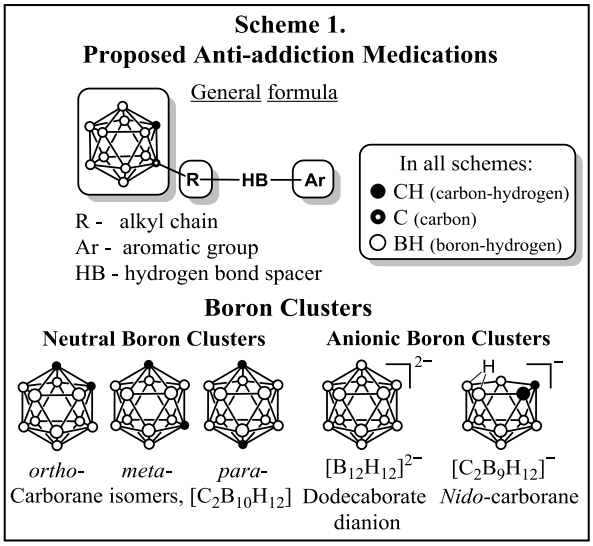
Grant No.: **Year:**

Grant Title: : _____

Boron-based Anti-addiction Medication

1. Purpose. We will prepare and study a series of new medications, which, we believe, can be efficacious for treating substance use disorder, specifically addiction to cocaine and methamphetamine. Specific goals:

1) Synthesis of a series of compounds of the general formula [B]-R-HB-Ar (Scheme 1), where [B] stands for icosahedral boron cluster; R is an extended alkyl chain, usually butyl, preferentially rigidified; HB - an amide or analogous hydrogen-bond containing spacer; and Ar - an aromatic group, preferentially extended to a di- or tri-aryl ring system.

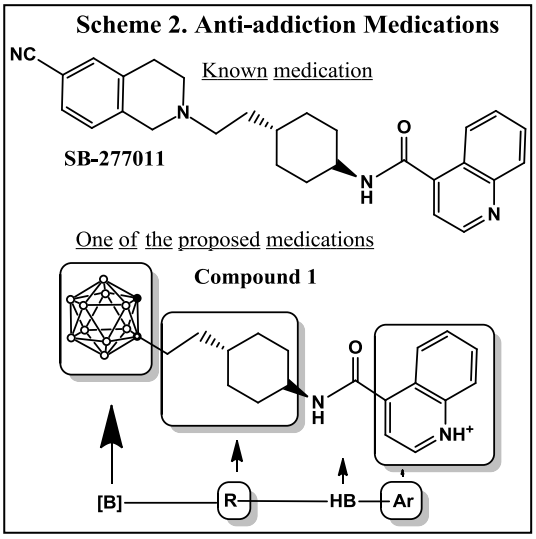


2) Thorough characterization of the resulting compounds by available analytical methods.

2. Project Background. Dopamine is an essential neurotransmitter in the central nervous system responsible for movement control. In addition, it is implicated in reward and reinforcement mechanisms, for what it is often referred to as a "feel-good" or more recently, a "motivation" neurotransmitter. Normally, dopamine is released by neurons in response to potential rewards (any "feel-good" stimulus) and then recycled back into the cell that released it, thus shutting off the signal between neurons. Virtually, all addictive drugs interfere with the dopamine system, preventing the dopamine from being recycled. Dopamine exerts its effects by binding to a group of dopamine receptors. Accumulation of excessive amounts of dopamine amplifies the dopamine signal by overloading dopamine receptors, and ultimately disrupts normal brain communication, which with repeated use may lead to addiction.

Medications to treat addiction target the same dopamine receptors as the drug of abuse by "tricking" the brain into thinking it is still getting the drug. Upon activating the dopamine receptor, the medication blocks it from binding dopamine and thus prevents the drug's euphoric and other effects. As a result, the person feels normal, and drug craving and withdrawal effects are reduced.

Currently, a few medications have been developed for opioids (heroin, morphine), tobacco (nicotine), and alcohol addiction. However, there is no approved treatment for cocaine and methamphetamine dependence. The best studied cocaine and methamphetamine anti-addiction medication that has been systematically tested in animal models of drug addiction is SB-277011 [1] (Scheme 2). Previous studies demonstrated that it significantly inhibits the rewarding effects of cocaine, heroin, nicotine, and methamphetamine, as well as reinstatement of drug-seeking behavior.[2] Compound SB-277011 had never reached clinical trials due to its high fat and poor water solubilities. In addition, SB-277011 was discovered to be significantly affected by metabolism,[3] resulting in its fast decomposition once it enters the blood stream. The subsequent generations of anti-addiction medications still display similar problems and present unwanted side effects, such as movement disorders (extrapyramidal syndrome), catalepsy, mood alterations, depression, anxiety, sedation, and memory impairment.[4]



Previous work has demonstrated that boron clusters (Scheme 1) are attractive building blocks to make new pharmaceuticals [5] due to their synthetic flexibility, aqueous stability, general

robustness, and remarkable bio-stability. Their fat and water solubilities can be tuned in a controlled manner *via* the use of different isomers (*ortho-*, *meta-*, or *para-*) or by making clusters anionic (*e.g.* $[B_{12}H_{12}]^{2-}$). They also display a range of unique interactions with biomolecules. Recent advances in medicinal research have shown significant promise for use of boron clusters in drug design.[6]

3. Project Need/Significance. According to the Journal of the American Medical Association, 900,000 Americans die each year from substance, alcohol, and tobacco abuse. Alcohol abuse alone causes 79,000 premature deaths annually. Recent data provided by the National Institute of Drug Abuse (NIDA) show that 20.6 million Americans (8% of the population) are currently classified as having substance dependence or abuse; amongst them, 1.4 million are current users of cocaine – one of the most abused drugs, and one for which there is no medication available.

Advances in addiction research are revealing long-lasting changes in the brains of individuals addicted to drugs, which supports the concept of addiction as a disease of the brain, termed substance use disorder. The dopamine system plays a central role in drug addiction, as well as in other neuropsychiatric disorders, including Parkinson's disease, dementia, and schizophrenia. The prevalence of Parkinson's disease and schizophrenia is about 1% of the total population, whereas the prevalence of drug addiction is even higher, creating a large disease burden.

Given the tremendous unmet need for efficacious and affordable anti-addiction treatment, we suggest the preparation of a new series of boron-based medication that, we believe, will prove superior to current medications in terms of efficacy and selectivity toward the targeted dopamine receptors. This study will be the first to use boron clusters to design new medication for the treatment of addiction.

4. Project Potential. A recently reported crystal structure of the dopamine receptor provides an opportunity to screen a series of newly designed compounds for their ability to interact with the active site of the dopamine receptor using computer modeling docking studies.[7] As a result, we were able to identify several promising candidates (e.g. compound **1**, Scheme 2) that showed an excellent fit to the active site of the dopamine receptor (Figure 1).

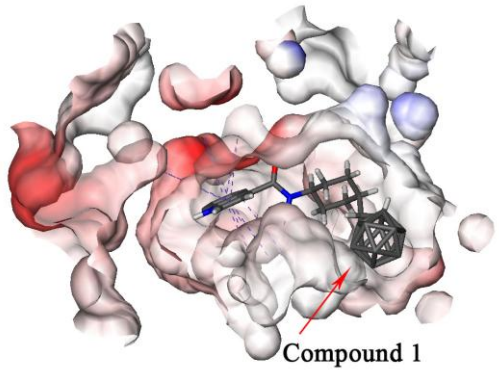


Figure 1. Active site of dopamine receptor.

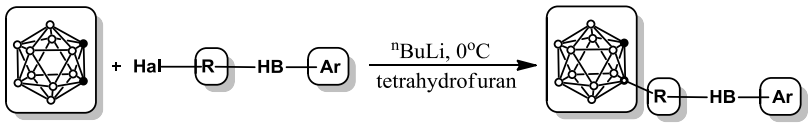
Our laboratory plans to synthesize compound **1** and a library of its structural analogs having the general formula [B]-R-HB-Ar. New compounds will be thoroughly characterized using a range of chemical analytical techniques. This should allow us to publish a short communication in a peer-reviewed journal and to start the collaborations necessary to evaluate the therapeutic effect of novel medications for treatment of addiction. Subsequent optimization of the prepared compounds based on their biomedical data is envisioned. Upon completion of this grant period, PI anticipates to have preliminary data sufficient to apply for extramural funding.

If funded, this project has a great potential of leading to effective anti-abuse treatment of cocaine and methamphetamine addictions, and potentially of other neuropsychiatric disorders associated with dopamine system (Parkinson's disease, dementia, and schizophrenia).

5. Methods. The first step will be to establish synthetic protocols for the preparation of the proposed compounds. In order to prepare the designed anti-addiction medications, a combination of organic, inorganic, and boron chemistry synthetic techniques will be employed.[8]

One of the synthetic routes to access compound **1** is displayed in Scheme 3. It starts with the formation of the R-HB-Ar functional group carrying a terminal halide ligand (Hal), which will be a point of attachment to a boron cluster. The following step is the derivatization of the carborane carbon-hydrogen (CH) unit using a strong base to remove mildly acidic CH protons and addition of the Hal-R-HB-Ar reagent (Scheme 3).

Scheme 3. Synthesis of Proposed Medication



The new library of the [B]-R-HB-Ar compounds will be thoroughly characterized using analytical instrumentation already available at TCU: nuclear magnetic resonance (NMR), X-ray diffraction (XRD), mass-spectrometry (MS), and infra-red spectroscopy (IR).

References:

[1] a) B. LeFoll, J.-C. Schwartz, P. Sokoloff, *Eur. Psychiatry* **2000**, *15*, 140; b) J.-C. Schwartz, J. Diaz, C. Pilon, P. Sokoloff, *Brain Res. Rev*. **2000**, 31, 277; c) G. Remington, S. Kapur, *Curr. Opin. Invest. Drugs* **2001**, *2*, 946.
[2] J.G. Gilbert, A.H. Newman, E.L. Gardner, C.R. Ashby Jr., C.A. Heidbreder, A.C. Pak, X.Q. Peng, Z.-X. Xi, *Synapse* **2005**, 17.
[3] N.E. Austin, S.J. Baldwin, L. Cutler, N. Deeks, P.J. Kelly, M. Nash, C.E. Shardlow, G. Stemp, K.M. Thewlis, A. Ayrton, P. Jeffrey, *Xenobiotica* **2001**, *31*, 677.
[4] a) C. Missale, S.R. Nash, S.W. Robinson, M. Jaber, M.G. Caron, *Phys. Rev.* **1998**, *78*, 189; b) C. Heidbreder, *CNS Neurol. Disord. - Dr.* **2008**, *7*, 410; c) V.J. Galani, D.G. Rana, *IJPFR* **2011**, *1*, 45.
[5] a) J.F. Valliant, K.J. Guenther, A.S. King, P. Morel, P. Schaffer, O.O. Sogbein, K.A. Stephenson, *Coord. Chem. Rev*. **2002**, *232*, 173; b) I.B. Sivaev, V.V. Bregadze, *Eur. J. Inorg. Chem*. **2009**, 1433; c) A.F. Armstrong, J.F. Valliant, *Dalton Trans*. **2007**, 4240; d) F. Issa, M. Kassiou, L.M. Rendina, *Chem. Rev*. **2011**, *111*, 5701; e) M. Scholz, E. Hey-Hawkins, *Chem. Rev*. **2011**, *111*, 7035.
[6] M.W. Lee, Jr., Y.V. Sevryugina, A. Khan, S.Q. Ye, *J. Med. Chem*. **2012**, *55*, 7290.
[7] E.Y.T. Chien, W. Liu, V. Katritch, G. Won Han, M.A. Hanson, L. Shi, A.H. Newman, J.A. Javitch, V. Cherezov, R. C. Stevens, *Science* **2010**, *330*, 1091.
[8] R.N. Grimes, *Carboranes*, Ed. 2, Elsevier: 2011.

BUDGET FORM

Account Code			Amount	Total
A. SALARIES – Student Assistants/Research Assistants/Junior Faculty Summer Pay (State projected period and number of hours for which assistant will be employed. **Rate of pay:** Be sure to consult the External Grants information page for the current minimum wage				
6104	**1.**	Summer salary	**$6,000.00**	
	2.			**$6,000.00**
B. TRAVEL (Itemize on separate sheet; do not include funds for presentation of research papers.)				
6220	**1.**	**Staff -**	**$**	
6222	**2.**	**Consultant -**	**$**	
6221	**3.**	**Foreign -**	**$**	**$**
C. PERMANENT EQUIPMENT (If requested equipment is presently available on campus, please explain, on separate sheet, why the available equipment cannot be used.)				
6340	**1.**		**$**	
	2.		**$**	
	3.		**$**	**$**
D. OTHER EXPENSES (Itemize on separate sheet, include costs.)				
6430	**1.**	**Supplies –**	$	
6437	**2.**	**Research Supplies -**	**$3,899.69**	
6341	**3.**	**Computer -**	**$**	
6365	**4.**	**Printing Services –**	**$**	
6360	**5.**	**Mail Services –**	**$**	
6445	**6.**	**Other –**	**$**	**$3,899.69**
			TOTAL BUDGET REQUEST	**$9,899.69**

Updated 2012-2013

BUDGET JUSTIFICATION:

As a junior faculty (hired in August 2013) holding a full-time, tenure-track position with the rank of Assistant Professor in Chemistry, I would like to request funding for Junior Faculty Summer Research Program. **$6,000.00**

RESEARCH SUPPLIES

Chemicals		
Solvents **$822**	anhydrous dichloromethane, 8L $283; anhydrous benzene, 2 L $113.5; anhydrous hexane, 2L $134; anhydrous tetrahydrofuran, 2L $152; anhydrous dimethylformamide, 2L $139.5	The variety of solvents will be needed for the various reactions that will be performed - in some cases it will be found that certain reactions work in certain solvents and not in others. Anhydrous solvents are more expensive, but it is necessary to use water-free solvents in order for the reactions to work.
Boron clusters **$2,000**	ortho-carborane 25g, $777; meta-carborane, 25g, $855; decaborane, 10g, $368	Boron clusters, like ortho-carborane, meta-carborane, and decaborane are starting materials.
Other reagents **$534.07**	1-(2-methoxyphenyl)piperazine, 100g, $104.63; 4-bromo-1-butene, 25g, $50; 1,4-dibromo-2-butene, 25g, $66.60; potassium phthalimide, 500g, $71.91; dichlorophenylpiperazine hydrochloride, 100g, $159; 1,4-dichlorobutane, 100g, $16.05; potassium triphosphate, 1kg, $35.34; potassium carbonate, 500g, $30.54	Boron clusters will be functionalized with organic groups, and for this we need a variety of organic and inorganic reagents.
Analyses (required for publication)		
NMR solvents **$223.70**	deuterated chloroform, 100g, $43.20, deuterated dichloromethane, 5g, $180.50.	In order to characterize the products of the reactions, we will need to dissolve them in deuterated solvents (solvents in which hydrogen atoms are replaced by their isotope deuterium), and take nuclear magnetic resonance (NMR) spectra of them in those solvents
NMR tubes **$182.50**	10 thin-walled Wilmad 535PP NMR tubes @ 18.25 each	NMR tubes are specialized glass tubes made to fit into the NMR spectrometer in order to take NMR spectra
Miscellaneous		
Gases **$137.42**	Each liquid nitrogen tank $68.71	Syntheses are conducted using Schlenk lines, a specially designed glassware which allows one to work under nitrogen atmosphere. Nitrogen tanks will be needed to supply nitrogen atmosphere.
Subtotal $3,899.69		

TOTAL $9,899.69

APPENDIX: Record of Scholarly Activity for the Past Three Years

PROFESSIONAL SOCIETY MEMBERSHIPS

- American Chemical Society (ACS), **2003**–present;
- American Crystallographic Association (ACA), **2006** –present.

PEER-REVIEWED PUBLICATIONS

- Synthesis of *closo*- and *nido*-biscarboranes with rigid unsaturated linkers as precursors to linear metallacarborane-based molecular rods. A.V. Safronov, Y.V. Sevryugina, K.R Pichaandi, S.S. Jalisatgi, M.F. Hawthorne. *Dalton Trans.* **2014**, *Advance Article*.

- Synthesis of [closo-$B_{12}(OH)_{11}NH_3$]−: A New Heterobifunctional Dodecaborane Scaffold for Drug Delivery Applications. O. Bondarev, A.A. Khan, X.Tu, Y.V. Sevryugina, S.S. Jalisatgi, M.F. Hawthorne, *J. Am. Chem. Soc.*. **2013**, *135*, 13204−13211.

- B-Mercaptocarboranes: a New Synthetic Route. K.Z. Kabytaev, T.A. Everett, A.V. Safronov, Y.V. Sevryugina, S.S. Jalisatgi, M.F. Hawthorne, *Eur. J. Inorg. Chem*. **2013**, 2488–2491.

- Carboranes Increase the Potency of Small Molecule Inhibitors of Nicotinamide Phosphoribosyltranferase. M.W. Lee, Jr., Y.V. Sevryugina, A. Khan, S.Q. Ye, *J. Med. Chem*. **2012**, *55*(16), 7290−7294.

- The Acid-induced Opening of [Closo-$B_{10}H_{10}]^{2-}$ as a New Route to 6-Substituted-nido-$B_{10}H_{13}$ Decaboranes and Related Carboranes. O. Bondarev, Y.V. Sevryugina, S.S. Jalisatgi, M.F. Hawthorne. *Inorg. Chem*. **2012**, *51*, 9935−9942.

- 8-Iodo-*ortho*-carborane – an Unfairly Forgotten Member of Iodocarborane Family: Synthesis and Structural Characterization. A.V. Safronov, Y.V. Sevryugina, S.S. Jalisatgi, R.D. Kennedy, C.L. Barnes, M.F. Hawthorne. *Inorg. Chem.* **2012**, *51*, 2629–2637.

US AND INTERNATIONAL PATENTS

- Cluster Boron Compounds and uses thereof. WO 2013/040222, March 22, **2013**.
- Small molecule inhibitors of Nicotinamide Phosphoribosyl Transferase (Nampt). PCT/US2012/066849, November 30, **2012**.

PRESENTATIONS AT SCHOLARLY MEETINGS

- Design of Novel Anti-addiction Medicine. Y.V. Sevryugina, M.R. VanGordon, 69th Southwest Regional Meeting of the ACS, Waco, TX, United States, November 16-19, **2013**, SWRM-216.

- Novel Anticancer Agents: Design and Synthesis of Boron-based Small Molecule Inhibitors of Nicotinamide Phosphoribosyltranferase (Nampt). Y.V. Sevryugina, A.

Khan, S.Q. Ye, M.W. Lee, Jr., 245th ACS National Meeting, New Orleans, LA, United States, April 7-11, **2013**.

- Hydroxy-undecahydro-(O-dichlorophosphoryl)-closo-dodecaborate(2−): Solvatomorphism, Monoclinic *C* and *I*-centered Cells and Challenging Disorders. Y. Sevryugina, O. Tutusaus, C.F. Campana, S.S. Jalisatgi, M.F. Hawthorne, 2012 ACA Annual Meeting, Boston, MA, July 28-August 1, **2012**.
- B-Iodinated *o*-Carboranes: C–H···I Hydrogen Bonding, Absolute Structure Determination and Merohedral Twinning in Space Group $P4_1$. Y. Sevryugina, A.V. Safronov, C.F. Campana, M.F. Hawthorne, 2011 ACA Annual Meeting, New Orleans, LA, United States, May 28–June 2, **2011**. Paper 05.01.5, p. 15, **oral**.
- Icosahedral Borane Scaffolds for Nanomolecular Delivery System. S. S. Jalisatgi, O. Tutusaus, Y. Sevryugina, K. Chan, M.W. Lee, M.F. Hawthorne, IME Boron XIV, Toronto, Canada, September 11-15, **2011**.
- Exhaustive Regiospecific Trimethylsilylation of $[closo\text{-}B_{12}(OH)_{12}]^{2-}$. M.W. Lee, Y.V. Sevryugina, M.F. Hawthorne, IME Boron XIV, Toronto, Canada, September 11-15, **2011**.

For TCU/RCAF Use Only:
- □ New/seed money
- □ Continuing/renewal

EVALUATION SHEET

Name: Yulia Sevryugina	**Deptartment:** Chemistry
Project Title: Boron-based Anti-addiction Medication	

Proposals will be evaluated on the basis of the following:		Points Possible	Points Awarded
0.	**Progress Report** (**Only for continuing/renewal projects).** One page maximum. The explanation must clearly delineate the reason for continued funding and include evidence of external grant submission concerning the proposal to be renewed – OR – include evidence of non-availability of fund for this work. Missing progress reports will deduct 15 points from continuing/renewal applications.	**-15**	_____
1.	**Abstract.** Has the investigator provided a summary statement that covers the main point of the project, the problem intended to solve, relevant background, expected methodologies, and major conclusions? Is the abstract 200 words or less?	**5**	_____
2.	**Purpose.** Is the purpose of the project clearly stated in a concise introductory paragraph? Based on this statement, is it clear exactly what the investigator hopes to produce?	**5**	_____
3.	**Project Background.** Is there an adequate review of the pertinent previous work (either by the investigator or others) so that it is clear how the proposed project fits into the current state of knowledge or artistry?	**10**	_____
4.	**Project Need/Significance.** Has the investigator provided a convincing argument that the proposed project will make an important contribution to the field of study or area of artistry?	**15**	_____
5.	**Project Potential.** Has the investigator provided an explanation of: **1)** how this project will contribute to his/her scholarly/artistic development, **2)** how this project will allow the investigator to seek extramural funding in this area of scholarly/artistic activity, and **3)** the potential for publication, or other appropriate form of external recognition, based on the activities of the projects?	**10**	_____
6.	**Methods.** Are the project activities clearly described, and does it appear that they will allow the investigator to reach the objective(s) described in the **Purpose**?	**15**	_____
7.	**Budget and Budget Justification.** Is the budget clearly described? Is each area of expenditure justified. Is overall cost of the project reasonable?	**30**	_____
8.	**Record of Scholarly Activity.** Has the investigator provided a record of their scholarly activity (publications, presentations, performances, and external funds)? Does this show active scholarship over the past three years, and that the current project will add to the investigator's scholarly development (see **Project Potential**)?	**10**	_____
Extra Points.	New faculty (in first or second year of appointment) who have not yet received a TCU RCAF Grant.	**15**	_____
Deductions.			
	1) Limited minor errors	**-10**	_____
	2) Major errors (in number or substance)	**-20**	_____
	3) Extreme errors	**-40**	_____
MAXIMUM TOTAL POINTS		**100 (115 if new faculty)**	_____