



## Frontiers Trailblazer Application Form

PI name: **Stephen D. Simon**

**Proposed Trailblazer Project Title: Celebrating the failures of medical research using a graphic novel format**

### **Abstract (≤ 500 words)**

Research organizations are very adept at publicizing their successes, but the information from their failures is equally important. Understanding the causes of research failures will create a needed sense of humility among researchers that will encourage them to take great care in conducting their work and help place future research on a more solid foundation. The goal of this project is to prepare two case studies of spectacular research failures, failures that led to serious harm to patients. The first case study involved the first human tests of a drug, TGN 1412, that led to the hospitalization and permanent disability of six research volunteers. The second case study involves a high-profile clinical trial of personalized medicine in the treatment of ovarian cancer where the study had to be stopped early because the data behind the personalized medicine algorithm were completely and totally wrong. These two case studies will use a graphic novel format and be licensed liberally to allow the research community to use and adapt this work to help teach the next generation of researchers. They will also serve as a model for future case studies in research failures using a graphic novel format.

### **Lay Language Summary (≤ 200 words)**

Research organizations are very adept at publicizing their successes, but the information from their failures is equally important. Understanding the causes of research failures will create a needed sense of humility among researchers that will encourage them to take great care in conducting their work and help place future research on a more solid foundation. The goal of this project is to prepare two case studies of spectacular research failures, failures that led to serious harm to patients. The first case study involved the first human tests of a drug, TGN 1412, that led to the hospitalization and permanent disability of six research volunteers. The second case study involves a high-profile clinical trial of personalized medicine in the treatment of ovarian cancer where the study had to be stopped early because the data behind the personalized medicine algorithm were completely and totally wrong. These two case studies will use a graphic novel format and be licensed liberally to allow the research community to use and adapt this work to help teach the next generation of researchers. They will also serve as a model for future case studies in research failures using a graphic novel format.

## **Proposed Trailblazer Project Description.**

### **Introduction**

The medical research community relies on a very effective publicity machine.<sup>1</sup> They are quick to tout the advances they have made. But equally important is to publicize the miserable failures of medical research. These findings “pollute the literature and waste precious resources.”<sup>2</sup> Only by understanding what has gone wrong can medical science avoid repeating these failures.

I have always been interested in the failures in medical research because so many of them can be tied directly to failures in following well-established guidelines in Statistics and Data Science.<sup>3</sup> I talk about many of these on my blog and they make excellent teaching examples in my classroom.



I am proposing a series of case studies in scientific failure. Failure comes in many forms, but I am most concerned with high stakes failures where bad and dangerous advice is disseminated, and people are directly harmed by the research. I want to develop these case studies using a graphic novel format.

## **Background**

A graphic novel is a story told where free hand drawings comprise much of the story telling. Many people use the terms graphics novel and comic book interchangeably. Though there are some subtle differences between the two, the differences are not worth the trouble. It might be tempting to dismiss a graphics novel or a comic book as something just for kids, but this is belied by the Pulitzer Prize Letters Award given to Art Spiegelman in 1992 for his graphic novel, Maus.<sup>4</sup>

The pioneer in using a graphic novel format to teach science was Larry Gonick, who published The Cartoon Guide to Computer Science in 1983, The Cartoon Guide to Genetics (with Mark Wheelis) also in 1983, The Cartoon Guide to Physics (with Art Huffman) in 1991, and The Cartoon Guide to Statistics (with Woolcott Smith) in 1994. It is Mr. Gonick's work that inspired my efforts in this area.

## **Previous work**

A graphic novel format is ideal for studies of research failure because these failures are laden with suffering and raw emotion that can be more effectively described with images and words rather than by words alone. I am not an artist, but I have paid an artist to develop a series of images for one case study, the TGN 1412 trial.<sup>5</sup> These images only filled in half of the story but should give a rough idea of how a graphic novel format would work.

TGN 1412 is an experimental drug that was intended to treat leukemia and arthritis. It attempted to stimulate the patient's immune system. The initial animal studies were promising, but the first trial in human subjects was a terrible disaster. Eight healthy volunteers were recruited for the study, and six of the patients suffered severe problems shortly after receiving the drug (two of the eight patients were given a placebo). Figure 1 shows one of the images used in this presentation.

The details of the suffering are rather gruesome. The stricken patients were "writhing, vomiting and screaming in agony as their temperatures soared and their organs began to fail. Fighting for their lives, some of the human guinea pigs saw their heads swell like balloons, while several had to have body parts amputated."<sup>6</sup>

## **Approach**

### **Phase 1: Complete additional drawings for the TGN 1412 trial**

The original images were drawn by Julie Berman, a professional artist,<sup>7</sup> and paid from my personal funds. The more abstract elements of this case study need to be completed. These include an illustration of the mechanism of action of the drug (binding to a CD-28 receptor) and an explanation of what a Cytokine storm is. Other images would flesh out some of the concerns about the trial.

The first phase of this work will be to get additional images from Ms. Berman to complete the work of this case study. The drawings would follow the same general format as the earlier files. In particular, the images would be black and white and text free, allowing adaptation to a variety of formats and easy translation, if there is interest, into different languages.



**Figure 1.** A research volunteer and one of the two placebo patients, Raste Khan, watches as one of the other patients convulses in pain.

The individual images, the text for the speaker notes, and a complete PowerPoint presentation will be placed on my website and github repository. Everything would be made available under the Creative Commons Attribution 3.0 license.<sup>8</sup>

## **Phase 2. Case study of the Duke ovarian cancer research scandal.**

In 2006, a research team at Duke University published a research paper that used “gene expression signatures” to identify individual responses to various chemotherapy drugs.<sup>9</sup> This was an early example of personalized medicine. The results led to the development of a large-scale clinical trial to test the efficacy of using the gene expression signatures to guide treatment options for patients with ovarian cancer. The study was shut down before completion because of concerns raised about the original research.<sup>10</sup> The authors made several attempts to address the concerns but failed and the original study was formally withdrawn in 2011. There have been several popular press accounts of this over time.<sup>11, 12, 13</sup>



In phase 2 of this grant, the basic timeline and history of this publication and its retraction will be outlined. A separate artist will be commissioned to produce images that can be matched with this outline to produce a graphic novel format documenting one of the most prominent failures in personalized medicine. The use of an independent artist will encourage diversity in the presentation style.

We will use the same publication strategy for this case study: publication on the web and at a github site of both the images and the accompanying speaker notes. All the work will be published under the Creative Commons 3.0 Attribution license.

### **Regulatory review**

This work does not require approval by an institutional review board because it relies solely on publicly available data.

### **Proprietary information**

Nothing in this grant or in any of the work associated with this grant is proprietary. You can share the information in this grant freely under the Creative Commons 3.0 Attribution license.

### **Specific publication plan for results of this study.**

The short-term product of this grant will be two complete case studies documenting serious failures in the research process. These case studies will be distributed on my website and github repository in PowerPoint format, making it easy for researchers and educators to use these case studies in classes on research methodology and ethics in research. The information will also be provided in a simple text format, allowing the re-use of these case studies in research posters or as informational handouts.

### **Plan to seek NIH funding and anticipated date for future study.**

I am seeking additional pilot funding for this grant including two internal grant mechanisms within the University of Missouri-Kansas City. If all three efforts are successful, there should be four complete case studies, each illustrated by a different artist, that can serve as a model for larger efforts, possibly publishable as a book.

The long-term goal is to obtain NIH funding through the R25 grant mechanism (Education Projects), to support the development of a range of case studies in a graphic novel format. There are several promising Program Announcement, such as PAR-19-258 (NIDA Research Education Program for Clinical Researchers and Clinicians), Par-18-476 (Cancer Research Education Grants Program - Curriculum or Methods Development) and many others. There is a similar program announcement through NSF, 19-609 (Ethical and Responsible Research). I will seek NIH and NSF funding as soon as I have two complete case studies to offer as preliminary data, possibly as early as July 2021.

### **Summary**

There is a need to recognize and learn from research failures. This grant proposes the development of case studies of research failure using a graphic novel format. These case studies would be made available in an open format to encourage their use in research training.

The underlying rationale for highlighting research failures is not to cast aspersion on the research community. Rather, it is an attempt to get researchers to approach their work with a sense of humility. If they recognize the



failures of others and the underlying causes of these failures, they will use greater care in their own work and provide a more stable and robust foundation for research findings in the future.

## References

1. Woolston C. Public relations: For your information. *Nature*, 2014 Apr 30; 509: 123-125.
2. Woodgett J. We must be open about our mistakes. *Nature*, 2012 Sep 05; 489: 7.
3. Thiese MS, Walker S, Lindsey J. Truths, Lies, and Statistics. *J Thorac Dis*, 2017 Oct; 9(10): 4117-4124.
4. The Pulitzer Prizes. Special Awards and Citations. <https://www.pulitzer.org/prize-winners-by-category/260>. Retrieved 2019-11-29.
5. Simon SD, Berman J. The TGN 1412 trial (very preliminary draft). <http://www.pmean.com/cases/Tgn1412Popwerpoint.pdf>. Retrieved 2019-11-29.
6. Evans S. How six fit young men were left disfigured and fighting for lives after 'Elephant Man' drugs trial. *The Daily Mirror*, 2017 Feb 21. <https://www.mirror.co.uk/news/uk-news/how-six-fit-young-men-9860903>. Retrieved 2019-11-29.
7. Berman J. Julia Berman Gallery. <http://www.juliaberman.com/gallery/index.php>. Retrieved 2019-11-29.
8. Creative Commons. Creative Commons Attribution License 3.0. <https://creativecommons.org/licenses/by/3.0/us/>. Retrieved 2019-11-29.
9. Potti A, Dressman HK, Bild A, et al. Genomic signatures to guide the use of chemotherapeutics. *Nature Medicine*, 2006; 12: 1294–1300.
10. Baggerly KA, Coombes KR. Deriving Chemosensitivity from cell lines: Forensic bioinformatics and reproducible research in high-throughput biology. *The Annals of Applied Statistics*, 2009; 3(4): 1309–1334.
11. Pollack A. F.D.A. Says Cancer Test Failed to Get Its Approval. *The New York Times*, 2008 Oct 08. <https://www.nytimes.com/2008/10/09/business/09cancer.html>. Retrieved 2019-11-29.
12. Kolata G. How Bright Promise in Cancer Testing Fell Apart. *The New York Times*, 2011 Jul 07. <https://www.nytimes.com/2011/07/08/health/research/08genes.html>. Retrieved 2019-11-29.
13. Singer N. Duke Suspends Researcher and Halts Cancer Studies. *The New York Times Prescription blog*, 2010 Jul 20. <https://prescriptions.blogs.nytimes.com/2010/07/20/duke-suspends-researcher-halts-cancer-studies/>. Retrieved 2019-11-29.

**DETAILED BUDGET FOR INITIAL BUDGET PERIOD  
DIRECT COSTS ONLY**

FROM  
2020-07-01

THROUGH  
2021-06-30

List PERSONNEL (*Applicant organization only*)  
Use Cal, Acad, or Summer to Enter Months Devoted to Project  
Enter Dollar Amounts Requested (*omit cents*) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mnths	Acad. Mnths	Summer Mnths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Stephen Simon	PD/PI					0	0	0
<b>SUBTOTALS</b>						0	0	0

CONSULTANT COSTS	
EQUIPMENT ( <i>Itemize</i> )	
SUPPLIES ( <i>Itemize by category</i> )	
TRAVEL	
INPATIENT CARE COSTS	
OUTPATIENT CARE COSTS	
ALTERATIONS AND RENOVATIONS ( <i>Itemize by category</i> )	
OTHER EXPENSES ( <i>Itemize by category</i> ) Stipend, Julia Berman Stipend, second artist to be named	5000

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	5000
<b>SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD</b> ( <i>Item 7a, Face Page</i> )		<b>\$ 5000</b>
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	
<b>TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD</b>		<b>\$</b>

## **BUDGET JUSTIFICATION**

I do not have sufficient artistic talent myself to prepare the graphic novel format and will collaborate with Julia Berman and a second artist to be named. They will prepare images that illustrate the case studies provided above. The artists will pay for all the materials they need and no travel will be required.

The fees for these images will be negotiated on a per image basis. All work will become my property which I will allow sharing across the research community using an open source license. If the funds are insufficient to complete all of the work needed, I will supplement using two internal UMKC grant mechanisms that I am applying for or with my own funds.

I will provide the overall framework and the notes to accompany these images at no charge.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Stephen D. Simon

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

POSITION TITLE: Professor / Independent Statistical Consultant

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 Iowa	B.A.	06/77	Mathematics
University of Iowa	M.S.	12/78	Statistics
University of Iowa	Ph.D.	12/82	Statistics

**A. Personal Statement**

As a statistical consultant with over 30 years of experience, I have worked on pretty much any type of study imaginable, though I have specialized mostly in health care research since 1987. I have taught many formal and informal training classes in the use of statistical software, including SAS, SPSS, and R. I am currently the President of the Kansas City R Users Group and have given many presentations for them. With the assistance of a database administrator, I am developing a new class, Introduction to SQL, as I have found SQL to be vital in any analysis of electronic health record data.

I have an outstanding track record in dissemination of research results. I have over 90 peer reviewed publications, four of which have won major awards. I have published a book about the statistical aspects of Evidence-Based Medicine and have a contract to produce a second book. I am the author of a major website and blog ([www.pmean.com](http://www.pmean.com), [blog.pmean.com](http://blog.pmean.com)) with over 1,700 pages about Statistics, Evidence-Based Medicine, and research ethics.

**B. Positions and Honors****Positions and Employment**

1979 – 1981 Research Assistant, Statistical Consulting Center, University of Iowa  
 1981 – 1987 Assistant Professor, Department of Applied Statistics and Operations Research, Bowling Green State University, Bowling Green, Ohio  
 1987 – 1987 Research Statistician, Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio  
 1987 – 1996 Chief, Statistics Activity, Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Cincinnati, Ohio  
 1996 – 2008 Research Biostatistician, Office of Medical Research, Children's Mercy Hospital, Kansas City, Missouri, with an adjunct faculty appointment at the University of Missouri-Kansas City  
 2008 – present Part-time Independent Statistical Consultant, P.Mean Consulting, Leawood, Kansas  
 2008 – present Part-time Professor (currently 44% effort), Department of Biomedical and Health Informatics, University of Missouri-Kansas City, Kansas City, Missouri

## Other Experience and Professional Memberships

1984 - present Member, American Statistical Association

## Honors

1990 Public Health Service Achievement Medal given for producing cost savings and greater operational efficiency through the use of micro-computer analysis of statistical data.

1990 Alice Hamilton Award given to a paper I co-authored (Schrader et al Reproductive Toxicology 1988; 2: 183-190).

1991 Alice Hamilton Award given to a paper I co-authored (Schrader et al Reproductive Toxicology 1988; 2: 183-190).

1994 Public Health Service Commendation Medal given in July 1994 for my oversight of a laboratory modernization effort.

1997 Best presentation in the area of Teaching Statistics in the Health Sciences given for a talk at the Joint Statistical Meetings in Anaheim CA (Simon "Medical Statistics Case Studies on the Web").

1999 Alice Hamilton Award (Biological Sciences Category) given to a paper I co-authored (Moorman et al Reproductive Toxicology 1998;12(3):333-46).

2003 Editor's Award given to a paper I coauthored (Miller et al Am J Audiology 2003;24(1);16-18).

2012 Honorable mention and \$1,000 cash award given for R code that I submitted to the Applications of R in Business competition sponsored by Revolution Analytics.

## **C. Contribution to Science**

1. I've had the opportunity to work with many researchers and the biggest problem that most of them face is **poor patient accrual**. They struggle to find a way to recruit subjects quickly enough so that they could meet their sample size goals within a practical time frame. With a colleague at Kansas University Medical Center (KUMC), Byron Gajewski, and later with a graduate student at KUMC, Joyce Yu Jiang, we developed Bayesian models that could forecast the amount of time that a trial would take to reach a fixed sample size or to forecast the sample size for a trial that ended at a fixed date.

My work with accrual models have taught me that, by itself, the sample size calculation during the planning of a research study is insufficient. If it takes you ten years to complete a study that you thought would only take ten months, you are going to end up with a disaster.

- a. Jiang Y, Simon S, Mayo MS, Gajewski BJ. Modeling and validating Bayesian accrual models on clinical data and simulations using adaptive priors. *Stat Med*. 2015 Feb 20; 34(4): 613-29.
- b. Gajewski BJ, Simon SD. A One-Hour Training Seminar on Bayesian Statistics for Nursing Graduate Students. *The American Statistician*. August 1, 2008, 62(3): 190-194.
- c. Gajewski BJ, Simon SD, Carlson SE. Predicting accrual in clinical trials with Bayesian posterior predictive distributions. *Stat Med*. 2008 Jun 15;27(13):2328-40.

2. At Children's Mercy Hospital, I developed an interest in **Evidence Based Medicine**. I had attended many journal clubs and started wondering what level of evidence it takes to get doctors or other health care professionals to change their clinical practice. In my experience, doctors tended to be hypercritical of the research presented at journal clubs. It's far too easy to nitpick and find a minor issue, but this does not necessarily invalidate the findings of the study.

I presented some of my own views on critical appraisal in a series of articles for the *Journal of Andrology*. I also partnered with doctors to write a couple of editorials that addressed controversies in critical appraisal, especially the importance of defining a clinically important difference. The material from these articles and editorials plus additional content from my website formed the basis of a book published in 2006 by Oxford University Press.

My experience with Evidence Based Medicine has taught me the importance of a thoughtful approach to research design issues like blinding and concealed allocation so that the resulting research publications will be considered more persuasive during the critical appraisal step of Evidence Based Medicine.

- a. Simon SD. Statistical Evidence in Medical Trials. What Do the Data Really Tell Us? Oxford UK: Oxford University Press; 2006.
- b. Portnoy JM, Simon SD. Is 3-mm less drowsiness important?. *Ann Allergy Asthma Immunol.* 2003 Oct;91(4):324-5.
- c. Simon SD. Understanding the odds ratio and the relative risk. *J Androl.* 2001 Jul-Aug;22(4):533-6.

3. At the National Institute for Occupational Safety and Health (NIOSH), a branch of the Centers for Disease Control and Prevention, I worked with a toxicologist, Steven M. Schrader, on **male reproductive toxicology**. I should note that Dr. Schrader also supervised a strong program in female reproductive toxicology, and while I learned quite a bit about both sides of the equation, a different statistician served as co-author on the publications on female reproductive toxicology.

I was fortunate to arrive at NIOSH shortly after completion of a major longitudinal study of sperm samples in a healthy cohort of unexposed males. The longitudinal design required novel statistical measures and graphical displays. This data set produced many publications including two which won major awards.

In addition to the longitudinal study, I worked on the planning of studies in humans examining occupational exposures to non-ionizing radiation and lead, and helped develop a novel rabbit model for lead exposure.

My research in male reproductive toxicology taught me how to handle the complexities associated with longitudinal data and exposure studies.

- a. Grajewski B, Cox C, Schrader SM, Murray WE, Edwards RM, Turner TW, Smith JM, Shekar SS, Evenson DP, Simon SD, Conover DL. Semen quality and hormone levels among radiofrequency heater operators. *J Occup Environ Med.* 2000 Oct;42(10):993-1005.
- b. Schrader SM, Langford RE, Turner TW, Breitenstein MJ, Clark JC, Jenkins BL, Lundy DO, Simon SD, Weyandt TB. Reproductive function in relation to duty assignments among military personnel. *Reprod Toxicol.* 1998 Jul-Aug;12(4):465-8.
- c. Moorman WJ, Skaggs SR, Clark JC, Turner TW, Sharpnack DD, Murrell JA, Simon SD, Chapin RE, Schrader SM. Male reproductive effects of lead, including species extrapolation for the rabbit model. *Reprod Toxicol.* 1998 May-Jun;12(3):333-46.
- d. Schrader SM, Turner TW, Breitenstein MJ, Simon SD. Longitudinal study of semen quality of unexposed workers. I. Study overview. *Reprod Toxicol.* 1988;2(3-4):183-90.

4. At Bowling Green State University, I partnered with an Economics faculty, James P. Lesage, to study **numerical accuracy issues**. These publications started with the seminal data set for numerical accuracy, the Longley data set, and looked at a flexible alternative developed by Wampler. We developed an extension that could examine near collinearity involving the intercept and produced new benchmarks for Analysis of Variance.

Some of these benchmarks were adopted by the National Institute for Standards and Technology for their Statistical Reference Datasets project. I also produced a couple of pedagogical articles that clearly illustrated how problems with numerical accuracy can arise.

The work in this area gave me an early overview of the broad range of statistical software packages available for microcomputers. I have maintained this interest and can easily identify which, among several competing statistical packages, is the best for a particular data analysis.

- a. Simon SD, Lesage JP. Assessing the accuracy of ANOVA calculations in statistical software. *Computational Statistics and Data Analysis* 1990; 8(3); 325-332.
- b. Simon SD, Lesage JP. The impact of collinearity involving the intercept term on the numerical accuracy of regression. *Computer Science in Economics and Management* 1988; 1; 137-152.
- c. Simon SD. How to illustrate numerical accuracy problems on any computer. *Mathematics and Computer Education* 1987; 21(1); 11-15.
- d. Simon SD. To err isn't only human. *Computer Language* 1986; 3(3); 71-76.

