Interdisciplinary Research (IDR) Origination Awards

Cover Page

Project Title

Optimizing the magnetic properties of magnetite (Fe_3O_4) nanoparticles for medical diagnosis purposes

Principal Investigator(s) (full-time faculty)

Name (PI listed first)	Department	College
Karine Chesnel	Physics and astronomy	CPMS
Roger Harrison	Chemistry and Biochemistry	CPMS
Bill Pitt	Chemical Engineering	Engineering

Track: Track 1

Abstract

Nanotechnology has allowed tremendous advances in disease diagnosis. The most promising methods often use magnetic nanoparticles (MNPs) because they can be manipulated via external magnetic field and temperature, thus facilitating biomolecule detection. However, it has been observed that MNPs tend to aggregate, causing malfunctions. Here we propose to optimize the structural and magnetic properties of magnetite (Fe_3O_4) MNPs to avoid clumping in medical applications. In particular, we seek uniformly sized MNPs that will collectively align with an external field but return to zero net magnetization when the field is released (superparamagnetism). The MNPs are fabricated via chemical routes in the laboratory of Dr. Harrison. The fabrication is optimized to obtain the best size control, with particle diameters ranging from 10 to 100 nm. The structural properties of the particles are analyzed via x-ray diffraction (XRD) and electron microscopy (TEM). The particles' magnetic properties are studied via vibrating sample magnetometry (VSM) and x-ray magnetic scattering (XRMS) in the laboratory of Dr. Chesnel. Their magnetic susceptibility is measured under high magnetic field and at low temperature via field-cooling measurements, to identify the blocking temperature where the material transitions from superparamagnetic to magnetically frozen. The particle size is optimized to bring the blocking temperature close to body temperature. Finally, the particles are functionalized and tested for various biomolecule detection applications, such as the capture and concentration of bacteria, proteins, and viruses, in the laboratory of Dr. Pitt. The preliminary findings will support grant proposals which we intend to submit to the National Science Foundation (NSF) and the National Institutes of Health (NIH).

Summary of Plans for External Funding

This project will lead to two large proposals: one to the NSF National Nanotechnology Institute (physics and chemistry for better MNPs), and one to the NIH Institute of Allergy & Infectious Diseases (disease diagnostics with MNPs), both planned for late 2023.

BYU Interdisciplinary Research (IDR) Proposal

Optimizing the magnetic properties of magnetite (Fe_3O_4) nanoparticles
for medical diagnosis purposes

Team Members:
Dr. Karine Chesnel (Physics & Astronomy, CPMS) - Principal Investigator
Dr. Roger Harrison (Chemistry & Biochemistry, CPMS)
Dr. Bill Pitt (Chemical Engineering, College of Engineering)

Abstract

Nanotechnology has allowed tremendous advances in disease diagnosis. The most promising methods often use magnetic nanoparticles (MNPs) because they can be manipulated via external magnetic field and temperature, thus facilitating biomolecule detection. However, it has been observed that MNPs tend to aggregate, causing malfunctions. Here we propose to optimize the structural and magnetic properties of magnetite (Fe3O4) MNPs to avoid clumping in medical applications. In particular, we seek uniformly sized MNPs that will collectively align with an external field but return to zero net magnetization when the field is released (superparamagnetism). The MNPs are fabricated via chemical routes in the laboratory of Dr. Harrison. The fabrication is optimized to obtain the best size control, with particle diameters ranging from 10 to 100 nm. The structural properties of the particles are analyzed via x-ray diffraction (XRD) and electron microscopy (TEM). The particles' magnetic properties are studied via vibrating sample magnetometry (VSM) and x-ray magnetic scattering (XRMS) in the laboratory of Dr. Chesnel. Their magnetic susceptibility is measured under high magnetic field and at low temperature via field-cooling measurements, to identify the blocking temperature where the material transitions from superparamagnetic to magnetically frozen. The particle size is optimized to bring the blocking temperature close to body temperature. Finally, the particles are functionalized and tested for various biomolecule detection applications, such as the capture and concentration of bacteria, proteins, and viruses, in the laboratory of Dr. Pitt. The preliminary findings will support grant proposals which we intend to submit to the National Science Foundation (NSF) and the National Institutes of Health (NIH).

1. Problem statement

Magnetic nanoparticles (MNP) are extremely useful for biomolecule separation processes. Although MNPs are commercially available, they have problems which prevent their full use in many important applications. The underlying problem with commercial MNPs in nearly all applications is that after the MNPs are collected by a magnetic field and separated from the solution, it is very difficult to completely disperse them into a new solution after the magnetic field is removed. These clumps of MNPs, with their biomolecule payload, clog filters and the microfluidic devices that are being developed to analyze the biomolecules to diagnose disease. We do not know if this clumping is because the particles do not return to zero magnetization (slight retention of any magnetization, called remanence, will keep them clumped) or if there are surface adhesion phenomena that keep them aggregated even in the absence of magnetic field. Total dispersion is required to allow for the elution of small molecules that may have been collected on the MNPs' surface, such as DNA fragments, proteins, or other biomolecules. Also, there is a need to produce MNPs with surfaces able to be functionalized with biomolecules. Another goal is to produce functionalized surfaces on the MNPs that will prevent aggregation, and that at the same time will allow attachment of specific biomolecules to the surfaces, such as DNA, proteins, viruses, bacteria and eukaryotic cells.

We desire to synthesize MNPs with proven zero residual magnetization (called superparamagnetism, SPM) when the field is released. Various coatings will be placed on the MNPs and any aggregation with zero residual magnetism will be attributed to surface interactions.

2. Scientific and societal impacts

Specific attachment of biomolecules to truly superparamagnetic MNPs (i.e., with zero residual permanent magnetization) is essential in future development of microfluidic diagnostic instruments. The collection and concentration of mammalian cells, bacteria, viruses, proteins, DNA and RNA can be efficiently done using functionalized superparamagnetic MNPs. But to release these biomolecules into microfluidic diagnostic devices, the MNPs must be effectively dispersed, which required no residual magnetization. Then using appropriate chemistry, the collected molecules can be quantified, with or without eluting them from the MNPs, to rapidly diagnose disease. MNPs between 10 and 100 nm in size are perfect for use in microfluidic devices, which have flow channels from 10 to hundreds of micrometers (μm) in width. The use of microfluidic devices allows diagnosis of disease from less than a drop of blood, or a drop of other body fluid (sweat, saliva, tears, urine, etc.). The miniaturization of these diagnostic methods also allows them to be used in hospitals and clinics worldwide, and not just in large hospital labs in developed countries.

3. Methodology

MNPs, such as the ones shown in Fig. 1a, will be synthesized in the lab of Dr. Harrison using organic solution routes [Jana 2004, Altavilla 2005]. Various procedures and reaction temperatures will be used to achieve different particle sizes. Smaller MNPs will be fabricated from Fe(III) acetylacetonate, mixed with hexadecane, octadecene, oleic acid and oleyamine, and heated to 200 °C for 30 minutes, then heated under nitrogen at 290°C for another 30 minutes, and cooled to room temperature. Larger MNPs will be prepared by using iron(III) oleate but heating it to 320°C for 30 min. All of the NPs will be precipitated with ethanol and decanted. We plan on fabricating MNP of size ranging from 10 to 100 nm: typically 10 nm, 20 nm 50 nm and 100nm. The MNP size will be controlled by adjusting the reaction time and the temperature. To achieve high temperatures, high boiling point solvents will be utilized.

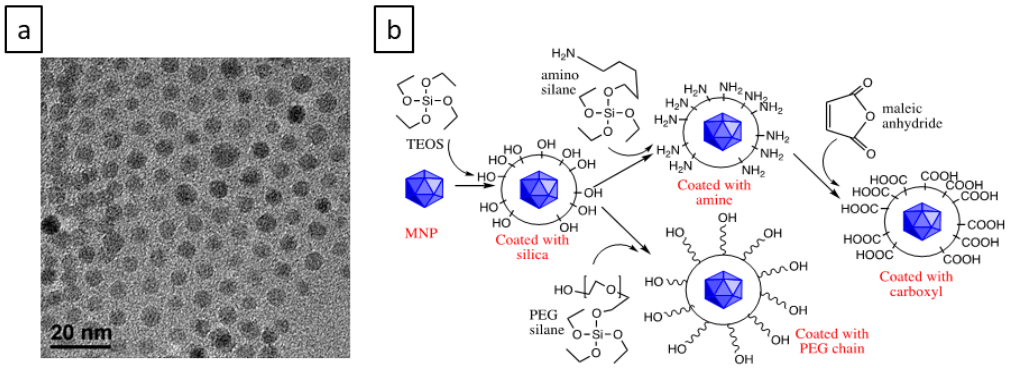

Figure 1: Synthesis and functionalization of MNPs. (a) TEM image of an assembly of our 5 nm Fe_3O_4 nanoparticles obtained by organic chemical synthesis. (b) Illustration of the functionalization process: TEOS is condensed on MNPs to form a silica shell with silanol groups on the surface. These coated MNPs react with PEG-silane to PEGylate the surface, or with amino-silane to aminate the surface. The aminated particle can be further reacted with an anydride to form a carboxylated surface.

Freshly synthesized particles will be stored under vacuum in a dessicator until coated with silica in the lab of Dr Pitt, for further functionalization, as illustrated in Fig. 1b. The Stober process [Rho 2014] and variations of it, will be used to produce the silica coating. Typically, MNPs are transferred to ethanol containing tetraethylorthosilicate (TEOS) and stirred in the presence of ammonia for several hours at room temperature. The thickness of the deposited silica coating will be varied by manipulating the concentration of TEOS and time of reaction. Variations in this process include varying the concentration of ammonia over time to reduce the tendency of MNP aggregation at short times [Sharifi 2018] or placing a poly(n-vinyl pyrrolidone) coating on the surface prior to the Stober process. The surfaces of these particles contain silanol groups (Si–OH).

The surface of the silica-coated MNP will be subsequently functionalized with various reactive groups. The surface can be coated with poly(ethyleneglycol) (PEG) by reaction with PEG-triethoxysilane in 50:50 methanol:water for several minutes as shown in the lower part of Fig. 1b. Amine groups will be placed on the surface by transferring the MNPs to a solution of amino triethoxysilane in 50:50 methanol:water for several minutes. This will produce an amine-terminated surface. An acid-terminated surface will be obtained by refluxing these amine-terminated MNPs in THF containing a cyclic anhydride such as malonic, maleic or succinic anhydride. These particles will be washed and stored under vacuum.

The MNPs will be imaged using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) as illustrated in Fig. 1a. These images will show the morphology of the MNPs and the thickness of the coating. From these images, the average MNP diameter will be determined. For the TEM imaging, the MNPs will be deposited on silicon nitride (Si_3N_4) membranes that are 50 to 100 nm to let the electronic and later the x-ray beams pass through.

The magnetic behavior of the MNPs will be characterized in the lab of Dr. Chesnel. For this purpose, magnetometry measurements will be carried out with a Vibrating Sample Magnetometer (VSM) on a Physical Property Measurements System (PPMS). The PPMS instrument includes a superconducting magnet allowing measurements up to 9 T (90,000 Oe) and sample cooling down to few Kelvins. As illustrated in Fig. 2, magnetization loops (Fig. 2a) as well as field-cooling (FC) and zero-field-cooling (ZFC) measurements (Fig. 2b) will be carried out by cooling samples down to 5 K under various magnetic fields to determine the blocking temperature T_B characterizing the possible super-paramagnetic (SPM) behavior of the MNPs assemblies. Above T_B, the collection of MNPs is expected to be SPM, while below T_B, it becomes magnetically blocked or frozen. [Chesnel 2014] These magnetometry measurements will allow to determine if our synthesized MNPs are truly SPM and can be further used and functionalized for biomedical applications involving magnetic field manipulation.

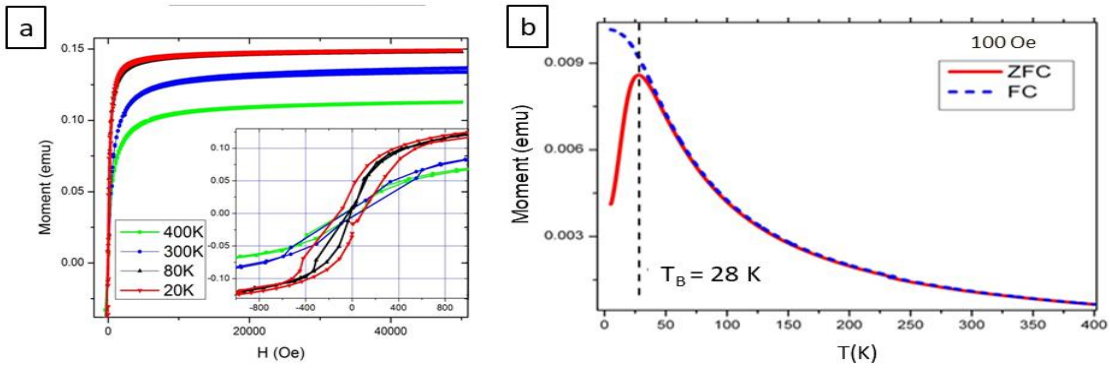

Figure 2: Magnetometry measurements carried on our Fe_3O_4 MNPs. (a) Magnetization loops measured on 8 nm MNPs at various temperatures; inset: zoom-in view near zero field. (b) Field cooled (FC) – zero field cooled (ZFC) measurements on 5 nm MNPs. The merging point between the FC and ZFC curves indicates the blocking temperature T_B, characterizing the superparamagnetism.

Additionally to magnetometry measurements, x-ray magnetic resonant scattering (XRMS) will be performed to access information about the nanoscale magnetic correlations between the MNPs, as illustrated in Fig. 3. The XRMS measurements will be carried out at synchrotron facilities (SLAC at Stanford, NSLS at Brookhaven National Lab) by the group of Dr Chesnel. To enhance the magneto-optical contrast and obtain magnetic information, the energy of the x-rays will be finely tuned to the L_3 edge of Fe, around 707 eV. To extract the magnetic signal from the charge signal, dichroism studies will be performed by circularly polarizing the x-ray light and switching the polarization helicity using an elliptical undulator (EPU). Deposited on silicon nitride membranes, the MNPs samples will be mounted on a cryogenic sample holder to allow sample cooling with liquid helium down to about 15 K. The sample holder will be inserted in pole pieces of an electromagnet allowing XRMS measurements with an *in-situ* magnetic field. The resulting XRMS scattering patterns, as shown in Fig. 3a will be collected on a 2D detector, a 2048 x 2048 pixels CCD camera from Princeton Instruments.

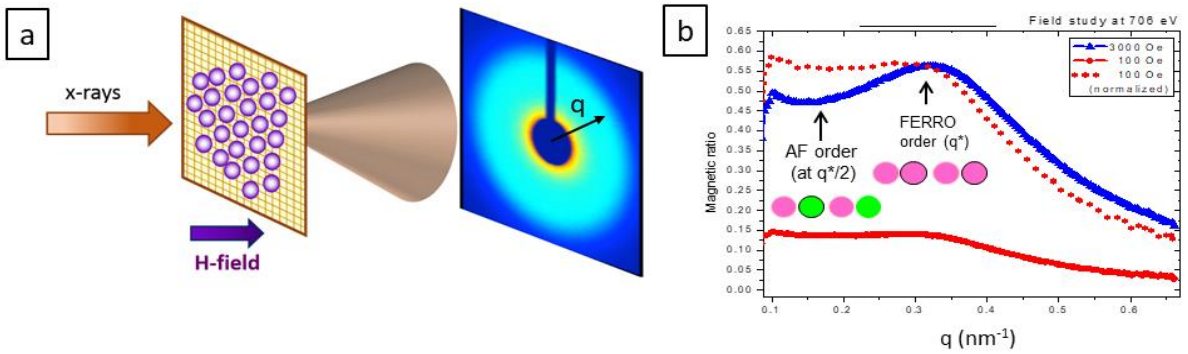

Figure 3: Illustration of x-ray resonant magnetic scattering (XRMS) measurements on MNP assemblies. (a) sketch of the setup showing illumination of MNP assemblies and 2D collection of scattering patterns, (b) Integrated XRMS signal as function of vector q, comparing high field (3000 Oe) and low field (100 Oe) for identifying nanoscale magnetic orders, i.e ferromagnetic and antiferromagnetic orders.

As illustrated in Fig. 3b, the XRMS measurements will allow accessing information about the nanoscale magnetic correlations between MNPs when self-assembled. Collected in various x-ray polarizations and magnetic field values, 2D scattering patterns, such as the one shown in Fig. 3a, will be integrated so to produce an intensity profile as function of vector q, as shown in Fig. 3b. Peaks and various features in these profiles indicate the presence of specific magnetic correlations between the MNPs, such as ferromagnetic order (parallel magnetic alignment) or antiferromagnetic order (antiparallel magnetic alignment). Comparing these profiles at high field and low field values will show how the MNPs tend to behave collectively under a driving field and when the field is released.

4. Expected outcomes

With this project, we plan to improve the magnetic properties of the MNPs for the mentioned medical applications, where a magnetic field is utilized to manipulate the MNPs. In particular, it is important that after being magnetically aligned and dragged by a magnetic field, the MNPs return to zero magnetization when the field is released so they can disperse, as illustrated in Fig. 4. Previous observations have shown that, the MNPs often form clusters, even in the absence of field. Visual observations in Dr Pitt's lab showed that after the MNPs are collected with a permanent magnet outside a glass test-tube, and the magnet removed, most of the clump is re-dispersed by rapid stirring, but little black flecks remain that cannot be re-dispersed. Our goal is to identify the cause of the clumping, being of magnetic origin or not, and then find ways to eliminate, or minimize it.

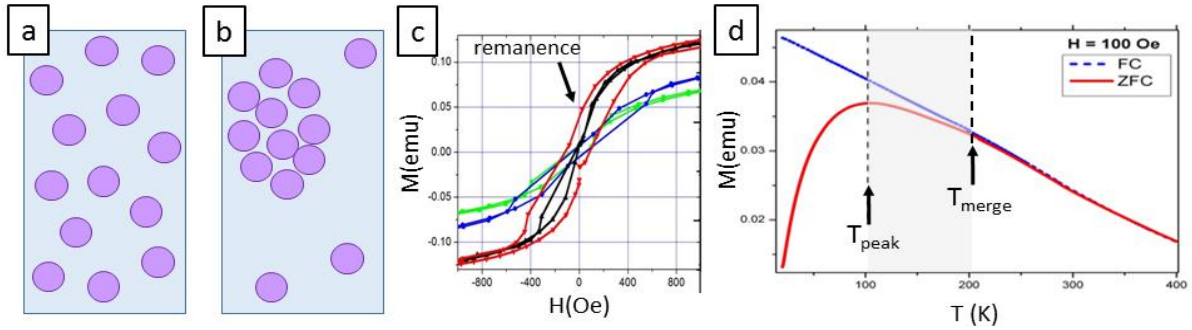

Figure 4: Illustration of clumping and magnetic couplings (a) a monodisperse solution of MNPS (b) clumping of MNPs in the solution (c) example of hysteresic magnetization curve, causing remanence (d) FC-ZFC curves where peak and merging temperature differ, indicating magnetic couplings between MNPs.

5. Measures of success and achievable milestones

The magnetometry measurements described in section 3 will allow us to identify if after a magnetic field has been applied and released, if there is any remanent magnetization in the MNPs. In particular, the presence of hysteresis in the magnetization loop, as shown in Fig. 4c, will generally be accompanied by magnetic remanence (non-zero magnetization M when field H = 0). Magnetic remanence may cause physical clumping between MNPs. Also, the FC-ZFC measurements will allow us to tell if there are magnetic couplings between MNPs. If the FC and ZFC curves don't merge at the peak of the ZFC curve but at a somewhat higher temperature, as illustrated in Fig. 4d, it indicates magnetic couplings between MNPs. Additionally, the XRMS measurements described in Fig. 3 will tell us if there are spatial magnetic correlations between individual MNPs. Our goal is to achieve MNPs that are completely independent magnetically in the absence of field, i.e., that would show a true superparamagnetic (SPM) behavior.

If signs of remanence and magnetic correlations is found in our MNPs, we will work on optimizing the structure and the size of the MNPs so to eliminate the magnetic correlation. It was shown that smaller MNPs tend to correlate less than bigger MNPs [Chesnel 2018]. Also, the MNPs could be coated with a non-magnetic layer that would prevent magnetic correlations but still allow the alignment and manipulation by a magnetic field. If no sign of remanence or correlations is found in our MNPs, it suggests that the observed clumping is not of magnetic origin, but either physical or chemical. We will then further study the origin of the clumping by electronic imaging (SEM, TEM). Depending on our finding, we will investigate ways to eliminate the clumping issue by modifying the chemical and structural composition of the MNPs.

The planned milestones for this project, if funded, will be the following:

April–Aug 2022	Fabrication of Fe_3O_4 MNPs of various sizes targeting 10 – 100 nm
Sep – Dec 2022	Coating and functionalization of the MNPs
Nov 2022 – April 2023	Magnetometry, FC/ZFC measurements of the coated MNPs and XRMS measurements at synchrotron facilities
May – Aug 2023	Analysis of the results, leading to modifying/ refining the chemical structure of the MNPs to minimize any existing remanence
Sep Dec 2023	Magnetic characterization of the optimized MNPs and publication of results

6. Interdisciplinary research partnerships

This multidisciplinary project requires the combined efforts of experts in chemistry, chemical engineering and magnetism. All the team members have years of expertise in their respective fields where they can contribute to the project. Dr Harrison is an expert in fabricating MNPs with various chemical routes, and in characterizing their structural properties [Chesnel 2014, Hancock 2015, Klomp 2020]. Dr Pitt is an expert in coating and functionalizing MNPs for drug delivery applications [Williams 2018]. Dr Chesnel is an expert in nanomagnetism and the use of x-ray synchrotron radiation to characterize magnetic properties of nano-objects [Cai 2014, Chesnel 2016, Chesnel 2018, Rackham 2019, Frandsen 2021]. This project cannot be completed without the combined expertise of the team members. Also, this project will lead to long-term collaborations, publications and successful applications in the medical field.

References

[Altavilla 2005]: Altavilla, Ciliberto, Gatteschi, Sangregorio, Advanced Materials **17**(8):1084 – 1087 (2005)

[Cai 2014]: Y. Cai, K. Chesnel, M. Trevino, A. Westover, R. Harrison, J. Hancock, S. Turley, A. Scherz, A. Reid, B. Wu, C. Graves, T. Wang, T. Liu, H. Durr, J. App. Phys. **115**, 17B537 (2014)

[Chesnel 2014]: K. Chesnel, M. Trevino, Y. Cai, J. Hancock, S. Smith, R. Harrison, J. Phys. **521**, 012004 (2014)

[Chesnel 2016]: K. Chesnel. A. Safsten, M. Rytting, E.E. Fullerton, Nature Communications **7**, 11648 (2016)

[Chesnel 2018]: Chesnel, Griner, Smith, Cai, Trevino, Newbold, Wang, Liu, Jal, Reid, Harrison, Magnetochemistry, 4, 42-58 (2018)

[Frandsen 2021]: B. A. Frandsen, C. Read, J. Stevens, C. Walker, M. Christiansen, R. G. Harrison, K. Chesnel, Phys. Rev. Materials **5** (5), 054411 (2021)

[Klomp 2020]: S. Klomp, C. Walker, M. Christiansen, B. Newbold, D. Griner, Y. Cai, P. Minson, J. Farrer, S. Smith, B. J. Campbell, R. Harrison, K. Chesnel, IEEE Trans. Magn. **56** (11), 2300109 (2020)

[Jana 2004]: N. Jana, Y Cheng, X, Peng, Chem. Mater.,**16** (20), pp 3931–3935 (2004)

[Hancock 2015]: Hancock, Rankin, Hammad Salam, Chesnel, Harrison, J. Nanosci. Nanotech. 15, 3809-3815 (2015)

[Rho 2014]: W.-Y. Rho, H.-M. Kim, S. Kyeong, Y.-L. Kang, D.-H. Kim, H. Kang, C. Jeong, D.-E. Kim, Y.-S. Lee, B.-H. Jun, J. Industr. Engin. Chemistry **20**, 2646-2649 (2014)

[Sharafi 2018]: Z. Sharafi, B. Bakhshi, J. Javidi and S. Adrangi, Iran J. Pharm. Research **17**, 386-395 (2018)

[Williams 2018] J.B Williams, C.M. Buchanan,W.G. Pitt, Pharmaceutical. Nanotechnology, **6**(2), 1-8 (2018)

Budget narrative:

To accomplish this project, we request $60,000 per year, for two years.

The funds will be distributed between the three groups, as described below, to support students and to buy chemicals and supplies. Some of the funds will be used for travel for synchrotron experiments at National Laboratories.

Karine Chesnel group: $ 25,000 per year

- 1 grad student, partial support: $10,000
- 2 undergrad students, partial support: $4000
- Supplies for magnetometry VSM measurements: $1000
- Cryogenics for XRMS measurements: $2000
- Travel support to run synchrotron measurements at National Laboratories: $8000

Roger Harrison group: $ 17,500 per year

- 1 grad student, partial support: $8000
- 2 undergrad students, partial support: $4000
- Chemicals and other lab supplies: $2500
- Analytical: SEM, TEM, XPS, SIMS, DLS, zeta potential: $3000

Bill Pitt group: $ 17,500 per year

- 1 grad student, partial support: $5000
- 2 undergrad students, partial support: $5000
- Chemicals and other lab supplies: $4500
- Analytical: SEM, TEM, XPS, SIMS, DLS, zeta potential: $3000

We will follow the same distribution of funds for each two years.

Plan for external funding following the IDR award

If funded, the faculty of this project will meet monthly to review progress and prepare two large proposals, both planned for late 2023:

- A proposal to the NSF National Nanotechnology Institute, which will focus on investigating the physical and chemical properties of the MNPs of various size and chemical structures. Dr. Chesnel will be the lead on this proposal. Anticipated 3 years of funding at around $500K each year, involving students from all three labs.

- A proposal to the NIH Institute of Allergy & Infectious Diseases, focusing on further optimizing the magnetic properties of the MNPs for disease diagnostics and drug delivery applications. Aims will be to produce surfaces that will not self-adhere, and yet will collect virus particles from culture or body fluids, such as blood. Dr. Pitt will be the lead on this proposal. Anticipated 5 yrs of funding at around $500K each year, involving students from all three labs.

Karine CHESNEL

Professional Preparation

Ecole Normale Supérieure, France	Physics & Chemistry	B.S.	1997
University Joseph Fourier, France	Physics	M.S.	1999
University Joseph Fourier, France	Physics	PhD	2002
Lawrence Berkeley National Laboratory	Physics	Post-Doc	2003-2006
CNRS, Toulouse, France	Physics	Post-Doc	2007

Appointments

2016 - present	Associate Professor, Department of Physics and Astronomy, Brigham Young University, UT, USA
2008 - 2016	Assistant Professor, Department of Physics and Astronomy, Brigham Young University, UT, USA

Five publications most related to this proposal

1. B. A. Frandsen, C. Read, J. Stevens, C. Walker, M. Christiansen, R. G. Harrison, and **K. Chesnel.** « Superparamagnetic dynamics and blocking transition in Fe_3O_4 nanoparticles probed by vibrating sample magnetometry and muon spin relaxation» Phys. Rev. Materials **5** (5), 054411 (2021)
2. S. Klomp, C. Walker, M. Christiansen, B. Newbold, D. Griner, Y. Cai, P. Minson, J. Farrer, S. Smith, B. J. Campbell, R. Harrison and **K. Chesnel** "Size-dependent crystalline and magnetic properties of 5 to 100 nm Fe_3O_4 nanoparticles: superparamagnetism, Verwey transition and FeO-Fe_3O_4 core-shell formation" IEEE Trans. Magn. **56** (11), 2300109 (2020)
3. J. Rackham, B. Newbold, S. Kotter, D. Smith, D. Griner, R. Harrison, A. Reid. M. Transtrum, **K. Chesnel** "Modeling interparticle magnetic correlations in magnetite nanoparticle assemblies using x-ray magnetic scattering data" AIP Advances, 9, 035033 (2019)
4. **K. Chesnel,** D. Griner, D. Smith, Y. Cai, M. Trevino, B. Newbold, T. Wang, T. Liu, E. Jal, A. Reid, R. Harrison, "Unraveling magnetic ordering in Fe3O4 nanoparticle assemblies via x-rays" Magnetochemistry **4,** 42-58 (2018)
5. **K. Chesnel,** M. Trevino, Y. Cai, J. Hancock, S. Smith, R. Harrison. "Particle size effects on the magnetic behavior of 5 to 11 nm Fe3O4 nanoparticles" J. Physics **521**, 012004 (2014)

Five other significant publications

1. **K.Chesnel**, A. Westover, C. Richards, B. Newbold, M. Healey, L. Hindman, B. Dodson, K. Cardon, D. Montealegre, J. Metzner, T. Schneider, B. Böhm, F. Samad, L. Fallarino and O. Hellwig "Morphological stripe-bubble transition in remanent magnetic domain patterns of Co/Pt multilayer films and its dependence on Co thickness" Phys. Rev. B, 98, 224404 (2018)
2. **K. Chesnel**. A. Safsten, M. Rytting, E.E. Fullerton "Shaping nanoscale magnetic domain memory in exchange-coupled ferromagnets by field cooling" Nature Communications **7**, 11648 (2016)
3. **K. Chesnel,** B. Wilcken, M. Rytting, S.D. Kevan, E.E Fullerton, "Field mapping and temperature dependence of magnetic domain memory induced by exchange couplings" New J. Phys **15**, 023016 (2013)
4. **K. Chesnel,** E.E Fullerton, M. J. Carey, J.B. Kortright, S.D. Kevan, "Magnetic memory in ferromagnetic thin films via exchange coupling" Phys. Rev. B **78**, 132409 (2008)
5. J. B. Kortright, O. Hellwig, **K. Chesnel**, S.Sun, and E. Fullerton, "Interparticle magnetic correlations in dense Co nanoparticle assemblies" Phys. Rev. B **71**, 012402 (2005)

Synergistic activities

- Implementation of a full magnetometry (VSM, EHE, MOKE)/ magnetic imaging (MFM) laboratory (built from scratch) at BYU
- Interdisciplinary collaborations with Chemistry and Chemical Engineering departments at BYU, U of Utah, UC San Diego, Chemnitz University of Technology, Germnay, SPINTEC, France
- Involvement of undergraduate students in synchrotron experiments at National Laboratories (NSLS II at Brookhaven Nat. Lab., APS at Argonne Nat. Lab., SLAC, ALS, SOLEIL, ESRF…)
- Contributions to experimental developments / upgrades at synchrotron endstations (beamline 13-3 at SSRL, SLAC; beamline 4-ID-C at the APS, Argonne, bealine 23-ID at NSLS II)
- Dissemination of knowledge: presentations and seminars (most recents)
    - MMM 2022, virtual, 14 January 2022
    - TMS 2021, x-ray imaging workshop, virtual, 16 March 2021 (invited)
    - CMD 2020 GEFES, virtual, 31 August 2020 (invited)
    - Magnetism and Magnetic Materials MMM 2019, Las Vegas, November 2019 (invited)
    - Boston University, Physics department, Boston, MA, April 2019 (colloquium)
    - Magnetism and Magnetic Materials 2018, Rome, Italy, October 2018 (keynote talk)
    - CEA Saclay – SOLEIL synchrotron, Paris, France, October 2018 (seminar)
    - EMN Nanomagnetism, Milan, Italy, July 2018 (invited talk)
    - BIT's NanoScience & Technology meeting, Singapore, October 2016 (invited talk)
    - SPINTEC, MINATEC, Grenoble, France, July 2016 (seminar)
    - EMN summer 2016 meeting, Cancun, Mexico, June 2016 (invited talk)

Roger G. Harrison

Professional Preparation

Utah State University	Chemistry	B.S. 1986
University of Utah	Inorganic Chemistry	Ph.D. 1993
University of Minnesota	Bioinorganic Chemistry	Postdoctoral, 1993-1995

Appointments

Professor of Chemistry	2016 - present	Brigham Young University
Associate Professor of Chemistry	2001- 2016	Brigham Young University
Assistant Professor of Chemistry	1995 - 2001	Brigham Young University

Publications from the last five years related to the project

B. Derden, A. Edwards, Z. Evans, B. Woolsey, C. Blair, N. G. Harrison, R. G. Harrison, "Synthesis of zinc oxide nanoplates and their use for hydrogen sulfide adsorption" *J Sol-Gel Sci Technol* **2022**, accepted.

B. A. Frandsen, C. Read, J. Stevens, C. Walker, M. Christiansen, R. G. Harrison, K. Chesnel, "Superparamagnetic dynamics and blocking transition in Fe_3O_4 nanoparticles probed by vibrating sample magnetometry and muon spin relaxation" *Phys. Rev. Materials* **2021**, 5, 054411.

S. Klomp, C. Walker, M. Christiansen, C. Wilkinson, B. Newbold, D. Griner, Y. Cai, P. Minson, J. Farrer, S. J. Smith, B. J. Campbell, R. G. Harrison, K. Chesnel, "Size-dependent crystalline and magnetic properties of 5 to 100 nm Fe_3O_4 nanoparticles: superparamagnetism, Verwey transition and core-shell formation" *IEEE Trans. Magn.*, **2020**, *56*, 2300109

J. Rackham, B. Newbold, S. Kotter, D. Smith, D. Griner, R. G. Harrison, Al H. Reid, M. Transtrum, K. Chesnel, "Modeling magnetic correlations in magnetite nanoparticle assemblies using x-ray magnetic scattering data" *AIP Advances*, **2019**, 9, 035033, doi: 10.1063/1.5080155.

K. Chesnel, D. Griner, D. Smith, Y. Cai, M. Trevino, B. Newbold, R. G. Harrison, T. Wang, T. Liu, E. Jal, A. Reid, "Unraveling nanoscale magnetic ordering in Fe_3O_4 nanoparticle assemblies via X-rays" *Magnetochemistry*, **2018**, 4, 42-58.

B. Hallac, J. Brown, E. Stavistski, R. G. Harrison, M. Argyle "In-Situ UV-Visible Assessment of Iron-Based High-Temperature Water-Gas Shift Catalysts Promoted with Lanthana: An Extent of Reduction Study" *Catalysts* **2018**, *8*, 63, doi:10.3390/catal8020063.

J. M. Hancock, W. M. Rankin, B. Woolsey, R. S. Turley, R. G. Harrison "Controlled Formation of ZnO Hexagonal Prisms Using Ethanolamines and Water" *J Sol-Gel Sci Technol* **2017**, *84*, 214-221.

Other recent significant publications from the last five years

P. A. Kim, D. Choe, H. So, S. Park, B. Suh, S. Jeong, K-T. Kim, C. Kim, R. G. Harrison, "A selective fluorescence sensor for hypochlorite used for the detection of hypochlorite in zebrafish" *Spectrochimica Acta A.*, **2021**, 261, 120059.

K. L. McGuire, P. Smit, D. H. Ess, J. T. Hill, R. G. Harrison, D. D. Busath, "Mechanism and kinetics of copper complexes binding to the influenza A M2 S31N and S31N/G34E channels" *Biophysical J.*, **2021**, 120/1, 168.

W. N. Chan, J. P. Warren, S. P. Krieger, B. L. Vestal, R. G. Harrison, "Separation and preconcentration of perrhenate from ionic solutions by ion exchange chromatography" *J. Chromatogr. A,* **2020**, *1631*, 461588.

A. Ahamed, R. G. Harrison, N. Nawar, S. J. Smith, M. M. Mostafa, "Synthesis, single crystal X-ray, spectroscopic characterization and biological activities of Mn^{2+}, Co^{2+}, Ni^{2+} and Fe^{3+} complexes" *J. Mol. Struct.*, **2020**, *1203*, 127240, doi:10.1016/j.molstruc.2019.127240.

T. Panahi, H. L. Anderson, K. I. Castro, J. D. Lamb, R. G. Harrison, "Distinguishing Amines with an Amino Acid Appended Resorcinarene-Based Cavitand" *Supramol. Chem.*, **2020**, *32*, 71-80.

K. McGuire, J. Hogge, A. Hintze, N. Liddle, N. Nelson, J. Pollock, A. Brown, S. Walker, J. Lynch, R. G. Harrison, D. D. Busath, "Copper Complexes as Influenza Antivirals: Reduced Zebrafish Toxicity" *Noble Metals in Medicine*, **2019**, doi: 10.5772/intechopen.88786

M. Yang, J. B. Chae, C. Kim, R. G. Harrison, "Visible Chemosensor for Fe(II), Co(II) and Cu(II) in Aqueous Solution" *Photochem Photobiol Sci*, **2019**, *18*, 1249-1258, DOI: 10.1039/C8PP00545A.

B. Raymond, K. C. Merrill, R. G. Harrison, S. D. Jarvis, R. J. Rasmussen, "The nicotine content of a sample of e-cigarette liquid manufactured in the United States" *J. Addiction Med.*, **2018**, *12*, 127-131.

J. M. Jung, C. Kim, R. G. Harrison "A Dual Sensor Selective for Hg^{2+} and Cysteine Detection" *Sens Actuators: B Chem*. **2018**, *255*, 2756-2763.

N. Gordon, K. McGuire, S. Wallentine, G. Mohl, J. Lynch, R. G. Harrison, D. Busath "Divalent copper complexes as influenza A inhibitors" *Antiviral Research* **2017**, *147*, 100-106.

J. M. Jung, J. J. Lee, E. Nam, M. H. Lim, C. Kim, R. G. Harrison "A zinc fluorescent sensor used to detect mercury(II) and hydrosulfide" *Spectrochimica Acta A.*, **2017**, *178*, 203-211.

T. Panahi, D. J. Weaver, J. D. Lamb, R. G. Harrison "A new approach for trace analysis of guanidine compounds in surface water with resorcinarene-based ion chromatography columns" *Analyst*, **2016**, *141*, 939-946.

Synergistic Activities

Associate Chair over Teaching, Department of Chemistry and Biochemistry, Brigham Young University, 2016-present. Evaluate teachers, assign classes, and solve student problems.

Secretary, International Organizing Committee for the International Symposium of Macrocyclic and Supramolecular Chemistry, 2010-present.

Learning and Curriculum Committee Chair, Department of Chemistry and Biochemistry, 10/2002-10/2013

Committee Chair for the formation and implementation of Chemistry 518, Advanced Inorganic Chemistry Laboratory. This is a senior level laboratory in advanced inorganic techniques taken by all chemistry majors. I chose the labs, supervised their trial, purchased equipment, and taught the course.

American Chemical Society Local Section High School Representative, 1/2000-present. Responsible for High School Chemistry Olympiad and Annual High School Awards Banquet.

BIOGRAPHICAL SKETCH

NAME: William G. Pitt

POSITION TITLE: Professor

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
Brigham Young University	B.S.	04/83	Chemical Engineering
University of Wisconsin-Madison	Ph.D.	12/87	Chemical Engineering
University of Minnesota-Twin Cities	Sabbatical	1994-95	Antibiotic delivery to oral bacteria
Montana State University	Sabbatical	2001-02	Antibiotic delivery to oral and industrial biofilms

A. Personal Statement

I have been doing research in drug delivery for 28 years. In my lab we make micelles, liposomes, solid nanoparticles, gas bubbles, and other nanostructures for drug delivery. We use magnetic nanoparticles to collect and separate DNA. We also collect bacteria on magnetic nanoparticles.

B. Positions and Honors

Positions and Employment

1982, 1983 Project Engineer, Terra Tek Research, Salt Lake City, UT : corrosion research, geochemistry
1983-1987 Research Assistant, Teaching Assistant, Dept of Chem. Eng., University of Wisconsin-Madison
1987-1993 Assistant Professor, Dept. of Chemical Engineering, Brigham Young University
1988-present Adjunct Asst, Assoc, Full Professor, Department of Bioengineering, University of Utah
1993-1998 Associate Professor, Chemical Engineering Dept., Brigham Young University
1998-present Professor, Chemical Engineering Dept., Brigham Young University

Honors

1994-1995 Lasby Visiting Professor, Dept. of Oral Sciences, Univ. of Minnesota, Minneapolis
1998 Outstanding Faculty Award, College of Engineering, Brigham Young University
2007-2012 Pope Professor of Chemical Engineering (endowed chair), Brigham Young University
2010 Outstanding Faculty Award, Department of Chemical Engineering, Brigham Young University
2013 Maesar Research and Creative Works Award, Brigham Young University
2016 Wesley P. Lloyd Award for Distinction in Graduate Education, Brigham Young University
2018-2023 Harvey Fletcher Professor of Chemical Engineering, Brigham Young University

C. Contributions to Science

1. Nanoparticle science. Our lab has expertise in making polymeric nanoparticles, including micelles, liposomes and solid nanoparticles. Most often these are used for drug delivery. We are now using magnetic nanoparticles which are derivatized to capture bacteria for rapid diagnostics of blood infection. In the recent past we synthesized submicron-sized l micelles and liposomes that are responsive to ultrasound – responsive in that these carriers sequester the cancer chemotherapeutic until ultrasound is applied. Thus ultrasound can be applied to a cancerous tissue and the drug released as the carriers circulate through the target tissue. Our most novel carrier is a 100-nm liposome that contains drug and a nanodroplet of non-toxic liquid perfluorocarbon that is triggered by ultrasound to change from a liquid to a gas phase, thus disrupting the liposomes. By placing endocytosis-activating ligands on the liposome surface, these are taken into the endosome and then disrupted, thus releasing drug directly to the cytosol. We also delivered plasmids and proteins with these liposomes. We successfully used some of these constructs in 2 NIH-funded research projects using a mouse model of colon cancer. Key papers in the area of bacterial diagnostics and drug delivery are listed below.

166. Richard A. Robison,* Taalin R. Hoj, Bradley McNeely, Kylie Webber, Evelyn Welling, William G. Pitt, Larry C. Ford, "A pentaplex real-time PCR assay for rapid identification of major beta-lactamase genes KPC, NDM, CTX, CMY, and OXA-48 directly from bacteria in blood", *J. Med. Microbiol.* **70**:001465 (2021).
165. AlSawaftah, N., Pitt, W.G., Husseini, G.A., "Dual-Targeting and Stimuli-Triggered Liposomal Drug Delivery in Cancer Treatment", *ACS Pharmacology and Translational Science*, **4**(3), 1028-1049 (2021).
164. Awad, N.S., Paul, V., Ter Haar, G., Allen, T., Pitt, W.G., and Husseini*, G.A., "Ultrasound-Responsive Nanocarriers in Cancer Treatment: A Review", *ACS Pharmacology & Translational Science*, **4**(2), 589-612 (2021).
162. Meena, G.G., Hanson, R.L., Wood, R.L, Brown, O.T., Stott, M.A., Robison, R.A., Pitt, W.G., Woolley, A.T., Hawkins, A.R., and Schmidt*, H., "3X Multiplexed Detection of Antibiotic Resistant Plasmids with Single Molecule Sensitivity", *Lab Chip*, **20**, 3763-3771 (2020).
161. Andersen, C., Pitt*, W.G., "Effect of dilution on separation of bacteria from blood by sedimentation", *Biotech. Progress*, **6**(1) e3056 (2020).
158. Hamilton, E.S., Ganjalizadeh, V., Wright, J.G., Pitt, W.G., Schmidt, H., Hawkins*, A.R., "3D hydrodynamic focusing in microscale channels formed with two photoresist layers", *Microfluidics and Nanofluidics*, **23**;122, 1-8 (2019).
156. Pitt*, W.G., Alizadeh, M., Blanco, R. Hunter, A.K., Bledsoe, C.G., McClellan, D.S., Wood, M.E., Wood, R.L., Ravsten, T.V., Hickey, C.L., Beard, C.W., Stepan, J.R., Carter, A., Husseini, G.A., Robison, R.A., Welling, E., Torgesen, R.N., Anderson, C., "Factors Affecting Rapid Separation of Bacteria from Blood", *Biotech. Progress*, **36**(1) 1-9, (2019).
153. Knob R., Hanson, R.L., Tateoka, O.B., Wood, R.L., Guerrero-Arguero, I., Robison, R.A., Pitt, W.G., Wooley*, A.T., "Sequence-specific sepsis-related DNA capture and fluorescent labeling in monoliths prepared by single-step photopolymerization in microfluidic devices", *J. Chromatography A*, **1562**, 12-18 (2018).
152. Williams, J.B., Buchanan, C.M., Pitt*, W.G., "Codelivery of Doxorubicin and Verapamil for Treating Multidrug Resistant Cancer Cells" *Pharm. Nanotech.*, **6**(2), 1-8 (2018).
150. J.B. Williams, C.M. Buchanan, G.A. Husseini, W.G. Pitt* "Cytosolic delivery of doxorubicin from liposomes to multidrug resistant cells via vaporization of perfluoropentane droplets", *J. Nanomedicine Res.*, **5(4)**, 00122 (2017). http://dx.doi.org/10.15406/jnmr.2017.05.00122
142. Rafeeq Tanbour, Ana M. Martins, William G. Pitt, Ghaleb A. Husseini*, "Drug Delivery Systems Based on Polymeric Micelles and Ultrasound: A Review", *Current Pharm. Design*, **22**(9), 1 (2016).
141. Chung-Yin Lin, Han-Yi Hsieh, William G. Pitt, Chiung-Yin Huang, I-Chou Tseng, Chih-Kuang Yeh, Kuo-Chen Wei*, and Hao-Li Liu*, "Focused Ultrasound-Induced Blood-Brain Barrier Disruption for Non-Viral, Non-Invasive, and Targeted Gene Delivery", *J. Controlled Release*, **212**, 1-9 (2015).
140. Javadi, M. and Pitt, W.G.*, "Insights into Ultrasonic Release from eLiposomes", *Letters in Applied NanoBioScience*, **4**,(1) 251-258 (2015).
139. Lattin, J.R., Javadi, M., McRae, M., and Pitt, W.G.*, "Cytosolic Delivery via the Endosome using Acoustic Droplet Vaporization, *J. Drug Targeting*, **23**(5), 469-479 (2015). http://dx.doi.org/10.3109/1061186X.2015.1009074
138. Husseini, G.A.*, Kherbeck, L., Pitt, W.G., Hubbell, J.A., Christensen, D.A., and Velluto, D., "Kinetics of Ultrasonic Drug Delivery from Targeted Micelles", *J. Nanosci. Nanotechnol.*, **15**(3), 2099-2104 (2015). http://dx.doi.org/10.1166/jnn.2015.9498
137. Lattin, J.R. and Pitt, W.G.*, "Factors Affecting Ultrasonic Release from eLiposomes", *J. Pharmaceutical Sciences*, **104**(4), 1373-1384 (2015). DOI: 10.1002/jps.24344
136. Pitt*, W.G., Zhao, Y., Jack, D. R., Perez, K.X., Jones, P.W., Marelli, R., Nelson, J.L., and Pruitt, J.D., "Extended Elution of Phospholipid from Silicone Hydrogel Contact Lenses", *J. Biomaterials Sci., Polymer Edn.*, **26**(4), 224-234 (2015). http://dx.doi.org/10.1080/09205063.2014.994947
135. Husseini, G.A.*, Pitt, W.G., Williams, J., and Javadi, M., "Investigating the Release Mechanisms of Calcein from eLiposomes at Higher Temperatures", *J. Colloid Sci. Biotech.* **3**(3), 239-244 (2014). http://dx.doi.org/10.1166/jcsb.2014.1100.
134. Chung-Yin Lin*, William G. Pitt, Hai-Li Liu, and Kuo-Chin Wei, "Development of Ultrasound Sensitive eLiposomes Containing Doxorubicin for Drug Delivery", *British J Pharm Res*, **4**(19), 2296-2311 (2014).
132. Husseini, G.A.*, Pitt, W.G., and Martins, A.M., "Ultrasonically triggered drug delivery: breaking the barrier", Colloids & Surfaces B: Biointerfaces, **123**, 364-386 (2014). http://dx.doi.org/10.1016/j.colsurfb.2014.07.051

Complete list of published work by W.G. Pitt in MyBibliography (showing 97 of 167 publications):
https://www.ncbi.nlm.nih.gov/sites/myncbi/william.pitt.1/bibliography/41164705/public/?sort=date&direction=descending

Current and Pending Support for Karine Chesnel

RECENT FUNDING

Project/Proposal Title: Student-centered research toward enhancing magnetic memory reliability
Source of Support: BYU Office of Research and Creative Activities - CPMS FAST
Primary Place of Performance: Brigham Young University, Provo, UT 84602
Support Start Date: 02/01/19
Support End Date: 01/31/21
Total Award Amount: $34,000

CURRENT

Project/Proposal Title: REU Site: Physics Research at Brigham Young University
Proposal/Award Number: 2051129
Source of Support: National Science Foundation, Undergraduate Research
Primary Place of Performance: Brigham Young University, Provo, UT 84602
Project/Proposal Support Start Date: 05/2021
Project/Proposal Support End Date: 04/2024
Total Award Amount: $370,586

PENDING

Project/Proposal Title: Nanoscale Magnetic Ordering and Fluctuation Dynamics in Fe3O4 nanoparticle assemblies
Source of Support: National Science Foundation, ENG/CBET, Nanoscale Interactions
Primary Place of Performance: Brigham Young University, Provo, UT 84602
Support Start Date: 03/2022
Support End Date: 02/2025
Total Award Amount: $594,420

Project/Proposal Title: Optimizing the structural and magnetic properties of magnetite (Fe_3O_4) nanoparticles for medical diagnosis purposes
Source of Support: BYU Office of Research and Creative Activities- BYU IDR Origination award
Support Start Date: 05/01/22
Support End Date: 04/31/24
Total Award Amount: $120,000

Current and Pending Support for Roger Harrison

PENDING
Macrocycles in Ion Chromatography
Thermo Fisher Inc.
BYU
$43,500
03/01/22
02/28/23
Pending
0 months committed

Optimizing the structural and magnetic properties of magnetite (Fe_3O_4) nanoparticles for medical diagnosis purposes
BYU Office of Research and Creative Activities
BYU
$120,000
05/01/22
04/31/23
Pending
0 months committed

Current and Pending Support for W. G. Pitt

CURRENT

NIH NIAID, R01AI116989 Hawkins is PI, Pitt is co-PI 4/1/2015 – 3/31/2022 0.75 calendar
$5.6MM in total direct costs. Pitt portion is about $800,000
Multiplexed, Non-Amplified, Nucleic Acid-Based Identification of Multidrug Resistant Pathogens Using an Integrated Optofluidic Platform
My specific research area is to develop the rapid separation technique to separate bacteria from whole blood in less than 10 minutes, and then lyse the bacteria and deliver the DNA to the next stage of the process.
OVERLAP: There is NO scientific overlap between this liposome project and the current proposal.

PENDING

NIH Pitt is the PI 10/1/2018 – 9/30/2023 5 years
NIAID $3,440,000
"Rapid Multiplexed Phenotypic Diagnostic: From Blood Draw to Antimicrobial Susceptibility in 2 Hours"
The major goals of this project are to isolate bacteria from blood by lysis and filtration or magnetic bead capture or platelet capture, and then grow them in single droplets in a microfluid device. My role (Pitt) is to direct the entire project, develop the collection and concentration, and assist in building integrated microfluidic system.
OVERLAP: There is some scientific overlap between this bacterial recovery project and the proposal in that we would explore magnetic beads as a potential capture mechanism.

Completed Research Support in past 3 years
1. "Mass-produced Inexpensive Paper-based SARS-CoV-2 Diagnostic Test Using Saliva for At-home Use". NIH/NIAID. $100,000 in total costs. May 1 – Sept 31, 2020. I was the co-PI on this project (1 grad student) to evaluate a rapid Covid detection technique. Brad Bundy was the PI. No overlap with the current proposal.

2. "MASS-PRODUCED, POINT-OF-CARE, AT-HOME, PAPER-BASED, COLORIMETRIC SARS-CoV-2/COVID19 SCREENING IN 30 MIN FOR LESS THAN $0.10" NIH/NIAID. $100,000 in total costs. June 1 – August 31, 2020. I was the co-PI on this project (1 grad student) to evaluate a rapid Covid detection technique. Brad Bundy was the PI. No overlap with the current proposal.

3. "At-home, Paper-based, Colorimetric, Extreme-low-cost SARS-CoV-2 Testing: Repurposing Pseudoknots as an RNA switch and Demonstrating Signal Amplification through Transcription-Translation Cascades" NIH/NIAID. $25,000 in total costs. May 1 – May 31, 2020. I was the co-PI on this project (1 grad student) to evaluate a rapid Covid detection technique. Brad Bundy was the PI. No overlap with the current proposal.

4. “Acoustically Activated Delivery of Small Molecules to the Skin”, L’Oreal Inc. $50,000 in total costs. Aug 15, 2016 – Aug 14, 2018. I am the PI on this project to develop drug delivery carriers for delivery of lipids and proteins to the dermis of the skin. No overlap with the current proposal.