Have a research idea?

***SYNERGY** can help you design a project to test your hypothesis…*

whether it's a pilot study to start your research career, or transitioning from a career development award to an RO1 - we are here to help!

Online Resources, web-links

Trails to Translational Research:

A step-by-step resource navigation guide to designing your research project

On-site Resources, web-links, contact

Off-site Resources, web-links

DARTMOUTH SYNERGY
Clinical and Translational Science Institute
Mentoring and Education Committee

Overview: 10 steps to designing your research project

- 1. Identify the 'Need / Gap in knowledge' and refine your 'Research Question'
- 2. Garner local support for your research role
- 3. How can your Research Question be answered most efficiently?
- 4. What specific scientific objectives or "Aims" will help answer this research question?
- 5. Identify the Study Design that can answer your Research Question
- 6. Sample Size estimation & power calculations
- 7. Work out the Logistics of your study
- 8. Define your Data collection, data storage and data management plans
- 9. Design a Statistical Analysis plan
- 10. Write and submit your Research Protocol for internal review

General SYNERGY Resource Requests link:
https://inspire.dartmouth.edu/

Project planning
https://geiselmed.dartmouth.edu/synergy-guides/home

Contact for general questions:
Angeline.Andrew@Dartmouth.edu

Search publications:
www.ncbi.nlm.nih.gov/pubmed
http://apps.webofknowledge.com

Search funded grants: www.nih.reporter

Search conference abstracts

Lecture: **Developing research questions, aims & hypotheses**
https://ilearn.tuftsctsi.org/account/login.aspx

- **1. Identify the 'Need' / 'Gap in knowledge' and refine your 'Research Question'**
  - What problem will your project address?
  - What is holding back the field?
  - Is an answer to this question relevant and impactful, or merely scientifically interesting?
  - What work is already being done on this topic? Who are the current leaders in the field?
  - Is there a niche for you?

Scientific Mentor

Talk to colleagues about clinical challenges

Talk to colleagues at other sites

Community Engagement Research Support group
Guide meaningful collaborations that address community-defined health priorities
https://synergy.dartmouth.edu/community-engagement-research
Deborah.J.Johnson@Dartmouth.edu

Maximizing the Mentee-Mentor Relationship (2-day workshop for individuals are early in their careers)
https://catalyst.harvard.edu/services/formal-mentoring/

- **2. Garner local support for your research role**
  - How will answering this 'Research Question' fit in with your career goals?
  - Talk with your Department / Section leadership about your research plans and the effort and time involved
  - Engage a Scientific Mentor for regular feedback and political support
  - Start building your team
    - Identify colleagues with complementary expertise e.g. clinical specialty, statistical analysis

Career Development Mentor

Department / Section Leader

Scientific Mentor

Contact your **Departmental Research Liaison** for:

- Referral to a scientific mentor
- Help identifying which SYNERGY Resource you need first

Departmental Research Liaisons:

BASIC SCIENCES DEPARTMENTS	LIAISON/FACULTY NAME
Biochemistry and Cell Biology	Charles Barlowe, PhD
Biomedical Data Science	Michael Whitfield, PhD
Epidemiology	Margaret Karagas, PhD
Microbiology and Immunology	William Green, PhD
Molecular and Systems Biology	Jay Dunlap, PhD

CLINICAL DEPARTMENTS	LIAISON/FACULTY NAME
Anesthesiology	Brian Sites, MD
Community Family Medicine	Adam Sorscher, MD
Medicine	Richard Enelow, MD; Corey Siegel, MD
Neurology	Barbara Jobst, MD
Obstetrics/Gynecology	Elizabeth Erekson, MD
Orthopedic Surgery	James Heckman, MD
Pathology	Wendy Wells, MD
Pediatrics	Paul Palumbo, MD
Psychiatry	Matthew Friedman, MD, PhD
Radiology	John Weaver, PhD
Surgery	Phil Goodney, MD
The Dartmouth Institute (TDI)	Martha Bruce, PhD, MPH

(Current list: https://synergy.dartmouth.edu/research-mentoring-and-education)

3. How can your 'Research Question' be answered most efficiently?

Search for public datasets:
e.g. Gene expression data:
https://www.ncbi.nlm.nih.gov/geo/

- Is there existing data, or do you need to perform primary data collection?

Center for Translational Population Research
Assistance on using the extensive Medicare database
https://synergy.dartmouth.edu/ctpr
Anna.Tosteson@Dartmouth.edu

- How many patients in the Dartmouth-Hitchcock system meet your study criteria?
  - Search the Electronic Health Records

Informatics for Integrating Biology and the Bedside
Identify sets of patients from integrated data sources at Dartmouth-Hitchcock
https://synergy.dartmouth.edu/biomedical-informatics
Alfredo.Tirado-Ramos@Dartmouth.edu

DH: QlikView one-year de-identified
https:hc-qlikview.hitchcock.org

- Are there archived tissue samples?

DH Pathology Translational Research Laboratory
https://cancer.dartmouth.edu/scientists-researchers/pathology-shared-resource
Greg.Tsongalis@Hitchcock.org

SYNERGY Bioregistry Core
Biosamples linked to lifestyle, exposures, and behavior
https://synergy.dartmouth.edu/bioregistry
Margaret.Karagas@Dartmouth.edu

- Can you piggyback onto an on-going study? Or Is someone at nearby using a similar cell/animal model?

Browse a compilation of regional resources
https://www.eagle-i.net/

Lecture: **Formulating research question, hypothesis and objectives**
https://www.youtube.com/watch?v=QGCXyvMgfXg

Examples of "Specific Aims" pages for a grant:

- https://accelerate.ucsf.edu/files/TICR_GrantWritingPt3Examples.pdf
- http://www.biosciencewriters.com/NIH-Grant-Applications-The-Anatomy-of-a-Specific-Aims-Page.aspx

- **4. What specific scientific objectives or "Aims" will help answer this research question?**
  - These scientific objectives are often called "**Specific Aims**" when you are applying for grant funding
  - e.g. Specific Aim 1. Compare survival time of patients newly diagnosed with *(disease)* who are randomized to drug *x,* compared to placebo.

Scientific Mentor

SYNERGY Research Development Workshop
Tutorial
https://synergy.dartmouth.edu/research-development-workshop
Angeline.Andrew@Dartmouth.edu

SYNERGY Biostatistics and Research Design Core
Revise Specific Aims
https://synergy.dartmouth.edu/research-design-and-epidemiology
Brock.Christensen@Dartmouth.edu

Lecture: Experimental and observational study design
https://ilearn.tuftsctsi.org/account/login.aspx

- **5. Identify the Study Design that can answer your Research Question**
  - Think "**P I C O**":
    - **P**articipant selection:
      - Organism strain & model design, or participant source
      - Define Inclusion / Exclusion criteria
    - **I**ntervention or Exposure(s): e.g. drug treatment
    - **C**omparison: e.g. within subjects over time, or between exposed / unexposed groups?
    - **O**utcome(s):
      - primary outcome? (e.g. survival time)
      - Secondary outcome?

SYNERGY Biostatistics and Research Design Core
Overall study design and methods
https://synergy.dartmouth.edu/research-design-and-epidemiology
Brock.Christensen@Dartmouth.edu
Tor.Tosteson@Dartmouth.edu

- Are you interested in real-world/'usual' conditions, or 'ideal' conditions?
- Observational study or intervention study?

SYNERGY Imaging Sciences Group-
study design specialized for image analysis (e.g. MRI, DTI, EEG, TMS)
wishart@dartmouth.edu

Summarize the motivation and Specific Aims of the project on the 1st page of your grant proposal.

- E.g. The first page dissected by color:

MicroRNA dysregulation and bladder cancer prognosis

Bladder cancer is the fourth most common malignancy in U.S. men and more than half of non-muscle invasive cases experience recurrent disease. Patients with low stage/grade tumors can remain disease free for many years, but high grade (HG), poorly differentiated tumors or those with carcinoma *in situ* (Tis) often recur within one year. These patients with TaHG, T1, or Tis tumors are at high-risk for tumor recurrence and progression. A subset of patients experience frequently recurring tumors that are refractory to treatment. Molecular markers that identify the most clinically challenging rapidly recurrent and refractory bladder cancer phenotypes and potentially modifiable new molecular therapeutic targets are critically needed.

MicroRNAs (miRNAs) are a class of non-protein coding RNA molecules that are frequently dysregulated in tumors and show promise as therapeutic targets. Compared to messenger RNAs (mRNAs), miRNAs are shorter in length and have a longer half-life, making them stable and potentially reliable as clinical prognostic biomarkers. MiRNAs play a critical role in gene regulation by binding to specific mRNA sites, often leading to cleavage and degradation of that mRNA. Abnormally high levels of a miRNA thus decrease the mRNA and protein levels of its target. Likewise, low expression of a miRNA can release a suppressed target gene. Whether they act as oncogenes, or as tumor suppressors, dysregulated miRNAs allow cells to escape from regulatory control, proliferating to form tumors.

The long term goal of this research program is to identify prognostic molecular markers. Our objective in this application is to identify miRNAs dysregulated in primary non-invasive bladder tumors that recur, and demonstrate their value as prognostic miRNA markers useful for managing the clinically challenging (TaHG, T1, Tis) subgroups of the patient population. We have assembled a unique population-based tissue bank of bladder tumors with extensive exposure, recurrence, progression and survival data from a large epidemiologic study cohort encompassing n=1062 non-invasive urothelial cell carcinoma (UCC) patients. Working with our highly interdisciplinary and interactive translational research team, we will comprehensively search for new prognostic miRNAs specifically in a subset of high-risk, clinically challenging non-invasive cases. The prognostic significance of the most promising miRNAs will then be assessed in our large population-based bladder cancer cohort.

Specific Aim 1: To identify dysregulated miRNAs associated with rapid recurrence of TaHG/T1/Tis bladder tumors. We will test primary tumors from subsets of patients with clinically challenging non-invasive histologic types (TaHG/T1/Tis) by evaluating the expression level of miRNAs in the primary tumor tissue in relation to early recurrent disease. Using the RNA-Seq method of comprehensively assessing miRNA expression will allow us to efficiently identify novel dysregulated miRNAs associated with recurrence, as well as to assess *a priori* prognostic miRNAs.

Specific Aim 2: To assess the prognostic value of a prioritized and confirmed dysregulated miRNA in a large population-based study with long-term patient follow-up.

- Prioritize: Dysregulated prognostic miRNAs will be prioritized based on the statistical significance and magnitude of the expression association, the abundance of the miRNA, the prevalence of dysregulation, as well as evidence from the primary literature, including: functional effects on tumorigenesis, or inverse associations of the miRNA with known targets.
- Confirm: MiRNAs will be technically confirmed in priority order by RT-qPCR and *in situ* hybridization assays will be used to assess the miRNA distribution among cell-types, focusing on miRNAs expressed in the urothelial carcinoma cells.
- Assess: Expanding to the full population-based epidemiologic study, we will finally assess the confirmed priority miRNA in slides from our entire cohort of non-muscle invasive urothelial cell carcinoma primary tumors by *in situ* hybridization. We will examine the prognostic value by analyzing miRNA dysregulation in relation to long-term patient outcomes (time to first recurrence, to progression, and to death).

Impact: Successful pursuit of these aims will identify a prognostic miRNA marker that can be used to tailor management of clinically challenging bladder cancer cases. Enabling early detection and aggressive treatment of rapidly recurrent and refractory phenotypes would reduce disease mortality. Dysregulated miRNAs are also potentially viable novel therapeutic targets for this malignancy. Clinical trials have demonstrated the efficacy of antagonists of over-expressed miRNAs (anti-miRs) as a gene therapy approach and trials of microRNA replacement therapies are also beginning. The bladder is an especially attractive candidate organ for these new lines of therapy because tumors are accessible via intravesical instillation.

- Where are we now?
  - Current knowledge
  - Identify the Gap or unmet "critical need"
- What needs to be done to fill this gap?
  - Long term goal
- Why are we the ones to address this need?
  - Unique features of team or resource
- What can we do now?
  - Objective in this application
  - Central hypothesis
  - **Specific Aims**
    - **"To identify the …"**
    - **"To assess the …"**
- What is the payoff?
  - Expected outcomes
  - Positive impact

Calculating sample size & power lecture
https://ilearn.tuftsctsi.org/account/login.aspx

- **6. Sample size estimation & power calculations**
  - What is a clinically relevant effect size?
  - What is the level of variability in your measures
  - How many animals or participants do you need to see this effect?
  - What proportion of available participants to you expect to enroll? So how many do you need to approach?
  - Is the study design plan feasible (here)?

SYNERGY Biostatistics and Research Design Core

Advice on choice of Statistical design and sample-size calculations.

https://synergy.dartmouth.edu/biostatistics-consultation

Tor.Tosteson@Dartmouth.edu

Research recruitment and participation lectures
https://ilearn.tuftsctsi.org/account/login.aspx

- **7. Work out the logistics of your study**
  - How will you recruit participants and incentivize participation?
  - Who will actually engage and track the participants?
  - Who will collect the biospecimens?
  - How will they be transported to the lab doing the assays?
  - Where will biospecimens be stored and how will the location be tracked?
  - QA / QC procedures for the assays.
  - Electronic health record Dataset

SYNERGY Recruitment and Retention Core
https://synergy.dartmouth.edu/recruitment-and-retention
laurie.s.lester@dartmouth.edu

Dartmouth-Hitchcock Clinical Research Unit
https://med.dartmouth-hitchcock.org/dh_clinical_research_unit.html
Barbara.A.Moskalenko@hitchcock.org

eSample (?)

Robotic freezers in Pathology
https://cancer.dartmouth.edu/scientists-researchers/pathology-shared-resource
Amber.Erskine@hithcock.org

DH Analytics Institute
Export DH data from Data Warehouse
http://one.hitchcock.org/intranet/departments/the-analytics-institute
Submit ticket at dhsm.hitchcock.org
Rebecca.M.Malila@hitchcock.org
Gouri.Chakraborti@hitchcock.org

REDCap user training video library
https://projectredcap.org/resources/videos/

- **8. Define your Data collection, data storage and data management plans**
  - Will your project use protected health information? https://ehr20.com/resources/phi-elements/
  - How will you meet data privacy and security requirements?
  - Will you lose data if your computer fails?
  - How will you enter, access, and move your data?

DartFS
1TB shared lab directory at no cost for faculty members
https://rc.dartmouth.edu/index.php/dartfs/

REDCap
Research Electronic Data Capture

Secure environment to manage data, a tool for building online surveys and automated export procedures for data analysis.

DHMC data:
Gouri.Chakraborti@Hitchcock.org
Data from other institutions:
REDCap@dartmouth.edu

SYNERGY Biomedical Informatics Core
Support on data integration, data management, text mining and visual analytics. Procedures for research data security
https://synergy.dartmouth.edu/biomedical-informatics
Alfredo.Tirado-Ramos@Dartmouth.edu

- **9. Design a Statistical Analysis plan**
  - Appropriate statistical and quantitative methods for your data.

SYNERGY Biostatistics and Research Design Core
Overall study design and methods
https://synergy.dartmouth.edu/research-design-and-epidemiology
Brock.Christensen@Dartmouth.edu
Tor.Tosteson@Dartmouth.edu

QBS | Dartmouth

Masters students
study design, data processing, statistical analysis and machine learning
https://geiselmed.dartmouth.edu/qbs/
Shaniqua.jones@dartmouth.edu

- See below you have specialized data types, e.g.
  - Qualitative data
  - GeoSpatial Data
  - Imaging data

Introduction to Mixed Methods Research
integrating qualitative and quantitative data (2 hrs/wk online)
https://catalyst.harvard.edu/services/mmr-online/

GeoSpatial Consulting
geocoding, travel time, census data, density and proximity calculations
heather.carlos@dartmouth.edu

Brain Science and the SYNERGY Imaging Sciences Groups
image acquisition, and state of the art image processing, analysis (e.g. MRI, DTI, EEG, TMS)
wishart@dartmouth.edu

CONSORT Guidelines for Reporting Clinical Trials
http://www.consort-statement.org/

Lecture: Developing a Research Study Protocol
https://ilearn.tuftsctsi.org/account/login.aspx

10a. Write and submit your Research Protocol for internal review - Human studies

- Does your Department or Center do pre-review of research protocols?
  (E.g. Cancer Center Review Committee)

Dartmouth College Institutional Review Board (IRB):

Dartmouth Committee for Protection of Human Subjects (CPHS)
Phone: (603) 646-6482 Email: cphs.tasks@dartmouth.edu

Protocol and consent templates
http://www.dartmouth.edu/~cphs/tosubmit/forms/

Appropriate level of review for your project?
http://www.dartmouth.edu/~cphs/tosubmit/categories.html

Required training
http://www.dartmouth.edu/~cphs/tosubmit/education/index.html

Dartmouth-Hitchcock – submit to :

D-HH Human Research Protection Program (IRB)
Phone: (603) 650-1846 Email: IRB@hitchcock.org

Login to access templates
https://dhirb.huronresearchsuite.com/IRB/

CITI (Collaborative IRB Training Initiative) online tutorial
http://www.citiprogram.org/

ALSO:

- Meet educational training requirements for investigators and personnel working on the project
- Does your funding agency need to approve your research protocol?

10b. Write and submit your Research Protocol for internal review – Animal studies

- Does your Department or Center do pre-review of research protocols?
  (E.g. Cancer Center Review Committee)
- Submit full research protocol :

Dartmouth Institutional Animal Care and Use Committee (IACUC)

Reviews protocols using live vertebrate animals

http://www.dartmouth.edu/iacuc/protocol_submission.html

Training requirements for using live vertebrate will vary by project

http://www.dartmouth.edu/iacuc/training.html

ALSO:

- Meet educational training requirements for investigators and personnel working on the project
- Does your funding agency need to approve your research protocol?

Summary: 10 steps to designing your research project

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Project planning
https://geiselmed.dartmouth.edu/synergy-guides/home

DARTMOUTH SYNERGY
Clinical and Translational Science Institute
Mentoring and Education Committee

Applying for grant funding?

Grant-writing Training
Full-day Workshops on grantsmanship (December)
Cynthia.L.Stewart@Dartmouth.edu
www.grantcentral.com

GrantGPS
Professional editing, comprehensive review of content by a compensated outside scientific reviewer, also organizational support
603-650-1605
Cynthia.L.Stewart@Dartmouth.edu

SYNERGY Advanced Certificate in Clinical Translational Research
Tutorials on developing your research proposal
https://synergy.dartmouth.edu/advanced-certificate
Angeline.Andrew@Dartmouth.edu

NIH Grant Application Examples, with accompanying reviews
https://www.niaid.nih.gov/grants-contracts/sample-applications

- Some internal funding sources
  - Hitchcock Foundation $30k
  - Norris Cotton Cancer Center Pilots
    - Individual $25k (Assistant Professor)
    - Multi-PI $50k
  - SYNERGY Pilots $25-50k
    - Translational Research Pilots
    - Community Engaged Research Pilots
  - American Cancer Center Institutional Research Grants $30k
  - Neukom Institute CompX Faculty Grants Program $20k

SYNERGY RESEARCH DEVELOPMENT WORKSHOP

A four-session tutorial on developing your clinical translational research project Specific Aims

FOUR WEDNESDAYS

May 6th, 13th, 20th, & 27th

4:00- 6:00 pm

Registration Deadline February 1st, 2020

Learn more at
synergy.dartmouth.edu/research-development-workshop

DARTMOUTH SYNERGY
Clinical and Translational Science Institute