Innovation through the Lens of Women's Health Research: A rising tide lifts all boats!

Linda G. Griffith

Professor of Biological Engineering, MIT

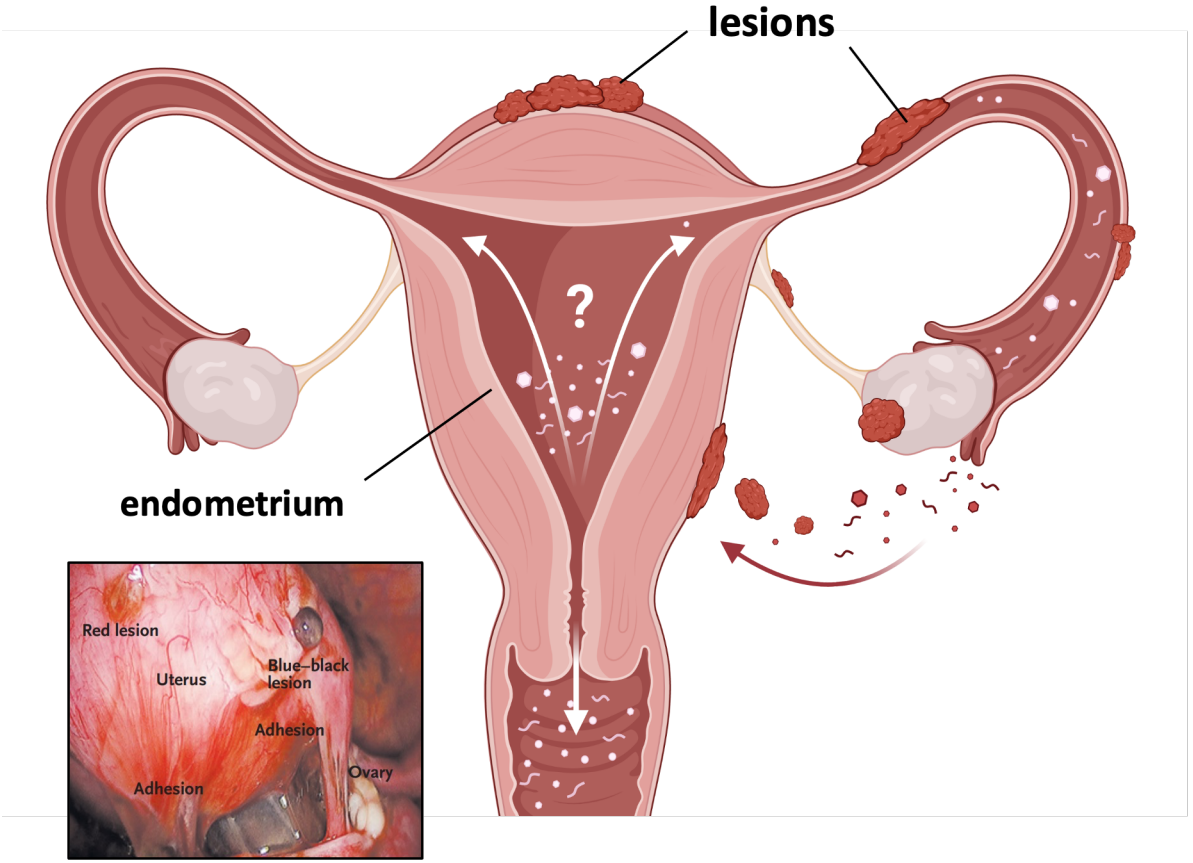
20 October 2021

Virtual (from Cambridge, MA)

Endometriosis: *A Chronic Inflammatory Disease*

Ectopic Growth of endometrium (glands & stroma)

- Affects ~10% of women
- Causes debilitating pain, infertility, anemia
- Onset often in teens, 7-10 years to diagnosis
- Surgery is required for diagnosis



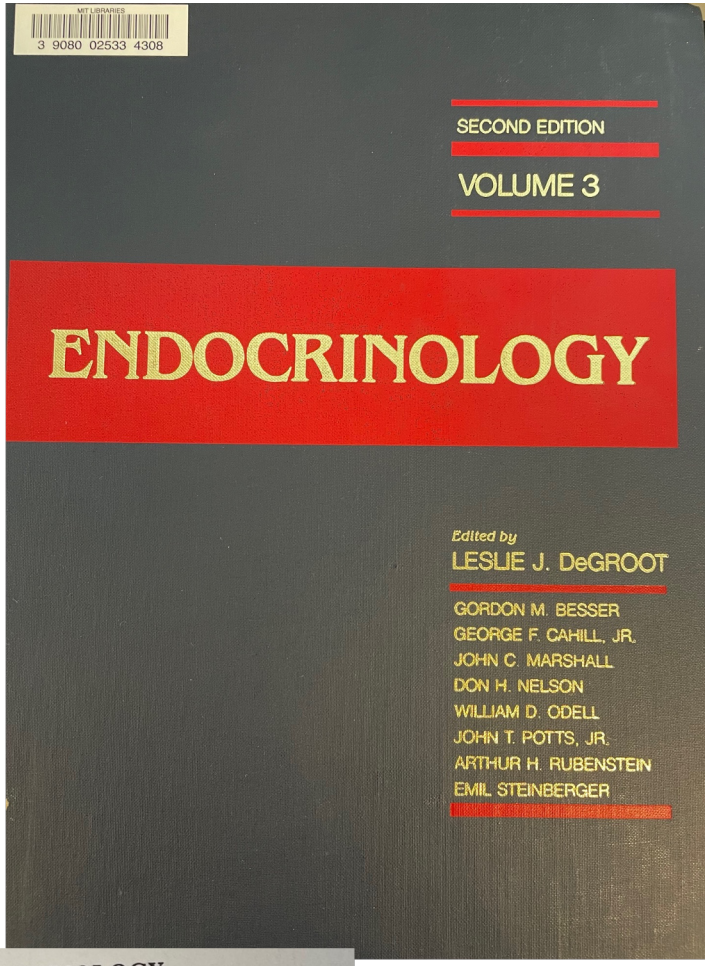
Treatments

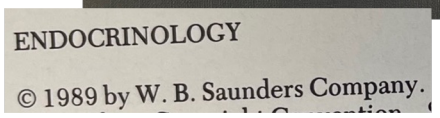
- oral contraceptives
- Lupron
- aromatase inhibitors
- danazol
- surgery (surgery, ….)

Giudice, *NEJM* 2010; Burney & Giudice ,Fert & Stert 2012; Vercellini , Viganò , Somigliana , Fedele , Nat Rev Endocrine 2014
Giudice, *NEJM* 2010; Potlog-Nahari *Fertility & Sterility* 2004

The Typical Endometriosis Patient…

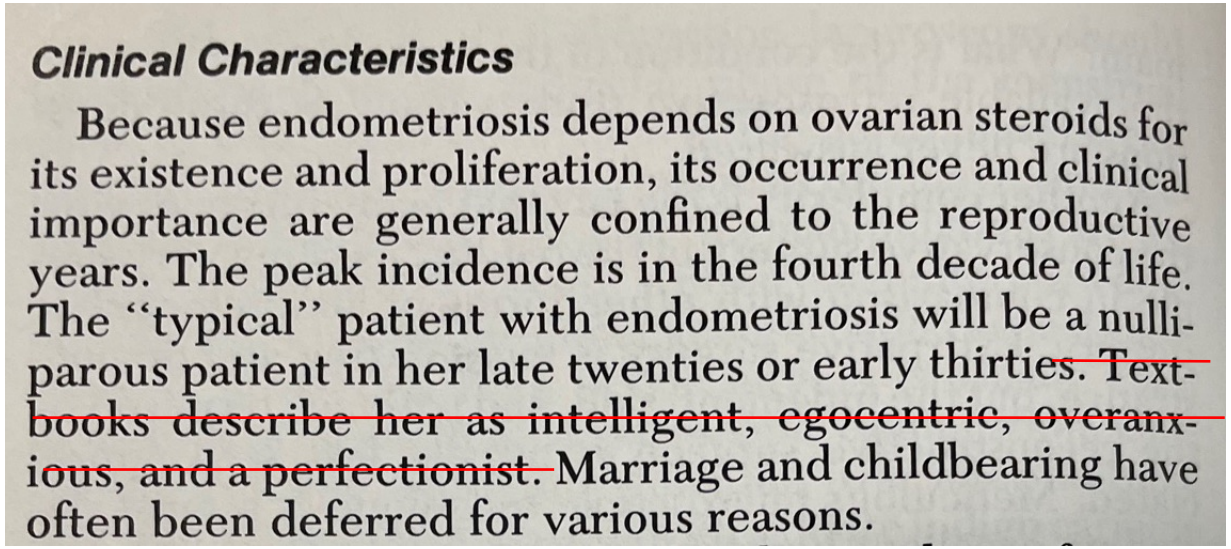
1989





"The 'typical' patient with endometriosis will be a nulliparous patient in her late twenties or early thirties. Textbooks* describe her as **intelligent, egocentric, overanxious, and a perfectionist**"

* such as this one



Clinical Characteristics

Because endometriosis depends on ovarian steroids for its existence and proliferation, its occurrence and clinical importance are generally confined to the reproductive years. The peak incidence is in the fourth decade of life. The "typical" patient with endometriosis will be a nulliparous patient in her late twenties or early thirties. Textbooks describe her as intelligent, egocentric, overanxious, and a perfectionist. Marriage and childbearing have often been deferred for various reasons.

…Or, (Severe) Diagnosis Bias?!

2006: My reaction when female Ob/Gyn tells my sister:

"Colonoscopy is negative –
Your daughter (age 15) is making things up to get out of going to school"

Actual diagnosis:
endometriosis (on bowel)

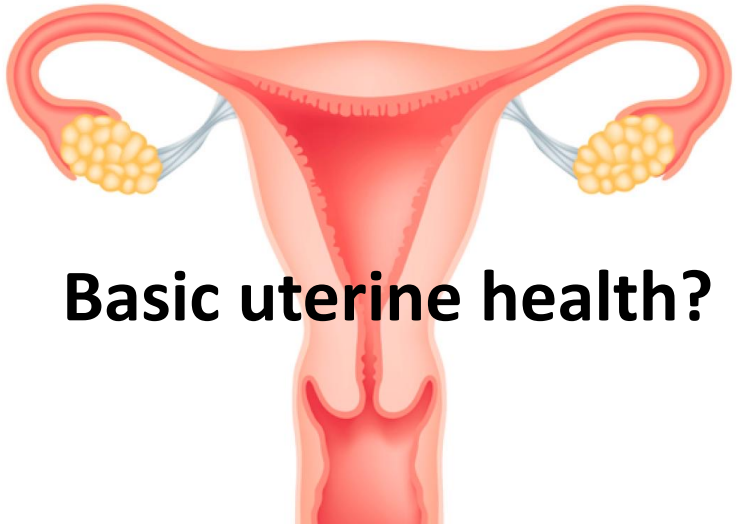
How far-reaching are the consequences of gaps in women's health funding, for women & for all? (We need more data!)

1. How does the lack of effective diagnosis & treatments for common gynecological (& women's health problems) affect general population health?

Healthy uterus / mom → healthy baby (toddler, teen, adult)

- Uterine & ovarian pathologies (heavy bleeding, fibroids, endometriosis, adenomyosis, Ashermann's, polycystic ovarian, vulvodynia) afflict at least xx %* of teens and yy%* 20s & zz%* 30s
- Fertility research / treatment ≠ uterine health research/treatment!

*estimates are >25%



Basic uterine health?

https://www.newhealthadvisor.org/Normal-Size-of-Uterus.html

https://www.healthgrades.com/right-care/tests-and-procedures/the-10-most-common-surgeries-in-the-u-s

2. Over 500, 000 hysterectomies per year in US (1/3 of all women by age 60)

- Hysterectomy associated with known increases in risk of heart disease, other illnesses (possibly due to poor management of diseases leading to hysterectomy?)
- Are all the health consequences really known? (Eg. insomnia leading to reduced immune function, increased infections, etc).

How far-reaching are the consequences of gaps in women's health funding? (We need more data!)

How much does cumulative excess morbidity of gynecology & female-skewed diseases contribute to the "women's pay gap"?

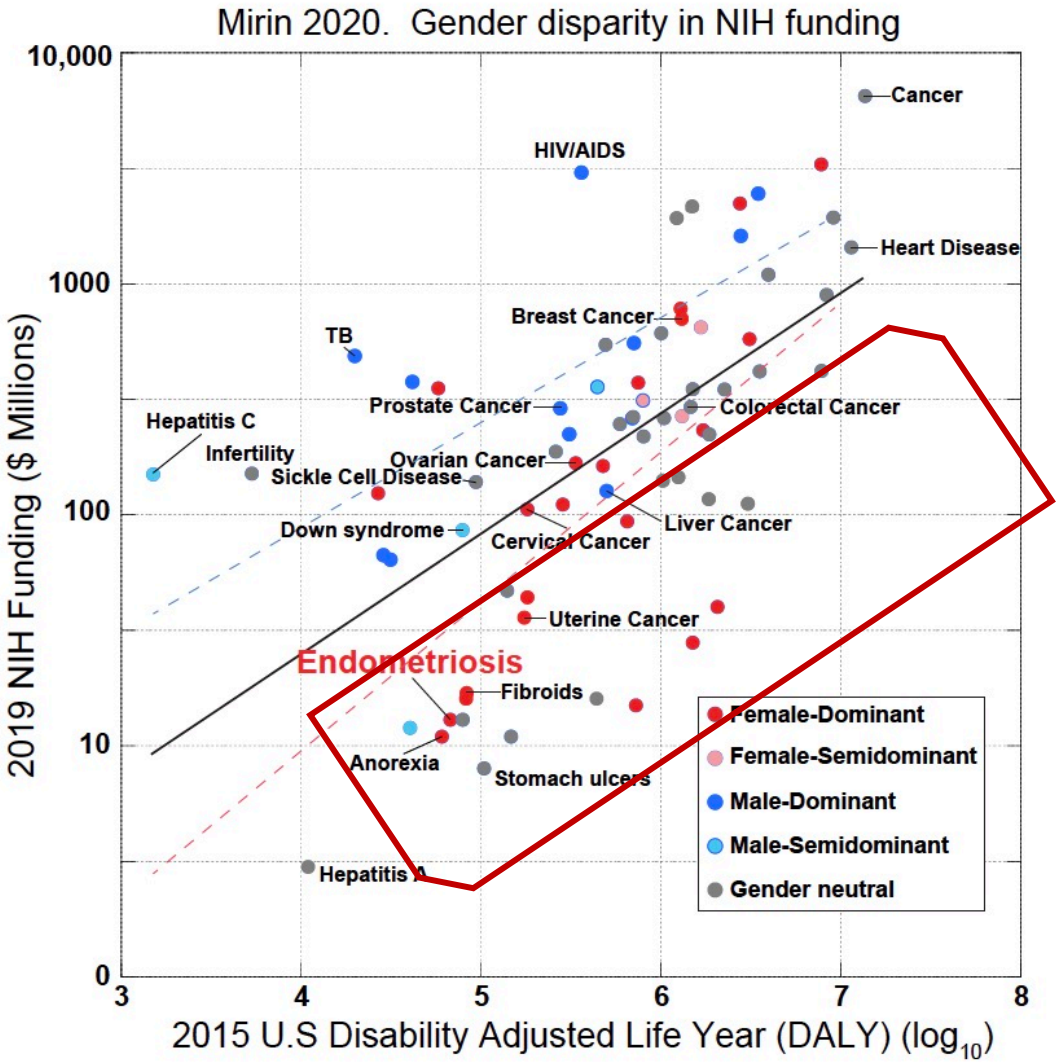
- Gynecology & female-skewed diseases are chronic, with lack of adequate treatments and high morbidity in productive life years
- Although relatively understudied, published data suggest women miss more work than men, because they themselves are sick (i.e., not just care-giver role)
- **Large, well-controlled economic studies in US are missing. We desperately need them!**

The herd of elephants in the room affecting women @ work

See eg. work of Emily Oster @ Brown

Gynecology* appears *very* underfunded – more analysis needed!

**Infertility, pregnancy ≠ gynecology*



Huge gaps in this analysis!
Because of huge gaps in NIH data and funding!

Example: Adenomyosis funding not represented

- There is no RCDC category, despite prevalence ~ endometriosis
- only 2 grants (both R01s) in the entire NIH Reporter
  - 2002-2006, NICHD (Epidemiology)
  - 2021 – continuing, NICHD (Basic science)
- DALYs are unknown – prevalence is ~ 10-fold underestimated
- NIH Reporter cites “89” projects – misleading!
  - only 2 are actually adenomyosis-focused
  - others mention adenomyosis incidentally

Plot by Ron Chandler, MSU, of data from Mirin, J. Women’s Health, 2021

Gynecology/ Women's Health funding is relatively unstable– unusually high reliance on special programs for major grants

Grant Topic Area	% funded grants, by mechanism	
	Unsolicited	Solicited (FOA/SEP)
All NIH Grants	**80**	**20**
Women's health	54	46
Gynecology		
Fibroids	43	57
Endometriosis	54	46
Vulvodynia	50	50

Data compiled by Elizabeth Barr, NIH ORWH, from RCDC queries

- **Unsolicited ("investigator initiated") proposals**
  - Investigator/team develops proposal idea
  - Three known submission deadlines per year, every year, allows investigators to submit when ready
  - Unsuccessful proposals can be re-submitted 2x, answering comments from reviewers
  - Investigators can seek NIH Program Manager feedback for improving proposal aims and impact before submission; this may be especially helpful to Early Stage Investigators

- **Solicited "Funding Opportunity Announcement" proposals**
  - NIH Program managers hold workshops, develop criteria, seek internal review and approval for FOA
  - Timing of public announcement is "whenever" (admin approval)
  - Investigators must write a grant that is "responsive" to the FOA criteria, typically within 8-10 weeks of FOA posting
  - Set-aside budget regardless of how many well-scored proposals
  - One-time submission; no revisions

Acknowledgements: Pierre Azoulay (MIT Sloan); Rem Koning (Harvard Business School)

How might unusually high reliance on special programs impair research on gynecology/women's health? (review process)

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- **Unsolicited ("investigator initiated") proposals are reviewed by *"Standing Study Sections"* – promotes robust community**
  - Stable cadre of reviewers who meet 3X per year (4-year terms)
  - Expertise of reviewers vetted by a nomination process
  - Additional reviewer vetting by ad hoc service before selection
  - Investigators submit when ready, can revise/resubmit
  - Proposal feedback provided by calibration against the arc of the field, helps young investigators, program managers can provide one-on-one feedback to improve proposals
- **Solicited ("Funding Opportunity Announcement/FOA") proposals are reviewed by ad hoc *"Special Emphasis Panels"***
  - Reviewers recruited for 1-time panel
  - Experienced reviewers / investigators are often conflicted by submission of proposals to FOA
  - No resubmission
  - no competing continuation of funded grants (one-off)

→Fields funded heavily by FOAs are at a disadvantage for building a robust research community

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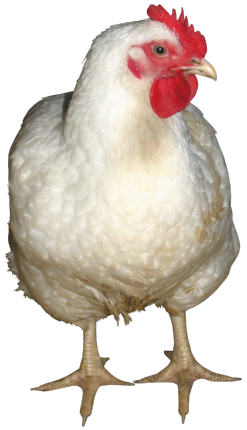
Outside analysis a must for this multi-faceted problem



Lack of dedicated funding for gynecology

- no “Institute for Reproductive Health”
- most funding is through “Child Health and Development”, which has many competing research areas
- ***What’s in a name….???!!***

Lack of experienced reviewers on standing study sections, broadly

- low “significance” scores for gynecology?
- Gynecology too complex ??

Lack of appropriate / accessible collaborative funding modes

- Many gynecology conditions are co-morbid

Need outside expert analysis of the entire application & funding process

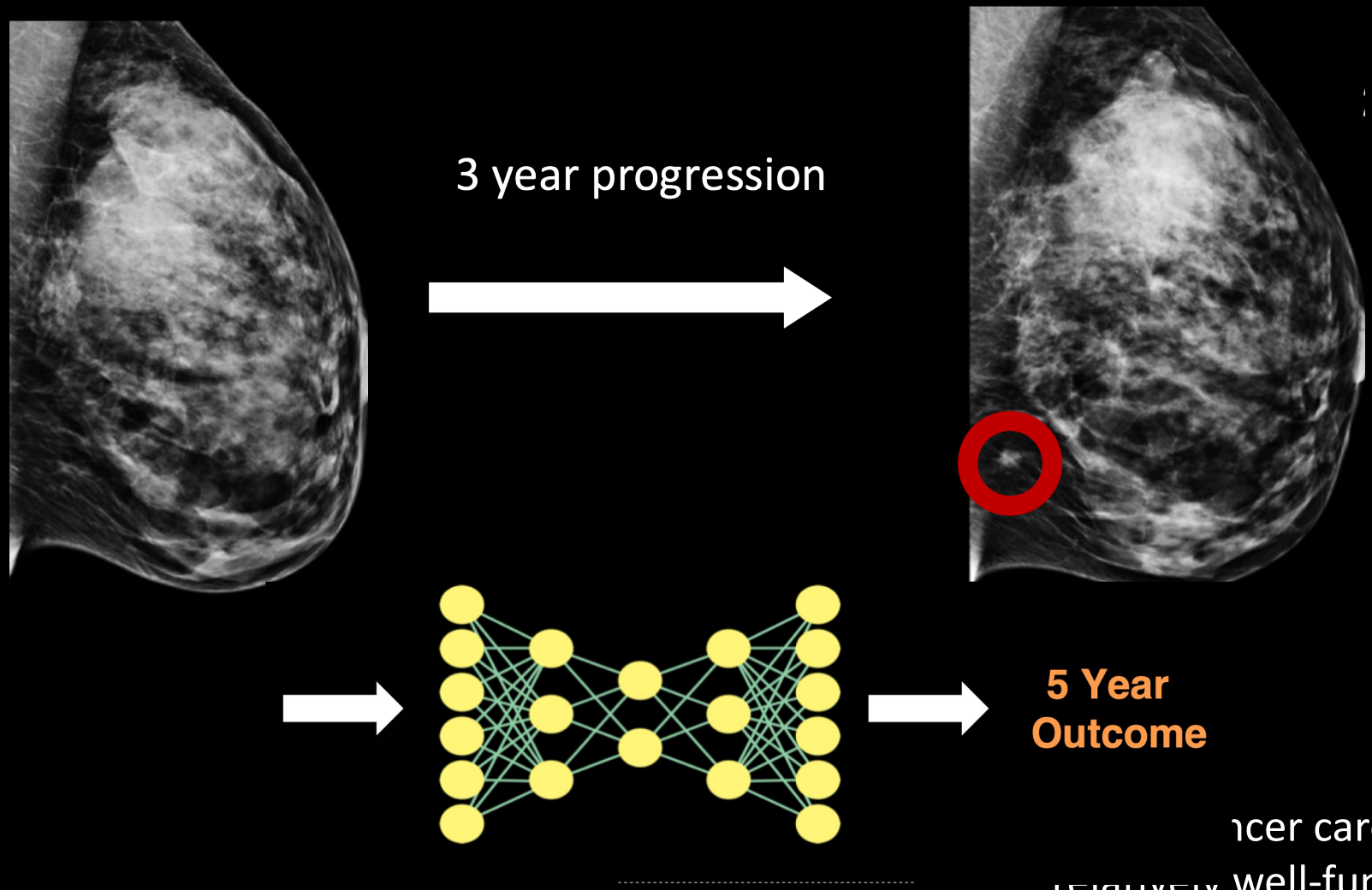
- Follow examples of outside analysis of confidential Census, IRS, EEOC, *etc.* data by scholars from NBER and NORC through creation of data enclaves *(analyses themselves may be $0 cost to NIH, funded by NSF, etc)*
- Key to data sharing agreements is that DATA are shared, not just outcomes (e.g. – who applied; what was actually in the application; confidential reviewer score data; were there hugely discordant scores *etc.*)
- How does expertise and bias play into proposal review (see e.g. work by Danielle Li, MIT Sloan)
- How might new modes of funding (eg through defined collaborative efforts) shift new investigators into gynecology/women’s health (see e.g. work by Kyle Myers, Harvard Business School)

Acknowledgements: Pierre Azoulay (MIT Sloan); Rem Koning (Harvard Business School)

Artificial Intelligence (AI): *Innovation Embraced in Medicine*

Predicting Future Cancer

Courtesy Regina Barzilay, MIT CSAIL



ncer care and research is
well-funded

Yala...Barzilay, *Science Translational Medicine*, 2021

AI/ Machine Learning Are Effective when:

- Images or (well-curated) data exist

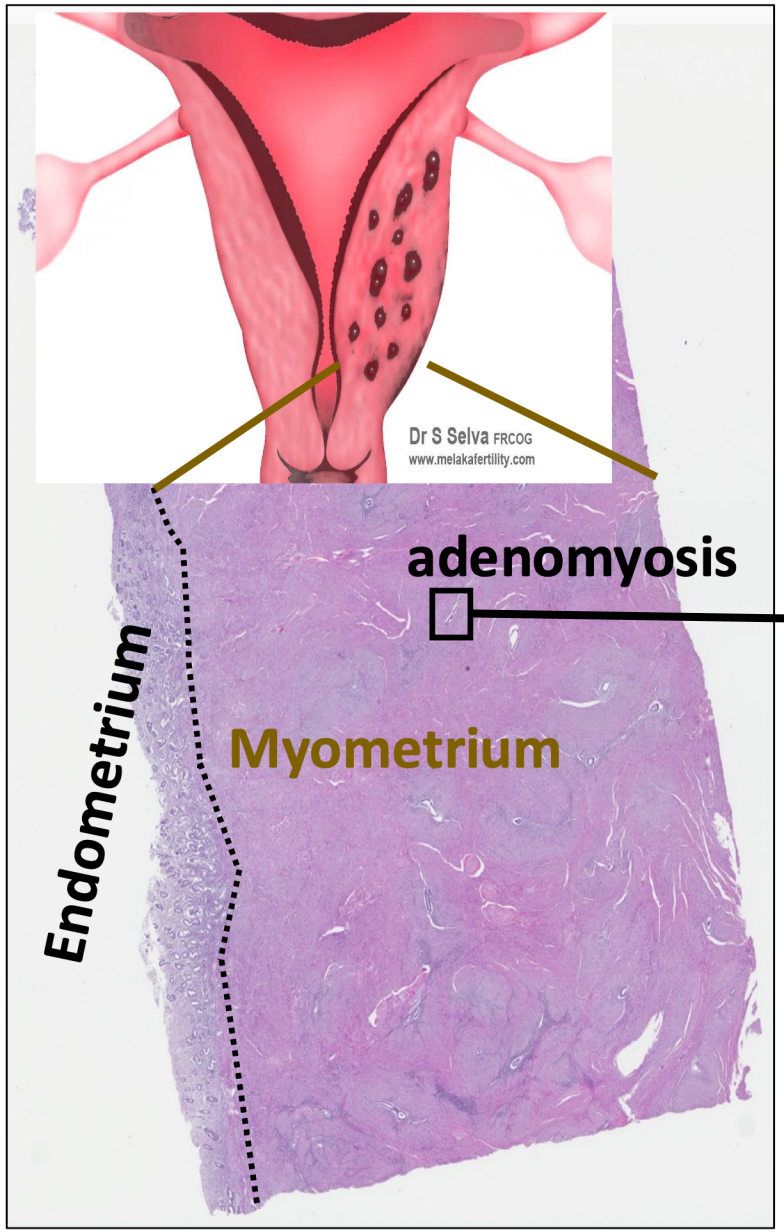
- Questions are well-posed to match the data

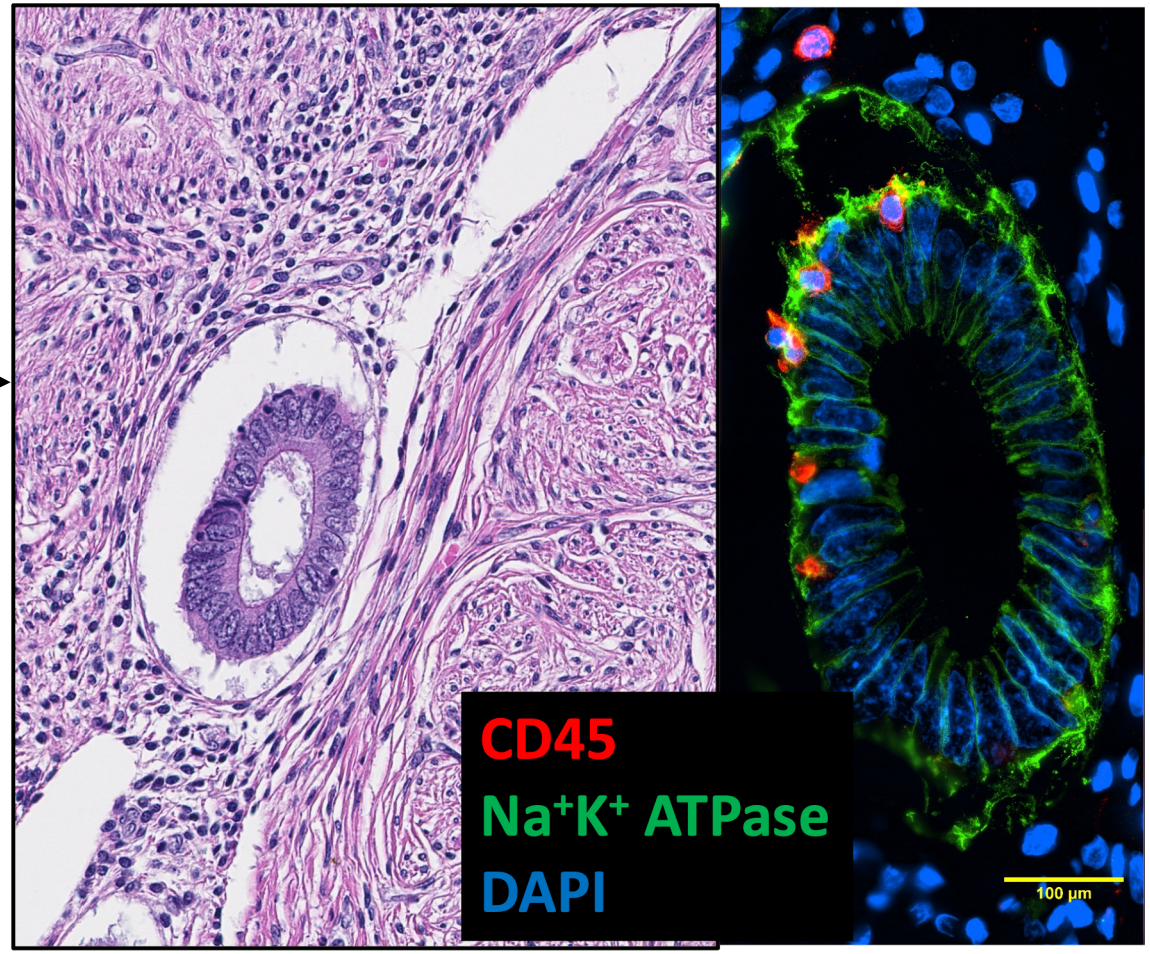
Most therapeutic *treatment* and *development* lies outside this realm

ESPECIALLY in Gynecology & Women's Health

AI & Adenomyosis?

Disease	Incidence (*% US population*)	# PubMed cites (*11 Oct. 2021*)
Crohn's/UC	~1%	60, 237
Adenomyosis	2-5%?	3, 115





Evan Chiswick, Keith Isaacson, Tony Guidi, Ed Boyden/lab, Linda Griffith, *unpublished*

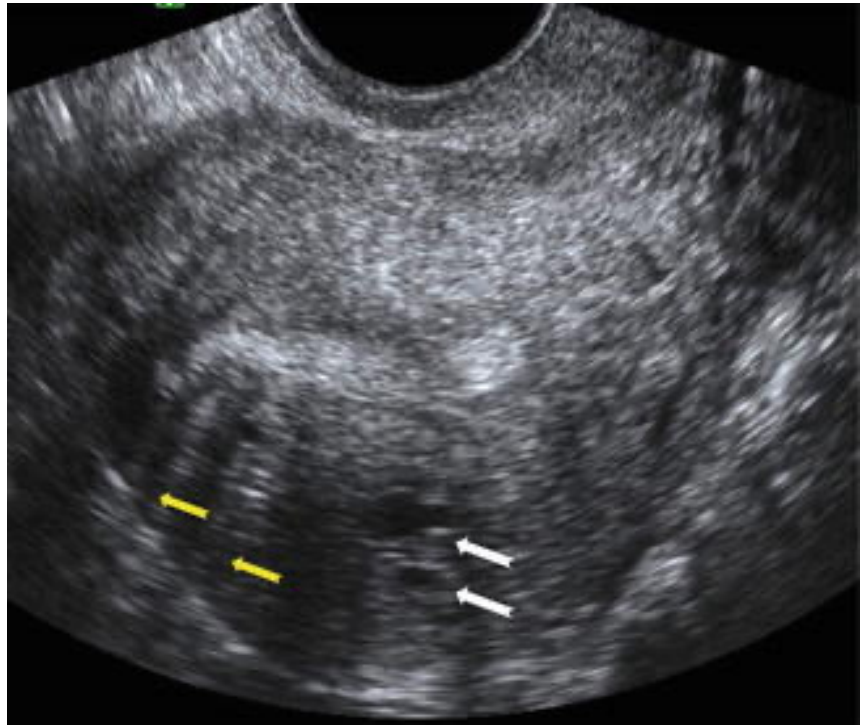
AI & Adenomyosis Diagnosis / Prognosis?

Difficult/impossible to "innovate" with current lack of infrastructure for basic studies…

With 500,000+ hysterectomies a year, we SHOULD be able to build the infrastructure for image-guided diagnosis!!

We SHOULD be able to build evidence-based infrastructure for biopsies on non-hysterectomy patients!

No $$ for infrastructure thus far.



https://obgynkey.com/adenomyosis-and-ultrasound-the-role-of-ultrasound-and-its-impact-on-understanding-the-disease/

No feasible biopsy process to correlate with all images yet exists

- Very difficult to "hit" lesion in hysteroscopic OR laparoscopic biopsy – clues in the adjacent myometrium?

AI & Adenomyosis - Therapy development?

*Genomic insights are only the tip of the iceberg

*not much genomics for adenomyosis, infer from endometriosis?

Science Signaling
AAAS

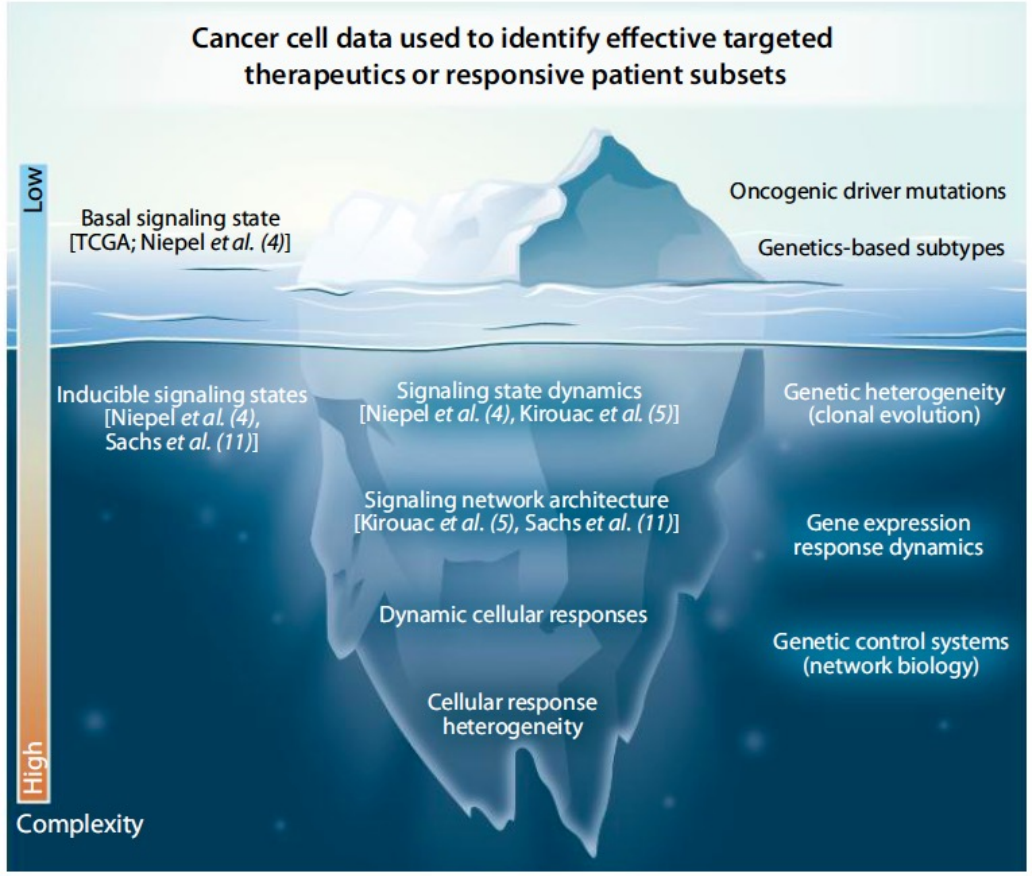
PERSPECTIVE

CANCER

What Lies Beneath: Looking Beyond Tumor Genetics Shows the Complexity of Signaling Networks Underlying Drug Sensitivity

Vito Quaranta* and Darren R. Tyson

The identification of "driver mutations" in cancers initiated rapid development of targeted drugs for the clinic. Despite promising outcomes initially in patients, the ultimate success of oncogene-targeted drugs has been hampered by the redundancy and remarkable complexity of cellular signaling pathways. Two studies in *Science Signaling* show that understanding these intricate networks and considering them during tumor classification and drug design can better predict drug response. These studies exemplify the potential of using systems analysis and computational modeling approaches to improve therapeutic strategies and outcomes in cancer patients.



www.SCIENCESIGNALING.org 24 September 2013 Vol 6 Issue 294

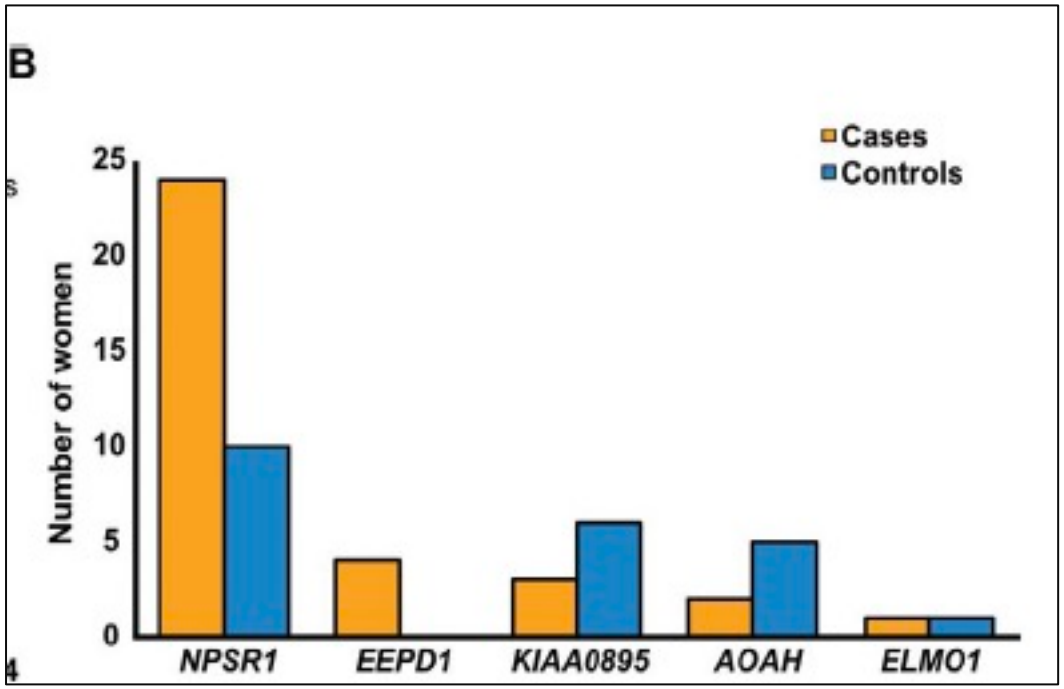
Caution: targeted drug discovery should not be disconnected from mechanistic understanding of dynamic signaling networks

AI/Genomics Analysis gives clues, not (yet) answers….

example for adenomyosis sister disease, endometriosis

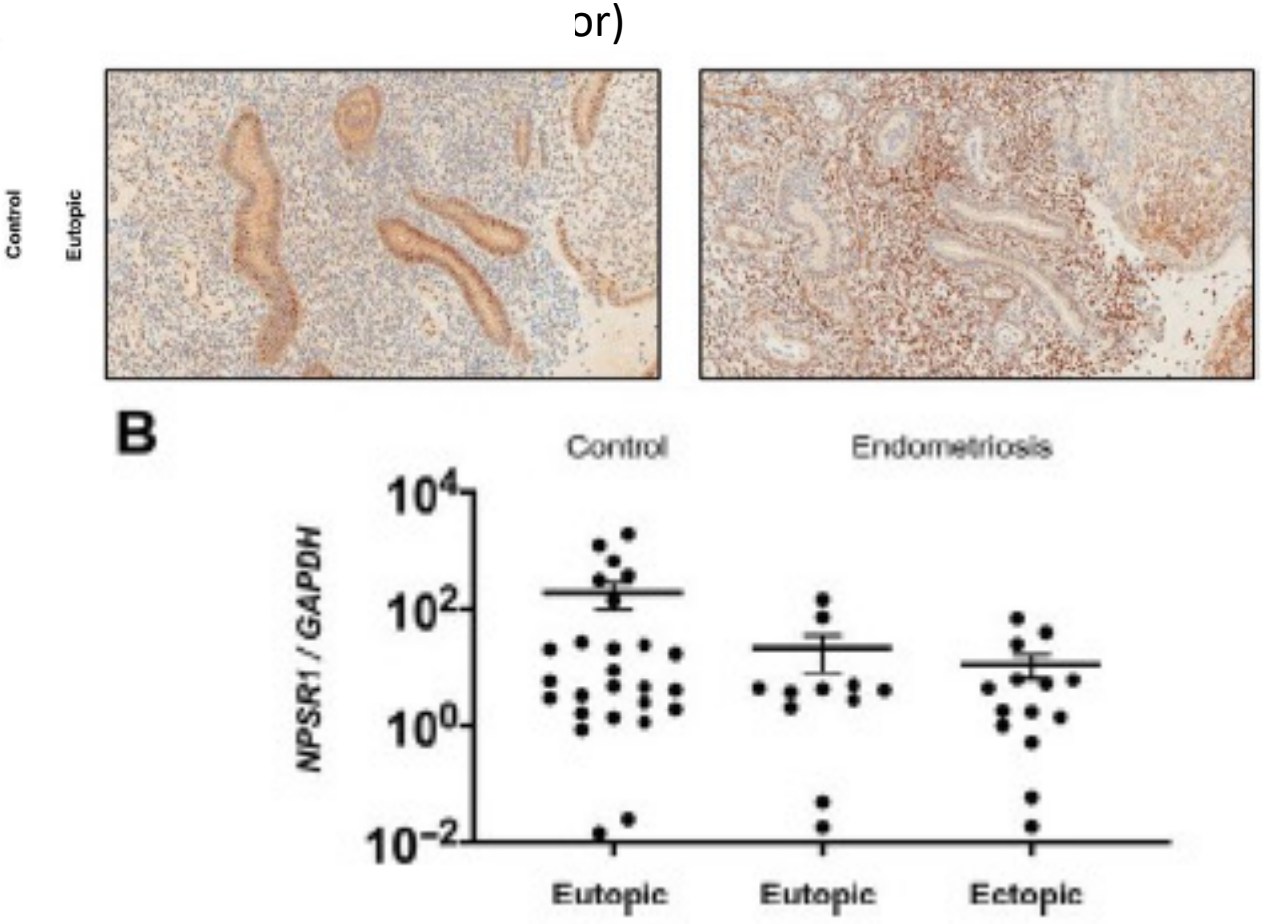
Genetic Linkage Study (Endometriosis), 32 families

Common variants observed in 11% European women



Endometrial Expression of NPSR1 / NPS

ɔr)



Tapmeier…Zondervan, Sci Trans Med, August 2021

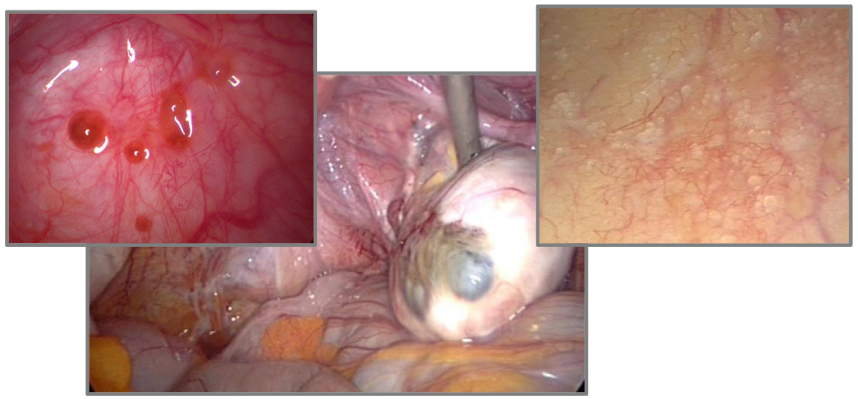
Neuropeptide S Receptor 1 is a Non-hormonal Treatment Target in Endometriosis

Endometriosis/adenomyosis is not one disease
– one drug (class) does not fit all!

Patient Heterogeneity

- age of onset
- symptoms
- immune system
- drug response
- co-morbidities

Lesion Heterogeneity, between/within patient(s)



- biology- glandular, fibrotic EMT, etc
- physiology – drug access?
- one drug for all lesions?

Molecular mechanistic stratification is needed!

Becker +, WERF EPHect Working Group Harmonization Project I, Fert & Stert (2014)

Hypotheses

- Patients can be grouped and treated according to different *molecular mechanisms* of disease (similar to cancer)

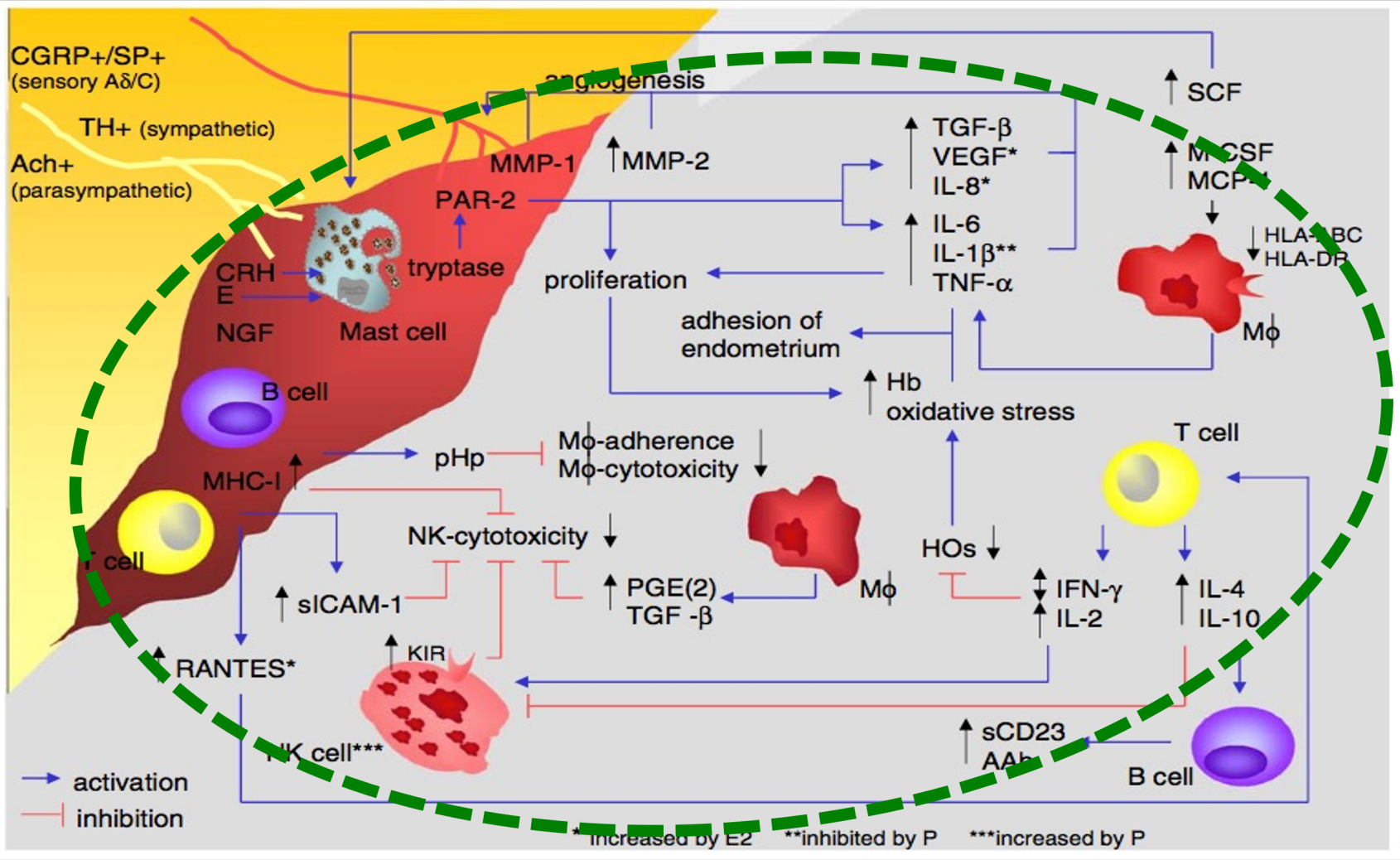
- Molecular mechanisms may correlate (or not) with symptoms rather than lesion burden

How do we find the mechanisms and groups?

Engineering Approach

Inflammation / Invasion PATHWAYS are Linked into Complex NETWORKS :

Cell-Cell Signaling Proteins (cytokines, chemokines, growth factors), Enzymes (proteases, kinases) etc.



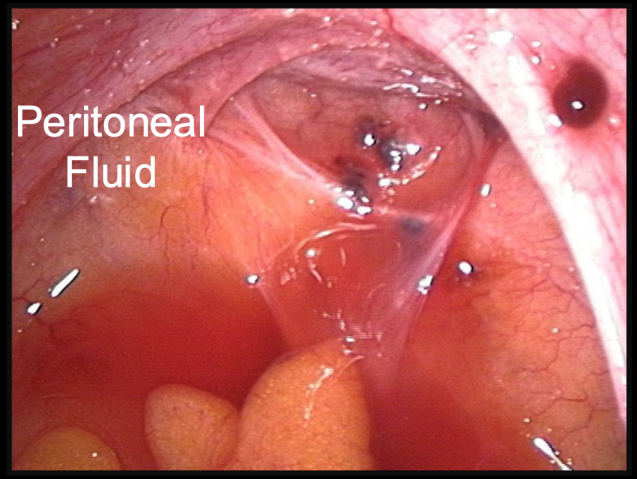
[Tariverdian. *Semin. Immunopathol.* (2006)]

Mechanism-based Molecular Classification of Endometriosis Patients

Identification of JNK as a new non-hormonal target *in a subset of patients*

Funded by an Anonymous Foundation (not NIH)

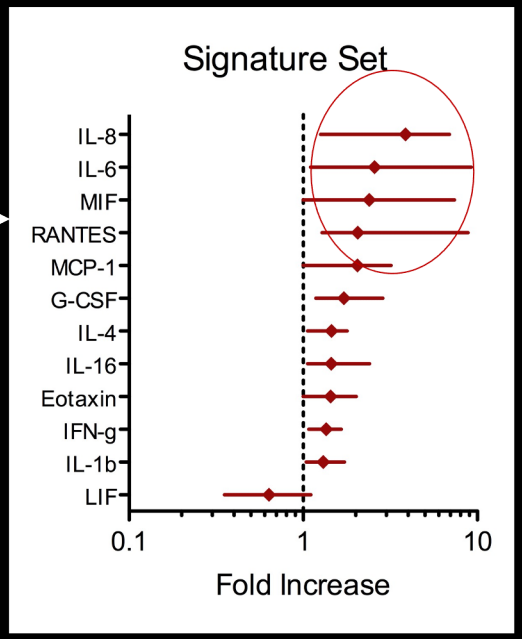
All (77) Patients (Stage I-IV) compared to Controls (20)



50-plex Luminex of cytokines

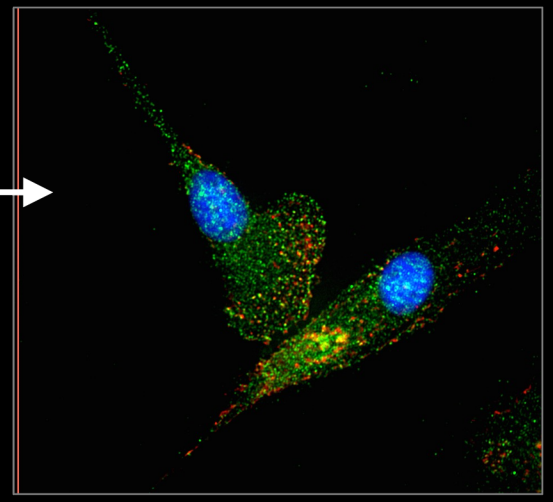
Consensus Signature

1/3 of patients, all disease stages



Multivariate Unsupervised Analysis

Jun kinase regulates inflammatory cytokine production

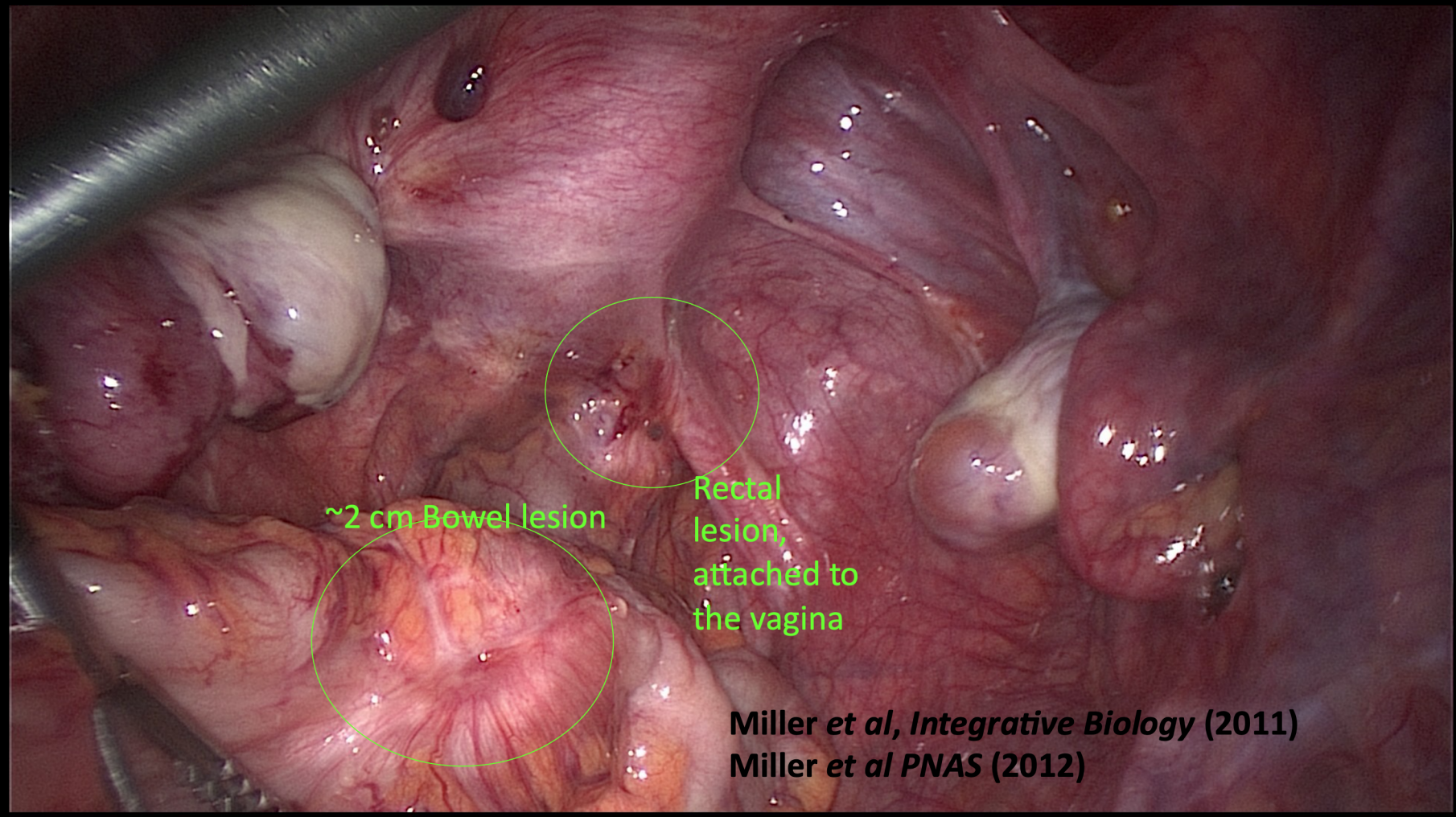


Reverse engineer immune network, test hypothesis in patient macrophages

Beste, Pfaeffle-Doyle, Prentice, Lauffenburger, Isaacson, Griffith, *Sci. Transl. Med.* (2014).

Replicated in a meta-study with Mauricio Abrão et al, São Paulo (in prep)

What are the consequences of inflammation on invasion of ectopic endometrial cells into underlying tissue? *Jnk also implicated*



Resection of 2 bowel endometriosis lesions + associated other endometriosis, Dr. Mauricio Abrão, Sirio Libanês Hospital 12 July 2011

JNK inhibitors have cured diverse patient populations of endometriosis!

(unfortunately, none are human)

Palmer et al., Reprod Sci. 2016

Hussein et al., Fertil Steril. 2016

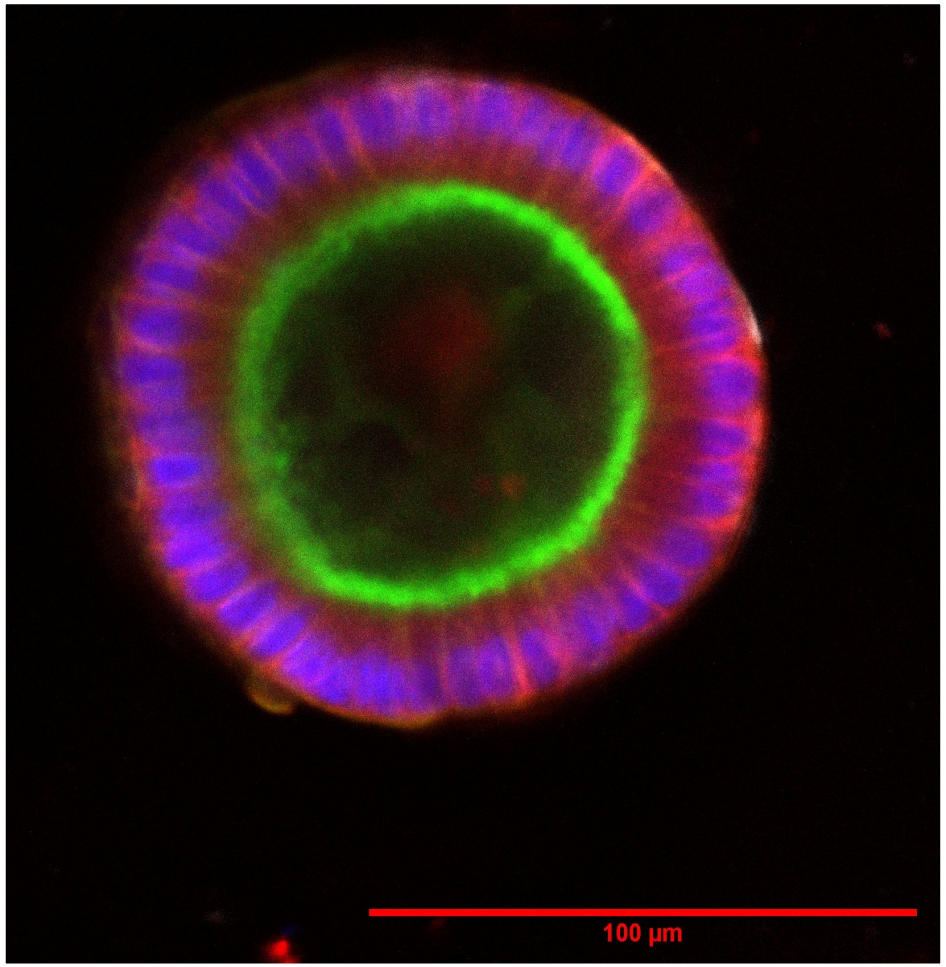
Clinical trial of JNKi (Preglem) unsuccessful –
Patient stratification issue? Drug chemistry/specificity?

Pharma: "we need efficacy models"

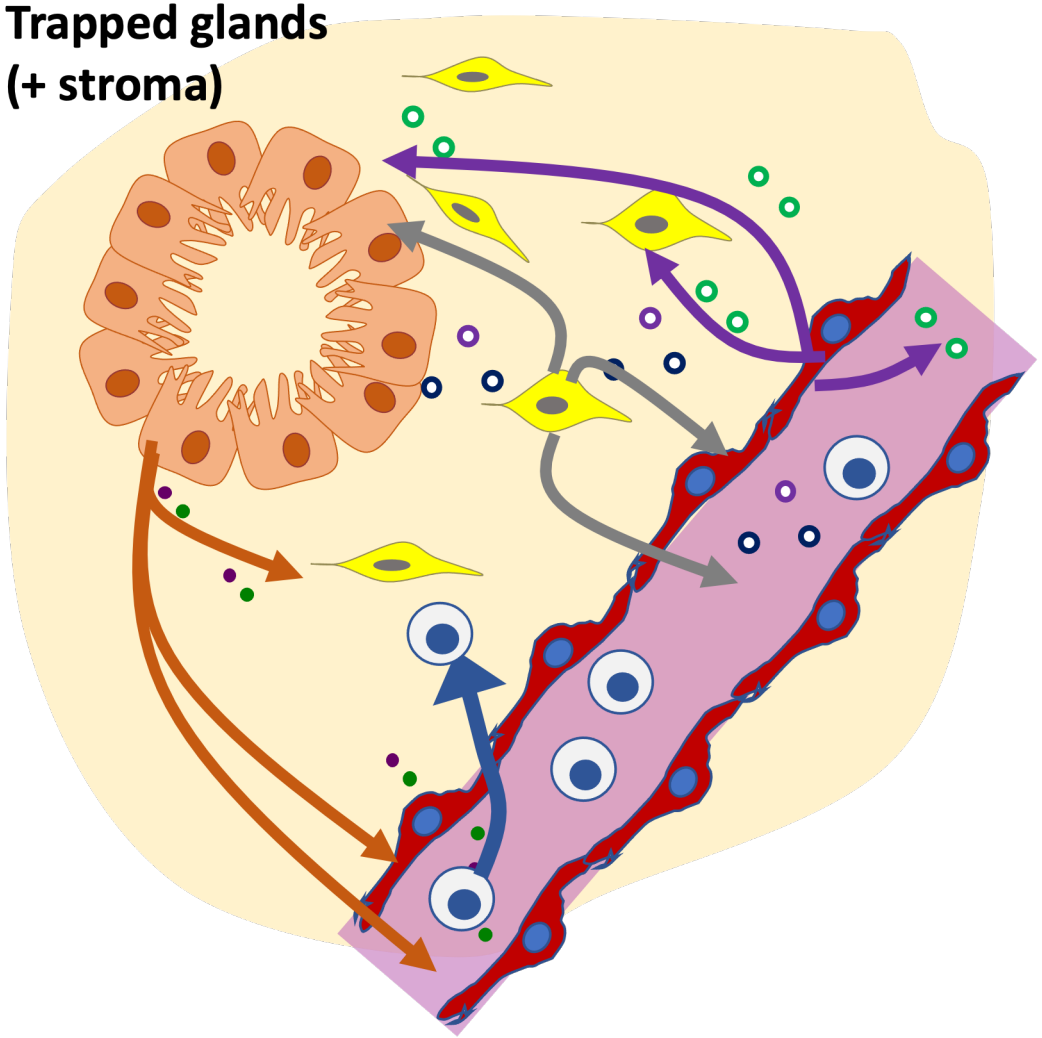
Modeling the Birth of Lesions With Tissue Engineering & Organs on Chips

Synthetic matrix/tissue engineering/Organ-on-chips supported by foundations and DARPA 2012 – 2017 then NIH 2019+ -

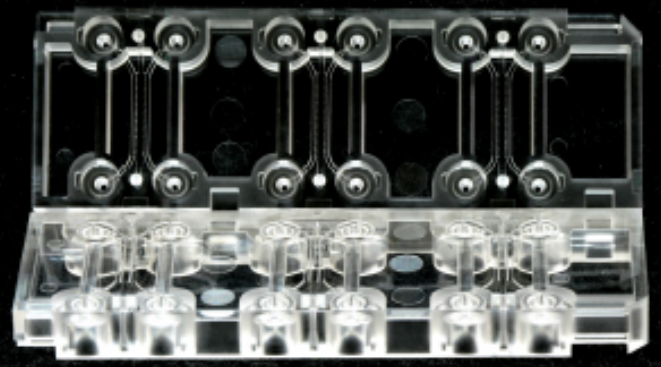
Endometrial Gland in Culture



Trapped glands
(+ stroma)



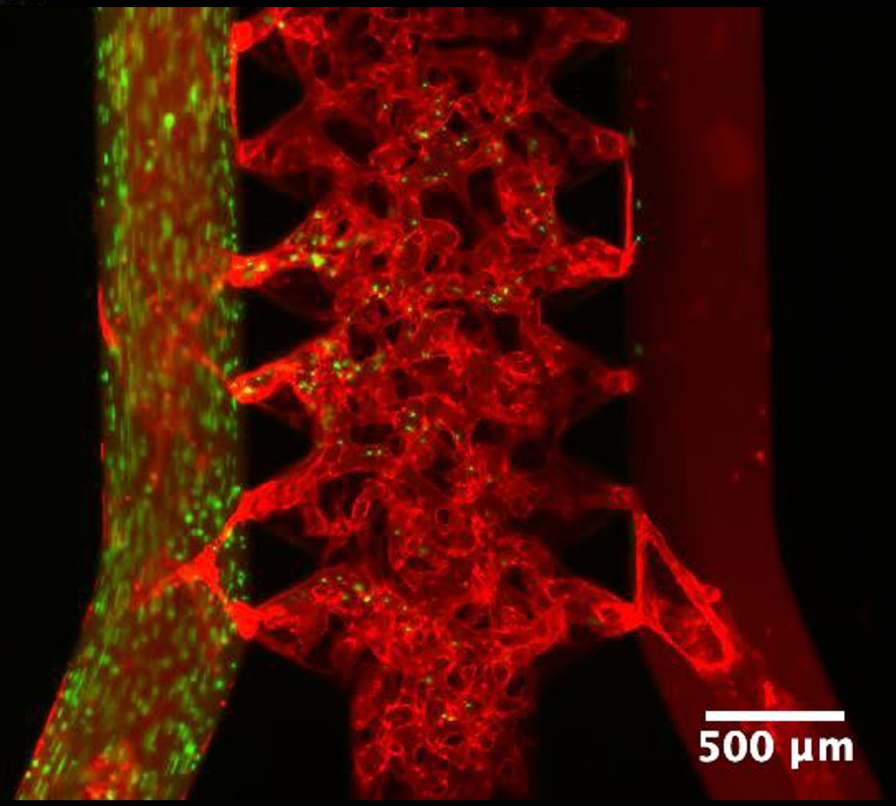
Recruitment of circulating (immune/stem) cells



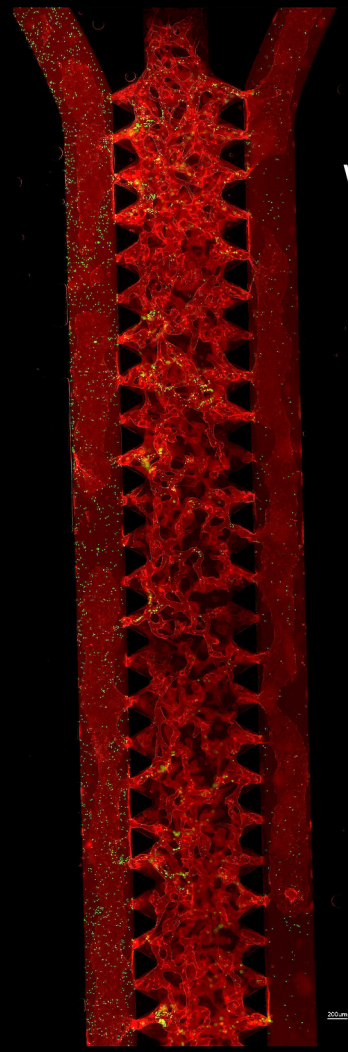
Microvascular networks driven by gravity flow in a commercial chip

Ellen Kan with
Roger Kamm lab

Human Monocytes (Cell Tracker)
HUVEC (UEA-1)



*real time

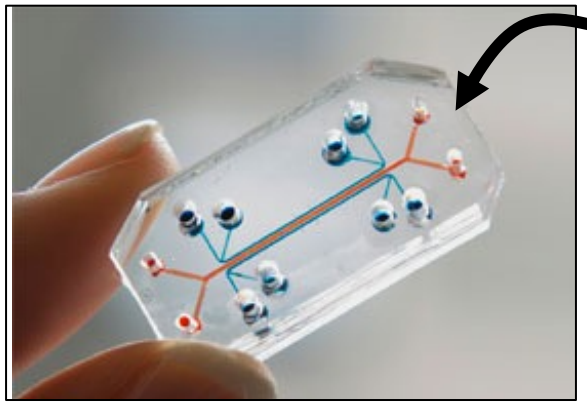


Whole channel view

Example of Women's health need driving innovation for all: Human on a chip – with protocols for sex dimorphism analysis

We MUST move beyond animal models – especially for chronic inflammatory diseases

Standard PDMS "Organ on Chip"
Wyss Institute (Ingber)

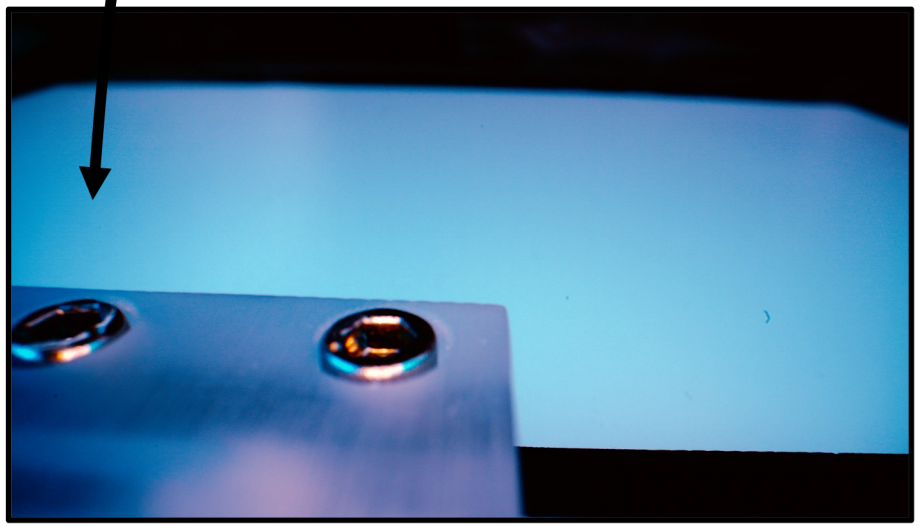


Sink for estradiol - cannot use for sex dimorphism!

V2.0 Hard Plastic: Endometriosis on a Chip
MIT (Griffith + Trumper)

NIH Tissue Chips Program 2019+

True microvasculature and control of estradiol/progesterone/testosterone!



Version 1.0 Hard Plastic, open system liver
MIT/Griffith-Trumper/CN BioInnovations

DARPA
Microphysiological Systems Program 2012-2019

The Emergence of "Biological Engineering" as a Model for a New Era of Trans-NIH collaboration

(Bio) Medical Engineering: Applications

Mechanical, electrical, materials engineering, etc applied to medical problems

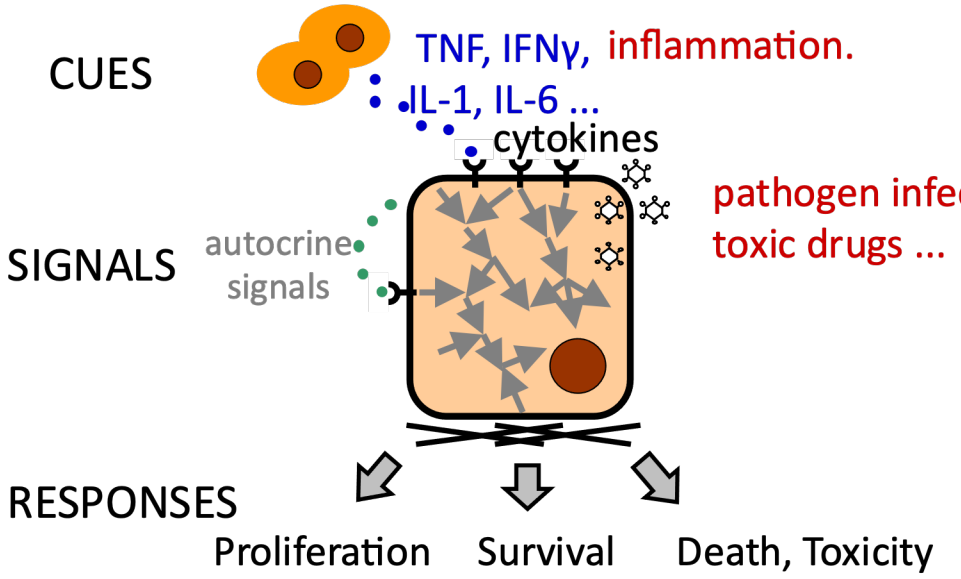
No particular need to know Biology, probably knows some physiology

Biological Engineering: a New Engineering Discipline

Engineering Analysis, Design, and Synthesis - based in Modern Molecular Life Science

Emphasis on Problem Definition! Must know biology

Not *essential* to know "instrumentation" or "fabrication"



Models tell you what to build

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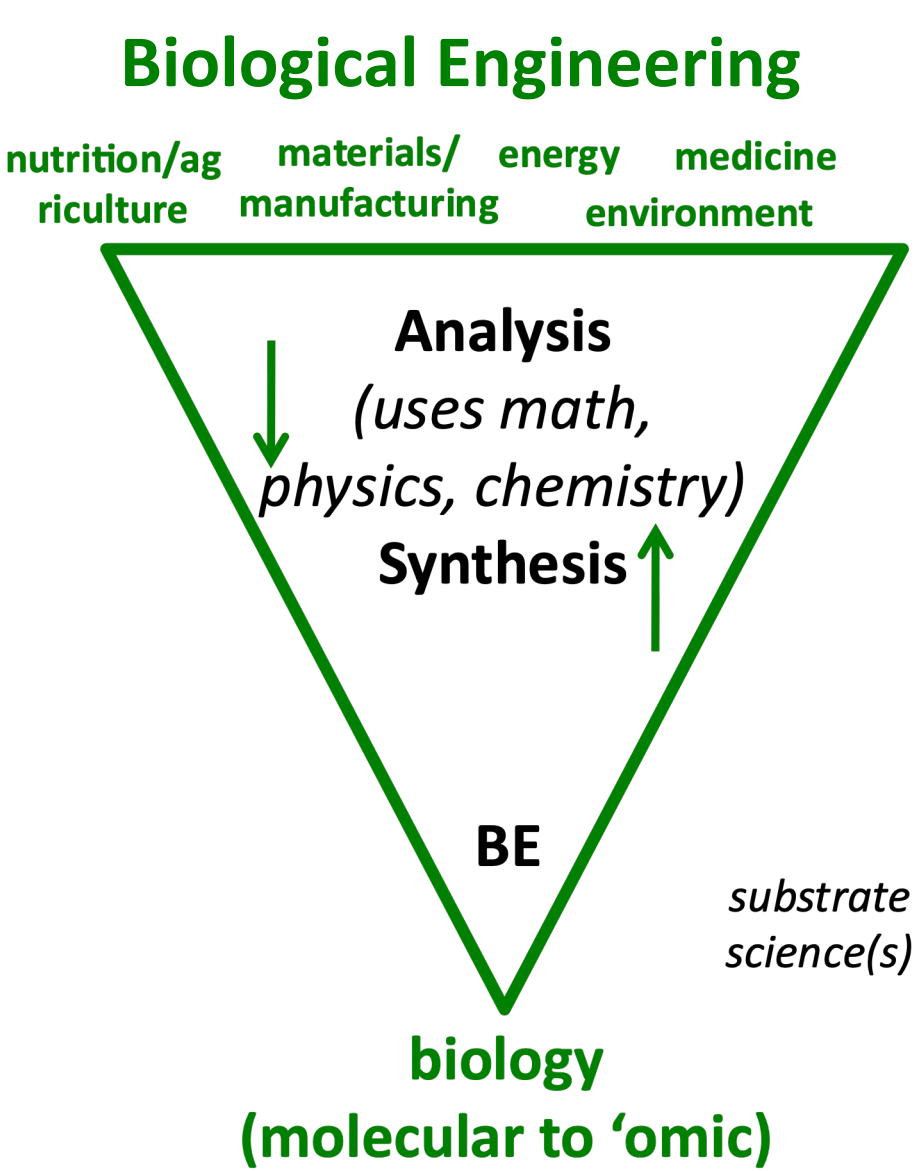
NATIONAL ACADEMY OF ENGINEERING

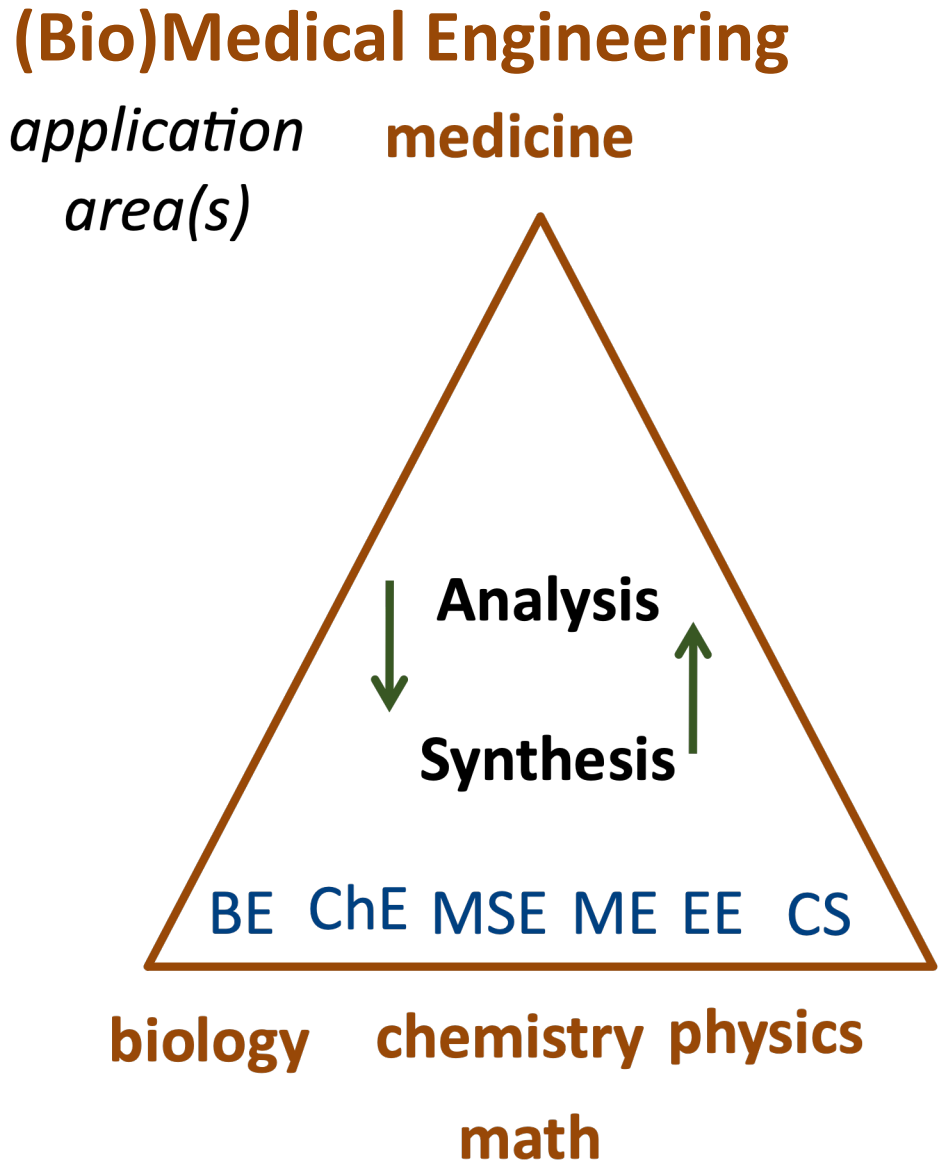
Bernard M. Gordon Prize for Innovation in Engineering Education

2021: Linda Griffith & Doug Lauffenburger, MIT

CITATION: For the establishment of a new biology-based engineering education, producing a new generation of leaders capable of addressing world problems with innovative biological technologies.

Biological Engineering As an Essential Discipline





Biological Engineering emerged organically over ~10 years

Ca. 1991

School of Engineering

AeroAstro
Chemical
Civil & Environmental
Electrical & Comp. Sci
Materials
Mechanical
Nuclear
Ocean

School of Science

Brain and Cognitive Sci.
Biology
Chemistry
Earth & Planetary Sci.
Math
Physics

Whitaker College

Health Sci & Technology
(Medical Engineering
Graduate Education)

Harvard Medical School MD programs

1985-2005
NSF "Biotech Process Engineering Center"
Chem. Eng. + Biol + Chem
Research, co-taught elective subjects

1993
Ad hoc inter-departmental UG BioEng Curriculum Committee formed: Should MIT have a "Biomedical Engineering" Major?

1993
Biology required for all students

1994
Formal pan-MIT grass roots faculty proposal to start a program "linking engineering to molecular life science @ MIT; MIT Admin says "yes"

1995 Biomedical Eng.Minor Degree
MIT's 1st interdepartmental Minor Degree
Requires: Biochem, Genetics, Cell Bio

1995 Center for Biomedical Engineering launched
Doug Lauffenburger recruited from UIUC Chem Eng/Cell Biol, for his pioneering work in "engineering cell biology"

1998 The Big Academic Experiment
"Division of Bioengineering & Environmental Health" launches in School of Engineering
6 faculty split appointments 50/50 with ChE, ME, EECS, etc ; 11 Toxicology faculty move to "BEEH"

1999
80+ students enrolled in BME Minor
>25% are Biology majors

1999
PhD in "Biological Engineering" launched

Biological Engineering emerged organically over ~10 years

Ca. 2000

School of Engineering

AeroAstro
Biological
Chemical
Civil & Environmental
Electrical & Comp. Sci
Materials
Mechanical
Nuclear
Ocean

School of Science

Brain and Cognitive Sci.
Biology
Chemistry
Earth & Planetary Sci.
Math
Physics

Whitaker College

Health Sci & Technology (Biomedical Engineering Graduate Education)

Harvard Medical School MD programs

2000
UG Committee begins developing curriculum for major in "Biol Eng." Emphasis on teaching collaborations between departments / schools

2001
Name change to "Biological Engineering (BE) Division"

2002
"BE Division" becomes permanent academic unit after formal MIT review

2003
"BE Division" becomes "BE Department", on par with all SoE Departments

2003 Biological Physical Chemistry launched
Molecular Thermo/Stat mech collaboration between ME & BE

2004
BE becomes "Course 20"

2005 Biological Engineering UG Major
First new UG major in 39 years

2005 Chem Dept joins "Biol P Chem"
Dean of Science Bob Silbey (Author of "Physical Chem, 4th Ed") + Moungi Bawendi*

2007 Biol Dept joins "Biol P Chem"
Biol Prof volunteered when Griffith had emergency endometriosis surgery

*Moungi and Linda started Lumicell + Precision Healing together (with others)

Gradual emergence of a now-established discipline

MIT requirement | BE requirement | BE core

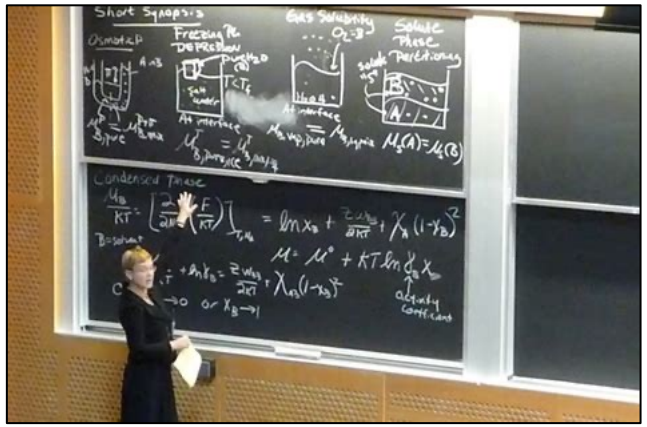
Years 1 and 2

Physics *(2 semesters)*
Calculus *(2 semesters)*
Biology
Chemistry

Differential equations
Programming and statistics
Organic chemistry
Biochemistry

Thermo of Biomolecular Systems
Intro to Biol. Eng. Careers
*Biological Eng lab *(wet)*

Year 3



Genetics
Cell biology

Analysis of biomolecular and cellular systems
Fields forces and flows in biol. systems
*BioEng lab *(instrumentation)*

Year 4

Senior design
(Thesis)

+ 3 Restricted Electives

Urgent Need for Workforce Development in Gynecology

- Research and teaching go hand in hand – top researchers usually want to teach (same for top clinical practioners)
- Lack of robust clinician-scientist research culture in gynecology filters into difficulty creating evidence-based practice guidelines
- *Tremendous* interest in gynecology research from young women in STEM – **when they ask, I have no good advice for them about funding**
- **I feel hesitant to encourage young scientists to study gynecology, due to uncertainties in funding**

How Addressing Women's Health "Raises All Boats" Structural Changes to Improve NIH collaboration for All

- *The need:* extensive collaboration across ICs to address systemic and co-morbid conditions in women, from childhood through menopause **with far more resources than are now available**
- *The need:* better dissemination of "biological engineering" concepts across NIH
- *The challenge:* Difficult to build collaborative projects across ICs as each IC has its own budget and agenda – is "tin-cupping" a sustainable plan for gynecology?
- *The potential:* staff throughout NIH see potential for collaboration
- *The suggestion:* Pilot a new mode of NIH collaboration with a Gynecology Center (or other means of dedicated funding for Gynecology) in NICHD
- *The caution:* An Institute should take the lead – not the Office of the Director or ORWH

Gynecology as an example of Women's Health Research that Desperately Needs A Quantum Change in Inter-IC Collaboration

NICHD

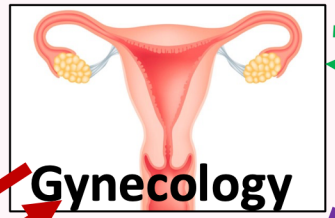
Child health

development

Fetal-maternal medicine

Fertility

Rehabilitation



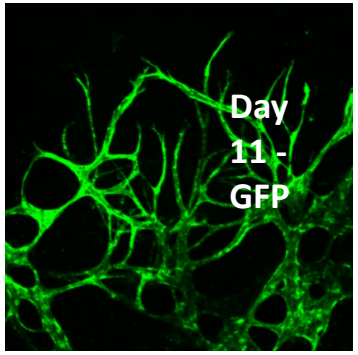
NINDS

- Chronic pain / quantitative metrics
- "brain fog" during drug treatment & menopause

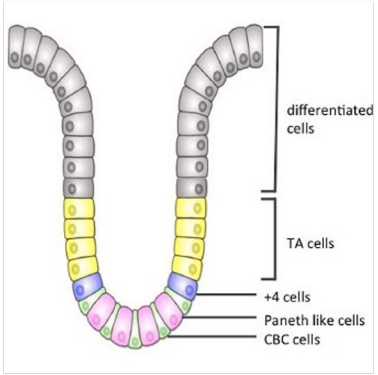
NIDDK

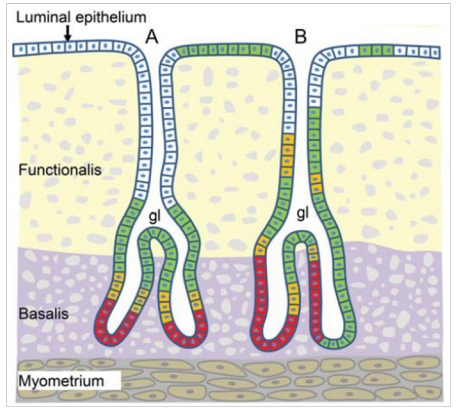
NHLBI

- Correlation with cardiovascular disease – genetic predisposition or drug treatment?



Example of Endometriosis / Adenomyosis





- GI co-morbidity in peri-menarchal girls developing dysmenorrhea ultimately endometriosis
- Prevention of kidney disease precipated by treatment for gynecological disease

Gynecology as an example of Women's Health Research that Can Potentially Benefit Broad Areas of Human Health

NICHD

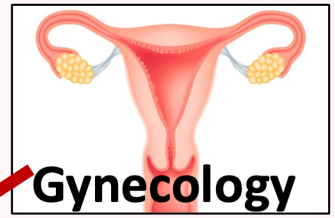
Child health

development

Fetal-maternal medicine

Fertility

Rehabilitation

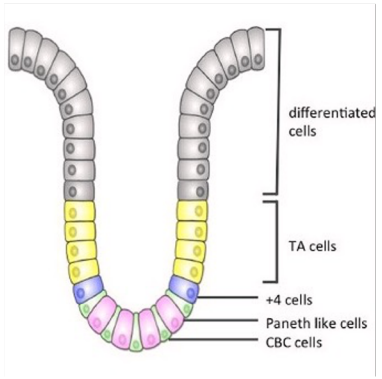


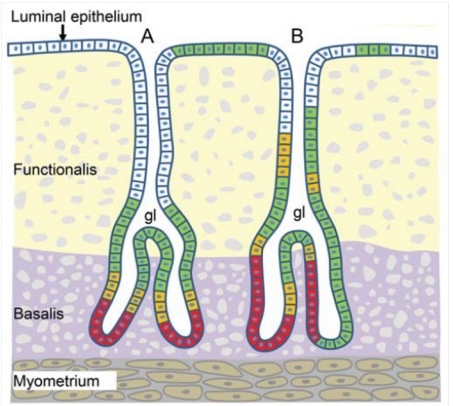
Better understanding of Normal and Pathological Menstruation Processes

NINDS

- Sex hormone regulation of migraine
- Chronic pain

NIDDK

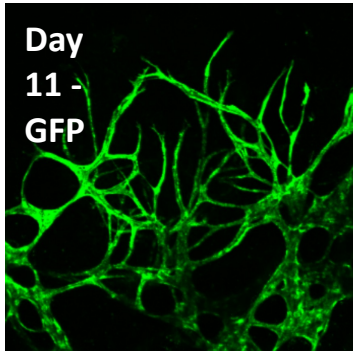




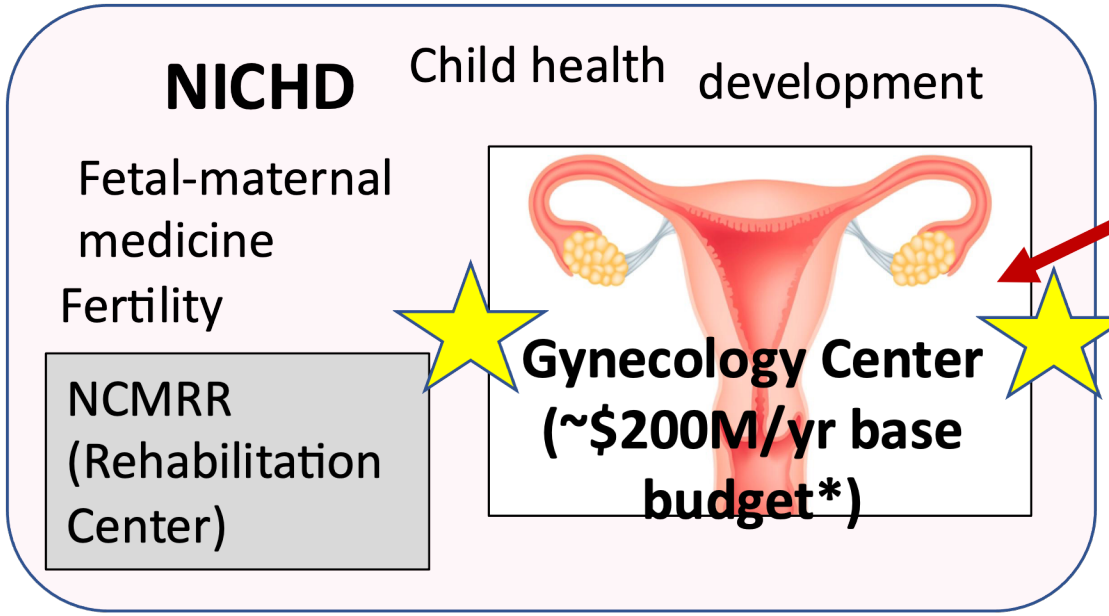
- Immunology of mucosal barriers
- Stem cell dynamics and plasticity in mucosal barriers

NHLBI

- Sex hormone regulation of vascular properties
- Endometrial vasculature dynamics as a model system for development and study of cardiovascular disease
- Neuroangiogenesis in health and disease



An Experiment – Gynecology as a new Collaborative NIH Model *a la* MIT Biological Engineering



NHLBI NINDS NIDDK ….etc

(~2%) budget to collaboration grants with Gyn. Center

- Emphasize investigator – initiated
- Basic science and translational science
- Include studies on younger patients (pre-teens even) with co-morbidities requiring collaboration across disciplines
- TRAINING PROGRAMS / WORKFORCE DEVELOPMENT

* Includes e.g. child-to-adult cohort studies

Pilot experiment with 2-3 institutes, small budget % to determine best operational model
Careful analysis needed to avoid downsides of the *Law of Unintended Consequences*

Key Elements:

- Substantial dedicated, protected funding for Gynecology within NICHD
- Substantial funding toward defined ways other ICs collaborate with Gynecology

Summary of recommendations

- Desperate need for outside analysis of funding disparities in Women's Health, especially in gynecology but also infectious disease, *etc.*
- Desperate need for better data on how women's health disparities influence wage gap for women (almost no studies exist for US!)
- NIH should encourage creation of an enclave allowing professionals from NBER, NORC, etc to analyze NIH data critically
- Women's health – often difficult to approach from genomic analysis -- motivates new "biological engineering" approaches to chronic diseases, benefitting all
- Gynecology offers a roadmap to an experiment for new models trans-NIH collaboration in research and workforce development
- Dedicated funding to Gynecology, and "Gynecology Collaboration", should be within an Institute and not in the OD
- Outside analysis of how to set up dedicated funding & a collaborative model is encouraged