

My Path to Research Independence

Professional Development Workshop and Mentored Mock Review
NCI Center to Reduce Cancer Health Disparities

July 19, 2021

John M. Carethers, M.D., M.A.C.P

C. Richard Boland Distinguished University Professor

John G. Searle Professor of Internal Medicine

University of Michigan



MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

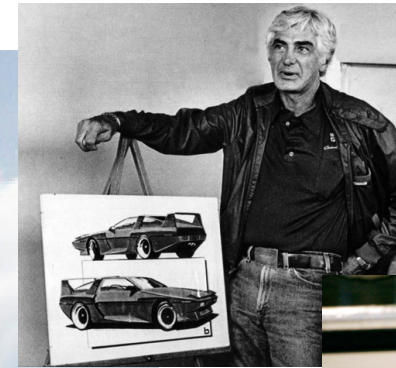
Early Points in My Career

- Detroit-born
- 10th child
- News carrier
- landscape caretaker and gardener
- Cass Tech H.S. grad
- Junior Achievement
- Family support and early role models
- Exploration of potential careers
- Worked 30 hours/week in undergrad tied to goals

Carethers Family circa 1973



Cass Technical High School – Detroit, Michigan



John DeLorean

Lily Tomlin
(with
Meryl
Streep)



Diana Ro

7. Noteworthy

- The mother of [aviation pioneer Charles Lindbergh](#), Mrs. Evangeline Land Lindbergh, was a chemistry teacher at Cass 1922-1942.
- The old school building is shown briefly in the film, *Four Brothers*.
- The student-led civil rights group, By Any Means Necessary ([BAMN](#)), has its largest chapter at Cass.
- On November 25-26 1927 the School Science and Mathematics Association held their annual convention at Cass
- In Summer 2008, Cass Technical High School student [Philip Johnson](#) landed a leading role in the Lifetime Original Movie, *America*.
- Alumnus John Carethers MD named Chairman of the department of Internal Medicine at the University of Michigan Medical School.
- From 2007 to 2009, [Triumph Church](#) of Detroit held a contract with [Detroit Public Schools](#) to conduct a weekly church service at the school's auditorium. [\[citation needed\]](#)

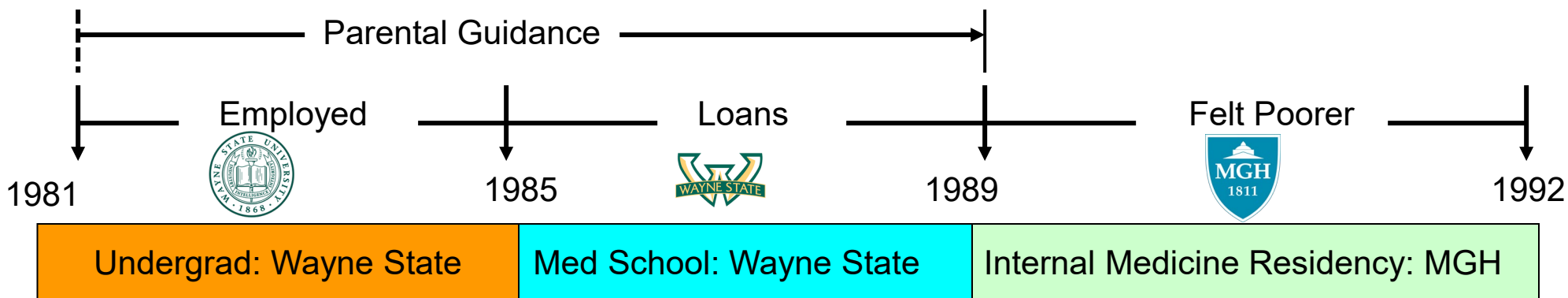


David Alan Grier

Pivotal Moments

- Choosing MD vs MD/PhD
- Post-fellowship – Stay at UM vs leave to go to UCSD
- Receiving mentorship – in science and for life
- Obtaining K08 and later Harold Amos award
- Obtaining first R01
- Being recognized for hard work
- Leadership positions

My Development Pathway



- Majorred in Molecular Biology and Biophysics - Minor in Chemistry
- no real lab experience
- good teachers
- mixed counselor advice
- MCAT in junior year
- role models** at Wayne State
- worked, lived at home



- Picked Wayne State over MSU and Michigan acceptances, turned down other interviews
- studied hard; finished at top of class
- research experience: Plastic Surgery and Endocrinology
- first publications
- borrowed \$ via loans
- lived at home



- Matched at MGH, one of the top programs in country
- no research
- great clinical experience
- lifelong relationships (letter writers)
- explored several fellowship options
- loved medical oncology
- role model** pointed me towards GI
- no duty hour restrictions



What Do I Do Now?

- **Clinician:** see patients that are high-risk for colon cancer
- **Research:** operate a translational laboratory focused on colorectal cancer genetics and disparities (NIH funded)
- **Education:** teach some undergrads (research), medical students, graduate students, residents and fellows (MD); talks nationally/internationally
- **Administration:** oversee Department of Internal Medicine (900 faculty and >1000 staff)
- **National:** involved in national medical organizations important to academic medicine

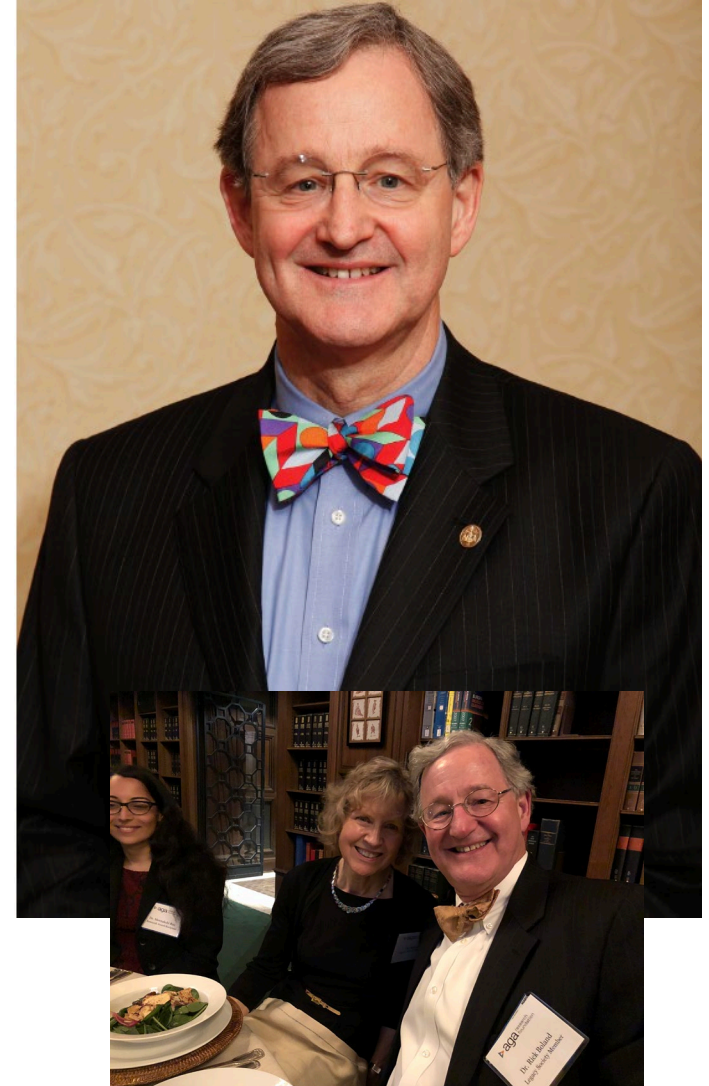
Outline

- My pathway towards independence in academia
 - The developing years with Rick Boland (mentor)
 - Alkylation and DNA MMR
 - 5-Fluorouracil and DNA MMR
 - Hamartomatous Polyposis Syndromes
- The Later Years
 - Measuring DNA MMR dysfunction
 - Inflammation and DNA MMR
 - DNA MMR and Disparities

Developing Years

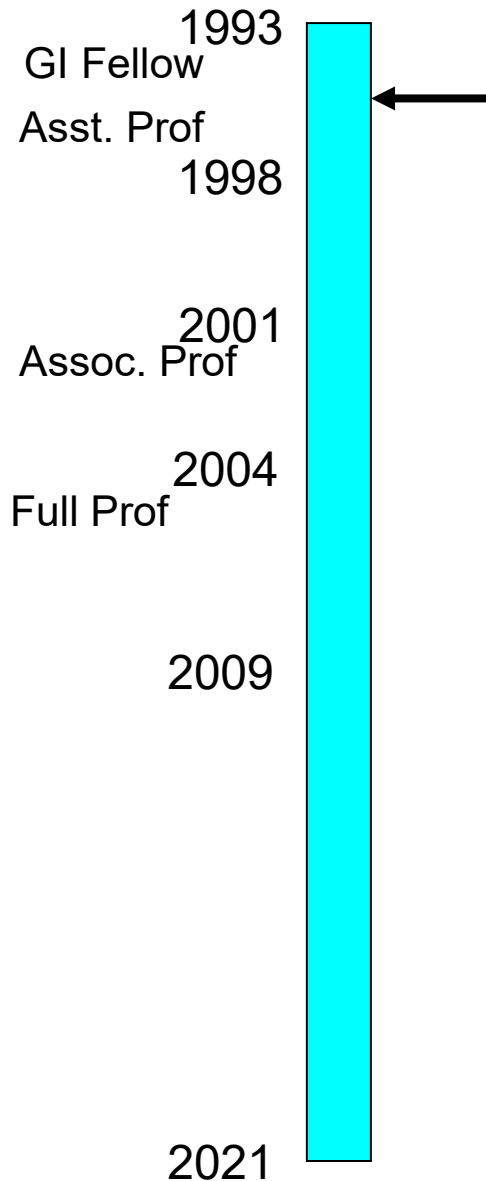
- GI Fellow 1992-1995
 - Joined Rick Boland's Lab in 1993 after his sabbatical
 - Juichi Sato, Minoru Koi, Gene Kraus, Mary Hawn, Sanjeev Cherian, Giancarlo Marra, DP Chauhan
 - Irwin Goldstein, Tom Kunkel, Asad Umar
 - Took MD Post-doc Summer Course (Steve Weiss)
 - Two projects
 - Major: *Griffonia simplicifolia* 1A4 lectin and apoptosis
 - Minor: alkylation damage and DNA MMR

C. Richard Boland, MD



Rick and Pat Boland

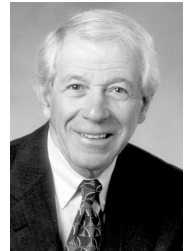
Project Timeline: Lectin



- *Griffonia simplicifolia* 1A4 lectin and apoptosis
- Wrote and obtained:
 - NRSA
 - ADHF grant
- Published ZERO papers



Rick Boland

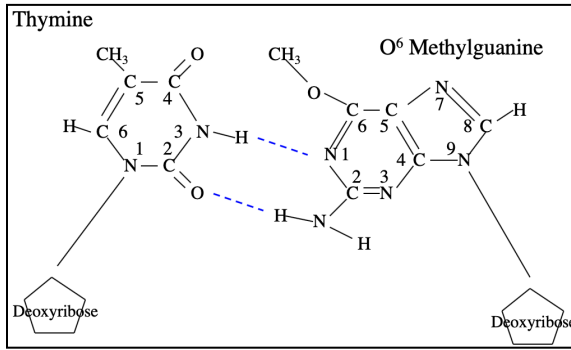


Irwin Goldstein

Lessons Learned

- Not every project becomes successful
- Have a major and minor project that is reasonable to investigate in timeline that you have

Cell Cycle and DNA MMR

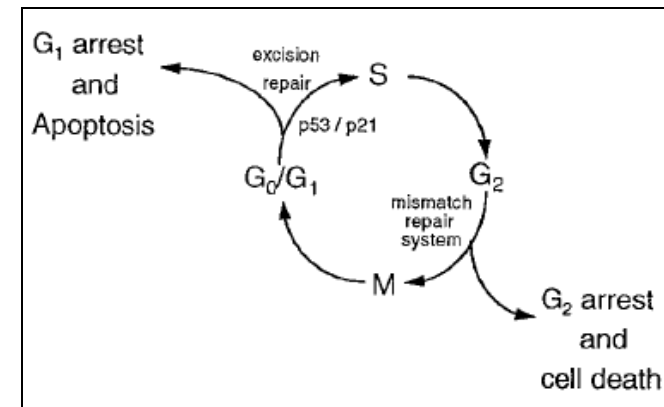
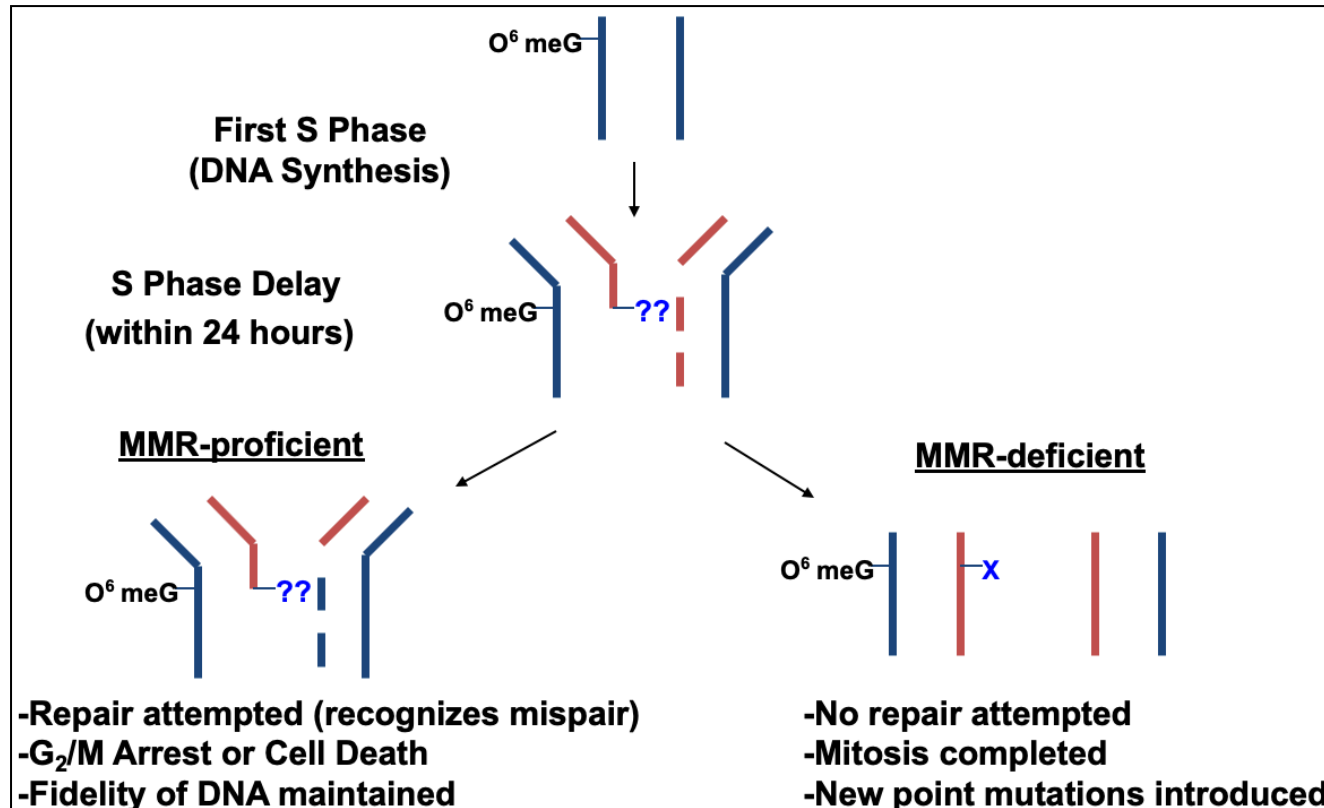


Competency in Mismatch Repair Prohibits Clonal Expansion of Cancer Cells Treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine

John M. Carethers,^{*} Mary T. Hawn,[‡] Dharam P. Chauhan,^{*} Michael C. Luce,[§] Giancarlo Marra,^{*} Minoru Koi,^{||} and C. Richard Boland^{*}

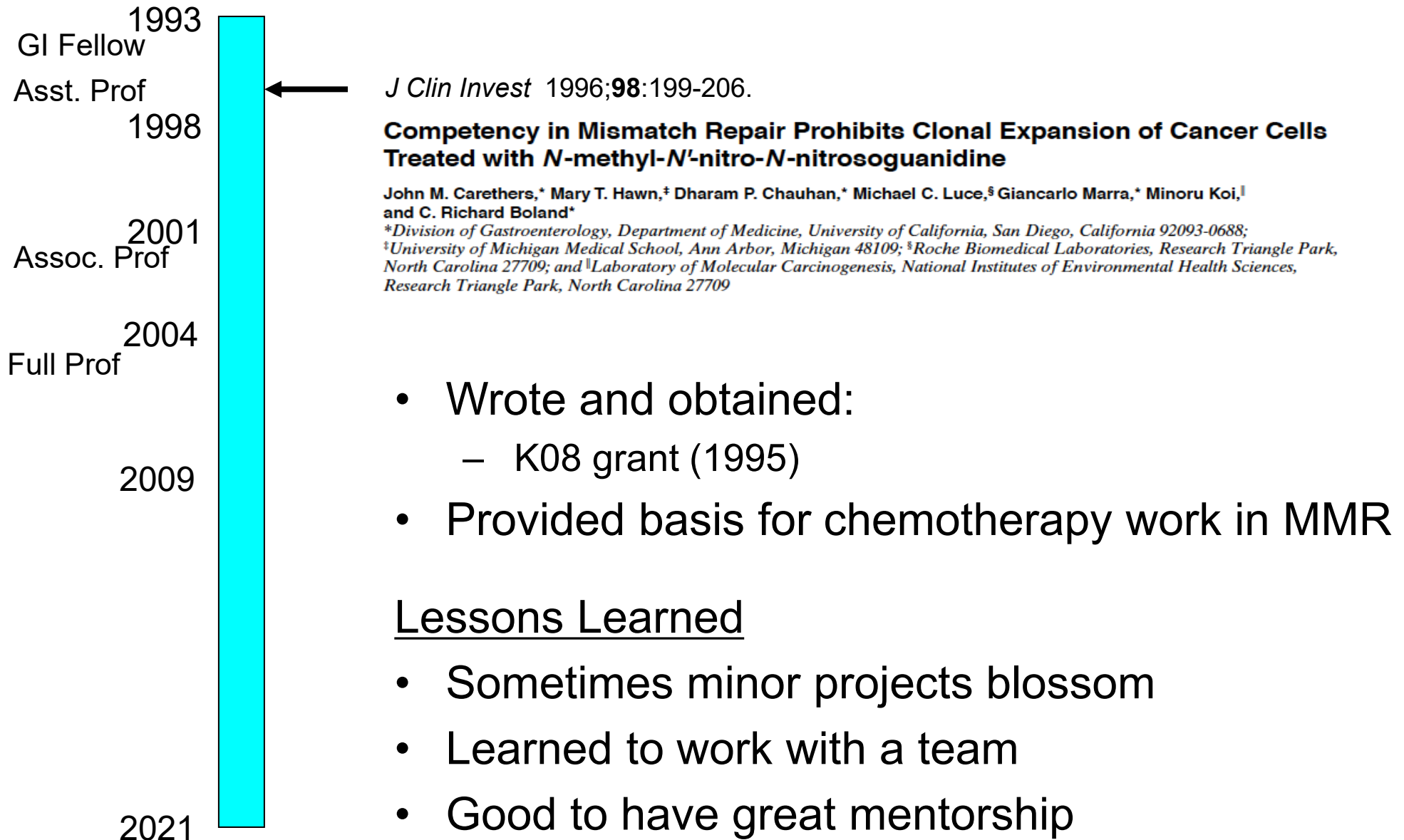
^{*}Division of Gastroenterology, Department of Medicine, University of California, San Diego, California 92093-0688;

[‡]University of Michigan Medical School, Ann Arbor, Michigan 48109; [§]Roche Biomedical Laboratories, Research Triangle Park, North Carolina 27709; and ^{||}Laboratory of Molecular Carcinogenesis, National Institutes of Environmental Health Sciences, Research Triangle Park, North Carolina 27709



MMR = post-synthetic repair

Project Timeline: MMR and Cell Cycle

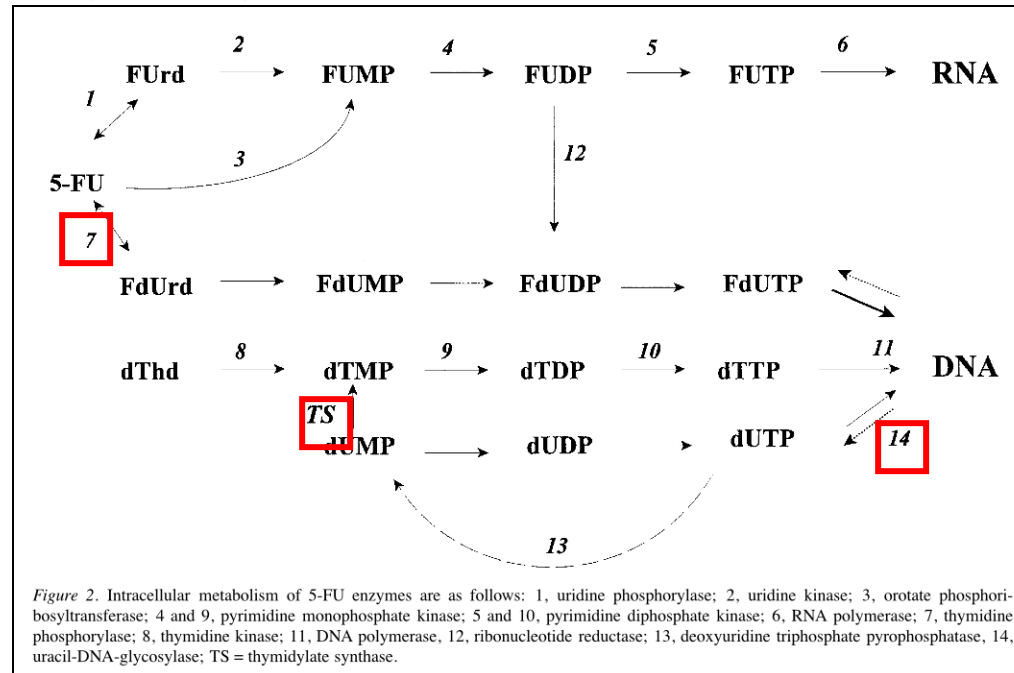
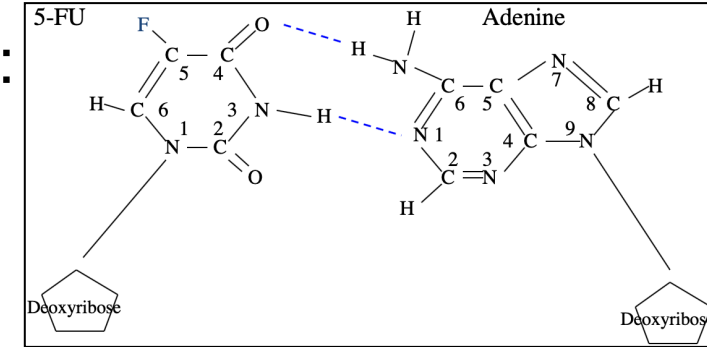


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5-Fluorouracil and Cell Toxicity

- Principle treatment for stage III colorectal cancer
- Cellular toxicity of this fluoropyrimidine due to:
 - Incorporation into all forms RNA
 - Blockage of thymidylate synthetase (TS)
 - Prohibits conversion of dUTP to dTTP
- DNA incorporation reported in breast cancer cells
 - Effect on toxicity thought to be minor mechanism



5-Fluorouracil and DNA MMR

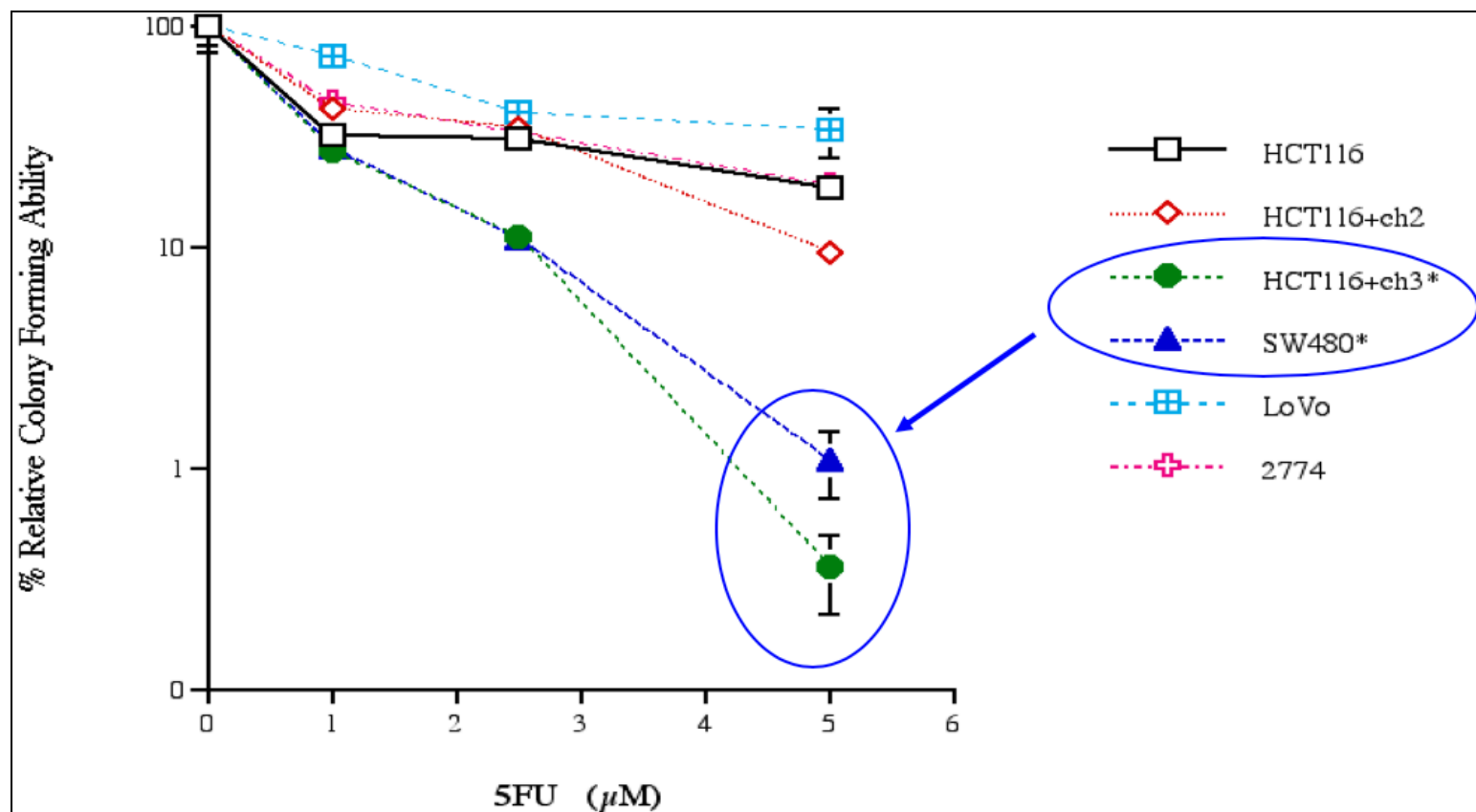
	Day 0	Day 5 0 μ M 5FU	Day 5 5 μ M 5FU
HCT116-GFP	50.6%	53.1%	*64.2%

Enrichment assay of a 50:50 mix of HCT116-GFP and HCT116+ch3 cells *(P<0.05)

Mismatch Repair Proficiency and In Vitro Response to 5-Fluorouracil

JOHN M. CARETHERS,^{*,†} DHARAM P. CHAUHAN,^{*} DANIEL FINK,^{*} SIBYLLE NEBEL,^{*} ROBERT S. BRESALIER,[§] STEPHEN B. HOWELL,^{*,†} and C. RICHARD BOLAND^{*,†,||}

^{*}Department of Medicine and [†]Cancer Center, University of California, and ^{||}Veterans Affairs Medical Center, San Diego, California; and [§]Henry Ford Hospital, Detroit, Michigan



5-Fluorouracil and CRC Patient Survival

Analysis	No. of Patients	P Value
<u>Based on MSI Status</u>		
MSI-H overall	36	0.99
non-MSI-H overall	168	
MSI-H with 5-FU	10	0.74
Non-MSI-H with 5-FU	56	
MSI-H without 5-FU	26	0.998
non-MSI-H without 5-FU	112	
<u>Based on 5-FU Status</u>		
No 5-FU overall	138	
5-FU overall	66	
No 5-FU with MSI-H	26	
5-FU with MSI-H	10	
No 5-FU with non-MSI-H	112	
5-FU with non-MSI-H	56	

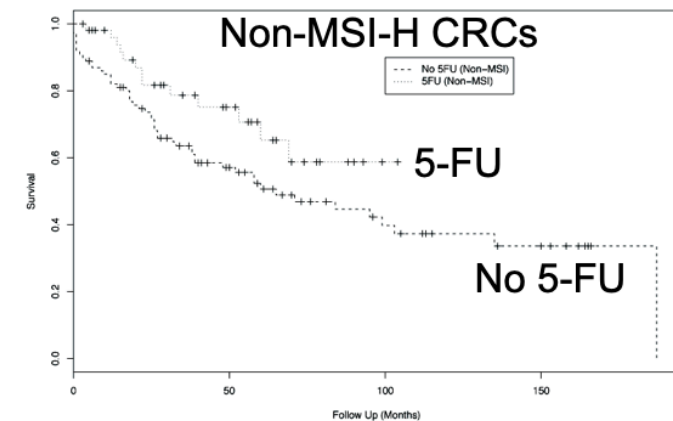
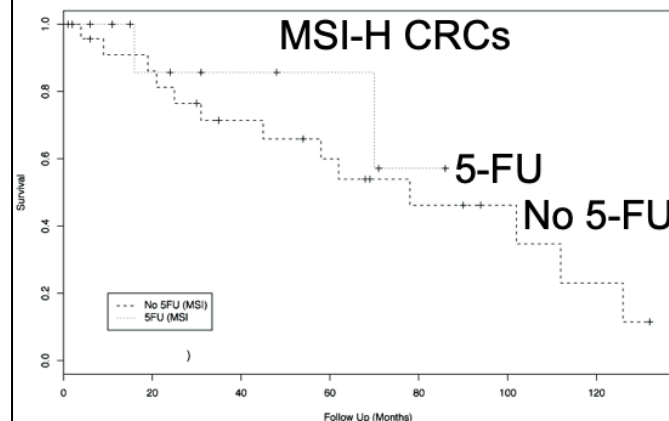
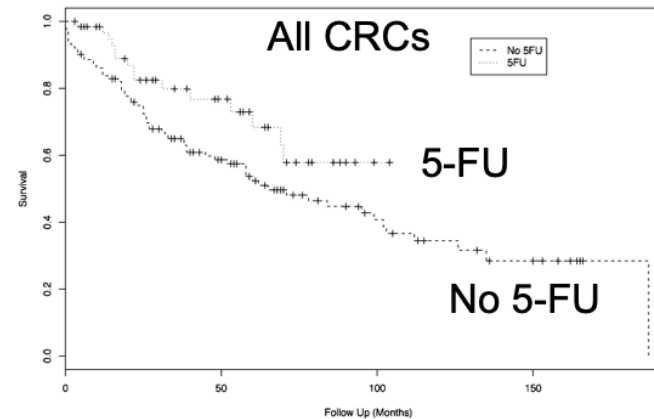
Use of 5-Fluorouracil and Survival in Patients With Microsatellite-Unstable Colorectal Cancer

JOHN M. CARETHERS,*†,§,¶ E. JULIETA SMITH,¶ CYNTHIA A. BEHLING,|| LANCHINH NGUYEN,* AKIHIRO TAJIMA,* RYAN T. DOCTORO,¶ BETTY L. CABRERA,¶ AJAY GOEL,* CHRISTIAN A. ARNOLD,* KATSUMI MIYAI,||,§ and C. RICHARD BOLAND*,§

*Department of Medicine, University of California, San Diego, California; †Cancer Center, University of California, San Diego, California; ‡Veterans Administration Research Service, San Diego, California; §Veterans Medical Research Foundation, San Diego, California; and

¶Department of Pathology, University of California, San Diego, California

No patient benefit with 5-FU for MSI-H CRC



Studies of 5-FU Treatment, Survival and MSI Status

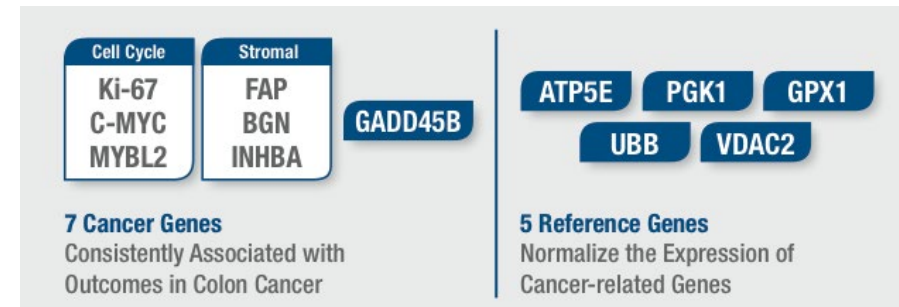
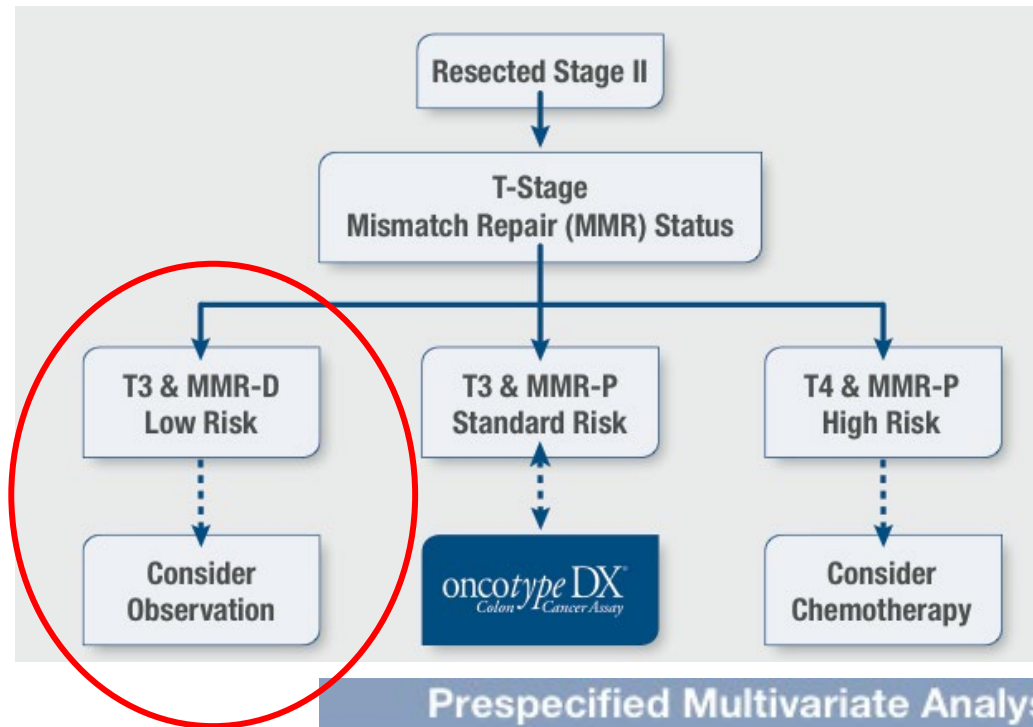
Table 3. Chemotherapy in Colorectal Cancer with Microsatellite Instability

First author	Year	Study design	Adjuvant chemotherapy regimen	No. of patients (MSI/MSS)	Benefit of chemotherapy in patients with MSI
Elsaleh ¹³⁵	2000	Consecutive patients	5-FU	63/669	Yes
Ribic ¹⁴¹	2003	Randomized controlled study	5-FU	95/475	No
Carethers ⁹⁴	2004	Consecutive patients	5-FU	36/168	No
de Vos tot Nederveen Cappel ¹⁴³	2004	Lynch syndrome patients	5-FU	28/0	No
Storojeva ¹³⁶	2005	Randomized controlled study	5-FU/mitomycin	21/139	No
Benatti ¹⁴²	2005	Consecutive patients	5-FU	256/1007	No
Popat ⁵¹	2005	Pooled data from multiple studies	5-FU	1277/6365	No
Lanza ¹³⁷	2006	Consecutive patients	5-FU	75/288	No
Jover ¹³⁸	2006	Consecutive patients	5-FU	66/688	No
Kim ¹²⁶	2007	Prospective study	5-FU/leucovorin	98/444	No
Des Guetz ¹³⁹	2009	Meta-analysis	—	454/2871	No
Bertagnolli ¹⁴⁰	2009	Randomized controlled study	5-FU/irinotecan/leucovorin	106/677	No

5-FU, 5-fluorouracil; MSS, microsatellite stable.

5FU may shorten survival in some MMR-deficient patients.

Stage II Prediction of CRC Behavior



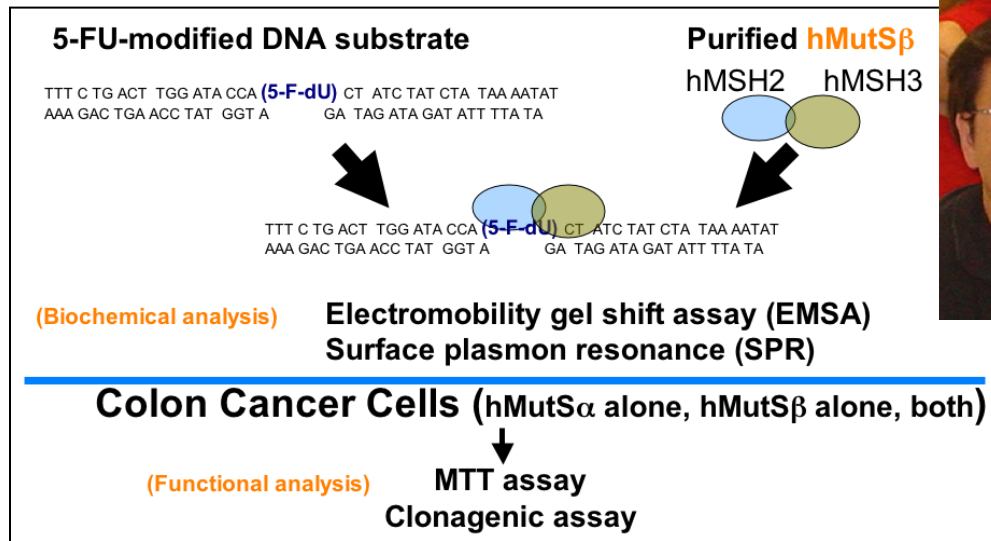
Gene Expression Levels Determine the Recurrence Score® (RS) Result¹

$$RS = +0.15 \times \text{Stromal Group} - 0.30 \times \text{Cell Cycle Group} + 0.15 \times \text{GADD45B}$$

Prespecified Multivariate Analysis, Surgery-Alone Patients (n=605)^{1,5}

Variable	Categories	Hazard Ratio (HR)	HR 95% CI	P Value
Recurrence Score	Continuous per 25 Units	1.61	(1.13, 2.29)	.008
MMR	13% Deficient vs 87% Proficient	0.32	(0.15, 0.69)	<.001
T-Stage	15% T4 vs 85% T3	1.83	(1.23, 2.75)	.005
Tumor Grade	29% High vs 71% Low	0.62	(0.40, 0.96)	.026
Number of Nodes Examined	62% <12 vs 38% ≥ 12	1.47	(1.01, 2.14)	.040
Lymphovascular Invasion	13% Present vs 87% Absent	1.40	(0.88, 2.23)	.175

5-Fluorouracil and MMR Mechanism



The Mismatch Repair Complex hMutS α Recognizes 5-Fluorouracil-Modified DNA: Implications for Chemosensitivity and Resistance

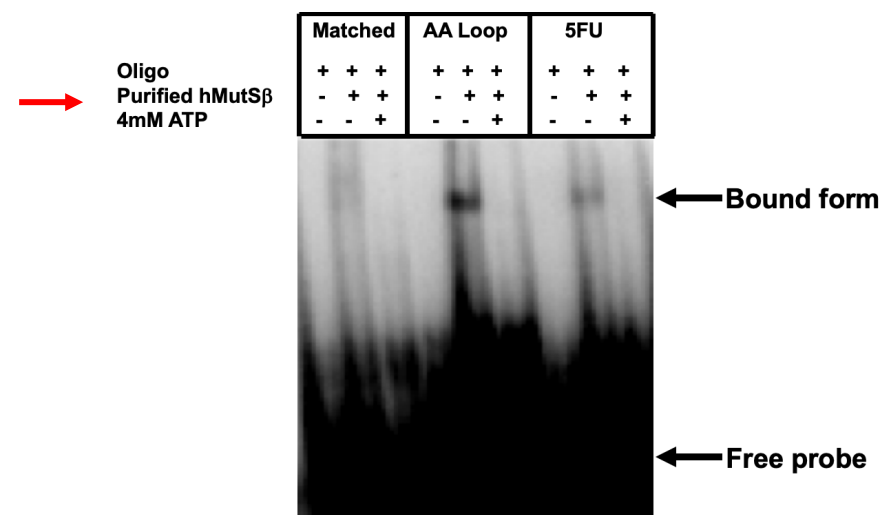
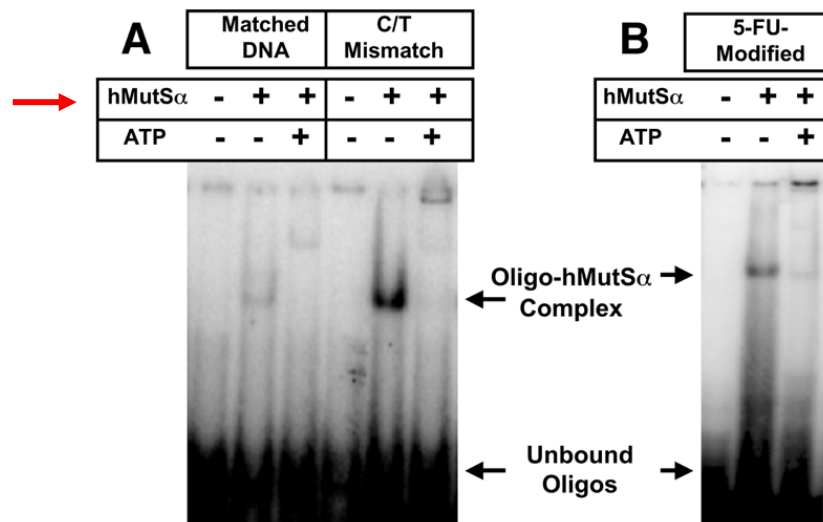
AKIHIRO TAJIMA,^{*,†} MARTIN T. HESS,[§] BETTY L. CABRERA,[†] RICHARD D. KOLODNER,^{*,§,¶} and JOHN M. CARETHERS^{*,†,||,¶}

^{*}Department of Medicine University of California, La Jolla, California; [†]Veterans Medical Research Foundation, San Diego, California; [§]Ludwig Institute for Cancer Research, La Jolla, California; [¶]Rebecca and John Moores Comprehensive Cancer Center, University of California, La Jolla, California; and ^{||}Veterans Administration Research Service, San Diego, California

Both hMutS α and hMutS β DNA Mismatch Repair Complexes Participate in 5-Fluorouracil Cytotoxicity

Akihiro Tajima^{2,3}, Moriya Iwaizumi^{1,2,3}, Stephanie Tseng-Rogenski¹, Betty L. Cabrera², John M. Carethers^{1,2,3*}

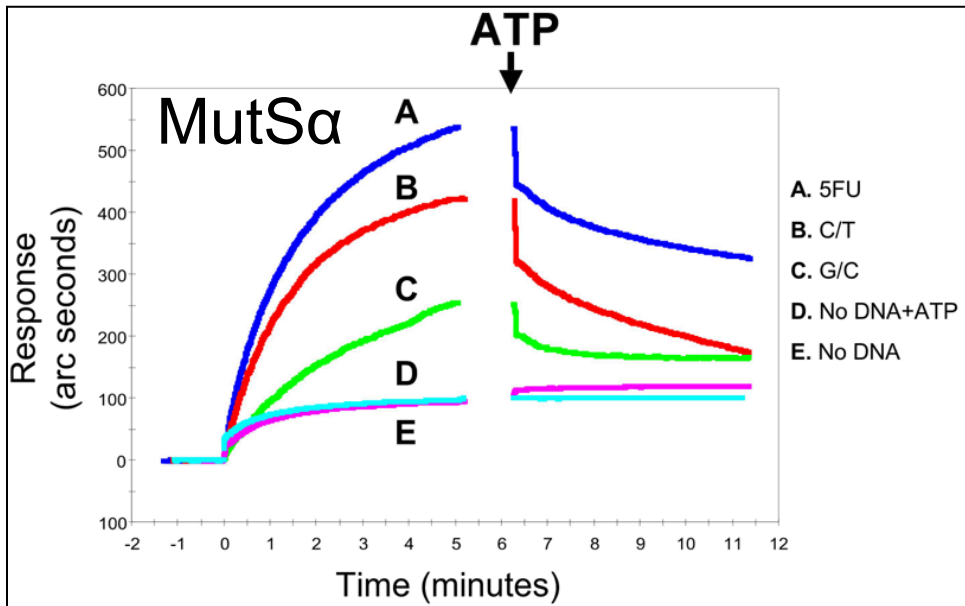
¹ Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States of America, ² Division of Gastroenterology, Department of Medicine, University of California San Diego, La Jolla, California, United States of America, ³ Moores Comprehensive Cancer Center, University of California San Diego, La Jolla, California, United States of America



Gastroenterology 2004;127:1678-1684

PLoS One 2011;6:e28117

5-Fluorouracil and MMR Mechanism



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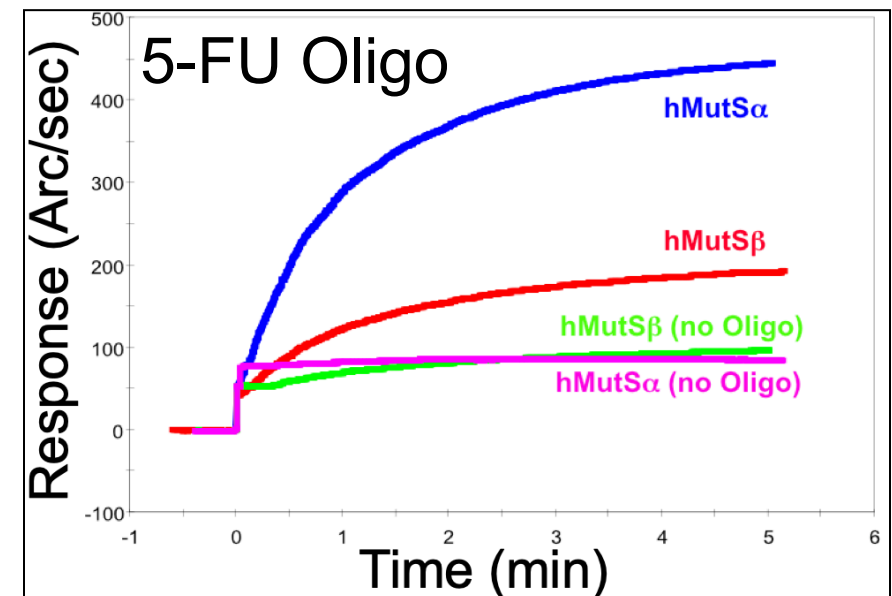
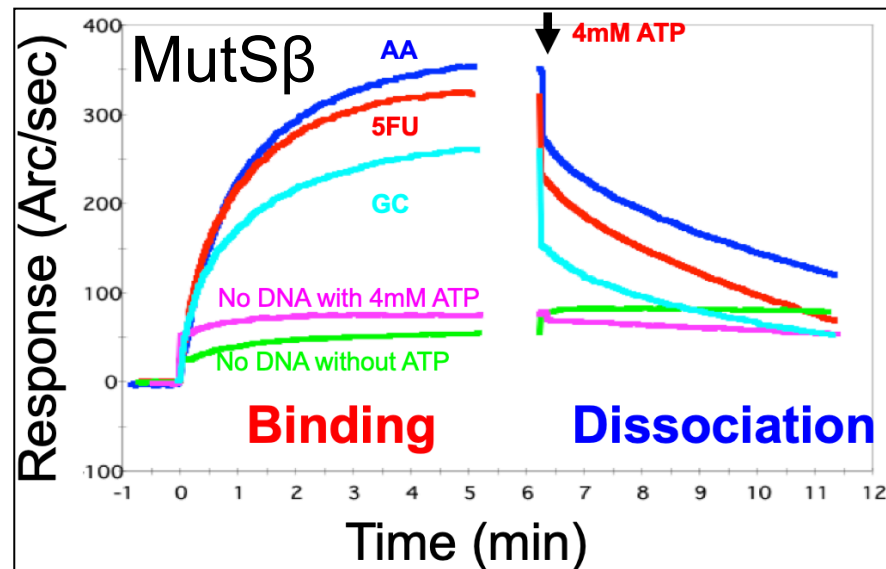
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5-Fluorouracil and MMR Mechanism

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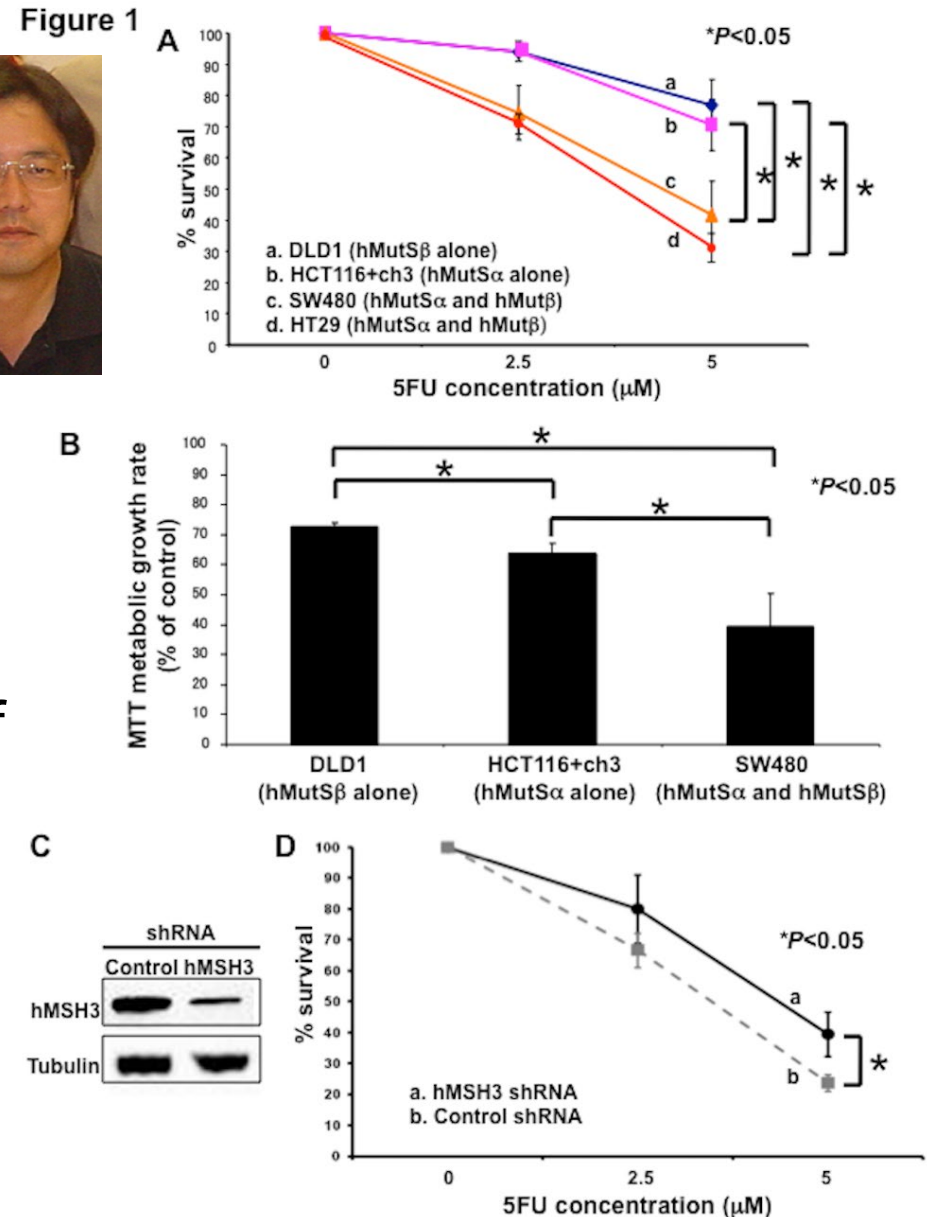
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- Clonogenic assays
- MTT growth assay
- Relative binding parallels degree of cell death

Figure 1

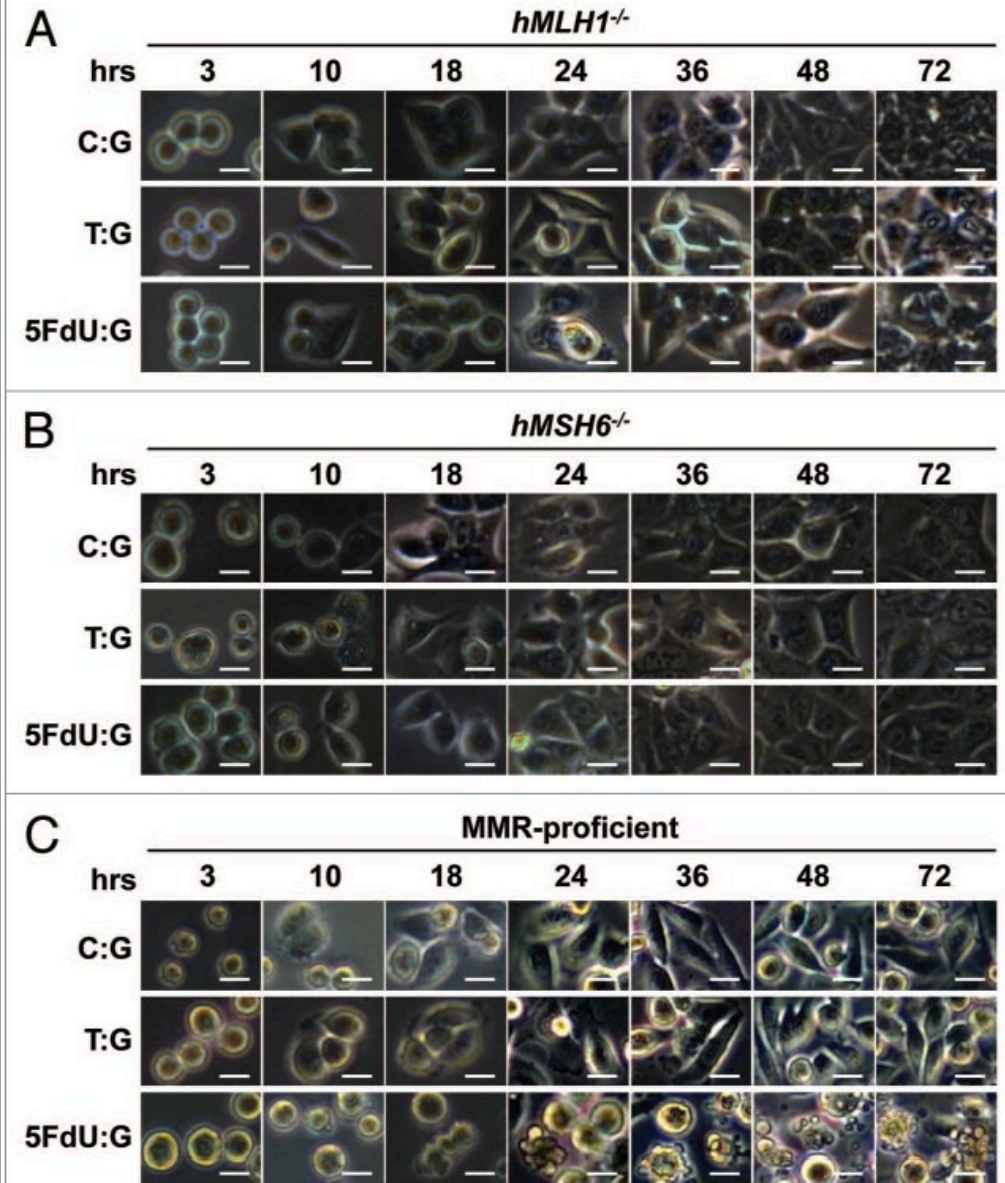
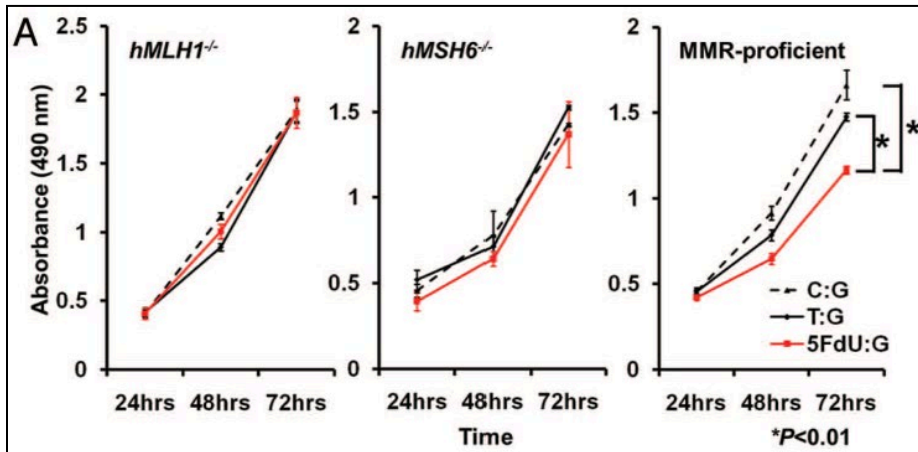
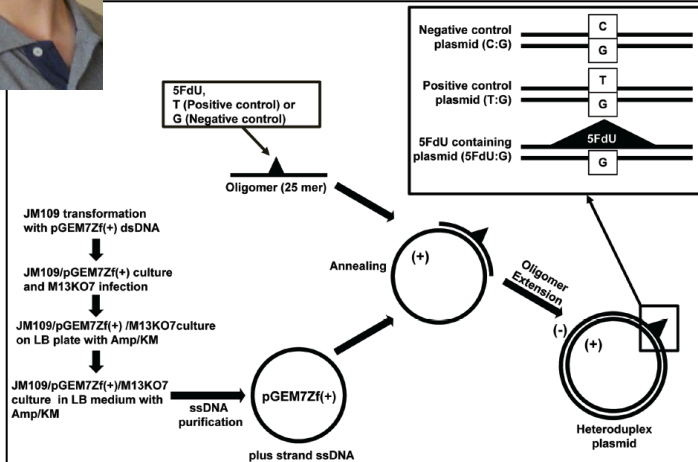
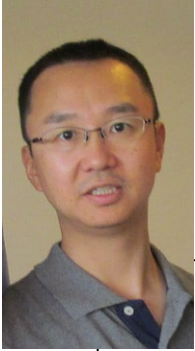


5-Fluorouracil and MMR Mechanism

DNA mismatch repair proficiency executing 5-fluorouracil cytotoxicity in colorectal cancer cells

Moriya Iwaizumi, Stephanie Tseng-Rogenski and John M. Carethers*

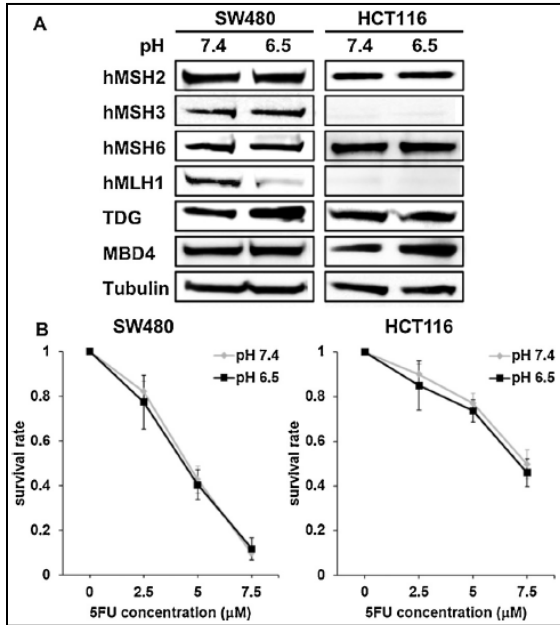
Division of Gastroenterology; Department of Internal Medicine; University of Michigan; Ann Arbor, MI USA



Plasmid 5-FU recognized by MMR for cell death

Cancer Biol Ther 2011;12:756-764

BER Can Rescue MMR-Deficient Recognition of 5-FU



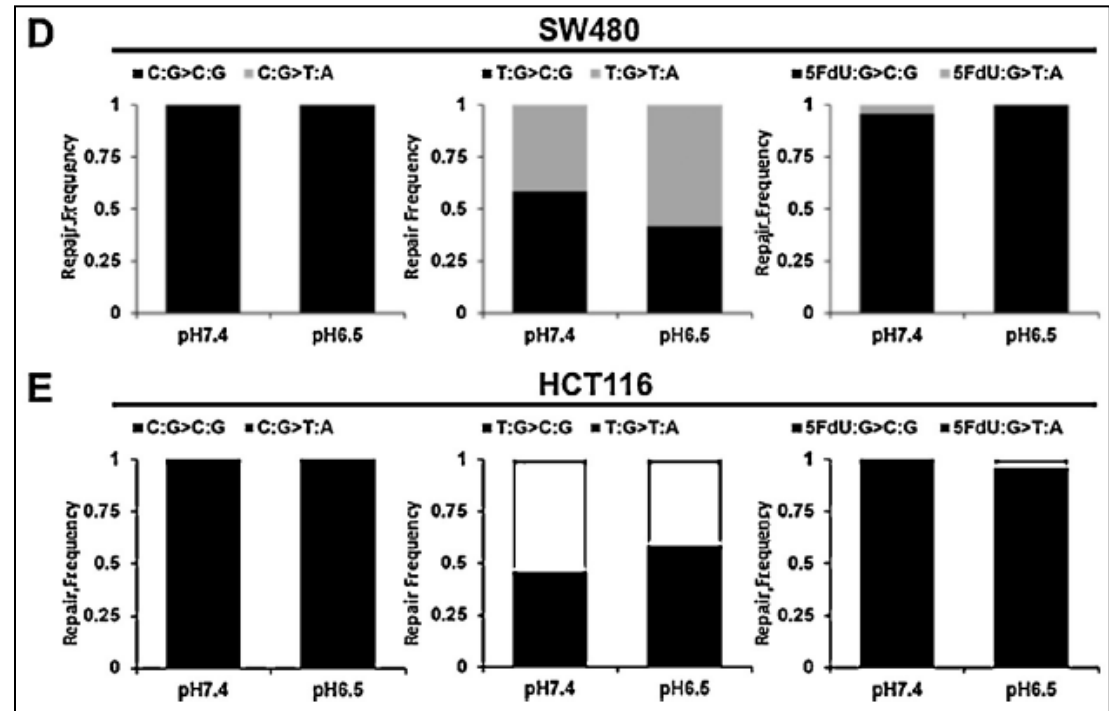
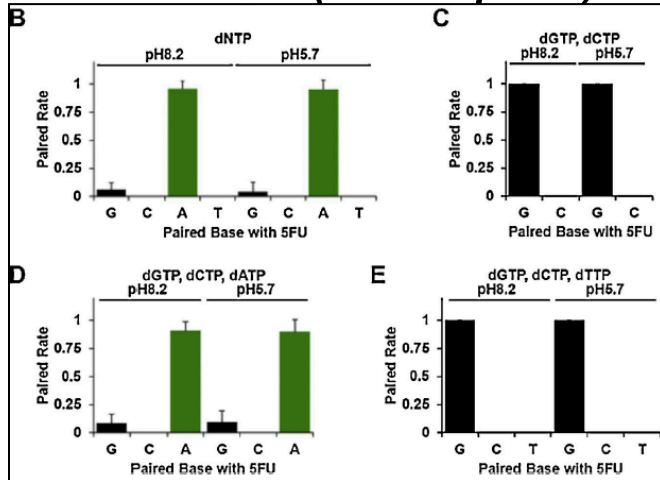
Acidic tumor microenvironment downregulates *hMLH1* but does not diminish 5-fluorouracil chemosensitivity

Moriya Iwaizumi, Stephanie Tseng-Rogenski, John M. Carethers*

Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States

In vitro, with BER and +/- MMR

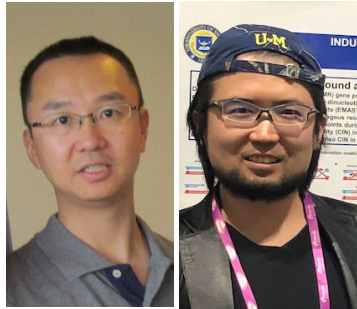
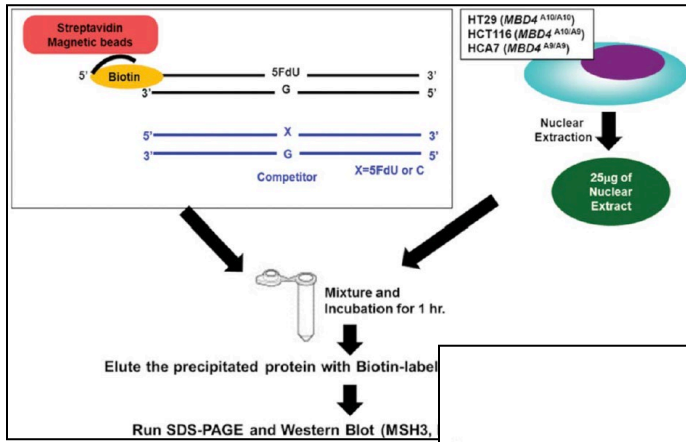
In silico (no repair)



5FdU:G repaired to C:G even w/o MLH1

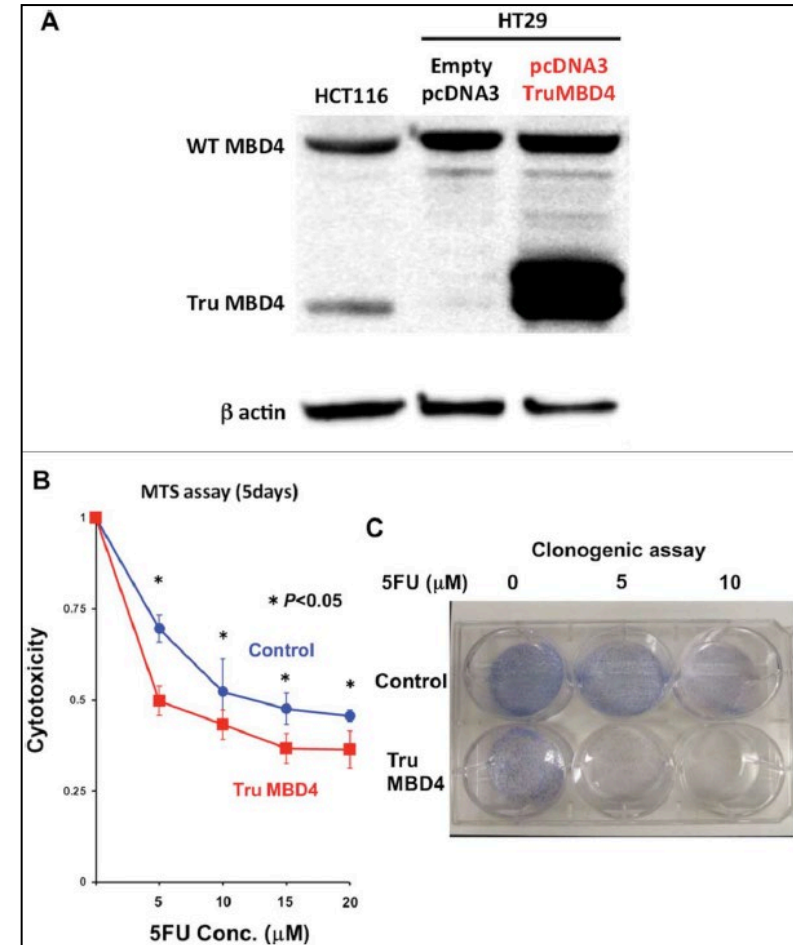
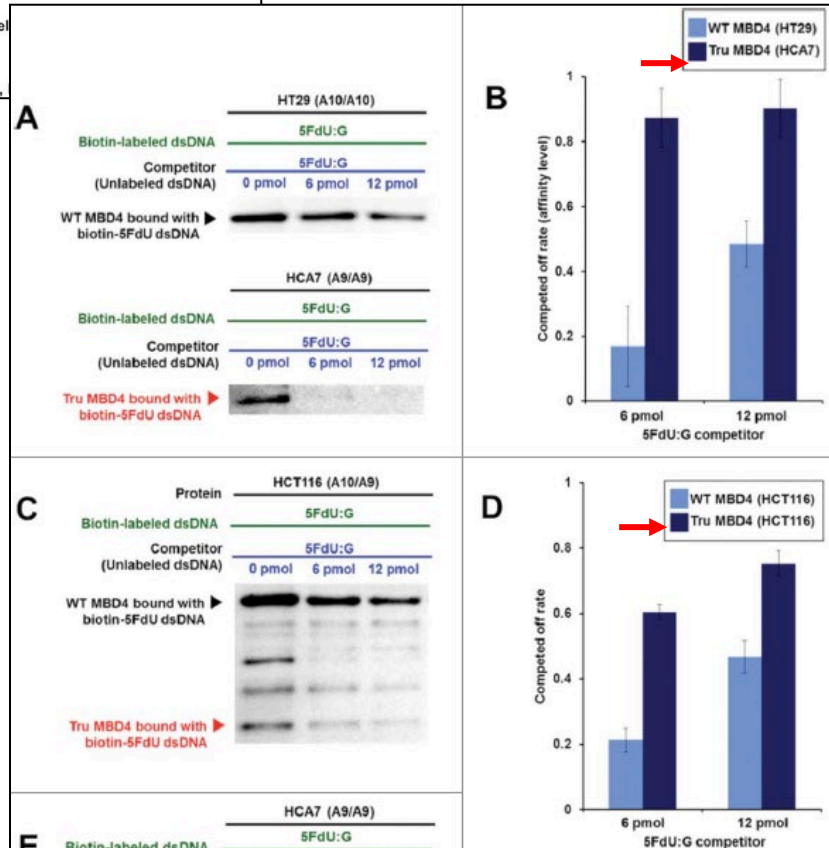
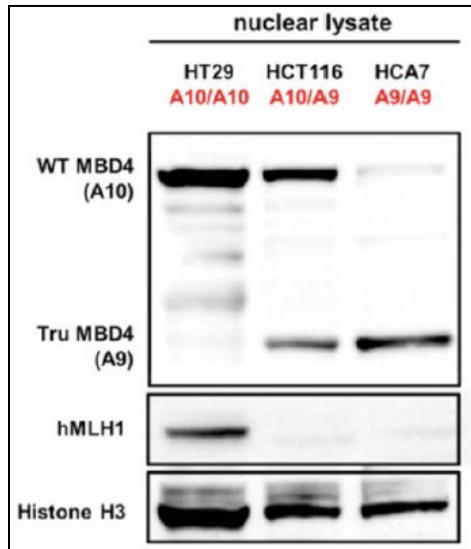
5FdU pairs with A>G

MBD4 Mutation Modifies 5-FU Sensitivity by MMR

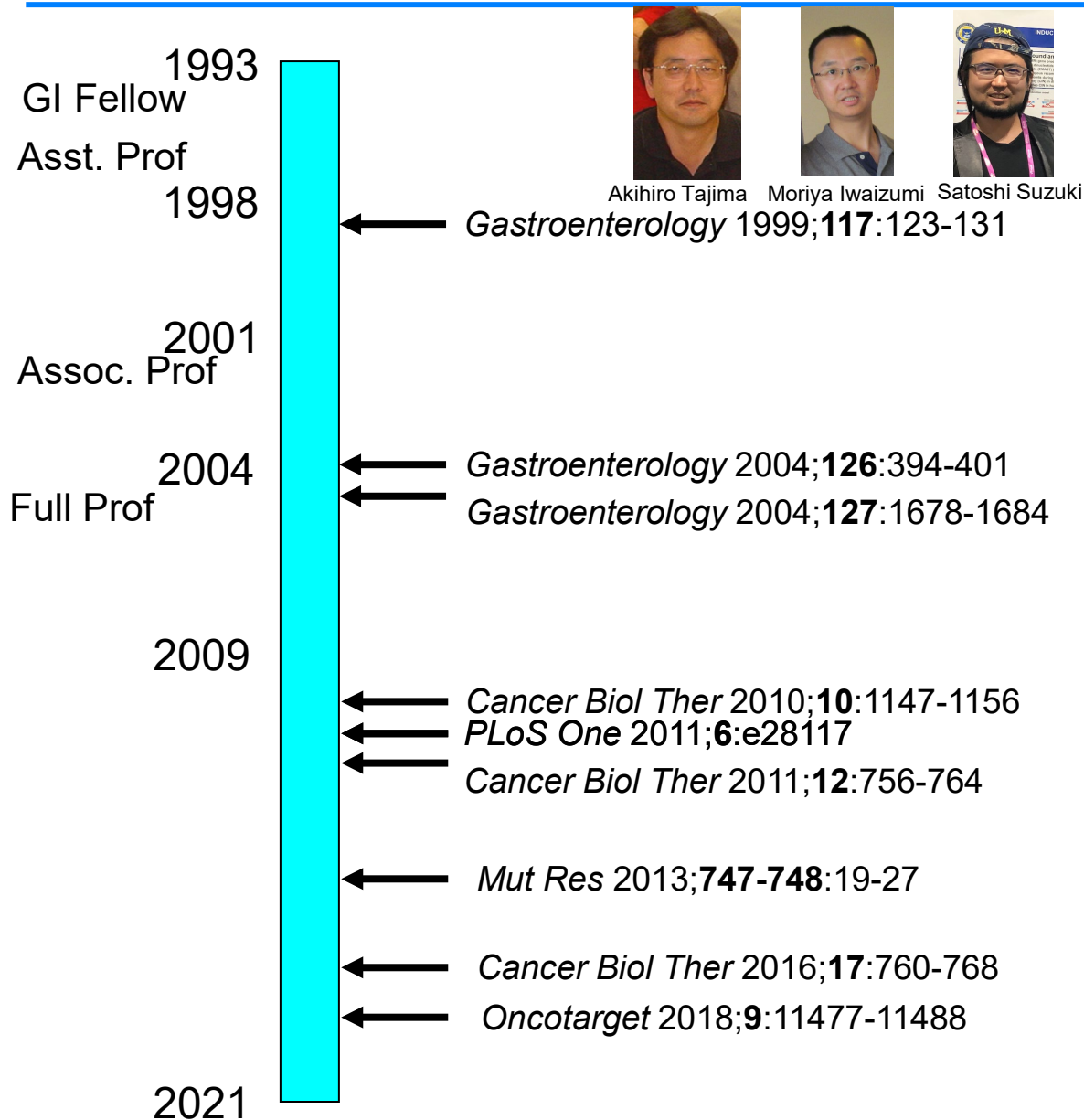


Production of truncated MBD4 protein by frameshift mutation in DNA mismatch repair-deficient cells enhances 5-fluorouracil sensitivity that is independent of *hMLH1* status

Satoshi Suzuki^a, Moriya Iwaizumi^{a,b}, Stephanie Tseng-Rogenski^b, Yasushi Hamaya^{a,b}, Hiroaki Miyajima^a, Shigeru Kanaoka^c, Ken Sugimoto^a, and John M. Carethers^b



Project Timeline: 5FU and MMR



- Extended work from K08
 - Formed basis for other MMR work
 - Followed a query from mentor
- Never funded by NIH
 - California and Foundation funding

Lessons Learned

- Great collaboration
- There is competition out there when you present at meetings
- Tell a story and follow through on it
- Basis for several recognition awards over time

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Bannayan-Riley-Ruvalcaba Syndrome

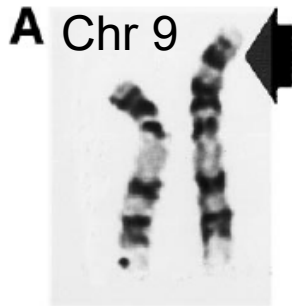


Localization of the Bannayan–Riley–Ruvalcaba Syndrome Gene to Chromosome 10q23

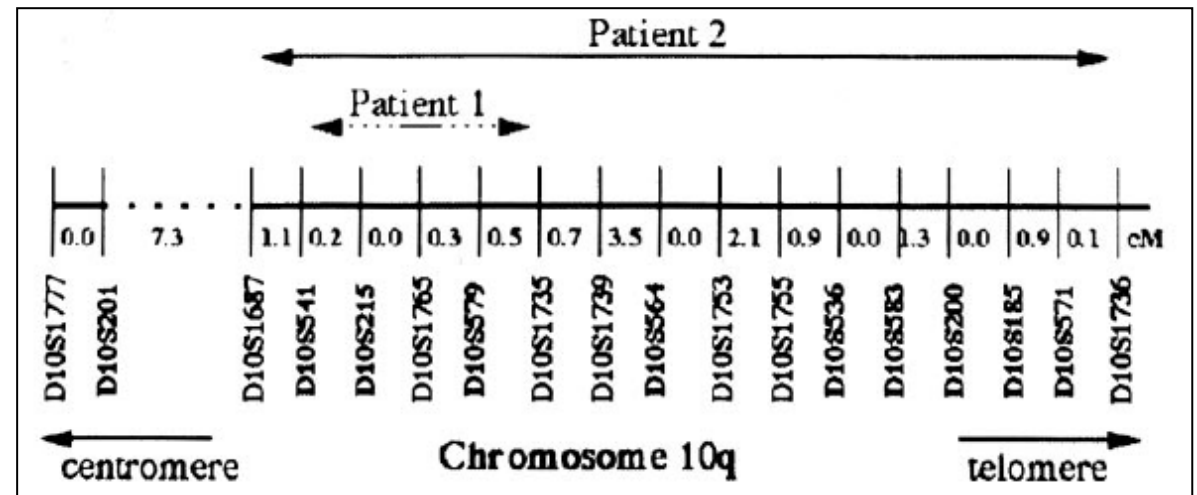
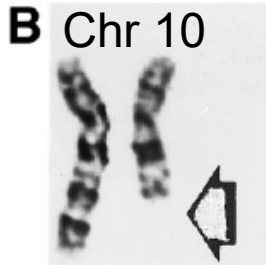
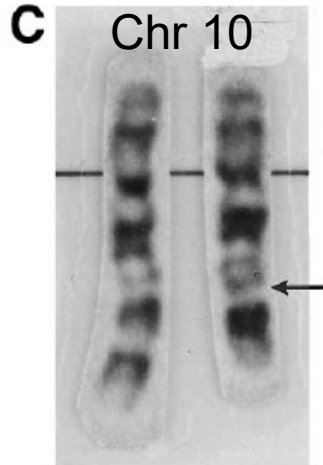
ANDREW F. ZIGMAN,* JOEL E. LAVINE,[‡] MARILYN C. JONES,^{‡,§} C. RICHARD BOLAND,^{||,¶,‡} and JOHN M. CARETHERS^{||,¶}

*Department of Surgery, ^{||}Division of Gastroenterology, Department of Medicine, [‡]Department of Pediatrics, and [¶]Cancer Center, University of California, and [§]Veterans Affairs Medical Center, San Diego; and [§]Children's Hospital, San Diego, California

Patient 1



Patient 2

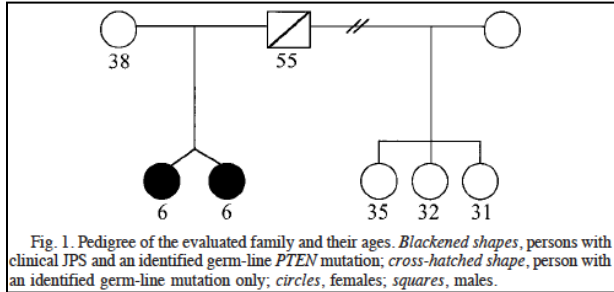


Patient 1: 46,XY,der(9)t(9;10)(p24.1;q 24.1),d er(10)del(10)(q23.2q24.1)t(9;1 0)(p24.1;q 23.2)

Patient 2: 46,XX,del(10)(q23.1q24.2)

Precise mapping showed overlap with Cowden's disease

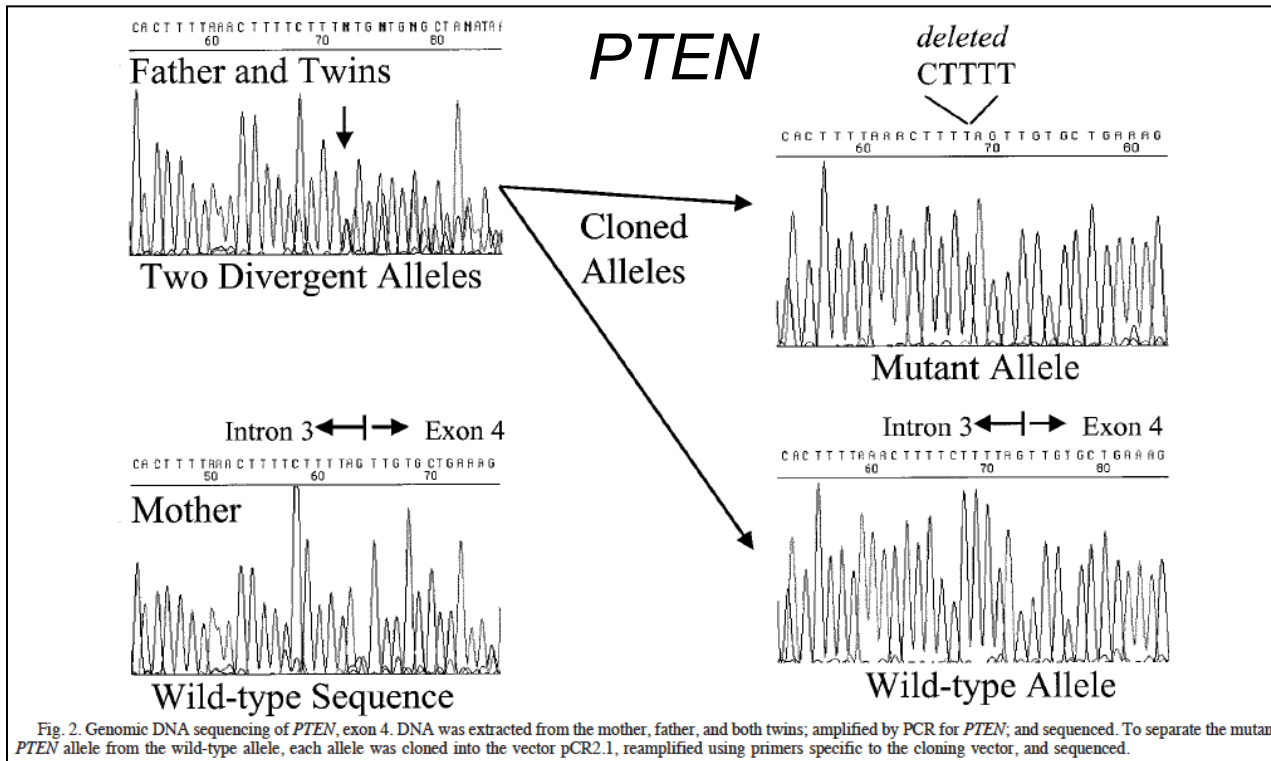
Unusual Phenotype with *PTEN* Mutation



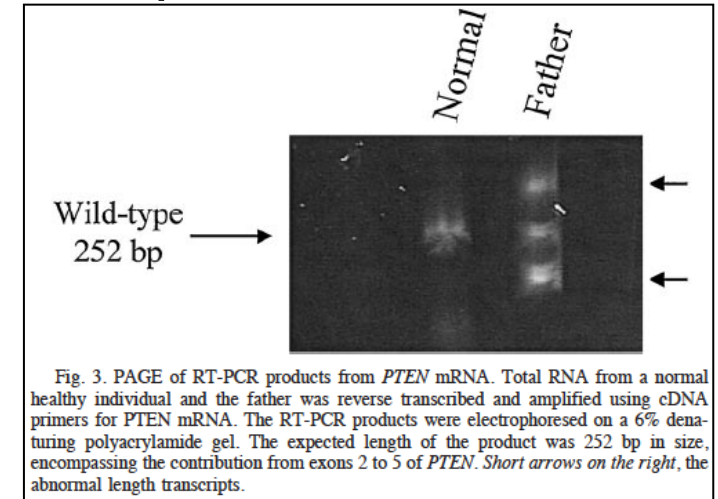
Genetic Heterogeneity in Familial Juvenile Polyposis¹

Sherry C. Huang, Christine R. Chen, Joel E. Lavine, Sharon F. Taylor, Robert O. Newbury, Thu-Thao T. Pham, Luigi Ricciardiello, and John M. Carethers²

Division of Gastroenterology and Nutrition, Department of Pediatrics [S.C.H., J.E.L., S.F.T.], and Division of Gastroenterology, Department of Medicine, and Cancer Center [C.R.C., T.T.T.P., L.R., J.M.C.], University of California, San Diego, California 92093; Department of Pathology, Children's Hospital, San Diego, California 92123 [R.O.N.], Veteran's Administration Research Service, San Diego, California 92161 [J.M.C.]



PTEN splice site variants



Germline *PTEN* mutation but phenotypically JPS

Genetics of Hamartomatous Polyposis Syndromes

(*disorganized* but mature tissue or cells indigenous to the site of origin)

Hamartomatous Syndrome	Chromosomal Location	Mutated Gene	Frequency in Germline
<u><i>PTEN</i> Hamartoma Syndrome</u>			
Cowden's Disease	10q22-23	<i>PTEN/MMAC1/TEP1</i>	>80%
Lhermitte-Duclos variant			
Bannayan-Riley-Ruvalcaba Syndrome	10q22-23	<i>PTEN/MMAC1/TEP1</i>	~60%
1997			
Juvenile Polyposis Syndrome	18q21.1	<i>SMAD4</i>	~20%
(with HHT overlap)	10q22-23	<i>BMPR1A/ALK3</i>	~25%
1998, 2001, 2005	9q34	<i>ENG</i>	?
Peutz-Jeghers Syndrome	19p13.3	<i>STK11/LKB1</i>	70-90%
1997			
Hereditary Mixed Polyposis Syndrome	15q13-q14 duplication	<i>GREM1</i> overexpression	?
2003/*2012			
Hyperplastic (Serrated) Polyposis Syndrome	17q22	<i>RNF43</i> (extremely rare)	?
1996-	?1p	<i>May not be familial</i>	

Nature Genetics* 2012;44**:699-703

BMP Signaling is Growth Suppressive in CRCs

Table 1. Genetic characteristics of the various cell lines used in this study

Cell Line	Microsatellite Status	Key Affected Genes	Key Restored Genes
HCT116	MSI-H	ACVR2, TGFBR2, hMLH1	
HCT116 + chr3	MSS	ACVR2	TGFBR2, hMLH1
HCT116 + chr2	MSI-H	TGFBR2, hMLH1	ACVR2
SW480	MSS	SMAD4	

MSI-H, high microsatellite instability; MSS, microsatellite stable; ACVR2, activin receptor 2; TGFBR2, transforming growth factor (TGF)- β receptor type 2; hMLH1, human mlh homolog 1.

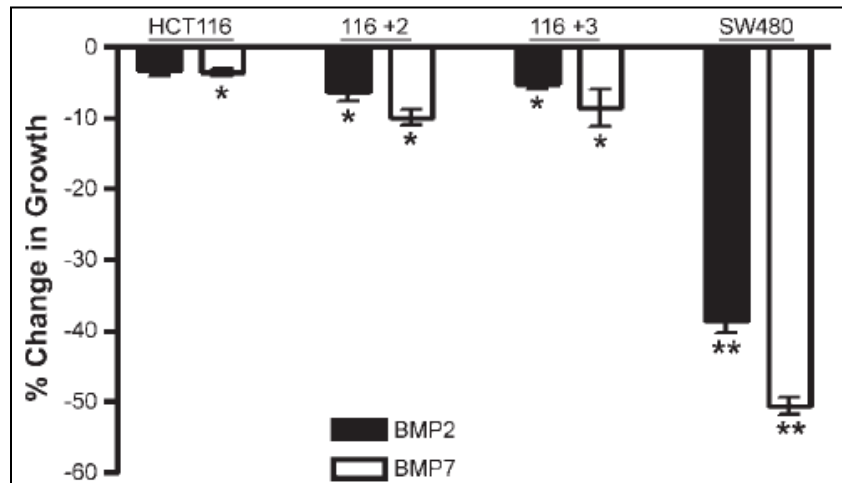


Fig. 3. Effect of BMP2 or BMP7 treatment on cell growth as assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in HCT116, HCT116 + chr2, HCT116 + chr3, and SW480 cells. Two-factor with replications ANOVA was used to determine P values: * $P < 0.05$ and ** $P < 0.01$.



Bone morphogenetic protein signaling and growth suppression in colon cancer

Stayce E. Beck,^{1,4} Barbara H. Jung,¹ Antonio Fiorino,¹ Jessica Gomez,¹ Eunice Del Rosario,¹ Betty L. Cabrera,¹ Sherry C. Huang,² Jimmy Y. C. Chow,¹ and John M. Carethers^{1,3,4,5,6}

Departments of ¹Medicine and ²Pediatrics, ³Rebecca and John Moores Comprehensive Cancer Center, and ⁴Biomedical Sciences Program, University of California, and ⁵Veterans Administration Research Service and ⁶Veterans Medical Research Foundation, San Diego, California

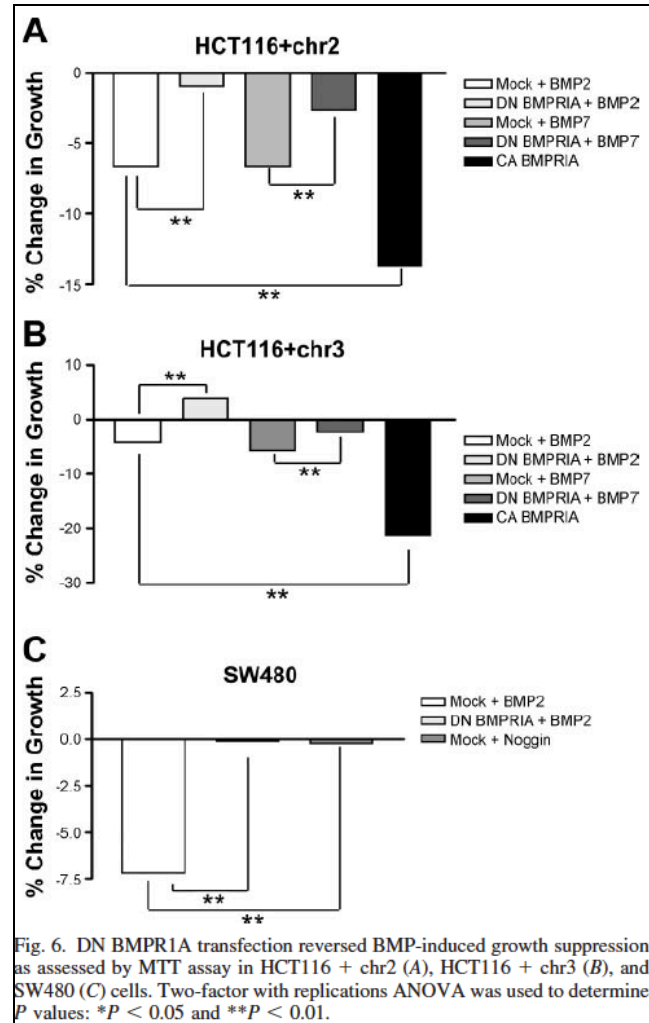
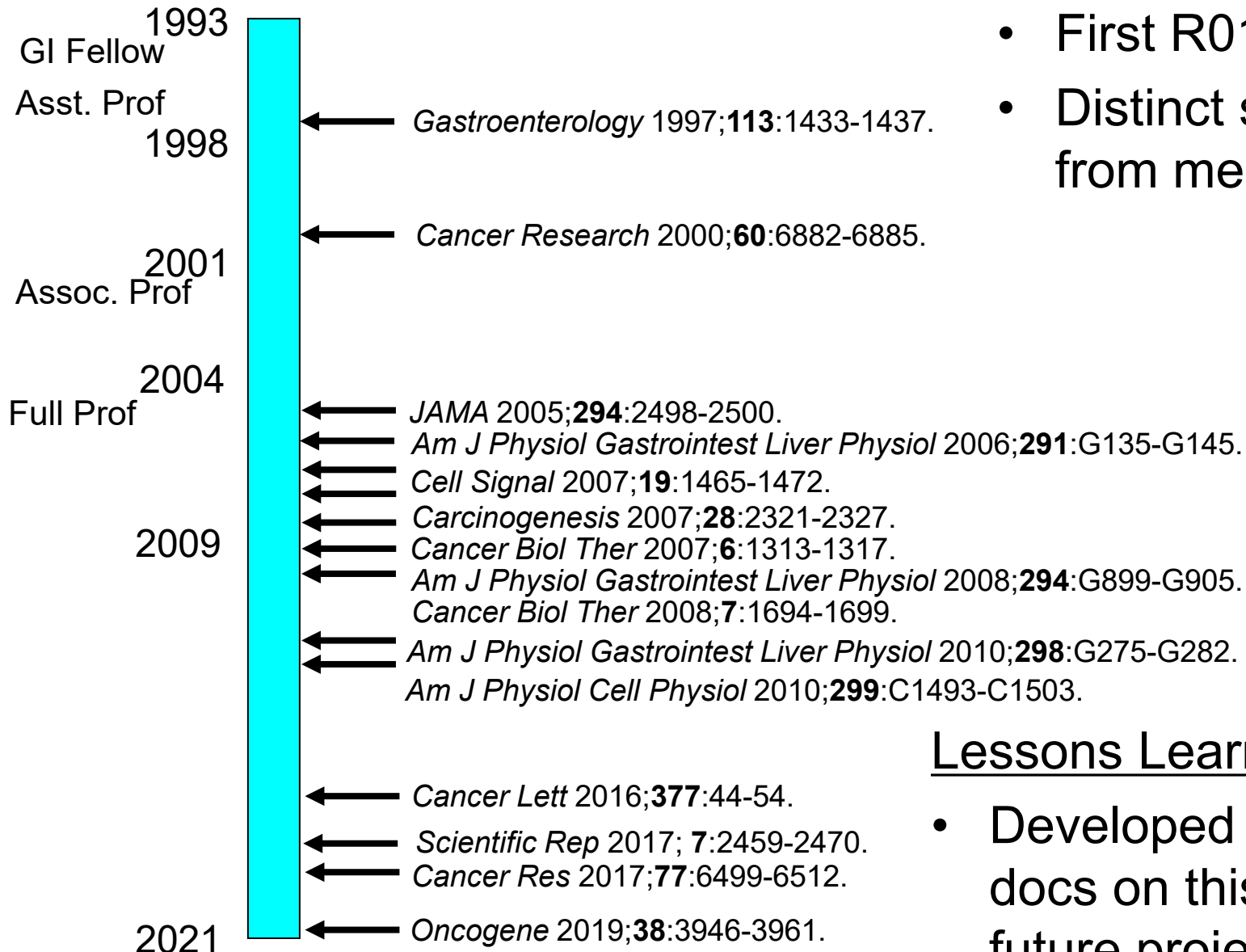


Fig. 6. DN BMPRIA transfection reversed BMP-induced growth suppression as assessed by MTT assay in HCT116 + chr2 (A), HCT116 + chr3 (B), and SW480 (C) cells. Two-factor with replications ANOVA was used to determine P values: * $P < 0.05$ and ** $P < 0.01$.

BMP suppression can be SMAD4-independent

Project Timeline: Hamartomatous Pathways



- First R01 on this subject
- Distinct separate project from mentor



Andrew Zigman



Sherry Huang



Stayce Beck



Jimmy Chow

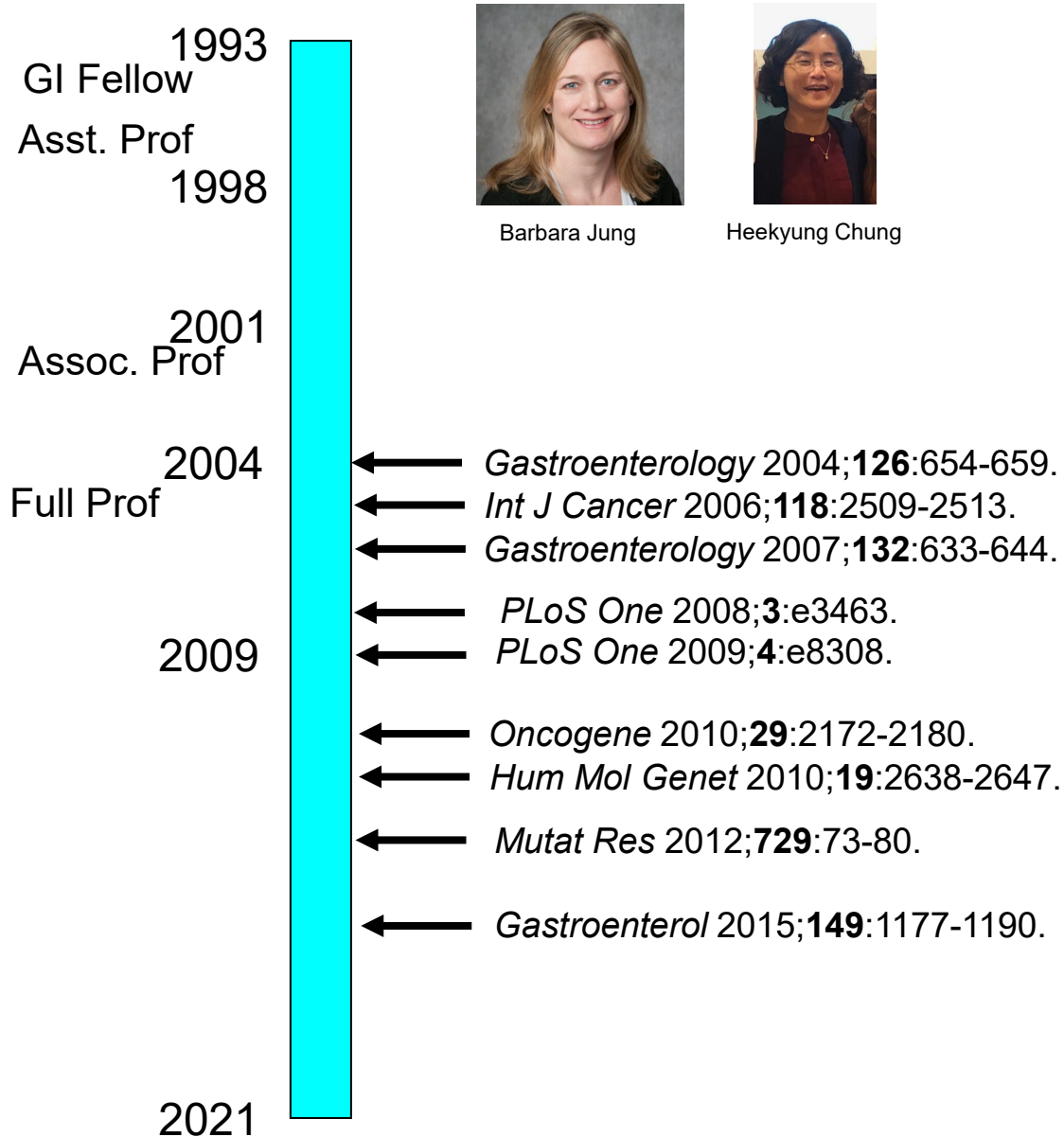
Lessons Learned

- Developed Pre-docs and Post-docs on this project for their future projects

Outline

- My pathway towards independence in academia
 - The developing years with Rick Boland (mentor)
 - Alkylation and DNA MMR
 - 5-Fluorouracil and DNA MMR
 - Hamartomatous Polyposis Syndromes
- The Later Years
 - Measuring DNA MMR dysfunction
 - Inflammation and DNA MMR
 - DNA MMR and Disparities

Project Timeline: MMR and Target Mutations

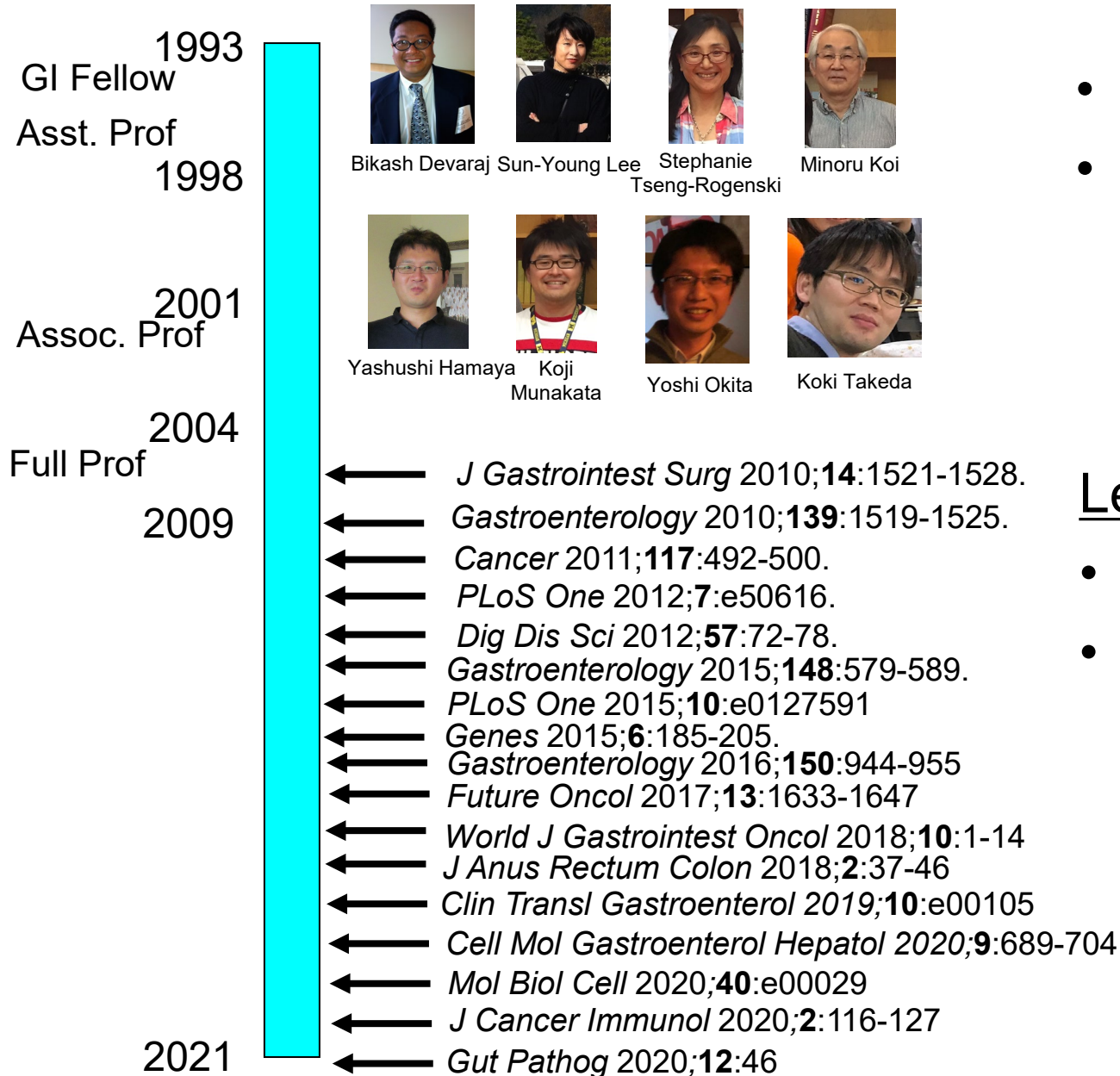


- NIH R01 and VA Merit funded
- Able to measure mutations in real time

Lessons Learned

- Trained great post-docs who now went on to bigger things and took project with them

Project Timeline: MMR and Inflammation



- NIH funded
- Describe relatively new MMR pathway

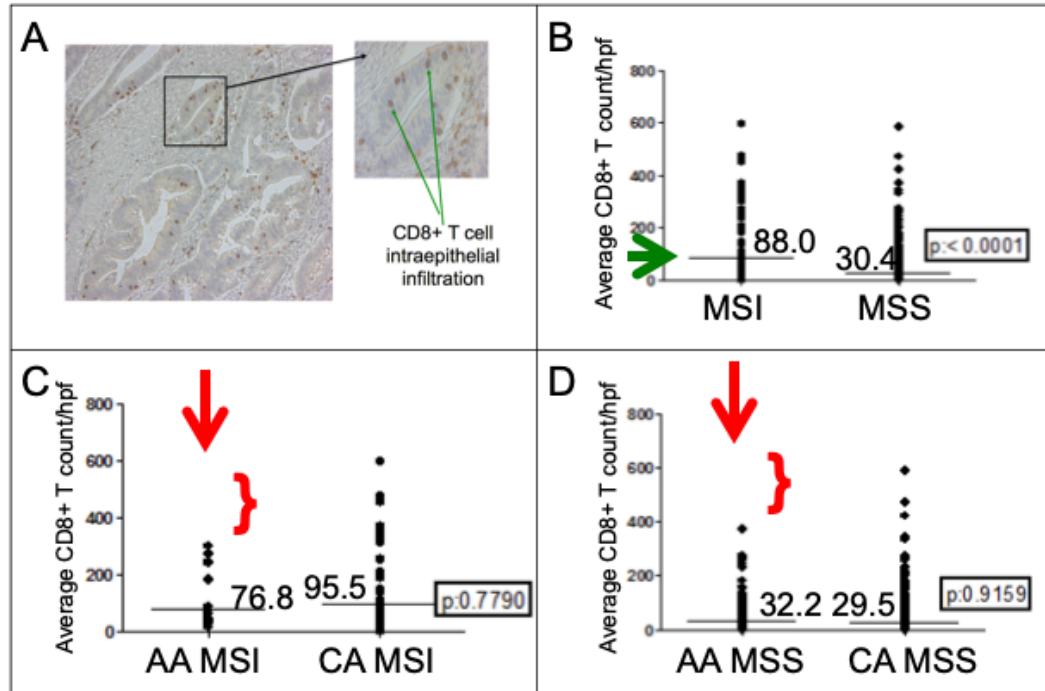
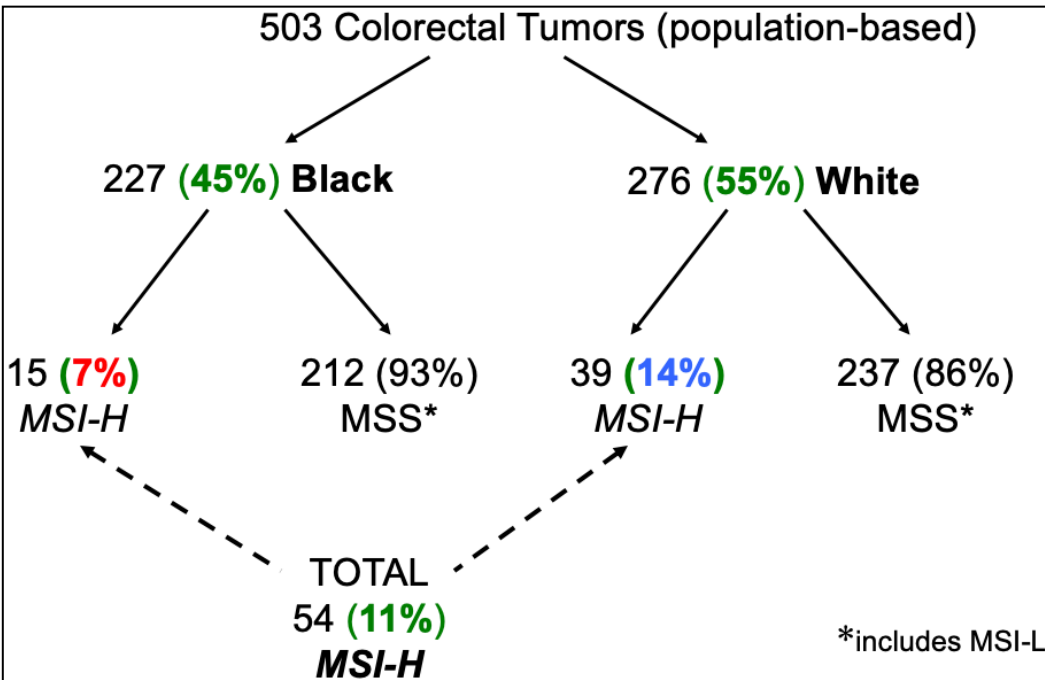
Lessons Learned

- Still discovering things
- Great projects for post-docs

Prevalence of MSI in AA CRCs

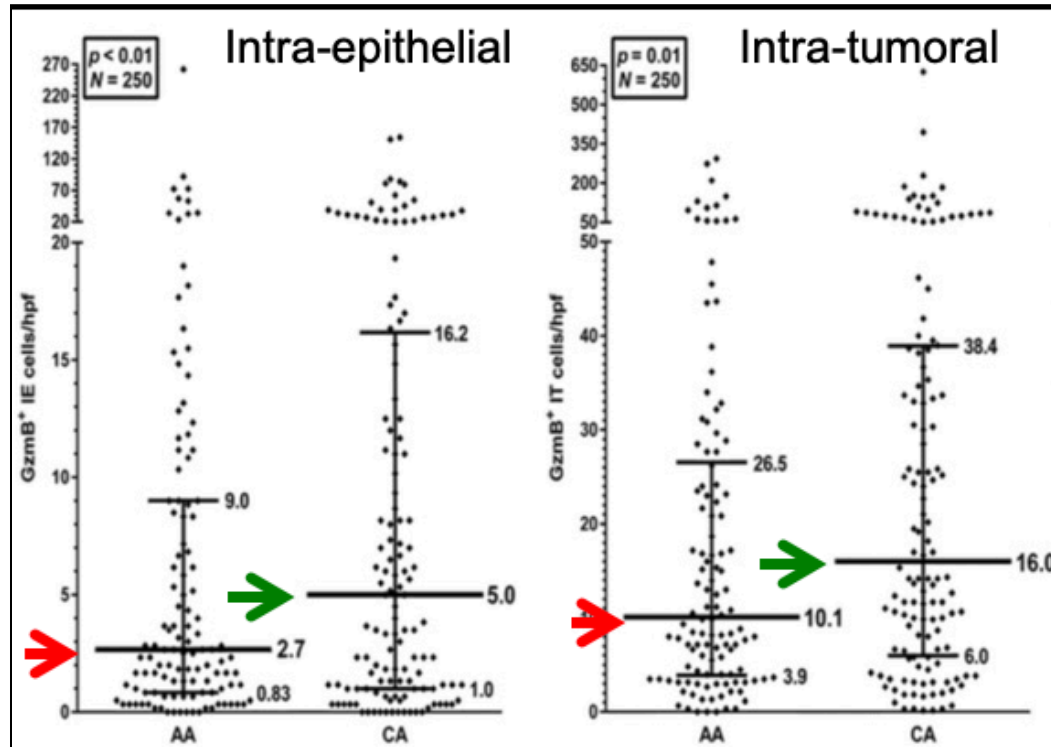
Influence of Race on Microsatellite Instability and CD8⁺ T Cell Infiltration in Colon Cancer

John M. Carethers^{1,4,6,*†}, Bhavya Murali^{2,3}, Bing Yang^{2,3}, Ryan T. Doctolero^{4,3}, Akihiro Tajima^{4,3}, Ranor Basa², E. Julieta Smith⁴, Monte Lee², Ryan Janke², Tina Ngo², Ruth Tejada², Ming Ji³, Matthew Kinseth², Betty L. Cabrera⁴, Katsumi Miyai⁵, Temitope O. Keku⁷, Christopher F. Martin⁷, Joseph A. Galanko⁸, Robert S. Sandler^{7,8}, Kathleen L. McGuire^{2†}



- CD8⁺ T cells are higher in MSI CRCs
- AA MSI and MSS CRCs **lack high counts of CD8⁺ T cells** c/w CA MSI and MSS CRCs

Immune Cell Population in AA CRCs



RESEARCH ARTICLE

Decreased Anti-Tumor Cytotoxic Immunity among Microsatellite-Stable Colon Cancers from African Americans

Ranor C. B. Basa¹*, Vince Davies¹*, Xiaoxiao Li¹*, Bhavya Murali¹*, Jinel Shah¹*, Bing Yang¹*, Shi Li², Mohammad W. Khan¹, Mengxi Tian¹, Ruth Tejada¹, Avan Hassan¹, Allen Washington, Jr¹, Bhramar Mukherjee², John M. Carethers³†, Kathleen L. McGuire¹‡*

- AA MSS CRCs show **reduced granzyme B⁺ T cells**
- Implications for less cytotoxicity for tumor cells

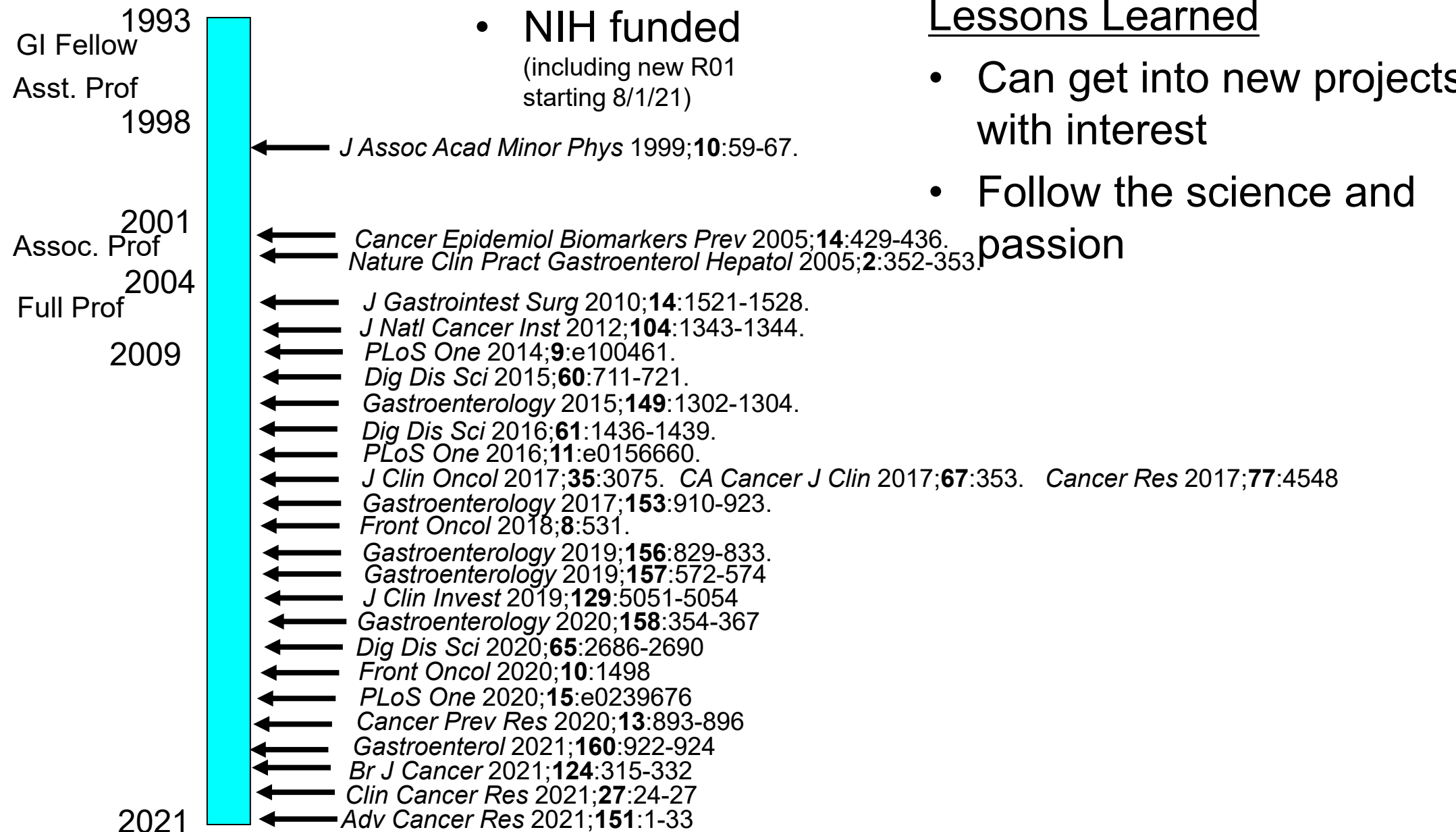
Cell Infiltration Markers	African American						Caucasian						Unadjusted Model	Adjusted Model
	N	mean	s.d.	median	range		N	mean	s.d.	median	range		P Value*	P value*
CD8 Intraepithelial	124	64.7	61.8	52.1	0.0	371.7	134	68.6	83.7	41.8	0.0	587.7	0.83	0.92
CD57 Intraepithelial	117	10.0	19.3	3.7	0.0	140.8	128	12.9	28.1	3.8	0.0	164.8	0.55	0.49
CD57 Intratumoral	117	51.7	55.6	29.8	0.0	298.0	128	62.8	69.9	38.2	0.2	362.3	0.32	0.94
GzmB Intraepithelial	118	10.2	27.8	2.7	0.0	262.3	131	14.0	24.9	5.0	0.0	154.3	<0.01	0.01
GzmB Intratumoral	118	25.5	46.2	10.1	0.0	293.7	131	40.0	73.7	16.7	0.2	625.5	0.01	0.06
IL 17 Intratumoral	111	189.8	140.1	165.7	2.0	656.7	123	182.8	127.0	154.8	0.0	551.8	0.63	0.87

*Unadjusted Model: Wilcoxon rank sum test

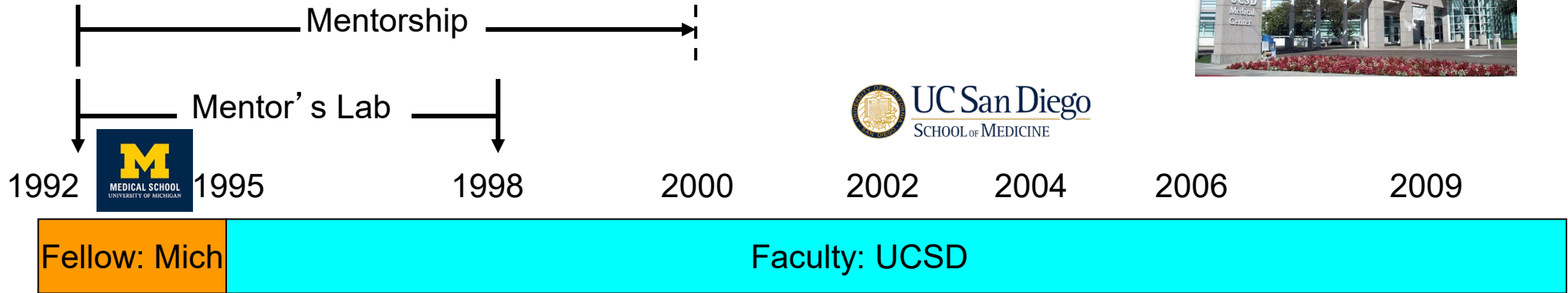
**Adjusted Model: Linear regression models with log transformed mean cell infiltration markers regressed on race, adjusted for gender

Fig 3. Summary statistics of the six cell infiltration biomarkers by race. The infiltration of cells positive for each of the markers (CD8, CD57, GzmB, and IL-17) are indicated, as is whether the data is for positive cells infiltrating the entire tumor (IT, epithelium and stroma) versus the epithelium alone (IE, intraepithelial).

Project Timeline: MMR and CRC Disparities



My Academic Career



- Univ of Michigan
- entered lab
- research focus
- grant writing
- married at end of fellowship
- T32
- K08
- RWJ
- moved To UCSD**
- own lab space
- first tech
- first post doc
- V Foundation
- Fellowship Dir**
- Preuss School
- FACP**
- R01
- CCRP
- VA Merit
- Div Chief**
- VA Sect Chief**
- Paid off Loans
- NCDD
- R01
- T32
- R24
- U54
- AGA Council**
- AGAF**
- ASCI**

Rank: Asst. Prof → Assoc. Prof → Prof →

Children: 1 → 2 → 3 → 4

Focus: CRC genetics, hereditary CRC, racial aspects of CRC

Networking: letters, recommendations, committees, grants, etc.

My Academic Career



2009

2012

2014

2016

2018

2020

2021

Faculty: University of Michigan

-Dept Chair
Univ. of MI

-U01

-R01

-R01

-Endowed Chair

-Taubman Scholar

-DUP

-ACP Dustan Award

-R01

-AAP

-NAM

-ACCA

- Am Acad Arts&Sci

-MM Alumni Award

-AAAS

-MACP

-FRCP

-WSU Dist Alum Award

-Williams Award

-AACR MICR Chair

-AACR Task Force Chair

-AAP President

-AGA President

-Senior Assoc Editor *Gastroenterology*

-APM Councilor

Publishing papers

Clinical care

Teaching

Administration

Training/Mentoring



Carethers' Laboratory

March 13, 2020



- Minoru Koi
- Stephanie Tseng-Rogenski
- Maide Raeker
- Koki Takeda
- Anand Venugopal
- Satoshi Suzuki
- Yoshiki Okita
- Carlos Zavala
- Bianca Arao
- Koji Munakata
- Takahito Kitajima
- Supal Mehta
- Alexander Worix
- Lizette Gutierrez
- Pierre Leconte
- Andre Enowtaku
- Jovan Pierre Charles
- Daniel Choi
- Carla Guarinos
- Paul K. Martin
- Yashushi Hamaya
- Sun-Young Lee
- Bikash Deveraj
- Moriya Iwaizumi



MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

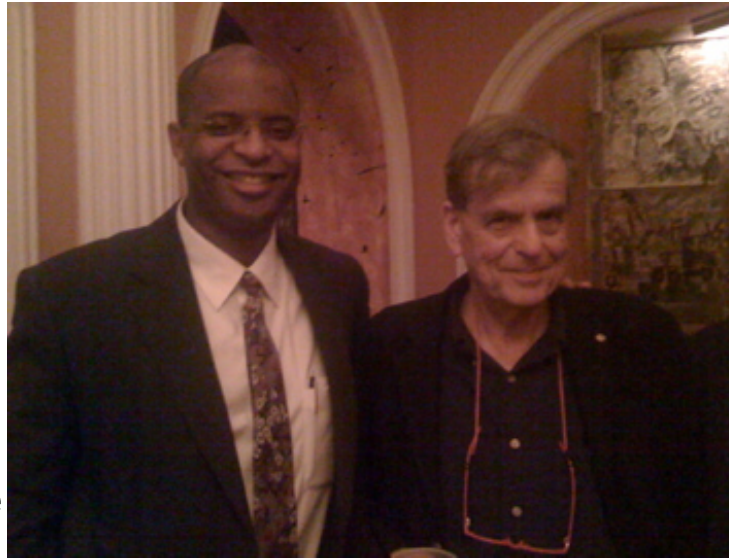
Keys to a Successful Career

- Work hard
- Persevere
- Focus on goals; don't let distractions derail you
- Emulate role models
- Find mentorship for advice on career development
- Be true and honest to yourself
- Social support; surround yourself with others with similar goals or who have your best interest
- Train the next generation – they will excite you!

The Benefits of Academia...



Roger Tsien
2008 Noble Laureate
UCSD Professor



Aaron Ciechanover
2004 Noble Laureate



Barry Marshall
2005 Noble Laureate

Bruce Beutler
2011 Noble Laureate



Gregg Semanza
2019 Noble Laureate



Joe Goldstein
1985 Noble Laureate



Thank you!

