

NAPS2

Two Decades of Success

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PF22

NAPS2: Innovation and Hard Work

- **Innovations:**

- Reverse engineering applied to CP as a complex disorder
- **SAPE** hypothesis as a new model of disease (progressive model)
- **TIGAR-O** classification system for multiple risk
- Modeling and simulation applied to complexity (e.g. CFTR)
- North American Pancreatitis Study Group (**NAPS2**)
- *PancreasFest* as an annual meeting of investigators & friends

- **Hard work:**

- >30 centers, >**100 investigators** > 10 years > 3000 subjects

- **Results:**

- Alcoholism is the single cause of CP in a *MINORITY* of cases
- Smoking is a major, independent risk factor for CP
- Multiple new genes discovered and replicated
- Revolutionary understanding of multiple pancreatic diseases
- Insights into pain mechanisms (QOL, stress genes)

NAPS2: >RAP-CP 3000 Cases/Controls

- **NAPS2 Sites (Site-PI) – Bold=NAPS2-CV**

- **Brigham & Women's MC**, Boston (Banks)
- Cedars-Sinai MC, Los Angeles (Simon Lo)
- **Dartmouth-Hitchcock MC**, NH (Gardner)
- Evanston NWU. Chicago (Brand)
- **Indiana Univ.**, Indianapolis, IN (Sherman)
- **Mayo Clinic Jacksonville**, FL (Lewis)
- **MUSC**, Charlestown, SC (Hawes)
- No. Mississippi MC, Tupelo, MS (Amann)
- Ochsner MC, New Orleans (Etemad)
- **St Louis Univ.** (Burton)
- Rush UMC, Chicago (DeMeo)
- **Univ. Alabama Birmingham (Wilcox)**
- Univ. Cincinnati (Gelrud)
- **Univ. Florida** (Forsmark)
- **Univ. Michigan** (Anderson)
- University of Pennsylvania (Kochman)
- **Univ. Pittsburgh**, UPMC (Slivka)
- Univ. Utah (DiSario)
- **Virginia Comm. U** (Sandhu)
- Washington Co, Hagerstown, MD (Money)
- Washington Hospital, DC (Steinberg)

- **Funding:** NIDDK, NPF, UPMC
- 2000-2014 (NAPS2, NAPS2-CV, NAPS2-AA)

- **NAPS2-AS (PI-Site)**

- + Aurora-St. Luke's MC, Milwaukee (Guda)
- + UABMD, Birmingham (Wilcox)
- + Griffin Hospital, Derby, CT (Muniraj)
- *Brigham & Woman's MC* (New PI: Conwell)
- *Indiana Univ.* (New PI: Cote)
- *MUSC* (New PI: Romagnuolo)
- *Pittsburgh Shadyside* (Brand, Gelrude)
- *St Louis Univ.* (PI: Alkaade)

- **NAPS2 – DNA & Biomarker Core**

- DNA - David Whitcomb MD PhD (DNA)
- Biomarkers – Brand, Papachristou
- Database manager – O'Connell
- Stello, Elinoff, Boggano, Hendricks, Solomon

- **NAPS2- Analysis Cores**

- Clinical Epidemiology – Yadav
- Epidemiology Data Center – Wisniewski
- Genetic modeling – Barmada, Langmead
- Computational Genetics – Devlin

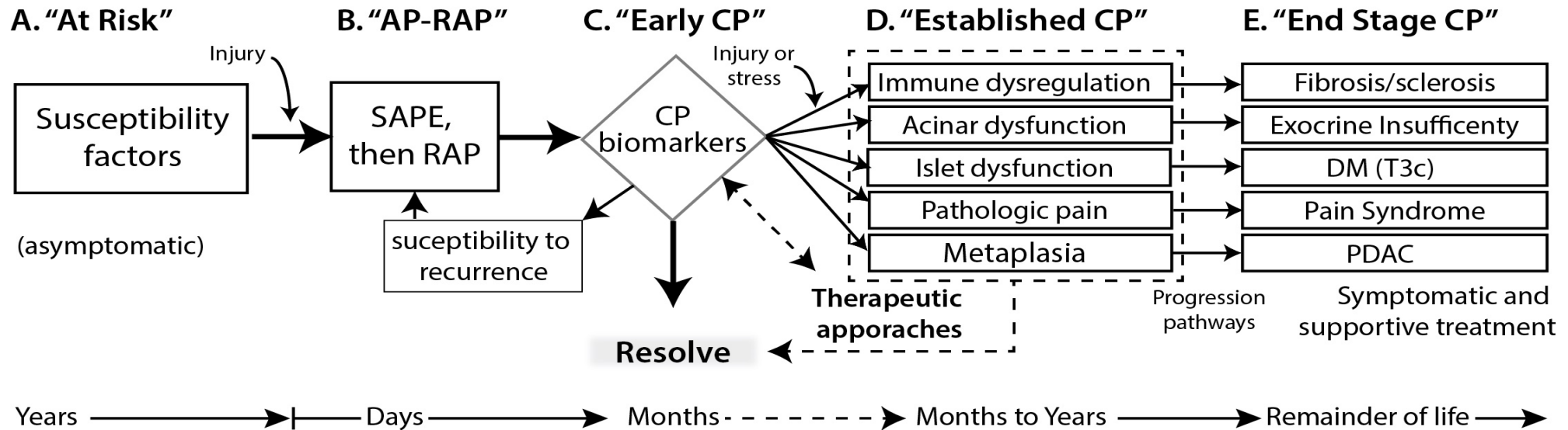
- **Collaborating Programs (Site PI)**

- Liverpool, England (Neoptolemos)
- Greifswald, Germany (Lerch)
- Penn Statue Univ, Hershey (Smith)
- Alzheimer's Disease Genetics Consortium
- NeuroGenetics Research Consortium

Organization of NAPS2

- Cooperative centers / 3 phases
 - **NAPS.** Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology*. 2008;8(4-5):520-31. PMID:18765957
 - **NAPS2 CV:** Conwell DL, Banks PA, Sandhu BS, Sherman S, Al-Kaade S, Gardner TB, et al. Validation of Demographics, Etiology, and Risk Factors for Chronic Pancreatitis in the USA: A Report of the North American Pancreas Study (NAPS) Group. *Dig Dis Sci*. 2017;62(8):2133-40. PMID:28600657
 - **NAPS2-AS:** Wilcox CM, Sandhu BS, Singh V, Gelrud A, Abberbock JN, Sherman S, et al. Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis. *Am J Gastroenterol*. 2016;111(10):1488-96. PMID:27527745
- INSPPIRE – Model used to start pediatric multicenter studies
- CAPER – invitation to young investigators to join studies
- CPDPC (PROCEED) - “NAPS2 on steroids”

Mechanistic Model



- 5 stages of pancreatitis
- TIGAR-O Etiology List
- SAPE Hypothesis

- Variable variability of:

- Acinar cells / nutrition
- Duct cells / CFTR-RD
- Islet cells / Type 2 / 3c DM
- Immunocytes / cytokines
- Nervous system (peripheral and central)
- DNA repair mechanisms / PDAC

NAPS2 – 50 peer-reviewed research papers

Alcohol and Smoking

- Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology*. 2008;8(4-5):520-31. PMID:18765957
- Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med*. 2009;169(11):1035-45. PMID:19506173
- Cote GA, Yadav D, Slivka A, Hawes RH, Anderson MA, Burton FR, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2010;9(3):266-73. PMID:21029787
- Yadav D, Slivka A, Sherman S, Hawes RH, Anderson MA, Burton FR, et al. Smoking Is Underrecognized as a Risk Factor for Chronic Pancreatitis. *Pancreatology*. 2011;10(6):713-9. PMID:21242712
- Muniraj T, Yadav D, Abberbock JN, Alkaade S, Amann ST, Anderson MA, et al. Increased awareness enhances physician recognition of the role of smoking in chronic pancreatitis. *Pancreatology*. 2019;19(4):500-6. PMID:30910452
- Jeon CY, Whitcomb DC, Slivka A, Brand RE, Gelrud A, Tang G, et al. Lifetime Drinking History of Persons With Chronic Pancreatitis. *Alcohol Alcohol*. 2019;54(6):615-24. PMID:31603464
- Jeon CY, Feldman R, Althouse A, AlKaade S, Brand RE, Guda N, et al. Lifetime smoking history and cohort-based smoking prevalence in chronic pancreatitis. *Pancreatology*. 2021. PMID:34116939

Genetics (1)

- Sass DA, Papachristou GI, Lamb J, Barmada MM, Brand RE, Money ME, et al. The MCP-1 -2518 A/G Polymorphism Is Not a Susceptibility Factor for Chronic Pancreatitis. *Pancreatology*. 2006;6(4):297-300.
- Lazarev M, Lamb J, Barmada MM, Dai F, Anderson MA, Max MB, et al. Does the pain-protective GTP cyclohydrolase haplotype significantly alter the pattern or severity of pain in humans with chronic pancreatitis? *Mol Pain*. 2008;4:58. PMID:19014702
- Muddana V, Lamb J, Greer JB, Elinoff B, Hawes RH, Cotton PB, et al. Association between calcium sensing receptor gene polymorphisms and chronic pancreatitis in a US population: Role of serine protease inhibitor Kazal 1type and alcohol. *World J Gastroenterol*. 2008;14(28):4486-91. PMID:18680227
- Brand H, Diergaard B, O'Connell MR, Whitcomb DC, Brand RE. Variation in the gamma-glutamyltransferase 1 gene and risk of chronic pancreatitis. *Pancreas*. 2013;42(5):836-40. PMID:23462328
- Greer JB, Larusch J, Brand RE, O'Connell MR, Yadav D, Whitcomb DC. ABO Blood Group and Chronic Pancreatitis Risk in the NAPS2 Cohort. *Pancreas*. 2011;40(8):1188-94. PMID:21792085
- Larusch J, Barmada MM, Solomon S, Whitcomb DC. Whole exome sequencing identifies multiple, complex etiologies in an idiopathic hereditary pancreatitis kindred. *JOP : Journal of the pancreas*. 2012;13(3):258-62. PMID:22572128
- Whitcomb DC, Larusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, et al. **Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. *Nature genetics***. 2012;44(12):1349-54. PMID:23143602

Genetics (2)

- LaRusch J, Jung J, General IJ, Lewis MD, Park HW, Brand RE, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genetics. 2014;10(7):e1004376. PMID:25033378
- LaRusch J, Lozano-Leon A, Stello K, Moore A, Muddana V, O'Connell M, et al. The Common Chymotrypsinogen C (CTRC) Variant G60G (C.180T) Increases Risk of Chronic Pancreatitis But Not Recurrent Acute Pancreatitis in a North American Population. Clin Transl Gastroenterol. 2015;6:e68. PMID:25569187
- Choi J, Oh TG, Jung H, Park KY, Shin H, Jo T, et al. Estrogen-Related Receptor gamma Maintains Pancreatic Acinar Cell Function and Identity by Regulating Cellular Metabolism. Gastroenterology. 2022. PMID:35461826
- Schneider A, Larusch J, Sun X, Aloe A, Lamb J, Hawes R, et al. Combined Bicarbonate Conductance-Impairing Variants in CFTR and SPINK1 Variants Are Associated With Chronic Pancreatitis in Patients Without Cystic Fibrosis. Gastroenterology. 2011;140(1):162-71. PMID:20977904
- Phillips AE, LaRusch J, Greer P, Abberbock J, Alkaade S, Amann ST, et al. Known genetic susceptibility factors for chronic pancreatitis in patients of European ancestry are rare in patients of African ancestry. Pancreatology. 2018;18(5):528-35. PMID:2985967
- Goodarzi MO, Nagpal T, Greer P, Cui J, Chen YI, Guo X, et al. Genetic Risk Score in Diabetes Associated With Chronic Pancreatitis Versus Type 2 Diabetes Mellitus. Clin Transl Gastroenterol. 2019;10(7):e00057. PMID:31232720
- Lasher D, Szabo A, Masamune A, Chen JM, Xiao X, Whitcomb DC, et al. Protease-Sensitive Pancreatic Lipase Variants Are Associated With Early Onset Chronic Pancreatitis. Am J Gastroenterol. 2019;114(6):974-83. PMID:30789418

Genetics (3)

- Dunbar E, Greer PJ, Melhem N, Alkaade S, Amann ST, Brand R, et al. Constant-severe pain in chronic pancreatitis is associated with genetic loci for major depression in the NAPS2 cohort. *J Gastroenterol.* 2020;55(10):1000-9. PMID:32681239
- Lewis MD, Talluri J, Wilcox CM, Abberbock JN, Tang G, Conwell DL, et al. Differences in Age at Onset of Symptoms, and Effects of Genetic Variants, in Patients With Early- vs Late-Onset Idiopathic Chronic Pancreatitis in a North American Cohort. *Clin Gastroenterol Hepatol.* 2020. PMID:32240833
- Dunbar EK, Greer PJ, Amann ST, Alkaade S, Banks P, Brand R, et al. Pain Experience in Pancreatitis: Strong Association of Genetic Risk Loci for Anxiety and PTSD in Patients With Severe, Constant, and Constant-Severe Pain. *Am J Gastroenterol.* 2021;116(10):2128-36. PMID:34236339
- Choi J, Oh TG, Jung H, Park KY, Shin H, Jo T, et al. Estrogen-Related Receptor gamma Maintains Pancreatic Acinar Cell Function and Identity by Regulating Cellular Metabolism. *Gastroenterology.* 2022. PMID:35461826
- (3 additional papers are in review / revision)

Sex, Ancestry, Age differences

- Romagnuolo J, Talluri J, Kennard E, Sandhu BS, Sherman S, Cote GA, et al. Clinical Profile, Etiology, and Treatment of Chronic Pancreatitis in North American Women: Analysis of a Large Multicenter Cohort. *Pancreas*. 2016;45(7):934-40. PMID:26967451
- Wilcox CM, Sandhu BS, Singh V, Gelrud A, Abberbock JN, Sherman S, et al. Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis. *Am J Gastroenterol*. 2016;111(10):1488-96. PMID:27527745
- Schwarzenberg SJ, Uc A, Zimmerman B, Wilschanski M, Wilcox CM, Whitcomb DC, et al. Chronic Pancreatitis: Pediatric and Adult Cohorts Show Similarities in Disease Progress Despite Different Risk Factors. *J Pediatr Gastroenterol Nutr*. 2019;68(4):566-73. PMID:30897605
- Jeon CY, Feldman R, Pendergast FJ, AlKaade S, Brand RE, Guda N, et al. Divergent trends in lifetime drinking and smoking between Black and White Americans diagnosed with chronic pancreatitis. *Pancreatology*. 2020;20(8):1667-72. PMID:33132046
- Lewis MD, Talluri J, Wilcox CM, Abberbock JN, Tang G, Conwell DL, et al. Differences in Age at Onset of Symptoms, and Effects of Genetic Variants, in Patients With Early- vs Late-Onset Idiopathic Chronic Pancreatitis in a North American Cohort. *Clin Gastroenterol Hepatol*. 2020. PMID:32240833

EPI and Diabetes

- Kanakis A, Vippera K, Papachristou GI, Brand RE, Slivka A, Whitcomb DC, et al. Bone health assessment in clinical practice is infrequently performed in patients with chronic pancreatitis. *Pancreatology*. 2020. PMID:32826169
- Zhan W, Akshintala V, Greer PJ, Greer JB, Alkaade S, Anderson MA, et al. Low serum trypsinogen levels in chronic pancreatitis: Correlation with parenchymal loss, exocrine pancreatic insufficiency, and diabetes but not CT-based Cambridge severity scores for fibrosis. *Pancreatology*. 2020;20(7):1368-78. PMID:32967795
- Greer JB, Greer P, Sandhu BS, Alkaade S, Wilcox CM, Anderson MA, et al. Nutrition and Inflammatory Biomarkers in Chronic Pancreatitis Patients. *Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition*. 2019;34(3):387-99. PMID:30101991
- Rickels MR, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology*. 2013;13(4):336-42. PMID:23890130 (PancreasFest)
- Bellin MD, Whitcomb DC, Abberbock J, Sherman S, Sandhu BS, Gardner TB, et al. Patient and Disease Characteristics Associated With the Presence of Diabetes Mellitus in Adults With Chronic Pancreatitis in the United States. *Am J Gastroenterol*. 2017;112(9):1457-65. PMID:28741615
- Goodarzi MO, Nagpal T, Greer P, Cui J, Chen YI, Guo X, et al. Genetic Risk Score in Diabetes Associated With Chronic Pancreatitis Versus Type 2 Diabetes Mellitus. *Clin Transl Gastroenterol*. 2019;10(7):e00057. PMID:31232720
- Yadav D, Whitcomb DC, Tang G, Slivka A, Bellin M, North American Pancreatitis Studies C. Autoimmunity May Explain Diabetes in a Subset of Patients With Recurrent Acute and Chronic Pancreatitis: A Pilot Study. *Clin Gastroenterol Hepatol*. 2021;S1542-3565(21)01223-4. PMID:34793964

Pain / QOL in CP

- Amann ST, Yadav D, Barmada MM, O'Connell M, Kennard ED, Anderson M, et al. Physical and mental quality of life in chronic pancreatitis: a case-control study from the North American Pancreatitis Study 2 cohort. *Pancreas*. 2013;42(2):293-300. PMID:23357924
- Lazarev M, Lamb J, Barmada MM, Dai F, Anderson MA, Max MB, et al. Does the pain-protective GTP cyclohydrolase haplotype significantly alter the pattern or severity of pain in humans with chronic pancreatitis? *Mol Pain*. 2008;4:58. PMID:19014702
- Lazarev M, Lamb J, Barmada MM, Dai F, Anderson MA, Max MB, et al. Does the pain-protective GTP cyclohydrolase haplotype significantly alter the pattern or severity of pain in humans with chronic pancreatitis? *Mol Pain*. 2008;4:58. PMID:19014702
- Burton F, Alkaade S, Collins D, Muddana V, Slivka A, Brand RE, et al. Use and perceived effectiveness of non-analgesic medical therapies for chronic pancreatitis in the United States. *Alimentary pharmacology & therapeutics*. 2011;33(1):149-59. PMID:21083584
- Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. *Gut*. 2011;60(1):77-84. PMID:21148579
- Machicado JD, Amann ST, Anderson MA, Abberbock J, Sherman S, Conwell DL, et al. Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities. *Am J Gastroenterol*. 2017;112(4):633-42. PMID:28244497

Pain / QOL (continued)

- Wilcox CM, Yadav D, Tian Y, Gardner TB, Gelrud A, Sandhu BS, et al. Chronic Pancreatitis Pain Pattern and Severity are Independent of Abdominal Imaging Findings. *Clin Gastroenterol Hepatol*. 2014;13(3):552-60. PMID:25424572
- Dunbar EK, Greer PJ, Amann ST, Alkaade S, Banks P, Brand R, et al. Pain Experience in Pancreatitis: Strong Association of Genetic Risk Loci for Anxiety and PTSD in Patients With Severe, Constant, and Constant-Severe Pain. *Am J Gastroenterol*. 2021;116(10):2128-36. PMID:34236339
- Vipperla K, Kanakis A, Slivka A, Althouse AD, Brand RE, Phillips AE, et al. Natural course of pain in chronic pancreatitis is independent of disease duration. *Pancreatology*. 2021. PMID:33674197
- Saloman JL, Tang G, Stello KM, Hall KE, Wang X, AlKaade S, et al. Serum biomarkers for chronic pancreatitis pain patterns. *Pancreatology*. 2021. PMID:34602367
- Anderson MA, Akshintala V, Albers KM, Amann ST, Belfer I, Brand R, et al. Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group. *Pancreatology*. 2016;16(1):83-94. PMID:26620965 (PancreasFest)

Other

- Park WG, Li L, Appana S, Wei W, Stello K, Andersen DK, et al. Unique circulating immune signatures for recurrent acute pancreatitis, chronic pancreatitis and pancreatic cancer: A pilot study of these conditions with and without diabetes. *Pancreatology*. 2019;Epub 2019 Nov 25. PMID:31791885
- Das R, Clarke B, Tang G, Papachristou GI, Whitcomb DC, Slivka A, et al. Endoscopic sphincterotomy (ES) may not alter the natural history of idiopathic recurrent acute pancreatitis (IRAP). *Pancreatology*. 2016;16(5):770-7. PMID:27450967

Multiple additional papers are in review or preparations

Paradigm Shifts

- Importance of Smoking in CP
- Complex trait genetics (RAP / CP / Diabetes / Pain)
- Chronic pain / QOL / mechanistic insights
- Model of CP (AP→RAP→CP)
 - Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. *Pancreatology*. 2016;16:218-24. PMID:26924663
 - Whitcomb DC, Shimosegawa T, Chari ST, Forsmark CE, Frulloni L, Garg P, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. *Pancreatology*. 2018;S1424-3903(18):30113-3. PMID:29793839

Congratulations: "The Team"

- "I put a man on the moon"
- In memory of:
 - Frank Burton MD
 - John Baillie MD
 - M. Michael Barmada PhD