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Study Identification

Unique Protocol ID: 22-08-1235
Brief Title: Evaluate Established Anti-DEFA5 mAbs Diagnostic Efficacy and Safety in IBD
Official Title: Evaluate Established Anti-DEFA5 mAbs Diagnostic Efficacy and Safety in IBD
Secondary IDs:

Study Status

Record Verification: November 2022
Overall Status: Not yet recruiting
Study Start: June 1, 2023 [Anticipated]
Primary Completion: May 31, 2025 [Anticipated]
Study Completion: June 30, 2025 [Anticipated]

Sponsor/Collaborators

Sponsor: Meharry Medical College
Responsible Party: Principal Investigator
Investigator: Amosy M'Koma [amkoma]
Official Title: Professor
Affiliation: Meharry Medical College

Collaborators:

Oversight

U.S. FDA-regulated Drug:
U.S. FDA-regulated Device:
U.S. FDA IND/IDE:
Human Subjects Review: Board Status: Exempt
Data Monitoring: Yes

Study Description

Brief Summary: Investigators propose to validate efficacy and safety of the detection of DEFA5 in the diagnosis of the colonic IBD using longitudinal vs. cross-sectional studies of known patient clinical data to correlate with their endoscopy biopsy data. 30% of colonic IBD patients cannot be accurately diagnosed (CC vs. UC) in a timely manner even when a state-of-the-art classification system of combined clinical, endoscopic, radiologic and histologic tools is used. When the diagnostic classification for these two diseases is inconclusive, the condition is termed indeterminate colitis (IC). Here, the central medical challenge is the discrimination of IBD into the specific subtypes with high accuracy, as it greatly affects surgical care of patients. Diagnostic accuracy of IC into either authentic UC or CC is of utmost importance when determining a patient's candidacy for

RPC-IPAA surgery, the standard curative surgical procedure for UC. Further, incorrect diagnosis and treatment carry potential morbidity from inappropriate and unnecessary surgery and costs. The success outcomes of RPC-IPAA surgery and convalescence depend on correct diagnosis. To address IBD diagnosis ambiguity and delays in IBD clinical settings, investigators developed a proteomic signature to discriminate between UC and CC patients that also will predict the outcome of IC patients for their eventual progress to either UC or CC. Our published data has shown robust evidence supporting presence of human alpha-defensin 5 (DEFA5) in areas of the colon mucosa with aberrant expression of apparent Paneth cell-like cells (PCLCs) or crypt cell-like cells (CCLCs), which identifies an area of colonic ileal metaplasia, consistent with the diagnosis of CC. DEFA5 bioassay discriminated CC and UC in a cohort of all IC patients with accuracy. A fit logistic model with group CC and UC as the outcome and the DEFA5 as independent variable differentiator with a positive predictive value of 96%. These findings were obtained solely from colectomy specimens for both the discovery and validation analyses. Investigators believe that use of endoscopy biopsies would be indifferent, which is the purpose of this prospective patient centered clinical study. Investigators propose to demonstrate that UC and CC, the two unsolved medical subtypes of pathology with no drugs for a cure, can accurately be distinguished molecularly by examining CCLCs-secreted DEFA5 in colonic endoscopy biopsies instantly. Our proposal is highly innovative, as it highlights the robustness of DEFA5 and its clinical relevance to IBD is both in science and the anticipated impact, as investigators seek to better understand difficulty to determine ‘subtypes” and translate that to improve diagnosis, treatment, clinical outcomes, and quality of life for patients and the realm of clinical care. DEFA5 immunoreactivity in colonic endoscopy biopsies could be a rapid potential diagnostic signature to resolve IC into authentic UC and CC with a first clinic endoscopy biopsy. IC is likely to be eliminated for good.

Detailed Description: The clinical relevance of this proposed screen is that it would lead to the elusive and accurate diagnosis to circumvent the inexact IC patients into authentic CC and UC with a first clinic endoscopy biopsy. The central medical challenge in endoscopic medicine and colorectal surgery is the discrimination of colonic IBD into the subtypes with high accuracy because it greatly affects surgical care of patients. Incorrect diagnosis and surgery carry potential morbidity from inappropriate and unnecessary surgery and cost. Our published data has shown robust evidence supporting presence of human alpha-defensin 5 (DEFA5) in areas of the colon mucosa with aberrant expression of apparent Paneth cell-like cells (PCLCs) / crypt cell-like cells (CCLCs), which identifies an area of colonic ileal metaplasia, consistent with the diagnosis of CC. Investigators propose to demonstrate that UC and CC, the two unsolved medical subtypes of GI pathology with no drugs for a cure, may accurately be distinguished molecularly by examining CCLCs-secreted DEFA5 in colonic endoscopy biopsies instantly. Our proposal is highly innovative, as it highlights the robustness efficacy and safety of DEFA5 and its clinical relevance in IBD diagnostics. The goal of this proposal is to develop a clinical approach to circumvent diagnostic ambiguity and delay, as well as permit timely and accurate diagnosis of colonic IBD. DEFA5 immunoreactivity in colonic endoscopy biopsies could be a potential diagnostic signature that accurately diagnoses CC and provides the basis to resolve ambiguity in the diagnosis of IBD to not only circumvent diagnostic delay, but also permit timely, accurate diagnosis and timely prescription of appropriate treatment options, an Affordable, Sensitive, Specific, User-friendly, Robust and Rapid, Equipment-free, and Deliverable (ASSURED) bioassay that may delineate subtypes of IBD during the first clinic endoscopy biopsy visit. This bioassay is specific, sensitive, linear, affordable, low risk, and less invasive. Investigators hypothesize that aberrant expression of DEFA5 secreting CCLCs in colonic crypt of IBD patients may be exploited as a reliable diagnostic signature to highly differentiate CC from UC in otherwise IC patients during the first clinic visit endoscopy biopsy without delay. Investigators foresee no issues pertaining

to this proposal as an established sampling error by endoscopic biopsy making it does not interfere with results and apropos of this project that each biopsy has complement CCLCs with co-localized DEFA5 clearly restricted in areas of the mucosa with aberrant CCLCs identifies a ubiquitously colonic ileal metaplasia that is consistent with the diagnosis of authentic CC. If successful, widespread use of this approach would not only revolutionize provide accurate diagnoses and the correct treatment regimens for IBD patients, but also it will improve health outcomes and patient quality of life, while reducing medical complications and/or unnecessary drugs, surgeries, & costs.

Conditions

Conditions: Inflammatory Bowel Diseases
Ulcerative Colitis
Crohn's Colitis
Indeterminate Colitis

Keywords: Inflammatory bowel disease
Crohn's colitis
Ulcerative colitis
Indeterminate colitis
DEFA5
Molecular diagnostics
Colonic biopsies
Colonic ileal metaplasia

Study Design

Study Type: Observational

Observational Study Model: Cohort

Time Perspective: Cross-Sectional

Biospecimen Retention: Samples With DNA

Biospecimen Description: The research outlined is consistent with the Non-human Welfare Act Criteria because investigators receive de-identified specimens and data from an IRB approved repository, and investigators do not have access to the link by which investigators may re-identify the specimens and data with their source. The research involves the use of human tissue acquired previously using the third-party good faith broker mechanism. Since all identifiers are striped, the tissue samples are considered non-human subjects. Each specimen is assigned a unique barcode identifier to maintain the patient's confidentiality. In no case is the patient's name ever revealed to the users. All information accompanying the specimen(s) uses the bar code identifier.

Enrollment: 230 [Anticipated]

Number of Groups/Cohorts: 5

Groups and Interventions

Groups/Cohorts	Interventions
Crohn's colitis Correlate patient longitudinal study of clinical data and their biopsy data. Investigators will determine DEFA5 levels from endoscopy biopsies from known authentic CC patients.	Diagnostic Test: Diagnostic Test The challenge is the discrimination of IBD into the subtypes with accuracy because it affects surgical care of patients. Investigators have developed a signature discriminator between UC&CC that also predicts the outcome of IC patients into

Groups/Cohorts	Interventions
	authentic UC/CC. This is a bioassay that is specific, sensitive, linear, affordable, minimal risk, non-invasive and constitutes an inexpensive, simple to use, point-of-care test format. Our published data have shown robust evidence supporting presence of DEFA5 in the colon crypt mucosa with aberrant expression of apparent crypt-cell-like cells (CCLCs) in areas identified with ectopic colon ileal metaplasia consistent with CC. Investigators propose to validate that UC/CC, the two unsolved medical sub-types of pathology can accurately be distinguished among IC patients by examining CCLCs secreted DEFA5 levels in endoscopy biopsies instantly. Diagnostics relies on the expression/localization/activation of DEFA5 and the ectopic CCLCs in the mucosal crypt of CC patients.
Ulcerative colitis Correlate patient longitudinal study of clinical data and their biopsy data. Investigators will determine DEFA5 levels from endoscopy biopsies from known authentic UC patients.	Diagnostic Test: Diagnostic Test The challenge is the discrimination of IBD into the subtypes with accuracy because it affects surgical care of patients. Investigators have developed a signature discriminator between UC&CC that also predicts the outcome of IC patients into authentic UC/CC. This is a bioassay that is specific, sensitive, linear, affordable, minimal risk, non-invasive and constitutes an inexpensive, simple to use, point-of-care test format. Our published data have shown robust evidence supporting presence of DEFA5 in the colon crypt mucosa with aberrant expression of apparent crypt-cell-like cells (CCLCs) in areas identified with ectopic colon ileal metaplasia consistent with CC. Investigators propose to validate that UC/CC, the two unsolved medical sub-types of pathology can accurately be distinguished among IC patients by examining CCLCs secreted DEFA5 levels in endoscopy biopsies instantly. Diagnostics relies on the expression/localization/activation of DEFA5 and the ectopic CCLCs in the mucosal crypt of CC patients.
Indeterminate colitis Correlate patient longitudinal study of clinical data and their biopsy data. Investigators will determine DEFA5 levels from endoscopy biopsies from	Diagnostic Test: Diagnostic Test The challenge is the discrimination of IBD into the subtypes with accuracy

Groups/Cohorts	Interventions
known IC patients (into authentic UC and CC)	because it affects surgical care of patients. Investigators have developed a signature discriminator between UC&CC that also predicts the outcome of IC patients into authentic UC/CC. This is a bioassay that is specific, sensitive, linear, affordable, minimal risk, non-invasive and constitutes an inexpensive, simple to use, point-of-care test format. Our published data have shown robust evidence supporting presence of DEFA5 in the colon crypt mucosa with aberrant expression of apparent crypt-cell-like cells (CCLCs) in areas identified with ectopic colon ileal metaplasia consistent with CC. Investigators propose to validate that UC/CC, the two unsolved medical sub-types of pathology can accurately be distinguished among IC patients by examining CCLCs secreted DEFA5 levels in endoscopy biopsies instantly. Diagnostics relies on the expression/localization/activation of DEFA5 and the ectopic CCLCs in the mucosal crypt of CC patients.
Diverticulitis Correlate patient longitudinal study of clinical data and their biopsy data. Investigators will determine DEFA5 levels from endoscopy biopsies from known diverticulitis.	Diagnostic Test: Diagnostic Test The challenge is the discrimination of IBD into the subtypes with accuracy because it affects surgical care of patients. Investigators have developed a signature discriminator between UC&CC that also predicts the outcome of IC patients into authentic UC/CC. This is a bioassay that is specific, sensitive, linear, affordable, minimal risk, non-invasive and constitutes an inexpensive, simple to use, point-of-care test format. Our published data have shown robust evidence supporting presence of DEFA5 in the colon crypt mucosa with aberrant expression of apparent crypt-cell-like cells (CCLCs) in areas identified with ectopic colon ileal metaplasia consistent with CC. Investigators propose to validate that UC/CC, the two unsolved medical sub-types of pathology can accurately be distinguished among IC patients by examining CCLCs secreted DEFA5 levels in endoscopy biopsies instantly. Diagnostics relies on the expression/localization/activation of DEFA5 and the ectopic CCLCs in the mucosal crypt of CC patients.

Groups/Cohorts	Interventions
Ileum Positive control	Diagnostic Test: Diagnostic Test The challenge is the discrimination of IBD into the subtypes with accuracy because it affects surgical care of patients. Investigators have developed a signature discriminator between UC&CC that also predicts the outcome of IC patients into authentic UC/CC. This is a bioassay that is specific, sensitive, linear, affordable, minimal risk, non-invasive and constitutes an inexpensive, simple to use, point-of-care test format. Our published data have shown robust evidence supporting presence of DEFA5 in the colon crypt mucosa with aberrant expression of apparent crypt-cell-like cells (CCLCs) in areas identified with ectopic colon ileal metaplasia consistent with CC. Investigators propose to validate that UC/CC, the two unsolved medical sub-types of pathology can accurately be distinguished among IC patients by examining CCLCs secreted DEFA5 levels in endoscopy biopsies instantly. Diagnostics relies on the expression/localization/activation of DEFA5 and the ectopic CCLCs in the mucosal crypt of CC patients.

Outcome Measures

Primary Outcome Measure:

1. Assesse investigator's two newly developed anti-DEFA5 monoclonal antibodies for immunohistochemistry and sandwich ELISAs, and determines the most effective one or both for bioassay kit for IBD diagnostics. [Time Frame: Six months]

Secondary Outcome Measure:

2. Assess expression of DEFA5 biomarker in colonic biopsies from known patients with the diagnosis of IBD i.e., UC, CC, IC, and none-IBD i.e., diverticulitis, diverticulosis, & ileum as positive control, this will differentiate UC vs. CC and IC into authentic UC and CC. [Time Frame: 12 months]

Eligibility

Study Population: A sample size of 230 subjects is sufficient to detect a clinically significant difference of 19% between the PPVs of CC and UC using a one-tailed test of proportions between the two groups with 80% statistical power and a 5% level of significance. This 19% difference represents 80% probability that subjects in the CC group with a positive screening test truly have the disease and 77% PPV for subjects in UC group. Investigators will add non-IBD samples, 46 in the DV arm and 46 in CP arm to strengthen the results.

Sampling Method: Probability Sample

Minimum Age:

Maximum Age:

Sex: All

Gender Based: No

Accepts Healthy Volunteers: Yes

Criteria: Inclusion Criteria:

There will be no specific recruitment of subjects for this research. Subjects are consented, in general, for the collection of tissue and serum for banking purposes. Not specifically for this project. Biopsies and serum collections are performed routinely as standard of care and no specific procedures are performed on the subjects for this grant.

Exclusion Criteria:

No children

Contacts/Locations

Central Contact Person: Kimberly Thomas, RN, CCRP
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Central Contact Backup:

Study Officials: Amosy E M'Koma, MD, MS, PhD
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Locations: **United States, Tennessee**
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IPDSharing

Plan to Share IPD: Undecided
IPD will be obtained (i) directly with study PI or (ii) request via a data repository

References

Citations: **[Study Results]** Williams AD, Korolkova OY, Sakwe AM, Geiger TM, James SD, Muldoon RL, Herline AJ, Goodwin JS, Izban MG, Washington MK, Smoot DT, Ballard BR, Gazouli M, M'Koma AE. Human alpha defensin 5 is a candidate biomarker to delineate inflammatory bowel disease. PLoS One. 2017 Aug 17;12(8):e0179710. doi: 10.1371/journal.pone.0179710. eCollection 2017. Erratum in: PLoS One. 2017 Dec 6;12 (12):e0189551. PubMed 28817680

[Study Results] Rana T, Korolkova OY, Rachakonda G, Williams AD, Hawkins AT, James SD, Sakwe AM, Hui N, Wang L, Yu C, Goodwin JS, Izban MG, Offodile RS, Washington MK, Ballard BR, Smoot DT, Shi XZ, Forbes DS, Shanker A, M'Koma AE. Linking bacterial enterotoxins and alpha defensin 5 expansion in the Crohn's colitis: A new insight into the etiopathogenetic and differentiation triggers driving colonic inflammatory bowel disease. PLoS One. 2021 Mar 9;16(3):e0246393. doi: 10.1371/journal.pone.0246393. eCollection

2021. PubMed 33690604

[Study Results] Ballard BR, M'Koma AE. Gastrointestinal endoscopy biopsy derived proteomic patterns predict indeterminate colitis into ulcerative colitis and Crohn's colitis. World J Gastrointest Endosc. 2015 Jun 25;7(7):670-4. doi: 10.4253/wjge.v7.i7.670. PubMed 26140094

[Study Results] Korolkova OY, Myers JN, Pellom ST, Wang L, M'Koma AE. Characterization of Serum Cytokine Profile in Predominantly Colonic Inflammatory Bowel Disease to Delineate Ulcerative and Crohn's Colitides. Clin Med Insights Gastroenterol. 2015 May 6;8:29-44. doi: 10.4137/CGast.S20612. eCollection 2015. PubMed 26078592

[Study Results] M'Koma AE. Diagnosis of inflammatory bowel disease: Potential role of molecular biometrics. World J Gastrointest Surg. 2014 Nov 27;6(11):208-19. doi: 10.4240/wjgs.v6.i11.208. Review. PubMed 25429322

[Study Results] Seeley EH, Washington MK, Caprioli RM, M'Koma AE. Proteomic patterns of colonic mucosal tissues delineate Crohn's colitis and ulcerative colitis. Proteomics Clin Appl. 2013 Aug;7(7-8):541-9. doi: 10.1002/prca.201200107. Epub 2013 May 8. PubMed 23382084

[Study Results] M'Koma AE, Seeley EH, Washington MK, Schwartz DA, Muldoon RL, Herline AJ, Wise PE, Caprioli RM. Proteomic profiling of mucosal and submucosal colonic tissues yields protein signatures that differentiate the inflammatory colitides. Inflamm Bowel Dis. 2011 Apr;17(4):875-83. doi: 10.1002/ibd.21442. Epub 2010 Aug 30. PubMed 20806340

Links:

Available IPD/Information: