Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA.

4. **Grant Contact Person's Telephone Number:** 814-935-1081

5. **Grant SAP Number:** 4100047645

6. **Project Number and Title of Research Project:** 1 - Vitamin D and Crohn's Disease: From the Bench to the Bedside

7. **Start and End Date of Research Project:** 7/1/2009 –6/30/2012

8. **Name of Principal Investigator for the Research Project:** Margherita T. Cantorna, PhD

9. **Research Project Expenses**.

   9(A) Please provide the amount of health research grant funds spent on this project for the entire duration of the grant, including any interest earned that was spent:

   $ 96,016

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
Bingaman	Hershey Coordinator	10%	$10,469
McDaniels	Graduate Student	5%	$3,593
Chen	Graduate Student	5%	$3,593
Ooi	Graduate Student	5%	$3,593

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
Cantorna	PI	10%
Smith	Co-PI	10%
Hartman	Co-PI	10%
Weaver	UP Coordinator	15%
Mitchell	UP Diet Assessment Center	10%
Smith	Technician	5%
Anson	Hershey researcher	5%
Yang	Post-doc	5%
Zhang	Graduate Student	5%
Zeky	Undergraduate Student	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_X____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No___X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes__X____ No_____

If yes, please describe your plans:

We have already submitted to the Crohn's and Colitis Foundation of America in the Fall of 2012. We are in the process of revising that application to resubmit it. In addition, we are planning on submitting a grant to the National Institutes of Health within the next six months. We are looking for program announcements and research funding announcements at the NIH for this submission.

12. Future of Research Project. What are the future plans for this research project?

Based on our results we plan to propose a placebo controlled and longer term study for efficacy in a large population of patients. In addition, we want to determine by what mechanisms vitamin D regulates human immune function and immune function in Crohn's patients in particular.

13. **New Investigator Training and Development**. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes__X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female	1		4	1
Unknown				
Total	**1**		**4**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	1		4	1
Unknown				
Total	**1**		**4**	**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White	1		1	
Black				
Asian			3	1
Other				
Unknown				
Total	**1**		**4**	**1**

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No____X_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

If yes, please describe the collaborations:

Two of the three PIs have recently moved to Emory (Hartman) and the NIH extramural program (Smith). Therefore the future collaborative research and proposals will include collaborations with Dr. Hartman at Emory and possibly intramural researchers at the NIH that collaborate with Dr. Smith.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes___X____ No_____

If yes, please describe involvement with community groups that resulted from the research project:

Researchers interacted with the local chapter of the Crohn's and Colitis Foundation to identify potential participants in the study. After making the initial contacts several researchers participated in local fund raising events.

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Broad objectives/Aims: The incidence of autoimmune diseases like inflammatory bowel disease (IBD) has increased in developed countries over the last 50 years. We propose that decreased outdoor activity and increased pollution and diets that lack adequate vitamin D have combined to create large fluctuations in vitamin D status in developed countries and especially in populations that experience winter. Experimentally we've shown that changes in vitamin D status result in more severe forms of experimental IBD. In addition, active vitamin D (1,25(OH)2D3) completely blocks the development of experimental IBD. The vitamin D hypothesis proposes that vitamin D regulates the development and function of the immune system and that changes in vitamin D status affect the development of the resultant immune response and the development of diseases like IBD. Our hypothesis is that because of low dietary vitamin D intakes and malabsorption of many nutrients, Crohn's patients will have low circulating vitamin D levels that are detrimental for their health. We plan to give Crohn's patients 1000 IU of vitamin D/d and determine whether this dose is well tolerated, induces an increase in circulating vitamin D levels and has any additional health benefits (improved bone markers, Crohn's disease activity scores, inflammatory markers).
B) Research Design: The plan is to conduct a phase I trial of vitamin D supplementation in adult patients with mild to moderate Crohn's disease. Patients will be recruited from both Hershey and State College. Because the study is a feasibility study no placebo controls will be included. Instead patients will serve as their own controls. Baseline and 6 month data collection will be done on diet, serum vitamin D levels, inflammation, bone mineral density, Crohn's activity scores and quality of life surveys.

Expected Research Outcomes and Benefits
The expected outcomes are 1) to identify what the dietary intakes and circulating levels of vitamin D are in the patient pool, 2) to determine whether vitamin D supplementation will

improve vitamin D status, and 3) to determine whether increased vitamin D intakes are associated with health benefits in the Crohn's patients including bone mineral densities, Crohn's activity scores, and quality of life. The information we gather in this study will be used to determine whether a larger clinical study is worthwhile, whether additional selection criteria in the recruitment of Crohn's patients are necessary, whether vitamin D is well tolerated and adequate for improving vitamin D status, and whether clinical and immunologic improvement is seen over the 6-month study period. In addition, the clinical data will be used to help develop new mechanistic experiments aimed at determining what aspects of the immune response and/or health of the Crohn's patients are improved with vitamin D supplementation.

Methods

Study Design. The study design was that of an open-labeled prospective clinical trial and was conducted at two locations both at the Pennsylvania State University, the College of Medicine (Hershey, PA) and the main campus (University Park, PA). Patients with confirmed Crohn's disease between the ages of 18-70 and of either gender were recruited into the study. Inclusion criteria required patients to have CDAI scores between 150-400 and serum levels of 25(OH)D_3 below 40 ng/ml. Patients were allowed to continue maintenance IBD medications and multivitamins. Patients with ulcerative colitis or other inflammatory bowel conditions were ineligible. Exclusion criteria also included patients with an ostomy or receiving corticosteroid therapy. A total of 31 Crohn's patients were screened for the trial and of those 18 were deemed eligible and completed the 24 wk study. All subjects gave their informed written consent before the start of the study. All procedures were approved by the Institutional Review Board of the Pennsylvania State University. The trial has been registered at https://register.clinicaltrials.gov and the trial # is NCT00742781. The primary outcome was to determine the oral dose of vitamin D needed to raise the serum level of 25(OH)D_3 to 40 ng/ml in Crohn's patients.

Vitamin D intervention. The vitamin D_3 supplement (cholecalciferol) was purchased from Nutraceutical Sciences Institute (Lexington, KY) and the capsules contained 1000 IU of vitamin D_3. Eligible participants were started on 1000 IU/d of vitamin D_3 administered orally once daily for 2 weeks after which the vitamin D status was evaluated and patients with serum levels of 25(OH)D_3 below 40 ng/ml had the dose raised to 2000 IU/d. The serum 25(OH)D_3 levels were measured every two weeks and the dose escalated by 1000 IU/d increments until serum 25(OH)D_3 levels above 40 ng/ml were achieved or they were taking 5000 IU/d vitamin D_3. All patients were evaluated at baseline, 2 wk, 12 wk and 24 wk. Treatment compliance was assessed via log sheets, returned capsule counts, and serum 25(OH)D_3 values.

Serum Measurements. Serum 25(OH)D_3 was measured using 25(OH)-Vitamin D direct ELISA kit (Immundiagnostik AG, Bensheim, Germany) according to the manufacturer's instructions. Serum transaminases, serum calcium, parathyroid hormone (PTH), alkaline phosphatase (ALP), albumin were done to evaluate safety and toxicity from vitamin D. Erythrocyte sedimentation rate (ESR) was monitored as an indicator of inflammation. Serum vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF-α), interleukin (IL)-10, and IL-17 were measured using a multiplex human kit (Millipore, St. Charles, MO) according to the manufacturer's instructions.

Disease activity and overall health assessment. A diary was provided to all patients to record daily bowel function, abdominal pain, sense of general well-being, and anti-diarrhea medication for 7 d prior to office visits to calculate the CDAI score. In addition, patients were asked about any adverse effects or changes in medications. The standard CDAI score criteria were utilized with a score of 220 or greater indicative of active disease, a score of 150 or below indicative of remission, a 70 point or greater decline indicative of a favorable response, and a 100 point or greater increase in score indicative of a flare-up. The number of subjects having a 100-pt decline was also assessed. The IBD questionnaire (IBDQ) was used to measure disease-specific quality of life. Baseline and wk 24 follow-up physical activity levels were assessed via the short version of the International Physical Activity Questionnaire (IPAQ) (http://www.ipaq.ki.se).

Dietary Assessment. Dietary intakes were collected and analyzed at the Penn State Diet Assessment Center (University Park, PA) via a series of unannounced three telephone 24-hour recalls (two weekday and one weekend day). The background dietary intake of vitamin D and other related nutrients (e.g. calcium) were assessed in this way. Data was collected at baseline and 24 wks. Nutrient calculations including both dietary and supplement intake were assessed using the Minnesota Nutrition Data System for Research (NDS-R) version 4.06.

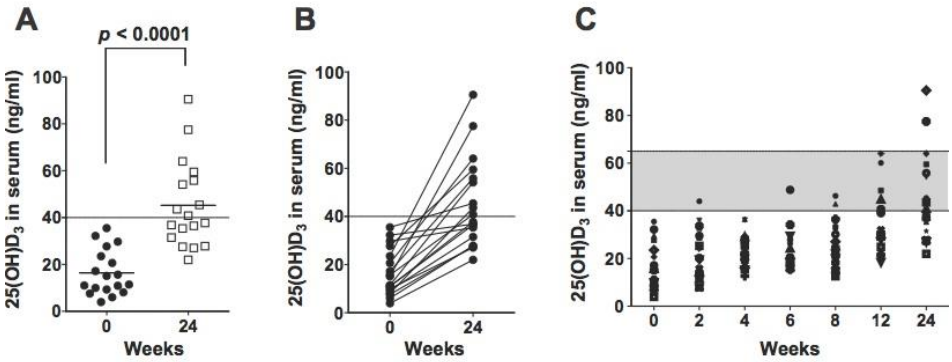
Dual energy X-ray absorptiometry (DEXA) Scan**.** The bone mineral density (BMD) of proximal femur measured by DEXA was performed at the beginning and end of the study by a trained technician. The T-score and Z-score were calculated according to age and gender.
Statistical analysis. Graphs and some basic statistics were generated using GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, California, USA). Baseline and 24 week values were evaluated to determine if they were normally distributed and compared using either a t-test and/or the Wilcoxon rank sum comparisons. Individual changes in lab tests, CDAI scores, and IBDQ values for a given patient were calculated to assess differences due to the supplementation therapy. Regression analyses were done using PROC GLM in SAS (version 9.3, SAS Institute, Cary, NC).

Results
Baseline characteristics of the patients. Based on an initial telephone conversation a total of 31 subjects were evaluated for entry into the study. Of the 31 subjects 10 subjects were ineligible largely due to having CDAI scores outside of the 150-400 score range. None of the screen failures were due to serum $25(OH)D_3$ levels above the 40 ng/ml threshold. Three additional patients withdrew from the study leaving a total of 18 patients who completed the study. The main reason stated for withdrawal from the study was compliance with scheduling the multiple visits required to determine appropriate vitamin D dosage (early bi-weekly visits). We originally had wanted to have 30 patients finish the study. The difficulty we think was the location and the early visits that precluded individuals from coming in bi-weekly. Future studies will not use 5000 IU/d and we should be able to recruit more easily.

The study had 61% females and 39% males with a broad age range of 18 to 66 and a mean age of 38. The mean body mass index (BMI) was 24 $\pm$ 3 kg/m2 with a broad range of BMI values from a low of 18 to a high of 30. Patients were on several different conventional IBD treatments including anti-TNF-α biologic agents (n=5), purine analogs (n=4), aminosalicylates (n=9) and

opioid receptor antagonists (n=4). Several patients were on more than one treatment (n=5) and 2 patients were not on any Crohn's maintenance drugs.

Figure.1

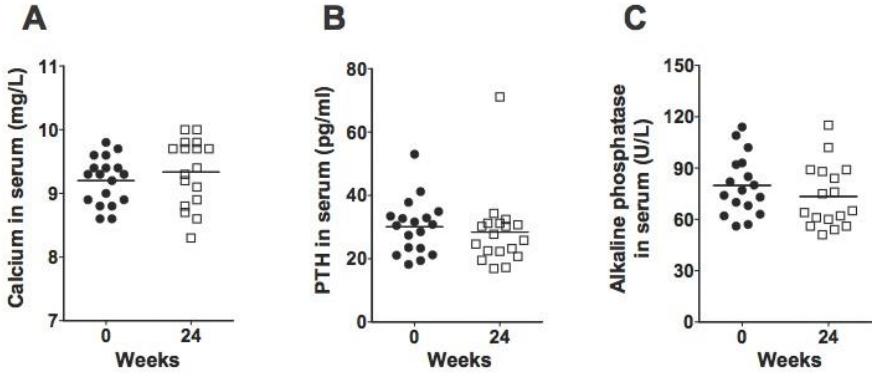


Participants were allowed to continue on multi-vitamins that contained vitamin D. At baseline 67% of the Crohn's patients were taking nutritional supplements that contained between 120-800 IU/d of vitamin D. Baseline vitamin D status of the Crohn's population was low even among those consuming multivitamin supplements (including vitamin D). Serum samples were obtained from 25 Crohn's patients at baseline. Thirteen of the 25 Crohn's patients (52%) had frank vitamin D deficiency at screening with serum 25(OH)D_3 levels below 12 ng/ml. The mean 25(OH)D_3 value of the patients entering the study was 16 $\pm$ 10 ng/ml (Fig. 1A).

<u>Vitamin D supplementation raises serum 25(OH)D_3 levels.</u> Vitamin D_3 supplementation for 24 weeks effectively and significantly raised serum 25(OH)D_3 levels to 45 $\pm$ 19 ng/ml from 16 $\pm$ 10 ng/ml (Fig. 1A). Two weeks of 1000 IU/d of vitamin D_3 was not adequate for raising 25(OH)D_3 levels in any of the 18 individuals in the study. In 14 of the 18 patients (78%) the maximal dose of 5000 IU/d was needed for the 24 wk study. Two of the patients that required less than 5000 IU/d of vitamin D_3 had higher levels of 25(OH)D_3 at baseline (over 30 ng/ml). Two patients had a dose reduction of vitamin D_3 from 5000 to 4000 IU/d due to unrelated health problems and those two patients remained on the lower dose of 4000 IU/d for the remainder of the study. Even on the maximum dose of 5000 IU/d dose for 24 weeks half of the participants failed to achieve serum 25(OH)D_3 levels above 40 ng/ml. Fig.1B shows the beginning and ending value of 25(OH)D_3 for each individual patient. Those subjects who started with higher vitamin D levels at baseline had reduced improvement in serum 25(OH)D_3 and those that started with low vitamin D levels showed the greatest improvement (Fig. 1B). The maximum increase in serum 25(OH)D_3 was 67 ng/ml, and smallest increase was 5 ng/ml. (Fig. 1B). There was a gradual improvement in serum 25(OH)D_3 levels over the six month supplementation (Fig. 1C). By week 24 two patients had serum 25(OH)D_3 levels above our targeted range of 65 ng/ml (Fig. 1C). Compliance was good based on the pill counts and was 96% (range 72%-100%) for the study overall. The improvement in serum vitamin D status was not associated with a change in serum PTH (from 30 $\pm$ 9 to 28 $\pm$12 pg/ml), calcium (from 9.2 $\pm$ 0.4 to 9.3 $\pm$0.5 mg/dL), or alkaline phosphatase (from 80 $\pm$ 17 to 73 $\pm$18 U/L) following 24 wk vitamin D_3 supplementation (Fig. 2). There was a small but insignificant increase in the BMD of both the right and left hip Z-score after 24 weeks of vitamin D_3 intake (data not shown). PTH and calcium values were all within the normal range both at the start and at the end of the study suggesting that the vitamin D_3 dose was not in the

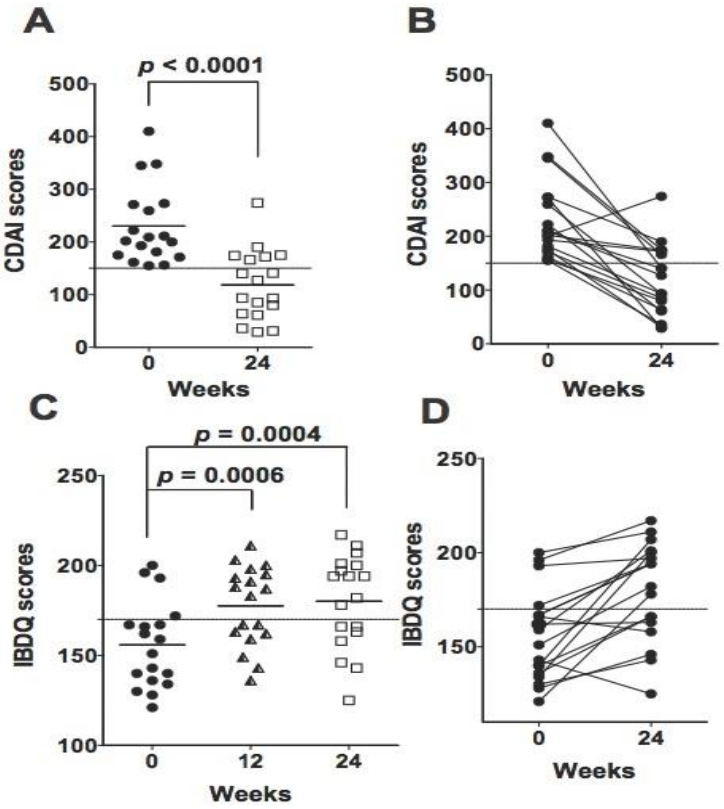
toxic range for any patient. There was no significant correlation between 25(OH)D_3 and either PTH or calcium at either time point.

Figure. 2



Crohn's disease severity**.** The mean CDAI score for patients at the beginning of the study was 230 ±74 indicating active disease (Fig. 3A). After 24 weeks of vitamin D the CDAI scores were below 150 for 67% of the participants (Fig. 3). The mean CDAI scores after 24 weeks vitamin D_3 supplementation also suggested that the patients were in remission. The mean CDAI score at follow-up was 118 ± 66 (Fig. 3A) with 12 out of 18 patients (67%) in remission with CDAI < 150. Furthermore, 17 patients (95%) achieved a response, with an average decrease in CDAI score of 112 ± 81 points after vitamin D supplement use for 24 weeks (Fig. 3). The maximum decrease was 269 points (from 410 to 141) with 78% of the patients experiencing a decrease in CDAI score of >70 points. Of the remaining participants three experienced a decrease of less than 70 points (decrease of 21-69 points) and 1 experienced an increase of 74 points. Two of the non-responders were patients that started with high serum 25(OH)D_3 and ended up on less than 5000 IU/d vitamin D_3. Based on univariate Pearson Correlations was no relationship between CDAI and 25(OH)D_3 status either before or following 24 week vitamin D_3 supplementation. The change in CDAI scores was inversely related to CDAI score at baseline indicating that patients with high CDAI scores at baseline showed the greatest vitamin D treatment effects (See Supplementary Table 1 online). CDAI scores showed a positive association with serum PTH before supplementation but the relationship disappeared after supplementation.

Figure. 3



Baseline IBDQ scores of 156 ± 24 were reported indicating poor quality of life (Fig. 3C). After supplementation for 12 weeks, 56% of patients had more favorable IBDQ scores with mean values of 178 ± 22 (p=0.0006) (Fig. 3C). At wk 24, the IBDQ scores were maintained and were also significantly higher than at baseline 180 ± 26 (p=0.0004) but not different from the 12 wk scores (Fig. 3C). The one patient that showed an increase in CDAI score also showed a decreased IBDQ score from 143 to 125 after 24 wks and as noted previously, a serum 25(OH)D_3 level that didn't reach the 40 ng/ml target (32 ng/ml after 24 wk) (Fig. 1 and 3). There was a significant inverse correlation between CDAI scores and IBDQ score both before and after supplementation. Serum 25(OH)D_3 level and the change in serum 25(OH)D_3 level after supplementation revealed a positive correlation with IBDQ score but not before.

Multiple linear regression analyses showed that at follow-up mean CDAI score was decreased by 112 points (96 for women, 95% CI=55-138; 136 for men, 95%=CI 83-189) after accounting for gender, change in serum vitamin D and baseline CDAI score (data not shown). Change in serum vitamin D over the follow-up time was marginally associated with change in CDAI score (p=0.09). In addition, at follow-up the mean IBDQ scores increased by 24 points (24 for women, 95% CI = 10-37; and 25 for men, 95% CI = 7-42) after accounting for gender, change in serum vitamin D, and baseline IBDQ. Change in serum vitamin D over the follow-up time was significantly associated with change in IBDQ score (p=0.0302). The addition of other covariates including BMI, age, and baseline serum vitamin D did not affect the results in either model.

Dietary status. The diets of all participants were evaluated using a series of 3-24 hour recall surveys at baseline and follow-up 24 weeks later. The nutrient intakes are reported as totals and the overall intakes per 1,000 kcal since individuals who consume more energy would be more likely to consume more nutrients. There were not significant changes in the dietary composition of most nutrients between baseline and 24 weeks (Table 1). As part of the evaluation, supplement use was recorded at baseline and 24 weeks for all participants (Table 2). There were nine patients already taking vitamin D supplements at baseline that ranged from 120-800 IU/d or 3-20 μg/d vitamin D (Table 2). At the end of the trial all but 1 of the original nine patients were still taking the vitamin D supplements. At baseline the mean total vitamin D intakes were below the DRI for all but two participants who were supplementing their vitamin D intakes. Dietary vitamin D, supplemental vitamin D (as background) and total vitamin D did not change significantly between baseline and 24 weeks (Table 2). There was an increase in the use of calcium supplements at 24 weeks compared to baseline calcium supplement use (Table 1). This resulted in an increase in total calcium ($p<0.06$) and a significant difference in total calcium reported for 1,000 kcal energy intake between 24 wk and baseline (Table 1). There were no differences in the intakes of vitamin A, vitamin C, vitamin E, iron, selenium or zinc between baseline and 24 wk follow-up (Table 1).

Table 1. Selected Dietary Characteristics of Participants (n=18)[1]

	Baseline mean (SD)	Follow-up mean (SD)	[2]Change mean (SD)	[3]p-value
Energy (kcal)	1739 (603)	1542 (444)	189 (431)	0.10
Carbohydrates (% kcal)	51 (9.8)	51 (5.4)	0 (10.3)	0.83
Protein (% kcal)	17 (4.6)	18 (4.3)	-1 (4.6)	0.56
Fat (% kcal)	32 (7.2)	31 (4.0)	1 (8.3)	0.63
Dietary calcium (mg)	670 (388)	648 (279)	-1 (290)	0.99
(mg /1,000 kcal)	379 (155)	442 (203)	-73 (160)	0.09
Calcium supplements (mg)	228 (576)	506 (970)	-250 (418)	**0.03**
Total calcium (mg)	897 (606)	1153 (879)	-251 (490)	0.06
(mg/1,000 kcal)	538 (408)	791 (648)	-245.2 (320)	**0.008**
Dietary vitamin D (μg)	3.7 (2.4)	5.3 (6.6)	-1.7 (6.8)	0.33
(μg/1,000 kcal)	2.2 (1.5)	3.9 (5.1)	-1.7 (4.8)	0.17
[4]Vitamin D supplement (μg)	4.9 (5.9)	4.8 (5.5)	0.6 (3.5)	0.48
Total vitamin D (μg)	8.5 (6.4)	10.1 (9.5)	-1.0 (5.6)	0.46
(μg/1,000 kcal)	5.3 (4.5)	7.2 (7.0)	1.6 (3.7)	0.11
Total vitamin A (μg RAE)	1322 (1005)	1365 (914)	62 (348)	0.49
(μg RAE/1,000 kcal)	799 (691)	954 (707)	-88.78 (338.1)	0.31
Total vitamin C (mg)	113 (106)	272 (746)	-173 (754)	0.37
(mg/1,000 kcal)	64 (53)	139 (327)	-80 (334)	0.35
Total vitamin E (mg ATE)	19 (16)	22 (17)	-2.0 (10.8)	0.48
(mg ATE/1,000 kcal)	11 (10)	15 (12)	-3 (9)	0.19
Total iron (μg)	37 (41)	38 (61)	2 (30)	0.78
(μg/1,000 kcal)	24 (31)	27 (46)	-1.1 (19)	0.82
Total selenium (μg)	114 (54)	103 (46)	13 (49)	0.31
(μg/1,000 kcal)	67 (26)	68 (27)	0.15 (27)	0.98
Total zinc (mg)	9.3 (4.5)	9.9 (5.5)	-0.66 (4.9)	0.59
(mg/1,000 kcal)	5.2 (1.3)	6.5 (3.5)	-1.2 (3.0)	0.12

[1]Values for the daily recommended intakes (DRI) for people aged 19-30 are as follows. For all nutrients except iron the lower value is for females, higher value is for males, and if there is only one value it is the same DRI for males and females: 1000 mg calcium, 15μg vitamin D, 700-900 μg vitamin A, 75-90 mg vitamin C, 15 mg vitamin E, 8-18 μg iron, 55 μg selenium, and 8-11 zinc.
[2]Change calculated as baseline – follow-up.
[3]p-value is for significant change between time points.
[4]There were 9 users of multi-vitamin supplements that contained vitamin D at baseline; all but 1 of these remained multi-vitamin users at follow-up. Background vitamin D supplement use ranged between 3-20 μg/d or 120-800 IU/d.

<u>Secondary outcomes.</u> Serum from the Crohn's patients before and after vitamin D_3 supplementation was assessed to determine whether there were changes in markers of inflammation associated with the vitamin D_3 supplementation. CRP, ESR, TNF-α, IL-17, IL-10

and vascular endothelial growth factor (VEGF) were all found to not be affected by the vitamin D supplementation (data not shown).

IPAQ questionnaires showed that of the 14 patients evaluated there was the same level of physically activity before and after vitamin D_3 supplementation (data not shown). Three of the participants increased their activity, three of the participants decreased their activity and the remaining 8 had no change in physical activity following vitamin D_3 supplementation (data not shown). The IPAQ scores were therefore unaffected by the vitamin D_3 supplementation.

Adverse effects. There were no significant adverse effects that could be directly attributed to vitamin D_3 supplementation. Complaints among the patients that may have been related to the supplement included headache, dizziness, fatigue, abdominal pain, constipation, and rash. Fifteen subjects reported one or more adverse events. The most common reported adverse event was headache, which occurred in 5 (28%) subjects. Four (22%) subjects reported mild abdominal pain. Four (22%) subjects reported rash that resolved within 1 day. Four (22%) subjects reported fatigue. All of these reported adverse events were mild and no infectious or serious adverse events occurred during the treatment.

Conclusions: In a small clinical trial in central PA vitamin D_3 supplementation for 24wks effectively improved vitamin D status, decreased CDAI scores and improved IBDQ scores in 18 patients. By raising serum vitamin D levels Crohn's patients with mild to moderate symptoms exhibited a decrease in CDAI scores such that the majority of patients achieved remission. The effect of vitamin D_3 on the CDAI scores was remarkable with all but one patient having a decrease in CDAI score and 78 % of the patients had a drop of 70 points or more, which is considered a treatment response in the clinic. The vitamin D_3 effect was also reflected in the improved IBDQ scores, which is a second validated assessment tool used to monitor therapeutic efficacy in clinical trials of IBD. The IBDQ questionnaire consists of 32 questions scored in four domains: bowel symptoms, emotional health, systemic systems, and social function. As established by other investigators the IBDQ scores were significantly correlated to the CDAI scores at both baseline and 24 weeks indicating that vitamin D_3 effectively improved both quality of life and CDAI scores. Even with the small number of participants and the lack of a placebo the study points to a strong effect of vitamin D_3 supplementation on Crohn's disease symptoms. The primary goal of the study was to determine what dose of vitamin D_3 would be required to raise serum $25(OH)D_3$ levels into a target range of over 40 ng/ml. Consistent with what has been published by others we found that Crohn's patients have low serum $25(OH)D_3$ levels. Even though the majority of the patients were on vitamin D supplements at baseline, that level of supplementation was insufficient to sustain serum $25(OH)D_3$ above 40 ng/ml. In fact, half of the Crohn's patients screened for the study had frank vitamin deficiency with serum levels of $25(OH)D_3$ suggesting malabsorption. The maximal amount of vitamin D_3 (5000 IU/d) was needed to raise serum $25(OH)D_3$ above 40 ng/ml. The serum levels of $25(OH)D_3$ were slow to respond to the vitamin D_3 supplement and even between 12 weeks and 24 weeks serum $25(OH)D_3$ levels continued to go up even though the dose of vitamin D_3 was not changed. It seems likely that the increased level of $25(OH)D_3$ between the 12 week and 24 week time point reflect improvement in CDAI scores, a healthier gut and better absorption of the vitamin D supplement. There were no signs of vitamin D toxicity based on the fact that both calcium and PTH were unaffected by the vitamin D_3 supplementation. In addition, there were no reported

adverse events that required a decrease or discontinuation of the vitamin D dose. Although the higher serum levels of 25(OH)D_3 were not toxic there are no reported benefits associated with high serum levels of 25(OH)D_3. In future studies it would be prudent to check the serum 25(OH)D_3 levels at least every 3 months to monitor the 25(OH)D_3 levels and to adjust the vitamin D_3 supplementation downward if needed. This study suggests that in patients with mild to moderate Crohn's disease a safe and tolerable dose of vitamin D that effectively raises serum 25(OH)D_3 levels is 5000 IU/d.

Calcium intakes were increased in the participants at week 24 compared to baseline (Table 1). A closer inspection of the dietary data provided by the individuals seemed to indicate that some individuals at follow-up consumed a calcium supplement every day of the 3 days of recall but only two of the 3 days at baseline. Therefore, it seems unlikely that the relatively modest change in calcium for a few individuals would account for the observed changes in CDAI and IBDQ scores. Other known immune-modulatory nutrients including vitamin A, vitamin C, vitamin E, selenium, iron and zinc were not different between baseline and 24 wk follow-up. It is possible that at wk 24 absorption of numerous nutrients (other than vitamin D) had improved concomitant with the decrease in CDAI scores; in future vitamin D supplement research it would be interesting to determine the concentrations of other micronutrient biochemically.

The Crohn's patients in this study were on several different maintenance therapies except glucocorticoids. The rationale for the exclusion of the glucocorticoids was the fact that usually glucocorticoid treatment is used to suppress Crohn's disease flares and the goal was to have patients with active but mild to moderate Crohn's symptoms. The study was not powered to identify whether vitamin D_3 supplementation might be more or less effective based on the other treatments being used. However, since vitamin D reduced CDAI scores in all but one patient it seems that the exclusion of any of the common maintenance therapies may not be warranted.

Several serum proteins were measured in the patient population. Acute-phase proteins such as CRP have been shown to increase with inflammation and to correspond with active Crohn's disease. ESR measurements are another non-specific measure of inflammation. There was no effect of vitamin D_3 supplementation or improvement in CDAI on the levels of either CRP or ESR in this cohort. In addition, TNF-α and IL-17 were detectable but not affected by the vitamin D_3 supplementation. VEGF is another serum protein that has been shown to correlate with active Crohn's disease. There was no effect of vitamin D_3 on any of the serum proteins measured and there was no correlation between these inflammatory biomarkers and the improvement in CDAI scores seen. At this time it is unclear by what mechanisms vitamin D might be improving the CDAI scores. This would be an important area for future research.

This small pilot study establishes that vitamin D_3 supplementation of patients with mild to moderate Crohn's disease is effective at improving the quality of life and suppressing clinical symptoms to induce remission. An effective dose of vitamin D_3 for improving vitamin D status in Crohn's patients was identified as being 5000 IU/d. The major limitations of this study are the small sample size and lack of placebo control. The study suggests that future larger studies that include placebos and go on for longer periods of time are warranted.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X___Yes
_____No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X__Yes
_____No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

___6___Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

___30___Number of subjects originally targeted to be included in the study
___31 _ Number of subjects enrolled in the study
(but only 18 completed the study)

Note: Studies that fall dramatically short on recruit.tment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
___12__Males
___19__Females
_____ Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics

__31__Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
__31__Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

University Park – Centre County and Hershey – Dauphin County

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF

version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Therapeutic effect of vitamin D supplementation in a pilot study of Crohn's patients.	Linlin Yang, Veronika Weaver, Jill P. Smith, Sandra Bingaman, Terryl J. Hartman and Margherita T. Cantorna	Clinical and Translational Gastroenterology	June 2012	☐Submitted ☐Accepted ☒Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

We have plasma samples available that will be used for metabolomics analysis. Publications in the future may use that data.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be

single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

This small pilot study establishes that vitamin D_3 supplementation of patients with mild to moderate Crohn's disease is effective at improving the quality of life and suppressing clinical symptoms to induce remission. An effective dose of vitamin D_3 for improving vitamin D status in Crohn's patients was identified as being 5000 IU/d. The major limitations of this study are the small sample size and lack of placebo control. The study suggests that future larger studies that include placebos and go on for longer periods of time are warranted.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No X

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Margherita T. Cantorna	**Professor**
eRA COMMONS USER NAME (credential, e.g., agency login) mcantorna	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Illinois	BS	1982-86	Chemistry
University of Wisconsin	PhD	1986-90	Immunology
University of Wisconsin	Post-doc	1990-92	Biochemistry

A. Personal Statement

The Cantorna laboratory studies mucosal immunology and inflammatory bowel disease in particular. The focus is on nutritional control of immune function and in particular most of our work has been to understand how vitamin D regulates immune function. Other nutrients of interest include mushrooms, and iron. To that end we have established several models of autoimmunity including inflammatory bowel disease to identify the targets of vitamin D in the immune system. In addition to the mouse work, in the last several years we have begun to work in human patients to study the effects of vitamin D supplementation in humans. We have published one manuscript that used a vitamin D supplement in multiple sclerosis patients.

B. Positions and Honors

Positions and Employment

1986-1990 Research Assist., Dept. of Med. Micro. & Immunol. U.of WI-Madison
1990-1992 Postdoctoral Fellow, Dept. of Biochem. U. of WI-Madison
1992-1994 NIH-NRSA Postdoc. Fellow, Dept. of Biochem.U.of WI-Madison
1995-1997 Assistant Scientist Dept. of Biochem. U. of WI-Madison
1998-2004 Assistant Professor, Immunology and Nutrition, Nutrition Dept., Pennsylvania State University
2004-2005 Associate Professor, Immunology and Nutrition, Nutrition Dept., Pennsylvania State University
2005- 2010 Associate Professor, Molecular Immunology, Vet. and Biomed.Sci, Pennsylvania State Univ.
2010-present Professor, Molecular Immunology, Vet. and Biomed. Sci. Pennsylvania State Univ.

Other Experience, Honors and Professional Memberships

1990 Gustafsson Fellowship Award, Association for Gnotobiotics, Buffalo, NY.
1992-1994 National Research Service Award, National Cancer Institute
1998 Patent No. US005716946A- Multiple sclerosis treatment.
1998 American Association of Immunology Travel Award,10th International Congress of Immunology in New Delhi India.
1999 Patent No. US005891865A- Arthritis treatment.

2000 Patent No. US006071897A- Prevention of transplant rejection.
2002 Patent no. US006479474 - Dietary Calcium as a supplement of vitamin D compound treatment of multiple sclerosis.
2004 Ad Hoc member, NIH Review Panel, RFA CA04-004"Molecular Target for Nutrients in Prostate Cancer"
2004 Patent No. US006673782 -Treatment of Systemic Lupus Erythematosis.
2004-2006 Ad Hoc member NIH Review Panel, Immunity and Host Defense, Special Emphasis Panel ZRG1IHD.
2006 Member Cancer Prevention P01 review panel. National Cancer Institute, NIH
2006-2010 Member NIH Review Panel, Immunity and Host Defense
2006 Directors Challenge, National Institute of Environmental Health Sciences, Internal review panel
2009 Experimental Biology and Medicine, Top ten most read articles. "Mounting Evidence for Vitamin D as an Environmental Factor Affecting Autoimmune Disease Prevalence", 229:136-1142, 2004.
2010 Patent # 704980 Treatment of Inflammatory Bowel Disease with 2-methylene-19-nor-vitamin D compounds.
2010 Member ZDK1 GRB-7 Microbiota and Immunity Program Projects National Institutes of Health
2011-present Member NIH Review Panel, Integrative Nutrition and Metabolic Processes.
2011 Ad Hoc member, NIH Review Panel, Immunity and Host Defense
2011 Ad Hoc member, NIH Review Panel, National Advisory Council of Complementary and Alternative Medicine review panel
2011 Editor Journal of Nutritional Biochemistry
2012 Osborne and Mendel Award for outstanding recent basic research accomplishments in nutrition, American Society for Nutrition, Bethesda, MD

C. Selected Peer-reviewed Publications (Selected from 59 peer-reviewed publications)
Most relevant to the current application

1. Froicu, M., V. Weaver, T.A. Wynn, J. Welch, M. McDowell, and M.T. Cantorna. 2003. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. Mol. Endo. 17:2386-2392.
2. Froicu, M., Y. Zhu, and M.T. Cantorna. 2006. Vitamin D receptor signaling is required to control Th1 driven gastrointestinal immunity in IL-10 knockout mice. Immunol.117:310-318.
3. Froicu, M., and M. T. Cantorna. 2007 Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. BMC Immunol 8:5.
4. Yu, S., V. Weaver, K. Martin, and M.T. Cantorna. 2009. The effects of whole mushrooms during inflammation. BMC Immunol 10:12.
5. Yu. S., Bruce, D, M. Froicu, V. Weaver and Cantorna, M.T., 2008. Failure of T cell homing, reduced CD4/CD8αα intraepithelial lymphocytes and inflammation in the gut of vitamin D receptor KO miceProc. Natl. Acad. Sci. USA 105:20834-20839.
6. Bruce, D. and M. T. Cantorna. 2011. Intrinsic requirement for the vitamin D receptor for the development of CD8αα expressing T cells. J. Immunol. 186:2819-2825.
7. M. Pinkerton, V.Chinchilli, E. Banta, T. Craig, A. August, R. Bascom, M.T. Cantorna, E. Harvill, and F.T. Ishmael. 2013. Differential expression of microRNAs in exhaled breath condensates of patients with asthma, patients with chronic obstructive pulmonary disease, and healthy adults. J. Allergy Clin. Immunol. In press.
8. L. Yang, V. Weaver, J.P.Smith, S. Bingaman, T. J. Hartman, and M.T. Cantorna. 2013. Therapeutic effect of vitamin D supplementation in a pilot study of Crohn's patients. Clin Transl Gastroenterol. 4:e33.

Additional recent publications of importance to the field (in chronological order)

1. Cantorna, M. T., and B.D. Mahon. 2004. Vitamin D and autoimmunity: Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp. Biol. Med. 229:1136-1142.
2. Bruce, D, J. P. Whitcomb, A. August, M. A. McDowell and Cantorna, M.T. 2009 Elevated nonspecific immunity and normal Listeria clearance in young and old vitamin D receptor knockout mice. Inter Immunol. 2:113-122.
3. Yu, S. and M. T. Cantorna 2008. The vitamin D receptor is required for iNKT cell development. Proc. Natl. Acad. Sci. USA. 105:5207-5212.
4. Cantorna, M.T. 2010 Why do T cells express the vitamin D receptor? Ann N Y Acad Sci. 1217:77-82.
5. Bruce, D., S. Yu, J. H. Ooi, and M. T. Cantorna. 2011. Converging pathways lead to overproduction of IL-17 in the absence of vitamin D signaling. Inter. Immunol. 8:519-528.
6. Yu, S., J. Zhoa, and M.T. Cantorna. 2011. Invariant NKT cell defects in vitamin D receptor knockout mice prevents experimental lung inflammation. J. Immunol. 187:4907-4912.
7. Whitcomb, J.P., M. DeAgostino, M. Ballentine, J. Fu, M. Tenniswood, J. Walsh, M.T. Cantorna, and M.A. McDowell. 2011 The role of vitamin D and vitamin D receptor in immunity to *Leishmania major* infection. J. Parasitol. Res. In press.
8. Yu, S. and M.T. Cantorna 2011. Epigenetic regulation of invariant NKT cells following in utero vitamin D deficiency in mice. J. Immunol.186:1384-1390.

D. Research Support

Ongoing Research Support

1R01AT005378 Cantorna (PI)
National Institute of Health
"Vitamin D Fluctuations and the Mucosal Immune Response"
8/01/2009-7/31/2014
The Aims of this grant are to determine the effects of vitamin D on the homing, development and function of CD8$\alpha\alpha$/TCR$\alpha\beta$+ T cells in the gut.

1R01 NS067563 Cantorna (PI)
National Institute of Health
"Vitamin D and NKT Cell Regulation of Multiple Sclerosis"
4/1/2010-3/30/2015
The Aims of this grant are to determine the effect of vitamin D on iNKT cell development and function, specifically as they relate to multiple sclerosis.

Recently Completed
Clinical and Translational Science Award, Cantorna (PI), Hartman (Co-I), Smith (Co-I)
Pilot Project Grants Pennsylvania State University
"Vitamin D and Crohn's disease: from the bench to the clinic"
04/01/2009-3/31/2012

The Aims of this grant are to determine if there are health benefits to Crohn's disease patients from a 6 month vitamin D intervention.

Clinical and Translational Science Award, August (PI), Cantorna (Co-I)
Pilot Project Grants Pennsylvania State University
"T cells and macrophages in asthma and respiratory infections"
9/1/2009-8/30/2012
The Aims of this grant are to use human samples to study T cell and macrophage responses to various stimuli.

1R01DK070782 Cantorna (PI)
National Institute of Health
"Vitamin D regulation of Inflammatory Bowel Disease"
9/01/2006-7/31/2010
The Aims of this grant are to understand the mucosal immune response in the gut and the types of T cells that regulate the response in the gut. The role of vitamin D and 1,25(OH)2D3 in regulation of T reg and CD8+ T cells was the focus of this grant.