Novel Approach for Designing Supportive Care in Genetic Disorders of Gastrointestinal Tract: Three-Dimensional Polymer Model of Nutritional Therapies in Cystic Fibrosis, Ulcerative Colitis, and Crohn’s Disease

Paul Zarogoulidis1,2, Ioannis Kioumis1, Theodora Tsiouda1, Nikolaos Pezirkianidis1,*, Christos Ritzoulis1, Haidong Huang1, Wolfgang Hohenforst-Schmidt1, Dionyssos Spyropoulos3, Konstantinos Porpodis1, Georgia Pitsiou1, Sofia Lampaki1, John Organtzis1, Bianca Kathryn Malecki1,2, Sindre Evrik Saetre1,2, Konstantinos Zarogoulidis1, and Marek Malecki2,5,9

1Aristotle University of Thessaloniki, Thessaloniki, Greece, EU
2University of Duisburg-Essen, Duisburg, Germany, EU
3Theagenio Anticancer Hospital, Thessaloniki, Greece, EU
4Alexander Technological Educational Institute, Thessaloniki, Greece, EU
5II Military University Hospital, Shanghai, China
6Coburg Regional Hospital, Germany, EU
7Private Practice, Serres, Greece, EU
8Jagiellonian University Medical College, Krakow, Poland, EU
9Phoenix Biomolecular Engineering Foundation, San Francisco, CA, USA
10University of Wisconsin, Madison, WI, USA

Abstract

Introduction: Cystic Fibrosis (CF), Ulcerative Colitis (UC), and Crohn’s Disease (LCD) manifest as various, multiple symptoms from malfunctioning and/or damaged gastrointestinal tract, which plague the patients. These symptoms result from the dysfunctional expression products of the specific mutations of the genes, which either manifest upon birth (CF) or later in life in immuno-genetically susceptible individuals as diseases of gastrointestinal tract (LCD). They all may potentially lead to malnutrition of the patients. Since only correcting the mutated genes, may cure these diseases permanently, the works on the future safe gene therapies continue vigorously. However, the provision of the necessary nutrients to the suffering patients is requirement of the effective, supportive care at presence. In this realm, we have developed a model of the diseased gastrointestinal tract aimed to guide designing and testing various nutritional therapies.

Materials and Methods: It is well known that inflammatory bowel diseases induce crypts within the patients’ gastrointestinal tract. Therefore, we have bioengineered, a novel, three-dimensional model of the gastrointestinal tract to evaluate the rheology of different types of nutrients. The model was assembled out of the biocompatible, non-toxic polymer with openings leading to vials of different shapes and sizes.

Results and Conclusion: The newly developed three-dimensional model simulates effectively the structure and functions of the gastrointestinal tract of the patients with mild and severe Ulcerative Colitis, Crohn’s Disease, and Cystic Fibrosis. Modifications of the different nutrients, with properties complementing the changed by diseases functionalities of the patients’ gastrointestinal tracts, will help to design the proper supportive therapies; thus to prevent the patients’ malnutrition.

Keywords: Cystic Fibrosis; Crohn’s Disease; Ulcerative Colitis; Nutrition model; Bioengineering; Biotechnology

Introduction

Cystic Fibrosis, Ulcerative Colitis, and Crohn’s Disease originate with mutations of the genes and manifest with the symptoms within the gastrointestinal tract.

Specifically, Cystic Fibrosis is an autosomal recessive disorder caused by a mutation in the gene on chromosome 7, which is coding for the protein cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR is responsible for the transport of chloride and sodium ions across epithelial membranes, therefore a defective protein lead to thick and viscous secretions. Mutations at several different locations in the gene can all lead to Cystic Fibrosis manifesting with differing symptoms and with varying prognoses of the disease. Some mutations lead to production of a less functional protein, while others lead to no production at all. While the most common mutation is delta F508, over 1500 different mutations have been reported. The disease primarily affects the lungs, liver and pancreas. Increased PCO2 and respiratory acidosis is observed in advanced disease. Cystic fibrosis can be diagnosed before birth. Treatment of cystic fibrosis consists of bronchodilators, corticosteroids, antibiotics, enzyme replacement, insulin, bisphosphonates and vaccination during influenza exacerbation, and physiotherapy. Lung transplantation is eligible for final stage disease [1-6]. The vigorous work on gene therapy is rapidly progressing.

*Corresponding author: Marek Malecki, M.D., Ph.D., Phoenix Biomolecular Engineering Foundation, San Francisco, CA 91105, USA; telephone: 4157134370; fax: 4157134371; Email: mnn-pbmef@nms@pbmef.org

Received July 04, 2014; Accepted July 23, 2014; Published July 25, 2014


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Ulcerative Colitis is a chronic inflammatory disease of the gastrointestinal tract. While genetic susceptibility is at the core problem, the factor triggering the disease remains elusive. Dozens of genes have also been linked to ulcerative colitis, many of them involved in the protective function of the intestines. In addition, there is an increased incidence of inflammatory bowel disease in people that have a family member with inflammatory bowel disease, suggesting a genetic basis of these diseases. Ulcerative Colitis usually attacks the large intestine. It has exacerbation periods and disease free periods [7], all manifesting by chronic bloody diarrhea. It is mostly treated as an autoimmune disease, although symptoms might diminish spontaneously. Nutritional supplementation certainly improves the patients’ well-being. Pregnancy is possible during symptom free periods. [7-12].

Crohn’s Disease has genetic mutations as the causative factor. Perhaps the most important of these genes is the NOD2 gene, as people with a mutated NOD2 have a 20 times increased risk of the disease. Nevertheless, mutations in many other genes may contribute to developing full blown symptoms. Crohn’s Disease might affect any part of the gastrointestinal tract (GIT). Patients may present with a variety of symptoms such as vomiting, weight loss, abdominal pain and diarrhea. Moreover, other symptoms include eye inflammation, anemia, arthritis and skin rash [13]. The manifestation of this disease, in the genetically susceptible people, depends on the interaction of the immune system, environmental factors and bacteria. Nevertheless, Crohn’s Disease does not appear to have an autoimmune background [14-16]. Treatment consists of anti-inflammatory agents, immune system suppressors, antibiotics, surgery, nutritional support and symptomatic relief (anti-diarrheal, laxatives) [17]. Potential of immuno-gene therapy is intensively explored.

The rapid progress takes place in refining the genomic background for these diseases. This creates the solid foundations for developing strategies for gene therapy. Meanwhile, the treatments are aimed at providing to the patients some relief of symptoms they are suffering from.

This work was dedicated to compensating the problems resulting from disturbances of the gastrointestinal tract the patient suffer. In this realm, we have developed a three-dimensional polymer model for designing of therapeutic nutrition.

Material and Method

The rationale for the project was the well known fact, that that the aforementioned diseases of the gastrointestinal tract induce formation of crypts. These crypts have different sizes with different diameters of entrances. The result is that the nutrient may easily enter, but may have difficulties on exit. This phenomenon aggravates the symptoms of the disease. Therefore, we pursued the concept of designing and engineering of a spatial model of tract simulating pathologically altered gastrointestinal tract of the patients. In order to do that we used the Altech® breathing circuit LOT: 6259.1503.12, 120 cm limb Y connector with ports 2lt latex free. We acquired pipettes with two different diameters 5 mm and 7 mm. We cut out most of the suction tube leaving only 5 mm in length. Afterwards we punctured 10 holes in different parts of the circuit and clued the pipettes head and neck in between the beginning and end (Figure 1). We glued the neck of the pipettes with Pattex® silicone that was melted again with Pattex®-Henkel KGaA melting apparatus (Nr: 10172786 Duesseldorf) (Figure 2). We have chosen to use two different pipettes with different ‘necks’ in order to simulate two different types of crypts. We named the 7 mm diameter grade I and the 5 mm diameter grade II (Figure 3). Grade II was relevant to the worse, based on the fact that a crypt with a smaller entrance releases the nutritional material more difficult. We designed three different groups of nutritional material: a) Proteins b) Carbohydrates and c) Fat. For each group we designed additionally six subgroups with different pH and viscosity. Viscosity is the most important factor influencing the rheology and deposition of nutrition within the GI tract. We have to comment at this point that all pipettes had the same volume. We are currently designing and engineering a pump simulating the gastrointestinal tract movement, so that more information can be gathered regarding its function, as well as of administered nutrients.

Results and Conclusions

In all aforementioned diseases, Ulcerative Colitis, Crohn’s Disease, and Cystic Fibrosis, gastrointestinal tract of the patients is pathologically altered. This may lead to their malnutrition. Therefore, nutrition is the key element of the supportive care.

The newly developed three-dimensional model simulates effectively the structure and functions of the gastrointestinal tract of the patients.

![Figure 1: 3D Polymer Tude with endoluminal traps](image1)

![Figure 2: Pattex®-Henkel KGaA melting apparatus (Nr: 10172786 Duesseldorf, Germany).](image2)
with mild and severe. Modifications of the different nutrients, with properties complementing the changed by diseases functionalities of the patients’ gastrointestinal tracts, will help to design the proper supportive therapies; thus to prevent the patients’ malnutrition. This can be accomplished by well designed composition and properly adjusted administration of the nutritional therapy, which addresses the spatial changes (crypts) for each of these diseases. While there are already several nutritional supplements on the market that can be used by the patients additionally to their treatment, their selection may benefit from tests run on the model system, which we present herein. We continue experimenting with the different types of nutritional compounds, different viscosities, acid/bases gradients, osmolarity, etc in order to identify the optimal combinations for the particular patient. Optimization of nutrition rheology could contribute effectively to the adjudant treatment for these patients. In general, spatial models of the pathologically altered gastrointestinal tract are excellent starters for initial experimentation, as we can easily proceed to an in vitro or in vivo experimentation [18]. Further refinement of the model system described herein, should help us in designing optimal composition and properties of the provided nutrients, thus to improve supportive care of our patients.

Conflict of Interest Statement

The authors state no conflict of interest.

Sources of Funding for the Work

This work was supported by the funds from the National Institutes of Health [grant numbers: P41 RR000570 and from the Phoenix Biomolecular Engineering Foundation [grant number: 2006070101]] to Marek Malecki MD PhD - Principal Investigator. Administrators of the funding institutions and managers of the facilities had no influence on the project design and presented data.

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