HHS Public Access

Author manuscript

Nat Rev Gastroenterol Hepatol. Author manuscript; available in PMC 2015 June 24.

Published in final edited form as:

Nat Rev Gastroenterol Hepatol. 2014 October ; 11(10): 584–586. doi:10.1038/nrgastro.2014.149.

Dynamic imaging of gut function: allowing the blind to see

Bishnu P. Joshi and **Thomas D. Wang**

Department of Medicine, Division of Gastroenterology, University of Michigan, 109 Zina Pitcher Place BSRB 1522, Ann Arbor, MI 48109-220, USA (B.P.J., T.D.W.)

Abstract

Improved methods are needed to dynamically image gut behaviour to assess for neuromuscular degenerative diseases. So-called nanonaps (soluble nanoformulated naphthalocyanines) have been developed for oral administration to pass through the intestines and provide high contrast for visualizing bowel motion on photoacoustic imaging. Moreover, radiotracer labelling of these nanoparticles facilitates multimodal detection using PET.

Motility disorders of the intestines give rise to a number of nonspecific gastrointestinal symptoms, such as bloating, constipation, nausea, pain and vomiting. These complaints are among the most frequent reasons that patients have for seeing a doctor. Common causes include acid reflux, anticholinergic drugs (for example, antihistimines), small bowel bacterial overgrowth and IBS.[1] These symptoms can also be caused by disorders of the intestinal nervous (neuropathy) or muscular (myopathy) systems, including achalasia, gastroparesis, pseudo-obstruction and Hirschprung disease.[2] Routine laboratory studies are usually not useful in arriving at the diagnosis. Conventional whole-body imaging studies, including plain films (radiography), gastric emptying scans, barium studies, CT and MRI, are helpful but have limitations in speed for visualizing normal (or abnormal) gut contractile activity in real time. Endoscopy provides clear images of the mucosal surface at video rate, but offers little information to evaluate the electrical behaviour of the intestinal tract. Improved imaging methods that can assess the dynamic behaviour of gut function are, therefore, needed. Zhang *et al.* have developed a family of nanoparticles called “nanonaps” that can be used to visualize physiological gut function in mice using photoacoustic imaging to potentially address this unmet clinical need.[3]

This emerging imaging modality combines the use of light with sound to produce high-resolution images with deep tissue penetration to visualize bowel activity. These nanoparticles absorb light to generate sound waves. Imaging can be performed in real time, a speed much faster than that of most conventional whole-body methods. An example image using this approach is shown in Figure 1, for which orally administered nanonaps provide contrast throughout the intestines at a depth up to 5 mm. These nanocarriers contained naphthalocyanine dyes that are hydrophobic and can be encapsulated in micelles by self-assembly. This process occurs when intermolecular forces aggregate in a predetermined

Correspondence to: T.D.W. thomaswa@umich.edu.

Competing interests

The authors declare no competing interests.

manner at the critical micelle concentration. Pluronic F127, an FDA-approved biological surfactant, was used to create the protective micelles that formed spontaneously at freezing temperatures (4 °C). The 'frozen' nanonaps were able to pass through the intestines without being absorbed and were excreted intact in the faeces. This property allows the exogenous contrast agents to be administered orally, greatly improves the safety profile and increases potential for future human use. Nanotechnology offers tremendous potential for future clinical applications.[4] Nanostructured materials with different optical properties can be combined synergistically for use in multimodal imaging applications and for simultaneous diagnosis with therapy. These materials have both superparamagnetic and fluorescence properties that enable multimodal imaging to be performed by combining MRI with optical methods.[5] Also, the surface of the nanoparticle itself can be modified by labelling with organic dyes and radiotracers, enabling the combination of optical imaging with either PET or single-photon emission CT (SPECT).[6] PET images of ^{64}Cu-labelled nanonaps can be seen in the stomach at 0.5 h and in the small bowel and colon at 3 h (Figure 1b,c). The nanonaps can be tuned for maximum absorption over a wide range of near-infrared wavelengths with large absorption coefficients (>1,000). This region of light is used to maximize depth of tissue penetration and to generate strong photoacoustic signals with minimal interference from absorption by haemoglobin or scattering by tissue. The nanonap absorption peaks did not shift with increased optical densities, as is commonly seen with organic dyes, allowing predictable imaging parameters to be used with the contrast agent in high concentrations.

The nanonaps were found to be stable in the low pH (pH 2-4) environment of the stomach and to avoid enzymatic degradation from bile and pancreatic juices. Co-registered ultrasonography images were collected to provide real-time mapping of intestinal anatomy, which is useful for clarifying the interpretation of the photoacoustic images. The nanonaps were also labelled with ^{64}Cu, a PET tracer, to perform quantitative whole-body imaging and to demonstrate feasibility for multimodal imaging. The cellular toxicity of nanonaps on cells in culture did not exhibit any toxicity up to an absorbance of 100 OD, the highest value tested. Similarly, oral administration of 100 ODs of nanonaps to mice resulted in no noticeable inflammation or other toxic effects, and the intestinal villi and crypts appeared healthy on histological examination. Similar results were achieved at higher oral doses of 50,000 OD_{860}/kg. The ^{64}Cu-labelled nanonaps showed similar behaviour, and about 80% of nanonaps were excreted in the faeces.

Since the introduction of the first PET–CT imaging system in 1998 by Townsend and colleagues in collaboration with Siemens Medical, *in vivo* imaging methods that combine two or more different modalities have grown rapidly in popularity, and are becoming a standard part of medical practice.[7] Accurate registration of functional with anatomical images provides improved clinical relevance and interpretability of the images. Combinations of imaging modalities have dramatically changed the direction of this emerging field of molecular imaging. Also, by incorporating multiple imaging modalities, the physical characteristics of one method can be used to validate the performance of another, usually within the setting of a single imaging session. The development of nanonaps represents a major step forward toward this goal by demonstrating feasibility in

mice, paving the way for future clinical translation of nanoparticle-based multimodal imaging agents.

Highly desired properties of *in vivo* molecular probes include: high target-binding affinity; specific uptake and retention; rapid clearance from non-target tissues; high permeability; *in vivo* stability; ease of synthesis; flexiblity for modification; and nontoxic. Although nanonaps already meet many of the criteria, their surface can be functionalized by labelling with targeting moieties, such as antibodies or peptides, to achieve specific binding to expand applications in imaging and therapy. *In vivo* imaging performance can be further improved by modifying the nanoparticle surface properties for multiplexed detection in multiple spectral regions. These nanoparticles are also promising for use with intravenous administration because of their multimodal properties, intrinsic stability and small size. There remains considerable work to be done before these imaging agents can be used in clinical practice to perform multimodal imaging with photoacoustics and either ultrasonography or PET. However, the results of this study establish an important step forward for possible translation of nanonaps into the clinic.

Acknowledgements

NIH R01 CA142750, U54 CA163059

Biography

Bishnu P. Joshi, PhD, University of Michigan

Bishnu P. Joshi, PhD is a Research Investigator in the Department of Medicine at the University of Michigan. He received his Ph.D. in Bio-organic Chemistry at Inha University in South Korea in 2009 and performed post-doctoral training at the Unversity of Michigan. He uses his multidisciplinary expertise in organic chemistry, peptide chemistry, biochemistry, and molecular biology to develop peptide-based imaging agents that target cell surface proteins in variety of digestive tract cancers for diagnostic imaging and monitoring of therapy.

Thomas D. Wang, MD, PhD, University of Michigan

Thomas D. Wang is an Associate Professor in the Departments of Medicine, Biomedical Engineering, and Mechanical Engineering at the University of Michigan. He graduated from MIT (PhD) in 1996 and Harvard Medical School (MD) in 1998, and is a board certified gastroenterologist. Dr. Wang has over 25 years of experience in developing novel optical imaging instruments and molecular probes for the early detection and staging of cancer in the digestive tract. He has pioneered the development and in vivo use of wide area fluorescence imaging, dual axes confocal endomicroscopy, and fluorescent-labeled peptides.

References

1. Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Irritable bowel syndrome: a 10-yr natural history of symptoms and factors that influence consultation behavior. Am J Gastroenterol. 2008; 103:1229–39. PMID: 18371141. [PubMed: 18371141]

2. Sandler RS, Stewart WF, Liberman JN, Ricci JA, Zorich NL. Abdominal pain, bloating, and diarrhea in the United States: prevalence and impact. Dig Dis Sci. 2000; 45:1166–71. PMID: 10877233. [PubMed: 10877233]

3. Zhang Y, Jeon M, Rich LJ, Hong H, Geng J, Zhang Y, Shi S, Barnhart TE, Alexandridis P, Huizinga JD, Seshadri M, Cai W, Kim C, Lovell JF. Non-invasive multimodal functional imaging of the intestine with frozen micellar naphthalocyanines. Nat Nanotechnol. 2014 PMID: 24997526.

4. Cho HS, Dong Z, Pauletti GM, Zhang J, Xu H, Gu H, Wang L, Ewing RC, Huth C, Wang F, Shi D. Fluorescent, superparamagnetic nanospheres for drug storage, targeting, and imaging: a multifunctional nanocarrier system for cancer diagnosis and treatment. ACS Nano. 2010; 4:5398–404. PMID: 20707381. [PubMed: 20707381]

5. Kessinger CW, Khemtong C, Togao O, Takahashi M, Sumer BD, Gao J. In vivo angiogenesis imaging of solid tumors by alpha(v)beta(3)-targeted, dual-modality micellar nanoprobes. Exp Biol Med (Maywood). 2010; 235:957–65. PMID: 206600966. [PubMed: 20660096]

6. Cai W, Chen K, Li ZB, Gambhir SS, Chen X. Dual-function probe for PET and near-infrared fluorescence imaging of tumor vasculature. J Nucl Med. 2007; 48:1862–70. PMID: 17942800. [PubMed: 17942800]

7. Beyer T, Townsend DW, Brun T, Kinahan PE, Charron M, Roddy R, Jerin J, Young J, Byars L, Nutt R. A combined PET/CT scanner for clinical oncology. J Nucl Med. 2000; 41:1369–79. PMID: 17942800. PMID: 10945530. [PubMed: 10945530]

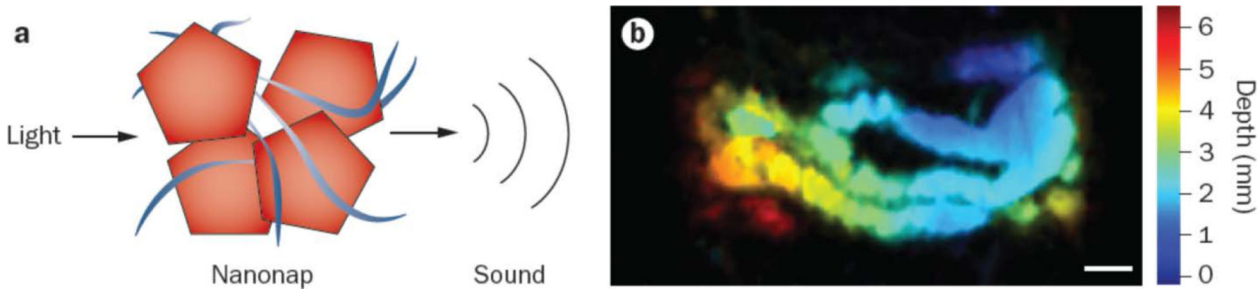

Figure 1. Use of nanonaps to visualize gut function

a | Nanonaps absorb light and produce sound to create photoacoustic images. **b** | Orally administered nanonaps provided contrast for depth-encoded photoacoustic image of mouse intestine with depth of 5 mm. With permission Nature Publishing Group © Zhang, Y. *et al. Nat. Nanotechnol.* doi:10.1038/nnano2014.130.