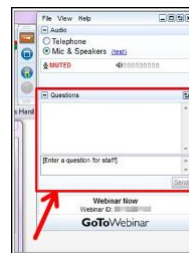


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**Thomas Cox**  
Professor of Chemistry,  
Butte College

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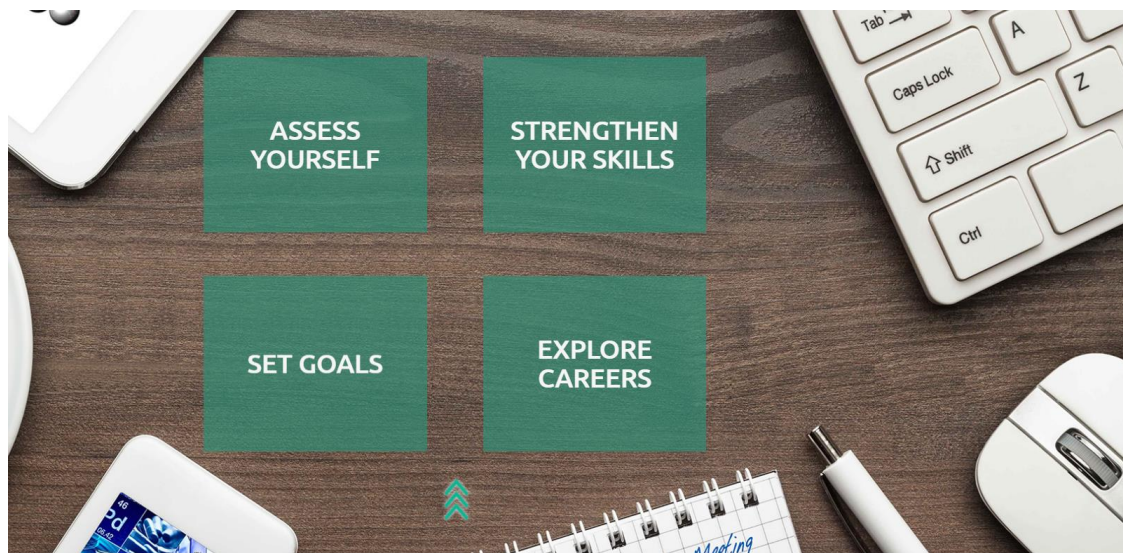
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**c&en** Features Steve Townsend in this free article!



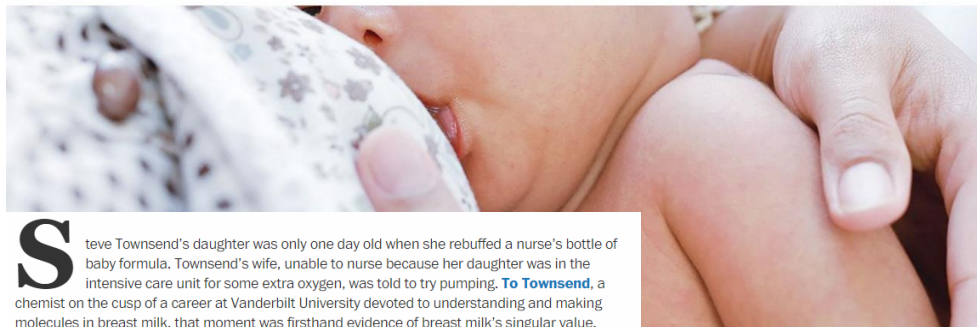
BIOCATALYSIS

## Synthesizing mothers' milk

Scientists are seeking ways to make beneficial but elusive sugars found in breast milk

by *Tien Nguyen*

JULY 1, 2018 | APPEARED IN VOLUME 96, ISSUE 27



**S**teve Townsend's daughter was only one day old when she rebuffed a nurse's bottle of baby formula. Townsend's wife, unable to nurse because her daughter was in the intensive care unit for some extra oxygen, was told to try pumping. **To Townsend**, a chemist on the cusp of a career at Vanderbilt University devoted to understanding and making molecules in breast milk, that moment was firsthand evidence of breast milk's singular value.

#### IN BRIEF

Mothers' milk contains a gold mine of health-boosting molecules called human milk oligosaccharides. First discovered a century ago, these highly complex molecules are only beginning to be synthesized. To tackle this task, researchers are using a bevy of methods, from old-school synthesis to genetically engineered bacteria. Their efforts are already bearing fruit: Companies are adding oligosaccharides to formula, while new studies hint at broader benefits to come.

<https://cen.acs.org/synthesis/biocatalysis/Synthesizing-mothersmilk/96/i27>

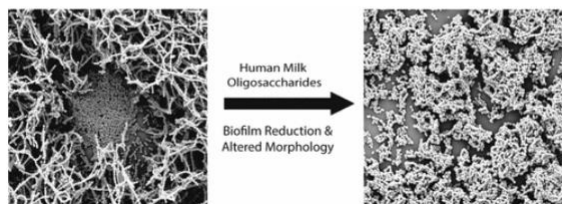
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Dorothy L. Ackerman, Ryan S. Doster, Jörn-Hendrik Weitkamp, David M. Aronoff, Jennifer A. Gaddy, and Steven D. Townsend

Publication Date (Web): June 1, 2017 (Article)

DOI: 10.1021/acsinfecdis.7b00064



<https://pubs.acs.org/doi/abs/10.1021/acsinfecdis.7b00064>

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# Nature's Elixir

## Antimicrobial Properties of Human Milk

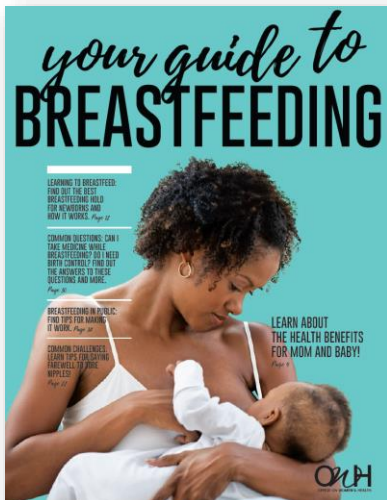


Featuring **Steve Townsend**  
Assistant Professor of Chemistry, Vanderbilt University

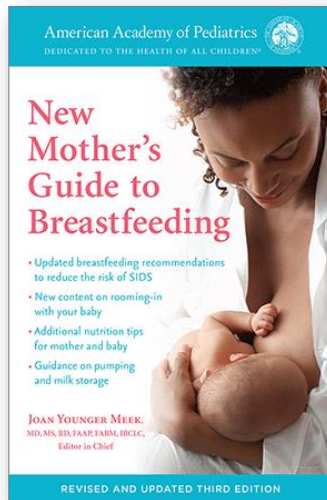
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GENERAL INFO

**Microbiome** Initiative



[www.womenshealth.gov/Breastfeeding](http://www.womenshealth.gov/Breastfeeding)



[www.aap.org](http://www.aap.org)

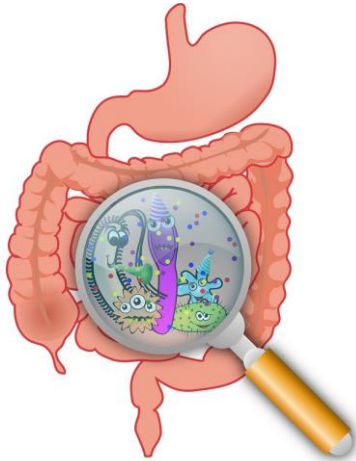


[www.who.int/topics/breastfeeding/en](http://www.who.int/topics/breastfeeding/en)

- 6 months exclusive
- 2 years and beyond w/ mixed diet

14



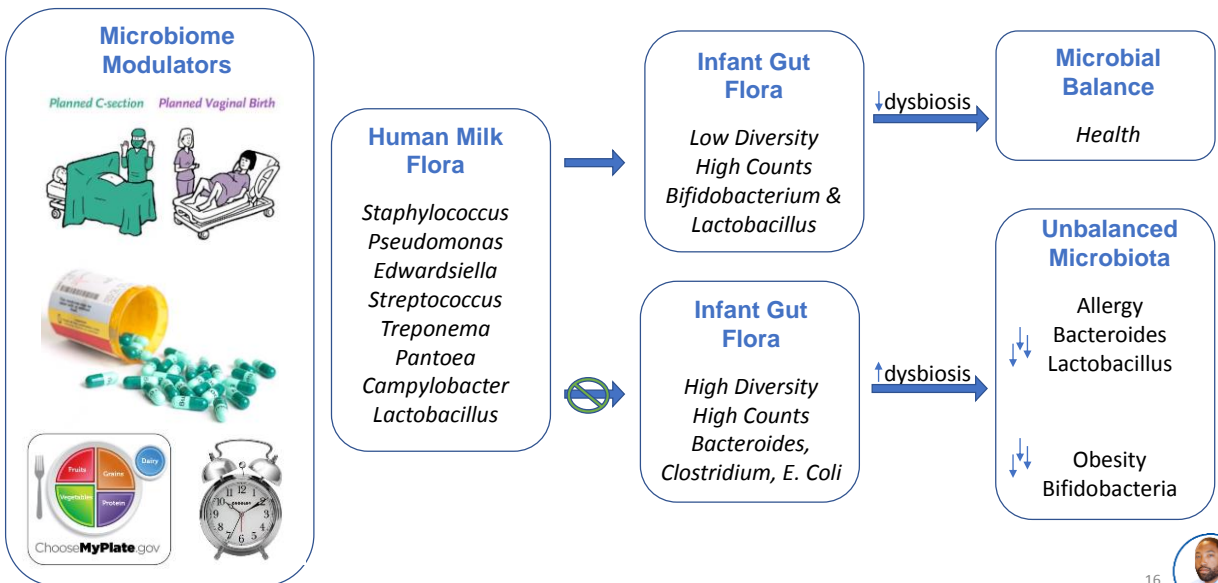


Who inhabits the milk microbiome?

What are the key factors influencing its activity?



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## Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



**Dysbiosis: What percentage of women receive antibiotics during labor and delivery?**

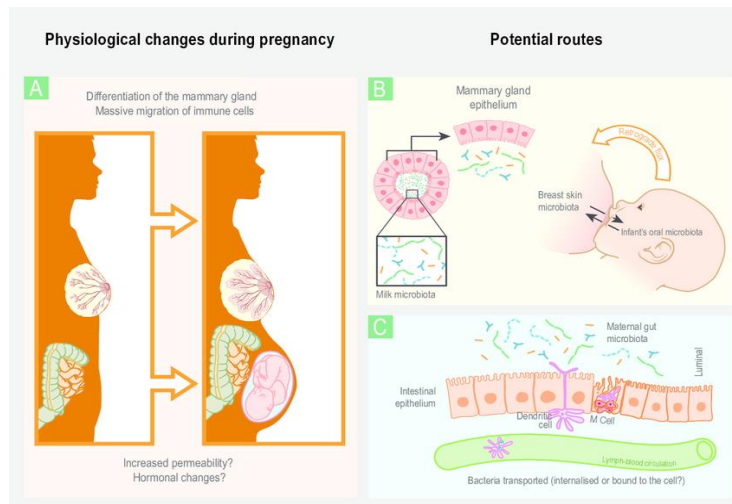
- About one-tenth
- About one-quarter
- About half
- About two-thirds
- About three-fourths

17

HUMAN MILK MICROBIOME

Microbiome Initiative

Increased Permeability



Retrograde Flux

Transported Via Immune Cells

P.V. Jeurink. *Beneficial Microbes*, 2013, 4, 17-30.

18





**Colostrum (< 5 days)**

Immunological  
 Secretory IgA  
 Lactoferrin  
 Leukocytes

Developmental  
 Epidermal Growth Factor  
 Minimal Lactose

Minerals  
 Na, Mg = High  
 K, Ca = Low

**Transitional (5 – 14 days)**

Na/K ratio declines  
 Lactose production increases  
 Immunological

**Mature (@ 4 – 6 weeks)**

*Immunologic instead of nutritional*

Morrow, A. *Pediatr. Clin. North Am.* **2013**, 60, 49.



Cells	Function
Macrophage	Infection protection T-cell activation
Stem Cells	Regeneration and Repair

Cytokines	Function
IL-6	B-cell activation
IL-8	Neutrophil recruitment
IL-10	Antibody induction
TNF-a	Immune activation

Immunoglobulins	Function
IgA	Inhibition of pathogen binding
sIgA	
IgG	Antimicrobial Activation of phagocytes
IgM	Agglutination

Others	Function
Lactoferrin	Anti-bacterial
Lactadherin	Anti-viral
Gangliosides	Anti-infectious
Mucins	Block pathogen adhesion

Morrow, A. *Pediatr. Clin. North Am.* **2013**, 60, 49.



## Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Sugars: Human milk contains > 200 unique oligosaccharides. **Which animal produces milk with equivalent oligosaccharide diversity?**

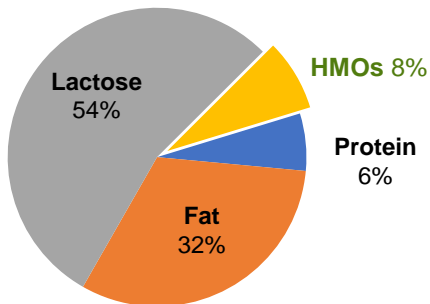
- Porcine (pig)
- Bovine
- Gorilla
- Chimpanzee
- Feline

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HUMAN vs. BOVINE

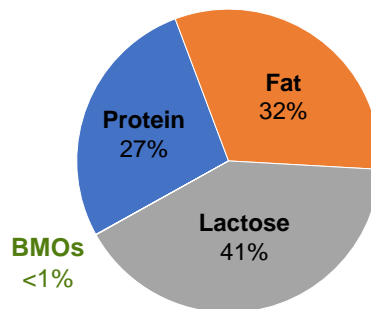
**Microbiome Initiative**

### Human Milk



**HMO** = human milk oligosaccharides - 200 unique oligosaccharides  
**BMO** = bovine milk oligosaccharides - 30 unique oligosaccharides

### Cow's Milk



Bode, L. *Glycobiology* **2012**, 22, 1147.  
 Sischo, J. *Dairy Sci.* **2017**, 100, 3883. 16.



22



lactoferrin  
secretory IgA  
lysozyme  
serum albumin

**Non-protein nitrogenated compounds (25%)**

urea/uric acid  
creatinine/creatinine  
amino acids  
nucleotides

**Take Home:** protein decreases between weeks 4-6

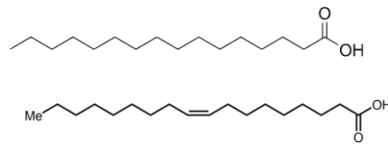
Morrow, A. *Pediatr. Clin. North Am.* **2013**, 60, 49.



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**Abundant Fats**

palmitic acid  
oleic acid



**Fat is cool...**

**Foremilk:** Low fat

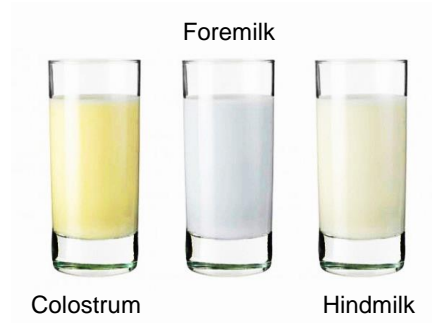
**Hindmilk:** High fat

**Night/Morning:** Low fat

**Afternoon/Evening:** High fat

**Fat is antimicrobial...**

Lypolytic activity

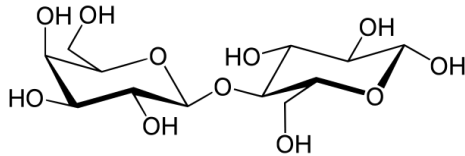


Morrow, A. *Pediatr. Clin. North Am.* **2013**, 60, 49.



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Structure of beta-D-Lactose

## Lactose

Least variable component in milk  
But...women who produce more milk  
produce more lactose

- Ca. 200 different HMOs observed
  - Vary from mom to mom
  - MW ranging from 500 to ca. 4000
  - 25-125 HMOs present
  - HMOs change over lactation
- **Not** metabolized
- Resist digestive enzymes and pH

Bode, L.; Jantscher-Krenn, E. *Adv. Nutr.* **2012**, *3*, 383S.

Newburg, D., *Biochemistry (Mosc.)* **2013**, *78*, 771.

25



w/ Craft. *ACS Infect. Dis.* **2018**, *4*, 77-83.

## Prebiotics (promote growth of symbiotes)

- Bifidobacterium – metabolize “short” HMOs
- Bacteroides – metabolize “long” HMOs

## Anti-adhesive antimicrobial agents

- *E. Coli*, *H. Pylori* – bind to sialylated HMOs
- *C. jejuni* - bind to fucosylated HMOs

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## SEMINAL RESULTS

## Microbiome Initiative



### HMOs from 5 donors

#### *S. agalactiae* (1 strain)

1. Growth inhibition up to 58%
2. Biofilm inhibition up to 26%
3. Alteration of biofilm architecture

### HMOs from 14 donors

#### *S. agalactiae* (3 strains)

1. Biofilm inhibition up to 80%
2. Growth inhibition up to 89%

#### *S. aureus* (MRSA)

1. Biofilm inhibition up to 60%
2. No growth inhibition

#### *A. baumannii*

1. Growth inhibition up to 11%
2. No biofilm inhibition

w/ Ackerman. *ACS Infect. Dis.*, **2017**, *3*, 595-605.

w/ Ackerman<sup>#</sup>, Craft<sup>#</sup>. *ACS Infect. Dis.*, **2018**, *4*, 315-324.

27

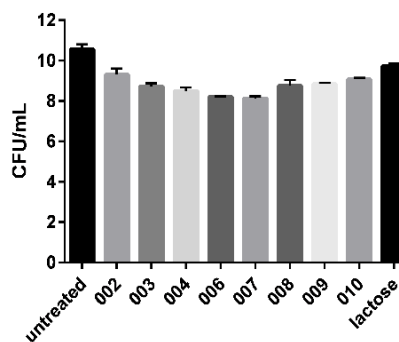
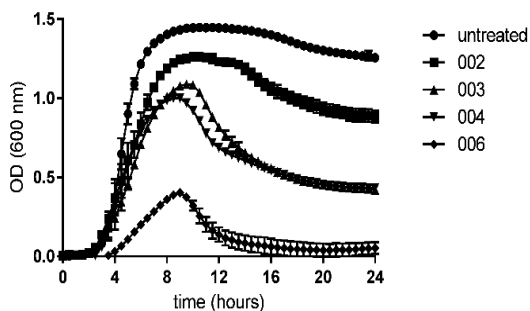


## FOLLOW-UP STUDY

## Microbiome Initiative



- Anaerobic Gram-positive
- Cause of infectious diarrhea
- Infection is triggered by antibiotic use



w/ Knippel and Huseman. Unpublished.

28



Strain CNCTC 10/84

Antibiotic	Fold Reduction	Classification
Ampicillin	2	$\beta$ -lactam
Penicillin	2	$\beta$ -lactam
Cefazolin	2	$\beta$ -lactam
Vancomycin	2	glycopeptide
Clindamycin	2	lincomycin
Gentamicin	8	aminoglycoside
Erythromycin	8	macrolide
Linezolid	2	oxazolidinone
Minocycline	32	tetracycline

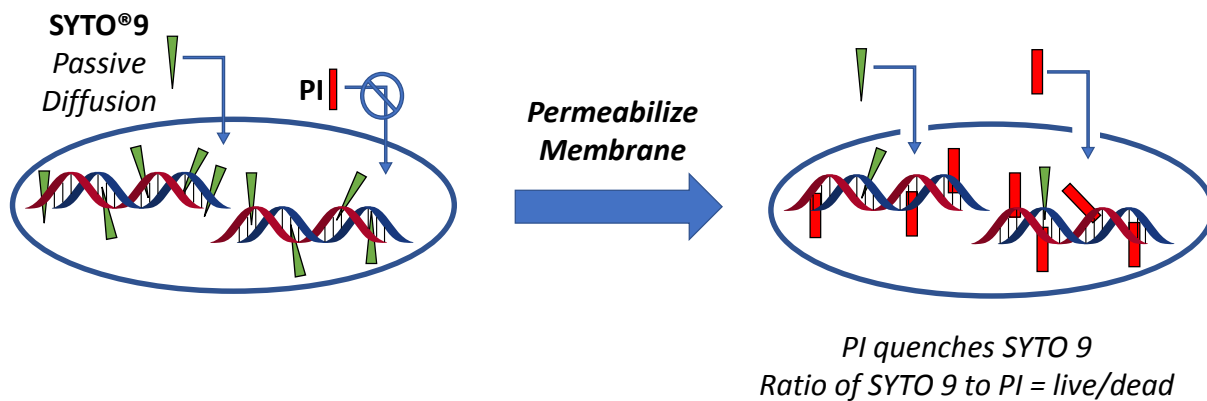
Strain GB590

Antibiotic	Fold Reduction	Classification
Ampicillin	0	$\beta$ -lactam
Penicillin	0	$\beta$ -lactam
Cefazolin	2	$\beta$ -lactam
Vancomycin	2	glycopeptide
Clindamycin	2	lincomycin
Gentamicin	16	aminoglycoside
Erythromycin	32	macrolide
Linezolid	2	oxazolidinone
Minocycline	8	tetracycline

Add 1% glucose  
Clindamycin = 16 fold reduction

w/ Craft. *ACS Chem. Bio.*, 2018. ASAP.

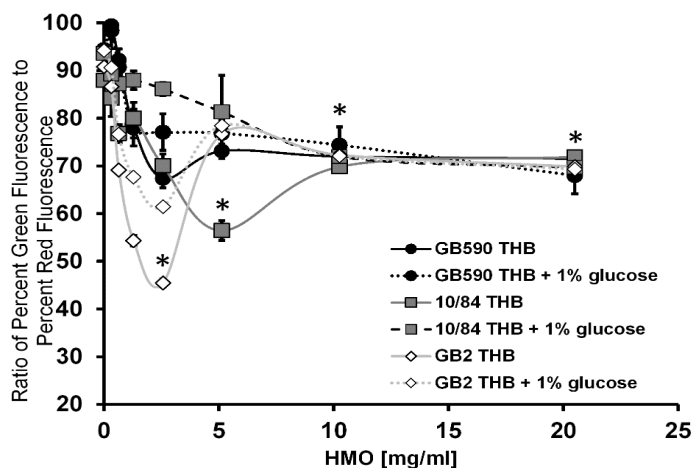
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w/ Craft. *ACS Chem. Bio.*, 2018. ASAP.

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## Conclusions

- **THB**: significant perturbation at  $\geq 2.56$  mM HMO
- **THB + 1% glc**: significant perturbation at  $\geq 10.25$  mg/mL HMO
- Strain specificity, growth specificity, dose dependent

w/ Craft. *ACS Chem. Bio.*, 2018. ASAP.

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## Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



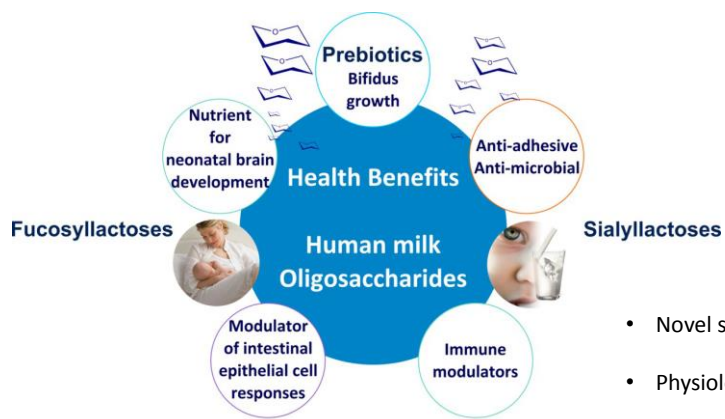
According to the most recent CDC breastfeeding report card, **which state in the U.S. had the highest percentage of babies that were breastfed?**

- California
- Idaho
- Hawaii
- Utah
- Minnesota

<https://www.cdc.gov/breastfeeding/pdf/2016breastfeedingreportcard.pdf>

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- Novel sources
- Physiologically relevant growth conditions
- Harnessing the power of chemical synthesis  
*"Any structure the mind can conceive is a candidate for total synthesis"* - Danishefsky

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Microbiome Initiative

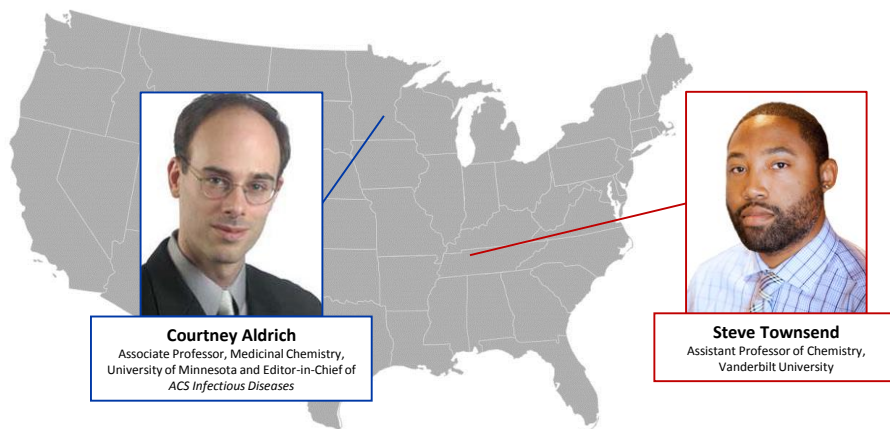


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## Nature's Elixir: Antimicrobial Properties of Human Milk



**Courtney Aldrich**

Associate Professor, Medicinal Chemistry,  
University of Minnesota and Editor-in-Chief of  
*ACS Infectious Diseases*

**Steve Townsend**

Assistant Professor of Chemistry,  
Vanderbilt University

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Publication Date (Web): June 1, 2017 (Article)

DOI: 10.1021/acsinfecdis.7b00064



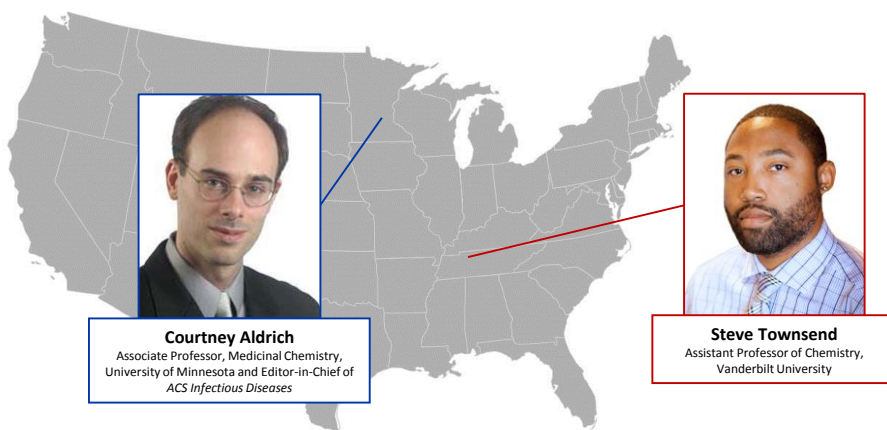
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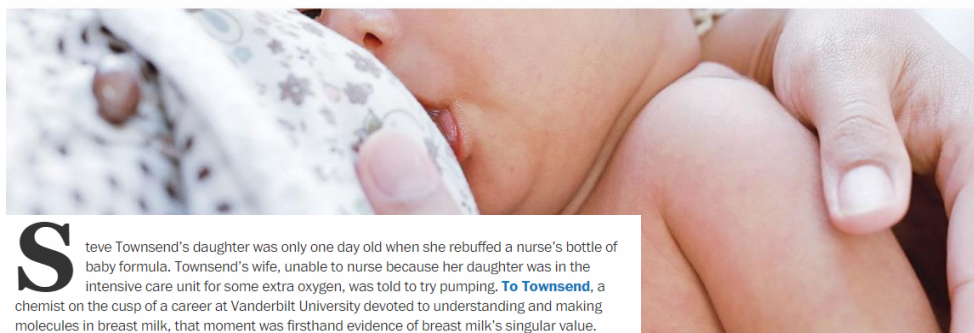
BIOCATALYSIS

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Scientists are seeking ways to make beneficial but elusive sugars found in breast milk

by *Tien Nguyen*

JULY 1, 2018 | APPEARED IN VOLUME 96, ISSUE 27



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<https://cen.acs.org/synthesis/biocatalysis/Synthesizing-mothersmilk/96/i27>

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**Thomas Cox**  
Professor of Chemistry,  
Butte College

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