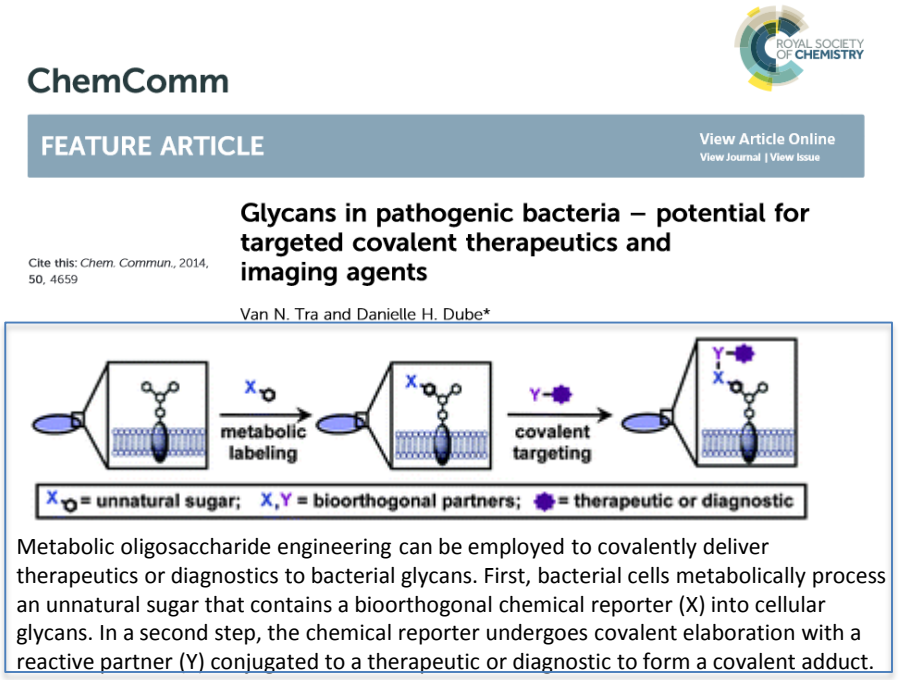
Deciphering *Helicobacter pylori*'s glycocode: uncovering & harnessing drug targets

Background:

- *Helicobacter pylori (Hp)* is the leading cause of duodenal ulcers and gastritis worldwide.
- Unfortunately, existing antibiotics frequently fail to eradicate *Hp* infection and cure these ailments.
- Virulence of *Hp* appears to be directly linked to the pathogen's ability to glycosylate proteins.
- Although *Hp* synthesizes a vast array of glycoproteins, what is not clear is the machinery responsible for their biosynthesis, how they can be harnessed to treat chronic *Hp* infection, and if they can be targeted selectively.
- The goals of this project were to identify *Helicobacter pylori (Hp)* glycosylation machinery that could serve as drug targets, to develop a strategy to inactivate *Hp* based on its distinctive glycans, and to assess the selectivity of our targeting strategy for *Hp* over other bacteria.



Metabolic oligosaccharide engineering can be employed to covalently deliver therapeutics or diagnostics to bacterial glycans. First, bacterial cells metabolically process an unnatural sugar that contains a bioorthogonal chemical reporter (X) into cellular glycans. In a second step, the chemical reporter undergoes covalent elaboration with a reactive partner (Y) conjugated to a therapeutic or diagnostic to form a covalent adduct.

Advance:

- Identification of fourteen mutant strains of *Hp* with glycosylation defects, six of which are in genes annotated as being involved in lipopolysaccharide (LPS) biosynthesis.
- These findings indicate that *Hp's* protein glycosylation pathway may intersect with its LPS biosynthesis pathway.
- Design and synthesis of a panel of *N*-azidoacetyl-containing variants of the rare bacterial sugars bacillosamine (Bac), *N*-acetylfucosamine (FucNAc), and 2,4-diacetamino-2,4,6- trideoxyhexose (DATDH) *N*-acetylfucosamine (FucNAc), and 2-acetamido-4-amino-2,4,6-trideoxy-galactose (AAT) AAT.
- Metabolic labeling experiments with this panel of sugars in *Hp* demonstrated that the bacillosamine derivative BacAz is efficiently incorporated into *Hp's* glycoproteins, and several azide-containing sugars from this panel were also found to be incorporated into surface-accessible glycoproteins of the pathogenic bacteria *Campylobacter jejuni*.
- Unlike *N*-acetylglucosamine (GlcNAc), Bac is expressed on the surface of select pathogenic bacterial strains and is not appreciably found on the surface of commensal bacteria.
- Results support the feasibility of developing new treatments for Hp-induced duodenal ulcers and gastritis.

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