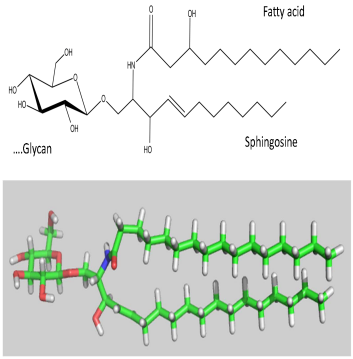


Biosynthesis of ABO glycolipids

Description

The biosynthesis of the ABO and all its related precursors such as H, I and P blood group system glycolipids (glycosphingolipids) all originate with glucose (GlcÎ²1) linked to a ceramide (Figure 5).

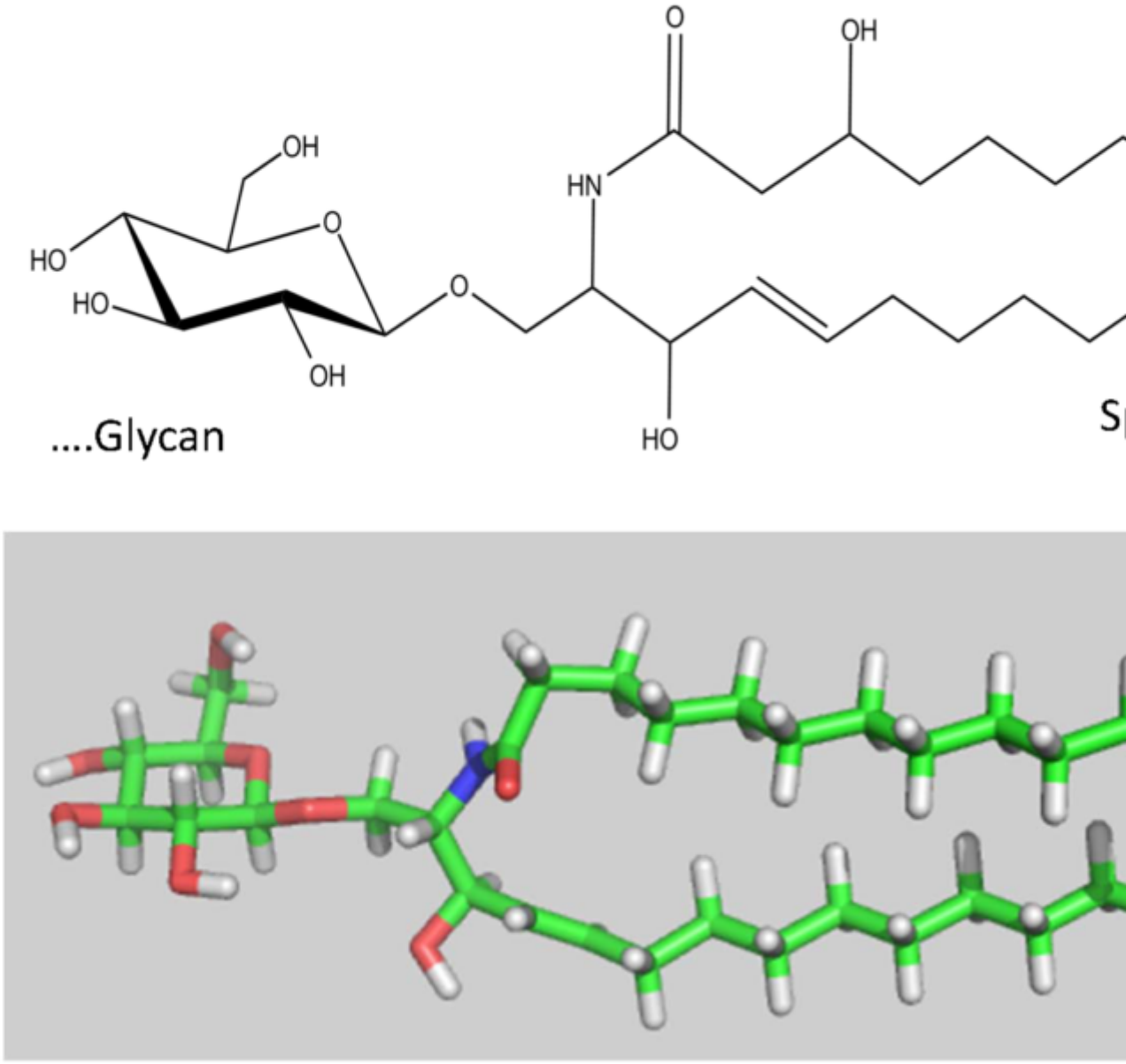


Figure 5. The glycosylceramide shown consists of glucose, fatty acid and shingosine. The molecular representation is drawn with PyMol (ref).

A galactose residue in Î²4 linkage (GalÎ²4) forms lactosylceramide (GalÎ²4GlcÎ²1-Cer) (Figure 6).

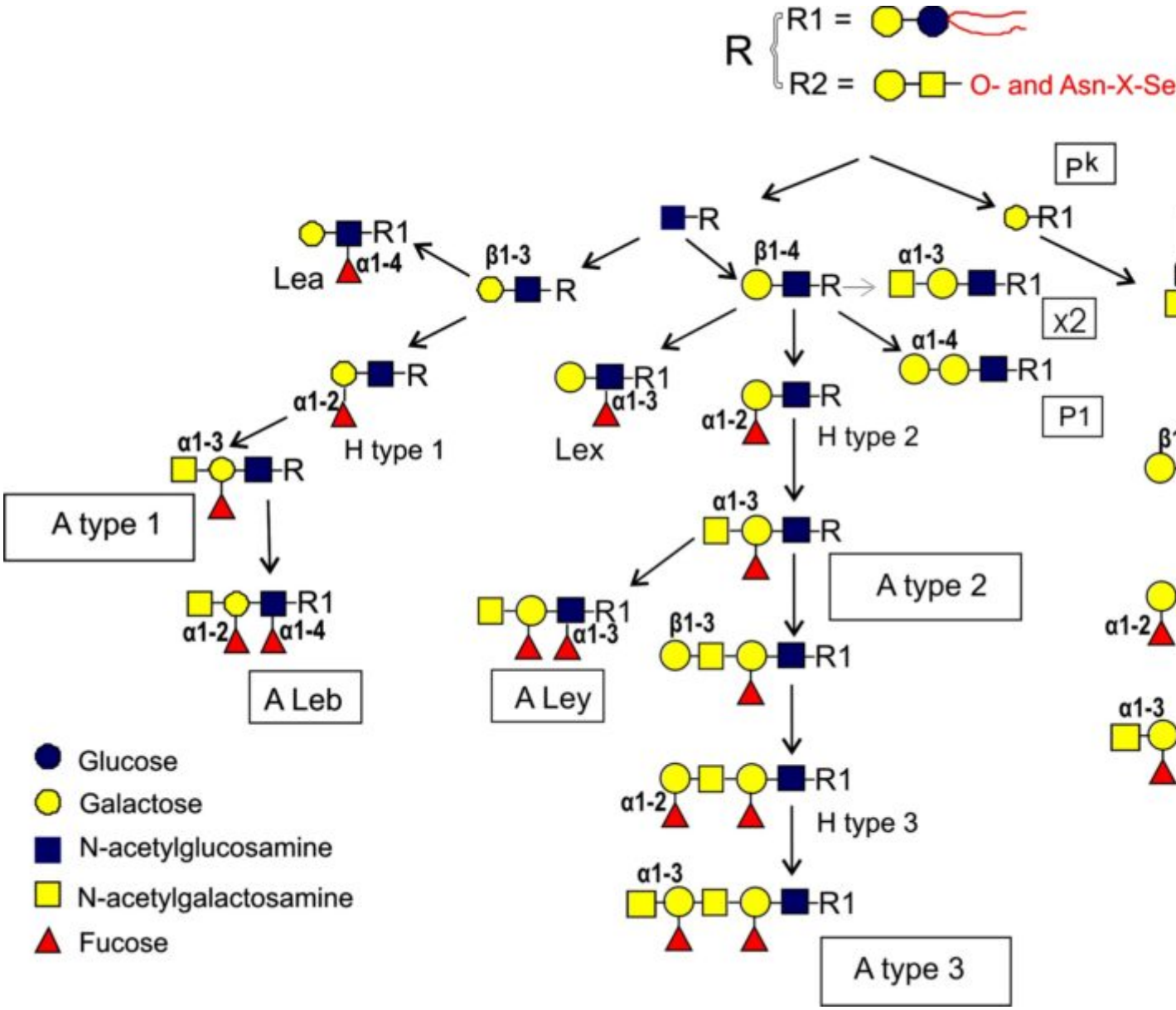


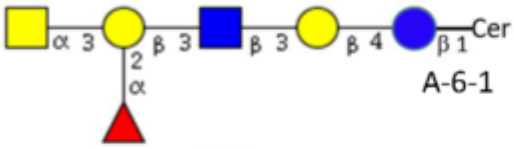
Figure 6. The biosynthesis path of the ABO and related antigens.

From this precursor two alternative pathways exist, one via lactotriaosylceramide towards type 1, 2, 3 precursors Rege et al., 1963Donald,1981Clausen et al., 1986Bremer et al., 1986, and the other via globotriaosylceramide (Gb3) towards type 4 precursor Bremer et al., 1984. In more detail, after lactotriaosylceramide (GlcNAcÎ²3GalÎ²4GlcÎ²1Cer) is formed and biosynthesis splits into two alternative pathways : the addition of Gal with a Î²3 linkage leads to lactotetraosylceramide (Lc-4 or type 1 precursor, GalÎ²3GlcNAcÎ²3GalÎ²4GlcÎ²1Cer) Reget et al., 1963, or Gal in Î²4 linkage leads to neolactotetraosylceramide (nLc-4 or type 2 precursor, GalÎ²4GlcNAcÎ²3GalÎ²4GlcÎ²1Cer) Reget et al., 1963. Both of these precursors can be fucosylated by the fucosyltransferase 2 (Fuc-TII) also known as the Se enzyme to form H type 1 and H type 2 antigens while the fucosyltransferase 1 (Fuc-TI) also known as the H enzyme can only modify the type 2 precursor to form H type 2. The H type 2 antigen may be extended by the action of GTA and GTB. The synthesis by GTA will be described in this section and in the section of the synthesis of glycoproteins. GTA adds the Î±3 GalNAc (Î±3 Gal) residue and thus forming A type 2 antigen Holgersson et al., 1992Hakomori et al., 1972 which may be further

extended with a FucÎ±2GalÎ²3 disaccharide forming the H type 3 (FucÎ±2GalÎ²3GalNAcÎ±3-R). This may also be further modified into A type 3 (â??repetitive Aâ?• or A type 3) (GalNAcÎ±3[FucÎ±2]GalÎ²3GalNAcÎ±3-R) Clausen et al., 1985 (Figure 4).

The biosynthesis of the type 4 pathway also originates from the lactosylceramide precursor where a Gal residue is added in an Î±4 linkage leading to globotriosylceramide (Gb3, also known as Pk) and then by adding a Î²3GalNAc to globotetraosylceramide, Gb4 (globoside or also known as the P antigen Kannagi et al., 1984 (Figure 4). From here three alternative pathways exist where Gb4 may be further extended into other structures. Elongation with the H-disaccharide forms H type 4 (globo-H) Kannagi et al., 1984Clausen et al., 1984 which can be further modified by the A1 transferase into A type 4 (A-7-4, globo-A) Clausen et al., 1984. The A2 transferase appears not able to convert H type 4 precursor into A-7-4 or at best very ineffectively Clausen et al., 1984Svensson et al., 2009. The other two pathways do not result in blood group A antigens. The addition of GalNAc with Î²3 linkage creates the p-Fs (para-Forssman) glycolipid Ando et al., 1982 while the addition of GalNAc with Î±3 linkage creates the Fs (Forssman) glycolipid Siddiquiet al., 1972Haslam & Baenziger, 1996Tamakawa et al., 1996. p-Fs is expressed in humans and Fs is widely seen as an animal antigen although a few publications have indicated its expression in human tissue, especially in tumors Hakomori et al., 1977Hakomori, 1984Breimer, 1985 and recently it has been established to be present on some human red cells as the blood group system, FORS Svensson et al., 2012. The antigens p-Fs and Fs (FORS1) although not blood group A antigens can react with some anti-A reagents Svensson et al., 2012. Figure 7 shows structurally characterized blood group A glycolipid structures known in red cell membranes and non-blood group A glycolipids that may cross-react with anti-A reagents.

A-4-6



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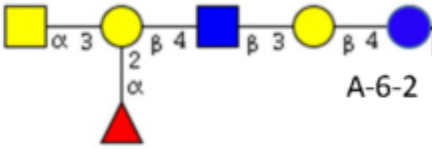

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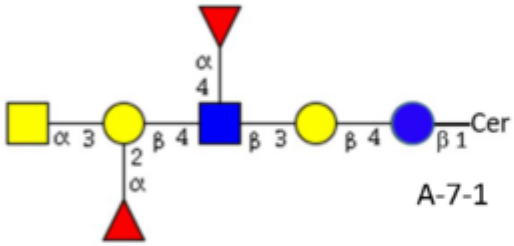

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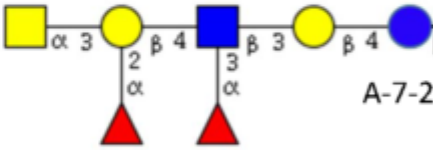

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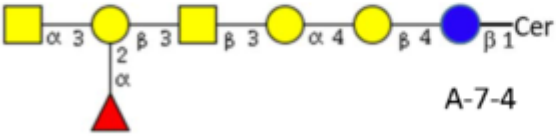

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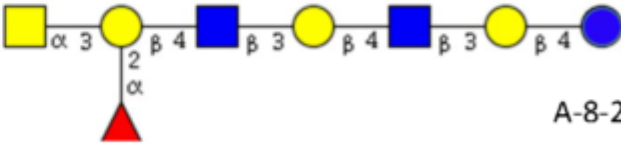

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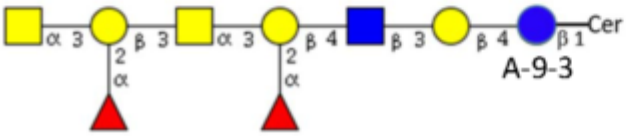

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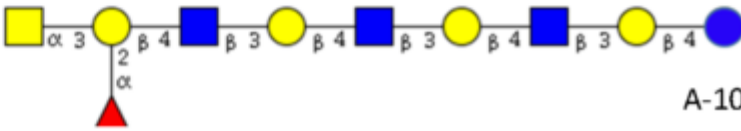

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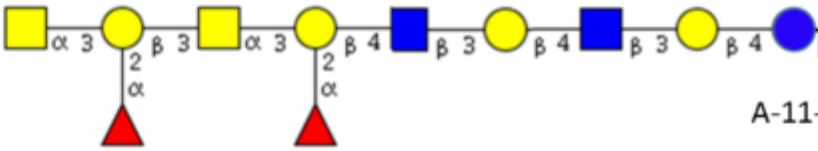

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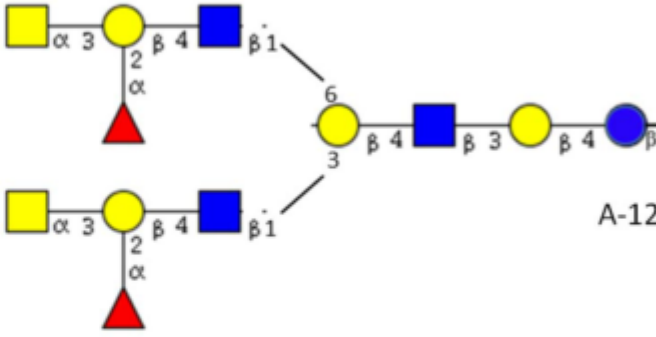

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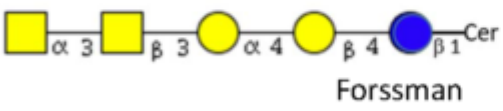
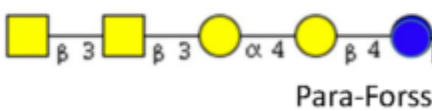
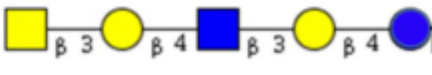


Forssman



Para-Forss

P-antigen



X2-antigen

Figure 7. Structurally characterized blood group A glycolipid structures known in red cell membranes. Also shown are related non-blood group A glycolipids that may cross-react with anti-A reagents.

Category

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