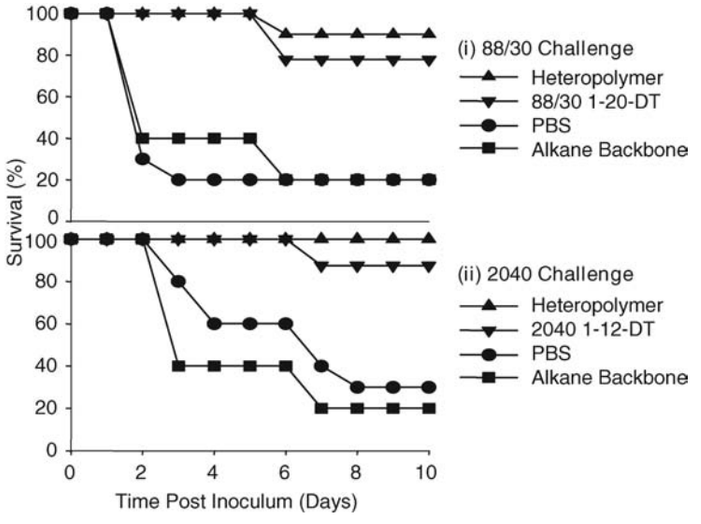

Figure 5 Heteropolymer with N-terminal and conserved peptide pendant side chains induces immunity to GABHS (group A β-hemolytic streptococci) challenge. The 88/30 (*i*) bacterial challenge strain is a clinical isolate from the Northern Territory of Australia and is represented on the heteropolymer construct by both an amino-terminal peptide and the conserved region epitope. In contrast, 2040 (*ii*) is a reference challenge strain that is only represented on the heteropolymer by the conserved region epitope. *Source*: From Ref. 71.

While these data are promising, a potential drawback of this approach is that while the polymerization technology utilizes consistent molar ratios of peptide, it cannot enable the specific ordering of the epitopes on the polymer backbone to be defined. Thus, it is expected that there would be batch-to-batch variation in the composition of the product, a factor that could affect immunogenicity and impede regulatory approval. New polymer chemistries are being developed that will enable the production of a product with a defined order of epitopes on the polymer. Alternative approaches would be to produce a polymer as a recombinant protein or as a DNA vaccine with all epitopes joined head to tail (see above).

MUCOSAL VACCINE FOR SEROTYPE-INDEPENDENT PROTECTION

School-age children are much more susceptible to GAS pharyngitis than adults. Furthermore, the siblings of a child with a streptococcal pharyngitis are five times more likely to acquire the organism than one of the parents. This decreased occurrence of streptococcal pharyngitis in adults might be explained by a nonspecific age-related host factor resulting in a decreased susceptibility to streptococci. Alternatively, protective antibodies directed to antigens common to a large number of GAS serotypes might arise as a consequence of multiple infections or exposures during childhood. This could result in an elevated response to conserved M protein epitopes. This latter hypothesis is partly supported by earlier studies on the immune response to the M protein where it was found that the B-repeat domain (Fig. 3) was clearly immunodominant (82). When rabbits were immunized with the whole M protein molecule, the first detectible antibodies were directed to the B-repeat region and rose steadily with time. It was only after repeated M protein immunization that antibodies were produced against the hypervariable A- and conserved C-repeat regions.

Unlike antibodies to the N-terminal region, it was clear that antibodies directed to the exposed C-repeat region were not opsonic (61). Because of this, experiments were performed to explore whether mucosal antibodies to this conserved region of M protein could play a role in protection from infection. Taking advantage of the pepsin cleavage site in the center of the M molecule (separating the variable and conserved regions) (Fig. 3), the recombinant M6 protein was cleaved and the N- and C-terminal fragments separated by SDS-PAGE and Western blotted. When the blots were reacted with different adult human sera, all adults tested had antibodies to the C-terminal conserved region while, as expected, only sera that were opsonic for the M6 organisms reacted with the N-terminal variable region (67,83,84). Similar studies performed with M proteins isolated from five different common serotypes (M3, M5, M6, M24, M29) revealed that sera from 10 of 17 adults tested did not have N-terminal-specific antibodies to these M types, while only two sera reacted with two serotypes and the remaining five sera with only one serotype. However, all sera tested reacted to the C-terminal fragment of the M molecule. Similar results were seen when salivary IgA from adults and children were tested in ELISA against the N- and C-terminal halves of the M6 molecule (V. A. Fischetti, unpublished data). In all, this is further evidence that the relative resistance of adults to streptococcal pharyngitis is clearly not due to the presence of type-specific antibodies to multiple types, but may perhaps be due to the presence of antibodies to conserved determinants.

From these findings it was reasoned that an immune response to the conserved region of the M molecule might afford protection by inducing a mucosal response to prevent streptococcal colonization and ultimate infection. In view of the evidence that the conserved C-repeat epitopes of the M molecule are immunologically exposed on the streptococcal surface (58), it should be possible to generate mucosal antibodies that are reactive to the majority of streptococcal types using only a few distinct conserved region antigens for immunization.

PASSIVE PROTECTION AT THE MUCOSAL SURFACE

sIgA is able to protect mucosal surfaces from infection by pathogenic microorganisms (85) despite the fact that its effector functions differ from those of serum-derived Igs (86). When streptococci are administered intranasally to mice, they are able