A Frost & Sullivan White Paper

3M™ Polisher ST—The Next Frontier in Downstream Processing

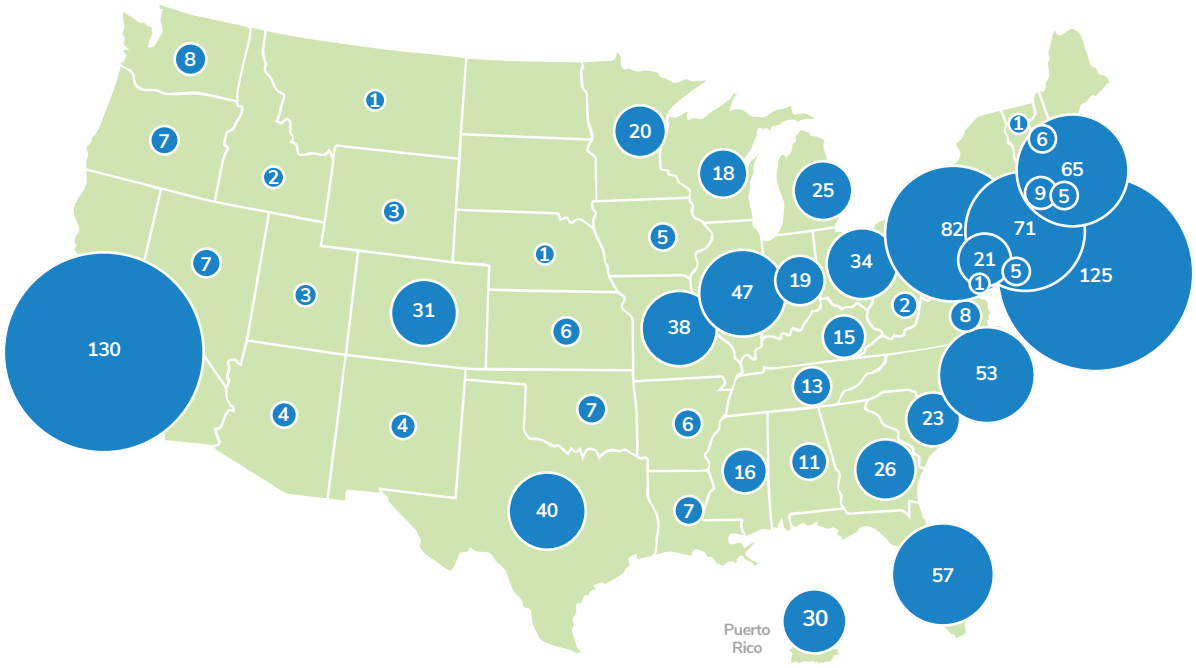
Powering clients to a future shaped by growth

FROST & SULLIVAN

ADVANCEMENTS IN NEXT-GENERATION THERAPIES— PAVING THE WAY FOR NOVEL BIOPROCESSING SOLUTIONS

Biopharmaceutical products (biologics) are transforming the treatment of many diseases like cancer, rheumatoid arthritis (RA), Hepatitis C, and Multiple Sclerosis (MS). Advances in biopharmaceutical innovation have transformed the treatment paradigms, helping patients slow disease progression and even disease remission for conditions such as RA. In the US and Puerto Rico alone, biopharmaceutical companies host approximately 1,100 manufacturing plants, producing cutting-edge therapies. Continued breakthroughs in biomanufacturing will be critical in addressing unmet patient needs and solving future healthcare challenges.

Figure 1: US Biopharmaceutical Manufacturing Facilities by State/Territory



Sources: NDP Analytics9; Hargreaves B10

Monoclonal antibodies (mAbs) and recombinant therapeutic proteins are the two largest biologics segments, comprising nearly 86.0% of the total biologics market in 2019. Producing these molecules consistently at a commercial scale is both complex and costly. The complexity is demonstrated by the variety of modifications on the molecule, including post-translational modifications, such as glycosylation, and degradation products, such as oxidation and hydrolysis, which affect the efficacy and safety of the drug. Similarly, progress in the mammalian cell culture process has resulted in significantly increased product titers, but also a substantial increase in process- and product-related impurities.

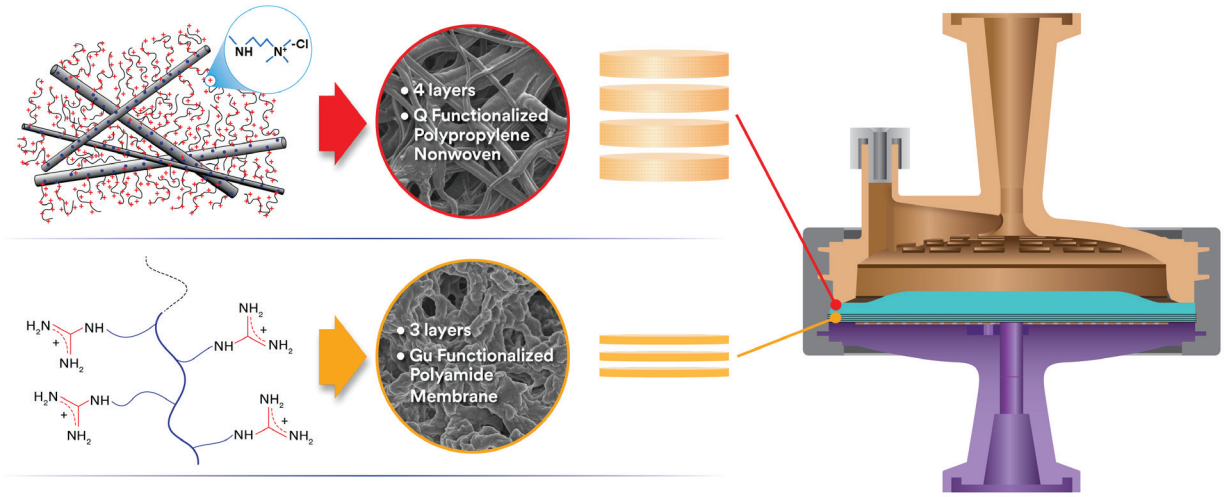
Due to the diverse physicochemical properties of these impurities, there is a constant need for new technologies that offer higher productivity and improved economics without sacrificing the process robustness required to meet final drug substance specifications. This paper outlines the performance of 3M™ Polisher ST technology, which allows the downstream polishing train to be restructured and simplified and chromatographic purity standards to be met with a reduced number of chromatographic steps.

3M™ POLISHER ST REPLACING PERFORMANCE ACROSS ALL PROCESS CONDITIONS

The need to launch innovative therapies faster and at lower costs has increasingly pushed biopharmaceutical companies to focus on improvements in manufacturing technologies. Downstream process development and manufacturing have become a strategic pivot for most companies to ensure the drug's safety, quality, identity, purity, and efficacy (SQIPE) to meet regulatory requirements for clinical trials and commercialization.

3M™ Polisher ST technology, which utilizes a guanidinium-functionalized polyamide membrane protected by a Q functionalized non-woven material, has demonstrated the viability of replacing the depth filtration and anion exchange chromatography (AEX) steps to achieve a simplified and cost-effective process. The platform is designed to reduce process- and product-related impurities and offer robust performance across a wide range of process conditions.

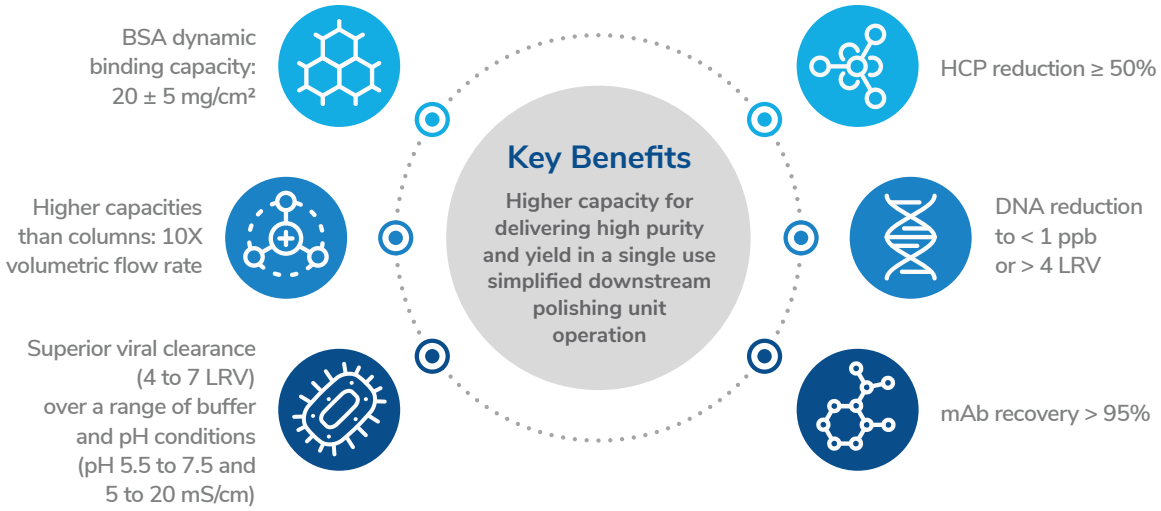
Figure 2: New chemistry design enabling true process potential: 3M™ Polisher ST (2020)



Monoclonal antibodies (mAbs) are complex biologic molecules, including size (e.g., 150 kDa IgG–900 kDa IgM), heterogeneity (e.g., glycosylation, deamidation, oxidation), structure (e.g., monomer, dimer, trimer, hexamer), charge (e.g., pI of 5.0–9.0), hydrophobicity, and genetic source (e.g., rodent, human). This intrinsic complexity mandates biopharmaceutical companies to adopt a new growth mindset to utilize new, innovative technologies and solutions.

3M™ Polisher ST technology offers a sandbox approach (Figure 2), providing both cost savings and greater efficiency, which are both imperative to biopharmaceutical manufacturing.

Figure 3: Why this platform will be a game-changer



It offers several advantages, including the ability to anticipate process yield, product purity and quality. Plus:

- >100 X mAb loading of typical Q resin (10+ kg/L target loading)
- Scalability from lab to manufacturing scale
- High salt and low pH tolerance
- Robust viral clearance across a wide range of conditions
- Viral nano-filter protection

Based on differential test results (factors listed above) in comparison to ADFs and, in particular, 3M™ Polisher ST technology's capability to remove HCP, DNA and high molecular weight (HMW) aggregate, it is clear this technology will eventually replace AEX by 2030.

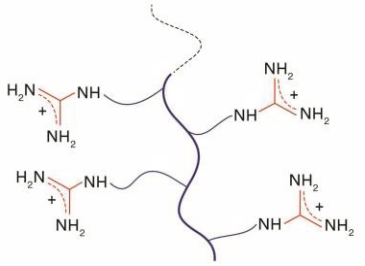
3M™ POLISHER ST VIRUS CLEARANCE CONQUERS MAB SOLUTIONS

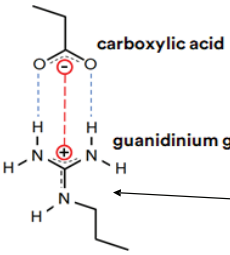
Adsorptive depth filters have been shown to provide viral clearance capability by either electrostatic adsorption or a combination of adsorption and mechanical entrapment. However, the implementation of adsorptive filters for claimable impurity and virus clearance in GMP manufacturing processes has been hindered by relatively poor and variable binding capacity (no consistency), lack of testing methods to demonstrate the post-usage filter integrity, and poor understanding of the viral clearance mechanism.

3M™ Polisher ST has demonstrated the highest impurity removal, including HCP levels, which appeared to be pH-independent.

Figure 4: Enabling Robust Viral Clearance Using New AEX Ligand Chemistry

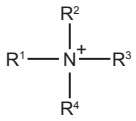
- Guanidinium functional group
- Novel 3M bio-inspired functional ligand design
- Large resonance structure stabilizes positive charge
- Multiple electrostatic-like interactions





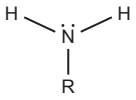
Capable of salt-bridging and hydrogen bonding

Current AEX Ligand Chemistries



Quaternary ammonium (Q)

- Conductivity sensitive



Primary amine (PA)

- Better salt tolerance
- Polyvalent buffer intolerant

Numerous experiments conducted strongly suggest that the HCP and DNA removal is governed predominantly by electrostatic interactions, but additional interactions such as hydrogen bonding also play an important role. They have also demonstrated that the 3M™ Polisher ST technology has a higher HCP removal capacity, resulting from salt tolerance.

Current regulations require the manufacturing process to demonstrate the ability to clear model viruses to ensure the safety of these cell-line-derived products prior to approval, with additional built-in safety for robustness. In the past, it has been demonstrated that greater than 3-4 log reduction of viruses can be achieved by using ADF post Protein A. 3M™ Polisher ST technology has demonstrated even higher clearance of viruses by filtration after low pH viral inactivation and neutralization.

To demonstrate the viral clearance, 3M™ Polisher ST technology was analyzed for clearance of murine viruses at low and high conductivities. Multiple studies have now demonstrated that 3M™ Polisher ST technology is at least as efficient at virus removal as equivalent columns, and due to the unique benefits of guanidium ligand mentioned above, often exceed columns in terms of virus clearance.

XMuLV, Reo-3 and PrV all showed >6 LRV clearance (detection limit) from pH 5-7.5, conductivities 3-20 mS/cm and in both monovalent (Acetate/Tris) and polyvalent (Citrate/Phosphate) buffers. MVM showed >4 LRV clearance from pH 5.5-7.5, conductivities 5-20 mS/cm and in both monovalent (Acetate/Tris) and polyvalent (Citrate/Phosphate) buffers.

3M™ Polisher ST technology has also been tested for viral clearance in actual mAb solutions. Six models covering a wide range of relevant conditions in DSP processes for mAbs were generated to represent real-life processes.

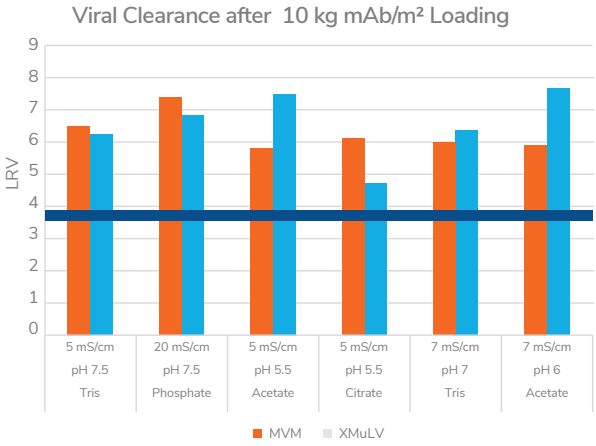
Figure 5: Robust viral clearance in mAb solutions

Viral Clearance studies were performed with MVM and XMuLV using mAb solutions representing legacy, modern and next-gen mAb feed streams.

The Tris pH 7.5 – 5 mS/cm MVM study was performed at Charles River. All other studies were performed at Texcell.

Feed Stream	Buffer	pH	Cond. (mS/cm)	Turbidity	Target HCP (ppm)	Target DNA (ppb)
Legacy	Tris	7.5	5	no	200	20
Legacy	Phosphate	7.5	20	no	200	20
Modern	Acetate	5.5	5	yes	500	1000
Modern	Citrate	5.5	5	no	500	50
NextGen	Tris	7.0	7	no	500	50
NextGen	Acetate	6.0	7	no	500	50

>4 LRV viral clearance was shown for all mAb feed streams



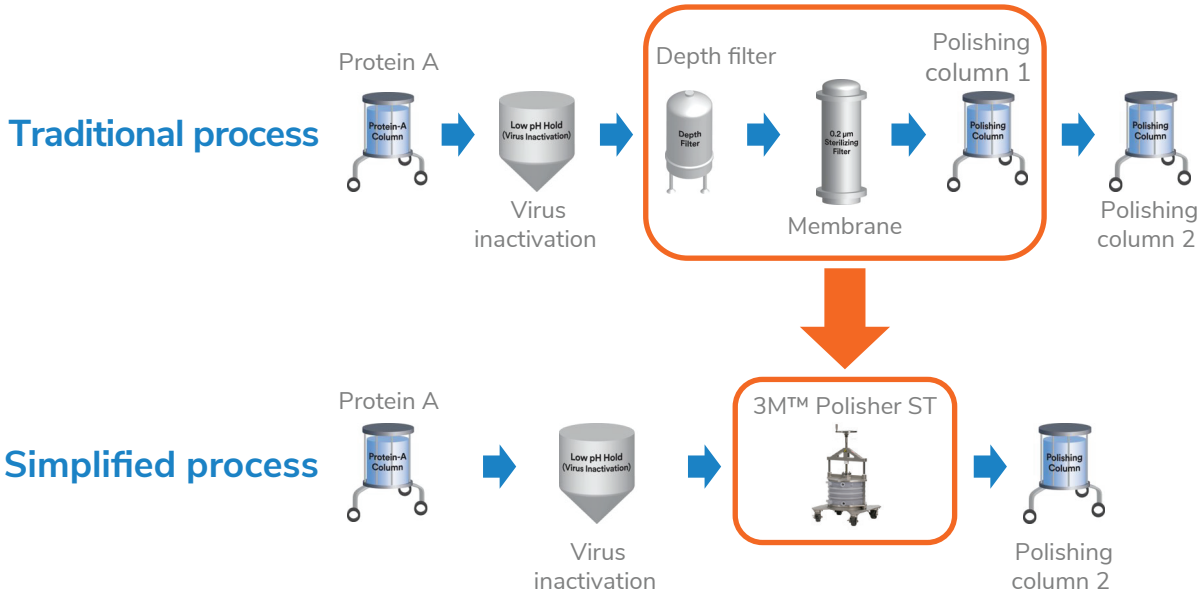
Robust viral clearance of 4 logs or more was shown for all conditions, including low pH, high conductivity or presence of turbidity. Interestingly, robust viral clearance was also observed in citrate buffer. Host cell protein removal was much lower in citrate, but process development scientists can still reliably use the product for viral clearance under these conditions.

3M™ POLISHER ST REPLACING CHROMATOGRAPHY COLUMN AT SCALE

Biopharmaceutical companies are approaching the limits of manufacturing productivity and scalability, and innovative downstream bioprocessing (DSP) solutions are required to address these challenging issues. The bottleneck in process-scale chromatography negates any advantages of scaling up earlier process units since bind-and-elute chromatography steps are driven by mass rather than volume.

This means that savings made upstream do not translate into increased productivity during purification. Larger columns also impact facility layouts, costs and infrastructure because space and buffer volumes for all steps also increase. As a consequence, pool and buffer volumes act as serious limitations when it comes to the introduction of high-titer processes into existing facilities.

Figure 6: Transition to Single-use Monolithic Systems



3M™ Polisher ST offers not only economic benefits and versatility, but it also has specific functional advantages over equivalent packed-bed columns. These are:

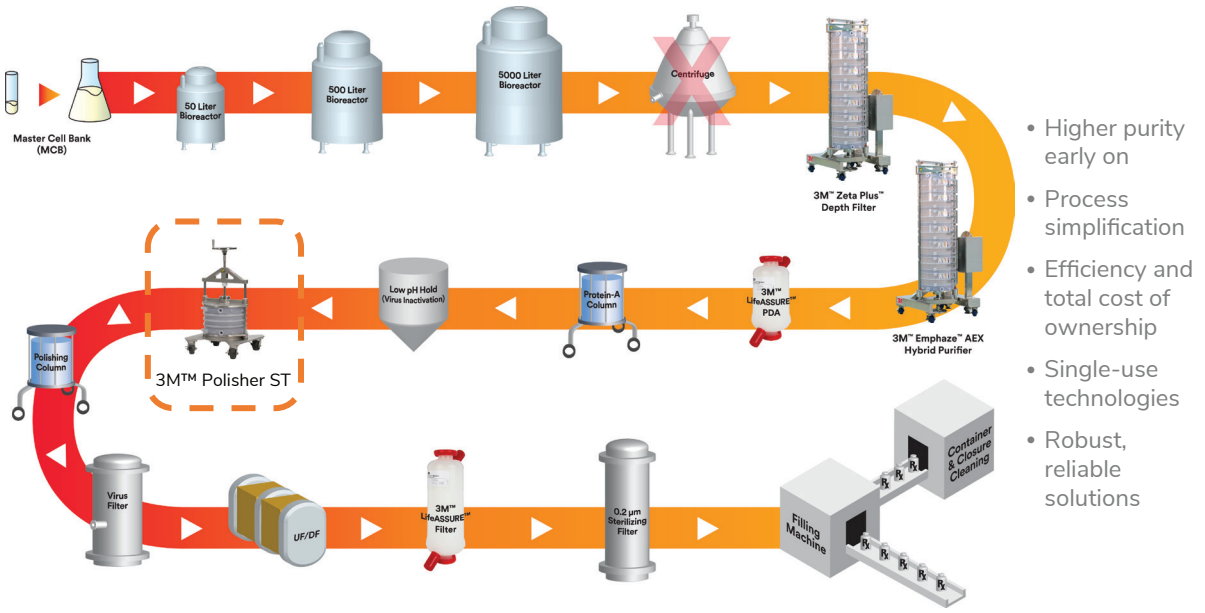
1. *Convenience* - There is no cleaning or validation, no packing, re-packing and recycling.
2. *Scalability* - A production scale capsule of 1.6 m² can replace a packed column of 80 liters. Capsules can be stacked for even higher loadings.
3. *Small footprint* – Use of one-fifth (20%) of the buffer volume compared to a column of equal capacity, saving time and money. Lower buffer volumes in the purification process drive down wastewater that needs to be handled for disposal.

DEVELOPING NEXT-GENERATION MAB PROCESS USING 3M™ ZETA PLUS DEPTH FILTER, 3M™ EMPHAZE AEX HYBRID PURIFIER AND 3M™ POLISHER ST

While upstream processing has led to increasing yields, downstream processing has remained a costly bottleneck: advances in titers over the past two decades shift the main manufacturing costs from USP toward DSP. There is a lot of space for improvement in DSP by leveraging process intensification techniques that allow replacing multi-use steps with high regulatory burden with single-use solutions.

3M has put together several platforms relating to each other in unique ways and will revolutionize bio-pharmaceutical manufacturing.

Figure 7: Enabling Robust Viral Clearance-Introduction of Single-use AEX Step



Open grades of 3M™ ZetaPlus depth filters with high capacity allow for a direct harvest, without the need for centrifugation. 3M™ Emphaze AEX Hybrid Purifier can replace the second depth filtration stage for removing small cell debris, thereby enabling higher purity earlier on in the DSP. This chromatographic clarification unit removes 4 to 5 logs of impurities like DNA and chromatin based on charge. This is a big step in process intensification as it can drive improved performance of capture columns, which will also result in >10-fold lower host cell protein levels that are normally seen in elution pools.

When 3M™ Emphaze AEX Hybrid Purifier is used in the clarification, turbidity after viral inactivation and neutralization will be much lower and, as a direct result, there is no longer a need for a depth filter step to deal with this turbidity.

Finally, 3M™ Polisher ST can replace the anion exchange polishing column and it does not need a depth filter or a membrane for protection, thereby combining multiple steps into one. The 3M™ Polisher ST will have 100 times the capacity of a traditional Q resin with a recommended target loading of 10 kg of mAb per m². The increased capacity means that a capsule can be used, which is much smaller than the traditional column.

THE ROAD AHEAD- TRIGGERING NEW PROCESS INTENSIFICATION TECHNOLOGIES

Biopharmaceutical companies face numerous challenges to meet the demand for intensified bioprocessing of mAbs. Performance limitations of current technologies, platforming requirements governing process design choices, and adherence to regulatory compliance to include steps for viral clearance have created a conundrum around mAb process trains and the need to make them more efficient, smaller, cost-effective and faster. 3M brings a world-class approach and a suite of technologies to diminish these hurdles. The approach relies on well-tested strategies to achieve very high purity early in the process train and then simplify by reducing the number of required steps. The technology portfolio enables replacing multi-use unit operations with robust single-use solutions that drive efficiency and reduce the total cost of ownership. The 3M™ Polisher ST is being tested in different polishing mAb process train layouts and will be on target to eventually replace the AEX flow-through column in any mAb process train, no matter the conditions. This is an excellent opportunity for biopharmaceutical companies to clear the bar on investments in new intensification technologies and demonstrate a clear increase in return on assets/investment (RoA/RoI) and plant productivity.

LIST OF ABBREVIATIONS

ADF = Adsorptive depth filtration

AEX= Anion exchange chromatography

DSP = Downstream processing

mAb = Monoclonal antibody

HCP = Host cell protein

DNA = Deoxyribonucleic acid

GMP = Good manufacturing practice

XMuLV = Xenotropic murine leukemia virus

Reo-3 = Reovirus type 3

PrV = Pseudorabies virus

MVM = Minute virus of mice

LRV = Log reduction value

NEXT STEPS

- **Schedule a meeting with our global team** to experience our thought leadership and to integrate your ideas, opportunities and challenges into the discussion.

- Interested in learning more about the topics covered in this white paper? Call us at 877.GoFrost and reference the paper you're interested in. We'll have an analyst get in touch with you.

- Visit our **Digital Transformation** web page.

- Attend one of our **Growth Innovation & Leadership (GIL)** events to unearth hidden growth opportunities.

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