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Next Generation Programable Automated Specimen Preparation Processors for Volume and Transmission Electron Microscopy: The ASP-2500™ and ASP-1500™

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Abstract Text

The key enabling breakthrough that enabled biospecimen Transmisssion Electron Microscopy (TEM), after the invention of the TEM, was the development of chemical fixation workflows incorporating aldehyde and osmium tetroxide fixatives, heavy metal staining, solvent dehydration, resin embedding, and ultramicrotomy [1]. Variations of this preparative methodology have proven to be the most reliable specimen preparation method for EM life science research, clinical diagnostics, and more recently for the exploding field of 3D volume EM (vEM) [2]. While today's TEM and vEM microscopes provide extensive automation, chemical specimen preparation in most labs remains a hands-on process of sequential immersion of specimens in a series of reagents every few minutes to hours over ~1-3 days for TEM, and ~3-5 days for vEM. While microwave and carousel processors aid some TEM tissue preparation protocols, these are not suitable for complex protocols, including immunolabeling and vEM preparation.

Microscopy Innovations changed this in 2015 with the introduction of the mPrep™ ASP-1000™ Automated Specimen Processor [3]. ASPs use natural-language, user-created scripts to provide automated protocols of any length or complexity for nearly any specimen or grid preparative task. The ASP then frees users from the tedious task of repetitive reagent exchanges while providing robotic reproducibility. ASPs also provide extremely fast specimen preparation times with a unique microfluidic reagent agitation system that further accelerates process times by providing near-zero reagent carryover. In 2023, the ASP-2000™ was introduced, adding programmable 0-100ºC reagent temperature control for tasks such as TCH heating for vEM, resin warming to facilitate infiltration, and cooling of labile biologicals for immuno-labeling. These capabilities were enabled with an all-new ASP Dashboard Control software, along with integrated best practice assistance, automated documentation (for clinical, pharmaceutical, research, and core labs) and easy sharing of protocols between any ASP-equipped lab, to enhance scientific reproducibility [4-5].

We now introduce the mPrep ASP-1500™ and ASP-2500™, with both physical design and Dashboard Control improvements driven by continuous applications development with ASP users (Fig. 1). The ASP-2500 (like the ASP-2000) provides 0-100ºC control, while the ASP-1500 does not control reagent temperature. The ASP-1500 and ASP-2500 are built to meet CE and related electrical, RF emission and safety certifications for world-wide installations, with a new integrated design that simplifies shipping and installation. With our mission to drive scientific reproducibility and collaborations, the new ASP Dashboard runs protocols created with earlier systems, while legacy ASPs are also easily upgraded to the newest Dashboard, usually at zero cost. The new Dashboard provides easy protocol script sharing with any ASP-equipped lab, further reduces reagent carryover to improve results and cut specimen preparation times, enhances reagent mixing and agitation modes for high-capacity specimen prep, provides enhanced best practice hover-help, and further expands process run documentation.

All ASP's use computational-fluid-dynamic-designed mPrep/s (micro-preparation of specimen) capsules that entrap specimens while the ASP provides bi-directional micro-fluidic reagent flow to drive gentle and effective reagent infiltration. This provides unprecedentedly fast specimen preparation times. Multiple publications, including two recent reviews of ASP Workflows in several EM labs, provide examples of TEM preparation in as little as 1 hour, and vEM preparation in just 5-8 hours, from aldehyde fixative rinse-out to ready for resin curing [5-6]. Dozens of publications over a decade of ASP use describe rapid, reproducible preparation of nearly any type of vertebrate, invertebrate, cellular, cell culture, and other specimens in research, core, clinical and pharmaceutical labs [3-10]. A recent clinical TEM paper described 3-years of daily ASP-1000 use to prepare up to 128 tissue specimens, from up to 16 patients, in just 2.5 hours while providing substantial reductions in hands-on effort and reagent consumption [10]. vEM labs have also documented how ASP vEM preparation provides the consistency needed to enable AI image segmentation for cancer and neuroscience preclinical research [6, 11].

The new ASP-1500, like the ASP-1000, is suitable when reagent temperature control is not necessary, such as for most TEM specimens, including clinical diagnostic applications. In contrast, when protocols require reagent thermal control, the ASP-2500 enables this, for example with 60°C TCH heating for vEM and 10°C cooling to minimize antibody label denaturation. In summary, the ASP-1500 and ASP-2500 provide new capabilities that build on a decade of fast, efficient ASP preparation of nearly any type of specimen for TEM, vEM and other microscopies, within core, research, clinical and pharmaceutical labs.

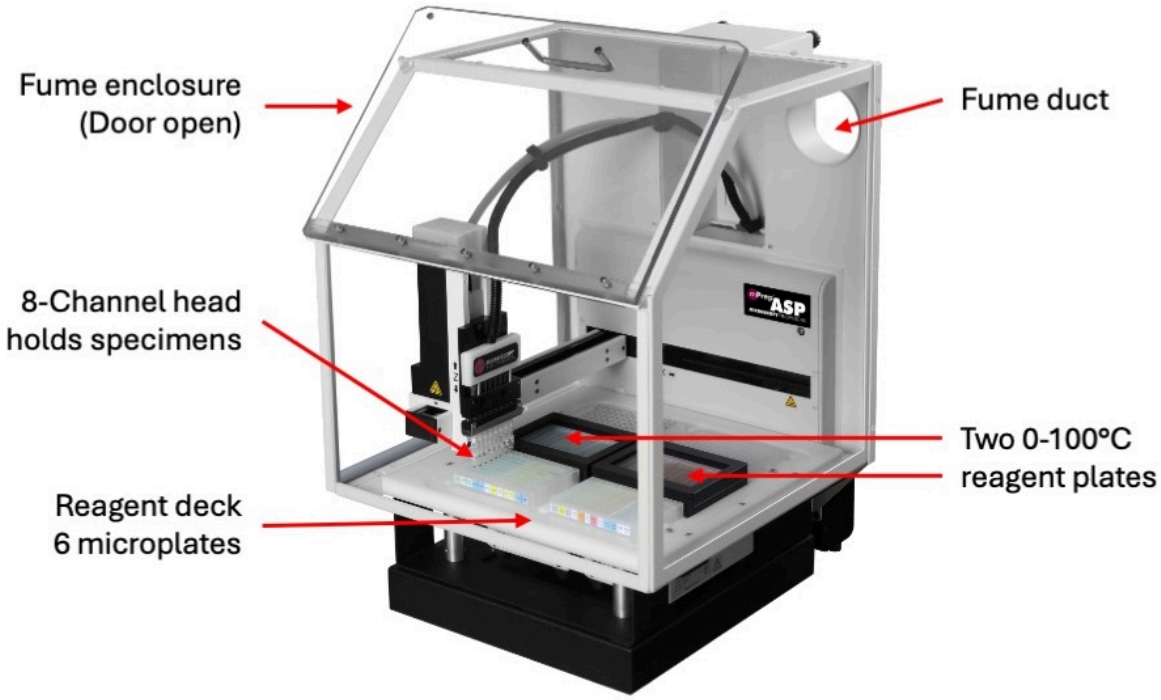

Fig. 1: The mPrep ASP-2500 has 6 microwell plate positions enabling up to 72 reagent protocol steps without user intervention. Two of these plates are under programmable temperature control from 0-100C. The 8-channel ASP-head, where specimen capsules (shown) or grid capsules are attached, enables simultaneous processing with up to 8 reagent protocols, such with and without a specific stain, titrations, and controls.

Keywords

Volume Electron Microscopy, Transmission Electron Microscopy, Automated, Specimen Preparation, AI, Image Segmentation, Research, Clinical, Diagnostic, Core Labs, Pharmaceutic, Preclinical, Neuroscience, Cancer, Reproducibility

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mPrep ASP-2500™ and ASP-1500™

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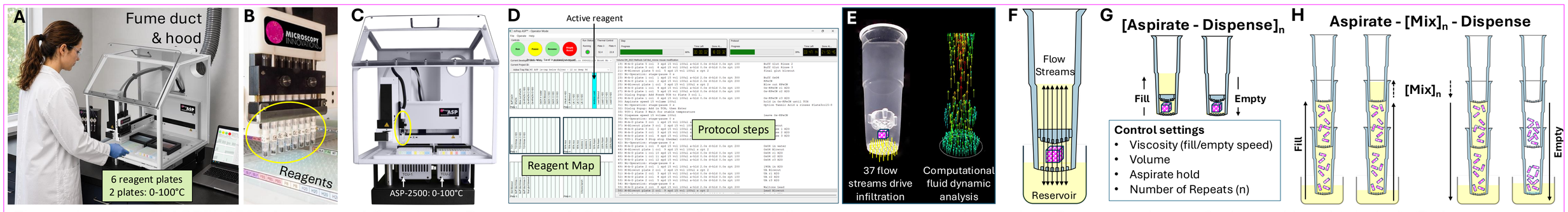


Figure 1: mPrep™ ASP™-2500 Automated Specimen Processor. **A-C**) ASP-robot & pump deliver reagents to specimens in mPrep capsules on 8-channel head (circled) (**B**) from reagents in 6 microplates, up to 72 reagents steps. Two 0-100°C controlled reagent plates on ASP-2500 (ASP-1500 no thermal control). **D**) ASP Dashboard maps reagent locations, follows Step-by-step protocol (easily modified & shared), active reagent, process timing, temperatures. **E-F)** Bi-directional microfluidic mixing for fast, gentle & uniform reagent infiltration. **G-H)** Mixing modes include *Aspirate-Dispense* **(G)** and *Aspirate-Mix-Dispense* **(H)** many specimens per capsule, stacked capsules, delicate specimens. Prepare 1-128 TEM specimens in <3 hrs, or 32 vEM specimens in ~5-8 hrs, using as little as 40 µl per specimen per reagent step [1-6, 14-16].

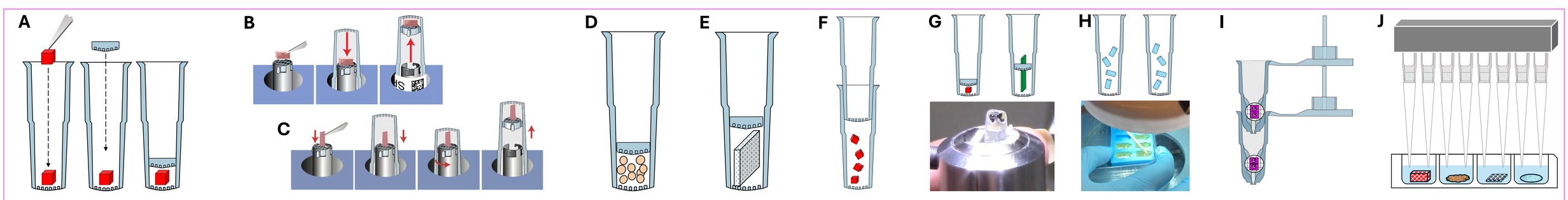


Figure 2: Workflows for most EM applications. A) mPrep/s (specimen) capsules entrap tissue, agar-enrobed specimens, pellets, organoids, etc. with mPrep/s screens placed and optionally oriented with the mPrep Workstation **(B-C)** or with the screen insertion tool. Or: **D**) Entrap several specimens. **E**) Planar specimens, e.g. cells on coverslips. **F**) High-throughput prep with 2 to 8 specimens per capsule capped with a second capsule, or trap high-pressure frozen specimens/planchets for cryo freeze-substitution [9]. **G)** Embed and section entrapped/oriented specimens, or **H)** remove and flat embed. **I**) Prepare TEM grids in mPrep/g capsules, such as for immunogold labeling [10-11]. **J**) Prepare specimens larger than ~4 x 9 mm (e.g. whole coverslips) in 24-well plates using pipette tip reagent delivery & agitation [12].

Introduction

In 2015 Microscopy Innovations introduced the first Automated Specimen Processor, the mPrep™ ASP-1000™, followed in 2023 by the ASP-2000™ which added protocol-controlled reagent temperatures. ASPs automate specimen & grid prep to assure reproducibility and free microscopists from time-consuming manual preparation [6,14].

Methods & Mission

We now introduce the mPrep ASP-1500™ and ASP-2500™ (Figure 1), developed through our mission to meet microscopists' needs for adaptable & reproducible automated specimen prep for biomedical research, diagnostics and more.

Proven Results

ASPs have prepared bio-specimens documented in more than 80 publications & presentations, including tissues from mammals, other vertebrates, invertebrates; cell suspensions & spheroids; immuno-labeling; and cell culture specimens. These have been prepared in research, core, clinical and pharma labs for vEM, TEM, SEM and other microscopies [1-8, 9-16]. vEM labs have documented how ASPs provide the consistency required for AI image segmentation for cancer and neuroscience preclinical research applications [13-14,16].

The new ASP-1500 & ASP-2500

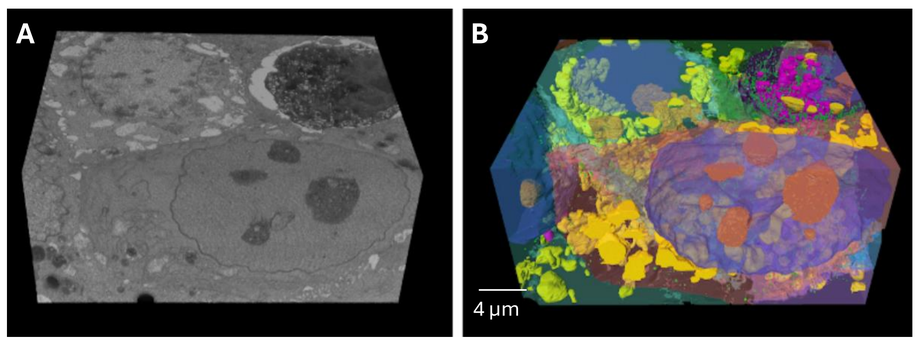
These new ASPs, like prior models, use natural-language, user-created protocol scripts and mPrep capsules to automate nearly any EM specimen or grid preparative task (Figures 1-2). New ASP-1500 and ASP-2500 enhancements, based on more than 10 years of customer experience and international demand, include:

Design & Engineering

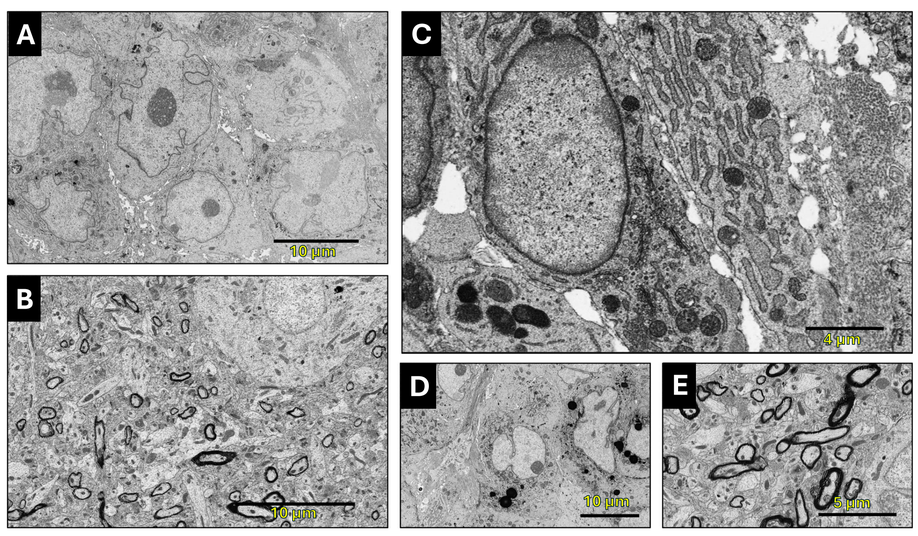
- Fume enclosure with exhaust flow "curtain", easy-open access door, a new clean design, & improved fume port
- International certifications: CE, RF, etc.
- Easier shipping , setup & lighter weight
- Easy upgrade from ASP-1500 to ASP-2500

User Interface & Prep Protocols

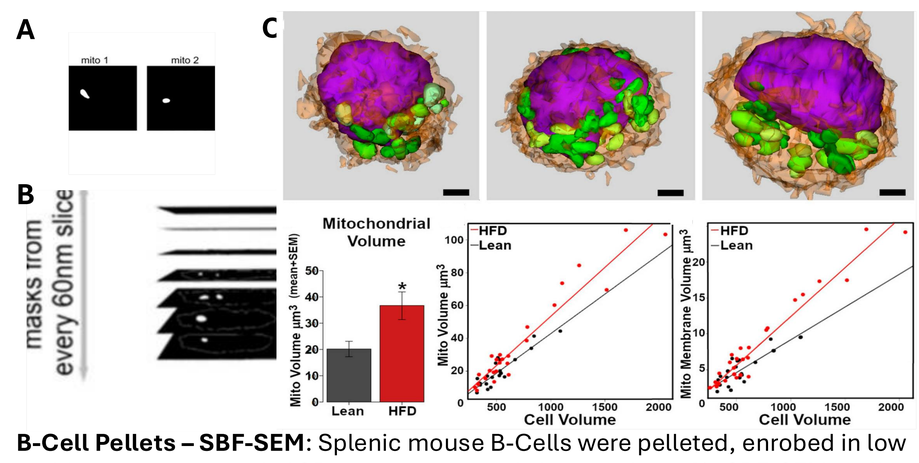
- Third Generation Control Software
- Enhanced microfluidic mixing control
- Reduced reagent carryover
- Compatibility with prior ASP protocols
- Help & User Guidance Updates
- Enhanced user alerts & documentation.



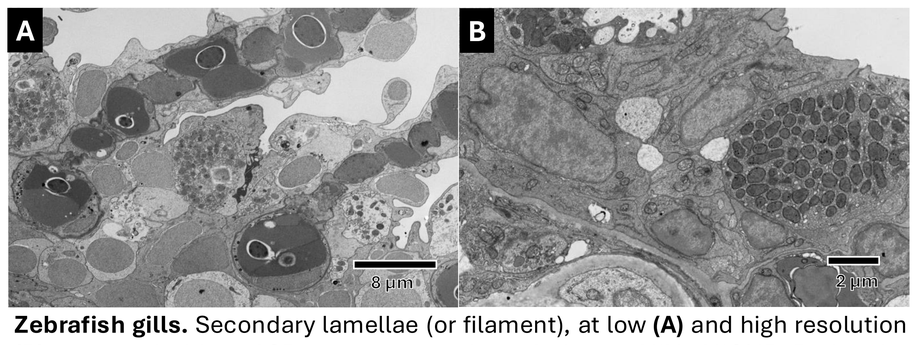
Human MCF7 Breast Cancer FIB-SEM. Cancer cell spheroids ASP-2000 prepared in <5 hrs with modified Hua protocol. **A**) Segmented vEM stacks. **B**) Segmentation trained from only 5% of manually annotated ground truth: **Nuclei, Nucleoli, Mitochondria**. FEI Helios G3 NanoLab DualBeam FIB-SEM. Oregon Health Science U. Knight Cancer Institute & Multiscale Microscopy Core [13-14].



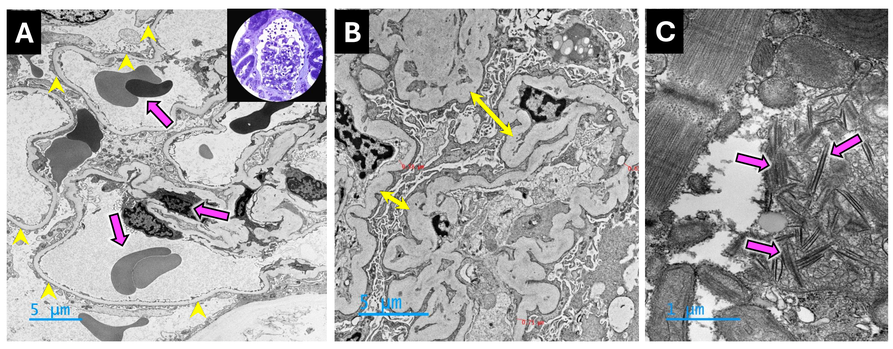
Brain and Pancreas. Tissues ASP-2000 prepared in <5 hrs with modified Hua protocol**.** SBF-SEM (**A & B**), FIB-SEM (**C-E**). **A**) Mouse Pancreas. **B**) Marmoset Brain. **C-D**) Mouse Pancreas. **E**) Marmoset Brain. Oregon Health Science University. Multiscale Microscopy Core [14].



B-Cell Pellets – SBF-SEM: Splenic mouse B-Cells were pelleted, enrobed in low melting agarose, and ASP-1000 processed for ~7.5hrs. **A**) SBF-SEM pellet volume image. **B**) Individual B-cell, **C**) Segmentation & analysis of individual B-Cells. **Mitochondria, Nucleus.** 3DEM Ultrastructure Core, Cleveland Clinic [8].



Zebrafish gills. Secondary lamellae (or filament), at low **(A)** and high resolution **(B),** prepared with an ASP-2000 process time of 3 hours. NIH - NICHD, Bethesda, Maryland [6].



Clinical Diagnostic Renal and Skeletal Muscle TEM. ASP-1000 prepared up to 128 biopsy tissue pieces per run in 2.5 hrs. Workflow requires only 1 person-hour effort. CAP, CLIA, ISO 15189 certified reference lab. **A**) Renal - TEM of healthy glomerulus with some foot process effacement around basement membranes (arrowheads), RBCs in capillary space, mesangial podocyte nuclei (arrows). Inset LM of the glomerulus. **B**) Renal - Patient with atrial fibrillation, coronary artery disease, bacteremia, diabetes mellitus, hypertension, pancreatic cancer, pericardial effusion. Note thickened basement membrane (double arrows). **C**) Skeletal muscle - Patient with mitochondrial cytopathy and active necrotizing myopathy. Note muscle with extensive paracrystalline inclusions (arrows). ARUP Laboratories, Salt Lake City, Utah [6,15].

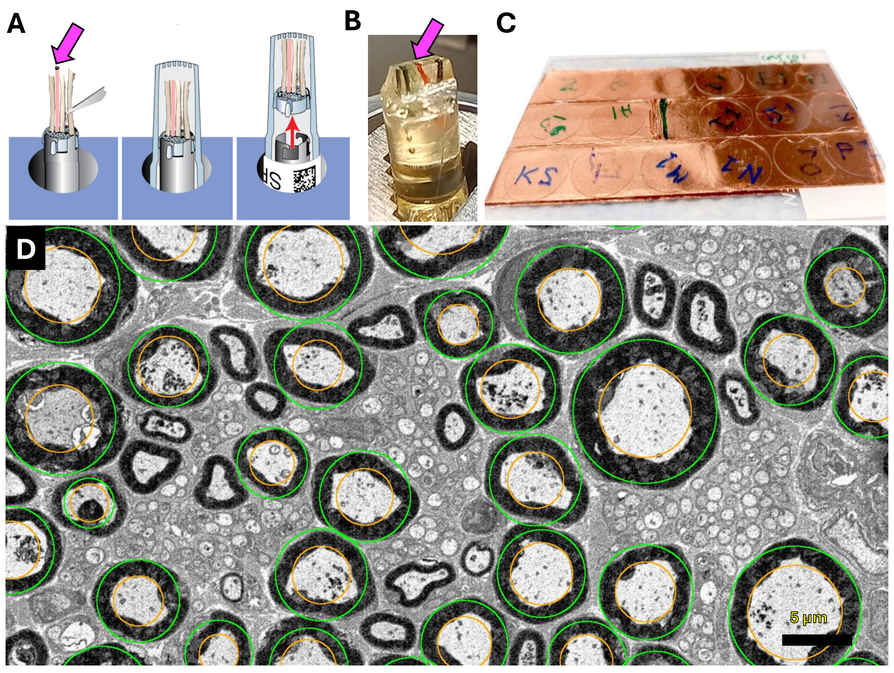


Figure 5: Peripheral Nerves. A) Three nerves oriented in one mPrep/s capsule with fiduciary thread (arrow), then ASP-prepared using a TEM-like ASP protocol with 90 minutes OsO_4 and **B)** resin embedded in the capsule (arrow). ASP-1000 preparation time ~4-hrs. **C)** 1 µm thick sections are mounted and UA and Pb stained on coverslips, then arrayed on copper tape. D) SEM image with auto-segmented axons for calculation of the myelin thickness G-ratios. 3DEM Ultrastructure Core, Cleveland Clinic Foundation, Ohio [16].

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