The Ice-Bucket Makeover: Portable Laboratory Cooling Gets with the Times

Data variability caused by differences in methods of acquisition and processing of human and animal samples (such as blood, nasal-, spinal-, mucosal fluid or tissue) is emerging as a major roadblock in post-genomic basic and clinical research (NCI Office of Biorepositories and Biospecimen Research (OBBR), June 2007). Worldwide efforts are currently under way to agree on a common standard operating procedure (SOP) or operating system for pre-analytical sample handling (see also www.isber.org/ibc.html, www.biospecimens.cancer.gov, www.web.genome.duke.edu/cores/ biorepository, www.oecd.org). Pre-analytical sample handling covers the spectrum from collection and preparation to storage of molecules, cells and tissues. The methods are often developed in an ad hoc fashion or inherited and adapted from older methods. The lack of standardisation, however, affects the quality and comparability of data across all fields of research and technological platforms. To advance personalised drug discovery and development, a new push for novel and improved methodologies for sample collection, preparation, shipment and quality assessment is required. This article will focus on temperature-sensitive bio-medical samples and will re-examine a century-old method for cooling and freezing.

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Benchtop sample temperature control, an integral part of most biomedical sample preparation and storage, remains in the 'middle ages' as it still depends on decades-old tools for cooling, freezing, snap-freezing or thawing, despite significant advances in analytical technologies. In particular, the ice bucket has been a ubiquitous feature of the laboratory for well over a century, and the simplicity of direct ice cooling seems to suggest that no improvements or substitutions are necessary or even possible. Since a very high percentage of life science work is conducted under cold conditions to prevent alteration or degradation of the biological materials, we had a fresh look at this proven yet sometimes messy method (*Figure 1*).

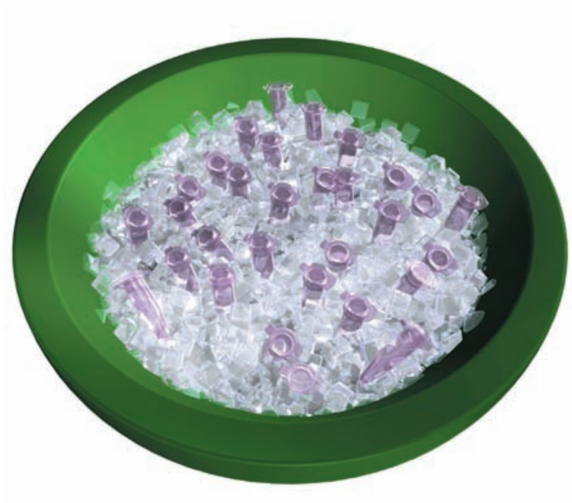

Figure 1. The Ice Bucket: a very messy, unorganised, error-prone and time-consuming, yet very common method of sample collection and cooling.

Although effective in keeping the samples cold, even the most careful placement of tubes in ice leaves a visually distorted array of tubes that move in position and angle as the ice melts. Scientific protocols consist of a long list of complex steps, many of which involve manipulating the contents of differing subsets of tubes. Even one instance of error through loss of label or disorganisation can alter the outcome of an experiment or assay, and may render the results meaningless or misleading. As a result, great losses in time and funds can unknowingly occur.

Another point of vulnerability in manual bench-top work is distraction and/or interruption. Proper execution of complex assay sequences requires intense operator focus. When a researcher's attention is interrupted unexpectedly, the opportunity for mistake in the order of tube manipulation sequence is enormous. For example, Kaiser Permanente discovered not long ago that interruptions were the main cause of medication errors. A reliable and visual place-keeper in the running sequence of events is often required to allow the technician to immediately recognise the step and tube where they left off at the time of interruption.

A third source of error is contamination or sample loss. Placing tubes in a melting ice environment exposes the tubes to excess moisture. Beads of melted ice can easily form near the opening of the tube, and when the tube cap is removed, the chance for contamination of the tube contents is significant. In addition, moisture on polyethylene or polypropylene tubes acts as an excellent lubricant, and greatly increases the likelihood of slippage errors, most of which result in sample loss that requires regeneration of the sample at the state where the error occurred.

A fourth source for error is timing. Assays are frequently dependent upon the timing sequence of the execution. Maintaining tubes in ice requires manual removal of the tube for opening and closing.

The additive sum of all like steps can be an impressive interval that can be difficult to predict, and insufficient allowance can easily confound the timing of a procedure. A means for accessing tubes without requiring individual holding and opening would be highly valuable.

With the existence or emergence of large genomic studies and other collaborative research studies, multi-site clinical trials, molecular epidemiology, pharmaco-genomics and molecular diagnostics, bench-top sample temperature control is in desperate need of a novel solution that enables a practical and inexpensive improvement in workflow, sample integrity and standardisation.

CoolRacks consist of arrays of receiver cavities for tubes rendered in a highly thermoconductive material. When in contact with ice or any thermal sink of like temperature (for example, dry ice, LN2, waterbath, heat block) the CoolRack will quickly adapt to the thermal sink temperature. The thermo-adaptive cavities allow placement of individual tubes resulting in a visually consistent array pattern that makes each tube easy to immediately identify and track (*Figure 2*).

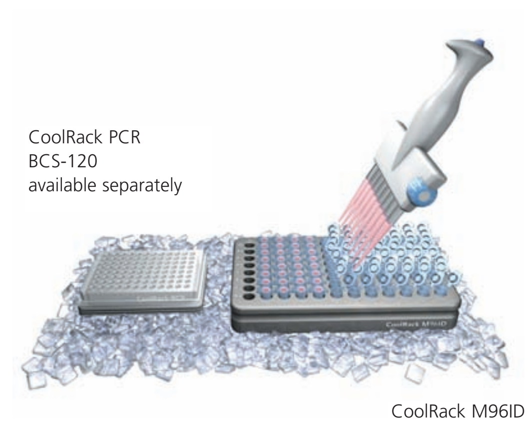

Figure 2. Highly Thermo-adaptive Sample Holder or CoolRacks. Simplified, fast, organised, protected, highly reproducible and standardised sample collection and cooling. This method can be used for standardising freezing, snap-freezing and thawing procedures as well.

As subsets of the tube array can be easily identified, experiments and assays can be logically organised to take direct advantage of indexing or natural human pattern recognition capability. Experimental sequences can be easily tracked in real time. As the CoolRack presents a stable base for the tubes, removal and holding of a tube is no longer necessary for opening or closing the tube or for adding or removing contents.

The time saving and fatigue reduction from elimination of manual tube holding greatly reduces the opportunity for operator error. In recognition of the value of this feature, redesigns of sample tube caps are now emerging on the market that take advantage of CoolRack design and benefits (Ergotubes by Biohit) and further reduce the time and effort for tube opening and closing. In addition, without the requirement for manual holding to open a tube, slippage errors are eliminated.

The CoolRack's cavities maintain a dry environment for the sample tube while quickly removing any heat resulting from environmental influx, effectively acting as a miniature refrigerator for each sample. The dry environment greatly reduces the opportunity for tube contents contamination.

Most importantly, however, the introduction of a simple and inexpensive technology such as the CoolRack method will result in an instant standardization of all temperature procedures for sample preparation, storage and transportation. Through the introduction of precision engineered, quality-controlled thermo-conductive CoolRacks, samples will be cooled, frozen or thawed in a highly reproducible manner. Sample temperature profiles will be identical and independent of user, time, site or location (*Figure 3*).

With the recognition that ice generated by conventional methods typically harbors biological contaminants, ice itself is often prohibited in critical environments such as sterile hoods, cleanrooms, GMP facilities, surgeries, and clinical settings.

When paired with an ice-free cold source and insulation, such as provided by a CoolBox, the CoolRack offers a large sample capacity, portable temperature management solution for the modern, contamination-free laboratory (*Figure 4*).

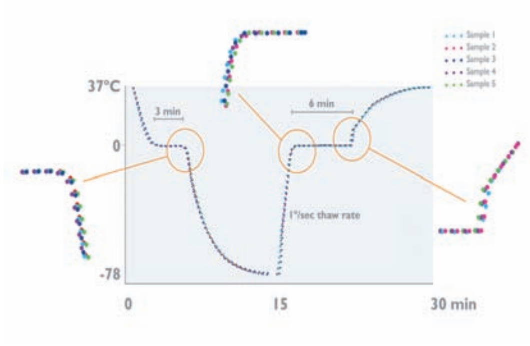

Figure 3. It's All About the Curves: Highly reproducible cooling, freezing, thawing through the use of precision engineered, novel alloy sample racks. (Method: The liquid content temperature of a 1.5ml microfuge tube containing 1ml of water was monitored by insertion of a thermocouple probe. The tube was transferred from a CoolRack in 37°C waterbath to a tube profile fitting CoolRack pre-equilibrated to -78°C on dry ice, then replaced into the 37°C CoolRack. The plot of 5 consecutive cycles demonstrates identical thermal profiles).

Figure 4. Ice-free cooling/freezing solutions. Uniform, all day, 're-chargeable' temperature management solution by combining thermo-conductive alloy sample racks with rechargeable cooling/freezing cartridge systems.

In summary, a closer examination and study of the decades-old 'ice bucket' method reveals that there are numerous limitations and pitfalls, all of which can be eliminated by the simple inclusion of highly thermo-conductive tube, plate or sample holders into sample collection, processing and handling. Quality controlled, precision-engineered novel alloy sample holders guarantee that each biomedical sample is cooled, (snap)- frozen or thawed the same way independent of time, operator or location.

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