



EXPERT INTERVIEW

Perspectives on Microsampling in Bioanalysis: Opportunities and Challenges in the era of the COVID-19 pandemic - An Interview with Dr. James Rudge



James Rudge

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Dr. James Rudge has served as Technical Director at Neoteryx since January of 2015. Prior to joining Neoteryx, Dr. Rudge worked for Phenomenex for 14 years and is a co-inventor of the Mitra Microsampling Device and the VAMS technology, which allows the precise, remote collection of volumetric samples. During his 14 years at Phenomenex, Dr. Rudge held a number of roles including Key Account Manager, Field Service Specialist, and latterly European Business Development Manager for Clinical. These roles allowed him to collaborate with customers on a wide range of projects regularly working in customer laboratories (globally) developing novel sample preparation and LC/LCMS methods.

Dr. Rudge graduated from the University of Wales (Swansea, UK) with a BSc. (Hons) in Biochemistry and a Ph.D. in Organic Chemistry where he worked on novel chemiluminescent probes for immunoassays.

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Could you please summarize your experience in bioanalysis and various microsampling techniques?

Around 2009 I became involved with microsampling for bioanalysis research when working with clients in the field, helping to set up novel bioanalytical assays specifically around sample preparation. One area which was emerging at the time was the use of DBS for PK studies. The advantage of this technique was that remote samples could be taken without the need of a phlebotomist. Furthermore, once dried, the samples were often stable under ambient conditions so they could be posted in the regular mail without the need for cold-chain shipping. These were advantages for companies running clinical trial research projects, especially when access to phlebotomy services and refrigeration was limited. I spoke to Dr. Neil Spooner, who was pioneering quantitative DBS work for the DMPK department at GSK, and he told me of the drawbacks of DBS filter paper cards. One drawback was of sample quality and the second was of quantitation. He told me that efforts were being made to improve

both challenges. One such solution, was to collect a fixed amount of blood in a capillary tube and then spot the blood onto a DBS paper. Wet microsampling using capillaries was a popular technique, and still is to this day. However, there are elements of risk associated with using glass. Also, filling such tubes without trapping air can be problematic. Yet, once the blood from the capillary tube was transferred to the DBS paper, then the whole spot could be extracted, either by manually cutting the spot out or using online extraction instrumentation.

This made me realize it might be possible to combine both the capillary and DBS into one device which has the benefits of both microsampling techniques but overcomes both issues associated with sample quality and hematocrit-related spot area biases. My idea was to put an absorptive material on the end of a tiny pipette, which would have the capacity to absorb a fixed volume of blood or other bio-fluid. A microsample could be collected in much the same way as volumetric capillary collection without the aforementioned drawbacks. Moreover, by using a martial-like paper, blood or other fluid could be dried like on a DBS card to deliver the same benefits around storage and transportation. With Dr. Spooner's encouragement and support, I made prototypes of DBS paper mounted on pipette tips. Dr. Spooner and Phil Denniff tested them at GSK and found that they absorbed blood independent of hematocrit. By doing this I, somewhat accidentally, invented the technique of volumetric absorptive microsampling. I have been fortunate to be involved with developing and refining this microsampling technique, and working with pharmaceutical researchers and others to demonstrate its utility for a wide range of bioanalytical research projects. The result of this work is the Mitra® device based on VAMS® technology, which we developed at Neoteryx. I have been fortunate to work with research groups in all corners of the world in microsampling method development for drug development and other applications.

How has COVID-19 changed the need and implementation of microsampling in research?

COVID-19 has changed how we live our lives, and the immediate threat of the virus has forced new social distancing measures. National lockdowns have caused an increased reliance on remote technologies. Simply put, people are less able or willing to leave the house, which includes onsite visits to brick-and-mortar facilities for specimen collection in research studies. Since the onset of the COVID-19 pandemic, Neoteryx has heard from many more researchers wanting to implement microsampling. For example, they want to use VAMS for remote collection of specimen microsamples for research, both for COVID-19 and for other studies that must continue despite lockdowns. There have been a number of COVID-19 sero-surveillance studies conducted with VAMS using remote, home-based blood collection with Mitra devices. For example, the National Institutes of Health (NIH) recently reported on their study of more than 8,000 remote microsamples from volunteers. The samples were analyzed to understand the degree of SARS-CoV-2 seroprevalence during the early part of the coronavirus pandemic in 2020. Also, more drugs are being evaluated for their efficacy in treating COVID-19. For example, a study reported in late 2020 used VAMS to collect microsamples to understand the prophylactic efficacy of the antimalarial drug Hydroxychloroquine. The COVID-19 pandemic has brought new awareness to the value of remote microsampling in both research and healthcare, and we anticipate that our remote microsampling technology will continue to be used in research studies of new drug therapies for life-threatening illnesses.

Do you think microsampling techniques will become a norm in clinical trials post COVID-19?

The pandemic has certainly shown that microsampling is a vital tool for remote, decentralized clinical trials. A quick look at clinicaltrials.gov today shows that there are over 3,000 new or recruiting clinical trials for COVID-19 alone. Recruitment of trial participants, especially during a pandemic is a real challenge, because people are isolating safe at

home, often on government advice. Yet, clinical trials are a vital tool to advance our understanding of vaccines and drugs that prevent or treat disease, which is an unfortunate paradox. I think remote microsampling will become a norm in clinical trials post-COVID-19. At Neoteryx, we have worked with many contract research organizations, pharmaceutical companies, and research agencies during the pandemic, whose studies proved that microsampling is a vital tool not only in drug trials, but also for huge serosurveillance studies.

I have heard that from an economic standpoint, the cost of having people attend clinics for clinical trials can cost up to \$1,000 per person per day. Remote microsampling can eliminate the need for such costly clinic visits. Some of our clients continue to offer participants an initial onsite visit for trial orientation or training, but subsequent trial visits, activities and specimen collection are conducted remotely.

Before the pandemic, microsampling was of interest where we saw some companies pioneering the remote approach in their trial designs, particularly for studies that involved sample collection across large geographical areas. There was less of a sense of urgency, however, to onboard microsampling widely. This is understandable, because clinical trials are costly and there is an element of risk involved with running an arm of a trial using a novel collection procedure. However, since the pandemic, and because of the pandemic, I have seen a huge surge of interest in remote microsampling. Starting in 2020, a number of companies began adopting a hybrid approach where participants are given a choice as to which sampling technique they prefer, or which sample types are to be collected. This approach is also discussed in a recent paper by AstraZeneca in *J Bioanalysis* (<https://doi.org/10.4155/bio-2020-0105>). Furthermore, an approach we are seeing more among our clients, is that they are designing their trials with mixed sampling from the start as an attempt to mitigate risk and to allow bridging between matrices. As the success of this approach and the benefits of remote microsampling are realized, I believe these will become the norm for clinical trial design, certainly in the medium term.

What are some pros and cons of the microsampling technique of your choice?

As someone who has been involved with developing volumetric absorptive microsampling, I am naturally biased towards this technique! A huge “pro” of the VAMS technology and this microsampling technique is that precise, quantitative biological samples can be easily collected from practically anyone, anywhere. This technique even works at the top of a mountain, as proven by the Medical University of Vienna!

Another “pro” of using VAMS, is that the microsamples are dried in transit, and the drying process often acts to preserve the molecule(s) of interest, which practically negates the need for cold-chain shipping. The “con” or disadvantage of VAMS is that it is dried blood, and so the blood is hemolyzed. This prevents harvesting of plasma or serum from the hematocrit. There are certain analytes, such as potassium, which require serum and hemolysis. Furthermore, some instruments require clear, non-hemolyzed, samples to allow for colorimetric measurements. Nevertheless, it is being proven that more and more analytes can be measured in different ways with great success from dried specimens, so these “cons” or disadvantages are a limitation of current bioanalytical equipment. As technology progresses, the need to harvest plasma or serum will decline, as demonstrated with analytes such as creatinine, which can now be analyzed accurately from dried blood extractions on an LCMS which is important in the study of new drug therapies that impact kidney function.

What technical hurdles you encountered during the early stages of this technology in your research?

For implementation of VAMS® methods in support of drug development research, I had to understand the importance of the role that hematocrit has on the assay. If the analyte does

not partition equally between hematocrit and the plasma, then when comparing assays to plasma, biases in the data can be observed. These “hurdles” or biases can be corrected or allowed for, and there are a number of excellent publications that explain how to deal with the issue. Another “hurdle” or challenge I have encountered pertaining to hematocrit is that, if extraction methodology has not been fully optimized, then negative biases can be observed with increasing percentage hematocrit levels. Moreover, the older the dried blood is on the Mitra® device tips, the more likely it is that negative extraction biases can be observed. However, both biases can be solved by optimizing the extraction conditions.

Finally, another hurdle, or question that needs to be addressed, is creation of appropriate calibrators (cals) and quality control samples (QCs). It is a requirement of regulatory authorities that cals and QCs should be produced in the same matrix as the sample matrix. For example, if capillary blood is to be tested, then cals and QCs should be prepared in blood, not in plasma. If an anticoagulant is used, then efforts should be made to bridge between native blood and blood with the anticoagulant added. One solution to this is to precoat tips with anticoagulant before sampling, and to compare samples with and without the blood stabilizer.

Do you have any advice for our readers who may be looking forward to implementing microsampling?

First, to get an overview of what is possible with microsampling, I would encourage the reader to read some of the excellent review papers on microsampling. Many of these address the points I have highlighted in response to your previous questions. Second, if the reader has access to an LC-MS or immunoassay (such as ELISA), then there is a very good chance that a robust method can be developed from microsamples. Indeed, the advances in sensitivity of instruments has improved significantly over the years. This means that, for some research studies, many molecules can be simultaneously measured from one tiny drop of a biofluid. This is quite remarkable when you stop to think about it!

Another point to think about is the nature of the analyte. Is it stable in the matrix and environmental conditions that the sample will be exposed to? One major benefit of using dried blood is that analytes, by and large, are much more stable than in wet blood. This allows for ambient storage and transportation, which can be critically important for research studies conducted in low-resource regions. For example, Swiss School of Tropical Medicine have reported on research projects where samples have been collected in the Ivory Coast then shipped back to the institute for extraction and analysis. Therefore, understanding analyte stability under such conditions is critical in order to validate a robust assay geared for remote specimen collection.

What are the three biggest challenges that need to be addressed in order to have a wide-spread adoption of microsampling in clinical trials?

1. A greater awareness that data obtained from microsamples can be just as good as data obtained from samples processed from traditional specimen collection techniques.
2. If the matrix is whole blood, then this should be the matrix used throughout the whole drug development cycle. The situation that exists presently for many drug development programs, is that early on in the development cycle (preclinical – phase 1 clinical), assays are often validated in plasma. As the drug development program transitions to phase II – IV, dried remote blood sampling becomes very attractive. The reason for this is that such trials are often international and multi-centered. At these later stages in the drug development cycle, switching to dried blood is highly attractive because it has the potential to eliminate cold-chain shipping, which is costly and adds risk to the sample integrity. Moreover, microsampling allows study participants to sample from home, which it is hoped, will improve participant recruitment and

- compliance to the clinical trial. However, if the bioanalytical work is conducted on wet plasma for the early stages in the development process, then bridging is needed to demonstrate that dried blood shows bioanalytical equivalency to plasma. However, if a decision is made to conduct all bioanalytical sampling from dried blood extracts in all stages, then this would negate the need to bridge between different sample types.
3. Logistics of sample collection, transportation, analysis and reporting need to be addressed early on in the development cycle. When a blood tube is exchanged with something very different (i.e., a Mitra microsampling device), then considerations for simple things like labelling become a critical factor to consider.

Could you share some of the most exciting developments that have happened in microsampling techniques in the last 5 years?

For me, microsampling is allowing groups from different parts of the world to collaborate in ways which would have been cost prohibitive with standard blood collection. Groups from all four corners of the world are now able to not only share data, but are able to share samples and even build inexpensive biobanks so that the same samples collected from one project can be used for completely new projects. These can be sent to a specialty laboratory, which is sometimes thousands of miles away. For example, in the field of omics blood microsampling can be conducted by one group to measure a proteome, and then sent to another group for SNP analysis. Indeed, if blood is too complex a matrix, then serum samples can be easily subsampled at a biobank at one center, dried and sent in the regular mail to another center for proteomic analysis without the need for stabilization. Microsampling techniques have enabled this inexpensive way to send biofluids, which has the potential to bring scientists closer and closer together, accelerating research as a result.

How do you see these techniques evolving in the next 5 years?

Collecting blood microsamples has the potential to negate the need for sample labelling which has increasingly become an issue when dealing with the logistics of remote samples. In future, I believe microsamples could be genetically screened for subject identity before measurement of the desired analyte of interest. This, of course, raises the problem of misuse of genetic information, but this boils down to more of an informatics problem than a scientific barrier. If the informatics data security problem can be solved, then using genomic DNA in blood as its own biometric identity maker, will ensure the data integrity of each microsample.

I also envision increased use of microsampling techniques for routine collection of other biofluids, such as saliva and urine. This application of microsampling could revolutionize toxicology sampling, for example. Although dried urine spots are a known technique, the low viscosity of urine compared to blood limits, from a practical standpoint, the amount of volume that can be collected on a filter paper. Volumetrically collecting the biofluid on a Mitra device, for example, would allow greater volumes to be collected in a smaller form factor, which aids in sample transportation and storage.

Finally, I envision greater use of liquid-handling robots to process microsamples, which will significantly improve the efficiency of sample processing. This would also allow a greater number of samples to be processed and would free up bioanalytical scientists to do other things, such as focusing on data analysis and assay design.

Do you see a need of an international consortium to champion and raise awareness for use of patient centric microsampling techniques in future clinical trials?

Yes, definitely see the need for an international consortium. I think that international conferences, such as CPSA (Clinical & Pharmaceutical Solutions Through Analysis) and the Patient Centric Sample Interest Group (which originated from ongoing conversations at CPSA events), have done an awful lot to move the patient-centric agenda to where it is

today. CPSA has created a platform for like-minded people to move the remote sampling agenda from a 'nice to have' option to the reality that it is a necessary approach that is becoming more relevant in the context of superbugs and global pandemics.

I highly encourage anyone who is interested in adopting patient-centric microsampling to attend CPSA events both online and in person (when the COVID-19 situation allows). Indeed, COVID-19 has inadvertently catalyzed and accelerated remote, patient-centric microsampling.