An Interview with Dr. Christoph Gassner of The Swiss Red Cross

Blood can be classified into 35 different groups. Some blood is so rare that a search for a compatible donor will span continents. Accordingly, a unit of rare blood can cost 30 times more than average. Rare blood can command north of $7,500 USD per liter/unit.

Receiving incompatible blood triggers alloimmunization and carries a consequent mortality risk that dramatically rises upon receiving such blood again from a subsequent transfusion. Regular recipients of blood, such as people with sickle cell anemia and beta thalassemia, depend upon a limited infrastructure of donated blood.

A better way to find and supply rare blood is in development by MassARRAY® community member Dr. Christoph Gassner, who leads the Swiss Red Cross' Department for Molecular Diagnostics and R&D in Zurich.

Gassner's team has developed an inexpensive MALDI-TOF genotyping-based screen for common and rare blood types. The cost of his MassARRAY-based panel may transform rare blood banking, as it can ensure the rare blood supply for the whole of Switzerland for a mere 80,000 Swiss Francs annually, including instrument amortization, labor, and associated costs.

A draft version of the screen, published last year in the journal Transfusion, demonstrated greater specificity, throughput, quality, and cost-efficiency than serology, the antibody-based approach that currently dominates blood banking worldwide. Since then, Dr. Gassner has screened thousands of patients using an improved panel and is assembling a new global initiative for safer, less costly blood banking.

Why can genotyping transform blood banking?

CG: Sometimes there are no commercial reagents for certain blood groups, so genotyping closes diagnostic gaps due to antibody unavailability for classical blood group detection. In genotyping, we are able to add more variants with only fractional increases in costs.

Traditionally, only the ABO blood group needs to match to avoid a lethal transfusion of incompatible blood. However, sometimes a patient's blood needs to be matched when he/she has already been immunized. Then the recipient has formed what we call an alloantibody against one, or some of the other 35 blood group systems. When we are confronted with such a patient, almost every single alloantibody may cause death during incompatible transfusion. Therefore, the correct blood type needs to be finely matched.

Despite genotyping's utility, why hasn't it been more widely adopted?

CG: There are commercial approaches and in-house approaches. All the commercial genotyping techniques have a certain cost and limitations with respect to the number of genetic variations analyzed. Generally speaking, the costs are quite high and the diagnostic output of genetic variations is quite low when compared to MALDI-TOF mass spectrometry. It's no wonder

the regular blood banks or transfusion services haven't adopted this technique very well.

The in-house methods have their own problems with respect to reliability and quality. We tested all this with our MALDI-TOF mass spectrometry genotyping technique and we were absolutely fascinated by the quality. Our research in *Transfusion* demonstrates the flexibility and accuracy of genotyping with the MassARRAY System and it further illustrates the limitations of fine blood matching by serology.

How has your genotyping program progressed thus far?

CG: In the last few years in Switzerland, we genotyped blood of 20,000 donors in Bern with an in-house method, and another 37,000 donors here in Zurich using the MassARRAY in a research program funded by the Humanitarian Foundation of the Swiss Red Cross. Roughly around 1% of all blood donors showed a rare blood variant, adding up to a total of 800 currently registered rare Swiss donors.

We lose about 10% of our rare donors every year, usually due to age, health, or donation restrictions like traveling to risky areas. We continuously look to resupply our rare donor list to make up for that loss. It will cost about 80,000 Swiss francs a year to maintain the number of donors within our rare blood donor program for all of Switzerland. That's not a lot of money, but it's been problematic to obtain.

What is your way around the financing challenge?

CG: Many specialists still assume that genotyping is expensive, despite the fact that it is becoming more affordable. The condensed MassARRAY panel we designed is an example of that.

We were able to condense additional genetic variations from 10 reaction tubes per donor to only two — at a cost around $30 per donor for the majority of common, extended, and rare blood groups. That is a huge price reduction, to about one-fifth what we published in *Transfusion Medicine Reviews* in 2013. It's less expensive and more comprehensive than classical serotyping; practically no other technique covers as many variants. About $20 of the cost covers extended blood groups such as Kell, Kidd, and Duffy, which have long established funding schemes. The remaining $10 is for rare blood types. This portion does not have a clear financing model yet.

Financing rare blood donor programs is an ongoing discussion that is taking place not only in Switzerland, but also around the world.

Do you see the hematology community worldwide changing blood donor screening practices?

CG: We've had some requests with bioinformatics specialists that are focused on HLA typing who are thinking about using genotyping and next generation sequencing with blood. Transplanting bone marrow and finding the correct donor is rumored to cost around €50,000. There is also interest in the potential of MALDI-TOF mass spectrometry for national programs for prenatal blood genotyping of fetal DNA from maternal plasma.

We are also looking into possible future solutions for electronic blood matching. The electronic matching provides the advantage of including important group systems on the donor and recipient side, which is not done regularly in hospitals today. If we have datasets of genotyped donors and recipients, we can electronically determine the best blood for everyone and avoid blood incompatibility right from the start. Not even allowing alloimmunization events because of perfectly matched blood. It's a huge goal that is probably not too far off. Perhaps it could be accomplished within a year or two.

This past October we started a new three-year collaboration between Bern and Zurich, with 4,000 and 8,000 annual donors to be genotyped

at each center, respectively. That's a potential of 36,000 donors over the course of the program. Zurich will use MALDI-TOF mass spectrometry. Both centers will confirm their genotyping results by serology as well. This is an ideal study now.

Why is blood genotyping research so advanced in Switzerland, especially when other nations have more people with rare blood types?

CG: Switzerland is not a member of the European Union, which offers a few key advantages such as having their own ministry of health (Bundesamt für Gesundheit, BAG). It doesn't exclusively rely on CE markings or FDA approval. If you can prove to Switzerland's BAG that the genotyping technology works well, is accurate, and has appropriate quality control mechanisms, you are allowed to continue with yearly-accredited audits. In countries like the U.S., you need to invest a lot of money for FDA approval before you are free to use the technology. I think that is a huge reason why we were able to find success here in Switzerland.

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