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Persistently low transplantation rate of ABO blood type O and highly sensitised patients despite alternative transplantation programs

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Summary

ABO blood type O and highly sensitised patients have the smallest chance to receive kidney transplantation. Do alternative donation programs increase this chance? In the period studied: 2323 patients were enlisted on the Rotterdam waiting list for a renal transplantation: 435 patients still waiting (WL), 464 delisted without transplantation (DWT). 1424 received deceased donor (DD, 535) or living donor (LD, 889, including 204 alternative) transplantation. Alternative LD programs in our centre are: paired kidney-exchange, altruistic with domino-paired donation and ABO-incompatible donation (ABOi). Compared to populations not transplanted, blood type O recipients are significantly underrepresented in DD and all LD transplantation populations, except the ABOi program. Highly sensitised patients are overrepresented in DD, but underrepresented in all LD transplantation populations. The high transplantation rate of highly sensitised patients was the result of Eurotransplant Acceptable mismatch program (AM). The LD ABOi and DD AM programs are the only alternative donation programs favourable for patients with low chances. While the contribution of direct LD transplantations will increase in time, the relative success rate of low-chance patients will decrease. Beside increasing LD ABOi transplantation, a new DD allocation model favouring both highly immunised and blood type O patients is essential.

Introduction

In our centre deceased donor transplantation (DD) was introduced in 1971 and living donor transplantation (LD) in 1981. Immunogenetic factors that influence the access to DD or LD renal transplantation are ABO blood type and HLA typing in combination with PRA (panel reactive antibody) [1]. The DD Eurotransplant allocation system (ETKAS) was introduced in 1996 because in the former allocation system patients with rare HLA phenotypes and HLA homozygous patients accumulated on the waiting list [2]. In ETKAS assignment of kidneys is done according to a point system [3,4]. Weights included are: Donor-recipient HLA mismatch grade, patients mismatch probability (probability for a 0 or 1 HLA mismatched kidney offer, adjusted for ABO blood type identical combinations and PRA level), waiting time, distance factor and National import/export balance. Extra points are given to high urgency patients and to children. As highly sensitised patients with HLA specific antibodies detectable in CDC and a virtual PRA higher than 85% turned out to be hard to match the acceptable mismatch (AM) program was developed for these patients. Highest priority, above the point system, is given to patients in this program [5]. For the AM program ABO identity is not required. Priority above the point system is also given to HLA identical

combinations. Before January 2011 ABO blood type identity was not required for HLA identical combinations. In the point system adjustment of allocation for ABO blood type is present only in the patients' HLA mismatch probability.

In time living donor kidney transplantation numbers increased and the last years living donor transplant numbers represent two thirds of the total number of transplantations performed in our centre [6]. Alternative living donation programs have been developed in order to circumvent the immunogenetic factors such as donor specific HLA antibodies or ABO incompatibility, enabling living donor transplantation in spite of them [7,8]. In our centre the Donor-exchange program was developed in 2004 to enable transplantation of incompatible couples [1]. The Domino-donation program is a combination of the altruistic donation program and the donor-exchange program that was developed in 2005 to increase the chances for transplantation [9]. Finally the ABO incompatible program was introduced in 2006 to enable transplantation for those couples that were ABO incompatible. Five years after the introduction of these programs we evaluate the success rate of populations with unfavourable immunogenetic factors in the different donation programs and compare them with direct living donor and deceased donor transplantation programs and with the population not (yet) transplanted.

Methods

The population studied consists of patients that had been or still were present on the Rotterdam kidney waiting list between January 1st 2000 and June 30th 2011. The database was merged with the Rotterdam transplantation database. For this study 2 populations were defined: Patients that were transplanted (T) and those that were not transplanted (NT) in the period studied. The patients NT are still on the waiting list for transplantation (WL) or were delisted without transplantation (DWT) because of death or because contra-indications for transplantation had developed. These contra-indications mostly were cardiovascular disease, and malignancies. Transplantations were defined as: deceased donor, direct living donor or alternative living donor transplantations. The latter were subdivided into: Donor-exchange, altruistic donor, domino-donor and ABO incompatible donor transplantations. The ABO blood type distribution and maximum percentage CDC–PRA in these populations were compared. For comparison PRA was subdivided into 4 categories: unsensitised: 0% (31.2% of the population), low: 1–4% (33.7% of the population), sensitised: 5–85% (30.5%% of the population) and highly sensitised: above 85% (4.6% of the population). Waiting time is defined from start of renal replacement therapy until transplantation, delisting or censoring in October 2011. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS), version 16.0. The Chi-square test was used to test the associations between two categorical nominal or ordinal variables. ANOVA was used to test associations between continuous variables. A P-value < 0.05 was considered significant. In order to predict transplantation versus DWT or still on the WL, univariate and multivariate Cox proportional Hazards analyses were performed. In SPSS (version 16), for each model: –2LL, the likelihood-ratio statistic, and the overall chi-square was used. Value considered significant is <0.05. Variables included were: patient gender (females), age, maximum PRA (0), and ABO blood type (A). For categorical variables the reference category is shown in brackets, age is included as a continuous variable. Separate analyses were performed with respectively LD or DD transplantations, only DD and only LD transplantations as the event studied.

Results

Between January 1st 2000 and June 30th 2011 2323 patients had been or still were on the Rotterdam waiting list for renal transplantation. Observation was until October 1st 2011. From these patients there were no missing values concerning follow-up and ABO blood type. Maximum PRA was lacking in 3 patients. Of these 2323 patients, 1424 (61.3%) received a living or deceased donor renal transplantation (Fig. 1). In the period studied 535 (23.0%) deceased donor transplantations, including 63 (2.7%) via the Acceptable mismatch program had been performed. 889 (38.3%) living donor transplantations including 204 (8.8%) alternative living donor transplantations were performed. The 204 alternative living donor transplantations were via the donor-exchange (41), the altruistic donor (71), the domino-donor (49), and the ABO incompatible donor transplantation programs (43). Pre-emptive transplantations were performed in 179/889 (20.1%) LD recipients, and in 6/535 (1.1%) deceased donor (DD) recipients. In the period studied 899 patients had not been transplanted (NT): 435 were still on the waiting list, 244 patients were delisted without a renal transplantation and 220 patients died while on the waiting list (Fig. 1). Of all patients enlisted, 20% had subsequently been delisted without a renal transplantation.

Table 1 shows the prevalence of ABO blood type O in the populations studied. Blood type O recipients are underrepresented in both living and deceased donor kidney transplantation populations compared to the population NT. The ABO blood type distribution of the populations is shown in Figure 2. In the donor-exchange program the prevalence of blood type B was higher than

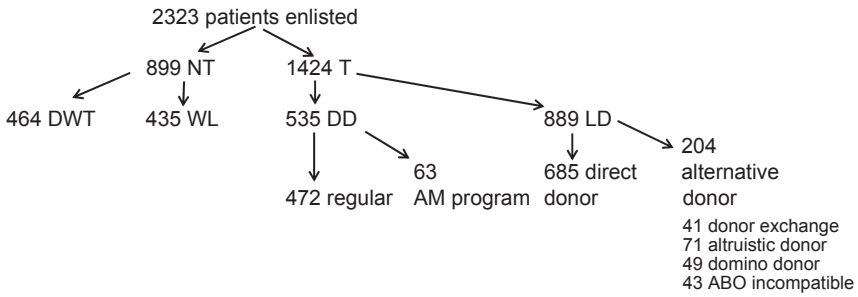

Figure 1 Diagram showing the pathways of patients after enlisting. NT, not transplanted; T, transplanted, DWT, delisted without transplant; WL, still on the waiting list; DD, deceased donor transplantation; LD, living donor transplantation.

Table 1. Prevalence of ABO blood type O and highly sensitised patients in the populations studied.

Population	Numbers	Percentage	*P*-value
Prevalence of ABO blood type 0			
Entire population	980/2323	42.2%	
Not transplanted (NT)	418/899	46.5%	0.003
DWT	216/464	46.6%	0.031**
Transplanted (T)	562/1424	39.5%	
DD	217/535	40.6%	0.023*
LD all programs	345/889	33.3%	<0.001
LD direct	257/685	37.5%	<0.001*
LD domino donor	10/49	20.4%	<0.001*
LD altruistic donor	34/71	47.9%	ns*
LD donor-exchange	14/41	34.1%	ns*
LD ABO incompatible	34/43	72.1%	0.001*
Prevalence of highly sensitised patients			
Entire population	106/2320	4.6%	
Not transplanted (NT)	48/898	5.3%	ns**
DWT	25/463	5.4%	ns**
Tranplanted (T)	53/1422	4.1%	
DD	51/535	9.5%	<0.001*
LD all programs	7/887	0.3%	<0.001*
LD direct	3/683	0.4%	<0.001*
LD domino donor	2/49	4.1%	ns*
LD altruistic donor	1/71	1.4%	ns*
LD donor-exchange	1/41	2.4%	ns*
LD ABO incompatible	0/43	0.0%	ns*

DWT, Delisted without transplant; DD, deceased dcncr; LD, living donor.
*Compared to NT, **Compared to T.

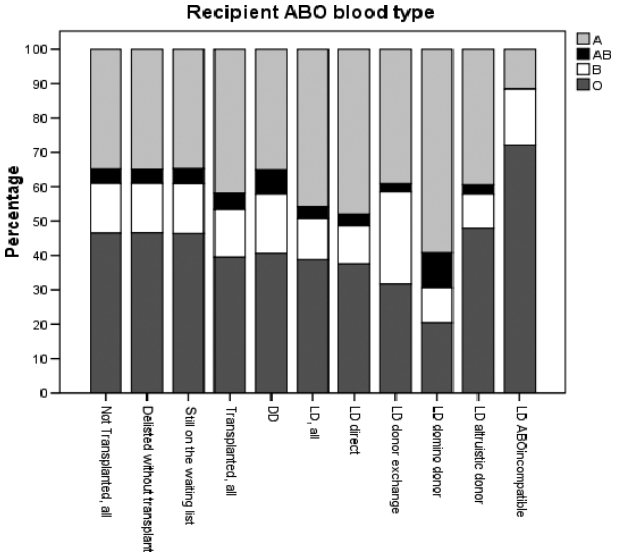

Figure 2 ABO blood type of population delisted without transplantation, waiting list patients, recipients of a deceased donor transplantation, or a living donor transplantation via the direct donation program or one of the alternative donation programs.

in the population NT (11/42, 26.2%, $P = 0.042$). In all other transplanted populations the prevalence of blood type B was not significantly different from the population NT. Table 2 shows waiting times from the various populations according to ABO blood type. In the DWT, and in the WL population there is a significant difference in waiting time between patients with blood types O and A, but not between patients with blood types O and B. In the DD transplantation population blood types O and B recipients waited significantly longer than blood types A and AB recipients.

From the population of blood type O *deceased donors* only 86.7% of kidneys had been allocated to O recipients and 13.3% had been allocated to non-O recipients. Via the AM program 42.6% (20/47) of O-donor kidneys had been allocated to non-O recipients, in the non-AM population this was 6.4% (13/202). In the population of recipients of a *direct living* donor 38.1% of blood type O kidneys had been transplanted to non-O recipients.

Highly sensitised patients are not underrepresented in the population T compared to the population NT (Table 1). The DWT and the WL populations had comparable percentages of highly sensitised patients (Fig. 3). However, there were significantly more sensitised patients (PRA 5–85%) in the former population [34.3% (159/464)

Table 2. Mean waiting time (years) and standard deviation according to ABO blood type and PRA category (ANOVA LSD).

Mean waiting time (years) and standard < deviation (ANOVA LSD)											
Delisted without transplantation		P1	P2	Waiting list	P1	P2	Recipients of deceased donor kidney	P1	P2	Recipients of living donor kidney	P1 and P2
ABO blood type											
A	2.1 ± 2.3	0.005	ns	0.8 ± 1.2	<0.001	0.017	3.1 ± 1.9	<0.001	0.017	1.6 ± 2.4	ns
AB	2.1 ± 3.3	ns	ns	1.9 ± 4.1	ns	ns	1.7 ± 1.6	<0.001	<0.001	1.0 ± 1.0	ns
B	2.4 ± 2.3	ns		1.6 ± 2.1	ns		3.8 ± 2.1	ns		1.6 ± 2.5	ns
O	2.8 ± 2.6		ns	1.7 ± 2.5		ns	4.2 ± 2.5		ns	1.5 ± 2.0	
Delisted without transplantation		P3		Waiting list	P3		Recipients of deceased donor kidney	P3		Recipients of living donor kidney	P3
Maximum PRA											
0	1.6 ± 1.4*	<0.001		0.8 ± 1.2*	<0.001		2.7 ± 2.1*	0.001		1.0 ± 1.4	0.026
1–4	2.1 ± 1.7*	<0.001		1.3 ± 1.8*	<0.001		3.3 ± 1.7**	ns		1.6 ± 2.1	ns
5–85	2.9 ± 2.2*	<0.001		1.9 ± 2.9*	<0.001		4.0 ± 2.5**	ns		2.0 ± 3.2	ns
86–100	7.1 ± 5.5*			4.1 ± 4.1*			4.0 ± 2.6			3.4 ± 2.6	

P1: Difference between blood type O and each other blood type is shown.
P2: Difference between blood type B and each other blood type is shown.
P3: Difference between PRA>85 and each other category is shown.
*Significantly different from all other PRA categories.
**Significantly different from all PRA categories but highly sensitized.

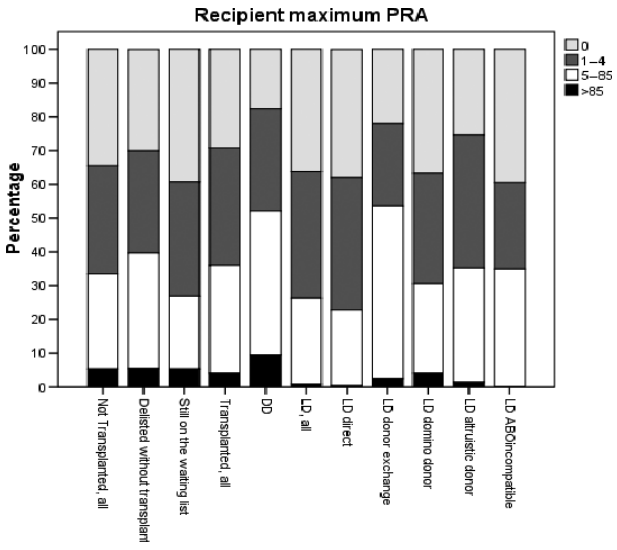

Figure 3 Maximum PRA of waiting list patients, recipients of a deceased donor transplantation, or a living donor transplantation via the direct donation program or one of the alternative donation programs.

respectively 21.6% (94/435) Fig. 3, $P < 0.001$]. In the DD transplantation population 9.5% of transplantations were in highly sensitised patients. Most of these patients were transplanted via the AM program [5]. Relatively more patients were highly sensitised or sensitised, and less patients had low or absent sensitisation (PRA 0–5) in the DD population in comparison to the population NT (Fig. 3). In contrast, in the LD transplantation population highly sensitised patients were underrepresented compared to the population NT. The percentage of sensitised patients (PRA 5–85) was higher in the population recipients of a kidney exchange donor (Fig. 3).

Table 2 shows the waiting times from the various populations according to PRA. In the populations DWT and on the WL highly sensitised patients had waited significantly longer in comparison to less immunised patients. In the DD transplanted population and in the LD transplantation population, highly immunised patients waited significantly longer than non-immunised patients. Overall DWT highly immunised patients have the longest waiting time. In the populations NT waiting time increased with increasing PRA. The difference was significant between all PRA categories.

Comparison of the DD and LD transplantation populations shows that the prevalence of ABO blood type O is not significantly different between these populations, however, there are significantly more sensitised and highly sensitised patients in the DD population compared to the LD population ($P < 0.001$).

Multivariate Cox proportional hazards analyses showed that the chance for either a LD or DD transplantation decreases with increasing recipient age (Table 3). Increasing recipient age decreases the chance for a LD renal transplantation, but increases the chance for DD transplantation. In comparison to patients with ABO blood

Table 3. Results of the Multivariate Cox proportional hazards analysis with Living donor (LD) or Deceased donor (DD) transplantation, respectively only LD and only DD transplantation as the event studied.

	LD or DD				DD				LD			
Transplantation type	Sig.	Exp(B)	95% CI for Exp(B)		Sig.	Exp(B)	95% CI for Exp(B)		Sig.	Exp(B)	95% CI for Exp(B)	
Age	<0.001	0.990	0.986	0.994	0.005	1.010	1.003	1.017	<0.001	0.980	0.976	0.985
Blood type ABO (A)	<0.001				<0.001				<0.001			
AB	0.165	1.194	0.928	1.534	<0.001	2.637	1.842	3.776	0.101	0.736	0.511	1.061
B	<0.001	0.696	0.592	0.818	0.563	0.929	0.723	1.193	<0.001	0.580	0.468	0.719
O	<0.001	0.605	0.538	0.680	<0.001	0.601	0.493	0.733	<0.001	0.623	0.538	0.720
gender (female)	0.371	0.951	0.852	1.062	0.756	1.029	0.860	1.230	0.216	0.916	0.796	**1**.053
PRAmax (0)	<0.001				0.002				<0.001			
1–4	<0.001	0.644	0.564	0.736	0.025	0.743	0.573	0.964	<0.001	0.637	0.546	0.744
5–85	<0.001	0.490	0.426	0.565	0.126	0.819	0.634	1.058	<0.001	0.378	0.316	0.451
86–100	<0.001	0.203	0.152	0.271	<0.001	0.495	0.338	0.724	<0.001	0.047	0.022	0.100

type A, blood type O patients have only 61% chance and patients with blood type B have only 70% chance for either LD or DD renal transplantation. (Table 3). Highly sensitised patients have only 20% chance for a renal transplantation in comparison to unsensitised patients. The Cox performed with *deceased donor kidney transplantation* as the event showed that ABO blood type significantly influenced this chance: in comparison to patients with blood type A patients with blood type O have a smaller chance (60%), patients with blood type AB have a higher chance (264%, $P < 0.001$). Highly sensitised patients have only 50% chance for DD transplantation in comparison to unsensitised patients. The Cox performed with *living donor kidney transplantation* as the event showed that patients with blood type O (62%) and B (58%) have a smaller chance compared to patients with ABO blood type A. The chance for living donor kidney transplantation decreases with increasing maximum PRA. Highly sensitised patients have only 5% chance for LD transplantation.

Discussion

In this study we show that of all patients enlisted, 20% had subsequently been delisted without a renal transplantation. In this population blood type O and highly sensitised patients are overrepresented. ABO blood type O recipients are underrepresented in the populations that received a kidney from a deceased donor, a direct living donor, a donor-exchange donor and a domino-donor. As donor and recipient are a couple in direct living donor transplantation, there is no opportunity for preferential allocation of O donor organs to random O recipients as there is in deceased donor transplantation. The reason why the donor-exchange and domino donation programs are unable to compensate for the lack of O recipients is that amongst the couples included O donors are underrepresented while there is a surplus of O recipients [1,10,11]. In contrast, ABO incompatible donation programs favour blood type O recipients, while blood-type O recipients are adequately transplanted in the altruistic donation program. However, though increasing numbers of blood type O patients are transplanted via these programs, this did not compensate for the low percentage of blood type O patients transplanted via the deceased and even lower percentage transplanted via direct living donor transplantation programs.

Highly sensitised patients are not underrepresented in the entire population of transplanted patients in comparison to the population not transplanted. In the deceased donor transplantation program, sensitised and highly sensitised patients are overrepresented in comparison to the population not transplanted. However, they are underrepresented in the combined living donor transplantation programs. In our population, highly sensitised patients received their kidneys primarily from a deceased donor, and to a lesser extend from domino donors and altruistic donors. A large proportion of the highly sensitised patients were transplanted via the deceased donor AM program [5]. In comparison to the population not transplanted, recipients of a deceased donor kidney are relatively less often unsensitised and more often sensitised and highly sensitised. Overall highly immunised patients still on the waiting list or DWT have the longest waiting time (Table 2). Most probably, apart from their high degree of sensitisation, this subgroup of patients has specific matching problems, for instance due to their rare HLA phenotypes, lack of acceptable mismatches or their blood type O. The results of the Cox proportional hazards analysis are in agreement with these results: Blood type O patients have only 61% chance for a renal transplantation in comparison to blood type A patients and

elevated PRA decreased the chances (Table 3). There is no interaction between ABO blood type and PRA which means that the chance for any renal transplantation in a highly sensitised patient with blood type O is only 12% ($0.20 \times 0.61 = 0.12$) in comparison to blood type A unsensitised patient.

The decreased rate of transplantation of blood-group O recipients in deceased donor kidney transplantation has been described before [12,13]. Blood type O patients wait longer for their transplantation and more often disappear from the waiting list without transplantation in comparison to non-O blood type recipients [12].

Our study shows that direct living donor transplantation makes things even worse. The alternative living donation programs in use in our centre enable living donor transplantation of a large number of patients that otherwise would have to wait for deceased donor transplantation. However, many of those really difficult to match candidates remain on the waiting list awaiting deceased donor transplantation. As living compared to deceased donor kidney transplantation rates increase in time all over Europe, this accumulation of blood type O and highly sensitised patients on the waiting list will increase exponentially if we do not change the rules.

There is no simple solution for the ABO blood type O and highly sensitised populations as their needs are conflicting. For both populations blood type O donors are needed. Several other solutions for the decreased living donor transplantation rate of blood type O recipients have been proposed: Altruistic unbalanced paired kidney exchange (inclusion of compatible couples with O-donors and non-O recipients) would certainly increase the chances for a match for the incompatible couples. However, the motivation of compatible couples to join an alternative program is low as they expect no profit [14]. As ABOi transplantation is the most successful program for blood type O patients, an increase in the number of LD transplantation centres offering ABOi transplantation would also be beneficial [15,16]. Another solution could be lowering the threshold for inclusion in living donor ABO incompatible transplantation. In centres without an operational ABO incompatible program, transplantation of ABO blood type A2 donors to recipients with low anti-A titers can possibly be performed without pre-treatment in both living and deceased donor transplantation [17,18]. List paired exchange that permits ABO incompatible exchanges, probably is favourable for the individual O recipient but harms those on the waiting list with blood type O who already have the longest waiting time [19]. The most successful and least risky strategy however would be upgrading the influence allotted to ABO blood type O in deceased donor organ sharing programs. Our study shows that, 13.3% of O-donor kidneys have been allocated to non-O recipients via ETKAS. Requirement of ABO identity for HLA identical combinations since January 2011 alleviates but does not solve the problem of blood type O patients. Still 8% of O-donor kidneys will be allocated to non-O recipients via the AM protocol, precluding restoration of the balance. As chances for highly immunised patients depend on the prevalence of HLA combinations needed, not all highly immunised patients have the same chance for a renal transplantation. To prevent unnecessary drainage of O-donor kidneys to the AM program, ABO identity should be required for those highly immunised patients with a reasonable chance to receive an ABO identical transplantation via the AM program. In order to increase the number of transplantations in blood type O patients, the influence of ABO blood type should be weighed more heavily and correction for ABO compatible combinations should be included. In Scandinavian countries, the USA and Australia blood type O donor kidneys are reserved for O-recipients [20–22]. In the UK O-kidneys are allocated to non-O recipients only under very special circumstances [23].

Although transplantation of highly sensitised patients in the DD program appears to be adequate, a small number of patients remains on the waiting list or is delisted without transplantation. If an incompatible living donor is available a desensitisation program might be an alternative strategy. However, pre-treatment and increased immunosuppressive treatment of the recipient is a heavy burden [24,25].

Conclusion

ABO blood type O patients are underrepresented in the deceased donor transplantation program, but the deceased donor Acceptable mismatch program is very successful in transplantation of highly sensitised patients. Via living donor kidney transplantation programs a large number of patients can be transplanted, but, in spite of alternative living donation programs, highly sensitised and ABO blood type O patients remain underrepresented. As the number of living donor kidney transplantations will increase in time the shift towards transplantation of patients with favourable factors will become more pronounced. As allocation of kidneys in living donation programs is restricted, the most successful strategy to increase transplantation of patients with unfavourable factors is via the deceased donor organ allocation program. Introduction of a new mathematical allocation model integrating the AM program and the HLA identical program in a point system that guarantees fair allocation to ABO blood type O patients and to highly sensitised patients would certainly improve clarity and fairness of the system.

Authorship

This work was not externally supported. JR: participated in research design and performance, data analysis and statistical analysis and in the writing of the manuscript. WW: participated in research design and performance and in the writing of the manuscript. FC, JW and JIJ: participated in the writing of the manuscript.

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