

Vaccination of mice with radiation-attenuated larvae of Schistosoma japonicum or S. mansoni

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Introduction Partial protection against challenge infections with normal cercariae of *Schistosoma mansoni* or *S. japonicum* has been induced by immunization with attenuated cercariae of either species. Immunization was successful in a number of different hosts including laboratory rodents and larger mammals. In most cases cercariae or schistosomula were irradiated with gamma or X-irradiation. There is ample evidence that such attenuated larval schistosomes may induce significant levels of resistance against infection (see reviews, e. g. 2, 23).

Comparatively much less attention has been paid to attenuation of cercariae by ultraviolet (uv) light, although this procedure has since long been shown to induce high levels of protection (3, 4, 12). When compared to gamma or X-irradiation, attenuation of cercariae with uv is considerably easier to perform and requires much less costly equipment. This leads us to investigate more closely the efficacy of this technique with the aim to use attenuated cercariae of *S. japonicum* as (part of) a vaccine against this parasite. *S. japonicum* is a zoonotic disease. In China, a significant risk of infection for humans derives from the infection of life-stock, which excrete parasite eggs and, by consequence, continue to contaminate with miracidia such areas, where snails still occur (5). We hypothesize that a vaccine for life-stock, including buffaloes, pigs and cattle, may contribute to the control of human schistosomiasis japonica.

As a basis for an uv-attenuated vaccine we established that an irradiation dose of 300 to 400 $\mu\text{Watt}\cdot\text{min}\cdot\text{cm}^{-2}$ of uv-light may induce resistance in mice (18). This confirmed earlier reports on the feasibility of immunization of mice with uv-attenuated cercariae of *S. japonicum*, although a different dose of irradiation was used by these authors (12). Our attenuation procedure proved later to be also efficient to immunize buffaloes and pigs against experimental infection in China (20, 21). Both animal species developed about 90% resistance against a challenge infection.

During later experimentation with mice it was realized that the effect of immunization was less consistent than we had previously assumed. Here we present data from immunizations of mice with cercariae of both *S. japonicum* or *S. mansoni*, which suggest that unidentified parameters influence the success of murine experiments. In addition we report initial attempts to identify the site, where immunity of mice might be induced by the uv-attenuated cercariae.

Materials and methods A Puerto Rican strain of *S. mansoni* was maintained in the laboratory through *Biomphalaria glabrata* snails and mice. Cercariae of *S. japonicum* were obtained from *Oncomelania hupensis* collected in Hubei province, P. R. China. *Oncomelania* snails were maintained under the conditions described by MOLONEY et al. (13). Schistosomula of *S. mansoni* were prepared by mechanical transformation (1). Mice of several strains and weighing 20 - 25 g were used.

Parasites and hosts

Irradiation of cercariae	<p>For gamma irradiation, suspensions of cercariae of <i>S. mansoni</i> were concentrated to about 1,000 larvae/ml, and irradiated by exposure to 20 krad from a ^{60}Co source. Cercariae of <i>S. mansoni</i> and of <i>S. japonicum</i> were irradiated with uv light at 254 nm. In Heidelberg, a low-pressure mercury vapour ultraviolet lamp (type N 16, Konrad Benda, Laborgeräte, D-6908 Wiesloch, FRG) was used, the energy output measured with UV-CM equipment (same company) with maximum sensitivity at 254 nm, and the zero value of the UV-CM calibrated for each experiment (18). In Glasgow a high intensity ultraviolet lamp (Mineralight & Blak Ray, model UVGL-58, from UVP Ltd., Cambridge), delivering its peak output at 254 nm, was used. The lamp was stationed in the horizontal position and its output at 254 nm measured at the beginning of each experiment using an UVX digital radiometer with a 254 nm uv tube, and with distance to either side of it. A platform was set up at 10 cm below the lamp, and a position marked where uv intensity was at maximum with $250 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$, varying by $\pm 7.0\%$ over a 3 cm radius. 8 ml of aquarium water containing cercariae at a concentration of approximately 700/ml were pipetted into a sterile plastic petri dish of 6 cm diameter, 1.5 cm depth, and placed at the optimum position below the uv lamp. Irradiation was carried out for the required time, usually 90 sec, supplying $350 - 400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$ of uv energy in both laboratories.</p> <p>Cercariae attenuated with uv were applied to the skin of mice within 1 min and those attenuated by gamma-radiation within 1 h.</p>
Infection, vaccination and challenge	<p>Normal and irradiation-attenuated cercariae were administered on the shaved abdominal or lateral skin of anesthetized mice using the "ring method" for <i>S. mansoni</i> (22) or by applying a cover-slip with a drop of water containing cercariae of <i>S. japonicum</i>. Immunizing and challenge cercariae were always applied to different sites. The time between the (last) immunization and the challenge infection was four weeks, except where stated otherwise.</p>
Recovery of schistosomula from lungs, lymph nodes and mesenteric veins	<p>Parasites were recovered from lungs and lymph nodes basically by published techniques (10, 19). In all cases the medium used was DMEM (GIBCO, Eggenstein, Germany) containing 10 units/ml heparin (Braun, Melsungen, FRG), and 5% heat-inactivated newborn calf serum (NCS). Chopped lung pieces were washed on a wire mesh to remove cells before incubation at 37°C for 3 h. Axillary lymph nodes were teased with forceps and incubated in macrowell cell culture plates at 37°C for 3 h. After incubation, the medium was filtered through a stainless steel sieve to remove the larger lung or lymph node fragments. The filtrates were concentrated by centrifugation at 200 - 300 g for 2 min and the schistosomula in the pellet were counted under a dissecting microscope. The medium used above to wash the chopped lung pieces was also checked for schistosomula. Challenge parasites were recovered from the hepatic portal system by perfusion (22) at five weeks (<i>S. japonicum</i>) or 6 to 7 weeks (<i>S. mansoni</i>).</p>
Results	<p>Results with <i>S. japonicum</i> are presented in table 1. No significant resistance was induced in mice immunized with uv-irradiated cercariae of <i>S. japonicum</i>, whether immunizations were given once, twice or three times with doses ranging from 300 to $400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$.</p> <p>Results with cercariae and schistosomula of <i>S. mansoni</i> are presented in tables 2 and 3, respectively. Uv-attenuated cercariae or schistosomula failed to induce resistance in some but not all experiments. However, gamma-attenuated larvae did so in both of the experiments performed.</p>
Resistance induced by attenuated larvae	
Lung and lymph node recovery of normal and attenuated <i>S. mansoni</i>	<p>Normal cercariae migrated through the lungs of mice with a peak at 6 to 7 days after infection. At this time point about 25% of the cercariae were recovered as schistosomula. Attenuation by gamma- (20 krad) or uv-irradiation ($100 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$) reduced the number of recoverable schistosomula dramatically and their values peaked at later time points (fig. 1). No worms were recovered from lungs after attenuation with $400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$.</p>

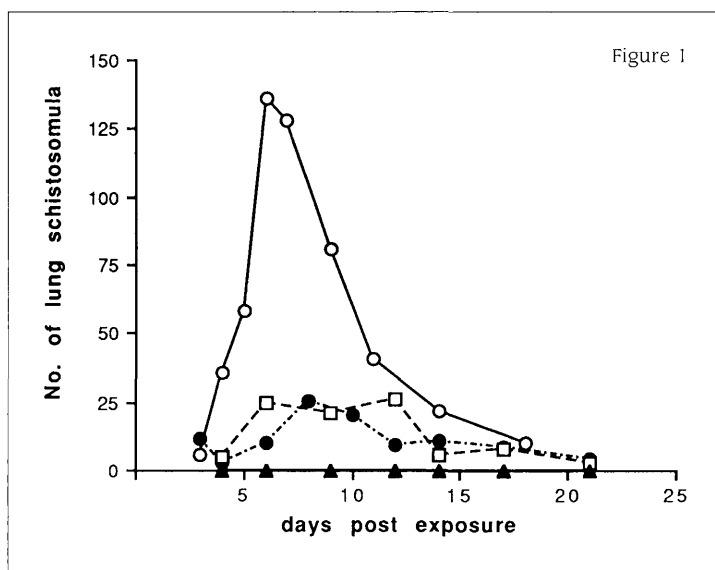
Table 1:

Vaccination of mice with uv-attenuated cercariae of *Schistosoma japonicum**

Experiment	Strain of mice	Number of mice	Irradiation dose $\mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$	Number of cercariae	Challenge (no. of cercariae)	Number of worms recovered	Resistance (%)	Significance
I	NMRI	10	—	—	150	71.5 ± 24.9		
		8	300	1×500	none	17.9 ± 11.9		
		9	300	1×500	150	79.9 ± 32.5^2	-11.7 ²	n. s.
		6	300	3×500	150	88.7 ± 29.6^2	-24.1 ²	n. s.
II	NMRI	15	—	—	150	78.3 ± 31.1		
		9	400	1×500	150	66.8 ± 33.4	14.7	n. s.
III	NMRI	8	—	—	150	114.8 ± 24.3		
		7	300	1×500	150	122.6 ± 18.0	- 6.8	n. s.
		8	400	1×500	150	105.0 ± 11.0	8.5	n. s.
IV	NMRI	9	—	—	150	95.3 ± 13.7		
		5	400	1×500	150	73.4 ± 25.1	23.0	n. s.
		5	350	1×500	150	82.8 ± 37.4	13.1	n. s.
		6	350	3×500	150	89.0 ± 14.3	6.6	n. s.
		10	400	3×500	150	87.2 ± 12.9	8.5	n. s.
V	C57/bl	8 ³	—	—	150	84.5 ± 23.6		
		2 ⁴	350	1×500	150	90.0 ± 9.9	6.5 ²	n. s.
		4 ³	400	1×500	150	65.3 ± 29.1	22.7	n. s.
		5	350	2×500	150	85.6 ± 14.2	- 1.3	n. s.
		3 ⁴	400	2×500	150	75.7 ± 34.0	10.4	n. s.

* All experiments were performed in Heidelberg.

- 1) Each immunization was with 500 cercariae/mouse given 1, 2 or 3 times and irradiated with 300, 350 or 400 $\mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$
- 2) If the number of "escape worms" derived from the immunization were deduced from these values, the resistance would have a positive value but would still not be significant.
- 3) One mouse died.
- 4) Two mice died.



Lung recovery of *Schistosoma mansoni* from mice following percutaneous infection. Each mouse was given 500 cercariae, which had received no treatment (\circ — \circ), 20 krad gamma irradiation (\square — \square) or uv-irradiation at $100 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$ (\bullet — \bullet) or $400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$ (\blacktriangle — \blacktriangle). Results are pooled from 4 independent experiments and each value represents the mean of 4 to 9 determinations.

When $100 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$ -attenuated cercariae were applied to the ventral abdominal skin of mice, about 2% could be recovered as schistosomula from the axial lymph-nodes six days later. Even though about 1% of the parasites resided in the lymph-nodes for about two weeks after immunization, these did not transform morphologically to the slender elongate shape which is typical for lung schistosomula, but remained rather short and stunted (not illustrated). About 8% developed to adult worms after seven weeks (tab. 2, exp. V). Following uv-attenuation with $400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$, less than 1% of the cercariae were recovered from lymph nodes and none were detectable by perfusion seven weeks later. Parasites irradiated with 20 krad also failed to develop to adult worms (tab. 2).

Table 2:

Vaccination of mice with uv-attenuated cercariae of *Schistosoma mansoni**

Experiment	Strain of mice	Number of mice	Irradiation dose $\mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$	kilorad	Number of cercariae	Challenge (no. of cercariae)	Number of worms recovered	Resistance (%)	Significance
I	NIH	7	—	—	—	150	67.1 ± 6.7	—	p < 0.001
		5	—	20	1 × 500	none	0	—	
		5	—	20	1 × 500	150	22.8 ± 3.5	66.0	
		5	400	—	1 × 500	none	0.4 ± 0.4	—	
		5	400	—	1 × 500	150	14.8 ± 5.5	78.5	
		5	800	—	1 × 500	none	1.0 ± 0.6	—	
		5	800	—	1 × 500	150	24.2 ± 6.2	65.4	
II	Balb/c	10	—	—	—	150	27.7 ± 6.6	—	n. s.
		4	400	—	1 × 500	none	0	—	
		5	400	—	1 × 500	150	25.8 ± 7.7	6.9	
III	Balb/c	10	—	—	—	150	55.9 ± 10.2	—	n. s.
		5	400	—	1 × 500	none	0.4 ± 0.4	—	
		5	400	—	1 × 500	150	41.8 ± 10.5	26.0	
IV	NMRI	9	—	—	—	200	82.1 ± 16.5	—	p < 0.0001
		8	—	20	1 × 500	none	0	—	
		7	—	20	1 × 500	200 ¹	16.0 ± 2.7	80.5	
		8	300	—	1 × 500	none	5.6 ± 2.9	—	
		7	300	—	1 × 500	200	35.1 ± 17.4	57.2	
		8	300	—	1 × 500	200 ¹	41.9 ± 21.9	55.9	
		8	300	—	2 × 500	200	62.7 ± 23.4	23.4	
		7	400	—	1 × 500	200	55.9 ± 7.8	32.0	
		7	400	—	2 × 500	200	28.0 ± 7.7	65.9	
V	NMRI	7	—	—	1 × 500	none	175.0 ± 30.0	—	p < 0.0001
		8	—	20	1 × 500	none	0	—	
		6	100	—	1 × 500	none	42.0 ± 12.1	—	
		6	400	—	1 × 500	none	0	—	

* Experiments I to III were performed in Glasgow, IV and V in Heidelberg.

1) The time between the last immunization and the challenge infection was 8 weeks.

Discussion We report here on several experiments in which we failed to induce expected levels of resistance in mice using uv-attenuated cercariae. Gamma-attenuated organisms also failed in one instance to induce resistance. Results were obtained independently in the laboratories in Heidelberg and in Glasgow. The data appear to be in conflict with our previous experience where immunization with gamma-attenuated cercariae of *S. mansoni* (17) and uv-attenuated cercariae of *S. japonicum* (18) successfully induced resistance. With respect to the procedure of uv-attenuation as performed in the laboratory in Heidelberg, we are not aware of any modification with respect to the previously employed procedures with mice (18) and with the successful experiments performed during the same time period with buffaloes and pigs in China (20, 21). In all instances, identical uv-equipment and, in part, the same persons were involved.

Conflicting in this situation is that the outcome of immunization experiments was less than uniformly successful in several previous reports.

Table 3:

Vaccination of mice with gamma or uv-attenuated schistosomula of *Schistosoma mansoni**

Experiment	Strain of mice	Number of mice	Irradiation dose		Number of cercariae	Challenge (no. of cercariae)	Number of worms recovered	Resistance (%)	Significance
			$\mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$	kilorad					
I	NIH	20	—	—	—	150	72.9 ± 7.1	—	
		10		20	1×500	none	0	—	
		10		20	1×500	150	58.5 ± 6.4	19.8	n. s.
		10	400		1×500	none	0	—	
		10	400		1×500	150	86.1 ± 6.7	-18.1	n. s.

* All experiments were performed in Glasgow.

In fact, among experiments by other authors, individual sets of data have repeatedly failed to induce the expected levels of resistance (see e. g. 11, 12, 16). Although we intentionally reported experiments here which seemingly do not support the validity of an attenuated cercarial vaccine, we continue to be convinced that this approach to induce resistance against schistosome infections is basically valid.

There is evidence suggesting that variability occurs between results of schistosome infections performed under defined and apparently identical conditions (6). Parameters other than the repeatedly advocated variability between schistosome strains of host species influence the outcome of infections. Although remaining still elusive, these parameters may influence results obtained even with individual batches of cercariae from otherwise identical origin. We rather take the present data to argue for the need to analyze in detail the mechanisms of immunity, which lead, in the majority of experimental situations, to a significant degree of resistance against schistosome infections.

Following gamma irradiation, larvae of *S. mansoni* have been shown to lose their ability to migrate with normal kinetics through the host's circulation. They were retarded in the skin or lungs, where the parasites die, and recoveries from the mesenterics were very much reduced (8, 9). With respect to uv-attenuation, the rate of development from cercariae to adults was less than 1 in 10,000 as determined from a total of 30,000 uv-irradiated cercariae given to buffaloes or pigs (20, 21). We now show that such organisms may migrate, in mice, in very low numbers only to the lungs, that this migration is delayed with respect to peak recovery of untreated larvae from this organ ($100 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$) and that no parasites survive to adulthood ($400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$). Thus, the pattern of migration inhibition is similar to the one which had been observed by others after gamma irradiation.

It may be noteworthy that the reduced exit of schistosomula from the skin is not by itself associated with the induction of resistance, since the low dose of $100 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$ resulted in a dramatic decrease of lung recovery values although it did not induce resistance in our earlier report. While this work was in progress, essentially similar data on lung recovery of uv-attenuated cercariae of *S. mansoni* were published by others (7). Thus, whether attenuation is achieved by gamma or uv-irradiation, death of parasites occurs before they reach the liver.

Gamma-irradiated larvae migrate in significant numbers to the lymph nodes of mice (14). We now show a similar migration pattern for uv-attenuated ones (irradiated at low dose), which remained for a considerable time period in lymph nodes. Lymph node schistosomula

lacked the elongated form of lung worms and were also rather less mobile. However, two week-old lymph node worms had developed a visible gut and suckers. This shows that uv-irradiation greatly impeded their development and that they may gradually die off in the lymph nodes. The requirement of lymphnodes, and not distant lymphoid organs, for the induction of immunity by attenuated *S. mansoni* had been demonstrated earlier (15).

The dominant feature of *Schistosoma mansoni* larvae attenuated with a high uv-dose ($400 \mu\text{W} \cdot \text{min} \cdot \text{cm}^{-2}$) appears to be that migration of parasites in mice does not apparently proceed beyond the skin. As a result, their residence in the skin may be prolonged with respect to untreated larvae. Current work would seem to support this hypothesis (GUI and RUPPEL, unpublished). Consequently, interaction with the immune system of the skin may occur in a different way following infection with normal or immunization with attenuated cercariae. Langerhans cells were recently shown to be important antigen-presenting cells in cutaneous leishmaniasis in mice (26). These cells may capture antigen in the skin, retain antigen in an immunogenic form for at least two days and present it to quiescent T cells in lymph nodes. It is also possible that the inhibition of protein synthesis seen in uv-irradiated schistosomula may lead to especially effective antigen presentation (24, 25). If antigen presentation by Langerhans cells of the skin would play a similar role with schistosome infections, this may happen more efficiently with prolonged residence of uv-attenuated parasites in the skin.

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Summary Experiments are presented, in which uv-attenuated larval *Schistosoma japonicum* and *S. mansoni* did not induce consistent resistance to infection in mice. The finding contrasts with other reports, including some from our own laboratories, where significant resistance was induced. The discrepancy is discussed. Most uv-attenuated *S. mansoni* could not be recovered from the lungs nor mesenteric veins of mice. It is suggested that uv-attenuated larvae die in the skin where they may present parasite antigen very effectively.

Key words *Schistosoma japonicum*, *Schistosoma mansoni*, ultraviolet light, gamma irradiation, mice, resistance to reinfection.

Zusammenfassung *Impfung von Mäusen mit Strahlungs-attenuierten Larven von Schistosoma japonicum oder S. mansoni*

Wir berichten über Experimente, in denen UV-attenuierte Larven von *Schistosoma japonicum* und *S. mansoni* keine konsistente Resistenz gegen eine Infektion in Mäusen induzierten. Diese Beobachtungen widersprechen anderen Berichten, darunter auch aus unseren eigenen Laborkolonien, in denen eine signifikante Resistenz induziert wurde. Dieser Gegensatz wird diskutiert. Die meisten UV-bestrahlten *S. mansoni* konnten weder aus den Lungen noch aus den Mesenterialvenen der Mäuse wieder gewonnen werden. Wir vermuten, daß die UV-attenuierten Larven in der Haut sterben, wo sie Parasitenantigen sehr effizient präsentieren können.

Schlüsselwörter *Schistosoma japonicum*, *Schistosoma mansoni*, ultraviolettes Licht, Gammabestrahlung, Mäuse, Resistenz gegen Infektion.

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