

# Antibody Research

*Anti "B" Cell Studies (Rituxan) – Trials of MS are being started this year (2004) to eliminate B cells, based on recent discovery of antibodies that destroy brain tissue and cause irreversible loss (atrophy)*

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## Results/Current Status

Successful antibody research has brought funding for Phase I clinical trials of Rituxan treatment for NMO MS patients. NMO stands for Neuromyelitis Optica (Devic's disease), an extremely severe form of MS that affects young adults and children, strikes spinal cord (paralysis) and optic nerves (blindness) and usually results in a bed-ridden condition and death within a few years of onset. Although attacks can initially respond to corticosteroids, disability rapidly ensues and there is no effective treatment for NMO. NMO, while a rare disease, is particularly frequent in African Americans and Asian populations and has been termed by some Asian MS.

A small Phase I trial of NMO patients has shown that Rituxan can be safely administered to these patients, and indicates a remarkable effect on preventing recurrence of attacks. Moreover, a surprising effect of REVERSING disability (vision and walking) was observed in some patients. We believe that this is proof of concept that disability in MS is linked to antibodies and the cells that make them, the B cells (Rituxan kills and eliminates all B cells).

Further funding is necessary to establish scientific research in order to investigate the mechanisms of action of Rituxan and understand why Rituxan is so effective in NMO. While NMO is a rare disease, this is a unique opportunity for the rationale design of anti-B cell strategies in the more common form of MS.

The UCSF research team has developed an extensive panel of laboratory assays in order to glean and maximize scientific information obtained from this trial. This information will best tell us how Rituxan works in MS, because NMO, according to the most recent data including some in Dr. Genain's lab, is a prototypal model of antibody-mediated MS. Thus the immunological studies will be yielding an invaluable set of data that cannot be obtained otherwise. The research blended in this trial, can be viewed as a large "capital investment" that will return gains to optimize future MS treatments with Rituxan.

## Proposed Funding

### 1. Establish scientific research in order to investigate the mechanisms of action of Rituxan and understand why Rituxan is so effective in NMO.

Funding for the above described immunological studies in the NMO trial:

2 full-time technicians @ \$100,000 per year each, 3 years \$ 600,000

Supplies for measuring:

Blood lymphocytes and their level of activity \$  
150,000

Antibodies and changes induced by Rituxan \$  
150,000

Cloning of existing antibody genes before Rituxan and  
reappearing ones after Rituxan (the lab will make  
harmless ones to use in future treatments of MS) \$  
500,000

Real time PCR machine with software and maintenance \$ 80,000

Equipment to fish myelin binding B cells from blood \$ 110,000

Equipment to make antibody microarrays, in order to  
Angle-fish all possible antibodies found in this disease \$ 50,000

~ \$1,600,000

## Proposed Future Trials

*The proposed trials are targeted for future funding. Clinical trials are very expensive, although obviously the goal for all research developed here. Four approaches below are examples of what private funding could do to accelerate the pace of combating MS.*

### 1. A trial for secondary progressive MS (overlaps with above). Rituxan or equivalent + plasmapheresis.

The next major goal is to design and implement a trial of Rituxan in secondary progressive and relapsing remitting MS patients who have a worsening condition and have already accumulated significant disability, such as requiring a cane, etc. *While large Rituxan trials are conducted nationwide following Dr. Genain's research achievement, these patients will be excluded from these trials which have strict entry criteria.*

Dr. Genain's team proposes to conduct a trial in secondary progressive MS patients, that will test the effect of Rituxan (B cell destruction) in combination with plasma exchange (removal of existing antibodies produced by plasmocytes-factories). This approach is unique and could TODAY impact the lives of already disabled MS patients. Chances are that this trial cannot be funded for another 4 or more years (either by NIH or Industry), before the results of the other trials are known. A pilot SPMS trial, submitted by Dr. Genain in 2002, was rejected by the ITN (Immune Tolerance Network-A spin off of NIH), which is now supporting several trials of Rituxan in other diseases based on the rationale outlined in the Genain proposal. Genentech, won't currently consider this trial because SPMS and patients that already walk with a cane are a high risk group. With appropriate private funding, however, the drug could be purchased and get this trial could commence within 3 months after FDA and IRB approval.

There is also red carpet resistance because both plasma exchange and Rituxan are outrageously expensive (plasma exchange: \$50,000 first month and then every 3 months [\$10,000], for 2 years total: Cost would be ~ \$90,000/year = \$180,000 per patient. Rituxan: \$30,000/year = \$60,000 per patient. Grand total: \$240,000 per patient. 200 patients in the 4 arms = \$48,000,000 for treatments alone. While this trial may be expensive, it pales to the 1996 estimate of societal cost of MS of > \$38 Billions in the US alone, not accounting for psychological and emotional burden to caregivers and their families.

- 2. A trial of Rituxan (or other anti-B cell agent: Amgen compound) designed for MS patients that have accumulated disability > 5.5 (E.g., have to use a cane or other device to be able to walk).**
- 3. A combination trial using Rituxan + Copaxone (B cell suppression + neuroprotection and neuroregeneration).**

Another interesting avenue is a trial of Rituxan + Copaxone. A lot of data indicates that copaxone actually REPAIRS myelin because it switches immune cells to make growth factors. The supplier of Copaxone, TEVA, may be interested in supplying the drug for the study.

- 4. A combination trial using Rituxan + Statins (or equivalent, non toxic drug discovered in Dr. Genain's lab. The latter 2 need pre-clinical studies in monkeys and possibly human CD20 transgenic mouse (mouse expressing their B cells to look like human ones, and therefore can be treated with Rituxan which will not destroy native mouse B cells).**

## Expected Outcomes

1. **A major expected result of Rituxan is that it will stop disability progression, short-term and long-term.**
2. If this occurs, proceed to design human MS trials with more selective agents (less toxic than general ablation of all B cells).

## Proposed Future Trial Funding

Cost of Phase I study if buying Rituxan:

\$ 48M\*

Logistic cost of trial (personnel, drug admin, MRI, labs, statistics, etc

\$ 40M

Research (Immunological and biomarker profiling): \$ 20M

*\*: note: there are creative ways to reduce cost, such as having plasma exchange picked up by insurance, etc.*