

Progress Report: The MacTel Project

At the 5-year mark of the collaboration, much has been learned,
but still no treatment is available.

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Idiopathic macular telangiectasia type 2 (MacTel) is a potentially blinding condition of the retinal vasculature in which pathologically dilated blood vessels form around the macula lutea. Damage to parafoveal photoreceptors leads eventually to permanent loss of vision.

MacTel was first fully described almost 30 years ago by Gass and Oyakawa,¹ but the condition is still poorly understood. An international research collaboration, the MacTel Project, was initiated in 2005 to bring together clinicians and bench scientists with the aims of improving our understanding of the clinical and pathologic features of the disease; raising awareness of the disease among clinicians; and identifying its causes and appropriate treatments.

This article briefly summarizes the project's rationale and some of what has been learned in the past 5 years about the disease's pathogenesis, epidemiology, and potential treatments.² This update is presented on behalf of all the scientists and clinicians participating in the MacTel Project.

THE MACTEL PROJECT

The MacTel Project comprises more than 30 centers in Europe, North America, the Middle East, and Australia, including clinical centers; genetics, reading, and coordinating centers; and several basic science

laboratories. The Scientific Executive Committee consists of Alan Bird, Emily Chew, Ian Constable, Marty Friedlander, Mark Gillies, Bob Graham, and Frank Holz.

The project encompasses a natural history observation study that identifies MacTel patients and follows the progression of their disease; a genetics study of MacTel patients and their family members designed to identify genes and genetic variants that may be associated with susceptibility for MacTel; and an eye donor program to study the histology and pathology of MacTel eyes.

A cohort of 400 participants has been enrolled and is being followed annually in order to fully characterize the nature of the condition and its progression. Relatives of the study subjects are screened for the genetic study.

The clinical research aims of the project include characterizing the clinical features and natural history of MacTel from the earliest to the vision-threatening stages; collecting genetic samples of affected individuals and their families; promoting and publicizing the disease among colleagues as an important subject for research; gathering evidence on the results of treatments that have been employed for patients with MacTel; and conducting pilot clinical trials of potential therapies for MacTel that are emerging as treat-

TABLE 1. VISUAL DYSFUNCTION DISPROPORTIONATELY GREATER THAN ACUITY LOSS

Characteristics	MacTel Natural History Cohort Median (NEI-VFQ-25 scores)	Reference Group Median (NEI-VFQ-25 scores)
General Health	50	69
General Vision	60	83
Ocular Pain	88	90
Near Activities	75	92
Distance Activities	83	93
Social Functioning	100	99
Mental Health	75	92
Role Difficulties	75	93
Dependency	100	99
Driving	88	87
Color Vision	100	98
Peripheral Vision	100	97

ments for other retinal vascular diseases.

The laboratory research objectives of the project include producing a more detailed understanding of the pathogenetic mechanisms of MacTel in both the early and critical stages; identifying a mouse model or models for MacTel; clarifying the genetic basis for MacTel in mouse models and humans; and identifying potential novel treatments, possibly including drugs, cytokines, or human progenitor cells.

In addition to these research initiatives, project members are also involved in developing and supporting a Web site to provide information for patients with MacTel.

MACTEL FEATURES

Although MacTel is uncommon, its prevalence is probably higher than most physicians believe. The early findings are subtle, so the diagnosis is likely often missed by optometrists and general ophthalmologists. MacTel was detected in 0.1% of subjects in the Beaver Dam study population over age 45 years (Ronald Klein, MD, personal communication), but this is probably an underestimate because identification was made based only on color photographs.

TABLE 2. HIGH PREVALENCE OF SYSTEMIC CONDITIONS

			P-values	
Condition	MacTel	NHANES*	Observed	Bootstrap
History of Coronary Heart Disease	14%	6%	.009	.009
History of Hypertension	62%	49%	<.001	<.001
Overweight**	84%	69%	<.001	<.001
History of Diabetes	33%	10%	<.001	<.001
History of Cancer	17%	14%	.385	.379
123 US MacTel participants used in the analysis				
*NHANES: National Health and Nutrition Examination Survey				
**Overweight defined as BMI ≥ 25				

No major new biomicroscopic features of MacTel have been identified since the early work of Gass and colleagues.^{1,3} The advent of optical coherence tomography (OCT) has allowed better characterization of the nature of the inner and outer lamellar cavities. Loss of central masking seen on autofluorescence studies, apparently due to loss of luteal pigment, is now recognized as probably the earliest and most sensitive and specific MacTel abnormality. Using adaptive optics, it is possible to image areas of photoreceptor damage in vivo.

The condition may remain stable for extended periods, sometimes interspersed with sudden decreases in vision. Patients' loss of visual function is disproportionately worse than the impairment of their visual acuity, which is only mildly affected in many cases (Table 1).⁴

In patients with MacTel, as compared with a reference population, there is a significantly higher prevalence of systemic conditions associated with vascular disease, including history of hypertension, history of diabetes, and history of coronary disease (Table 2).

Familial transmission is now recognized in a small proportion of people with MacTel (Figure 1); however, the nature of any related genetic defect or defects

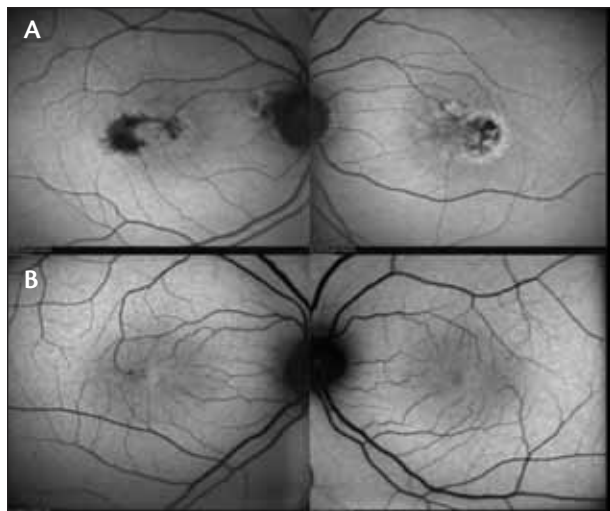


Figure 1. Familial transmission is now recognized in a small proportion of people with MacTel. The autofluorescence images of a mother with MacTel (A) and her daughter (B).

remains elusive. The MacTel genetic study team hopes that exome analysis in the affected population and relatives may be more successful in identifying related variants.

Histopathology studies of a single post-mortem specimen have shown a loss of Mueller cell markers from central retina, suggesting that Mueller cell death may be involved in the pathogenesis. One animal model in which the receptor for very low density lipoproteins is “knocked out” mimics many of the clinical characteristics of the disease and other models are being developed in the laboratories. Animal studies using the established model have shown an anti-oxidant diet and a special form of gene therapy to be effective in preserving visual function in these mice.

Treatment options are limited. No treatment has to date been shown to prevent progression. The variable course of progression of the disease makes it difficult to assess the efficacy of treatments. Retinal laser photocoagulation is not helpful. It is hoped that a better understanding of the pathogenesis of the disease may lead to better treatments.

The use of vascular endothelial growth factor (VEGF) inhibitors, which have proven so successful in treating age-related macular degeneration in the past 5 years, has been investigated in pilot studies for treatment of subretinal neovascularization in MacTel. Ranibizumab given before the development of subretinal neovascularization dramatically reduces the vascular leak seen on angiography, although microperimetry suggests that neural atrophy may still proceed in treated eyes.

CONCLUSIONS

At 5 years, the MacTel Project has gleaned an enormous amount of information about MacTel type 2, but the disease's pathogenesis remains obscure and no treatments are available.

Further study of subclinical disease will likely help to elucidate its underlying mechanisms. Goals of the MacTel Project now include further research to identify related gene defects, further development of animal models, the use of adaptive optics to study photoreceptor changes in the earliest clinical phenotype of the disease, identification of potential treatments, and ultimately a phase 3 clinical trial with one or more candidate therapies. Exploratory clinical trials may begin this year. Additionally, another post mortem sample of the condition would help to confirm histologic findings and might reveal further valuable insights.

With the progress made against this puzzling disease at the 5-year mark of the MacTel Project, the project investigators hope to stimulate other groups to join in the research. With the help of a generous grant, the investigators are now calling for projects, with the potential to allocate up to \$30,000 to successful applicants. We hope this funding opportunity will give us the chance to continue the work of the MacTel Project with new members and renewed vigor. ■

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For more on the MacTel Project, please visit the project's Web site: www.mactelresearch.org.

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