CALL FOR PROPOSALS

A seed grant for a basic or clinical study with relevance to melorheostosis may be funded at up to $30,000 for one year. The grant does not support indirect costs or principal investigators’ salaries.

A MESSAGE FROM THE BOARD OF DIRECTORS:

This grant is being offered by the Melorheostosis Association, an all volunteer organization of dedicated patients and parents of patients who suffer from this debilitating disease. Our association has established the world’s largest database of melorheostosis patients, many of whom have expressed their willingness to participate in research. We also have a bone and tissue repository at the NIH. Please feel free to contact us regarding any questions you may have. Kathleen Harper, President, kathleen@melorheostosis.org. FOR MORE INFORMATION REGARDING MELORHEOSTOSIS, PLEASE SEE THE ATTACHED DESCRIPTION.

A MESSAGE FROM DR. FRED KAPLAN, MEDICAL PANEL CHAIR

Although the condition is rare, it is my firm belief that lessons learned from melorheostosis research will be applicable to virtually every condition that affects the formation of bone and every condition that affects the formation of the skeleton. I believe that answers found for melorheostosis will reach far beyond those afflicted with melorheostosis to impact those who have more common conditions, such as arthritis and osteoporosis, which affect hundreds of millions of people worldwide. I look forward to my association with this exciting and important work.

INSTRUCTIONS FOR COMPLETING APPLICATION

Please submit your application to the Melorheostosis Association NO LATER THAN April 30, 2008:

BY MAIL TO:             BY FAX TO: 212 308-0794
Research Grant Application
Melorheostosis Association
410 East 50th Street
New York, NY 10022
MELORHEOSTOSIS

The name Melorheostosis (MEL) refers to “flowing hyperostosis” (dense bone) within the limbs. The x-ray findings have been likened to wax that has dripped down the side of a candle. MEL was first described in 1922, (1) Approximately 200 cases have been reported in the medical literature. (2, 3)

Clinical and radiographic features
MEL is a rare skeletal dysplasia characterized by a hyperostosis of cortical bone (2, 3). The hyperostotic bone lesions have a linear pattern and are mainly located along the diaphyses of tubular bones. They can extend internally into the medullary canal or externally with periosteal involvement resulting in the characteristic wavy outline of the affected bone. In some patients, smaller, spotty lesions, reminiscent of osteopoikilosis, can be observed in the epimetaphyseal regions of the affected bones. MEL lesions are most frequently found in the appendicular skeleton. They usually show an asymmetric distribution with involvement of one or more bones located in an area innervated by the same spinal sensory nerve. MEL can also affect the surrounding soft tissues including the subcutis, muscles, and blood vessels (4, 5). Soft tissue calcification, fibrosis, and blood or lymphatic vessel anomalies resulting in edema can be present. Sclerodermatous skin lesions or indurations and joint contractures are frequently observed and are usually the presenting symptoms in childhood. MEL can be asymptomatic but usually causes chronic pain and functional limitations because of joint contractures, bone deformities, and limb length discrepancy. MEL is predominantly a sporadic disorder. However, individuals with MEL have been observed in families with autosomal dominant osteopoikilosis or the Buschke-Ollendorff syndrome.

Laboratory Findings
Routine laboratory studies (e.g., blood calcium and phosphate levels and alkaline phosphatase activity) are normal.

Histopathological Findings
The skeletal lesion in MEL features thickening of the inner surface of bone during infancy and childhood, and then new bone formation occurs on the surface of bone during adult life. (3) Bony lesions are sclerotic (dense). Unlike in true scleroderma, the collagen of the scleroderma-like lesions of the skin in MEL appears normal. Hence, these skin findings have been called linear melorheostotic scleroderma. (4, 8)

Etiology and Pathogenesis
The precise cause of sporadic melorheostosis is not yet known. Heterozygous loss-of-function mutations in the LEMD3 gene can cause two related disorders, ie osteopoikilosis and the Buschke-Ollendorff syndrome (10). The LEMD3 protein is an inner nuclear membrane protein that can act as a specific repressor of TGFβ and BMP signaling through interaction with R-SMADs. Osteopoikilosis is usually a benign autosomal dominant skeletal dysplasia characterized by multiple small and round hyperostotic lesions in different parts of the skeleton (usually the epimetaphyseal regions of the tubular bones). The Buschke-Ollendorff syndrome is the association of osteopoikilosis and dermatofibrosis lenticularis disseminata. Inactivating germline mutations in the LEMD3 gene have also been identified in a few MEL patients that belong to a family with either osteopoikilosis or the Buschke-Ollendorff syndrome (11). However, in the great majority of sporadic patients with isolated MEL, no germline LEMD3 mutations are documented (11, 12). In a few cases, the possibility of a somatic LEMD3 mutation has been investigated but not found (10, 11). Despite the evidence that haploinsufficiency for LEMD3 can act as a predisposing factor for the development of MEL, the precise role of LEMD3 (and other components within the TGFβ signaling pathway) in the pathogenesis of isolated and sporadic MEL is not yet understood (9).
**Diagnosis**

The diagnosis of MEL is usually based on clinical evaluation and the finding of the characteristic radiographic abnormalities. Plain radiographs are usually sufficient to confirm the diagnosis. Scintigraphy reveals increased tracer uptake in the affected bone and soft tissue areas (7). Computed tomography and magnetic resonance imaging (MRI) are usually not needed for diagnosis but are helpful to understand possible complications. The bone and soft tissue lesions have low signal activities on all MRI sequences.

**Treatment**

The disease can be progressive with periodic exacerbations (6). There is currently no cure for the disorder. Surgery is possible to correct bone deformities and asymmetric bone growth. However, bone healing after osteotomy can be problematic in MEL patients. Soft tissue releases in children have a high failure rate, and are often complicated by abnormal scar formation. Contracture releases are more effective in adults and the outcome seems to improve with the use of rotation flaps. Prior to surgery, the application of external fixators spanning the contracture area might be considered, and this may even be the sole treatment (13). Pain management is usually a challenge because of the chronic and progressive character of the disorder.

# MELORHEOSTOSIS ASSOCIATION

## APPLICATION FOR RESEARCH GRANT

### TITLE OF RESEARCH PROJECT:

---

### APPLICANT INFORMATION

<table>
<thead>
<tr>
<th>Name (Last, First, M.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Address:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>City:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
</tbody>
</table>

### INSTITUTION

<table>
<thead>
<tr>
<th>Name of Current Institution/Employer:</th>
</tr>
</thead>
<tbody>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Address:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>City:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Name of Current Supervisor (include his/her title and degrees):</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Financial Representative of the Institution:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Print Name</td>
</tr>
</tbody>
</table>

### GRANT NOTIFICATION REQUIREMENTS

<table>
<thead>
<tr>
<th>Grants and contracts official to be notified if an award is made:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Address:</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>City:</td>
</tr>
</tbody>
</table>

### RESUME OR CURRICULUM VITAE

Please attach your resume or curriculum vitae indicating your:

<table>
<thead>
<tr>
<th>Education</th>
<th>Previous Research Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional Experience</td>
<td>Publications</td>
</tr>
</tbody>
</table>

---
RESEARCH PLAN

Please describe your research plan, making sure to cover the following topics:

- Research objectives
- Background information on the problem/question/hypothesis you will address in your research
- Methods and procedures you will use to reach your objectives
- The relationship of your work to melorheostosis

You may attach additional sheets if necessary, but please limit your description to no more than four pages.

Note: A report, if possible for publication, will be expected at the end of the grant.
Please attach a separate budget narrative to explain and justify any unusual budget items.

### I. Personnel
(Salary and fringe benefits)

<table>
<thead>
<tr>
<th>Amt. Requested</th>
<th>Amt. Requested from Other Sources or Donated</th>
<th>Total Expenses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### II. Equipment

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### III. Supplies

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IV. Other

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL**
I certify that, to the best of my knowledge and belief, all of the statements and information contained herein and on any attachments are true, correct, complete, and made in good faith.

I authorize the Melorheostosis Association to investigate all statements and/or information contained herein and to contact those people listed as references for the purposes of obtaining any and all information concerning my previous employment and education background as necessary for arriving at an award decision.

Applicant’s Signature: ___________________________ Date: ___________________________