Animal models of cutis laxa

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**Les Animaux Modèles de la Cutis Laxa**

4th Information Day on Cutis Laxa, Lyon, France, 17th September, 2011

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Why use animal models?

**Pourquoi Utiliser des Animaux Modèles**

- Discover the cause of cutis laxa in humans
  - Which gene is affected?
  - What are the physiological, pathological and biochemical changes that lead to cutis laxa?
- Test approaches to the treatment of cutis laxa
  - Small molecule drugs

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* Découvrir la cause de la Cutis Laxa chez les Humains
  - Quel gène est affecté ?
  - Quels sont les changements physiologiques, pathologiques et biochimiques qui induisent la Cutis Laxa ?

* Tester des approches de traitement de la Cutis Laxa
  - Très petites quantités de médicament


Yeast


Human skin cells


"Skin equivalent"

Which models to use?

- Use simplest and most economical model possible
- Move to models more similar to human to verify findings.


Mouse


Worm


Fruit fly


Zebra fish

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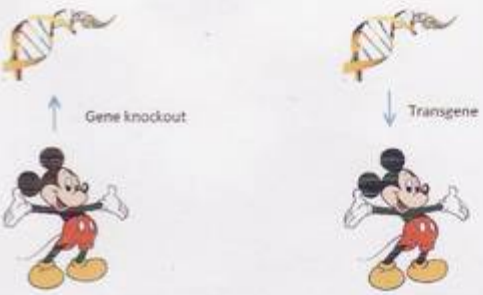
**Quels Modèles Utiliser ?**

- Utiliser les modèles les plus petits et les plus économiques possibles
- Vérifier les découvertes en utilisant des modèles de plus en plus proches de l'homme

Genetic manipulation of mice

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**Manipulation Génétique de la souris**

« Désactiver » le Gène « Remplacer » le gène

Example 1: fibulin 5 (FBLN5)
Autosomal recessive cutis laxa 1B


Fibulin 5 knockout mice
Yanagisawa et al. (2002)
Nature 415:168-171


Human fibulin 5 mutation
Loeys et al. (2002)
Hum Mol Genet

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**Example 1 : Fibuline 5 (FBLN 5)**
**Cutis Laxa Autosomale Récessive 1B**

Souris avec Fibuline5 Désactivée

Mutation Fibuline5 Chez l'humain

Example 2: fibulin 4 (FBLN4)
Autosomal recessive cutis laxa 1A


Fibulin 4 knockout mice
McLaughlin et al. (2006)
Mol Cell Biol 26:1700-1709


Human fibulin 4 mutation
Hucthagowder et al. (2006)
Am J Hum Genet 78:1075-1080

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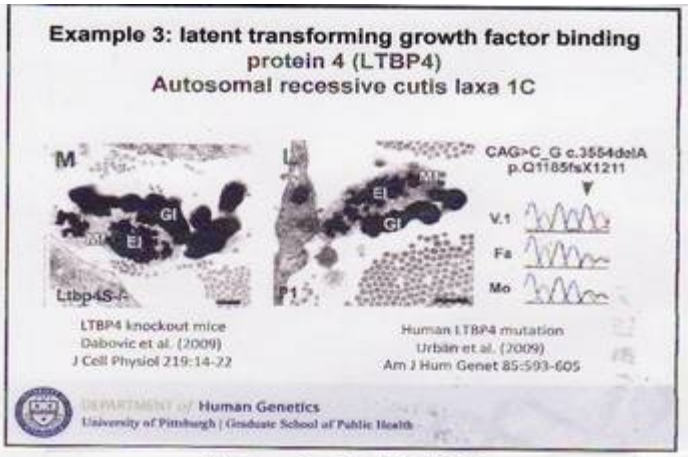
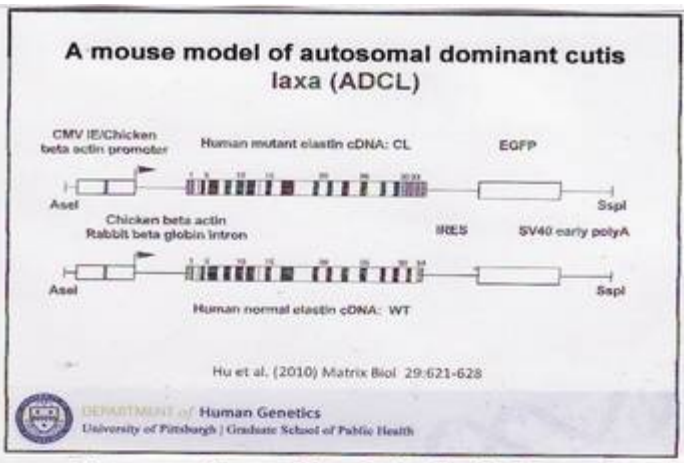
**Example 2 : Fibuline 4 ( FBLN 4)**
**Cutis Laxa Autosomale Récessive 1A**

Souris avec Fibuline4 Désactivée

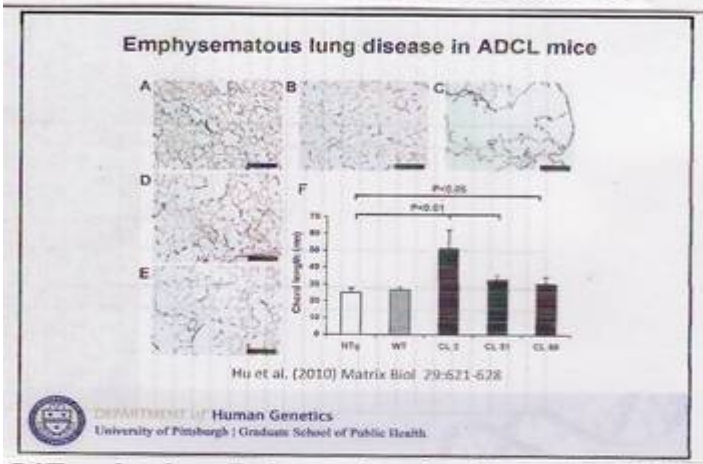
Mutation Fibuline4 Chez l'humain



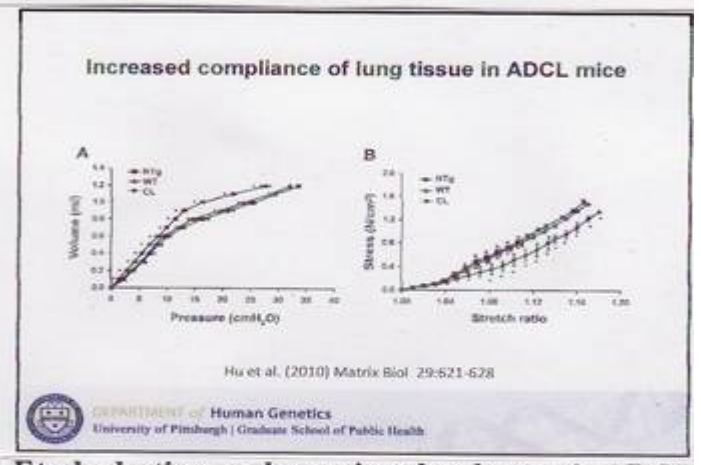

**Exemple 3 : LTBP4**
**Cutis Laxa Autosomale Récessive 1C**




**Une souris modèle de la Cutis Laxa Autosomale Dominante (ADCL)**

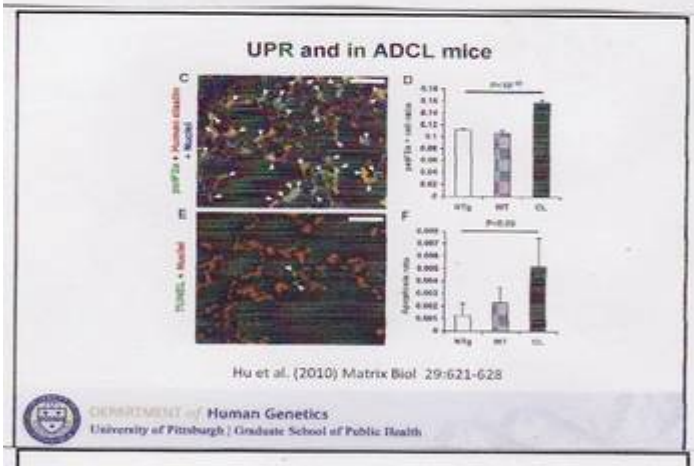


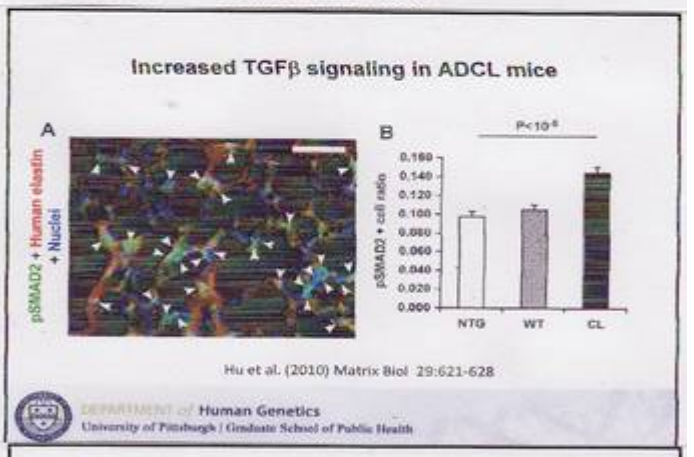

**L'Emphysème Pulmonaire chez la souris ADCL**

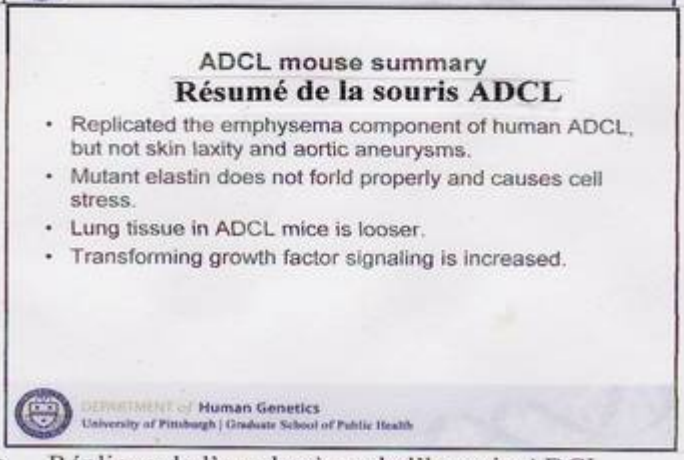



**Etude du tissu pulmonaire chez la souris ADCL**

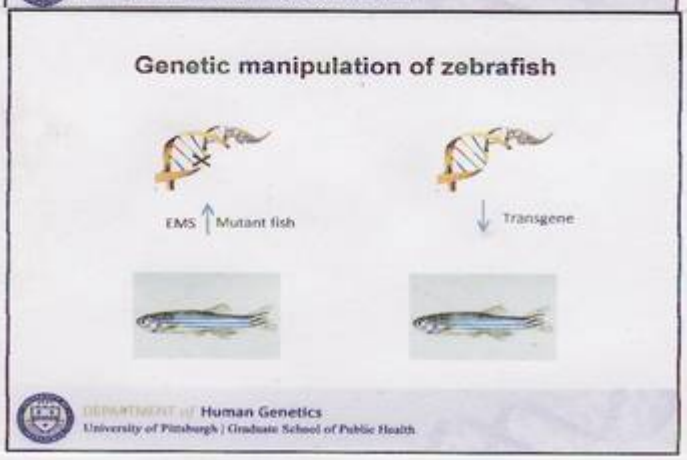
Pression Taux d'étirement



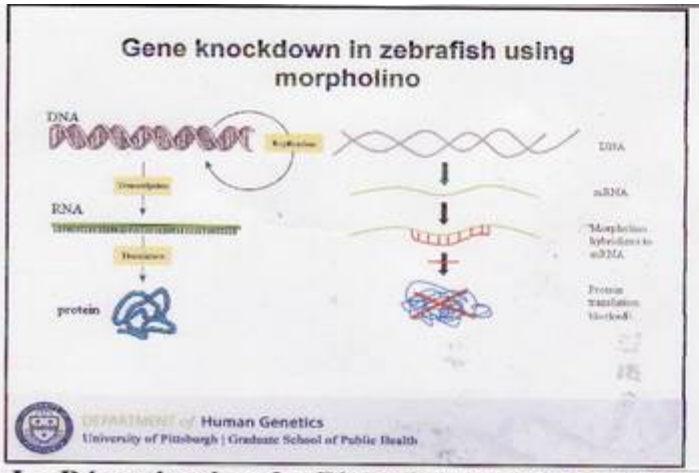



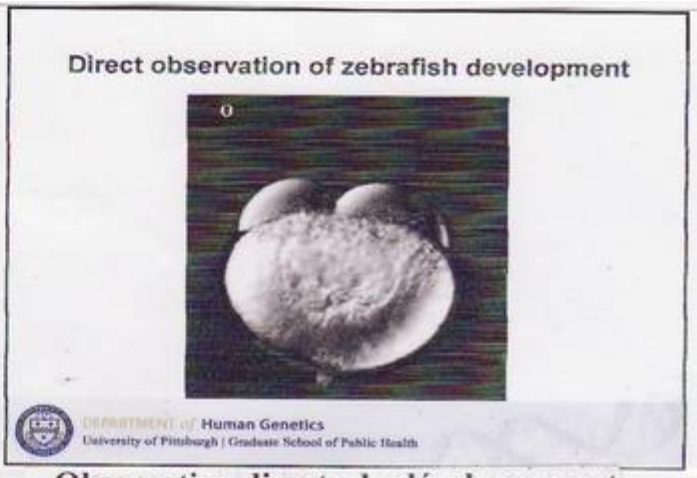

- Réplique de l'emphysème de l'humain ADCL, mais pas de la laxité cutanée, ni des anévrismes aortiques
- L'élastine mutée ne fonctionne pas correctement et cause un stress de la cellule
- Le tissu pulmonaire de la souris ADCL est plus lâche
- Le signal de l'hormone de croissance est accru



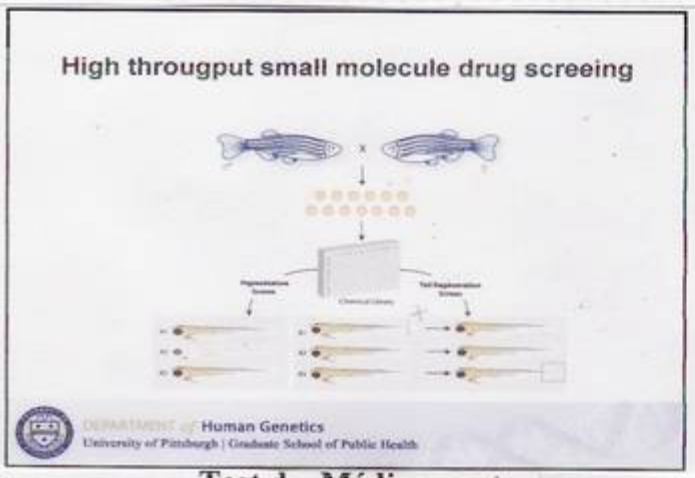

**Manipulation génétique du Poisson-Zèbre**



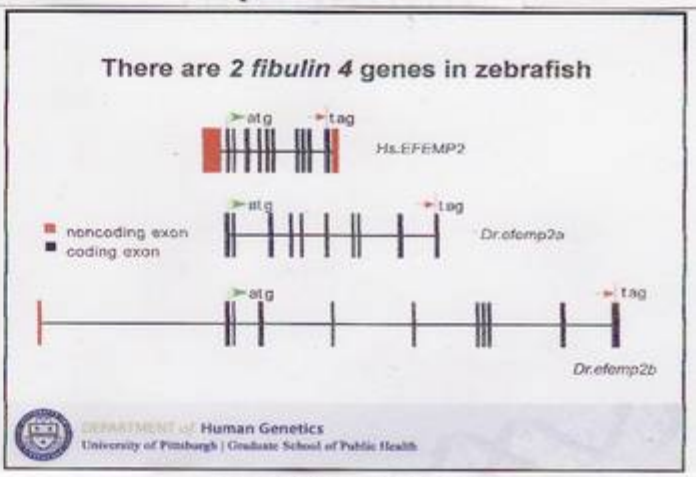

**La Désactivation du Gène chez le poisson-zèbre**



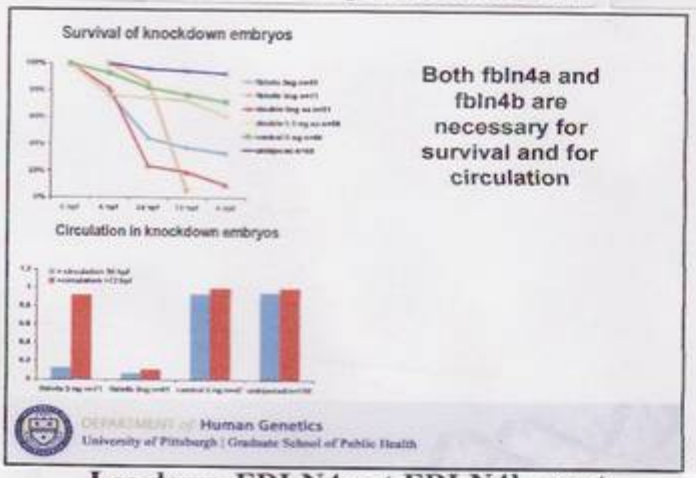

**Observation directe du développement du poisson-zèbre**



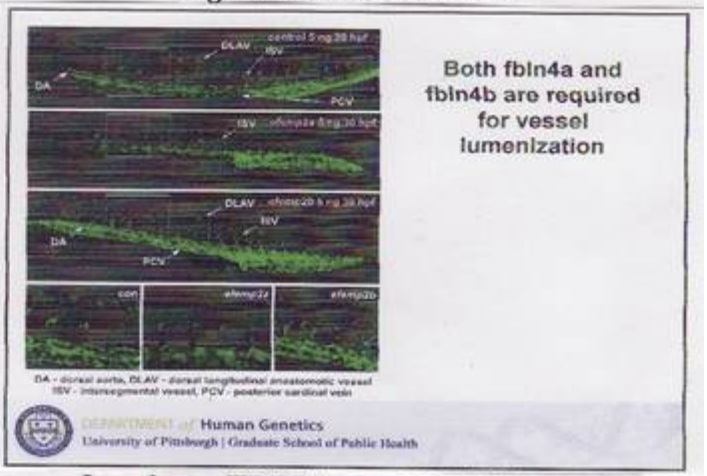

**Test de Médicaments : Gros débit et peu de molécules**



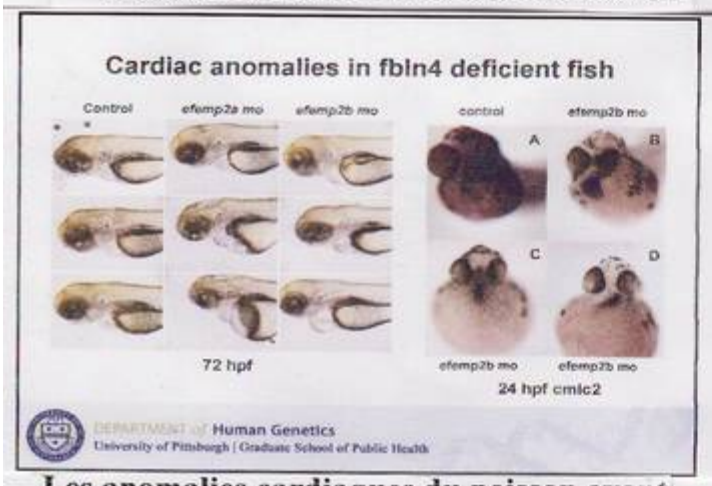

**Le poisson-zèbre a *2 gènes de la Fibuline 4***



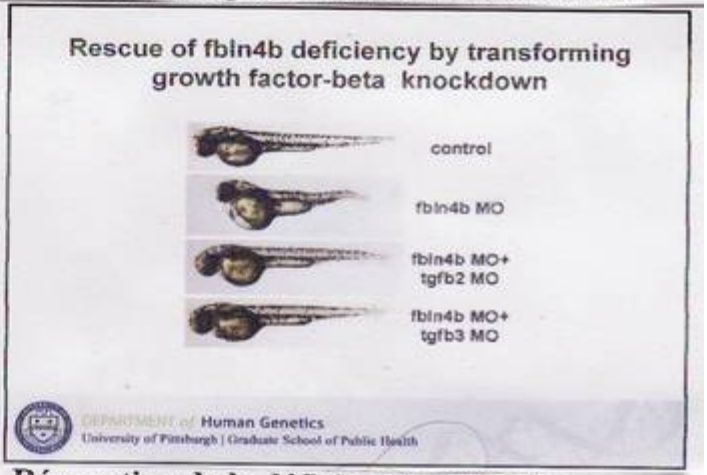

**Les deux, FBLN4a et FBLN4b, sont nécessaires à la survie et à la circulation**




**Les deux, FBLN4a et FBLN4b, sont nécessaires pour visualiser les vaisseaux**

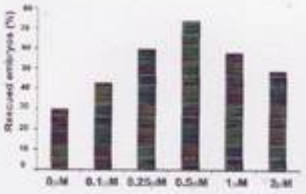



**Les anomalies cardiaques du poisson ayant une déficience en Fibuline4**




**Réparation de la déficience en FBLN4 par désactivation de l'hormone de croissance béta**

## Rescue of fibulin-4 deficiency with a chemical inhibitor of transforming growth factor

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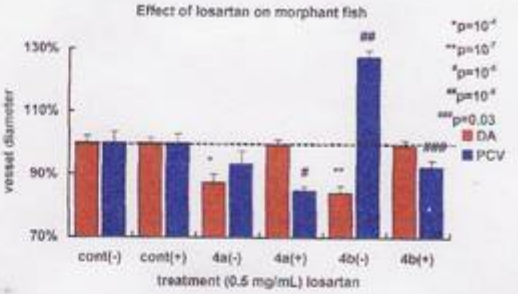
## Losartan rescues fbln4a and fbln4b deficiency

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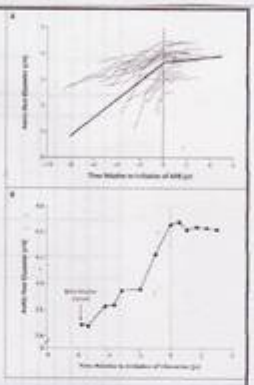
## Réparation de la déficience en FBLN4 par Inhibiteur chimique de l'hormone de croissance

### Losartan shows promise in an small, open label exploratory clinical trial of Marfan syndrome

- 18 patients with rapidly expanding aortic root
- Double blind losartan vs. atenolol trial ongoing n=600 in the US
- Several trials are ongoing in Europe



Brooke et al. (2008) N Engl J Med 358: 2787-2795

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## Le Losartan répare les déficiences de FBLN4a et FBLN4b

### Conclusions

- We have established a zebrafish model of fibulin-4 related cutis laxa (ARCL1A).
- Transforming growth factor beta inhibition either by genetic or chemical treatment can rescue the disease associated with fibulin-4 deficiency.
- Losartan, a blood pressure medication rescues the vascular anomalies caused by fibulin-4 loss.
- Zebrafish may be a useful tool for rapid screening and identification of drugs that may correct the the effects of cutis laxa mutations.

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## Le Losartan montre des possibilités dans un essai clinique pour le Syndrome de Marfan

* 18 patients ayant une base aortique évoluant rapidement
* Aux USA, essai en cours, en double aveugle, Losartan vs atenolol n=600
* Plusieurs essais sont en cours en Europe

* Nous avons créé un poisson-zèbre modèle de la Cutis Laxa FBLN4 (ARCL1a)
* L'inhibition de l'Hormone de croissance béta par taitement génétique ou chimique peut réparer la maladie associée à une déficience de la Fibuline4
* Le Losartan, médicament pour la tension, répare les anomalies vasculaires dues à l'absence de fibuline4
* Le poisson-zèbre peut être un outil utile pour tester rapidement et identifier les molécules qui pourraient corriger les effets des mutations de la cutis laxa.

## St. Louis

Washington University
Robert P. Mecham

Washington University
Robert P. Mecham

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## Urban Lab


## Cutis Laxa Research Clinics

- Bi-annual clinics held in Pittsburgh, Pennsylvania, USA
- Upcoming clinic: October 21st-22nd, 2011
- Website: www.hgen.pitt.edu/projects/cutislaxa
- Coordinators' E-mail: cutislax@pitt.edu

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