Zebrafish as a Model for Studies on Hereditary Multiple Exostosis

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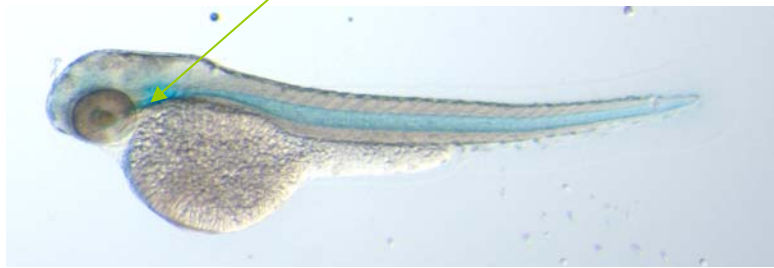
Overview

- Introduction to zebrafish (*Danio rerio*)
- Why fish is a good model for studies on skeletal disorders?
- Zebrafish mutants and HME
  - EXT2 and EXTL3
  - Role in skeletal development as well as other tissues

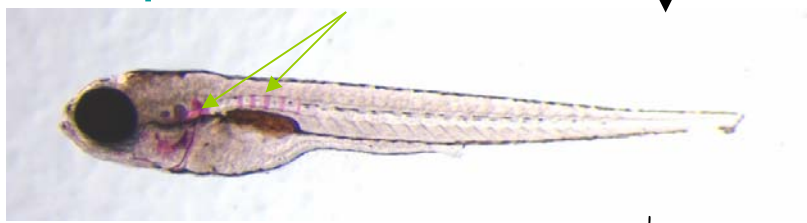
RO **Karlstrom** and DA **Kane**
A flipbook of zebrafish embryogenesis
Development (1996) 123:461

2-3dpf (cartilage begins to form)

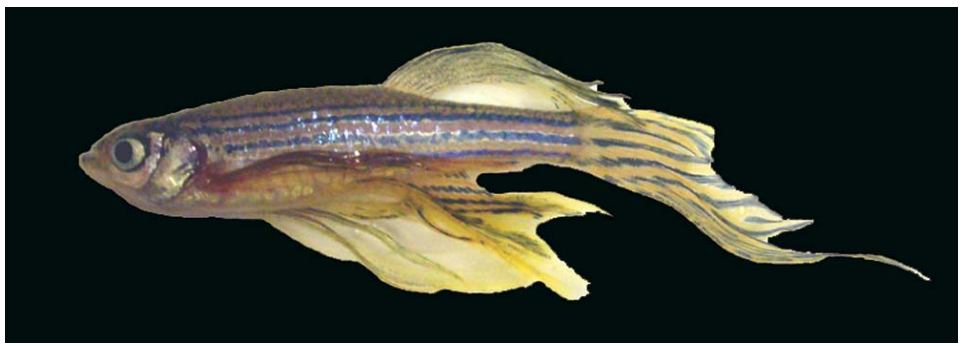


QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

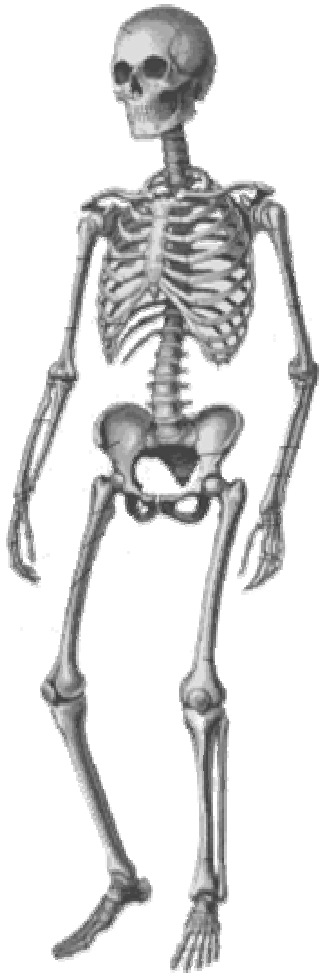
5-6dpf (first ossification)



3-4 months (adult)

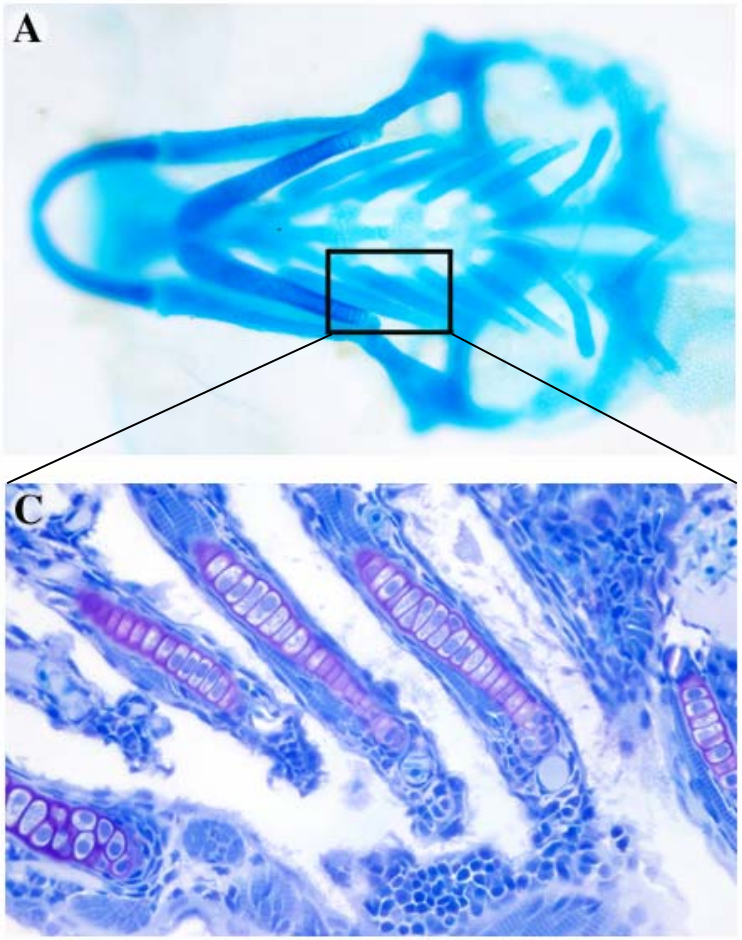


Why zebrafish is good model for studies on skeletal disorders?



Zebrafish as a model for skeletogenesis

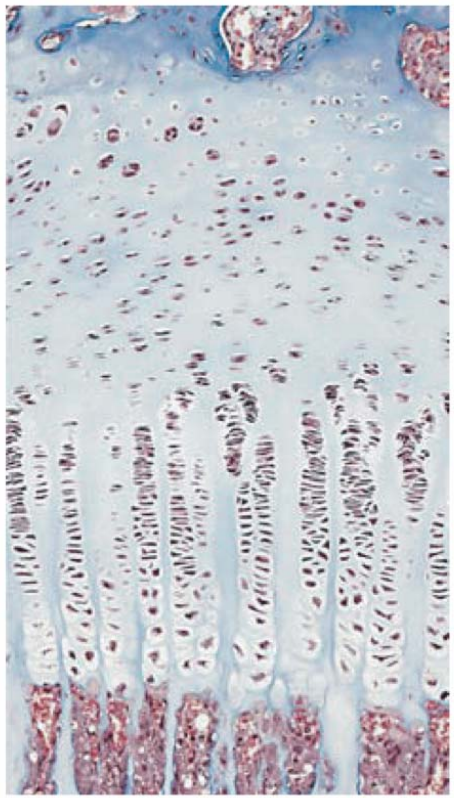
Craniofacial cartilage



wild type zebrafish

Ventral view

Growth plate



The *dackel* “family”

dackel (dak)

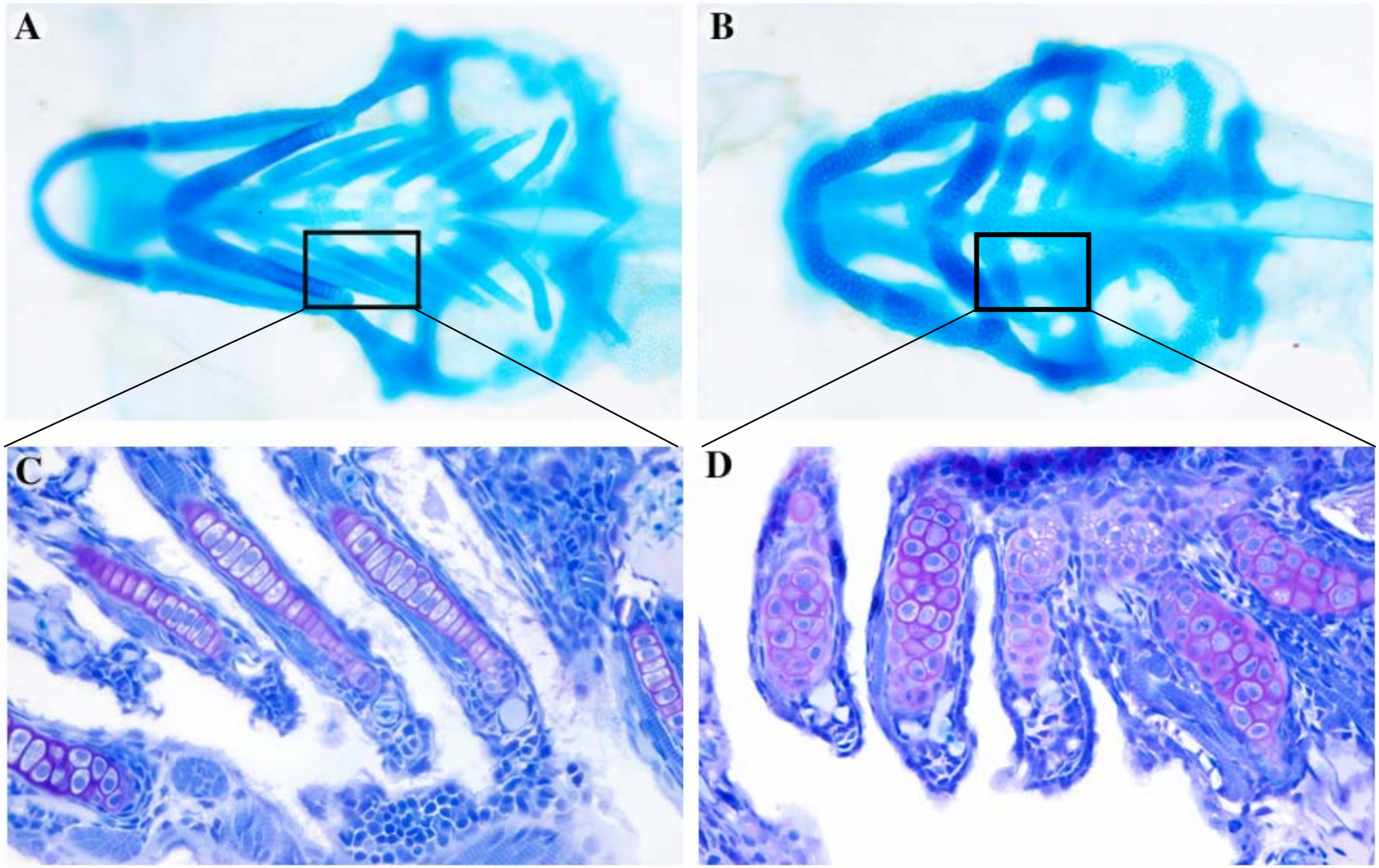
boxer (box)

pinscher (pic)

Forward genetic screen for fish showing cartilage phenotype.

-exostosis-like organisation of the chondrocytes

Zebrafish as a model for HME



wild type

dackel homozygous mutant

The *dackel* “family”

dackel (dak)

boxer (box)

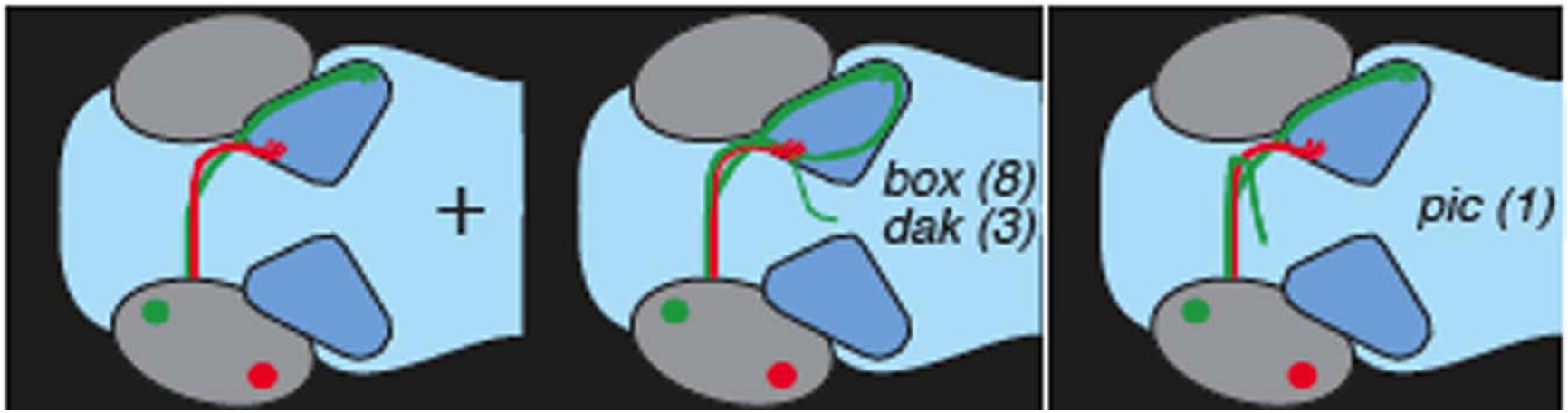
pinscher (pic)

Share pleiotropic phenotype:

-exostosis-like organisation of the chondrocytes

-missorting of the retinotectal projections

Axonal pathfinding: Retinotectal projections



Ventral view

Trowe *et.al., 1996*

See also: **Lee *et.al.*, 2004. Neuron. 16; 44(6): 947-960.**
Karlstrom *et.al.*, Development 123: 427-438.

The *dackel* “family”

dackel (dak)

boxer (box)

pinscher (pic)

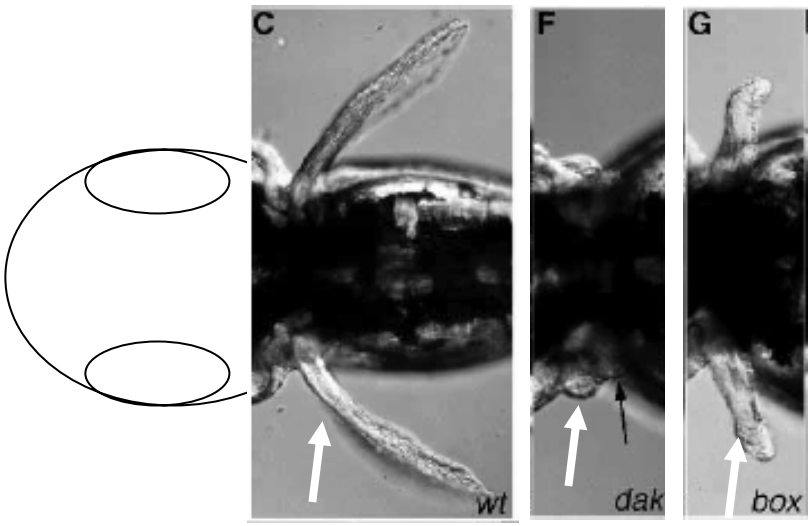
Share pleiotropic phenotype:

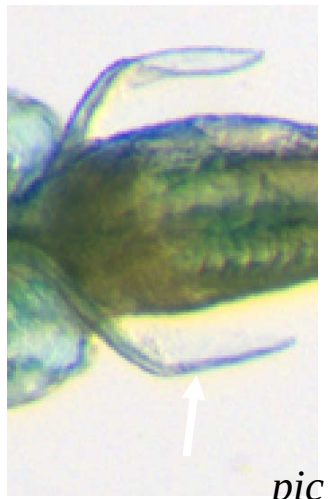
-exostosis-like organisation of the chondrocytes

-missorting of the retinotectal projections

-malformation of the pectoral fin

The pectoral fin





Ventral view

van Eeden et al., 1996

See also: **Norton *et.al.*, *2005*. Development. 132:4951-4962.**
Grandel *et.al.*, 2000. Development. 127: 4169-4178.

The *dackel* “family”

dackel (dak)

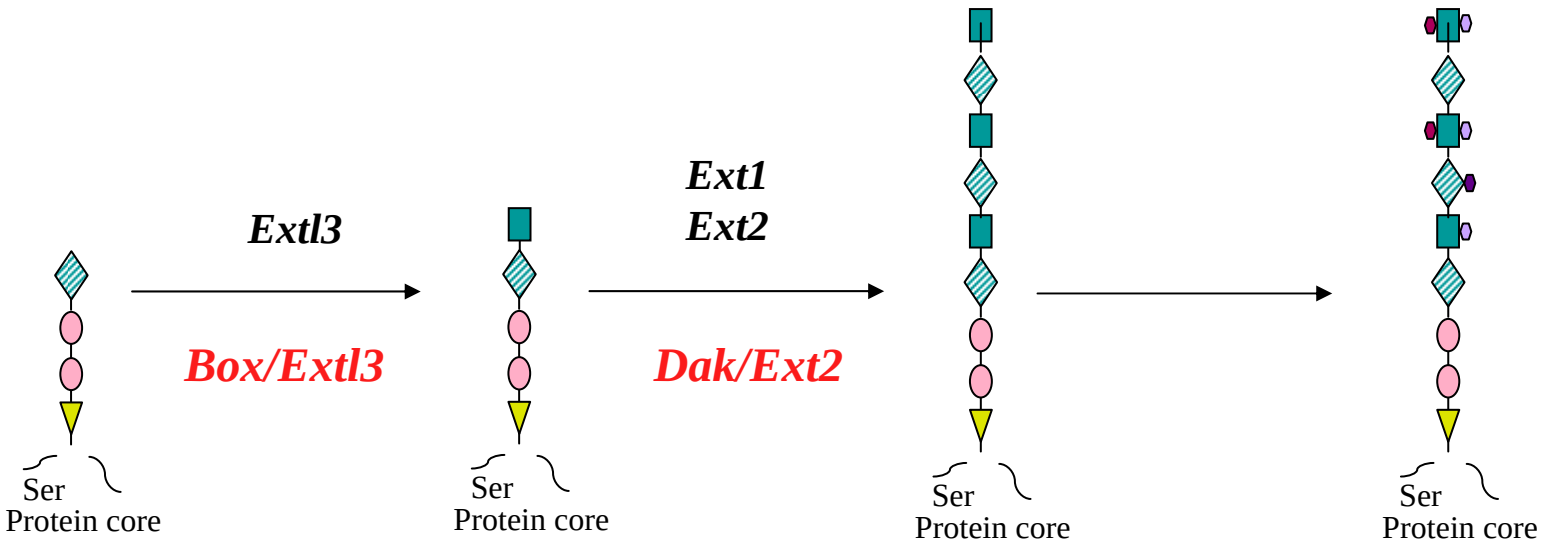
boxer (box)

pinscher (pic)

Common pleiotropic phenotype:

Genes involved in the same pathway

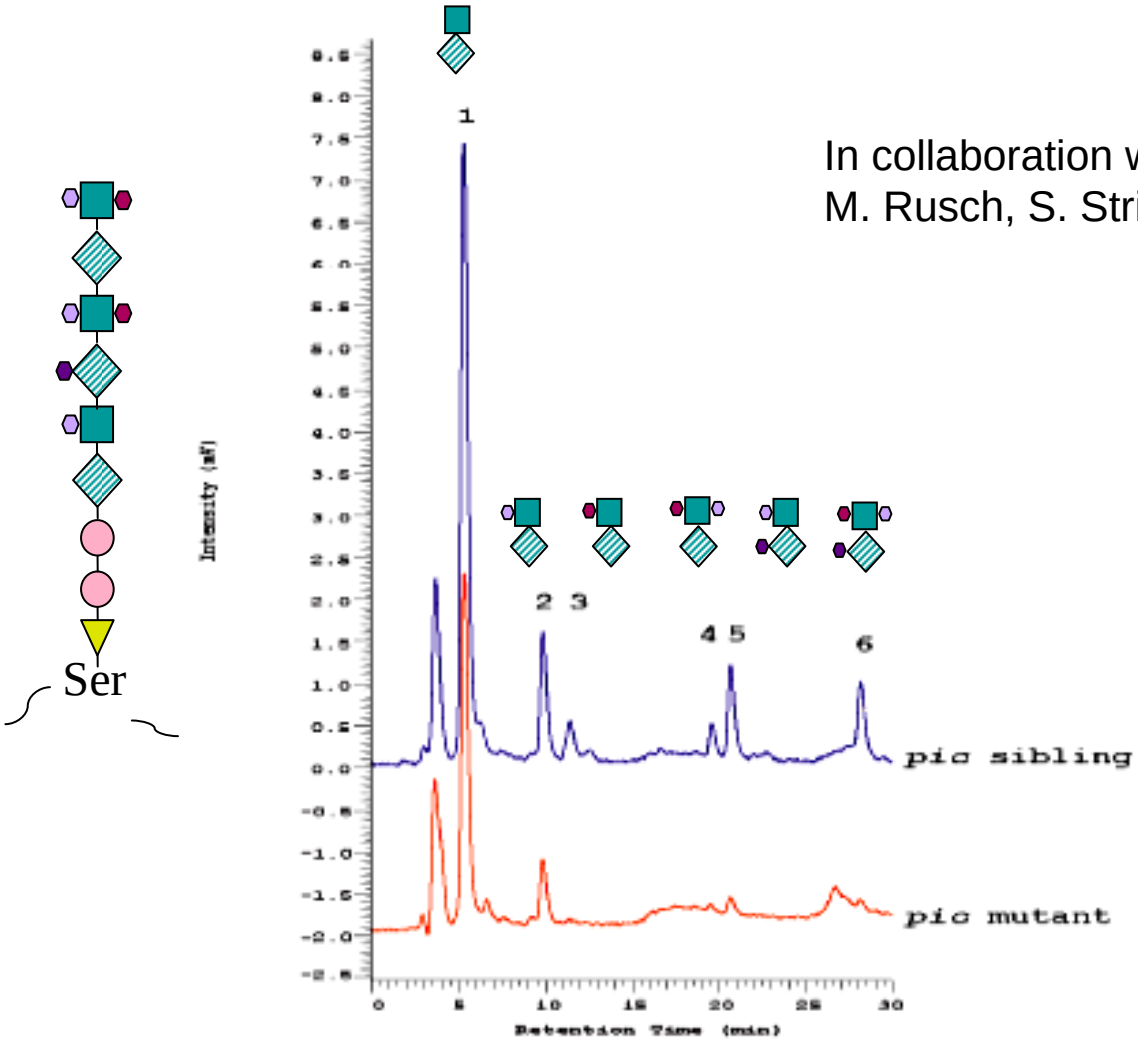
Cloning of *box* and *dak* revealed their role in HSPG biosynthesis:



Box/Extl3 and D*ak/Ext2* were cloned in collaboration with Chien lab

Pinscher?

HSPGs are reduced in *box, dak* and *pic* mutants



In collaboration with
M. Rusch, S. Stringer and S. Selleck

strong reduction also seen in *dak* and *box* mutants

How do exostosis develop?

Acknowledgments

- Roehl lab:
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- Chris Hill
- Johan Ledin / Carl Neumann

- Collaboration:
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  - S. Selleck lab,
  - S. Stringer lab

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