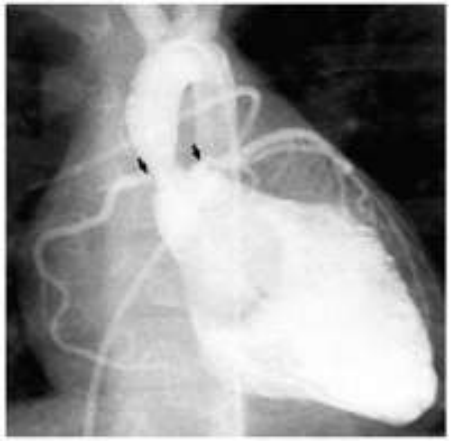
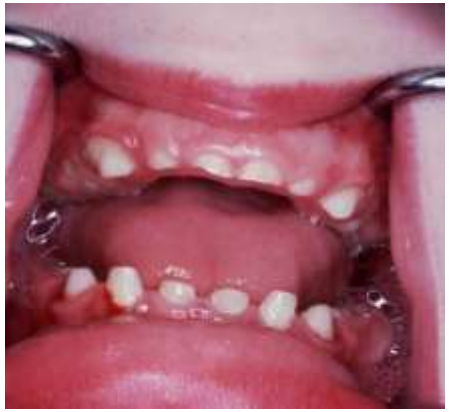
Genes and Human Behaviour: Analysing Mouse Models of Williams-Beuren Syndrome



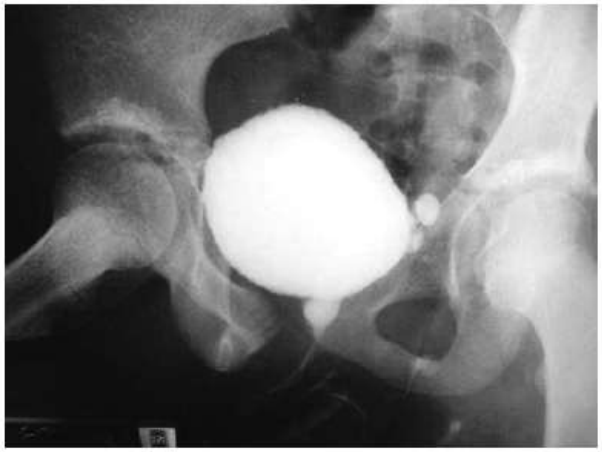
SVAS angiogram



Microdontia

Organ System		Incidence (%)
Ocular and visual		
Esotropia	Cross-eyed	50
Hyperopia	Long-sighted	50
Auditory		
Chronic otitis media	Middle ear inflammation	50
Hypersensitivity to sound		90
Dental		
Malocclusion		85
Microdontia		95
Cardiovascular		
Any abnormality (total)		80
SVAS		75
SVPS		25
PPS		50
Renal artery stenosis		45
Other arterial stenosis		20
VSD		10
Hypertension		50
Genitourinary		
Structural anomaly		20
Enuresis		50
Nephrocalcinosis		<5
Recurrent urinary tract infections		30
Gastrointestinal		
Feeding difficulties		70
Constipation		40
Colon diverticula		30
Rectal prolapse		15
Integument		
Soft lax skin		90
Inguinal hernia		40
Umbilical hernia		50
Prematurely gray hair		90
Musculoskeletal		
Joint hypermobility		90
Joint contractures		50
Radioulnar synostosis		20
Kyphosis		20
Lordosis		40
Awkward gait		60
Calcium		
Hypercalcemia		15
Hypercalciuria		30
Endocrine		
Hypothyroidism		2
Early puberty (but rarely true precocious puberty)		50
Diabetes mellitus		15
Obesity		30
Neurologic		
Hyperactive deep tendon reflexes		75
Chiari I malformation		10
Hypotonia (central)		80
Hypertonia (peripheral)		50

ELN ?



Bladder diverticula in a 7 yr old boy

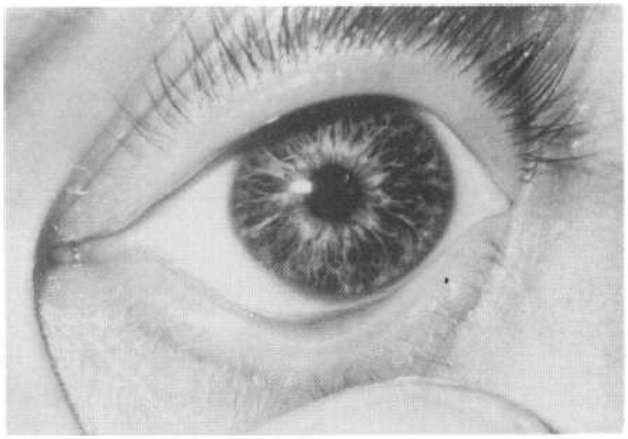


Figure 1 Stellate pattern of iris in a patient with Williams syndrome.

The craniofacial abnormalities in Williams-Beuren syndrome

Enlargement or overgrowth of soft tissue

- Wide smile
- Full lips
- Full cheeks
- Periorbital fullness
- Epicanthal folds (skin fold of the upper eyelid)
- Anteverted naris
- Long philtrum
- Low-set ears

Neuropathology of Williams-Beuren Syndrome

Sensory

High frequency hearing impairment but amplified perception of sound (hyperacusis/ auditory allodynia)

Motor

Gait abnormalities, difficulties descending stairs, changing surfaces

Saccade dysmetria

Learning and memory impairments

Reduced IQ: Range from severe mental retardation to within normal limits

Severe visuospatial construction deficit

Language – Relatively preserved (compared to other functions)

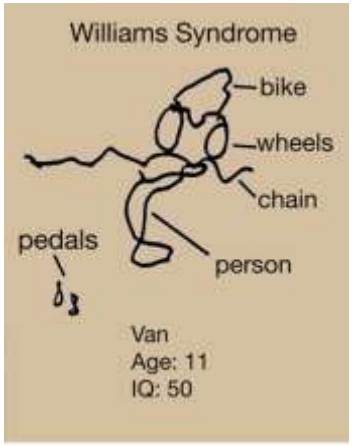
Auditory Rote memory: better than CA and IQ matched controls

Behaviour

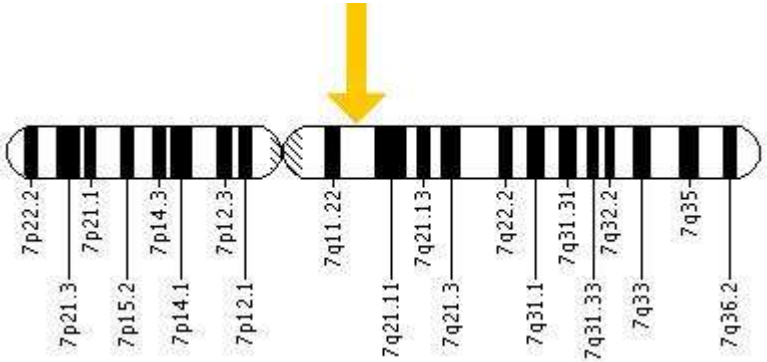
Reduced social anxiety

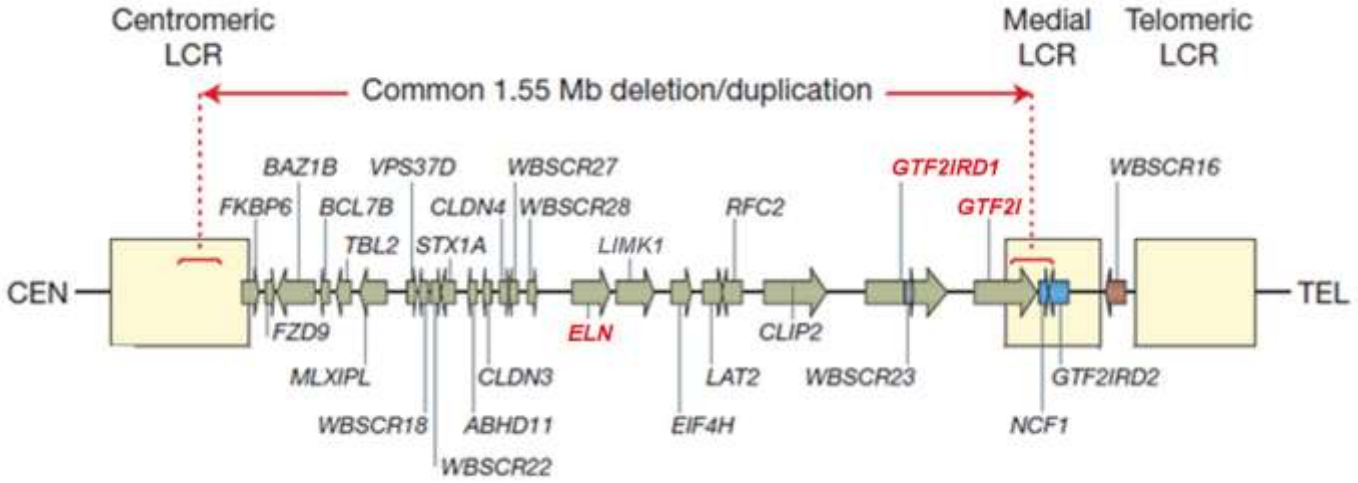
Increased non-social anxiety

Anticipatory anxiety

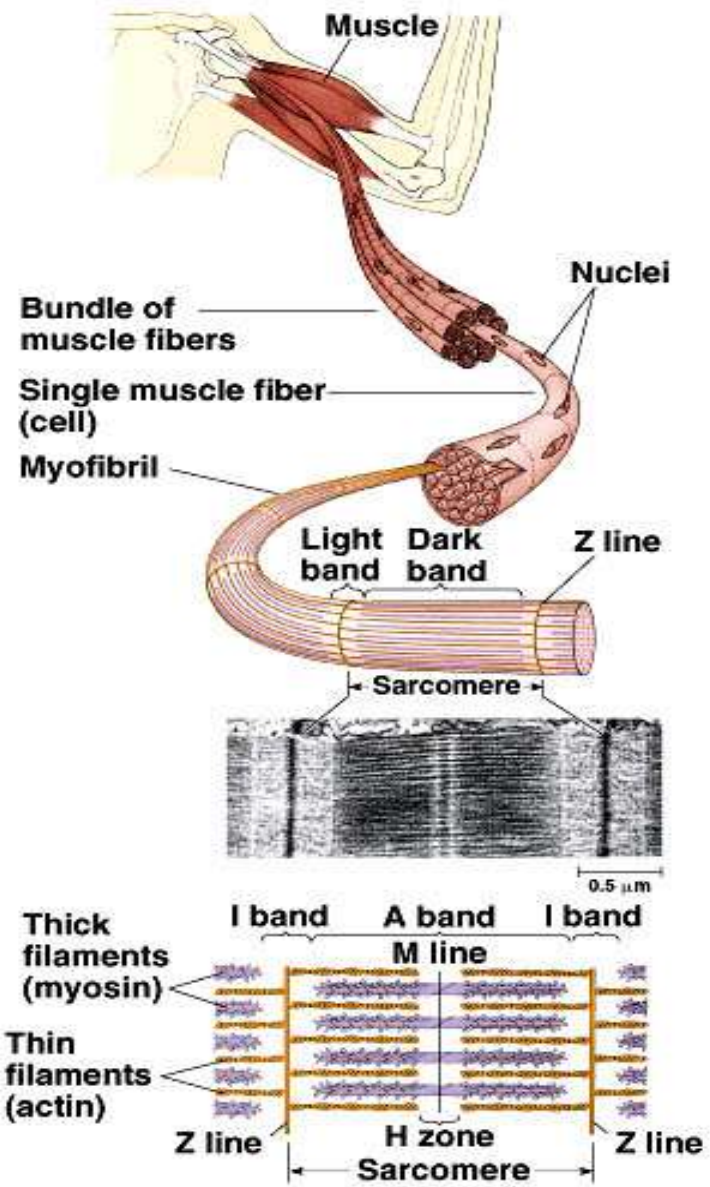


Williams syndrome is caused by a hemizygous microdeletion within Chr7q11.23



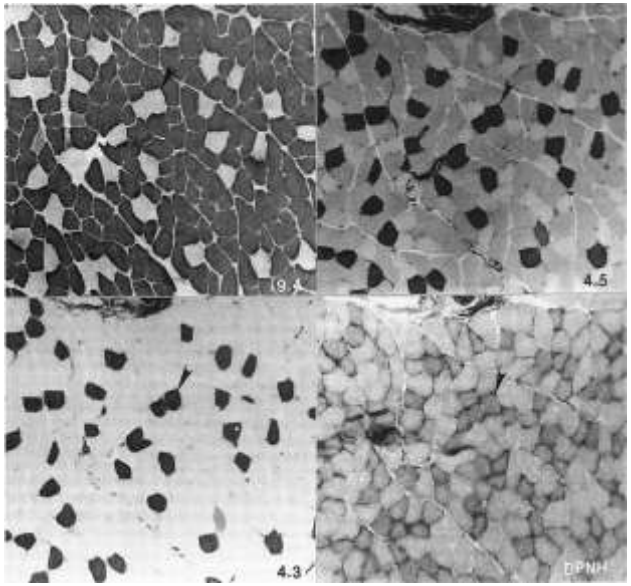


Lucy R. Osborne[1,*] and Carolyn B. Mervis[2]



Muscles, muscle fibres and myofibrils

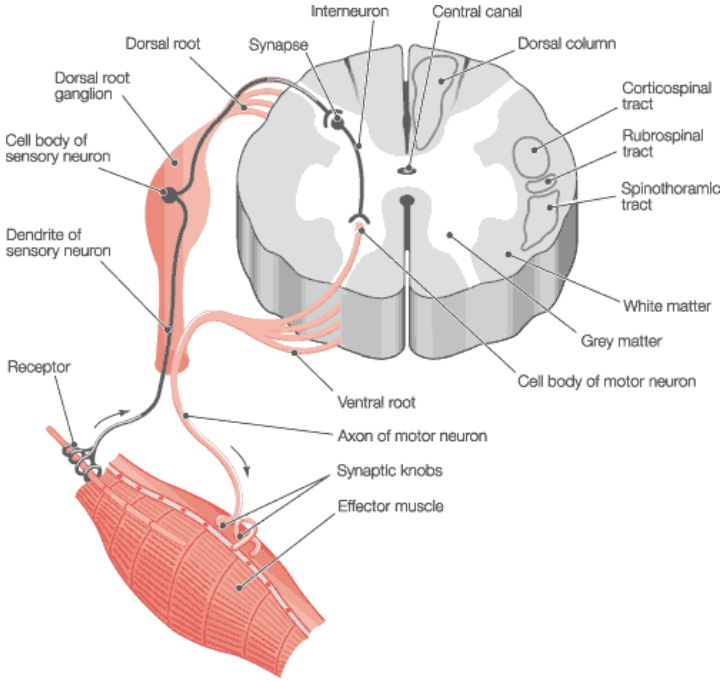
Properties of Muscle Fiber Types

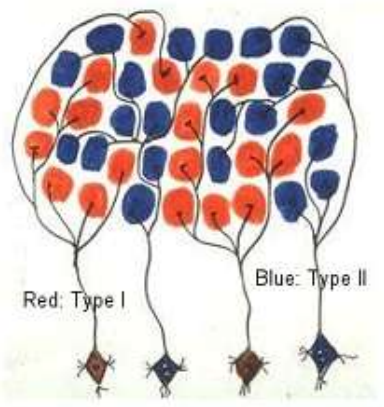


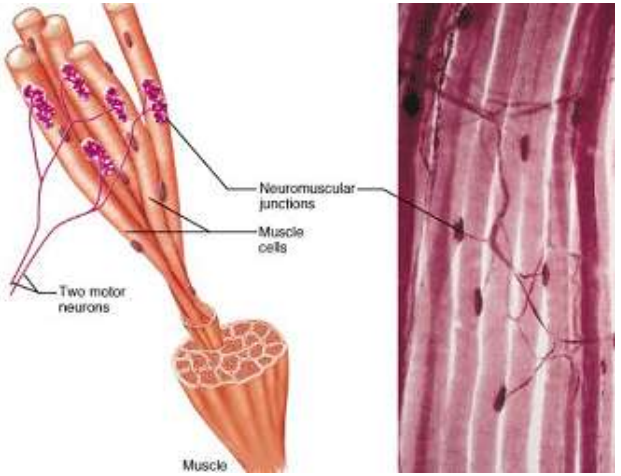
	Fast fibers			Slow fibers
Characteristic	**IIb**	**IIx**	**IIa**	**Type I**
V_{max} (speed of shortening)	Highest	Intermediate		Low
Resistance to fatigue	Low	High/moderate		High
Predominant energy system	Anaerobic	Combination		Aerobic
Myoglobin	Low	Medium		High
Capillary density	Low	Medium		High

Motor control of muscle fibres

Motor unit – the α-motor neuron and all the fibres under its control







Motor units

may control <5 muscle fibres in the eye or small hand muscles or >2000 fibres in the gastrocnemius

Importance of muscle functions

Athletic performance – marathon runners versus sprinters

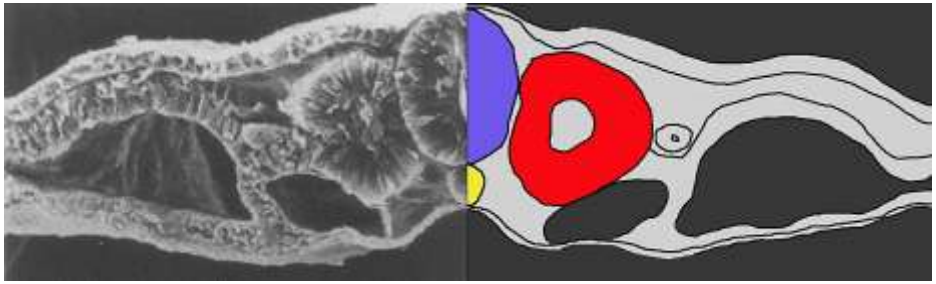
Ageing – preferential reduction of fast fibres in sarcopenia

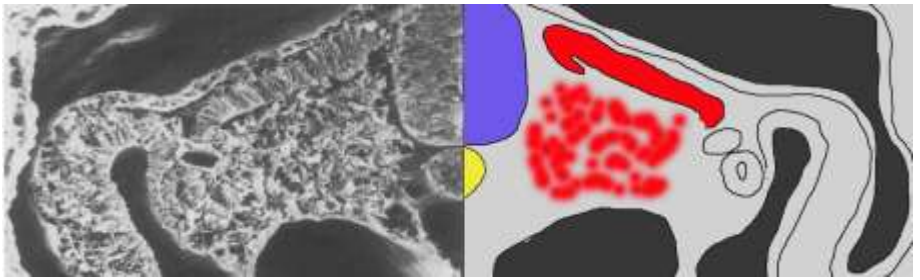
Disease – preferential loss of fast fibres in Duchenne muscular dystrophy; complete absence of fast fibres in some nemaline myopathy patients.

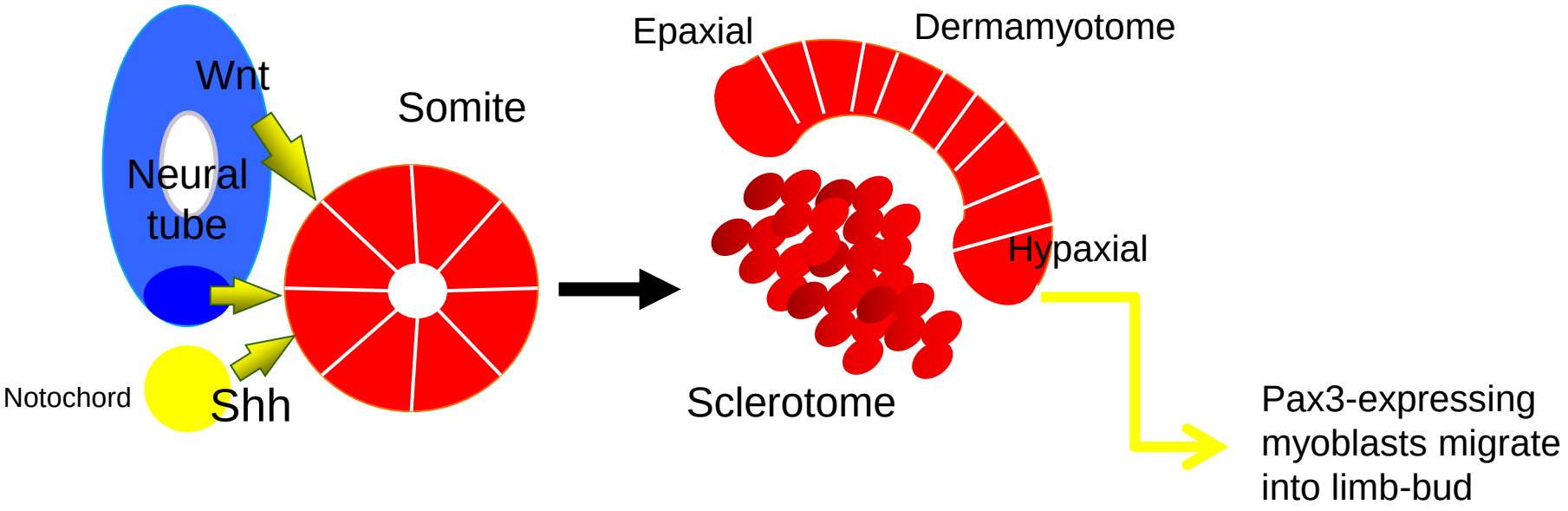
Atrophy responses – reduction of slow fibres in response to bed-rest, space flight and spinal cord injury.

Hypertrophy – maturation hypertrophy, hypertrophy in response to work demand e.g. resistance training.

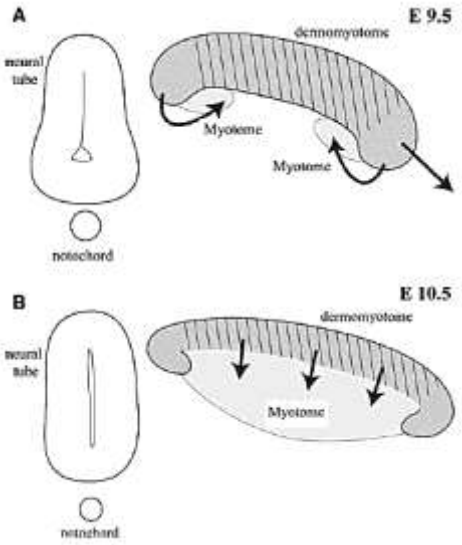
The origin of embryonic myoblasts in the chick







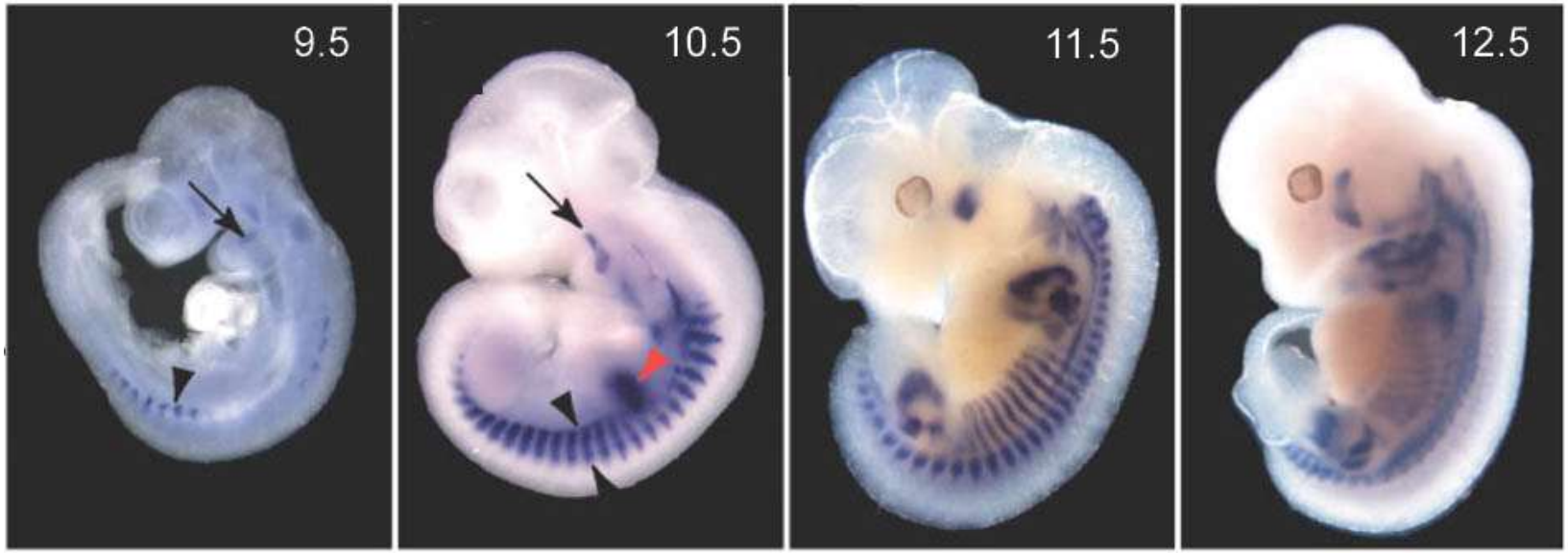
Myogenesis in the mouse



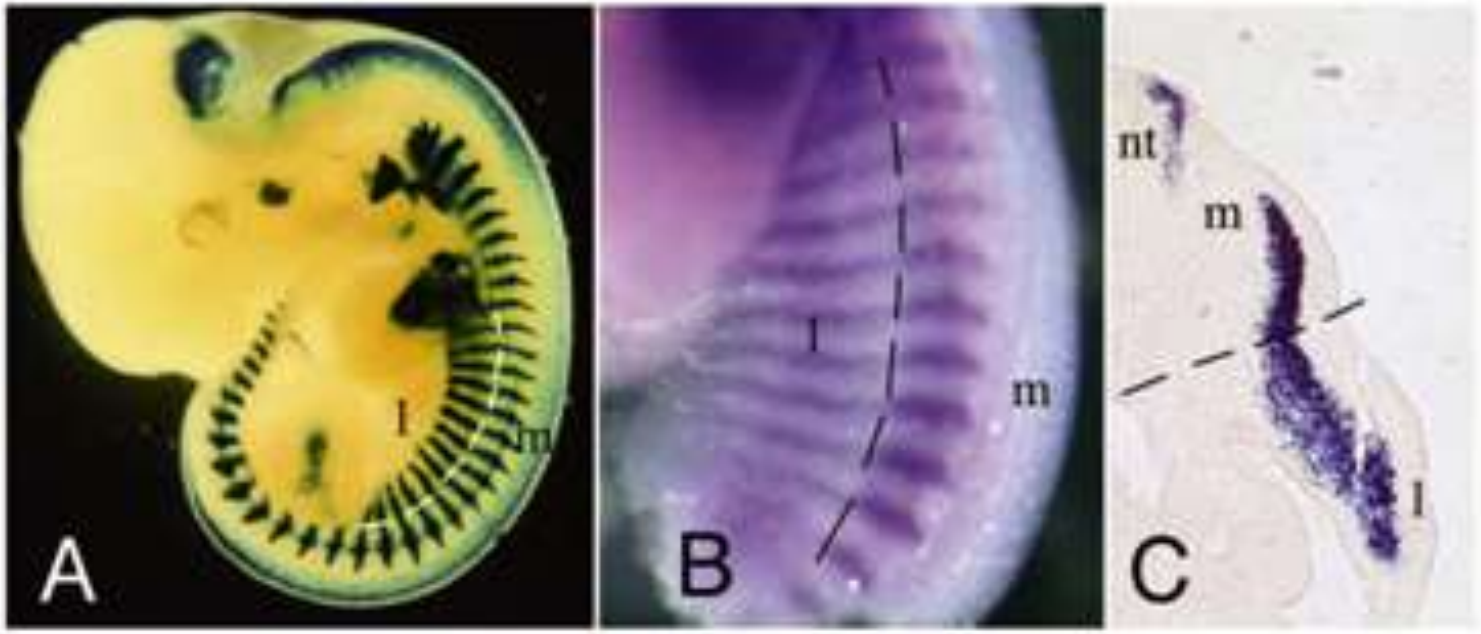
Formation of the myotome

Muscle progenitors delaminate from the edges of the dermamyotome to form the myotome. Some cells migrate into the limb buds. At E10.5 the dermamyotome disintegrates centrally and the main myotome is formed

Expression of the myogenic regulatory factor (MRF) gene MyoD



Epaxial and hypaxial components of the myotome E11.5 mouse embryos.



Eloy-Trinquet S , Nicolas J Development 2002;129:111-122

Myogenesis

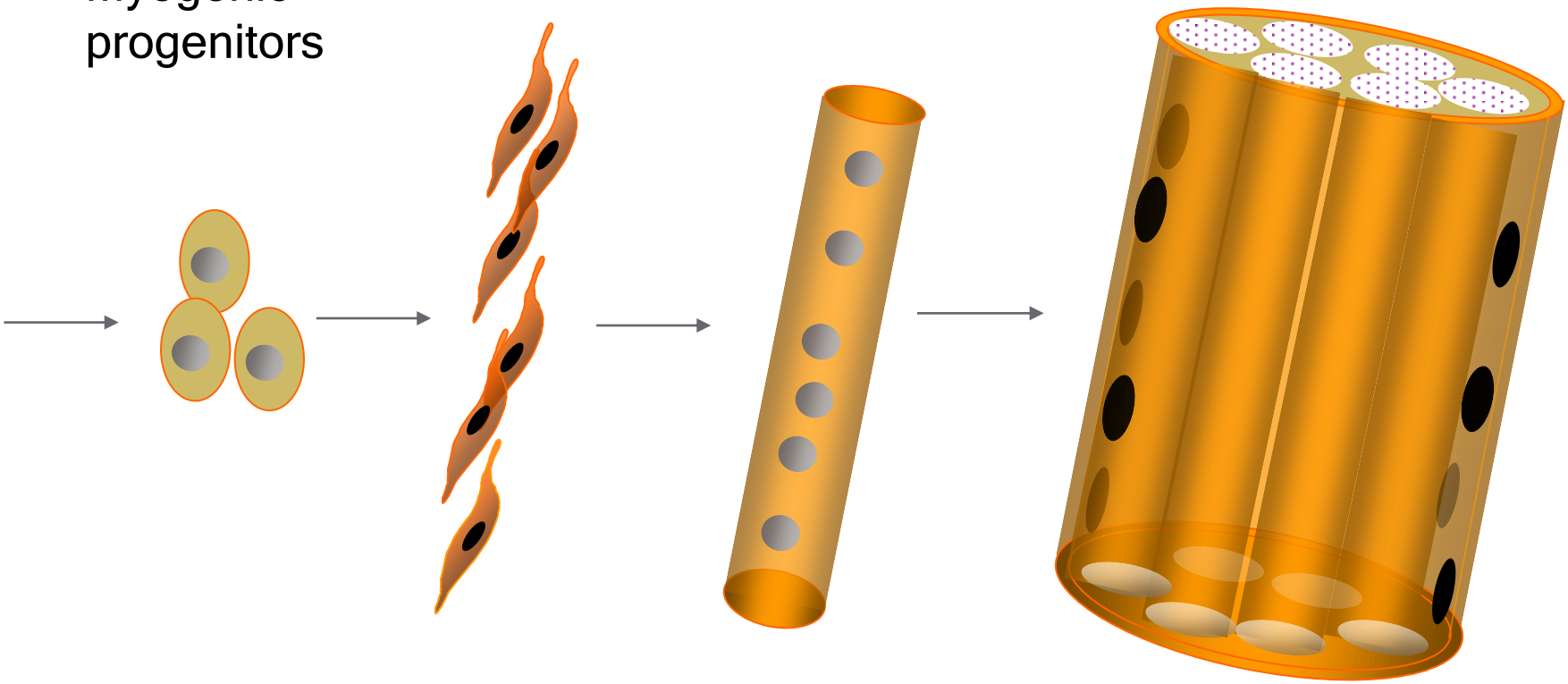
Proliferative phase

Maturation hypertrophy to increase size and expression of adult myofilament genes = mature muscle fiber

Myogenic progenitors

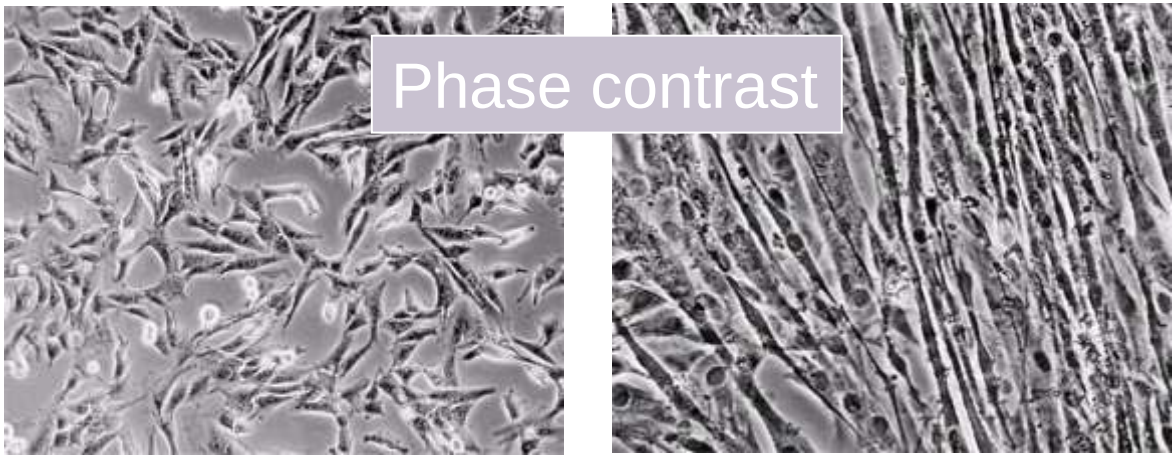
Myoblasts

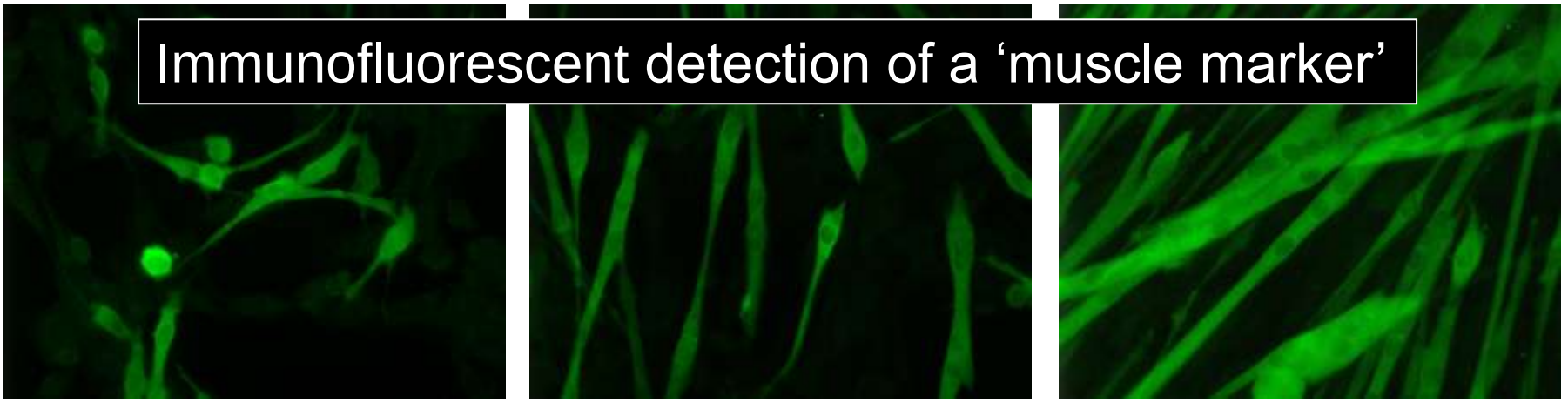
Myotube



Myoblast differentiation in culture

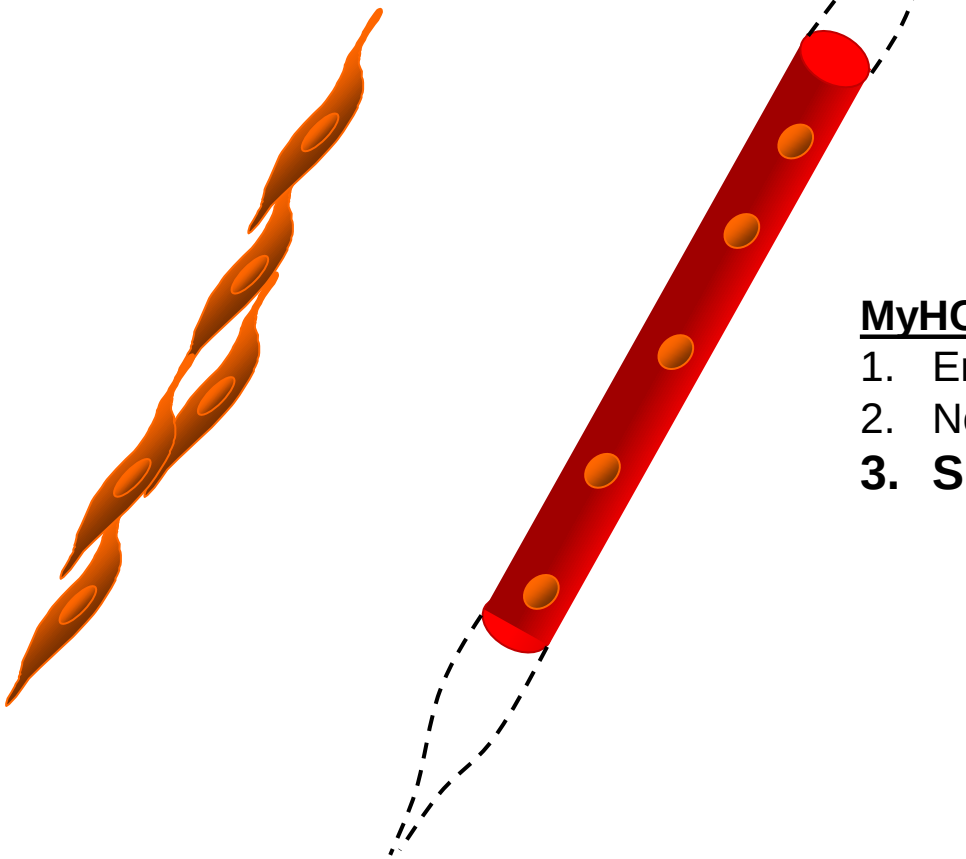
Myoblast Myocyte Myotube





Differentiation of **primary** myotubes in the mouse hind-limb (12-14 dpc) and the beginning of fibre type <u>patterning</u>

Fusion of myoblasts is ordered and synchronous. Nerve is not required for fusion or Myosin Heavy Chain Slow expression



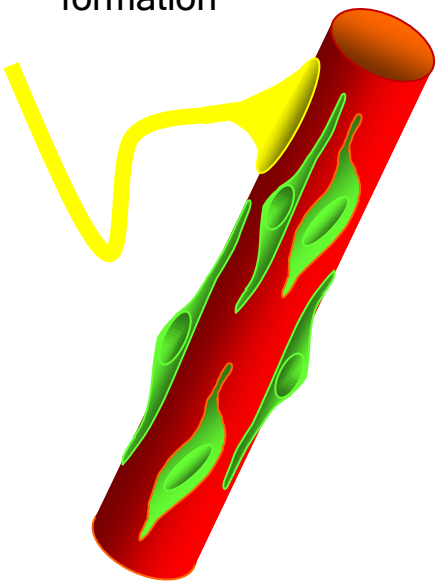
Tendon formation from sclerotome-derived cells – marked by expression of Scleraxis (Scx). Induced by the myotome.

<u>MyHC expression</u>

1. Embryonic
2. Neonatal
3. **Slow**

Secondary myotube formation – mouse hindlimb 14dpc – birth and continuing fibre type patterning

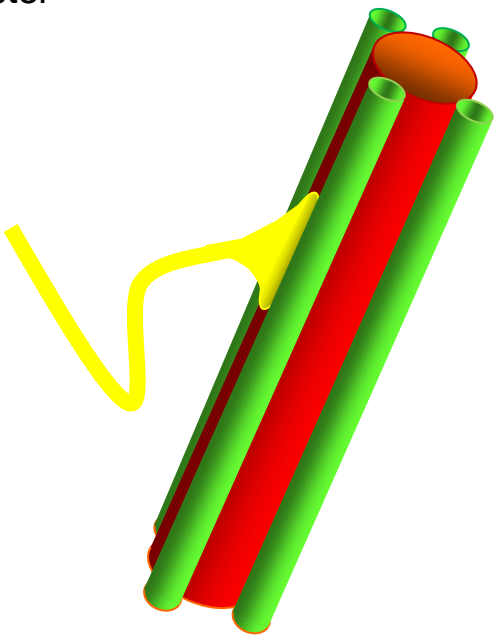
14-16 dpc - Pioneer motor axons contact primary myotubes. Necessary for survival of myotube and secondary myotube cluster formation



Secondary myotubes form in Clusters around primaries.

MyHC gene expression

1. Embryonic
2. Neonatal

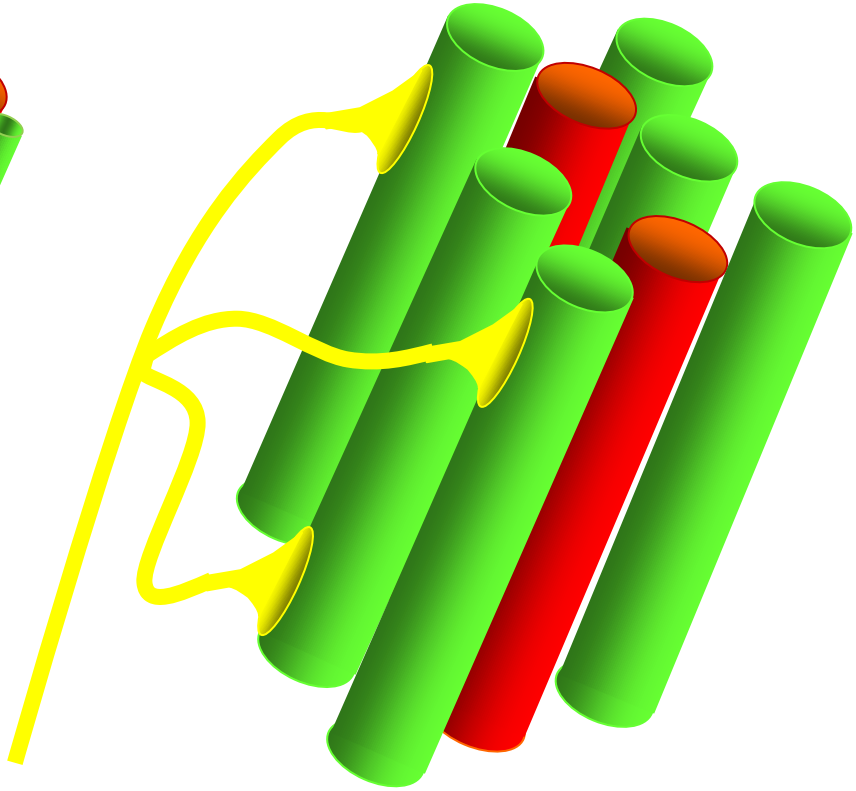


Late fetal stage- clusters disperse.

MyHC gene expression

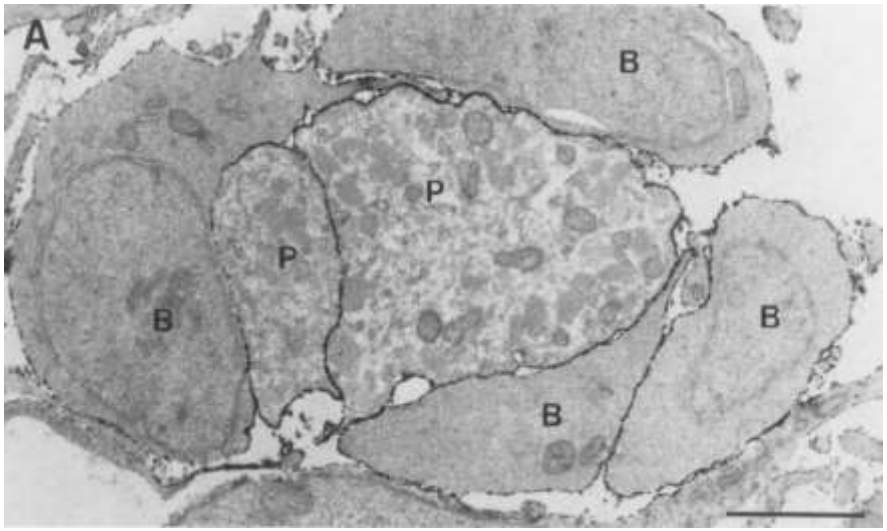
Primaries – slow MyHC

Secondaries - neonatal MyHC

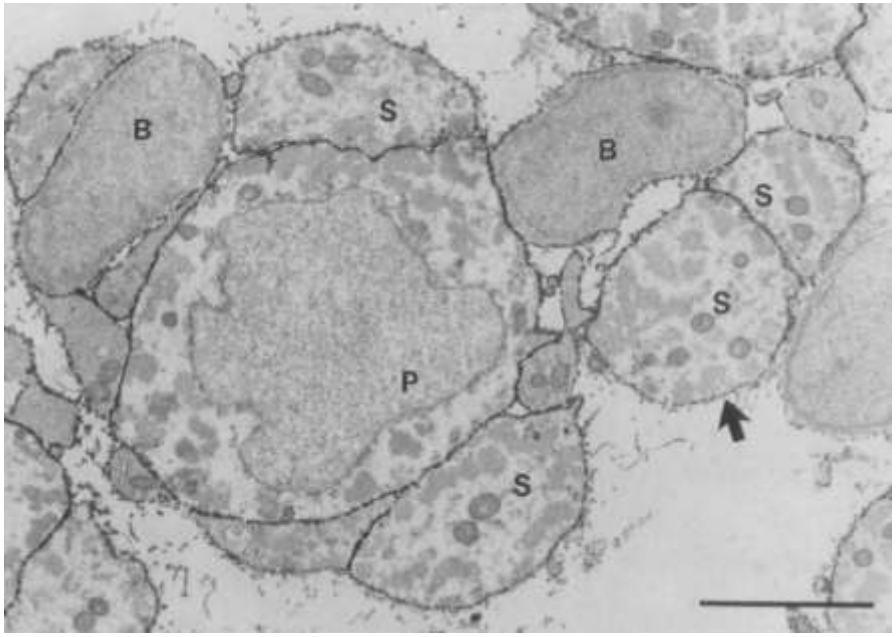


EM sections of developing iliofibularis muscle in chick embryos

Primary myogenesis

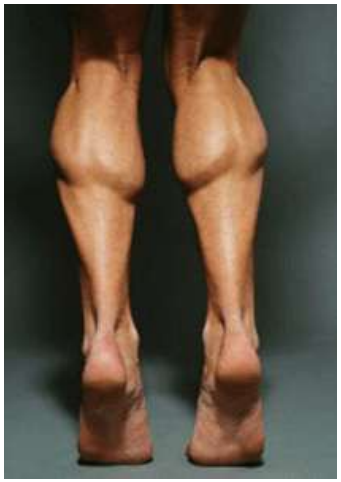


Secondary myogenesis

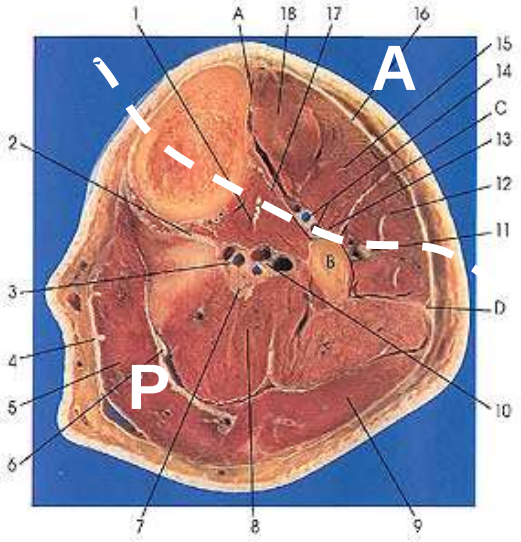


Barbara Fredette,* Urs Rutishauser,‡ and Lynn Landmesser*

Studying muscles in the mouse as a model of human muscle development – the lower hind limb

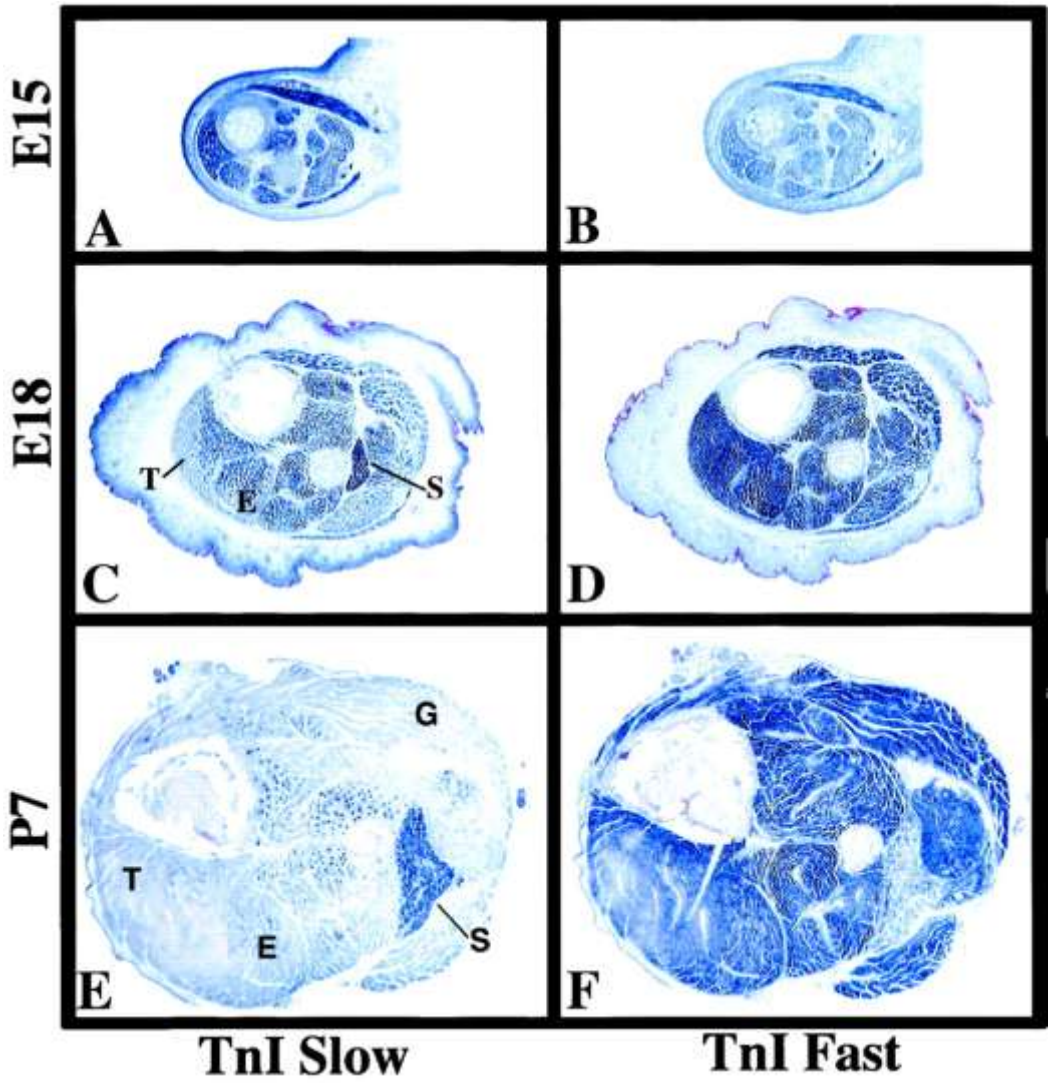


Approx plane of section



18 Tibialis anterior
15 Extensor digitorum longus EDL
12 Peroneus brevis and longus
17 Tibialis posterior
8 Soleus
9 Gastrocnemius medial head
5 Gastrocnemius lateral head

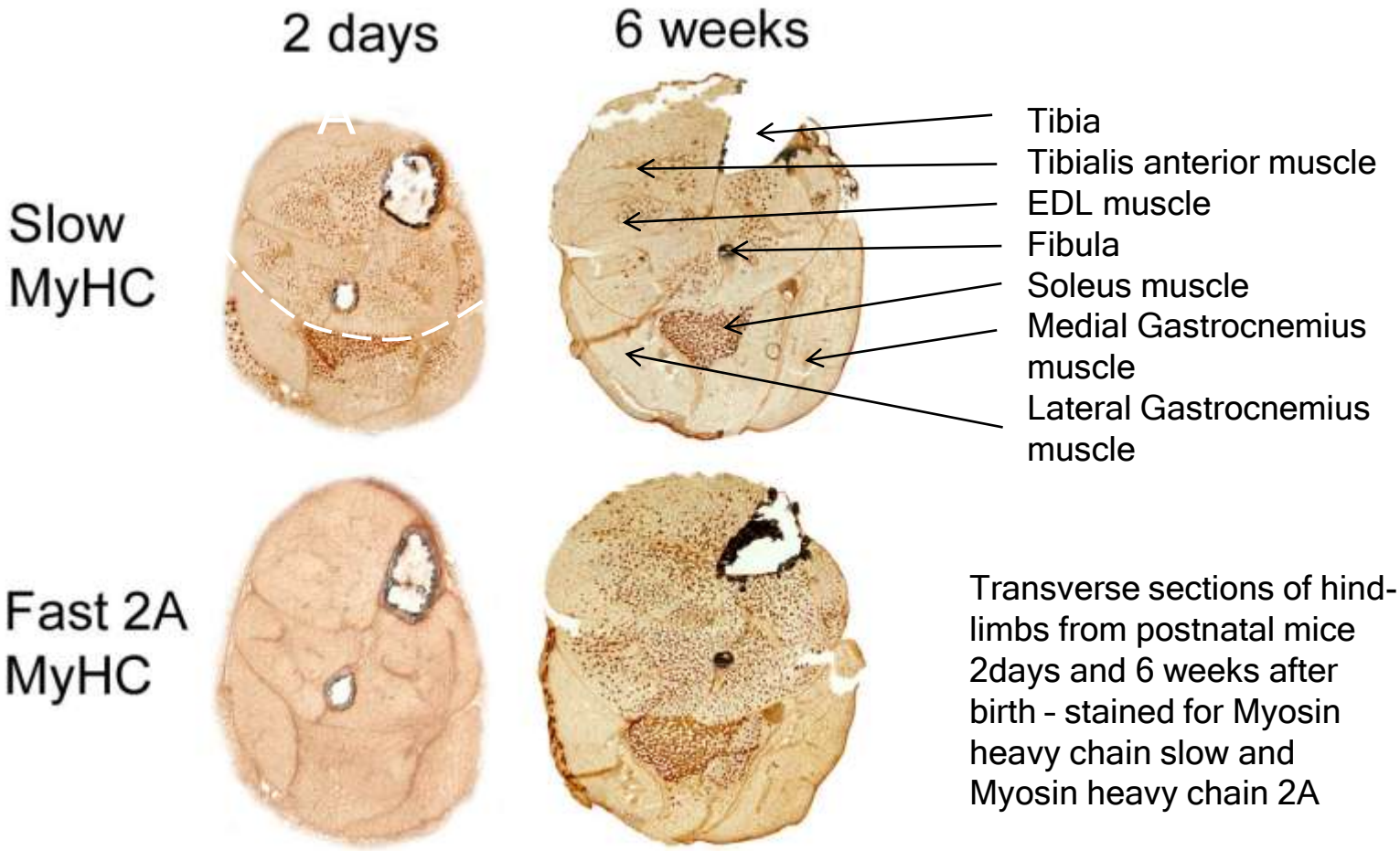
In situ hybridisation analysis of Troponin I isoforms in mouse crural sections



G = Gastrocnemius
S = Soleus
E = EDL
T = Anterior tibialis

Tnni1 is the gene that encodes the inhibitory subunit of the Troponin complex that is found in slow-twitch fibres.

Postnatal fibre CONVERSION: slow fiber number declines and neonatal MyHC is replaced by the adult fast fibre MyHCs



Transverse sections of hind-limbs from postnatal mice 2days and 6 weeks after birth – stained for Myosin heavy chain slow and Myosin heavy chain 2A

Plasticity and Regeneration of Adult Muscle

Muscle Adaptation to Exercise Training

Adaptations to exercise training, particularly elevation in oxidative capacity of exercised muscle but also some myosin isoform changes mainly in fast subtypes.

Cross-Reinnervation

Buller *et al*. (1960) – Motor nerves supplying the (slow) soleus and (fast) FDL muscles swapped around. Contraction speed of soleus got faster, FDL slower.

Chronic Low-Frequency Stimulation (CLFS)

Artificial electrical stimulation of a nerve supplying a fast muscle with a tonic pattern mimics the impulse pattern of a slow nerve and induces fast to slow transformation Pette et al. (1973).

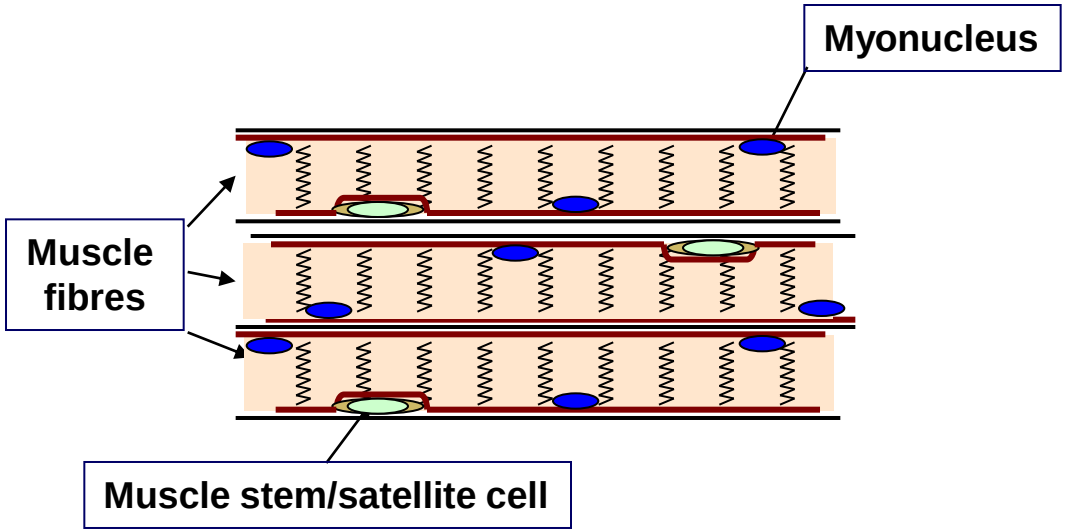
Pure Fibers, Hybrid fibers and the "Next-Neighbour Rule"

Analysis of myofilament isoforms in single fibers reveal the presence of "pure" and "hybrid" fibers containing, for example, MHC 2B and 2X. The percentage of hybrid fibers increases dramatically in transforming muscles. Transition occurs in a stepwise direction 2B->2X->2A->I. Hybrids fibres always contain a pair of "next-neighbour" isoforms.

Regeneration

Injured muscle can regenerate itself using a population of stem cells that are laid down during embryogenesis – called satellite cells. Satellite cells lie between the sarcolemma and the basal lamina of each muscle fibre and activated by injury.

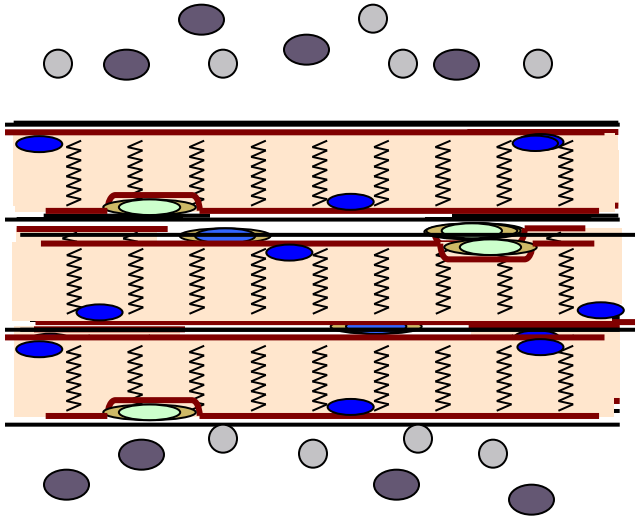
Skeletal Muscle during Injury



Normal Muscle

- Muscle fibres are post-mitotic.
- Muscle stem / satellite cells remain quiescent.

Skeletal Muscle during Injury



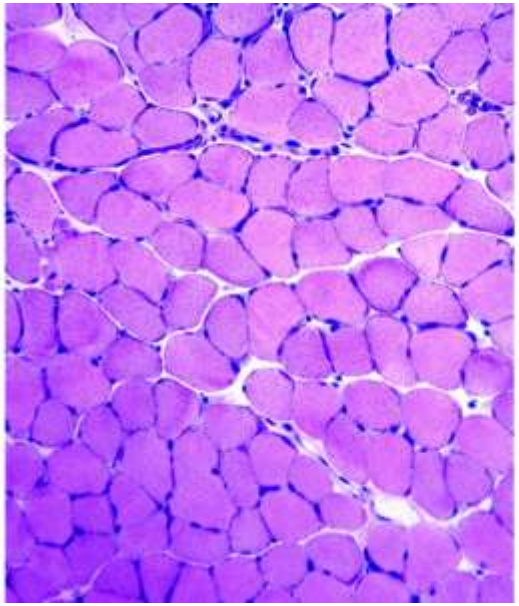
Injured Muscle

- Muscle stem / satellite cells are activated and proliferate.
- Cells, including inflammatory cells, transiently infiltrate the muscle bed.
- Post-mitotic satellite cells align and fuse to repair/form new muscle fibres.

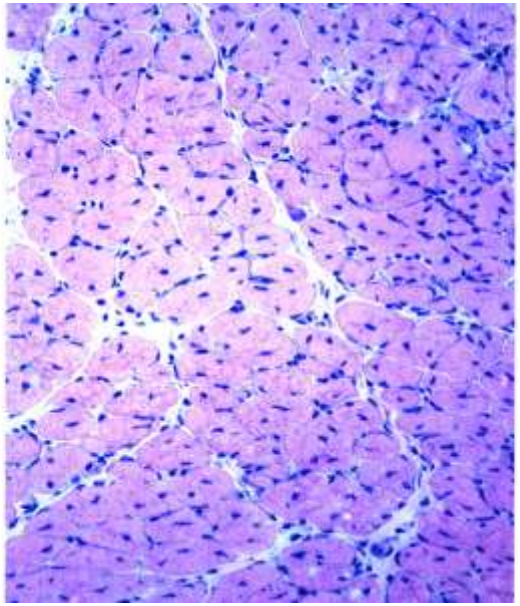
Notexin injury to mouse skeletal muscle

Australian tiger snake

Normal



10days regeneration



10 days ablated satellite cells