A major clinical progress to repair **nerve-gap lesions** was made, in the past twenty years, by demonstrating that an adequate functional recovery may be obtained by using simple **artificial nerve-guides**.

These simple devices are shaped as **cylindrical conduits** and protect the regrowth of neurites from the proximal stump towards the distal stump.

Artificial nerve-guides **do not provide any topographical matching** for the fibers **nor** they provide any **chemical guidance**. So, there is no way for fibers from the proximal stump to correctly match their original target territory. However, **artificial nerve-guide can achieve a high rate of clinical success** in some districts like the distal sensory nerves of the fingers of the Hand.

*How is this possible?*

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A known limiting factor in the clinical use of nerve-guides is the extension of the gap, as we do not have any artificial nerve-guide able to provide an adequate rate of recovery in gaps longer than 30 mm.

Significant research efforts have been poured into the improvement of the characteristics of artificial guides in terms of support they may provide for the cells (spinal cord neurons and Schwann cells), mostly in terms of local delivery of growth factors (both neurotropic and vasculotropic).

We found interesting to note that none of the engineered guides proved to be significantly more successful than the traditional simple hollow tubes.

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How is this possible?

At the **anatomical level**, the continuity of the **nerve fibers** (axons and dendrons) is interrupted, as well as the continuity of the **Schwann cells** row which accompanies each fiber, together with the integrity of **blood vessels** inside and around the nerve.

At the **physiological level** the first and most obvious consequence of the lesions is the loss of the function of the cut **nerve**. It **will not transmit any electrical impulse** to and from the neurons which contributed its fibers.
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It is important to remind that these neurons are alive after the lesion, so the repair process starts very soon.

We describe nerve regeneration in peripheral nerve-gap lesions as a complex process in which different types of cells and several chemical factors interact together. This interaction, when successful, leads to the achievement of the anatomical restoration of nerve fibers.
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We describe nerve regeneration in peripheral nerve-gap lesions as a complex process in which different types of cells and several chemical factors interact together. This interaction, when successful, leads to the achievement of the anatomical restoration of nerve fibers.

It is important to underline that this anatomical restoration is not the same as functional restoration.
The success of anatomical restoration of the nerve fiber can be ascribed to two occurrence:

1- new neurites come in contact with SC and proceed to form new fibers towards the distal;

2- new neurites come in contact with SC and they connect with not yet digested distal remains (in particular, with the laminin outside envelope).

This anatomical restoration may have little clinical significance if the target is mismatched.

It is the successful match of the distal target which can be clinically labelled as “nerve regeneration”.

How can simple hollow tubes achieved that?
Nerve Repair

Brain Plasticity
Nerve Repair

A primordial built-in mechanism for nerve repair which appeared before Brain Plasticity
The repair process starts quite immediately.

*Cleveland Clinic, 2006. Illustrator, David Schumick, BS, CMI.*
Unfortunately, fibroblasts in the nearby respond to the lesion as well and start a scar tissue formation. This reaction is extremely adverse to nerve regeneration and may definitively impede it.

However this reaction is physiological as it is very basic and primordial and likely older than the appearance of the peripheral nervous system itself.

Combining results from **in-vitro** studies, **in-vivo** studies, and **in-human** studies, it is possible to support the conclusion that the **physical environment** which is provided by the artificial nerve-guides plays a key role in their mechanism of action.

Merolli A. *Modelling peripheral nerve from studies on “the bands of Fontana” and on “artificial nerve-guides” suggests a new recovery mechanism which can concur with brain plasticity*. *Am J Neuroprotec Neuroregen* 2016, in press


Merolli A, et Al. *A more detailed mechanism to explain the “bands of Fontana” in peripheral nerves. Muscle Nerve* 2012 Oct;46(4):540-7


a Carbon Fiber suspended in culture
day 2

Human Schwann cells
day 4

nucleus

outfoldings (blebs)
Periodicity 38 um
Length of a white step 22 um
Length of a dark step 16 um
Step height 1 um
Lateral size of slope appr. 2 um
Merolli A, et Al. In-vivo regeneration of rat sciatic nerve in a double-halved stitch-less guide: a pilot study

Microsurgery, 2009
Schwann’s cell
Regeneration Chamber
7 days
34 days
regenerate
regenerate
in 2008
3D printing:
rapid prototyping PEG
digital nerve
second-look at 3 months
MEDIAN nerve at the wrist 43 years 25 mm gap 37 days after trauma

Second-look at 8 months
By the end of the 18th century the anatomist Felice Fontana described the structure of peripheral nerve, highlighting transverse and oblique bands clearly visible at low magnification.

These bands appear like spirals able to lengthen or shorten in accordance to the stretching of the nerve.

Fontana demonstrated that the bands are optical illusions created by the arrangements of nerve fibers.
A more detailed mechanism to explain the “bands of Fontana” in peripheral nerves
Merolli A, Mingarelli L, Rocchi L
Muscle Nerve 2012 46(4):540-547
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...because nerve fibers spirals at high pitch, so any small group of them pin-point located on one side can easily spread all around in a short distance...

...so, there is a high probability that at least some fibers reach the target ...
redundancy
redundancy
No Bands in Nerve Regenerate in the Rat

5 mm
MEDIAN nerve at forearm 28 years 25 mm gap 6 days after trauma
MEDIAN nerve at forearm 28 years 25 mm gap 6 days after trauma
MEDIAN nerve at forearm 28 years 25 mm gap 6 days after trauma

redundancy

Second-look at 13 months
MEDIAN nerve at forearm, 28 years, 25 mm gap, 6 days after trauma.

*Second-look* at 13 months.

*Redundancy*
SUMMARY

1-physical protection from the cellular action coming from nearby tissues.
Nerve-guides protect growing neurites from the scar tissue reaction

2-physical guidance along a preferred direction.
New neurites could spread all around (like it happens in Neuroma);
however, the guide helps in limiting this sprouting and in directing the growth
from proximal to distal.

3-defined and computable probability of correct match based on the physical structure.
The physical structure of the nerve, has highlighted by the study of the phenomenon of
the bands of Fontana, provide a probability of correct match by simple facing the stumps.

4-physical definition of a volume for growth factors.
This will help GF to reach the growing neurite with little dispersion around tissueS.

5-physical protection from outside mechanical stresses.
As far as the direction and load of outside mechanical stresses does not disrupt the
stump-to-guide coupling, growth inside the guide is quite shielded from mechanical stimuli.
In conclusions:

- the **physical environment** provided by artificial nerve-guide may be **key factor** in achieving a structural and functional restoration in peripheral nerve lesions;

- working on the **geometry of the guide** may be as important as on new biochemical and cellular cues but it may bring the advantage to find **an easier and less expensive** way to contribute to peripheral nerve regeneration.
thank you