Human Hepatocyte Growth Factor Promotes Functional Recovery in Primates after Spinal Cord Injury: past achievements and perspective for clinical trial

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Previous report

Introduction of HGF into spinal cord using HSV-1 vector in rat SCI model significantly reduced damaged area and promoted functional recovery.


Recombinant human HGF (rhHGF) administration into subarachnoid space from right after SCI in rat.

![Graph showing rhHGF and PBS administration over time](image)

- rhHGF n > 5
- PBS n > 5

Intrathecal administration

- rhHGF 200μg/2weeks
- PBS

![Histological images](image)

* indicates significant difference.
Objective assessment of *neurological hand function* after cervical SCI to predict the therapeutic effects of intrathecal rhHGF in human treatment.
Materials and Methods

- Animals and SCI models
  adult female common marmoset (n=5 for each; rhHGF and PBS group)
  modified MASCIS protocol
    20g weight-drop from 5cm height onto exposed dura matter at C5 level
    (*Iwanami et al, J. Neurosci Res. 2005*)
- Administration of rhHGF
  intrathecal catheter insertion right after SCI from C7 level
  administration of 400μg of rhHGF or PBS for 4 weeks by osmotic mini pump

**common marmoset cervical SCI model; rhHGF 400 mg / 4 weeks**

![](image)
Highlighted points in this scaling are:
- Extension of wrist
- Pronation of forearm
- Flexion and extension of fingers
- Position sense of four limbs

Reach and grasp performance against a pen:
8 weeks after SCI

1 day after SCI

Weight bearing and hand placement in walking
Motor function analysis using original open field scoring (full score: 31 points)

Intrathecal rhHGF significantly promoted hand function after SCI

Days after injury

All data are mean ± SEM.
* P < 0.05, ** P < 0.01 Mann-Whitney test

Kitamura et al, PLoS one, November 2011 | Volume 6 | Issue 11 | e27706
Spinal tracts described by DTT in ventral white matter reflected spared rim of LFB-positive myelinated area at 12 weeks after SCI, suggesting the efficacy of DTT in vivo.
LFB staining at 12 weeks after SCI

Intrathecal rhHGF significantly spared rim of intact white matter

**P<0.01
*P<0.05 by t-test
Intrathecal rhHGF significantly preserved corticospinal tract

CaMK2α-positive corticospinal tract (CST) fibers in intact spinal cord

Intrathecal rhHGF significantly preserved corticospinal tract

CaMK2α-positive area ratio to intact spinal cord (%)
Intrathecal rhHGF did not give rise to abnormal sprouting of CGRP-positive fibers in lamina III at 12 weeks after SCI.
Exactly for clinical application

What we have to do next was
- Determine the therapeutic time window of rhHGF
- Determine the minimal-effective dose in rat thoracic SCI model

Delayed administration from 4 days after SCI also promoted functional recovery, even at much lower dose of rhHGF.
Time to move!

✓ Therapeutic effects and mechanisms in rat SCI model
✓ Therapeutic effects of intrathecal rhHGF in rat and primate SCI model
✓ Therapeutic time window and minimal effective dose

Plan for clinical trial

2011-2012  Phase I  clinical trial in people with ALS
2013-      Phase I  clinical trial in people with SCI

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