Universität Zürich[UZH]

Center of Experimental Rheumatology

Complex Regional Pain Syndrome (CRPS): Basic research and involvement of patient research partners

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1. Background

CRPS occurs after limb injury, trauma, or surgery

Clinical changes	Changes in affected limb
Sensory	allodynia, hyperalgesia,
Vasomotor	temperature, skin color
Sudomotor/ edema	swelling, sweating changes,
Motor	reduced range of motion, weakness, tremor, dystonia, pain with movement
Trophic	hair/nail/skin changes.



CRPS-affected (right) and non-affected hand (left)

Challenges in CRPS symptoms and diagnosis

CRPS patients often face disbelief because pain can seem disproportionate to the injury, visible symptoms may fluctuate, and diagnosis relies on clinical criteria rather than a definitive molecular or imaging test. The absence of a definitive diagnostic test contributes to patient heterogeneity. This can lead to inconclusive pathobiological findings and hinder targeted therapy development.

2. Aim & Significance

Aim: To combine molecular CRPS research with public outreach and patient research partner (PRP) involvement, linking biological mechanisms with patient-validated, and patient-centered research.

Significance: Objective molecular evidence can help counter disbelief, while PRP involvement ensures that CRPS research is conducted with patients and addresses outcomes relevant to them.

3. Involvement of PRP

Established PRP infrastructure for rheumatology research

- Published framework for PRP involvement in rheumatology research [1].
- Established 5-step model: infrastructure, recruitment, training, early involvement, ongoing support.
- Built network of ~80 PRPs and matched PRPs to ~20 projects.

CRPS outreach & recruitment into the PRP network

- Organized "*Forschung im Dialog*" for CRPS patients and relatives at Balgrist.
- 40 participants, >80 interested people.
- Program:
  i. CRPS research at Balgrist
  ii. Lab tour at Balgrist Campus
  iii. Introduction to PRP network



CRPS patient testimonials after event:

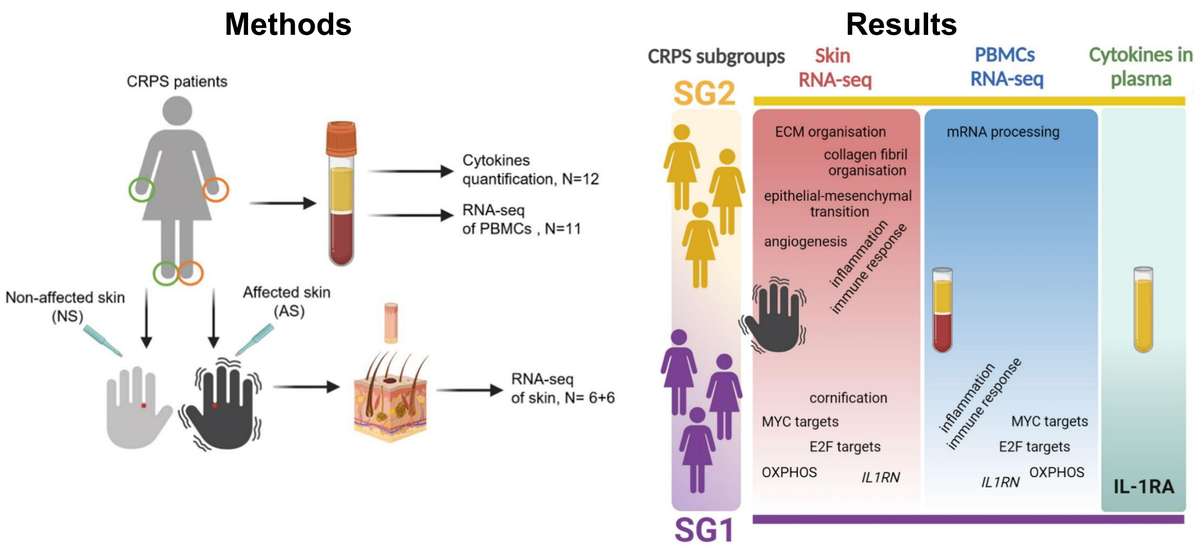
"Research helps show that CRPS pain is real – not imagined."
"Being invited into the research dialogue gives me back a sense of agency."
"Biological evidence can turn disbelief into validation."

Trained CRPS PRPs integrated in a SNSF project

- Recruited 2 CRPS PRPs from the PRP network.
- Completed PRP schooling. PRPs took part in SNSF project kick-off.
- Dedicated PRP meeting used to co-develop PRP contributions to recruitment, communication, patient retention, and study workflow.

4. Molecular evidence of CRPS pathobiology

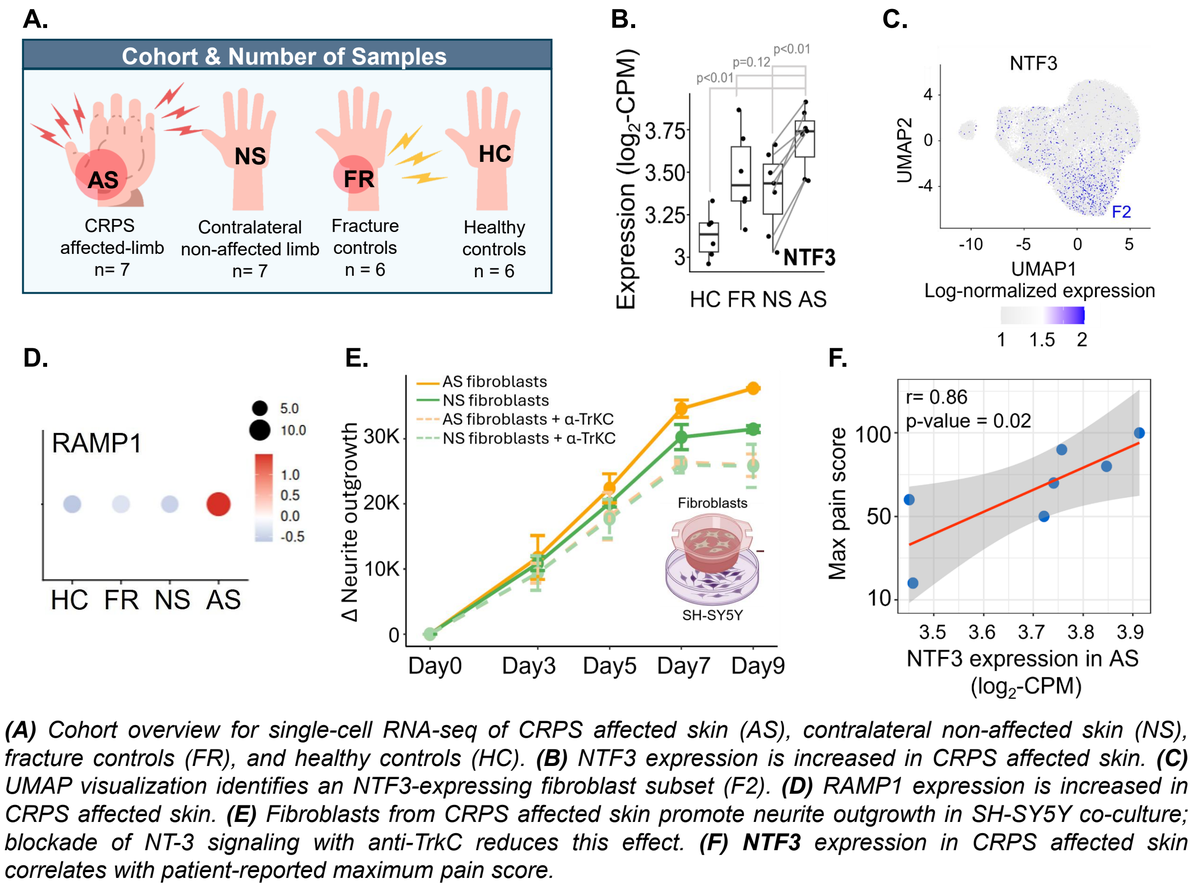
Identification of two biological subgroups of CRPS type I [2]



Identification of two biological CRPS type I subgroups (SG) by skin–blood molecular profiling. *Affected/non-affected skin, PBMCs, and plasma from unilateral CRPS type I patients were profiled by RNA-seq and cytokine analysis. Two molecular subgroups emerged: SG2 with stronger affected-skin inflammation/fibrosis signatures, and SG1 with stronger PBMC inflammation and higher plasma IL-1RA, supporting skin–blood molecular stratification for targeted diagnostics and therapies.*

NT-3/RAMP1-high fibroblasts link CRPS skin pathology to pain and neurite outgrowth

Single-cell RNA-seq of CRPS skin identified an expanded neuron-associated fibroblast subset characterized by high NTF3 and RAMP1 expression. NTF3 correlated with pain and CRPS fibroblasts promoted neurite outgrowth via NT-3/TrkC. Together, these findings support a pain-associated fibroblast–neuron mechanism in CRPS skin.



(A) *Cohort overview for single-cell RNA-seq of CRPS affected skin (AS), contralateral non-affected skin (NS), fracture controls (FR), and healthy controls (HC).* ***(B)*** *NTF3 expression is increased in CRPS affected skin.* ***(C)*** *UMAP visualization identifies an NTF3-expressing fibroblast subset (F2).* ***(D)*** *RAMP1 expression is increased in CRPS affected skin.* ***(E)*** *Fibroblasts from CRPS affected skin promote neurite outgrowth in SH-SY5Y co-culture; blockade of NT-3 signaling with anti-TrkC reduces this effect.* ***(F)*** ***NTF3*** *expression in CRPS affected skin correlates with patient-reported maximum pain score.*

5. Conclusions

- Basic molecular research demonstrates that CRPS pain is associated with measurable biological changes, including molecular subgroups and a pain-associated NT-3/RAMP1-high fibroblast subset.
- Communicating these findings through outreach and integrating trained CRPS PRPs into research can strengthen validation, agency, trust, and patient-centered study design.

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References:
[1] Buerki et al. RMD open. 2025, 11(1):e005263.
[2] Perez Vertti Valdes. Mol Med. 2025, 31(1):94.