Technical Meeting on Advances in Boron Neutron Capture Therapy

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Clinical trial investigations on BNCT by molecular and network medicine

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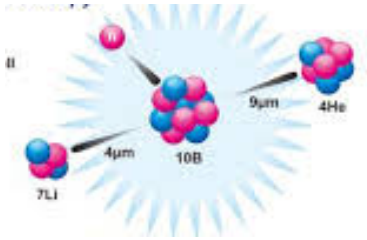
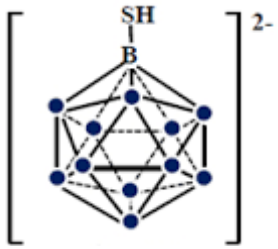
All authors are partners in the "RENOVATE Consortium"

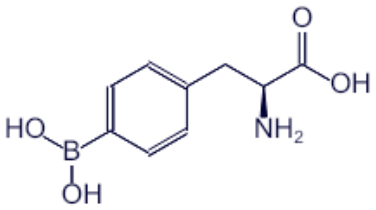


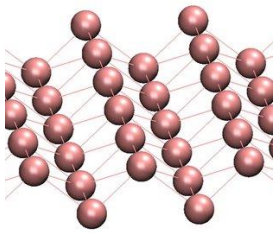


Recent improvements of accelerator-based neutron sources for hospitals will increase the application of BNCT cancer therapy. However, even after tumor-selective BNCT, recurrence may occur.

The reasons for such recurrences after BNCT have not been fully elucidated, but they may reflect tumor characteristics.

It is required to improve by biomedical investigations the understanding of the biochemical and physiological aspects.

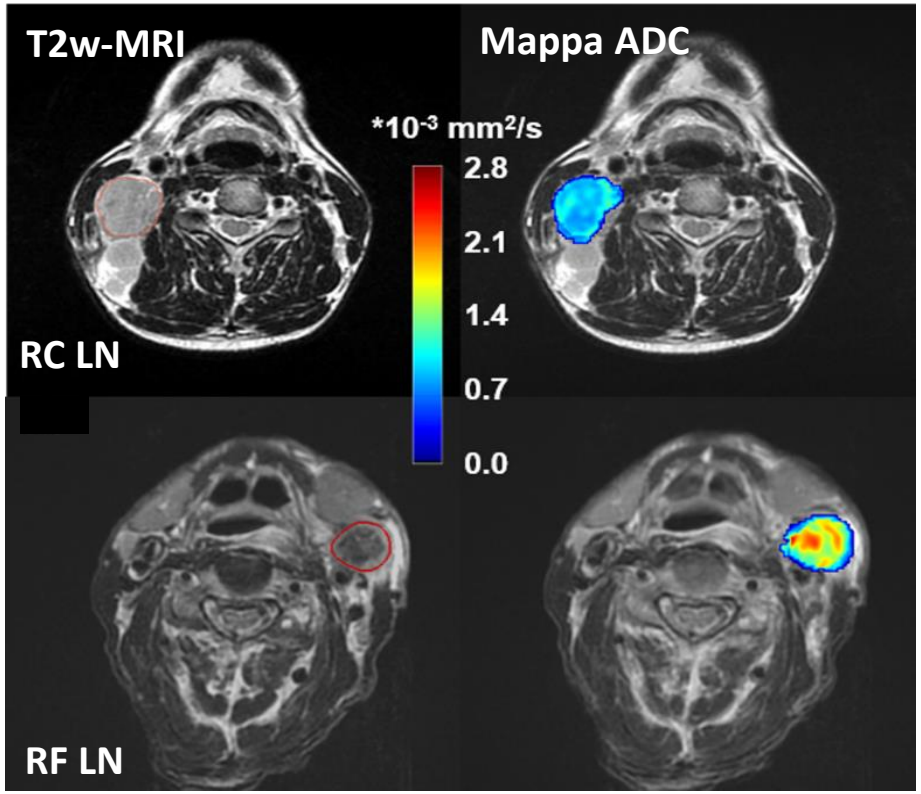




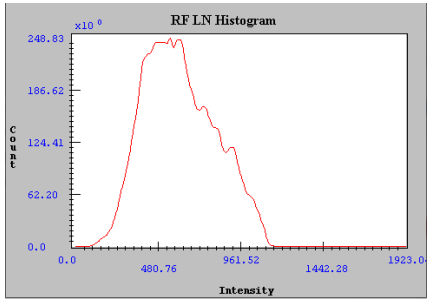
In the treatment of (HNSCC), the early prediction of residual malignant lymph nodes (LNs) is currently required.

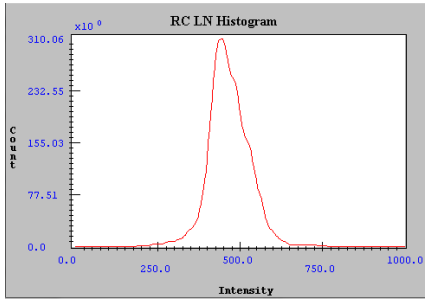
Rizzo & co-workers suggest that TA on T2w-MRI and ADC can be combined together to obtain a more accurate prediction of response to CRT.

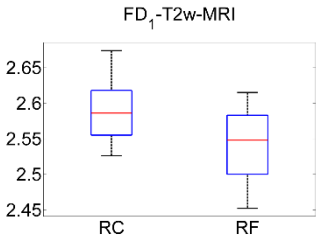
Prediction of tumor response to RT in HNC

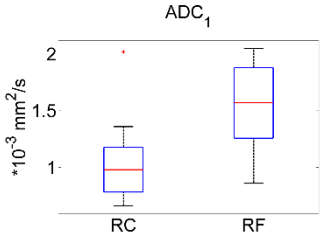


- **30** patients considered (19 with RC LNs; 11 with RF LNs)
- Features selection with **Spearman correlation**
- Prediction with **Fisher's Linear Discriminant Analysis**
- **Leave-one-out** validation





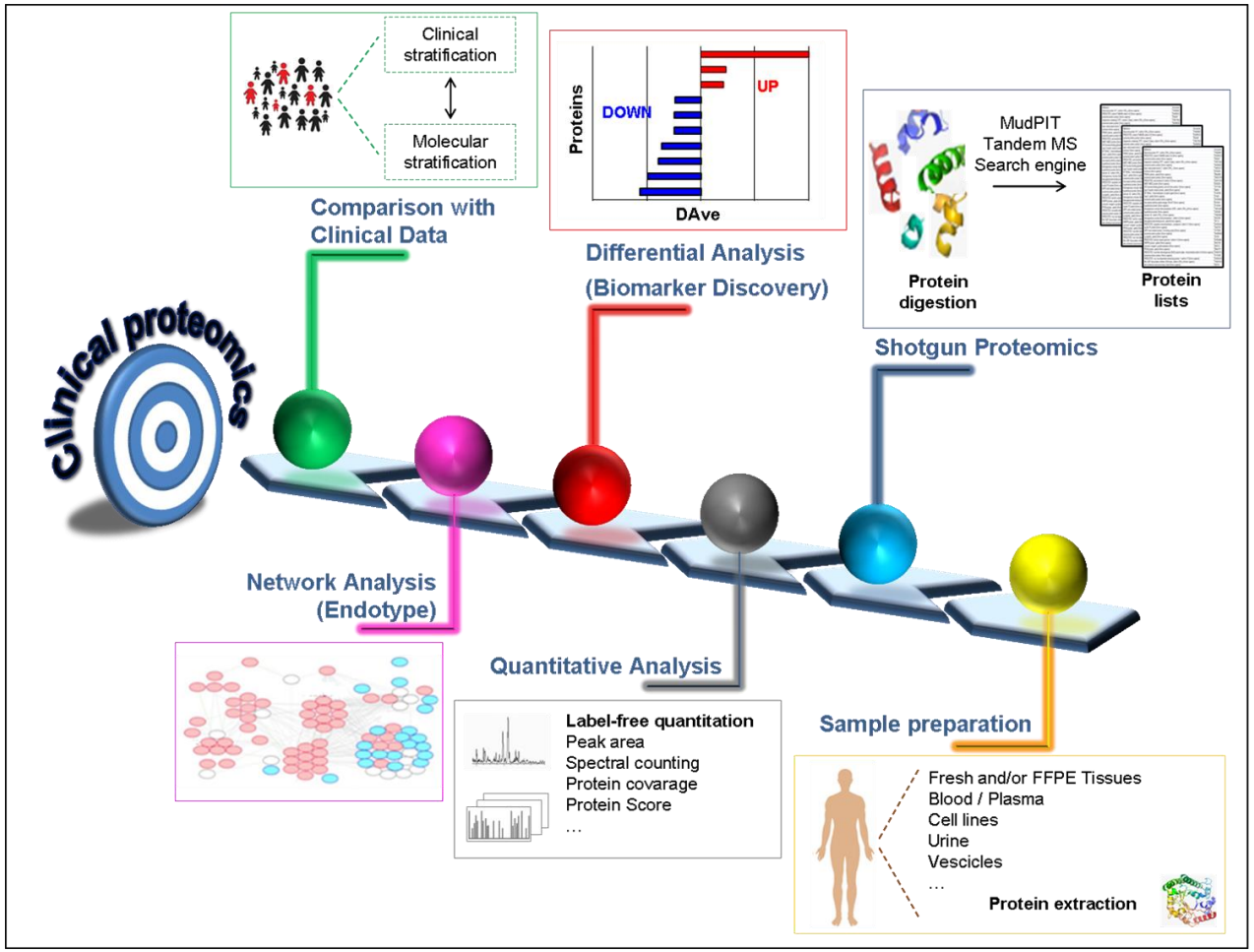




- RF LNs more hetero-geneous, but with less complexity (necrosis areas)
- RC LNs more homogeneous and complex (absence of necrosis areas)

Scalco et al, 2016. Physica Medica. 32: 1672-1680.

In this context, innovative molecular profiles, can be of great importance to facilitate improvements of radiotherapy, specifically for BNCT.

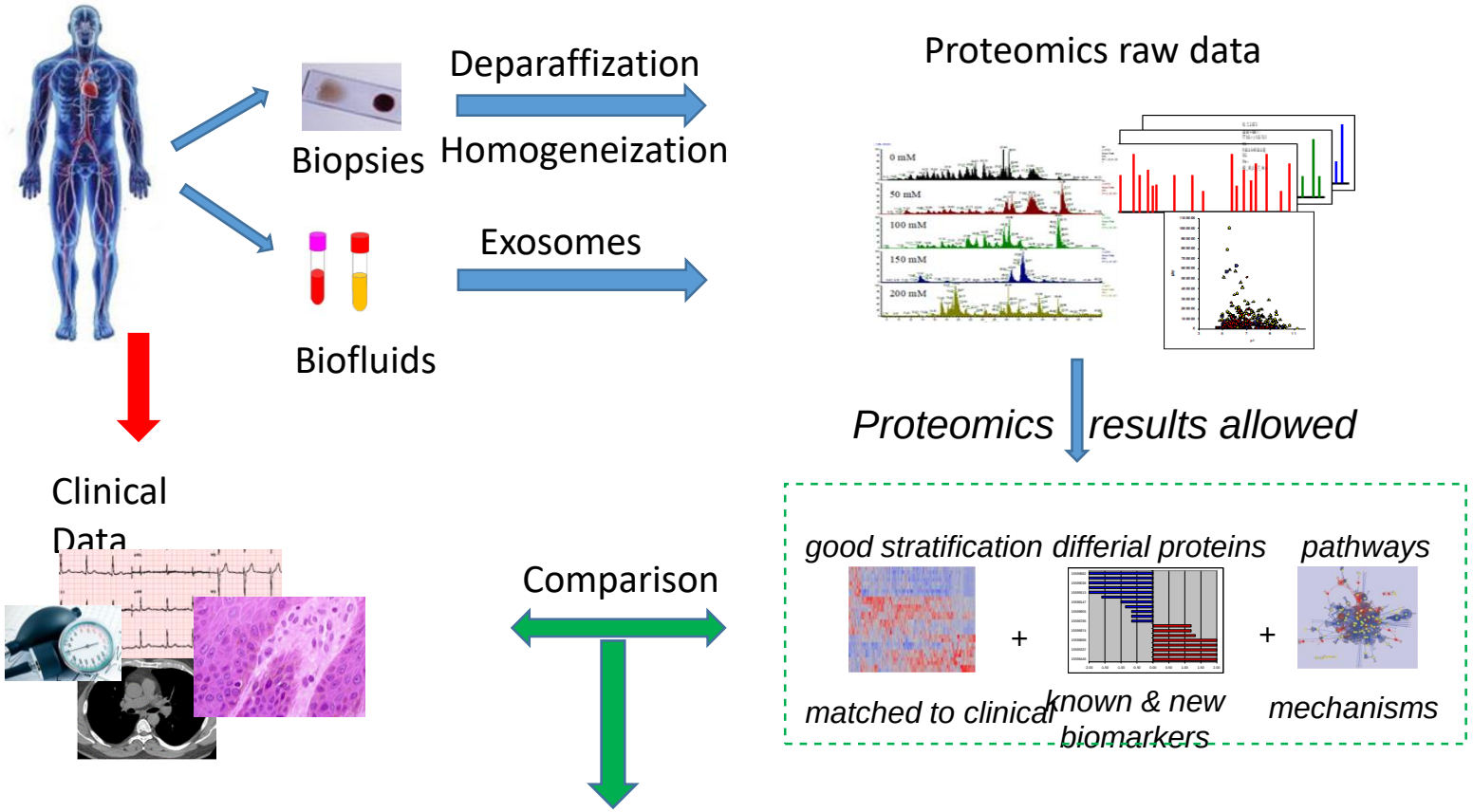


In particular, the great progress of proteomics methodologies, allow a deeper investigation of human diseases and their therapies.

The main aims of clinical proteomics concern:

1) characterization of profiles related to specific physio-pathological conditions;
2) biomarker discovery for diagnosis and useful for monitoring therapy;
3) evaluation of metabolic clusters grouping the biomarkers involved in the disease
4) investigation of molecular mechanism (endotypes) correlating clinical stratification and disease etiology, useful to develop a target therapy.

Shotgun proteomics may be used to analyze a wide range of samples, including tissue, fresh. Frozen and paraffined, cell lines and biofluids (exosome, mainly)



Personalized Medicine

- Biomarkers for early diagnosis and predictive of therapy effect
- Disease- and therapy-related pathways (endotypes)

Non-invasive monitoring of the development of the disease and the therapeutic effect may be performed by analyzing the circulating exosomes.

Exosomes are a mirror of physio-pathological states of subjects, and they are a very important complement to the traditional biopsies.

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Proteome Profiling of Neuroblastoma-Derived Exosomes Reveal the Expression of Proteins Potentially Involved in Tumor Progression

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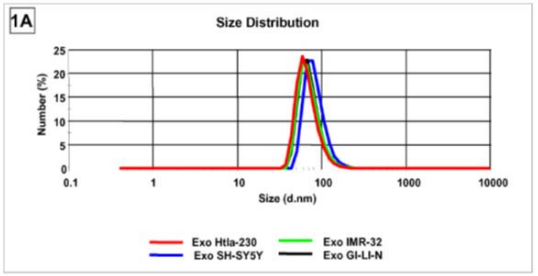
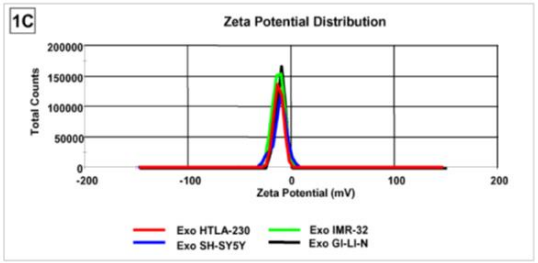
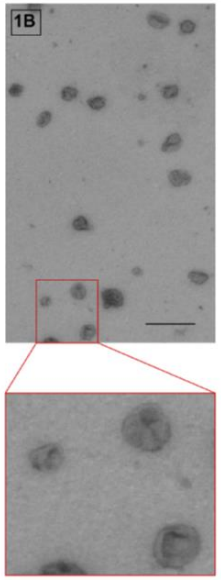






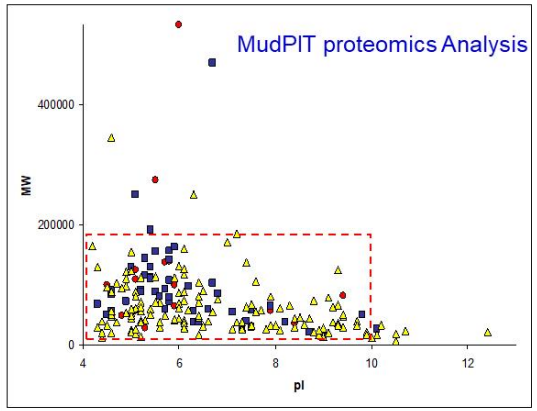
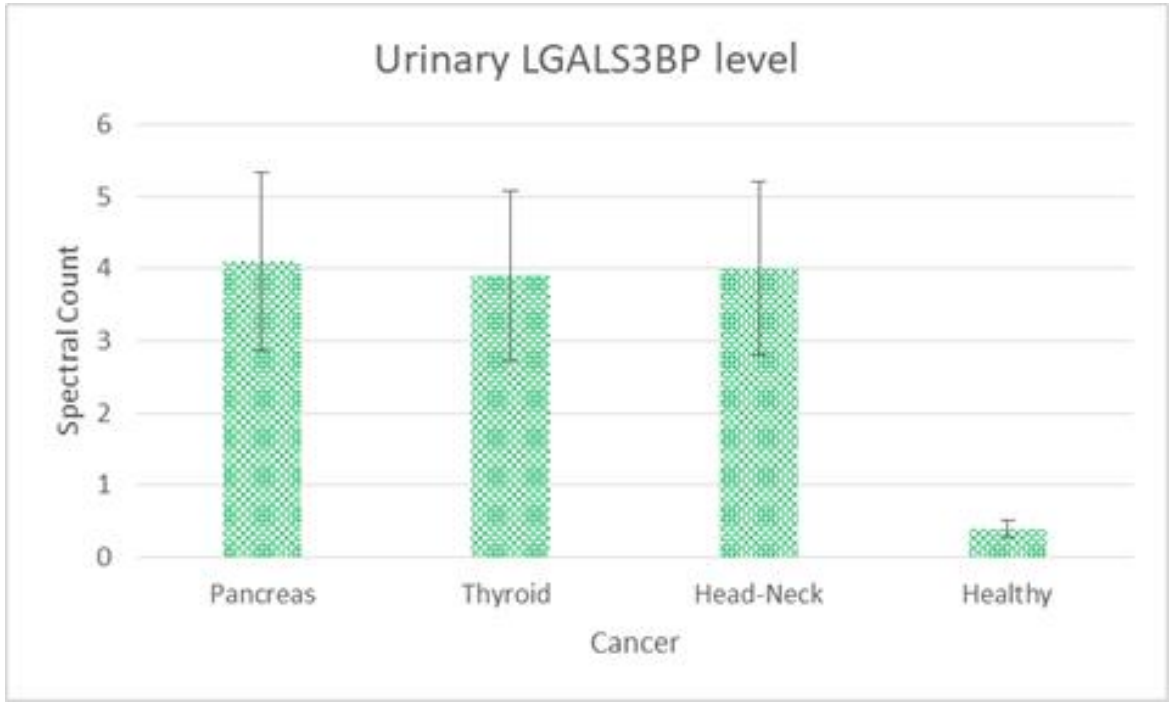


Figure 1. Physical charachterization of NB cell-derived exosomes. Size distribution (panel A) and Zeta Potential (panel C) of NB cell-derived

The combination of non-invasive samples with shotgun proteomics, integrated by network analysis, is contributing the developing of a Clinical Proteomics strategy, involving the characterization of biomarkers and perturbed molecular pathways in relation to disease states.

Biomarkers of pathological states can be detected in biofluids, including inflammatory proteins, such as galectin-3 binding protein (LGALS3BP).

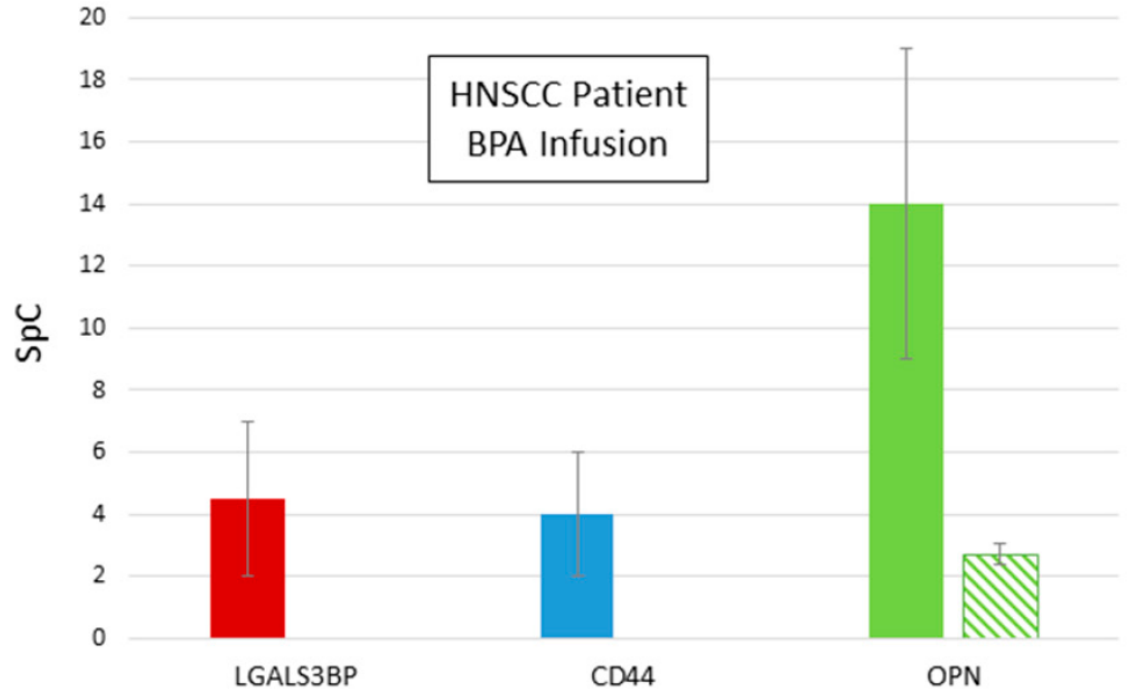
This protein is detectable in urine of cancer patients, such as pancreas, thyroid and head-neck (HNC) tumors, and it resulted overexpressed in comparison to healthy.



Masutani & Mauri, Chapter 22
in Neutron Capture Therapy - Principles and Applications

In relation to boron infusion,by means of proteomics a reduction in three proteins has been observed: galectin 3 Binding Protein (LGALS3BP), CD44, and OPN (SPP1)

These glycoproteins are involved in inflammatory processes and possibly tumor progression.

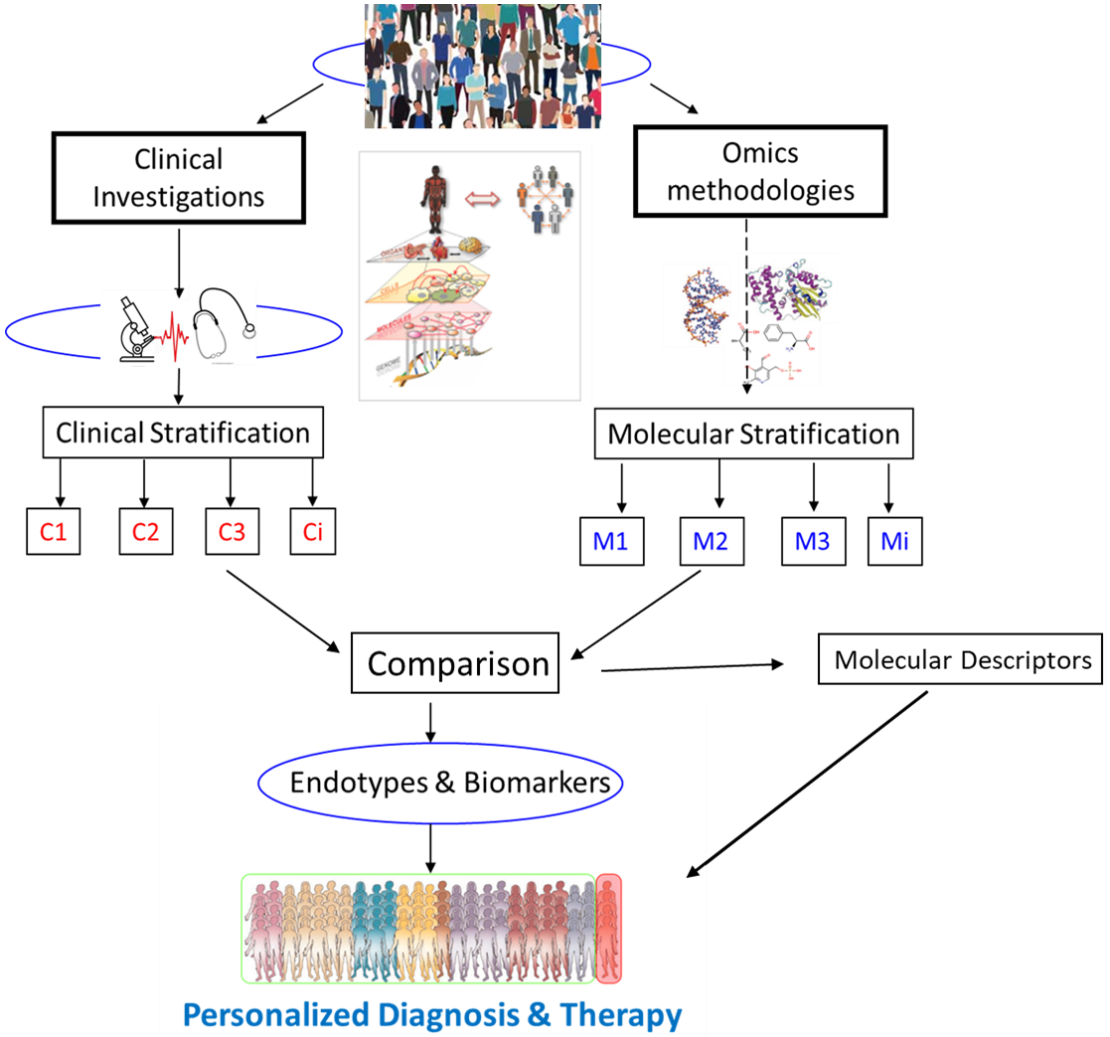


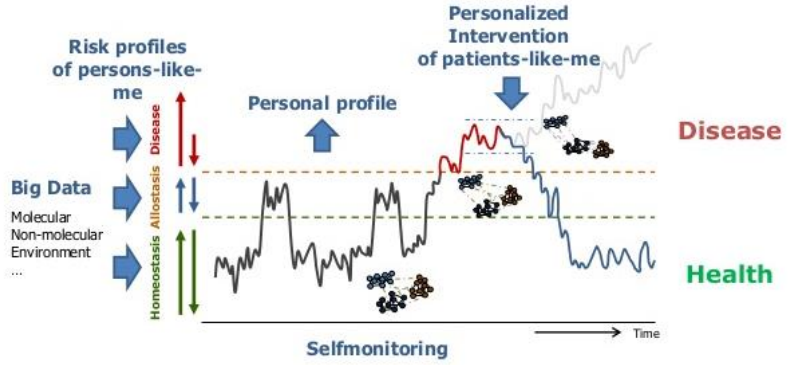
Protein levels before (solid fill) and after infusion (diagonal lines fill)

The three proteins were reduced or even absent in urine that was sampled after boron compound infusion.

*Ferrari et al., Molecules **2019**, 24, 794*

Boron Neutron Capture Therapy will take advantages from molecular investigations. In particular, with such tools it becomes possible to study the effects due to each step of treatment: boron infusion and neutron beam irradiation.

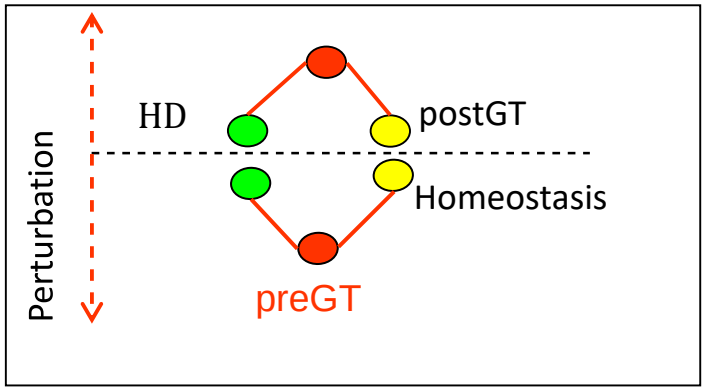


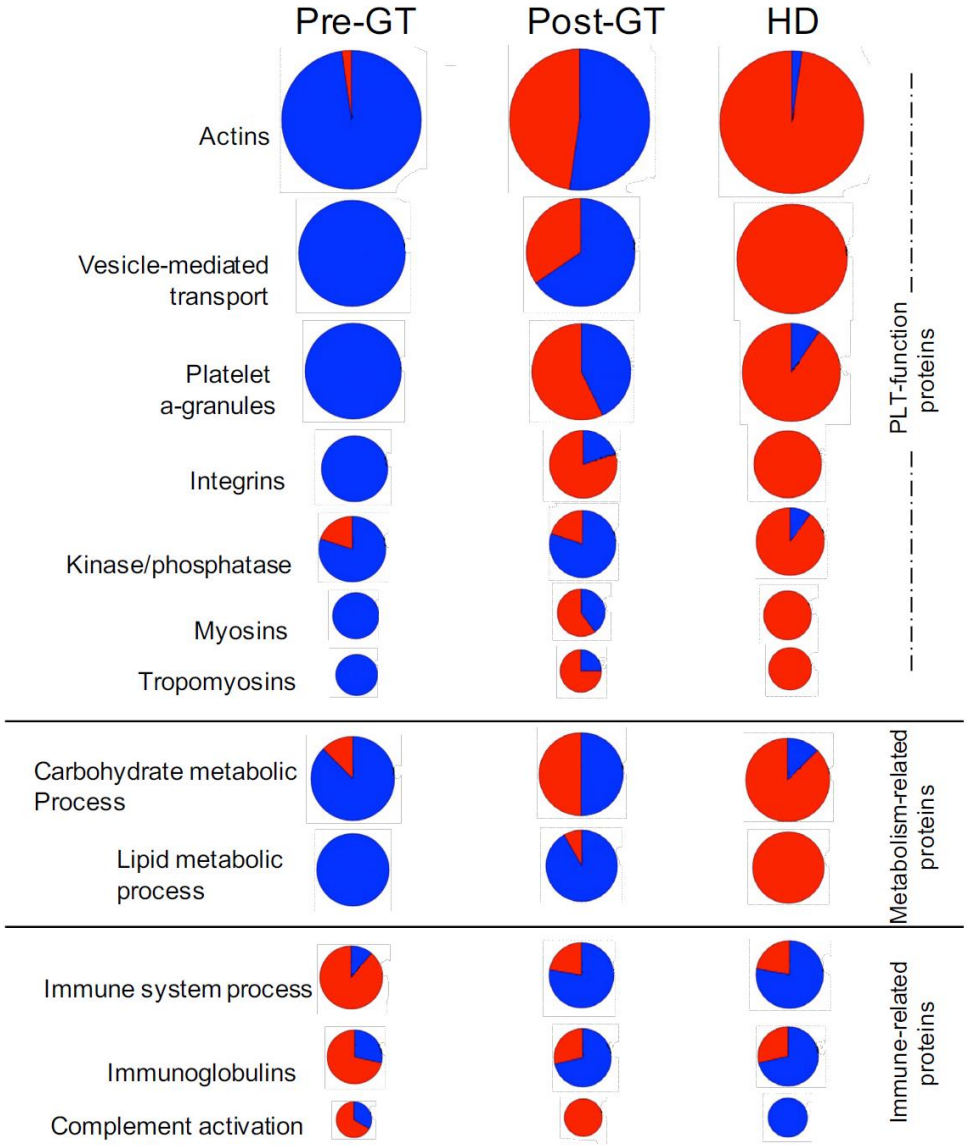


Adapted from Jan van der Greef (2013)

Proteome Recovery *index* (PR*i*) is a new algorithm allowing the identification of disease- and therapy-related pathways, recovered by after treatment.

As an example, it was characterized in WAS patients (Pre-GT) the pathways perturbed and recovered to healthy (HD) after gene therapy (Post-GT).

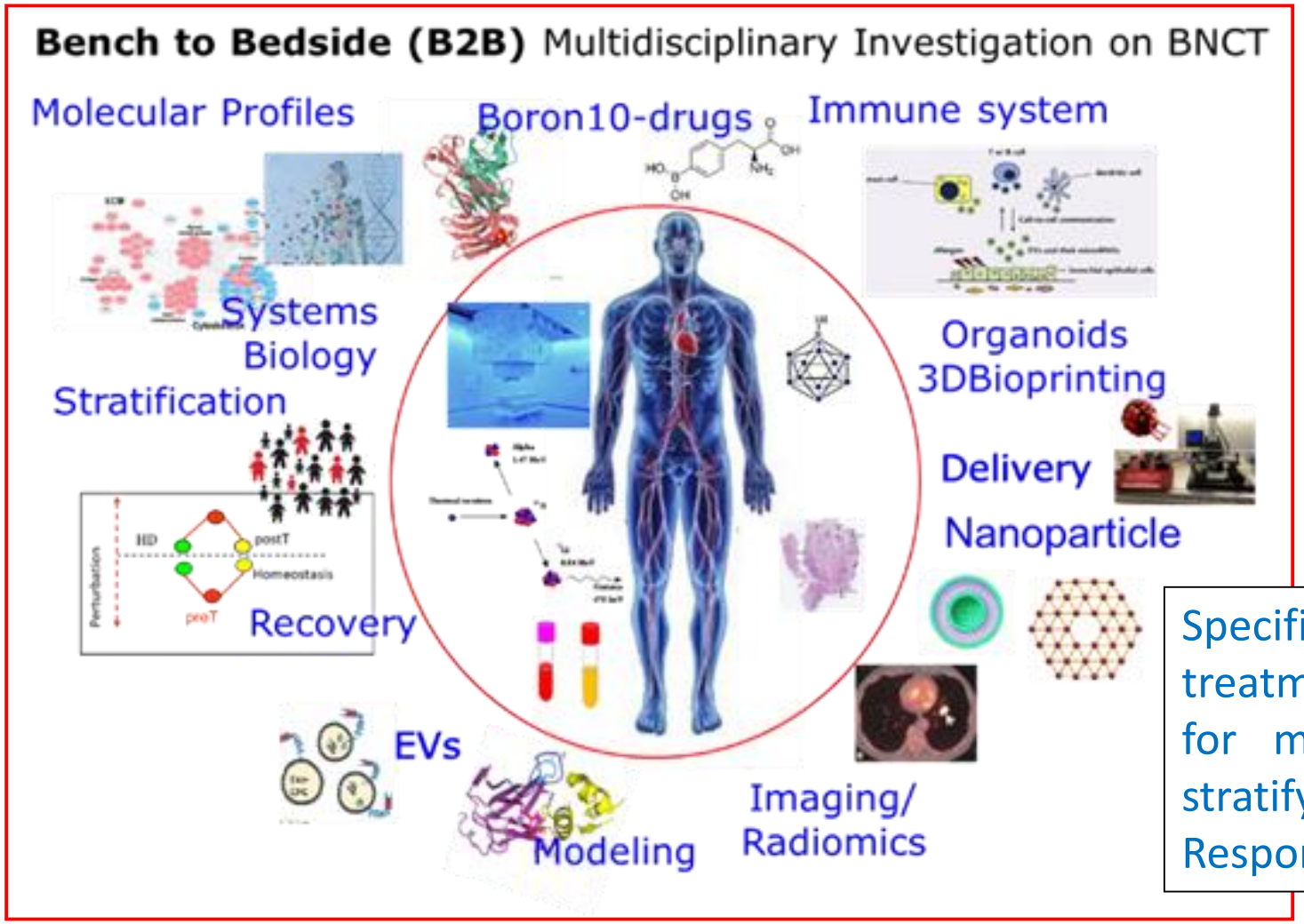




THE JOURNAL OF Allergy AND Clinical Immunology

Sereni et al., JACI (2019)

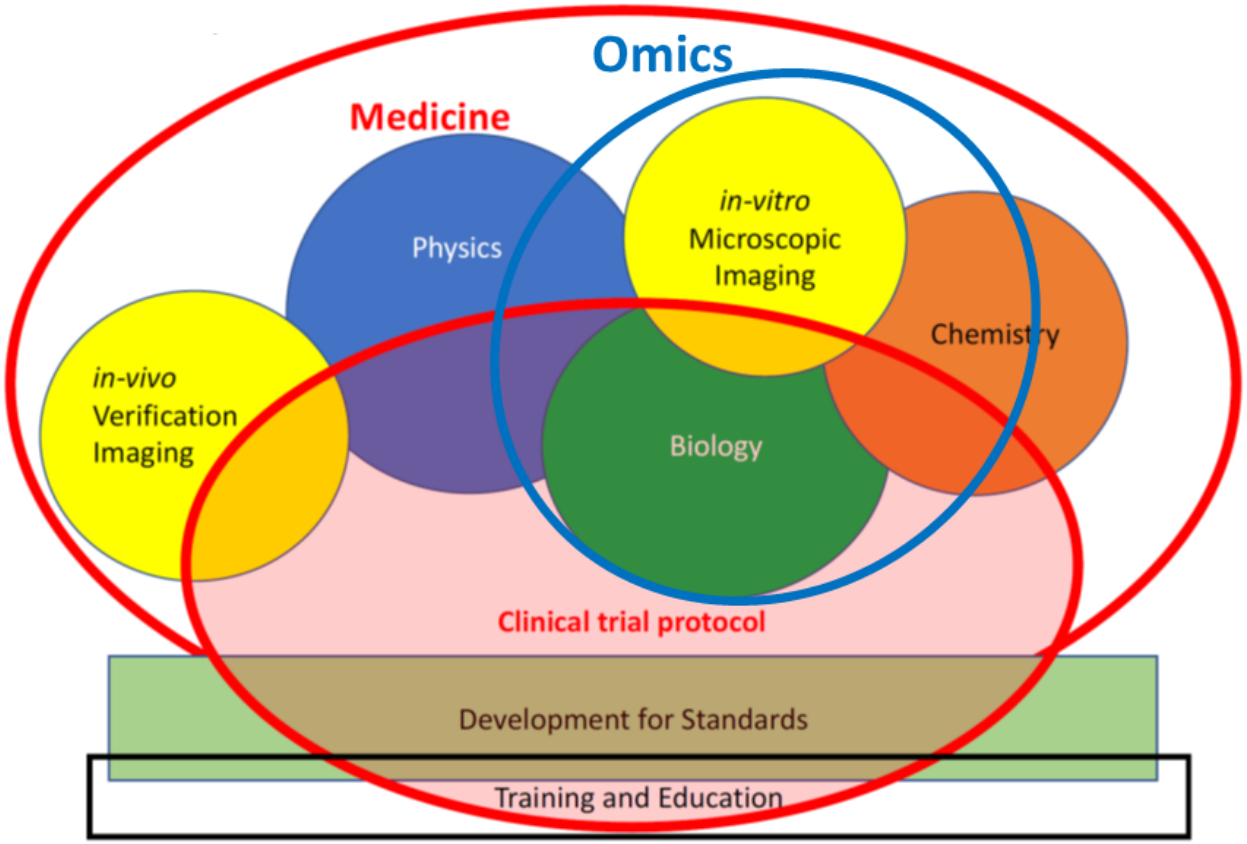
Multidisciplinary investigation integrates **physical-molecular-medical studies** of **neutron therapy**, including radiomics, **new boron-containing drugs and delivery approaches**



Specifically, molecular profiles of patients before treatment, characterization of biomarkers useful for monitoring efficacy and side effects, and stratifying subjects can allow the predictive Responders and Non-Responders to therapy

In the next future, this strategy will permit the monitoring of therapeutic efficacies and identification of disease- and therapy-related pathways.

These are important issues for developing a future Precision/Personalized Medicine in BNCT, involving the characterization of different subtypes of cancers, determined by different biomarkers leading to the eligibility of the patients to specific therapeutic treatments.



Modified from RENOVATE presentation

In this context *RENOVATE Consortium* will be of primary importance to *accelerate* synergic activities for BNCT.

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