ULICE WP 3
„Biologically based expert system for individualised patient allocation“

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Objectives of WP 3

Objectives This work-package aims at developing a novel radiobiologically-driven software prototype which allows:

- biologically-based decision making for rational individualised allocation of tumours of different entities, stages and biology to treatment with photon beams vs. proton beams vs. ion beams (expert system module);
- biological stratification of prospective and retrospective uni- and multi-centre clinical data for state-of-the-art multiplexed analysis of the value of hadron beams for tumours of different entities, stages and biology (research tool module).

Motivation and Aim

- Scientific-based allocation of patients to different treatment modalities
- Limited availability of hadron beam therapy facilities
- Patient selection is essential for resource optimization

Development of a software prototype with two different aspects:

- Expert system module: Support to decision making about the best treatment option for an individual patient, based on radiobiological aspects of the tumor and patient features: photons vs protons vs carbon ions
- Research tool module: Multiparameter analysis of clinical data to determine the value of hadron therapy for different tumor entities, stage and biology

Defining the strategy

- The previous tasks are not easy:
  - Lack of accessible, individual clinical patient data
  - Series of patients not comparable
  - No randomized trials (lack of comprehensive data on tumor reactions against high and low LET radiation)

- First task: definition of strategy (What is our goal - What is possible)
- Several concepts are possible

Concept I: Retrospective analysis

- Retrospective analysis of individual patient outcome data, treated with all three modalities
- This requires the creation of a database
- Collection of retrospective patient data practically not feasible
- Many series of patients treated with carbon therapy, many more with proton therapy but very heterogeneous data
  - different dose prescriptions
  - different fractionation
  - different physical beam properties

➡ Retrospective joint outcome analysis even on individual patient data is not possible

➡ Only qualitative assessment

Concept II: Decision based on tumor parameters

- Basic assumption: similar dose distributions delivered by protons and carbon ions
- Comparison of protons (low LET) versus carbon ions (high LET)
- Prediction based on a set of parameters that describe features of a specific tumor, e. g.:
  - alpha/beta ratio
  - hypoxia
  - proliferation
  - tumor volume
- Implies, calculation of the therapeutic gain:

$$f = \frac{RBE_{Tumor}^{HiLET} \,/\, RBE_{OAR}^{HiLET}}{RBE_{Tumor}^{LoLET} \,/\, RBE_{OAR}^{LoLET}}$$

(Ando et al 2005)

Concept II: Decision based on tumor parameters

- Determination of the RBE:
  - modelling or experimental data
  - RBE = RBE(LET, D, …), e.g., Joiner, Scholz

- Only modelling is possible

➡ Normal tissue must be included

➡ Treatment planning

Concept III: prospective decision tool

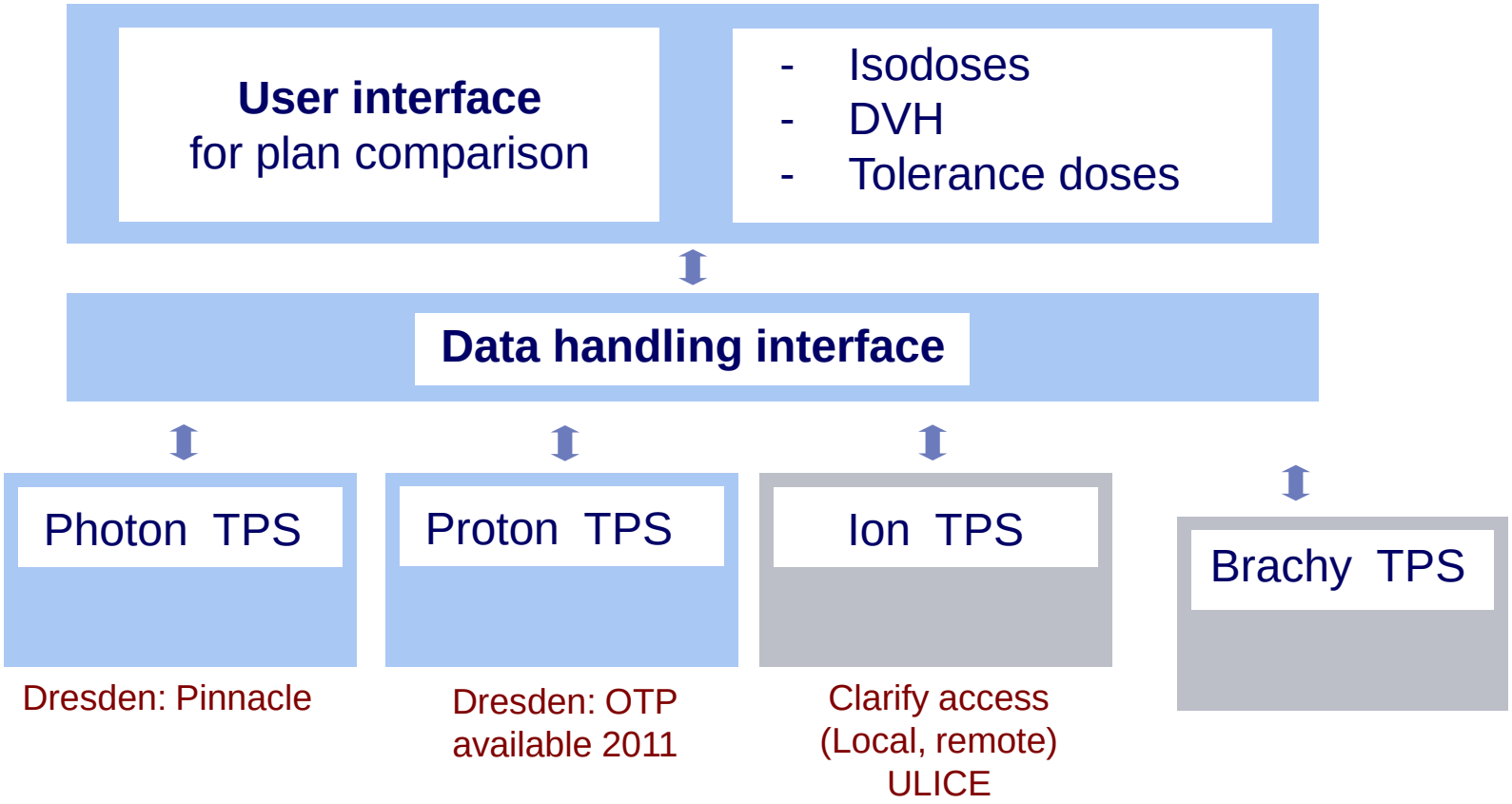
- Decision on the best treatment has to be based on the available methods:
  - clinical expertise
  - current irradiation machines
  - and treatment planning systems
- The first level of the comparison between modalities must be based on comparative treatment planning
- Normal tissue reaction has to be included in the analysis
- The introduction of quantitative criteria for the comparison is required: Different TCP and NTCP models will be implemented

Concept III: prospective decision tool

- The third decision level: Other tumor and patient features will be integrated into the system, e. g., age, co-morbidities, hypoxia info, gene profiling info
- The tool will allow the validation of the models (**Research tool)**

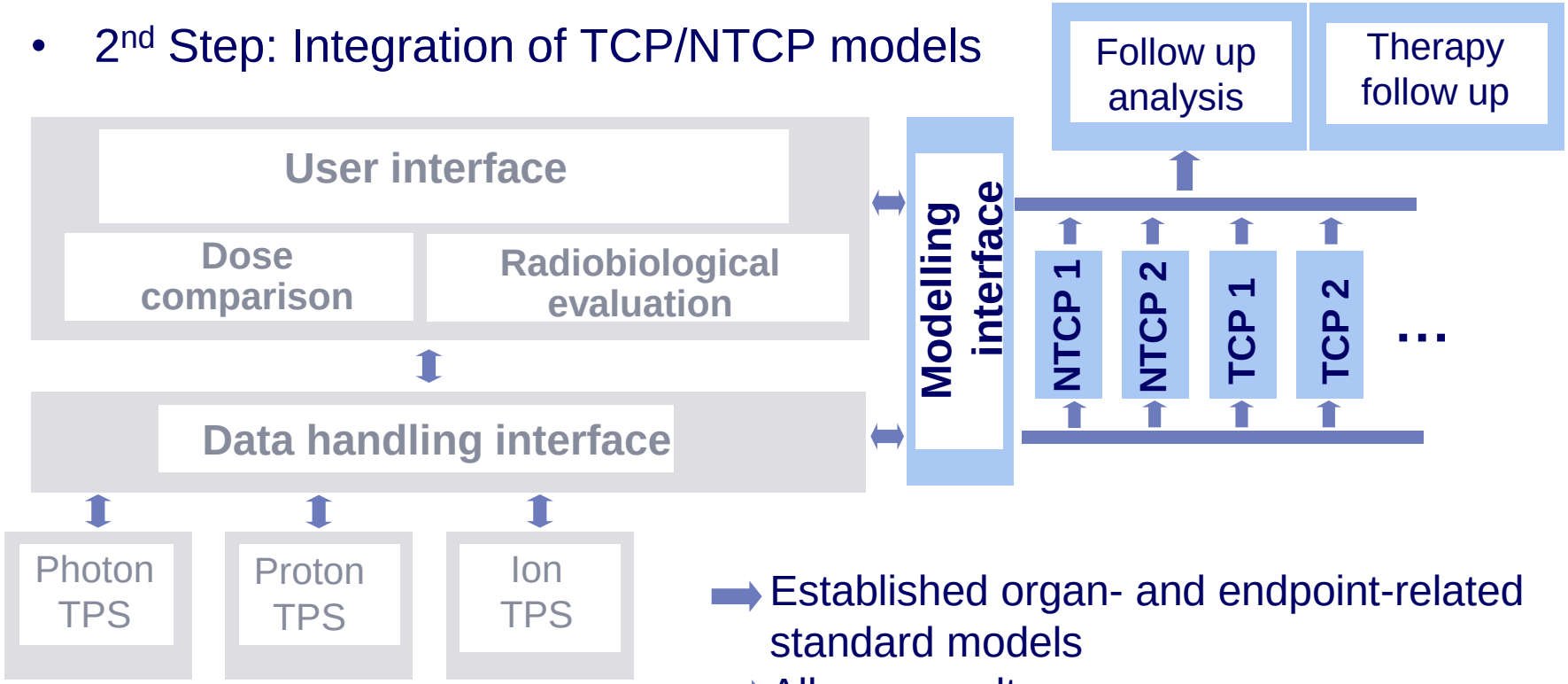
Concept III: prospective decision tool

- 1st Step: Prototype in Dresden



Concept III: prospective decision tool

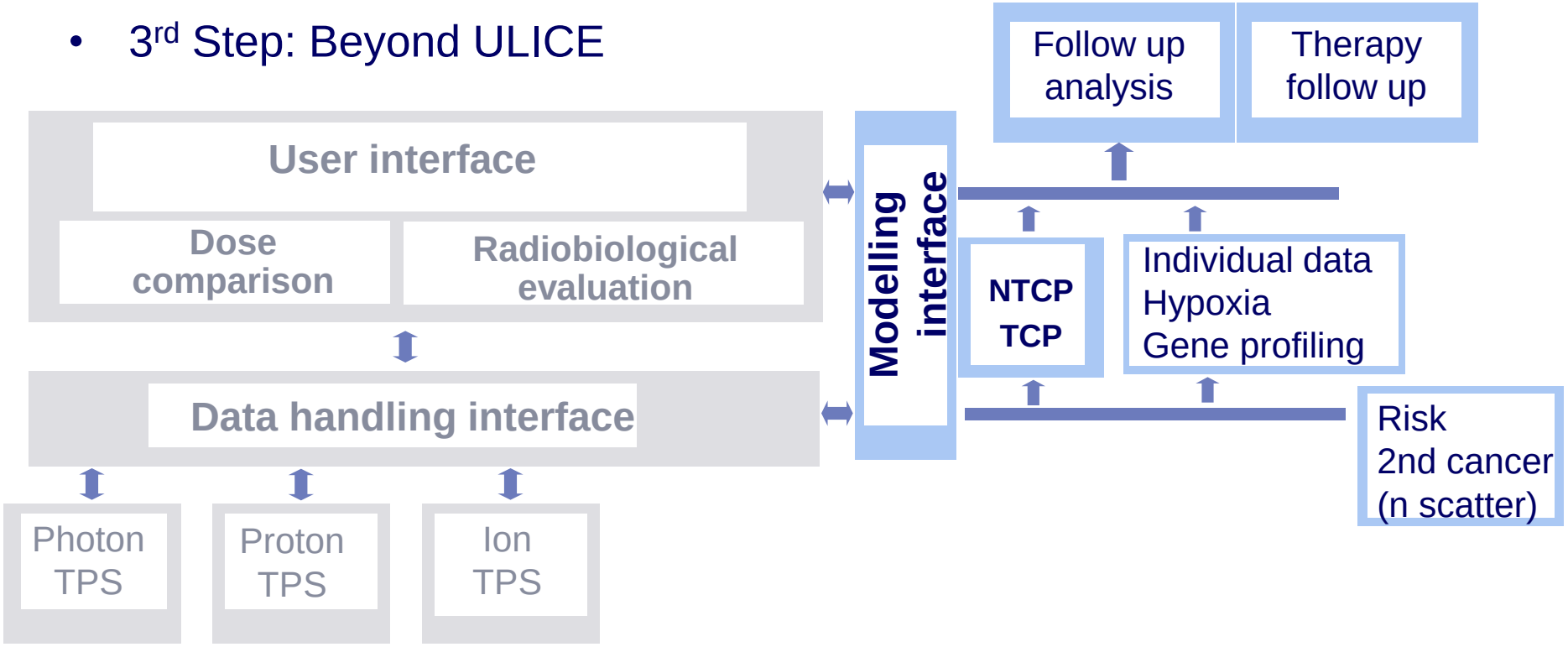
- 2nd Step: Integration of TCP/NTCP models



- Established organ- and endpoint-related standard models
- Allegro results

Concept III: prospective decision tool

- 3rd Step: Beyond ULICE



Work in progress: Deliverables

3.1	Evaluation of the world-wide radiobiological data base for rational decision making in prescription of different hadron beams	Michael Baumann
3.2	Development of unified protocols for measurement of radiobiological relevant parameters in individual patients and generation of exemplary data sets	Vincent Grégoire

R. Gahbauer (UCL Brussels)

A. Santiago (TU Dresden)

Work in progress: Deliverables

3.1/3.1	List of radiobiological relevant parameters determining tumour control dependent on the beam quality	M 18	Apr 2011
3.2/3.2	Report of different methods available for measurement of radiobiological relevant parameters in patients	M 18	Apr 2011
3.3/3.1	Report on data of the radiobiological effects of different beams on tumours	M 18	Apr 2011
3.4/3.3	Structure of the software modules	M 18	Apr 2011
3.5/3.2	Provision of exemplary molecular imaging data sets to WP 5	M 18	Apr 2011

R. Gahbauer: D3.2

A. Santiago: D3.1 and D3.3

WP 3.2: Selection criteria

Selection criteria low vs high LET: Resistance as indication for ions

1. Tumors succesfully treated with high LET
2. Expected benefit from high LET due to:
    - hypoxia
    - proliferation
    - repair characteristics
3. Location near sensitive structures
4. Consider normal tissue consequences (paediatric tumors)

WP 3.2: Selection criteria

5. General selection criteria:
   - Subset selection most important: High frequency of occurrence, high clinical variability and range in prognosis
   - Subset selection not very important: low frequency of occurrence, historically bad outcomes and known resistance

6. Predictive Methods to quantify resistance in individual patients:
   - Individual history, estimation of growth rate, clinical judgement
   - Imaging: PET, Nuclear Medicine imaging, fMRI
   - Molecular, genetic profiling, genetic expression and hypersensitivities
   - Hypoxia (polarometric measurements, markers of, PET, MRI etc)
   - Repair characteristics (linear quadratic parameters NT/Tumor)

WP 3.1: Evaluation of the radiobiological data

- Review has been performed, report will be finished in time
- Main conclusions (shaped the software tool concept!):
  - Retrospective analysis: only qualitative
- Review rationale for high LET:
  - RBE studies, from the perspective of the therapeutic gain
- Decision based on set of tumor / NT parameters not possible

➡ Modelling RBE

WP 3.1: Evaluation of the radiobiological data

- Besides, other parameters which determine LTC
  - Tumor volume, location (determines D)
- Account for individuality:
  1. Treatment planning (C12, proton, photons)
  2. Prospective assessment (TCP/NTCP)
  3. Patient features, tumor features